Université de Montréal

Synthèse totale de la pactamycine et d'une sélection d'analogues, progrès vers la synthèse totale de la daphniglaucine C et brève étude d'une transposition allylique réductrice

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Cette thèse intitulée :

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progrès vers la synthèse totale de la daphniglaucine C et brève étude d'une transposition allylique réductrice

présentée par :

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Résumé

Il y a plus de cinquante ans, la pactamycine a été isolée en tant qu'agent antitumoral potentiel. Il a été réalisé plus tard qu'il s'agissait en fait d'un agent antibactérien capable d'inhiber la synthèse de protéines lors du procédé de traduction. Récemment, il a même été démontré que certains de ses analogues possèdent des propriétés antiprotozoaires prometteuses. La présente thèse détaille la première synthèse totale de la pactamycine, entreprise au sein du groupe Hanessian, ainsi que la préparation d'une sélection d'analogues testés pour leurs propriétés biologiques.

En outre, la daphniglaucine C appartient à une vaste famille de composés naturels isolés des feuilles du *daphniphyllum* au cours des dix dernières années. Bien que relativement peu d'information soit connue par rapport à l'activité biologique de la daphniglaucine C, la synthèse de celle-ci représente certainement un défi intéressant pour un chimiste organicien. Au passage, nos efforts vers la synthèse totale du composé cible auront permis d'explorer l'emploi de plusieurs méthodes en vue de la formation de centres quaternaires. De plus, un réarrangement réductif atypique, catalysé au palladium à partir d'alcools allyliques non-activés, a été étudié et employé afin de générer une sélection de pyrrolidines polysubstituées.

Mots-clés

Pactamycine, daphniglaucine C, pyrrolidines polysubstituées, aminocyclopentitol, alkaloïdes, antibiotique, anticarcinogène, antiprotozoaire, synthèse totale et diastéréosélective, réarrangements sigmatropiques, centres quaternaires, alcools allyliques, palladium, réarrangement de Payne.

Abstract

Although pactamycin was first isolated as a potential antitumoral drug, further studies highlighted its capacities in inhibiting protein synthesis, and thus its potency as an antibacterial agent. Furthermore, it was recently discovered that some of its analogs display promising antiprotozoal activity. The present thesis reports and details the first total synthesis of pactamycin, pursued in the Hanessian lab over the last few years, as well as the preparation of a selection of analogs thereby tested for their biological properties.

Daphniglaucin C belongs to a large family of natural compounds isolated from the leaves of *daphniphyllum* over the last decade. Although relatively little is known as to the biological activity of daphniglaucin C, its synthesis poses an obvious and interesting challenge for organic chemists. En route towards its total synthesis, the use of several methods for the formation of quaternary centers was explored. Moreover, an atypical reductive allylic transposition, catalyzed by palladium from unactivated allylic alcohols, was studied and used to generate a variety of polysubstituted pyrrolidines.

Keywords

Pactamycin, daphniglaucin C, polysubstituted pyrrolidines, aminocyclopentitol, alkaloids, antibiotic, anticarcinogenic, antiprotozoal, total synthesis, diastereoselective synthesis, sigmatropic rearrangements, quaternary centers, allylic alcohols, palladium, Payne rearrangement.

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Ac	acétyle
ABCN	1,1'-azobis(cyclohexanecarbonitrile)
AIBN	1,1'-azobis(isobutyronitrile)
Ar	groupement aromatique
ARN*m*	acide ribonucléique messager
ARN*t*	acide ribonucléique de transfert
Boc	*tert*-butyloxycarbonyle
BEMP	2-*tert*-butyl-imino-2-diéthylamino-1,3-diméthylperhydro-1,2,3-diazaphosphorine
BINAP	2,2'-bis(diphénylphosphino)-1,1'-binaphthyle
Bn	benzyle
Bu	butyle
Bz	benzoyle
CBS	catalyseur de Corey-Bakshi-Shibata
CCM	chromatographie sur couche mince
Cp	cyclopentadiényle
CSA	acide camphorsulfonique
DBU	diaza(1,3)bicyclo[5.4.0]undécane
DCE	1,2-dichloroéthane
DIAD	diisopropylazidodicarboxylate
DIBAL	diisobutylaluminium
DIPEA	diisopropyléthylamine
DMAP	diméthylaminopyridine
1,2-DME	1,2-diméthoxyéthane
DMA	diméthylacétamide
DMF	diméthylformamide
DMP	Dess-Martin periodinane
DMSO	diméthylsulfoxyde
Et	éthyle

HMPA	hexaméthylphosphoramide
IBX	acide iodoxobenzoïque
IC_{50}	concentration inhibitrice à 50%
Im	imidazole
IR	infra-rouge
KHMDS	*N,N*-bis(triméthylsilyl)amidure de potassium
LDA	diisopropylamidure de lithium
LiHMDS	*N,N*-bis(triméthylsilyl)amidure de lithium
M	molaire
***m*CPBA**	acide méta-chloroperbenzoïque
Me	méthyle
MIC	concentration minimale inhibitrice
MHz	mégahertz
Ms	mésyle
NaHMDS	*N,N*-bis(triméthylsilyl)amidure de sodium
NBS	*N*-bromosuccinimide
NBS	*N*-chlorosuccinimide
NOE	effet nucléaire d'Overhauser
NMO	*N*-méthyl-morpholine-*N*-oxyde
NMP	*N*-méthyl-2-pyrrolidone
Ns	nosyle
GP	groupement protecteur
PDC	dichromate de pyridinium
Ph	phényle
pTSA	acide para-toluènesulfonique
Pyr	pyridine
RMN	résonance magnétique nucléaire
TBAF	fluorure de tétra-*N*-butylammonium
TBAI	iodure de tétra-*N*-butylammonium
TBME	*tert*-butoxyméthane
TBS	*tert*-butyldiméthylsilane

TEA	triéthylamine
TES	triéthylsilane
Tf	triflyle
TFA	acide trifluoroacétique
THF	tétrahydrofurane
TIPS	triisopropylsilane
TMS	tétraméthylsilane
t.a.	température ambiante
TPAP	perruthénate de tétrapropylammonium
Tr	trityle
Ts	tosyle

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En premier lieu, j'aimerais remercier le professeur Hanessian pour m'avoir accepté dans son groupe et pour m'avoir permis de travailler sur des projets passionnants avec beaucoup de latitude. Je garderai, entre autres, un bon souvenir de nos longues discussions au tableau.

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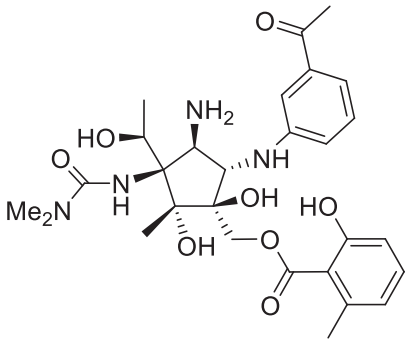
Chapitre I

Synthèse totale de la pactamycine

1.1 Propriétés du composé cible et historique

La pactamycine a été isolée pour la première fois en 1961 par Bhuyan et Argoudelis sans que sa structure ne puisse être élucidée.[1] On a tôt fait de remarquer ses activités antibiotique et antitumorale exceptionnelles, mais sa toxicité a empêché son développement en tant que médicament. Ce n'est que près de dix ans plus tard qu'une première structure de la pactamycine a été proposée grâce à une étude impliquant la dégradation chimique.[2] Deux ans plus tard, cette structure a été révisée et sa stéréochimie assignée en ayant recours à la cristallographie aux rayons-X d'un dérivé de la pactamycine (*Figure 1.1*).[3] Ce n'est qu'en 1972 qu'a été publié le premier spectre RMN ^{13}C de la structure révisée de la pactamycine, corroborant l'assignation effectuée précédemment.[4] C'est à l'aide d'un processus de fermentation de la bactérie *Streptomyces pactum* var *pactum* dans des conditions légèrement acides (pH 6,5–7,0) à 32 °C qu'on peut obtenir le composé cible avec un rendement acceptable (216 µg de pactamycine/mL de ferment).[5]



pactamycine (**1.1**)

Figure 1.1 : Structure de la pactamycine

Une étude effectuée par Argoudelis *et al* a permis d'identifier et de caractériser deux nouveaux congénères de la pactamycine : la pactamycate (**1.2**), cristalline, et la de-6-MSA-pactalactame (**1.8**), premier congénère isolé ne possédant pas l'unité salicylique (**1.9**) caractéristique de la pactamycine et de la pactamycate (*Figure 1.2*). Une autre vague de congénères a été découverte un peu plus tard, en 1986, dont la 7-épipactamycine (**1.4**)[6] et un autre congénère originalement appelé cranomycine[7] et reconnu comme étant en fait la 7-désoxypactamycine (**1.5**). En même temps, deux autres congénères ont été découverts et identifiés comme la 8''-hydroxypactamycine (**1.6**) et la

8''-hydroxypactamycate (**1.3**).[8] Le plus récent des congénères identifiés est celui nommé jogyamycine (**1.7**, la 7-désoxy-de-6-MSA-pactamycine selon l'appellation usuelle), découvert en 2012.[9]

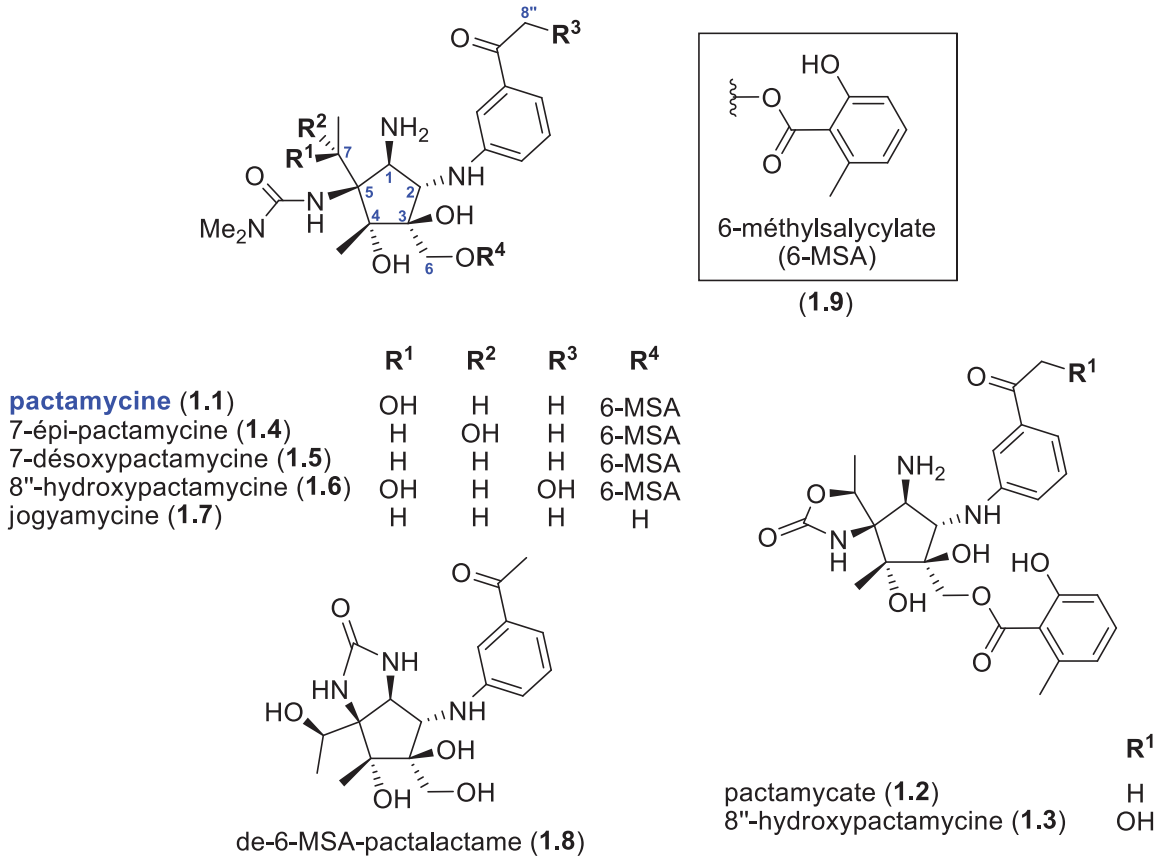


Figure 1.2 : Structure des congénères connus de la pactamycine

La pactamycine a été un des premiers composés appartenant à la classe des aminocyclitols à être isolé.[10] Même si les aminocyclitols se retrouvent rarement dans la nature, le caractère unique de leur structure et l'activité biologique qu'ils montrent généralement en ont fait un objet d'étude répandu.[11] Cette classe comprend quelques composés déjà synthétisés dont les propriétés ont fait l'objet d'études approfondies, tels que la trehazolamine (**1.10**), l'allosamizoline (**1.11**), la mannostatine (**1.12**) et l'aristeromycine (**1.13**), tous quatre étant des métabolites des streptomycètes (*Figure 1.2*).[12] La structure de la pactamycine, en comparaison, montre un noyau cyclopentane octasubstitué et six centres chiraux adjacents, faisant sans doute de celle-ci le métabolite le plus complexe des aminocyclopentitols.

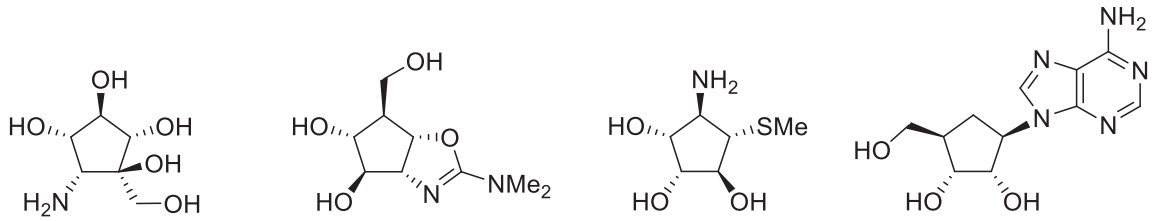


Figure 1.3 : Sélection d'aminocyclopentitols connus

Depuis la découverte de la pactamycine, les voies biosynthétiques menant à sa formation ont été élucidées en grande partie.[13] Tel qu'illustré dans le *Schéma 1.1*, la pactamycine est constituée de trois structures cycliques dérivant chacune de voies biosynthétiques différentes. Il a été démontré que le premier et principal cycle, le cyclopentitol, est dérivé du glucose (**1.14**) (*Schéma 1.1*). La formation de l'acide 6-méthylsalicylique, quant à elle, implique des enzymes de type polycétides-synthases (PKS) et utilise l'acide acétique comme précurseur (voir **1.15**). Finalement, la biosynthèse de la portion *m*-aminoacétophénone (**1.16**) est similaire à celle du shikimate et a donc pour précurseur le glucose, elle aussi. La biosynthèse de la pactamycine implique aussi l'incorporation tardive de groupements méthyles et d'amines. Il a été démontré que les deux atomes de carbone du *N*-méthyle et trois atomes des substituants du noyau cyclopentane sont dérivés de la S-adénosylméthionine (SAM, **1.17**). L'ensemble de ces conclusions a été possible grâce à des expériences d'incubation avec des composés isotopiquement marqués. Toutefois, il subsiste quelques incertitudes quant au mécanisme d'incorporation et quant à la source de certains atomes dans le cycle aromatique du motif aminoacétophénone.

Plus récemment, deux études indépendantes de Kudo,[14] Mahmud[15] et leurs collègues respectifs ont mené au clonage de la séquence de gènes capable de former la pactamycine. Ces travaux ont permis, d'une part, de corroborer globalement les voies biosynthétiques établies, et, d'autre part, de proposer une voie un peu plus élaborée pour expliquer la formation du noyau cyclopentitol à partir du glucose.

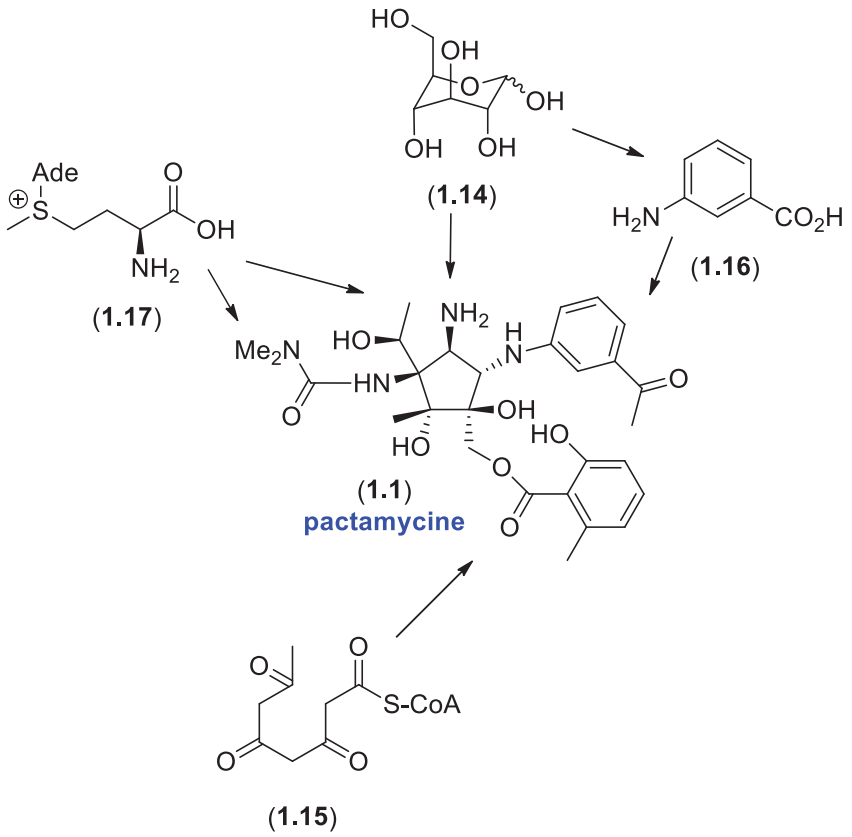


Schéma 1.1 : Biosynthèse de la pactamycine, par Kobayashi

Bien que la pactamycine ait été originalement étudiée pour ses propriétés antitumorales (IC_{50} = [0,5–2,0] mg/kg pour une dizaine de types de cellules cancéreuses), il s'est avéré qu'elle possédait surtout un potentiel intéressant en tant qu'antibiotique (MIC = [0,012–6,5] µg/mL pour une dizaine de sources bactériennes). On a tôt fait d'attribuer cette activité à ses capacités à inhiber la synthèse de protéines lors du procédé de traduction génétique, tant dans les systèmes eucaryotes que procaryotes.[16] Dans ce procédé de traduction, l'ARN*m*, véritable étalon contenant toute l'information requise quant à la séquence d'acides aminés à assembler, est associé au ribosome bactérien. Celui-ci assure à son tour l'arrangement d'ARN*t* afin que chacun des acides aminés associés à ces derniers soit assemblé dans l'ordre désiré. Il existe trois sites distincts où l'ARN*t* peut se lier au ribosome : le site d'entrée (A), le site d'élongation (P) et le site de sortie (E). Il est à mentionner, cependant, que le premier ARN*t* à s'associer au ribosome entre directement au site P lors du procédé d'initiation de la traduction. L'essentiel des enzymes et coenzymes impliqués dans le procédé de traduction, ainsi que les sites ribosomaux E, P et A sont illustrés dans le *Schéma 1.2.*

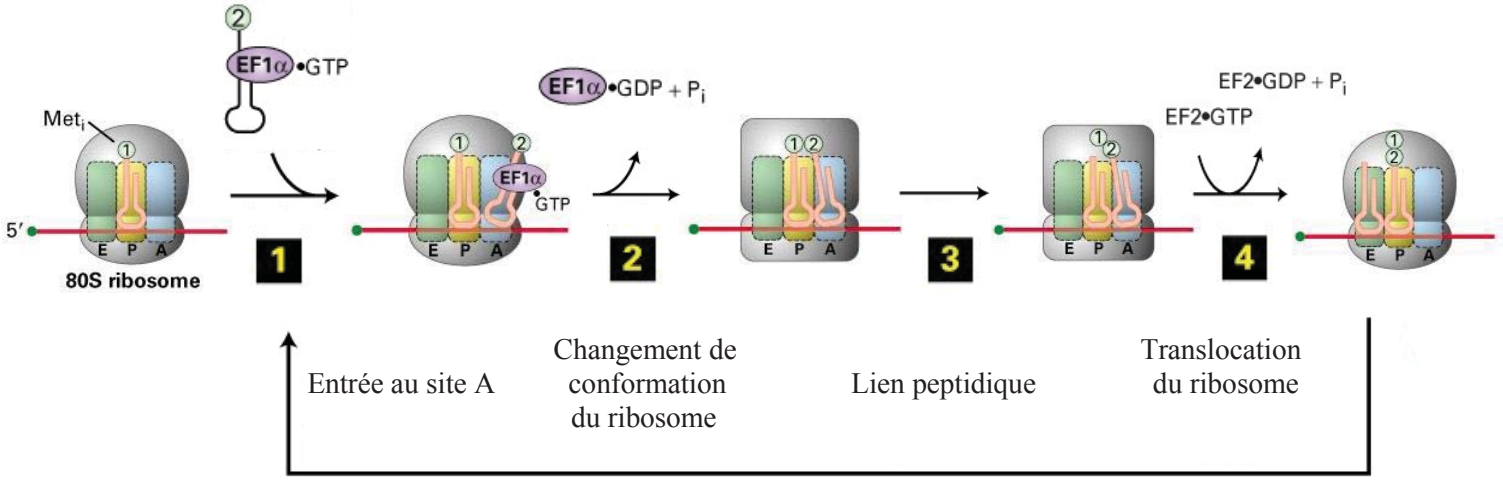


Schéma 1.2 : Modèle général de traduction avec emphase sur les sites ribosomaux[17]

Or, on croyait la pactamycine capable de s'associer au ribosome et d'empêcher l'entrée de l'ARN*t* au niveau du site P de celui-ci, soit par compétition directe, soit *via* un changement de conformation du ribosome. En conséquence, l'initiation du procédé de traduction était compromise. Cette hypothèse a d'ailleurs été rapportée dans la première revue sur le sujet, dans laquelle il était toutefois mentionné qu'il y avait encore un doute à ce sujet.[18] Ce n'est qu'en 2004, après quelques observations abondant en ce sens,[19] que le paradigme a été officiellement revisité par le laboratoire de Dinos, cette fois-ci proposant que la pactamycine inhibe la traduction principalement au niveau de la translocation au site E, et non au niveau du procédé d'initiation.[20] La pactamycine serait reconnue par la petite sous-unité ribosomale 30S et, d'une part, réduirait la flexibilité de cette dernière en complexant deux bases histidines et, d'autre part, éloignerait le codon E de quelque 12 Å, rendant ainsi la translocation et la synthèse des protéines beaucoup plus difficiles (voir *Schéma 1.2*).

La sous-unité ribosomale 30S est une cible importante pour une vaste gamme d'antibiotiques.[21] L'élucidation de sa structure a donc permis de réviser nos connaissances quant aux interactions entre le ribosome et les substrats inhibiteurs, dont la spectinomycine, la paromomycine et la streptomycine.[22] Les interactions clés entre la pactamycine (en jaune) et le ribosome sont aujourd'hui connues (*Figure 1.4*). Celles-ci impliquent notamment quelques ponts-hydrogène et un empilement π entre l'aniline de la pactamycine, son unité salycilique et le résidu provisoirement numéroté 693. Cet empilement π a pour effet d'imiter deux bases d'ARN*m* consécutives.[23] L'ensemble de

ces interactions induit un changement de conformation au niveau du ribosome qui, tel qu'expliqué précédemment, provoque l'inhibition de la traduction.

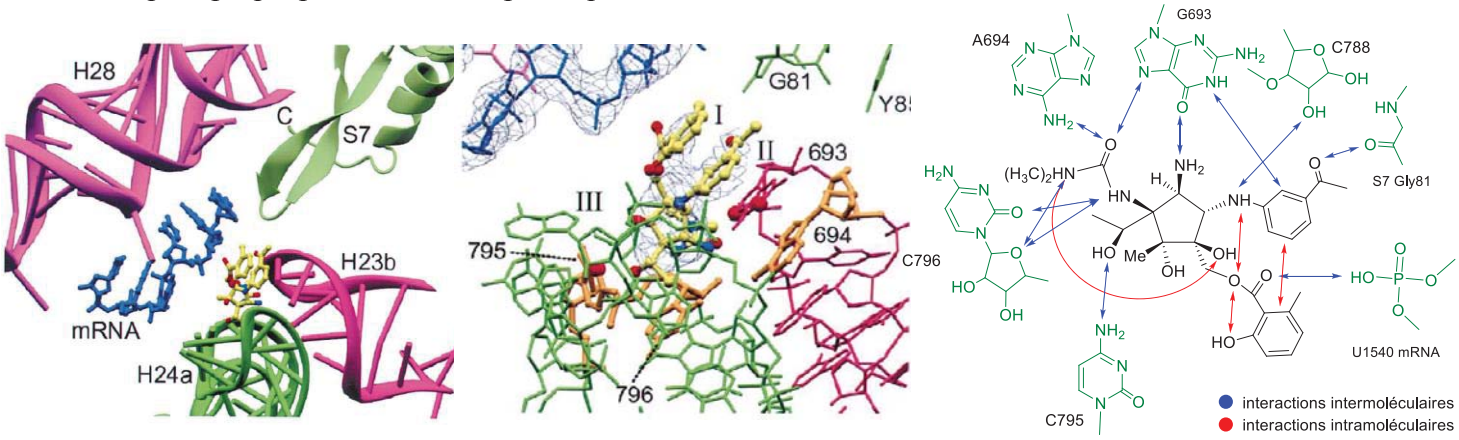


Figure 1.4 : Interactions clés entre la pactamycine et l'unité ribosomale impliquée[22]

En plus des propriétés antibactériennes et anticarcinogéniques, il a été découvert récemment que la pactamycine, et en particulier certains de ses congénères et analogues, possédaient des propriétés antiprotozoaires intéressantes.[15] Assez, d'ailleurs, pour qu'on parle aujourd'hui de la pactamycine comme d'un des composés cibles potentiels les plus intéressants à cet égard.[24]

1.2 Synthèses partielles publiées

Au moment où les travaux détaillés dans la présente thèse ont été entrepris, seulement deux équipes de recherche avaient travaillé à la synthèse partielle de la pactamycine. La première synthèse, celle du groupe d'Isobe,[25] a été publiée en 2005 et utilisait comme réactif de départ le diacétone-D-glucose **1.18**, commercialement disponible. Une série de manipulations, décrite dans le *Schéma 1.3*, a permis d'installer une amine tertiaire *via* un réarrangement sigmatropique d'Overman (de **1.20** à **1.21**) dirigé vers la face la moins encombrée du sucre.[15]

Le trichloroacétamide, une fois réarrangé, a été attaqué de façon intramoléculaire par l'alcool libre afin de former un carbamate cyclique tel qu'en **1.24** qui a été maintenu tout au long de la synthèse. Les deux acétonides retrouvés dans le composé de départ (**1.18**) ont tour à tour été hydrolysés afin de décomposer une partie du sucre et d'en faire

un précurseur approprié pour la fermeture du cyclopentane substitué (**1.27**). Cette fermeture s'est ensuite effectuée à l'aide d'une réaction de Pauson-Khand intramoléculaire et achevait de constituer la charpente de la pactamycine. L'intermédiaire avancé **1.29** a été obtenu en vingt-et-une étapes avec environ 5,5% de rendement global et nécessitant l'emploi de quatre groupements protecteurs différents (six au total).

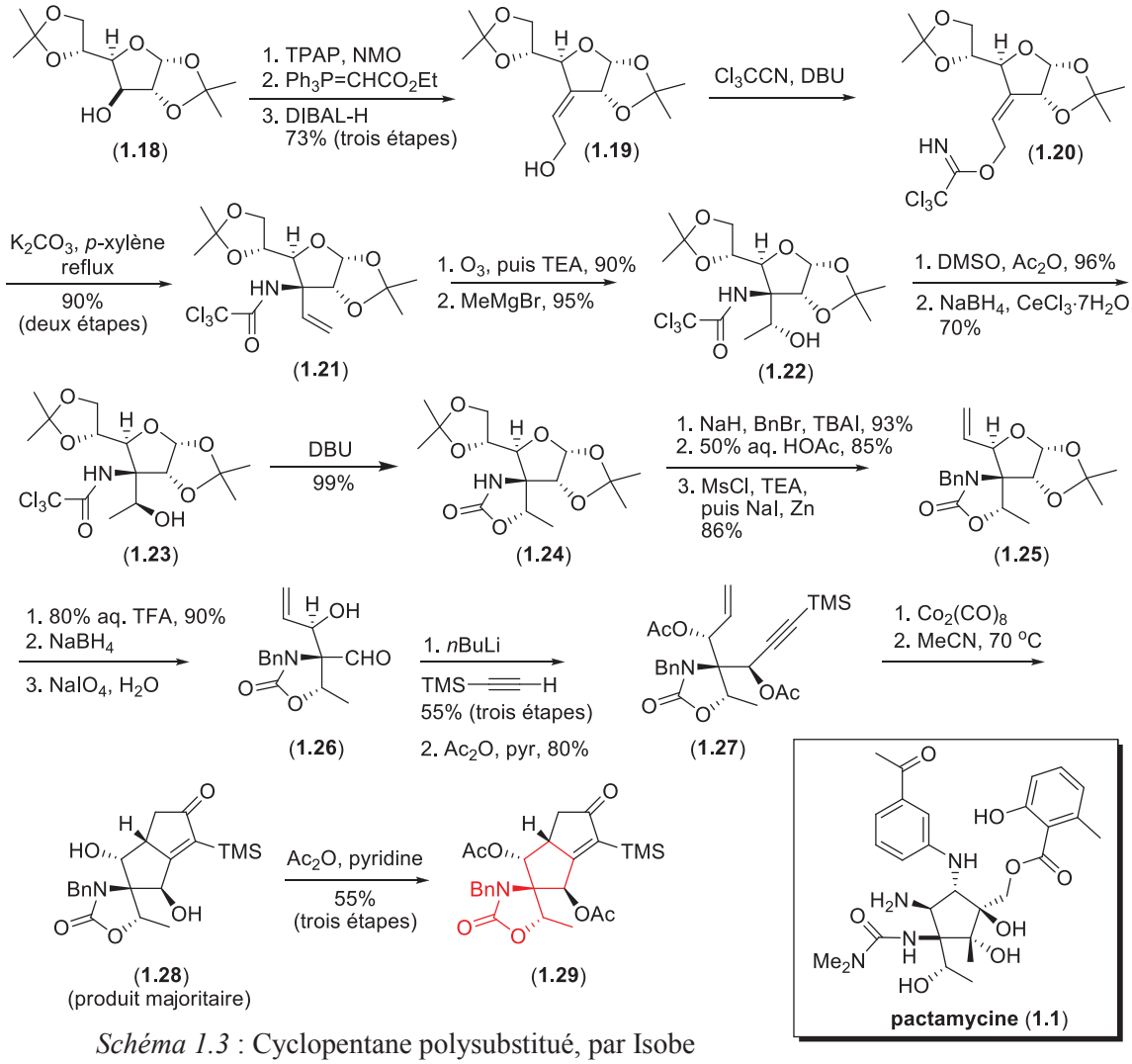


Schéma 1.3 : Cyclopentane polysubstitué, par Isobe

L'autre synthèse partielle existante a été réalisée deux ans plus tard par le groupe de Knapp.[26] Celui-ci a procédé à la synthèse de ce qu'il appelle le « noyau oxygéné » de la pactamycine (**1.40**), c'est-à-dire un cyclopentane sur lequel tous les groupements fonctionnels contenant un atome d'oxygène ont été stéréosélectivement incorporés (*Schéma 1.4*).

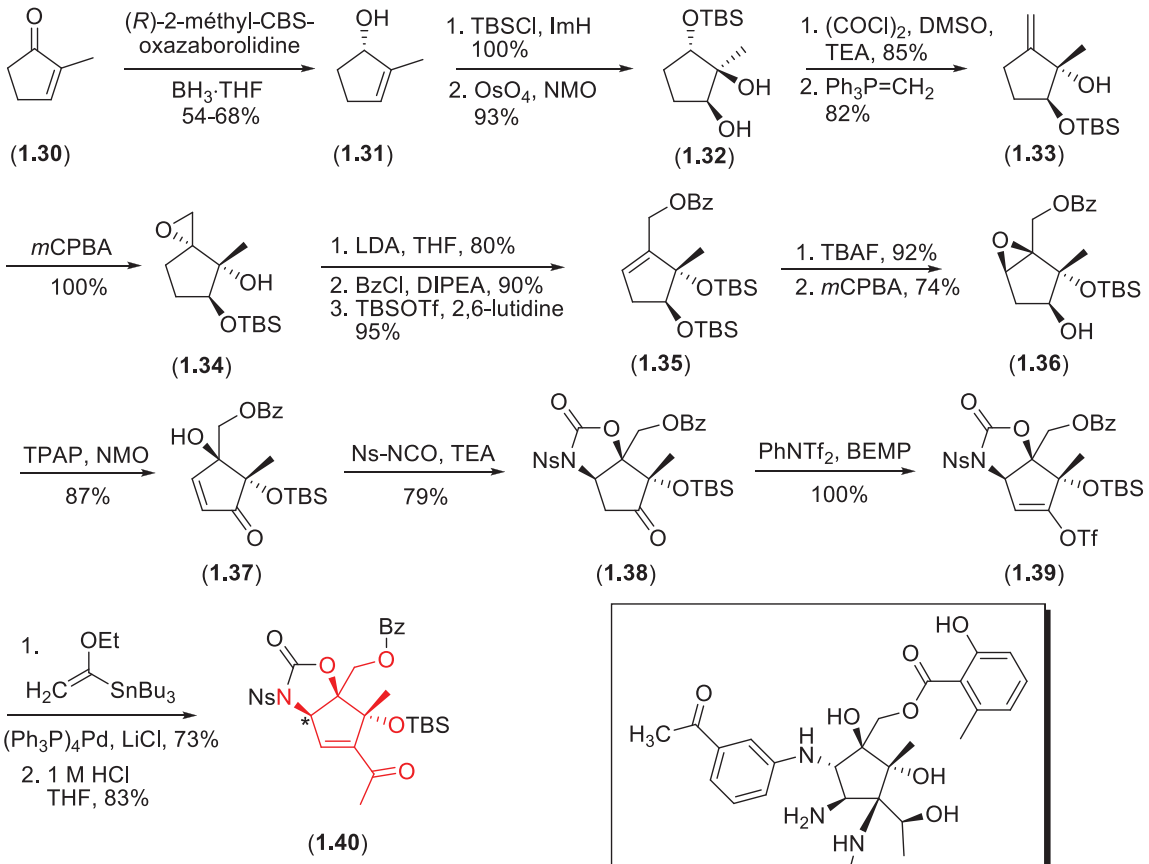


Schéma 1.4 : Voie empruntée par Knapp

À partir du 2-méthyl-cyclopent-2-én-1-one (**1.30**), l'installation des centres chiraux a été assurée d'emblée par une transformation énantiosélective en utilisant le réactif de Corey-Bakshi-Shibata (voir *Schéma 1.4*). Une exploitation conséquente de la topologie du cyclopentène obtenu a ensuite permis d'obtenir un diol (**1.32**) transformé à son tour afin d'installer les atomes d'oxygène restants. Le carbamate cyclique tel qu'en **1.38**, seul groupement fonctionnel contenant ici un atome d'azote, a été installé *in situ* à l'aide d'un isocyanate additionné de façon intramoléculaire à l'énone, par une réaction d'addition de Michael. Au total, la stratégie de Knapp, qui comporte seize étapes, dont cinq fonctionnalisations diastéréosélectives, donne un rendement global d'environ 2,0% et utilise quatre groupements protecteurs.

Après les travaux relatés dans la présente thèse, il s'avère que trois nouvelles synthèses partielles ont été publiées. La première, effectuée en 2012 par le groupe de Johnson,[27] préconise une approche différente des deux synthèses présentées précédemment. Plutôt que d'avoir recours rapidement à un motif cyclopentane polysubstitué, leur approche préconise la formation précoce du centre quaternaire aminé contenant l'urée (voir *Schéma 1.5*). Pour ce faire, une fonction diazo a été introduite par réaction de transfert depuis l'acétoacétate de méthyle (**1.41**), pour ensuite effectuer une insertion N-H catalysée au rhodium et déjà rapportée[28] afin d'obtenir **1.43**. Ensuite, ce produit a lui aussi été soumis à des conditions connues[29] afin d'effectuer l'allylation menant à **1.44** de façon racémique. Le groupe de Johnson a d'ailleurs démontré qu'il était possible d'obtenir le composé **1.44** de façon énantioenrichie (r.e. 92 : 8) en utilisant le (*R*)-BINAP comme catalyseur lors de l'allylation, dans des conditions non-optimisées, mais a préféré poursuivre la synthèse de la cible moléculaire sous forme d'un mélange racémique. Pour cette raison, la stéréochimie des intermédiaires obtenus par le groupe de Johnson à partir de ce point a été représentée par des traits pleins.

Par la suite, une série de transformations a permis d'obtenir l'énone **1.48**, sur laquelle a été ajouté un réactif de Grignard afin d'obtenir un nouveau stéréocentre tel qu'en **1.49**. La diastéréosélectivité de cette dernière transformation a été expliquée par le modèle dit de Cram-chélate où le groupement éthyl-OTBS serait plus gros que le groupement allyle. Une cyclisation par métathèse d'alcènes a ensuite été effectuée sous les conditions usuelles de Grubbs pour obtenir le cyclopentène substitué **1.50**, ensuite dihydroxylé pour fournir **1.51** sans qu'une explication ne soit toutefois fournie quant à l'obtention du diastéréoisomère voulu. Le cyclopentane polysubstitué **1.51** a ensuite été protégé sous forme d'acétonide tel qu'en **1.53**, dont la structure a pu être confirmée par analyse de diffraction des rayons-X. Des efforts ont été effectués afin d'oxyder le carbone en position vacante, ou même d'introduire l'aniline, mais en vain. Néanmoins, la synthèse décrite ici a été effectuée en quinze étapes avec un rendement global de 5,0% et fait usage de trois groupements protecteurs différents.

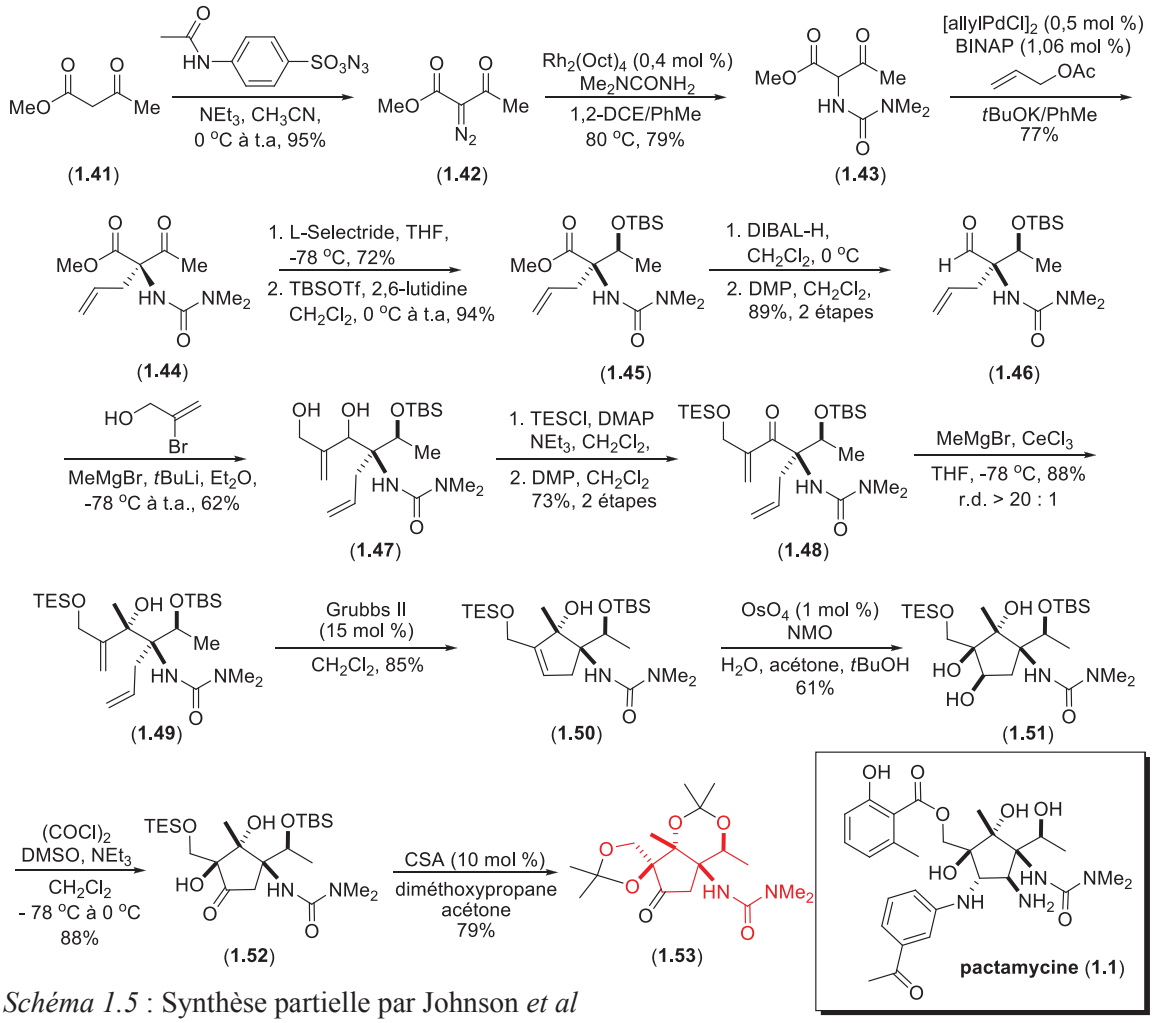


Schéma 1.5 : Synthèse partielle par Johnson *et al*

Le groupe de Looper a aussi travaillé à la synthèse partielle de la pactamycine.[30] La synthèse a été entamée par la formation d'une oxazoline **1.54** à partir de la D-thréonine, ensuite allylée et transformée afin de fournir **1.55** (*Schéma 1.6*). Par la suite, une cyclisation a été effectuée pour fournir le cyclopentène substitué **1.57**, qui a lui-même été transformé en époxyde **1.61**. L'activation de l'époxyde à l'aide de $BF_3 \cdot Et_2O$ a permis de favoriser une réaction en cascade tirant profit de la proximité de quelques groupements fonctionnels et installant deux centres stéréogéniques simultanément pour fournir **1.65**. Cette synthèse partielle par Looper, dont l'élégance et l'originalité sont manifestes, n'inclue seulement qu'onze étapes, avec un rendement global de 4,2%, et ne nécessite la protection que de deux groupements fonctionnels.

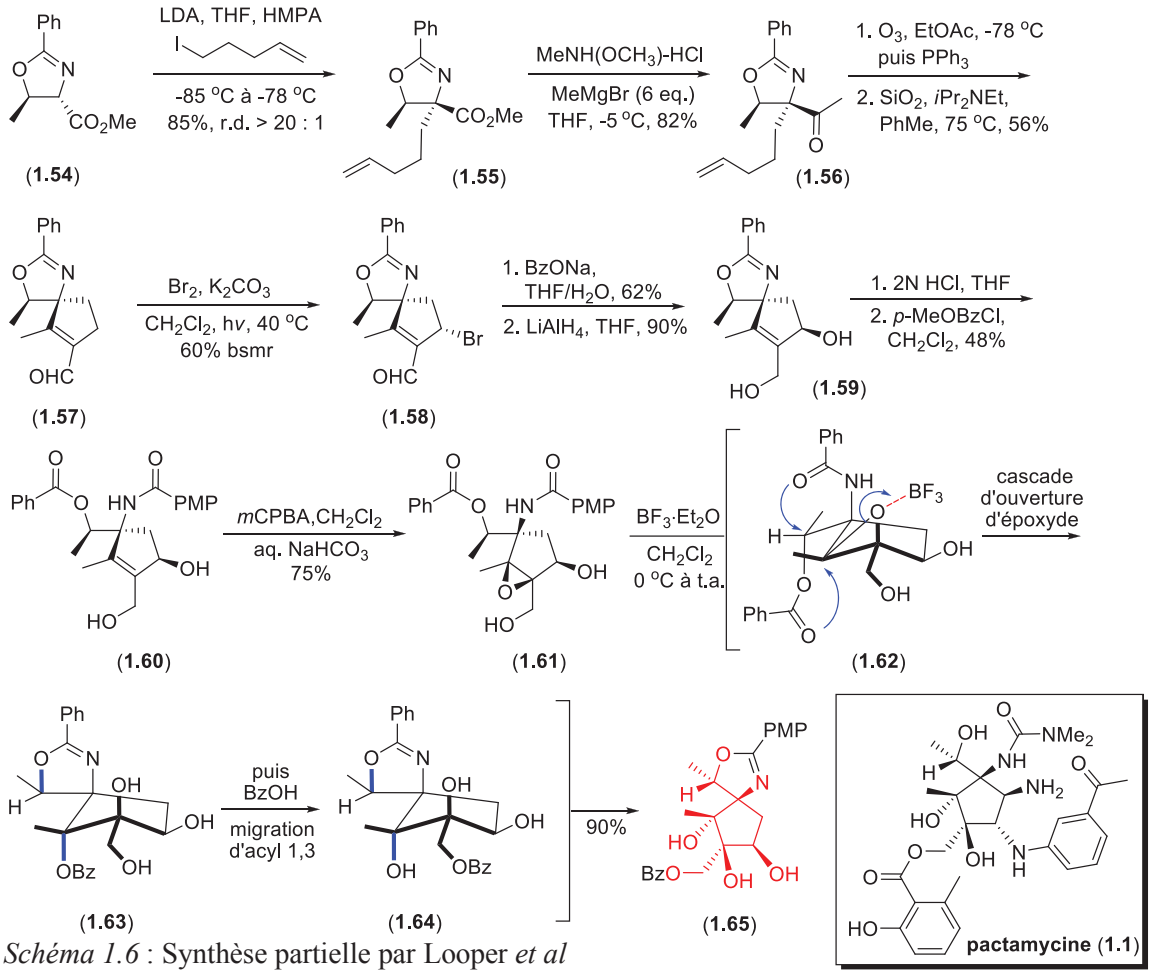


Schéma 1.6 : Synthèse partielle par Looper *et al*

Finalement, le groupe de Nishikawa et Isobe a publié une deuxième approche vers la synthèse de la pactamycine.[31] Après avoir initialement envisagé de construire le motif cyclopentène à l'aide d'une cyclisation de Pauson-Khand, tel que décrit dans le *Schéma 1.3*, ils ont découvert que la fonctionnalisation d'intermédiaires avancés (tel que **1.29**) en route vers la pactamycine était impossible. L'approche vers la synthèse de la pactamycine a donc été révisée, en tirant avantage de l'intermédiaire avancé **1.66**. Plutôt que de soumettre celui-ci à une cyclisation de Pauson-Khand, une série de manipulations a permis d'obtenir l'aldéhyde **1.68** protégé, précurseur pour une cycloaddition permettant d'obtenir l'isoxazoline **1.70** réarrangée instantanément en aziridine **1.71** (*Schéma 1.7*). Cette aziridine a été ouverte et transformée afin d'obtenir **1.74**. Malheureusement, ils ont établi, *a posteriori*, que la stéréochimie en positions 4 et 6 (montrée dans le *Schéma 1.7*) n'était pas celle affichée par la pactamycine. La stratégie révisée de Nishikawa et Isobe a cette fois-ci utilisé vingt-sept étapes et cinq groupements protecteurs, et permet un rendement global de 1,7%.

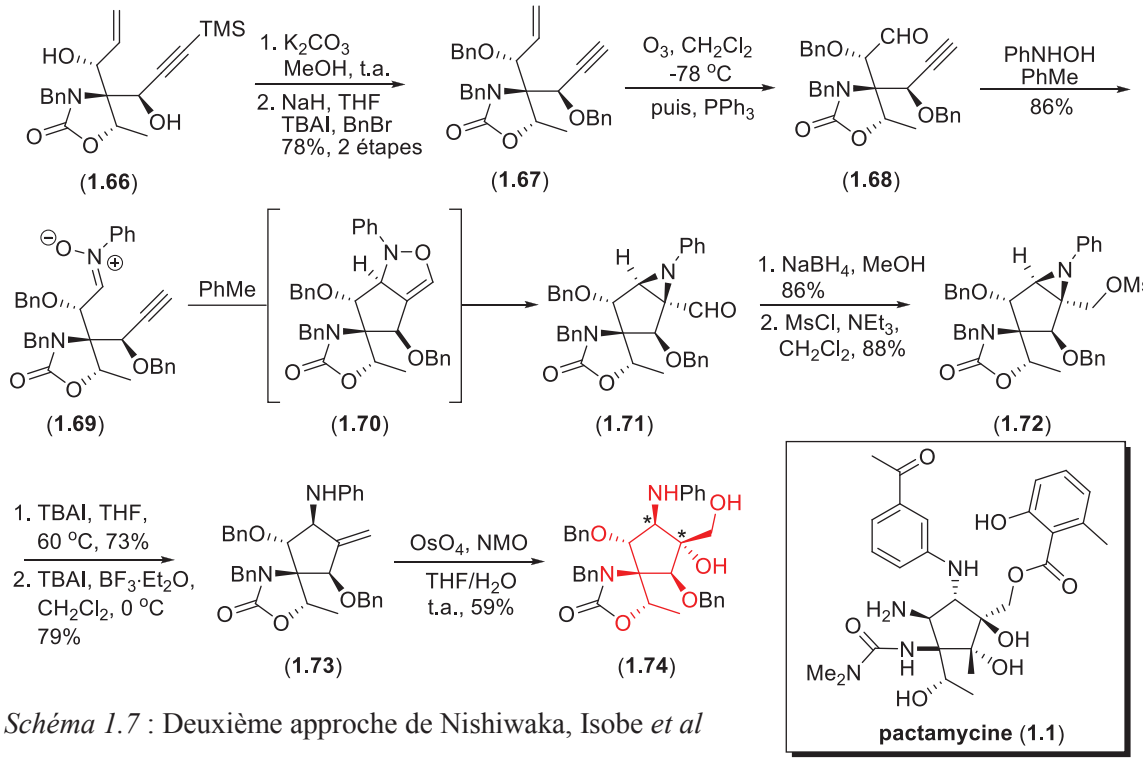


Schéma 1.7 : Deuxième approche de Nishiwaka, Isobe *et al*

Malgré le fait qu'il soit relativement facile et abordable d'obtenir la pactamycine grâce à la fermentation de cultures bactériennes, celle-ci possède une structure d'une complexité intéressante pour le chimiste de synthèse. Même si elle ne se compare pas, en termes de grosseur, à plusieurs classiques de la synthèse totale, la pactamycine possède néanmoins six centres chiraux adjacents, ce qui fait d'elle un défi de synthèse considérable. En outre, toutes voies de synthèse devraient tenir compte du fait que le composé cible affiche un cyclopentane octasubstitué et très dense. Le défi de la synthèse ira ainsi en grandissant au fur et à mesure qu'elle progressera, l'installation de nouveaux groupements fonctionnels étant de plus en plus difficile à accomplir. En outre, les groupements fonctionnels qu'on retrouve dans le composé final incluent une amine alkylique, une aniline, une urée, un ester, quatre alcools (dont un phénol) et une cétone. Il sera donc nécessaire de planifier la synthèse afin de permettre l'incorporation de cette riche liste de groupements en temps opportuns.

Ainsi, l'article 1 ci-joint (Section 1.3 et Annexe IV) rapporte la première synthèse totale de la pactamycine (**1.1**) et de la pactamycate (**1.2**) dans ses grands traits.[32] L'article 2 (Section 1.4 et Annexe IV), quant à lui, en détaille plus amplement ses vicissitudes, et relate au passage la synthèse des composés de-6-MSA-pactamycine (**2.4**) et de-6-MSA-pactamycate (**2.5**).

Tandis que le Dr. Shayamapada Banerjee a entâmé la synthèse de la pactamycine et a travaillé à élaborer une voie sans issue décrite dans l'article 2, Juan Del Valle et Fabien Lecomte ont travaillé à améliorer cette voie. Pour sa part, Benoît Deschênes-Simard a eu pour mandat d'élucider la structure des intermédiaires de synthèse par analyse de diffraction des rayons-X. Jianbin Zhang a étudié plus en profondeur les prérequis pour l'ouverture régiosélective d'époxydes modèles avec des anilines, mais ces résultats ne sont présentés que brièvement dans les articles 1 et 2. Finalement, le Dr. Vakiti et moi avons travaillé conjointement à l'essentiel de la synthèse totale décrite. Alors que, initialement, le Dr. Vakiti travaillait à incorporer l'amine en position 1 sur des intermédiaires avancés déjà obtenus par le Dr. Banerjee, j'ai développé une nouvelle voie préconisant l'installation précoce de cette amine. C'est finalement cette stratégie qui a été utilisée pour obtenir la charpente de la pactamycine. Par la suite, le Dr. Vakiti et moi avons travaillé à achever la fonctionnalisation de la pactamycine. Plus précisément, le Dr. Vakiti a largement contribué à former l'urée en position 5, groupement fonctionnel très difficile à installer, tel qu'expliqué dans les articles 1 et 2.

1.3 Article 1

Total Synthesis of Pactamycin

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Among the plethora of microbial secondary metabolites produced by the soil bacterium of the *Streptomyces* family is pactamycin, a structurally unique member of aminocyclopentitol-containing natural products.

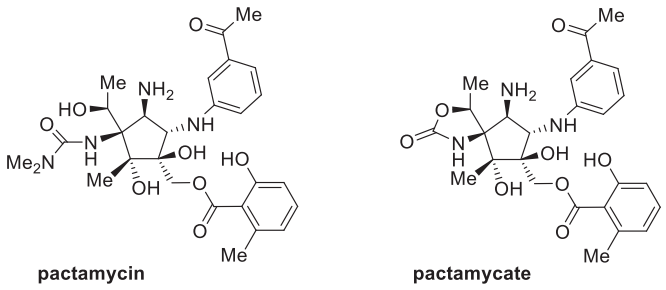


Figure 1.5: Structures of pactamycin and pactamycate.

Pactamycin was isolated in 1961 from a fermentation broth of *Streptomyces pactum* var *pactum* by scientists at the former Upjohn Company.[1] It exhibited activity against Gram-positive and Gram-negative bacteria, in addition to potent in vitro and in vivo cytotoxic effects.[2] Its further development as a chemotherapeutic agent was curtailed due to its toxicity. The potent protein synthesis inhibitory activity of pactamycin is attributed to the stage of translocation from the A and P sites to the P and E sites during formation of certain m-RNA-t-RNA complexes in prokaryotes as well as in eukaryotes.[3] Pioneering X-ray crystallographic studies[4] involving binding to the 30S site of *Thermus thermophilus* showed unique interactions, whereby pactamycin adopts a spatial orientation so as to mimic an RNA nucleotide. The two aromatic moieties stack against each other like consecutive RNA bases, while the core cyclopentane motif mimics the RNA sugar-phosphate backbone, which results in an intricate network of H-bonded interactions within the 30S site of the ribosome. Recent elegant studies on the biosynthesis of pactamycin by Mahmud and coworkers[5] revealed a gene cluster which also produced pactamycate, de-6-MSA-pactamycin and de-6-MSA-pactamycate, the natural congeners lacking the 6-methyl salicylic acid moiety.

A proposed structure of pactamycin was reported in 1970 by the Upjohn scientists as a result of seminal studies involving chemical degradation.[6] It was subsequently corrected in 1972 from X-ray crystallographic studies, as shown in Figure 1.5.[7] To the best of our knowledge, pactamycin is the most densely functionalized naturally-occuring aminocyclopentitol.[8] In spite of its unique architecture and rich history in the realm of

RNA structure and function,[3-5] efforts toward the synthesis of pactamycin and its congeners have been sparse. Knapp,[9] Isobe[10] and their respective coworkers recently reported conceptually different approaches toward the construction of the aminocyclopentane core motif. Herein, we communicate the first total synthesis of pactamycin and its naturally-occurring congener, pactamycate (Figure 1.5).

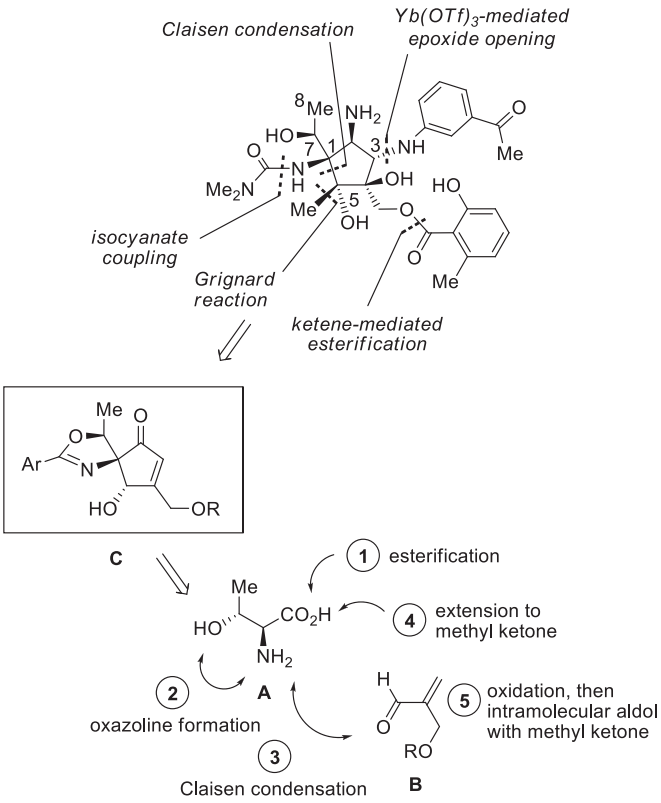


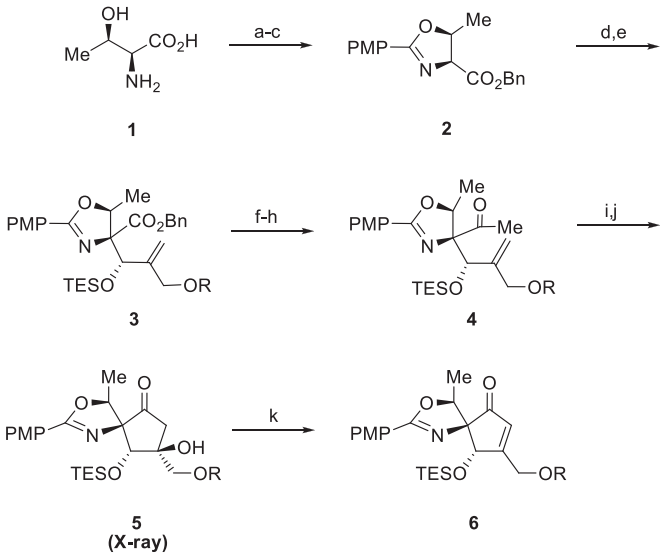
Figure 1.6: Strategic bond disconnections and key transformations shown in their order of execution. **A** = L-threonine; **B** = O-protected 2-hydroxymethyl acrolein; **C** = core cyclopentenone intermediate.

In considering a synthetic strategy, we were cognizant that the densely functionalized cyclopentane core harboring three contiguous tertiary centers would require a judicious choice of well-orchestrated bond forming sequences. Furthermore, we wanted to adopt a modular approach for the introduction of substituents and appendages in order to allow for diversification to eventually prepare bioactive analogues while eliminating toxicity.

Analysis of the structure of pactamycin led to the choice of L-threonine as a partially hidden chiron, representing C1, C2, C7 and C8, and ensuring the stereochemistry of the secondary hydroxyl group in the hydroxyethyl appendage, as well as the position of the amine group at C1 (Figure 1.6). The cyclopentenone core (**C**) would arise from a sequence of well-documented reactions culminating with an intramoleculer aldol condensation. Systematic manipulation of the cyclopentenone (**C**) would then eventually lead to pactamycin. Straightforward as this plan may have been, its execution was met with several unexpected roadblocks particularly involving the elaboration of the *N,N*-dimethylurea group at C1, and the proximity of functional groups (vide infra).

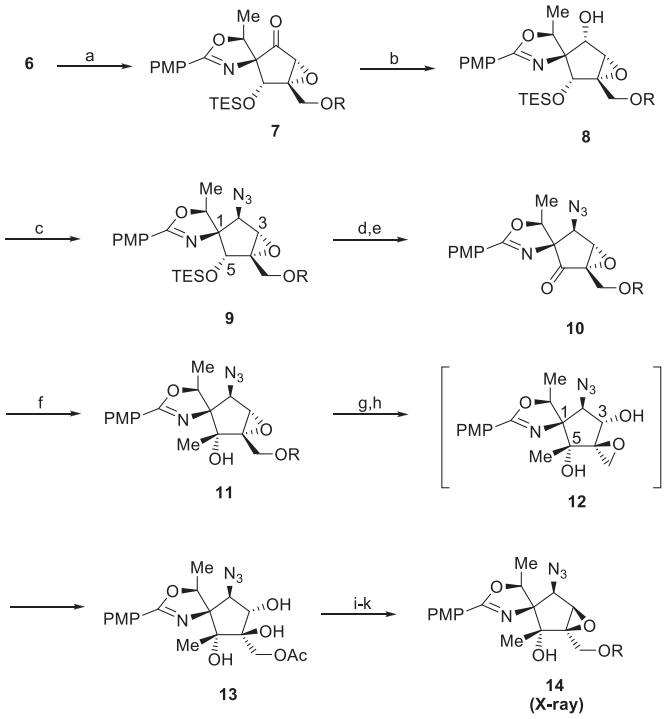
A 3-step sequence starting with L-threonine (**1**) led to the PMP-oxazoline derivative **2** (Scheme 1.8).[11,12] Formation of the enolate with LiHMDS, and condensation with O-TBDPS-2-hydroxymethyl acrolein, followed by protection with TESOTf afforded **3** as a single isomer. Reduction of the benzyl ester to the aldehyde, treatment with MeMgBr and oxidation afforded the methyl ketone **4**. Ozonolytic cleavage of the exocyclic methylene group, followed by a highly stereoselective Mukaiyama-type intramolecular aldol condensation afforded **5** as a crystalline intermediate. Upon treatment with trichloroacetyl chloride in pyridine, β-elimination took place to give the cyclopentenone **6**.

From this point on, it was imperative to introduce the epoxide and hydroxyl group in that order, while securing the desired stereochemistries that would allow introduction of an azide group with inversion at C2, and the aniline moiety regioselectively at C3. In the event, base-induced epoxidation of **6** afforded epoxide **7**, which was stereoselectively reduced under Luche conditions to give **8** (Scheme 1.9). The formation of the α-oriented epoxide and secondary alcohol as in **8** was imperative, because the S_N2 azide displacement of the corresponding triflate in the diastereomeric β-epoxide in a related series was unsuccessful.



Scheme 1.8: Synthesis of the cyclopentenone intermediate **6**, R = TBDPS, PMP = *p*-MeO-phenyl, TES = triethylsilyl. a) BnOH, *p*TSA, benzene, reflux, 67%; b) *p*-anisoylchloride, TEA, DCM, r.t., 64%; c) $SOCl_2$, MeCN, 0 °C, 85%; d) LiHMDS, THF, -78 °C, O-TBDPS-2-hydroxymethylacrolein; e) TESOTf, 2,6-lutidine, DCM, 0 °C to r.t., 67%, 2 steps; f) DIBAL-H, DCM, -78 °C; g) MeMgBr, Et_2O, 0 °C, 87%, 2 steps; h) $(COCl)_2$, DMSO, TEA, DCM, -78 °C to r.t., 91%; i) O_3, DCM, -78 °C, then DMS, 84%; j) $TiCl_4$, DCM, DIPEA, TMSCl, 0 °C, 85%; k) Cl_3CCOCl, pyr., DCM, r.t., 89%.

Although the azide group could be easily introduced *via* the triflate ester of **8** to give **9**, it became necessary to "invert" the stereochemistry of the epoxide in order to contemplate the stereo- and regioselective introduction of the aniline moiety by opening at C3. This operation was postponed in favor of the obligatory C-methyl branching at C5. Thus, selective cleavage of the O-TES ether and oxidation to the ketone gave **10**, which was treated with MeMgBr to give **11** as a single diastereomer. An X-ray structure of the phenyl oxazoline analog of **10** confirmed its structure and absolute configuration.[12] The "inversion" of the epoxide in **11** was achieved by treatment of the corresponding primary alcohol with $Zn(OTf)_2$ in AcOH to give the C4-inverted triol **13**. Presumably, this arose from the spiroepoxide **12** which underwent solvolysis to afford the primary acetate as in **13**. A 2-step sequence restored the robust TBDPS ether group, and the resulting triol was converted in situ to the epoxide **14** via the secondary triflate (70% overall yield from **11**). An X-ray crystal structure validated the suggested sequence of inversions in going from **11** to **14**.



Scheme 1.9: Synthesis of the epoxide **14**, R = TBDPS, PMP = *p*MeO-phenyl. a) H_2O_2 (30% w/w), 20% NaOH, MeOH-DCM, 0 ºC, 75%, (88% bsmr); b) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH-DCM, 0 ºC, 92%; c) Tf_2O, pyr. DMAP, 0 ºC, then Bu_4NN_3, toluene, r.t., 87%; d) TFA: MeCN: H_2O (1:8:1), 0 ºC to r.t., 93%; e) DMP, DCM, 0 ºC, 96%; f) MeMgBr, THF, -78 ºC; g) TBAF, THF, 0 ºC, 86%, 2 steps; h) $Zn(OTf)_2$, AcOH, 80 ºC; i) K_2CO_3, MeOH, r.t.; j) TBDPSCl, TEA, DMAP, r.t., 85%, 3 steps; k) Tf_2O, pyr. DMAP, DCM, -78 ºC to 0 ºC, 96%.

Highly stereoselective epoxide opening at C3 with the aniline derivative **15** in the presence of $Yb(OTf)_3$[13] afforded the core structure **16** as the sole regioisomer (Scheme 1.10). Cleavage of the oxazoline moiety with aqueous HCl[14] led to the *p*-methoxybenzoyl ester, which was transformed to the acetonide **18** in straightforward manner.

Formation of an intermediate isocyanate in the presence of diphosgene,[15] then treatment with dimethylamine gave the urea **19** in excellent yield. Treatment of the ester with DIBAL-H, followed by oxidative cleavage of the olefin to the methyl ketone, and hydrolysis of the acetonide function led to **20**. Esterification with the cyanomethyl ester **21**,[16] then reduction of the azide group in the presence of Lindlar's catalyst, afforded pactamycin which was purified by silica gel chromatography. Synthetic pactamycin

exhibited spectroscopic and chiroptical properties identical to the originally published data.[6,12] Furthermore, ^{1}H NMR data at 700 MHz, ^{13}C NMR data at 400 MHz, HPLC data, as well as single crystal X-ray structures of several intermediates provide hitherto unavailable characterization features for future synthetic endeavours.[12] Pactamycin is reported to be unstable in solution as evidenced by a change in optical rotation in different solvents, losing some of its biological activity with time.[6]

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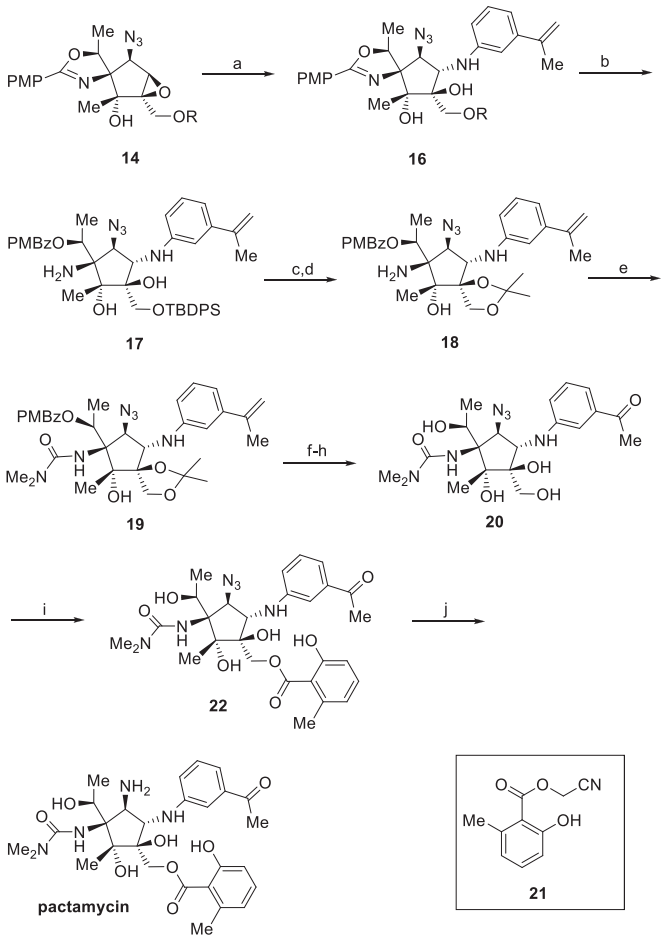
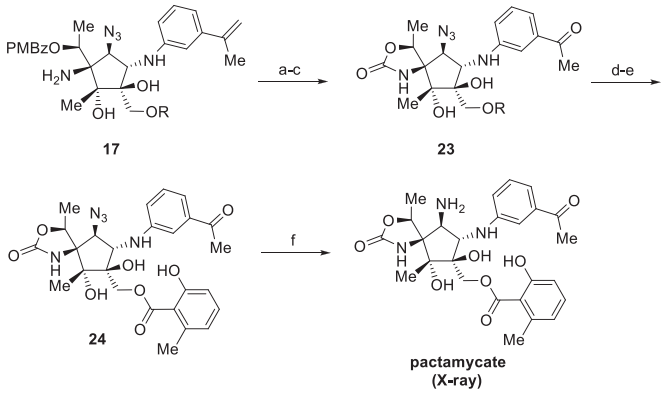


Scheme 1.10: Synthesis of pactamycin from the epoxide **14**, R = TBDPS, PMP = *p*-MeO-phenyl, PMBz = *p*-MeO-benzoyl. a) 3-(prop-1-en-2-yl)aniline (**15**), $Yb(OTf)_3$, toluene, 80 °C, 81%, (91% bsmr); b) 2*N* HCl, THF, r.t., 63%, (83% after two cycles); c) TASF, DMF, 0 °C to r.t., 95%; d) 2,2-DMP:DCM (1:5), CSA, 0 °C to r.t., 86%; e) $Cl_3COCOCl$, activated charcoal, TEA, THF, -46 °C, then $HNMe_2$, -46 °C to r.t., 86%; f) DIBAL-H, DCM, -78 °C., 90%; g) OsO_4, THF:acetone:H_2O (5:5:1), cat. NMO, then $NaIO_4$, THF-H_2O, r.t., 80%; h) TFA:MeCN:H_2O (5:1:1), 0 °C to r.t., 85%; i) cyanomethyl 2-hydroxy-6-methylbenzoate (**21**), K_2CO_3, DMA, r.t., 96%; j) Lindlar's cat., H_2, MeOH-EtOH, 85%.

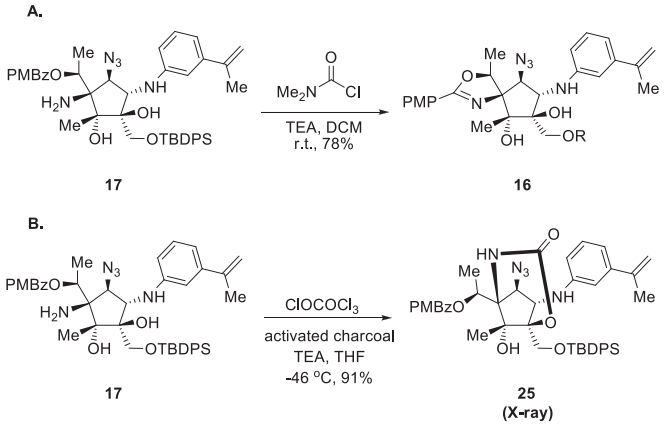
The synthesis of crystalline pactamycate[6], a naturally occurring congener,[5a] is shown in Scheme 1.11. Treatment of **17** with DIBAL-H, then diphosgene,[15] resulted in the formation of the corresponding cyclic carbamate. Oxidative cleavage of the *exo*-methylene group in the latter afforded **23**, which was converted in two steps to the 2-azido precursor **24**. Hydrogenation in presence of Lindlar's catalyst gave crystalline pactamycate. An X-ray crystal structure confirmed the structure of pactamycin and the original assignment of its absolute configuration for the first time (Scheme 1.11).[7,12]



Scheme 1.11: Synthesis of pactamycate, R = TBDPS. a) DIBAL-H, DCM, -78 °C, 89%; b) $Cl_3COCOCl$, activated charcoal, TEA, THF, -46 °C, 86%; c) OsO_4, THF:acetone:H_2O (5:5:1), cat. NMO, then $NaIO_4$, THF-H_2O, r.t., 82%; d) TASF, DMF, 0 °C to r.t., 93%; e) cyanomethyl 2-hydroxy-6-methylbenzoate (**21**), K_2CO_3, DMA, r.t., 98%; f) Lindlar's cat., H_2, MeOH-EtOH, 83%.

The successful and seemingly straightforward total synthesis of pactamycin described in this paper underscores the importance (and frustrations) of many unwanted transformations due to the proximity of reactive functional groups anchored on the cyclopentane core. For example, having introduced the primary amino group at C1 in intermediate **17** by acidic hydrolysis of the oxazoline **16**, there only remained to convert it to the *N,N*-dimethylurea, bringing us within a few steps from the intended target, pactamycin. In practice, various attempts at reaction of **17** with *N,N*-dimethylcarbamoyl chloride resulted in the formation of the precursor oxazoline **16** (Scheme 1.12A). In fact, triethylamine and DMAP alone effected the same transformation to **16**. Attempted formation of the desired *N,N*-dimethylurea by treatment of **17** with diphosgene to give an

intermediate isocyanate, then quenching with dimethylamine, formed the six-membered cyclic carbamate **25** in 91% yield even at -46ºC (Scheme 1.12B)! This remarkably facile reaction, spanning a tertiary alcohol and a highly hindered amine, demonstrates the importance and unexpected consequences of spatial proximity in a confined architecture such as found in **17**.



Scheme 1.12: Unexpected results arising from the closeness of functional groups on the polysubstituted cyclopentane core structure, PMP = *p*-MeO-phenyl, PMBz = *p*-MeO-benzoyl.

The total synthesis of pactamycin and pactamycate by the route described herein was achieved in twenty-nine linear steps and 3.0% overall yield starting with the known oxazoline **2** readily available from L-threonine.[11] The modular introduction of functional groups allows for a great deal of flexibility in the quest for the synthesis of less toxic congeners that maintain their antibacterial and cytotoxic activities.[17] Efforts toward these goals are presently being actively pursued in our laboratory.

CCDC 805348-805351 and 811840 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Keywords: natural product synthesis · pactamycin · pactamycate· polysubstituted cyclopentane · total synthesis

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[2] B. K. Bhuyan, A. Dietz, C. G. Smith, *Antimicrob. Agents Chemother*. **1962**, 184-190.

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[6] a) P. F. Wiley, H. K. Jahnke, F. MacKellar, R.B. Kelly, A. D. Argoudelis, *J. Org. Chem.* **1970**, *35*, 1420-1425; b) For the ^{13}C NMR spectrum of the corrected structure of pactamycin, see: D. D. Weller, A. Haber, K. L. Rinehart Jr., P. F. Wiley, *J. Antibiot.* **1978**, *31*, 997-1006.

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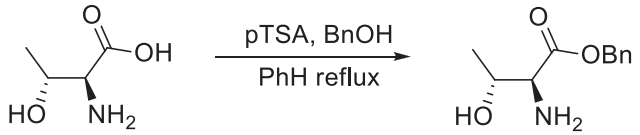
General information. All non-aqueous reactions were run in flame-dried glassware under a positive pressure of argon with exclusion of moisture from reagents and glassware using standard techniques for manipulating air-sensitive compounds. Anhydrous solvents were obtained using standard drying techniques. Unless stated otherwise, commercial grade reagents were used without further purification. Reactions were monitored by analytical thin-layer chromatography (TLC) performed on pre-coated, glass-backed silica gel plates. Visualization of the developed chromatogram was performed by UV absorbance, aqueous cerium ammonium molybdate, iodine, or aqueous potassium permanganate. Flash chromatography was performed on 230-400 mesh silica gel with the indicated solvent systems. Melting points are uncorrected. Infrared spectra were recorded on a FT-IR spectrometer and are reported in reciprocal centimeters (cm^{-1}). Routine nuclear magnetic resonance spectra were recorded either on AV-300, AV-400, or AV-700 spectrometer. Chemical shifts for ^{1}H NMR spectra are recorded in parts per million from tetramethylsilane with the solvent resonance as the internal standard ($CHCl_3$, δ 7.27 ppm). Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, m = multiplet and br = broad) and coupling constant in Hz. Chemical shifts for ^{13}C NMR spectra are recorded in parts per million from tetramethylsilane using the central peak of the solvent resonance as the internal standard ($CDCl_3$, δ 77.00 ppm). All spectra were obtained with complete proton decoupling. Optical rotations were determined at 589 nm at ambient temperature. Data are reported as follows: $[\alpha]_D$ concentration (c in g/100 mL), and solvent. High-resolution mass spectra were performed by the Centre régional de spectroscopie de masse de l'Université de Montréal using fast atom bombardment (FAB) or electrospray ionization (ESI) techniques. Low-resolution mass spectra were obtained using electrospray ionization (ESI).

Experimental procedures:

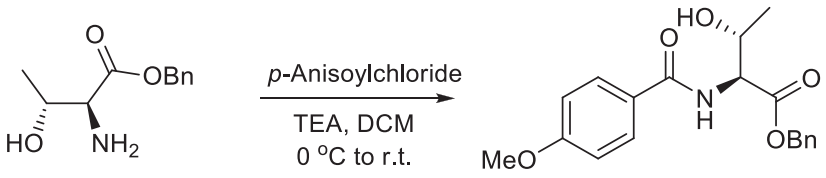
(2*S*,3*R*)-benzyl 2-amino-3-hydroxybutanoate:



L-Threonine (**1**)

A suspension of L-Threonine (23.0 g, 193.1 mmol) in 200 mL of 4:1 benzene:BnOH was treated with *p*-toluenesulfonic acid monohydrate (40.3 g, 212.4 mmol). The flask was fitted with a Dean-Stark trap and heated under reflux for 24 h (~115 ^{o}C) with azeotropic removal of water. The reaction was cooled to r.t. and benzene was removed *in vacuo*. To the mixture was added water, and the aqueous layer was washed with EtOAc (2 x 200 mL). The organic washes were back-extracted with water (4 x 100 mL) and the combined aqueous layers were then basified to pH > 9 using KOH pellets. The aqueous solution was finally extracted with EtOAc (5 x 200 mL) and the organic layers dried over Na_2SO_4 and evaporated to give the crude amino ester as colorless oil. To the oil was added 100 mL of petroleum ether with stirring and the turbid mixture was kept over 48 h at 4 ^{o}C to get the desired ester as crystalline. After decanting the solution, the crystals were dried to give the pure benzyl ester as a white solid (27.0 g, 67%). $[\alpha]_D^{20}$ = –4.2 (*c* = 1.00, MeOH); M.P. = 67 – 68 ^{o}C; IR (neat): ν_{max} = 3446, 2928, 2810, 1731, 1587, 1455, 1330, 1294, 1174, 972, 920, 877, 826, 752, 698 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44 – 7.38 (5H, m), 5.19 (2H, s), 4.14 – 3.71 (1H, m, *J* = 6.0 Hz), 3.33 (1H, d, *J* = 5.2 Hz), 2.19 (2H, br s), 1.22 (3H, d, *J* = 6.4 Hz); HRMS (ESIMS): calcd for $C_{11}H_{16}NO_3$ $[M+H]^+$ 210.11247, found 210.11244.

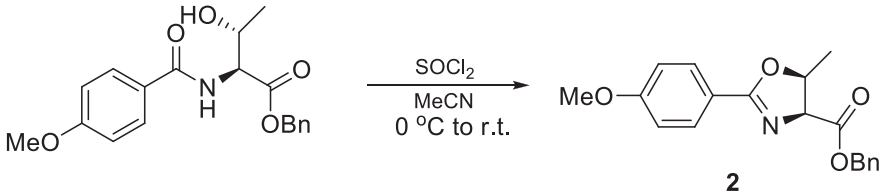
(2*S*,3*R*)-benzyl 3-hydroxy-2-(4-methoxybenzamido)butanoate:



To a stirred solution of benzyl ester (27.0 g, 129.1 mmol) in dry DCM (250 mL) was added TEA (21.6 mL, 155.0 mmol) at 0 ^{o}C under argon atmosphere and stirred for 10 min. The reaction mixture was warmed to room temperature and *p*-anisoyl chloride (17.8 mL, 129.1 mmol) was added and stirred for 2 h at r.t. It was quenched with saturated aqueous NH_4Cl solution and the organic phase was separated. The aqueous phase was washed three times with dichloromethane, the combined organic phases were dried over sodium sulfate and concentrated *in vacuo*. Purification by column chromatography 50%

EtOAc in hexanes afforded pure colorless and odorless crystals (28.4 g, 64%). $[\alpha]_D^{20}$ = +24.5 (*c* = 1.00, $CHCl_3$); IR (neat): ν_{max} = 3373, 2974, 2840, 1746, 1633, 1607, 1539, 1505, 1456, 1385, 1350, 1309, 1257, 1180, 1123, 1028, 841, 765, 754, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.81 (2H, d, *J* = 4.4 Hz), 7.33 – 7.23 (5H, m), 7.05 (1H, d, *J* = 4.4 Hz), 6.89 (2H, d, *J* = 4.4 Hz), 5.21 (2H, dd, *J* = 8.4, 6.0 Hz), 4.86 (1H, dd, *J* = 4.4, 1.2 Hz), 4.46 (1H, m), 3.83 (3H, m), 2.93 (1H, br s), 1.26 (3H, d, *J* = 3.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.6, 165.1, 159.9, 132.7, 126.6, 126.1, 125.8, 125.6, 111.2, 65.7, 64.8, 55.4, 52.8, 17.5; HRMS (ESIMS): calcd for $C_{19}H_{22}NO_5$ $[M+H]^+$ 344.14925, found 344.14958.

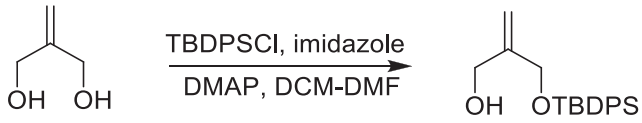
(4*S*,5*S*)-benzyl 2-(4-methoxyphenyl)-5-methyl-4,5-dihydrooxazole-4-carboxylate (2):



2

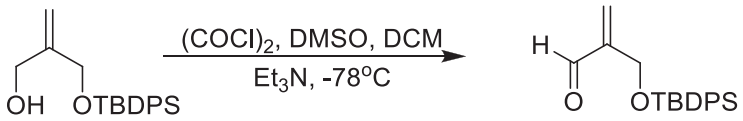
To a stirred solution of the amide (28.0 g, 81.6 mmol) in dry acetonitrile (250 mL) was added thionyl chloride (7.1 mL, 97.9 mmol) at 0 °C under argon atmosphere. The reaction mixture was warmed to room temperature and stirred for 10 h, then quenched with aqueous saturated $NaHCO_3$ solution and extracted three times with EtOAc. The combined organic phases were washed with brine, dried over sodium sulfate and concentrated *in vacuo* to afford yellow solid, which was crystallised by adding, 50 mL of ethyl acetate and cooling at 4 °C for 16 h. After filtration, oxazoline (22.6 g, 85%) was obtained as pale yellow crystals. M.P. = 85 – 87 °C; $[\alpha]_D^{20}$ = +15.2 (*c* = 1.00, $CHCl_3$); IR (neat): ν_{max} = 3459, 2987, 2957, 2933, 1745, 1643, 1609, 1512, 1456, 1364, 1351, 1253, 1233, 1181, 1168, 1084, 1028, 839, 757, 703 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.95 (2H, d, *J* = 8.9 Hz), 7.41 – 7.28 (5H, m), 6.92 (2H, d, *J* = 8.9 Hz), 5.25 and 5.21 (2H, ABq, *J* = 12.2 Hz), 5.02 – 5.00 (2H, m), 3.84 (3H, s), 1.31 (3H, d, *J* = 5.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.7, 165.6, 162.1, 135.0, 130.0, 128.3, 128.2, 128.1, 119.3, 113.3, 77.2, 71.2, 66.5, 54.9, 15.9; HRMS (ESIMS): calcd for $C_{19}H_{20}NO_4$ $[M+H]^+$ 326.13868, found 326.13803.

2-((tert-butyldiphenylsilyloxy)methyl)prop-2-en-1-ol:



To a stirred solution of diol (15.0 g, 170.2 mmol) in dry DCM (150 mL) and dry DMF (150 mL), imidazole (17.39 g, 255.4 mmol) and DMAP (2.08 g, 17.0 mmol) were added at 0 ^{o}C and stirred for 10 min, to it was added TBDPSCl (47.9 mL, 187.3 mmol) drop wisely at 0 ^{o}C and stirring was continued for 6 h at r.t. After completion, the reaction mixture was diluted with ether (600 mL) and washed with water (200 mL x 3) and brine (100 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Flash column chromatography of the crude mass using 15% ethyl acetate in hexanes afforded the TBDPS ether (38.85 g, 70%) as a colorless viscous liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.74 – 7.78 (4H, m), 7.43 – 7.50 (6H, m), 5.20 (2H, d, *J* = 15.0 Hz), 4.22 (2H, s), 2.17 (1H, br s), 1.14 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 147.6, 136.0, 133.7, 130.3, 128.2, 11.5, 65.9, 54.8, 27.3, 19.7. The product could not be seen on ESI-MS or HRMS.

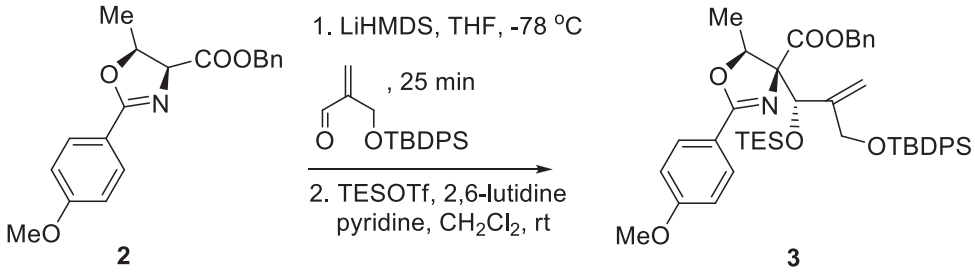
2-((tert-butyldiphenylsilyloxy)methyl)acrylaldehyde:



To a solution of oxalylchloride (20.1 mL, 229.9 mmol) in dry CH_2Cl_2 (800 mL) at –78 °C, DMSO (34.8 mL, 490.5 mmol) was added slowly in drop wise manner, with stirring under argon atmosphere. After 15 min stirring, alchol (50.0 g, 153.3 mmol dissolved in 100 mL of dry CH_2Cl_2) was added in to the reaction mixture. After 0.5 h of stirring at –78 °C, Et_3N (106.8 mL, 766.5 mmol) was added and stirred for another 0.5 h at –78 °C and then for 0.5 h at 0 °C. The reaction mixture was then quenched with saturated aqueous NH_4Cl solution (300 mL) and extracted with $CHCl_3$ (2 x 500 mL). The combined organic layers were washed with water (500 mL), brine (200 mL), dried (Na_2SO_4) and

concentrated *in vacuo*. Purification by column chromatography 5% EtOAc in hexanes afforded pure colorless oil (47.7 g, 96%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.65 (1H, s), 7.74 (4H, d, *J* = 7.5 Hz), 7.43 – 7.50 (6H, m), 6.78 (1H, s), 6.21 (1H, s), 4.56 (2H, s), 1.19 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 193.0, 148.8, 135.1, 132.7, 132.5, 129.5, 127.5, 60.1, 26.5, 19.0. The product could not be seen on ESI-MS or HRMS.

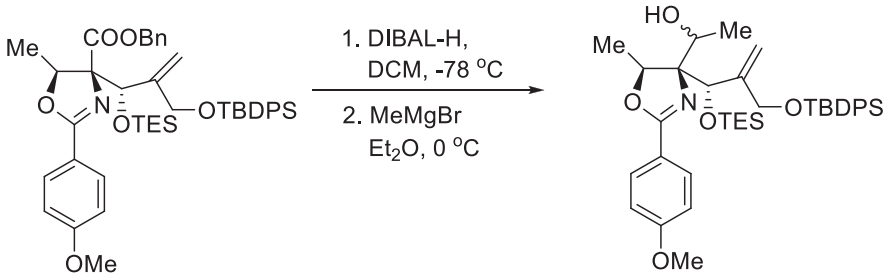
Silyl ether (3):



To a stirred solution of LiHMDS (36.91 mL, 1.0 *M* in THF, 36.91 mmol) in THF (300 mL) was added dropwise with a solution of oxazoline (10.0 g, 30.76 mmol) in THF (50 mL) at –78 °C under argon and stirred for 30 min. To the above enolate, a solution of α,β-unsaturated aldehyde (14.96 g, 46.14 mmol) in THF (50 mL) was added dropwisely at -78 °C and the reaction mixture was stirred for 25 min. The reaction mixture was then quenched very slowly with saturated aqueous NH_4Cl solution at –78 °C. The quench was continued at such low temperatures for an additional 1 h. The reaction mixture was then extracted with ether (500 mL x 3), washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. A crude yellowish and viscous paste was obtained and dried again by making an azeotrop with toluene two times. Without further purification, the crude allylic alcohol was solubilized in dry dichloromethane (200 mL), TESOTf (7.02 mL, 36.91 mmol) and 2,6-lutidine (5.37 mL, 46.14 mmol) were added at 0 °C and stirred for 2 h at rt. The reaction mixture was diluted with ether and washed with saturated aqueous $NaHCO_3$ solution. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Flash column chromatography on silica gel using 15% ethyl acetate in hexane afforded the silylether **3** (15.73 g, 67%, 2 steps) as a pale yellow liquid. $[\alpha]_D^{20}$ = +19.5 (*c* = 1.00, $CHCl_3$); IR (neat): ν_{max} = 2957, 2878, 1739, 1729, 1644, 1612, 1514, 1470, 1428, 1359, 1254, 1112, 912, 840, 742, 702 cm^{-1}; ^{1}H

NMR (400 MHz, $CDCl_3$): δ = 7.79 (2H, d, *J* = 8.8 Hz), 7.63 (2H, d, *J* = 6.7 Hz), 7.53 (2H, d, *J* = 6.7 Hz), 7.44 – 7.21 (11H, m), 6.79 (2H, d, *J* = 8.8 Hz), 5.56 (1H, s), 5.26 (1H, s), 5.25 and 5.16 (2H, ABq, *J* = 12.3 Hz), 4.77 (1H, q, *J* = 6.6 Hz), 4.66 (1H, s), 4.44 and 4.30 (2H, ABq, *J* = 15.3 Hz), 3.85 (3H, s), 1.23 (3H, d, *J* = 6.6 Hz), 1.03 (9H, s), 0.91 (9H, t, *J* = 7.8 Hz), 0.59 (6H, q, *J* = 7.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.6, 164.3, 162.0, 147.8, 135.5, 135.4, 135.3, 133.7, 133.5, 130.8, 129.4, 129.3, 128.6, 128.3, 128.1, 127.5, 127.4, 119.9, 114.1, 113.3, 85.8, 79.5, 79.4, 66.7, 63.4, 55.2, 26.7, 19.2, 17.3, 6.9, 4.6; HRMS (ESIMS): calcd for $C_{45}H_{58}NO_6Si_2$ $[M+H]^+$ 764.37972, found 764.38087.

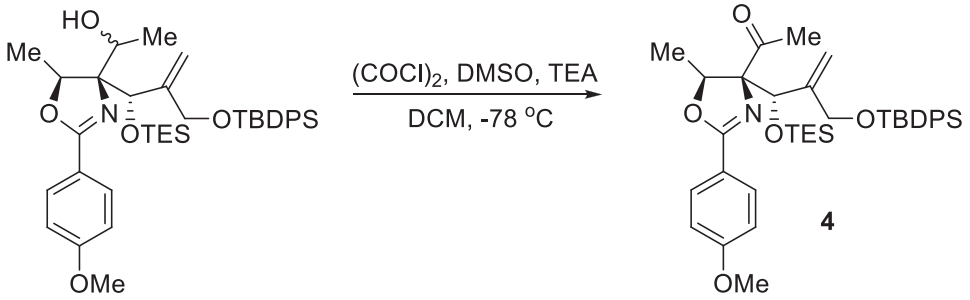
Hydroxy disilyl ether:



To a magnetically stirred solution of benzyl ester **3** (37.4 g, 48.99 mmol) in dry dichloromethane (350 mL) at –78 °C DIBAL-H (147 mL, 1.0 *M* solution in toluene, 146.98 mmol) was added dropwise and stirred for 1 hr. The reaction was followed by Mass Spectroscopy and additional DIBAL-H portions (0.5 eq.) were added every 30 min until complete consumption of starting material. The reaction was quenched with 20% potassium sodium tartrate solution and allowed to reach r.t., then Et_2O was added and the mixture was stirred for 2 h at r.t. The organic phase was separated and the aqueous layer was extracted twice with ether. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude material, a mixture of aldehyde and hemiacetal, was usually not isolated and engaged right away in the next reaction. The above viscous liquid was dissolved in ether (350 mL) and treated with MeMgBr (81.7 mL, 3.0 *M* solution in ether, 244.9 mmol) at 0 °C and stirred for 1 h. The reaction was then quenched with aqueous saturated NH_4Cl solution, extracted with ether, dried over Na_2SO_4 and concentrated under reduced pressure. Flash column chromatography using

20% ethyl acetate in hexanes as eluant afforded an unseparable diastereomeric mixture (2:1 by ^{1}H NMR) of alcohol (28.7 g, 87% 2 steps) as a colorless viscous liquid. IR (neat): ν_{max} = 3428, 2956, 2876, 1644, 1611, 1514, 1463, 1427, 1371, 1306, 1255, 1171, 1112, 1070, 915, 839, 740, 702 cm^{-1}; HRMS (ESIMS): calcd for $C_{39}H_{56}NO_5Si_2$ $[M+H]^+$ 674.36915, found 674.36919. The ^{1}H NMR, ^{13}C NMR and $[\alpha]_D$ data was compiled, but refers to a mixture of diastereomers. The two alcohols were hence engaged in the next chemical transformation.

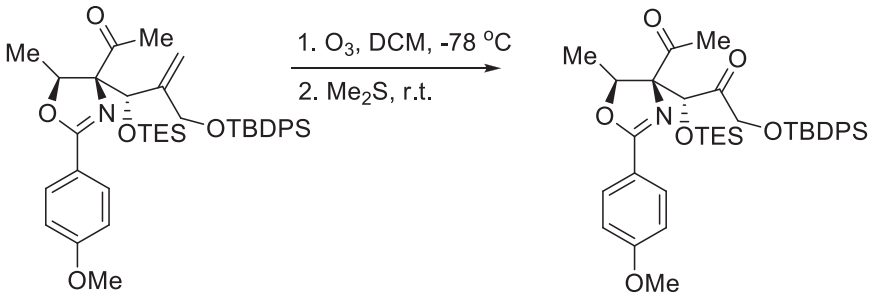
Methyl ketone (4):



To a solution of oxalylchloride (5.54 mL, 63.52 mmol) in dry CH_2Cl_2 (350 mL) at –78 °C, DMSO (9.62 mL, 135.44 mmol) was added slowly in drop wise manner, with stirring under argon atmosphere. After 15 min stirring, oxazoline alcohol (28.5 g, 42.33 mmol dissolved in 50 mL of dry CH_2Cl_2) was added in to the reaction mixture. After 0.5 h of stirring at –78 °C, Et_3N (29.5 mL, 211.6 mmol) was added and stirred for another 0.5 h at –78 °C and then for 0.5 h at 0 °C. The reaction mixture was then quenched with saturated aqueous NH_4Cl solution and extracted with CH_2Cl_2 (300 mL x 2). The combined organic layers were washed with water, brine, dried over Na_2SO_4 and concentrated *in vacuo*. Flash column chromatography on silica gel using 15% ethyl acetate in hexanes afforded the methyl ketone **4** (25.86 g, 91%) as colorless liquid. $[\alpha]_D^{20}$ = –18.2 (*c* = 1.00, $CHCl_3$). IR (neat): ν_{max} = 2956, 2877, 1713, 1644, 1610, 1513, 1461, 1350, 1255, 1170, 1111, 1082, 1056, 904, 839, 740, 701 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 (2H, d, *J* = 8.9 Hz), 7.62 (2H, d, *J* = 9.4 Hz), 7.53 (2H, d, *J* = 8.0 Hz), 7.46 – 7.25 (6H, m), 6.84 (2H, d, *J* = 9.4 Hz) 5.57 (1H, s), 5.23 (1H, s), 4.70 (1H, q, *J* = 6.6 Hz), 4.63 (1H, s), 4.39

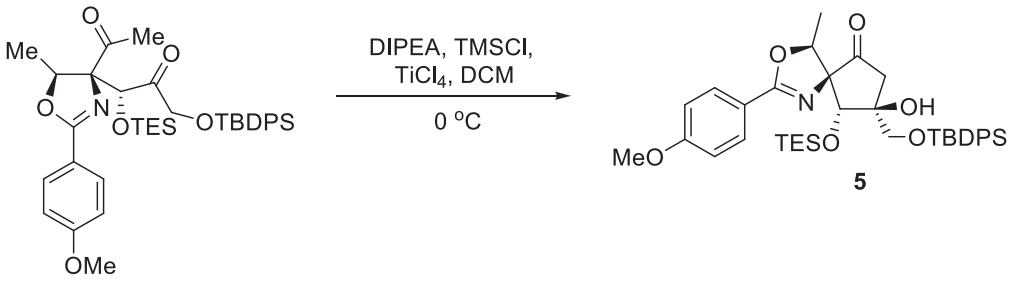
and 4.30 (2H, ABq, J = 15.5 Hz), 3.87 (3H, s), 2.27 (3H, s), 1.24 (3H, d, J = 6.6 Hz), 1.02 (9H, s), 0.94 – 0.90 (9H, m), 0.59 – 0.53 (6H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 211.0, 163.9, 161.8, 147.5, 135.4, 135.0, 133.3, 133.2, 129.8, 129.5, 129.3, 127.8, 127.5, 119.9, 113.7, 113.5, 88.5, 80.5, 79.8, 62.9, 55.0, 30.9, 26.4, 18.9, 17.3, 6.5, 4.3; HRMS (ESIMS): calcd for $C_{39}H_{54}NO_5Si_2$ $[M+H]^+$ 672.35350, found 672.35453.

Diketone:



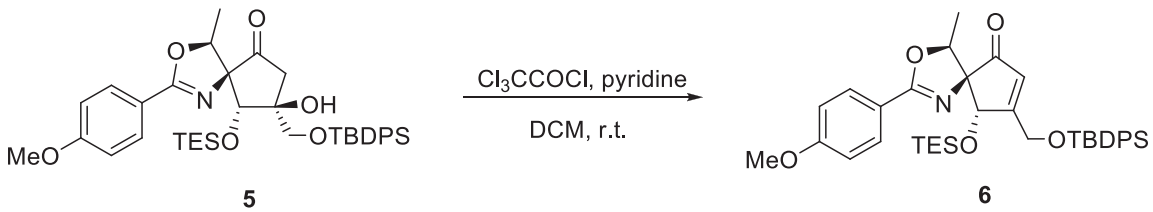
To a solution of olefin (25.6 g, 38.13 mmol) in dichloromethane (200 mL) was passed O_3 gas at –78 °C until the color become light blue. The excess O_3 gas was removed by passing argon gas. The ozonide was decomposed with Me_2S (28 mL, 381.32 mmol) at –78 °C. The mixture was stirred overnight at r.t. The solvent was removed under reduced pressure and flash column chromatography on silica gel using 18% ethyl acetate in hexanes afforded the diketone (21.57 g, 84%) as a colorless viscous liquid. $[\alpha]_D^{20}$ = +27.0 (c = 1.00, $CHCl_3$); IR (neat): ν_{max} = 2957, 2878, 1727, 1713, 1641, 1610, 1514, 1462, 1427, 1356, 1256, 1170, 1113, 1088, 1030, 821, 742, 702 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.93 (2H, d, J = 8.9 Hz), 7.68 – 7.35 (10H, m), 6.93 (2H, d, J = 8.9 Hz), 5.34 (1H, q, J = 6.7 Hz), 4.67 (1H, s). 4.56 and 4.45 (2H, ABq, J = 18.4 Hz), 3.89 (3H, s), 2.25 (3H, s), 1.30 (3H, d, J = 6.7 Hz), 1.04 (9H, s), 0.78 (9H, t, J = 7.8 Hz), 0.43 (6H, q, J = 7.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 210.2, 207.8, 165.7, 162.4, 135.6, 135.5, 132.9, 132.8, 130.3, 129.9, 129.7, 127.9, 127.6, 119.9, 113.8, 87.9, 78.7, 76.1, 70.0, 55.4, 30.2, 26.7, 19.2, 17.3, 6.6, 4.6; HRMS (ESIMS): calcd for $C_{38}H_{52}NO_6Si_2$ $[M+H]^+$ 674.33277, found 674.33561.

Hydroxy-cyclopentanone (5):



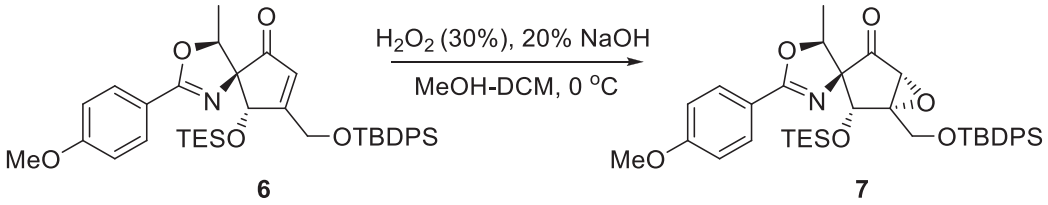
To a magnetically stirred solution of diketone (1.0 g, 1.48 mmol) in dry dichloromethane (40 mL) was added diisopropyl ethylamine (0.78 mL, 4.46 mmol) and a catalytic amount of TMSCl (0.1 mL) at 0 °C. After having stirred for 5 min, $TiCl_4$ (1.78 mL, 1.0 *M* solution in dichloromethane, 1.78 mmol) added dropwisely to the reaction mixture and stirred for 15 min. The reaction was then quenched with cold water and extracted with ether, dried over Na_2SO_4 and concentrated under reduced pressure. Flash column chromatography on silica gel using 25% ethyl acetate in hexanes afforded the hydroxy-cyclopentanone **5** (850 mg, 85%) as pale yellow crystals. $[\alpha]_D^{20}$ = +76.3 (*c* = 1.00, $CHCl_3$); IR (neat): ν_{max} = 3590, 2956, 2858, 1751, 1644, 1610, 1514, 1463, 1427, 1362, 1256, 1171, 1105, 1030, 840, 740, 703 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.85 (2H, d, *J* = 8.9 Hz), 7.73 – 7.68 (4H, m), 7.49 – 7.43 (6H, m), 6.89 (2H, d, *J* = 8.9 Hz), 4.86 (1H, q, *J* = 6.6 Hz), 4.50 (1H, s), 4.03 (1H, d, *J* = 9.3 Hz), 3.85 (3H, s), 3.79 (1H, s, OH), 3.47 (1H, d, *J* = 9.3 Hz), 2.92 and 2.59 (2H, ABq, *J* = 19.6 Hz), 1.12 (9H, s), 1.06 (3H, d, *J* = 6.6 Hz), 0.83 (9H, t, *J* = 7.8 Hz), 0.52 (6H, q, *J* = 7.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 210.9, 177.9, 166.2, 162.3, 135.5, 135.3, 132.7, 132.6, 130.2, 130.1, 130.0, 127.9, 127.8, 127.6, 119.4, 113.5, 84.8, 82.0, 77.8, 76.6, 66.3, 55.3, 48.0, 26.8, 19.3, 17.1, 6.6, 4.8; HRMS (ESIMS): calcd for $C_{38}H_{52}NO_6Si_2$ $[M+H]^+$ 674.33277, found 674.33492.

Cyclopentenone (6):



To a solution of hydroxy ketone (20.85 g, 30.96 mmol) in CH_2Cl_2 (60 mL) was added pyridine (15 mL) and trichloroacetyl chloride (6.95 mL, 61.93 mmol) dropwisely at rt and stirred for 8 h at rt. The reaction mixture was diluted with ether and washed with 0.1 *N* HCl, water and brine. The organic layer was dried over Na_2SO_4 concentrated under reduced pressure. Flash column chromatography on sila gel using 10% ethyl acetate in hexanes afforded the cyclopentenone **6** (18.06 g, 89%) as colorless viscous liquid. $[\alpha]_D^{20}$ = +108.8 (*c* = 1.00, $CHCl_3$); IR (neat): ν_{max} = 2957, 2878, 1722, 1715, 1641, 1610, 1514, 1456, 1428, 1361, 1335, 1256, 1151, 1112, 1087, 1035, 910, 824, 740, 703 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.92 (2H, d, *J* = 8.8 Hz), 7.70 – 7.66 (4H, m), 7.48 – 7.28 (6H, m), 6.90 (2H, d, *J* = 8.8 Hz), 6.54 (1H, s), 5.12 (1H, q, *J* = 6.6 Hz), 4.99 (1H, s), 4.66 and 4.46 (2H, ABq, *J* = 18.9 Hz), 3.81 (3H, s), 1.35 (3H, d, *J* = 6.6 Hz), 1.13 (9H, s), 0.76 (9H, t, *J* = 7.9 Hz), 0.44 (6H, q, *J* = 7.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.5, 178.1, 166.5, 162.4, 135.5, 135.4, 132.8, 132.7, 130.3, 130.1, 128.1, 128.0, 127.8, 119.9, 113.7, 85.9, 77.6, 77.3, 62.6, 55.4, 26.8, 19.4, 17.2, 6.6, 4.7; HRMS (ESIMS): calcd for $C_{38}H_{50}NO_5Si_2$ $[M+H]^+$ 656.32220, found 656.32302.

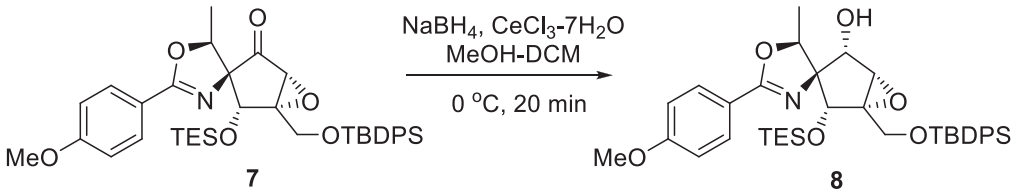
Epoxy-ketone (7):



To a stirred solution of cyclopentenone **6** (17.85 g, 27.23 mmol) in MeOH:DCM (110 mL, 7:1) at 0 °C, H_2O_2 (30% in water, 61 mL) and NaOH (20% aq. solution, 15 mL) were added dropwise and stirred for 2 h. The reaction was quenched with aqueous saturated Na_2SO_3 solution and extracted three times with ether. The organic layer was dried over Na_2SO_4 and concentrated under vacuum. Flash column chromatography using 8% ethyl acetate in hexanes afforded the epoxy-ketone **7** (13.71 g, 75%) as colorless liquid and 30% ethyl acetate in hexanes afforded the epoxide with TES deprotected product (2.23 g, 16%). $[\alpha]_D^{20}$ = +3.6 (*c* = 1.00, $CHCl_3$); IR (neat): ν_{max} = 2957, 2878, 1760,

1644, 1610, 1514, 1463, 1428, 1355, 1326, 1256, 1151, 1105, 1033, 825, 740, 703 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.97 (2H, d, *J* = 8.7 Hz), 7.67 – 7.64 (4H, m), 7.49 – 7.41 (6H, m), 6.92 (2H, d, *J* = 8.7 Hz), 5.23 (1H, q, *J* = 6.5 Hz), 4.63 (1H, s), 4.26 and 3.78 (2H, ABq, *J* = 11.9 Hz), 1.24 (3H, d, *J* = 6.5 Hz), 1.09 (9H, s), 0.83 (9H, t, *J* = 8.0 Hz), 0.50 (6H, q, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 204.0, 165.9, 161.9, 135.3, 135.1, 132.2 132.1, 130.0, 129.8, 129.7, 127.6, 127.6, 127.4, 119.5, 113.2, 82.5, 74.3, 69.0, 59.1, 58.3, 55.0, 29.3, 26.4, 18.8, 16.2, 6.2, 4.4, 4.3; HRMS (ESIMS): calcd for $C_{38}H_{50}NO_6Si_2$ $[M+H]^+$ 672.31712, found 672.31720.

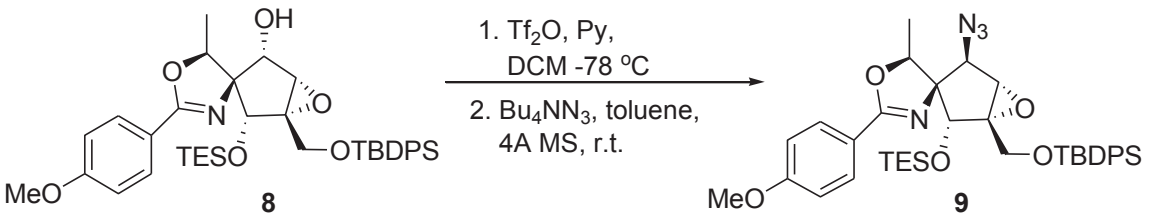
Epoxy-alcohol (8):



7 **8**

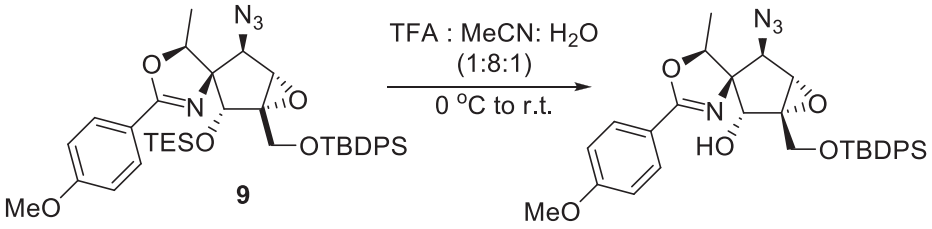
To a solution of epoxyketone **7** (13.6 g, 20.26 mmol) in MeOH:DCM (60 mL, 1:1) was added $CeCl_3 \cdot 7H_2O$ (15.09 g, 40.51 mmol) at 0 °C and stirred for 10 min. Then, $NaBH_4$ (766 mg, 20.26 mmol) was added portion wise and stirred for 1 h. The reaction was then quenched with slow addition of saturated aqueous NH_4Cl solution and extracted three times with ethyl acetate. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. Flash column chromatography using 10% ethyl acetate in hexanes eluant afforded the epoxyalcohol **8** (12.55 g, 92%) as a viscous liquid. $[\alpha]_D^{20}$ = –36.6 (*c* = 1.00, $CHCl_3$); IR (neat): ν_{max} = 3356, 2956, 2877, 1640, 1514, 1456, 1427, 1366, 1257, 1153, 1107, 1035, 832, 740, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.76 (2H, d, *J* = 8.8 Hz), 7.69 – 7.67 (4H, m), 7.47 – 7.41 (6H, m), 6.88 (2H, d, *J* = 8.8 Hz), 5.14 (1H, q, *J* = 6.8 Hz), 4.53 (1H, s), 4.21 (1H, s), 4.15 and 3.65 (2H, ABq, *J* = 11.6 Hz), 3.87 (3H, s), 3.75 (1H, s), 3.30 (1H, s), 1.55 (3H, d, *J* = 6.8 Hz), 1.10 (9H, s), 0.80 (9H, t, *J* = 8.0 Hz), 0.46 (6H, q, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.5, 161.7, 135.4, 135.2, 132.8, 132.5, 129.8, 129.6, 129.5, 127.5, 127.4, 119.6, 113.1, 79.0, 77.2, 76.8, 76.6, 62.8, 59.8, 57.9, 54.9, 26.5, 18.9, 16.6, 6.2, 4.5; HRMS (ESIMS): calcd for $C_{38}H_{52}NO_6Si_2$ $[M+H]^+$ 674.33277, found 674.33519.

Epoxy-azide (9):



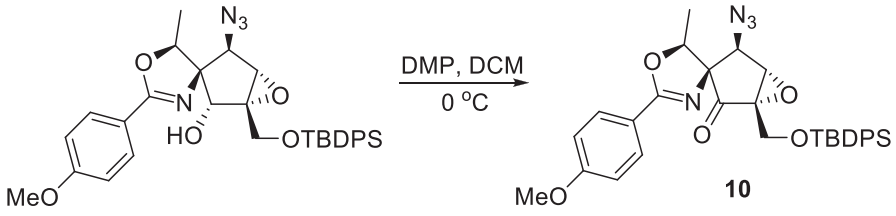
To a solution of pyridine (15 mL) in dry DCM (90 mL) was added triflic anhydride (3.82 mL, 22.7 mmol) at –78 °C with stirring under argon atmosphere. After 10 min stirring, epoxy-alcohol **8** (10.2 g, 15.1 mmol dissolved in 20 mL of dry DCM) was added to the reaction mixture at –78 °C and stirred at 0 °C for 1 h. The mixture was then quenched with aqueous saturated solution of $NaHCO_3$, extracted with DCM (100 mL x 2), and washed with 0.1 *N* HCl, brine, dried over Na_2SO_4 and concentrated in *vacuo*. The secondary triflate intermediate was purified by flash column chromatography on silica gel, using 5% ethylacetate in hexanes. The triflate was then subjected to S_N2 displacement, by dissolving it into 120 mL toluene with preactivated 4Å molecular sieves (3 g) and tetrabutylammonium azide (21.5 g, 75.7 mmol) was added at r.t under argon. The conversion was finished in three days, after which the suspension was filtered and washed with EtOAc (100 mL x 3), the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Flash column chromatography on silica gel (8% EtOAc/hexanes) was used to afford epoxy-azide **9** (9.1 g, 86%) as a colorless oil. $[\alpha]_D^{20}$ = –44.4 (*c* = 1.00, $CHCl_3$); IR (neat): ν_{max} = 2956, 2877, 2110, 1644, 1610, 1514, 1463, 1427, 1360, 1257, 1113, 1033, 916, 837, 738, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.89 (2H, d, *J* = 12.0 Hz), 7.68 – 7.63 (4H, m), 7.42 – 7.37 (6H, m), 6.87 (2H, d, *J* = 12.0 Hz), 5.08 (1H, q, *J* = 8.8 Hz), 4.58 (1H, s), 4.12 (1H, s), 4.09 and 3.54 (2H, ABq, *J* = 15.6 Hz), 3.82 (3H, s), 3.18 (1H, s), 1.26 (3H, d, *J* = 8.8 Hz), 1.06 (9H, s), 0.76 (9H, t, *J* = 10.2 Hz), 0.42 (6H, q, *J* = 10.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.9, 162.2, 136.0, 135.7, 133.3, 132.9, 130.3, 130.1, 130.0, 128.0, 127.9, 120.7, 113.7, 80.9, 77.9, 77.4, 66.4, 63.1, 60.1, 56.6, 55.5, 27.0, 19.4, 17.1, 6.8, 5.1; HRMS (ESIMS): calcd for $C_{38}H_{51}N_4O_5Si_2$ $[M+H]^+$ 699.33925, found 699.34028.

Epoxy-alcohol:



The epoxy-azide **9** (9.08 g, 13.0 mmol) was dissolved in a 1:8:1 mixture of TFA:MeCN:H_2O (48 mL) at 0 °C while maintained under argon. The reaction was carried out during 4 h, after which the transformation was monitored on ESI-MS and the reaction was slowly quenched with a saturated solution of $NaHCO_3$ at 0 °C. The reaction mixture was extracted three times with EtOAc, dried over Na_2SO_4 and concentrated *in vacuo*. The intermediate was purified by flash chromatography on silica gel (20% EtOAc/ hexanes), to afford epoxy alcohol (7.06 g, 93%) as a colorless oil. $[\alpha]_D^{20} = -75.3$ (*c* = 1.00, $CHCl_3$); IR (neat): ν_{max} = 3443, 2934, 2859, 2110, 1633, 1612, 1514, 1463, 1427, 1360, 1257, 1113, 1031, 910, 824, 734, 703 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.95 (2H, d, *J* = 8.9 Hz), 7.73 – 7.70 (4H, m), 7.50 – 7.42 (6H, m), 6.93 (2H, d, *J* = 8.9 Hz), 5.20 (1H, q, *J* = 6.6 Hz), 4.67 (1H, s), 4.19 (1H, s), 4.08 and 3.96 (2H, ABq, *J* = 11.9 Hz), 3.87 (3H, s), 3.38 (1H, s), 2.77 (1H, br s), 1.36 (3H, d, *J* = 6.6 Hz), 1.09 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.4, 162.5, 135.8, 135.7, 132.6, 130.2, 130.1, 128.2, 128.1, 120.2, 113.8, 81.3, 78.1, 78.0, 65.8, 63.1, 62.7, 56.9, 55.6, 27.0, 19.4, 17.2; HRMS (ESIMS): calcd for $C_{32}H_{37}N_4O_5Si$ $[M+H]^+$ 585.25493, found 585.25321.

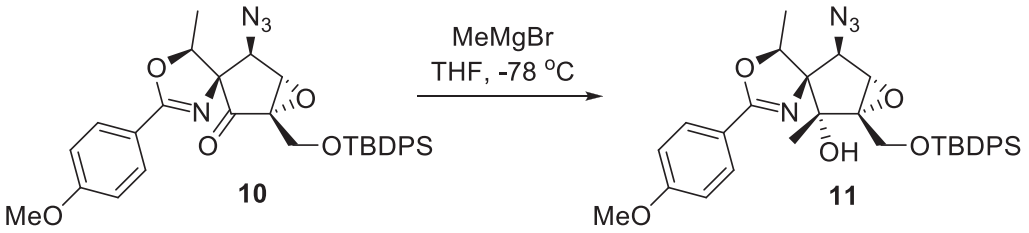
Epoxy-ketone (10):



To a stirred solution of epoxy alcohol (7.02 g, 12.02 mmol) in DCM (125 mL) was added Dess-Martin periodinane (6.2 g, 14.4 mmol) at 0 °C and the reaction mixture was stirred

at r.t. for 2 h. The reaction mixture was quenched with $Na_2S_2O_3/NaHCO_3$ (7:1) aqueous saturated solution (40 mL). The mixture was stirred vigorously until the two layers were seperated. The crude product was extracted with ether (100 mL x 3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography using 10% ethyl acetate/hexanes afforded the epoxy-ketone **10** (6.72 g, 96%) as a colorless viscous foam. $[\alpha]_D^{20}$ = –143.0 (*c* = 1.00, $CHCl_3$); IR (neat): ν_{max} = 2933, 2859, 2113, 1761, 1643, 1610, 1514, 1463, 1427, 1358, 1259, 1171, 1114, 1030, 909, 824, 737, 703 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.97 (2H, d, *J* = 8.8 Hz), 7.70 – 7.66 (4H, m), 7.47 – 7.42 (6H, m), 6.93 (2H, d, *J* = 8.8 Hz), 4.69 (1H, q, *J* = 6.5 Hz), 4.46 (1H, s), 4.22 and 4.16 (2H, ABq, *J* = 12.9 Hz), 4.11 (1H, s), 3.87 (3H, s), 1.48 (3H, d, *J* = 6.5 Hz), 1.07 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 204.1, 166.9, 162.9, 135.8, 135.6, 132.8, 132.6, 130.8, 130.1, 128.1, 128.0, 119.4, 113.9, 82.6, 81.7, 62.9, 59.9, 59.5, 56.8, 55.5, 26.9, 19.4, 17.6; HRMS (ESIMS): calcd for $C_{32}H_{35}N_4O_5Si$ $[M+H]^+$ 583.23712, found 583.23975.

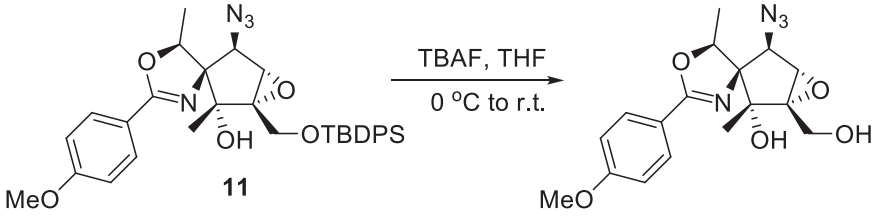
Epoxy-alcohol (11):



To a stirred solution of epoxy-ketone **10** (6.70 g, 11.51 mmol) in dry THF (70 mL) was added MeMgBr (9.6 mL, 3.0 *M* solution in ether, 28.78 mmol) at –78 °C under argon and stirred for 3 h. The reaction mixture was quenched with saturated aqueous NH_4Cl solution and extracted with ethyl acetate (100 mL x 3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Purification by column chromatography using 20% EtOAc in hexanes afforded epoxyalcohol **11** (6.27 g, 91%) as a colorless liquid. $[\alpha]_D^{20}$ = –54.8 (*c* = 1.00, $CHCl_3$); IR (neat): ν_{max} = 3531, 2934, 2858, 2110, 1643, 1610, 1514, 1427, 1356, 1256, 1170,

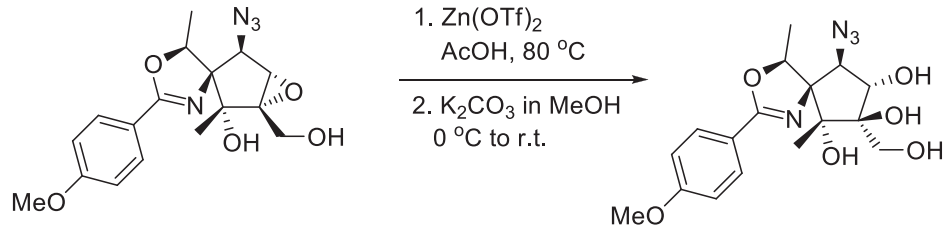
1113, 1044, 911, 823, 744, 703 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.98 (2H, d, *J* = 8.8 Hz), 7.74 – 7.72 (4H, m), 7.48 – 7.28 (6H, m), 6.92 (2H, d, *J* = 8.8 Hz), 5.31 (1H, q, *J* = 6.6 Hz), 4.37 and 3.76 (2H, ABq, *J* = 12.1 Hz), 4.09 (1H, s), 3.87 (3H, s), 3.45 (1H, s), 3.08 (1H, s), 1.54 (3H, s), 1.38 (3H, d, *J* = 6.6 Hz), 1.10 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.6, 162.4, 135.8, 135.7, 132.5, 132.4, 130.6, 130.3, 130.2, 128.2, 128.8, 120.6, 113.7, 86.1, 81.3, 79.4, 69.4, 63.0, 59.0, 55.6, 26.9, 21.9, 19.4, 17.7; HRMS (ESIMS): calcd for $C_{33}H_{39}N_4O_5Si$ $[M+H]^+$ 599.26842, found 599.27110.

Epoxy diol:



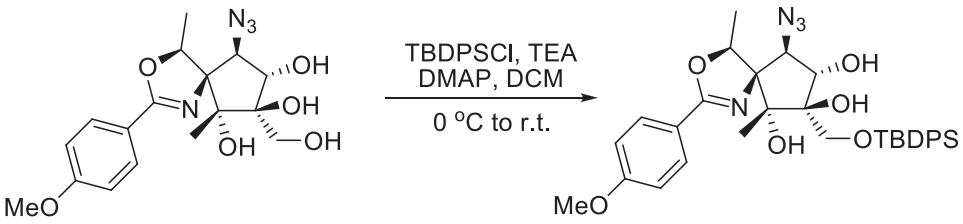
To the solution of epoxyalcohol **11** (6.22 g, 10.40 mmol) in THF (40 mL) was added TBAF (12.5 mL, 1.0 *M* in THF, 12.48 mmol) at 0 °C. The reaction mixture was stirred at r.t. for 1.5 h, a saturated aqueous NH_4Cl solution was then added and the aqueous phase was extracted three times with EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Purification was achieved by flash chromatography using 80% EtOAc in hexanes to afforded epoxydiol (3.55 g, 95%) as colorless viscous liquid. $[\alpha]_D^{20}$ = –71.5 (*c* = 1.00, $CHCl_3$); IR (neat): ν_{max} = 3418, 2936, 2110, 1643, 1609, 1514, 1455, 1356, 1256, 1171, 1092, 1029, 910, 841, 744, 703 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.95 (2H, d, *J* = 8.8 Hz), 6.93 (2H, q, *J* = 8.8 Hz), 5.16 (1H, q, *J* = 6.6 Hz), 4.26 and 3.85 (2H, ABq, *J* = 12.7 Hz), 4.06 (1H, s), 3.87 (3H, s), 3.63 (1H, s), 2.52 (1H, s), 2.36 (1H, br s), 1.49 (3H, s), 1.38 (3H, d, *J* = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.9, 162.5, 130.6, 120.2, 113.9, 86.9, 80.7, 79.2, 70.2, 62.6, 59.8, 59.3, 55.6, 21.1, 17.6; HRMS (ESIMS): calcd for $C_{17}H_{21}N_4O_5$ $[M+H]^+$ 361.15065, found 361.15048.

Tetrol:



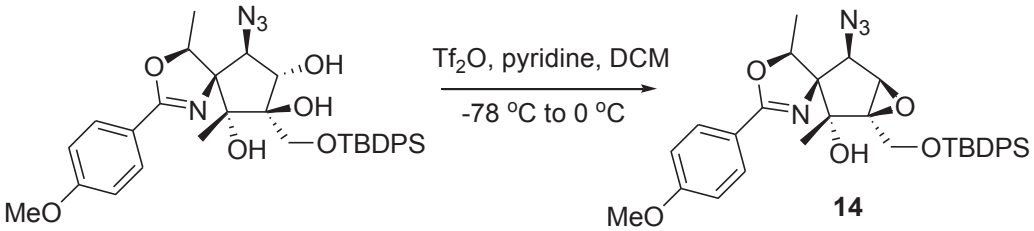
To the stirred solution of epoxy alcohol (3.50 g, 9.72 mmol) in AcOH (50 mL) was added $Zn(OTf)_2$ (7.07g, 19.4 mmol) and stirred at 80 °C for 2 days. The reaction mixture was then cooled to 0 °C, quenched with an aqueous saturated $NaHCO_3$ solution, extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4, concentrated under reduced pressure. The crude mixture was usually engaged in the following transformation without purification, hence reacted the monoacetate product, as well as some diacetate side-product (characterized) and enhancing the yield for this sequence. The crude mixture from the previous reaction was dissolved in a 10% solution of K_2CO_3 in MeOH (40 mL) at 0 °C and stirred for 1 h at r.t. The reaction was quenched with aqueous saturated NH_4Cl solution and the aqueous phase was extracted three times with EtOAc. The intermediate was purified by flash chromatography on silica gel using 70% EtOAc in hexanes to give tetrol (3.20 g, 87%, 2 steps). Spectroscopic data for the diacetate intermediate: IR (neat): $[\alpha]_D^{20}$ = +23.4 (*c* = 1.00, $CHCl_3$); IR (neat): ν_{max} = 3443, 2936, 2102, 1745, 1640, 1610, 1515, 1367, 1256, 1171, 1048, 901, 842, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.86 (2H, d, *J* = 8.7 Hz), 6.93 (2H, d, *J* = 8.7 Hz), 5.64 (1H, d, *J* = 6.0 Hz), 5.60 (1H, s), 4.88 (1H, q, *J* = 6.6 Hz), 4.57 and 4.26 (2H, ABq, *J* = 11.9 Hz), 3.89 (1H, d, *J* = 6.0 Hz), 3.85 (3H, s), 3.27 (1H, s), 2.14 (3H, s), 2.13 (3H, s), 1.57 (3H, d, *J* = 6.6 Hz), 1.24 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.0, 169.4, 164.2, 162.5, 131.3, 118.2, 113.5, 113.3, 84.8, 82.5, 82.0, 81.3, 78.3, 67.7, 63.3, 55.1, 20.7, 20.5, 16.9, 16.5; HRMS (ESIMS): calcd for $C_{21}H_{27}N_4O_8$ $[M+H]^+$ 463.18234, found 463.18258. Spectroscopic data for the tetrol: $[\alpha]_D^{20}$ = +54.5 (*c* = 1.00, $CHCl_3$); IR (neat): ν_{max} = 3605, 3443, 3256, 2936, 2101, 1644, 1609, 1514, 1455, 1364, 1256, 1166, 1104, 1042, 901, 835, 744, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.87 (2H, d, *J* = 8.7 Hz), 6.92 (2H, d, *J* = 8.7 Hz), 5.70 (1H, br s), 4.91 (1H, q, *J* = 6.6 Hz), 4.56 (1H, s), 4.04 and 4.02 (2H, ABq, *J* = 12.1 Hz), 3.94 (1H, d, *J* = 5.3 Hz), 3.87 (3H, s), 3.50 (2H, br s), 3.09 (1H, br s), 1.59 (3H, d, *J* = 6.6 Hz), 1.24 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.1, 162.8, 130.5, 118.8, 113.8, 85.1, 84.7, 83.7, 80.8, 78.6, 70.3, 63.3, 55.5, 17.1; HRMS (ESIMS): calcd for $C_{17}H_{23}N_4O_6$ $[M+H]^+$ 379.16121, found 379.16127.

Triol:



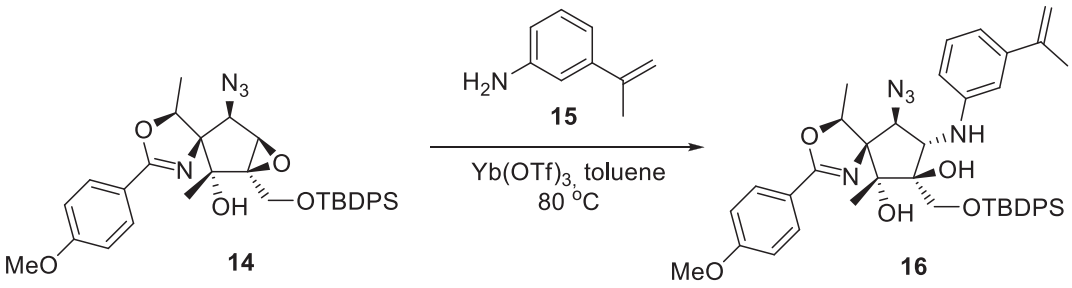
A solution of tetrol (3.1 g, 8.20 mmol) in DCM (40 mL) was added TEA (5.72 mL. 41.0 mmol), TBDPSCl (2.52 mL, 9.84 mmol) and DMAP (200 mg, 1.6 mmol) at 0 °C. The reaction mixture was stirred for 4 h at r.t. The reaction was quenched with aqueous saturated NH_4Cl solution and extracted twice with dichloromethane. The intermediate was purified by flash chromatography on silica gel using EtOAc in Hexanes to afford triol (4.95 g, 98%) as clear oil. $[\alpha]_D^{20}$ = +41.2 (*c* = 1.00, $CHCl_3$); IR (neat): ν_{max} = 3430, 2933, 2858, 2102, 1644, 1611, 1514, 1463, 1427, 1366, 1258, 1171, 1104, 927, 823, 742, 705 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.88 (2H, d, *J* = 8.8 Hz), 7.80 (2H, d, *J* = 6.3 Hz), 7.74 (2H, d, *J* = 6.3 Hz), 7.51 – 7.44 (6H, m), 6.93 (2H, d, *J* = 8.8 Hz), 5.56 (1H, br s, OH), 4.93 (1H, q, *J* = 6.6 Hz), 4.56 (1H, t, *J* = 6.0 Hz), 4.14 and 4.09 (2H, ABq, *J* = 11.0 Hz), 3.98 (1H, d, *J* = 4.9 Hz), 3.86 (3H, s), 3.64 (1H, s), 3.39 (1H, d, *J* = 6.3 Hz), 1.60 (3H, d, *J* = 6.6 Hz), 1.18 (3H, s), 1.13 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.0, 162.9, 136.0, 135.8, 132.1, 131.6, 130.7, 130.5, 130.4, 128.3, 128.2, 119.1, 114.0, 85.4, 85.2, 84.3, 80.9, 78.9, 71.0, 66.2, 55.6, 27.1, 19.3, 17.5, 17.3; HRMS (ESIMS): calcd for $C_{33}H_{41}N_4O_6Si$ $[M+H]^+$ 617.27899, found 617.27653.

Epoxy-alcohol (14):



To a stirred solution of triol (4.9 g, 7.95 mmol) in dry DCM (50 mL) was added pyridine (5 mL) and triflic anhydride (2.67 mL, 15.9 mmol) at –78 ^{o}C under argon atmosphere. The reaction was warmed to 0 ^{o}C and stirred for 1 h. The reaction mixture was quenched with an aqueous saturated $NaHCO_3$ solution and stirred for 30 min to form the epoxide *in situ*. The reaction mixture was extracted three times with dichloromethane and purified by flash column chromatography on silica gel using 10% EtOAc in hexanes to afforded epoxide **14** (4.5 g, 96%) as pale yellow crystals. $[\alpha]_D^{20}$ = +102.7 (*c* = 1.00, $CHCl_3$); IR (neat): ν_{max} = 3480, 2961, 2934, 2860, 2101, 1644, 1634, 1611, 1514, 1463, 1428, 1361, 1346, 1305, 1258, 1171, 1153, 1113, 1035, 910, 841, 822, 736, 703 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.97 (2H, d, *J* = 8.9 Hz), 7.70 (4H, t, *J* = 6.8 Hz), 7.54 – 7.44 (6H, m), 6.92 (2H, d, *J* = 8.9 Hz), 4.92 (1H, q, *J* = 6.5 Hz), 4.41 and 3.65 (2H, ABq, *J* = 11.5 Hz), 4.02 (1H, s), 3.86 (3H, s), 3.68 (1H,s), 3.49 (1H, s), 1.49 (3H, d, *J* = 6.5 Hz), 1.31 (3H, s), 1.11 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.4, 162.5, 135.8, 135.7, 132.0, 131.7, 130.8, 130.6, 130.5, 128.3, 128.2, 120.2, 113.7, 83.8, 81.1, 78.5, 77.5, 62.8, 62.7, 62.5, 55.5, 30.0, 19.2, 17.8; HRMS (ESIMS): calcd for $C_{33}H_{39}N_4O_5Si$ $[M+H]^+$ 599.26842, found 599.26858.

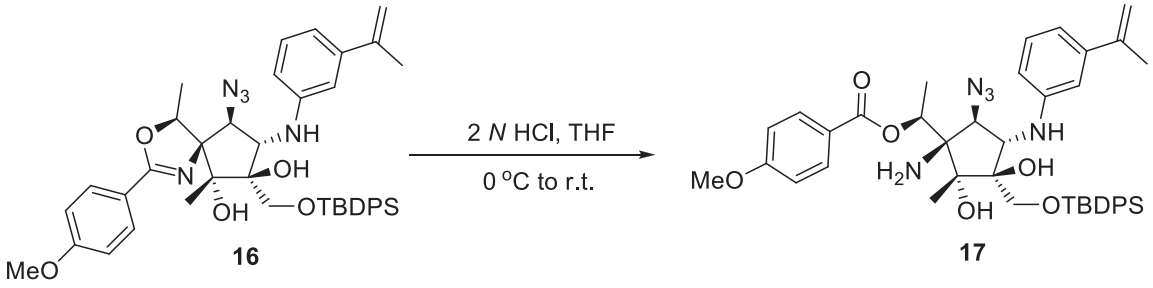
Substituted aniline (16):



To a stirred solution of epoxyalcohol **14** (2.50 g, 4.18 mmol) in toluene (75 mL), the aniline derivative **15** (5.56 g, 41.8 mmol) and $Yb(OTf)_3$ (1.29 g, 2.09 mmol) were added at r.t. and heated at 80 ^{o}C and stirred for 9 h at the same temperature. The reaction mixture was cooled to r.t., then quenched with water (50 mL) and extracted with ethyl acetate (100 mL x 2). The combined organic layers were washed with 0.5 *N* HCl, saturated aqueous $NaHCO_3$ solution, dried over anhydrous Na_2SO_4 and concentrated

under reduced pressure. The residue was purified by flash column chromatography using 10% ethyl acetate in hexanes to afford the core structure of pactamycin **16** (2.47 g, 81%) as a pale yellow viscous liquid. Further elution at 12% EtOAc in hexanes recovered the unreacted epoxide **14** (284 mg, 11%). If that much aniline was not added, competing Payne rearrangement product was observed. The aniline derivative was prepared upon simple Wittig olefination onto *m*-acetophenone. $[\alpha]_D^{20}$ = +6.7 (*c* = 1.00, $CHCl_3$); IR (neat): ν_{max} = 3417, 2934, 2858, 2099, 1641, 1605, 1580, 1514, 1463, 1427, 1364, 1258, 1171, 1113,1034, 908, 822, 736, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.90 (2H, d, *J* = 8.9 Hz), 7.67 (2H, d, *J* = 8.0 Hz), 7.65 – 7.37 (6H, m), 7.28 (2H, t, *J* = 8.1 Hz), 7.16 (1H, t, *J* = 8.9 Hz), 6.93 (3H, t, *J* = 8.9 Hz), 6.81 (1H, s), 6.64 (1H, d, *J* = 8.1 Hz), 5.66 (1H, s), 5.32 (1H, s), 5.05 (1H, m), 4.98 (1H, q, *J* = 6.6 Hz), 4.90 (1H, s), 4.47 (1H, d, *J* = 9.8 Hz), 4.18 (1H, t, *J* = 6.6 Hz), 4.16 and 3.84 (2H, ABq, *J* = 11.1 Hz), 3.97 (1H, d, *J* = 6.5 Hz), 3.87 (3H, s), 2.11 (3H, s), 1.61 (3H, d, *J* = 6.6 Hz), 1.19 (3H, s), 1.12 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.0, 162.7, 146.9, 143.5, 142.5 135.8, 135.5, 134.7, 131.1, 131.0, 130.5, 130.3, 130.0, 129.3, 128.0, 127.9, 127.7, 118.9, 115.3, 113.8, 112.1, 111.9, 110.7, 84.6 (2), 80.1, 78.7, 71.0, 68.1, 66.4, 55.4, 26.9, 21.8, 19.0, 17.3, 17.1; HRMS (ESIMS): calcd for $C_{42}H_{50}N_5O_5Si$ $[M+H]^+$ 732.35757, found 732.35788.

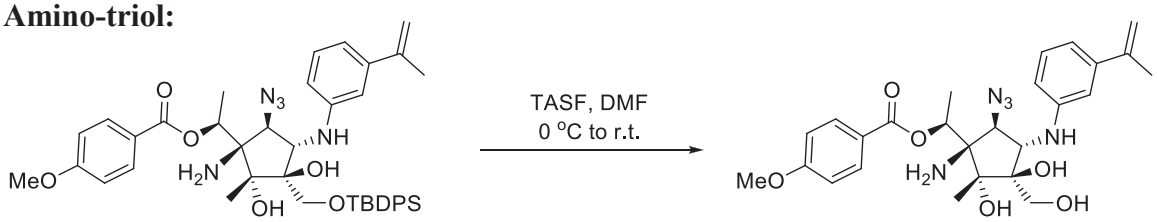
Amino-ester (17):



To a stirred solution of oxazoline **16** (2.27 g, 3.10 mmol) in THF (25 mL) was added 2.0 *N* HCl (10 mL) at 0 °C and allowed to warm up to room temperature. After being stirred for 14 h at r.t., the reaction mixture was cooled to 0 °C, quenched with a saturated aqueous $NaHCO_3$ solution and extracted with ethyl acetate (100 mL x 3). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification by column chromatography using 10%

EtOAc in hexanes recovered the oxazoline **16** (726 mg, 32%) and 25% EtOAc in hexanes afforded amino-ester **17** (1.46 g, 63%) as pale yellow viscous liquid. The cumulative yield after two cycles was 83%. $[\alpha]_D^{20}$ = +106.8 (*c* = 1.00, $CHCl_3$); IR (neat): ν_{max} = 3394, 2934, 2858, 2106, 1703, 1604, 1580, 1512, 1462, 1427, 1328, 1259, 1168, 1113, 1073, 1030, 822, 757, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 8.02 (2H, d, *J* = 8.9 Hz), 7.60 (2H, d, *J* = 6.8 Hz), 7.49 (2H, d, *J* = 6.8 Hz), 7.41 – 7.17 (7H, m), 6.98 (2H, d, *J* = 8.9 Hz), 6.90 (1H, d, *J* = 7.9 Hz), 6.75 (1H, s), 6.65 (1H, dd, *J* = 1.9, 8.1 Hz), 5.78 (1H, q, *J* = 6.5 Hz), 5.32 (1H, s), 5.04 (1H, m), 4.88 (1H, s), 4.56 (1H, d, *J* = 11.1 Hz), 4.25 (1H, dd, *J* = 4.5, 11.1 Hz), 4.01 and 3.77 (2H, ABq, *J* = 11.0 Hz), 3.95 (1H, d, *J* = 4.5 Hz), 3.91 (3H, s), 2.11 (3H, s), 1.37 (3H, d, *J* = 6.5 Hz), 1.27 (3H, s), 1.06 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.1, 163.7, 146.4, 143.6, 142.6, 135.8, 135.6, 131.7, 131.3, 131.2, 130.1, 129.9, 129.3, 127.9, 127.8, 122.4, 115.5, 113.8, 112.2, 112.1, 111.0, 83.8, 80.8, 74.1, 70.9, 70.5, 66.9, 65.5, 55.5, 26.9, 21.9, 19.0, 18.1, 15.2; HRMS (ESIMS): calcd for $C_{42}H_{52}N_5O_6Si$ $[M+H]^+$ 750.36814, found 750.36939.

Amino-triol:

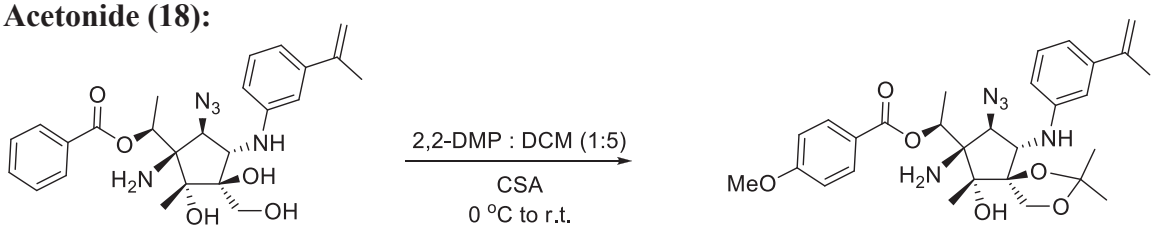


17

To a stirred solution of amino diol **17** (505 mg, 0.67 mmol) in dry DMF (5 mL) was added TAS-F (557 mg, 2.02 mmol) at 0 °C under argon and allowed to room temperature. After being stirred for 1 h at r.t., the reaction mixture was cooled to 0 °C, quenched with a pH=7 phosphate buffer solution and extracted with ethyl acetate (50 mL x 3). The combined organic layers were washed with water (40 mL x 3), brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography using 70% ethyl acetate in hexanes to afford the pure amino triol (327 mg, 95%) as amorphous solid. $[\alpha]_D^{20}$ = +135.5 (*c* = 1.00, $CHCl_3$); IR (neat): ν_{max} 3386, 2938, 2106, 1703, 1604, 1580, 1511, 1456, 1325, 1259, 1168, 1101, 1074, 1028, 885, 847, 770, 696 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 8.01 (2H, d, *J* = 8.5 Hz), 7.22 (1H,

t, J = 7.9 Hz), 6.97 (2H, d, J = 8.3 Hz), 6.93 (1H, d, J = 7.6 Hz), 6.87 (1H, s), 6.71 (1H, d, J = 7.9 Hz), 5.72 (1H, q, J = 6.5 Hz), 5.38 (1H, s), 5.09 (1H, s), 4.46 (1H, d, J = 10.7 Hz), 4.24 (1H, d, J = 10.7 Hz), 4.12 (1H, br s), 3.90 (3H, s), 3.88 (2H, s), 3.81 (1H, s), 2.79 (1H, br s), 2.16 (3H, s), 1.36 (3H, d, J = 6.5 Hz), 1.33 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.2, 164.0, 146.5, 143.4, 142.7, 131.8, 129.4, 121.8, 116.5, 114.0, 113.3, 112.5, 111.8, 83.8, 82.0, 73.6, 71.5, 70.7, 67.2, 63.0, 55.5, 21.9, 17.8, 15.3; HRMS (ESIMS): calcd for $C_{26}H_{34}N_5O_6$ $[M+H]^+$ 512.25036, found 512.25114.

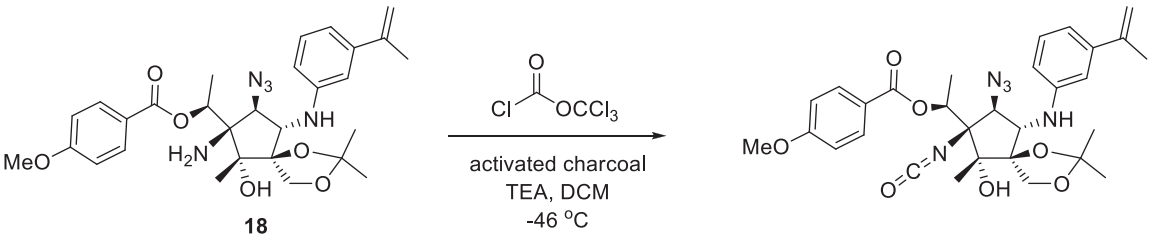
Acetonide (18):



18

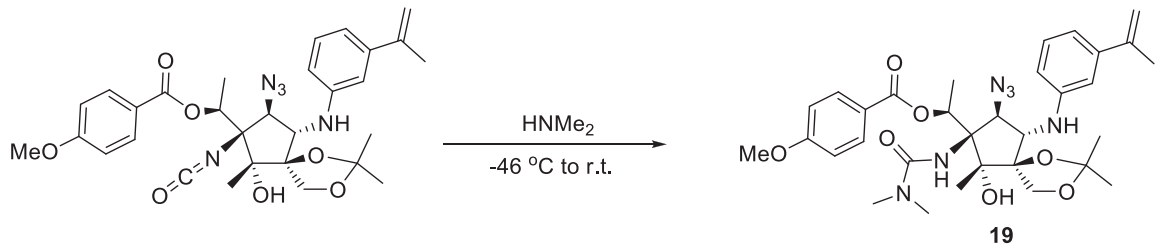
To a stirred solution of amino triol (306 mg, 0.60 mmol) in dry DCM (5 mL), CSA (167 mg, 0.72 mmol) and 2,2-dimethoxy propane (1 mL) were added sequentially at 0 °C under argon and allowed to room temperature. After being stirred for 2 h at r.t., the reaction mixture was cooled to 0 °C, quenched with saturated aqueous $NaHCO_3$ solution and extracted with DCM (50 mL x 2). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude residue (284 mg, 86%) was characterized and directly used for the next step without further purification. $[\alpha]_D^{20}$ = +65.2 (c = 1.00, $CHCl_3$); IR (neat): ν_{max} = 3389, 2918, 2849, 2102, 1694, 1605, 1581, 1512, 1455, 1373, 1319, 1259, 1169, 1151, 1101, 1059, 1031, 908, 854, 772, 730, 695 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.07 (2H, d, J = 8.7 Hz), 7.22 (1H, t, J = 7.9 Hz), 6.97 (2H, d, J = 8.7 Hz), 6.90 (1H, d, J = 7.9 Hz), 6.80 (1H, s), 6.65 (1H, d, J = 7.9 Hz), 5.50 (1H, q, J = 6.5 Hz), 5.38 (1H, s), 5.09 (1H, s), 4.54 (1H, d, J = 11.7 Hz), 4.32 and 4.25 (2H, ABq, J = 10.1 Hz), 4.27 (1H, s), 3.90 (3H, s), 3.53 (1H, s), 2.17 (3H, s), 2.07 (2H, br s), 1.44 (6H, s), 1.41 (3H, d, J = 6.5 Hz), 1.20 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.0, 164.2, 146.3, 143.5, 142.8, 132.2, 129.4, 121.7, 115.8, 113.9, 112.4 (2), 111.0, 110.9, 91.5, 84.5, 75.4, 73.6, 69.6, 67.1, 65.9, 55.5, 26.3, 25.3, 21.9, 17.7, 15.5; HRMS (ESIMS): calcd for $C_{29}H_{38}N_5O_6$ $[M+H]^+$ 552.28166, found 552.28253.

Isocyanate:



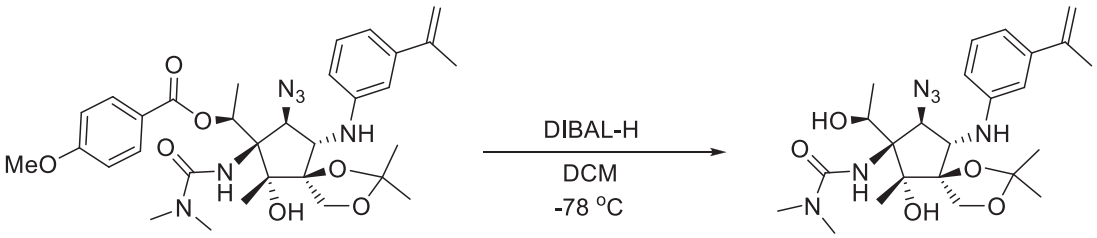
To a stirred solution of acetonide **18** (265 mg, 0.48 mmol) in dry THF (5 mL), activated charcoal (24 mg), Et_3N (0.14 mL, 0.96 mmol) and diphosgene (0.09 mL, 0.72 mmol) were added slowly at –46 °C under argon and stirred for 15 min. Then, the reaction was quenched with saturated aqueous $NaHCO_3$ solution and extracted with ethyl acetate (50 mL x 2). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Flash column chromatography using 20% ethyl acetate in hexanes eluted the stable isocyanate (247 mg, 89%) as a colorless liquid. $[\alpha]_D^{20}$ = +22.8 (*c* = 1.00, $CHCl_3$); IR (neat): ν_{max} = 3389, 2988, 2849, 2270, 2103, 1687, 1604, 1581, 1512, 1382, 1320, 1260, 1169, 1104, 1064, 1029, 896, 854, 771, 730, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 8.08 (2H, d, *J* = 8.9 Hz), 7.23 (1H, t, *J* = 7.9 Hz), 6.99 (2H, d, *J* = 8.9 Hz), 6.93 (2H, d, *J* = 7.9 Hz), 6.80 (1H, s), 6.64 (1H, dd, *J* = 1.9, 6.0 Hz), 5.50 (1H, q, *J* = 6.3 Hz), 5.39 (1H, s), 5.11 (1H, s), 4.58 (1H, d, *J* = 11.7 Hz), 4.39 (1H, s), 4.34 and 4.24 (2H, ABq, *J* = 10.1 Hz), 4.17 (1H, dd, *J* = 2.5, 9.2 Hz), 3.92 (3H, s), 3.50 (1H, d, *J* = 2.5 Hz), 2.17 (3H, s),1.48 (3H, s), 1.46 (3H, s), 1.45 (3H, d, *J* = 6.3 Hz), 1.28 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.9, 164.4, 146.0, 143.4, 142.9, 132.4, 129.5, 124.1, 121.1, 116.2, 114.1, 112.6, 112.4, 111.4, 111.0, 90.8, 85.7, 75.7, 73.8, 72.4, 66.9, 66.0, 55.6, 26.0, 25.2, 21.8, 18.1, 16.2; HRMS (ESIMS): calcd for $C_{30}H_{36}N_5O_7$ $[M+H]^+$ 578.26092, found 578.26124.

Dimethyl urea (19):



To the isocyanate (240 mg, 0.42 mmol) was added neat 0.5 mL dimethyl amine (upon condensing the gas at –46 °C) and the reaction mixture was left warming to room temperature. It was directly subjected to flash column chromatography using 30% ethyl acetate in hexanes to afford dimethyl urea **19** (252 mg, 97%) as a colorless liquid. $[\alpha]_D^{20}$ = +100.4 (*c* = 1.00, $CHCl_3$); IR (neat): ν_{max} = 3398, 2987, 2939, 2108, 1709, 1651, 1605, 1582, 1512, 1372, 1257, 1168, 1101, 1057, 1031, 849, 757, 695 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 8.00 (2H, d, *J* = 8.9 Hz), 7.17 (1H, t, *J* = 7.8 Hz), 6.96 (2H, d, *J* = 8.9 Hz), 6.88 (1H, d, *J* = 7.8 Hz), 6.83 (1H, d, *J* = 2.0 Hz), 6.68 (1H, dd, *J* = 2.0, 7.8 Hz), 6.50 (1H, q, *J* = 6.5 Hz), 5.75 (1H, s), 5.33 (1H, s), 5.06 (1H, s), 4.41 (1H, d, *J* = 9.8 Hz), 4.20 (1H, d, *J* = 9.8 Hz), 4.16 (1H, s), 3.97 and 3.95 (2H, ABq, *J* = 7.3 Hz), 3.87 (3H, s), 2.93 (6H, s), 2.13 (3H, s), 1.57 (3H, s), 1.56 (3H, d, *J* = 6.6 Hz), 1.43 (3H, s), 1.35 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.6, 163.6, 158.0, 147.1, 143.6, 142.7, 131.6, 129.3, 122.2, 116.1, 113.9, 112.6, 112.3, 111.1, 109.9, 90.3, 83.0, 72.1, 70.9, 68.3, 66.1, 65.3, 55.5, 36.6, 29.7, 26.0, 25.8, 22.4, 21.9, 17.1; HRMS (ESIMS): calcd for $C_{32}H_{43}N_6O_7$ $[M+H]^+$ 623.31877, found 623.31983.

Urea-diol:

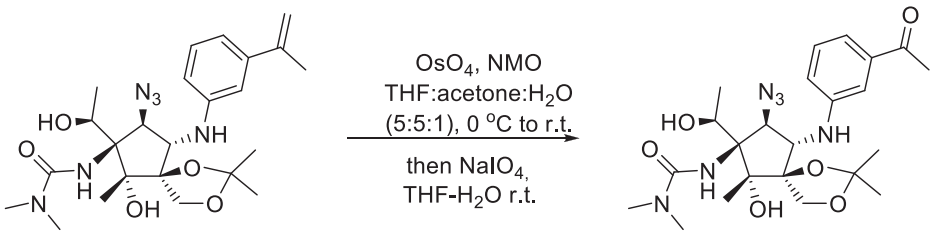


19

To a stirred solution of dimethyl urea **19** (240 mg, 0.39 mmol) in dry DCM (5 mL), DIBAL-H (1.54 mL, 1.0 *M* in toluene, 1.54 mmol) was added slowly at –78 °C under argon and stirred for 1.5 h. The reaction mixture was then quenched with slow addition of methanol and warmed to room temperature. A saturated aqueous potassium sodium tartrate solution was added to the reaction mixture and stirred for 1 h. The reaction mixture was extracted with ethyl acetate (50 mL x 2), the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Flash column chromatography using 25% ethyl acetate in hexanes eluted the urea diol (170 mg,

90%) as colorless liquid. $[\alpha]_D^{20}$ = +38.2 (*c* = 1.00, $CHCl_3$); IR (neat): ν_{max} = 3377, 2926, 2105, 1644, 1602, 1581, 1537, 1487, 1372, 1325, 1259, 1117, 1061, 855, 787, 757, 695 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.48 (1H, d, *J* = 11.3 Hz), 7.23 (1H, t, *J* = 7.8 Hz), 6.92 (1H, d, *J* = 7.8 Hz), 6.73 (1H, d, *J* = 2.0 Hz), 6.57 (1H, d, *J* = 7.8 Hz), 5.44 (1H, s), 5.38 (1H, s), 5.24 (1H, d, *J* = 11.2 Hz), 5.10 (1H, s), 4.65 (1H, s), 4.28 (1H, s), 3.95 (1H, q, *J* = 6.5 Hz), 3.93 (1H, d, *J* = 11.2 Hz), 3.69 (1H, s), 3.03 (6H, s), 2.16 (3H, s), 1.47 (3H, s), 1.46 (3H, s), 1.42 (3H, s), 1.21 (3H, d, *J* = 6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.3, 145.8, 143.4, 143.0, 129.6, 115.9, 112.6, 112.1, 110.6, 91.4, 88.5, 73.9, 73.2, 72.8, 66.6, 65.4, 36.7, 26.4, 25.7, 21.9, 20.8, 17.8; HRMS (ESIMS): calcd for $C_{24}H_{37}N_6O_5$ $[M+H]^+$ 489.28199, found 489.28014.

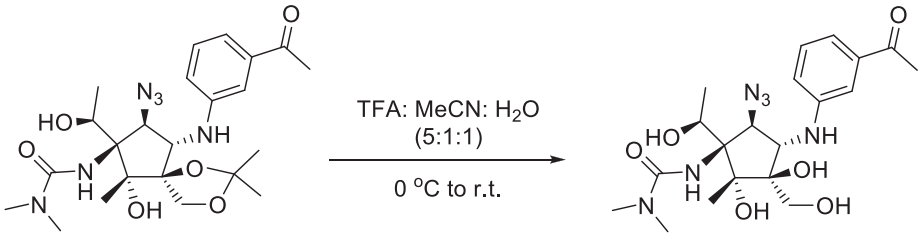
Methyl ketone:



To a stirred solution of olefin compound (160 mg, 0.33 mmol) in THF (2 mL), acetone (2 mL) and H_2O (0.4 mL) were added NMO (192 mg, 1.64 mmol) and catalytic amount of OsO_4 (0.1 mL, 4% wt in H_2O) at 0 °C and stirred for 2 h at r.t. A saturated aqueous sodium bisulfite solution was added to the reaction mixture and stirred for 30 min. The reaction mixture was extracted with ethyl acetate (50 mL x 2), the combined organic layers were washed with water, brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Flash column chromatography using 75% ethyl acetate in hexanes eluted the tetrol as clear oil, which was directly used for the next reaction without characterisation. To the stirred solution of above tetrol in THF (3 mL) and H_2O (3 mL) was added $NaIO_4$ (105 mg, 0.49 mmol) at r.t. and stirred for 3 h. The reaction mixture was extracted with ethyl acetate (50 mL x 2) and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Flash column chromatography using 25% ethyl acetate in hexanes eluted the methyl ketone (129 mg, 80% in 2 steps) as colorless liquid. $[\alpha]_D^{20}$ = +58.7 (*c* = 1.00, $CHCl_3$); IR (neat): ν_{max} = 3373, 2989, 2935, 2105, 1682,

1643, 1602, 1538, 1488, 1372, 1323, 1264, 1231, 1114, 1061, 855, 757, 689 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.47 (2H, d, *J* = 11.3 Hz), 7.36 – 7.30 (2H, m), 7.23 (1H, s), 6.84 (1H, d, *J* = 7.4 Hz), 5.43 (1H, s), 5.38 (1H, d, *J* = 11.2 Hz), 4.64 (1H, s), 4.27 and 4.23 (2H, ABq, *J* = 11.2 Hz), 3.94 (1H, d, *J* = 11.2 Hz) 3.93 (1H, q, *J* = 6.5 Hz), 3.02 (6H, s), 2.61 (3H, s), 1.45 (6H, s), 1.41 (3H, s), 1.20 (3H, d, *J* = 6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 198.1, 158.2, 146.1, 138.5, 129.8, 118.4, 117.8, 111.8, 110.7, 91.3, 88.3, 74.2, 72.9, 72.7, 66.7, 65.3, 36.6, 26.6, 26.3, 25.7, 20.6, 17.7; HRMS (ESIMS): calcd for $C_{23}H_{35}N_6O_6$ $[M+H]^+$ 491.26126, found 491.26189.

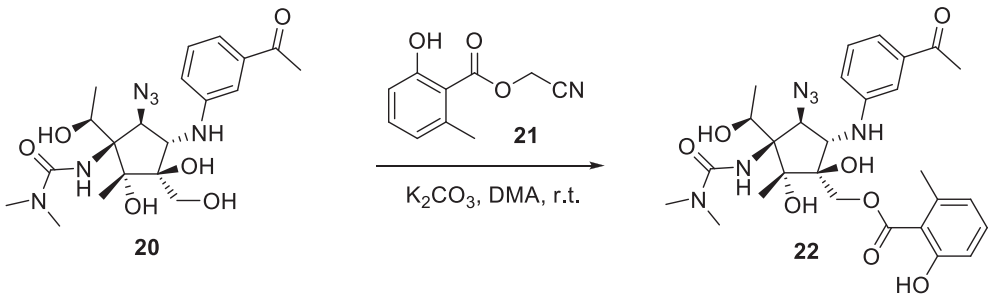
Keto-tetrol (20):



20

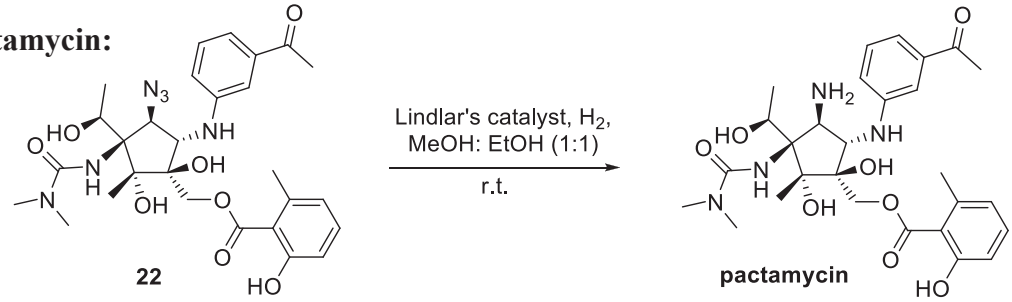
To the stirred solution of methyl ketone (120 mg, 0.25 mmol) in acetonitrile (0.3 mL) and H_2O (0.3 mL); TFA (1.5 mL) was added at 0 °C and stirred for 45 min at r.t., then the reaction mixture was cooled to 0 °C and quenched very slowly with saturated aqueous $NaHCO_3$ solution and extracted with ethyl acetate (50 mL x 2). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated in *vacuo*. Flash column chromatography using 70% ethyl acetate in hexanes eluted tetrol **20** (94 mg, 85%) as colorless liquid. $[\alpha]_D^{20}$ = +52.2 (*c* = 1.00, $CHCl_3$); IR (neat): ν_{max} = 3410, 2935, 2104, 1681, 1634, 1603, 1538, 1373, 1326, 1240, 1110, 1037, 756, 689 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.55 (1H, d, *J* = 11.2 Hz), 7.32 – 7.20 (2H, m), 7.19 (1H, s), 6.83 (1H, d, *J* = 6.3 Hz), 5.53 (1H, s), 5.34 (1H, d, *J* = 11.2 Hz), 4.58 (1H, s), 4.09 and 3.63 (2H, ABq, *J* = 11.8 Hz), 4.00 (1H, m), 3.89 (1H, d, *J* = 11.2 Hz), 3.67 (1H, br s), 3.60 (1H, s), 2.99 (6H, s), 2.51 (3H, s), 1.41 (3H, s), 1.20 (3H, d, *J* = 6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 198.6, 158.5, 146.2, 138.3, 129.8, 118.7, 118.6, 112.1, 88.3, 84.3, 74.1, 73.8, 72.8, 66.6, 61.0, 36.7, 26.6, 20.4, 17.8; HRMS (ESIMS): calcd for $C_{20}H_{31}N_6O_6$ $[M+H]^+$ 451.22996, found 451.23004.

Methyl salicylate ester (21):



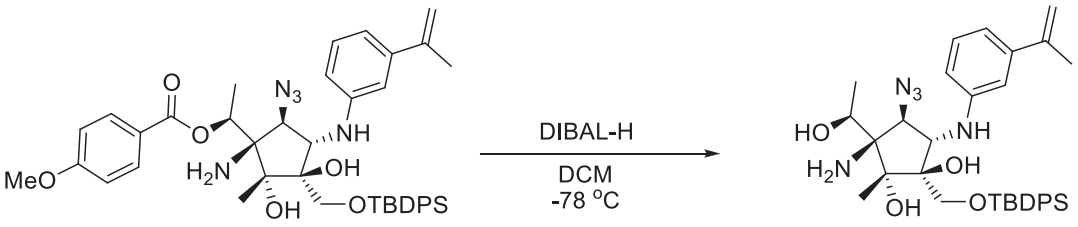
To a stirred solution of the cyanomethyl ester **21** (72 mg, 0.38 mmol) in dry dimethylacetamide (1.5 mL) was added K_2CO_3 (39 mg, 0.28 mmol) at r.t. and stirred for 1 h under argon atmosphere. The above freshly made ketene was added to the stirred solution of tetrol (85 mg, 0.19 mmol) in dimethylacetamide (1.5 mL) at r.t. and stirred for 10 min. The reaction mixture was then cooled to 0 ^oC, quenched with saturated aqueous NH_4Cl solution and extracted with ethyl acetate (40 mL x 3). The combined organic layers were washed with water (30 mL x 3), brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Flash column chromatography using 40% ethyl acetate in hexanes afforded methyl salicylate ester **22** (106 mg, 96%) as a colorless liquid. $[\alpha]_D^{20}$ = +40.4 (*c* = 1.00, $CHCl_3$); IR (neat): ν_{max} = 3412, 2935, 2104, 1681, 1644, 1604, 1582, 1532, 1439, 1372, 1325, 1252, 1214, 1110, 756 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 10.90 (1H, br s), 7.64 (1H, d, *J* = 11.3 Hz), 7.29 – 7.21 (4H, m), 6.84 (1H, s), 6.78 (1H, d, *J* = 8.3 Hz), 6.61 (1H, d, *J* = 7.5 Hz), 5.57 (1H, s), 5.48 (1H, d, *J* = 11.3 Hz), 4.83 (1H, s), 4.83 and 4.71 (2H, ABq, *J* = 12.2 Hz), 4.02 (1H, m), 3.98 (1H, d, *J* = 11.3 Hz), 3.67 (1H, s), 3.39 (1H, br s), 3.01 (6H, s), 2.53 (3H, s), 2.37 (3H, s), 1.54 (3H, s), 1.22 (3H, d, *J* = 6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 198.3, 172.0, 162.5, 158.4, 145.9, 140.8, 138.3, 134.4, 129.8, 123.0, 118.8, 118.3, 115.6, 112.0, 111.9, 88.7, 83.7, 74.5, 73.6, 73.1, 67.0, 65.2, 36.7, 26.5, 23.9, 20.5, 17.6; HRMS (ESIMS): calcd for $C_{28}H_{37}N_6O_8$ $[M+H]^+$ 585.26674, found 585.26702.

Pactamycin:



To a solution of azido ester **22** (44 mg, 0.075 mmol) in EtOH (1 mL) and MeOH (1 mL) was added Lindlar's catalyst (20 mg) and H_2-filled ballons was applied for 3 h. It was then filtered through a short pad of celite and the filter cake was washed with 10% MeOH in dichloromethane. The filtrate and washings were combined and concentrated *in vacuo*. Flash column chromatography using 2% MeOH in diclorometh ane afforded pactamycin (36 mg, 85%) as a pale yellow amorphous solid. $[\alpha]_D^{20}$ = +30.4 (*c* = 1.00, $CHCl_3$) and $[\alpha]_D^{20}$ = +22.6 (*c* = 0.73, 95% EtOH); IR (neat): ν_{max} = 3379, 2932, 1667, 1604, 1519, 1462, 1440, 1372, 1328, 1296, 1253, 1214, 1108, 911, 804, 781, 731, 702 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$): δ = 10.95 (1H, br s), 7.93 (1H, d, *J* = 11.0 Hz), 7.29 – 7.19 (5H, m), 6.84 – 6.80 (2H, m), 6.66 (1H, d, *J* = 7.4 Hz), 5.79 (1H, br s), 5.69 (1H, d, *J* =10.6 Hz), 4.86 and 4.81 (2H, ABq, *J* = 12.4 Hz), 3.95 (1H, m), 3.83 (1H, d, *J* = 10.6 Hz), 3.01 (6H, s), 2.98 (1H, s), 2.57 (3H, s), 2.40 (3H, s), 1.57 (3H, s), 1.06 (3H, d, *J* = 6.4 Hz); ^1H NMR (400 MHz, $CDCl_3$ + D_2O): δ = 7.29 – 7.25 (3H, m), 7.19 (1H, s), 6.83 – 6.81 (2H, m), 6.66 (1H, d, *J* = 7.4 Hz), 4.85 and 4.80 (2H, ABq, *J* = 12.3 Hz), 3.93 (1H, q, *J* = 6.4 Hz), 3.82 (1H, s), 3.01 (6H, s), 2.96 (1H, s), 2.57 (3H, s), 2.40 (3H, s), 1.56 (3H, s), 1.06 (3H, d, *J* = 6.4 Hz); ^1H NMR (400 MHz, DMF – D_7): δ = 7.55 (1H, br s), 7.40 (1H, s), 7.25 – 7.18 (3H, m), 7.04 (1H, m), 6.78 (1H, d, *J* = 8.2 Hz), 6.67 (1H, d, *J* = 7.5 Hz), 5.92 (1H, d, *J* =10.0 Hz), 5.77 (1H, br s), 4.81 and 4.52 (2H, ABq, *J* = 11.6 Hz), 3.98 (1H, q, *J* = 6.4 Hz), 3.95 (1H, d, *J* = 10.0 Hz), 3.03 (1H, s), 2.97 (6H, s), 2.53 (3H, s), 2.18 (3H, s), 1.49 (3H, s), 0.98 (3H, d, *J* = 6.4 Hz); ^1H NMR (400 MHz, DMF – D_7 + D_2O): δ = 7.37 (1H, s), 7.26 – 7.20 (2H, m), 7.03 (1H, m), 6.74 (1H, d, *J* = 8.2 Hz), 6.58 (1H, d, *J* = 7.5 Hz), 4.73 and 4.55 (2H, ABq, *J* = 11.6 Hz), 3.97 (1H, q, *J* = 6.4 Hz), 3.95 (1H, s), 3.00 (1H, s), 2.95 (6H, s), 2.52 (3H, s), 2.15 (3H, s), 1.47 (3H, s), 0.98 (3H, d, *J* = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 198.5, 172.5, 162.7, 159.2, 146.6, 141.2, 138.3, 134.5, 129.6, 123.0, 118.7, 118.4, 115.7, 112.1, 110.8, 88.8, 84.9, 74.3, 71.5, 68.8, 65.3, 63.2, 36.9, 26.7, 24.0, 21.1, 18.1; HRMS (ESIMS): calcd for $C_{28}H_{39}N_4O_8$ $[M+H]^+$ 559.27624, found 559.27733.

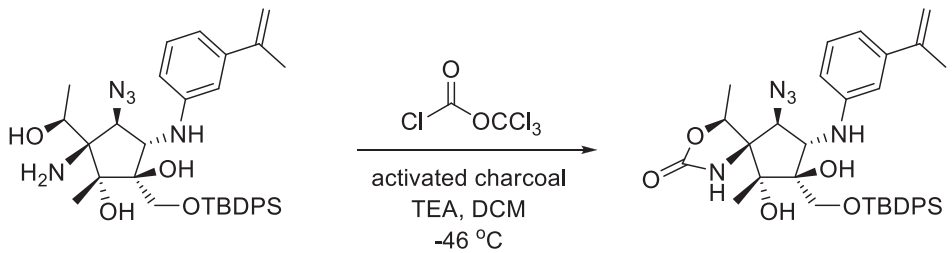
Amino triol (17):



17

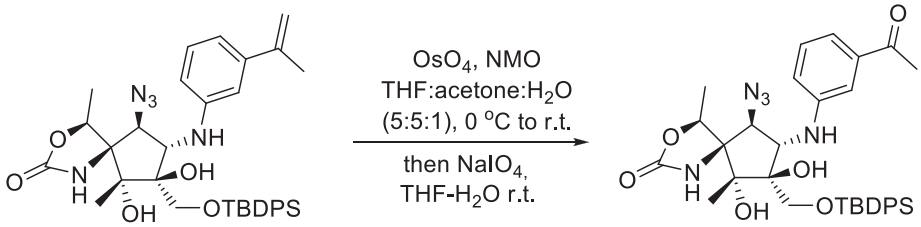
To a stirred solution of urea amino triol **17** (420 mg, 0.56 mmol) in dry DCM (10 mL), DIBAL-H (2.80 mL, 1.0 *M* in toluene, 2.80 mmol) was added slowly at –78 °C under argon and stirred for 2 h. The reaction mixture was then quenched with slow addition of methanol (2 mL) and warmed to room temperature. A saturated aqueous potassium sodium tartrate solution was added to the reaction mixture and stirred for 1 h. The reaction mixture was extracted with ethyl acetate (80 mL x 2), the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Flash column chromatography using 85% ethyl acetate in hexanes eluted the amino triol (307 mg, 89%) as colorless liquid. $[\alpha]_D^{20}$ = +123.4 (*c* = 1.00, $CHCl_3$); IR (neat): ν_{max} = 3380, 2932, 2858, 2106, 1602, 1580, 1428, 1375, 1328, 1262, 1113, 1058, 891, 822, 740, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.64 (2H, d, *J* = 6.8 Hz), 7.52 (2H, d, *J* = 6.8 Hz), 7.45 – 7.17 (7H, m), 6.91 (1H, d, *J* = 8.0 Hz), 6.75 (1H, br s), 6.59 (1H, d, *J* = 8.0, Hz), 5.33 (1H, s), 5.05 (1H, s), 4.86 (1H, br s), 4.56 (1H, d, *J* = 10.9 Hz), 4.29 (1H, q, *J* = 6.6 Hz), 4.19 (1H, dd, *J* = 4.5, 10.8 Hz), 4.04 and 3.81 (2H, ABq, *J* = 10.8 Hz), 3.88 (1H, d, *J* = 4.0 Hz), 2.11 (3H, s), 1.43 (3H, s), 1.22 (3H, d, *J* = 6.6 Hz), 1.10 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.1, 143.2, 142.2, 135.5, 135.3, 130.8, 129.9, 129.7, 129.0, 127.6, 127.5, 115.1, 111.8, 111.7, 110.6, 84.7, 80.5, 73.5, 69.6, 68.2, 66.8, 65.1, 26.6, 21.5, 18.7, 18.6, 17.8; HRMS (ESIMS): calcd for $C_{34}H_{46}N_5O_4Si$ $[M+H]^+$ 616.33136, found 616.33098.

Cyclic carbamate:



To a stirred solution of amino triol (290 mg, 0.47 mmol) in dry THF (6 mL), activated charcoal (24 mg), Et_3N (0.13 mL, 0.94 mmol) and diphosgene (0.08 mL, 0.71 mmol) were added slowly at –46 ºC under argon and stirred for 15 min., then the reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution and extracted with ethyl acetate (50 mL x 2). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Flash column chromatography using 40% ethyl acetate in hexanes eluted the cyclic carbamate (269 mg, 89%) as colorless liquid. $[\alpha]_D^{20}$ = +15.1 (*c* = 0.75, $CHCl_3$); IR (neat): ν_{max} = 3402, 2932, 2858, 2103, 1738, 1602, 1428, 1386, 1325, 1263, 1113, 1073, 895, 822, 758, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.62 (2H, d, *J* = 6.8 Hz), 7.56 (2H, d, *J* = 6.8 Hz), 7.47 – 7.29 (6H, m), 7.16 (1H, t, *J* = 7.9 Hz), 6.91 (1H, d, *J* = 7.8 Hz), 6.77 (1H, br s), 6.61 (1H, d, *J* = 7.8 Hz), 6.02 (1H, s), 5.37 (1H, s), 5.10 (1H, s), 4.89 (1H, q, *J* = 6.5 Hz), 4.22 (1H, d, *J* = 10.2 Hz), 4.11 (1H, s), 4.03 (2H, s), 3.94 and 3.90 (2H, ABq, *J* = 10.8 Hz), 3.74 (1H, s), 2.15 (3H, s), 1.48 (3H, d, *J* = 6.5 Hz), 1.36 (3H, s), 1.05 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.7, 145.7, 143.1, 142.2, 135.2, 135.1, 131.7, 131.2, 129.7, 129.0, 127.6, 127.6, 115.5, 112.1, 111.9, 110.7, 83.1, 81.3, 75.9, 72.2, 70.5, 66.4, 62.3, 26.5, 21.5, 18.8, 17.4, 16.0; HRMS (ESIMS): calcd for $C_{35}H_{44}N_5O_5Si$ $[M+H]^+$ 642.31062, found 642.31184.

Methyl ketone (23):

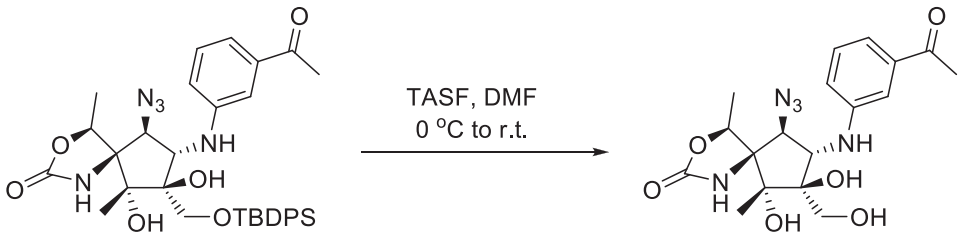


23

To a stirred solution of cyclic carbamate (180 mg, 0.28 mmol) in THF (2 mL), acetone (2 mL) and H_2O (0.4 mL); were added NMO (164 mg, 1.4 mmol) and catalytic amount of OsO_4 (0.1 mL, 4% wt in H_2O) at 0 ºC and stirred for 2 h at r.t. Saturated aqueous sodium bisulfite solution was added to the reaction mixture and stirred for 30 min. The reaction

mixture was extracted with ethyl acetate (50 mL x 2), the combined organic layers were washed with water, brine, dried over anhydrous Na_2SO_4 and concentrated in *vacuo*. Flash column chromatography using 80% ethyl acetate in hexanes eluted the tetrol as clear oil, which was directly used for the next reaction without characterisation. To the stirred solution of above tetrol in THF (3 mL) and H_2O (3 mL); was added $NaIO_4$ (90 mg, 0.42 mmol) at r.t. and stirred for 3 h. The reaction mixture was extracted with ethyl acetate (50 mL x 2) and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Flash column chromatography using 40% ethyl acetate in hexanes eluted the methyl ketone **23** (148 mg, 82% in 2 steps) as a colorless liquid. $[\alpha]_D^{20}$ = +14.7 (*c* = 1.00, $CHCl_3$); IR (neat): ν_{max} = 3373, 2932, 2858, 2105, 1746, 1681, 1603, 1428, 1356, 1360, 1268, 1113, 1078, 909, 822, 739, 703 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.57 (2H, d, *J* = 6.8 Hz), 7.50 (2H, d, *J* = 6.8 Hz), 7.45 – 7.25 (8H, m), 7.22 (1H, s), 6.85 (1H, d, *J* = 7.8 Hz), 5.98 (1H, s), 4.83 (1H, q, *J* = 6.5 Hz), 4.31 (1H, d, *J* = 9.6 Hz), 4.01 (2H, s), 3.92 and 3.83 (2H, ABq, *J* = 10.8 Hz) 3.73 (1H, s), 3.54 (1H,s), 2.56 (3H, s), 1.47 (3H, d, *J* = 6.5 Hz), 1.38 (3H, s), 1.03 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 198.3, 157.7, 146.5, 138.1, 135.5, 135.4, 131.8, 131.5, 130.2, 130.1, 129.8, 128.0, 127.9, 118.8, 117.7, 112.7, 83.6, 82.0, 75.9, 72.2, 70.6, 66.7, 62.8, 26.8, 26.7, 19.1, 17.6, 16.8; HRMS (ESIMS): calcd for $C_{34}H_{42}N_5O_6Si$ $[M+H]^+$ 644.28989, found 644.29092.

Trihydroxy-carbamate:

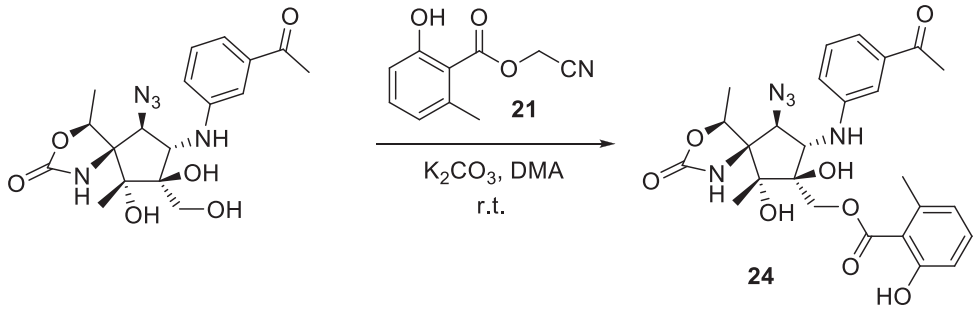


23

To a stirred solution of methyl ketone **23** (125 mg, 0.19 mmol) in dry DMF (2 mL) was added TAS-F (157 mg, 0.57 mmol) at 0 °C under argon and allowed towarm up to room temperature. After being stirred for 1 h at r.t., the reaction mixture was cooled to 0 °C, quenched with a pH 7 phosphate buffer solution and extracted with ethyl acetate (30 mL

x 3). The combined organic layers were washed with water (20 mL x 3), brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography using 95% ethyl acetate in hexanes to afford the pure triol (73 mg, 93%) as an amorphous solid. $[\alpha]_D^{20}$ = +37.9 (*c* = 0.88, DMF); IR (neat): ν_{max} = 3355, 2938, 2106, 1738, 1668, 1601, 1388, 1359, 1327, 1268, 1186, 1067, 896, 822, 768, 688 cm^{-1}; ^1H NMR (400 MHz, Acetone – D_6): δ = 7.45 (1H, s), 7.26 (1H, m), 7.08 (1H, m), 6.54 (1H, s), 5.56 (1H, d, *J* = 9.3 Hz), 4.84 (1H, s), 4.78 (1H, q, *J* = 6.5 Hz), 4.60 (1H, s), 4.33 (1H, d, *J* = 8.5 Hz), 4.16 (2H, t, *J* = 8.9 Hz), 4.06 and 3.69 (2H, ABq, *J* = 11.3 Hz) 3.06 (1H, br s), 2.53 (3H, s), 1.50 (3H, d *J* = 6.5 Hz), 1.45 (3H, s); ^{13}C NMR (100 MHz, Acetone – D_6): δ = 198.4, 158.1, 149.1, 139.1, 130.0, 118.3, 118.1, 113.0, 83.5, 82.6, 75.9, 71.4, 68.8, 67.3, 63.5, 26.7, 17.7, 17.4; HRMS (ESIMS): calcd for $C_{18}H_{24}N_5O_6$ $[M+H]^+$ 406.17211, found 406.17289.

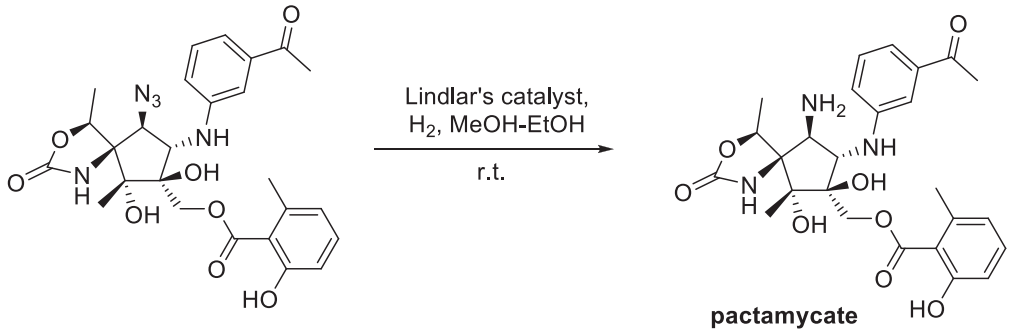
Keto-salicylate (24):



To a stirred solution of the cyanomethyl ester **21** (43 mg, 0.22 mmol) in dry dimethylacetamide (1 mL) was added K_2CO_3 (23 mg, 0.17 mmol) at r.t. and stirred for 1 h under argon atmosphere. The above freshly made ketene was added to the stirred solution of triol (45 mg, 0.11 mmol) in dimethylacetamide (1 mL) at r.t. and stirred for 10 min. The reaction mixture was then cooled to 0 ^oC and quenched with saturated aqueous NH_4Cl solution and extracted with ethyl acetate (40 mL x 3). The combined organic layers were washed with water (30 mL x 3), brine, dried over anhydrous Na_2SO_4 and concentrated in *vacuo*. Flash column chromatography using 40% ethyl acetate in hexanes afforded keto salicylate **24** (59 mg, 98%) as colorless liquid and not stable at room

temperature. $[\alpha]_D^{20}$ = +60.8 (*c* = 1.00, $CHCl_3$); IR (neat): ν_{max} = 3380, 2938, 2104, 1738, 1667, 1604, 1440, 1388, 1359, 1327, 1253, 1152, 1106, 756 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$ + CD_3OD): δ = 7.22 – 7.15 (2H, m), 6.86 (1H, m), 6.73 (1H, d, *J* = 7.6 Hz), 6.64 (1H, d, *J* = 7.6 Hz), 4.80 (1H, q, *J* = 6.5 Hz), 4.62 and 4.54 (2H, ABq, *J* = 12.0 Hz), 4.07 (1H, d, *J* = 4.8 Hz), 4.04 (1H, d, *J* = 4.8 Hz), 2.48 (3H, s), 2.36 (3H, s), 1.48 (3H, d, *J* = 6.5 Hz), 1.34 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.4, 171.2, 161.4, 158.5, 146.4, 141.0, 137.6, 134.1, 129.6, 123.0, 119.3, 118.5, 115.3, 112.7, 112.0, 83.5, 82.8, 72.6, 70.7, 67.4, 64.8, 60.4, 26.6, 23.5, 17.6, 16.0; HRMS (ESIMS): calcd for $C_{26}H_{30}N_5O_8$ $[M+H]^+$ 540.20889, found 540.20901.

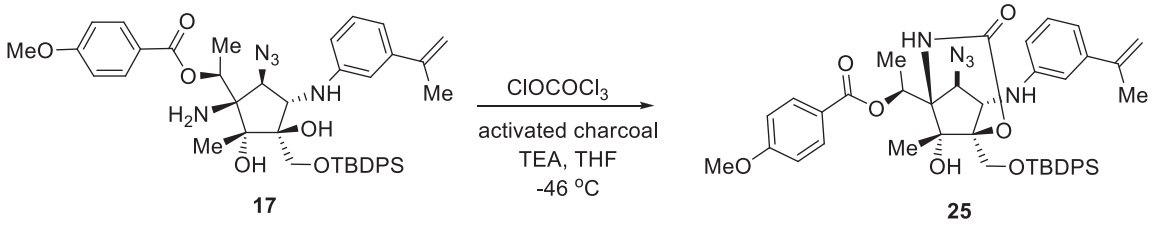
Pactamycate:



To a solution of azido ester **24** (18 mg, 0.03 mmol) in EtOH (1 mL), MeOH (1 mL) was added Lindlar's catalyst (10 mg) and H_2-filled ballons was applied for 3 h. It was then filtered through a short pad of celite and the filter cake was washed with 10 % MeOH in dichloromethane. The filtrate and washings were combined and concentrated *in vacuo*. Flash column chromatography using 6% MeOH in dichloromethane, afforded pactamycate (14 mg, 83%) as a pale yellow solid, which was crystalysed in EtOH. M.P = 204 – 206 ^oC; $[\alpha]_D^{20}$ = +23.8 (*c* = 0.48, DMF); IR (neat): ν_{max} = 3592, 3369, 2917, 2849, 1732, 1668, 1603, 1464, 1358, 1263, 1106, 1068, 897, 782, 690 cm^{-1}; ^1H NMR (400 MHz, CD_3OD): δ = 7.33 (1H, s), 7.22 – 6.92 (3H, m), 6.68 – 6.63 (2H, m), 4.84 (1H, q, *J* = 6.6 Hz), 4.65 and 4.44 (2H, ABq, *J* = 11.8 Hz), 3.66 (1H, d, *J* = 7.4 Hz), 3.59 (1H, d, *J* = 7.4 Hz), 2.45 (3H, s), 2.25 (3H, s), 1.58 (3H, d, *J* = 6.6 Hz), 1.39 (3H, s); ^1H NMR (400 MHz, DMF – D_7): δ = 7.50 (1H, s), 7.22 – 7.11 (4H, m), 6.94 (1H, br s), 6.82 (1H, d, *J* =

8.2 Hz), 6.72 (1H, d, *J* = 7.5 Hz), 5.94 (1H, d, *J* = 7.2 Hz), 4.74 (1H, q, *J* = 6.5 Hz), 4.69 and 4.35 (2H, ABq, *J* = 11.6 Hz), 3.74 (1H, t, *J* = 8.9 Hz), 3.57 (1H, d, *J* = 8.9 Hz), 2.51 (3H, s), 2.25 (3H, s), 1.54 (3H, d, *J* = 6.5 Hz), 1.39 (3H, s), ^{1}H NMR (400 MHz, DMF – D_7 + D_2O): δ = 7.43 (1H, s), 7.20 – 7.08 (4H, m), 6.80 (1H, d, *J* = 8.2 Hz), 6.69 (1H, d, *J* = 7.5 Hz), 4.76 (1H, q, *J* = 6.5 Hz), 4.61 and 4.36 (2H, ABq, *J* = 11.6 Hz), 3.66 (1H, d, *J* = 8.8 Hz), 3.55 (1H, d, *J* = 8.8 Hz), 2.49 (3H, s), 2.17 (3H, s), 1.52 (3H, d, *J* = 6.5 Hz), 1.35 (3H, s); ^{13}C NMR (100 MHz, DMF – D_7): δ = 198.7, 169.0, 158.9, 157.0, 150.9, 138.8, 138.6, 132.0, 129.6, 122.1, 120.3, 117.9, 116.7, 114.5, 112.7, 83.0, 81.5, 76.7, 71.6, 71.1, 67.8, 59.4, 26.8, 20.4, 17.9, 16.9; HRMS (ESIMS): calcd for $C_{26}H_{32}N_3O_8$ $[M+H]^+$ 514.21839, found 514.21855.

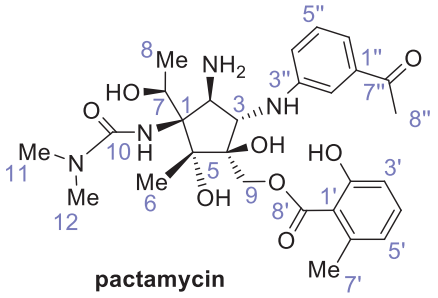
Cyclic carbamate (25):

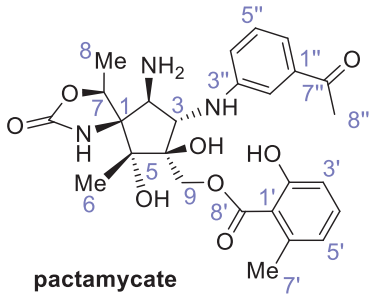


To a stirred solution of amino diol **17** (38 mg, 0.05 mmol) in dry THF (2 mL), activated charcoal (10 mg), Et_3N (0.014 mL, 0.102 mmol) and diphosgene (0.009 mL, 0.076 mmol) were added slowly at –46 ºC under argon and stirred for 15 min., then the reaction was quenched with saturated aqueous $NaHCO_3$ solution and extracted with ethyl acetate (30 mL x 2). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Flash column chromatography using 20% ethyl acetate in hexanes eluted the cyclic carbamate **25** (36 mg, 91%) as white crystals. $[\alpha]_D^{20}$ = +55.1 (*c* = 1.00, $CHCl_3$); IR (neat): ν_{max} = 3324, 2929, 2856, 2106, 1707, 1698, 1605, 1581, 1512, 1323, 1259, 1169, 1104, 1071, 847, 769, 702 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.03 (2H, d, *J* = 8.9 Hz), 7.61 (2H, d, *J* = 6.8 Hz), 7.47 – 7.36 (6H, m), 7.25 – 7.20 (4H, m), 6.97 (1H, d, *J* = 7.9 Hz), 6.93 (2H, d, *J* = 8.9 Hz), 6.78 (1H, s), 6.64 (1H, d, *J* = 7.9 Hz), 6.05 (1H, s), 5.56 (1H, q, *J* = 6.6 Hz), 5.33 (1H, s), 5.08 (1H, s), 4.33 (1H, br s), 4.42 (1H, d, *J* = 4.5 Hz), 4.26 (1H, d, *J* = 4.5 Hz), 4.20 and 3.86 (2H,

ABq, J = 11.2 Hz), 3.87 (3H, s), 2.12 (3H, s), 1.57 (3H, d, J = 6.6 Hz), 1.35 (3H, s), 1.10 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.2, 163.9, 150.7, 145.7, 143.3, 142.9, 135.8, 135.5, 131.9, 130.6, 130.6, 130.5, 130.2, 129.5, 128.1, 127.9, 121.6, 116.3, 113.9, 112.6, 111.9, 110.9, 85.4, 78.6, 68.8, 66.9, 66.6, 63.7, 55.4, 26.9, 21.9, 18.9, 17.0, 16.9; HRMS (ESIMS): calcd for $C_{43}H_{50}N_5O_7Si$ $[M+H]^+$ 776.34740, found 776.34663.

NMR COMPARISON





^{1}H NMR Comparison Table – Natural and synthetic pactamycin in DMF – D_7 + D_2O

Position	Natural[a]	Synthetic
8	0.98 (3H, d)	0.98 (3H, d)
6	1.49 (3H, s)	1.47 (3H, s)
7'	2.20 (3H, s)	2.15 (3H, s)
8''	2.50 (3H, s)	2.52 (3H, s)
11, 12	2.94 (6H, s)	2.95 (6H, s)
2	3.97 (1H, s)	3.00 (1H, s)
3	4.00 (1H, s)	3.95 (1H, s)
7	4.03 (1H, q)	3.97 (1H, q)
9	4.54 and 4.78 (2H, dd)	4.55 and 4.73 (2H, ABq)
aromatic	6.70-7.30 (7H, m)	6.58-7.37 (7H, m)

^{1}H NMR Comparison Table – Natural and synthetic pactamycate in DMF – D_7 + D_2O

Position	Natural[a]	Synthetic
6	1.38 (3H, s)	1.35 (3H, s)
8	1.54 (3H,d)	1.52 (3H, d)
7'	2.24 (3H, s)	2.17 (3H, s)
8''	2.46 (3H, s)	2.49 (3H, s)
2	3.56 (1H, d)	3.55 (1H, d)
3	3.73 (1H, d)	3.66 (1H, d)
9	4.39 and 4.65 (2H, dd)	4.36 and 4.61 (2H, ABq)
7	4.73 (1H, q)	4.76 (1H, q)
aromatic	6.72-7.12 (7H, m)	6.69-7.43 (7H, m)

^{13}C NMR Comparison Table – Natural and synthetic pactamycin in $CDCl_3$

Position	Natural[b]	Synthetic
1	71.5	71.5
2	63.3	63.2
3	68.9	68.8
4	84.7	84.9
5	88.8	88.8
6	21.1	21.1
7	74.2	74.3
8	18.1	18.1
9	65.3	65.3
10	159.2	159.2
11 and 12	36.8	36.9
1'	112.4	112.1
2'	162.4	162.7
3'	115.5	115.7
4'	134.2	134.5
5'	123.0	123.0
6'	141.2	141.2
7'	23.8	24.0
8'	172.2	172.5
1''	138.2	138.3
2''	110.9	110.8
3''	146.7	146.6
4''	118.8	118.7
5''	129.6	129.6
6''	118.3	118.4
7''	198.7	198.5
8''	26.7	26.7

^{1}H NMR Comparison Table – Natural and synthetic pactamycate in CD_3OD

Position	Natural[c]	Synthetic
6	1.38 (3H, s)	1.39 (3H, s)
8	1.58 (3H,d)	1.58 (3H, d)
7'	2.24 (3H, s)	2.25 (3H, s)
8''	2.44 (3H, s)	2.45 (3H, s)
2	3.60(1H, d)	3.59 (1H, d)
3	3.67 (1H, d)	3.66 (1H, d)
9	4.45 and 4.64 (2H, dd)	4.44 and 4.65 (2H, ABq)
7	4.84 (1H, q)	4.84 (1H, q)
aromatic	6.60-7.40 (7H, m)	6.63-7.33 (7H, m)

[a] P. F. Wiley, H. K. Jahnke, F. MacKellar, R.B. Kelly, A. D. Argoudelis, *J. Org. Chem.* **1970**, *35*, 1420-142.
[b] D. D. Weller, A. Haber, K. L. Rinehart Jr., P. F. Wiley, *J. Antibiot.* **1978**, *31*, 997-1006.
[c] T. Ito, N. Roongsawang, N. Shirasaka, W. Lu, P. M. Flatt, N. Kasanah, C. Miranda, T. Mahmud, *ChemBioChem* **2009**, *10*, 2253-2265.

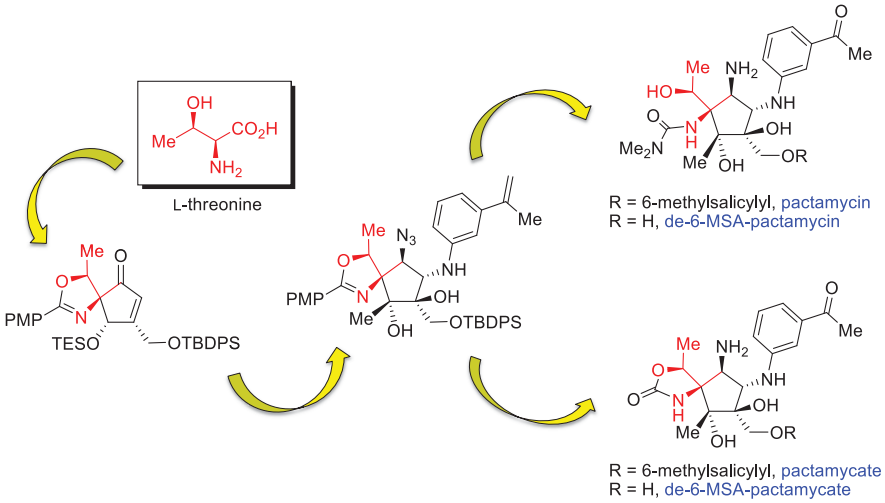
1.4 Article 2

Total Synthesis of Pactamycin and Pactamycate – a Detailed Account

Stephen Hanessian,* Ramkrishna Reddy Vakiti, Stéphane Dorich, Shyamapada Banerjee and Benoît Deschênes-Simard

J. Org. Chem. **2012**, *77*, 9458.

ABSTRACT: This article describes synthetic studies that culminated in the first total synthesis of pactamycin and pactamycate, and, in parallel, the two known congeners, de-6-MSA-pactamycin and de-6-MSA-pactamycate, lacking the 6-methylsalicylyl moiety. Starting with L-threonine as a *chiron*, a series of stereocontrolled condensations led to a key cyclopentenone harboring a spirocyclic oxazoline. A series of systematic functionalizations led initially to the incorrect cyclopentanone epoxide, which was "inverted" under solvolytic conditions. Installation of the remaining groups and manipulation of the oxazoline eventually led to pactamycin, pactamycate and their desalicylyl analogues.



INTRODUCTION

The plethora of microbial secondary metabolites produced by the soil bacterium of the Streptomyces family comprise a family of highly substituted aminocyclopentitol-containing natural products.[1] Among these are pactamycin (**1**) and pactamycate (**2**), two structurally unique and functionally rich metabolites (Figure 1.7). Related cyclopentane core structures, albeit with simpler substitution patterns, are encountered in allosamizoline (**5**), [2] mannostatin A (**6**), [2] and trehazolamine (**7**).[3] Early studies on the biosynthesis of pactamycin were reported by Rinehart and coworkers in 1978.[4] More recently, Kudo and coworkers[5] cloned the biosynthetic gene cluster involved in the

formation of the cyclopentane ring of pactamycin. Mahmud and co-workers[6] have shown pactamycin (**1**), pactamycate (**2**), de-6-MSA-pactamycin (**3**) and de-6-MSA-pactamycate (**4**) are produced from the same gene cluster.

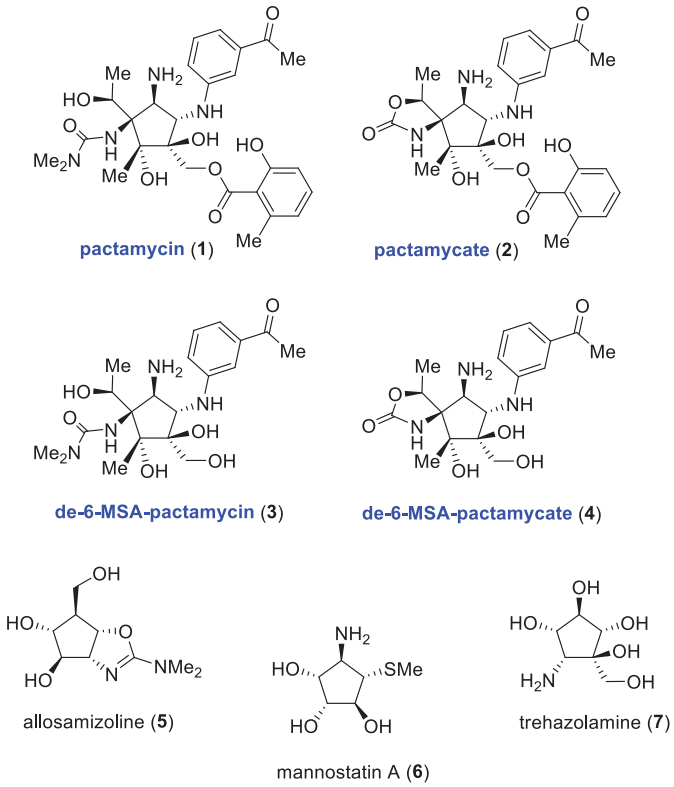
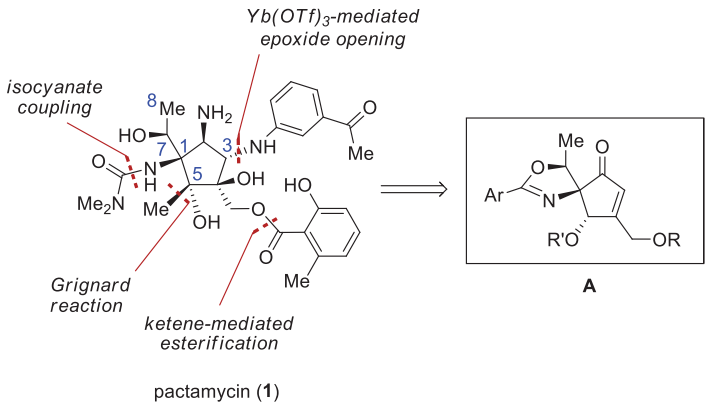


Figure 1.7: Structures of pactamycin, pactamycate, de-6-MSA-pactamycin, de-6-MSA-pactamycate, allosamizoline, mannostatin A, and trehazolamine

Pactamycin was isolated in 1961 from a fermentation broth of *Streptomyces pactum var pactum* by scientists at the former Upjohn Company.[7] Although it exhibited *in vitro* activity against certain Gram-positive and Gram-negative bacteria, as well as cytotoxicity toward cancer cell lines, its further development was curtailed due to its toxicity.[8] This can be attributed to its effect in arresting protein biosynthesis in eukaryotes as well as in prokaryotes.[9] Pioneering X-ray crystallographic studies by Ramakrishnan and coworkers[10] involving pactamycin bound to the 30S site of *Thermus thermophilus* showed unique interactions, whereby its two aromatic moieties are π-stacked against each other like consecutive RNA bases, while the core aminocyclopentitol motif mimics the RNA sugar-phosphate backbone. This results in an intricate network of H-bonded interactions with specific bases within the 30S site of the ribosome, as well as intramolecularly.

An initially proposed structure for pactamycin by the Upjohn scientists in 1970 based on chemical degradation studies[11] was subsequently corrected in 1972 as a result of an X-ray crystal structure of a derivative.[12] To the best of our knowledge, pactamycin is the most densely functionalized naturally-occurring aminocyclopentitol.[13] In spite of its unique architecture and rich history in the realm of other RNA-binding natural products, efforts toward its synthesis have been sparse. Conceptually different approaches toward the construction of the aminocyclopentitol core of pactamycin were reported by Isobe,[14] Knapp,[15] and more recently by Johnson,[16] Looper,[17] Nishikawa[18] and their respective coworkers.

In a preliminary Communication, we reported the first total synthesis of pactamycin (**1**) and pactamycate (**2**).[19] Herein, we provide a detailed account of our efforts, delineating initial studies that were met with a number of unexpected dead-ends and road blocks, necessitating revisions of synthetic approaches. Analysis of the structure of pactamycin reveals a number of challenges, not the least of which are the presence of three contiguous tertiary centers at C4, C5 and C1 (Scheme 1.13). We were cognizant that the densely functionalized core motif would require a judicious choice of carefully orchestrated bond-forming sequences, in which the order of execution would be crucial. Based on the existing functional groups and substituents on the cyclopentane core of pactamycin, a series of bond-forming sequences could be envisaged as shown in Scheme 1.13.

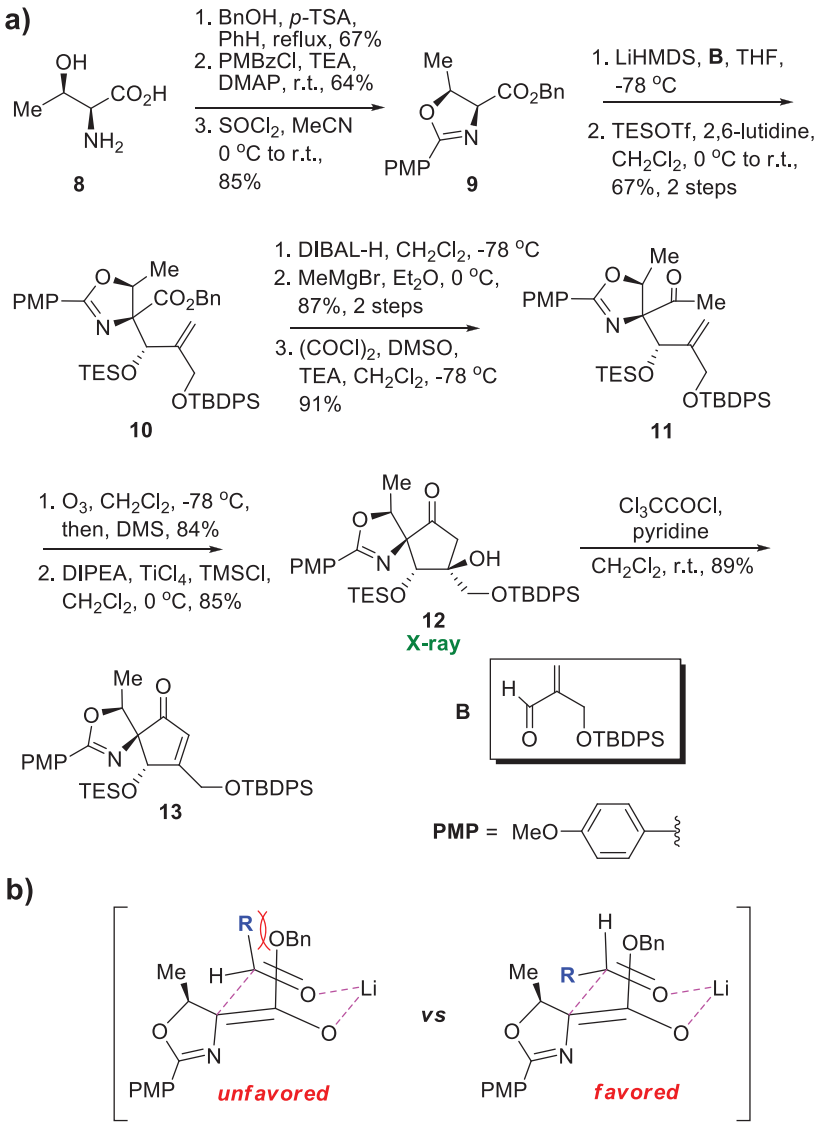


Scheme 1.13: Strategic bond disconnections to key intermediate cyclopentenone **A**

Straightforward as this plan may have appeared to be at the outset, we were unaware of the potential difficulties associated with effecting seemingly routine transformations as new substituents and appendages were sequentially introduced on the cyclopentane core. Considering the nature and placement of the substituents, we chose to secure the aminoalcohol unit comprising C1, and extending toward C2 (or C5) that could be further elaborated into the cyclopentane core motif. With this initial objective in mind, we chose L-threonine as a suitable *chiron* that would provide a hydroxyethyl appendage with the desired absolute configuration, and allowing further elaboration of the α-amino acid segment to introduce C-branching *via* enolate or Claisen condensation. Since the aminoalcohol portion of pactamycin was considered to be an inherent part of the molecule, we wanted to adopt a modular approach for the introduction of substituents around the cyclopentane core to allow for diversification in preparing potentially bioactive analogs and congeners with diminished toxicity. To this end, we chose the cyclopentenone core motif **A** as our initial objective for synthesis (Scheme 1.13).

RESULTS AND DISCUSSION

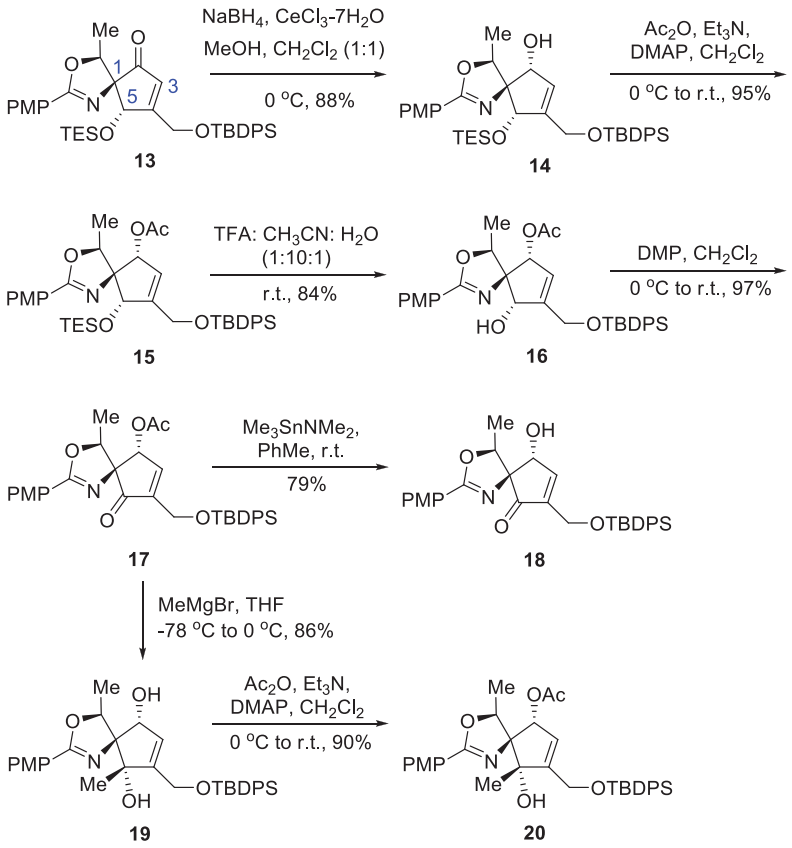
THE CYCLOPENTENONE CORE. A known 3-step sequence starting with L-threonine (**8**) led to the PMP-oxazoline derivative **9** (Scheme 1.14a).[20] Formation of the enolate with LiHMDS, and condensation with O-TBDPS-2-hydroxymethyl acrolein (**B**), followed by protection with TESOTf afforded **10** as a single isomer. The observed stereoselectivity can be rationalized based on a favored Zimmerman-Traxler transition state model (Scheme 1.14b). Reduction of the benzyl ester to the aldehyde, treatment with MeMgBr, and oxidation of the resulting alcohol, afforded the methyl ketone **11**. Ozonolytic cleavage of the exocyclic methylene group, followed by a highly stereoselective Mukaiyama-type intramolecular aldol condensation, proceeding *via* a presumed Ti-coordinated Si-enol ether or the corresponding Ti-enolate, afforded **12** as a shelf-stable crystalline product which was fully characterized by X-ray crystallography.[21] Treatment of **12** with trichloroacetyl chloride in pyridine led to the corresponding ester, which underwent *in situ* β-elimination to give the intended cyclopentenone **13**.



Scheme 1.14: a) Synthesis of the cyclopentenone intermediate **13**. b) Suggested transition state for the formation of **10**

ELABORATION OF THE CYCLOPENTENONE CORE (PLAN A). We started by exploring a sequence of reactions to introduce functional groups in a "clockwise manner" commencing with the carbonyl group at C2 in **13** (Scheme 1.15). Under a variety of conditions, reduction led almost exclusively to the (*R*)-allylic alcohol **14**. This result augured well for the introduction of an azide group at C2 (and eventually an amine), by an S_N2 reaction to secure the correct stereochemistry as found in pactamycin. Unfortunately, all attempts to prepare the triflate ester from **14** led to complex mixtures.

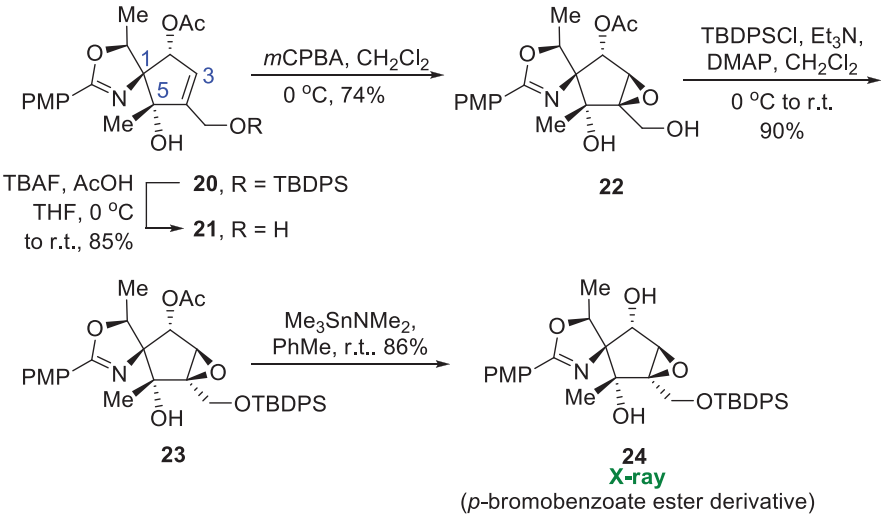
Conversion to the acetate ester **15** and treatment of the latter with $Pd(PPh_3)_4$ and NaN_3 or $TMSN_3$ under classical Tsuji-Trost conditions[22] was also unsuccessful, as starting material remained intact and could be recovered. Selective deprotection of the TES ether in **15** gave **16**, which was oxidized under Dess-Martin conditions to give ketone **17**. Deacetylation to **18** with trimethylstannyl dimethylamine,[23] followed by attempted conversion to the triflate ester led to decomposition. However, treatment of **17** with MeMgBr afforded **19** as a single isomer with the required orientation as found in pactamycin. Unfortunately, formation of the corresponding triflate or mesylate esters also failed, giving a complex mixture of products.



Scheme 1.15: Towards the pactamycin core, plan A (part 1)

We next decided to postpone the introduction of the azide group, in favor of the aniline moiety at C3. The acetate **20**, prepared from **19**, was transformed to the corresponding allylic alcohol **21**, which was treated with *m*CPBA to afford epoxide **22** (Scheme 1.16). Reprotection of the primary hydroxyl group as in **23**, followed by

deacetylation, led to **24**, whose structure was ascertained by X-ray crystallography of the corresponding *p*-bromobenzoate ester.[21] It is noteworthy that the direct epoxidation of **20** gave only trace amounts of **23**, and mainly entailed slow decomposition. Disappointingly, attempts to prepare the C2 triflate ester of **24** led to a complex mixture of products.

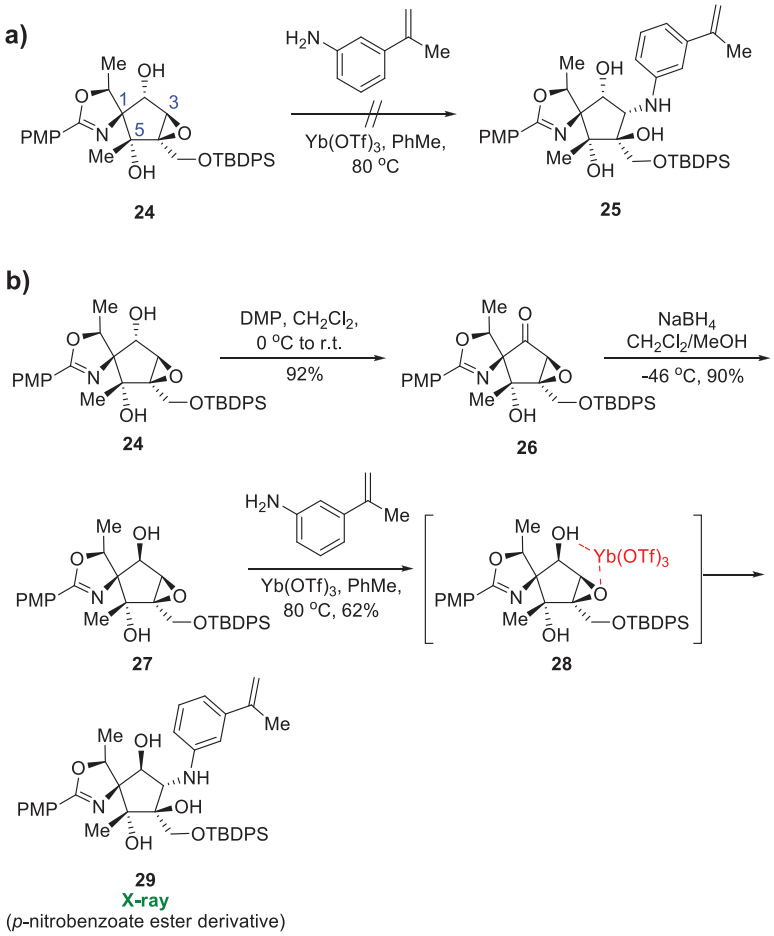


Scheme 1.16: Towards the pactamycin core, plan A (part 2)

Faced with yet another impasse in our attempts to functionalize C2, we proceeded to study conditions for the regioselective ring opening of the epoxide **24** with various anilines.[24] Preliminary model studies, to be discussed in a separate publication, with simple 1-hydroxy-2,3-epoxy-3-methyl cyclopentanes, with and without protecting groups utilizing various Lewis acids and anilines, resulted in exclusive opening at the tertiary carbon atom. Nevertheless, we hoped that the selectivity could be reversed due to the different topology, substitution pattern and steric effects in **24**. However, treatment with 3-isopropenyl aniline in the presence of $Yb(OTf)_3$ in toluene at 80 °C did not lead to **25**, but resulted in the formation of a complex mixture of products (Scheme 1.17a).

Oxidation of **24** to the corresponding ketone **26**, and reduction with $NaBH_4$ led to the C2 epimeric alcohol **27**. Much to our delight, treatment with 3-isopropenyl aniline in the presence of $Yb(OTf)_3$ now led to the expected aniline **29**. Definitive confirmation of

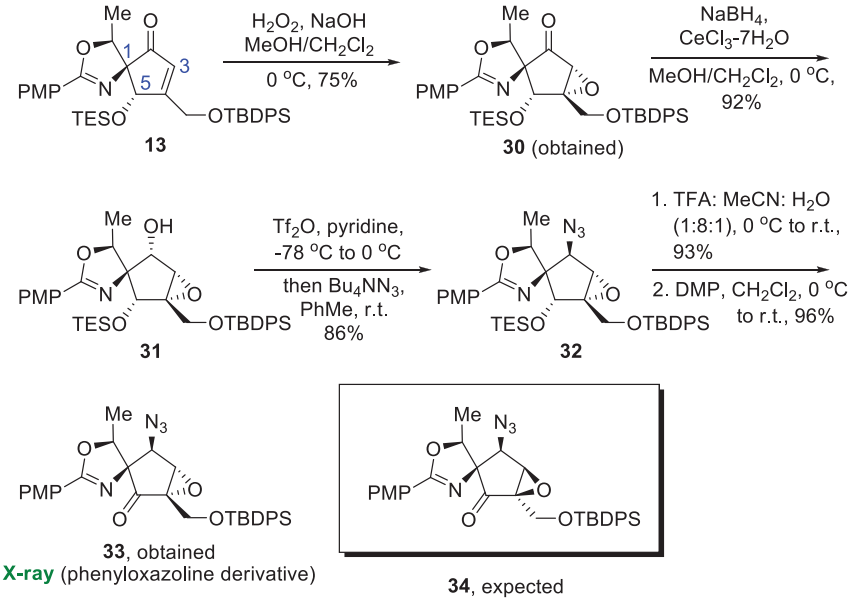
structure and stereochemistry was obtained from a single X-ray crystal structure determination of a *p*-nitrobenzoate ester derivative.[21] The successful regio- and stereoselective opening of the *syn*-oriented epoxyalcohol **27** can be explained by a favorable Yb-coordinated complex (**28**),[24] which presumably was not formed in the case of **24** with an *anti*-orientation of the C2 alcohol compared to **27** (Scheme 1.17b).



Scheme 1.17: Towards the pactamycin core, plan A (part 3): Introduction of the aniline moiety

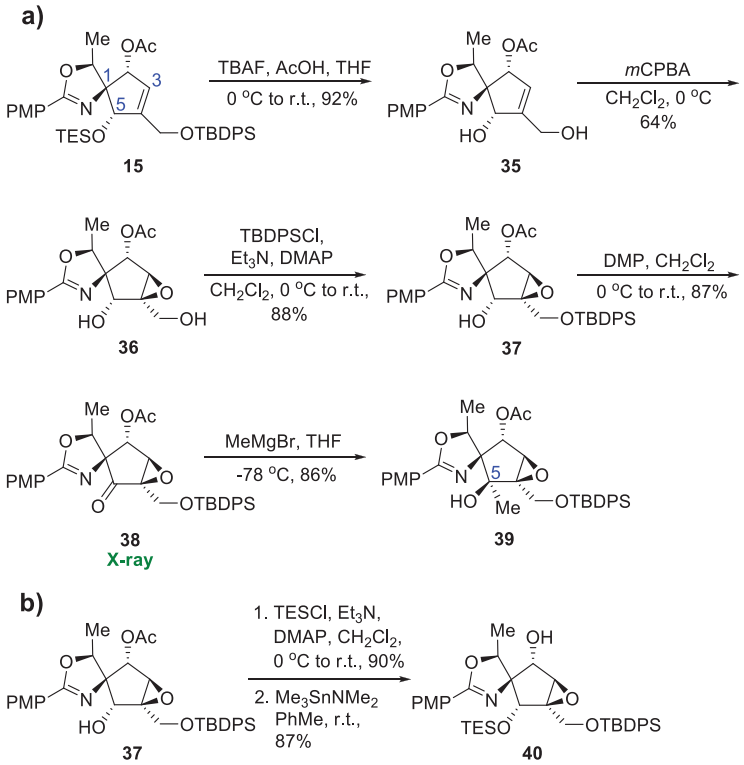
Reassessing our options, it was clear that substantial progress had been made in reaching the advanced stage of intermediate **29**, which possessed all the required functional appendages except at C2. Introduction of an azide group would require re-inversion of the C2 hydroxyl group in order to attempt S_N2 substitution on the triflate ester. However, our prior negative experiences along those lines (*vide supra*) dissuaded us from continuing this approach.

ELABORATION OF THE CYCLOPENTENONE CORE (PLAN B). We returned to the cyclopentenone core motif **13** and considered a different sequence of funtionalizations. Treatment of **13** with H_2O_2 cleanly afforded a product which we believed to be the "*up*" epoxide analogue of **30** as observed for **21**, due to the orientation of the bulky O-TES group (Scheme 1.18). Reduction of the ketone with $NaBH_4$ in the presence of $CeCl_3 \bullet 7H_2O$ gave a single alcohol at C2, which upon triflation and treatment with Bu_4NN_3 afforded a product containing the elusive azide group for the first time. However, not until the O-TES group was deprotected, and the resulting alcohol was oxidized did we become aware that epoxidation had occurred from the *opposite face* of the enone in **13** as evidenced from an X-ray structure.[21] Thus, epoxidation had led to **30**, which was reduced to **31**, and introduction of azide had led to **32** and **33** after silyl deprotection and oxidation, rather than the expected **34**. We presume that the combination of the spirooxazoline and the bulky O-TBDPS group (forced to occupy the *upper* face in order to avoid steric interactions with the "down" O-TES group) may have disfavored the approach of the hydroperoxide ion from the same side, eventually leading to the wrong epoxide **30**.



Scheme 1.18: Towards the pactamycin core, plan B (part 1): Introducing azide on the wrong epoxide

We therefore once again changed our order of reactions, now starting with **15** (Scheme 1.19a). Deprotection of the silyl ethers led to **35** which was smoothly epoxidized to **36** with *m*CPBA, then reprotected to give **37**. Oxidation to **38** and X-ray analysis confirmed the required "*up*" orientation of the epoxide. However, deprotection of the acetate ester in **38**, and attempted triflation led to decomposition. Having the ketone **38** in hand, we also attempted to introduce the methyl group at C5 using a Grignard reaction. In this case, however, attack occurred from the side *opposite* to the epoxide and the spirooxazoline to give the **39**, which stereochemistry was ascertained by spectral comparison with compound **23**, epimeric at C5. Conversion of **37** to **40** (a diastereomer of **31**) followed by attempted triflation led to yet another complex mixture (Scheme 1.19b).

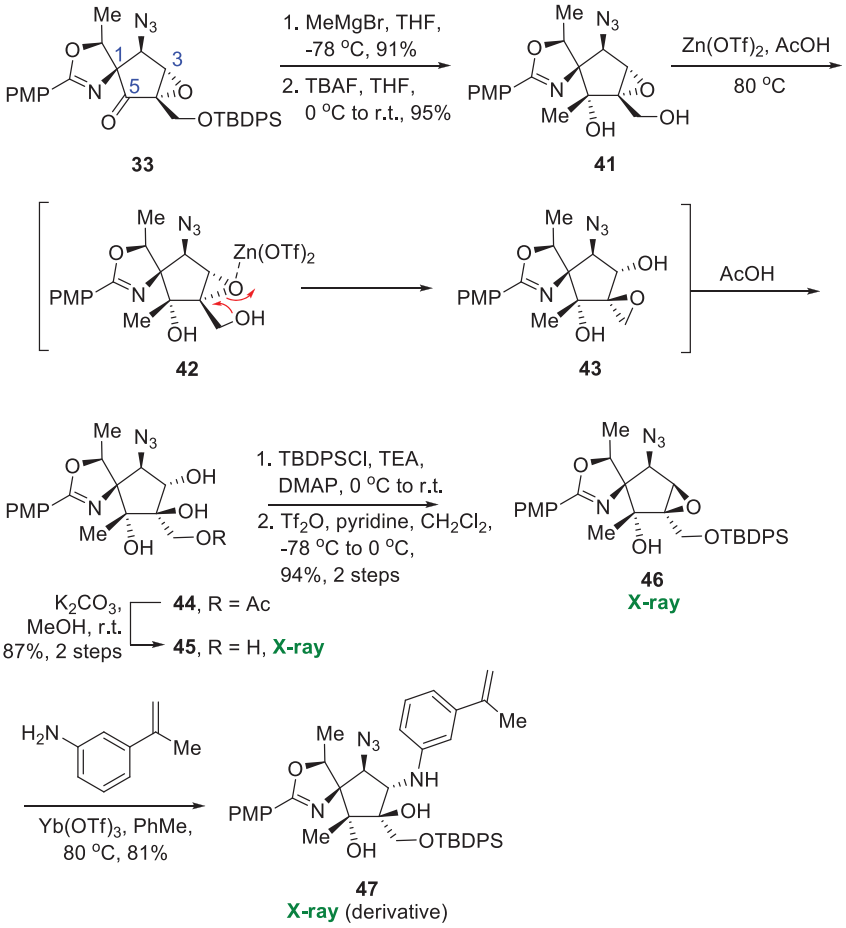


Scheme 1.19: Towards the pactamycin core, plan B (part 2): Introducing the correct epoxide

INVERTING THE EPOXIDE (PLAN C). From the various attempts to introduce an azide group at C2 with the correct stereochemistry, it was clear that a successful triflation and S_N2 azide displacement was possible only with a specific relative orientation of the

epoxy alcohol as found in **31**. We were therefore faced with an "*epoxide inversion*" issue. Treatment of the ketone **33** with MeMgBr, then silyl ether deprotection cleanly gave **41** (Scheme 1.20). For the "inversion" of the epoxide, we would rely on a regioselective solvolytic ring opening, followed by placing a leaving group at the resulting C3 alcohol, then treatment with an appropriate base to effect epoxide formation with the tertiary hydroxyl group at C4, acting as an internal nucleophile. A variety of conditions were tried to effect these transformations, but without success.[25] We then resorted to an activation of the epoxide with a Lewis acid in the presence of acetic acid as a nucleophile in the hope of obtaining the C4-inverted tertiary alcohol as the acetate ester. In the event, treatment of **41** with $Zn(OTf)_2$ in acetic acid[26] led directly to the primary acetate ester **44** in excellent yield.

Thus, configurational inversion at C3 and C4 had indeed been achieved, albeit by an alternative pathway than the one initially envisaged (*vide supra*). Presumably, solvolysis proceeded by initial activation of the epoxide by $Zn(OTf)_2$, as in **42**, followed by formation of a spiroepoxide **43** by intramolecular attack of the primary hydroxyl group with inversion of configuration of the tertiary C4 center. Subsequent regioselective ring opening with acetic acid at the primary carbon atom of the spiroepoxide, possibly activated by $Zn(OTf)_2$, led to **44** as the only product in good overall yield. A two-step sequence restored the TBDPS ether group, and the resulting triol was converted to the C3, C4-"inverted" epoxide **46** via the corresponding triflate (71% overall yield from **33**). An X-ray structure of **46** confirmed the structure of the latter intermediate. Highly regio- and stereoselective epoxide opening at C3 with 3-isopropenyl aniline in the presence of $Yb(OTf)_3$ afforded the advanced core structure **47** as the sole product.[21] It should be noted that activation of the epoxide **46** with $Yb(OTf)_3$ occurred in the absence of a coordinating hydroxyl group, and the regioselective opening with the aniline could be due to the inductive effect of the neighboring azido group, and to steric effects.

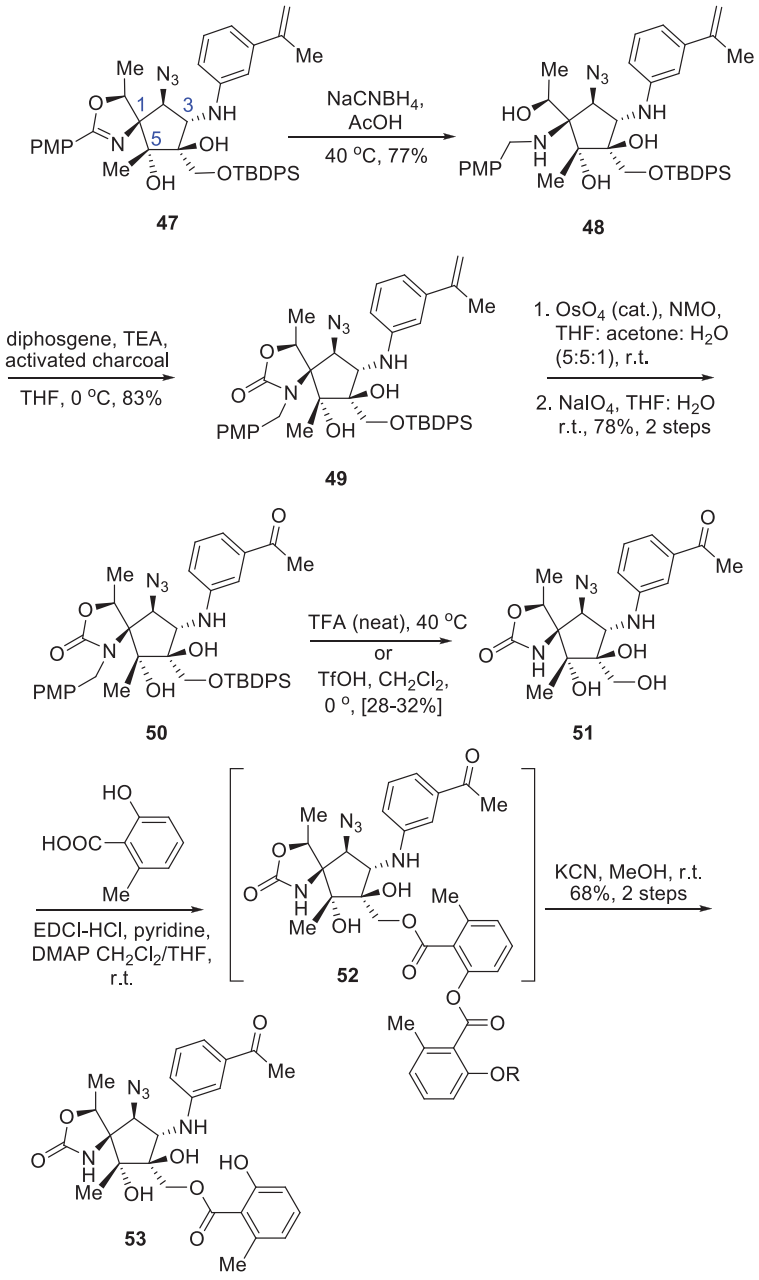


Scheme 1.20: Obtaining the core structure of pactamycin

TOWARDS PACTAMYCATE. Having secured the full complement of substituents directly attached to the cyclopentane core motif, we set our next objective towards the naturally occurring congener, pactamycate, previously obtained by acid treatment of pactamycin.[11] Studies by Mahmud and coworkers[6] on the biosynthesis of pactamycin led to the identification and isolation of pactamycate and its de-6-MSA-counterpart from the same gene cluster.

Our first steps towards pactamycate consisted in the conversion of **47** to the N-PMB derivative **48** by treatment with $NaCNBH_3$ in AcOH[20] (Scheme 1.21). Formation of the cyclic carbamate **49** using diphosgene in the presence of activated charcoal[27] was followed by an oxidative cleavage of the exocyclic methylene group to afford **50**.

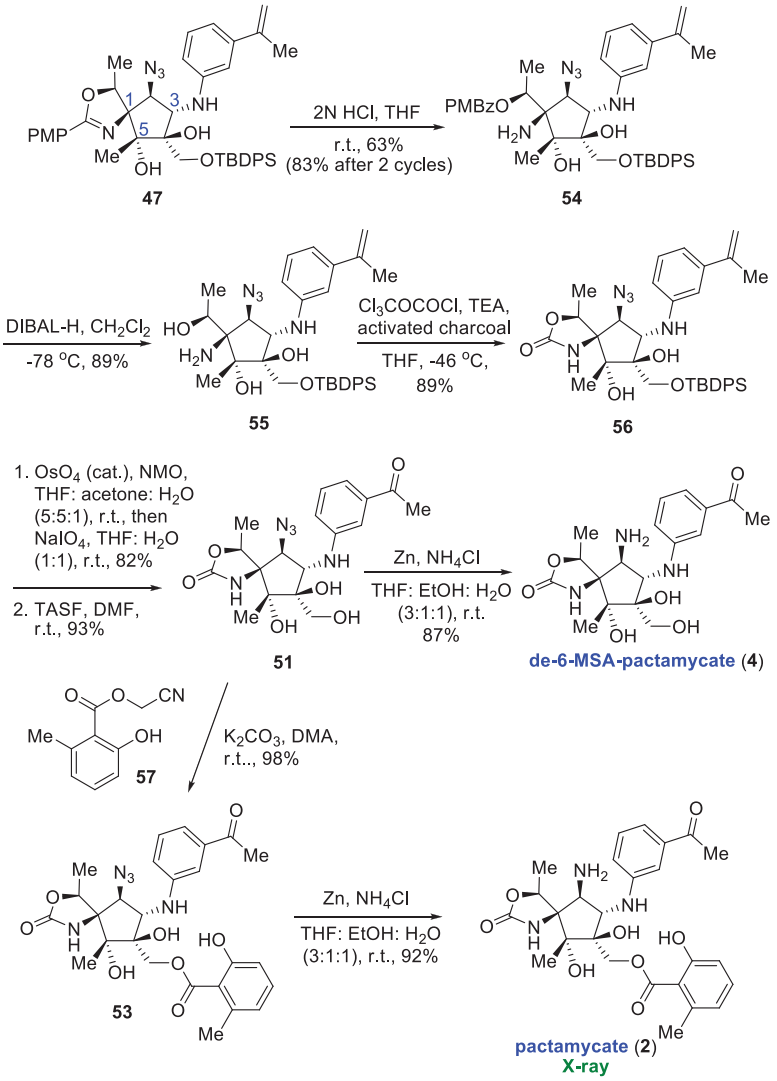
Treatment of **50** with ceric ammonium nitrate resulted in decomposition. However, treatment under strong acidic conditions removed the N-PMB group, albeit in modest yield, to furnish the 2-azido analog of de-6-MSA-pactamycate **51**.



Scheme 1.21: Towards pactamycate (first approach)

There remained to esterify the primary hydroxyl group and to reduce the azide group to reach pactamycate. Thus, treatment of **51** with 6-methylsalicylic acid in the presence of EDCI under standard conditions led to the formation of **52** as a mixture of oligomers containing two or more 6-MSA units as a result of multiple esterifications of the phenolic hydroxyl group in the initially formed 2-azido pactamycate. Treatment of **52** with KCN in MeOH[28] effected selective cleavage of the phenolic esters to afford the desired 2-azido pactamycate **53**.

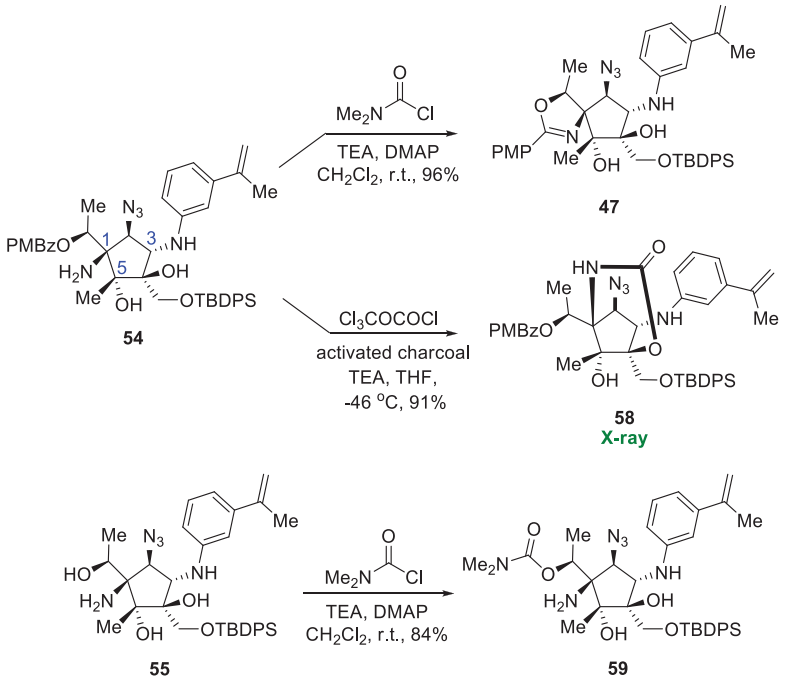
In view of the modest yield of deprotection of the N-PMB group, coupled with the unwanted double esterification of **51**, we sought an alternative approach to pactamycate (Scheme 1.22). The oxazoline group in **47** was cleaved under acidic conditions to afford the *p*-methoxybenzoate ester **54**. Treatment with DIBAL-H led to **55**, which when treated with diphosgene in the presence of activated charcoal gave the cyclic carbamate **56**. Oxidative cleavage of the exocyclic methylene group, followed by cleavage of the OTBDPS group in the presence of TASF[29] afforded **51**, which had been obtained in lower yields by the earlier route (see Scheme 1.21). Esterification of **51** was successfully achieved using cyanomethyl 2-hydroxy-6-methylbenzoate (**57**), according to Porco and coworkers[30] to afford **53**. Reductive cleavage of the azido group in presence of Zn powder in aqueous NH_4Cl[31] gave crystalline pactamycate (**2**) whose structure and absolute stereochemistry was validated by X-ray crystallography for the first time. De-6-MSA-pactamycate (**4**) could be obtained by reductive cleavage of the azido group in **51**, adopting the same methods used for **53**.



Scheme 1.22: Towards pactamycate (second approach)

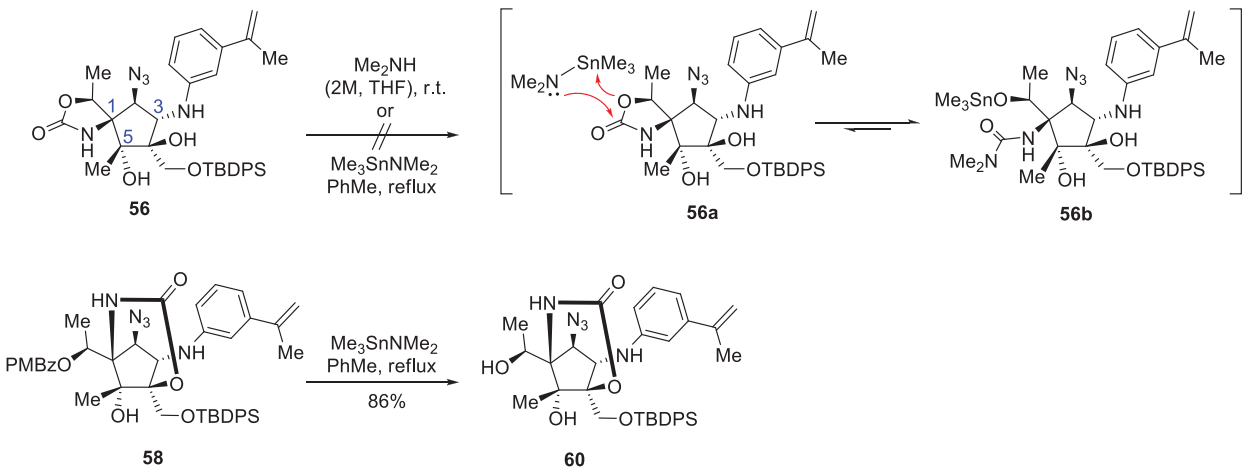
ONWARD TO PACTAMYCIN. The advanced intermediates **54** and **55** were exquisitely poised for a straightforward completion of the total synthesis of pactamycin. All that would be required was the formation of the dimethylurea by suitable functionalization of the exposed primary amino group. The availability of N,N-dimethylcarbonyl chloride as a reagent would practically ensure access to the desired N,N-dimethylurea from one or more of the aforementioned intermediates.[32] However, in practice, this turned out to be a frustrating experience and a reflection of the unexpected reactivities of an otherwise commonly reactive primary amino group in densely functionalized core motifs, such as **54** and **55** (Scheme 1.23). When **54** was treated with

N,N-dimethylcarbamoyl chloride under a variety of conditions, none of the desired N,N-dimethylurea was observed. Instead, the oxazoline **47**, formed by an intramolecular attack of the amino group on the PMBz ester and elimination of water, was recovered. Under forcing conditions, using NaH, TBAI and N,N-dimethylcarbamoyl chloride, only carbamoylation of **54** was observed. In an effort to obtain the intended urea *via* an intermediate isocyanate, we treated **54** with diphosgene in the presence of activated charcoal. Surprisingly, this led to the 6-membered cyclic carbamate **58**, resulting from an intramolecular attack of the tertiary alcohol on the isocyanate group. The structure of **58** was ascertained by X-ray analysis. Treatment of the aminotriol **55** with N,N-dimethylcarbamoyl chloride led to the formation of the carbamate **59**, leaving the amino group unperturbed.



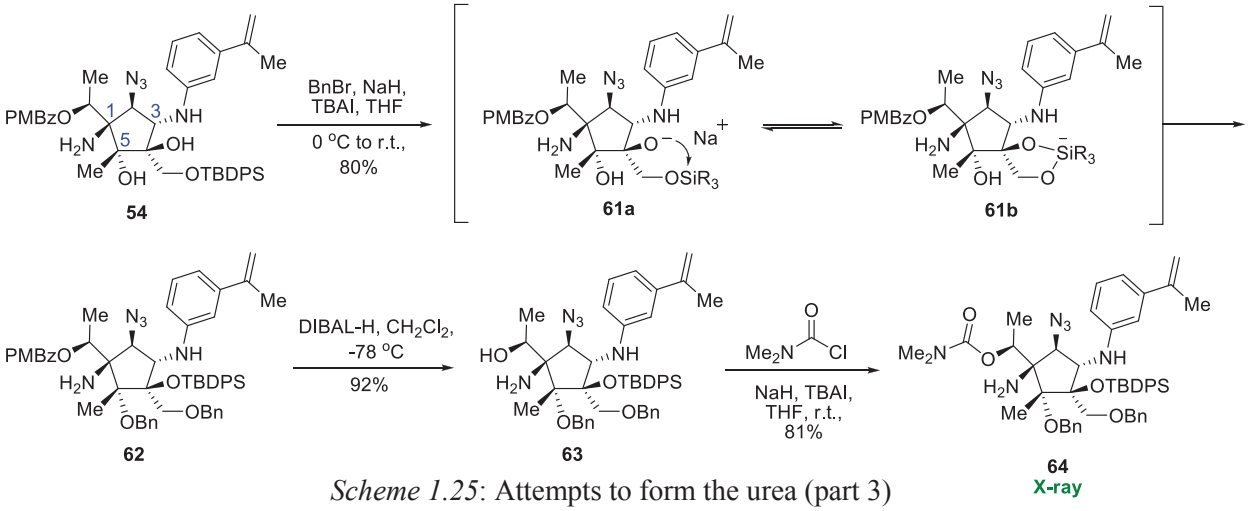
Scheme 1.23: Attempts to form the urea (part 1)

We then reasoned that treatment of the cyclic carbamates **47**, **56** and **58** with dimethylamine or trimethylstannyl dimethylamine (Me_3SnNMe_2) could result in the formation of the elusive N,N-dimethylurea, *via* a direct attack on the carbonyl group of the carbamate, or *via* a 4-center activation mode with transfer of the dimethylamine group (Scheme 1.24). However, in the presence of Me_3SnNMe_2 in refluxing toluene, **56** was found to be completely stable, while **58** gave the O-PMBz deprotected carbamate **60**.



Scheme 1.24. Attempts to form the urea (part 2)

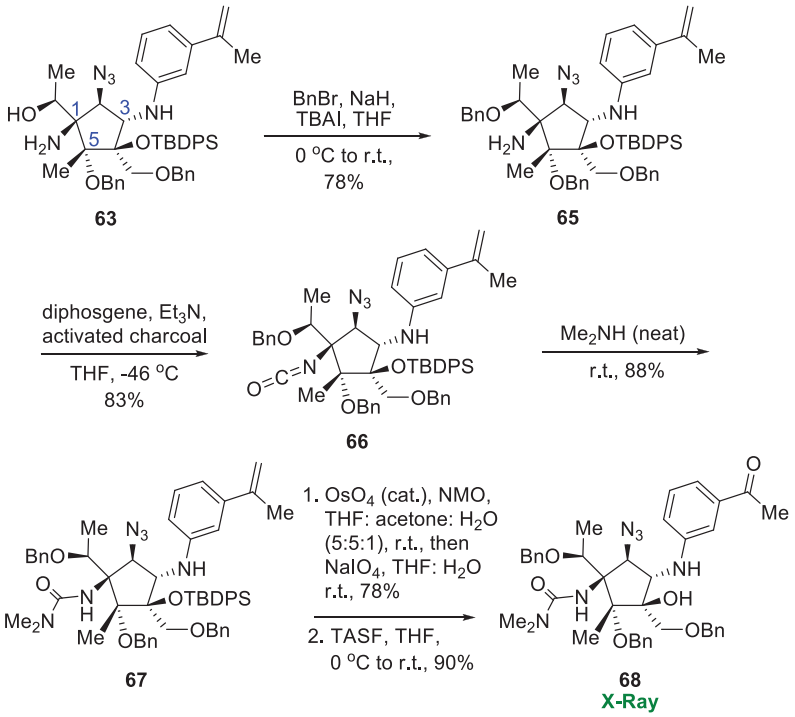
The unsuccessful attempts to prepare the N,N-dimethylurea derivative by selective acylation of the seemingly more nucleophilic primary amino group at C1 underscore the importance of proximity and steric effects in the densely functionalized cyclopentane core intermediates such as **54** and **55**. The extreme shielding of the amino group was further demonstrated in a last resort effort to achieve urea formation (Scheme 1.25). Thus, benzylation of the aminoester **54** in the presence of BnBr, NaH, and Bu_4NI in THF led unexpectedly to **62**, the structure of which was confirmed only after effecting two additional steps (*vide infra*). Realizing that benzylation had not occurred on the amino group from independent analysis, but as yet unaware of the exact placement of the two benzyl groups, we treated the product **62** with NaH, TBAI and N,N-dimethylcarbamoyl chloride, which resulted in recovery of starting material. Then, the amine **62** was reduced with DIBAL-H to cleave the PMB ester, and the resulting amino alcohol **63** was treated with N,N-dimethylcarbamoyl chloride in the presence of NaH, and Bu_4NI at r.t. The product turned out to be the carbamate **64**, the structure of which was confirmed by X-ray analysis. Remarkably, and against all predictions, benzylation had spared the primary amino group, and instead, had occurred on two adjacent diols albeit with an internal functional adjustment. Thus, the alkoxide initially formed from the tertiary alcohol at C4 of **54** had undergone an intramolecular silyl transfer reaction[33] via **61**, transposing the TBDPS group and exposing a primary alkoxide which was benzylated to give **62**!



Scheme 1.25: Attempts to form the urea (part 3)

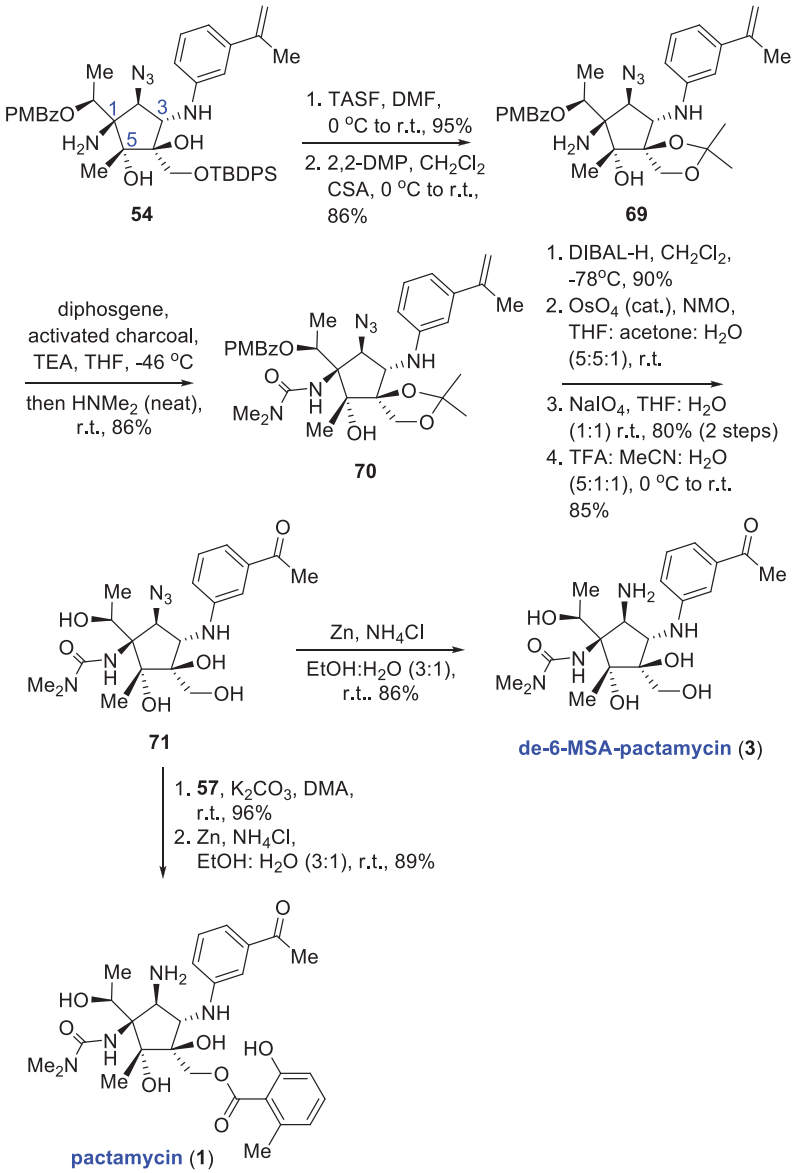
In an alternative approach, benzylation of intermediate **63** under the same conditions as for **54**, gave the tribenzyl ether **65** (Scheme 1.26). Treatment with diphosgene led to a chromatographically stable isocyanate **66** which was treated with neat dimethylamine to give the N,N-dimethylurea **67**, for the first time. Oxidative cleavage of the exocyclic methylene group led to the ketone, which was desilylated to give the crystalline urea derivative **68**. Clearly, without X-ray crystallographic evidence, it would have been very difficult to interpret the results shown in Schemes 1.25 and 1.26, spectroscopically or otherwise.

Although we became aware of the inertness of the primary amino group toward acylation and alkylation, we also learned that in the absence of an interfering hydroxyl at C4, we could nevertheless form isocyanates and even the desired N,N-dimethylurea as shown in Scheme 1.26. Rather than continuing with the fully protected intermediate **68**, we turned our attention instead to "neutralizing" the offending tertiary hydroxyl group at C4.



Scheme 1.26: Formation of the urea *via* the isocynate

Deprotection of the TBDPS ether in **54** led to an aminotriol which was converted to the acetonide **69** (Scheme 1.27). Formation of the isocyanate, then treatment with neat dimethylamine afforded the N,N-dimethylurea derivative **70** in 86% yield. Reductive cleavage of the PMB ester followed by the oxidative cleavage of the methylene group, and finally hydrolysis of the acetonide group gave **71**. Esterification as described for pactamycate (**2**), followed by reduction of the azido group gave pactamycin (**1**) in excellent yield.[21] In parallel, reduction of the azide group in **71** led to de-6-MSA-pactamycin (**3**).



Scheme 1.27: Completion of the total synthesis of pactamycin

CONCLUSION

We described a detailed account of our efforts towards the total synthesis of pactamycin, pactamycate, and their de-esterified counterparts. Starting with L-threonine as the chiral cornerstone, we proceeded to construct the cyclopentenone core motif **A** (Scheme 1), which served as the pivotal scaffold upon which we attempted to introduce

the required substituents in a systematic way. Initial failures and unexpected results forced us to explore alternative approaches to install functional groups in regio- and stereocontrolled reactions. At times, the difference between triumph and disaster hinged upon the judicious choice of methods and order of execution, such as the solvolytic "inversion" of the epoxide in presence of $Zn(OTf)_2$ and AcOH. Epoxide opening with an aniline moiety was possible only when a neighboring hydroxy group had a *syn* relationship, favoring a coordination with the Lewis acid $Yb(OTf)_3$, or when an azide group was present, exerting an inductive effect. Finally, the importance of proximity effects and steric shielding became manifest in the numerous vain attempts to acylate or benzylate the presumably more basic and nucleophilic primary amino group in the presence of highly hindered tertiary hydroxyl groups. In spite of these humbling experiences, logic, deductive reasoning, and a strong resolve prevailed in the end. Pactamycin (**1**) and pactamycate (**2**) were synthesized in 29 steps (3.1 %) and 26 steps (4.0 %) respectively, starting with the known oxazoline **9**. With the recent reports on the antiprotozoal activities of pactamycin,[6] the study of this unique amino cyclopentitol and its analogues expands their scope as valuable biological probes to interact with RNAs of diverse sources. Studies relative to such objectives are in progress and will be reported in due course.

EXPERIMENTAL SECTION

Experimental procedures and characterization data for the preparation of compounds **1**, **2**, **8**–**13**, **30**–**33**, **41**–**47**, **51**, **53**–**56**, **58**, **69**–**71** have been reported previously.[19]

(4*S*,5*R*,6*R*,9*S*)-8-((tert-Butyldiphenylsilyloxy)methyl)-2-(4-methoxyphenyl)-4-methyl-9-(tripropylsilyloxy)-3-oxa-1-azaspiro[4.4]nona-1,7-dien-6-ol (14). To a solution of cyclopentenone **13** (3.81 g, 5.81 mmol) in MeOH:CH_2Cl_2 (30 mL, 1:1) was added $CeCl_3 \cdot 7H_2O$ (4.33 g, 11.63 mmol) at 0 °C under argon atmosphere and the mixture was stirred for 10 min. Then, $NaBH_4$ (220 mg, 5.81 mmol) was added portion wise and stirred for 1 h at the same temperature. The reaction was then quenched with slow addition of a saturated aqueous NH_4Cl solution and extracted three times with EtOAc. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. Flash column chromatography using 25% EtOAc in hexanes eluent afforded the allylic alcohol **14** (3.37 g, 88%) as a viscous liquid; $[\alpha]_D^{20}$ –6.8 (*c* 1.00, acetone); IR (neat): ν_{max} 3178 (br, s), 3071, 2957, 2877, 1635, 1610, 1513, 1463, 1427, 1372, 1350,

1307, 1257, 1172, 1144, 1112, 1065, 1039, 1008, 974, 908, 875, 841, 741, 702, 611 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.86 (2H, d, *J* = 8.8 Hz), 7.75 – 7.72 (4H, m), 7.47 – 7.40 (6H, m), 6.90 (2H, d, *J* = 8.8 Hz), 6.30 (1H, d, *J* = 1.9 Hz), 5.10 (1H, q, *J* = 6.6 Hz), 4.72 (1H, s), 4.37 – 4.34 (3H, m), 3.86 (3H, s), 2.28 (1H, br s), 1.61 (3H, d, *J* = 6.6 Hz), 1.11 (9H, s), 0.85 (9H, t, *J* = 7.9 Hz), 0.56 – 0.49 (6H, m) ; ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.9, 162.0, 147.5, 135.6, 135.4, 133.5, 133.3, 130.1, 129.6, 129.2, 128.5, 127.6, 127.5, 120.4, 113.4, 86.0, 79.8, 78.9, 78.2, 61.3, 55.2, 26.7, 19.2, 16.6, 6.6, 4.7; HRMS-ESI (*m*/*z*): calcd. for $C_{38}H_{52}NO_5Si_2$ $[M+H]^+$ 658.33785, found 658.33952.

(4*S*,5*S*,6*R*,9*S*)-8-((tert-Butyldiphenylsilyloxy)methyl)-2-(4-methoxyphenyl)-4-methyl-9-(tripropylsilyloxy)-3-oxa-1-azaspiro[4.4]nona-1,7-dien-6-yl acetate (15). To a solution of allylic alcohol **14** (3.12 g, 4.75 mmol) in CH_2Cl_2 (20 mL) was added Et_3N (3.31 mL. 23.73 mmol), Ac_2O (0.67 mL, 7.12 mmol) and DMAP (58.6 mg, 0.48 mmol) at 0 °C under argon atmosphere. The reaction mixture was stirred for 1 h at r.t. The reaction was quenched with aqueous saturated NH_4Cl solution and extracted twice with CH_2Cl_2. The residue was purified by flash chromatography on silica gel using 15% EtOAc in hexanes to afford acetate **15** (3.16 g, 95%) as clear oil; $[\alpha]_D^{20}$ –22.4 (*c* 1.00, $CHCl_3$); IR (neat): ν_{max} 3072, 2957, 2935, 2877, 1743, 1640, 1610, 1513, 1462, 1427, 1369, 1306, 1254, 1238, 1169, 1145, 1112, 1071, 1034, 968, 911, 875, 841, 823, 741, 703, 613 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.92 (2H, d, *J* = 8.9 Hz), 7.73 – 7.71 (4H, m), 7.47 – 7.40 (6H, m), 6.93 (2H, d, *J* = 8.9 Hz), 6.04 (1H, s), 5.73 (1H, s), 5.13 (1H, q, *J* = 6.8 Hz), 4.65 (1H, s), 4.33 (2H, q, *J* = 6.8 Hz), 3.86 (3H, s), 2.07 (3H, s), 1.56 (3H, d, *J* = 6.8 Hz), 1.12 (9H, s), 0.82 (9H, t, *J* = 7.9 Hz), 0.54 – 0.48 (6H, m) ; ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.2, 164.0, 162.0, 148.2, 135.5, 135.4, 133.3, 133.2, 129.9, 129.7, 127.7, 127.6, 124.1, 120.5, 113.5, 86.3, 80.7, 79.0, 77.8, 61.2, 55.3, 26.7, 21.2, 19.2, 16.5, 6.6, 4.7; HRMS-ESI (*m*/*z*): calcd. for $C_{40}H_{54}NO_6Si_2$ $[M+H]^+$ 700.34842, found 700.34801.

(4*S*,5*S*,6*R*,9*S*)-8-((tert-Butyldiphenylsilyloxy)methyl)-9-hydroxy-2-(4-methoxyphenyl)-4-methyl-3-oxa-1-azaspiro[4.4]nona-1,7-dien-6-yl acetate (16). The disilyl ether **15** (1.72 g, 2.46 mmol) was dissolved in a 1:10:1 mixture of TFA:MeCN:H_2O (18 mL) at r.t. and stirred for 3 h at the same temperature. The transformation was monitored on ESI-MS and the reaction mixture was slowly quenched with a saturated solution of $NaHCO_3$ at 0 °C. The reaction mixture was extracted three times with EtOAc, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel using 20% EtOAc in hexanes to afford allylic alcohol **16** (1.21 g, 84%) as a colorless oil; $[\alpha]_D^{20}$ –65.1 (*c* 1.00, $CHCl_3$); IR (neat): ν_{max} 3072, 3014, 2959, 2933, 2857, 1739, 1632, 1610, 1513, 1462, 1427, 1371, 1307, 1255, 1236, 1171, 1112, 1031, 840, 823, 744, 703, 612 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.86 (2H, d, *J* = 8.9 Hz), 7.75 – 7.73 (4H, m), 7.47 – 7.42 (6H, m), 6.92 (2H, d, *J* = 8.9 Hz), 6.18 (1H, d, *J* = 1.9 Hz), 5.63 (1H, s), 5.19 (1H, q, *J* = 6.7 Hz), 4.50 (2H, s), 4.24 (1H, s), 3.86 (3H, s), 3.02 (1H, br s), 2.07 (3H, s), 1.44 (3H, d, *J* = 6.7 Hz), 1.12 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.7, 164.0, 162.2, 150.3,

135.5, 135.4, 133.1, 133.0, 130.1, 129.7, 127.7, 127.6, 126.2, 83.4, 81.0, 80.0, 77.7, 61.6, 55.3, 26.7, 21.2, 19.1, 16.0; HRMS (ESIMS): calcd. for $C_{34}H_{40}NO_6Si$ $[M+H]^+$ 586.26194, found 586.26182.

(4*S*,5*S*,6*R*)-8-((tert-Butyldiphenylsilyloxy)methyl)-2-(4-methoxyphenyl)-4-methyl-9-oxo-3-oxa-1-azaspiro[4.4]nona-1,7-dien-6-yl acetate (17). To a stirred solution of allylic alcohol **16** (1.13 g, 1.93 mmol) in CH_2Cl_2 (20 mL) was added Dess-Martin periodinane (900 mg, 2.12 mmol) at 0 °C under argon atmosphere and the reaction mixture was stirred at r.t. for 2 h. The reaction mixture was quenched with $Na_2S_2O_3/NaHCO_3$ (7:1) aqueous saturated solution (20 mL) at 0 °C. The mixture was stirred vigorously until the two layers were separated at r.t. The crude product was extracted with ether (60 mL x 3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel using 15% EtOAc in hexanes afforded the enone **17** (1.09 g, 97%) as a colorless viscous foam; $[\alpha]_D^{20}$ –183.5 (*c* 1.00, $CHCl_3$); IR (neat): ν_{max} 2932, 1733, 1723, 1633, 1609, 1513, 1427, 1369, 1257, 1226, 1112, 1027, 839, 742, 703, 668 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.88 (2H, d, *J* = 8.9 Hz), 7.69 – 7.65 (5H, m), 7.47 – 7.39 (6H, m), 6.91 (2H, d, *J* = 8.9 Hz), 5.93 (1H, d, *J* = 1.9 Hz), 5.06 (1H, q, *J* = 6.7 Hz), 4.56 – 4.48 (2H, m), 3.86 (3H, s), 2.13 (3H, s), 1.50 (3H, d, *J* = 6.7 Hz), 1.12 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.9, 169.5, 165.5, 162.5, 150.7, 147.4, 135.5, 135.4, 132.9, 132.7, 130.4, 129.9, 129.8, 127.9, 127.8, 119.4, 113.6, 81.3, 79.4, 59.0, 55.4, 26.8, 21.1, 19.3, 16.1; HRMS-ESI (*m*/*z*): calcd. for $C_{34}H_{38}NO_6Si$ $[M+H]^+$ 584.2463, found 584.2467.

(4*S*,5*R*,9*R*)-7-((tert-Butyldiphenylsilyloxy)methyl)-9-hydroxy-2-(4-methoxyphenyl)-4-methyl-3-oxa-1-azaspiro[4.4]nona-1,7-dien-6-one (18). To a solution of enone **17** (70 mg, 0.12 mmol) in toluene (3 mL) was added (dimethylamino)trimethyltin (0.1 mL, 0.60 mmol) dropwisely at r.t. under argon atmosphere and stirred for 3 h. Toluene was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel using 25% EtOAc in hexanes afforded the allylic alcohol **18** (51.4 mg, 79%) as colorless oil; $[\alpha]_D^{20}$ –147.9 (*c* 1.00, $CHCl_3$); IR (neat): ν_{max} 3222 (br s), 3072, 2958, 2932, 2858, 1715, 1626, 1609, 1513, 1462, 1427, 1360, 1307, 1258, 1172, 1113, 1030, 906, 868, 839, 823, 736, 702, 610 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.88 (2H, d, *J* = 8.9 Hz), 7.71 – 7.67 (4H, m), 7.65 (1H, d, *J* = 1.9 Hz), 7.47 – 7.41 (6H, m), 6.90 (2H, d, *J* = 8.9 Hz), 4.98 (1H, d, *J* = 1.9 Hz), 4.94 (1H, q, *J* = 6.7 Hz), 4.56 – 4.48 (2H, m), 3.85 (3H, s), 2.24 (1H, br s), 1.60 (3H, d, *J* = 6.7 Hz), 1.13 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.8, 165.7, 162.5, 154.4, 145.7, 135.5, 133.0, 132.8, 130.3, 129.9, 129.8, 127.9, 127.8, 119.6, 113.6, 83.2, 80.6, 76.4, 58.9, 55.3, 26.8, 19.2, 16.0; HRMS-ESI (*m*/*z*): calcd. for $C_{32}H_{36}NO_5Si$ $[M+H]^+$ 542.23573, found 542.23740.

(4*S*,5*R*,6*S*,9*R*)-7-((tert-Butyldiphenylsilyloxy)methyl)-2-(4-methoxyphenyl)-4,6-dimethyl-3-oxa-1-azaspiro[4.4]nona-1,7-diene-6,9-diol (19). To a stirred solution of enone **17** (823 mg, 1.41 mmol) in dry THF (15 mL) was added MeMgBr (2.35 mL, 3.0 *M* solution in ether, 7.06 mmol) at –78 °C under argon

atmosphere and stirred for 30 min. Then the temperature was raised to 0 °C and stirred for 20 min. The reaction mixture was quenched with saturated aqueous NH_4Cl solution and extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Purification by column chromatography on silica gel using 35% EtOAc in hexanes afforded allylic alcohol **19** (676 mg, 86%) as a colorless liquid; $[\alpha]_D^{20}$ +29.4 (*c* 1.00, $CHCl_3$); IR (neat): ν_{max} 3402 (br), 3072, 2960, 2932, 2857, 1634, 1610, 1513, 1462, 1427, 1361, 1334, 1308, 1256, 1171, 1112, 1034, 996, 952, 912, 840, 824, 743, 702, 612 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.88 (2H, d, *J* = 8.9 Hz), 7.75 – 7.70 (4H, m), 7.49 – 7.43 (6H, m), 6.91 (2H, d, *J* = 8.9 Hz), 6.22 (1H, br s), 5.25 (1H, q, *J* = 6.6 Hz), 4.52 (1H, d, *J* = 8.0 Hz), 4.44 (2H, s), 3.86 (3H, s), 2.90 (1H, s), 2.07 (1H, d, *J* = 8.0 Hz), 1.63 (3H, d, *J* = 6.6 Hz), 1.21 (3H, s), 1.11 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.2, 162.1, 150.6, 135.6, 135.5, 132.8, 132.7, 131.7, 130.1, 130.0, 129.9, 127.8, 120.4, 113.6, 85.1, 83.9, 79.1, 77.7, 61.2, 55.3, 26.8, 19.1, 17.9, 17.2; HRMS-ESI (*m*/*z*): calcd. for $C_{33}H_{40}NO_5Si$ $[M+H]^+$ 558.26703, found 558.26887.

(4*S*,5*S*,6*R*,9*S*)-8-((tert-Butyldiphenylsilyloxy)methyl)-9-hydroxy-2-(4-methoxyphenyl)-4,9-dimethyl-3-oxa-1-azaspiro[4.4]nona-1,7-dien-6-yl acetate (20). To a solution of allylic alcohol **19** (658 mg, 1.18 mmol) in CH_2Cl_2 (20 mL) was added Et_3N (0.82 mL. 5.90 mmol), Ac_2O (0.17 mL, 1.77 mmol) and DMAP (14 mg, 0.12 mmol) at 0 °C under argon atmosphere. The reaction mixture was stirred for 1 h at r.t. The reaction was quenched with aqueous saturated NH_4Cl solution and extracted twice with CH_2Cl_2. The residue was purified by flash chromatography on silica gel using 25% EtOAc in hexanes to afford acetate **20** (637 mg, 90%) as clear oil; $[\alpha]_D^{20}$ –37.0 (*c* 1.00, $CHCl_3$); IR (neat): ν_{max} 3220 (br), 2933, 2857, 1739, 1643, 1609, 1513, 1454, 1427, 1370, 1336, 1309, 1254, 1226, 1169, 1112, 1086, 1028, 950, 840, 824, 744, 703, 671, 612 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.88 (2H, d, *J* = 8.9 Hz), 7.74 – 7.70 (4H, m), 7.48 – 7.41 (6H, m), 6.92 (2H, d, *J* = 8.9 Hz), 6.30 (1H, d, *J* = 2.3 Hz), 5.60 (1H, d, *J* = 2.3 Hz), 5.23 (1H, q, *J* = 6.6 Hz), 4.45 (2H, s), 3.87 (3H, s), 2.11 (3H, s), 1.92 (1H, s), 1.43 (3H, d, *J* = 6.6 Hz), 1.11 (9H, s), 1.08 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.4, 162.9, 162.2, 154.6, 135.6, 135.5, 133.2, 133.1. 130.1, 129.8, 129.7, 127.7, 127.6, 126.1, 84.9, 83.5, 80.9, 77.4, 60.4, 55.4, 26.8, 21.5, 19.2, 17.2, 17.1; HRMS-ESI (*m*/*z*): calcd. for $C_{35}H_{42}NO_6Si$ $[M+H]^+$ 600.2776, found 600.2790.

(4*S*,5*S*,6*R*,9*S*)-9-Hydroxy-8-(hydroxymethyl)-2-(4-methoxyphenyl)-4,9-dimethyl-3-oxa-1-azaspiro[4.4]nona-1,7-dien-6-yl acetate (21). To a solution of silyl ether **20** (624 mg, 1.04 mmol) in THF (10 mL) was added AcOH (2 drops) and TBAF (1.15 mL, 1.0 *M* in THF, 1.15 mmol) at 0 °C under argon atmosphere. The reaction mixture was stirred at r.t. for 1 h, a saturated aqueous NH_4Cl solution was then added and the aqueous phase was extracted three times with EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel using 60% EtOAc in hexanes to afford allylic alcohol **21** (320 mg, 85%) as clear oil; $[\alpha]_D^{20}$ –56.5 (*c* 1.00, $CHCl_3$); IR (neat): ν_{max} 3401 (br), 2973, 2936, 2840, 1732, 1634, 1609, 1514, 1454, 1422, 1371,

1338, 1308, 1255, 1172, 1090, 1022, 953, 910, 842, 732 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.88 (2H, d, *J* = 8.9 Hz), 6.92 (2H, d, *J* = 8.9 Hz), 6.26 (1H, d, *J* = 2.2 Hz), 5.57 (1H, d, *J* = 2.2 Hz), 5.25 (1H, q, *J* = 6.6 Hz), 4.37 (2H, d, *J* = 9.7 Hz), 3.85 (3H, s), 3.21 (1H, br s), 2.08 (3H, s), 1.44 (3H, d, *J* = 6.6 Hz), 1.18 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.3, 163.5, 162.4, 155.0, 130.2, 126.4, 119.7, 113.7, 84.7, 83.7, 77.5, 58.6, 55.4, 21.4, 17.2, 17.0; HRMS-ESI (*m*/*z*): calcd. for $C_{19}H_{24}NO_6$ $[M+H]^+$ 362.15981, found 362.16011.

(1*R*,2*R*,3*S*,4*S*,5*R*,5'*S*)-2-Hydroxy-1-(hydroxymethyl)-2'-(4-methoxyphenyl)-2,5'-dimethyl-5'H-6-oxaspiro[bicyclo[3.1.0]hexane-3,4'-oxazole]-4-yl acetate (22). To the solution of allylic alcohol **21** (316 mg, 0.875 mmol) in CH_2Cl_2 (15 mL) was added *m*CPBA (647 mg, 70% in water, 2.63 mmol) at 0 °C under argon atmosphere. The reaction mixture was stirred for 2 h at the same temperature. A saturated aqueous Na_2SO_3 solution was added to the reaction mixture at 0 °C and stirred for 30 mins. The reaction mixture was then diluted with EtOAc, washed with a saturated aqueous $NaHCO_3$ solution. The aqueous phase was extracted two times with EtOAc, the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel using 80% EtOAc in hexanes to afford epoxy alcohol **22** (244 mg, 74%) as a colorless oil; $[\alpha]_D^{20}$ –15.0 (*c* 1.00, $CHCl_3$); IR (neat): ν_{max} 3418 (br), 2937, 1738, 1634, 1610, 1514, 1455, 1422, 1372, 1308, 1255, 1226, 1172, 1092, 1030, 908, 841, 732 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.91 (2H, d, *J* = 8.9 Hz), 6.92 (2H, d, *J* = 8.9 Hz), 5.43 (1H, s), 5.24 (1H, q, *J* = 6.5 Hz), 4.17 (1H, d, *J* = 12.7 Hz), 4.07 (1H, d, *J* = 12.7 Hz), 3.86 (3H, s), 3.75 (1H, s), 2.44 (1H, s), 2.16 (3H, s), 1.33 (3H, d, *J* = 6.5 Hz), 1.22 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.9, 163.0, 162.4, 130.4, 119.8, 113.6, 84.0, 81.0, 77.8, 67.7, 59.6, 58.0, 55.4, 21.2, 17.5, 16.7; HRMS-ESI (*m*/*z*): calcd. for $C_{19}H_{24}NO_7$ $[M+H]^+$ 378.1547, found 378.1558.

(1*R*,2*R*,3*S*,4*S*,5*R*,5'*S*)-1-((tert-Butyldiphenylsilyloxy)methyl)-2-hydroxy-2'-(4-methoxyphenyl)-2,5'-dimethyl-5'H-6-oxaspiro[bicyclo[3.1.0]hexane-3,4'-oxazole]-4-yl acetate (23). To a solution of epoxy alcohol **22** (220 mg, 0.583 mmol) in CH_2Cl_2 (10 mL) was added Et_3N (0.2 mL. 1.46 mmol), TBDPSCl (0.16 mL, 0.64 mmol) and DMAP (7 mg, 0.06 mmol) at 0 °C under argon atmosphere. The reaction mixture was stirred for 4 h at r.t., then quenched with aqueous saturated NH_4Cl solution and extracted twice with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel using 25% EtOAc in hexanes to afford silyl ether **23** (323 mg, 90%) as clear oil; $[\alpha]_D^{20}$ –11.6 (*c* 1.00, $CHCl_3$); IR (neat): ν_{max} 3486 (br), 3072, 2960, 2934, 2858, 1746, 1641, 1610, 1513, 1455, 1428, 1372, 1334, 1308, 1254, 1232, 1170, 1113, 1064, 1030, 910, 841, 823, 735, 703, 614 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.93 (2H, d, *J* = 8.9 Hz), 7.74 – 7.69 (4H, m), 7.48 – 7.42 (6H, m), 6.92 (2H, d, *J* = 8.9 Hz), 5.42 (1H, s), 5.30 (1H, q, *J* = 6.5 Hz), 4.25 (1H, d, *J* = 11.6 Hz), 3.90 (1H, d, *J* = 11.6 Hz), 3.86 (3H, s), 3.58 (1H, s), 3.21 (1H, s), 2.17 (3H, s), 1.35 (3H, d, *J* = 6.5 Hz), 1.24 (3H, s), 1.09 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.9, 162.4, 161.9, 135.3, 135.2, 132.0, 131.9,

130.0, 129.7, 129.6, 127.5, 119.7, 113.2, 83.7, 80.6, 77.5, 76.5, 66.3, 61.1, 60.0, 55.0, 26.4, 20.9, 18.8, 17.3, 17.2; HRMS-ESI (*m*/*z*): calcd. for $C_{35}H_{42}NO_7Si$ $[M+H]^+$ 616.2725, found 616.2733.

(1*R*,2*R*,3*R*,4*S*,5*R*,5'*S*)-1-((tert-Butyldiphenylsilyloxy)methyl)-2'-(4-methoxyphenyl)-2,5'-dimethyl-5'H-6-oxaspiro[bicyclo[3.1.0]hexane-3,4'-oxazole]-2,4-diol (24). To a solution of acetate **23** (270 mg, 0.44 mmol) in toluene (5 mL) was added (dimethylamino)trimethyltin (0.36 mL, 2.19 mmol) dropwisely at r.t. under argon atmosphere and stirred for 3 h. Toluene was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel using 50% EtOAc in hexanes afforded the epoxy alcohol **24** (216 mg, 86%) as colorless oil; $[\alpha]_D^{20}$ +4.4 (*c* 1.00, $CHCl_3$); IR (neat): ν_{max} 3326 (br), 2933, 2858, 1632, 1610, 1513, 1454, 1427, 1361, 1332, 1308, 1257, 1174, 1113, 1045, 944, 910, 841, 824, 735, 703, 614 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.92 (2H, d, *J* = 8.8 Hz), 7.73 – 7.70 (4H, m), 7.50 – 7.42 (6H, m), 6.91 (2H, d, *J* = 8.8 Hz), 5.27 (1H, q, *J* = 6.5 Hz), 4.43 (1H, br s), 4.33 (1H, d, *J* = 11.3 Hz), 4.32 (1H, s), 3.85 (3H, s), 3.80 (1H, d, *J* = 11.3 Hz), 3.55 (1H, s), 1.55 (3H, d, *J* = 6.5 Hz), 1.27 (3H, s), 1.11 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.4, 162.3, 135.5, 135.4, 131.8, 130.3, 130.2, 128.1, 128.0, 120.2, 113.5, 83.4, 81.7, 77.9, 74.8, 65.3, 63.1, 62.4, 55.3, 26.8, 19.1, 17.5, 17.2; HRMS-ESI (*m*/*z*): calcd. for $C_{33}H_{40}NO_6Si$ $[M+H]^+$ 574.26194, found 574.26272.

(1*R*,2*R*,3*R*,5*S*,5'*S*)-1-((tert-Butyldiphenylsilyloxy)methyl)-2-hydroxy-2'-(4-methoxyphenyl)-2,5'-dimethyl-5'H-6-oxaspiro[bicyclo[3.1.0]hexane-3,4'-oxazol]-4-one (26). To a stirred solution of epoxy alcohol **24** (125 mg, 0.218 mmol) in CH_2Cl_2 (5 mL) was added Dess-Martin periodinane (102 mg, 0.24 mmol) at 0 °C under argon atmosphere and the reaction mixture was stirred at r.t. for 2 h. The reaction mixture was quenched with $Na_2S_2O_3/NaHCO_3$ (7:1) aqueous saturated solution (10 mL) at 0 °C. The mixture was stirred vigorously until the two layers were separated at r.t. The crude product was extracted with Et_2O (20 mL x 3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel using 25% EtOAc in hexanes afforded the epoxy ketone **26** (115 mg, 92%) as a colorless oil; $[\alpha]_D^{20}$ +142.5 (*c* 1.00, $CHCl_3$); IR (neat): ν_{max} 3478 (br), 3072, 2933, 2858, 1753, 1627, 1610, 1513, 1462, 1427, 1362, 1306, 1257, 1170, 1113, 1033, 910, 840, 823, 800, 737, 703, 612 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.91 (2H, d, *J* = 9.0 Hz), 7.74 – 7.69 (4H, m), 7.52 – 7.46 (6H, m), 6.89 (2H, d, *J* = 9.0 Hz), 4.94 (1H, q, *J* = 6.6 Hz), 4.46 (1H, d, *J* = 11.8 Hz), 3.85 (3H, s), 3.82 (1H, d, *J* = 11.8 Hz), 3.20 (1H, s), 1.68 (3H, d, *J* = 6.6 Hz), 1.52 (3H, s), 1.11 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 204.0, 165.4, 162.3, 135.5, 131.6, 131.4, 130.5, 130.4, 128.1, 128.0, 119.9, 113.4, 82.7, 78.8, 78.5, 67.4, 61.9, 59.7, 55.3, 26.7, 19.4, 19.1, 16.4; HRMS-ESI (*m*/*z*): calcd. for $C_{33}H_{38}NO_6Si$ $[M+H]^+$ 572.24629, found 572.24675.

(1*R*,2*R*,3*R*,4*R*,5*R*,5'*S*)-1-((tert-Butyldiphenylsilyloxy)methyl)-2'-(4-methoxyphenyl)-2,5'-dimethyl-5'H-6-oxaspiro[bicyclo[3.1.0]hexane-3,4'-oxazole]-2,4-diol (27). To a solution of epoxy ketone **26** (78

mg, 0.137 mmol) in MeOH:CH_2Cl_2 (1:1, 3 mL) was added $NaBH_4$ (5.2 mg, 0.137 mmol) at –46 °C under argon atmosphere and stirred for 1 h. The reaction was then quenched with slow addition of saturated aqueous NH_4Cl solution and extracted three times with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. Flash column chromatography on silica gel using 35% EtOAc in hexanes eluent afforded the epoxy alcohol **27** (71 mg, 90%) as a colorless oil; $[\alpha]_D^{20}$ +31.0 (*c* 1.00, $CHCl_3$); IR (neat): ν_{max} 3474 (br), 2931, 1638, 1610, 1513, 1427, 1361, 1256, 1112, 1030, 840, 744, 702, 614 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.96 (2H, d, *J* = 8.9 Hz), 7.73 – 7.68 (4H, m), 7.51 – 7.43 (6H, m), 6.91 (2H, d, *J* = 8.9 Hz), 5.08 (1H, q, *J* = 6.5 Hz), 4.46 (1H, d, *J* = 8.0 Hz), 4.33 (1H, d, *J* = 11.5 Hz), 4.01 (1H, s), 3.86 (3H, s), 3.66 (1H, d, *J* = 11.5 Hz), 3.37 (1H, s), 2.66 (1H, d, *J* = 8.0 Hz), 1.52 (3H, d, *J* = 6.5 Hz), 1.30 (3H, s), 1.11 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.1, 162.3, 135.6, 135.5, 131.9, 131.7, 130.4, 130.3, 130.2, 128.0, 127.9, 120.0, 113.5, 81.5, 80.7, 78.4, 72.3, 64.3, 64.0, 62.8, 55.4, 26.8, 19.0, 18.8, 17.3; HRMS-ESI (*m*/*z*): calcd. for $C_{33}H_{40}NO_6Si$ $[M+H]^+$ 574.26194, found 574.26343.

(4*S*,5*R*,6*R*,7*S*,8*S*,9*S*)-7-((tert-Butyldiphenylsilyloxy)methyl)-2-(4-methoxyphenyl)-4,6-dimethyl-8-(3-(prop-1-en-2-yl)phenylamino)-3-oxa-1-azaspiro[4.4]non-1-ene-6,7,9-triol (29). To a stirred solution of epoxy alcohol **27** (56 mg, 0.098 mmol) in toluene (3 mL), the aniline derivative (130 mg, 0.98 mmol) and $Yb(OTf)_3$ (61 mg, 0.049 mmol) were added at r.t. under argon atmosphere. The reaction mixture was heated to 80 °C and stirred for 9 h, then cooled to r.t., quenched with water (5 mL) and extracted with EtOAc (50 mL x 2). The combined organic layers were washed with 0.5 *N* HCl, saturated aqueous $NaHCO_3$ solution, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel using 40% EtOAc in hexanes to afford the aniline **29** (43 mg, 62%) as a pale yellow viscous liquid; $[\alpha]_D^{20}$ +20.5 (*c* 1.00, $CHCl_3$); IR (neat): ν_{max} 3421 (br), 2932, 1635, 1604, 1586, 1514, 1427, 1364, 1257, 1171, 1105, 1038, 822, 737, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.92 – 6.69 (18H, aromatic protons), 5.32 (1H, s), 5.07 (1H, q, *J* = 6.4 Hz), 5.03 (1H, s), 4.68 – 4.58 (2H, m), 4.40 (1H, dd, *J* = 11.2, 4.8 Hz), 4.17 – 4.12 (2H, m), 3.99 (1H, br s), 3.88 (3H, s), 3.83 (1H, d, *J* = 10.8 Hz), 2.25 (1H, d, *J* = 11.6 Hz), 2.10 (3H, s), 1.60 (3H, d, *J* = 6.4 Hz), 1.19 (3H, s), 1.12 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.2, 162.9, 147.8, 143.8, 142.3, 135.8, 135.6, 131.4, 131.3, 130.4, 130.2, 130.0, 129.1, 128.0, 127.9, 118.9, 114.9, 113.8, 112.4, 111.9, 111.0, 84.4, 83.6, 80.9, 80.3, 79.4, 72.8, 66.7, 55.5, 27.0, 21.9, 19.0, 17.3, 17.1; HRMS-ESI (*m*/*z*): calcd. for $C_{42}H_{51}N_2O_6Si$ $[M+H]^+$ 707.35235, found 707.35109.

(4*S*,5*S*,6*R*,9*S*)-9-Hydroxy-8-(hydroxymethyl)-2-(4-methoxyphenyl)-4-methyl-3-oxa-1-azaspiro[4.4]nona-1,7-dien-6-yl acetate (35). To the solution of silyl ether **15** (1.07g, 1.53 mmol) in THF (10 mL) was added TBAF (3.21 mL, 1.0 *M* in THF, 3.21 mmol) at 0 °C under argon atmosphere. The reaction mixture was stirred at r.t. for 1.5 h, a saturated aqueous NH_4Cl solution was then added and the aqueous phase was extracted three times with EtOAc. The combined organic layers were dried over

Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel using 80% EtOAc in hexanes to afford diol **35** (489 mg, 92%) as colorless viscous liquid; $[\alpha]_D^{20}$ –87.7 (*c* 1.00, $CHCl_3$); IR (neat): ν_{max} 3351 (br), 1733, 1631, 1514, 1422, 1372, 1308, 1255, 1173, 1028, 914, 841, 746 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.80 (2H, d, *J* = 8.9 Hz), 6.86 (2H, d, *J* = 8.9 Hz), 6.06 (1H, s), 5.54 (1H, s), 5.21 (1H, q, *J* = 6.7 Hz), 4.34 (3H, br s), 4.18 (1H, br s), 3.82 (3H, s), 2.03 (3H, s), 1.43 (3H, d, *J* = 6.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.0, 164.7, 162.4, 150.6, 130.2, 126.7, 119.5, 113.6, 83.28, 80.89, 79.38, 78.17, 59.37, 55.32, 21.16, 16.11; HRMS-ESI (*m*/*z*): calcd. for $C_{18}H_{22}NO_6$ $[M+H]^+$ 348.14416, found 348.14499.

(1*S*,2*R*,3*S*,4*S*,5*R*,5'*S*)-2-Hydroxy-1-(hydroxymethyl)-2'-(4-methoxyphenyl)-5'-methyl-5'H-6-oxaspiro[bicyclo[3.1.0]hexane-3,4'-oxazole]-4-yl acetate (36). To the solution of diol **35** (431 mg, 1.24 mmol) in CH_2Cl_2 (15 mL) was added *m*CPBA (918 mg, 70% in water, 3.73 mmol) at 0 °C under argon atmosphere. The reaction mixture was stirred for 2 h at the same temperature. A saturated aqueous Na_2SO_3 solution was added to the reaction mixture at 0 °C and stirred for 30 mins. The reaction mixture was then diluted with EtOAc, washed with saturated aqueous $NaHCO_3$ solution. The aqueous phase was extracted two times with EtOAc, the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel using 90% EtOAc in hexanes to afford epoxy diol **36** (286 mg, 64%) as a colorless oil; $[\alpha]_D^{20}$ –41.5 (*c* 1.00, $CHCl_3$); IR (neat): ν_{max} 3364 (br), 3008, 2937, 1746, 1633, 1610, 1514, 1455, 1422, 1373, 1334, 1308, 1256, 1230, 1173, 1088, 1029, 904, 842, 732, 688 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.84 (2H, d, *J* = 8.8 Hz), 6.85 (2H, d, *J* = 8.8 Hz), 5.30 (1H, s), 5.20 (1H, q, *J* = 6.5 Hz), 4.26 (1H, d, *J* = 12.7 Hz), 4.24 (1H, br s), 3.93 (1H, s), 3.82 (1H, d, *J* = 12.7 Hz); 3.80 (3H, s), 3.65 (1H, s), 2.11 (3H, s) 1.27 (3H, d, *J* = 6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.7, 163.5, 162.4, 130.4, 119.7, 113.6, 82.3, 78.4, 76.9, 76.3, 67.3, 60.5, 59.7, 55.3, 21.1, 16.4; HRMS-ESI (*m*/*z*): calcd. for $C_{18}H_{22}NO_7$ $[M+H]^+$ 364.13908, found 364.13963.

(1*S*,2*R*,3*S*,4*S*,5*R*,5'*S*)-1-((tert-Butyldiphenylsilyloxy)methyl)-2-hydroxy-2'-(4-methoxyphenyl)-5'-methyl-5'H-6-oxaspiro[bicyclo[3.1.0]hexane-3,4'-oxazole]-4-yl acetate (37). To a solution of epoxy alcohol **36** (269 mg, 0.74 mmol) in CH_2Cl_2 (10 mL) was added Et_3N (0.31 mL. 2.22 mmol), TBDPSCl (0.21 mL, 0.82 mmol) and DMAP (9 mg, 0.074 mmol) at 0 °C under argon atmosphere. The reaction mixture was stirred for 4 h at r.t, then quenched with aqueous saturated NH_4Cl solution and extracted twice with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel using 30% EtOAc in hexanes to afford silyl ether **37** (392 mg, 88%) as clear oil; $[\alpha]_D^{20}$ –28.7 (*c* 1.00, $CHCl_3$); IR (neat): ν_{max} 3466 (br), 3071, 3011, 2932, 2857, 1747, 1630, 1609, 1512, 1462, 1427, 1373, 1332, 1308, 1254, 1228, 1171, 1113, 1087, 1031, 841, 823, 744, 703, 612 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.92 (2H, d, *J* = 8.9 Hz), 7.72 – 7.68 (4H, m), 7.47 – 7.41 (6H, m), 6.90 (2H, d, *J* = 8.9 Hz), 5.39 (1H, s), 5.36 (1H, q, *J* = 6.5 Hz), 4.21 (1H, d, *J* = 11.6 Hz),

4.03 (1H, d, J = 11.6 Hz), 3.96 (1H, d, J = 3.1 Hz), 3.85 (3H, s), 3.58 (1H, s), 3.27 (1H, d, J = 3.1 Hz), 2.15 (3H, s), 1.31 (3H, d, J = 6.5 Hz), 1.09 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.5, 163.1, 162.3, 135.5, 135.4, 132.3, 132.2, 130.3, 130.1, 130.0, 127.9, 120.1, 113.5, 82.5, 78.5, 77.9, 76.5, 65.3, 62.8, 60.6, 55.3, 26.7, 21.1, 19.1, 16.4; HRMS-ESI (m/z): calcd. for $C_{34}H_{40}NO_7Si$ $[M+H]^+$ 602.25686, found 602.25821.

(1*R*,3*S*,4*S*,5*R*,5'*S*)-1-((tert-Butyldiphenylsilyloxy)methyl)-2'-(4-methoxyphenyl)-5'-methyl-2-oxo-5'H-6-oxaspiro[bicyclo[3.1.0]hexane-3,4'-oxazole]-4-yl acetate (38). To a stirred solution of epoxy alcohol **37** (132 mg, 0.22 mmol) in CH_2Cl_2 (5 mL) was added Dess-Martin periodinane (140 mg, 0.33 mmol) at 0 °C under argon atmosphere and the reaction mixture was stirred at r.t. for 2 h. The reaction mixture was quenched with $Na_2S_2O_3$/$NaHCO_3$ (7:1) aqueous saturated solution (5 mL) at 0 °C. The mixture was stirred vigorously until the two layers were separated at r.t. The crude product was extracted with Et_2O (30 mL x 3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel using 25% EtOAc in hexanes afforded the epoxy ketone **38** (115 mg, 87%) as colorless crystals; m.p. 123–125 °C; $[\alpha]_D^{20}$ –136.4 (*c* 1.00, $CHCl_3$); IR (neat): ν_{max} 3072, 3010, 2959, 2933, 2858, 1754, 1723, 1631, 1609, 1513, 1463, 1427, 1372, 1353, 1309, 1257, 1220, 1170, 1113, 1086, 1058, 1030, 908, 864, 842, 739, 703, 616 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91 (2H, d, J = 8.9 Hz), 7.71 – 7.67 (4H, m), 7.47 – 7.39 (6H, m), 6.90 (2H, d, J = 8.9 Hz), 5.57 (1H, s), 5.16 (1H, q, J = 6.5 Hz), 4.36 (1H, d, J = 12.4 Hz), 4.10 (1H, s), 4.03 (1H, d, J = 12.4 Hz), 3.86 (3H, s), 2.14 (3H, s), 1.37 (3H, d, J = 6.5 Hz), 1.09 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 203.8, 169.3, 164.7, 162.6, 135.6, 135.2, 132.9, 132.6, 130.6, 129.9, 129.8, 127.8, 127.7, 119.2, 113.6, 79.4, 79.1, 73.3, 61.2, 59.6, 57.2, 55.4, 26.7, 20.9, 19.3, 16.8; HRMS-ESI (m/z): calcd. for $C_{34}H_{38}NO_7Si$ $[M+H]^+$ 600.24121, found 600.24208.

(1*R*,2*S*,3*S*,4*S*,5*R*,5'*S*)-1-((tert-Butyldiphenylsilyloxy)methyl)-2-hydroxy-2'-(4-methoxyphenyl)-2,5'-dimethyl-5'H-6-oxaspiro[bicyclo[3.1.0]hexane-3,4'-oxazole]-4-yl acetate (39). To a stirred solution of epoxy ketone **38** (66 mg, 0.11 mmol) in dry THF (3 mL) was added MeMgBr (0.07 mL, 3.0 *M* solution in ether, 0.22 mmol) at –78 °C under argon atmosphere and stirred for 1 h. The reaction mixture was quenched with saturated aqueous NH_4Cl solution and extracted with EtOAc (20 mL x 3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Purification by column chromatography on silica gel using 30% EtOAc in hexanes afforded epoxy alcohol **39** (58 mg, 86%) as a colorless liquid; $[\alpha]_D^{20}$ –56.8 (*c* 1.00, $CHCl_3$); IR (neat): ν_{max} 3444 (br), 2957, 2932, 2857, 1745, 1636, 1609, 1513, 1462, 1427, 1373, 1337, 1309, 1255, 1236, 1171, 1113, 1080, 1049, 906, 841, 823, 741, 704, 687, 609 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87 (2H, d, J = 8.9 Hz), 7.79 – 7.75 (4H, m), 7.45 – 7.41 (6H, m), 6.93 (2H, d, J = 8.9 Hz), 5.12 (1H, s), 5.11 (1H, q, J = 6.5 Hz), 4.49 (1H, d, J = 11.6 Hz), 4.33 (1H, s), 3.87 (3H, s), 3.71 (1H, d, J = 11.6 Hz), 2.15 (3H, s), 1.37 (3H, d, J = 6.5 Hz), 1.20 (3H, s), 1.09 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.8, 163.4, 162.8, 135.7, 135.6, 133.2, 133.1,

130.4, 129.7, 129.6, 127.7, 127.6, 118.9, 113.8, 81.7, 78.9, 78.1, 75.3, 69.2, 68.9, 60.5, 55.4, 26.7, 21.3, 19.3, 17.1, 9.9; HRMS-ESI (*m*/*z*): calcd. for $C_{35}H_{42}NO_7Si$ $[M+H]^+$ 616.27251, found 616.27303.

(1*R*,3*R*,4*S*,5*R*,5'*S*)-1-((tert-Butyldiphenylsilyloxy)methyl)-4-hydroxy-2'-(4-methoxyphenyl)-5'-methyl-5'H-6-oxaspiro[bicyclo[3.1.0]hexane-3,4'-oxazol]-2-one (alcohol of 38). To a solution of epoxy ketone **38** (40 mg, 0.067 mmol) in toluene (3 mL) was added (dimethylamino)trimethyltin (0.055 mL, 0.33 mmol) dropwisely at r.t. under argon atmosphere and stirred for 3 h. Toluene was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel using 35% EtOAc in hexanes afforded the epoxy alcohol (32.5 mg, 87%) as a colorless oil; $[\alpha]_D^{20}$ –93.7 (*c* 1.00, $CHCl_3$); IR (neat): ν_{max} 3230 (br), 3072, 2932, 2858, 1753, 1614, 1513, 1462, 1427, 1355, 1309, 1259, 1174, 1113, 1058, 1030, 996, 863, 841, 823, 798, 743, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.90 (2H, d, *J* = 8.8 Hz), 7.72 – 7.70 (4H, m), 7.46 – 7.39 (6H, m), 6.88 (2H, d, *J* = 8.8 Hz), 5.12 (1H, q, *J* = 6.5 Hz), 4.65 (1H, s), 4.35 (1H, d, *J* = 12.5 Hz), 4.09 (1H, d, *J* = 12.5 Hz), 4.08 (1H, s), 3.84 (3H, s), 2.85 (1H, br s), 1.50 (3H, d, *J* = 6.5 Hz), 1.06 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 205.4, 164.9, 162.6, 135.7, 135.6, 133.0, 132.6, 130.6, 129.9, 129.8, 127.8, 119.4, 113.6, 80.7, 79.7, 71.4, 62.4, 61.5, 57.4, 55.3, 26.7, 19.2, 17.0; HRMS-ESI (*m*/*z*): calcd. for $C_{32}H_{36}NO_6Si$ $[M+H]^+$ 558.23064, found 558.23177.

(1*R*,2*R*,3*S*,4*S*,5*R*,5'*S*)-1-((tert-Butyldiphenylsilyloxy)methyl)-2'-(4-methoxyphenyl)-5'-methyl-2-(tripropylsilyloxy)-5'H-6-oxaspiro[bicyclo[3.1.0]hexane-3,4'-oxazole]-4-yl acetate (TES ether of 37). To a solution of epoxy alcohol **37** (223 mg, 0.37 mmol) in CH_2Cl_2 (10 mL) was added Et_3N (0.1 mL. 0.74 mmol), TESCl (0.075 mL, 0.45 mmol) and DMAP (5 mg, 0.04 mmol) at 0 °C under argon atmosphere. The reaction mixture was stirred for 4 h at r.t, then quenched with aqueous saturated NH_4Cl solution and extracted twice with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel using 25% EtOAc in hexanes to afford silyl ether (239 mg, 90%) as clear oil; $[\alpha]_D^{20}$ –33.8 (*c* 1.00, $CHCl_3$); IR (neat): ν_{max} 3071, 3000, 2956, 2935, 2877, 1746, 1637, 1610, 1512, 1460, 1427, 1372, 1323, 1308, 1254, 1228, 1169, 1112, 1075, 1031, 1009, 901, 841, 740, 703, 613 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.94 (2H, d, *J* = 8.8 Hz), 7.74 – 7.72 (4H, m), 7.45 – 7.40 (6H, m), 6.93 (2H, d, *J* = 8.8 Hz), 5.31 (1H, s), 5.10 (1H, q, *J* = 6.5 Hz), 4.21 (1H, d, *J* = 12.0 Hz), 3.94 (1H, s), 3.90 (1H, d, *J* = 12.0 Hz), 3.87 (3H, s), 3.71 (1H, s), 2.09 (3H, s), 1.34 (3H, d, *J* = 6.5 Hz), 1.08 (9H, s), 0.90 (9H, t, *J* = 7.9 Hz), 0.65 – 0.61 (6H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.7, 162.9, 162.2, 135.8, 135.7, 133.2, 133.1, 130.3, 129.6, 127.6, 120.3, 113.5, 84.3, 78.5, 78.1, 76.2, 67.7, 60.0, 59.9, 55.3, 26.8, 21.0, 19.3, 16.3, 6.7, 4.8; HRMS-ESI (*m*/*z*): calcd. for $C_{40}H_{54}NO_7Si_2$ $[M+H]^+$ 716.34333, found 716.34461.

(1*R*,2*R*,3*R*,4*S*,5*R*,5'*S*)-1-((tert-Butyldiphenylsilyloxy)methyl)-2'-(4-methoxyphenyl)-5'-methyl-2-(tripropylsilyloxy)-5'H-6-oxaspiro[bicyclo[3.1.0]hexane-3,4'-oxazol]-4-ol (40). To a solution of disilyl ether (186 mg, 0.26 mmol) in toluene (5 mL) was added (dimethylamino)trimethyltin (0.21 mL, 1.3 mmol)

dropwisely at r.t. under argon atmosphere and stirred for 3 h. Toluene was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel using 30% EtOAc in hexanes afforded the epoxy alcohol **40** (152 mg, 87%) as a colorless oil; $[\alpha]_D^{20}$ –10.2 (*c* 1.00, $CHCl_3$); IR (neat): ν_{max} 3256, 2956, 1630, 1513, 1462, 1427, 1328, 1307, 1256, 1173, 1112, 841, 741, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.95 (2H, d, *J* = 8.9 Hz), 7.76 – 7.72 (4H, m), 7.45 – 7.38 (6H, m), 6.93 (2H, d, *J* = 8.9 Hz), 5.03 (1H, q, *J* = 6.5 Hz), 4.30 (1H, d, *J* = 11.8 Hz), 4.28 (1H, d, *J* = 11.7 Hz), 3.91 (1H, s), 3.87 (3H, s), 3.86 (1H, d, *J* = 11.8 Hz), 3.73 (1H, s), 1.89 (1H, d, *J* = 11.8 Hz), 1.52 (3H, d, *J* = 6.5 Hz), 1.09 (9H, s), 0.92 (9H, t, *J* = 7.9 Hz), 0.70 – 0.63 (6H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.0, 162.2, 135.8, 135.7, 133.3, 133.0, 130.3, 129.7, 129.6, 127.6, 120.6, 113.5, 83.4, 78.7, 78.4, 74.6, 67.2, 61.0, 60.5, 55.4, 26.8, 19.3, 16.4, 6.8, 4.8; HRMS-ESI (*m*/*z*): calcd. for $C_{38}H_{52}NO_6Si_2$ $[M+H]^+$ 674.33277, found 674.33367.

(1*S*,2*R*,3*R*,4*S*,5*S*)-4-Azido-1-((tert-butyldiphenylsilyloxy)methyl)-3-((S)-1-hydroxyethyl)-3-(4-methoxybenzylamino)-2-methyl-5-(3-(prop-1-en-2-yl)phenylamino)cyclopentane-1,2-diol (48). To a stirred solution of oxazoline **47** (170 mg, 0.232 mmol) in dry AcOH (4 mL) was added $NaCNBH_3$ in portions (59 mg, 0.93 mmol) at r.t. under argon atmosphere. The reaction mixture heated to 40 °C and stirred for 12 h. Then, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution and extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Purification by column chromatography on silica gel using 30% EtOAc in hexanes afforded *N*-PMB amino alcohol **48** (132 mg, 77%) as a colorless liquid; $[\alpha]_D^{20}$ +60.8 (*c* 1.00, $CHCl_3$); IR (neat): ν_{max} 3413 (br), 2932, 2858, 2106, 1602, 1581, 1513, 1471, 1428, 1373, 1327, 1250, 1175, 1113, 1071, 1035, 890, 822, 738, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.64 – 6.58 (18H, aromatic protons), 5.30 (1H, s), 5.04 (1H, s), 5.01 (1H, s), 4.54 (1H, q, *J* = 6.7 Hz), 4.36 (1H, d, *J* = 10.1 Hz), 4.29 (1H, d, *J* = 6.5 Hz), 4.21 (1H, d, *J* = 10.1 Hz), 4.14 (1H, m), 4.04 (1H, d, *J* = 11.1 Hz), 3.98 (1H, d, *J* = 12.4 Hz), 3.81 (3H, s), 3.76 (1H, d, *J* = 11.1 Hz), 2.09 (3H, s), 1.62 (3H, s), 1.52 (3H, d, *J* = 6.7 Hz), 1.11 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.9, 146.8, 143.6, 142.5, 135.8, 135.6, 132.2, 131.1, 131.0, 130.3, 130.0, 129.3, 129.2, 128.0, 127.9, 115.4, 114.1, 112.2, 112.1, 111.0, 86.0, 80.4, 73.4, 69.7, 69.5, 66.0, 55.3, 47.5, 27.0, 21.9, 20.7, 19.5, 19.0; HRMS-ESI (*m*/*z*): calcd. for $C_{42}H_{54}N_5O_5Si$ $[M+H]^+$ 736.38887, found 736.38914.

(4*S*,5*R*,6*R*,7*S*,8*S*,9*S*)-9-Azido-7-((tert-butyldiphenylsilyloxy)methyl)-6,7-dihydroxy-1-(4-methoxybenzyl)-4,6-dimethyl-8-(3-(prop-1-en-2-yl)phenylamino)-3-oxa-1-azaspiro[4.4]nonan-2-one (49). To a stirred solution of *N*-PMB amino alcohol **48** (125 mg, 0.17 mmol) in dry THF (4 mL), activated charcoal (12 mg), Et_3N (0.17 mL, 1.19 mmol) and diphosgene (0.02 mL, 0.17 mmol) were added slowly at 0 °C under argon atmosphere and stirred for 1 h. Then, the reaction was quenched by slow addition of a saturated aqueous $NaHCO_3$ solution and extracted with EtOAc (50 mL x 2). The combined organic layers were washed with brine, filtered, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Flash column chromatography on silica gel using 25% EtOAc in hexanes eluted the cyclic carbamate **49** (108 mg, 83%)

as a colorless liquid; $[\alpha]_D^{20}$ +5.8 (*c* 1.00, $CHCl_3$); IR (neat): ν_{max} 3366 (br), 2932, 2858, 2106, 1725, 1603, 1584, 1514, 1428, 1407, 1362, 1247, 1178, 1113, 1086, 1051, 908, 821, 782, 738, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.54 – 6.39 (18H, aromatic protons), 5.33 (1H, s), 5.09 (1H, s), 4.87 (1H, d, *J* = 15.8 Hz), 4.78 (1H, d, *J* = 15.8 Hz), 4.77 (1H, d, *J* = 12.4 Hz), 4.76 (1H, q, *J* = 6.2 Hz), 4.15 (1H, d, *J* = 10.9 Hz), 3.97 (1H, d, *J* = 10.9 Hz), 3.74 (3H, s), 3.71 (1H, s), 3.40 (1H, br s), 2.86 (1H, s), 2.78 (1H, s), 2.12 (3H, s), 1.54 (3H, d, *J* = 6.2 Hz), 1.44 (3H, s), 1.07 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.3, 158.4, 146.2, 143.4, 142.1, 135.3, 131.8, 131.4, 130.2, 129.8, 129.1, 128.9, 128.0, 127.9, 115.9, 113.6, 112.7, 112.0, 110.8, 84.4, 81.9, 75.4, 74.6, 66.7, 66.2, 65.9, 55.1, 46.7, 26.9, 21.8, 19.8, 19.1, 17.2; HRMS-ESI (*m*/*z*): calcd. for $C_{43}H_{52}N_5O_6Si$ $[M+H]^+$ 762.36814, found 762.36649.

(4*S*,5*R*,6*R*,7*S*,8*S*,9*S*)-8-(3-Acetylphenylamino)-9-azido-7-((tert-butyldiphenylsilyloxy)methyl)-6,7-dihydroxy-1-(4-methoxybenzyl)-4,6-dimethyl-3-oxa-1-azaspiro[4.4]nonan-2-one (50). To a stirred solution of olefin **49** (103 mg, 0.135 mmol) in THF (2 mL), acetone (2 mL) and H_2O (0.4 mL) were added NMO (79 mg, 0.677 mmol) and OsO_4 (0.1 mL, 4% wt in H_2O) at 0 °C and stirred for 2 h at r.t. A saturated aqueous sodium bisulphite solution was added to the reaction mixture and stirred for 30 min. The reaction mixture was extracted with EtOAc (50 mL x 3), the combined organic layers were washed with water, brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Flash column chromatography on silica gel using 70% EtOAc in hexanes eluted the tetrol as clear oil, which was directly used for the next reaction without characterisation. To the stirred solution of above tetrol in THF (1.5 mL) and H_2O (1.5 mL) was added $NaIO_4$ (43 mg, 0.2 mmol) at r.t. and stirred for 3 h. The reaction mixture was extracted with EtOAc (50 mL x 3) and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Flash column chromatography on silica gel using 30% EtOAc in hexanes eluted the methyl ketone **50** (81 mg, 78% in 2 steps) as a colorless liquid; $[\alpha]_D^{20}$ +7.5 (*c* 1.00, $CHCl_3$); IR (neat): ν_{max} 3365 (br), 2933, 2106, 1727, 1715, 1673, 1604, 1514, 1247, 1179, 1084, 909, 821, 735, 703 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.54 – 7.14 (15H, aromatic protons), 6.80 (1H, d, *J* = 8.7 Hz), 6.65 (1H, m), 4.85 (1H, d, *J* = 23.1 Hz), 4.80 (1H, d, *J* = 23.1 Hz), 4.77 (1H, q, *J* = 6.4 Hz), 4.15 (1H, d, *J* = 10.8 Hz), 4.14 (1H, d, *J* = 11.0 Hz), 4.02 (1H, d, *J* = 10.8 Hz), 3.73 (3H, s), 3.70 (1H, s), 3.64 (1H, d, *J* = 11.0 Hz), 3.05 (1H, br s), 2.82 (1H, br s), 2.53 (3H, s), 1.54 (3H, d, *J* = 6.4 Hz), 1.44 (3H, s), 1.06 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.2, 159.2, 158.5, 146.4, 138.0, 135.4, 135.3, 131.6, 131.2, 130.4, 129.8, 129.3, 129.2, 128.1, 128.0, 118.7, 117.9, 113.6, 112.9, 84.5, 81.9, 75.3, 74.5, 66.8, 65.9, 65.7, 55.2, 46.7, 26.9, 26.7, 20.1, 19.1, 17.3; HRMS-ESI (*m*/*z*): calcd. for $C_{42}H_{50}N_5O_7Si$ $[M+H]^+$ 764.3474, found 764.34611.

De-6-MSA-pactamycate (4). To a stirred solution of azide **51** (35 mg, 0.086 mmol) in THF:EtOH:H_2O (3:1:1, 2.5 mL) were added ammonium chloride (14 mg, 0.26 mmol), zinc powder (8.5 mg, 0.13 mmol) at r.t. and stirred for 6 h. Then, the reaction mixture was quenched with aqueous ammonia (10 mL) and extracted with CH_2Cl_2 (50 mL x 2). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography

on silca gel using 8% MeOH in $CHCl_3$ afforded de-6-MSA-pactamycate **4** (28.5 mg, 87%) as a pale yellow solid; m.p. 93–95 °C; $[\alpha]_D^{20}$ –16.5 (*c* 1.00, MeOH); IR (neat): ν_{max} 3372 (br), 2939, 1732, 1674, 1602, 1385, 1359, 1335, 1267, 1063, 894, 777, 690 cm^{-1}; ^1H NMR (400 MHz, CD_3OD): δ 7.38 (1H, s), 7.21 – 7.18 (2H, m), 7.00 (1H, m), 4.82 (1H, q, *J* = 6.6 Hz), 3.91 (1H, d, *J* = 11.5 Hz), 3.53 (1H, d, *J* = 11.5 Hz), 3.52 (1H, d, *J* = 7.9 Hz), 3.49 (1H, d, *J* = 7.9 Hz), 2.54 (3H, s), 1.53 (3H, d, *J* = 6.6 Hz), 1.34 (3H, s); ^{13}C NMR (100 MHz, CD_3OD): δ 201.6, 161.1, 150.8, 139.1, 130.2, 119.2, 117.9, 113.2, 84.0, 83.0, 78.5, 72.6, 71.2, 63.8, 60.7, 26.9, 17.6, 17.2; HRMS-ESI (*m*/*z*): calcd. for $C_{18}H_{26}N_3O_6$ $[M+H]^+$ 380.18161, found 380.18276.

(*S*)-1-((1*R*,2*R*,3*S*,4*S*,5*S*)-1-Amino-5-azido-3-((tert-butyldiphenylsilyloxy)methyl)-2,3-dihydroxy-2-methyl-4-(3-(prop-1-en-2-yl)phenylamino)cyclopentyl)ethyl dimethylcarbamate (59). To a solution of amino triol **55** (48 mg, 0.078 mmol) in CH_2Cl_2 (3 mL) were added Et_3N (0.065 mL. 0.47 mmol), *N*, *N*-dimethylcarbamoyl chloride (0.02 mL, 0.23 mmol) and DMAP (2 mg, 0.016 mmol) at r.t. under argon atmosphere and stirred for 12 h. The reaction was then quenched with aqueous saturated NH_4Cl solution and extracted twice with CH_2Cl_2. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel using 40% EtOAc in hexanes afforded carbamate **59** (45 mg, 84%) as a clear oil; $[\alpha]_D^{20}$ +86.2 (*c* 1.00, $CHCl_3$); IR (neat): ν_{max} 3385 (br), 2931, 2857, 2105, 1687, 1601, 1580, 1488, 1396, 1330, 1268, 1195, 1112, 887, 822, 738, 703 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.63 – 6.56 (15H, aromatic protons and NH_2), 5.36 (1H, q, *J* = 6.5 Hz), 5.33 (1H, s), 5.04 (2H, s), 4.60 (1H, d, *J* = 11.2 Hz), 4.18 (1H, dd, *J* = 11.2, 3.6 Hz), 3.97 (1H, d, *J* = 10.9 Hz), 3.87 (1H, d, *J* = 10.9 Hz), 3.74 (1H, d, *J* = 11.2 Hz), 2.98 (3H, s), 2.96 (3H, s), 2.11 (3H, s), 1.29 (3H, d, *J* = 6.5 Hz), 1.26 (3H, s), 1.04 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.2, 146.4, 143.6, 142.5, 135.8, 135.6, 132.2, 132.0, 129.9, 129.7, 129.3, 127.8, 127.7, 115.3, 112.3, 112.1, 111.0, 83.8, 82.1, 74.2, 72.6, 69.4, 67.9, 64.4, 36.7, 35.9, 26.9, 21.9, 19.1, 17.9, 15.7; HRMS-ESI (*m*/*z*): calcd. for $C_{37}H_{51}N_6O_5Si$ $[M+H]^+$ 687.36847, found 687.37043.

(1*S*,5*R*,6*S*,7*S*,8*R*)-6-Azido-1-((tert-butyldiphenylsilyloxy)methyl)-8-hydroxy-5-((S)-1-hydroxyethyl)-8-methyl-7-(3-(prop-1-en-2-yl)phenylamino)-2-oxa-4-azabicyclo[3.2.1]octan-3-one (60). To a solution of cyclic carbamate **58** (47 mg, 0.06 mmol) in dry toluene (3 mL) was added (dimethylamino)trimethyltin (0.1 mL, 0.6 mmol) dropwisely at r.t. under argon atmosphere, then the reaction mixture heated to reflux and stirred for 3 h. Toluene was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel using 55% EtOAc in hexanes afforded diol **60** (33 mg, 86%) as a colorless oil; $[\alpha]_D^{20}$ +88.4 (*c* 1.00, $CHCl_3$); IR (neat): ν_{max} 3398 (br), 2931, 2857, 2107, 1699, 1602, 1582, 1390, 1326, 1263, 1113, 891, 822, 759, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.61 – 6.74 (15H, aromatic protons and OH), 6.18 (1H, s), 5.30 (1H, s), 5.06 (1H, t, *J* = 1.5 Hz), 4.85 (1H, s), 4.47 (1H, d, *J* = 5.1 Hz), 4.31 (1H, d, *J* = 11.0 Hz), 4.20 (1H, m), 4.19 (1H, d, *J* = 11.2 Hz), 4.01 (1H, m), 3.83 (1H, d, *J* = 11.2 Hz), 2.10 (3H, s), 1.52 (3H, d, *J* = 6.6 Hz), 1.30 (3H, s), 1.09 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.7,

145.7, 143.3, 143.0, 135.8, 135.5, 130.6, 130.4, 130.2, 129.6, 128.2, 128.0, 116.3, 112.6, 111.8, 110.9, 85.0, 78.5, 74.5, 67.1, 66.8, 65.9, 64.0, 27.0, 21.9, 20.7, 18.9, 16.8; HRMS-ESI (*m*/*z*): calcd. for $C_{35}H_{44}N_5O_5Si$ $[M+H]^+$ 642.31062, found 642.31084.

(*S*)-1-((1*R*,2*R*,3*S*,4*S*,5*S*)-1-Amino-5-azido-2-(benzyloxy)-3-(benzyloxymethyl)-3-(tert-butyldiphenylsilyloxy)-2-methyl-4-(3-(prop-1-en-2-yl)phenylamino)cyclopentyl)ethyl 4-methoxybenzoate (62). To a solution of amino diol **54** (330 mg, 0.44 mmol) in THF (10 mL) were added NaH (88 mg, 60% dispersion in mineral oil, 2.2 mmol) benzyl bromide (0.13 mL, 1.1 mmol) and TBAI (81 mg, 0.22 mmol) at 0 °C. The reaction mixture was stirred for 2 h at r.t., then quenched with aqueous saturated NH_4Cl solution and extracted with EtOAc (100 mL x 2). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel using 15% EtOAc in hexanes afforded the dibenzyl ether **62** (328 mg, 80%) as colorless viscous liquid; $[\alpha]_D^{20}$ +106.7 (*c* 1.00, $CHCl_3$); IR (neat): ν_{max} 3416 (br), 2934, 2858, 2098, 1707, 1604, 1580, 1511, 1318, 1276, 1257, 1168, 1103, 1029, 771, 738, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.16 – 6.66 (28H, aromatic protons), 5.78 (1H, s), 5.68 (1H, q, *J* = 6.4 Hz), 5.43 (1H, dd, *J* = 8.0, 1.8 Hz), 5.17(1H, s), 5.00 (1H, t, *J* = 1.4 Hz), 4.16 (1H, d, *J* = 8.9 Hz), 4.11 (1H, d, *J* = 8.9 Hz), 3.97 (1H, q, *J* = 11.6 Hz), 3.91 (3H, s), 3.71 (1H, d, *J* = 12.3 Hz), 3.62 (1H, d, *J* = 1.8 Hz), 3.53 (1H, d, *J* = 9.9 Hz), 3.43 (1H, d, *J* = 9.9 Hz), 3.26 (1H, d, *J* = 12.3 Hz), 2.01 (3H, s), 1.92 (3H, s), 1.39 (3H, d, *J* = 6.4 Hz), 1.13 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.2, 163.5, 145.7, 143.4, 141.9, 137.2, 136.8, 136.7, 135.7, 135.0, 134.1, 131.7, 129.7, 129.0, 128.9, 128.8, 128.7, 128.2, 128.0, 127.6, 127.3, 127.0, 122.9, 114.7, 113.8, 111.8, 111.3, 110.8, 91.9, 90.6, 76.9, 74.2, 71.9, 70.2, 67.7, 67.6, 66.6, 55.5, 27.6, 21.9, 20.0, 14.7, 13.5; HRMS-ESI (*m*/*z*): calcd. for $C_{56}H_{64}N_5O_6Si$ $[M+H]^+$ 930.46204, found 930.45989.

(*S*)-1-((1*R*,2*R*,3*S*,4*S*,5*S*)-1-Amino-5-azido-2-(benzyloxy)-3-(benzyloxymethyl)-3-(tert-butyldiphenylsilyloxy)-2-methyl-4-(3-(prop-1-en-2-yl)phenylamino)cyclopentyl)ethanol (63). To a stirred solution of *p*-methoxy benzyl ester **62** (307 mg, 0.33 mmol) in dry CH_2Cl_2 (12 mL), DIBAL-H (1.65 mL, 1.0 *M* in toluene, 1.65 mmol) was added slowly at –78 °C under argon atmosphere and stirred for 1.5 h. The reaction mixture was then quenched with slow addition of MeOH and warmed to room temperature. A saturated aqueous potassium sodium tartrate solution was added to the reaction mixture and stirred for 1 h. The reaction mixture was extracted with CH_2Cl_2 (100 mL x 2), the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel using 35% EtOAc in hexanes afforded amino alcohol **63** (242 mg, 92%) as colorless liquid; $[\alpha]_D^{20}$ +27.8 (*c* 1.00, $CHCl_3$); IR (neat): ν_{max} 3399 (br), 3029, 2933, 2858, 2097, 1600, 1580, 1492, 1453, 1427, 1328, 1258, 1109, 1027, 975, 784, 739, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.92 – 6.65 (24H, aromatic protons), 5.93 (1H, t, *J* = 1.9 Hz), 5.42 (1H, dd, *J* = 8.0, 2.0 Hz), 5.19 (1H, s), 5.00 (1H, t, *J* = 1.5 Hz), 4.76 (1H, d, *J* = 9.7 Hz), 4.41 (1H, d, *J* = 9.7 Hz), 4.08 (1H, m), 4.05 (1H, d, *J* = 11.2 Hz), 3.98 (1H, d, *J* = 11.2 Hz), 3.61 (1H, d, *J* = 12.1 Hz), 3.55 (1H, d, *J* = 10.0 Hz), 3.47 (1H, d,

J = 2.0 Hz), 3.46 (1H, d, *J* = 10.0 Hz), 2.02 (3H, s), 1.90 (3H, s), 1.12 (3H, d, *J* = 6.5 Hz), 1.09 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.8, 143.4, 141.9, 137.8, 137.3, 136.7, 135.6, 135.0, 134.0, 129.6, 129.1, 129.0, 128.4, 128.2, 128.0, 127.9, 127.6, 127.3, 127.0, 114.7, 111.8, 111.2, 111.0, 91.5, 90.7, 78.0, 71.9, 69.7, 69.4, 67.6, 67.3, 66.8, 27.6, 21.8, 20.0, 18.6, 13.7; HRMS-ESI (*m*/*z*): calcd. for $C_{48}H_{58}N_5O_4Si$ $[M+H]^+$ 796.42526, found 796.42568.

(*S*)-1-((1*R*,2*R*,3*S*,4*S*,5*S*)-1-Amino-5-azido-2-(benzyloxy)-3-(benzyloxymethyl)-3-(tert-butyldiphenylsilyloxy)-2-methyl-4-(3-(prop-1-en-2-yl)phenylamino)cyclopentyl)ethyl dimethylcarbamate (64). To a solution of amino alcohol **63** (42 mg, 0.053 mmol) in dry THF (2 mL) were added NaH (8.5 mg, 60% dispersion in mineral oil, 0.21 mmol), *N*, *N*-dimethylcarbamoyl chloride (0.01 mL, 0.106 mmol) and TBAI (4 mg, 0.01 mmol) at r.t. under argon atmosphere and stirred for 6 h. The reaction was then quenched with aqueous saturated NH_4Cl solution and extracted twice with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel using 20% EtOAc in hexanes afforded carbamate **64** (37 mg, 81%) as pale yellow crystals; m.p. 153–155 °C; $[\alpha]_D^{20}$ +42.5 (*c* 1.00, $CHCl_3$); IR (neat): ν_{max} 3416 (br), 2933, 2099, 1698, 1600, 1493, 1393, 1270, 1187, 1109, 909, 736, 702 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 – 6.67 (24H, aromatic protons), 5.78 (1H, s), 5.42 (1H, d, *J* = 8.0 Hz), 5.38 (1H, q, *J* = 6.4 Hz), 5.16 (1H, s), 4.99 (1H, s), 4.36 (1H, d, *J* = 8.7 Hz), 4.22 (1H, d, *J* = 8.7 Hz), 3.98 (1H, d, *J* = 11.2 Hz), 3.90 (1H, d, *J* = 11.2 Hz), 3.71 (1H, d, *J* = 12.3 Hz), 3.56 (1H, s), 3.55 (1H, d, *J* = 9.9 Hz), 3.42 (1H, d, *J* = 9.9 Hz), 3.29 (1H, d, *J* = 12.3 Hz), 3.07 (3H, s), 3.00 (3H, s), 2.00 (3H, s), 1.90 (3H, s), 1.31 (3H, d, *J* = 6.4 Hz), 1.11 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.4, 145.7, 143.4, 141.8, 137.3, 137.0, 136.7, 136.5, 135.7, 135.1, 134.1, 129.6, 129.1, 129.0, 128.9, 128.7, 128.2, 128.1, 128.0, 127.6, 127.3, 127.0, 114.6, 111.8, 111.2, 110.9, 91.7, 90.5, 76.6, 74.5, 71.9, 70.0, 67.7, 67.5, 66.6, 36.6, 36.1, 27.6, 21.8, 20.0, 15.4, 13.2; HRMS-ESI (*m*/*z*): calcd. for $C_{51}H_{63}N_6O_5Si$ $[M+H]^+$ 867.46237, found 867.4628.

(1*S*,2*S*,3*R*,4*R*,5*S*)-2-Azido-4-(benzyloxy)-3-((S)-1-(benzyloxy)ethyl)-5-(benzyloxymethyl)-5-(tert-butyldiphenylsilyloxy)-4-methyl-N1-(3-(prop-1-en-2-yl)phenyl)cyclopentane-1,3-diamine (65). To a solution of amino alcohol **63** (186 mg, 0.234 mmol) in dry THF (5 mL) were added NaH (38 mg, 60% dispersion in mineral oil, 0.94 mmol), BnBr (0.04 mL, 0.35 mmol) and TBAI (9 mg, 0.02 mmol) at 0 °C under argon atmosphere and stirred for 3 h. The reaction was then quenched with aqueous saturated NH_4Cl solution and extracted twice with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel using 10% EtOAc in hexanes afforded amino tribenzyl ether **65** (162 mg, 78%) as clear oil; $[\alpha]_D^{20}$ +67.5 (*c* 1.00, $CHCl_3$); IR (neat): ν_{max} 3417 (br), 3029, 2933, 2858, 2098, 1600, 1579, 1494, 1453, 1427, 1329, 1266, 1109, 976, 909, 820, 784, 736, 701 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00 – 6.68 (29H, aromatic

protons), 5.96 (1H, s), 5.53 (1H, dd, *J* = 8.0, 2.0 Hz), 5.22 (1H, s), 5.03 (1H, t, *J* = 1.4 Hz), 4.77 (1H, d, *J* = 11.4 Hz), 4.47 (1H, d, *J* = 9.9 Hz), 4.40 (1H, d, *J* = 11.4 Hz), 4.32 (1H, d, *J* = 9.9 Hz), 4.16 (1H, q, *J* = 6.3 Hz), 4.13 (1H, d, *J* = 11.7 Hz), 4.01 (1H, d, *J* = 11.7 Hz), 3.69 (1H, d, *J* = 12.2 Hz), 3.56 (1H, d, *J* = 2.1 Hz), 3.53 (1H, d, *J* = 9.9 Hz), 3.47 (1H, d, *J* = 9.9 Hz), 3.28 (1H, d, *J* = 12.2 Hz), 2.05 (3H, s), 1.96 (3H, s), 1.35 (3H, d, *J* = 6.3 Hz), 1.11 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.9, 143.4, 141.8, 138.6, 137.8, 137.3, 136.7, 135.6, 135.2, 134.8, 134.2, 129.5, 129.0, 128.9, 128.7, 128.4, 128.1, 127.9, 127.8, 127.7, 127.6, 127.5, 127.4, 127.2, 126.9, 114.5, 111.8, 111.1, 111.0, 92.5, 90.5, 78.4, 71.8, 70.9, 70.0, 67.7, 67.2, 66.3, 27.6, 21.9, 20.0, 13.8, 13.4; HRMS-ESI (*m*/*z*): calcd. for $C_{55}H_{64}N_5O_4Si$ $[M+H]^+$ 886.47221, found 886.47332.

N-((1*S*,2*S*,3*R*,4*R*,5*S*)-5-Azido-3-(benzyloxy)-4-((S)-1-(benzyloxy)ethyl)-2-(benzyloxymethyl)-2-(tert-butyldiphenylsilyloxy)-4-isocyanato-3-methylcyclopentyl)-3-(prop-1-en-2-yl)aniline (66). To a stirred solution of amine **65** (146 mg, 0.165 mmol) in dry THF (5 mL), activated charcoal (15 mg), Et_3N (0.07 mL, 0.49 mmol) and diphosgene (0.04 mL, 0.33 mmol) were added slowly at –46 °C under argon and stirred for 20 min. Then, the reaction was quenched with saturated aqueous $NaHCO_3$ solution and extracted with EtOAc (50 mL x 2). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Flash column chromatography on silica gel using 8% EtOAc in hexanes eluted the stable isocyanate **66** (125 mg, 83%) as a colorless liquid; $[\alpha]_D^{20}$ +49.5 (*c* 1.00, $CHCl_3$); IR (neat): ν_{max} 3417 (br), 3029, 2933, 2858, 2258, 2098, 1600, 1581, 1454, 1329, 1267, 1110, 909, 821, 737, 701 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 – 6.73 (29H, aromatic protons), 6.07 (1H, s), 5.65 (1H, dd, *J* = 8.0, 1.9 Hz), 5.20 (1H, s), 5.02 (1H, s), 4.82 (1H, d, *J* = 11.5 Hz), 4.44 (1H, d, *J* = 10.3 Hz), 4.39 (1H, d, *J* = 11.5 Hz), 4.37 (1H, d, *J* = 10.3 Hz), 4.28 (1H, q, *J* = 6.2 Hz), 4.10 (1H, dd, *J* = 11.7, 4.0 Hz), 3.83 (1H, d, *J* = 11.7 Hz), 3.70 (1H, d, *J* = 12.0 Hz), 3.52 (1H, d, *J* = 4.0 Hz), 3.50 (1H, d, *J* = 9.9 Hz), 3.44 (1H, d, *J* = 12.0 Hz), 3.33 (1H, d, *J* = 9.9 Hz), 2.04 (3H, s), 1.96 (3H, s), 1.41 (3H, d, *J* = 6.2 Hz), 1.14 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.7, 143.3, 142.0, 137.9, 137.6, 137.4, 136.8, 136.0, 135.3, 134.6, 129.4, 129.1, 129.0, 128.7, 128.5, 128.1, 128.0, 127.6, 127.5, 127.4, 127.3, 127.1, 127.0, 125.4, 115.1, 112.0, 111.3, 111.1, 93.0, 88.3, 77.7, 75.6, 73.6, 72.1, 69.6, 68.7, 67.5, 66.8, 27.2, 21.8, 19.9, 14.8, 13.9.

3-((1*R*,2*R*,3*S*,4*S*,5*S*)-5-Azido-2-(benzyloxy)-1-((S)-1-(benzyloxy)ethyl)-3-(benzyloxymethyl)-3-(tert-butyldiphenylsilyloxy)-2-methyl-4-(3-(prop-1-en-2-yl)phenylamino)cyclopentyl)-1,1-dimethylurea (67). To an isocyanate **66** (96 mg, 0.105 mmol) was added neat 0.2 mL dimethyl amine (upon condensing the gas at –46 °C) and the reaction mixture was left warming to room temperature. It was directly subjected to flash column chromatography using 20% EtOAc in hexanes to afford urea **67** (89 mg, 88%) as a colorless oil; $[\alpha]_D^{20}$ +8.6 (*c* 1.00, $CHCl_3$); IR (neat): ν_{max} 3400 (br), 3030, 2931, 2857, 2100, 1666, 1602, 1581, 1524, 1496, 1454, 1361, 1334, 1243, 1172, 1108, 1028, 909, 821, 780, 733, 701 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 – 6.41 (29H, aromatic protons), 5.58 (1H, s), 5.39 (1H, s), 5.08 (1H, s), 4.89 (1H, d, *J* = 11.8 Hz), 4.68 (1H, q, *J* = 6.1 Hz), 4.62 (1H, d, *J* = 11.8 Hz), 4.50 (1H, d, *J* = 11.0 Hz), 4.42 (1H, br s),

4.11 – 3.97 (4H, m), 3.87 (1H, d, *J* = 10.1 Hz), 3.64 (1H, d, *J* = 10.1 Hz), 2.90 (6H, s), 2.18 (3H, s), 1.91 (3H, s), 1.14 (3H, d, *J* = 6.1 Hz), 0.92 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.9, 147.2, 143.9, 141.5, 139.2, 139.0, 137.1, 136.2, 135.9, 135.3, 134.7, 129.2, 129.1, 128.6, 128.5, 128.3, 128.1, 128.0, 127.9, 127.2, 127.1, 127.0, 126.8, 126.7, 114.2, 111.7, 111.4, 110.7, 91.0, 86.1, 74.9, 72.9, 70.9, 70.4, 69.2, 67.2, 65.7, 62.3, 36.5, 27.5, 21.9, 19.9; HRMS-ESI (*m*/*z*): calcd. for $C_{58}H_{69}N_6O_5Si$ $[M+H]^+$ 957.50932, found 957.5084.

3-((1*R*,2*R*,3*S*,4*S*,5*S*)-4-(3-Acetylphenylamino)-5-azido-2-(benzyloxy)-1-((S)-1-(benzyloxy)ethyl)-3-(benzyloxymethyl)-3-(tert-butyldiphenylsilyloxy)-2-methylcyclopentyl)-1,1-dimethylurea (methylketone of 67). To a stirred solution of olefin **67** (70 mg, 0.073 mmol) in THF (1 mL), acetone (1 mL) and H_2O (0.2 mL) were added NMO (60 mg, 0.51 mmol) and OsO_4 (0.05 mL, 4% wt in H_2O) at 0 °C and stirred for 2 h at r.t. A saturated aqueous sodium bisulphite solution was added to the reaction mixture and stirred for 30 min. The reaction mixture was extracted with EtOAc (30 mL x 3), the combined organic layers were washed with water, brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Flash column chromatography on silica gel using 70% EtOAc in hexanes eluted the diol as clear oil, which was directly used for the next reaction without characterisation. To the stirred solution of above diol in THF (1 mL) and H_2O (1 mL) was added $NaIO_4$ (24 mg, 0.11 mmol) at r.t. and stirred for 2 h. The reaction mixture was extracted with EtOAc (30 mL x 3) and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Flash column chromatography on silica gel using 30% EtOAc in hexanes eluted the methyl ketone (55 mg, 78% in 2 steps) as a colorless liquid; $[\alpha]_D^{20}$ +23.2 (*c* 1.00, $CHCl_3$); IR (neat): ν_{max} 3434 (br), 2931, 2857, 2099, 1665, 1603, 1585, 1524, 1358, 1272, 1237, 1172, 1108, 910, 821, 733, 701, 607 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62 – 7.08 (29H, aromatic protons), 6.62 (1H, br s), 6.38 (1H, s), 4.84 (1H, d, *J* = 8.0 Hz), 4.66 (1H, d, *J* = 12.1 Hz), 4.56 (1H, m), 4.45 (1H, d, *J* = 11.1 Hz), 4.19 (1H, m), 4.04 – 3.98 (2H, m), 3.92 (1H, d, *J* = 11.3 Hz), 3.86 (1H, d, *J* = 10.1 Hz), 3.59 (1H, d, *J* = 10.1 Hz), 2.94 (6H, s), 2.62 (3H, s), 1.89 (3H, s), 1.12 (3H, d, *J* = 6.4 Hz), 0.91 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.3, 158.6, 147.3, 139.3, 138.8, 137.6, 137.0, 136.1, 136.0, 135.1, 134.4, 129.3, 129.2, 128.8, 128.7, 128.4, 128.3, 128.1, 128.0, 127.2, 127.1, 126.9, 126.8, 126.5, 117.2, 116.7, 112.8, 90.9, 85.8, 73.0, 70.9, 68.9, 67.9, 65.7, 61.7, 36.6, 27.4, 26.8, 19.9.

3-((1*R*,2*R*,3*S*,4*S*,5*S*)-4-(3-Acetylphenylamino)-5-azido-2-(benzyloxy)-1-((S)-1-(benzyloxy)ethyl)-3-(benzyloxymethyl)-3-hydroxy-2-methylcyclopentyl)-1,1-dimethylurea (68). To a stirred solution of silyl ether (44 mg, 0.046 mmol) in dry DMF (2 mL) was added TAS-F (38 mg, 0.138 mmol) at 0 °C under argon and allowed to room temperature. After being stirred for 1 h at r.t., the reaction mixture was cooled to 0 °C, quenched with a pH=7 phosphate buffer solution and extracted with EtOAc (50 mL x 3). The combined organic layers were washed with water (30 mL x 3), brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel using 50% EtOAc in hexanes to afford the pure keto alcohol **68** (30 mg, 90%) as pale yellow crystals; m.p. 127–128 °C; $[\alpha]_D^{20}$

+53.1 (*c* 1.00, $CHCl_3$); IR (neat): ν_{max} 3385 (br), 2931, 2102, 1674, 1602, 1538, 1358, 1269, 1173, 1111, 910, 734, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.37 – 7.15 (19H, aromatic protons), 6.92 (1H, d, *J* = 7.6 Hz), 6.32 (1H, s), 5.64 (1H, s), 4.81 (1H, q, *J* = 6.3 Hz), 4.68 (1H, d, *J* = 11.0 Hz), 4.66 (1H, d, *J* = 10.8 Hz), 4.59 (1H, d, *J* = 10.8 Hz), 4.52 – 4.49 (2H, m), 4.37 (1H, dd, *J* = 11.1, 4.3 Hz), 3.94 (1H, d, *J* = 10.0 Hz), 3.85 (1H, d, *J* = 7.1 Hz), 3.54 (1H, d, *J* = 10.0 Hz), 2.97 (6H, s), 2.56 (3H, s), 1.72 (3H, s), 1.40 (3H, d, *J* = 6.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.6, 158.4, 147.3, 138.5, 138.1, 138.0, 129.6, 128.6, 128.5, 128.2, 127.8, 127.7, 127.6, 127.5, 127.4, 118.0, 117.4, 113.0, 92.3, 82.4, 76.6, 74.0 72.4, 71.4, 71.2, 70.5, 68.5, 66.8, 36.7, 26.7, 14.9, 14.4; HRMS-ESI (*m*/*z*): calcd. for $C_{41}H_{49}N_6O_6$ $[M+H]^+$ 721.37081, found 721.37077.

De-6-MSA-pactamycin (3). To a stirred solution of azide **71** (24 mg, 0.044 mmol) in EtOH:H_2O (3:1, 2 mL) were added NH_4Cl (7 mg, 0.133 mmol), zinc powder (4.5 mg, 0.067 mmol) at r.t. and stirred for 6 h. Then, the reaction mixture was quenched with aqueous ammonia (10 mL) and extracted with CH_2Cl_2 (30 mL x 2). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography on silca gel using 5% MeOH in $CHCl_3$ afforded de-6-MSA-pactamycin **3** (19.5 mg, 86%) as a pale yellow oil; $[\alpha]_D^{20}$ +32.5 (*c* 1.00, $CHCl_3$); IR (neat): ν_{max} 3383 (br), 2935, 1678, 1603, 1520, 1440, 1359, 1334, 1269, 1091, 1042, 912, 782, 732, 689 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.86 (1H, br s), 7.29 – 6.85 (5H, aromatic protons and NH_2), 5.56 (1H, br s), 5.48 (1H, d, *J* = 9.9 Hz), 4.13 (1H, d, *J* = 11.7 Hz), 3.93 (1H, m), 3.76 (1H, d, *J* = 9.9 Hz), 3.75 (1H, d, *J* = 11.7 Hz), 3.01 (6H, s), 2.97 (1H, s), 2.56 (3H, s), 1.47 (3H, s), 1.06 (3H, d, *J* = 6.4 Hz); ^1H NMR (400 MHz, $CDCl_3$+D_2O): δ = 7.29 – 6.85 (4H, aromatic protons), 4.14 (1H, d, *J* = 11.8 Hz), 3.92 (1H, q, *J* = 6.4 Hz), 3.75 (1H, s), 3.70 (1H, d, *J* = 11.8 Hz), 3.00 (6H, s), 2.93 (1H, s), 2.52 (3H, s), 1.45 (3H, s), 1.04 (3H, d, *J* = 6.4 Hz); ^1H NMR (400 MHz, CD_3OD): δ = 7.27 – 7.24 (3H, aromatic protons), 6.93 (1H, m), 4.07 (1H, q, *J* = 6.5 Hz), 3.94 (1H, d, *J* = 11.5 Hz), , 3.74 (1H, d, *J* = 2.1 Hz), 3.68 (1H, d, *J* = 11.5 Hz), 3.01 (1H, d, *J* = 2.1 Hz), 2.98 (6H, s), 2.56 (3H, s), 1.42 (3H, s), 1.04 (3H, d, *J* = 6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 198.8, 159.3, 146.9, 138.1, 129.5, 119.1, 118.4, 110.6, 88.5, 84.9, 73.9, 71.7, 68.1, 62.9, 61.7, 36.9, 26.6, 21.3, 18.2; ^{13}C NMR (100 MHz, CD_3OD): δ 201.7, 161.2, 149.4, 139.5, 130.7, 119.7, 118.5, 113.3, 89.6, 85.6, 74.4, 72.9, 69.4, 64.1, 62.3, 37.3, 27.1, 22.0, 18.9; HRMS-ESI (*m*/*z*): calcd. for $C_{20}H_{33}N_4O_6$ $[M+H]^+$ 425.23946, found 425.23998.

ASSOCIATED CONTENT

Supporting Information

Copies of the ^1H and ^{13}C NMR spectra of new compounds (PDF) and CIF files for compounds **2**, **12**, **24** (*p*-bromobenzoate ester derivative), **29** (*p*-nitrobenzoate ester derivative), **33** (phenyloxazoline derivative), **38**, **45**, **46**, **47** (derivative), **58**, **64**, **68**. This material is available free of charge via the Internet at http://pubs.acs.org.

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1.5 Conclusions et perspectives

La première synthèse totale de la pactamycine a été rapportée cinquante ans après son isolement. Au passage, nos travaux ont démontré la faisabilité d'ouvertures d'époxydes activées à l'ytterbium, en plus de fournir de nombreux exemples de réarrangements de Payne dans le cas d'aminocyclitols. En somme, l'expérience a démontré qu'il était important d'incorporer les différents groupements fonctionnels dans le bon ordre, sans quoi l'encombrement stérique grandissant empêchait d'accomplir la synthèse.

De manière plus importante, la synthèse totale de la pactamycine représente la première étape d'un projet beaucoup plus ambitieux, celui de préparer des analogues non naturels préservant les propriétés biologiques de la pactamycine.

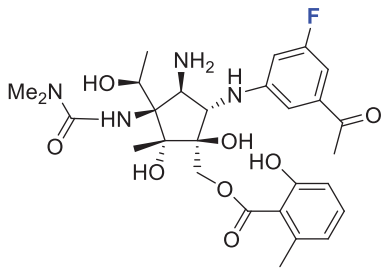
Chapitre II

Synthèse d'une sélection d'analogues de la pactamycine et étude de leurs propriétés biologiques

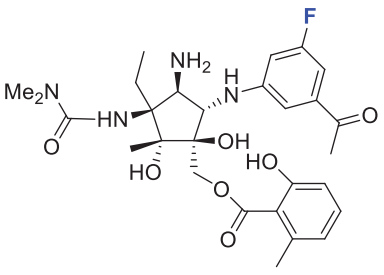
2.1 Synthèses d'analogues connues

En plus d'une liste relativement généreuse de congénères de la pactamycine (voir *Figure 1.2*) dont les dernières entrées sont très récentes, quelques analogues synthétiques ont déjà été préparés. Les connaissances acquises par le groupe de Rinehart lors de l'étude de la biosynthèse de la pactamycine leur ont permis de synthétiser trois analogues fluorés grâce à une expérience de *feeding* (*Figure 2.1*).[33] En ajoutant la 5-fluoroaniline au milieu usuel contenant déjà notamment une culture de *Streptomyces pactum* var *pactum*, du glucose, du peptone, de la tryptone, de l'extrait de levure, de la mélasse et du gruau, il a été possible d'obtenir la 5''-fluoropactamycine (**2.1**) et, dans une moindre mesure, la 5''-fluoropactamycate (**2.3**), la 7-désoxy-5''-fluoropactamycine (**2.2**) et deux autres produits non-identifiés. De ces composés, seules les propriétés biologiques de la 5''-fluoropactamycine ont été assignées sommairement. Il s'est avéré que celle-ci possédait le même pouvoir antibactérien envers le *Bacillus subtilis* et le même pouvoir anticarcinogénique contre les cellules de leucémie LI210 que la pactamycine elle-même.

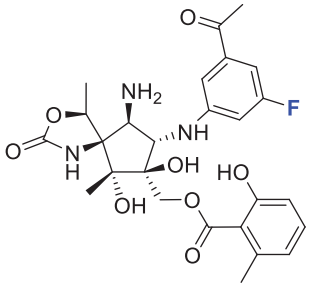
Il est important de noter que les concentrations de 5-fluoroaniline étaient optimales à 0,358 mmol/L et permettaient d'obtenir 0,6 mg/L de l'analogue fluoré d'intérêt (**2.1**). Des concentrations supérieures empêchaient la formation de pactamycine ou de quelconques congénères. De plus, il est à noter que la même expérience a été tentée avec la 5-méthylaniline, sans qu'aucune incorporation de celle-ci ne puisse être notée. Il s'agit là d'une démonstration éloquente des limitations de l'expérience de *feeding*.



(**2.1**)
5''-fluoropactamycine



(**2.2**)
7-désoxy-5''-fluoropactamycine

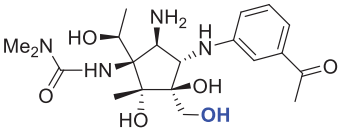


(**2.3**)
5''-fluoropactamycate

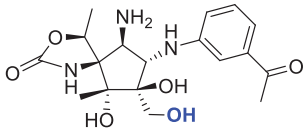
Figure 2.1 : Biosynthèse des analogues 5''-fluorés par Rinehart *et al*

Le groupe de Mahmud, ayant quant à lui travaillé au clonage de gènes produisant la pactamycine,[15] a été capable de générer un corpus impressionnant d'analogues non-naturels en ayant recours à la mutation de gènes (*Figure 2.2*). En réprimant sélectivement un ou plusieurs gènes connus comme étant impliqués dans la biosynthèse de la pactamycine, le groupe de Mahmud a été capable de surpasser les limitations de l'expérience de *feeding*. En plus de la dé-6-MSA-pactamycine (**2.4**) et la dé-6-MSA-pactamycate (**2.5**), il leur a été possible de produire la *N*,*N*-didéméthylpactamycine (**2.6**), la *N*,*N*-didéméthyl-7-désoxypactamycine (**2.7**), la 7-déméthyl-7-désoxypactamycine (**2.8**) et la de-6-MSA-7-déméthyl-7-désoxypactamycine (**2.9**).

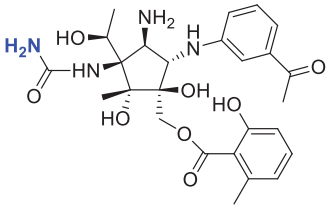
En premier lieu, la de-6-MSA-pactamycine a été reconnue comme étant aussi active que la pactamycine (1–10 µL), autant contre les bactéries Gram-positives que Gram-négatives (*Mycobacterium smegmatis*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, et *Escherichia coli*). Au même titre que la pactamycate, la de-6-MSA-pactamycate n'a par contre montré aucune activité antibactérienne. Par ailleurs, l'activité anticarcinogénique de la de-6-MSA-pactamycine et de la de-6-MSA-pactamycate contre les cellules de colon HT-29 suggère une activité comparable à celle des composés parents respectifs, la pactamycine et la pactamycate.



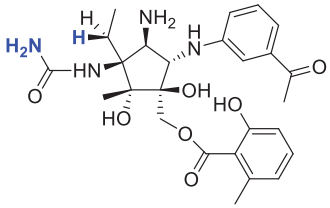
(**2.4**)
de-6-MSA-pactamycine



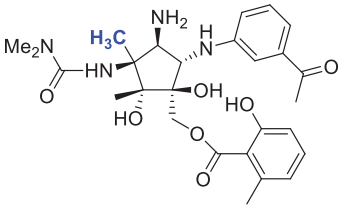
(**2.5**)
de-6-MSA-pactamycate



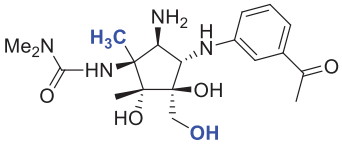
(**2.6**)
N,*N*-didéméthylpactamycine



(**2.7**)
N,*N*-didéméthyl-7-désoxypactamycine



(**2.8**)
7-déméthyl-7-désoxypactamycine



(**2.9**)
de-6-MSA-7-déméthyl-7-désoxypactamycine

Figure 2.2 : Biosynthèse d'analogues par répression de gènes, par Mahmud *et al*

Déjà, l'étude de Mahmud a permis d'établir quelques conclusions importantes en vue d'une étude de relation structure à activité (SAR) plus complète : (1) la présence de la *N*,*N*-diméthylurée est importante pour maintenir l'activité biologique, autant antibactérienne qu'anticarcinogénique; (2) ni la perte du groupement hydroxyl en position 7, ni celle de l'ester salicylique (6-MSA) ne semblent affecter l'activité antibactérienne du composé, ni sa cytotoxicité. Ce dernier point est pour le moins surprenant, étant donné l'étude proposée par Ramakrishnan qui démontre l'importance de l'empilement π entre l'aniline, l'ester salicylique et un résidu du ribosome pour l'activité biologique (voir *Figure 1.4*). La *Figure 2.3* démontre donc l'essentiel des modifications chimiques qui ont pu être apportées jusqu'à aujourd'hui afin de générer une variété d'analogues de la pactamycine. Comme toute cette stratégie repose sur l'expérience de *feeding* ou l'ingénierie biologique, il en découle quelques limitations importantes. Notre approche nous permettrait donc de diversifier les analogues par voies chimiques, là où ces autres méthodes ne le permettent pas.

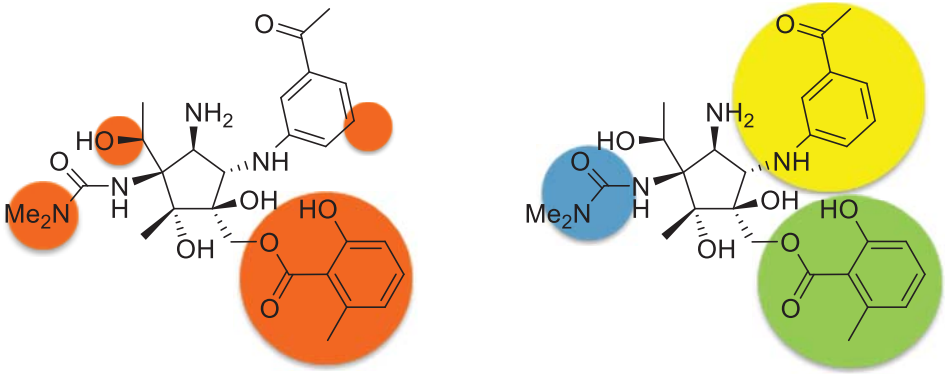


Figure 2.3 : Positions modifiées à ce jour (à gauche) et analogues potentiels de première génération avec notre voie (à droite)

L'article 3 ci-joint (Section 2.2 et Annexe IV) montre donc la synthèse de huit analogues préparés selon les voies de synthèses préétablies et abordées au Chapitre 1 (articles 1 et 2). De plus, les analyses des propriétés antibiotiques, anticarcinogéniques et antiprotozoaires y sont rapportées et mises en relief par rapport aux données connues de la pactamycine (**1.1**). La synthèse d'analogues a principalement été réalisée par les Drs.

Vakiti et Chattopadhyay. J'ai alors pu étudier les propriétés biologiques de ces analogues sous la supervision du professeur Christian Lavallée.

2.2 Article 3

Probing Functional Diversity in Pactamycin toward Antibiotic, Antitumor, and Antiprotozoal Activity

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Abstract

A total of eight new analogs of pactamycin were prepared and tested alongside pactamycin and three of its natural congeners for antibacterial, anticancer and antiprotozoal activities. The present study highlights the effects of changing the urea and aniline groups especially with regard to anticancer and antiprotozoal activities.

Keywords Pactamycin, analogs, urea, aniline, antibacterial, anticancer, antiprotozoal.

Introduction

Pactamycin represents a structurally unique natural product belonging to the aminocyclopentitol family[1] (Figure 2.4). Its isolation in 1961 from a fermentation broth of *Streptomyces pactum* by the former Upjohn Company scientists,[2] was followed by its structure elucidation by chemical and spectroscopic methods,[3] and eventually as a derivative by X-ray crystallography.[4] Early studies by the Upjohn group have shown that pactamycin exhibited in vitro activity against a limited panel of Gram-positive and Gram-negative bacteria as well as cytotoxicity against some cancer cell lines.[5] However, further interest in pactamycin was curtailed because of its toxicity.

The highly functionalized and unique structure of pactamycin has generated interest in recent years on several fronts.[6] Pioneering X-ray crystallographic studies of a pactamycin-RNA complex from *Thermus thermophilus* by Ramakrishnan and coworkers[7] showed a unique mode of binding at the 30S site. Early studies on the biosynthesis of pactamycin were reported by Rinehart and coworkers[8]. More recently, Kudo and coworkers[9] cloned the biosynthetic gene cluster involved in the formation of the cyclopentane ring of pactamycin. Elegant studies by Mahmud and coworkers[10] on the biosynthesis of pactamycin have traced its components to small molecule precursors by isotopic labelling. Furthermore, they have identified the biosynthetic gene cluster that produces pactamycin (**1**), de-6-methylsalicylyl pactamycin (**2**), pactamycate (**3**), de-6-methylsalicylyl pactamycate (**4**), and 7-deoxypactamycin (**5a**) (Figure 2.4).

Synthetic approaches toward the synthesis of the cyclopentane core of pactamycin were sparse except for preliminary reports from the Isobe[11] and Knapp[12] groups in 1995 and 1997 respectively. A total synthesis of pactamycin and pactamycate was reported in 2011 by our group.[13] More recently, conceptually different approaches to the substituted core structure of pactamycin were independently divulged by Johnson,[14] Looper,[15] and Nishikawa.[16]

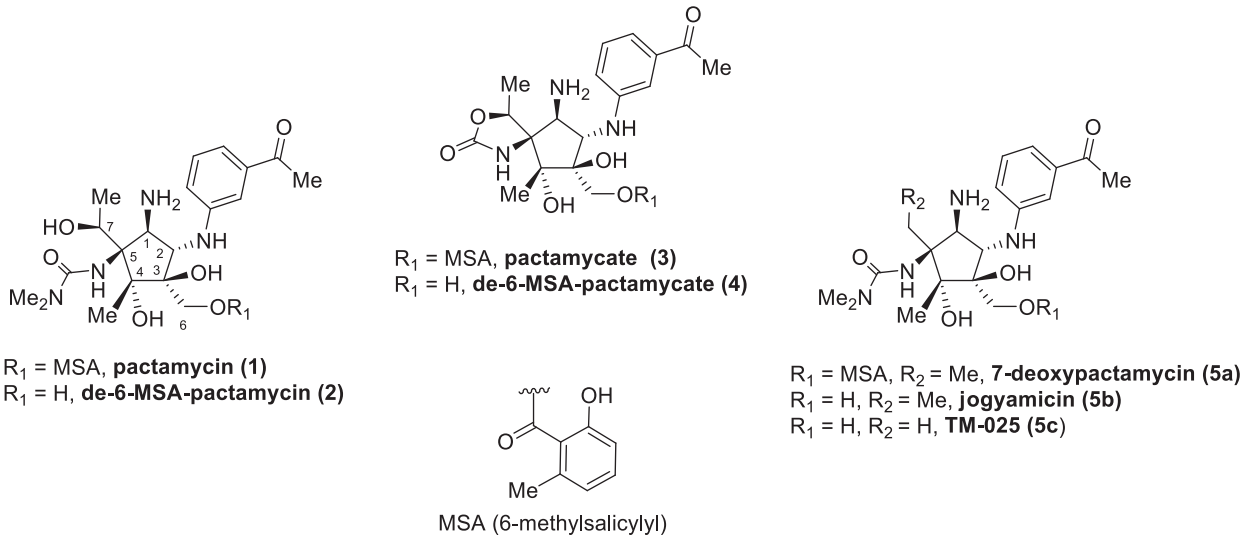


Figure 2.4: Structures of pactamycin, pactamycate, their de-6-methylsalicylyl analogs, jogyamicin, 7-deoxypactamycin, and TM-025

In spite of the sustained interest in the mode of action of pactamycin as an inhibitor of protein biosynthesis in prokaryotes,[6] and the intriguing interactions with RNA's,[7] little was known regarding its activity beyond the limited testing done at the former Upjohn Company.[5] Recently, interest in pactamycin and its relatively few congeners available from biosynthetic studies in small amounts has been highlighted by the discovery of its antiprotozoal activity. Thus, Õmura and coworkers[17] reported that 7-deoxypactamycin (**5a**) exhibited activity against *Trypanosoma brucei* and *Plasmodium falciparum* at levels that were 8-fold higher in potency compared to pactamycin. In a more recent report, Õmura and coworkers[18] showed that jogyamycin (**5b**), the de-6-methylsalicylyl 7-deoxypactamycin congener, was also a potent antitrypanosomal agent and considerably better than pactamycin. Finally, superior activity of a new metabolite of pactamycin (**5c,** TM-025) against malaria parasites was recently divulged by Mahmud and coworkers.[19]

Results and discussion

Chemistry

Our synthesis plan toward pactamycin was conceived so as to allow the preparation of functionally modified analogs.[13] We were intrigued by the role that the unusual 6-methyl salicylyl ester (6-MSA) moiety in pactamycin could play in the in vitro activity as an antibiotic when our work began some years ago. Only within the past three years has it been demonstrated that de-6-methylsalicylyl pactamycin (**2**) and its 7-modified congeners were endowed with equal if not better antiprotozoal activity, but diminished antibacterial activity.[19] With this knowledge, we focussed on the synthesis of de-6-methylsalicylyl pactamycin analogs in which the aniline and urea moieties were modified, starting from appropriate advanced intermediates[13] (Figure 2.5).

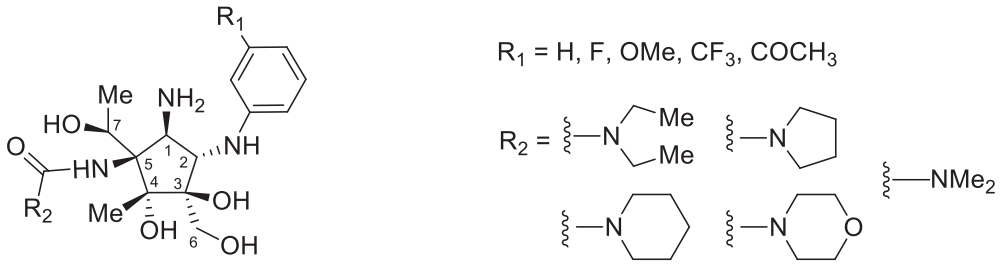
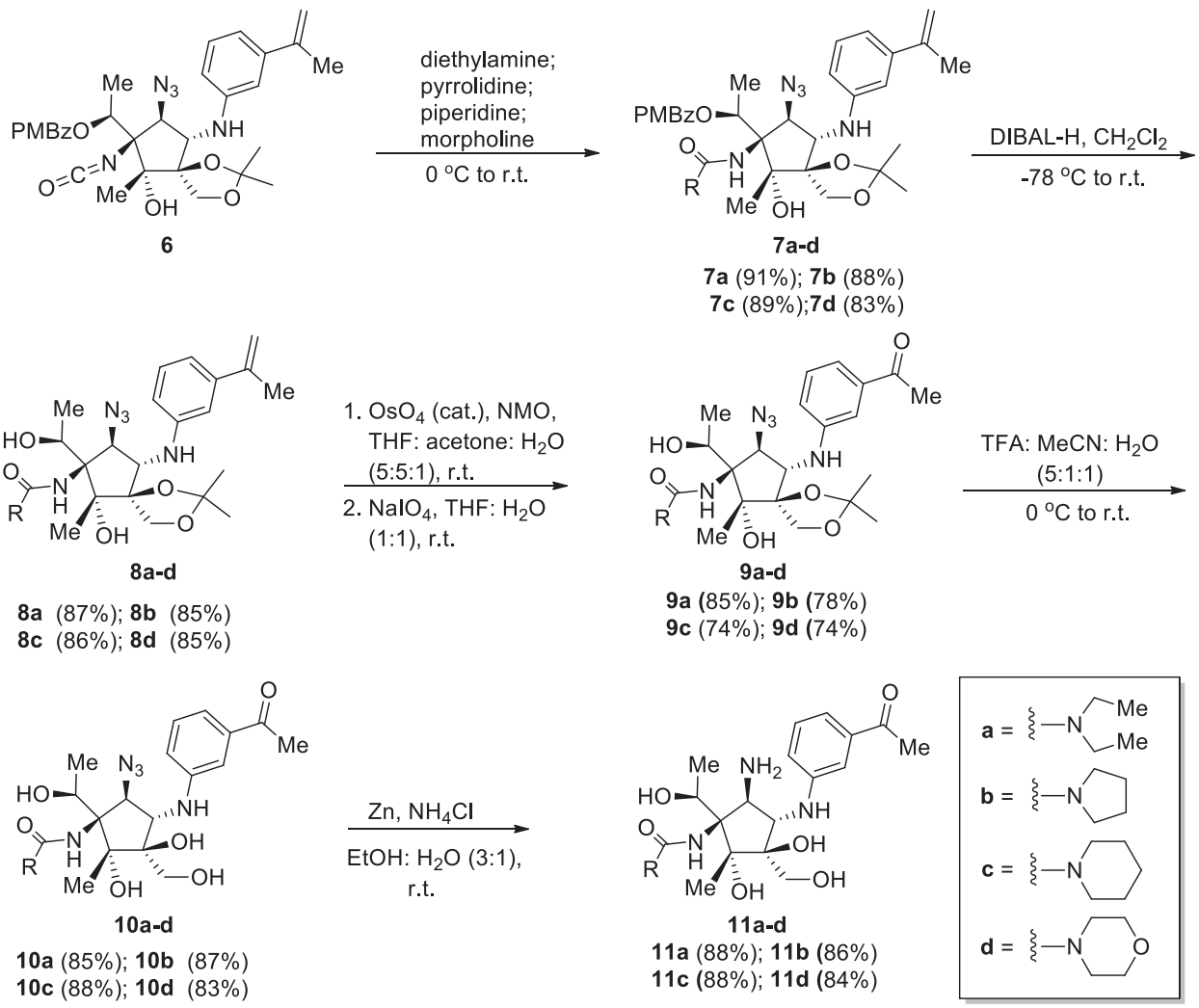


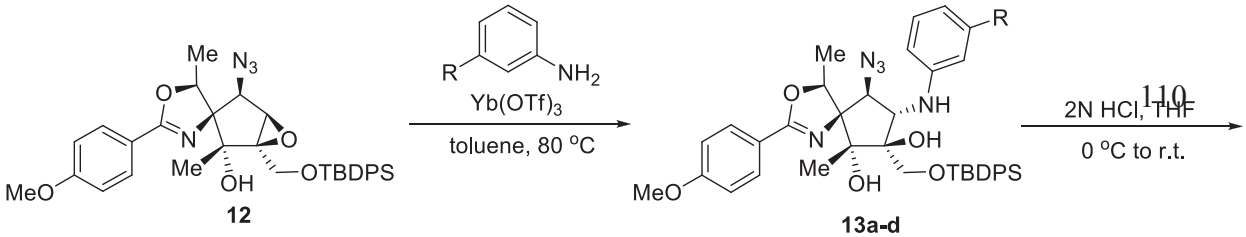
Figure 2.5: Two series of modifications toward the pactamycin analogs

Maintaining the original aniline moiety with the *m*-acetyl group, we prepared a series of *N*,*N*-dialkyl ureas (**11a-d**) varying the bulk of the substituents by treating the isocyanate **6**[13] with a series of amines. The resulting substituted ureas (**7a-7d**), were converted to the 7-hydroxy analog by treatment with DIBAL-H to give **8a-8d**. Subsequent oxidative transformation to the ketones **9a-9d**, cleavage of the acetal to **10a-10d,** and Zn-mediated reduction of the azide group led to the *N*,*N*-disubstituted urea analogs of de-6-methylsalicylyl pactamycin **11a-11d** (Scheme 2.1).



Scheme 2.1: Synthesis of disubstituted urea analogs of de-6-methylsalicylyl pactamycin

Next, keeping the *N*,*N*-dimethylurea group, we substituted the original *m*-acetyl-1-aniline moiety at C2 by aniline and *m*-substituted anilines (**19a-d**) (Scheme 2.2). Thus $Yb(OTf)_3$ mediated cleavage of the epoxide group in **12**[13] in the presence of four different anilines gave the aniline analogs **13a-13d** as single diastereomers.[20] Acid-catalyzed cleavage of the oxazoline moiety afforded the aminoalcohols **14a-14d**, which were converted to the isocyanates **15a-15d**. Treatment with dimethylamine led to the *N*,*N*-dimethylurea derivatives **16a-16d**, which were eventually converted to **19a-19d** as described in Scheme 2.3.



Scheme 2.2: Synthesis of de-6-methylsalicylyl aniline analogs of pactamycin

Biological Activity Studies

The antibacterial activities of these and related derivatives against a panel of six representative microorganisms are shown in Table 1. Pactamycin and de-6-MSA pactamycin remained the most active against *E. coli* and *S. aureus*, closely followed by the *m*-fluoro, and *m*-trifluoromethyl aniline analogs. Modification of the urea group led to diminution or loss of activity showing its paramount importance.

Table 2.1: Antibacterial activities (minimum inhibitory concentration) for compounds **1-4**, **11a-d** and **19a-d**

Compound	*E.coli* (mg/L)	*S. aureus* (mg/L)	*K. pneumoniae* (mg/L)	*A. baumanii* (mg/L)	*P. aeruginosa* (mg/L)	*E. faecalis* (mg/L)
1	16	0.12	32	16	128	128
2	4	2	8	128	128	64
2*	8	8	16	128	>128	>128
3	>128	>128	>128	>128	>128	>128
4	>128	>128	>128	>128	>128	>128
4*	>128	>128	>128	>128	>128	>128
11a	>128	4	>128	>128	>128	128
11b	64	8	128	>128	>128	128
11b*	64	8	128	>128	>128	128
11c	>128	>128	>128	>128	>128	>128
11d	>128	>128	>128	>128	>128	>128
19a	32	64	64	>128	>128	>128
19b	8	4	32	64	>128	128
19c	64	16	>128	128	>128	>128
19d	16	2	128	64	>128	64
19d*	32	2	128	64	>128	128

* compounds tested after 24 hrs storage at 0 ^{o}C

The cytotoxicity of the same analogs against a panel of four cancer cell lines is shown in Table 2. Excellent activity was exhibited against a colorectal HCT116 cell lines by pactamycin (**1**) and de-6-MSA pactamycin (**2**). Among the modified urea analogs, the pyrrolidine urea **11b** appeared to be the best. Unfortunately, all other analogs were either inactive or weakly active against the other cell lines.

Table 2.2: Cytotoxicity values for compounds **1-4**, **11a-d** and **19a-d**

Compound	HCT116 (colorectal) IC50 (μM)	PC3 (prostate) IC50 (μM)	WI-38 (lung) IC50 (μM)	MDA-231 (breast) IC50 (μM)
1	0.07	0.24	>1	0.5
2	0.07	0.31	>1	0.26
3	>1	>1	>1	>1
4	>1	>1	>1	>1
11a	0.23	0.40	>1	0.44

11b	0.09	0.15	>1	0.12
11c	>1	>1	>1	>1
11d	>1	>1	>1	>1
19a	0.81	>1	>1	>1
19b	0.19	>1 (35%)	>1 (34%)	>1
19c	0.39	>1	>1	>1
19d	0.10	0.75	>1 (42%)	0.38

Table 2.3: Typical antimalarial activity for compounds **1-4**, **11a-d** and **19a-d**[21]

Compound	D6 IC50 (nM)	Dd2 IC50 (nM)	7G8 IC50 (nM)
1	<2.5	<2.5	2.5
2	<2.5	<2.5	2.5
3	>2500	>2500	>2500
4	>2500	>2500	>2500
11a	29	40	42
11b	9	9	10
11c	>2500	2003	1596
11d	>2500	>2500	>2500
19a	14.6	13.9	18.5
19b	6.5	7.4	<2.5
19c	13.7	11.5	19.8
19d	6.7	3.5	<2.5

The most interesting results were obtained against *Plasmodium falciparum* (Table 3). A clear demarcation in the tolerance of *N*,*N*-dialkylurea groups was observed as the size increased. Thus, the threshold of activity was maintained up to the pyrrolidine urea (**11b**) (IC_{50} = 9 nM), but rapidly fell for the piperidine and morpholine analogs (**11c**, **11d**). Among the anilines, excellent activity was observed in the case of the *m*-fluoro and *m*-trifluomethyl aniline analogs (**19b** and **19d**) against the D6 strain. In addition the same analogs were also highly active against chloroquine-resistant Dd2 and 7G8 strains.

Conclusion

In conclusion, we have prepared a series of modified urea and aniline analogs of de-6-MSA pactamycin and studied the influence of systematic modifications on the biological activities compared to pactamycin and de-6-MSA pactamycin. Antibacterial

activity against *E. coli* and *S. aureus* was maintained only in the *m*-fluoro and *m*-trifluoromethyl aniline analogs. There appears to be a limit to steric tolerance in the antitumor activity of urea analogs against colorectal cancer cell line with the pyrrolidine analog of de-6MSA pactamycin being the most active. Variation in the *m*-position of the aniline resulted in excellent activity against *Plasmodium falciparum* indicating better tolerance compared to changes in the urea moiety. Moreover, equally high activity was observed against chloroquine-resistant strains by the *m*-fluoro and *m*-trifluoromethyl anline analogs. Further studies toward a better understanding of structure-activity relationships toward an extended panel of tumor cell lines and protozoal organisms will be reported in due course.

Experimental

General

All non-aqueous reactions were run in flame-dried glassware under a positive pressure of argon with exclusion of moisture from reagents and glassware using standard techniques for manipulating air-sensitive compounds. Anhydrous solvents were obtained using standard drying techniques. Unless stated otherwise, commercial grade reagents were used without further purification. Reactions were monitored by analytical thin-layer chromatography (TLC) performed on pre-coated, glass-backed silica gel plates. Visualization of the developed chromatogram was performed by UV absorbance, aqueous cerium ammonium molybdate, iodine, or aqueous potassium permanganate. Flash chromatography was performed on 230-400 mesh silica gel with the indicated solvent systems. Melting points are uncorrected. Infrared spectra were recorded on a FT-IR spectrometer and are reported in reciprocal centimeters (cm^{-1}). Routine nuclear magnetic resonance spectra were recorded either on AMX-300, AV-300, AV-400, or AV-700 spectrometer. Chemical shifts for ^{1}H NMR spectra are recorded in parts per million from tetramethylsilane with the solvent resonance as the internal standard ($CHCl_3$, δ 7.27 ppm). Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, m = multiplet and br = broad) and coupling constant in Hz. Chemical shifts for ^{13}C NMR spectra are

recorded in parts per million from tetramethylsilane using the central peak of the solvent resonance as the internal standard ($CDCl_3$, δ 77.00 ppm). All spectra were obtained with complete proton decoupling. Optical rotations were determined at 589 nm at ambient temperature. Data are reported as follows: $[\alpha]_D$ concentration (*c* in g/100 mL), and solvent. High-resolution mass spectra were performed by the Centre régional de spectroscopie de masse de l'Université de Montréal using fast atom bombardment (FAB) or electrospray ionization (ESI) techniques. Low-resolution mass spectra were obtained using electrospray ionization (ESI).

General procedure for synthesis of compounds 7a-d

To isocyanate **6** (49 mg, 0.085 mmol) was added 0.1 mL of secondary amines (neat) at 0 ^oC and the reaction mixture was left warming to room temperature. It was directly subjected to flash column chromatography using [40-50]% ethyl acetate in hexanes to afford **7a-d** as colorless oils.

(*S*)-1-((5*S*,6*R*,7*R*,8*S*,9*S*)-8-Azido-7-(3,3-diethylureido)-6-hydroxy-2,2,6-trimethyl-9-((3-(prop-1-en-2-yl)phenyl)amino)-1,3-dioxaspiro[4.4]nonan-7-yl)ethyl 4-methoxybenzoate (7a). Yield: 91% (50 mg from 49 mg); $[\alpha]_D^{20}$ +90.9 (*c* 1.00, $CHCl_3$); IR (neat): ν_{max} 3403, 2977, 2107, 1708, 1644, 1605, 1582, 1511, 1257, 1168, 1032, 849, 769 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.98 (2H, d, *J* = 8.9 Hz), 7.17 (1H, t, *J* = 8.0 Hz), 6.94 (2H, d, *J* = 8.9 Hz), 6.89- 6.85 (2H, m), 6.69 (1H, dd, *J* = 8.0, 1.8 Hz), 6.57 (1H, q, *J* = 6.6 Hz), 5.66 (1H, s), 5.33 (1H, s), 5.06 (1H, t, *J* = 1.4 Hz), 4.42 (1H, d, *J* = 9.8 Hz), 4.25- 4.20 (3H, m), 3.97 (2H, s), 3.88 (3H, s), 3.34- 3.20 (4H, m), 2.13 (3H, s), 1.58 (1H, d, *J* = 6.6 Hz), 1.57 (3H, s), 1.43 (3H, s), 1.35 (3H, s), 1.15 (6H, t, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.5, 163.5, 156.7, 147.2, 143.5, 142.6, 131.6, 129.2, 122.3, 116.0, 113.8, 112.5, 112.2, 111.1, 109.9, 90.2, 83.0, 71.9, 70.6, 68.1, 65.9, 65.2, 55.4, 41.7, 26.0, 25.7, 22.4, 21.8, 17.2, 13.9; HRMS-ESI (*m/z*): calcd. for $C_{34}H_{47}N_6O_7$ $[M+H]^+$ 651.35007, found 651.35183.

(*S*)-1-((5*S*,6*R*,7*R*,8*S*,9*S*)-8-Azido-6-hydroxy-2,2,6-trimethyl-9-((3-(prop-1-en-2-yl)phenyl)amino)-7-(pyrrolidine-1-carboxamido)-1,3-dioxaspiro[4.4]nonan-7-yl)ethyl 4-methoxybenzoate (7b). Yield : 88% (66 mg from 67 mg); $[\alpha]_D^{20}$ +88.8 (*c* 1.00, $CHCl_3$); IR (neat): ν_{max} 3388, 2979, 2107, 1709, 1649, 1605, 1511, 1382, 1257, 1168, 849, 757 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.99 (2H, d, *J* = 8.9 Hz), 7.14 (1H, t, *J* = 7.9 Hz), 6.95 (2H, d, *J* = 8.9 Hz), 6.87 (1H, d, *J* = 14.1 Hz), 6.86 (1H, d, *J* = 1.9 Hz), 6.69 (1H, dd, *J* = 7.9, 1.9 Hz), 6.47 (1H, q, *J* = 6.6 Hz), 5.56 (1H, s), 5.33 (1H, s), 5.06 (1H, s), 4.42 (1H, d, *J* = 9.8 Hz), 4.29- 4.19 (3H, m), 4.01- 3.93 (2H, m), 3.88 (3H, s), 3.41- 3.21 (4H, m), 2.13 (3H, s), 1.91 (1 H, br s), 1.93- 1.87 (4H, m), 1.43 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.6, 163.5, 156.4, 147.2, 143.6,

142.6, 131.6, 129.2, 122.3, 116.0, 113.8, 112.5, 112.2, 111.1, 109.8, 90.2, 82.8, 71.9, 70.6, 68.3, 65.9, 65.2, 55.4, 45.7, 26.0, 25.7, 25.6, 22.4, 21.8, 17.2; HRMS-ESI (*m/z*): calcd. for $C_{34}H_{45}N_6O_7$ $[M+H]^+$ 649.33442, found 649.33597.

(*S*)-1-((5*S*,6*R*,7*R*,8*S*,9*S*)-8-Azido-6-hydroxy-2,2,6-trimethyl-7-(piperidine-1-carboxamido)-9-((3-(prop-1-en-2-yl)phenyl)amino)-1,3-dioxaspiro[4.4]nonan-7-yl)ethyl 4-methoxybenzoate (7c). Yield: 89% (72 mg from 70 mg); $[\alpha]_D^{20}$ +85.7 (*c* 1.00, $CHCl_3$); IR (neat): ν_{max} 3406, 2937, 2108, 1708, 1643, 1605, 1581, 1511, 1382, 1326, 1256, 1168, 1101, 1031, 850, 769 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.99 (2H, d, *J* = 8.9 Hz), 7.17 (1H, t, *J* = 7.9 Hz), 6.95 (2H, d, *J* = 8.9 Hz), 6.87 (1H, d, *J* = 7.7 Hz), 6.86 (1H, d, *J* = 2.0 Hz), 6.69 (1H, dd, *J* = 7.8, 1.9 Hz), 6.51 (1H, q, *J* = 6.6 Hz), 5.80 (1H, s), 5.33 (1H, s), 5.06 (1H, t, *J* = 1.4 Hz), 4.41 (1H, d, *J* = 9.8 Hz), 4.26- 4.20 (3H, m), 3.99- 3.97 (2H, m), 3.88 (3H, s), 3.42- 3.38 (2H, m), 3.33- 3.28 (2H, m), 2.13 (3H, s), 1.62- 1.51 (12H, m), 1.43 (3H, s), 1.28 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.6, 163.6, 157.0, 147.1, 143.5, 142.6, 131.6, 129.2, 122.3, 116.0, 114.0, 113.8, 112.5, 112.2, 111.1, 109.8, 90.2, 82.9, 71.9, 70.7, 68.1, 66.0, 65.2, 60.4, 55.4, 45.5, 25.9, 25.7, 25.5, 24.5, 22.3, 21.8, 17.2; HRMS-ESI (*m/z*): calcd. for $C_{35}H_{47}N_6O_7$ $[M+H]^+$ 663.35007, found 663.3517.

(*S*)-1-((5*S*,6*R*,7*R*,8*S*,9*S*)-8-Azido-6-hydroxy-2,2,6-trimethyl-7-(morpholine-4-carboxamido)-9-((3-(prop-1-en-2-yl)phenyl)amino)-1,3-dioxaspiro[4.4]nonan-7-yl)ethyl 4-methoxybenzoate (7d). Yield: 83% (59 mg from 62 mg); $[\alpha]_D^{20}$ +81.9 (*c* 1.00, $CHCl_3$); IR (neat): ν_{max} 3406, 2984, 2109, 1708, 1605, 1581, 1511, 1382, 1257, 1168, 1116, 1030, 849, 768 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.00 (2H, d, *J* = 8.9 Hz), 7.15 (1H, t, *J* = 7.8 Hz), 6.95 (2H, d, *J* = 8.9 Hz), 6.88 (1H, d, *J* = 7.8 Hz), 6.84 (1H, d, *J* = 1.9 Hz), 6.69 (1H, dd, *J* = 7.9, 1.9 Hz), 6.44 (1H, q, *J* = 6.6 Hz), 5.77 (1H, s), 5.33 (1H, s), 5.06 (1H, t, *J* = 1.4 Hz), 4.40 (1H, d, *J* = 9.9 Hz), 4.28 (1H, d, *J* = 9.2 Hz), 4.22 (1H, d, *J* = 9.9 Hz), 4.11 (1H, s), 4.00- 3.94 (2H, m), 3.88 (3H, s), 3.71- 3.60 (4H, m), 3.42- 3.28 (4H, m), 2.13 (3H, s), 1.57 (3H, d, *J* = 6.6 Hz), 1.55 (3H, s), 1.42 (3H, s), 1.35 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.7, 163.7, 157.2, 147.0, 143.5, 142.6, 131.6, 129.2, 122.1, 116.1, 113.9, 112.5, 112.3, 111.1, 109.9, 90.2, 82.8, 71.6, 70.6, 68.2, 66.4, 66.1, 65.2, 55.4, 44.3, 25.9, 25.7, 22.2, 21.8, 17.2; HRMS-ESI (*m/z*): calcd. for $C_{34}H_{45}N_6O_8$ $[M+H]^+$ 665.32934, found 665.33075.

General procedure for synthesis of 8a-d.

To a stirred solution of **7a-d** (49 mg, 0.075 mmol) in dry CH_2Cl_2 (3 mL), DIBAL-H (0.26 mL, 1.5 *M* in toluene, 0.385 mmol) was added slowly at –78 °C under argon and the mixture was stirred for 1.5 h. The reaction mixture was then quenched by slow addition of methanol and warmed to room temperature. A saturated aqueous potassium sodium tartrate solution was added, the reaction mixture stirred for 1 h, then extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Flash column chromatography using [20-25]% ethyl acetate in hexanes gave compounds **8a-d** as colorless liquids.

3-((5*S*,6*R*,7*R*,8*S*,9*S*)-8-Azido-6-hydroxy-7-((*S*)-1-hydroxyethyl)-2,2,6-trimethyl-9-((3-(prop-1-en-2-yl)phenyl)amino)-1,3-dioxaspiro[4.4]nonan-7-yl)-1,1-diethylurea (8a). Yield : 87% (34 mg from 49 mg); $[\alpha]_D^{20}$ +19.3 (*c* 1.00, $CHCl_3$); IR (neat): ν_{max} 3424, 2983, 2935, 2104, 1635, 1602, 1580, 1528, 1489, 1455, 1407, 1374, 1287, 1259, 1216, 1118, 1057, 890, 855, 784 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.67 (1H, d, *J* = 11.2 Hz), 7.23 (1H, t, *J* = 7.9 Hz), 6.92 (1H, d, *J* = 7.7 Hz), 6.73 (1H, s), 6.57 (1H, dd, *J* = 8.0, 2.0 Hz), 5.39 (1H, s), 5.38 (1H, s), 5.29 (1H, d, *J* = 11.2 Hz), 5.10 (1H, s), 4.85 (1H, s), 4.30 (1H, d, *J* = 9.9 Hz), 4.26 (1H, d, *J* = 9.9 Hz), 3.98- 3.88 (2H, m), 3.69 (1H, s), 3.35 (2H, q, *J* = 7.1 Hz), 2.16 (3H, s), 1.47 (3H, s), 1.44 (3H, s), 1.43 (3H, s), 1.24 (6H, t, *J* = 7.1 Hz), 1.20 (3H, d, *J* = 6.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.3, 145.8, 143.4, 143.0, 129.6, 115.8, 112.6, 112.1, 110.6, 110.5, 91.4, 88.7, 73.9, 73.5, 72.8, 66.3, 65.5, 42.3, 26.3, 25.9, 21.9, 21.0, 17.8, 13.8; HRMS-ESI (*m/z*): calcd. for $C_{26}H_{41}FN_6O_5$ $[M+H]^+$ 517.31329, found 517.31392.

***N*-((5*S*,6*R*,7*R*,8*S*,9*S*)-8-Azido-6-hydroxy-7-((*S*)-1-hydroxyethyl)-2,2,6-trimethyl-9-((3-(prop-1-en-2-yl)phenyl)amino)-1,3-dioxaspiro[4.4]nonan-7-yl)pyrrolidine-1-carboxamide (8b).** Yield : 85% (52 mg from 65 mg); $[\alpha]_D^{20}$ +30.0 (*c* 1.00, $CHCl_3$); IR (neat): ν_{max} 3408, 2984, 2104, 1634, 1602, 1581, 1531, 1487, 1396, 1325, 1258, 1212, 1146, 1060, 856, 784, 730 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.54 (1H, d, *J* = 11.4 Hz), 7.23 (1H, t, *J* = 7.9 Hz), 6.92 (1H, d, *J* = 7.9 Hz), 6.73 (1H, s), 6.57 (1H, dd, *J* = 8.0, 2.0 Hz), 5.38 (1H, s), 5.24 (1H, s), 5.23 (1H, d, *J* = 11.0 Hz), 5.11(1H, t, *J* = 1.3 Hz), 4.67 (1H, s), 4.27 (2H, s), 4.01- 3.91 (2H, m), 3.69 (1H, s), 3.49- 3.37 (4H, m), 2.16 (3H, s), 2.02- 1.98 (4H, m), 1.46 (6H, s), 1.43 (3H, s), 1.24 (3H, d, *J* = 6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.8, 145.8, 143.4, 142.9, 129.6, 115.8, 112.6, 112.1, 110.6, 110.5, 91.4, 88.4, 73.8, 73.1, 72.9, 66.6, 65.4, 45.9, 26.3, 25.6, 21.9, 20.8, 17.8 ; HRMS-ESI (*m/z*): calcd. for $C_{26}H_{39}FN_6O_5$ $[M+H]^+$ 515.29764, found 515.29897.

***N*-((5*S*,6*R*,7*R*,8*S*,9*S*)-8-azido-6-hydroxy-7-((*S*)-1-hydroxyethyl)-2,2,6-trimethyl-9-((3-(prop-1-en-2-yl)phenyl)amino)-1,3-dioxaspiro[4.4]nonan-7-yl)piperidine-1-carboxamide (8c).** Yield : 86% (48 mg from 70 mg); $[\alpha]_D^{20}$ +29.6 (*c* 1.00, $CHCl_3$); IR (neat): ν_{max} 3374, 2986, 2935, 2855, 2104, 1631, 1602, 1579, 1528, 1374, 1258, 1209, 1120, 1059, 890, 855, 784, 730 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.52 (1H, d, *J* = 11.3 Hz), 7.23 (1H, t, *J* = 7.9 Hz), 6.92 (1H, d, *J* = 7.6 Hz), 6.73 (1H, s), 6.57 (1H, dd, *J* = 8.1, 2.0 Hz), 5.51 (1H, s), 5.38 (1H, s), 5.25 (1H, d, *J* = 11.3 Hz), 5.10 (1H, s), 4.67 (1H, s), 4.28 (2H, s), 4.39- 3.91 (2H, m), 3.69 (1H, s), 3.51- 3.47 (2H, m), 3.40- 3.35 (2H, m), 2.16 (3H, s), 1.70- 1.60 (6H, m), 1.59 (3H, s), 1.46 (3H, s), 1.45 (3H, s), 1.43 (3H, s), 1.21(3H, d, *J* = 6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.4, 145.8, 143.4, 143.0, 129.6, 115.9, 112.6, 112.1, 110.6, 91.3, 88.5, 74.1, 73.2, 72.6, 66.7, 65.5, 45.7, 29.7, 26.4, 25.9, 25.6, 24.4, 21.9, 20.8, 17.8; HRMS-ESI (*m/z*): calcd. for $C_{27}H_{41}N_6O_5$ $[M+H]^+$ 529.31329, found 529.31370.

***N*-((5*S*,6*R*,7*R*,8*S*,9*S*)-8-Azido-6-hydroxy-7-((*S*)-1-hydroxyethyl)-2,2,6-trimethyl-9-((3-(prop-1-en-2-yl)phenyl)amino)-1,3-dioxaspiro[4.4]nonan-7-yl)morpholine-4-carboxamide (8d).** Yield : 85% (39 mg from 58 mg); $[\alpha]_D^{20}$ +39.7 (*c* 1.00, $CHCl_3$); IR (neat): ν_{max} 3377, 2986, 2106, 1640, 1602, 1580, 1538, 1373, 1263, 1210, 1119, 1059, 855, 730 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.25- 7.21 (2H, m), 6.92 (1H, d, *J* = 7.8 Hz), 6.73 (1H, s), 6.57 (1H, dd, *J* = 8.0, 1.9 Hz), 5.51 (1H, s), 5.38 (1H, s), 5.21 (1H, d, *J* = 11.4 Hz), 5.10 (1H, s), 4.57 (1H, s), 4.28 (2H, ABq, *J* = 9.9 Hz), 4.02- 3.92 (2H, m), 3.77- 3.74 (4H, m), 3.70 (1H, s), 3.54- 3.50 (2H, m), 3.41- 3.37 (2H, m), 2.16 (3H, s), 1.46 (3H, s), 1.45 (3H, s), 1.42 (3H, s), 1.21 (3H, d, *J* = 6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.2, 145.4, 143.0, 142.7, 129.3, 115.6, 112.3, 111.8, 110.3, 110.2, 91.0, 88.1, 73.7, 72.8, 72.2, 66.5, 66.2, 65.1, 44.1, 26.0, 25.2, 21.5, 20.4, 17.5; HRMS-ESI (*m/z*): calcd. for $C_{26}H_{39}FN_6O_6$ $[M+H]^+$ 531.29256, found 531.29410.

General procedure for synthesis of 9a-d

To a stirred solution of **8a-d** (34 mg, 0.066 mmol) in THF (1 mL), acetone (1 mL) and H_2O (0.2 mL) were added NMO (54 mg, 0.46 mmol) and a catalytic amount of OsO_4 (0.1 mL, 4% wt in H_2O) at 0 ºC. After stirring for 2 h at r.t., a saturated aqueous sodium bisulfite solution was added, the reaction mixture stirred for 30 min, then extracted with ethyl acetate. The combined organic layers were washed with water, brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Flash column chromatography using 80% ethyl acetate in hexanes gave the tetrol as clear oil, which was directly used for the next reaction without characterisation. To the stirred solution of above tetrol in THF (1 mL) and H_2O (1 mL) was added $NaIO_4$ (28 mg, 0.13 mmol) at r.t. and stirred for 3 h. The reaction mixture was extracted with ethyl acetate and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Flash column chromatography using [40-50]% ethyl acetate in hexanes gave compounds **9a-d** as colorless liquids.

3-((5*S*,6*R*,7*R*,8*S*,9*S*)-9-((3-Acetylphenyl)amino)-8-azido-6-hydroxy-7-((*S*)-1-hydroxyethyl)-2,2,6-trimethyl-1,3-dioxaspiro[4.4]nonan-7-yl)-1,1-diethylurea (9a). Yield : 85% in 2 steps (29 mg from 34 mg); $[\alpha]_D^{20}$ +30.5 (*c* 1.00, $CHCl_3$); IR (neat): ν_{max} 3373, 2985, 2935, 2105, 1682, 1634, 1603, 1531, 1436, 1374, 1358, 1288, 1119, 1057, 855, 783, 688 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.66 (1H, d, *J* = 11.2 Hz), 7.39- 7.31 (2H, m), 7.23 (1H, s), 6.83 (1H, d, *J* = 7.6 Hz), 5.42 (1H, d, *J* = 11.1 Hz), 5.37 (1H, s), 4.82 (1H, s), 4.25 (2H, ABq, *J* = 11.0 Hz), 3.96 (1H, d, *J* = 11.1 Hz), 3.90 (1H, m), 3.64 (1H, s), 3.34 (4H, q, *J* = 7.2 Hz), 2.61 (3H, s), 1.47 (3H, s), 1.43 (6H, s), 1.24 (6H, t, *J* = 7.2 Hz), 1.19 (3H, d, *J* = 6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.2, 157.2, 146.2, 138.6, 129.9, 118.5, 117.9, 111.8, 110.8, 91.3, 88.6, 74.2, 73.4, 72.8, 66.4, 65.5, 42.3, 26.7, 26.3, 26.0, 20.9, 17.7, 13.8; HRMS-ESI (*m/z*): calcd. for $C_{25}H_{39}N_6O_6$ $[M+H]^+$ 519.29256, found 519.29356.

***N*-((5*S*,6*R*,7*R*,8*S*,9*S*)-9-((3-Acetylphenyl)amino)-8-azido-6-hydroxy-7-((*S*)-1-hydroxyethyl)-2,2,6-trimethyl-1,3-dioxaspiro[4.4]nonan-7-yl)pyrrolidine-1-carboxamide (9b):** Yield : 78% in 2 steps (39 mg from 50 mg); $[\alpha]_D^{20}$ +37.4 (*c* 1.00, $CHCl_3$); IR (neat): ν_{max} 3184, 2984, 2104, 1681, 1637, 1602, 1534, 1487, 1398, 1357, 1324, 1263, 1146, 1060, 914, 855, 781, 731, 688 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.52 (1H, d, *J* = 11.4 Hz), 7.37- 7.32 (2H, m), 7.22 (1H, s), 6.83 (1H, m), 5.37 (1H, d, *J* = 11.1 Hz), 5.22 (1H, s), 4.66 (1H, s), 4.24 (2H, ABq, *J* = 9.9 Hz), 3.95 (1H, m), 3.93 (1H, d, *J* = 11.1 Hz), 3.63 (1H, s), 3.50- 3.38 (4H, m), 2.60 (3H, s), 2.07- 1.97 (4H, m), 1.46 (3H, s), 1.45 (3H, s), 1.45 (3H, s), 1.23 (3H, d, *J* = 6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.2, 156.7, 146.2, 138.6, 129.9, 118.5, 117.9, 111.9, 110.7, 91.3, 88.4, 74.0, 73.0, 72.9, 66.7, 65.4, 45.9, 26.7, 26.3, 25.7, 25.6, 20.7, 17.8; HRMS-ESI (*m/z*): calcd. for $C_{25}H_{37}N_6O_6$ $[M+H]^+$ 517.27691, found 517.27822.

***N*-((5*S*,6*R*,7*R*,8*S*,9*S*)-9-((3-Acetylphenyl)amino)-8-azido-6-hydroxy-7-((*S*)-1-hydroxyethyl)-2,2,6-trimethyl-1,3-dioxaspiro[4.4]nonan-7-yl)piperidine-1-carboxamide (9c).** Yield : 74% in 2 steps (34 mg from 46 mg); $[\alpha]_D^{20}$ +38.8 (*c* 1.00, $CHCl_3$); IR (neat): ν_{max} 3371, 2988, 2937, 2857, 2106, 1682, 1603, 1532, 1487, 1438, 1373, 1357, 1323, 1270, 1233, 1209, 1125, 1059, 1023, 913, 854, 781, 732, 688 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.49 (1H, d, *J* = 11.3 Hz), 7.38- 7.35 (2H, m), 7.31 (1H, s), 6.83 (1H, m), 5.49 (1H, s), 5.65 (1H, d, *J* = 11.2 Hz), 4.65 (1H, s), 4.25 (2H, ABq, *J* = 9.9 Hz), 3.98- 3.90 (2H, m), 3.64 (1H, s), 3.52- 3.46 (2H, m), 3.40- 3.34 (2H, m), 2.60 (3H, s), 2.19 (1H, s), 1.68- 1.60 (6H, m), 1.47 (3H, s), 1.45 (3H, s), 1.43 (3H, s), 1.19 (3H, d, *J* = 6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.2, 157.4, 146.2, 138.6, 129.9, 118.6, 117.9, 111.8, 110.7, 91.3, 88.5, 74.3, 73.2, 72.6, 66.7, 65.4, 45.7, 26.7, 26.3, 25.7, 24.4, 20.7, 17.8; HRMS-ESI (*m/z*): calcd. for $C_{26}H_{39}N_6O_6$ $[M+H]^+$ 531.29256, found 531.29356.

***N*-((5*S*,6*R*,7*R*,8*S*,9*S*)-9-((3-Acetylphenyl)amino)-8-azido-6-hydroxy-7-((*S*)-1-hydroxyethyl)-2,2,6-trimethyl-1,3-dioxaspiro[4.4]nonan-7-yl)morpholine-4-carboxamide (9d):** yield : 74% in 2 steps (29 mg from 39 mg); $[\alpha]_D^{20}$ +43.6 (*c* 1.00, $CHCl_3$); IR (neat): ν_{max} 3378, 2987, 2935, 2858, 2107, 1682, 1637, 1602, 1537, 1437, 1374, 1304, 1265, 1119, 1060, 1021, 914, 854, 781, 732 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.36- 7.34 (2H, m), 7.28- 7.19 (2H, m), 6.83 (1H, m), 5.49 (1H, s), 5.34 (1H, d, *J* = 11.2 Hz), 4.56 (1H, s), 4.25 (1H, ABq, *J* = 10.0 Hz), 3.96 (1H, m), 3.93 (1H, d, *J* = 11.2 Hz), 3.80- 3.70 (4H, m), 3.65 (1H, s), 3.55- 3.49 (2H, m), 3.41- 3.36 (2H, m), 2.60 (3H,s), 2.19 (3H, s), 1.46 (3H, s), 1.44 (3H, s), 1.42 (3H, s), 1.20 (3H, d, *J* = 6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.2, 157.5, 146.1, 138.6, 129.9, 118.7, 117.9, 111.8, 110.7, 91.3, 88.4, 74.4, 73.1, 72.6, 66.9, 66.7, 65.4, 44.5, 26.7, 26.3, 25.6, 20.6, 17.8; HRMS-ESI (*m/z*): calcd. for $C_{25}H_{37}N_6O_7$ $[M+H]^+$ 533.27182, found 533.27306.

General procedure for synthesis of 10a-d

To the stirred solution of **9a-d** (29 mg, 0.056 mmol) in acetonitrile (0.2 mL) and H_2O (0.2 mL), TFA (1 mL) was added at 0 °C and stirred for 45 min at r.t, then the reaction mixture was cooled to 0 °C and

quenched very slowly with a saturated aqueous $NaHCO_3$ solution and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Flash column chromatography using 83-95% ethyl acetate in hexanes gave compounds **10a-d** as colorless liquids.

3-((1*R*,2*R*,3*S*,4*S*,5*S*)-4-((3-Acetylphenyl)amino)-5-azido-2,3-dihydroxy-1-((*S*)-1-hydroxyethyl)-3-(hydroxymethyl)-2-methylcyclopentyl)-1,1-diethylurea (10a). Yield : 87% (23 mg from 29 mg); $[\alpha]_D^{20}$ +31.6 (*c* 1.00, $CHCl_3$); IR (neat): ν_{max} 3418, 2977, 2934, 2103, 1681, 1633, 1603, 1531, 1439, 1358, 1302, 1113, 1056, 917, 783, 757, 688 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.64 (1H, d, *J* = 11.2 Hz), 7.38- 7.30 (2H, m), 7.25 (1H, s), 6.87 (1H, d, *J* = 7.2 Hz), 5.47 (1H, s), 5.38 (1H, d, *J* = 11.2 Hz), 4.70 (1H, s), 4.17 (1H, d, *J* = 11.6 Hz), 3.97 (1H, m), 3.91 (1H, d, *J* = 11.2 Hz), 3.66 (1H, d, *J* = 11.6 Hz), 3.63 (1H, s), 3.41-3.25 (4H, m), 3.22 (1H, s), 2.57 (3H, s), 2.23 (1H, br s), 1.44 (3H, s), 1.25- 1.20 (9H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.8, 157.9, 146.6, 138.9, 130.3, 119.3, 119.0, 112.7, 89.0, 84.8, 74.7, 74.2, 73.7, 67.0, 61.6, 42.7, 27.1, 21.1, 18.2, 14.2; HRMS-ESI (*m/z*): calcd. for $C_{22}H_{35}N_6O_6$ $[M+H]^+$ 479.26126, found 479.26241.

***N*-((1*R*,2*R*,3*S*,4*S*,5*S*)-4-((3-Acetylphenyl)amino)-5-azido-2,3-dihydroxy-1-((*S*)-1-hydroxyethyl)-3-(hydroxymethyl)-2-methylcyclopentyl)pyrrolidine-1-carboxamide (10b).** Yield : 87% (26 mg from 32 mg); $[\alpha]_D^{20}$ +22.2 (*c* 1.00, $CHCl_3$); IR (neat): ν_{max} 3396 (br), 2978, 2937, 2937, 2875, 2103, 1681, 1633, 1603, 1531, 1487, 1402, 1326, 1234, 1136, 755, 689 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.56 (1H, d, *J* = 11.2 Hz), 7.34- 7.23 (2H, m), 6.86 (1H, d, *J* = 7.2 Hz), 5.35 (1H, s), 5.34 (1H, d, *J* = 11.6 Hz), 4.59 (1H, s), 4.15 (1H, d, *J* = 11.2 Hz), 3.98 (1H, m), 3.94 (1H, d, *J* = 11.2 Hz), 3.66 (1H, d, *J* = 11.6 Hz), 3.62 (1H, s), 3.42 (4H, br s), 3.33 (1H, s), 1.99 (4H, br s), 1.45 (3H, s), 1.24 (3H, d, *J* = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.4, 157.0, 146.2, 138.4, 129.9, 118.8, 118.6, 112.3, 88.4, 84.4, 73.9, 73.0, 66.6, 61.2, 46.0, 26.6, 25.6, 20.6, 17.8; HRMS-ESI (*m/z*): calcd. for $C_{22}H_{33}N_6O_6$ $[M+H]^+$ 477.24561, found 477.24459.

***N*-((1*R*,2*R*,3*S*,4*S*,5*S*)-4-((3-Acetylphenyl)amino)-5-azido-2,3-dihydroxy-1-((*S*)-1-hydroxyethyl)-3-(hydroxymethyl)-2-methylcyclopentyl)piperidine-1-carboxamide (10c).** Yield : 88% (21 mg from 26 mg); $[\alpha]_D^{20}$ + 26.8 (*c* 1.00, $CHCl_3$); IR (neat): ν_{max} 3381, 2937, 2856, 2103, 1681, 1627, 1603, 1531, 1487, 1442, 1325, 1270, 1114, 1060, 912, 732 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.55 (1H, d, *J* = 11.2 Hz), 7.37- 7.31 (2H, m), 7.26 (1H, s), 6.87 (1H, d, *J* = 7.2 Hz), 5.60 (1H, s), 5.35 (1H, d, *J* = 11.2 Hz), 4.62 (1H, s), 4.16 (1H, d, *J* = 11.6 Hz), 3.99 (1H, m), 3.91 (1H, d, *J* = 11.2 Hz), 3.67 (1H, d, *J* = 11.6 Hz), 3.63 (1H, s), 3.49- 3.36 (4H, m), 3.20 (1H, s), 2.58 (3H, s), 1.66- 1.60 (6H, m), 1.46 (3H, s), 1.22 (3H, d, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.3, 157.6, 146.2, 138.5, 129.9, 118.9, 118.5, 112.4, 88.4, 84.4, 74.3, 73.7, 73.2, 66.7, 61.2, 45.9, 26.7, 25.8, 24.4, 20.6, 17.8; HRMS-ESI (*m/z*): calcd for $C_{23}H_{35}N_6O_6$ $[M+H]^+$ 491.26126, found 491.26460.

***N*-((1*R*,2*R*,3*S*,4*S*,5*S*)-4-((3-Acetylphenyl)amino)-5-azido-2,3-dihydroxy-1-((*S*)-1-hydroxyethyl)-3-(hydroxymethyl)-2-methylcyclopentyl)morpholine-4-carboxamide (10d).** Yield : 83% (22 mg from 28 mg); $[\alpha]_D^{20}$ +35.6 (*c* 1.00, $CHCl_3$); IR (neat): ν_{max} 3378, 2977, 2921, 2859, 2104, 1675, 1627, 1603, 1537, 1434, 1395, 1359, 1333, 1304, 1260, 1118, 1077, 1003, 916, 786, 730, 686 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.38- 7.32 (2H, m), 7.26- 7.23 (2H, m), 6.87 (1H, d, *J* = 7.2 Hz), 5.61 (1H, s), 5.34 (1H, d, *J* = 11.6 Hz), 4.52 (1H, s), 4.17 (1H, d, *J* = 11.6 Hz), 4.01 (1H, m), 3.92 (1H, d, *J* = 11.6 Hz), 3.76- 3.73 (4H, m), 3.65 (1H, d, *J* = 11.6 Hz), 3.63 (1H, s), 3.51- 3.46 (2H, m), 3.43- 3.38 (2H, m), 3.23 (1H, s), 2.58 (3H, s), 2.12 (1H, s), 1.45 (3H, s), 1.22 (3H, d, *J* = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.3, 157.8, 146.1, 138.5, 130.0, 119.1, 118.6, 112.3, 88.4, 84.5, 74.3, 73.7, 73.1, 66.8, 66.5, 61.1, 44.6, 26.7, 20.5, 17.8; HRMS-ESI (*m/z*): calcd. for $C_{22}H_{33}N_6O_7$ $[M+H]^+$ 493.24052, found 493.24255.

General procedure for synthesis of 11a-d

To a stirred solution of **10a-d** (10 mg, 0.021 mmol) in EtOH:H_2O (3:1, 2 mL) were added ammonium chloride (33 mg, 0.62 mmol), zinc powder (20 mg, 0.31 mmol) at r.t. and stirred for 6 h. The reaction mixture was quenched with aqueous ammonia (2 mL) and extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography using [5-8]% methanol in chloroform to give compounds **11a-d**.

3-((1*R*,2*R*,3*S*,4*S*,5*S*)-4-((3-Acetylphenyl)amino)-5-amino-2,3-dihydroxy-1-((*S*)-1-hydroxyethyl)-3-(hydroxymethyl)-2-methylcyclopentyl)-1,1-diethylurea (11a). Pale yellow oil, yield : 88% (8.4 mg from 10 mg); $[\alpha]_D^{20}$ +41.2 (*c* 0.33, $CHCl_3$); IR (neat): ν_{max} 3381, 2976, 2931, 1679, 1603, 1515, 1359, 1298, 1081, 1056, 913, 784, 732 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.05 (1H, d, *J* = 10.0 Hz), 7.28- 7.21 (2H, m), 7.05 (1H, s), 6.84 (1H, m), 5.68 (1H, s), 5.50 (1H, d, *J* = 10.4 Hz), 4.13 (1H, d, *J* = 11.6 Hz), 3.92 (1H, m), 3.76 (1H, d, *J* = 11.6 Hz), 3.42- 3.29 (4H, m), 2.96 (1H, s), 2.57 (3H, s), 2.10- 1.82 (4H, m), 1.48 (3H, s), 1.37- 1.13 (6H, m), 1.05 (3H, d, *J* = 6.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.6, 158.2, 146.9, 138.3, 129.6, 118.9, 118.4, 110.9, 88.7, 84.7, 74.2, 71.5, 68.2, 62.6, 61.8, 42.2, 26.7, 21.5, 18.2, 13.8; HRMS-ESI (*m/z*): calcd for $C_{22}H_{37}N_4O_6$ $[M+H]^+$ 453.27076, found 453.26901.

***N*-((1*R*,2*R*,3*S*,4*S*,5S)-4-((3-acetylphenyl)amino)-5-amino-2,3-dihydroxy-1-((*S*)-1-hydroxyethyl)-3-(hydroxymethyl)-2-methylcyclopentyl)pyrrolidine-1-carboxamide (11b).** Pale yellow solid, yield : 86% (9.8 mg from 12 mg); $[\alpha]_D^{20}$ +29.5 (*c* 1.00, $CHCl_3$); IR (neat): ν_{max} 3381, 2977, 2918, 2875, 1679, 1603, 1519, 1486, 1398, 1357, 1337, 1235, 1136, 1072, 911, 781, 731, 689 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.89 (1H, d, *J* = 10.8 Hz), 7.28- 7.24 (2H, m), 7.19 (1H, s), 6.84 (1H, d, *J* = 3.2 Hz), 6.74 (1H, s), 5.49 (1H, s), 5.46 (1H, d, *J* = 10.8 Hz), 4.13 (1H, d, *J* = 11.6 Hz), 3.94 (1H, m), 3.77- 3.72 (2H, m), 3.43 (4H, br s), 2.96 (1H, s), 2.55 (3H, s), 1.97 (4H, br s), 1.49 (3H, s), 1.08 (3H, d, *J* = 6.4 Hz); ^{13}C NMR (100 MHz,

$CDCl_3$): δ 198.7, 157.8, 146.9, 138.2, 129.6, 119.0, 118.4, 110.8, 88.6, 84.8, 73.9, 71.7, 68.0, 62.6, 61.8, 46.0, 29.7, 26.7, 25.6, 21.5, 18.2; HRMS-ESI (*m/z*): calcd. for $C_{22}H_{35}N_4O_6$ $[M+H]^+$ 451.25511, found 451.25380.

***N*-((1*R*,2*R*,3*S*,4*S*,5*S*)-4-((3-Acetylphenyl)amino)-5-amino-2,3-dihydroxy-1-((*S*)-1-hydroxyethyl)-3-(hydroxymethyl)-2-methylcyclopentyl)piperidine-1-carboxamide (11c).** Pale yellow solid, yield : 88% (7.5 mg from 9 mg); $[\alpha]_D^{20}$ +24.2 (*c* 0.45, $CHCl_3$); IR (neat): ν_{max} 3379, 2935, 2850, 1678, 1602, 1515, 1442, 1273, 1060, 910, 731, 688 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.93 (1H, d, *J* = 10.4 Hz), 7.28- 7.20 (3H, m), 6.85 (1H, d, *J* = 6.8 Hz), 5.63 (1H, s), 5.47 (1H, d, *J* = 10.0 Hz), 4.11 (1H, d, *J* = 11.6 Hz), 3.94 (1H, m), 3.78- 3.73 (2H, m), 3.49- 3.39 (4H, m), 3.08 (1H, s), 2.58 (3H, s), 1.66- 1.60 (6H, m), 1.49 (3H, s), 1.06 (3H, d, *J* = 6.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.6, 158.6, 146.9, 138.3, 129.7, 118.9, 118.4, 111.0, 88.6, 84.7, 74.1, 71.3, 68.3, 62.7, 61.8, 45.9, 26.7, 25.8, 24.5, 21.5, 18.2; HRMS-ESI (*m/z*): calcd. for $C_{23}H_{37}N_4O_6$ $[M+H]^+$ 465.27076, found 465.27025.

***N*-((1*R*,2*R*,3*S*,4*S*,5*S*)-4-((3-Acetylphenyl)amino)-5-amino-2,3-dihydroxy-1-((*S*)-1-hydroxyethyl)-3-(hydroxymethyl)-2-methylcyclopentyl)morpholine-4-carboxamide (11d).** Pale yellow solid, yield : 84% (8.8 mg from 11 mg); $[\alpha]_D^{20}$ +29.3 (*c* 0.75, $CHCl_3$); IR (neat): ν_{max} 3381, 2917, 2850, 1678, 1603, 1515, 1440, 1359, 1335, 1303, 1269, 1118, 1072, 909, 732 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.65 (1H, d, *J* = 10.4 Hz), 7.35- 7.28 (2H, m), 7.20 (1H, s), 6.84 (1H, d, *J* = 3.2 Hz), 5.55 (1H, s), 5.50 (1H, d, *J* = 10.4 Hz), 4.13 (1H, d, *J* = 11.6 Hz), 3.94 (1H, m), 3.78 (5H, br s), 3.53- 3.40 (4H, m), 2.95 (1H, s), 2.57 (3H, s), 1.47 (3H, s), 1.05 (3H, d, *J* = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.7, 158.8, 146.8, 138.3, 129.7, 118.9, 118.5, 110.8, 88.6, 84.8, 74.0, 71.4, 68.4, 66.6, 62.7, 61.6, 44.7, 26.7, 21.3, 18.2; HRMS-ESI (*m/z*): calcd. for $C_{22}H_{35}N_4O_7$ $[M+H]^+$ 467.25003, found 467.24941.

General procedure for synthesis of 13a-d

To a stirred solution of **12** (130 mg, 0.217 mmol) in toluene (4 mL), the anilines (0.2 mL, 2.173 mmol) and $Yb(OTf)_3$ (67.5 mg, 0.108 mmol) were added at r.t. and heated at 80 °C and stirred for 9-26 h at the same temperature. The reaction mixture was cooled to r.t., then quenched with water and extracted with ethyl acetate. The combined organic layers were washed with 0.5 *N* HCl, saturated aqueous $NaHCO_3$ solution, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography using 10% ethyl acetate in hexanes to afford compounds **13a-d** as pale yellow viscous liquids. Further elution at 12% EtOAc in hexanes recovered the unreacted epoxide.

(4*S*,5*R*,6*R*,7*S*,8*S*,9*S*)-9-Azido-7-(((tert-butyldiphenylsilyl)oxy)methyl)-2-(4-methoxyphenyl)-4,6-dimethyl-8-(phenylamino)-3-oxa-1-azaspiro[4.4]non-1-ene-6,7-diol (13a). Yield : 74% (110 mg from 130 mg); $[\alpha]_D^{20}$ +6.56 (*c* 1.00, $CHCl_3$); IR (neat): ν_{max} 3409, 2938, 3864, 2102, 1642, 1606, 1516, 1466,

1430, 1366, 1349, 1312, 1259, 1173, 1153, 1108, 1059, 1033, 842, 824, 746, 703, 616 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.87 (2H, d, *J* = 9.0 Hz), 7.64 (1H, d, *J* = 1.4 Hz), 7.62 (1H, d , *J* = 1.6 Hz), 7.49- 7.37 (6H, m), 7.27- 7.13 (4H, m), 6.91 (2H, d, *J* = 9.0 Hz), 6.75 (1H, tt, *J* = 1, 7.3 Hz), 6.69 (2H, dd, *J* = 1, 7.6 Hz), 5.58 (1H, s), 4.95 (1H, q, *J* = 6.6 Hz), 4.85 (1H, s), 4.38- 4.30 (2H, m), 4.13 (1H, d, *J* = 11.1Hz), 3.97-3.89 (1H, m), 3.83 (3H, s), 3.80 (1H,d, *J* = 11.1Hz), 1.59 (3H, d, *J* = 6.6 Hz), 1.17 (3H, s), 1.08 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.0, 162.7, 147.0, 135.8, 135.5, 131.1, 131.0, 130.4, 130.2, 129.4, 127.8, 118.9, 117.7, 113.1, 84.5, 84.4, 80.1, 78.6, 71.0, 68.1, 66.4, 55.3, 26.9, 18.9, 17.3, 17.0; HRMS (ESIMS): calcd for $C_{39}H_{46}N_5O_5Si$ $[M+H]^+$ 692.3263, found 692.3268.

(4*S*,5*R*,6*R*,7*S*,8*S*,9*S*)-9-Azido-7-(((tert-butyldiphenylsilyl)oxy)methyl)-8-((3-fluorophenyl)amino)-2-(4-methoxyphenyl)-4,6-dimethyl-3-oxa-1-azaspiro[4.4]non-1-ene-6,7-diol (13b). Yield : 83% (98 mg from 110 mg); $[\alpha]_D^{20}$ +2.3 (*c* 1.00, $CHCl_3$); IR (neat): ν_{max} 3392, 2933, 2107, 1704, 1606, 1512, 1259, 1168, 1104, 1073, 822, 770, 738, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): *δ* 7.80 (2H, d, *J* = 8.9 Hz), 7.55 (2H, dd, *J* = 1.2, 7.9 Hz), 7.40 (2H, dd, *J* = 1.2, 7.9 Hz), 7.40-7.26 (4H, m), 7.21- 7.17 (2H, m), 7.03- 6.96 (1H, m), 6.83 (2H, d, *J* = 8.9 Hz), 6.39- 6.26 (4H, m), 5.48 (1H, s), 4.88 (1H, q, *J* = 6.6 Hz), 4.71 (1H, s), 4.73 (1H, d, *J* = 9.7 Hz), 4.19 (1H, dd, *J* = 6.8, 9.7 Hz), 4.00 (1H, d, *J* = 11.1 Hz), 3.85 (1H,d , *J* = 6.8 Hz), 3.76 (3H, s), 3.72 (1h, d, *J* = 11.1 Hz), 1.51 (3H, d, *J* = 6.6 Hz), 1.11 (3H, s), 1.01 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 165.3, 164.1, 162.9, 162.7, 148.9, 148.8, 135.8, 135.5, 131.1, 130.9, 130.5, 130.4, 130.4, 130.3, 130.1, 129.7, 127.9, 127.8, 127.7, 118.8, 113.7, 108.7, 104.3, 104.1, 100.0, 99.7, 84.5, 84.4, 84.3, 80.1, 78.6, 70.8, 68.2, 66.3, 55.3, 26.9, 18.9, 17.4, 17.0; HRMS (ESIMS): calcd for $C_{39}H_{45}FN_5O_5Si$ $[M+H]^+$ 710.31685, found 710.31712.

(4*S*,5*R*,6*R*,7*S*,8*S*,9*S*)-9-Azido-7-(((tert-butyldiphenylsilyl)oxy)methyl)-2-(4-methoxyphenyl)-8-((3-methoxyphenyl)amino)-4,6-dimethyl-3-oxa-1-azaspiro[4.4]non-1-ene-6,7-diol (13c). Yield : 86% (140 mg from 150 mg); $[\alpha]_D^{20}$ +5.14 (*c* 1.00, $CHCl_3$); IR (neat): ν_{max} 3418, 2934, 2099, 1641, 1610, 1514, 1496, 1463, 1455, 1427, 1364, 1345, 1305, 1258, 1213, 1170, 1113, 1055, 1037, 908, 840, 822, 794, 739, 702 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): *δ* 7.87 (2H, d, *J* = 8.9.0 Hz), 7.64 (2H, dd, *J* = 1.4, 8.0 Hz), 7.48 (2H, dd , *J* = 1.4, 8.0 Hz), 7.44- 7.30 (4H, m), 7.29- 7.21 (2H, m), 7.06 (1H, t, *J* = 8.0 Hz), 6.90 (2H, d, *J* = 8.9 Hz), 6.35- 6.24 (3H, m), 5.56 (1H, br s), 4.94 (1H, q, *J* = 6.6Hz), 4.81 (1H, s), 4.46- 4.36 (1H, m), 4.35-4.26 (1H, m), 4.13 (1H, d, *J* = 11.0 Hz), 3.91 (1H, d, *J* = 6. Hz), 3.82 (3H, s), 3.80 (1H, d, *J* = 11.0 Hz), 3.71 (3H, s), 1.58 (3H, d, *J* = 6.6 Hz), 1.16 (3H, s), 1.08 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 164.0, 162.7, 160.9, 148.4, 135.7, 135.5, 131.1, 130.4, 130.2, 130.1, 127.9, 127.8, 118.9, 113.7, 105.9, 103.7, 98.7, 84.5, 80.0, 78.6, 70.9, 68.1, 66.4, 55.3, 54.9, 26.9, 18.9, 17.3, 17.0; HRMS (ESIMS): calcd for $C_{40}H_{48}N_5O_6Si$ $[M+H]^+$ 722.3368, found 722.3369.

(4*S*,5*R*,6*R*,7*S*,8*S*,9*S*)-9-Azido-7-(((tert-butyldiphenylsilyl)oxy)methyl)-2-(4-methoxyphenyl)-4,6-dimethyl-8-((3-(trifluoromethyl)phenyl)amino)-3-oxa-1-azaspiro[4.4]non-1-ene-6,7-diol (13d). Yield : 52% (122 mg from 200 mg); 20 eq. of *m*-trifluoromethyl aniline was required; $[\alpha]_D^{20}$ +2.4 (*c* 1.00, $CHCl_3$); IR (neat): ν_{max} 3415, 2934, 2098, 1639, 1611, 1514, 1427, 1344, 1258, 1167, 1115, 1068, 743, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.90 (2H, d, *J* = 8.9 Hz), 7.62 (2H, d, *J* = 6.8 Hz), 7.47-7.34 (6H, m), 7.28-7.22 (4H, m), 6.98 (1H, d, *J* = 7.7 Hz), 6.94 (2H, d, *J* = 8.9 Hz), 6.85- 6.80 (2H, m), 5.61 (1H, s), 4.98 (1H, q, *J* = 6.6 Hz), 4.78 (1H, s), 4.60 (1H, d , *J* = 9.6 Hz), 4.33 (1H, dd, *J* = 6.8, 9.6 Hz), 4.07 (1H, d , *J* = 11.2 Hz), 3.94 (1H, d, *J* = 6.8 Hz), 3.85- 3.82 (4H, m), 1.61 (3H, d, *J* = 6.6 Hz), 1.21 (3H, s), 1.10 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.2, 162.8, 147.2, 135.7, 135.4, 131.0, 130.9, 130.5, 130.3, 130.1, 129.9, 128.0, 127.9, 118.9, 115.4, 114.2, 114.1, 113.8, 109.8, 109.6, 84.5, 84.4, 80.1, 78.6, 70.9, 68.1, 66.4, 55.4, 26.9, 19.0, 17.4, 17.0; HRMS (ESIMS): calcd for $C_{40}H_{45}F_3N_5O_5Si$ $[M+H]^+$ 760.31366, found 760.31417.

General procedure for synthesis of 14a-d

To a stirred solution of **13a-d** (56 mg, 0.081 mmol) in THF (1.4 mL) was added 2.0 *N* HCl (0.6 mL) at 0 ºC and the solution was allowed to warm up to room temperature. After being stirred for 18 h at r.t., the reaction mixture was cooled to 0 ºC, quenched with a saturated aqueous $NaHCO_3$ solution and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification by column chromatography using 10% EtOAc in hexanes gave the starting oxazoline (33-39%). Elution with [10-25]% EtOAc in hexanes afforded compounds**14a-d** as pale yellow viscous liquids.

(*S*)-1-((1*R*,2*R*,3*S*,4*S*,5*S*)-1-Amino-5-azido-3-(((tert-butyldiphenylsilyl)oxy)methyl)-2,3-dihydroxy-2-methyl-4-(phenylamino)cyclopentyl)ethyl 4-methoxybenzoate (14a). Yield : 53% (30 mg from 56 mg); $[\alpha]_D^{20}$ +96.8 (*c* 1.00, $CHCl_3$); IR (neat): ν_{max} 3391, 2934, 2170, 1704, 1604, 1511, 1463, 1382, 1316, 1259, 1168, 1104, 1072, 1029, 846, 821, 747, 701, 504 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.02 (2H, d, *J* = 8.9 Hz), 7.59 (2H, d, *J* = 6.8 Hz), 7.48 (2H, d, *J* = 6.8 Hz), 7.44- 7.26 (4H, m), 7.26- 7.17 (4H, m), 6.95 (2H, d, *J* = 8.9 Hz), 6.76 (1H, t, *J* = 7.3 Hz), 6.66 (2H, d, *J* = 7.8 Hz), 5.76 (1H, q, *J* = 6.5 Hz), 4.86 (1H, s), 4.47 (1H, d, *J* = 11.2 Hz), 4.23 (1H, dd, *J* = 4.6, 11.1 Hz), 4.04 (1H, d, *J* = 11.0 Hz), 3.92 (1H, d, *J* = 4.6 Hz), 3.88 (3H, s), 3.73 (1H, d, *J* = 11.0 Hz), 1.34 (3H, d, *J* = 6.5 Hz), 1.26 (3H, s), 1.04 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.0, 163.6, 146.5, 135.7, 135.6, 131.6, 131.3, 131.3, 130.0, 129.8, 129.5, 127.7, 122.3, 117.8, 113.8, 113.3, 83.7, 80.8, 74.0, 70.8, 70.5, 66.8, 65.4, 55.4, 26.9, 18.9, 18.1, 15.1; HRMS (ESIMS): calcd for $C_{39}H_{48}N_5O_6Si$ $[M+H]^+$ 710.3368, found 710.3371.

(*S*)-1-((1*R*,2*R*,3*S*,4*S*,5*S*)-1-Amino-5-azido-3-(((tert-butyldiphenylsilyl)oxy)methyl)-4-((3-fluorophenyl)amino)-2,3-dihydroxy-2-methylcyclopentyl)ethyl 4-methoxybenzoate (14b). Yield : 53% (30 mg from 55 mg); $[\alpha]_D^{20}$ +105.6 (*c* 1.00, $CHCl_3$); IR (neat): ν_{max} 3418, 2935, 2100, 1640, 1621, 1614,

1515, 1495,1427, 1365, 1346, 1258, 1171, 1152, 1114, 1057, 1033, 840, 823, 740, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.92 (2H, d, J =8.9 Hz), 7.49 (2H, d, J = 6.7 Hz), 7.41 (2H, d, J = 6.7 Hz), 7.30 (2H, q, J = 7.3 Hz), 7.27- 7.15 (4H, m), 7.02 (1H, m), 6.89 (2H, d, J = 8.9 Hz), 6.34 (1H, dt, J = 1.8, 8.4 Hz), 6.28 (1H, dd, J = 1.8, 8.1 Hz), 6.22 (2H, td, J = 2.2, 11.5 Hz), 5.67 (1H, q, J = 6.5 Hz), 4.73 (1H, s), 4.51 (1H, d, J = 11.0 Hz), 4.07 (1H, dd, J = 4.6, 11.0 Hz), 3.88- 3.80 (5H, m), 3.68 (1H, d, J = 11.0 Hz), 1.28 (3H, d, J = 6.5 Hz), 1.17 (3H, s), 0.96 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.1, 163.7, 148.3, 135.7, 135.5, 131.6, 131.3, 131.3, 131.1, 130.6, 130.5, 130.1, 129.9, 127.7, 127.8, 122.3, 113.8, 109.0, 104.4, 100.1, 99.9, 83.7, 80.8, 74.1, 70.8, 70.6, 66.8, 65.4, 55.5, 26.9, 18.9, 18.1, 15.2; HRMS (ESIMS): calcd for $C_{39}H_{47}FN_5O_6Si$ $[M+H]^+$ 728.3274, found 728.3286.

(*S*)-1-((1*R*,2*R*,3*S*,4*S*,5*S*)-1-Amino-5-azido-3-(((tert-butyldiphenylsilyl)oxy)methyl)-2,3-dihydroxy-4-((3-methoxyphenyl)amino)-2-methylcyclopentyl)ethyl 4-methoxybenzoate (14c). Yield : 45% (65 mg from 140 mg); $[\alpha]_D^{20}$ +99.2 (*c* 1.00, $CHCl_3$); IR (neat): ν_{max} 3395, 3072, 2934, 2858, 2107, 1704, 1605, 1512, 1496, 1463, 1428, 1259, 1212, 1168, 1104, 1073, 1030, 822, 770, 737, 702 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.00 (2H, d, J = 9.0 Hz), 7.58 (2H, dd, J = 1.4, 8.0 Hz), 7.50 (2H, d, J = 1.4, 8.0 Hz), 7.43-7.20 (7H, m), 7.08 (1H, d, J = 8.0 Hz), 6.96 (2H, d, J = 9.0 Hz), 6.33 (1H, dd, J = 2.2, 8.1 Hz), 6.24 (1H, dd, J = 2.0, 8.0 Hz), 6.20 (1H, t, J = 2.2 Hz), 5.74 (1H, q, J = 6.5 Hz), 4.82 (1H, s), 4.52 (1H, d, J = 11.2 Hz), 4.18 (1H, dd, J = 2.7, 11.2 Hz), 3.98 (1H, d, J = 10.9 Hz), 3.90 (1H, d, J = 4.5 Hz), 3.88 (3H, s), 3.74 (1H, d, J = 10.9 Hz), 3.72 (3H, s), 1.36 (3H, d, J = 6.5 Hz), 1.24 (3H, s), 1.04 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.1, 163.6, 160.9, 147.9, 135.8, 135.6, 131.6, 131.4, 131.3, 130.2, 130.1, 129.8, 127.8, 127.7, 122.4, 113.8, 106.1, 103.8, 99.0, 83.8, 80.8, 74.1, 70.9, 70.5, 66.9, 65.4, 55.0, 26.9, 18.9, 18.1, 15.1; HRMS (ESIMS): calcd for $C_{40}H_{50}N_5O_7Si$ $[M+H]^+$ 740.3474, found 740.34816.

(*S*)-1-((1*R*,2*R*,3*S*,4*S*,5*S*)-1-Amino-5-azido-3-(((tert-butyldiphenylsilyl)oxy)methyl)-2,3-dihydroxy-2-methyl-4-((3-(trifluoromethyl)phenyl)amino)cyclopentyl)ethyl 4-methoxybenzoate (14d). Yield : 53% (124 mg from 230 mg); $[\alpha]_D^{20}$ +102.4 (*c* 1.00, $CHCl_3$); IR (neat): ν_{max} 3392, 2934, 2107, 1698, 1606, 1512, 1423, 1344, 1259, 1167, 1114, 1069, 1030, 847, 821, 770, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.01 (2H, d, J =8.7 Hz), 7.55 (2H, d, J = 7.4 Hz), 7.47 (2H, d, J = 7.4 Hz), 7.39 (2H, q, J = 7.7 Hz), 7.31- 7.21 (6H, m), 6.97 (3H, d, J = 8.7 Hz), 6.81 (1H,s), 6.75 (1H, d, J = 8.2 Hz), 5.80- 5.73 (1H, m), 4.79 (1H, s), 4.73 (1H, d, J = 10.9 Hz), 4.20 (1H, dd, J = 4.5, 10.9 Hz), 3.93 (1H, d, J = 4.5 Hz), 3.92- 3.88 (4H, m), 3.79 (1H, d, J = 11.0 Hz), 1.35 (3H, d, J = 6.5 Hz), 1.27 (3H, s), 1.04 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.1, 163.7, 146.7, 135.7, 135.6, 131.6, 131.3, 130.1, 129.9, 129.9, 127.8, 127.7, 122.3, 115.7, 114.1, 114.1, 113.8, 109.5, 109.5, 83.7, 80.8, 74.1, 70.8, 70.3, 66.9, 65.3, 55.4, 26.8, 18.9, 18.0, 15.1; HRMS (ESIMS): calcd for $C_{40}H_{47}F_3N_5O_6Si$ $[M+H]^+$ 778.32422, found 778.32531.

General procedure for synthesis 15 a-d

To a stirred solution of **14a-d** (94 mg, 0.134 mmol) in dry DMF (3 mL) was added TAS-F (110 mg, 0.401 mmol) at 0 °C under argon and allowed to room temperature. After being stirred for 1 h at r.t., the reaction mixture was cooled to 0 °C, quenched with a pH=7 phosphate buffer solution and extracted with ethyl acetate. The combined organic layers were washed with water, brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure.

To a stirred solution of crude amino triol in dry DCM (2 mL), CSA (37.3 mg, 0.16 mmol) and 2,2-dimethoxypropane (0.4 mL) were added sequentially at 0 °C under argon and warm up to room temperature. After being stirred for 2 h at r.t., the reaction mixture was cooled to 0 °C, quenched with saturated aqueous $NaHCO_3$ solution and extracted with DCM. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure.

To a stirred solution of crude acetonide in dry THF (2 mL), activated charcoal (10 mg), Et_3N (0.037 mL, 0.266 mmol) and diphosgene (0.024 mL, 0.199 mmol) were added slowly at –46 °C under argon and the reaction mixture was stirred for 60 min. The reaction was quenched with saturated aqueous $NaHCO_3$ solution and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Flash column chromatography using [22-26]% ethyl acetate in hexanes gave compounds **15a-d** as colorless liquids.

(*S*)-1-((1*R*,2*R*,3*S*,4*S*,5*S*)-1-Amino-5-azido-2,3-dihydroxy-3-(hydroxymethyl)-2-methyl-4-(phenylamino)cyclopentyl)ethyl 4-methoxybenzoate (15a). Yield : 86% (63 mg from 94 mg); $[\alpha]_D^{20}$ +14.27 (*c* 1.00, $CHCl_3$); IR (neat): ν_{max} 3390, 2989, 2934, 2271, 2105, 1688, 1604, 1511, 1455, 1382, 1317, 1260, 1169, 1065, 1029, 848, 771, 750, 694 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.02 (2H, d, *J* = 8.9 Hz), 7.24 (2H, d, *J* = 7.4 Hz), 6.97 (2H, d, *J* = 8.9 Hz), 6.78 (1H, t, *J* = 7.4 Hz), 6.69 (2H, d, *J* = 7.7 Hz), 5.48 (1H, q, *J* = 6.4 Hz), 4.52 (1H, br s), 4.35 (1H, br s), 4.31 (1H, d, *J* = 10.1 Hz), 4.21 (1H, d, *J* = 10.1 Hz), 4.12 (1H, br s), 3.89 (3H, s), 3.46 (1H, d, *J* = 2.6 Hz), 1.45- 1.40 (9H, m), 1.24 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.9, 164.0, 132.3, 129.7, 124.0, 121.1, 118.5, 114.0, 113.5, 111.3, 90.8, 85.6, 75.5, 73.8, 72.4, 67.0, 65.9, 55.5, 26.0, 25.1, 18.0, 16.1; HRMS (ESIMS): calcd for $C_{27}H_{32}N_5O_7$ $[M+H]^+$ 538.2296, found 538.2308.

(*S*)-1-((1*R*,2*R*,3*S*,4*S*,5*S*)-1-Amino-5-azido-4-((3-fluorophenyl)amino)-2,3-dihydroxy-3-(hydroxymethyl)-2-methylcyclopentyl)ethyl 4-methoxybenzoate (15b). Yield : 81% (45 mg from 70 mg); $[\alpha]_D^{20}$ +11.79 (*c* 1.00, $CHCl_3$); IR (neat): ν_{max} 3398, 2988, 2939, 2272, 2104, 1687, 1606, 1512, 1496, 1382, 1261, 1169, 1070, 1029, 851, 771 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.05 (2H, d, *J* = 8.9 Hz), 7.17 (1H, ABq, *J* = 8.1 Hz), 6.97 (2H, d, *J* = 8.9 Hz), 6.50- 6.36 (3H, m), 5.48 (1H, q, *J* = 6.3 Hz), 4.67 (1H, d, *J* = 11.5 Hz), 4.42 (1H, s), 4.27 (1H, d, *J* = 10.1 Hz), 4.18 (1H, d, *J* = 10.1 Hz), 4.06 (1H, dd, *J* = 2.6, 11.5 Hz), 3.89 (3H, s), 3.43 (1H, d, *J* = 2.6 Hz), 1.44- 1.41 (9H, m), 1.24 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.8, 165.3, 164.4, 162.9, 147.9, 147.8, 132.3, 130.9, 130.8, 124.0, 121.0, 114.0, 111.5, 109.0, 109.0,

105.1, 104.9, 100.5, 100.2, 90.6, 85.5, 75.5, 73.7, 72.3, 67.0, 65.8, 55.5, 26.0, 25.2, 17.9, 16.1; HRMS (ESIMS): calcd for $C_{27}H_{31}FN_5O_7$ $[M+H]^+$ 556.2202, found 556.2220.

(*S*)-1-((1*R*,2*R*,3*S*,4*S*,5*S*)-1-Amino-5-azido-2,3-dihydroxy-3-(hydroxymethyl)-4-((3-methoxyphenyl)amino)-2-methylcyclopentyl)ethyl 4-methoxybenzoate (15c). Yield : 47% (39 mg from 110 mg); $[\alpha]_D^{20}$ +11.2 (*c* 1.00, $CHCl_3$); IR (neat): ν_{max} 3389, 2990, 2938, 2271, 2104, 1688, 1606, 1512, 1496, 1383, 1318, 1261, 1212, 1169, 1103, 1064, 1030, 909, 854, 733, 689 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.05 (2H, d, *J* = 8.9 Hz), 7.14 (1H, t, *J* = 8.1 Hz), 6.97 (2H, d, *J* = 8.9 Hz), 6.34 (1H, dd, *J* = 2.2, 7.7 Hz), 6.30 (1H, dd, *J* = 1.7, 8.0 Hz), 6.24 (1H, t, *J* = 2.2 Hz), 5.48 (1H, q, *J* = 6.3 Hz), 4.53 (1H, d, *J* = 11.6 Hz), 4.38 (1H, s), 4.28 (1H, d, *J* = 10.1 Hz), 4.20 (1H, d, *J* = 10.1 Hz), 4.10 (1H, dd, *J* = 2.6, 11.6 Hz), 3.88 (3H, s), 3.79 (3H, s), 3.47 (1H, d, *J* = 2.6 Hz), 1.45 (3H, s), 1.43 (3H, d, *J* = 6.3 Hz), 1.42 (3H, s), 1.25 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.8, 164.3, 161.0, 147.5, 132.3, 130.4, 124.0, 121.1, 114.0, 111.3, 106.2, 103.9, 99.4, 90.7, 85.5, 75.5, 73.7, 72.4, 66.9, 65.9, 55.5, 55.1, 26.0, 25.1, 18.0, 16.1; HRMS (ESIMS): calcd for $C_{28}H_{34}N_5O_8$ $[M+H]^+$ 568.24019, found 568.24056.

(*S*)-1-((1*R*,2*R*,3*S*,4*S*,5*S*)-1-Amino-5-azido-2,3-dihydroxy-3-(hydroxymethyl)-2-methyl-4-((3-(trifluoromethyl)phenyl)amino)cyclopentyl)ethyl 4-methoxybenzoate (15d). Yield : 82% (54 mg from 80 mg); $[\alpha]_D^{20}$ +19.0 (*c* 1.00, $CHCl_3$); IR (neat*):* ν_{max} 3382, 2969, 2104, 1687, 1605, 1513, 1342, 1317, 1261, 1168, 1124, 1069, 852, 771, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.05 (2H, d, *J* = 8.9 Hz), 7.33 (1H, t, *J* = 7.8 Hz), 7.02 (1H, d, *J* = 7.8 Hz), 6.97 (2H, d, *J* = 8.9 Hz), 6.78 (1H, t, *J* = 7.4 Hz), 6.89 (1H, s), 6.85 (1H, d, *J* = 8.1 Hz), 5.49 (1H, q, *J* = 6.3Hz), 4.75 (1H, d, *J* = 11.5 Hz), 4.47 (1H, s), 4.35 (1H, br s), 4.24 (2H, ABq, *J* = 10.1 Hz), 4.15- 4.09 (1H, m), 3.88 (3H, s), 3.47 (1H, d, *J* = 2.7 Hz), 2.04 (1H, s), 1.45-1.43 (9H, m), 1.26 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.9, 164.4, 146.3, 132.3, 130.1, 125.4, 124.1, 122.7, 121.0, 115.8, 114.9,114.0, 111.5, 110.0, 110.0, 90.6, 85.6, 75.4, 73.8, 72.3, 66.9, 66.9, 65.8, 55.5, 25.9, 25.2, 17.9, 16.1; HRMS (ESIMS): calcd for $C_{28}H_{31}F_3N_5O_7$ $[M+H]^+$ 606.21701, found 606.21775.

4.1.9. General procedure for synthesis of 16a-d

To **15a-d** (82 mg, 0.152 mmol) was added neat 0.5 mL dimethylamine (upon condensing the gas at –46 °C) and the reaction mixture was left warming to room temperature. It was directly subjected to flash column chromatography using [32-40]% ethyl acetate in hexanes to afford compounds **16a-d** as colorless liquids.

(*S*)-1-((5*S*,6*R*,7*R*,8*S*,9*S*)-8-Azido-7-(3,3-dimethylureido)-6-hydroxy-2,2,6-trimethyl-9-(phenylamino)-1,3-dioxaspiro[4.4]nonan-7-yl)ethyl 4-methoxybenzoate (16a). Yield : 88% (78 mg from 82 mg); $[\alpha]_D^{20}$ +96.8 (*c* 1.00, $CHCl_3$); IR (neat): ν_{max} 3401, 2987, 2937, 2109, 1711, 1652, 1605, 1512, 1372, 1317, 1258, 1168, 1101, 1057, 1030, 848, 732, 694 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.98 (2H, d, *J* = 9.0 Hz), 7.18 (2H, t, *J* = 7.6 Hz), 6.94 (2H, d, *J* = 9.0 Hz), 6.79- 6.69 (3H, m), 6.44 (1H, q, *J* = 6.5 Hz), 5.70 (1H, s), 4.39

(1H, d, J = 9.8 Hz), 4.15 (1H, d, J = 9.8 Hz), 4.15- 4.09 (1H, m), 3.99- 3.89 (2H, m), 3.86 (3H, s), 2.90 (6H, s), 1.54- 1.52 (6H, m), 1.39 (3H, s), 1.30 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.5, 163.3, 157.9, 147.2, 131.6, 129.4, 122.2, 118.4, 113.8, 113.5, 109.8, 90.1, 82.8, 72.0, 70.6, 68.0, 65.9, 65.1, 55.4, 36.5, 29.6, 25.6, 22.4, 17.0; HRMS (ESIMS): calcd for $C_{29}H_{39}N_6O_7$ $[M+H]^+$ 583.28747, found 583.28885.

(*S*)-1-((5*S*,6*R*,7*R*,8*S*,9*S*)-8-Azido-7-(3,3-dimethylureido)-9-((3-fluorophenyl)amino)-6-hydroxy-2,2,6-trimethyl-1,3-dioxaspiro[4.4]nonan-7-yl)ethyl 4-methoxybenzoate (16b). Yield : 93% (12 mg from 12 mg); $[\alpha]_D^{20}$ +78.0 (c 1.00, $CHCl_3$); IR (neat): ν_{max} 3405, 2932, 2109, 1709, 1650, 1607, 1513, 1495, 1372, 1317, 1258, 1168, 1102, 1058, 1031, 848, 768, 733 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 (2H, d, J = 8.9 Hz), 7.14- 7.06 (1H, m), 6.94 (2H, d, J = 8.9 Hz), 6.53- 6.38 (4H, m), 5.67 (1H,s), 4.39 (1H, d, J = 9.8 Hz), 4.29 (1H, d, J = 8.4 Hz), 4.10 (2H, d, J = 9.8 Hz), 3.93- 3.86 (5H, m), 2.89 (6H, s), 1.54 (3H, m), 1.52 (3H, d, J = 6.6 Hz), 1.39 (3H, s), 1.31 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.7, 164.5, 163.6, 162.4, 157.9, 149.1, 149.0, 131.6, 130.6, 130.4, 122.1, 113.8, 109.8, 109.3, 105.0, 104.8, 100.4, 100.0, 89.8, 82.6, 72.0, 70.1, 67.8, 65.8, 65.1, 55.4, 36.5, 25.6, 22.4, 17.0; HRMS (ESIMS): calcd for $C_{29}H_{38}FN_6O_7$ $[M+H]^+$ 601.2781, found 601.2804.

(*S*)-1-((5*S*,6*R*,7*R*,8*S*,9*S*)-8-Azido-7-(3,3-dimethylureido)-6-hydroxy-9-((3-methoxyphenyl)amino)-2,2,6-trimethyl-1,3-dioxaspiro[4.4]nonan-7-yl)ethyl 4-methoxybenzoate (16c). Yield : 86% (36 mg from 39 mg); $[\alpha]_D^{20}$ +90.9 (c 1.00, $CHCl_3$); IR (neat): ν_{max} 3397, 2988, 2937, 2109, 1710, 1658, 1606, 1512, 1496, 1463, 1372, 1258, 1213, 1167, 1102, 1054, 1031, 849, 732 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.97 (2H, d, J = 9.0 Hz), 7.08 (1H, t, J = 8.7 Hz), 6.94 (2H, d, J = 9.0 Hz), 6.44 (1H, q, J = 6.5 Hz), 6.38- 6.27 (3H, m), 5.70 (1H, s), 4.38 (1H, d, J = 9.8 Hz), 4.24- 4.09 (3H, m), 3.95- 3.89 (2H, m), 3.86 (3H, s), 3.75 (3H, s), 2.89 (6H, s), 1.53 (3H, s), 1.53 (3H, d, J = 6.5 Hz), 1.39 (3H, s), 1.33 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.6, 163.5, 160.8, 157.9, 148.6, 131.6, 130.1, 122.2, 113.8, 109.8, 106.5, 103.4, 99.6, 90.0, 82.8, 72.0, 70.6, 68.0, 65.9, 65.1, 55.4, 55.0, 36.5, 26.0, 25.7, 22.3, 17.0; HRMS (ESIMS): calcd for $C_{30}H_{41}N_6O_8$ $[M+H]^+$ 613.29804, found 613.29907.

(*S*)-1-((5*S*,6*R*,7*R*,8*S*,9*S*)-8-Azido-7-(3,3-dimethylureido)-6-hydroxy-2,2,6-trimethyl-9-((3-(trifluoromethyl)phenyl)amino)-1,3-dioxaspiro[4.4]nonan-7-yl)ethyl 4-methoxybenzoate (16d). Yield : 93% (54 mg from 54 mg); $[\alpha]_D^{20}$ +101.07 (c 1.00, $CHCl_3$); IR (neat): ν_{max} 3403, 2938, 2109, 1708, 1651, 1606, 1512, 1452, 1343, 1258, 1167, 1122, 1068, 1031, 849, 766, 697 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 (2H, d, J = 8.9 Hz), 7.31- 7.24 (2H, m), 7.00- 6.85 (5H, m), 6.47 (1H, q, J = 6.5 Hz), 5.70 (1H, s), 4.48- 4.44 (1H, m), 4.39 (1H, d, J = 9.9 Hz), 4.23 (1H, s), 4.16 (1H, d, J = 9.9 Hz), 3.97- 3.93 (2H, m), 3.85 (3H, s), 2.89 (6H, s), 1.56- 1.54 (6H, m), 1.39 (3H, s), 1.30 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.5, 163.6, 157.9, 147.4, 131.5, 128.2, 125.5, 122.8, 12212, 116.3, 114.7, 114.7, 113.8, 109.9, 109.7, 109.6,

90.0, 82.7, 71.7, 7036, 68.0, 65.7, 65.1, 55.4, 36.5, 36.5, 25.9, 25.6, 22.2, 17.1; HRMS (ESIMS): calcd for $C_{30}H_{38}F_3N_6O_7$ $[M+H]^+$ 651.27486, found 651.27541.

General procedure for synthesis of 17 a-d

To a stirred solution of **16a-d** (74 mg, 0.127 mmol) in dry DCM (3.5 mL), DIBAL-H (0.34 mL, 1.5 *M* in toluene, 0.51 mmol) was added slowly at –78 ^oC under argon and stirred for 1.5 h. The reaction mixture was then quenched with slow addition of methanol and warmed to room temperature. A saturated aqueous potassium sodium tartrate solution was added to the reaction mixture and stirred for 1 h, extracted with ethyl acetate, the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Flash column chromatography using [24-28]% ethyl acetate in hexanes gave compounds **17 a-d** as colorless liquids.

3-((5*S*,6*R*,7*R*,8*S*,9*S*)-8-Azido-6-hydroxy-7-((*S*)-1-hydroxyethyl)-2,2,6-trimethyl-9-(phenylamino)-1,3-dioxaspiro[4.4]nonan-7-yl)-1,1-dimethylurea (17a). Yield : 91% (52 mg from 74 mg); $[\alpha]_D^{20}$ +40.9 (*c* 1.00, $CHCl_3$); IR (neat): ν_{max} 3419, 2988, 2935, 2106, 1644, 1602, 1538, 1505, 1372, 1311, 1260, 1139, 1117, 1061, 1047, 860, 750, 693, 532 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.44 (1H, d, *J* = 11.4 Hz), 7.24 (1H, t, *J* = 8.6 Hz), 6.77 (1H, t, *J* = 7.3 Hz), 6.61 (2H, d, *J* = 8.6 Hz), 5.41 (1H, s), 5.18 (1H, d, *J* = 11.2 Hz), 4.60 (1H, s), 4.24 (2H, s), 4.00- 3.84 (2H, m), 3.65 (1H, s), 3.00 (6H, s), 1.44 (3H, s), 1.43 (3H, s), 1.39 (3H, s), 1.17 (3H, d, *J* = 6.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.3, 145.8, 129.7, 118.2, 113.1, 110.5, 97.3, 83.3, 74.0, 73.1, 72.7, 66.7, 65.4, 36.7, 26.3, 25.6, 20.7, 17.7; HRMS (ESIMS): calcd for $C_{21}H_{33}N_6O_5$ $[M+H]^+$ 449.25069, found 449.25239.

3-((5*S*,6*R*,7*R*,8*S*,9*S*)-8-Azido-9-((3-fluorophenyl)amino)-6-hydroxy-7-((*S*)-1-hydroxyethyl)-2,2,6-trimethyl-1,3-dioxaspiro[4.4]nonan-7-yl)-1,1-dimethylurea (17b). Yield : 98% (43 mg from 56 mg); $[\alpha]_D^{20}$ +41.8 (*c* 1.00, $CHCl_3$); IR (neat): ν_{max} 3380, 2995, 2933, 2108, 1737, 1622, 1593, 1536, 1515, 1498, 1375, 1339, 1260, 1214, 1181, 1156, 1062, 1049, 967, 941, 857, 757, 685 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.45 (1H, d, *J* = 11.4 Hz), 7.24- 7.21 (1H, m), 6.54 (1H, ddt, *J* = 0.8, 2.3, 8.5 Hz), 6.37 (1H, ddd, *J* = 0.8, 2.3, 8.1 Hz), 6.30 (1H, td, *J* = 2.3, 11.4 Hz), 5.39 (1H, s), 5.31 (1H, d, *J* = 11.2 Hz), 4.62 (1H, s), 4.21 (2H, ABq, J = 9.9 Hz), 3.98- 3.85 (1H, m), 3.80 (1H, d, *J* = 11.2 Hz), 3.62 (1H, s), 2.99 (6H, s), 1.43 (6H, s), 1.38 (3H, s), 1.21 (3H, d, *J* = 6.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.4, 163.0, 158.2, 147.8, 147.7, 130.9, 130.8, 110.7, 108.9, 108.9, 104.8, 104.6, 100.0, 99.8, 91.2, 88.3, 74.2, 73.0, 72.8, 66.7, 65.3, 36.7, 26.3, 25.6, 20.6, 17.7; HRMS (ESIMS): calcd for $C_{21}H_{31}FN_6NaO_5$ $[M+Na]^+$ 489.2232, found 489.2254.

3-((5*S*,6*R*,7*R*,8*S*,9*S*)-8-Azido-6-hydroxy-7-((*S*)-1-hydroxyethyl)-9-((3-methoxyphenyl)amino)-2,2,6-trimethyl-1,3-dioxaspiro[4.4]nonan-7-yl)-1,1-dimethylurea (17c). Yield : 75% (36 mg from 62 mg);

$[\alpha]_D^{20}$ +47.5 (*c* 1.00, $CHCl_3$); IR (neat): ν_{max} 3418, 2988, 2936, 2106, 1643, 1614, 1538, 1495, 1373, 1308, 1259, 1212, 1164, 1139, 1061, 1046, 856, 761, 733, 689 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.47 (1H, d, *J* = 11.3 Hz), 7.13 (1H, t, *J* = 8.1 Hz), 6.34 (1H, dd, *J* = 2.2, 8.1 Hz), 6.22 (1H, dd, *J* = 1.7, 8.1 Hz), 6.16 (1H, t, *J* = 2.2 Hz), 5.41 (1H, s), 5.22 (1H, d, *J* = 11.3 Hz), 4.63 (1H, s), 4.23 (2H, s), 3.93 (1H, sept, *J* = 6.5 Hz), 3.84 (1H, d, *J* = 11.3 Hz), 3.78 (3H, s), 3.65 (1H, s), 2.99 (6H, s), 1.43 (3H, s), 1.42 (3H, s), 1.38 (3H, s), 1.18 (3H, d, *J* = 6.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.1, 158.3, 147.2, 130.5, 110.5, 106.0, 103.6, 99.0, 91.3, 83.3, 74.0, 73.1, 72.7, 66.6, 65.3, 55.1, 36.7, 26.3, 25.5, 20.7, 17.7; HRMS (ESIMS): calcd for $C_{22}H_{35}N_6O6$ $[M+H]^+$ 479.26126, found 479.26244.

3-((5*S*,6*R*,7*R*,8*S*,9*S*)-8-Azido-6-hydroxy-7-((*S*)-1-hydroxyethyl)-2,2,6-trimethyl-9-((3-(trifluoromethyl)phenyl)amino)-1,3-dioxaspiro[4.4]nonan-7-yl)-1,1-dimethylurea (17d). Yield : 91% (110 mg from 130 mg); $[\alpha]_D^{20}$ +44.0 (*c* 1.00, $CHCl_3$); IR (neat): ν_{max} 3377, 2988, 2936, 2105, 1641, 1535, 1148, 1373, 1343, 1281, 1163, 1122, 1062, 855, 785, 693 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.46 (1H, d, *J* = 11.3 Hz), 7.31 (1H, t, *J* = 7.9 Hz), 7.00 (1H, d, *J* = 7.6 Hz), 6.82 (1H, s), 6.77 (1H, d, *J* = 8.2 Hz), 5.42 (2H, d, *J* = 11.3 Hz), 4.67 (1H, s), 4.22 (2H, ABq, *J* = 9.9 Hz), 3.96- 3.87 (1H, s), 3.85 (1H, d, *J* = 11.3 Hz), 3.6 (1H, s), 2.99 (6H, s), 1.43 (3H, s), 1.43 (6H, s), 1.39 (3H, s), 1.21 (3H, d, *J* = 6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.2, 146.1, 130.1, 125.4, 122.7, 116.0, 114.6, 114.5, 110.7, 109.3, 109.2, 91.2, 88.2, 74.9, 72.8, 66.6, 65.3, 41.9, 36.6, 26.2, 25.6, 20.5, 17.7; HRMS (ESIMS): calcd for $C_{22}H_{32}F_3N_6O_5$ $[M+H]^+$ 517.23808, found 517.23916.

General procedure for synthesis of 18 a-d

To the stirred solution of **17a-d** (13 mg, 0.029 mmol) in acetonitrile (0.1 mL) and H_2O (0.1 mL); TFA (0.5 mL) was added at 0 °C and the solution was stirred at 33 °C for variable times (90 min for **17a**, 75 min for **17b** and 60 min for **17c**, r.t. for 90 min in the case of **17d**), cooled to 0 °C , quenched very slowly with saturated aqueous $NaHCO_3$ solution and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Flash column chromatography using [70-80]% ethyl acetate in hexanes gave compounds **18a-d** as colorless liquids.

3-((1*R*,2*R*,3*S*,4*S*,5*S*)-5-Azido-2,3-dihydroxy-1-((*S*)-1-hydroxyethyl)-3-(hydroxymethyl)-2-methyl-4-(phenylamino)cyclopentyl)-1,1-dimethylurea (18a). Yield : 76% (9 mg from 13 mg); $[\alpha]_D^{20}$ +13.5 (*c* 1.00, $CHCl_3$); IR (neat): ν_{max} 3412, 2928, 2104, 1634, 1602, 1537, 1506, 1374, 1307, 1249, 1110, 1036, 912, 752, 734, 694 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.44 (1H, d, *J* = 11.4 Hz), 7.30- 7.21 (2H, m), 6.80 (1H, t, *J* = 7.3 Hz), 6.67 (2H, d, *J* = 7.8 Hz), 5.51 (1H, s), 5.13 (1H, d, *J* = 10.7 Hz), 4.53 (1H, s), 4.17 (2H, d, *J* = 11.8 Hz), 4.03- 3.91 (1H, m), 3.81 (1H, d, *J* = 8.9 Hz), 3.64 (1H, s), 3.62 (1H, d, *J* = 11.8 Hz), 3.00 (6H, s), 2.15 (1H, br s), 1.74 (1H, br s), 1.41 (3H, s), 1.21 (3H, d, *J* = 6.5 Hz); ^{13}C NMR (100 MHz,

$CDCl_3$): δ 158.5, 145.7, 129.7, 118.7, 113.9, 88.2, 84.6, 73.9, 73.8, 72.9, 66.8, 61.4, 36.7, 20.4, 17.7; HRMS (ESIMS): calcd for $C_{18}H_{29}N_6O5$ $[M+H]^+$ 409.21939, found 409.22051.

3-((1*R*,2*R*,3*S*,4*S*,5*S*)-5-Azido-4-((3-fluorophenyl)amino)-2,3-dihydroxy-1-((*S*)-1-hydroxyethyl)-3-(hydroxymethyl)-2-methylcyclopentyl)-1,1-dimethylurea (18b). Yield : 85% (10 mg from 12.5 mg); $[\alpha]_D^{20}$ +18.9 (*c* 1.00, $CHCl_3$); IR (neat): ν_{max} 3408, 2931, 2104, 1622, 1590, 1538, 1374, 1334, 1248, 1180, 1152, 1110, 1037, 763, 733 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.51 (1H, d, *J* = 11.3 Hz), 7.20- 7.13 (1H, m), 6.47 (1H, dt, *J* = 2.0, 8.4 Hz), 6.41 (1H, dd, *J* = 1.8, 8.2 Hz), 6.35 (1H, td, *J* = 2.2, 11.3 Hz), 5.50 (1H, s), 5.29 (1H, d, *J* = 11.3 Hz), 4.56 (1H, s), 4.10 (1H, d, *J* = 11.6 Hz), 4.00- 3.91 (1H, m), 3.77 (1H, d, *J* = 11.3 Hz), 3.65- 3.60 (2H, m), 3.17 (1H, s), 2.99 (6H, s), 2.07 (1H, br s), 1.73 (1H, br s), 1.40 (3H, s), 1.22 (3H, d, *J* = 6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.4, 163.0, 158.5, 147.7, 147.6, 130.9, 130.8, 109.4, 109.4, 105.3, 105.0, 100.7, 100.4, 88.3, 84.4, 74.0, 73.8, 73.0, 66.7, 61.2, 36.7, 36.6, 20.4, 17.7; HRMS (ESIMS): calcd for $C_{18}H_{28}FN_6O_5$ $[M+H]^+$ 427.20997, found 427.21009.

3-((1*R*,2*R*,3*S*,4*S*,5*S*)-5-Azido-2,3-dihydroxy-1-((*S*)-1-hydroxyethyl)-3-(hydroxymethyl)-4-((3-methoxyphenyl)amino)-2-methylcyclopentyl)-1,1-dimethylurea (18c). Yield : 70% (9 mg from 14 mg); $[\alpha]_D^{20}$ +16.9 (*c* 1.00, $CHCl_3$); IR (neat): ν_{max} 3413, 2929, 2104, 1615, 1537, 1514, 1374, 1305, 1261, 1212, 1164, 1110, 1038, 913, 762, 733 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.45 (1H, d, *J* = 11.3 Hz), 7.14 (1H, t, *J* = 8.1 Hz), 6.37 (1H, dd, *J* = 1.7, 8.1Hz), 6.26 (1H, dd, *J* = 1.2, 8.1 Hz), 6.22 (1H, t, *J* = 1.7 Hz), 5.50 (1H, s), 5.14 (1H, d, *J* = 11.7 Hz), 4.54 (1H, s), 4.17 (1H, d, *J* = 11.7 Hz), 4.02- 3.91 (1H, m), 3.84- 3.76 (4H, m), 3.65 (1H, s), 3.59 (1H, d, *J* = 11.7 Hz), 2.99 (6H, s), 1.81 (1H, br s), 1.61 (2H, br s), 1.41 (3H, s), 1.20 (3H, d, *J* = 6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.1, 158.5, 147.1, 130.6, 106.5, 104.2, 99.7, 88.2, 84.6, 73.9, 73.8, 73.0, 66.8, 61.4, 55.1, 36.7, 20.5, 17.7; HRMS (ESIMS): calcd for $C_{19}H_{30}N_6O_6$ $[M+H]^+$ 439.22996, found 439.23098.

3-((1*R*,2*R*,3*S*,4*S*,5*S*)-5-Azido-2,3-dihydroxy-1-((*S*)-1-hydroxyethyl)-3-(hydroxymethyl)-2-methyl-4-((3-(trifluoromethyl)phenyl)amino)cyclopentyl)-1,1-dimethylurea (18d). Yield : 82% (14 mg from 18 mg); $[\alpha]_D^{20}$ +26.9 (*c* 1.00, $CHCl_3$); IR (neat): ν_{max} 3408, 2934, 2104, 1633, 1538, 1488, 1375, 1342, 1284, 1164, 1122, 1068, 908, 787, 735, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.48 (1H, d, *J* = 11.3 Hz), 7.33 (1H, t, *J* = 7.8 Hz), 7.03 (1H, d, *J* = 7.8 Hz), 6.87 (1H, s), 6.81 (1H, d, *J* = 8.2 Hz), 5.50 (1H, s), 5.40 (1H, d, *J* = 11.3 Hz), 4.58 (1H, s), 4.13 (1H, d, *J* = 11.6 Hz), 4.02- 3.92 (1H, m), 3.84 (1H, d, *J* = 11.1 Hz), 3.63 (1H, d, *J* = 11.6 Hz), 3.60 (1H, s), 3.15 (1H, s), 2.99 (6H, s), 2.05 (1H, br s), 1.69 (1H, br s), 1.42 (3H, s), 1.23 (3H, d, *J* = 6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.4, 146.1, 132.2, 131.9, 130.2, 116.6, 115.0, 114.9, 109.8, 109.8, 88.3, 84.1, 74.1, 73.8, 73.8, 73.0, 66.5, 61.1, 36.7, 20.4, 17.7; HRMS (ESIMS): calcd for $C_{19}H_{28}F_3N_6O_5$ $[M+H]^+$ 477.20678, found 477.20767.

General procedure for synthesis of 19 a-d

To a stirred solution of **18a-d** (9 mg, 0.022 mmol) in EtOH:H_2O (3:1, 1.4 mL) were added ammonium chloride (35 mg, 0.662 mmol), zinc powder (22 mg, 0.331 mmol) at r.t. and the mixture was stirred for 8 h. The reaction mixture was quenched with aqueous ammonia (2 mL) and extracted with CH_2Cl_2, the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography using [4-5]% methanol in chloroform to give **19a-d** as a pale yellow oils.

3-((1*R*,2*R*,3*S*,4*S*,5*S*)-5-Amino-2,3-dihydroxy-1-((*S*)-1-hydroxyethyl)-3-(hydroxymethyl)-2-methyl-4-(phenylamino)cyclopentyl)-1,1-dimethylurea (19a). Yield : 80% (7 mg from 9 mg); $[\alpha]_D^{20}$ +29.3 (*c* 1.00, $CHCl_3$); IR (neat): ν_{max} 3382, 2927, 2724, 1603, 1505, 1373, 1297, 1089, 1041, 912, 750 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.85 (1H, d, *J* = 10.5 Hz), 7.20 (2H, t, *J* = 7.8 Hz), 7.05 (1H, s), 6.73 (1H, t, *J* = 7.3 Hz), 6.64 (2H, d, *J* = 7.8 Hz), 5.56 (1H, s), 5.20 (1H, d, *J* = 10.9 Hz), 4.11 (1H, d, *J* = 11.7 Hz), 3.99- 3.87 (1H, m), 3.72 (1H, d, *J* = 11.7 Hz), 3.67 (1H, d, *J* = 10.5 Hz), 2.99 (6H, s), 1.79 (5H, br s), 1.45 (3H, s), 1.05 (3H, d, *J* = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.4, 146.6, 129.6, 117.9, 113.4, 88.4, 84.8, 74.0, 71.3, 68.6, 62.4, 61.9, 36.8, 21.5, 18.2; HRMS (ESIMS): calcd. for $C_{18}H_{31}N_4O_5$ $[M+H]^+$ 383.2289, found 383.22804.

3-((1*R*,2*R*,3*S*,4*S*,5*S*)-5-Amino-4-((3-fluorophenyl)amino)-2,3-dihydroxy-1-((*S*)-1-hydroxyethyl)-3-(hydroxymethyl)-2-methylcyclopentyl)-1,1-dimethylurea (19b). Yield : 75% (7.6 mg from 10 mg); $[\alpha]_D^{20}$ +33.2 (*c* 1.00, $CHCl_3$); IR (neat): ν_{max} 3382, 2927, 1719, 1621, 1515, 1455, 1374, 1337, 1180, 1150, 1088, 1041, 918, 759 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.86 (1H, d, *J* = 10.8 Hz), 7.17- 7.03 (2H, m), 6.46- 6.28 (3H, m), 5.62 (1H, s), 5.39 (1H, d, *J* = 10.5 Hz), 4.06 (1H, d, *J* = 11.6 Hz), 3.97- 3.84 (1H, m), 3.73 (1H, d, *J* = 11.6 Hz), 3.60 (1H, dd, *J* = 1.4, 10.5 Hz), 2.99 (6H, s), 2.95 (1H, s), 1.77 (1H, br s), 1.45 (3H, s), 1.04 (3H, d, *J* = 6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.4, 162.9, 159.3, 148.3, 130.6, 109.5, 109.4, 104.3, 104.1, 99.9, 99.6, 88.4, 84.6, 73.9, 71.3, 68.4, 62.4, 61.7, 36.8, 21.4, 18.2; HRMS (ESIMS): calcd. for $C_{18}H_{30}FN_4O_5$ $[M+H]^+$ 401.21947, found 401.2182.

3-((1R,2*R*,3*S*,4*S*,5*S*)-5-Amino-2,3-dihydroxy-1-((*S*)-1-hydroxyethyl)-3-(hydroxymethyl)-4-((3-methoxyphenyl)amino)-2-methylcyclopentyl)-1,1-dimethylurea (19c). Yield : 80% (7 mg from 9 mg); $[\alpha]_D^{20}$ +36.3 (*c* 1.00, $CHCl_3$); IR (neat): ν_{max} 3385, 2934, 1614, 1515, 1455, 1374, 1212, 1162, 1090, 1041, 912, 823, 762, 732, 690 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.86 (1H, d, *J* = 10.7 Hz), 7.15- 7.02 (2H, m), 6.28 (1H, d, *J* = 8.2 Hz), 6.25 (1H, d, *J* = 8.2 Hz), 6.17 (1H, s), 5.56 (1H, s) 5.25 (1H, d, *J* = 10.7 Hz), 4.08 (1H, d, *J* = 11.7 Hz), 3.98- 3.87 (1H, m), 3.77 (3H,s), 3.69 (1H, d, *J* = 11.7 Hz), 3.60 (1H, d, *J* = 10.7 Hz), 3.05- 2.91 (7H, s), 1.81 (2H, s), 1.44 (3H, s), 1.05 (3H, d, *J* = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.0, 159.4, 148.0, 130.0, 106.4, 102.8, 99.4, 88.4, 84.7, 71.3, 68.6, 62.4, 61.9, 55.1, 36.8, 21.5, 18.2; HRMS (ESIMS): calcd for $C_{19}H_{33}N_4O_6$ $[M+H]^+$ 413.23946, found 413.23835.

3-((1*R*,2*R*,3*S*,4*S*,5*S*)-5-Amino-2,3-dihydroxy-1-((*S*)-1-hydroxyethyl)-3-(hydroxymethyl)-2-methyl-4-((3-(trifluoromethyl)phenyl)amino)cyclopentyl)-1,1-dimethylurea (19d). Yield : 75% (10 mg from 14 mg); $[\alpha]_D^{20}$ +32.7 (*c* 1.00, $CHCl_3$); IR (neat): ν_{max} 3381, 2933, 1614, 1520, 1449, 1374, 1346, 1283, 1164, 1122, 1068, 909, 787, 733, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.88 (1H, d, *J* = 10.7 Hz), 7.32- 7.20 (1H, m), 7.06 (1H, s), 6.96 (1H, d, *J* = 7.6 Hz), 6.81 (1H, s), 6.77 (1H, d, *J* = 8.0 Hz), 5.62 (1H, s), 5.48 (1H, d, *J* = 10.3 Hz), 4.06 (1H, d, *J* = 11.5 Hz), 3.97- 3.84 (1H, m), 3.73 (1H, d, *J* = 11.5 Hz), 3.67 (1H, d, *J* = 10.3 Hz), 2.99 (6H, s), 2.93 (1H, s), 1.86 (3H, br s), 1.45 (3H, s), 1.04 (3H, d, *J* = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.3, 146.8, 131.9, 131.6, 129.9, 125.5, 122.8, 116.4, 114.1, 114.1, 109.1, 109.1, 88.4, 84.5, 74.0, 73.9, 71.3, 68.6, 62.4, 61.5, 36.8, 21.4, 18.2; HRMS (ESIMS): calcd. for $C_{19}H_{30}F_3N_4O_5$ $[M+H]^+$ 451.21628, found 451.21758.

In vitro antimalarial activity

In vitro antimalarial activity was determined by the malaria SYBR Green-based fluorescence (MSF) assay described previously[22] with slight modification[21]. Stock solutions of each test drug were prepared in sterile distilled water at a concentration of 10mM. The drug solutions were serially diluted with culture medium and distributed to asynchronous parasite cultures on 96-well plates in quadruplicate in a total volume of 100µL to achieve 0.2% parasitemia with a 2% hematocrit in a total volume of 100µL. Automated pipetting and dilution were carried out with a programmable Precision 2000 robotic station (Bio-Tek, Winooski, VT). The Plates were then incubated for 72h at 37 ºC. After incubation, 100µL of lysis buffer with 0.2 µL/ml SYBR Green I (54,66) was added to each well. The plates were incubated at room temperature for an hour in the dark and then placed in a 96-well fluorescence plate reader (Spectramax Gemini-EM; Molecular Diagnostics) with excitation and emission wavelengths at 497 nm and 520 nm, respectively, for measurement of fluorescence. The 50% inhibitory concentration (IC_{50}) was determined by nonlinear regression analysis of logistic dose-response curves (GraphPad Prism software).

In vitro antibacterial activity

Mimimum inhibitory concentrations (MIC) were measured by a standard broth microdilution method following the Clinical Laboratory Standard Institute recommendations.[23] Isolates tested were *E. coli* ATCC 25922, *S. aureus* ATCC 25923, *K.*

pneumoniae ATCC 700603, a clinical isolate of *A. baumanii, P. aeruginosa* ATCC 27853 and *E. faecalis* ATCC 29212. Plates were read after an incubation period of 20 hours.

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2.3 Conclusions et perspectives

Dans le cadre de ce projet, quelques analogues de la pactamycine ont été préparés, puis testés pour leurs activités antibiotique, anticarcinogénique et antiprotozoaire. Il a

notamment été découvert qu'il existe une taille critique tolérée pour la fonction urée, au-delà de laquelle les activités anticarcinogénique et antiprotozoaire sont globalement affectées.

La facilité avec laquelle cette sélection d'analogues a été préparée laisse croire que plusieurs générations d'analogues pourraient être synthétisées grâce aux voies de synthèse établies. Il serait alors possible de varier davantange le motif aniline ou urée de la pactamycine, mais aussi, notamment, de masquer ou d'enlever quelques alcools afin de modifier les interactions clés entre l'analogue donné et le ribosome bactérien. Par ailleurs, la de-6-MSA pactamycine (**2.4**) synthétisée dans notre laboratoire a été envoyée au groupe Ramakrishnan dans l'espoir d'obtenir une structure cristalline qui permettrait d'élucider les interactions clés entre le ribosome et ce congénère pour lequel il manque l'unité salycylique.

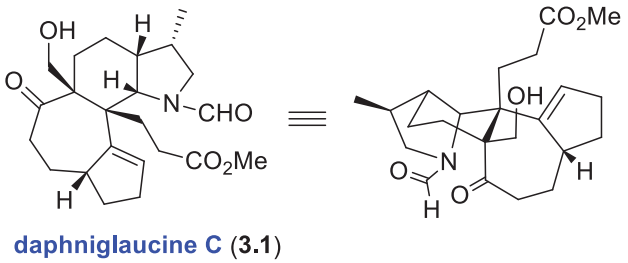
De manière plus personnelle, l'expérience en synthèse acquise dans le cadre de ce projet m'a alors permis d'entamer la synthèse totale de la daphniglaucine C, un autre produit naturel dont la structure et les propriétés sont très différentes de la pactamycine.

Chapitre III

Progrès vers la synthèse totale de la daphniglaucine C

3.1 Propriétés de la daphniglaucine C et historique

Par rapport à la pactamycine, l'histoire de la daphniglaucine C (**3.1**) est beaucoup plus courte et récente. Ce n'est qu'en 2003 que le groupe de Kobayashi a isolé le composé cible pour la première fois, des feuilles du *Daphniphyllum glaucescens*.[34] Sa structure, déterminée par RMN (*Figure 3.1*), montre six centres stéréogéniques (cinq adjacents), dont seule la stéréochimie relative est connue, et est caractérisée par un tétracycle hautement arquée. Par ailleurs, elle possède deux centres quaternaires vicinaux, situés près du centre de la molécule, et quelques groupements fonctionnels dont une cétone, un ester, un alcool, un alcène et un formamide. Très peu d'information a été obtenue par rapport à l'activité biologique de la daphniglaucine C : elle est capable d'inhiber la polymérisation de la tubuline (IC_{50} = 25 μM) et affiche une certaine cytotoxicité contre les cellules L1210 de la murine lymphoma (IC_{50} = 0,1 μg/mL).



daphniglaucine C (**3.1**)

Figure 3.1 : Structure de la daphniglaucine C

La daphniglaucine C est membre d'une vaste famille de composés naturels polycycliques isolés à partir du genre *daphniphyllum*. En plus de dix daphniglaucines connues (*Schéma 3.2*), dont la première a aussi été isolée en 2003,[35] il existe une multitude de classes de composés qui, à quelques exceptions près, affichent une haute ressemblance avec celles-ci, telles que les daphnilactones, les daphnezomines, les daphmanidines, les yuzurimines, les calycinines et les calyciphillines.[36] La *Figure 3.2* montre une sélection de composés de classes parentes, et représente la daphniglaucine C dans une perspective qui met en relief sa composition en trois dimensions. Il est à noter que, pour le reste de la présente thèse, une perspective différente permettant de mieux représenter le motif octahydroindole sera utilisée (voir *Figure 3.1*). Il n'en reste pas moins que, lorsque les daphniglaucines sont représentées en trois dimensions, leur très

haute ressemblance est frappante. Alors que celles-ci affichent toutes une charpente tétracyclique dont la stéréochimie est préservée, la daphniglaucine C est la seule qui ne possède pas le bicycle 5,5 surligné, ainsi qu'une amine tertiaire en jonction de cycle. Il est à noter que les daphniglaucines E et G (**3.5**) sont simplement des invertomères N–O. Il en va de même pour les daphniglaucines F et H (**3.6**).

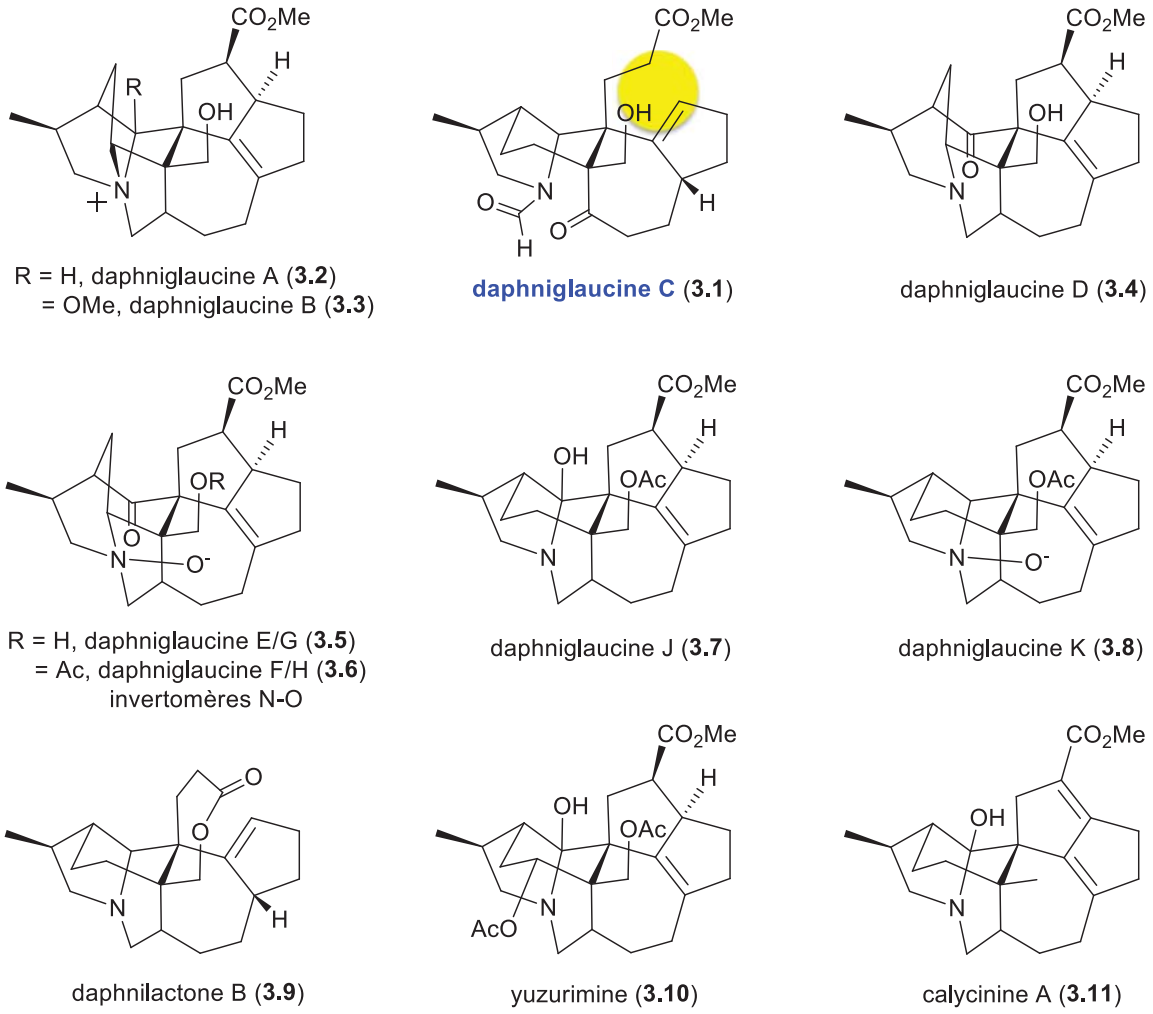


Figure 3.2 : La grande classe des daphniglaucines et quelques composés de la même famille

En même temps qu'il a isolé et caractérisé la daphniglaucine C, le groupe de Kobayashi a proposé une voie biosynthétique valide non seulement pour toutes les daphniglaucines, mais aussi pour plusieurs composés isolés du *Daphniphyllum glaucescens* (*Schéma 3.1*). Un intermédiaire énamine (**3.15**), correspondant à la charpente de la daphniglaucine C, serait obtenu par suite d'une fragmentation, puis tautomérisation,

d'un squelette secodaphnane (**3.14**), provenant lui-même d'une réaction ène depuis l'imine **3.13**. L'existence de cette imine, dérivée du squalènedialdéhyde (**3.12**), a été postulée il y a plus de vingt ans par Heathcock et a été corroboré depuis par plusieurs synthèses biomimétiques de divers produits naturels extraits du *daphnyphyllum*.[37] L'énamine **3.15** ainsi obtenue serait alors sujette à un clivage oxydatif, par exemple, afin de fournir la daphniglaucine C. Il est à noter que ces voies biomimétiques demeurent hypothétiques, et que celles-ci n'ont pas été revisitées ou confirmées par la suite. Par ailleurs, quelques détails ne sont pas fournis dans le cadre de cette proposition, notamment où et quand serait oxydée la position 21 (numérotation selon Kobayashi *et al*, voir *Schéma 3.1*). Plus particulièrement, il reste impossible de déterminer à quelle étape surviendrait la différenciation de la daphniglaucine C par rapport aux autres membres de sa famille.

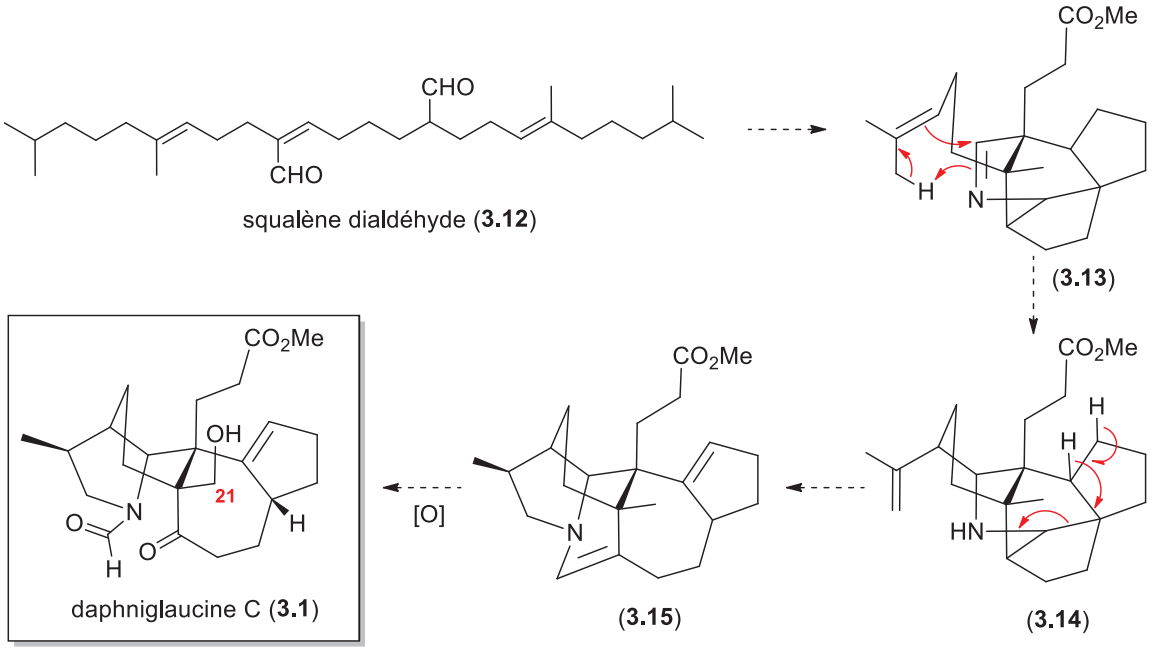


Schéma 3.1 : Biosynthèse pour les daphniglaucines, proposée par Kobayashi

Alors que certains composés de classes parentes de la daphniglaucine C ont été synthétisés, il n'existe toujours aucune synthèse totale ni partielle de cette dernière. Toutefois, quelques synthèses partielles ont été développées récemment pour les daphniglaucines en général, ou pour quelques composés de classes parentes.[38] Notamment, le groupe de Coldham a récemment établi une voie de synthèse préconisant l'emploi d'une réaction nitroso afin de synthétiser un précurseur tricyclique racémique

(**3.23**) des daphniglaucines (*Schéma 3.2*).[39] Il est toutefois important de souligner qu'un des trois cycles synthétisés dans cette approche (dessiné en rouge) est inutile, voire nuisible à la synthèse de la daphniglaucine C, celle-ci étant la seule à ne pas contenir ce cycle supplémentaire. Ce problème est d'ailleurs récurrent dans les synthèses partielles existantes.

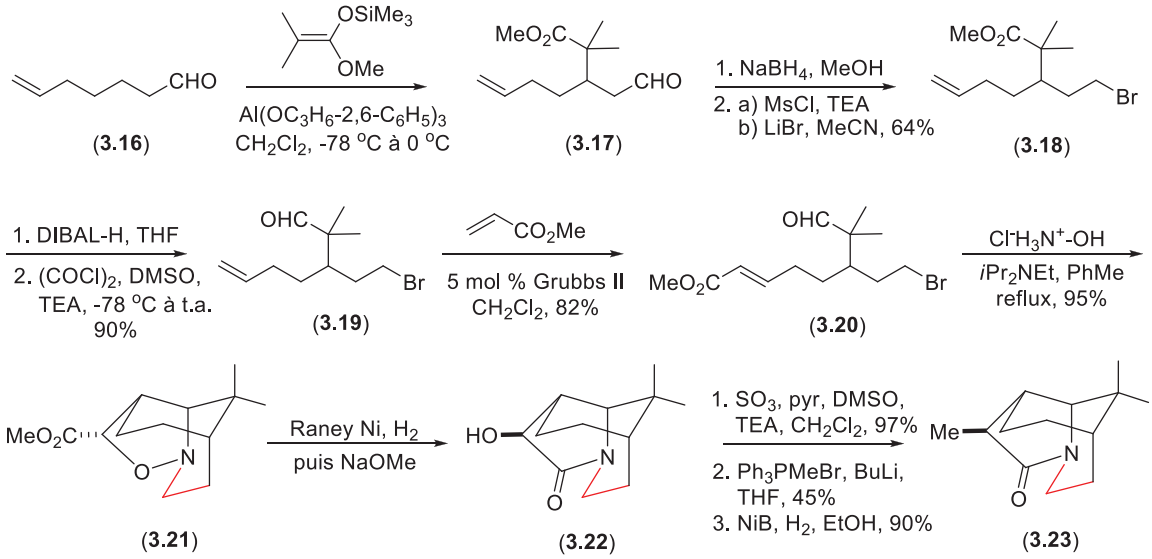


Schéma 3.2 : Synthèse partielle d'une daphniglaucine

Fort d'une riche expérience en synthèse totale de produits naturels contenant des octahydroindoles polysubstitués, tels que l'oscillarine (**3.24**), la dysinosine A (**3.25**), la chlorodysinosine A (**3.26**) et quelques composés similaires dont l'aeruginosine 205B (**3.27**) (voir *Figure 3.3*),[40] le groupe Hanessian a donc récemment entrepris d'établir une voie de synthèse pour la daphniglaucine C.

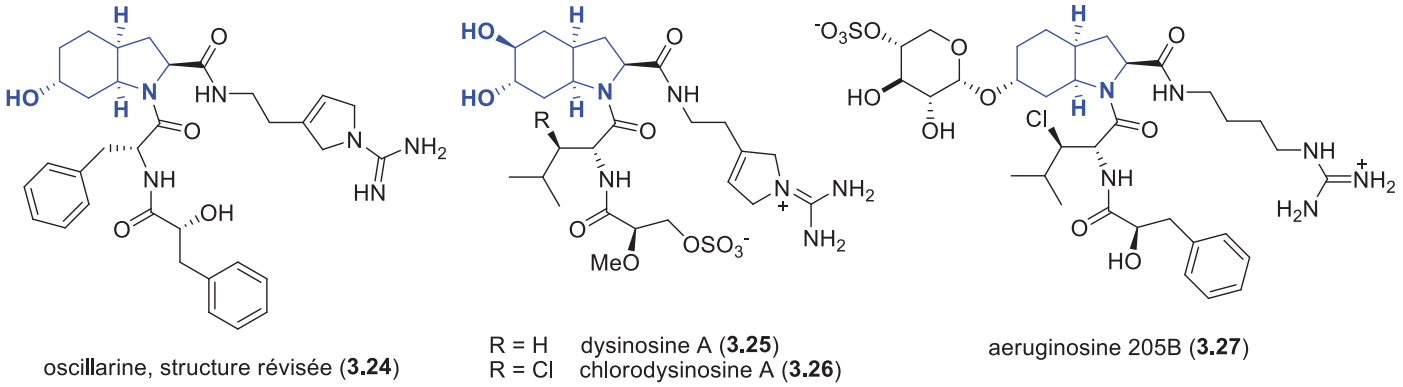


Figure 3.3 : Octahydroindoles par le groupe Hanessian

3.2 Première approche

Au cours des synthèses mentionnées ci-dessus (*Figure 3.3*), la formation des octahydroindoles a été assurée par une réaction d'aza-Prins. Or, il s'est avéré que des résultats préliminaires laissaient croire que cette stratégie ne serait pas appropriée pour les substrats pour lesquels il manquait un ester en position adjacente à l'azote tel que pour la daphniglaucine C.[41] Lorsque le projet m'a été attribué, il a donc déjà été convenu qu'une autre voie de synthèse serait plus prometteuse, et mes recherches ont abondé en ce sens.

La synthèse aurait recours à une méthodologie de synthèse faisant appel à des réactions énantiosélectives afin de fournir le cyclohexénol énantioenrichi **3.35** qui, lui, servirait de précurseur pour élaborer l'ényne **3.34**, puis l'octahydroindole **3.33** (*Schéma 3.3*).

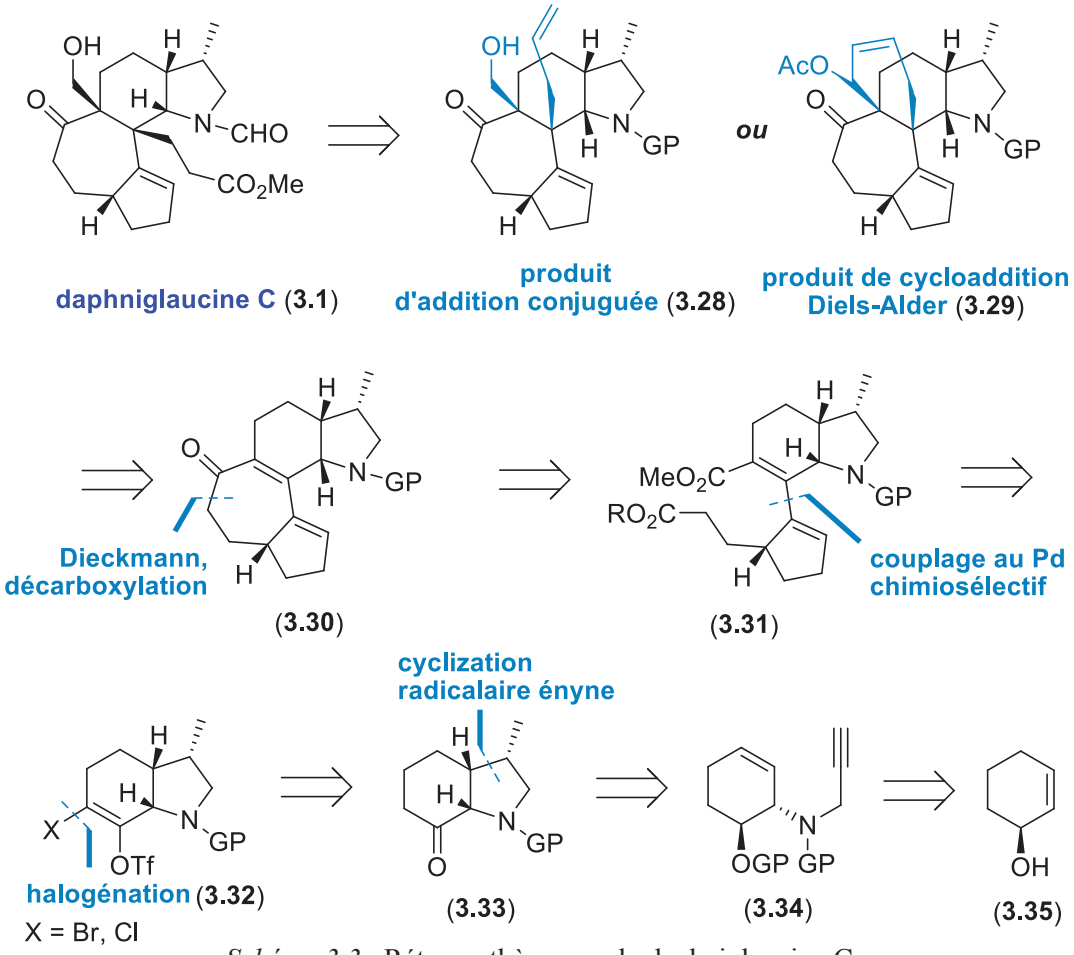


Schéma 3.3 : Rétrosynthèse pour la daphniglaucine C

L'octahydroindole pourrait à son tour être fonctionnalisé afin de fournir le triflate de bromoénol **3.32**, premier partenaire pour une approche convergente mettant en vedette un couplage de Stille avec un cyclopentène chiral monosubstitué. Le tricycle **3.31** obtenu par couplage au palladium pourrait ensuite être cyclisé pour obtenir la structure tétracyclique **3.30**, pour enfin installer les deux centres quaternaires vicinaux requis en tirant profit de la structure hautement convexe, dûe aux trois protons *syn* en jonction de cycle, par exemple à l'aide de réactions de Diels-Alder ou d'addition conjuguée.

Les premières étapes de la synthèse ont été entreprises sans réelles embûches (*Schéma 3.4*). La réduction de la cyclohex-2-énone (**3.36**) selon les conditions de Luche[42] a permis d'obtenir le cyclohex-2-énol (**3.35**) racémique. Afin d'épargner en peine et en argent, la voie a été explorée à partir de composés racémiques, après s'être assuré qu'il était possible d'obtenir le cyclohexénol (**3.35**) de façon chirale tel que décrit dans la littérature.[43] Pour cette approche, les traits pleins seront donc utilisés pour décrire la stéréochimie des mélanges racémiques, conformément à la convention utilisée plus tôt dans le Chapitre 1 (*Schéma 1.5*). Une époxydation de Prilezhaev dirigée à partir de **3.35** a permis d'obtenir l'époxyde **3.37**, dont l'alcool a été protégé sous forme d'éther benzylique tel qu'en **3.38**. En ayant recours à une méthode connue,[44] l'époxyde a été ouvert par suite d'élimination régiosélective afin de fournir l'alcool secondaire allylique **3.39**. Cet alcool a ensuite été sujet à un déplacement de Mitsunobu[45] avec une amine propargylique activée sous forme de sulfonamide pour fournir l'ényne **3.40**. Un léger travail d'optimisation a été nécessaire pour cette réaction : si plus d'un équivalent de sulfonamide était employé, il y avait formation concomitante du produit d'addition S_N2', dans un mélange inséparable. Par exemple, en exagérant ce phénomène et en fournissant à la réaction dix équivalents du sulfonamide propargylique, il a été possible d'obtenir encore plus de produit S_N2' que de produit S_N2 (1.8 : 1).

Par la suite, plusieurs options ont été envisagées afin de convertir l'ényne **3.40** en octahydroindole, telles que la cyclisation assistée au zirconium,[46] ou catalysée au ruthénium,[47] à l'indium,[48] ou au palladium.[49] C'est finalement la cyclisation radicalaire

(Bu_3SnH, AIBN)[50] qui a été employée pour fournir le bicycle **3.41** avec un rendement acceptable (83%) après protolyse du stannane vinylique. Par ailleurs, la structure du composé bicyclique a été confirmée par diffraction des rayons-X. Qui plus est, il a été jugé que cette méthode était très reproductible et facilement applicable sur grande échelle. À ce stade, il a donc été envisagé que la liaison double exocyclique en **3.41** pouvait être hydrogénée afin d'installer le troisième stéréocentre que contient la daphniglaucine C, soit le groupement méthyle en position 4 de la pyrrolidine.

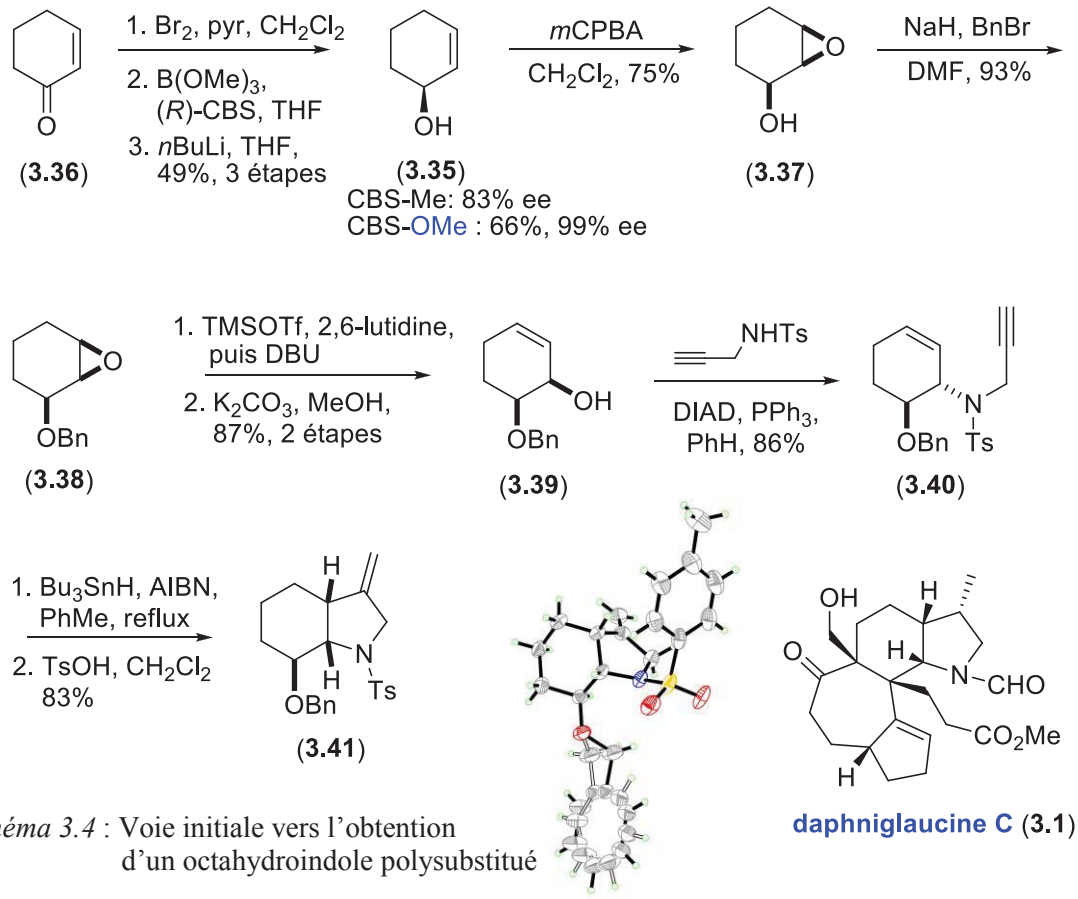
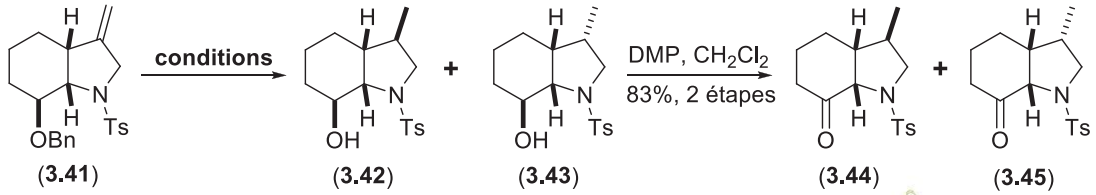


Schéma 3.4 : Voie initiale vers l'obtention d'un octahydroindole polysubstitué

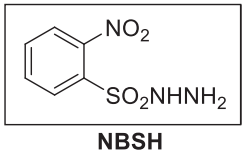
L'hydrogénation a donc été accomplie en même temps que l'hydrogénolyse de l'éther benzylique pour fournir les alcools **3.42** et **3.43** dans un mélange de diastéréoisomères inséparables. Par chance, l'oxydation de l'alcool secondaire en cétone a permis d'obtenir un mélange séparable des diastéréoisomères **3.44** et **3.45** faciles à analyser grâce à leurs propriétés cristallines. Il était espéré que l'hydrogénation de l'oléfine exocyclique procéderait par la face supérieure convexe du bicycle, générant

ainsi le diastéréoisomère désiré. Or, dans des conditions usuelles, l'hydrogénation a plutôt fourni majoritairement l'autre diastéréoisomère (r. d. = [3,5-3] : 1), à notre grande surprise! *A posteriori*, il a été postulé que la topologie du bicycle forçait justement le groupement tosyle à pointer directement vers le haut (peut-être même sous forme d'un invertomère prédominant), bloquait la face supérieure convexe, et menait donc à l'obtention du mauvais diastéréoisomère. L'analyse par diffraction des rayons-X de l'intermédiaire **3.41** confirme cette hypothèse, mais il faut préciser qu'il s'agit là de l'état solide, et qu'il peut justement y avoir des différences considérables entre la conformation de la molécule en solution et à l'état solide. Il n'en demeure par moins qu'il y avait un premier problème majeur au niveau de la synthèse proposée, et il fallait essayer d'inverser la diastéréosélectivité. En premier lieu, les conditions d'hydrogénation ont été modifiées dans l'espoir d'améliorer le ratio diastéréomérique (*Schéma 3.5*). Malheureusement, ni le catalyseur de Pearlman (dans le méthanol, l'acétate d'éthyle ou les deux), ni le palladium sur charbon ou les catalyseurs de Crabtree et Wilkinson n'ont permis d'obtenir l'autre diastéréoisomère désiré de façon majoritaire. En outre, l'emploi du diimide 2-nitrobenzènesulfonylhydrazine (NBSH), parfois employé pour de telles hydrogénations,[51] n'a permis aucune conversion. Cette brève sélection de conditions laissait donc croire qu'il allait être difficile de régler le problème sans changer la structure même de l'intermédiaire hydrogéné.

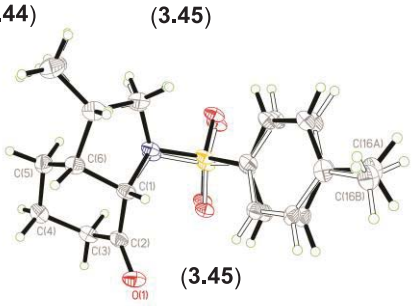


conditions

$Pd(OH)_2$, H_2, MeOH, 16 h	[3.5-3] : 1
$Pd(OH)_2$, H_2, EtOAc, 16 h	[3.5-3] : 1
$Pd(OH)_2$, H_2, MeOH/EtOAc (1 : 1), 16 h	[3.5-3] : 1
Pd/C, H_2, MeOH/EtOAc (1 : 1), 16 h	[3.5-3] : 1
$[Ir(COD)(PCy_3)(py)]PF_6$, H_2, CH_2Cl_2, 3 d	2 : 1*
$RhCl(PPh_3)_3$, H_2, CH_2Cl_2, 3 d	2 : 1*
NBSH, PhMe, 3 d	aucune réaction



NBSH



(**3.45**)

*sans hydrogénolyse du groupement benzyle

Schéma 3.5 : Problèmes de diastéréosélectivité de l'hydrogénation (1)

Par la suite, il a été raisonné que l'éther benzylique était peut-être le coupable indirect de ce problème de diastéréosélectivité : peut-être une interaction stérique défavorable entre cet éther et le sulfonamide forçait-elle ce dernier à adopter la conformation problématique? Pour éprouver cette théorie, l'éther benzylique en **3.41** a été déprotégé avant l'hydrogénation (plutôt que pendant) en utilisant du BBr_3 dans des conditions usuelles (*Schéma 3.6*). Malheureusement, l'hydrogénation sur l'alcool libre **3.46** a toujours donné le diastéréoisomère indésirable de façon majoritaire. Par ailleurs, cet alcool a ensuite été oxydé afin de fournir la cétone **3.47**, mais, encore une fois, l'hydrogénation de cette cétone a toujours fourni le mauvais diastéréoisomère majoritairement (1,4 : 1). Les catalyseurs de Wilkinson et Crabtree ont aussi été essayés pour effectuer l'hydrogénation de la cétone **3.47**, mais n'ont permis qu'un ratio diastéréomérique de 1 : 1.

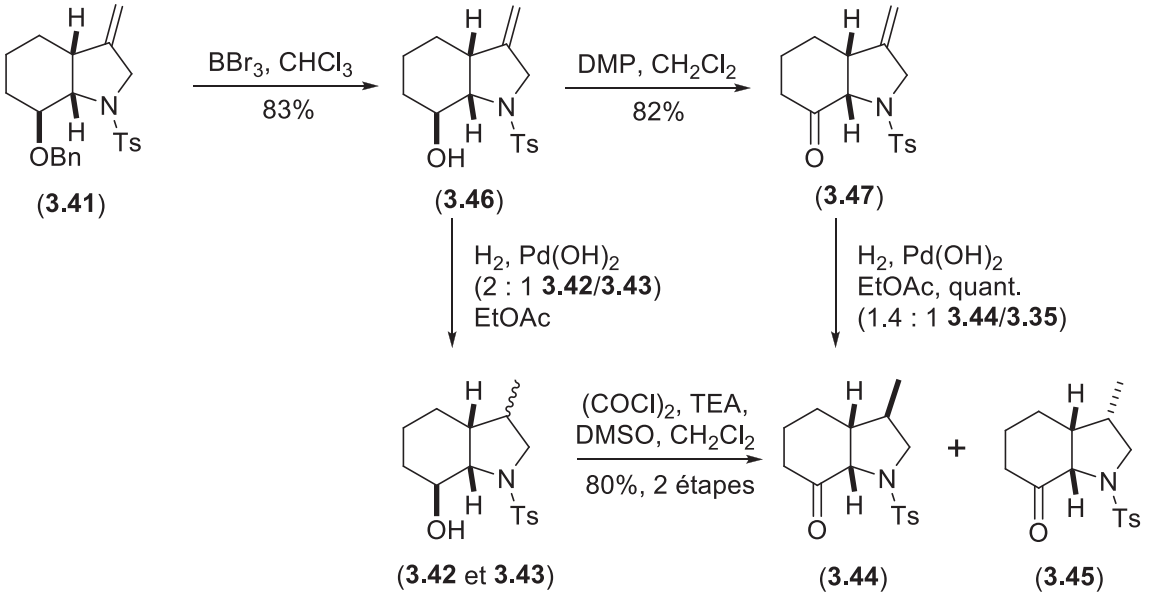


Schéma 3.6 : Problèmes de diastéréosélectivité de l'hydrogénation (2)

Finalement confrontés au fait que le problème était inhérent à la structure bicyclique, il a été convenu qu'il était préférable de changer le tosyle pour un groupement plus petit, afin que l'hydrogénation puisse opérer par la face supérieure, tel qu'envisagé initialement. Le groupement protecteur a donc été changé pour un mésyle en utilisant l'amine propargylique mésylée dans la réaction de Mistunobu décrite précédemment, puis en appliquant la même stratégie de cyclisation radicalaire ényne pour obtenir

l'intermédiaire **3.49** (*Schéma 3.7*). L'hydrogénation n'a toutefois permis d'obtenir qu'un ratio diastéréomérique de 2,4 : 1, toujours en faveur du mauvais diastéréoisomère. L'information a été validée après oxydation du mélange d'alcools **3.50** vers les cétones **3.51** et **3.52**, puis séparation des ces deux diastéréoisomères. Il s'est d'ailleurs avéré que le diastéréoisomère **3.52**, celui désiré, a pu être analysé par diffraction des rayons-X.

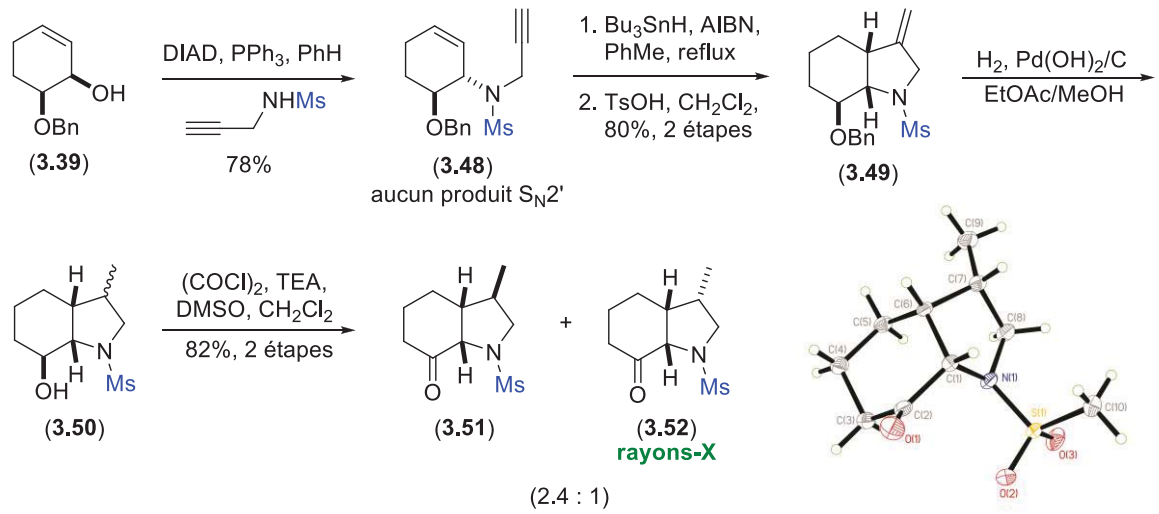


Schéma 3.7 : Formation du bicycle mésylé **3.49** et hydrogénation

Puisqu'il n'a pas été suffisant de troquer le tosyle pour un mésyle, il a été convenu qu'il fallait utiliser un groupement encore plus petit. Pour ce faire, une réaction de Birch[52] a été effectuée avec du lithium[53] à partir de l'alcène **3.41** pour assurer d'abord le clivage du groupement tosyle. Il a été découvert que l'aminoalcool **3.53** obtenu était instable, et devait être rapidement utilisé. D'une part, cet aminoalcool **3.53** a ensuite été reprotégé sous forme d'acétyle qui, après hydrogénation, a permis l'obtention d'un ratio diastéréomérique amélioré de 1,5 : 1 (**3.54**) (*Schéma 3.8*). Mais, finalement, c'est en tentant l'hydrogénation directement sur l'amine libre **3.53** que le diastéréoisomère désiré a été obtenu de façon majoritaire (5 : 1). Le calcul des ratios diastéréomériques obtenus par hydrogénation de l'amine libre et de l'acétamide a été possible grâce à une comparaison avec le spectre RMN du produit **3.54**, obtenu en outre après déprotection de l'intermédiaire connu **3.42**. Chronologiquement, ces résultats ont été obtenus beaucoup plus tard. La section à venir fera donc état du bicycle tosylé **3.45** comme intermédiaire d'intérêt.

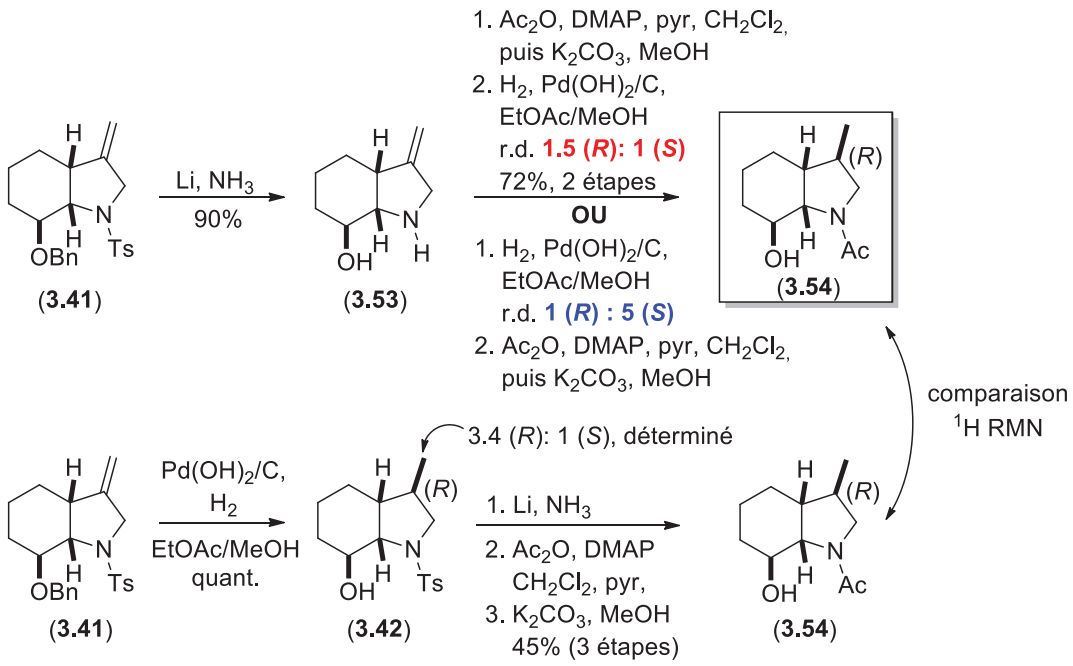


Schéma 3.8 : Problèmes de diastéréosélectivité de l'hydrogénation (3)

Afin de poursuivre la synthèse telle que planifiée initialement (voir *Schéma 3.3*), il était maintenant nécessaire de fonctionnaliser régiosélectivement la cétone en **3.45**. Or, les premiers tests d'alkylation de la cétone **3.45** ont été effectués avec le réactif de Mander[54] et ont mené à la formation d'un mélange complexe découlant probablement de la formation de plus d'un régioisomère, diastéréoisomère, tautomère, et de combinaisons de ceux-ci. Afin de simplifier l'analyse, c'est vers la formation de l'éther d'énol silylé que l'attention a été tournée afin d'éviter, à tout le moins, de former plusieurs diastéréoisomères d'alkylation et tautomères potentiels. Or, l'emploi de bases telles que LiHMDS, NaHMDS, KHMDS, ou LDA, utilisées dans le THF, n'ont permis d'obtenir qu'un mélange de régioisomères inséparable de 2 : 1 (**3.55** et **3.56**) en faveur du régioisomère désiré (*Schéma 3.9*) avec des rendements modestes [34-52%]. Aucune amélioration tangible n'a été observée en changeant le solvant pour de l'éther éthylique, ni en ajoutant l'hexaméthylphosphoramide (HMPA) comme co-solvant, ou même en changeant l'ordre d'addition des réactifs. À la lumière de ces résultats, il semble donc que l'intermédiaire **3.45** avait une réelle propension à la substitution en jonction de cycle, possiblement en raison du pKa du proton à cette position expliqué par la présence du groupement protecteur tosyle.

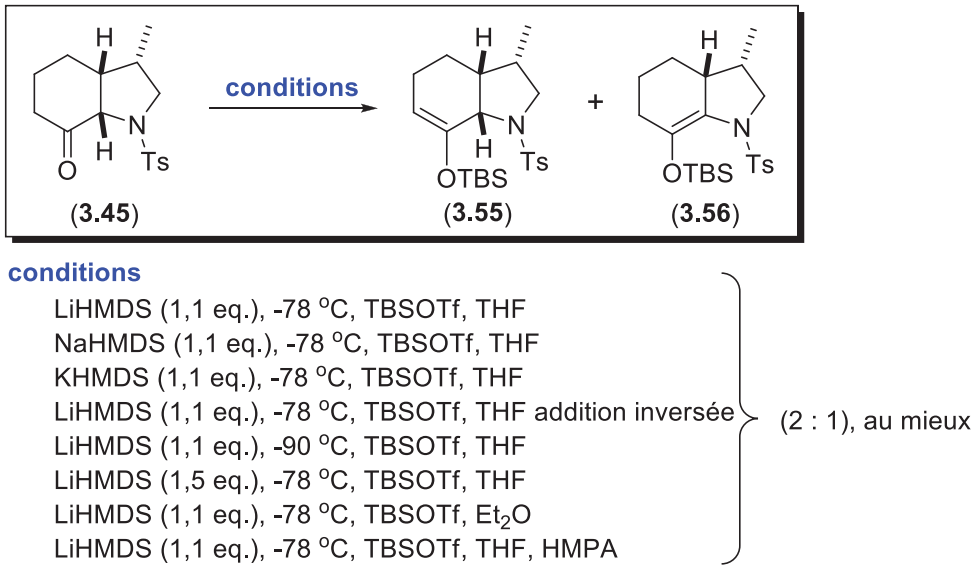


Schéma 3.9 : Tentative de fonctionnalisation régiosélective de l'intermédiaire **3.45**

Or, il existe une option facile à essayer dans ces cas où la régiosélectivité est problématique, soit celle de former, puis déprotoner, une hydrazone plutôt que la cétone de départ.[55] Cette stratégie met donc l'accent sur l'aspect stérique impliqué dans l'α-alkylation et amoindrit l'importance du pKa des sites potentiellement déprotonés.[56] L'hydrazone **3.57**, une fois formée avec un rendement acceptable, n'a toutefois pu être alkylée, ou peut-être même déprotonée, en utilisant le LiHMDS, le LDA, le *s*BuLi ou même le *t*BuLi pour bases, combinées à des électrophiles comme le réactif de Mander, l'iodure de méthyle ou même simplement l'oxyde de deutérium (*Schéma 3.10*).

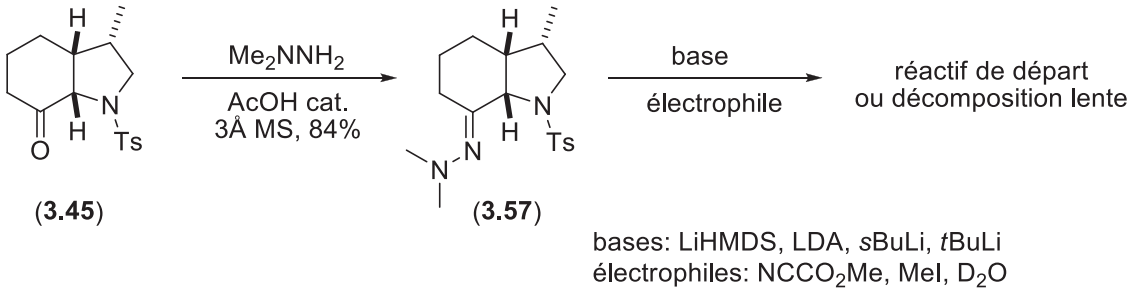
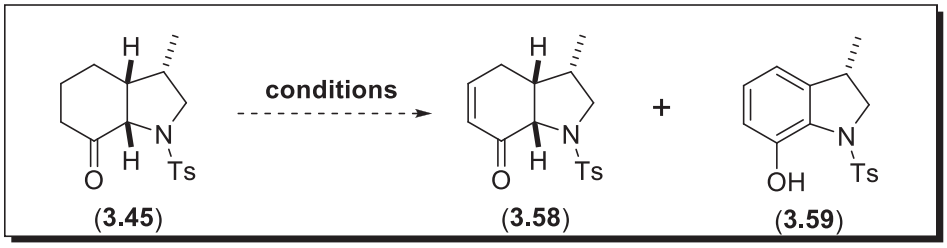


Schéma 3.10 : Tentative de fonctionnalisation régiosélective à l'aide de l'hydrazone **3.57**

Postulant qu'il s'agissait effectivement d'un problème de pKa, le recours à l'énol, plutôt qu'à l'énolate, a alors été préconisé. Plusieurs méthodes permettant de transformer une cétone en énone, combinées à une transformation de Baylis-Hilman, auraient permis de fonctionnaliser la cétone régiosélectivement en deux étapes. À cet effet, l'emploi d'IBX pour oxyder la cétone **3.45** en énone a été préconisé prioritairement.[57] Cette méthode, essayée dans le DMSO, seule ou en présence de toluène ou de benzène, n'a pas permis d'obtenir le produit désiré (*Schéma 3.11*). Ce n'est qu'en changeant le co-solvant pour de l'hexafluorobenzène, connu pour faciliter la réaction, que 38% du produit désiré **3.58** a pu être observé après trois jours, avec formation concomitante du phénol **3.59**, produit de sur-oxydation de la cétone **3.45**. En deuxième lieu, l'oxydation des cétones avec des dérivés du sélénium[58] a donc été tentée en traitant la cétone **3.45** avec de l'anhydride benzènesélénique. Les meilleurs résultats ont été obtenus en utilisant seulement 1,1 éq. d'anhydride et en chauffant dans le toluène, mais toujours avec un rendement modeste (29%) avec formation du sous-produit phénolique **3.59** indésirable. De plus, l'élimination a été tentée en deux étapes avec un réactif de chlorure de phénylsélénium oxydé par la suite, mais cette stratégie n'a permis de fournir que le sous-produit phénolique **3.59**.



oxydation au IBX

DMSO/PhMe (2 : 1), 1,5 à 5 eq., 75 °C	aucune réaction	
DMSO/PhH (2 : 1), 1,5 à 5 eq., 75 °C	traces	25%
DMSO/C_6F_6 (2 : 1), 1,5 à 5 eq., 75 °C	38%	15%
DMSO, 1,5 à 3 eq., 60 à 105 °C	aucune réaction	

oxydation au sélénium

$(PhSeO)_2O$ 1,5 à 3 eq., THF, reflux 2 d	---	traces
$(PhSeO)_2O$ 1,1 eq., PhMe, 80 °C à reflux, 2 d	29%	12%
$(PhSeO)_2O$ 5,0 eq., PhMe, 85 °C, 2 d	13%	45%
PhSeCl (1,1 eq.), EtOAc, puis pyr/H_2O_2	---	34%

Schéma 3.11 : Tentative de formation sélective de l'énone **3.58**

Dans un autre ordre d'idée, une transformation connue permet de convertir les cétones en bromoénals en une seule étape (*Schéma 3.12*).[59] Cette réaction fait encore appel à un mécanisme où est préconisée la formation d'un énol (plutôt qu'un énolate). Il était alors espéré que cette transformation puisse être régiosélective dans le cas de la cétone **3.45**, d'autant qu'elle forçait la formation d'un alcène tétrasubstitué, impossible dans le cas de l'autre régiomère en jonction de cycle. Malheureusement, le traitement de la cétone **3.45** avec le tribromure de phosphore, dans le DMF, n'a permis aucune transformation, sinon quelque décomposition après un jour.

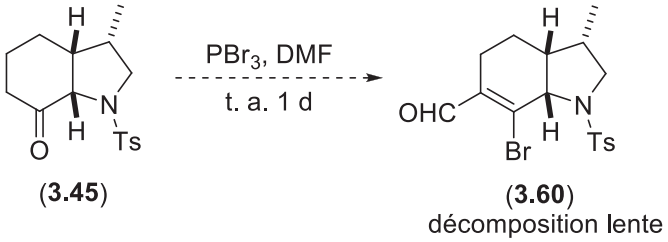


Schéma 3.12 : Tentative de formation sélective de l'énal **3.60**

Dans la même optique, il existait une autre option pour fonctionnaliser la cétone : celle de former une énaminone régiosélectivement (*Schéma 3.13*). Ces énaminones sont parfois employées en synthèse et permettent la fonctionnalisation sélective en position 4 de l'énone après ajout de réactifs de Grignard.[60] De cette façon, il aurait été possible de continuer l'élaboration du polycycle caractéristique de la daphniglaucine C. La formation de l'énaminone **3.61** a donc été essayée dans des conditions usuelles. La cétone **3.45** a été chauffée dans le toluène en présence de *N*,*N*-diméthylformamide diméthylacétal, ne permettant toutefois que de la décomposition à reflux. En changeant pour le *tert*-butoxybis(diméthylamino)méthane[61] (réactif de Bredereck) souvent employé dans de tels cas, la conversion n'a toujours pas été possible.

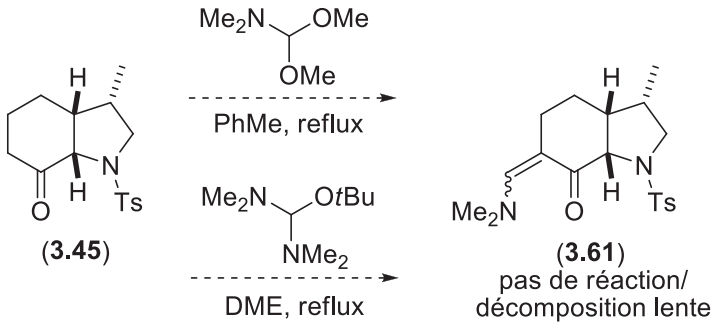
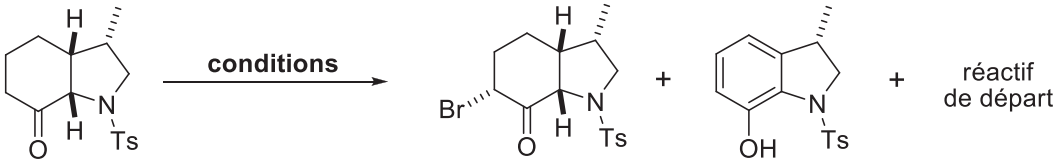


Schéma 3.13 : Tentative de formation de l'énaminone **3.61**

Poursuivant ainsi cette idée d'avoir recours à un énol plutôt qu'à un énolate, l'α-halogénation des cétones a été tentée. Plutôt que d'employer des conditions où l'on a recours à la formation d'un énolate et à un électrophile tel que le brome moléculaire ou le *N*-bromosuccinimide (NBS), l'α-halogénation a donc été tentée en traitant directement la cétone **3.45** avec un agent bromant, sans base.[62] À notre grand bonheur, la fonctionnalisation régiosélective a d'abord été accomplie en utilisant du brome moléculaire dans le chloroforme et a permis, en plus, de former un seul diastéréoisomère **3.62** (*Schéma 3.14*). Toutefois, le rendement de cette transformation était peu reproductible (51-92%), et menait une fois de plus à la formation du phénol **3.59** de façon minoritaire (5-33%). L'obtention de ce dernier sous-produit était pour le moins surprenante, et était probablement expliquée par une séquence de déhydrobromation-bromation à partir de **3.62**.[63] Dans une tentative d'optimisation de l'α-bromation, il a été découvert que la vitesse d'addition du brome moléculaire affectait grandement le rendement obtenu, et qu'il était optimal d'ajouter celui-ci très rapidement (voir partie expérimentale) à 0 °C. En outre, le solvant a été changé pour l'acétonitrile, solvant communément employé pour une telle réaction, mais n'a mené qu'à une lente conversion moins sélective. En utilisant le NBS, en particulier en excès (5-6 éq.), la transformation a pu être améliorée pour atteindre un rendement de 96%. Par contre, cette réaction a été rapidement délaissée, étant très lente (effectuée en trois à quatre jours) et souffrant de graves problèmes de reproductibilité à plus grosse échelle.



conditions	(3.62)	(3.59)	réactif de départ
Br_2 (1,0 eq.), $CHCl_3$, 0 °C	[51-92]%	[5-33]%	---
Br_2 (1,0 eq.), MeCN, 0 °C à t.a.	28%	13%	38%
NBS (10 eq.), pTsOH (3,0 eq.), MeCN, t.a., 4 d	48%	---	33%
NBS (6,0 eq.), AcOH, 60 °C, 3 d	96%	---	---

Schéma 3.14 : Halogénation diastéréo- et régiosélective de la cétone **3.45**

L'α-bromocétone **3.62** pouvait être utilisée dans différentes transformations afin de fournir un produit tricyclique clé évoqué au schéma rétrosynthétique (voir **3.31**, *Schéma 3.3*), et ce produit pouvait ultimement être transformé en produit tétracyclique polysubstitué en route vers la daphniglaucine C. Dans un premier lieu, il a été tenté d'effectuer une élimination sur la bromocétone **3.62** afin d'accéder à l'énone **3.58** qui, encore une fois, aurait permis une fonctionnalisation en ayant recours à la réaction de Baylis-Hilman (*Schéma 3.15*). En utilisant les méthodes usuelles et recommandées, telles que le 1,8-diazabicyclo[5.4.0]undéc-7-ène (DBU), ou le carbonate de lithium et de calcium, il a toutefois été impossible de promouvoir l'élimination du bromure.[64]

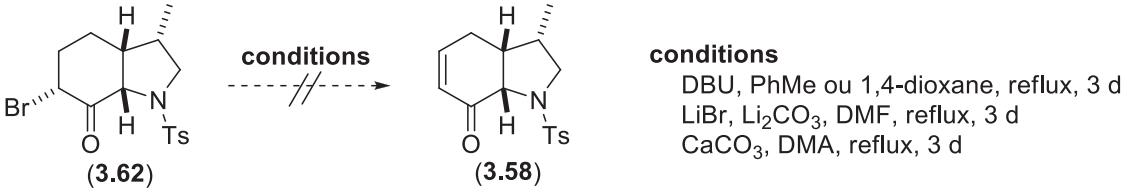
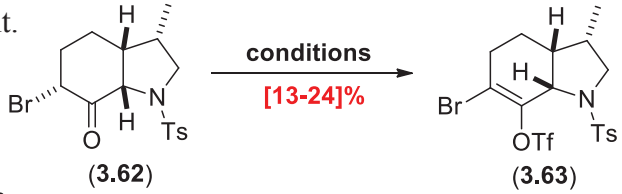


Schéma 3.15 : Tentatives d'élimination de la bromocétone **3.62**

Si l'élimination n'a pas été possible, au moins l'acidité du proton du côté de l'halogène devrait-elle être augmentée, de telle sorte qu'un traitement basique devrait, en théorie, favoriser la formation d'un énolate, régiosélectivement, cette fois-ci. Or, il s'avère qu'il existe quelques travaux portant sur la formation et le couplage chimiosélectif de triflates d'halogénoénol.[65] Il est intéressant de constater que, pour de tels motifs, le couplage au palladium est prévu s'effectuer au niveau du triflate, chimiosélectivement.



conditions

LHMDS (1,05 eq.), Tf_2O, THF, -78 °C (à t.a.)
LHMDS (1,05 eq.), Tf_2O (prémixé), THF, -78 °C
LHMDS (1,05 eq.), Tf_2O/HMPA, THF, -78 °C
KHMDS (1,05 eq.), Tf_2O, THF, -78 °C
LHMDS (1,05 eq.), Tf_2O, Et_2O, -78 °C
LHMDS (1,05 eq.), PhOTf, DMF, -78 °C à t.a. (aucune conversion)
LHMDS (1,05 eq.), réactif de Comins, THF, -78 °C à t.a.
LHMDS (1,05 eq.), réactif de Comins (prémixé), THF, -78 °C à t.a.
LHMDS (1,05 eq.), réactif de Comins, THF/HMPA, -78 °C à t.a.
LHMDS (1,05 eq.), réactif de Comins, Et_2O, -78 °C à t.a.

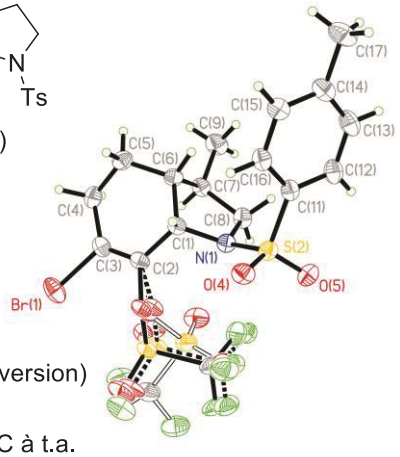


Schéma 3.16 : Formation du triflate de bromoénol **3.63**

La formation du triflate de bromoénol **3.63** a donc été tentée en traitant la bromocétone **3.62** avec du KHMDS ou du LiHMDS dans l'éther ou le THF (*Schéma 3.16*). Cependant, en utilisant l'anhydride triflique, le triflate de phénol[66] ou le réactif de Comins,[67] un maximum de 24% de produit désiré a pu être observé, même en tentant ces réactions sur plus d'un jour. Il a été compris un peu plus tard qu'il s'agissait probablement là d'un problème de réactivité. Dans tous les cas, l'énolate n'a pas été transformé quantitativement en triflate, et l'eau ajoutée au milieu réactionnel afin de parachever la réaction était suffisante, une fois déprotonée par la base HMDS, pour effectuer un déplacement S_N2 sur le site bromé, site activé par la cétone adjacente (*Schéma 3.17*). En autant de temps qu'il en fallait pour que le milieu réactionnel revienne à température ambiante durant l'extraction, l'acyloine **3.64** était donc formée de façon majoritaire, par inversion parfaite de la stéréochimie en alpha de la cétone. Puis, en quelques heures seulement, il y avait épimérisation de l'acyloine **3.64**, donnant un mélange 1 : 1 des diastéréoisomères **3.64** et **3.65**. Fait intéressant à noter : l'acyloine épimérisable n'était pas sujette à une transposition de la cétone et de l'alcool, même si celle-ci était facilement imaginable.

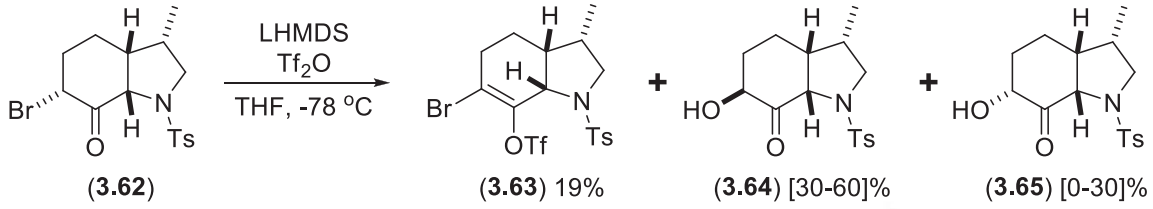
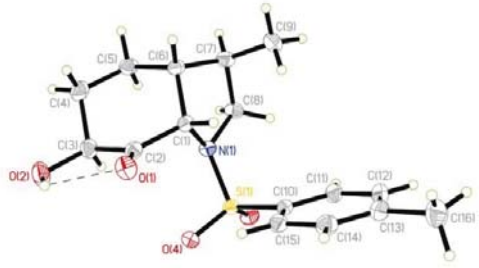


Schéma 3.17 : Formation du triflate de bromoénol **3.63** et des acyloines **3.64** et **3.65**



Pour bien comprendre cette transformation, la bromocétone **3.62** a été engagée dans une réaction de déplacement S_N2 avec de l'acétate de tétrabutylammonium pour générer l'acyloine acétylée **3.66**, et celle-ci a été comparée avec le produit d'acétylation de l'acyloine **3.64** (*Schéma 3.18*). Il a ainsi été possible de démontrer la réelle propension qu'avait le site bromé à être engagé dans une réaction de substitution.

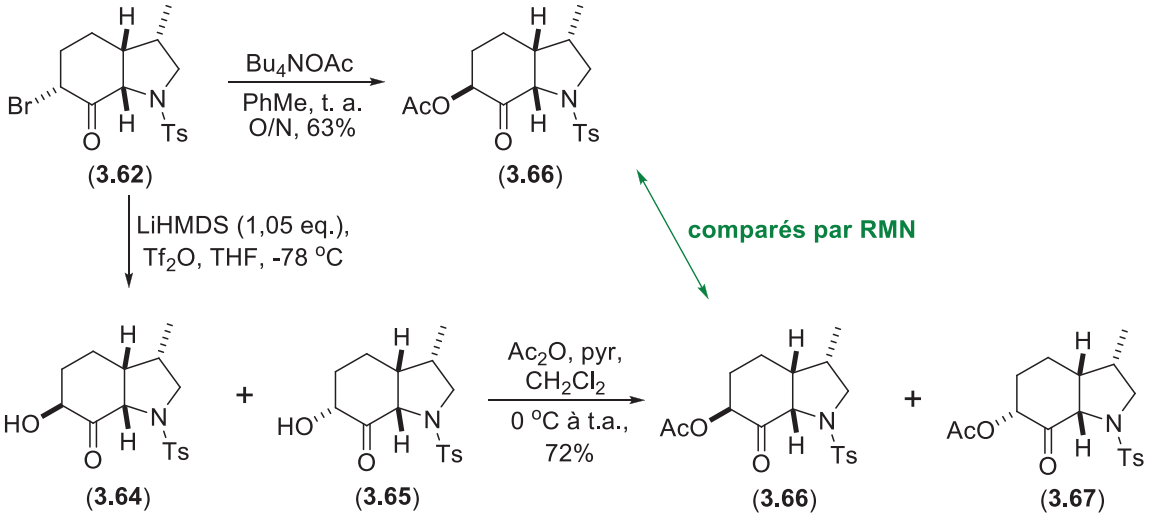


Schéma 3.18 : Déplacement avec Bu_4NOAc, et comparaison avec l'acyloine **3.66**

En outre, la facilité de cette transformation a été corroborée par l'épimérisation de la bromo-cétone en présence de bromure de tétrabutylammonium à température ambiante (*Schéma 3.19*).

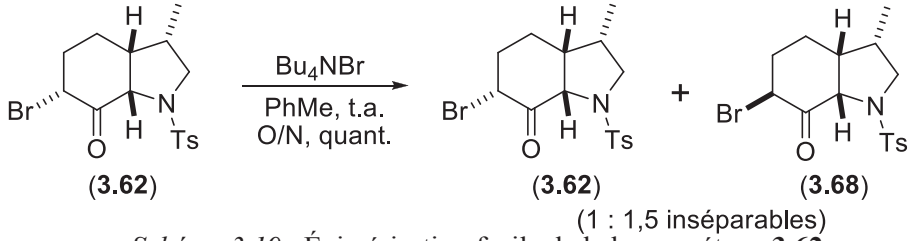


Schéma 3.19 : Épimérisation facile de la bromocétone **3.62**

Encouragé par la réactivité du site halogéné dans la formation des produits **3.64**, **3.66** et **3.68**, et par le potentiel d'un tel déplacement pour élaborer le tricycle désiré, il a été tenté de former une liaison C-C en traitant l'α-bromocétone **3.62** avec du cyanure de potassium (*Schéma 3.20*).[68] À notre grand désarroi, l'attaque du cyanure s'est effectuée cette fois-ci directement sur la cétone, afin de générer le cyano-époxyde **3.69** cristallin. Il a été trouvé qu'il existe bel et bien de tels exemples de réactivité dans la littérature.[69]

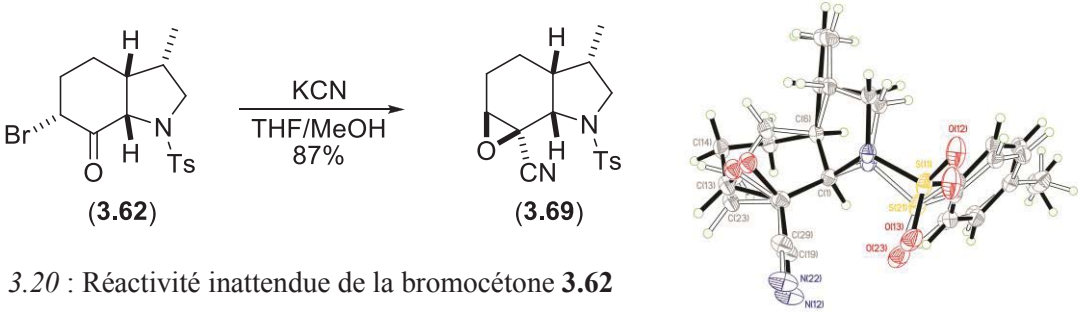
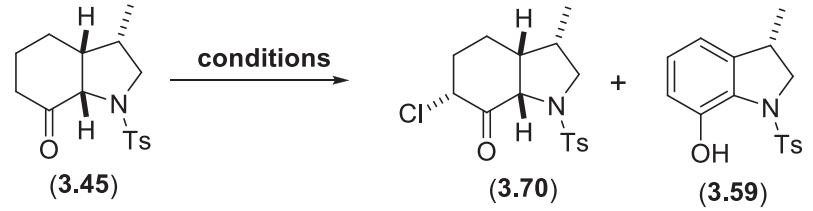


Schéma 3.20 : Réactivité inattendue de la bromocétone **3.62**

Dans un dernier effort, il a été convenu qu'une chlorocétone pouvait être formée, puis transformée en énol de chlorotriflate[70] à son tour, ou afficher des propriétés différentes de la bromocétone **3.62** et permettre ainsi l'élaboration d'un intermédiaire polycyclique. C'est en utilisant du *N*-chlorosuccinimide (NCS) en présence d'acide *p*-toluènesulfonique que la chlorocétone **3.70** a pu être formée avec un rendement de 92%, cette fois-ci plus reproductible (*Schéma 3.21*), sans que ne soit formé le phénol **3.59** observé plus tôt (voir *Schéma 3.14*). Toutefois, des problèmes de reproductibilité ont été notés lorsque la réaction était effectuée sur plus grosse échelle (100 mg et plus). Et, de toute façon, la formation de l'énol de chlorotriflate correspondant posait des problèmes similaires à ceux observés lors de la formation de l'énol de bromotriflate **3.63**.



conditions	(3.70)	(3.59)
NCS (1,0 eq.), DMSO, 70 °C	---	26% + 68% SM
NCS (1,0 eq.), pTsOH (1,5 eq.), MeCN, t.a., 3 d	26% + 68% SM	---
NCS (5,0 eq.), pTsOH (1,5 eq.), MeCN, t.a., 3 d	92%	---

Schéma 3.21 : Formation de la chlorocétone **3.70**

À ce stade, il était plutôt décourageant de constater que, après plusieurs mois d'efforts et malgré plusieurs stratégies différentes, l'issue de la fonctionnalisation régiosélective de la cétone **3.45** demeurait sans solution.

3.3 Approche et rétrosynthèse revisitées

Pendant que s'accumulaient les échecs et les problèmes dans le cadre de l'approche détaillée précédemment, le Dr. Helge Menz avait entrepris la synthèse de la calyciphilline B (**3.71**),[71] un composé naturel provenant de la même famille que la daphniglaucine C (*Schéma 3.22*). Comme ces deux produits partagent aussi un noyau pyrrolidine similaire, il a été envisagé de développer une synthèse convergente pour

ceux-ci, utilisant les mêmes réactifs de départ. Il a été convenu que la 3-hydroxyproline (**3.72**), précurseur évident pour une pyrrolidine polysubstituée, pouvait servir de point de départ pour l'élaboration des deux composés cibles polycycliques.

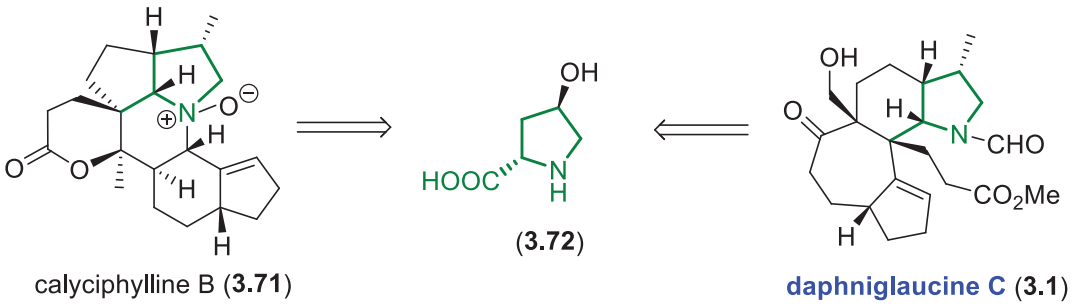


Schéma 3.22 : Structures de la calyciphilline B et daphniglaucine C et leur chiron commun

L'essentiel de la rétrosynthèse a donc été ajusté selon cette prémisse que l'hydroxyproline (**3.72**) pouvait servir de charpente pour le motif pyrrolidine retrouvé dans la daphniglaucine C (*Schéma 3.23*). Après protection et fonctionnalisation en position 3, un diester (**3.74**) ainsi formé pourrait être cyclisé pour donner un hexahydroindole (**3.73**) qui serait alors couplé et utilisé essentiellement tel qu'il en était convenu dans le premier plan rétrosynthétique (voir *Schéma 3.3*).

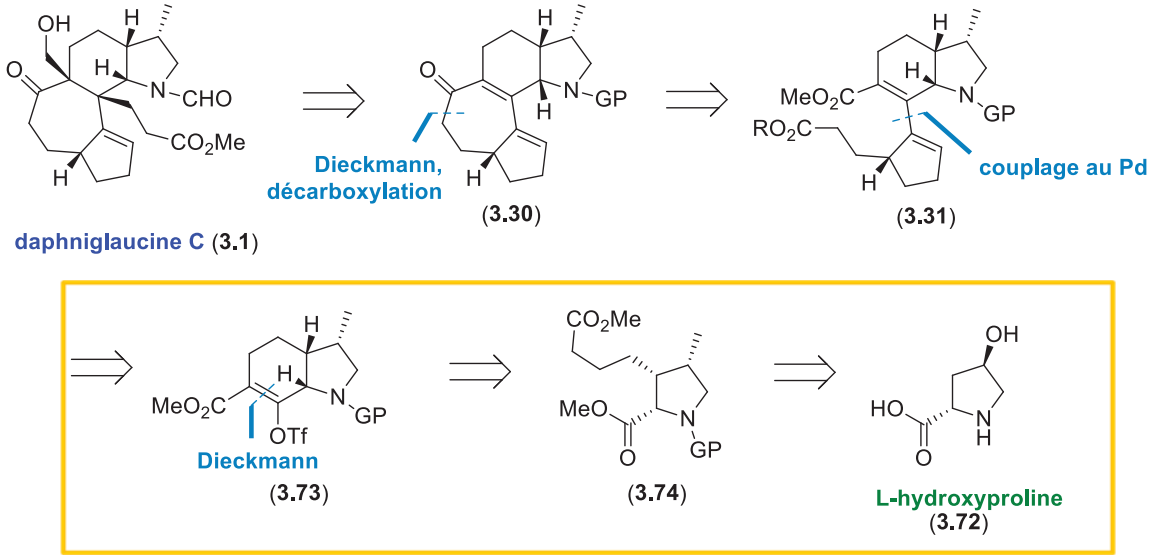


Schéma 3.23 : Rétrosynthèse de la daphniglaucine C (deuxième approche)

À la lumière de l'information obtenue lors des déboires de la première approche, ce plan présentait deux avantages cruciaux : premièrement, le méthyle en position 3 de la pyrrolidine pourrait être installé sans avoir à subir les caprices de la topologie d'un bicycle (bien qu'il était initialement prévu de tirer profit de celle-ci) et, surtout, il permettrait d'obtenir directement un bicycle fonctionnalisé sous forme de β-cétoester pouvant être facilement transformé en partenaire de couplage de Stille.

Le *Schéma 3.24* montre donc l'apport du Dr. Helge Menz en voie de l'obtention du composé bicyclique **3.82**, en mettant l'accent (en orange) sur quelques problèmes à régler afin d'améliorer cette séquence. Chacune de ces étapes sera couverte et détaillée dans la présente section.

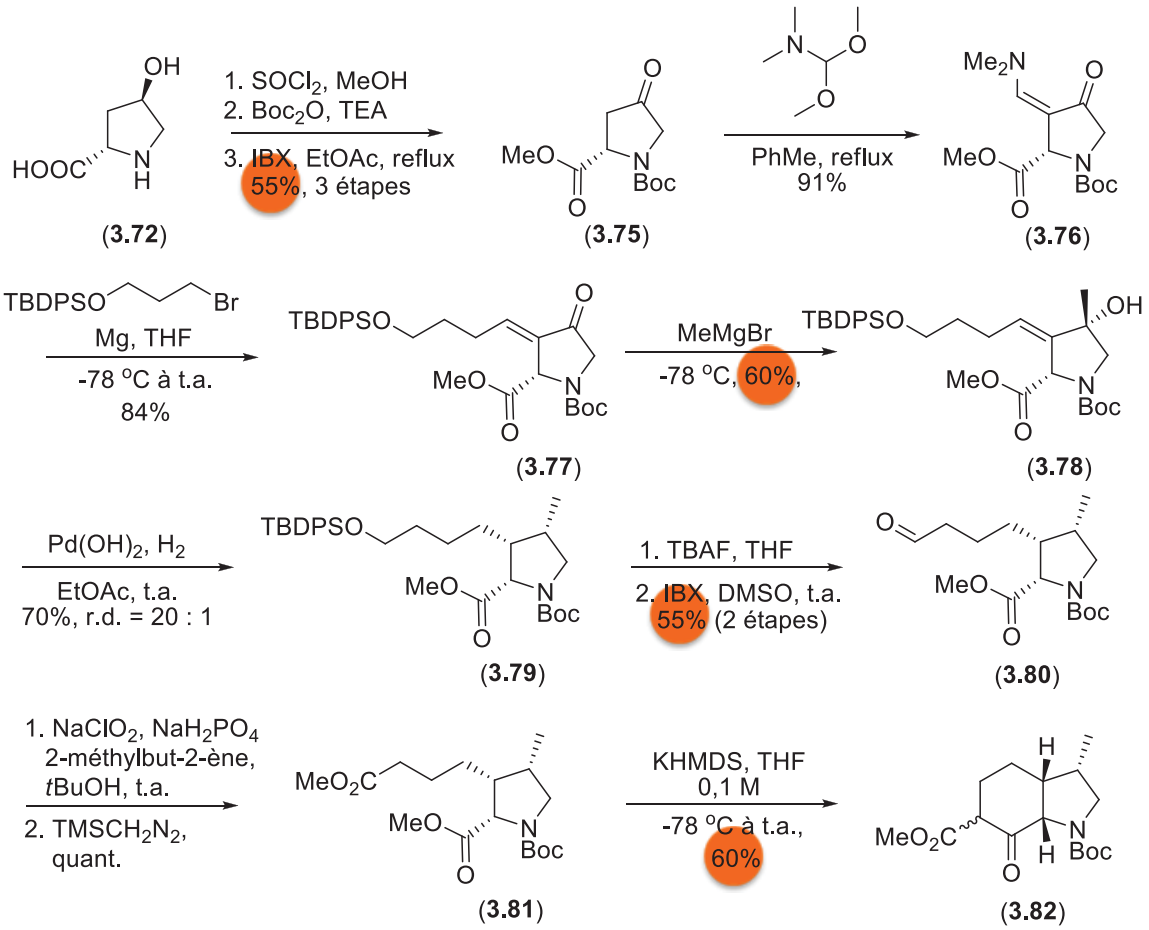


Schéma 3.24 : Schéma vers l'obtention du bicycle **3.82** tel que réalisé par le Dr. Helge Menz

Tel que mentionné plus tôt, le premier objectif de la synthèse consistait en l'obtention d'une pyrrolidine 2,3,4-trisubstituée de configuration *syn*. Après avoir passé plusieurs semaines à essayer de reproduire sans succès les résultats de Sardina *et al* selon lesquels il était possible d'obtenir ces motifs,[72] les efforts ont été tournés vers une approche jugée plus sûre, bien que plus longue. La 3-hydroxyproline (**3.72**), commercialement disponible, a d'abord été oxydée en pyrrolidinone **3.75** après protection (*Schéma 3.25*). Alors que le Dr. Helge Menz utilisait initialement l'IBX pour effectuer cette transformation avec un rendement de 58%, le procédé a été amélioré en utilisant du TEMPO, avec de l'acide trichloroisocyanurique en tant que cooxydant, permettant un rendement quantitatif.[73]

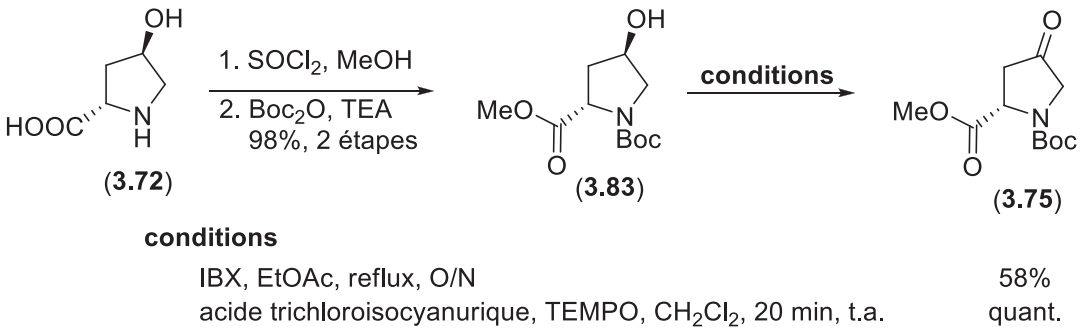


Schéma 3.25 : Obtention de la pyrrolidinone **3.75**

L'objectif aurait alors été de travailler tout de suite à la formation du deuxième centre stéréogénique (en position 3), mais des études préliminaires effectuées par le Dr. Helge Menz laissaient croire qu'une 4-prolinone substituée en position 3 était très facilement épimérisable. La formation de l'énaminone **3.76** a donc été préférée (voir *Schéma 3.13*),[74] ce groupement fonctionnel étant connu pour réagir en position β en présence de nucléophiles (*Schéma 3.26*). Plutôt que d'hydrogéner cet intermédiaire directement, il était planifié de « masquer » la cétone en y ajoutant un méthyle (**3.85**), afin d'éviter que le stéréocentre créé par hydrogénation n'épimérise. L'alcool tertiaire hydrogéné (**3.86**) serait par la suite éliminé, puis l'alcène **3.87** serait hydrogéné par la face supérieure pour donner la pyrrolidine 2,3,4-trisubstituée désirée. Même si ce plan semblait laborieux, il permettrait d'établir chacun des centres stéréogéniques requis d'une façon plus certaine.

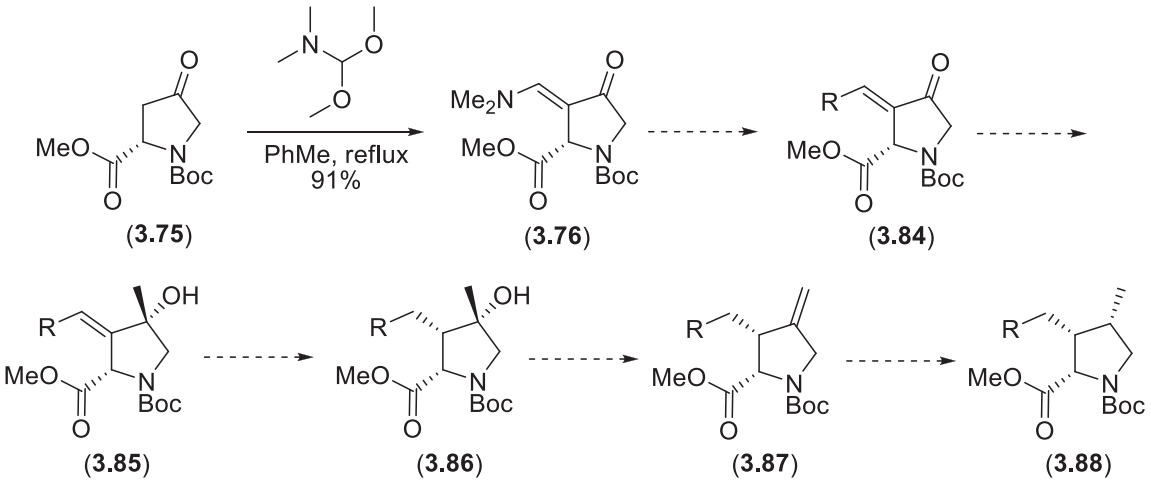


Schéma 3.26 : Plan vers la formation de la pyrrolidine 2,3,4-trisubstituée

Tel que prévu, la préparation d'un réactif de Grignard à partir du 3-bromo-1-benzoxypropane, puis l'ajout de celui-ci sur l'énaminone **3.76** a donné lieu à de l'addition 1,4 afin de générer sélectivement l'énone **3.89** (*Schéma 3.27*). Alors que les premiers résultats obtenus par le Dr. Helge Menz provenaient de l'utilisation d'un réactif de Grignard protégé sous forme d'éther silylé TBDPS (*Schéma 3.24*), il a été préféré d'utiliser un groupement benzyle pouvant être déprotégé de façon concomitante lors de l'hydrogénation à venir, afin de sauver une étape. Ensuite, alors que le Dr. Helge Menz a éprouvé quelques difficultés afin de promouvoir l'addition 1,2 chimiosélective du méthyl-Grignard sur l'énone obtenue, le problème a été réglé plus tard en ayant recours à une méthodologie développée par le groupe de Knochel préconisant l'emploi de sels de lanthanum.[75] L'alcool allylique tertiaire **3.90** a donc été obtenu chimiosélectivement dans un ratio de 5 : 1 en faveur du diastéréoisomère (*S*) en améliorant le rendement de 60% à 88%. Rappelons que le plan était ici d'hydrogéner l'alcène exocyclique tel qu'en **3.90** afin d'installer le deuxième stéréocentre voulu, tout en procédant à l'hydrogénolyse de l'éther benzylique. Or, il s'est avéré que l'alcool allylique **3.90**, sous des conditions d'hydrogénation usuelles, a directement donné l'alcène tétrasubstitué **3.91**! Cet alcène a pu, à son tour, être hydrogéné facilement pour donner la pyrrolidine 2,3,4-trisubstituée **3.92** à laquelle nous avions longtemps aspiré lors de l'approche précédente, dans un ratio diastéréoisomérique supérieur à 20 : 1. La transformation de l'alcool allylique **3.90** en alcène tétrasubstituée (**3.91**) a fait l'objet d'une étude plus approfondie afin de déterminer

les mécanismes à évoquer, les conditions optimales possibles, et l'identité des groupements fonctionnels tolérés. Ces résultats seront détaillés au Chapitre 4 intitulé « Brève étude d'une transposition allylique réductrice ».

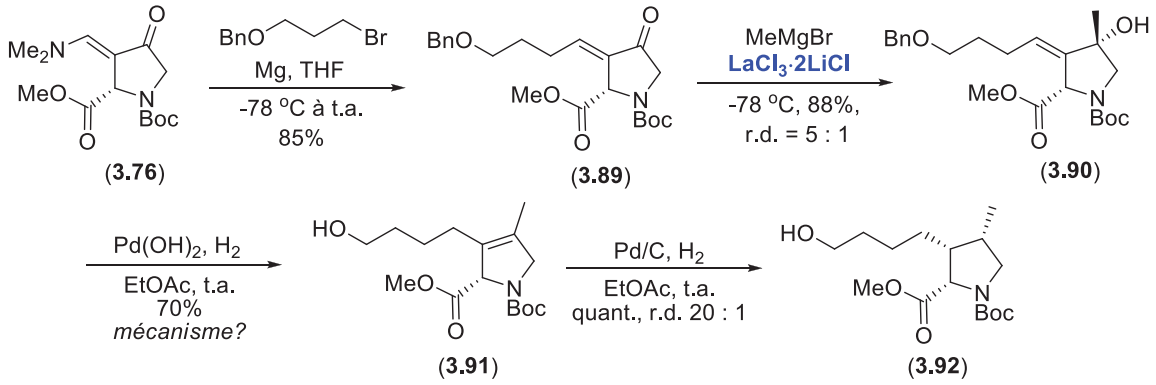


Schéma 3.27 : Résultats inattendus lors de l'hydrogénation de l'alcool allylique **3.90**

Une fois la pyrrolidine **3.92** obtenue, l'alcool a été transformé en ester méthylique à l'aide d'une séquence de trois étapes préconisant l'emploi d'IBX afin d'obtenir l'aldéhyde **3.80**, puis une oxydation de Pinnick[76] afin de transformer cet aldéhyde en acide carboxylique (*Schéma 3.28*). Ce dernier a ensuite été estérifié dans des conditions usuelles pour fournir le diester **3.81**. Plus tard, il a été découvert que la bisoxydation de l'alcool **3.92** à l'acide carboxylique **3.93** pouvait être effectuée avec un rendement quantitatif en une seule étape selon une méthode développée récemment par Porcheddu *et al.*[77] Il s'agit là d'une modification de la méthodologie utilisée précédemment pour obtenir la pyrrolidone **3.75**, cette fois-ci utilisant une quantité catalytique de NaBr converti *in situ* en NaOBr capable d'oxyder l'aldéhyde en acide carboxylique.

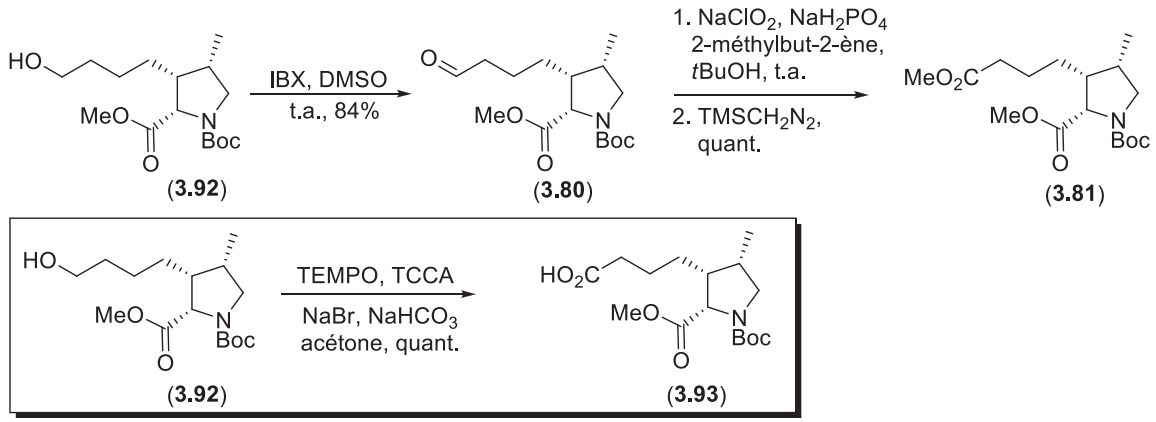
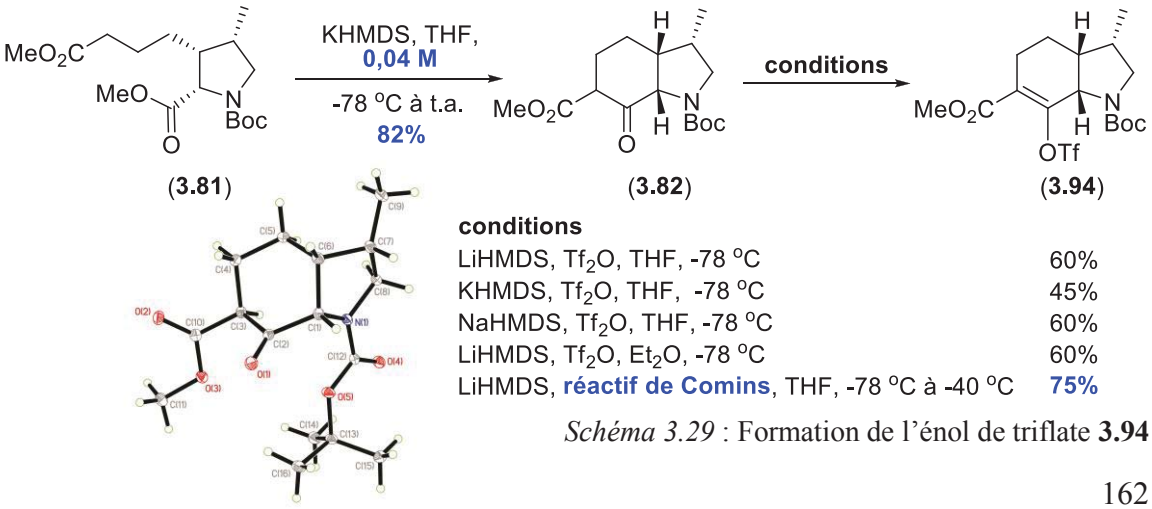


Schéma 3.28 : Formation du diester **3.81**

Le diester **3.81** était alors prêt pour une cyclisation d'aldol intramoléculaire de type Dieckmann[78] pour générer le bicycle octahydroindole substitué, tel que prévu (voir *Schéma 3.23*). Le premier test effectué par le Dr. Helge Menz laissait présager qu'il était possible d'effectuer cette transformation dans des conditions usuelles (KHMDS, THF, 0,01 M), mais qu'un léger travail d'optimisation serait nécessaire. Il s'est avéré que le rendement a pu être amélioré de 60% à 74%, puis à 82% (reproductible) en changeant simplement la concentration de la réaction de 0,01 M, à 0,02 M, à 0,04 M. Puisque le rendement était cette fois-ci acceptable, l'optimisation a été arrêtée à ce stade. Il est important de souligner que le produit de cyclisation **3.82**, dont la structure et la stéréochimie ont été certifiées par analyse de diffraction des rayons-X, correspond en tous points au bicycle fonctionnalisé qui était espéré dans la section précédente : il s'agit maintenant du diastéréoisomère désiré et, surtout, le β-cétoester est un dérivé fonctionnalisé régiosélectivement de la cétone **3.45**.

Après avoir amélioré la voie de synthèse établie par le Dr. Helge Menz afin d'obtenir l'intermédiaire **3.82**, il a été facile de transformer le β-cétoester **3.82** en triflate vinylique **3.94**. Toutefois, les premiers tests n'ont pas donné d'excellents rendements, encore une fois. Pas plus le LiHMDS que le NaHMDS ou le KHMDS, dans le THF en présence d'anhydride triflique (Tf_2O) n'a-t-il permis d'obtenir le produit **3.94** avec un rendement de plus de 60% (*Schéma 3.29*). La substitution du THF pour l'éther diéthylique n'a permis aucune amélioration. Finalement, le rendement a pu être augmenté jusqu'à 75% en utilisant le réactif de Comins[67] comme source de triflate plutôt que l'anhydride triflique, cette fois-ci en ayant réchauffé à -40 °C pendant quatre heures.



conditions	
LiHMDS, Tf_2O, THF, -78 °C	60%
KHMDS, Tf_2O, THF, -78 °C	45%
NaHMDS, Tf_2O, THF, -78 °C	60%
LiHMDS, Tf_2O, Et_2O, -78 °C	60%
LiHMDS, **réactif de Comins**, THF, -78 °C à -40 °C	**75%**

Schéma 3.29 : Formation de l'énol de triflate **3.94**

3.3.1 Formation du stannane 3.100

L'intermédiaire **3.94** correspondant à un des deux partenaires de couplage de Stille nécessaire à l'obtention d'un composé tricyclique vers la daphniglaucine C, l'attention a été tournée momentanément vers l'obtention d'un cyclopentene substitué pouvant être couplé à ce dernier fragment (voir *Schéma 3.23*). Alors que quelques stratégies ont été originalement considérées ou essayées à cet effet,[79] le groupe de Knochel avait déjà travaillé à l'élaboration courte et efficace de tels motifs, démontrant l'utilité de sels mixtes de zinc-cuivre pour la synthèse rapide d'iodures vinyliques et cycliques (*Schéma 3.30*).[80] Cette approche, introduisant la chiralité simplement à l'aide du réactif de CBS pour obtenir **3.97**,[81] préconisait l'emploi de phosphates allyliques déplacés de façon S_N2'. Il est à noter que quelques problèmes de reproductibilité ont été rencontrés initialement, mais ont été réglés en assurant une activation efficace du zinc métallique à l'aide de dibromoéthane et de chlorure de triméthylsilyl.[82] Afin de convertir l'iodure vinylique **3.99** en stannane, partenaire de couplage en vue de la réaction de Stille prévue, deux stratégies globales existaient : le couplage en présence de réactifs diétains,[83] et une séquence d'échange halogène-métal, suivi d'une transmétallation.[84] Alors que la première méthode n'a donné lieu à aucune conversion après plusieurs jours, la deuxième méthode a permis de fournir le stannane **3.100**, prêt pour un couplage de Stille.

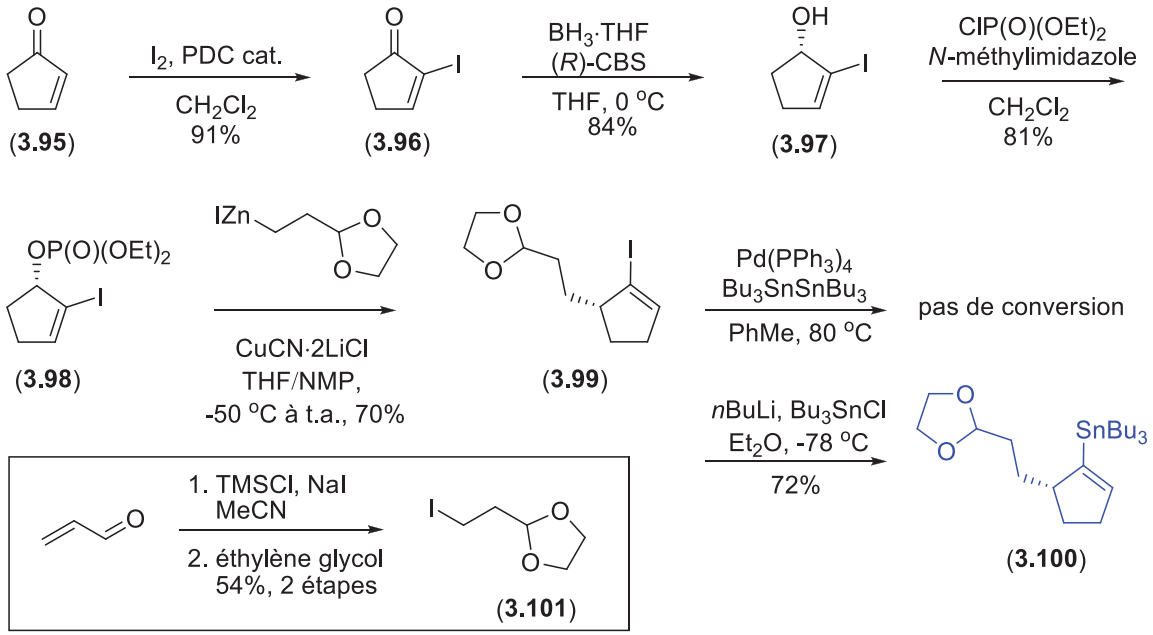


Schéma 3.30 : Synthèse de l'autre partenaire de couplage **3.100**

Les premières tentatives de formation de **3.100** ont été effectuées dans le THF, mais la réaction était moins sélective et souffrait de problèmes de reproductibilité, ne permettant que des rendements de 30-40%. Surtout, cette réaction était incomplète, rendant le produit apolaire difficile à séparer du réactif de départ. Alors que l'emploi de HMPA, ou de *t*BuLi, ou encore un changement de concentration à 1 M n'ont rien changé, la réaction a été améliorée de façon significative en employant plutôt de l'éther diéthylique comme solvant, permettant cette fois un rendement de 72% très reproductible, sur plus grosse échelle. Les deux partenaires de couplage de Stille étant prêts, ceux-ci ont été couplés dans des conditions usuelles de Stille à l'aide de $Pd_2(dba)_3$ (*Schéma 3.31*). Tel qu'il est généralement recommandé dans le cas de partenaires de couplage encombrés, l'emploi de triphénylarsine ($AsPh_3$) a été préconisé, afin d'accélérer la réaction et d'empêcher le transfert d'une chaîne butyle (venant du stannane **3.100** encombré).[85] Le premier essai, effectué à une concentration de 0,2 M, a permis d'obtenir directement le produit tricyclique **3.102** avec un rendement de 61%. En changeant simplement la concentration à laquelle le couplage était effectué (0,4 M), le rendement a été progressivement amélioré à 89%, et est maintenant reproductible.

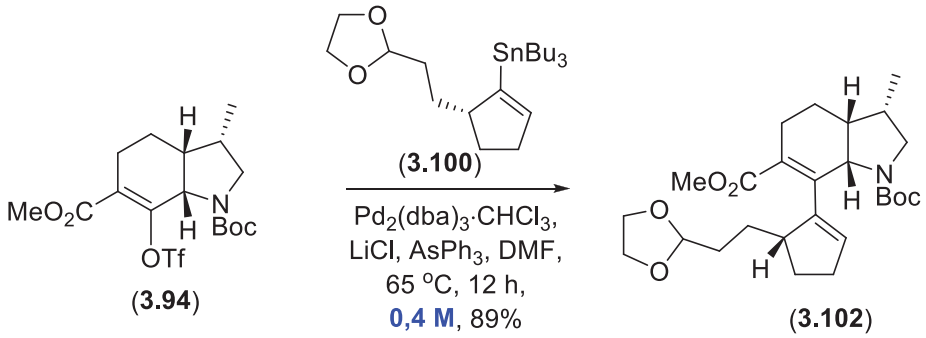
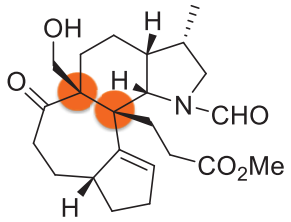


Schéma 3.31 : Couplage de Stille vers la formation du composé tricyclique **3.102**

Ayant en main un intermédiaire prometteur (**3.102**) en vue de compléter la synthèse de la daphniglaucine C, plusieurs options s'offraient à nous. L'obtention d'un intermédiaire tétracyclique tel que **3.30** (*Schéma 3.3*) a été reportée, puisque l'intermédiaire tricyclique **3.102** permettait déjà de mettre à l'épreuve quelques transformations en vue d'obtenir un ou deux des centres quaternaires contenus dans le composé cible.

3.4 Tentatives de formation des centres quaternaires
3.4.1 Emploi d'intermédiaires tricycliques

Si la formation de centres quaternaires demeure un des plus grands défis de synthèse à ce jour,[86] il est indéniable que le défi est accru dans le cas de la daphniglaucine C qui contient deux centres quaternaires vicinaux (*Figure 3.4*).[87] Conscients des difficultés potentielles reliées à l'installation de centres quaternaires de nature néopentylique, nous avons tout de même entrepris de fonctionnaliser l'ester α,β-insaturé **3.102** que nous avions déjà en main.



daphniglaucine C (**3.1**)

Figure 3.4 : La daphniglaucine C et ses deux centres quaternaires vicinaux

3.4.1.1 Cycloaddition [3+2] de Trost

À cet effet, une méthode développée par Trost,[88] et largement employée depuis,[89] permet d'effectuer des cycloadditions de type [3+2] en réagissant un triméthylméthylène (TMM) avec des alcènes activés dont des esters α,β-insaturés, tel qu'en **3.102** (*Schéma 3.32*). L'avantage d'une telle réaction est qu'elle aurait permis d'installer les deux centres quaternaires d'un seul coup, en étant assurés que ceux-ci seraient formés en relation *syn*, sur la même face du tricycle. De plus, cette méthode permet bel et bien de former des centres quaternaires. Une transformation de l'alcène obtenu en cétone, puis une oxydation de type Bayer-Villiger permettrait alors d'obtenir une lactone qui pourrait à son tour être fonctionnalisée afin d'obtenir les chaînes contenues dans la daphniglaucine C. Toutefois, malgré la notoriété de cette réaction, il n'en existe aucun exemple sur des diènes, tel que contient le composé **3.102**, à notre connaissance. Néanmoins, cette méthode, essayée dans le THF, le toluène, le DMF ou le DMSO selon ses conditions classiques, n'a permis aucune formation du produit désiré. Ce n'est qu'en chauffant dans le DMSO qu'une lente décomposition de **3.102** a été observée.

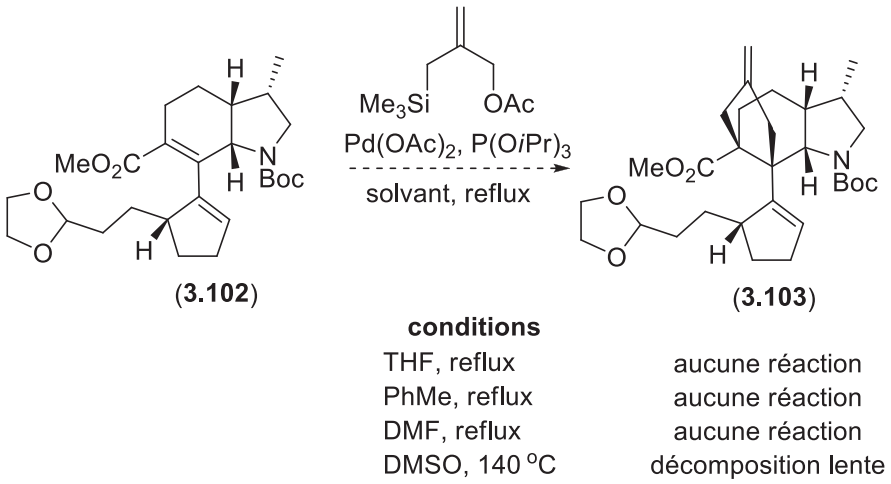


Schéma 3.32 : Tentatives de cycloaddition [3+2] avec l'intermédiaire **3.102**

3.4.1.2 Cycloaddition de Diels-Alder

En outre, les cycloaddition de Diels-Alder ont été largement employées dans le cas de formation de centres quaternaires, même de façon intermoléculaire.[90] Cependant, il existe beaucoup moins d'exemples de réaction du diène de Danishefsky (**3.104**) ou de l'acétate de 1,3-butadiène (**3.105**) avec des esters α,β-insaturés tels que **3.102**.[91] Surtout, il n'existe aucun exemple de formation de centres quaternaires sur des systèmes diéniques tels qu'ici. Néanmoins, il aurait été possible de modifier chimiquement le nouveau cyclohexène obtenu afin d'en construire les deux chaînes latérales contenues dans le composé cible.

Pour point de départ, la réaction de Diels-Alder a donc été essayée dans des conditions thermiques dans le toluène, mais n'a mené à aucune formation des produits désirés **3.106** ou **3.107** (*Schéma 3.33*). Même en changeant le solvant pour le DMSO, aucune transformation désirée n'a pu être observée. Alors qu'il aurait été logique de tenter de faciliter cette réaction par l'ajout d'acides de Lewis, il a été remarqué que la présence d'un acétal et d'un carbamate Boc en **3.102**, tous deux sensibles aux acides de Lewis, aurait dû compliquer la tâche. Cette stratégie a donc été délaissée, du moins à partir de l'intermédiaire **3.102**.

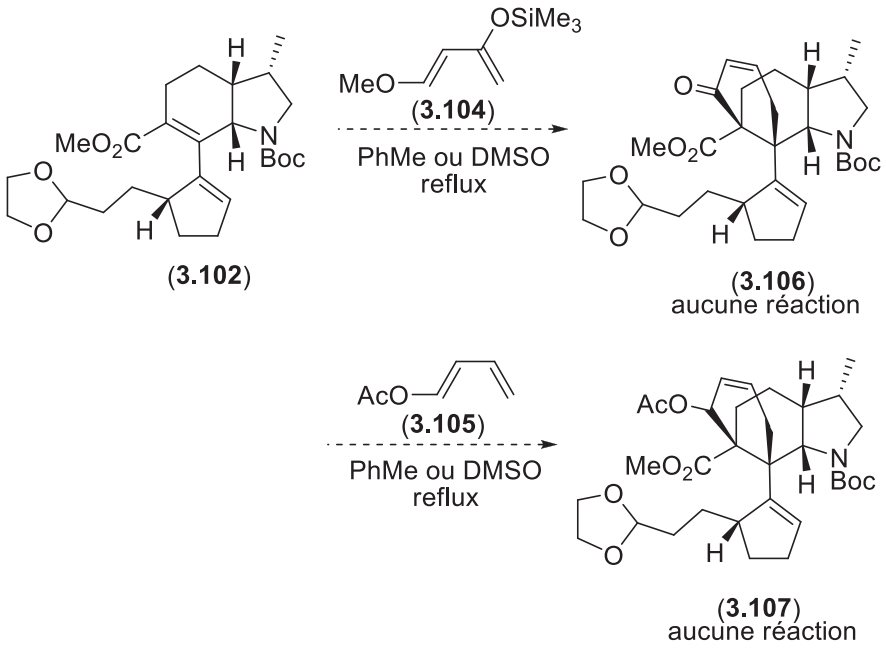


Schéma 3.33 : Tentatives de cycloaddition Diels-Alder avec l'intermédiaire **3.102**

3.4.1.3 Cyanation

La cyanation conjuguée est une réaction très employée et étudiée en ce qui a trait à la formation de liaisons carbone-carbone, y compris celle de centres quaternaires.[92] Il existe trois grandes catégories de réactifs utiles à la cyanation d'alcènes activés : les cyanures d'alkalins, les cyanures de dialkylaluminium et les cyanures de trialkylaluminium de lithium. Les deux dernières catégories ont l'avantage clair et éprouvé de minimiser la formation de sous-produits, notamment les produits d'hydrolyse du nitrile obtenu. Des deux dernières catégories, celle des cyanures de dialkylaluminium est reconnue comme étant la plus active, et il a été démontré à maintes reprises qu'elle permet de former des centres quaternaires, même à des positions sujettes à l'effet néopentylique.[93] Cependant, il est à noter que la très vaste majorité de ces réactions est effectuée sur des énones; il en existe très peu d'exemples sur les esters insaturés. Puisqu'il s'agissait tout de même d'un test rapide à effectuer, l'ester tricyclique **3.102** a été soumis à ces conditions en utilisant le cyanure de diéthylaluminium, commercialement disponible, dans une tentative d'addition 1,4 de cyanure (*Schéma 3.34*). Malheureusement, et sans grande surprise, aucune addition conjuguée n'a été observée. Ce n'est qu'au bout de trois jours qu'une déprotection lente de l'acétal en **3.102** a été observée, probablement en raison de l'acidité de Lewis du réactif d'aluminium.

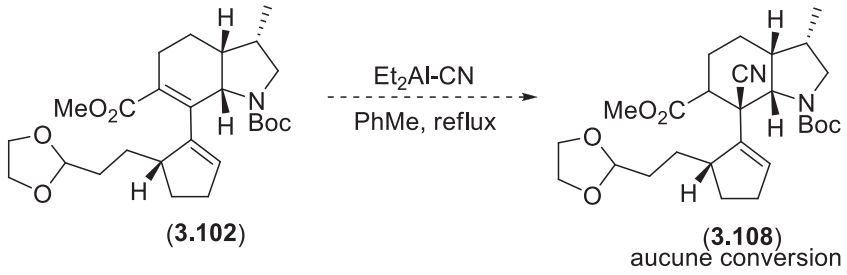


Schéma 3.34 : Tentatives de cyanation de l'intermédiaire **3.102**

3.4.1.4 Addition conjuguée de phosphonamides

L'addition conjuguée représentait aussi une option évidente à essayer pour générer au moins un centre quaternaire. Alors que l'addition de cuprates et de réactifs de ce type a été remise à plus tard (*vide infra*), l'addition de phosphonamides allyliques a été essayée à ce stade (*Schéma 3.35*). L'emploi de phosphonamides est connu depuis longtemps, et cette méthode en particulier a été enrichie au sein de notre laboratoire.[94] Celle-ci permet non seulement de former des centres quaternaires, mais le permet aussi sur des esters α,β-insaturés. Le phosphonamide allylique **3.110** a donc été préparé en deux étapes à partir de produit commerciaux[95] et l'ajout de ce dernier sur la 3-méthyl-cyclohex-2-énone (**3.109**) a été reproduit sans qu'aucun problème ne soit rencontré. Par contre, l'ajout de ce même phosphonamide achiral sur l'ester **3.102** s'est soldé en échec, ne fournissant qu'un mélange complexe sans qu'aucun produit d'addition ne puisse être isolé, ou même observé par analyse du mélange réactionnel brut.

Suite à l'échec de ces deux dernières transformations, une approche différente a été tentée : l'addition radicalaire conjuguée. Alors qu'une addition conjuguée normale pouvait en théorie mener à la formation d'une nouvelle liaison carbone-carbone en position 4 autant qu'en position 6, cette dernière favoriserait peut-être l'addition 1,4 caractérisée par la formation d'un radical tertiaire, plus stable qu'un radical secondaire si l'addition 1,6 était à envisager.

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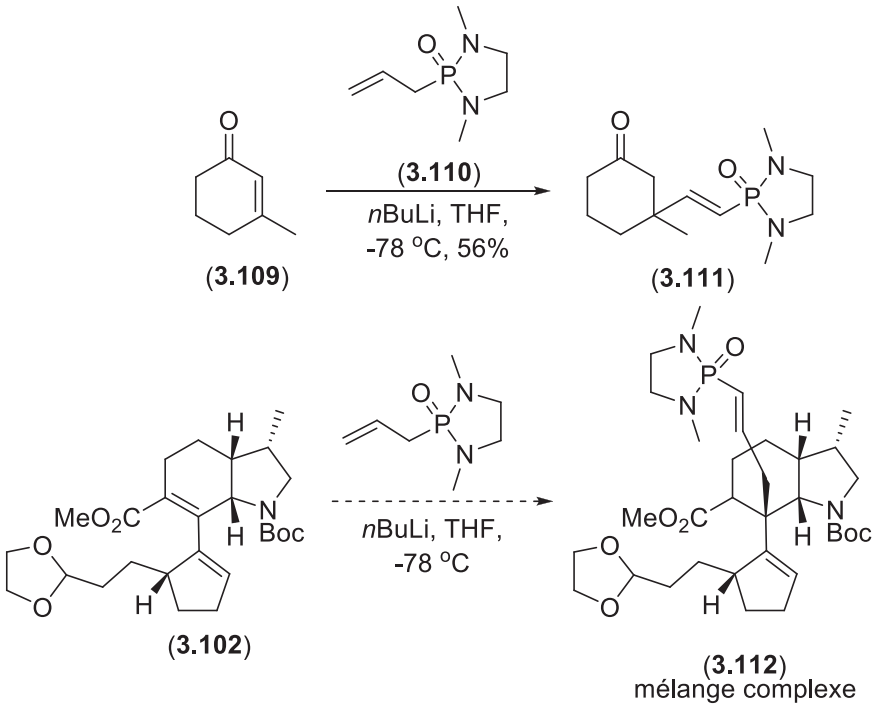


Schéma 3.35 : Addition de phosphonamides sur les intermédiaires **3.102** et **3.109**

3.4.1.5 Addition conjuguée radicalaire

Alors qu'il existe une multitude d'exemples quant à la faisabilité de l'addition radicalaire conjuguée dans sa version intramoléculaire, beaucoup moins de méthodes font état d'additions conjuguées radicalaires intermoléculaires. Surtout, toutes ces méthodes d'additions radicalaires conjuguées possibles, telles que celles promues par le SmI_2,[96] le Ti(III)[97] et le triéthylaluminium ou le triéthylborane,[98] ne permettent de l'addition que sur les énones, et non les esters insaturés. Ces deux constats, liés au fait que très peu de ces méthodes permettent la formation de centres *quaternaires* en particulier, ne laissaient finalement pas autant de choix que prévu! L'ester **3.102** a donc été traité avec du titanium(III), lui-même préparé par réduction au zinc d'un complexe Cp_2TiCl_2 (*Schéma 3.36*). Au-delà des couleurs attendues, caractéristiques de la formation efficace d'un complexe au Ti(III), aucune transformation désirée n'a pu être observée, et le réactif de départ a pu être réisolé.

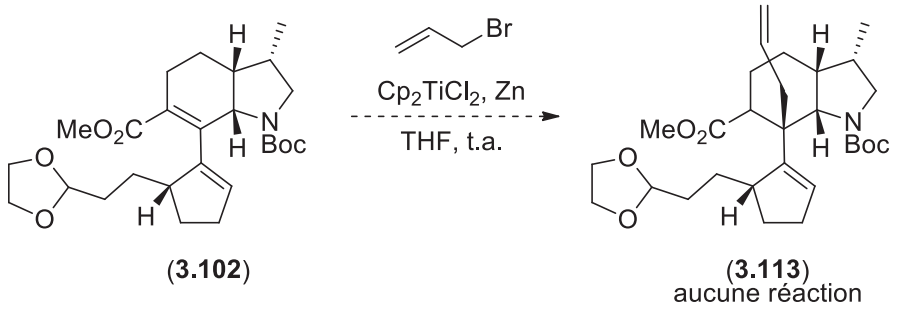


Schéma 3.36 : Tentative d'addition conjuguée radicalaire sur l'intermédiaire **3.102**

Confrontés à la pluralité de nos échecs vers l'installation des centres quaternaires, et de moins en moins convaincus que l'ester **3.102** possède la réactivité nécessaire, une autre approche a alors été préconisée : celle du réarrangement sigmatropique. Heureusement, il existe beaucoup d'options au niveau de ces réarrangements : notamment les réarrangements de Cope, de Claisen, de Johnson-Claisen, d'Ireland-Claisen, d'oxy-Cope, de Wittig-Still, et d'Eschenmoser-Claisen. Qui plus est, chacune de ces transformations implique des particularités mécanistiques différentes et des améliorations distinctes. Il y avait donc fort à parier que quelques-unes de ces réactions intramoléculaires pouvaient effectivement réussir là où toutes les réactions précédemment détaillées avaient échoué. Encore plus encourageant : non seulement les réarrangements sigmatropiques permettent la formation de centres quaternaires, mais ils constituent en fait une des principales stratégies pour celle-ci.[87]

3.4.1.6 Réarrangements sigmatropiques [3,3]

Afin de tester certains de ces réarrangements, il était toutefois nécessaire de préparer leur précurseur respectif. Or, le premier réarrangement testé a été celui de Johnson-Claisen (*Schéma 3.37*).[99] Bien qu'il s'agisse d'un des réarrangements les moins doux, c'est grâce à ce réarrangement que le Dr. Helge Menz, un collègue qui travaillait sur la synthèse totale de la calyciphilline B (tel que mentionné précédemment), a trouvé une rare méthode permettant la formation du centre quaternaire tel que contient le composé **3.117**. Les conditions employées dans le cas de la calyciphilline B étaient elles-mêmes empruntées du groupe de Bach ayant à effectuer cette transformation sur un

substrat similaire.[100] Puisqu'il y a une forte similarité entre **3.116** et les intermédiaires obtenus jusqu'ici pour la daphniglaucine C, l'ester **3.102** a été réduit à l'aide du réactif DIBAL-H afin de générer l'alcool allylique **3.114**. Il semblait par ailleurs impossible de réduire l'ester en aldéhyde chimisoélectivement. Ensuite, cet alcool a été chauffé à reflux dans l'orthoacétate de méthyle comme solvant en présence d'hydroquinone jusqu'à conversion d'une tache moins polaire sur CCM, et cet intermédiaire, présumément l'acétal de cétène, a été chauffé jusqu'à évaporation graduelle de l'orthoester, tel que décrit. Ce n'est qu'après un jour qu'il devenait évident que la réaction n'induisait que la décomposition lente de l'acétal de cétène intermédiaire.

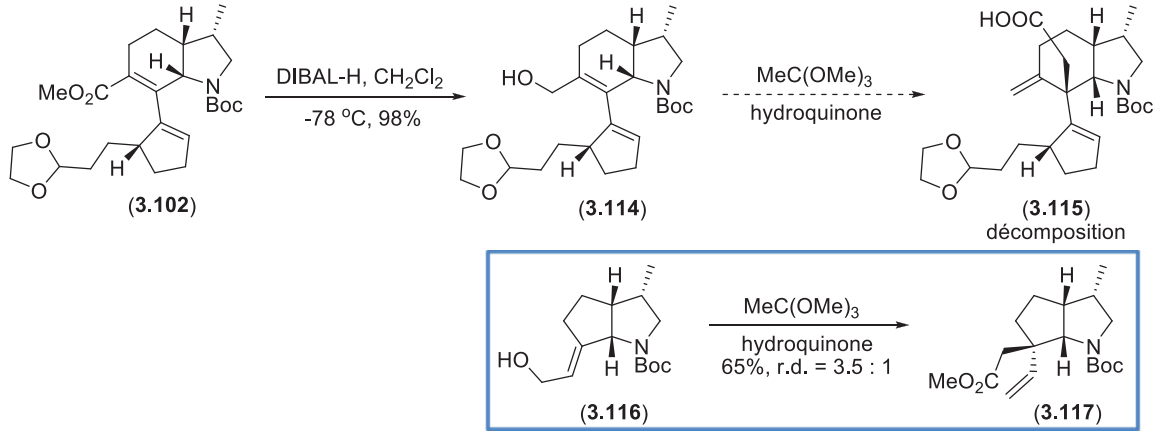


Schéma 3.37 : Tentative de réarrangement de Johnson-Claisen de l'intermédiaire **3.114**

Or, la différence de réactivité entre **3.102** et **3.116** pouvait probablement s'expliquer par deux différences entre leur structure : l'intermédiaire tricyclique **3.102** est le seul à posséder un groupement acétal, sensible à l'acide, et un diène (et non simplement un alcène). Il est à noter que le carbamate Boc, groupement aussi sensible à l'acide et donc peut-être responsable de la décomposition encourue, est aussi présent dans l'intermédiaire **3.116**. Par ailleurs, la résistance du Boc envers les acides a été démontrée à quelques reprises par la suite dans le cas de l'intermédiaire **3.102** (*vide infra*).

Afin d'offrir une chance plus sérieuse au réarrangement de Johnson-Claisen, une option évidente s'offrait alors à nous : changer l'acétal tel qu'en **3.114**. Pour ce faire, il a été pratique d'utiliser l'intermédiaire **3.114** et ainsi éviter d'avoir deux esters susceptibles

d'être réduits sans discernement (*Schéma 3.38*). L'alcool allylique **3.114** a donc été soumis à des conditions d'hydrolyse classiques (HCl 1 N dans le THF) afin de fournir l'aldéhyde correspondant avec un rendement modeste, mais probablement optimisable. L'aldéhyde a été oxydé selon les conditions de Pinnick afin de fournir un acide carboxylique qui, dans son mélange brut, a été converti en ester méthylique tel qu'en **3.118**. Encore une fois, l'intermédiaire **3.118** a permis de tester les conditions de Johnson-Claisen et, malheureusement, n'a donné rien de mieux que de la décomposition, tel qu'observé précédemment.

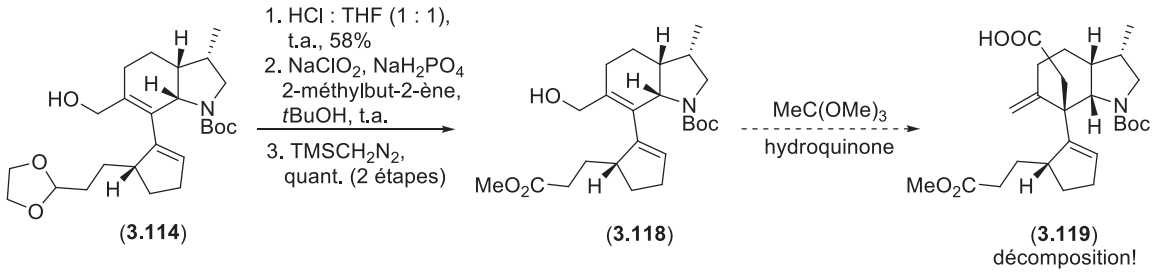


Schéma 3.38 : Tentative de réarrangement de Johnson-Claisen, prise 2

Bien qu'il ait été décourageant de constater que le réarrangement de Johnson-Claisen ne convenait pas pour la formation du centre quaternaire alors qu'il l'avait été pour l'intermédiaire **3.116**, il restait à ce stade beaucoup d'autres types de réarrangements à essayer, dont certains sous des conditions plus douces. Entre autres, il a été possible de tester le réarrangement d'Eschenmoser,[101] permettant lui aussi la formation de centres quaternaires.[102] L'alcool allylique **3.114** a donc été chauffé en présence de diméthylacétal de diméthylacétamide en utilisant le toluène comme solvant, mais aucune transformation n'a pu être observée jusqu'à reflux (*Schéma 3.39*). Ce n'est qu'en changeant le solvant pour du xylène et en chauffant pendant deux jours qu'une lente décomposition a été observée. Autant dans le cas du réarrangement d'Eschenmoser que Johnson-Claisen, une lente évaporation du solvant a par ailleurs été préconisée lors des réarrangements, sans que cette stratégie n'améliore les chances de transformation.

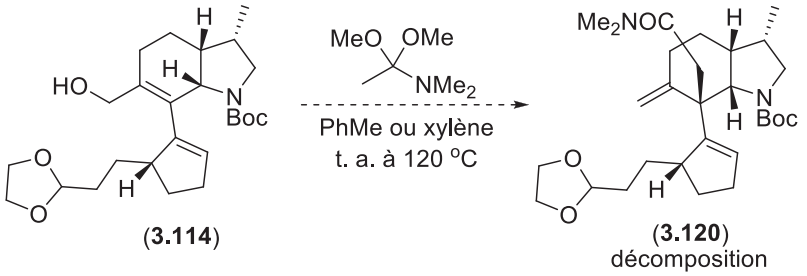


Schéma 3.39 : Tentative de réarrangement d'Eschenmoser avec l'intermédiaire **3.114**

Ensuite, il a été possible de tester le réarrangement d'Ireland-Claisen[103] sans trop avoir à modifier les intermédiaires en main (*Schéma 3.40*). L'acétate **3.121** a été préparé à partir de l'alcool allylique **3.114** dans des conditions usuelles (Ac_2O, Et_3N, DMAP). Par la suite, c'est sans grande difficulté que l'éther d'énol silylé correspondant (**3.122**) a pu être préparé sélectivement, bien que par une conversion partielle (48%, 92% bsmr). Cet énol silylé a d'ailleurs pu être isolé par chromatographie sur silice, et était très stable, même à température ambiante! Cependant, lorsque l'énol silylé **3.122** a été chauffé à reflux dans le THF ou le toluène, aucune conversion désirée n'a pu être observée. Ce n'est qu'en chauffant à reflux dans le 1,4-dioxane qu'une décomposition lente a été notée. Bien qu'il soit en effet possible de catalyser cette réaction grâce à quelques acides de Lewis,[104] ce type de réarrangement sigmatropique a été laissé de côté.

Avec l'intermédiaire **3.114** en main, un autre réarrangement sigmatropique a facilement pu être essayé: celui d'oxy-Cope.[105] L'alcool allylique **3.114** a donc été oxydé en aldéhyde selon les conditions de Dess-Martin, puisque le réactif de DIBAL-H était incapable de réduire chimiosélectivement l'ester méthylique en aldéhyde. Par la suite, un réactif d'allyl Grignard a été ajouté sur l'aldéhyde, afin de fournir le mélange d'alcools secondaires **3.124** dans un ratio diastéréomérique de 4 : 3. Puisque la nouvelle chaîne ajoutée était en rotation libre, il a été impossible d'assigner aisément la stéréochimie respective des diastéréoisomères. Par contre, ceux-ci étant séparables, les deux alcools ont simplement été engagés séparément dans les mêmes conditions d'oxy-Cope.

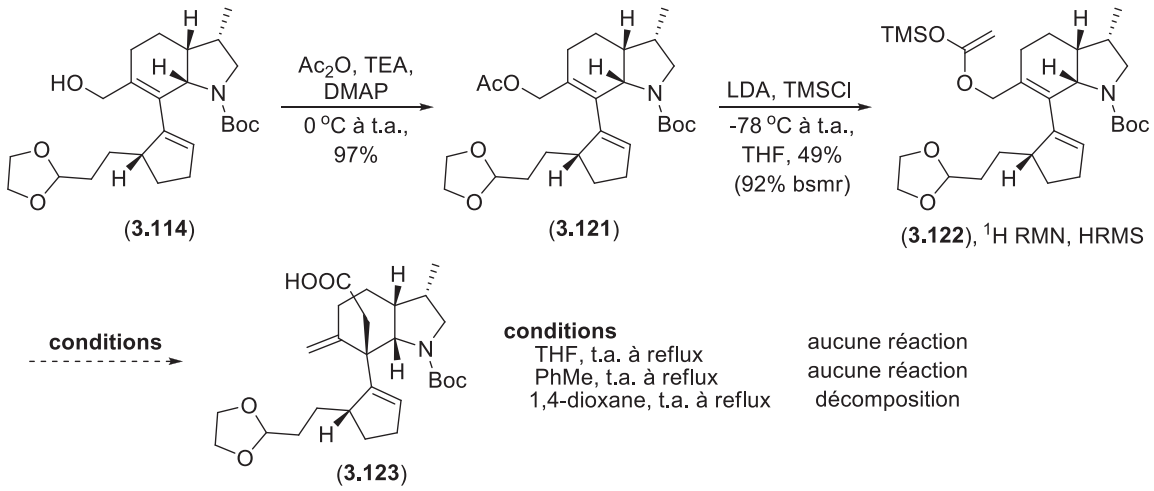


Schéma 3.40 : Tentative de réarrangement d'Ireland-Claisen avec l'intermédiaire **3.121**

À cet effet, une base a été utilisée afin d'effectuer un réarrangement oxy-Cope anionique, connu depuis longtemps comme étant plus efficace qu'un réarrangement d'oxy-Cope neutre.[106] Des bases possibles à utiliser, les bases à contre-ion potassium sont les plus populaires : puisque le potassium est plus gros, il coordonne l'alcoolate de façon moins efficace, ce qui entraîne un affaiblissement de la liaison C1-C2 et un réarrangement plus facile (*Schéma 3.41*). Malheureusement, les alcools secondaires **3.124**, traités séparément avec le KHMDS dans le THF, le toluène ou le diglyme, n'ont donné qu'une décomposition lente, et aucun produit désiré n'a été observé. Même la base forte KH a été employée, sans qu'aucune transformation ne soit observée après reflux dans le toluène. Il subsistait quelques options intéressantes, dont l'emploi d'éthers couronnes ou des micro-ondes (*vide infra)*, mais l'absence totale de réaction a dissuadé toute tentative abondant en ce sens.

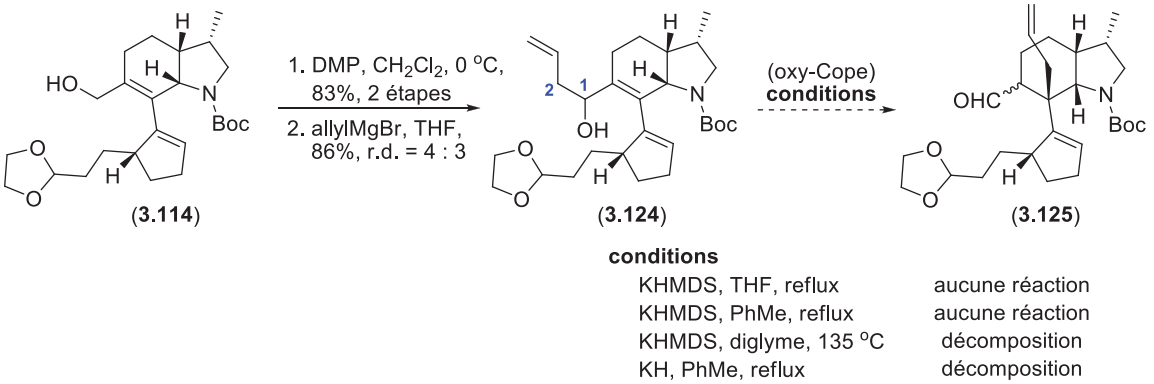


Schéma 3.41 : Tentative de réarrangement d'oxy-Cope avec **3.124**

3.4.1.7 Réarrangement de Wittig-Still

Ayant amenuisé considérablement la liste possible de réarrangements sigmatropiques pouvant être effectués à partir des intermédiaires tricycliques **3.114** et **3.124**, une option moins populaire, mais tout aussi pertinente, a été tentée : le réarrangement de Wittig-Still.[107,108] En effet, même si celui-ci préconise l'emploi d'étain, parfois toxique, et d'une base très forte telle que le butyllithium, il possède l'avantage indéniable d'être lui aussi promu par un changement de pKa du réactif de départ vers le produit. Car en allant du réactif de départ au produit attendu, on obtient un alcoolate beaucoup plus stable que le carbanion primaire formé par transmétallation. C'est probablement pourquoi ces réactions sont, à tout le moins, effectuées à plus basses températures que les autres réarrangements sigmatropiques essayés jusqu'ici.

Il est aussi utile de noter que cette réaction est capable de mener à la formation de centres quaternaires, bien que dans de rares exemples et avec des rendements parfois peu convaincants (*Schéma 3.42*),[109] mais qu'aucune réaction connue ne fait état de son emploi dans le cas de systèmes diéniques tels que celui en **3.114**. La formation d'un produit de réarrangement [2,3] est connue pour procéder de façon concertée, alors qu'un sous-produit de réarrangement [1,2] est parfois observé et connu pour être le produit d'une dissociation-recombinaison radicalaire, qui elle-même peut mener à la formation de sous-produits dans le cas d'intermédiaires sensibles aux radicaux.[110] De façon générale, il est toutefois reconnu que la formation de sous-produits radicalaires peut être circonvenue en maintenant la réaction à basse température.

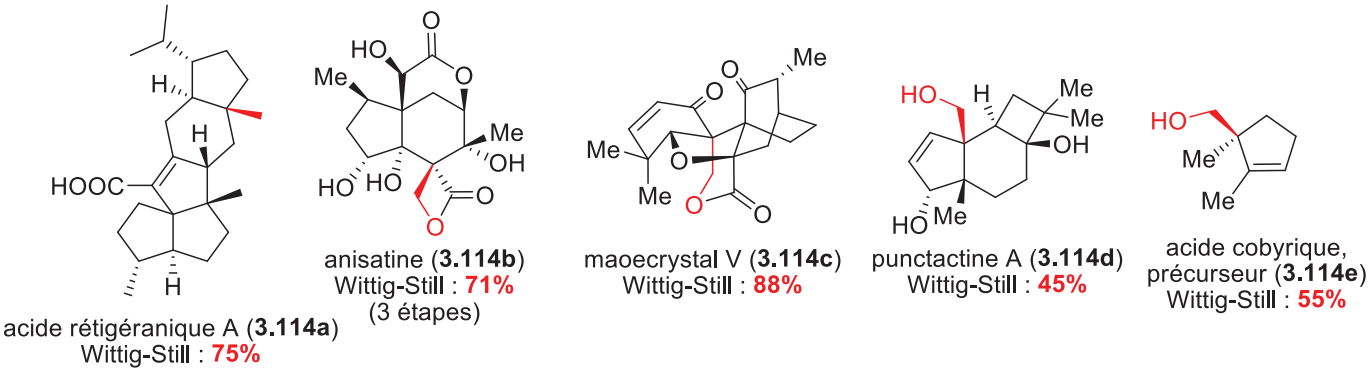


Schéma 3.42 : Exemples de réarrangements de Wittig-Still en synthèse totale de produits naturels

Afin de tester le réarrangement de Wittig-Still, l'éther d'étain **3.126** a été préparé dans des conditions usuelles à partir de l'alcool allylique **3.114** avec un rendement de 85% (*Schéma 3.43*). Ce réactif d'étain a ensuite été traité avec du buthyllithium, à -78 ^{o}C dans le THF, tel que largement prescrit pour un tel réarrangement. Après 4 h à cette température, la réaction a été arrêtée en traitant le milieu réactionnel avec du chlorure d'ammonium. Deux produits ont alors été isolés : le produit **3.128** (38%), provenant sans doute d'une transmétallation de **3.126** sans qu'aucun réarrangement n'ait été observé, et très étonnamment, le produit **3.114** (22%)! Or, ce dernier produit, formellement obtenu par voie de « déméthylstannylation », n'a jamais été rapporté comme sous-produit d'une réaction de Wittig-Still, à notre connaissance. La réaction a été répétée afin de s'assurer que le produit de départ **3.126** n'était pas simplement contaminé par l'alcool **3.114** avant réaction, mais les produits obtenus étaient toujours les mêmes. Puisque le produit **3.128** majoritaire a été isolé, la réaction a été réessayée en laissant cette fois-ci le milieu réactionnel revenir à température ambiante pendant 1 h. Malheureusement, seulement le produit **3.114** a encore été isolé (27%). Alors que tout laissait croire que cette réaction était inappropriée pour le substrat **3.126**, une rencontre fortuite a inspiré l'essai d'une troisième condition, cette fois-ci traitant l'éther d'étain **3.126** avec un large excès de buthyllithium (10 eq.) dans l'hexane, directement à -10 ^{o}C. Alors que ces conditions semblaient peut-être un peu fortes, elles ont néanmoins permis d'observer la formation du produit **3.127** désiré avec un rendement modeste de 25%, avec formation concomitante des produits **3.114** et **3.129**, produits inséparables. Il est toutefois à mentionner que la stéréochimie du produit attendu (**3.127**) n'a pas pu être confirmée par noesy. La stéréochimie dessinée est présumée, étant donné la topologie du polycycle.

Étant confrontés à un mélange réactionnel plus complexe qu'attendu compte tenu de la présence de l'intermédiaire **3.114**, la réaction de réarrangement de Wittig-Still a eu besoin d'un peu plus d'affection. Alors que la formation du sous-produit de réarrangement [1,2] (**3.129**) est en effet détaillée et connue pour procéder selon un mécanisme de dissociation-recombinasion radicalaire,[110] comment le produit **3.114** pouvait-il être obtenu dans de telles conditions (*Schéma 3.44*)? S'agissait-il d'une attaque du *n*Buli, agissant comme nucléophile plutôt que comme base, afin d'opérer directement

la déméthylstannylation? S'agissait-il, alternativement, d'une α-élimination effectuée à partir du carbanion **3.130**, générant ainsi l'alcool **3.114** et un carbène? Ou s'agissait-il finalement d'une α-élimination, peut-être plus probable, effectuée à partir d'un ylure d'étain stabilisé **3.131**? De plus, nonobstant le mécanisme à évoquer, la formation du sous-produit **3.114** était-elle explicable par la présence du diène, altérant considérablement l'énergie des orbitales HOMO-LUMO impliquées dans le réarrangement?

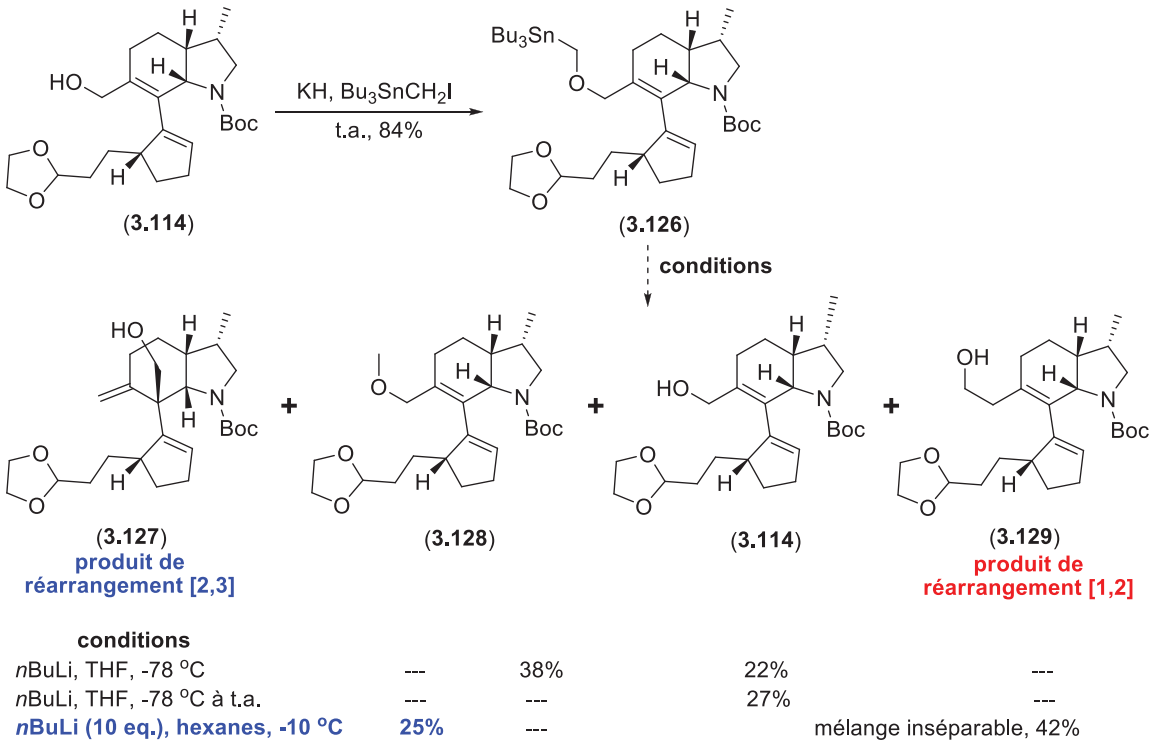


Schéma 3.43 : Tentative de réarrangement de Wittig-Still avec l'intermédiaire **3.126**

Tel que mentionné précédemment, la formation de sous-produits tels que **3.114** n'est pas rapportée dans la littérature, probablement parce que les réarrangements de Wittig-Still sont typiquement effectués en une seule étape à partir de l'alcool allylique. La présence d'alcool allylique aurait alors pu être attribuée à une formation incomplète de l'éther d'étain intermédiaire, alors qu'il y avait plus à chercher. La réponse à ces questions permettrait peut-être au passage d'identifier un mécanisme alternatif de la réaction de Wittig-Still négligé jusqu'à maintenant, ou, du moins, d'augmenter considérablement le rendement du produit attendu **3.127**.

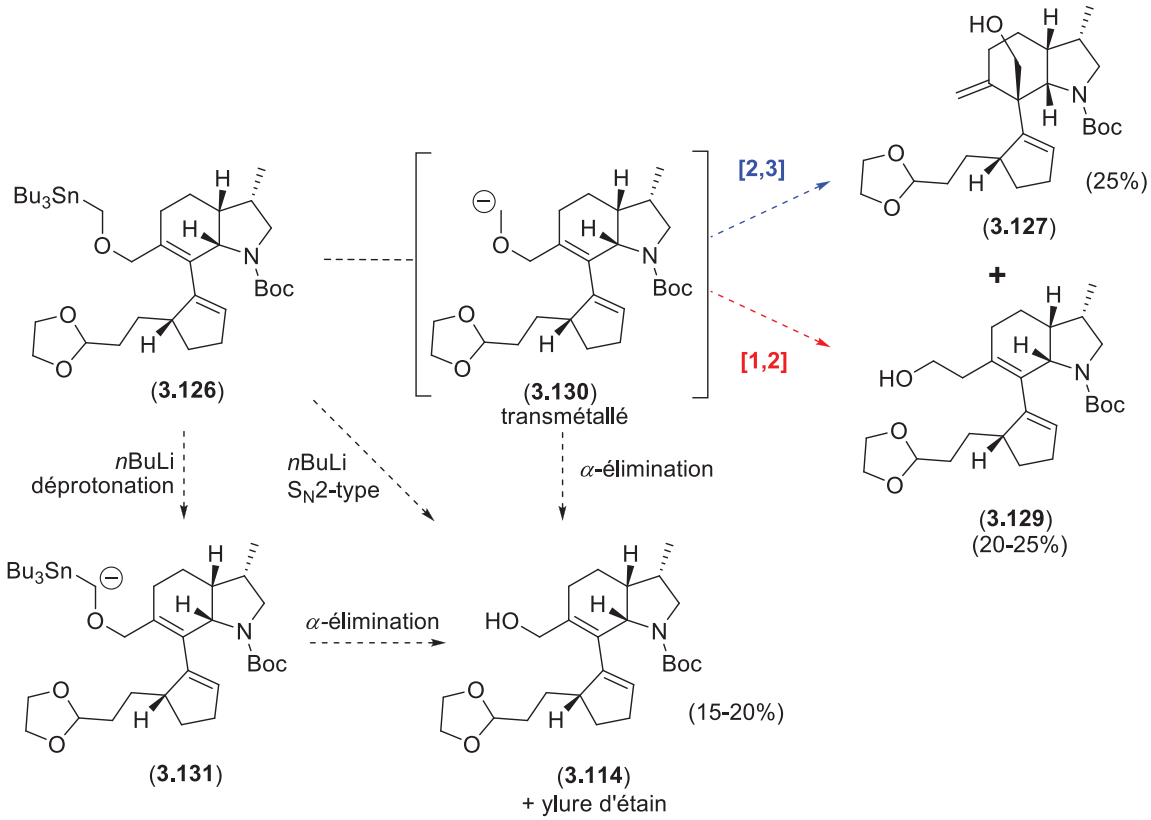


Schéma 3.44 : Mécanismes possibles expliquant la formation des produits **3.114**, **3.127** et **3.129**

Afin de répondre à ces questions et d'éviter de gaspiller quelques grammes d'un intermédiaire précieux, l'optimisation a été effectuée sur un substrat test (*Schéma 3.45*). Celui-ci a été préparé à partir de la diénone **3.132**, elle-même préparée en deux étapes connues à partir de la cyclohexa-1,3-dione.[111] Une réduction chimiosélective à l'aide des conditions de Luche, puis la formation de l'éther d'étain ont permis d'obtenir l'intermédiaire **3.133** en quantité appréciable. Par contre, et à notre grande surprise, le traitement de cet éther d'étain selon des conditions usuelles de Wittig-Still a permis d'obtenir le produit désiré de réarrangement [2,3] (**3.134**, 40%), ainsi que du produit de réarrangement [1,2] (**3.135**, 33%), sans qu'il n'y ait formation problématique de l'alcool allylique anticipé. Il fallait donc se rendre à l'évidence : pour des raisons inconnues encore à ce jour, le substrat test **3.133** était inapproprié pour étudier la formation d'un alcool allylique homologue à **3.114**.

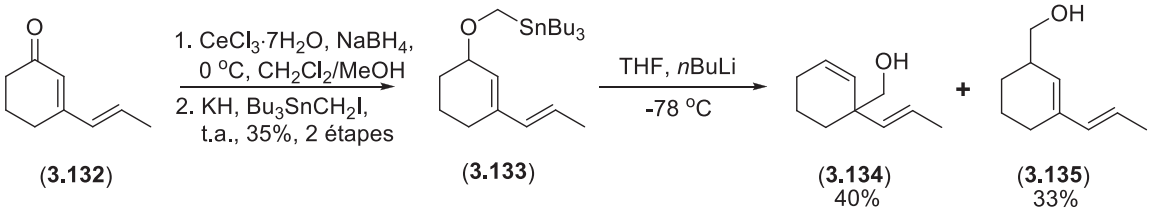
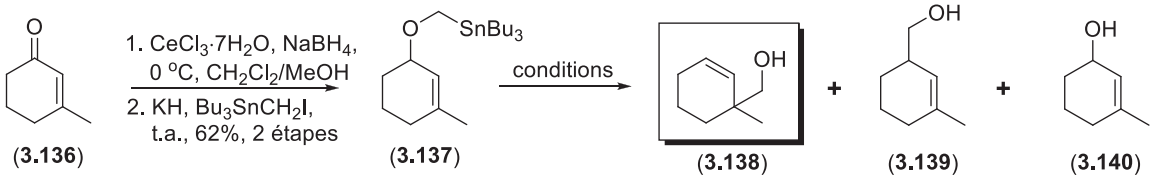


Schéma 3.45 : Formation d'un substrat test pour étudier le réarrangement de Wittig-Still

Alternativement, l'énone **3.136** a donc été préparée en utilisant les méthodes précédemment évoquées. L'énone a ensuite été réduite sous les conditions de Luche, et l'éther d'étain **3.137** a été formé sans embûche (*Schéma 3.46*). Le traitement de l'intermédiaire **3.137** avec le *n*BuLi dans le THF à -78 °C a mené cette fois-ci à l'obtention exclusive de l'alcool allylique **3.140**, homologue au sous-produit **3.114**. Il était maintenant possible d'essayer d'optimiser la réaction de Wittig-Still avec un substrat qui montrait la même propension à former **3.140**. En premier lieu, la base a été changée pour le *s*BuLi, puis le *t*Buli, en utilisant toujours le THF à -78 °C, sans que l'issue de la réaction n'ait été modifiée. Ensuite, le milieu réactionnel a été chauffé lentement jusqu'à température ambiante, pendant 1 h, pour finalement permettre la formation du produit de réarrangement [2,3] désiré (**3.138**, 30-33%) ainsi que du sous-produit de réarrangement [1,2] (**3.139**, 33-37%) tant avec le *t*BuLi qu'avec le *n*Buli. Il s'agissait donc d'un bien pour un mal : à basse température, il y avait formation majoritaire de l'alcool allylique **3.140**, alors qu'à plus haute température, il y avait formation concomitante d'un produit de réarrangement [1,2] (**3.139**), probablement de façon radicalaire. Il est à noter que l'ajout d'un agent capable de piéger les radicaux n'aurait pas amélioré la réaction : il aurait modifié la formation de **3.139**, sans pour autant faciliter la formation de **3.138**.

Ensuite, la réaction a donc été réessayée en traitant toujours l'éther d'étain **3.137** avec du *n*BuLi à -78 °C, mais en permettant au milieu réactionnel de réchauffer lentement à -20 °C pendant 8 h. Sous ces conditions, le rendement du produit de réarrangement [2,3] a été augmenté à 48%, aux dépens du produit de réarrangement [1,2], dont le rendement a diminué à 22%. Pour donner encore plus de relief à cet effet de température, la réaction a aussi été tentée à -40 °C. Dans ce cas, le produit **3.138** a été obtenu avec un rendement légèrement inférieur de 44%, alors que le sous-produit **3.139** a été obtenu avec un rendement légèrement supérieur mais reproductible de 29%. Par ailleurs, seules quelques traces de l'alcool allylique **3.140** ont été observées par RMN ^{1}H. Une autre expérience a été effectuée à l'aide de ce substrat test en traitant le substrat **3.137** avec du *n*BuLi, mais en maintenant cette température pendant 4 h, après quoi le milieu réactionnel a été réchauffé à 0 °C. Sous ces conditions, il y a eu formation majoritaire de l'alcool **3.140**, et formation minoritaire des produits **3.138** (22%) et **3.139** (13%). Cette

dernière expérience laissait donc croire que le produit **3.140** était un produit cinétique, alors que les deux autres produits étaient thermodynamiques. De plus, la même transformation essayée dans l'éther diéthylique, ou en utilisant du HMPA comme cosolvant a permis des rendements variables, mais inférieurs à ceux obtenus dans le THF. Finalement, lorsque le solvent a été remplacé par l'hexane, une distribution de rendements similaire à celle obtenue dans le THF a été observée.



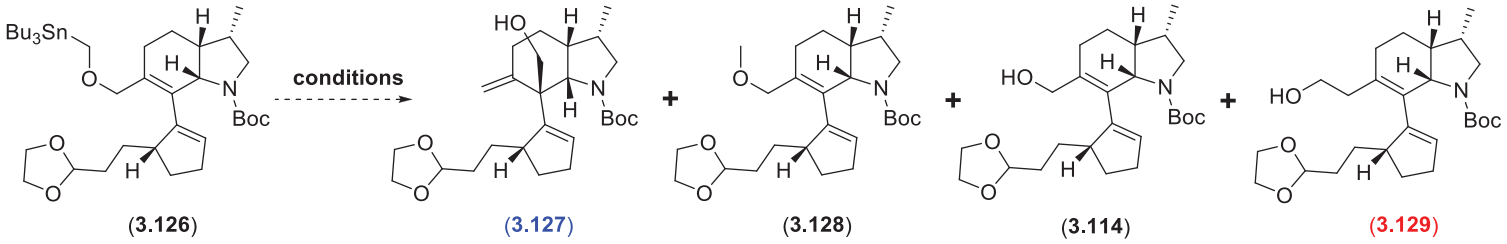
(**3.136**) (**3.137**) (**3.138**) (**3.139**) (**3.140**)

conditions	(**3.138**)	(**3.139**)	(**3.140**)
*n*BuLi, THF, -78 °C, 4 h	--	--	35%
*s*BuLi, THF, -78 °C, 4 h	--	--	38%
*t*BuLi, THF, -78 °C, 4 h	--	--	35%
*t*BuLi, THF, -78 °C, puis 0 °C, 1 h	30%	37%	--
*n*BuLi, THF, -78 °C, puis 0 °C, 1 h	33%	33%	--
***n*BuLi, THF, -78 °C, puis -20 °C, 8 h**	**48%**	**22%**	**--**
*n*BuLi, THF, -78 °C, puis -40 °C, 8 h	44%	29%	traces
*n*BuLi, THF, -78 °C (4 h), puis 0 °C, 1 h	22%	13%	40%
*n*BuLi, Et_2O, -78 °C, puis -20 °C, 8 h	18%	32%	6%
*n*BuLi, THF/HMPA (10 : 1), -78 °C, puis -20 °C, 8 h	20%	12%	35%
*n*BuLi, hexanes, -78 °C, puis -20 °C, 8 h	48%	28%	10%

Schéma 3.46 : Optimisation du réarrangement de Wittig-Still avec le substrat test **3.137**

Espérant transposer ces connaissances acquises quant à l'importance de la température dans le réarrangement de Wittig-Still, les études d'optimisation avec le substrat **3.126** ont été reprises (*Tableau 2.1*). Force a été d'admettre qu'un simple changement de température n'était pas, dans ce cas, suffisant pour optimiser la réaction (entrées 3-8). Une brève étude de changement de solvants a donc été entreprise, dans l'optique que certains de ces solvants pourraient décourager la formation de radicaux libres, et donc que la température pourrait être variée davantage afin d'obtenir un produit **3.127** majoritaire (entrées 9-13).[112] Toutefois, la réaction effectuée dans l'éther éthylique, le toluène, le *tert*-butoxyméthane (TBME) ou en présence de HPMA n'a permis aucune amélioration.

Tableau 3.1 : Optimisation du réarrangement de Wittig-Still avec l'intermédiaire **3.127**



entrée	conditions	3.127	3.128	3.114	3.129
1	nBuLi (1,2 eq.), THF, -78 °C	--	38%	22%	--
2	nBuLi (1,2 eq.), THF, -78 °C, O/N	--	--	27%	--
3	nBuLi (10 eq.), hexanes, -10 °C	25%	--	(1,5 : 1) 42%	
4	nBuLi (1,2 eq.), hexanes, -10 °C	25%	--	(1,5 : 1) 42%	
5	nBuLi (1,2 eq.), hexanes, -40 °C	19%	23%	(3 : 1) 47%	
6	nBuLi (1,2 eq.), hexanes, -20 °C	25%	--	(1,5 : 1) 42%	
7	nBuLi (1,2 eq.), hexanes, 0 °C	22%	--	(1 : 2) 39%	
8	nBuLi (1,2 eq.), hexanes, t.a.	22%	--	(1 : 4) 33%	
9	nBuLi (1,2 eq.), PhMe, -20 °C	22%*	--	(1 : 2) 44%	
10	nBuLi (1,2 eq.), THF, -20 °C	--	--	(2 : 1) 59%	
11	nBuLi (1,2 eq.), Et_2O, -20 °C	--	--	(1 : 2) 44%	
12	nBuLi (1,2 eq.), TBME, -20 °C	15%	--	(1 : 1,2) 47%	
13	nBuLi (1,2 eq.), THF/HMPA, -20 °C	mélange complexe			

* produit impur.

À ce stade, il était décourageant de constater que, après une douzaine de nouvelles conditions essayées, il n'était toujours pas possible d'optimiser la réaction de Wittig-Still avec le substrat **3.126**. D'autre part, ces réactions destructives consumant notre lot d'intermédiaires tricycliques à une vitesse étonnante, il était peut-être préférable de laisser cette stratégie de côté pour se concentrer sur d'autres options permettant de meilleurs rendements et, surtout, permettant d'accéder à la daphniglaucine C en moins d'étapes. Notamment, peut-être serait-il salutaire d'utiliser l'intermédiaire **3.102** afin de former l'énone tétracyclique prévue (*Schéma 3.47*, voir *Schéma 3.1*). L'obtention de cette énone permettrait de tester de nouveau toutes les stratégies détaillées précédemment et, plus important encore, de le faire avec un intermédiaire cétone plus électrophile que l'ester correspondant.

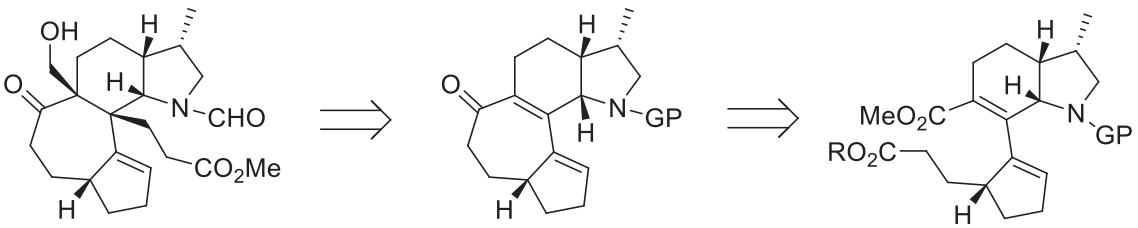


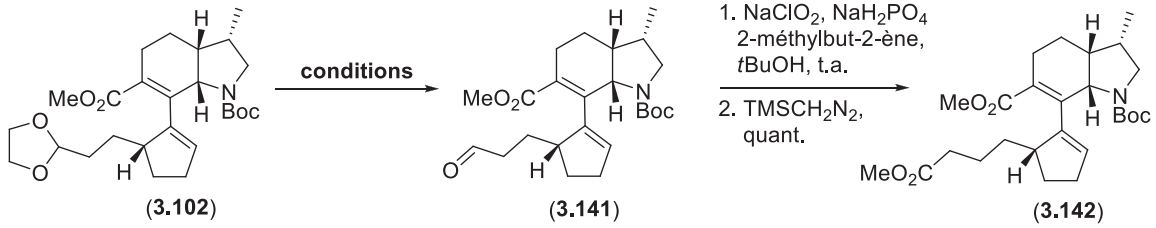
Schéma 3.47: Vers la formation d'une énone tétracyclique

Afin d'accéder à l'énone désirée, il fallait d'abord déprotéger l'acétal afin d'obtenir, après oxydation, un diester pouvant être cyclisé (tel que de **3.81** à **3.82**) pour fournir un composé tétracyclique (*Schéma 3.48*). Or, avant même d'effectuer la déprotection de l'acétal tel qu'en **3.102**, quelques scénarios potentiels ont été envisagés afin d'obtenir directement un stannane cyclopenténique, homologue de **3.100**, possédant une chaîne latérale avec un ester. Cette approche aurait pour avantages principaux d'être plus convergente et d'épargner peut-être quelques difficultés quant à une déprotection chimiosélective d'un acétal en présence d'un Boc, défi n'étant pas sans laisser quelques appréhensions. Il est à noter que, puisque la dernière étape pour la préparation du stannane **3.100** employait une base forte, il était impossible d'avoir un ester comme précurseur à cette étape : Knochel *et al* ont d'ailleurs démontré qu'un échange halogène-métal effectué sur les iodures vinyliques de type **3.99** menait à une cyclisation rapide afin de fournir différents substrats bicycliques.[80] En conséquence, quelques tests préliminaires de déprotection chimiosélective de l'acétal en présence du stannane vinylique sur le composé **3.100** ont été effectués et laissaient présager qu'il allait être difficile, voire impossible, d'obtenir le cyclopentène substitué avec ester avant le couplage de Stille.

Les efforts ont donc été axés sur la déprotection chimiosélective de l'acétal en présence du Boc, tel que contient l'intermédiaire **3.102**. La première méthode ayant été essayée préconisait l'emploi de triflate d'indium(II),[113] capable de déprotection chimiosélective en présence de Boc. Cette méthode, existant surtout pour les cétals, fonctionne présumément selon un mécanisme de trans-cétalisation avec l'acétone utilisée comme solvant. La transformation avec **3.102** a permis d'obtenir 60% de l'aldéhyde **3.141**, après deux jours à température ambiante. Après un recyclage, le rendement pouvait être augmenté à 83%. La réaction n'était certainement pas parfaite et, en plus de

déprotéger partiellement le carbamate Boc, elle affichait un grave problème de reproductibilité tant en termes de temps réactionnel que de rendement. Alors que les auteurs n'en faisaient aucune mention, il a été découvert que la réaction était impossible en présence de tamis moléculaire, et que l'humidité pouvait donc grandement affecter cette transformation.

Même si cette réaction a tout de même été utilisée souvent, quelques efforts ont été investis afin de trouver une alternative plus chimiosélective, reproductible et efficace. Deux méthodes distinctes, l'une avec le TESOTf,[114] et l'autre avec le $TrBF_4$,[115] ont été essayées, mais n'ont mené qu'à la décomposition rapide du réactif de départ. C'est beaucoup plus tard et avec surprise qu'il a été découvert que la simple protolyse avec le HCl (1 N, THF) à température ambiante permettait d'obtenir très sélectivement l'aldéhyde **3.141** désiré (88%) de façon reproductible. Cet aldéhyde a alors été facilement converti en ester méthylique **3.142** en deux étapes, à l'aide de la réaction de Pinnick décrite précédemment.



conditions

$In(OTf)_3$, acétone, t.a., 2 d	60%, 83% bsmr
$In(OTf)_3$, acétone, μW, t.a., 2 d	28%
TESOTf, TEA, CH_2Cl_2, 0 °C	décomposition
$TrBF_4$, CH_2Cl_2, 0 °C	décomposition
1N HCl, THF (1 : 1), t.a., 16 h	**88%**

Schéma 3.48 : Conversion de l'acétal **3.102** vers le diester **3.142**

3.4.1.8 Addition conjuguée

Avant de se concentrer sur la formation du tétracyclique en route vers la daphniglaucine C tel qu'ébauché dans le schéma rétrosynthétique, il nous est apparu qu'une transformation effectuée au stade de l'intermédiaire **3.142** permettrait d'accéder à la charpente du composé cible en une seule étape! L'addition conjuguée d'un cuprate,[116] idée évidente et négligée jusqu'à présent, permettrait ici de générer un énolate qui, lui,

pourrait cycliser à la manière d'une réaction de Dieckmann afin d'obtenir le composé tétracyclique contenant déjà les deux centres quaternaires vicinaux (*Schéma 3.49*). En premier lieu, un réactif de Grignard, en l'occurrence le 3-buténylMgBr, a été utilisé conjointement avec le CuBr·DMS et le TMSCl[117] afin de générer un organocuivreux dans l'éther ou dans le THF, sans qu'il ne soit toutefois possible de former le produit désiré. Ensuite, l'emploi de HMPA ou de DMAP,[118] conseillés comme agents activateurs pour les réactions d'addition conjuguée d'organocuivreux, a aussi été essayé sans succès. Dans un autre ordre d'idée, les réactifs de Yamamoto[119] utilisent une quantité stoechiométrique de $BF_3 \cdot Et_2O$ conjointement aux réactifs habituels des cuprates. Ceux-ci, pourtant connus pour être très actifs, ont été essayés ici sans succès. Même en essayant d'utiliser un groupement méthyle comme nucléophile, il a été impossible de noter quelque transformation vers **3.143**. En outre, l'emploi de dichlorométhane comme solvant, modification reconnue pour améliorer la réactivité des ajouts de cuprates, a été testé mais n'a encore une fois entraîné aucune transformation.[120] De plus, les réactifs de plus haut ordre[121] (parfois appelés réactifs de Lipschutz) ont été essayés dans l'éther diéthylique ou dans le THF, sans que ceux-ci ne réussissent là où les autres méthodes avaient échoué. Dans un dernier effort, la réaction de Sakurai, pourtant ouvertement reconnue comme étant inappropriée dans le cas d'ajouts sur les esters, a été essayée selon ses conditions classiques et dans l'optique que, cette fois-ci, le milieu réactionnel pouvait être chauffé sans que le nucléophile ne se décompose. C'est toutefois le carbamate Boc qui a été déprotégé rapidement dans ces conditions.

Après ces quelques tentatives, il devenait évident qu'il y avait un grave problème de réactivité avec l'intermédiaire **3.142**, aussi réfractaire à l'ajout de nucléophiles radicalaires et, entre autres, de réactifs de cyanation. Afin d'éviter un encombrement stérique trop intense avec le groupement *tert*-butyle du carbamate Boc, l'unité cyclopentène serait fort probablement perpendiculaire au système conjugué. D'une part, la liaison double 5,6 ne serait donc pas susceptible d'être attaquée par un nucléophile, n'étant pas conjuguée, et, d'autre part, cette conformation imposerait un effet pseudo-néopentylique à la liaison double 3,4 rendant l'addition conjuguée difficile avant que ne décomposent les nucléophiles utilisés.

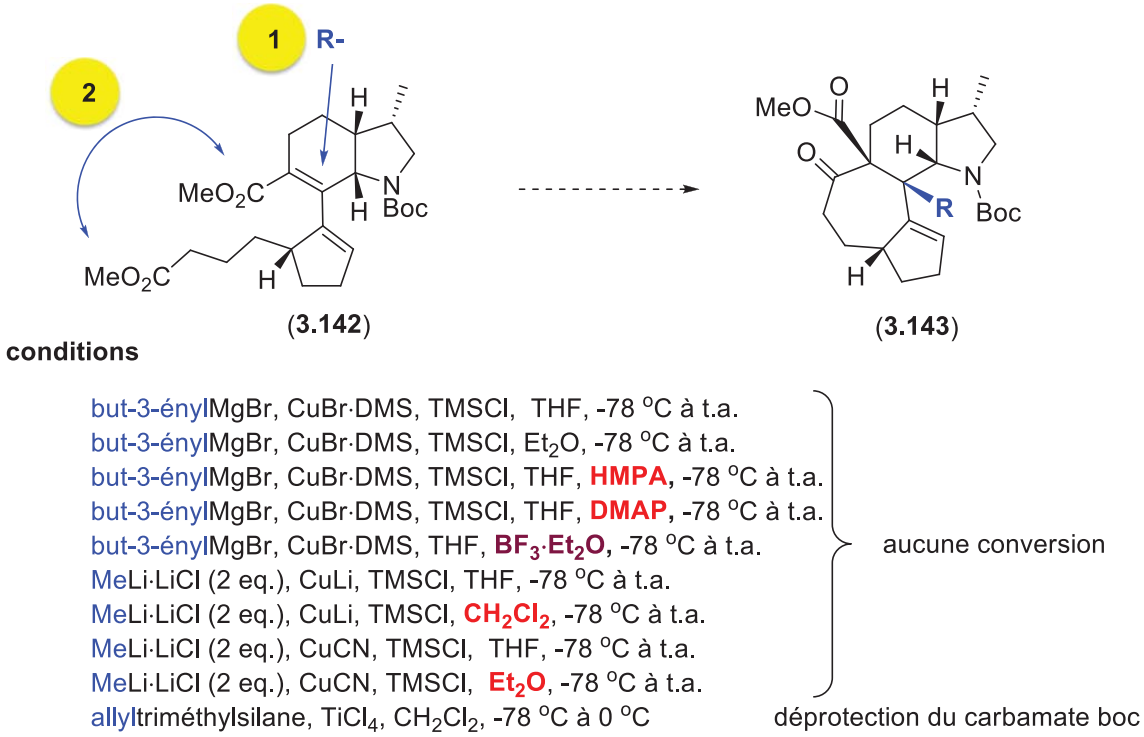


Schéma 3.49 : Tentatives de séquence tandem addition-cyclisation vers **3.143**

Après ces quelques tentatives infructueuses de formation de centre(s) quaternaire(s), il était rassurant de savoir si, au moins, le tétracycle **3.30**, intermédiaire envisagé lors de la rétrosynthèse, pouvait être obtenu (*Schémas 3.1* et *3.23*). Tel que mentionné précédemment, une des méthodes possibles assurant la formation de tels cycles consiste en la cyclisation de Dieckmann, déjà utilisée pour la formation de l'octahydroindole **3.82**. Or, s'il est plus rare d'en voir des exemples pour la formation de cycles à sept membres, ces derniers ne sont pas impossibles à former.[122] Quelques lectures nous ont convaincus qu'il serait peut-être préférable d'effectuer la cyclisation dans des conditions plus fortes. Par contre, le diester **3.142**, traité à l'hydrure de sodium dans le benzène d'abord à 0 °C, puis réchauffé à t.a., puis au reflux, n'a fini que par se décomposer (*Schéma 3.50*). De même, l'emploi de potassium de *tert*-butanolate dans le 1,4-dioxane n'a mené qu'à une décomposition lente du réactif de départ. C'est finalement en utilisant les bases HMDS que le β-cétoester **3.144** a pu être formé. Les meilleurs résultats ont été obtenus en traitant le diester avec du KHMDS à -78 °C, puis en laissant réchauffer le milieu réactionnel à t.a. pendant 30 min. Cependant, le cétoester **3.144**, dont

visiblement un seul diastéréoisomère était formé, était aussi isolé avec son tautomère énol **3.145** dont la purification n'était pas commode. Pour pallier à ce problème technique, il a été préférable d'engager directement le mélange brut de **3.144** et **3.145** dans la décarboxylation désirée. En traitant donc le mélange de tautomères avec de l'hydroxyde de potassium dans le THF/H_2O (2 : 1) à 65 °C, il a été possible d'isoler la cétone tétracyclique **3.146** avec un rendement de 62% sur deux étapes, rendement indubitablement meilleur que si la séquence était accomplie en deux étapes distinctes (environ 35%). Il est à noter que la saponification avec une base oxygénée a été préférée à la méthode de décarboxylation de Krapcho,[123] de peur que ces dernières conditions ne mènent à la déprotection du carbamate Boc.

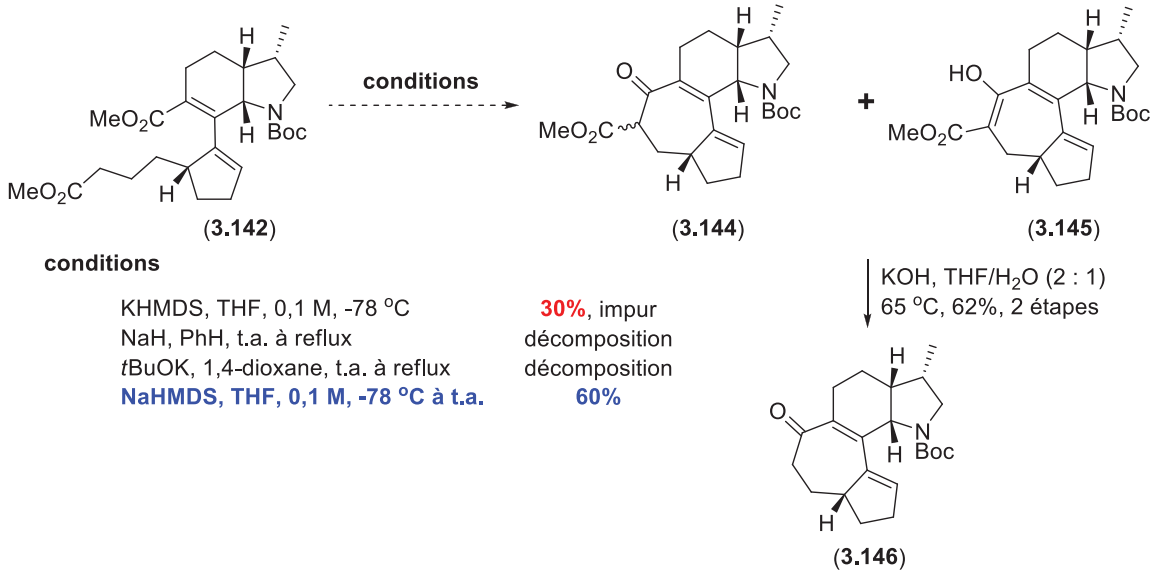


Schéma 3.50 : Cyclisation de Dieckmann vers l'obtention du composé tétracyclique **3.146**

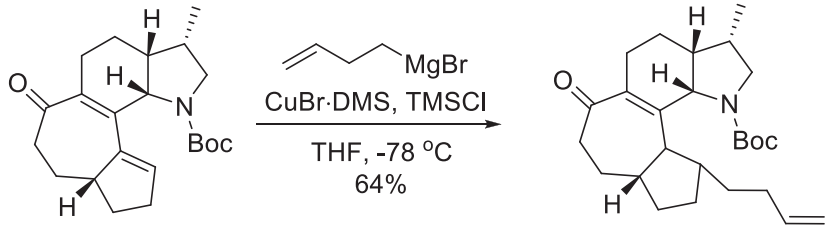
En outre, cette dernière séquence nécessaire à la formation de l'énone **3.146** pourrait peut-être être améliorée. Toutefois, l'instabilité relative de cette énone laisse croire qu'elle décomposerait lentement lors de l'étape de décarboxylation, de toute façon. Dans cette optique, il aurait peut-être été préférable d'utiliser un ester différent, qui aurait pu être facilement décarboxylé dans des conditions chimiosélectives et douces.

3.4.2 Emploi de quelques intermédiaires tétracycliques

3.4.2.1 Addition conjuguée

L'obtention de l'énone tétracyclique consistait quand même en une légère consolation après ces nombreux échecs quant à l'installation de centres quaternaires. La diénone **3.146**, beaucoup plus électrophile que le diester **3.102**, et adoptant une conformation beaucoup moins libre et plus rigide, permettrait peut-être d'obtenir le noyau structurel de la daphniglaucine C en revisitant notamment les réactions de Diels-Alder, de cycloaddition, de cyanation, d'addition conjuguée (radicalaire ou autre) et de réarrangements sigmatropiques.

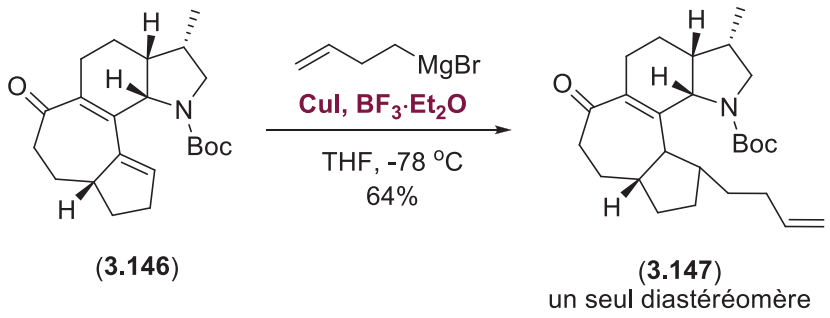
Il va sans dire que le premier type de transformation essayé a été l'ajout de cuprates, puisqu'il est aussi connu que celui-ci peut mener à la formation de deux centres vicinaux après piégeage de l'énolate formé.[124] Cette fois-ci, en utilisant un réactif de Gilman[125] (*Schéma 3.51*), il y a rapidement eu l'addition du butényl pour former un seul diastéréoisomère, mais en position 6 pour former le produit **3.147**! Les expériences noesy n'ont pas permis de confirmer de quel diastéréoisomère il s'agissait.



(**3.146**) (**3.147**)
un seul diastéréomère

Schéma 3.51 : Addition conjuguée avec l'énone **3.146**

Confrontés cette fois-ci à un problème de régiosélectivité (et non de réactivité comme dans le cas de l'ester **3.102**), il subsistait tout de même une alternative intéressante. Les réactifs de Yamamoto, en plus d'être caractérisés par une réactivité améliorée tel que déjà mentionné (*vide supra*), procèdent par un mécanisme différent capable de favoriser l'addition 1,4 par rapport à l'addition 1,6 dans le cas des substrats simples. Ces réactifs ont donc été essayés une fois de plus dans l'espoir de pouvoir former le centre quaternaire (*Schéma 3.52*). Malheureusement, cette option n'a permis que de former exactement le même produit **3.147** observé précédemment, avec le même rendement.



(**3.146**)

(**3.147**)
un seul diastéréomère

Schéma 3.52 : Addition conjuguée avec l'énone **3.146** à l'aide d'un réactif de Yamamoto

En outre, Alexakis, Mauduit et leurs collègues respectifs ont récemment travaillé au développement de catalyseurs de type NHC afin de promouvoir l'addition-1,4 de cuprates sur des énones de façon énantiosélective.[126] Leur découverte est importante car elle s'inscrit dans une courte liste de méthodologies capables de résoudre ce problème d'énantiosélectivité, sans solution depuis longtemps, mais aussi parce que leur méthodologie paraît capable de promouvoir alternativement l'addition-1,4 ou l'addition-1,6 sur des diénones choisies.

Cet article était certainement d'importance primordiale pour le présent projet : non seulement il était effectivement capable de promouvoir l'addition sélective 1,4 sur des diénones tests, il faisait état de la formation de centres quaternaires et, qui plus est, avec un réactif de butényle approprié à l'élaboration des chaînes latérales contenues dans la daphniglaucine C (*Schéma 3.26*). Heureusement, le professeur Mauduit, ancien étudiant du groupe Hanessian, a été courtois au point de nous envoyer un échantillon généreux de son catalyseur NHC le plus puissant, à cette seule différence qu'il était sous forme de contre-ion PF_6^-, plus stable, alors que la publication faisait état d'un contre-ion Cl^- rendant le catalyseur hygroscopique. Après avoir demandé si le contre-ion n'avait pas d'importance sur l'issue de la réaction, il a été possible de tester l'efficacité de ce catalyseur sur une diénone test **3.132**, diénone déjà employée dans le cadre de ce projet, ainsi que dans leur article. Malheureusement et à notre grande surprise, ces résultats n'ont pas pu être reproduits! Trois tentatives de catalyse n'ont permis que de l'ajout sélectif 1,6 pour générer **3.148**, comme si le ligand NHC n'avait aucun effet (*Schéma 3.53*).

Ce n'est qu'après plusieurs correspondances avec le professeur Mauduit et une autre enveloppe transatlantique que le ligand NHC avec contre-ion chlorure a pu être testé, tel que décrit originalement, pour réaliser qu'il y avait bel et bien une différence majeure entraînée par l'identité du contre-ion, et qu'il était maintenant possible de générer **3.149** sans problème et de façon reproductible. Le groupe Mauduit continue d'étudier le comportement global de ses catalyseurs et à éprouver sa nouvelle théorie selon laquelle, *a priori*, un quelconque sel de chlorure de magnésium pourrait être formé et affecter le mécanisme inconnu d'addition de cuprates catalysée par NHC.

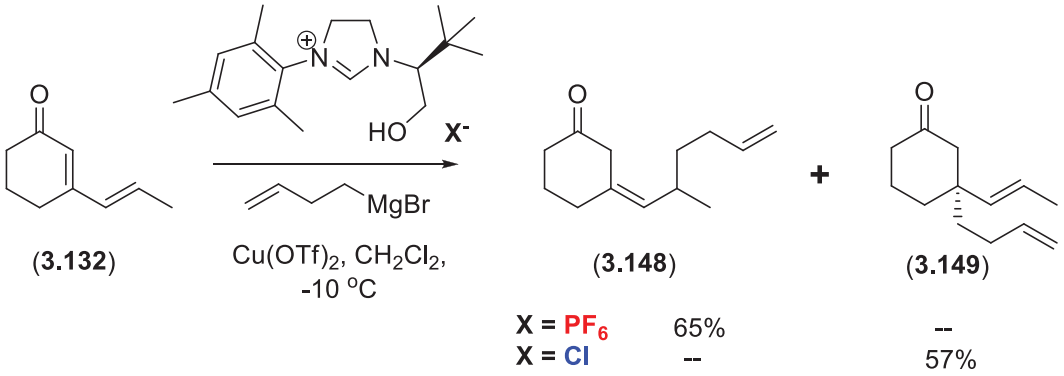


Schéma 3.53 : Test de la catalyse au NHC de Mauduit, Alexakis *et al*

Ces résultats encourageants laissaient présager qu'il serait possible de former le centre quaternaire désiré avec cette seule modification. Malheureusement, lorsqu'appliquée dans le cas du substrat **3.146** plus complexe (*Schéma 3.54*), aucune conversion n'a pu être observée, même en prolongeant le temps de réaction à un jour ou en laissant le milieu réactionnel réchauffer jusqu'à température ambiante.

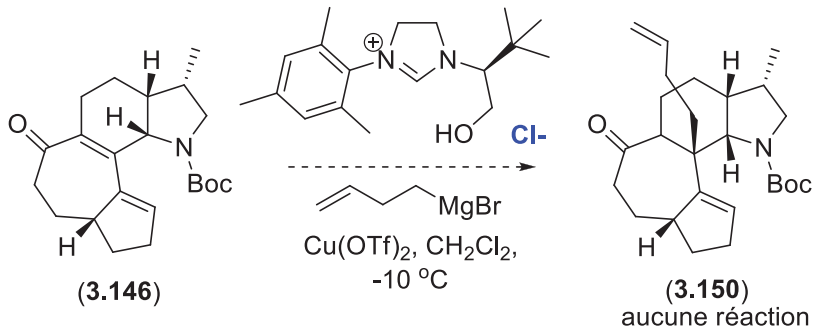
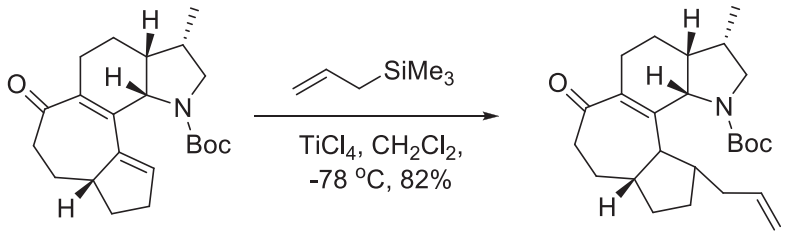


Schéma 3.54 : Tentative d'addition conjuguée catalysée par NHC sur l'énone **3.146**

Après ces quelques essais infructueux utilisant les réactifs de cuprates, une autre idée a été tentée. L'addition de Sakurai, ineffective dans le cas de l'ester **3.102**, avait cette fois-ci de meilleures chances de réussite. Il est à noter que ce type de réaction est connu pour l'ajout sur les diénones, et procède habituellement à l'ajout en position 1,6.[127] C'est donc sans grande surprise que l'allylation a elle aussi procédé en position 1,6 avec un rendement de 82% (*Schéma 3.55*).



(**3.146**) (**3.151**)

Schéma 3.55 : Addition de Sakurai avec l'énone **3.160**

3.4.2.2 Addition conjuguée radicalaire

Une fois de plus, l'addition radicalaire conjuguée a alors été considérée. Ayant cette fois-ci affaire à une énone (voir *Schéma 3.36*), peut-être était-il possible de tirer avantage de la réactivité accrue de cette dernière. En effet, il existe beaucoup plus de méthodes promouvant l'addition conjuguée radicalaire sur les diénones, tel que les réactifs de titane(III), d'aluminium et de samarium précédemment mentionnés (*vide supra*). En premier lieu, la réaction promue au titane(III), essayée précédemment, a été encore une fois tentée, cette fois-ci sur l'énone **3.146**, mais sans que celle-ci ne puisse entraîner une quelconque transformation, sinon de la décomposition lente (*Schéma 3.56*). L'énone a ensuite été soumise aux conditions d'addition radicalaire conjuguée en employant un peroxyde et un sel d'aluminium comme initiateurs.[128] Un produit d'addition d'un allyle en position 1,6 a alors été obtenu sous forme d'un seul diastéréoisomère, présumément de stéréoconfiguration (*R*) en comparant avec le produit de Sakurai obtenu précédemment, **3.151**.

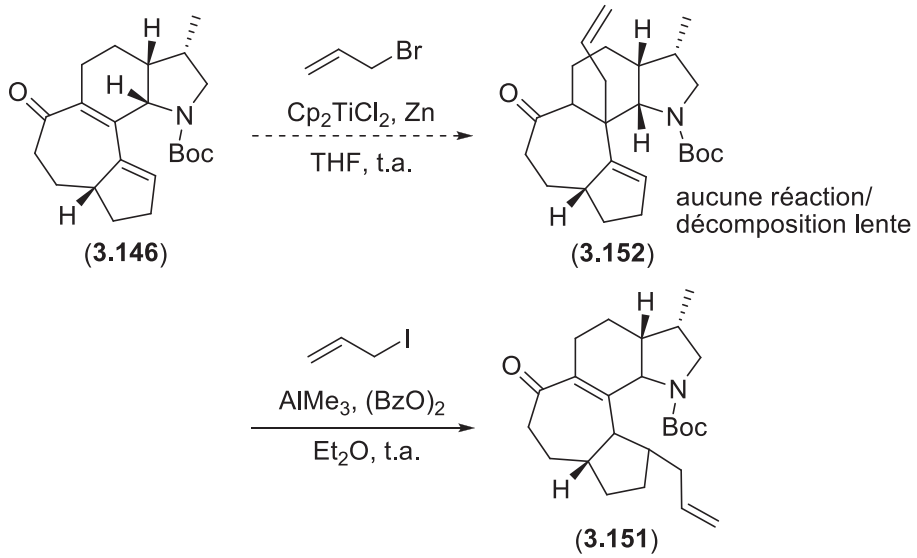


Schéma 3.56 : Additions radicalaires conjuguées avec l'énone **3.146**

3.4.2.3 Cycloadditions [3+2] de Trost

À court d'options quant aux additions nucléophiles ou radicalaires conjuguées, d'autres types de réactions intermoléculaires ont été mises de l'avant, à commencer par celles capables de générer les deux centres quaternaires vicinaux du même coup. En premier lieu, la littérature fait état de la faisabilité de la cycloaddition [3+2] de TMM, tentée avec l'intermédiaire **3.102** (*vide supra)*, avec les énones. Cette stratégie a donc été essayée de nouveau, en utilisant une fois de plus les conditions usuelles (*Schéma 3.57*). Malheureusement, aucune transformation n'a pu être observée dans le THF ou le toluène, alors que de la décomposition lente a été observée en changeant pour le DMSO à 140 °C.

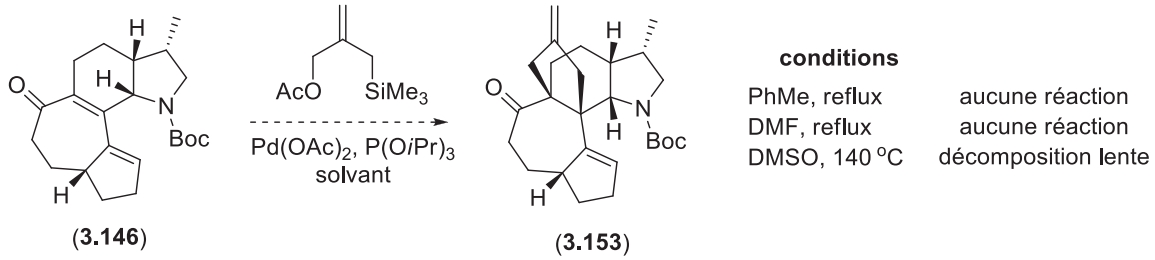


Schéma 3.57 : Tentative de cycloaddition [3+2] avec l'énone **3.146**

3.4.2.4 Cyanation

Par ailleurs, la cyanation, elle aussi tentée avec l'intermédiaire tricyclique **3.102**, avait plus de chances de réussite avec l'énone **3.146**, plus électrophile. La cyanation a donc été tentée d'emblée avec le cyanure de diéthylaluminium, source commerciale,

puissante et plus propre de cyanure (voir *Schéma 3.34* et explications connexes). Une fois de plus, la cyanation n'a toutefois pas été observée dans le THF, même après avoir chauffé deux jours à reflux (*Schéma 3.58*).

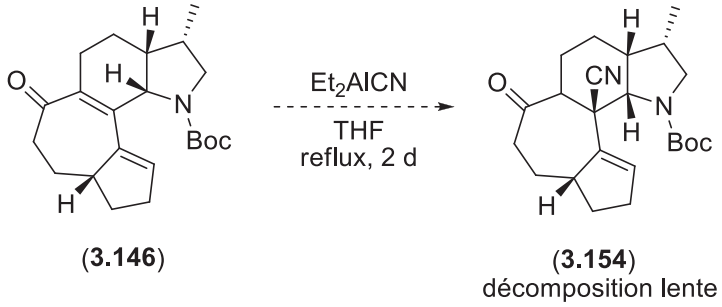


Schéma 3.58 : Tentative de cyanation de l'énone **3.146**

3.4.2.5 Cycloadditions de Diels-Alder

En dernier lieu, la cycloaddition de Diels-Alder, elle aussi connue pour réagir avec les énones,[129] a été essayée tant avec le diène de Danishefsky qu'avec l'acétate de 1,3-buténol pour tenter d'obtenir respectivement les structures pentacycliques **3.155** ou **3.156**. Encore une fois, aucune conversion vers un produit désiré n'a pu être observée, même après deux jours à reflux dans le toluène (*Schéma 3.59*), et le réactif de départ a pu être isolé en grande partie.

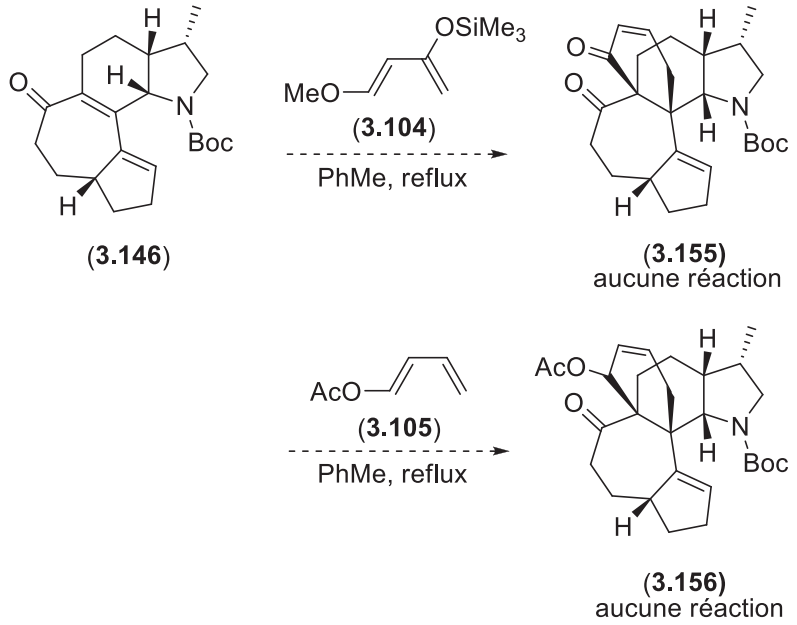


Schéma 3.59 : Tentative de cycloaddition de Diels-Alder avec l'énone **3.146**

3.4.2.6 Réarrangements sigmatropiques

Une fois de plus confrontés à l'échec évident des réactions intermoléculaires en vue d'installer les centres quaternaires requis, cette fois-ci plus en raison du manque de *sélectivité* qu'en raison du manque total de réactivité, nos efforts ont été à nouveau tournés vers l'emploi de réactions intramoléculaires. La diénone **3.146** a donc été réduite selon diverses conditions afin d'obtenir l'alcool **3.157**, précurseur évident pour quelques réarrangements sigmatropiques (*Schéma 3.60*). La première condition essayée, la réduction de Luche à 0 °C, a permis d'obtenir un mélange de diastéréoisomères inséparables de 2,5 : 1. Il a été impossible de déterminer la stéréochimie de ces diastéréoisomères en utilisant les expériences noesy. Les mêmes conditions de réduction de Luche, effectuées à des températures plus froides, ont permis d'augmenter le ratio diastéréoisomérique à 3,3 : 1 (à -40 °C), puis à 5,0 : 1 (à -78 °C). Alternativement, l'autre diastéréoisomère a pu être obtenu majoritairement dans un ratio de 1 : 2 en utilisant le L-Selectride® comme plus grosse source d'hydrure.

(**3.146**) (**3.157**)

conditions

$NaBH_4$, $CeCl_3 \cdot 7H_2O$, $MeOH/CH_2Cl_2$, 0 °C	r.d. = 2,5 : 1
$NaBH_4$, $CeCl_3 \cdot 7H_2O$, $MeOH/CH_2Cl_2$, -40 °C	r.d. = 3,3 : 1
$NaBH_4$, $CeCl_3 \cdot 7H_2O$, $MeOH/CH_2Cl_2$, -78 °C	**r.d. = 5,0 : 1**
L-Selectride®, THF, -78 °C	**r.d. = 1 : 2**

Schéma 3.60 : Réduction chimiosélective de la cétone telle qu'en **3.146**

Même s'il reste impossible d'en être certain, l'hypothèse est que l'alcool obtenu grâce au traitement au L-Selectride®, source d'hydrure plus grosse, est l'alcool (*S*) dérivé simplement d'une attaque de l'hydrure par la face supérieure, moins encombrée.[130] Un dérivé *p*-nitrobenzoate des deux diastéréoisomères a été préparé dans l'espoir de générer quelques intermédiaires cristallins ou, du moins, de changer les propriétés physiques des diastéréoisomères au point de pouvoir séparer ceux-ci physiquement. Cependant, ces

esters ont été obtenus sous forme d'huile et étaient toujours inséparables. Malgré l'obtention d'un mélange diastéréomérique inséparable, il a été possible de tester la faisabilité du réarrangement de Johnson-Claisen sur de tels intermédiaires (*Schéma 3.61*). Le mélange a donc été dilué dans l'orthoacétate de méthyle en présence d'hydroquinone mais, encore une fois, seule une décomposition lente a été observée lorsque le milieu réactionnel a été chauffé à environ 110 °C.

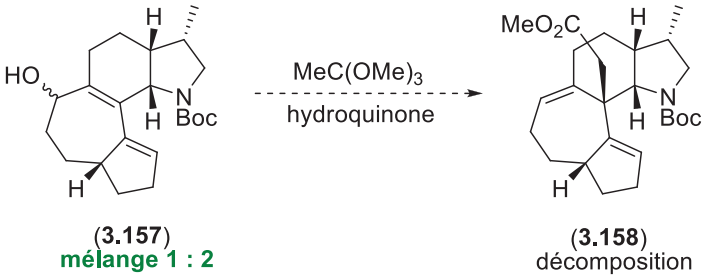


Schéma 3.61 : Tentative de réarrangement de Johnson-Claisen avec l'intermédiaire **3.157**

Toujours dans l'espoir de séparer les deux diastéréoisomères obtenus, les acétates **3.159** ont été préparés sous des conditions usuelles à partir des alcools allyliques **3.157** (*Schéma 3.62*). Dans la foulée, même si ces acétates étaient encore une fois inséparables, il a été possible d'éprouver la faisabilité du réarrangement d'Ireland-Claisen. Après avoir formé l'acétate de cétène silylé tel qu'en **3.160**, il a été impossible de promouvoir le réarrangement de celui-ci dans le THF, le toluène ou le 1,4-dioxane.

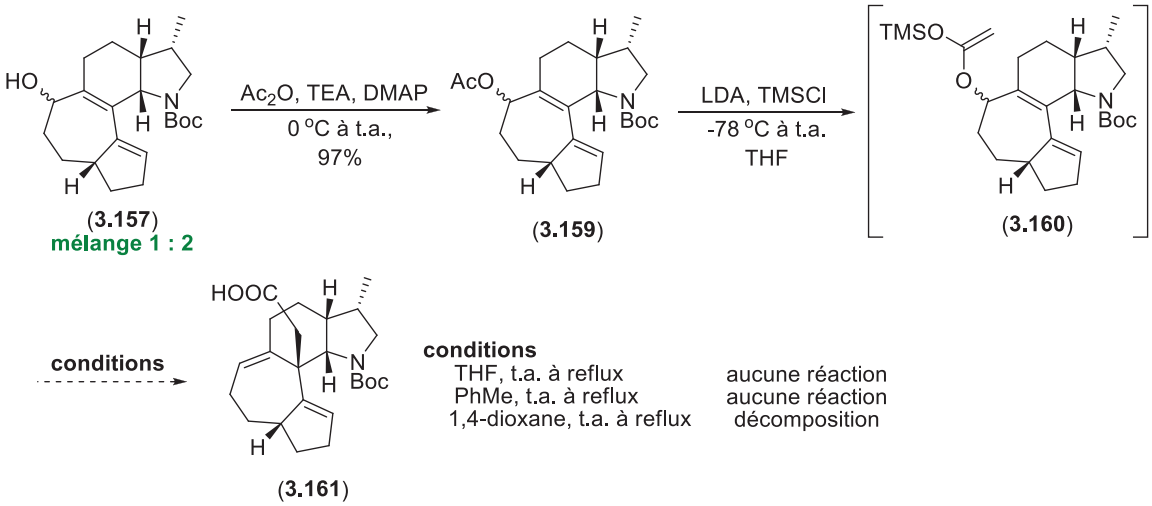


Schéma 3.62 : Tentative de réarrangement d'Ireland-Claisen avec l'intermédiaire **3.159**

Après ces tentatives infructueuses de réarrangements de Johnson-Claisen et d'Ireland-Claisen, l'option du réarrangement de Wittig-Still a été tentée. Cette réaction avait déjà fait ses preuves dans le cadre de ce projet (voir *Schéma 3.43*, *3.44* et *Tableau 3.1*), par contre, celle-ci ne serait peut-être pas appropriée dans le cas de substrats cycliques. Par exemple, il est facile d'imaginer que l'état de transition de type enveloppe (**3.162b**) menant au produit [2,3], déjà difficile à former, serait peut-être impossible à former dans le cas d'un polycycle. Toutefois, dans l'espoir de reproduire notre chance d'auparavant, l'éther d'étain **3.162** a été préparé à partir du mélange diastéréomérique **3.157** dans les conditions détaillées plus tôt (*Schéma 3.63*). Il est à mentionner que, malheureusement, les réactifs d'étains **3.162** étaient encore inséparables. Néanmoins, le réarrangement de Wittig-Still a été tenté à ce stade sur le mélange de diastéréoisomères selon une des conditions optimales développées précédemment. Malheureusement, seul l'alcool allylique **3.157** (dont le ratio diastéréomérique n'avait pas changé) a pu être isolé, le reste ayant rapidement décomposé. Étant incertains quant à l'identité des diastéréoisomères utilisés, l'autre mélange a été utilisé, toujours sans succès.

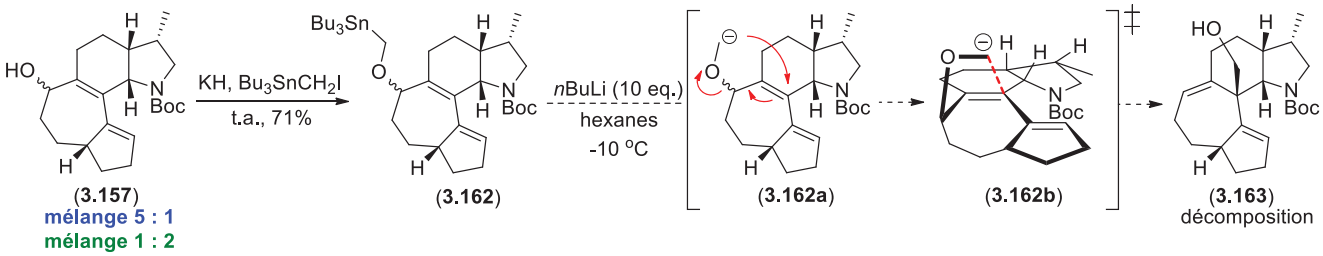


Schéma 3.63 : Tentative de réarrangement de Wittig-Still avec l'intermédiaire **3.162**

Un autre type de réarrangement sigmatropique a donc été tenté, soit le réarrangement d'oxy-Cope. Afin d'en générer le précurseur, la méthodologie de Knochel permettant l'ajout de nucléophiles sélectivement en 1,2 (*vide supra*) a encore une fois été employée à bon escient (*Schéma 3.64*). En plus d'être très régiosélective en 1,2, l'addition n'a généré qu'un seul diastéréoisomère, présumément celui dessiné ci-dessous. Il est d'ailleurs fâcheux de constater qu'il est possible de promouvoir l'addition 1,6 sur l'énone **3.146** (à l'aide entre autres de cuprates) et l'addition 1,2 (à l'aide de la méthodologie de Knochel), mais pas l'addition 1,4! Le réarrangement de l'alcool allylique **3.164**, très sensible à l'acide, n'a cependant pas pu être promu en utilisant le KHMDS ou le KH comme bases.

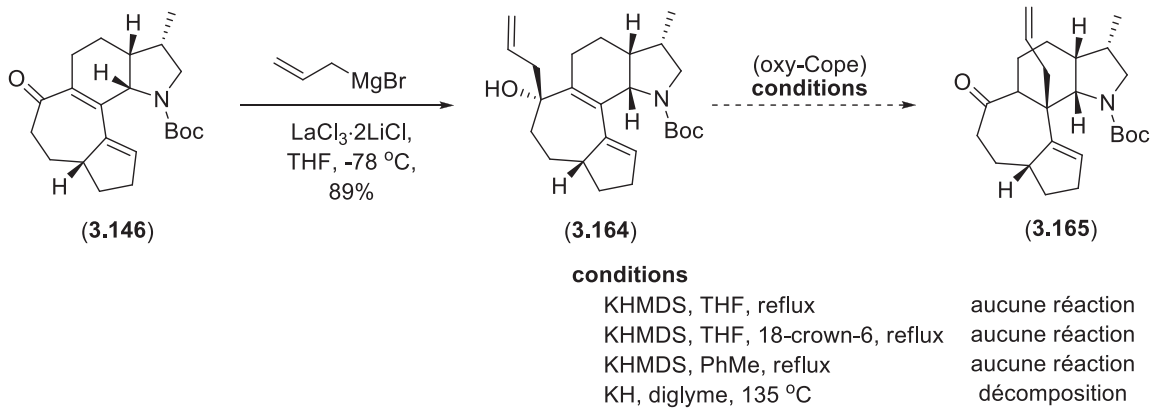


Schéma 3.64 : Tentative de réarrangement d'oxy-Cope avec l'intermédiaire **3.164**

Avant d'abandonner cette stratégie générale de réarrangements sigmatropiques au niveau d'intermédiaires tétracycliques, une dernière option a été envisagée. S'il est possible de concevoir des réarrangements [2,3] ou [3,3] pour de tels systèmes, qu'en est-il des réarrangements [4,3]? Il existe effectivement bien peu d'information quant à la faisabilité, les mécanismes et la tolérance de tels réarrangements.[131] Si un réarrangement [4,3] pouvait être promu, il serait possible d'obtenir directement la chaîne latérale à trois atomes de carbone **3.167** telle que dans la daphniglaucine C, à partir d'un intermédiaire allylé tel que **3.166** (*Schéma 3.65*).

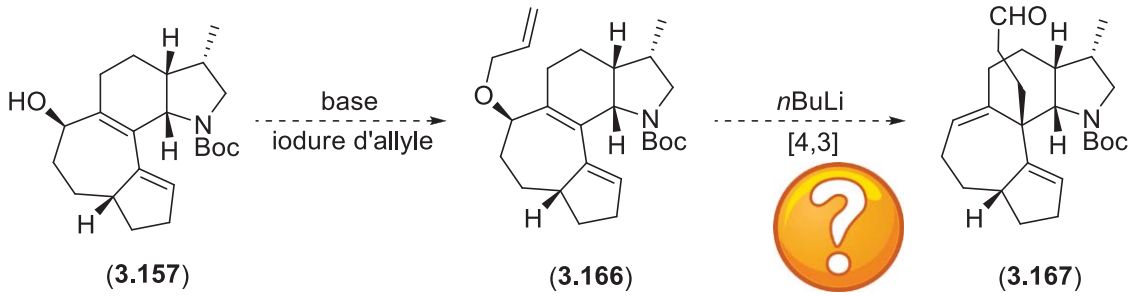


Schéma 3.65 : Plan vers un réarrangement [4,3]?

Cependant, la difficulté d'un tel réarrangement saute aux yeux : le réarrangement [4,3] désiré n'est qu'une voie possible sur tant d'autres (voir *Schéma 3.66*). Il est d'ailleurs à noter qu'en plus des huit produits dessinés, les réarrangements [2,6] et [4,6], provenant d'une migration de l'allyle jusqu'en position 6, ne doivent pas être négligés.

D'abord, la déprotonation pourrait théoriquement engendrer deux carbanions stabilisés différents, **3.175** et **3.176**. Néanmoins, une sélectivité pourrait être espérée dans ce cas, la déprotonation désirée formant un carbanion secondaire (**3.176**), plus stable que le carbanion tertiaire **3.175** sauf exceptions. De cette façon, plusieurs sous-produits potentiels pourraient être évités. Le deuxième point compliquant cette réaction vient du fait que le réarrangement [4,3] est interdit par la symétrie des orbitales, et qu'il serait donc sûrement plus facile d'obtenir les produits de réarrangement [1,4] ou [2,3], qui eux sont permis par la symétrie des orbitales. En fait, le peu d'information existant à ce sujet laisse croire qu'il faudrait espérer un mécanisme radicalaire afin d'obtenir le produit réarrangé [4,3].[131]

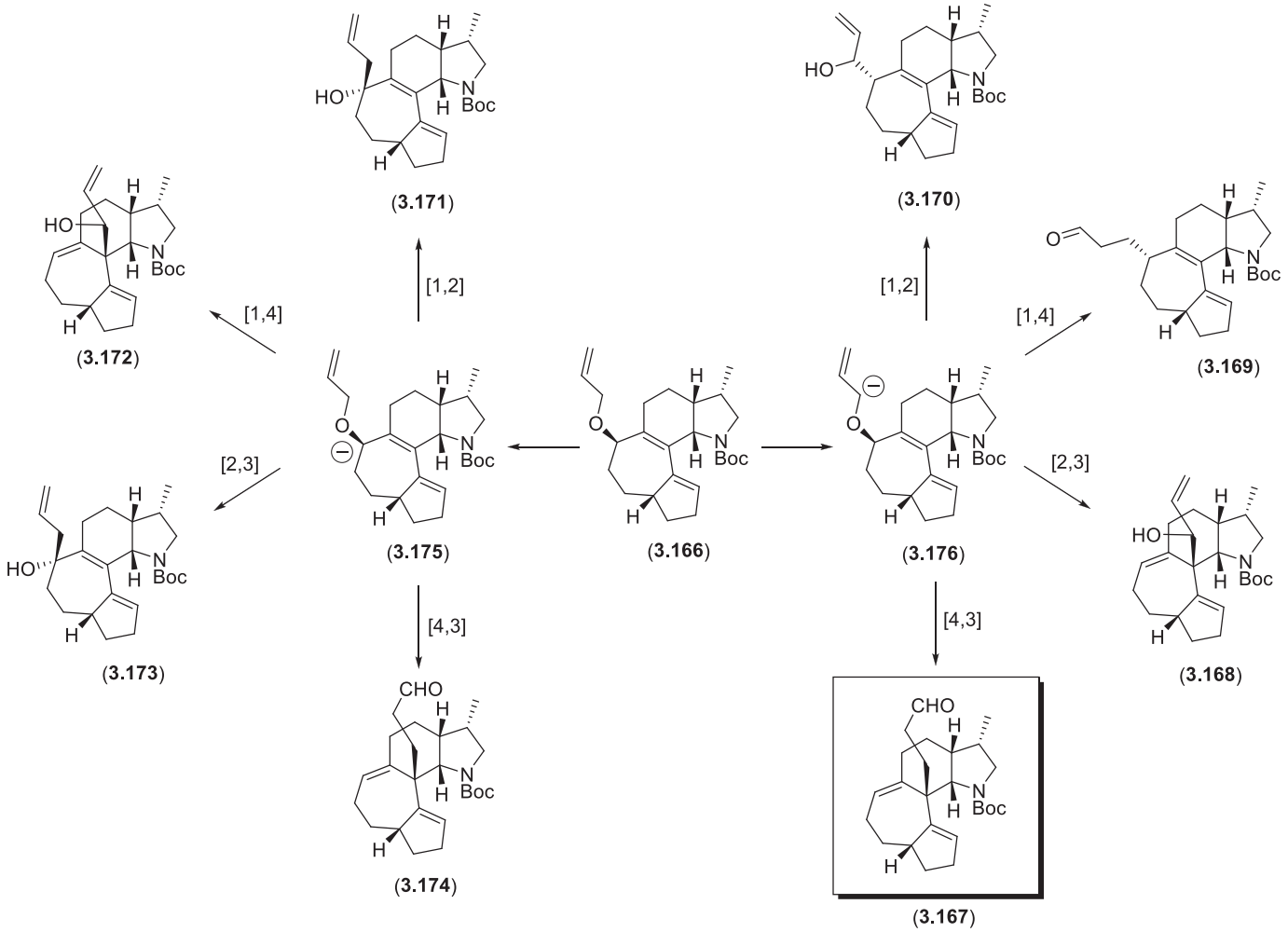


Schéma 3.66 : Intermédiaires possiblement engendrés lors de réarrangements à partir de **3.166**

Afin de tester rapidement la viabilité de ce plan, et pour éviter de gaspiller inutilement des intermédiaires précieux tels que **3.157**, un substrat test a été préparé pour la cause. En utilisant toujours **3.132** comme précurseur de départ, l'alcool allylique a été cette fois-ci allylé dans des conditions usuelles et non-optimisées afin d'obtenir l'éther d'allyl **3.177** en grande quantité (*Schéma 3.67*). Un traitement au *n*BuLi, à -78 °C, dans le THF, n'a permis que d'observer le produit de réarrangement [1,2] majoritaire (**3.178**, 45%), ainsi que le produit de réarrangement [1,4] minoritaire (**3.179**, 17%). Afin de vérifier si cette sélectivité s'expliquait par la présence d'un diène, un autre substrat test (**3.180**) a été préparé de façon similaire. Selon les mêmes conditions de réarrangement, les deux mêmes produits de réarrangement [1,2] (**3.181**) et [1,4] (**3.182**) ont été obtenus avec des rendements de 45% et 12% respectivement, rendements presque identiques à ceux obtenus à partir de **3.177**. Fait intéressant à noter : le produit de réarrangement [1,2] majoritaire est formé par un mécanisme radicalaire, alors que le produit minoritaire est permis par la symétrie des orbitales. Néanmoins, les deux produits observés n'étaient pas caractérisés par une migration de la chaîne allyle, tel qu'il aurait été souhaitable.

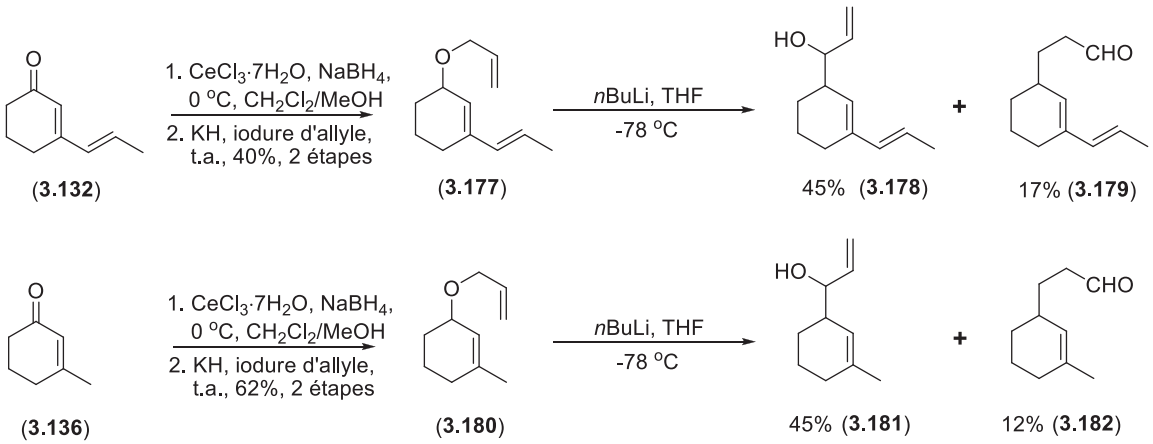


Schéma 3.67 : Tentatives de réarrangement 1,4 avec les substrats test **3.177** et **3.180**

Pour résoudre ce problème, on pourrait croire qu'il aurait été possible d'effectuer le réarrangement sur un substrat acyclique,[107] et ainsi de faciliter la formation d'un état de transition à sept membres. Or, un substrat acyclique aurait pour problème incontournable et majeur que la déprotonation ne pourrait plus être régiosélective, générant deux carbanions secondaires (comme **3.175** *vs* **3.176**), à moins d'installer sélectivement un site où, par exemple, une transmétallation pourrait être effectuée chimiosélectivement. Les

résultats de cette brève étude de faisabilité de réarrangements [4,3] ou [2,3], ainsi que ceux portant sur la formation de centres quaternaires à l'aide du réarrangement de Wittig-Still (*Schémas 3.40* et *3.41*) ont fait l'objet d'une courte publication en préparation.

À ce stade-ci, un constat (voire un examen de conscience) était inévitable : après plusieurs tentatives de réactions intermoléculaires et intramoléculaires visant à installer le(s) centre(s) quaternaire(s) désiré(s), autant sur des intermédiaires tricycliques tels que **3.102** que sur des intermédiaires tétracycliques tels que **3.146**, aucune méthode convaincante n'avait été trouvée. Or, tous les intermédiaires utilisés avaient pour dénominateur commun qu'ils possédaient un système diène, ce qui faisait d'eux des intermédiaires non-testés pour la très vaste majorité des réactions détaillées ci-haut. Peut-être était-il alors préférable de faire disparaître momentanément la deuxième liaison double en position-5,6, sous-estimée jusqu'à maintenant quant au biais stéréoélectronique qu'elle imposait?

3.5 Stratégies visant à enlever momentanément l'alcène en position 5,6

Dans un premier temps, cette stratégie a été tentée dans le cas de l'intermédiaire tétracyclique **3.146**. Plusieurs options existaient afin de faire disparaître la liaison double posant potentiellement problème : en plus de nombreuses réactions intermoléculaires, cette liaison double pouvait simplement être attaquée de façon intramoléculaire par le carbamate, une fois activée. Pour ce faire, il est typiquement possible d'activer l'alcène avec un réactif électrophile.

C'est dans cette optique que la bromocarbamoylation[132] de l'intermédiaire **3.146** a été effectuée en traitant celui-ci avec du brome moléculaire dans le dichlorométhane ou le chloroforme (*Schéma 3.68*). Le produit **3.183** a été obtenu avec un rendement de 88% sous forme d'un seul diastéréoisomère. La confirmation de la structure et de la stéréochimie du produit obtenu a été possible grâce à une analyse par diffraction des rayons-X.

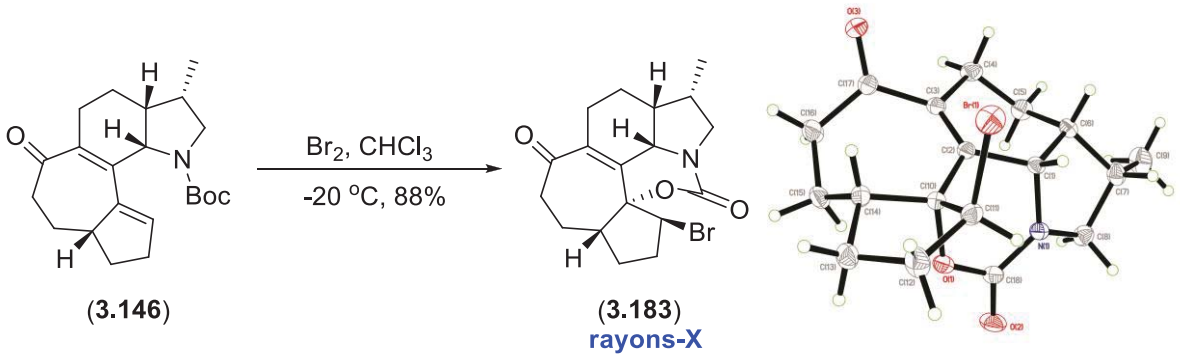


Schéma 3.68 : Bromocarbamoylation de l'intermédiaire **3.146**

Il a été possible, dès cette étape, de tester deux options permettant potentiellement d'installer les centres quaternaires. Ayant maintenant affaire à une énone, et non à une diénone, il était impossible d'obtenir quelque produit d'addition 1,6. L'ajout de cuprate sous les conditions usuelles a donc été essayé, sans toutefois permettre de conversion (*Schéma 3.69*). Tel que démontré dans la structure cristalline obtenue, l'atome de brome serait fort probablement directement dans la trajectoire Burgi-Dunitz empruntée par le nucléophile. Pour essayer de pallier à ce problème, la réaction de Sakurai a alors été essayée, dans l'espoir que celle-ci procèderait d'une façon telle que le recouvrement orbitalaire serait différent, ou qu'une augmentation de température suffirait à promouvoir l'addition conjuguée de l'allyle. Malheureusement, cette réaction n'a permis, encore une fois, qu'une lente décomposition du réactif de départ.

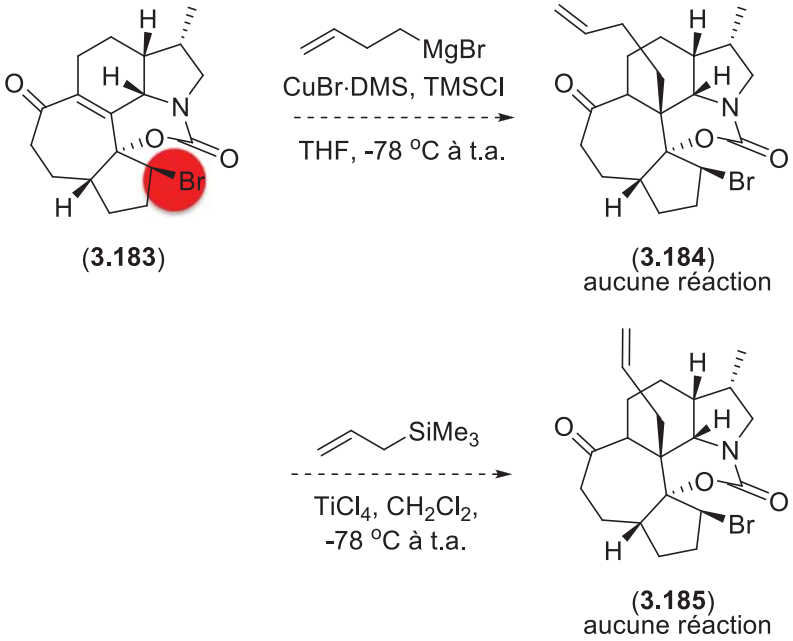
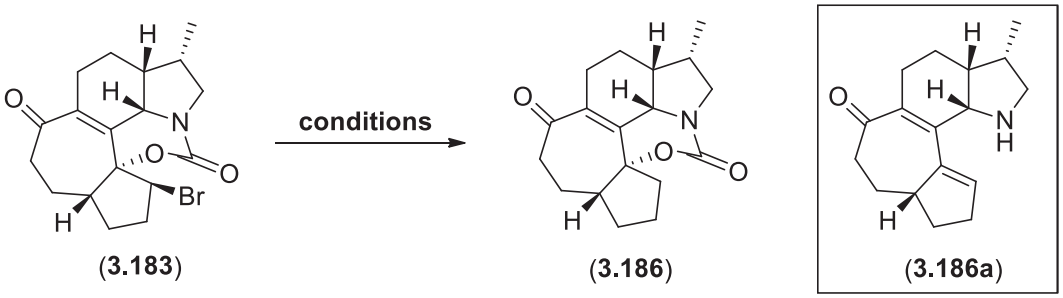


Schéma 3.69 : Tentatives d'addition conjuguée avec le bromocarbamate **3.183**

L'atome de brome étant présumément trop gros pour permettre l'attaque d'un quelconque nucléophile, il a été convenu qu'il serait préférable de travailler à enlever celui-ci. Le produit obtenu, le carbamate pentacyclique **3.183**, pourrait être converti vers la daphniglaucine C après ouverture du carbamate, puis élimination de l'alcool résultant. Pour commencer, les conditions de débromation usuelles,[133] avec du Bu_3SnH et un initiateur, ont été essayées (*Schéma 3.70*). Aucune conversion n'étant observée, l'ajout d'excès d'initiateur et de tributylétain n'a mené qu'à une décomposition lente du réactif de départ. Une méthode alternative préconisant l'emploi plus doux de phénylsilane en tant que solvant et agent réducteur[134] a été utilisée, mais a mené lentement à la décomposition de la bromo-énone **3.183** sans qu'aucun produit attendu ne soit observé. Dans un dernier effort, une troisième méthode radicalaire a été essayée, faisant appel à des radicaux d'indium[135] et dont le mécanisme est clairement différent des deux autres méthodes utilisées. Malheureusement, une fois de plus, aucune réaction n'a pu être observée dans le THF à reflux.

En outre, les conditions d'hydrogénolyse, largement employées pour la débromation (ou la déshalogénation en général), ont été essayées. Dans un premier lieu, les catalyseurs les plus doux ont été testés afin d'éviter que l'énone ne soit réduite au passage. Un excès de nickel de Raney, bien connu pour la débromation (même de produits avec des carbonates adjacents)[136] a été ajouté sans hydrogène[137] au bromo-carbamate **3.183** dans le méthanol et agité pendant deux jours, sans qu'aucune transformation ne soit observée. Finalement, ce n'est qu'en ajoutant de l'hydrogène que, finalement, le produit « d'élimination » **186a** a été observé, correspondant en fait à la diénone dont le carbamate aurait été déprotégé. Dans l'espoir de changer le mécanisme de l'hydrogénation en changeant le métal utilisé, le catalyseur de Pearlman[138] et le catalyseur de Lindlar[139] ont été utilisés à leur tour, mais n'ont permis aucune transformation après plusieurs jours, même après ajout de plusieurs équivalents de catalyseur. Même en augmentant la pression à 60 bars, dans le cas du catalyseur de Pearlman, aucune transformation n'a été observée.



(**3.183**) (**3.186**) (**3.186a**)

conditions

Bu_3SnH, ABCN, PhMe, reflux	aucune réaction/ décomposition
$PhSiH_3$, ABCN, 110 °C	décomposition
Bu_3SnH, $InCl_3$, THF, reflux	aucune réaction
Raney-Ni (excès), MeOH	aucune réaction
Raney-Ni (excès), H_2, MeOH	"élimination" (**186a**)
$Pd(OH)_2$, H_2, MeOH	aucune réaction
$Pd(OH)_2$, H_2, MeOH (60 bars)	aucune réaction
catalyseur de Lindlar, H_2, MeOH	aucune réaction
PtO_2, H_2, MeOH,	sur-réduction
Pd/C, H_2, MeOH	"élimination" lente (**186a**)

Schéma 3.70 : Tentative de débromation de l'intermédiaire **3.183**

Dans l'espoir qu'un catalyseur plus puissant pourrait faire l'affaire, le catalyseur d'Adams a été essayé, mais celui-là s'est justement avéré trop puissant et a mené à la mono- et di-réduction de l'énone pour fournir un mélange complexe de sous-produits. Dans un dernier lieu, le palladium sur charbon (Pd/C)[140] a, quant à lui, lentement mené à l'élimination observée avec le nickel de Raney. Peu importe le métal utilisé, il semblait donc y avoir une forte propension en **3.183** à restaurer le système diénone conjugué, facteur enthalpique, et décarboxyler le carbamate, facteur entropique.

Puisque les méthodes classiques d'hydrogénolyse, d'élimination et de réduction radicalaire avaient échoué, il a été tenté d'enlever le bromure avec un hydrure.[141] *A priori*, cette option assurerait de ne pas former de radicaux, dont la nocivité a été prouvée dans le cas de ces intermédiaires, ni de promouvoir l'élimination. Plutôt que de protéger la cétone momentanément afin d'éviter que celle-ci ne soit réduite au passage, il a été prévu que le fait de réduire la cétone, puis de la réoxyder, sauverait en fait une étape à la synthèse (*Schéma 3.71*). La bromo-énone **3.183** a donc été traitée avec plus de deux équivalents de Super-Hydride©, réduisant effectivement la cétone en position 1,2 et ne

fournissant qu'un diastéréoisomère. L'alcool allylique **3.187** ainsi formé a été isolé, caractérisé, puis resoumis aux conditions de réduction. Par contre, il a fallu un certain temps pour comprendre que la deuxième réduction avait plutôt lieu au niveau du carbamate cyclique pour donner l'époxyde **3.188**. Bien que cet époxyde était invisible par spectrométrie de masse et instable sur silice, la réaction était heureusement assez propre pour pouvoir interpréter ces informations simplement à partir de la spectrométrie RMN sur le mélange brut.

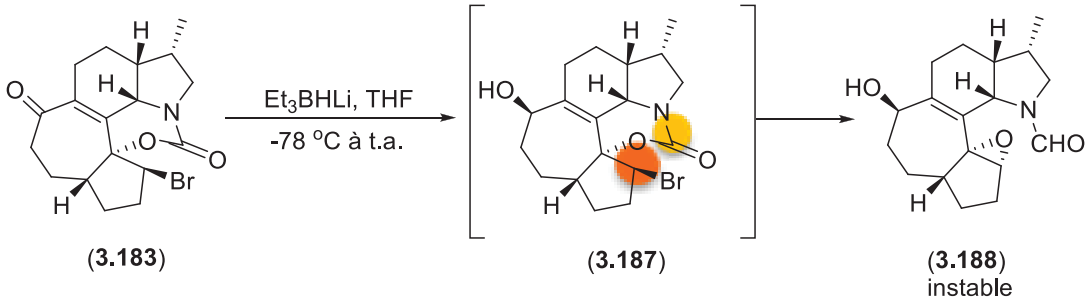
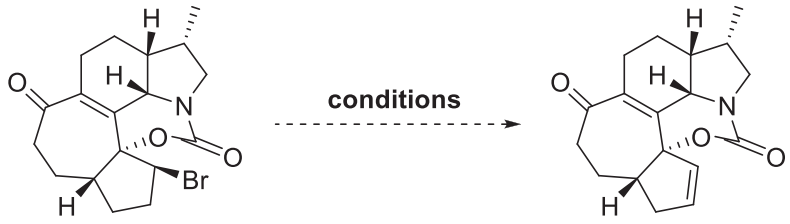


Schéma 3.71 : Tentative de débromation de l'intermédiaire **3.183** (plan B)

Dans un dernier effort quant à la débromation du bromocarbamate **3.183**, une stratégie différente a été utilisée. Plutôt que de tenter par quelque méthode de substituer formellement l'atome de brome à un atome d'hydrogène, il serait peut-être possible d'effectuer l'élimination de l'atome de brome, afin de fournir l'alcène **3.189** (*Schéma 3.72*), en fait un carbamate allylique. Après formation des centres quaternaires, ce carbamate allylique pourrait être employé dans des conditions de Tsuji-Trost hydrogénatives afin de restaurer l'alcène tel que contenu dans le composé cible. Bien qu'un tel type d'élimination ne soit pas particulièrement facile, il existe une poignée de conditions tout indiquées pour le faire, nécessitant certainement toutes une haute température (voir *Schéma 3.15*).

En premier lieu, le carbonate de lithium a été utilisé dans le DMF à reflux, sans qu'aucune réaction ne puisse être observée. En deuxième lieu, le DBU a été employé dans le toluène à reflux et a mené après un jour à un produit qui, bien que visible sur CCM, n'a jamais pu être isolé. Alternativement, le DBU dans le dioxane, à reflux, menait au même produit en quatre heures. Encore aujourd'hui, il est difficile de comprendre pourquoi le produit, pourtant visible sur CCM, n'a jamais pu être isolé. Peut-être était-il

possible d'observer ce produit brièvement en raison de son instabilité, due justement au fait que le carbamate, doublement allylique, pouvait facilement former un carbocation destructif? Néanmoins, il reste que le produit désiré **3.189** n'a jamais pu être obtenu ou observé, même après simple évaporation du solvant et spectrométrie RMN du mélange réactionnel brut.



(**3.183**) (**3.189**)

conditions

Li_2CO_3, DMF, 100 °C	aucune réaction
DBU, PhMe, reflux	décomposition
DBU, dioxane, 140 °C	décomposition

Schéma 3.72 : Tentative de débromation de l'intermédiaire **3.183** (plan C)

Face à l'impossibilité de débromer le bromocarbamate **3.183**, il était espéré que la formation d'un iodocarbamate, plus labile, pourrait mener plus facilement au produit désiré. Même s'il existe quelques exemples d'iodocarbamoylation dans la littérature,[142] ceux-ci sont plus rares, surtout à partir de carbamates Boc où il y a perte d'isoprène concomitante.[143] Or, la diénone **3.146**, traitée à l'iode dans le chloroforme ou le dichorométhane, a donc été transformée en iodocarbamate **3.190** avec un faible rendement (21%, 32% bsmr, *Schéma 3.73*). Alors que la bromocarbamoylation s'effectuait en trente minutes à -40 °C, l'iodocarbamoylation était lente et incomplète à cette température. La température a été graduellement augmentée à 0 °C, puis à température ambiante, sans que la réaction ne puisse être complétée. Même en changeant le nombre d'équivalents d'iode, ou en préservant le milieu réactionnel à -40 °C pendant 16 h, la réaction n'a pas pu être améliorée. Il aurait probablement été possible d'optimiser grandement la réaction en changeant le solvant utilisé, ou en employant plutôt du NIS comme agent iodant, mais aucun effort n'a été investi en ce sens. L'iodocarbamate **3.190** a donc été soumis globalement aux mêmes conditions de déshalogénation qu'avec le bromocarbamate **3.183**. Dans un premier lieu, les méthodes et exemples de déiodation

radicalaires abondent dans la littérature.[144] Dans cet ordre d'idée, la déiodation a été essayée avec le tributylétain en présence d'initiateur 1,1'-azobis(cyclohexanecarbonitrile) (ABCN), mais celle-ci n'a mené qu'à une lente décomposition de l'iodocarbamate, sans qu'aucun produit désiré ne puisse être observé. L'emploi du catalyseur de Lindlar, lui aussi prescrit pour une telle transformation,[145] n'a permis aucune transformation encore une fois, même après plusieurs jours et après ajout de plusieurs équivalents de catalyseur. Le palladium sur charbon (Pd/C),[146] quant à lui, n'a mené qu'au même produit d'élimination observé plus tôt, cette fois-ci beaucoup plus rapidement.

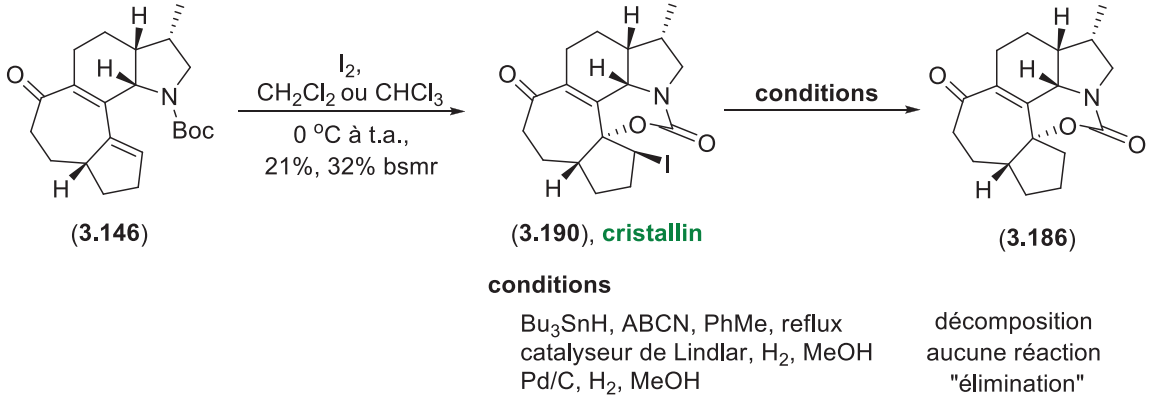


Schéma 3.73 : Formation de l'iodocarbamate **3.190** et tentative de déiodation de celui-ci

Encore une fois, l'iodocarbamate **3.190** a été traité avec du Super-Hydride© selon la stratégie détaillée précédemment. Alors que, une fois de plus, le produit de réduction-1,2 (**3.191**) a pu être obtenu chimiosélectivement et sous forme d'un seul diastéréoisomère (*Schéma 3.74*), la deuxième réduction n'a donné que le même produit observé lors de la tentative de réduction de l'intermédiaire **3.188**.

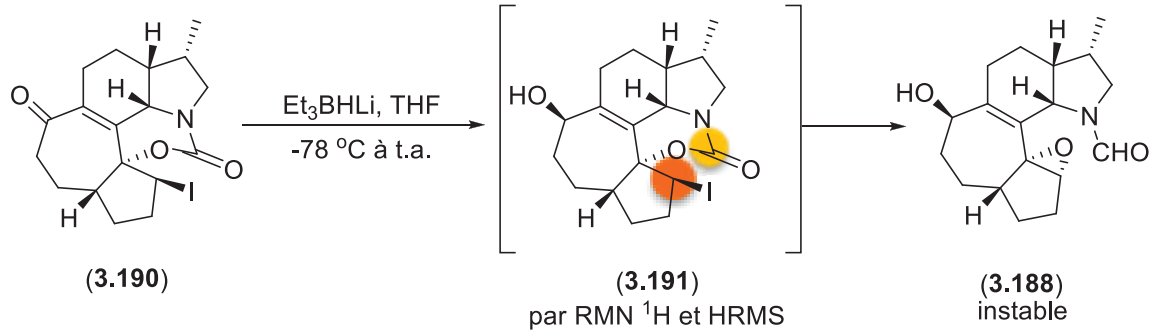
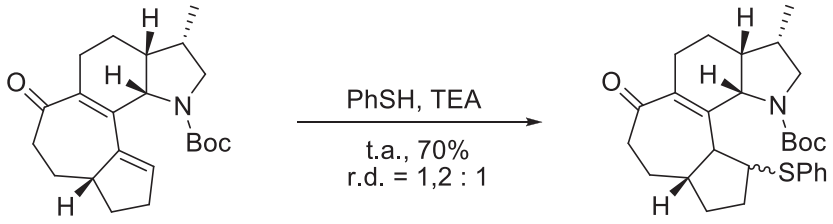


Schéma 3.74 : Tentative de déiodation de l'intermédiaire **3.190** (plan B)

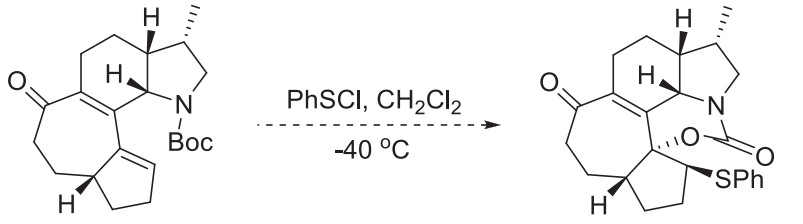
Face à une autre stratégie globalement inadéquate, les halogénocarbamates ont été délaissés pour se concentrer sur d'autres méthodes articulées autour de la disparition momentanée de l'alcène-5,6 présumé coupable de biais électronique. Plutôt que d'installer un gros atome d'halogène empêchant l'attaque d'un nucléophile (voir *Schéma 3.56*), l'ajout d'un groupement capable, au contraire, de chélater et de faciliter l'attaque d'un nucléophile a été testé. Les thioéthers, entre autres, sont connus pour améliorer les additions de cuprates en coordonnant ces réactifs et les rendant ainsi plus disponibles pour une addition conjuguée ou un déplacement S_N2 avec des tosylates.[147] Par l'entremise d'une addition de thia-Michael sur l'énone **3.146**, dans des conditions usuelles,[148] le thioéther **3.192** a donc été formé avec un rendement de 70% (*Schéma 3.75*). Par contre, alors que l'ajout des autres nucléophiles n'avait mené qu'à la formation d'un seul diastéréoisomère (voir notamment *Schémas 3.51, 3.52, 3.55* et *3.64*), l'addition 1,6 du thiophénol a formé deux diastéréoisomères non-identifiés et inséparables dans un mélange de 1,2 : 1. Pour ces raisons, l'ajout d'un cuprate n'a pas été tenté à partir de l'intermédiaire **3.192**.



(**3.146**) (**3.192**)

Schéma 3.75 : Addition de thia-Michael avec **3.146**

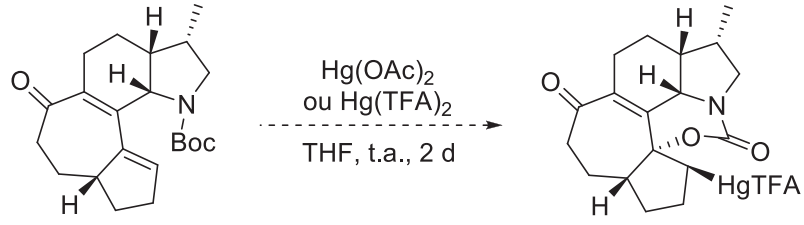
Plutôt que d'avoir recours à une addition de thia-Michael sur la diénone **3.146** électrophile, une réaction chélétropique utilisant l'énone comme nucléophile a alors été préconisée.[149] La formation d'un thionium, si possible, entraînerait peut-être une carbamoylation afin de former **3.193**, analogue de **3.183** différent en ça qu'il contient maintenant un thioéther capable de coordonner des nucléophiles, plutôt qu'un brome ou un iode encombrant (*Schéma 3.76*). Le chlorure de sulfényl, préparé facilement à partir du thiophénol et du NCS,[150] a été ajouté à **3.140** dans le dichlorométhane, en quantité stoechiométrique, à -40 °C. Malheureusement, seule une décomposition rapide a été observée dans ces conditions.



(**3.146**) (**3.193**) décomposition rapide

Schéma 3.76 : Tentative de formation d'un thionium avec **3.146**

En outre, il existe quelques méthodes possibles afin d'effectuer la mercuration d'alcènes, notamment l'oxymercuration et l'aminomercuration.[151] Si les rapports de mercuricarbamoylation n'existent toutefois pas, cette stratégie garde l'avantage indéniable qu'elle permet d'avoir recours à un vaste choix d'autres conditions afin de mener éventuellement à une énone telle que **3.189**. C'est donc dans cette optique que l'énone **3.146** a été traitée avec de l'acétate de mercure(II) ou du triflate de mercure(II), en espérant promouvoir la formation de **3.194** (*Schéma 3.77*). Malheureusement, aucune transformation n'a pu être observée après deux jours à t.a., alors qu'un reflux dans le THF n'a permis qu'une lente décomposition.



(**3.146**) (**3.194**) aucune réaction

Schéma 3.77 : Tentative de mercuricarbamoylation avec **3.146**

Après ces quelques essais infructueux d'halogénocarbamoylation, de thia-Michael, de sulfonium et de mercuricarbamoylation avec la diénone **3.146**, il est devenu tentant de considérer ces options à partir d'intermédiaires tricycliques tels que **3.102**. L'absence d'une cétone réactive, peut-être la cause de certains problèmes lors des dernières réactions détaillées, permettrait peut-être de faire disparaître l'alcène et de

former enfin les centres quaternaires requis. S'inspirant des résultats encourageants obtenus avec la diénone tétracyclique **3.146**, la bromocarbamoylation a été effectuée une fois de plus en utilisant du brome moléculaire, à -40 °C, pour former le bromocarbamate **3.195** avec un rendement de 82% (*Schéma 3.78*). Un sous-produit mineur de déprotection de l'acétal a été observé.

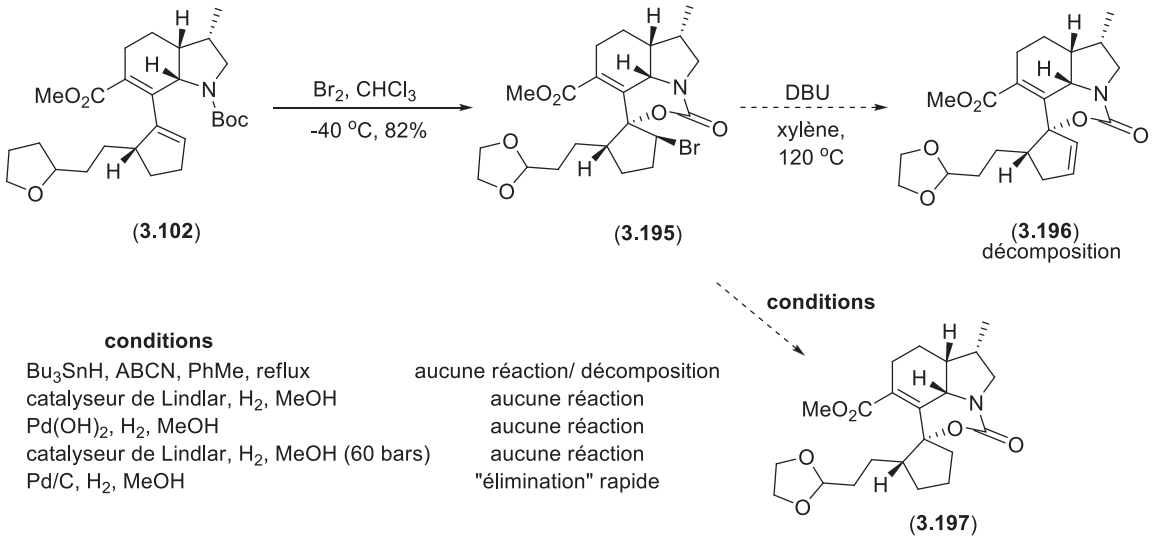


Schéma 3.78 : Formation du bromocarbamate tricyclique **3.195** et tentatives de débromation

La débromation du carbamate tétracyclique **3.195** a ensuite été tentée en utilisant les conditions usuelles de débromation radicalaire montrées précédemment (*vide supra*). Elle n'a toutefois permis qu'une lente décomposition après un jour et/ou ajout de plusieurs équivalents de tributylétain et d'initiateur radicalaire. Dans la même optique qu'avec l'intermédiaire **3.183**, la débromation a donc été tentée dans des conditions d'hydrogénolyse. En utilisant le catalyseur de Lindlar ou de Pearlman, aucune réaction n'a été observée, même sous une pression de 60 bars d'hydrogène dans le cas du catalyseur de Lindlar. Dans un dernier lieu, le traitement au palladium sur charbon a mené à une lente élimination, tel qu'observé avec **3.183**. Puisque, malheureusement, les tentatives de débromation du carbamate tricyclique **3.195** ne donnaient que les mêmes sous-produits qu'auparavant, les essais abondant en ce sens ont vite avorté.

Tant qu'à avoir l'intermédiaire bromé **3.195** en main, la réduction de l'ester contenu dans celui-ci a été effectuée à l'aide du réactif de DIBAL-H pour fournir l'alcool allylique **3.198** (*Schéma 3.79*). Il a alors été possible de tenter la débromation de nouveau, en espérant que l'absence d'un groupement ester stabilisant découragerait l'élimination observée à plusieurs reprises lors de tentatives d'hydrogénolyse de tels intermédiaires (voir *Schéma 3.70*, *3.74* et *3.78*). Malheureusement, un survol rapide des principales options disponibles, telles que précédemment essayées, laissait présager que la débromation était encore une fois problématique.

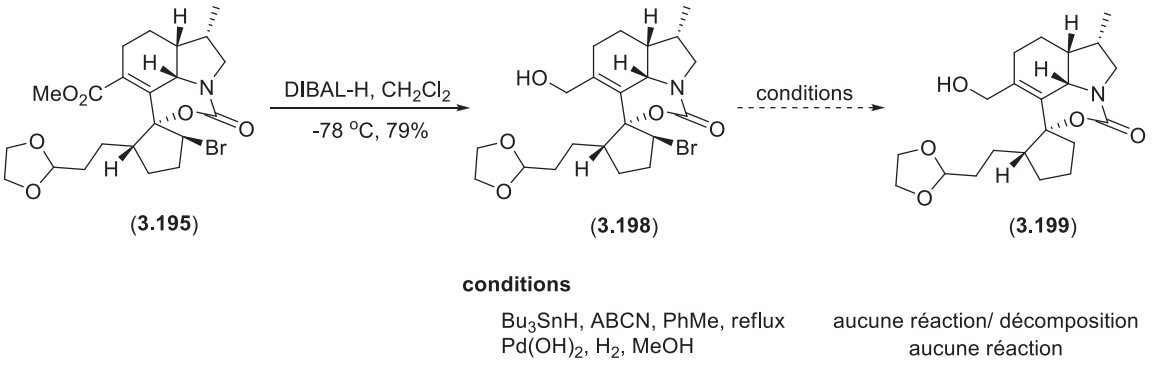


Schéma 3.79 : Réduction de **3.195** en **3.198** et tentatives de débromation

En gardant toutefois en tête que l'idée principale de ces transformations était de « masquer » temporairement l'alcène supplémentaire dont le biais électronique était peut-être néfaste, l'alcool allylique **3.198** représentait en soi un précurseur intéressant pour la formation de centres quaternaires. Il était effectivement possible d'éprouver une fois de plus la liste de réarrangements sigmatropiques disponibles à partir d'alcools allyliques, tel que précédemment (*vide supra*). Les réactions de Johnson-Claisen et d'Eschenmoser ont donc été essayées dans les mêmes conditions que précédemment, mais sans succès, ne menant qu'à la décomposition lente de l'intermédiaire **3.198** (*Schéma 3.80*). La formation de l'éther d'étain **3.202** a ensuite été tentée en vue d'effectuer un réarrangement de Wittig-Still, risqué en présence de l'atome de brome, mais demeurant la seule méthode ayant permis la formation d'un centre quaternaire dans le cadre de ce projet. Cependant, seule une décomposition rapide du bromocarbamate **3.198** a été observée en utilisant le KH ou le KHMDS comme base et à différentes températures (-78 °C à t.a.).

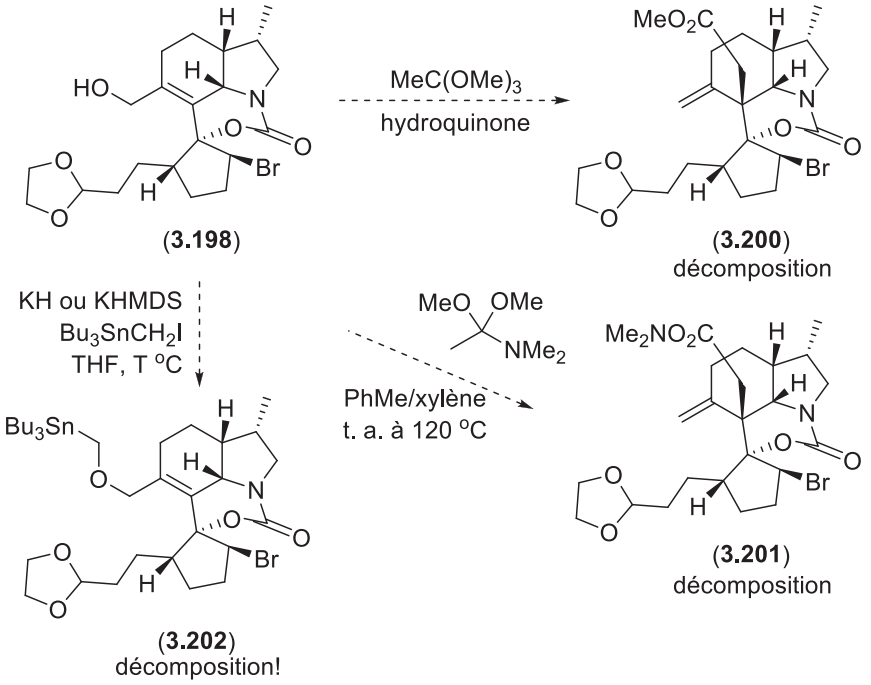


Schéma 3.80 : Tentatives de réarrangements sigmatropiques avec l'intermédiaire **3.198**

En outre, l'acétate **3.203** a été formé à partir de l'alcool allylique **3.198** (*Schéma 3.81*). Ainsi, la formation de l'acétal de cétène silylé a pu être accomplie tel qu'en **3.204**. Malheureusement, le réarrangement d'Ireland-Claisen de cet intermédiaire dans le 1,4-dioxane à reflux n'a pas été possible. Une fois de plus, il semblait que l'atome de brome encombrant compromettait la faisabilité des réarrangements sigmatropiques essayés, à l'instar des additions conjuguées en voie d'obtenir **3.184** et **3.185**.

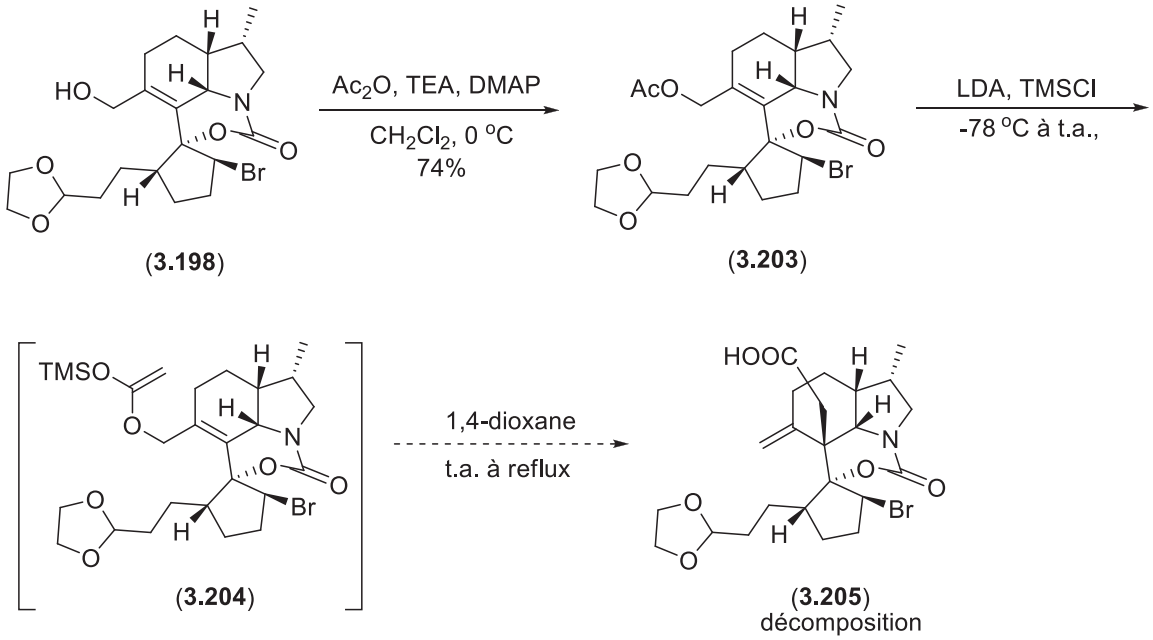


Schéma 3.81 : Formation de l'acétate **3.203** et tentative de réarrangement d'Ireland-Claisen

Tandis que l'option de l'addition de thia-Michael était impensable dans le cas de cet ester α,β-insaturé en raison de la faible électrophilie de ce dernier, la formation du thionium a alors pu être essayée, une fois de plus. En utilisant encore le chlorure de sulfényle (PhSCl), fraîchement préparé, c'est cette fois-ci la lactonisation qui a été promue afin de former la lactone **3.206** sélectivement (*Schéma 3.82*)! Aucune trace d'un produit de carbamoylation n'a été observée et, surtout, la lactone **3.206** a été obtenue sous forme d'un seul diastéréoisomère, celui dessiné à la suite de l'interprétation des études nOe. Bien qu'il soit difficile de le voir en deux dimensions, il était encourageant de constater que le thioéther était effectivement très près de l'énone, et que la coordination avec un réactif de cuprate, par exemple, n'était pas impensable. Les réactifs de Lipschutz et Gilman ont alors été utilisés dans des conditions usuelles. Alors que, dans le premier cas, aucune réaction n'a été observée même après réchauffement lent et graduel du milieu réactionnel, le réactif de Gilman n'a mené à -20 ^{0}C qu'à la formation d'un mélange complexe où un nouveau signal de méthyle était introuvable.

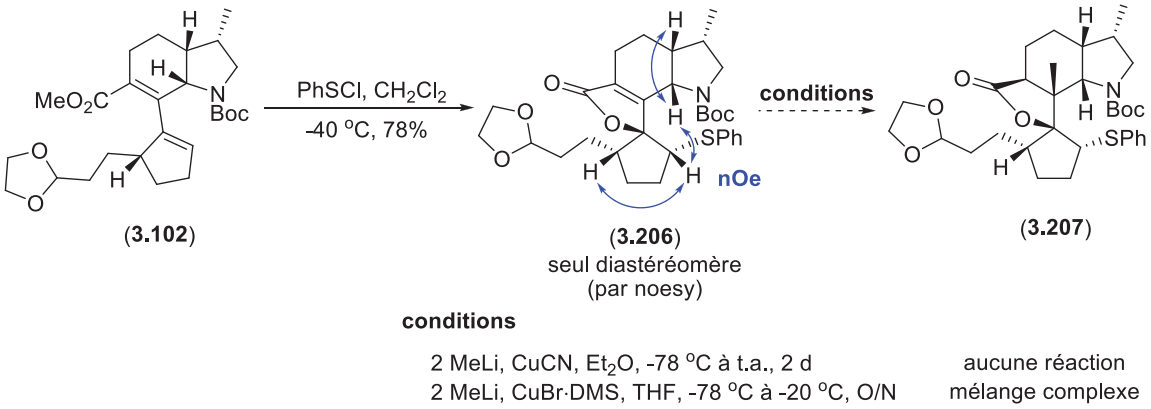


Schéma 3.82 : Formation de la lactone **3.206** et ajout de cuprates sur cette dernière

La mercurilactonisation, qui avait échoué dans le cas de la diénone **3.146**, a été ressayée. En premier lieu, l'utilisation d'acétate de mercure(II) dans le THF n'a mené à aucune transformation, même après deux jours et après avoir chauffé le milieu réactionnel à reflux (*Schéma 3.83*). Ce n'est qu'en utilisant le trifluoroacétate de mercure(II) qu'une réaction a été observée, mais, plutôt que d'avoir promu la carbamoylation tel qu'espéré, c'est en fait la mercurilactonisation qui a été obtenue, soit l'organomercurien **3.208**.

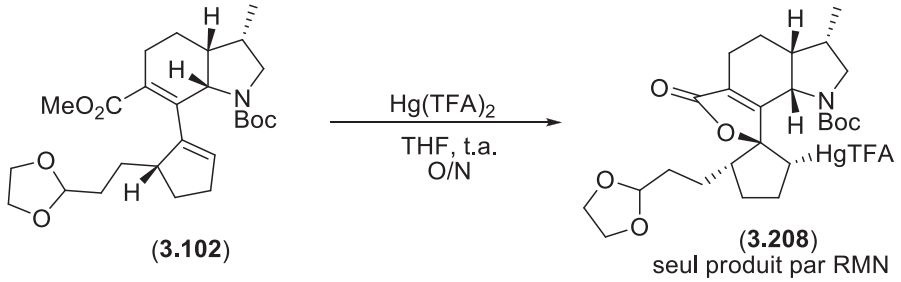


Schéma 3.83 : Oximercuration de l'intermédiaire **3.102**

Cette transformation est très étrange puisque, à notre connaissance, les mercurilactonisations sont toujours effectuées à partir d'acides carboxyliques et non d'esters comme ici. Tel que souvent observé dans le cas des dernières réactions présentées précédemment (voir *Schémas 3.51, 3.52, 3.55* et *3.64*), un seul diastéréoisomère a été obtenu. Il fallait ensuite tenter la démercuration de l'intermédiaire **3.208** pour ainsi recourir à une lactone tétracyclique telle que **3.209** (*Schéma 3.84*) beaucoup moins encombrée que **3.207**. La condition la plus largement employée, soit le borohydrure de sodium en présence d'hydroxyde de sodium,[152] a d'abord été utilisée, mais n'a mené qu'à une rapide décomposition du réactif de départ. Probablement que l'hydrure était capable de réduire la lactone et, surtout, la démercuration est connue pour procéder selon un mécanisme radicalaire sous de telles conditions. Or, il a été observé maintes fois dans le cadre de ce projet que les intermédiaires radicaux sont susceptibles de mener à une décomposition rapide (*vide supra*). Une deuxième méthode de démercuration, faisant usage d'un amalgame de sodium et de mercure et étant connue pour procéder de façon non-radicalaire,[153] a été essayée, mais n'a mené qu'à la formation d'un mélange complexe.

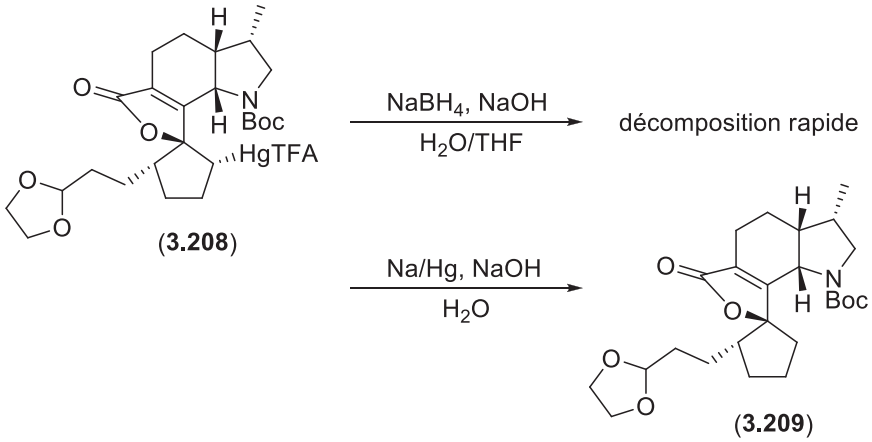


Schéma 3.84 : Démercuration de l'intermédiaire **3.208**

Face à ces multiples échecs en voie de l'obtention d'intermédiaires tels que **3.197**, **3.199**, ou **3.209**, une transformation plus directe a été envisagée. Plutôt que d'avoir recours à la mercurilactonisation (ou mercuricarbamoylation), et d'avoir à réduire le composé organomercurien résultant, la palladocarbamoylation devrait donner accès à un complexe tel que **3.210** pouvant directement fournir l'alcène **3.196** (*Schéma 3.85*). Bien que, à l'instar de la mercuration, il existe plusieurs variantes de cette réaction, tel que l'oxypalladation ou l'aminopalladation,[154] il n'existe toutefois aucun rapport de palladocarbamoylation tel que tenté ici.

Afin d'éprouver la faisabilité de cette transformation, un bref survol des conditions les plus employées dans le cas d'oxypalladation a été effectué. Or, en traitant l'ester **3.102** avec de l'acétate de palladium dans le THF, l'acétonitrile ou le DMSO, ou du chlorure de palladium dans le dichlorométhane à reflux, il n'a été possible d'observer aucune transformation désirée. Cette stratégie a donc été mise de côté, en pensant qu'il devait finalement y avoir une raison pour laquelle cette transformation n'avait effectivement jamais été rapportée auparavant.

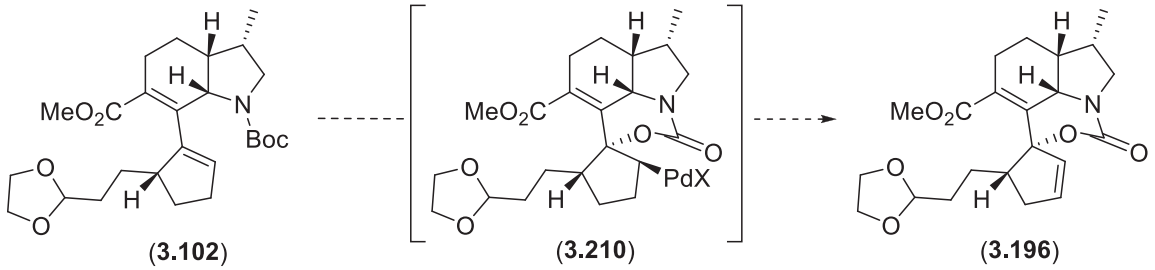


Schéma 3.85 : Tentatives de palladocarbamoylation avec l'intermédiaire **3.102**

Cette méthode représentait toutefois la dernière tentative dans le but de faire disparaître momentanément l'alcène en position 5,6 et, globalement, la dernière stratégie afin d'installer les centres quaternaires manquants en vue d'obtenir la daphniglaucine C (**3.1**).

3.6 Conclusion et perspectives

Pour conclure, quelques progrès ont été accomplis vers la synthèse totale de la daphniglaucine C (**3.1**). À partir de la prolinone **3.74** commerciale, l'intermédiaire tétracyclique **3.146** a notamment été préparé en quinze étapes (dont dix purifications sur silice), avec un rendement global de 14,2% et en utilisant trois groupements protecteurs (*Schéma 3.86*).

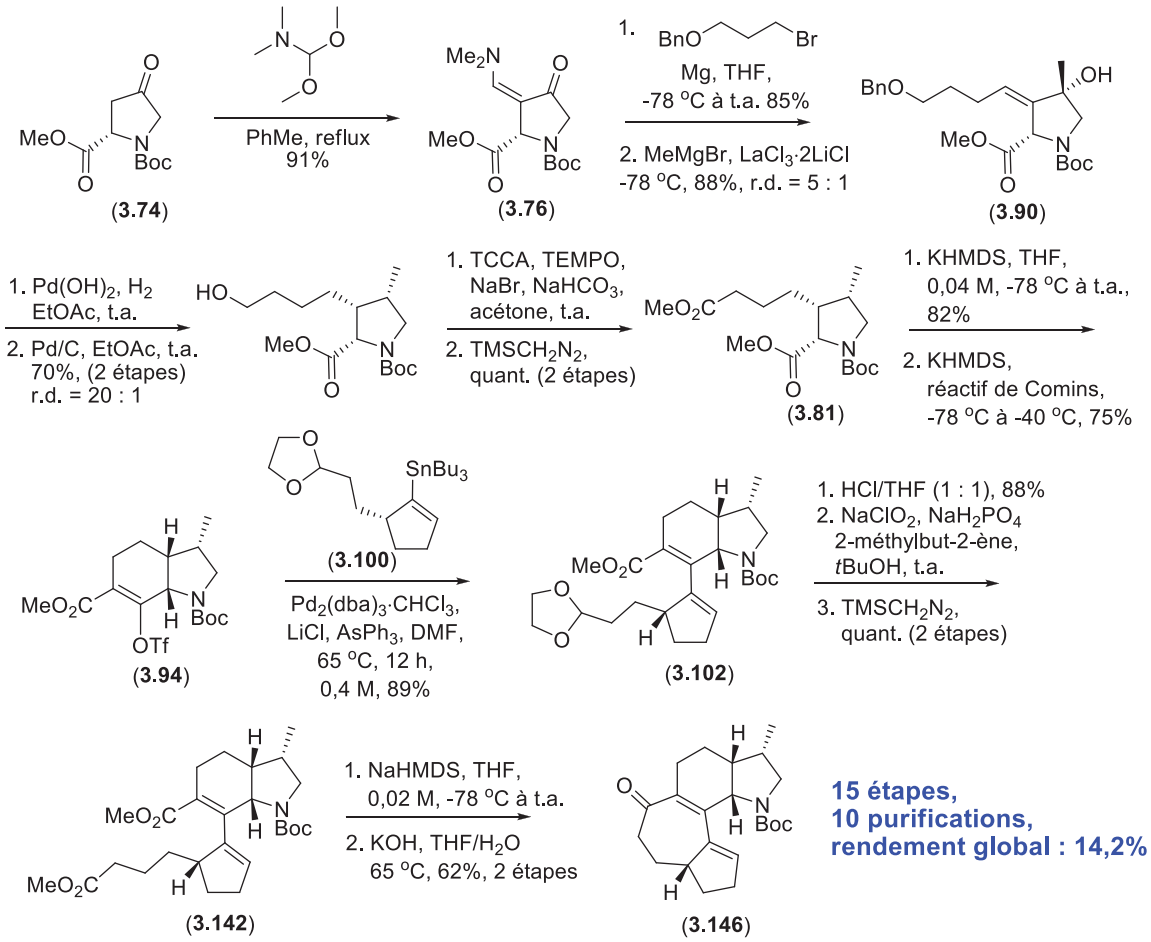


Schéma 3.86 : Synthèse de l'intermédiaire tétracyclique **3.146** depuis **3.74**

Aucune méthode efficace de formation des centres quaternaires contenus dans la daphniglaucine C n'a pu être trouvée, même si de nombreux efforts ont abondé en ce sens. Par contre, certains intermédiaires sont peut-être un peu plus prometteurs que d'autres afin de terminer la synthèse totale entreprise. Entre autres, l'intermédiaire **3.127**,

produit de réarrangement de Wittig-Still tricyclique, est en fait le seul produit affichant un centre quaternaire. Après s'être assuré qu'il s'agit bel et bien du diastéréoisomère désiré, et après avoir tenté plus sérieusement l'optimisation de son obtention, il serait possible d'utiliser cet intermédiaire dans une série de transformations menant à la daphniglaucine C (*Schéma 3.87*).

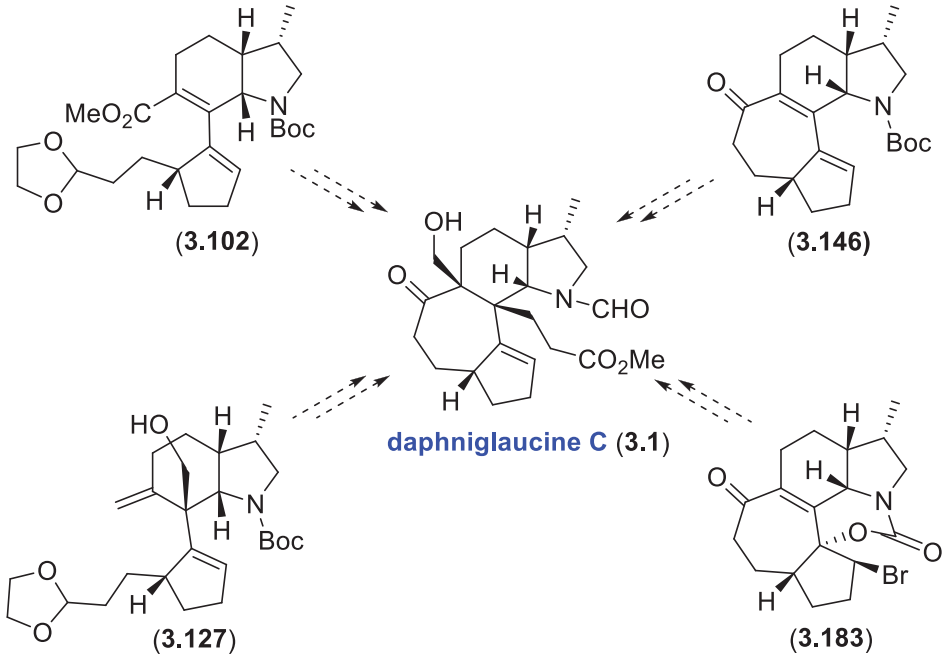


Schéma 3.87 : Intermédiaires d'intérêt vers la synthèse totale de la daphniglaucine C

En outre, les intermédiaires **3.146** et **3.183** pourraient eux aussi être considérés comme prioritaires en vue de compléter la synthèse totale de la daphniglaucine C. D'une part, il reste plusieurs méthodes de débromation à tester en voie d'obtenir des intermédiaires d'intérêt à partir de **3.183** et pour lesquels l'alcène en position 5,6 serait « neutralisé ». Plusieurs options pourraient alors mener au produit cible.

D'autre part, quelques méthodes de formation de centres quaternaires peuvent encore être essayées à partir de la diénone **3.146**, comme par exemple l'ajout de phosphonamides, l'addition conjuguée radicalaire promue au samarium, ou la formation d'un cyclopropane en position 3,4 qui pourrait être ouvert en son apex. Par ailleurs, il serait peut-être avantageux d'échanger ou de simplement enlever le groupement protecteur Boc afin d'éprouver de nouveau la longue liste de méthodes vers la formation

de centres quaternaires. Il est possible que l'encombrement stérique qu'impose ce dernier groupement ait été sous-estimé jusqu'à présent. Si les intermédiaires en main permettent bel et bien la synthèse totale de la daphniglaucine C, il serait éventuellement très intéressant d'investir quelques efforts vers la synthèse d'autres daphniglaucines, puisque celles-ci partagent une charpente hautement similaire (voir *Figure 3.2*).

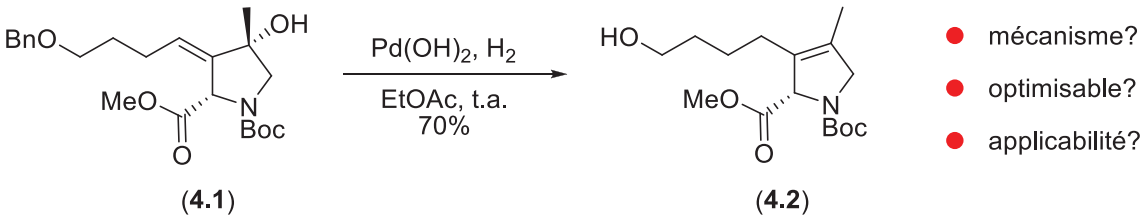
En outre, il serait possible de tirer profit de la synthèse établie jusqu'ici afin de préparer une vaste gamme d'analogues non-naturels de la daphniglaucine C. Par exemple, il est facile d'imaginer des analogues pour lesquels le groupement formamide pourrait être échangé pour un amide différent. Ou encore, l'ester pourrait être changé ou carrément enlevé du composé cible. Les propriétés biologiques des analogues obtenus, ainsi que celles de la daphniglaucine C elle-même, pourraient ensuite être explorées davantage.

Chapitre IV

Brève étude d'une transposition allylique réductrice

4.1 Découverte et mise en contexte

Dans le cadre du projet de synthèse totale de la daphniglaucine C (chapitre 3), il a été découvert que l'hydrogénation de l'intermédiaire **3.83**, initialement censée fournir le produit **3.79**, a plutôt mené à la formation d'un produit formel de transposition allylique réductrice (voir *Schémas 3.24, 3.26, 3.27*). Or, il était dans notre intérêt d'étudier cette réaction plus en détail afin de comprendre quel(s) mécanisme(s) étai(en)t à évoquer et, conséquemment, d'utiliser cette transformation dans le cadre d'une stratégie plus générale afin d'obtenir un large éventail de pyrrolines et de pyrrolidines polysubstituées (*Schéma 4.1*). Les résultats de ce chapitre ont été obtenus en collaboration avec Salma Kassem, une étudiante stagiaire à la maîtrise.



(**4.1**) (**4.2**)

Schéma 4.1 : Transposition allylique réductrice observée

D'abord, il est intéressant de remarquer que, malgré l'âge et l'omniprésence de la réaction d'hydrogénation, il n'existe à notre connaissance que deux exemples de désoxygénation avec transposition allylique telle que décrite dans nos travaux. Certes, il existe plusieurs cas de désoxygénation d'alcools benzyliques dans de telles conditions, mais très peu d'alcools simplement *allyliques*. En premier lieu, le groupe de Camplo[155] a décrit une transformation similaire dans des travaux publiés en 2005 (*Schéma 4.2*). Bien que les produits décrits soient différents des nôtres, il n'est pas impossible que les mêmes intermédiaires soient obtenus, mais que ceux-ci soient hydrogénés plus facilement. Alors que la transposition de **4.1** permet d'obtenir un alcène tétrasubstitué (**4.2**) stable, le groupe de Camplo obtient probablement un alcène trisubstitué, peut-être plus facile à hydrogéner vers **4.5**. Malgré le manque d'information quant à cette transformation (rendements, quantité de catalyseur, mécanisme), le groupe d'Odinokov[156] en montre un deuxième exemple probant avec la transposition régiosélective d'un alcool allylique sur un analogue de cholestérol (*Schéma 4.2*).

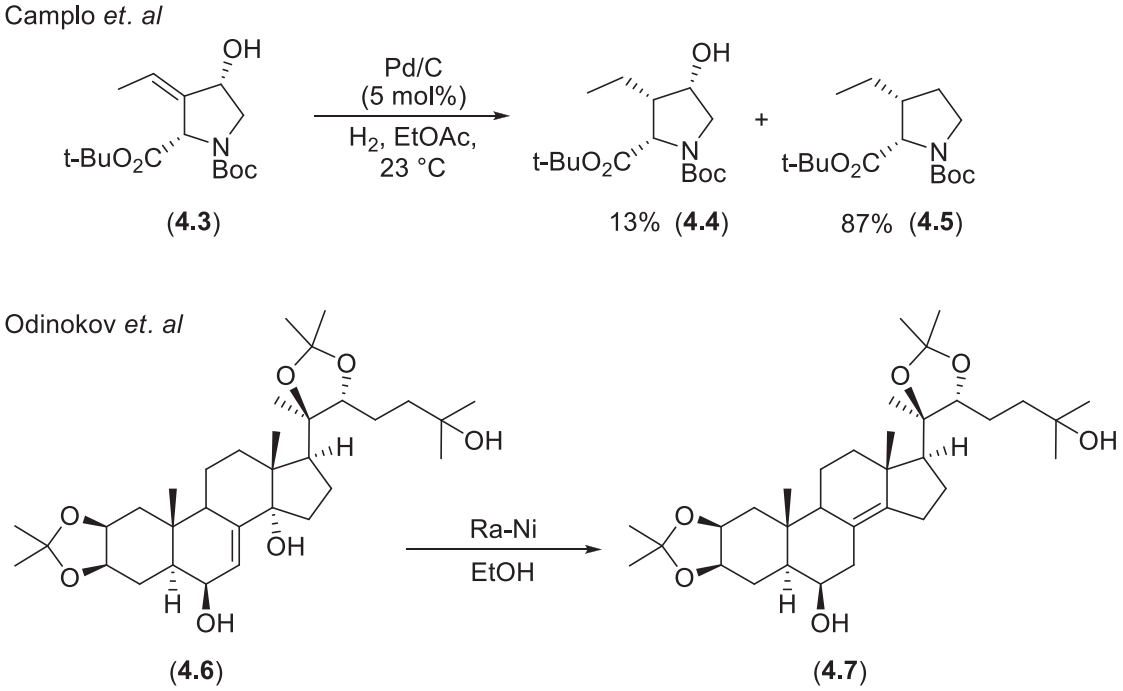


Schéma 4.2 : Travaux antérieurs de Campo, Odinokov et leurs collaborateurs respectifs

4.2 Brève optimisation

Afin de comprendre un peu mieux la réaction de transposition allylique réductrice, un alcool allylique test a été préparé à partir de l'énaminone **4.8** (*Schéma 4.3*) en deux étapes à l'aide de la méthode précédemment utilisée (voir *Schéma 3.27*). Il est à noter que l'alcool allylique résultant a été obtenu à partir de l'énone **4.9** sous forme de mélange diastéréomérique (r.d. = 5 : 1) séparable (**4.10** et **4.11**).

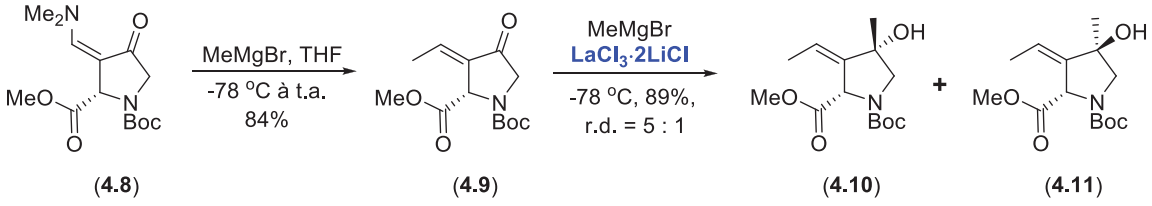


Schéma 4.3 : Préparation de l'alcool allylique test **4.10**

Ayant en main plusieurs grammes de l'intermédiaire **4.10**, différents catalyseurs ont alors été employés dans une tentative d'optimisation de la transformation étudiée (*Tableau 4.1*). En premier lieu, nous nous sommes assurés que la réaction de transposition allylique réductrice était bel et bien reproductible dans le cas de ce substrat-ci (entrée 1). Il s'est avéré que trois produits ont été obtenus à partir de **4.10** en présence du catalyseur de Pearlman et d'hydrogène : le composé **4.12** (63%), produit attendu, l'isomère désoxygéné **4.13** (10%) et l'alcool tertiaire **4.14** (10%). Le dernier intermédiaire **4.14** est fort probablement provenu d'une hydrogénation simple, sans qu'il n'y ait de transposition allylique réductrice; C'est en fait le produit qui était initialement attendu lorsque la réaction a été effectuée pour la première fois. Il est également à noter qu'il était impossible d'obtenir le produit **4.12** en resoumettant l'alcool tertiaire **4.14** aux mêmes conditions d'hydrogénation. La présence de la liaison double était donc capitale pour la faisabilité de la désoxygénation. Il s'est avéré qu'un temps réactionnel plus long permettait l'isomérisation quantitative du produit **4.13** vers le produit attendu **4.12**, améliorant ainsi le rendement global de 63% à 68% de façon reproductible (entrée 2). L'isomérisation a probablement eu lieu lentement afin de fournir un alcène tétrasubstitué, encore plus stable que l'alcène trisubstitué de départ. Qui plus est, il est à noter qu'aucune transposition allylique n'a été observée à partir de l'alcool allylique diastéréomérique **4.11**.

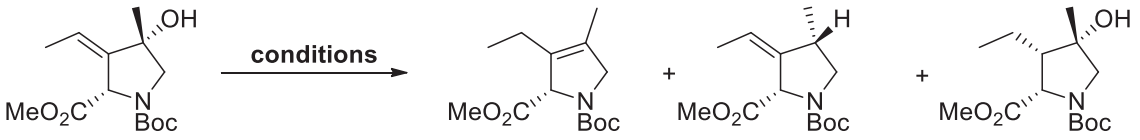
Ensuite, différents catalyseurs ont été essayés, à commencer par le catalyseur de Wilkinson et de Crabtree (entrée 3-4), pour avoir une idée des résultats obtenus par catalyse homogène. Malheureusement, ces deux essais n'ont permis aucune transformation, même en augmentant la quantité de catalyseur à un équivalent, ou en attendant plusieurs jours. Le catalyseur d'Adams a par la suite été testé (entée 5), mais celui-ci n'a permis d'obtenir que du produit hydrogéné sans transposition, avec un rendement de 98%. Puisque les deux réactions décrites par Camplo et Odinokov faisaient état de deux catalyseurs plus doux, soit le nickel de Raney et le catalyseur de Lindlar (entrées 6 et 7), ces conditions ont été essayées. Par contre, ni l'un ni l'autre n'a été capable d'induire une quelconque transformation.

En outre, une série d'expériences a été réalisée (entrées 8 à 11) afin de déterminer l'importance ou l'effet de l'état d'oxydation du palladium. Le chlorure de palladium(II), de même que l'acétate de palladium(II) ont échoué à effectuer une quelconque transformation. Néanmoins, l'activité du catalyseur d'acétate de palladium(II) a pu être restaurée en ajoutant de la triphénylphosphine au milieu réactionnel, permettant d'obtenir 39% de produit désiré après quatre jours, de même que 18% du régioisomère **4.13**. Dans le même ordre d'idée, le Pd_2dba_3, source de palladium(0), a permis d'obtenir très lentement 60% du produit désiré **4.12**, de même que 15% du régiomère **4.13** et 20% de l'alcool tertiaire **4.14**. Cette série de résultats tend à confirmer que seule la présence de palladium à l'état d'oxydation 0 est nécessaire afin d'effectuer la transposition allylique réductrice. Afin de compléter ces résultats, le palladium déposé sur charbon (Pd/C) a été à raison de 5% mol, mais n'a malheureusement mené qu'à l'hydrogénation rapide de l'alcool allylique **4.10** afin de fournir l'alcool tertiaire **4.14** avec un rendement de 95%.

À ce moment, il a été stipulé que le palladium(0), nécessaire à la transposition allylique réductrice, était simplement présent en trop grande quantité et menait alternativement au produit hydrogéné **4.12**. Cette hypothèse a été mise à l'épreuve en diminuant graduellement la quantité de palladium(0) présent dans le milieu réactionnel (entrées 12 à 17). En diminuant de 5% mol à 0,5% mol, il a donc été possible d'observer la formation lente de l'alcool allylique hydrogéné (34%) comme avant, mais surtout de l'alcène tétracyclique désiré, bien qu'en rendement modeste (11%)!

L'ensemble des conditions regroupées dans le *Tableau 4.1* démontre la difficulté à optimiser la transposition allylique réductrice ou, d'un point de vue différent, notre chance d'avoir essayé de prime abord les conditions optimales pour celle-ci. Il semblait effectivement que le catalyseur de Pearlman, probablement lentement transformé en palladium(0) en présence d'hydrogène[157] avait la réactivité parfaite pour promouvoir la transposition allylique réductrice vers **4.12**, sans qu'il n'y ait d'hydrogénation trop rapide menant à la formation de **4.14**.

Tableau 4.1 : Optimisation de la transposition allylique réductrice (catalyseurs)



(**4.10**) (**4.12**) (**4.13**) (**4.14**)

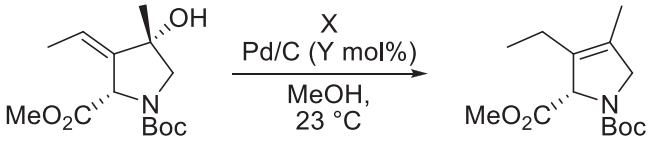
entrée	catalyseur	mol (%)	temps	4.12 (%)	4.13 (%)	4.14 (%)
1	$Pd(OH)_2/C$	5	3 h	63	10	10
2	$Pd(OH)_2/C$	5	16 h	68	-	10
3	$RhCl(PPh_3)_3$	5	3 d		n.r.	
4	$[Ir(cod)(PCy_3)(py)]PF_6$	5	3 d		n.r.	
5	PtO_2	5	16 h	-	-	98
6	Raney nickel	5	3 d		n.r.[d]	
7	catalyseur de Lindlar	5	24 h		n.r.	
8	$PdCl_2$	5	2 d		traces[a]	-
9	$Pd(OAc)_2$	5	4 d		traces[a]	-
10	$Pd(OAc)_2 + PPh_3$	5	4 d	39	18	-
11	Pd_2dba_3	5	3 d	60	15	20
12	Pd/C	5	1 h	-	-	95
13	Pd/C	1	1 h	9	-	87
14	Pd/C	0,25	16 h		traces[a]	
15	Pd/C	0,5	16 h	11	-	34
16	Pd/C	0,5[b]	16 h	13	-	39
17	Pd/C	0,5[c]	2 d	25	-	23

Concentration : 0,2 M si non-spécifiée
[a]traces visibles; [b]concentration : 0,1 M; [c] concentration : 0,05 M; [d] aussi essayé dans le MeOH

À ce point-ci, une stratégie différente a donc été essayée en vue d'optimiser la transposition allylique réductrice. Puisque le palladium(0) sur charbon était capable de promouvoir la transposition lorsque la charge du catalyseur était réduite, peut-être serait-il salutaire de préserver ce catalyseur, mais de changer la source d'hydrogène ? En premier lieu, l'ammonium de formate a été essayé sans succès : après une journée, il n'y a eu aucune transformation observée, même en augmentant la charge du palladium à 5%

mol et en ajoutant jusqu'à 10 eq. de formate d'ammonium (*Tableau 4.2*). Ensuite, le poly(méthylhydroxysiloxane) (PMHS, 10 eq.), reconnu comme agent réducteur de liaisons doubles,[158] a été utilisé en maintenant une faible charge de Pd/C (1% mol). À notre grand bonheur, non seulement la réaction était-elle rapide (habituellement 40 min) et reproductible, mais elle permettait aussi de former l'alcène **4.12** avec un rendement amélioré (80%, entrée 2). Par contre, le PMHS ayant un point d'ébullition de 205 °C, il était difficile de se débarrasser de celui-ci étant donné la faible polarité des produits isolés. Même un lavage biphasique hexane/acétonitrile, parfois prescrit pour de tels problèmes, n'aidait en rien. C'est seulement après trois ou quatre purifications sur silice qu'il était possible d'isoler l'alcène **4.12** pur, sans impuretés liées au PMHS. Pour ces raisons techniques, la quantité de PMHS contenue dans le milieu réactionnel a été réduite à 5 eq. (entrée 3), puis à 2 eq. (entrée 4), pour un rendement et un temps réactionnel identiques. Par contre, même avec 2 eq., il n'était pas très pratique d'utiliser le PMHS en raison de sa propension à contaminer l'alcène **4.12** apolaire. Une purification sur silice n'était jamais suffisante.

Tableau 4.2 : Optimisation de la transposition allylique réductrice (sources réductrices)



(**4.10**) (**4.12**)

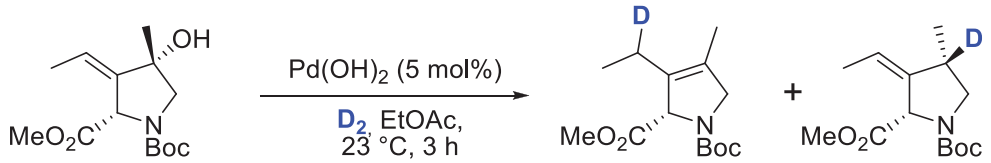
entrée	X	Y	temps	(4.12) %
1	HCO_2NH_4, 2 eq.	1-5	1 d	n.r.
2	PMHS, 10 eq.	1	40 min	80
3	PMHS, 5 eq.	1	40 min	80
4	PMHS, 2 eq.	1	40 min	80
5	Et_3SiH, 5 eq.	5	40 min	78*
6	Et_3SiH, 10 eq.	1	40 min	78*
7	Et_3SiH, 5 eq.	1	40 min	82
8	**Et_3SiH, 2 eq.**	**1**	**40 min**	**82**

*Quelques sous-produits ont été observés sous forme de traces

Pour ces raisons, le PMHS a été remplacé par le triéthylsilane (Et_3SiH). [159] En utilisant 5 eq. de Et_3SiH avec 5% mol Pd/C (entrée 5) ou 10 eq. de Et_3SiH avec 1% mol Pd/C (entrée 6), la réaction permettait la formation de 78% de l'alcène **4.12**, avec formation concomitante de traces de l'alcool tertiaire **4.14**. En diminuant à 5 eq., puis 2 eq. avec 1% mol Pd/C (entrées 7-8), c'est là qu'il s'est agi d'une réelle amélioration par rapport aux conditions de départ (*Tableau 4.1*, entrée 1) : en plus d'un rendement supérieur et reproductible de 82%, le produit **4.12** a pu être obtenu rapidement et de façon très propre, simplement après une purification sur silice.

4.3 Études mécanistiques

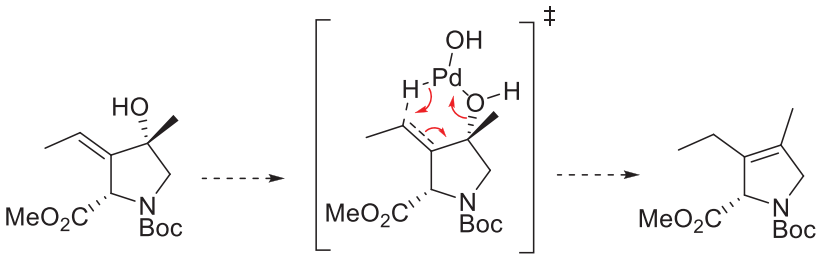
Par ailleurs, il était intéressant de tenter d'élucider le mécanisme impliqué dans cette transposition allylique réductrice. Les informations ainsi acquises aideraient peut-être à comprendre un peu mieux les limitations inhérentes de la méthodologie potentielle que nous avions en main. En ce sens, il est peut-être utile de rappeler les conclusions acquises jusqu'ici : (1) la présence de palladium(0) est essentielle à la transposition allylique réductrice, mais ce dernier entraîne simplement la réduction vers **4.14** s'il est trop abondant; (2) si le régioisomère **4.13** est isolé, il peut être simplement isomérisé dans les conditions réactionnelles précédentes. Par contre, l'isomérisation inverse est impossible; (3) l'alcool tertiaire **4.14** ne peut jamais être transformé en produit **4.12** ni désoxygéné, même s'il est isolé, puis réengagé dans les conditions réactionnelles d'hydrogénation; (4) le diastéréoisomère **4.11** ne réagit pas aux conditions de transposition allylique. De plus, une simple expérience de deutération, en substituant l'hydrogène habituellement employé par le deutérium moléculaire, a permis de constater qu'il y avait monodeutération tel qu'en **4.15** et **4.16**, et nulle part ailleurs (*Schéma 4.4*).



(**4.10**) (**4.15**) (**4.16**)

Schéma 4.4 : Expérience de deutération de **4.10**

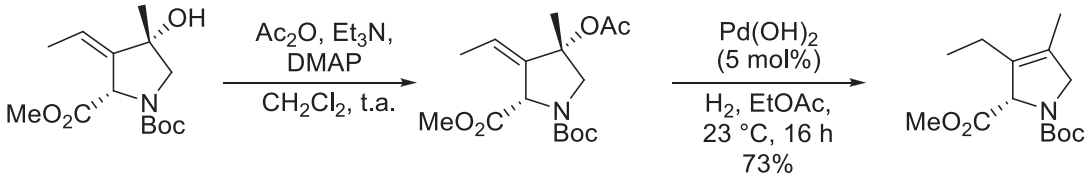
Il existe plusieurs mécanismes possibles pouvant expliquer la transposition allylique réductrice. En premier lieu, il n'est pas impossible d'imaginer un mécanisme concerté impliquant une coordination de l'alcool tertiaire avec le palladium, suivie d'un réarrangement de type « ène » (*Schéma 4.5*). Ce mécanisme permettrait la formation du produit attendu, mais n'expliquerait toutefois pas la formation du sous-produit **4.13**. Tel que mentionné précédemment, l'alcène trisubstitué **4.13** est facilement isomérisé vers l'alcène tétrasubstitué **4.12**, et non l'inverse.



(**4.10**) (**4.17**) (**4.12**)

Schéma 4.5 : Mécanisme 1 - réarrangement de type « ène »

De plus, une expérience simple a permis de démontrer que l'acétate **4.18**, formé dans des conditions usuelles à partir de **4.10**, était quand même enclin à subir une transposition allylique réductrice, et ce, même sans que ne soit possible la coordination entre l'alcool et le palladium (*Schéma 4.6*). Même s'il est envisageable que le mécanisme expliquant le réarrangement de l'acétate allylique **4.18** soit différent de celui avec l'alcool **4.10**, il reste néanmoins possible d'écarter ce mécanisme, au moins partiellement.



(**4.10**) (**4.18**) (**4.12**)

Schéma 4.6 : Tentative d'infirmation du mécanisme 1

Dans un autre ordre d'idée, la transposition allylique réductrice pourrait procéder en plusieurs étapes, à commencer par une élimination E_2 afin de fournir, par exemple, l'alcène exocyclique **4.19** (*Schéma 4.7*). Ce diène serait alors rapidement hydrogéné afin de fournir **4.13**, puis, après isomérisation, **4.12**.

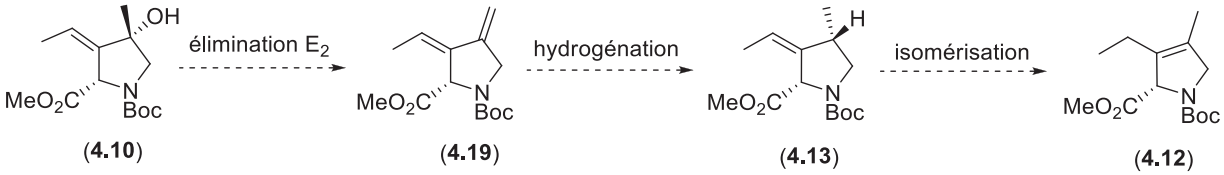


Schéma 4.7 : Mécanisme 2 - élimination E_2, suivie d'une hydrogénation

Afin de tester cette hypothèse, l'analogue *tert*-butyle **4.20** a été préparé dans des conditions usuelles, puis soumis aux conditions permettant la transposition allylique réductrice (*Schéma 4.8*) sans qu'aucune transformation ne soit observée. L'échec de cette dernière réaction tend à démontrer la plausibilité du mécanisme d'élimination E_2, alors que l'analogue **4.20** ne pouvait pas former le diène tel qu'en **4.19**. Par contre, peut-être était-il difficile d'effectuer la transposition allylique avec cet intermédiaire simplement en raison d'un encombrement stérique accru. Les conclusions quant à la crédibilité du mécanisme d'élimination E_2 ne pouvaient donc pas reposer que sur cette expérience.

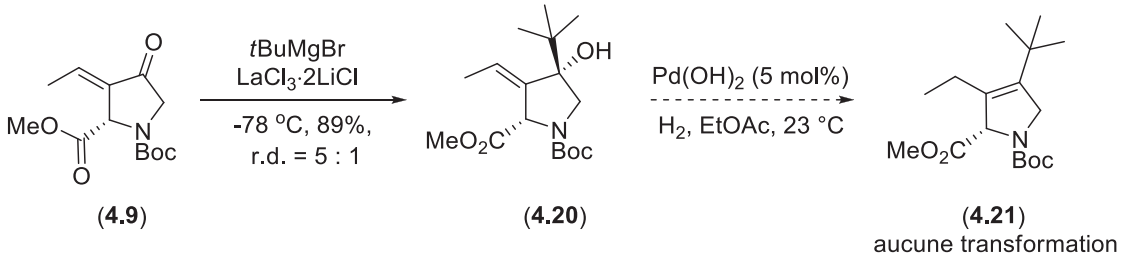
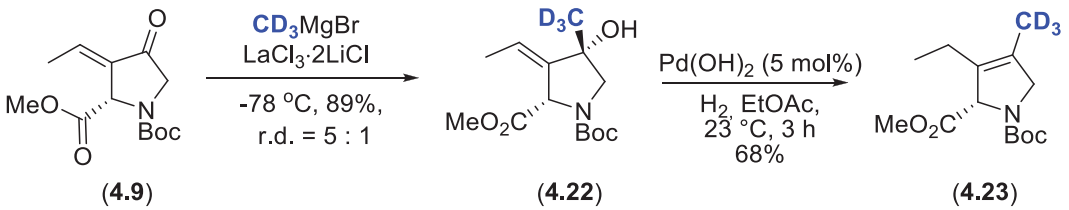


Schéma 4.8 : Tentative d'infirmation du mécanisme 2

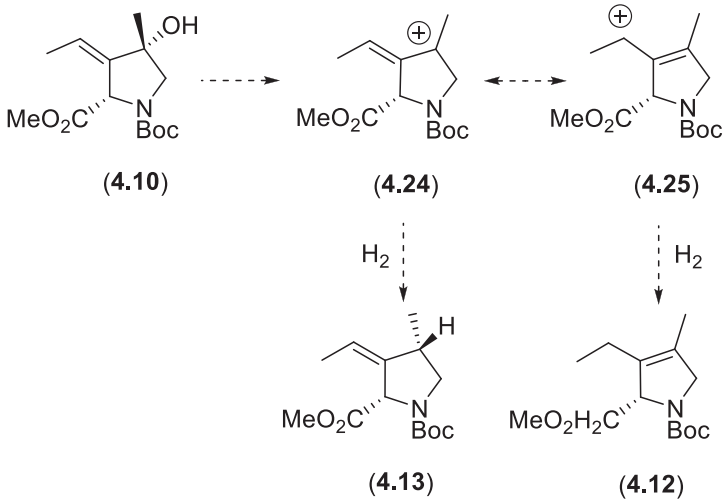
Pour éprouver ce mécanisme de façon plus crédible, l'analogue deutéré **4.22** a été préparé, puis soumis aux conditions permettant la transposition allylique réductrice (*Schéma 4.9*). L'expérience était simple : si l'élimination avait bel et bien lieu, il y aurait perte inévitable d'un des trois atomes de deutérium au passage. Or, les trois atomes de deutérium ont été préservés (**4.23**), infirmant cette deuxième hypothèse d'élimination E_2, du moins vers le diène **4.19**. De plus, si un diène avait été formé, la polydeutération de celui-ci aurait été observée lors de l'expérience montrée plus tôt (Schéma 4.4).



(**4.9**) (**4.22**) (**4.23**)

Schéma 4.9 : Tentative d'infirmation du mécanisme 2

Une troisième option a donc été considérée : la formation d'un carbocation, suivie d'un parachèvement de ce carbocation par l'hydrogène (*Schéma 4.10*). Le carbocation tertiaire **4.24** pourrait se réarranger en carbocation secondaire **4.25** afin d'expliquer la formation de l'isomère **4.12**. Toutefois, cette hypothèse est peu probable, étant donné le coût enthalpique associé à la formation de ce carbocation secondaire moins stable. De façon plus logique, le carbocation tertiaire **4.24** serait parachevé par l'hydrogène, et ce produit pourrait ensuite être sujet à une isomérisation catalysée par le palladium, simplement.



(**4.10**) (**4.24**) (**4.25**) (**4.13**) (**4.12**)

Schéma 4.10 : Mécanisme 3 – formation d'un carbocation

Malheureusement, les tentatives de piégeage du carbocation à l'aide de méthanol ou d'aniline ont été infructueuses, laissant croire encore une fois que le mécanisme proposé est inapproprié.

En outre, les rares études portant sur l'hydrogénolyse des alcools insaturés, presque seulement benzyliques,[160] invoquent un état de transition selon lequel le palladium est directement inséré dans la liaison C-O de l'alcool sous forme de matrice (*Schéma 4.11*). Un atome d'hydrogène, présent sur un autre atome de palladium en surface, pourrait alors déplacer la liaison double de façon S_n2', ou simplement hydrogénolyser la liaison C-Pd-O afin de fournir respectivement les produits **4.12** et **4.13**. Cette idée, bien que peu détaillée dans la littérature, pourrait expliquer pourquoi deux différents régiomères peuvent être formés, et pourquoi l'acétate **4.18** peut lui aussi réagir (admettant que l'insertion au palladium est aussi possible avec un acétate). Elle pourrait aussi expliquer pourquoi le produit deutéré **4.22** ne perd aucun deutérium dans ces conditions, et qu'une seule incorporation de deutérium est observée lorsque la transposition est effectuée avec du deutérium.

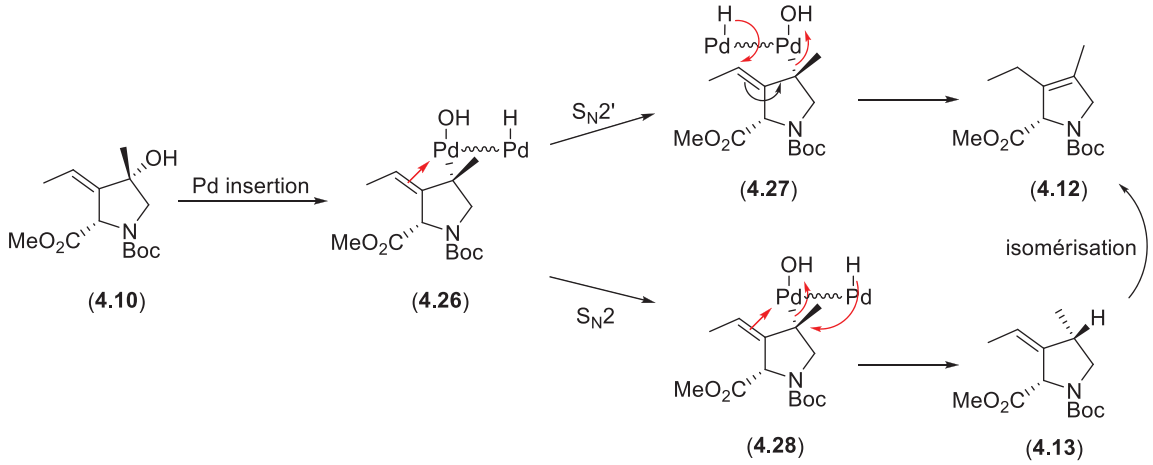


Schéma 4.11 : Mécanisme 4 – hydrogénolyse directe (McQuillin)

En dernier lieu, un mécanisme plus connu d'activation allylique de type Tsuji-Trost pourrait être considéré (*Schéma 4.12*). Bien que cette méthode emploie normalement des acétates ou des carbonates allyliques, il a été démontré récemment qu'il est aussi possible d'utiliser des alcools allyliques non-activés, tels qu'en **4.29** et **4.30**, grâce à une activation par ponts-hydrogène avec de l'eau.[161] Or, autant les catalyseurs de Pearlman que le palladium sur charbon, permettant des rendements optimaux de transposition allylique, contiennent effectivement de l'eau.[162] L'alcool allylique activé, en présence du palladium, serait donc amené à former un complexe π-allyl.

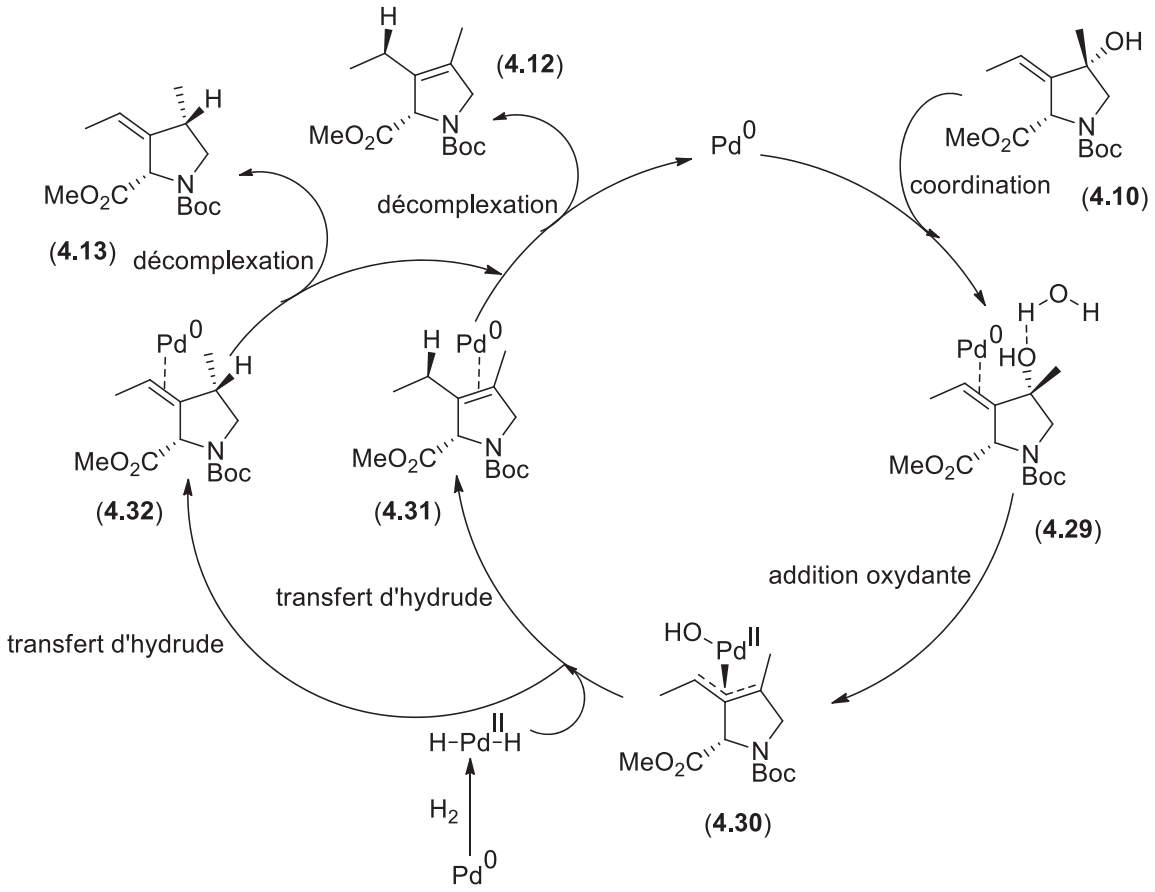


Schéma 4.12 : Mécanisme 5 – formation d'un complexe π-allyl

La différence majeure entre les deux derniers mécanismes est au niveau de la coordination du palladium : alors que, dans le mécanisme simple d'hydrogénolyse (*Schéma 4.11*), le palladium s'insère vers la face inférieure de la pyrrolidine, la formation d'un complexe π-allyl implique une attaque du palladium vers la face supérieure. Pour tenter d'expliquer sommairement lequel des deux mécanismes est le plus plausible, un modèle Hyperchem a été calculé (*Figure 4.1*).[163] De ce modèle, on retient sans surprise que le carbamate Boc impose un caractère sp^2 à la liaison C−N. En conséquence, l'ester méthylique semblerait adopter une conformation axiale afin de minimiser la tension allylique A-1,2 avec ce dernier groupement. L'ester méthylique étant vers l'arrière, c'est donc dire que la face inférieure de la pyrrolidine semble plus encombrée. Il serait donc plus logique d'envisager une attaque du palladium vers la face supérieure, afin de former un complexe π-allyl, qu'une insertion du palladium entre la liaison C-OH selon le mécanisme proposé par McQuillin.

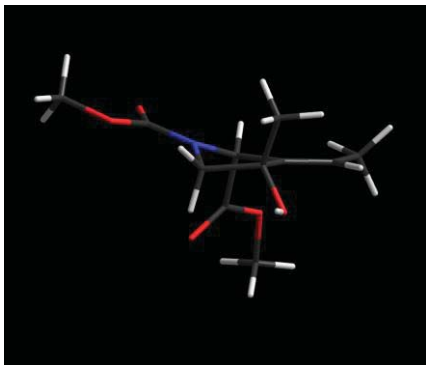


Figure 4.1 : Représentation HyperChem de la pyrrolidine **4.10**

Il est aussi à noter que cette remarque corrobore, *a priori*, l'observation selon laquelle il est difficile d'assujettir l'autre diastéréoisomère **4.11** à la transposition allylique : le palladium, ayant à attaquer cette fois-ci vers la face inférieure de la pyrrolidine, aurait à subir l'encombrement stérique de l'ester méthylique. Cela ne serait pas le cas si l'hydrogénolyse de type McQuillin était observée.

En outre, les deux derniers mécanismes proposés pourraient expliquer pourquoi il était difficile de soumettre l'analogue *tert*-butyle **4.20** à la transposition allylique (par rapport à son homologue **4.10**) : dans le cas de cet intermédiaire, tant la face inférieure que la face supérieure seraient encombrées, de telle sorte que le palladium pourrait difficilement former le complexe π-allyl ou procéder à l'insertion du lien C-O tel que nécessaire. Par ailleurs, cette étude, bien que brève et sommaire, nous laissait croire qu'il serait possible d'appliquer cette modeste méthodologie à la formation de pyrrolidine polysubstituée.

4.4 Étendue de la réaction

Une brève étude de l'étendue de la réaction a été accomplie, dans le but de permettre la synthèse rapide de 3-pyrrolines ou de pyrrolidines 2,3,4-trisubstituées. Toujours à partir de l'énaminone **4.8**, différents nucléophiles ont été utilisés afin de générer une variété d'énones (composés **4.33a-i**, *Schéma 4.13*). Ces énones ont été à leur tour converties en alcools allyliques sans embûches majeures, si ce n'est que les diastéréoisomères obtenus étaient souvent inséparables (**4.34a-i**).

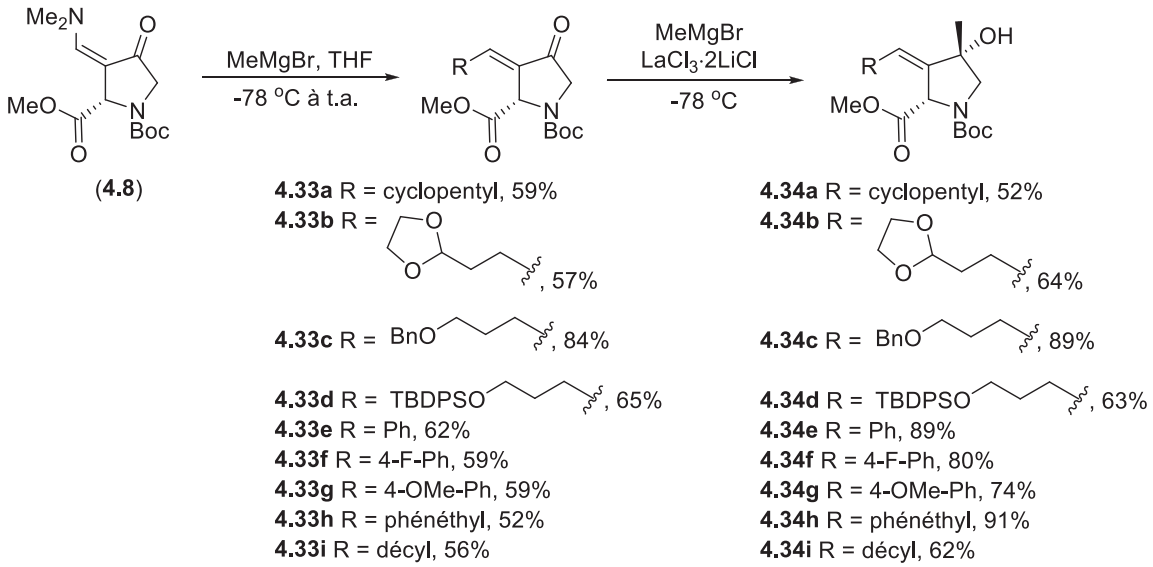


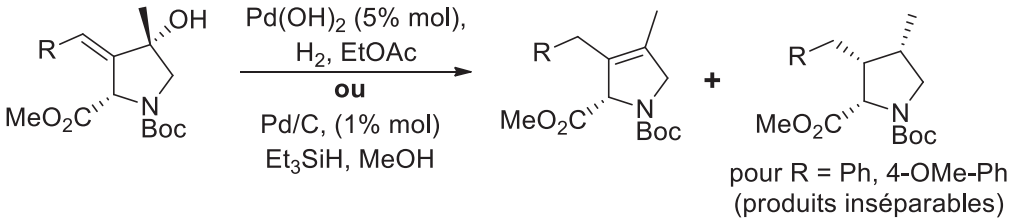
Schéma 4.13 : Préparation des alcools allyliques en vue de tester l'étendue des substrats

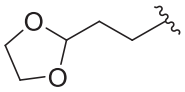
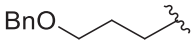
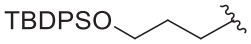
Ayant en main cette modeste collection d'alcools allyliques, la transposition allylique réductrice a été testée en utilisant en alternance les deux méthodes optimales, soit $Pd(OH)_2$, H_2 et Pd/C, Et_3SiH (*Tableau 4.3*). Il est apparu qu'un changement de structure pouvait affecter grandement la faisabilité du réarrangement désiré, ainsi que la distribution de produits. Les alcools allyliques avec groupements alkyles ou phénéthyle (entrées 1-7) ont permis un réarrangement sans grand problème et avec un rendement acceptable. Cependant, il a parfois été nécessaire d'ajouter plusieurs équivalents de triéthylsilane afin de promouvoir complètement la transformation. Alors que, dans le cas de l'intermédiaire méthyle (**4.10**), une amélioration significative a pu être observée en utilisant le triéthylsilane avec Pd/C (*Tableau 4.2*), il s'est avéré qu'il en était tout autre dans le cas d'une chaîne avec éther benzylique (entrée 4), pour laquelle le catalyseur de Pearlman était optimal.

En outre, il a été observé que les alcools allyliques avec groupements aryles possédaient une réactivité intéressante. Quand, dans le cas du groupement 4-fluorophényle (entrée 9) les conditions de transposition ont rapidement mené à un mélange complexe, les groupements phényle et 4-OMe-phényle (entrée 8 et 10) ont permis un réarrangement relativement propre, mais aussi partiellement une sur-réduction pour mener à la pyrrolidine 2,3,4-trisubstituée en une étape! Même si cette deuxième

transformation n'est pas surprenante (il s'agit, après tout, de conditions d'hydrogénation), il est intéressant de noter que seuls ces deux substrats ont permis une sur-réduction. Car, même en tentant de forcer l'hydrogénation de l'alcène tétrasubstitué obtenu en augmentant le nombre d'équivalents de triéthylsilane (jusqu'à 20 eq.), de Pd/C (jusqu'à 5% mol) ou le temps réactionnel (jusqu'à deux jours), il a été impossible d'observer directement le produit pyrrolidine attendu. Néanmoins, lorsque le nombre d'équivalents de triéthylsilane a été ajusté à 1.2 eq., il a été possible d'obtenir l'alcène tétrasubstitué correspondant, sans sur-hydrogénation.

Tableau 4.3 : Étendue de la transposition allylique réductrice



entrée	R	rendement (%)[a]
1	méthyle	68 (82)
2	cyclopentyle	73
3		77
4		70[a] (mélange complexe)
5		61
6	décyle	(72)[b]
7	phénéthyle	(67)[b]
8	Ph	(67)
9	4-F-Ph	mélange complexe
10	4-OMe-Ph	(62)[b]

[a] Rendements entre parenthèses obtenus à l'aide de la deuxième méthode : Pd/C (1% mol), Et_3SiH (2 éq.);
[b] nécessitait plus de 5 éq. de triéthylsilane;
[c] utilisé avec 1.2 éq. de triéthylsilane.

4.5 Conclusion et perspectives

En conclusion, une transposition allylique réductrice surprenante a été observée en soumettant l'alcool allylique et tertiaire **4.10** aux conditions normales d'hydrogénation. Les meilleurs rendements pour cette transformation ont pu être obtenus en utilisant une combinaison de catalyseur de Pearlman et d'hydrogène, ou encore de palladium sur charbon (Pd/C) et de triéthylsilane (Et_3SiH). Une brève étude mécanistique suggère que la désoxygénation procède par un mécanisme concerté de type *Tsuji-Trost*. Par ailleurs, une modeste sélection d'alcools allyliques et tertiaires (**4.34a-i**) a été synthétisée et soumise aux conditions optimales de transposition allylique, globalement avec succès.

Dans un premier lieu, il serait intéressant de convertir les alcènes tétrasubstitués obtenus (*Tableau 4.3*) en pyrrolidines pour ainsi compléter l'étude et s'assurer que différentes pyrrolidines 2,3,4-trisubstituées peuvent être formées avec un rendement global et dans un ratio diastéréomérique acceptables. À l'avenir, il serait aussi intéressant de modifier davantage les pyrrolidines utilisées, par exemple en utilisant un groupement protecteur différent, ou par suite d'une substitution en position 5. En outre, une piperidine polysubstituée pourrait être synthétisée et soumise aux conditions de transposition allylique. Toutes ces modifications auraient pour but ultime de comprendre les limitations structurelles que tolère la transposition allylique. Idéalement, il serait alors possible de promouvoir alternativement l'hydrogénation simple ou la transposition allylique à partir d'une liste d'alcools allyliques beaucoup plus étoffée.

Chapitre V

Partie expérimentale

5.1 Notes générales sur la partie expérimentale

5.1.1 Instrumentation

L'acquisition de spectres de résonance magnétique nucléaire de protons (RMN ^{1}H) et de carbones (RMN ^{13}C) a été effectuée à l'aide d'appareils de type Bruker AV-300 et Bruker AV-400. Les déplacements chimiques sont exprimés en parties par million (ppm) selon l'échelle δ et ont pour référence le tétraméthylsilane (TMS); les constantes de couplage sont, quant à elles, exprimées en Hertz (Hz). Le code suivant fut employé en ce qui a trait à la multiplicité : singulet (s), doublet (d), triplet (t), quadruplet (q), doublet de doublets (dd), multiplet (m) et pic large (br).

La spectrométrie de masse de basse résolution (LRMS) a été enregistrée à partir d'un spectromètre Thermo Finnigan MSQ (Single Quadrupole). Les spectres de masse à haute résolution (HRMS) ont été enregistrés sur un spectromètre Kratos MS-50 TCA ou VG-autospec-C1.

La spectroscopie infrarouge (IR) a été effectuée à l'aide d'un spectrophotomètre Perkin-Elmer FTIR Paragon 1000. Les points de fusion non-corrigés ont été déterminés à l'aide d'un appareil Büchi B-540. Les pouvoirs rotatoires spécifiques ont été mesurés avec un polarimètre PerkinElmer 343 à la longueur d'onde du sodium de 589 nm et à température ambiante (22 °C).

5.1.2 Chromatographie et solvants

Lorsque mentionné, la séparation des intermédiaires a été effectuée à l'aide de chromatographie éclair en utilisant un gel de silice Kieselgel 60. Les solvants utilisés comme éluants ont généralement été distillés préalablement.

5.1.3 Solvants

Le tétrahydrofurane (THF), le dichlorométhane (DCM), l'éther diéthylique (Et_2O) et le toluène (PhMe) anhydres ont été séchés à l'aide d'un système SDS (*Solvent Delivery System*).

5.1.4 Notes

Lorsque nécessitant des conditions anhydres, la verrerie a été séchée à la flamme. Dans tous les cas, le montage réactionnel a ensuite été maintenu sous argon. Le sulfate de sodium était l'agent de séchage utilisé par défaut. Tel que permis par le *Guide de présentation et d'évaluation des mémoires de maîtrise et des thèses de doctorat*, la partie expérimentale a été rédigée en anglais et présentée en annexe afin d'assurer un lectorat scientifique élargi.

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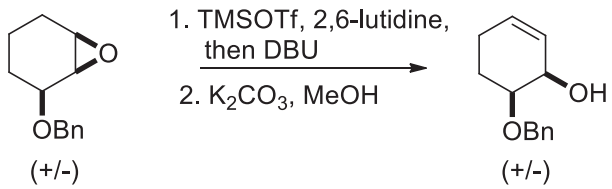
Annexes

Annexe I – Partie expérimentale relative à la daphniglaucine C

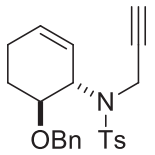
Allylic alcohol (3.39)



A solution of the known syn-epoxyether* **3.38** (0.260 g, 1.27 mmol) in toluene (8 mL) under argon was treated with trimethylsilyltrifluoromethanesulfonate (0.246 mL, 1.34 mmol) followed by 2,6-lutidine (0.741 mL, 6.37 mmol). After stirring for 30 min at r.t., DBU (0.964 mL, 6.37 mmol) was added and the reaction was stirred for 18 h. The reaction mixture was then diluted with 1M HCl (10 mL), extracted with Et_2O (3 × 10 mL), and the organic layers dried over Na_2SO_4 and evaporated. The crude residue was taken up in 10 mL of MeOH and K_2CO_3 (0.260 g, 1.88 mmol) was added at r.t. The mixture was stirred for 1 h, aftwer which TLC showed the presence of a new spot and consumption of the TMS ether intermediate. The reaction was filtered and concentrated *in vacuo*, and the crude material was purified by flash chromatography over silica gel (hexanes/EtOAc = 80/20) to give the pure allylic alcohol 3.39 as a pale yellow liquid (0.226 g, 87%). All spectroscopic data was in accordance with that reported.

* Calvani, F.; Crotti, P.; Gardelli, C.; Pineschi, M. *Tet. Lett.* **1994**, *50*, 12999.

Enyne (3.40)

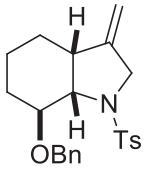


(+/-)

A solution of the allylic alcohol **3.39** (5.50 g, 26.9 mmol) in dry benzene (80 mL) was cooled to 0 °C and treated sequentially with (*N*-Ts)-propargylamine (5.50 g, 26.9 mmol), triphenylphosphine (9.96 g, 37.7 mmol), and DIAD (7.42 mL, 37.7 mmol) under argon.

The reaction was stirred 18 h at r.t., diluted with water (50 mL), extracted with Et_2O (3 × 30 mL), dried over Na_2SO_4, and concentrated. The crude material was purified by flash chromatography over silica gel (hexanes/EtOAc = 85/15) to give the sulfonamide **3.40** as a colorless oil (9.18 g, 86%). IR (neat): ν_{max} = 3291, 2932, 1734, 1335, 1158, 1092 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.81 (2H, d, *J* = 11.2 Hz), 7.42 – 7.10 (7H, m), 5.90 (1H, m), 5.30 (1H, m), 4.59 (2H, m), 4.47 (1H, d, *J* = 15.6 Hz), 4.20 (1H, dd, *J* = 24.8, 2.8 Hz), 3.88 (1H, dd, *J* = 24.8, 2.8 Hz), 3.76 (1H, m), 2.38 (3H, s), 2.13 (3H, m), 1.71 (1H, m), 1.19 (1H, d, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 142.7, 138.4, 137.5, 132.0, 128.9, 128.4, 128.1, 127.8, 127.3, 125.4, 79.9, 75.4, 71.8, 70.4, 59.9, 32.9, 26.4, 23.4, 21.3, 21.2; HRMS (ESIMS): calcd $C_{23}H_{25}NO_3S$ $[M+H]^+$ 396.16279, found 396.16278.

Alkene (3.41)

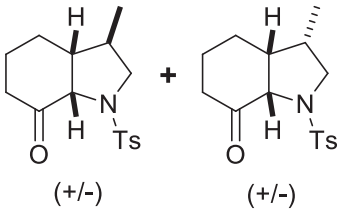


(+/-)

A solution of the allylic sulfonamide **3.40** (9.00 g, 22.7 mmol) and AIBN (0.373 g, 2.275 mmol) in 100 mL benzene under argon was gradually heated to reflux. During the warming, tributyltin hydride (7.96 mL, 29.6 mmol) was slowly added. The reaction was maintained at reflux for 4 h, after which TLC indicated consumption of the starting material. After cooling to r.t., solid *p*-toluenesulfonic acid monohydrate (5.62 g, 29.6 mmol) was added and the solution stirred for 30 min until TLC showed no vinylstannane intermediate remaining. The reaction was carefully neutralized and washed with 10% aq. Na_2CO_3 (100 mL), dried over Na_2SO_4, and concentrated. The crude solid was absorbed onto silica gel and purified by flash chromatography (hexanes/EtOAc = 85/15) to give the pure perhydroindole **3.41** as a hard white solid (8.90 g, 83%). IR (neat): ν_{max} = 2941, 2107, 1350, 1163, 1095 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.73 (2H, d, *J* = 8.2 Hz), 7.42 (2H, d, *J* = 8.5 Hz), 7.35 (2H, t, *J* = 7.1 Hz), 7.29 (1H, d, *J* = 7.2 Hz), 7.25 (2H, d, *J* = 8.0 Hz), 4.93 (1H, d, *J* = 2.2 Hz), 4.78 (1H, q, *J* = 2.4 Hz), 4.66 (2H, dd, *J* = 15.5, 12.1 Hz), 4.05 (2H, dd, *J* = 76.9, 15.7 Hz), 3.83 (1H, t, *J* = 7.5 Hz), 3.35 – 3.28 (1H, m), 2.39 (3H, s), 2.33 (1H, brs), 1.99 – 1.93 (1H, m), 1.81 – 1.73 (1H, m), 1.56 – 1.45 (2H, m), 1.42 –

1.27 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.6, 142.9, 138.6, 135.3, 129.4, 129.3, 128.1, 128.0, 127.8, 127.3, 127.1, 127.0, 126.9, 105.0, 75.5, 71.0, 65.0, 51.1, 42.2, 28.8, 23.7, 21.1, 18.5; HRMS (ESIMS): calcd $C_{23}H_{27}NO_3S$ $[M+H]^+$ 398.17844, found 398.17965.

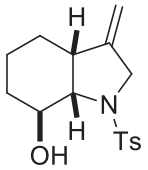
Octahydroindole (3.44, 3.45)



Typical procedure : The exocyclic alkene **3.41** (132 mg, 0.3320 mmol) was dissolved in MeOH:EtOAc (2: 1, 75 mL) and a catalytic amount of 20% $Pd(OH)_2/C$ was added at r.t. Then, the mixture was stirred under an atmosphere of hydrogen for 18 h, filtered through Celite (with CH_2Cl_2 rinsings) and the filtrate was concentrated to give a 3.6: 1 mixture of diastereomeric secondary alcohols as a white solid (100 mg, 97%). ^{1}H NMR of major isomer, (300 MHz, $CDCl_3$): δ 7.76 (2H, d, *J* = 8.1 Hz), 7.36 (2H, d, *J* = 8.1 Hz), 3.93 (1H, brs), 3.75 (1H, dd, *J* = 9.3 Hz, 7.5 Hz), 3.64 – 3.57 (1H, m), 3.34 (1H, t, *J* = 8.1 Hz), 2.72 (1H, t, *J* = 8.1 Hz), 2.47 (3H, s), 2.20 – 2.01 (2H, m), 1.60 (2H, m), 1.45 – 1.16 (4H, m), 0.86 (3H, d, *J* = 6.3 Hz); ESI/MS for $C_{16}H_{23}NO_3S$ calculated $(M + H^+)$ 310, found 310. Without further purification, the crude mixture of diastereomeric secondary alcohols was engaged in the next oxidation step. To a flask containing oxalyl chloride (2 M in CH_2Cl_2, 0.324 mL, 0.647 mmol) under argon was added 1 mL of dry CH_2Cl_2 (1 mL). The flask was cooled to -78 ^{o}C and DMSO (0.099 mL, 1.391 mmol) was added dropwise. After stirring 15 min at -78 ^{o}C, a solution of diastereomeric perhydroindoles (0.100 g, 0.323 mmol) in dry CH_2Cl_2 (1 mL) was slowly added. After stirring 20 min, triethylamine (0.450 mL, 3.230 mmol) was added and the reaction was allowed to warm to r.t. and stirred an additional 1 h. The mixture was diluted with 1M HCl (5 mL), extracted with CH_2Cl_2 (3 × 10 mL), dried over Na_2SO_4, and evaporated to give the crude product. Separation of the diastereomeric ketones by careful flash chromatography over silica gel (hexanes/EtOAc = 80/20) gave the major diastereomer **3.44** as a white solid (0.065 g, 66%, 83% based on theoretical

maximum). IR (neat): ν_{max} = 2940, 1725, 1292, 1167, 1033 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.83 (2H, d, *J* = 8.0 Hz), 7.33 (2H, d, *J* = 6.3 Hz), 4.29 (1H, d, *J* = 8.0 Hz), 3.51 (1H, t, *J* = 8.0 Hz), 2.86 (1H, t, *J* = 8.8 Hz), 2.56 (1H, m), 2.44 (3H, s), 2.42 (1H, m), 2.15 (1H, m), 1.91 (3H, m), 1.74 (2H, m), 0.84 (3H, d, *J* = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 206.8, 143.0, 135.0, 129.1, 127.4 (the two latter accounting for two carbon atoms from the tosyl group), 67.8, 53.2, 49.6, 39.4, 34.5, 24.2, 24.1, 21.2, 15.5; HRMS (ESIMS): calcd for $C_{16}H_{21}NO_3Na$ $[M+Na]^+$ 330.11344, found 330.11311.

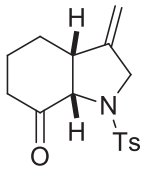
Alcohol (3.46)



(+/-)

Under argon and in a flame-dried flask, a solution of the benzyl ether **3.41** (315 mg, 0.7932 mmol) in dry CH_2Cl_2 (4 mL) was cooled to 0 °C and BBr_3 (1.0 M in hexanes, 835 μL, 0.8329 mmol) was slowly added. The reaction was stirred for 5 min, and then quenched with a saturated solution of $NaHCO_3$ (10 mL). The biphasic mixture was separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The solvent was removed under reduced pressure and purification of the residue by flash chromatography (hexanes/Et_2O = 70/30) gave the title compound (200 mg, 83%) as a thick colorless oil. IR (neat): ν_{max} = 3520, 2938, 2866, 1672, 1597, 1338, 1158, 1094 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.73 (2H, d, *J* = 8.2 Hz), 7.31 (2H, d, *J* = 8.0 Hz), 5.00 (1H, brs), 4.80 (1H, brs), 4.05 (2H, brs), 3.51 (1H, t, *J* = 8.4 Hz), 3.35 (2H, m), 2.41 (3H, s), 2.18 (1H, brs), 1.93 (1H, d, *J* = 12.6 Hz), 1.85 (1H, d, *J* = 14.5 Hz), 1.56 – 1.40 (2H, m), 1.40 – 1.14 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.1, 143.6, 134.5, 129.6, 126.2 (the two latter accounting for two carbon atoms from the tosyl group), 105.4, 70.4, 66.9, 51.6, 41.3, 31.6, 22.7, 21.2, 18.5; HRMS (ESIMS): calcd for $C_{16}H_{22}NO_3SNa$ $[M+Na]^+$ 330.11344, found 330.11360.

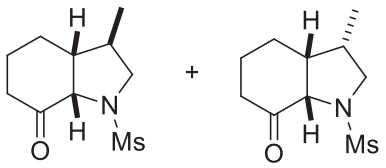
Keto-alkene (3.47)



(+/-)

The secondary alcohol **3.46** (55 mg, 0.1791 mmol) was dissolved in wet CH_2Cl_2 (2 mL) and Dess-Martin periodinane (99 mg, 0.2330 mmol) was added at 0 °C. The mixture was allowed to stir as such for 1 h until complete consumption of the starting meterial, after which the reaction mixture was washed with an aqueous saturated solution of sodium thiosulfate (5 mL). The aqueous phase was separated from the organic phase, and the former was washed with CH_2Cl_2 (3 × 5 mL). The solvent was removed under reduced pressure, and purification of the residue was achieved by flash chromatography (hexanes/EtOAc = 80/20) to give the title compound (45 mg, 82%) as a colorless oil. IR (neat): ν_{max} = 2940, 2870, 1728, 1347, 1162, 1097 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.79 (2H, d, *J* = 8.2 Hz), 7.36 (2H, d, *J* = 8.1 Hz), 4.96 (1H, brs), 4.91 (1H, brs), 4.13 (1H, d, *J* = 3.9 Hz), 3.95 (2H, dd, *J* = 45.1, 14.3 Hz), 3.10 (1H, brs), 2.79 – 2.65 (1H, m), 2.45 (3H, s), 2.45 – 2.38 (1H, m), 2.00 – 1.79 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 206.4, 144.3, 143.4, 134.0, 129.2, 127.6 (the two latter accounting for two carbon atoms from the tosyl group), 106.7, 68.2, 50.8, 48.0, 39.0, 25.2, 23.9, 21.2; HRMS (ESIMS): calcd for $C_{16}H_{20}NO_3SNa$ $[M+Na]^+$ 328.09779, found 328.09754.

Mesyl-ketone (3.51, 3.52)



(+/-) (+/-)

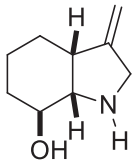
A solution of the allylic alcohol **3.39** (1.271 g, 6.228 mmol) in dry benzene (80 mL) was cooled to 0 °C and treated sequentially with (*N*-Ms)-propargylamine (1.16 g, 8.720 mmol), triphenylphosphine (2.287 g, 8.720 mmol), and DIAD (1.71 mL, 8.720 mmol) under argon. The reaction mixture was stirred 18 h at r.t., diluted with water (50 mL), extracted with

Et_2O (3 × 30 mL), dried over Na_2SO_4, and concentrated. The crude material was purified by flash chromatography over silica gel (hexanes/EtOAc = 85/15) to give the enyne **3.49** as a colorless oil (1.51 g, 77%). A solution of the allylic sulfonamides (1.33 g, 4.16 mmol) and ABCN (0.100 g, 0.416 mmol) in dry benzene (75 mL) under argon was gradually heated to reflux. During the warming, tributyltin hydride (2.19 mL, 8.12 mmol) was slowly added. The reaction mixture was maintained at reflux for 4 h after which TLC indicated consumption of the enyne starting material. After cooling to r.t., solid *p*-toluenesulfonic acid monohydrate (1.54 g, 8.12 mmol) was added and the solution stirred for 30 min until no vinylstannane intermediate remained. The reaction mixture was carefully neutralized and washed with 10% aq. Na_2CO_3 (20 mL), dried over Na_2SO_4, and concentrated. The crude solid was absorbed onto silica gel and purified by flash chromatography (hexanes/EtOAc = 85/15 to 70/30) to give the pure perhydroindole as a hard white solid (1.04 g, 80%). The exocyclic alkene **3.50** (400 mg, 1.25 mmol) was dissolved in MeOH:EtOAc (2:1, 15 mL). To the solution at r.t. was added a catalytic amount (5-15% mol) of 20% $Pd(OH)_2/C$ and the mixture was put under 1 atm of H_2. The reaction mixture was stirred for 18 h, filtered through Celite (with CH_2Cl_2 rinsings) and the filtrate was concentrated to give a 2.4: 1 mixture of diastereomeric perhydroindoles as a white solid (290 mg, quant). Without further purification, the crude mixture of diastereomeric secondary alcohols was engaged in the next oxidation step. To a flask containing oxalyl chloride (2 M in CH_2Cl_2, 0.386 mL, 0.772 mmol) under argon was added of dry CH_2Cl_2 (1 mL). The flask was cooled to -78 ºC and DMSO (120 µL, 1.66 mmol) was added dropwise. After stirring 15 min at -78 ºC, a solution of the previous crude diastereomeric mixture (90 mg, 0.3861 mmol) in dry CH_2Cl_2 (1 mL) was slowly added. After stirring 20 min, triethylamine (0.450 mL, 3.230 mmol) was added and the reaction mixture was allowed to warm up to r.t. and stirred an additional 1 h. The mixture was diluted with 1M HCl (5 mL), extracted with CH_2Cl_2 (3 × 5 mL) dried over Na_2SO_4, and evaporated to give the crude product. Separation of the diastereomeric ketones by careful flash chromatography (hexanes/Et_2O = 90/10 to 50/50 with 10% EtOAc increments) over silica gel gave the two octahydroindoles **3.51** and **3.52** as a ratio of 2.4: 1 (0.065 g, 69%). Minor (crystalline) diastereomer **3.52**. R_f = 0.25 (hexanes/EtOAc = 50/50), [$KMnO_4$].

For compound **3.51**, *up (S)*-diastereomer: IR (neat): ν_{max} = 2944, 1768, 1601, 1254, 1206, 1131 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 4.54 (1H, d, *J* = 8.2 Hz), 3.46 (1H, dd, *J* = 8.5, 8.4 Hz), 3.16 (3H, s), 3.07 (1H, dd, *J* = 8.5, 8.4 Hz), 2.43 – 2.35 (3H, m), 2.04 – 1.88 (3H, m), 1.85 – 1.67 (2H, m), 1.03 (3H, d, *J* = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 208.1, 68.5, 52.6, 49.0, 40.0, 39.9, 34.4, 23.5, 22.4, 14.9; HRMS (ESIMS): calcd for $C_{10}H_{18}NO_3SNa$ $[M+Na]^+$ 254.08214, found 328.08271.

For compound **3.52**, *down (R)*-diastereomer: IR (neat): ν_{max} = 2942, 1724, 1337, 1150 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 3.99 (1H, d, *J* = 6.6 Hz), 3.46 (1H, dd, *J* = 10.0, 8.1 Hz), 3.46 (1H, dd, *J* = 10.0, 8.1 Hz), 3.00 (3H, s), 2.74 – 2.66 (2H, m), 2.42 – 2.35 (2H, m), 2.13 – 2.06 (1H, m), 1.84 – 1.72 (2H, m), 1.84 – 1.72 (1H, m), 1.02 (3H, d, *J* = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 209.0, 68.5, 53.6, 47.1, 37.4, 36.2, 36.1, 25.1, 21.7, 13.1; HRMS (ESIMS): calcd for $C_{10}H_{18}NO_3SNa$ $[M+Na]^+$ 254.08214 found 328.08221.

Aminoalcohol (3.53)

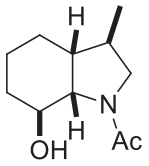


(+/-)

A dry three-necked round-bottomed flask was equipped with a cold trap and condensed 3-4 mL ammonia at -78 °C. Then, freshly cut lithium chips (50-60 mg, approx. 10 eq.) were washed with hexanes and introduced in the flask, after which a deep-blue color was observed persistently. After 10 min, a solution of compound **3.41** (300 mg, 0.7547 mmol) in dry THF (5 mL) was added slowly to the mixture. After 1 h, full conversion was reached and the reaction was thus quenched upon addition of MeOH (10 mL). The mixture was left stirring open-flask for 1 h to get rid of the bulk of ammonia. The solvent was then directly removed under vacuum, and the residue was purified by chromatography ($MeOH/CH_2Cl_2$ = 20/80) to give the aminoalcohol **3.53** as a yellowish paste (104 mg, 90%). IR (neat): ν_{max} = 3344, 2934, 1668, 1451, 1072 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 4.96 (1H, d, *J* = 2.3 Hz), 4.83 (1H, d, *J* = 2.6 Hz), 3.98 (2H, brs), 3.67 (2H, ABq, *J* = 49.1, 16.0 Hz), 3.27 – 3.20 (1H, m), 3.06 (1H, t, *J* = 8.1 Hz), 2.73 (1H, brs), 1.96 – 1.82 (2H, m), 1.69 – 1.55 (1H, m), 1.53 – 1.47 (1H, m), 1.42 – 1.16 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 142.5,

106.4, 66.3, 65.9, 47.1, 41.7, 32.0, 22.5, 18.8; HRMS (ESIMS): calcd for $C_9H_{16}NO$ $[M+H]^+$ 154.12264, found 154.12255.

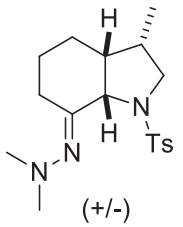
Acetamide (3.54)



(+/-)

A solution of the aminoalcohol **3.53** (20 mg, 0.1306 mmol) in CH_2Cl_2 (1 mL) was cooled to 0 °C and DMAP (cat.), pyridine (25 μL, 0.3132 mmol), and Ac_2O (30 μL, 0.3132 mmol) were added. The reaction mixture was allowed to warm up to r.t. and stirred for 2 h, after which full conversion could be observed. The reaction mixture was thus quenched with a 1 N HCl solution (5 mL), the aqueous and organic phases were separated and the aqueous phase was further extracted with EtOAc (3 × 5 mL). The crude mixture was then taken up in wet MeOH (5 mL) and added K_2CO_3 (22 mg, 0.1567 mmol) at 0 °C. After 2 h, the residue was purified by flash chromatography (MeOH/CH_2Cl_2 = 5/95) to give the acetate **3.54** (8 mg, 72%) as a colorless liquid. R_f = 0.3 (EtOAc), [$KMnO_4$]. IR (neat): ν_{max} = 3357, 1618, 1450 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 5.08 (1H, s), 4.94 (1H, s), 4.13 (1H, brs), 4.10 (2H, ABq, *J* = 24.7, 14.2 Hz), 3.41 – 3.33 (1H, m), 2.89 (1H, brs), 2.10 (3H, s), 2.06 – 2.00 (2H, m), 1.97 – 1.89 (1H, m), 1.63 – 1.52 (2H, m), 1.40 – 1.21 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.4, 144.4, 105.7, 73.5, 64.4, 51.9, 41.4, 32.9, 22.7, 21.9, 18.7; HRMS (ESIMS): calcd for $C_{11}H_{17}NO_2$ $[M+H]^+$ 196.13321, found 196.13348.

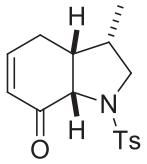
Hydrazone (3.57)



(+/-)

To a solution of ketone **3.44** (60 mg, 0.1954 mmol) in dry MeOH (1 mL) were added activated 3Å molecular sieves (100 mg), *N*,*N*-dimethylhydrazine (150 μL, 1.954 mmol) and 3 drops of AcOH at r.t. The reaction mixture was then stirred O/N, after which H_2O (5 mL) and CH_2Cl_2 (5 mL) was added and the biphasic mixture was separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL). The solution was then dried over Na_2SO_4 and the solvent was removed under reduced pressure. Purification of the residue by flash chromatography (hexanes/EtOAc = 60/40) gave the title compound (52 mg, 84%) as a colorless liquid. IR (neat): ν_{max} = 2939, 2864, 1449, 1350, 1162 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.85 (2H, d, *J* = 8.2 Hz), 7.36 (2H, d, *J* = 8.2 Hz), 3.48 (1H, d, *J* = 3.8 Hz), 3.48 (1H, dd, *J* = 10.3, 10.2 Hz), 3.25 (1H, dd, *J* = 10.4, 10.3 Hz), 3.25 (1H, d, *J* = 13.2 Hz), 2.60 (6H, s), 2.45 (3H, s), 2.31 – 2.22 (1H, m), 2.11 – 2.07 (1H, m), 2.04 – 1.90 (2H, m), 1.68 – 1.32 (3H, m), 0.92 (3H, d, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.0, 142.9, 132.5, 129.2, 127.8 (the two latter accounting for two carbon atoms from the tosyl group), 66.6, 53.4, 47.2 (accounting for two carbon atoms from the hydrazone), 46.4, 34.6, 25.3, 24.8, 21.3, 21.2, 12.2; HRMS (ESIMS): calcd for $C_{18}H_{28}N_3O_2S$ $[M+H]^+$ 350.18967, found 350.19047.

Enone (3.58)

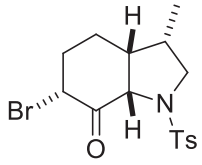


(+/-)

Typical protocol: to a solution of ketone **3.44** (26 mg, 0.0841 mmol) in DMSO: hexafluorobenzene (2: 1, 1.8 mL) maintained under argon was added IBX (57 mg, 0.202 mmol) at r.t., and the reaction mixture was slowly brought to 65 °C. After three days, the reaction mixture was cooled back to r.t., diluted with Et_2O (5 mL) and filtered on Celite. The organic phase was then removed under reduced pressure. Purification of the residue by flash chromatography (hexanes/EtOAc = 80/20 to 40/60 with 10% EtOAc increments) gave the enone **3.58** (10 mg, 38%) as a white solid, as well as some phenol by-product (4 mg, 15%). In an attempt to minimize the formation of over-oxidized product, a separate experiment was performed using only 1.5 eq. of IBX. However, no significant

improvement could be seen. IR (neat): ν_{max} = 2930, 2861, 1733, 1694, 1168 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.94 (2H, d, *J* = 8.3 Hz), 7.36 (2H, d, *J* = 8.2 Hz), 6.80 – 6.72 (1H, m), 6.08 – 6.00 (1H, m), 4.59 (1H, d, *J* = 7.1 Hz), 3.36 (1H, dd, *J* = 9.4, 7.8 Hz), 3.03 (1H, dd, *J* = 9.4, 9.4 Hz), 2.79 – 2.69 (1H, m), 2.48 – 2.41 (1H, m), 2.45 (3H, brs), 2.11 – 1.98 (2H, m), 1.01 (3H, d, *J* = 6.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 194.9, 146.7, 143.3, 136.7, 129.4 (accounting for two carbon atoms from the tosyl group), 128.1, 127.9 (accounting for two carbon atoms from the tosyl group), 64.8, 53.1, 44.4, 35.9, 29.4, 25.2, 15.7; HRMS (ESIMS): calcd for $C_{16}H_{20}NO_3SNa$ $[M+Na]^+$ 328.09779, found 328.09908.

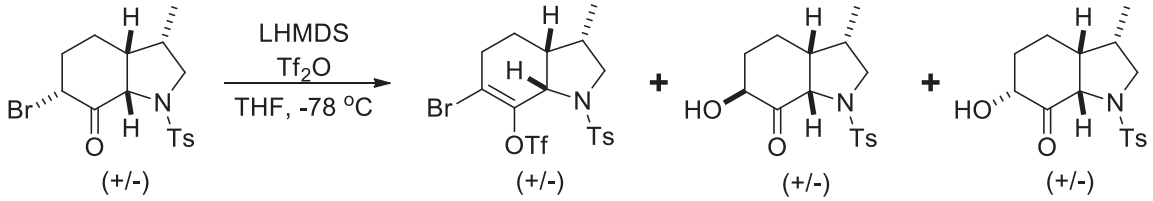
Bromoketone (3.62)



(+/-)

Typical protocol: a solution of the ketone **3.44** (400 mg, 1.302 mmol) in $CHCl_3$ (8 mL) was cooled to 0 ºC and added bromine (67 μL, 1.302 mmol) very rapidly under vigorous stirring. After 5 min, sodium thiosulfate (5 mL) was added to the reaction mixture, the aqueous phase was rapidly extracted with $CHCl_3$ (3 × 10 mL) and the combined organic phases were dried over sodium sulfate. The solvent was removed under reduced pressure, and purification of the residue by flash chromatography (hexanes/EtOAc = 80/20) gave the bromoketone **3.62** (464 mg, 92%) as a thick colorless oil. IR (neat): ν_{max} = 2932, 1734, 1351, 1165 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.82 (2H, d, *J* = 8.3 Hz), 7.36 (2H, d, *J* = 8.0 Hz), 4.90 (1H, d, *J* = 7.3 Hz), 4.60 (1H, dd, *J* = 6.0, 3.7 Hz), 3.55 (1H, dd, *J* = 9.4, 7.5 Hz), 2.88 (1H, dd, *J* = 9.4, 8.1 Hz), 2.46 (3H, s), 2.34 – 2.23 (2H, m), 2.19 – 2.05 (2H, m), 1.99 – 1.93 (1H, m), 1.80 – 1.73 (1H, m), 0.89 (3H, d, *J* = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.8, 143.3, 134.4, 129.3, 129.1, 127.3, 64.9, 53.2, 50.2, 48.9, 34.5, 31.8, 21.2, 21.0, 15.7; HRMS (ESIMS): calcd for $C_{16}H_{21}[^{79}Br]NO_3S$ $[M+H]^+$ 386.04200, found 386.04253.

Bromoenol triflate (3.63) and acyloins (3.64, 3.65)



Typical protocol: a solution of the bromoketone **3.62** (20 mg, 0.0517 mmol) in dry THF (1 mL) was cooled to -78 °C and treated with LiHMDS (1.0 M in toluene, 55 μL). The reaction mixture was left stirring for 1h, after which triflic anhydride (10 μL, 0.0620 mmol) was added slowly to the mixture. The reaction was left stirring as such for variable times (see Chapter 3), after which the reaction was quenched using a saturated solution NH_4Cl (5 mL). The reaction was then allowed to warm up to r.t., and extractions with EtOAc (3 × 5 mL) were carried out after variable times. The combined organic layers were dried over sodium sulfate, and the solvent was removed under reduced pressure. Purification of the residue by flash chromatography (hexanes/EtOAc = 70/30 to 40/60) gave the title compounds **3.63** (5 mg, 19%), **3.64** (5 mg, 30%), and **3.65** (5 mg, 30%), as crystalline compounds.

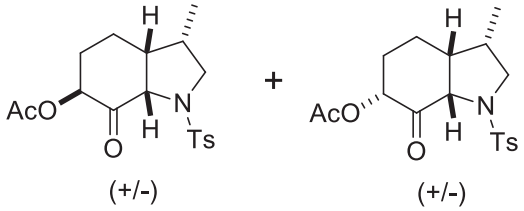
For compound **3.63**: = 0.5 (hexanes/EtOAc = 70/30), [$KMnO_4$], [CAM]. IR (neat): ν_{max} = 2938, 1421, 1355, 1205, 1168, 1094 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.80 (2H, d, *J* = 8.2 Hz), 7.36 (2H, d, *J* = 8.1 Hz), 4.73 (1H, d, *J* = 7.2 Hz), 3.62 (1H, dd, *J* = 10.4, 8.2 Hz), 2.94 (1H, t, *J* = 10.3 Hz), 2.72 – 2.56 (1H, m), 2.46 (3H, s), 2.22 – 2.12 (1H, m), 1.90 – 1.75 (2H, m), 1.72 – 1.64 (1H, m), 1.56 – 1.48 (1H, m), 0.86 (3H, d, *J* = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.7, 142.9, 134.0, 129.4, 127.6 (the two latter accounting for two carbon atoms from the tosyl group), 118.6, 70.2, 61.4, 54.8, 44.5, 32.5, 31.2, 26.1, 20.8, 15.7; HRMS (ESIMS): calcd for $C_{17}H_{20}NBrF_3O_5S_2$ $[M+H]^+$ 517.99129, found 517.99212.

For compound **3.64**: R_f = 0.3 (hexanes/EtOAc = 40/60), [$KMnO_4$], [CAM]. IR (neat): ν_{max} = 3458, 2923, 1725, 1346, 1161, 1091 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.76 (2H, d, *J* = 8.2 Hz), 7.41 (2H, d, *J* = 7.9 Hz), 4.93 – 4.87 (1H, m), 3.91 (1H, dd, *J* = 10.6, 6.8 Hz), 3.63 (1H, d, *J* = 4.7 Hz), 3.39 (1H, d, *J* = 4.6 Hz), 2.78 (1H, dd, *J* = 10.6, 2.2 Hz), 2.49 (3H, s), 2.50 – 2.36 (2H, m), 2.19 – 2.05 (2H, m), 1.85 – 1.77 (2H, m), 0.51 (3H, d, *J* = 7.1

Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 208.6, 143.9, 130.8, 129.4, 127.8 (the two latter accounting for two carbon atoms from the tosyl group), 71.6, 65.5, 54.3, 51.7, 36.6, 36.0, 25.2, 21.3, 19.0; HRMS (ESIMS): calcd for $C_{16}H_{21}NO_4SNa$ $[M+Na]^+$ 346.10835, found 346.10854.

For compound **3.65**: R_f = 0.25 (hexanes/EtOAc = 40/60), [$KMnO_4$], [CAM]. IR (neat): ν_{max} = 3479, 2924, 1732, 1338, 1164 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.87 (2H, d, *J* = 8.2 Hz), 7.35 (2H, d, *J* = 8.1 Hz), 4.69 (1H, d, *J* = 8.1 Hz), 4.28 – 4.22 (1H, m), 3.56 (1H, d, *J* = 4.1 Hz), 3.44 (1H, t, *J* = 8.2 Hz), 2.92 (1H, t, *J* = 9.4 Hz), 2.47 (3H, s), 2.30 – 2.23 (1H, m), 2.20 – 2.11 (1H, m), 2.04 – 1.95 (2H, m), 1.95 – 1.80 (2H, m), 0.96 (3H, d, *J* = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 206.7, 143.1, 135.8, 129.1, 127.3 (the two latter accounting for two carbon atoms from the tosyl group), 74.0, 67.1, 52.8, 43.2, 33.8, 31.3, 21.2, 19.1, 14.5; HRMS (ESIMS): calcd for $C_{16}H_{21}NO_4SNa$ $[M+Na]^+$ 346.10802, found 346.10802.

Acetylated acyloins (3.66, 3.67)



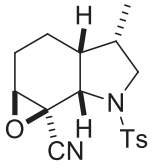
A solution of the acyloin **3.64** and **3.65** (10 mg, 0.03095 mmol) in dry CH_2Cl_2 (1 mL) was cooled to 0 ºC and DMAP (cat.), NEt_3 (4 µL, 0.0371 mmol), and Ac_2O (4 µL, 0.0371 mmol) were added. The reaction mixture was allowed to warm up to r.t. and stirred for 20 min, after which full conversion could be observed. The reaction mixture was thus quenched with a 1 N HCl solution (5 mL), the aqueous and organic phases were separated and the aqueous phase was further extracted with EtOAc (3 × 5 mL). The residue was purified by flash chromatography (hexanes/EtOAc = 80/20) to give the acetylated acyloins (8 mg, 72%) as colorless liquids.

For the *up*-diastereomer (**3.66**): R_f = 0.4 (hexanes/EtOAc = 40/60), [$KMnO_4$], [CAM]. IR (neat): ν_{max} = 2927, 1733, 1351, 1235, 1163 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.77 (2H, d, *J* = 8.3 Hz), 7.37 (2H, d, *J* = 8.0 Hz), 5.71 – 5.63 (1H, m), 3.96 (1H, d, *J* = 5.7 Hz), 3.78 (1H, dd, *J* = 11.3, 7.2 Hz), 2.87 (1H, dd, *J* = 10.3, 4.2 Hz), 2.46 (3H, s), 2.29 – 2.15

(2H, m), 2.19 (3H, s), 2.08 – 1.80 (4H, m), 0.64 (3H, d, J = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 202.0, 169.1, 143.6, 132.4, 129.6, 127.8 (the two latter accounting for two carbon atoms from the tosyl group), 74.1, 66.7, 53.9, 50.6, 35.7, 31.2, 23.6, 21.2, 20.5, 17.8; HRMS (ESIMS): calcd for $C_{18}H_{23}NO_5SNa$ $[M+Na]^+$ 388.11891, found 388.12004.

For the *down*-diastereomer (**3.67**): IR (neat): ν_{max} = 2926, 1745, 1344, 1238, 1166, 1038 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.87 (2H, d, J = 8.3 Hz), 7.33 (2H, d, J = 8.0 Hz), 5.23 (1H, dd, J = 12.5, 6.1 Hz), 4.73 (1H, d, J = 8.2 Hz), 3.39 (1H, t, J = 8.4 Hz), 2.97 (1H, t, J = 9.3 Hz), 2.45 (3H, s), 2.21 – 2.04 (3H, m), 2.16 (3H, s), 1.95 – 1.73 (3H, m), 0.98 (3H, d, J = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.9, 169.2, 143.0, 136.1, 129.1, 127.4 (the two latter accounting for two carbon atoms from the tosyl group), 74.8, 67.9, 52.7, 48.8, 33.7, 27.7, 21.2, 20.3, 19.7, 14.7; HRMS (ESIMS): calcd for $C_{18}H_{23}NO_5SNa$ $[M+Na]^+$ 388.11891, found 388.11881.

Cyanoepoxide (3.69)

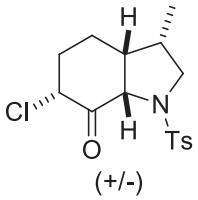


(+/-)

To a solution of the bromoketone **3.62** (68 mg, 0.1757 mmol) in THF: MeOH (1: 1, 1 mL) was slowly added potassium cyanide (14 mg, 0.2108 mmol) at 0 °C. After 15 min, the conversion was complete and water (5 mL) was thus added to the mixture. The biphasic mixture was separated and the aqueous phase was extracted with EtOAc (3 × 5 mL). The solvent was removed under reduced pressure and purification of the residue by flash chromatography (hexanes/Et_2O = 80/20 to 60/40) gave the title compound (49 mg, 87%) as a whitish solid. R_f = 0.3 (hexanes/EtOAc = 60/40), [$KMnO_4$], [CAM]. IR (neat): ν_{max} = 2960, 1349, 1163, 1092 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.89 (2H, d, J = 8.2 Hz), 7.37 (2H, d, J = 8.0 Hz), 4.18 (1H, d, J = 7.1 Hz), 3.72 (1H, brs), 3.55 (1H, dd, J = 10.3, 6.6 Hz), 2.99 (1H, dd, J = 10.3, 4.6 Hz), 2.45 (3H, s), 2.12 – 2.00 (2H, m), 1.98 – 1.89 (1H, m), 1.60 – 1.53 (1H, m), 1.48 – 1.42 (2H, m), 0.61 (3H, d, J = 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.6, 134.0, 129.4, 127.9 (the two latter accounting for two carbon

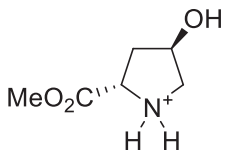
atoms from the tosyl group), 118.3, 60.9, 57.7, 54.2, 48.3, 42.9, 35.4, 21.2, 20.4, 19.3, 17.3; HRMS (ESIMS): calcd for $C_{17}H_{20}N_2O_3SNa$ $[M+Na]^+$ 355.10868, found 355.10893.

Chloroketone (3.70)



Typical protocol: to a solution of the ketone **3.44** (35 mg, 0.1140 mmol) in CH_3CN (1.5 mL) was added NCS (17 mg, 0.1254 mmol) and pTSA (4 mg, 0.0228 mmol) at r.t., after which the mixture was brought to 40 °C. After 12 h, water (10 mL) was added and the aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic phases were dried over sodium sulfate, and the solvent was removed under reduced pressure. Purification of the residue by flash chromatography (hexanes/EtOAc = 80/20) gave the title compound (36 mg, 92%) as a white solid. IR (neat): ν_{max} = 2959, 1738, 1454, 1348, 1165 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.79 (2H, d, *J* = 8.2 Hz), 7.37 (2H, d, *J* = 8.0 Hz), 4.73 (1H, dd, *J* = 7.5, 4.0 Hz), 4.51 (1H, d, *J* = 6.5 Hz), 3.66 (1H, dd, *J* = 9.7, 7.5 Hz), 2.84 (1H, dd, *J* = 9.7, 6.6 Hz), 2.46 (3H, s), 2.31 – 2.26 (1H, m), 2.19 – 2.05 (3H, m), 1.99 – 1.93 (1H, m), 1.80 – 1.73 (1H, m), 0.78 (3H, d, *J* = 6.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.2, 143.5, 133.5, 129.3, 129.2, 127.5, 127.3, 65.5, 59.9, 53.4, 49.6, 34.8, 33.2, 21.5, 21.2, 16.6; HRMS (ESIMS): calcd for $C_{16}H_{21}NO_3ClSNa$ $[M+Na]^+$ 342.09252, found 342.09319.

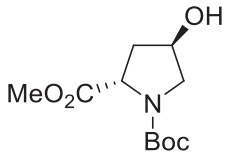
2*S*,4*R*)-4-Hydroxypyrrolidine-2-carboxylic acid methyl ester hydrochloride



Trans-4-hydroxy-*L*-proline (10.0 g, 76.0 mmol) was dissolved in MeOH (52 mL) and the resulting suspension was cooled to 0 °C. Thionyl chloride (7.8 mL, 106.4 mmol) was then added dropwise. The resulting mixture was stirred at 0 °C for 30 min, then allowed to warm

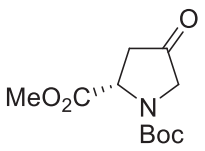
up to room temperature and stirred for an extra 12 h. The solvent was removed under reduced pressure and the remaining oil was transfered in cold diethyl ether (100 mL). The resulting white solid was filtered, washed with cold diethyl ether (2 × 50 mL), then dried to give 13.4 g (73.8 mmol, 97%) of the desired hydrochloride salt as colorless needles. If necessary, it can be recrystallized from MeOH/EtOAc. The analytical data are in complete agreement with that previously reported (*J. Org. Chem*. **1996**, *61*, 4748).

(2*S*,4*R*)-1-*tert*-butyl-2-methyl-4-hydroxypyrrolidine-1,2-dicarboxylate (3.83)



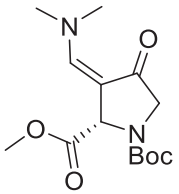
The hydrochloride salt reported above (25.0 g, 138.8 mmol) was dissolved in 1,4-dioxane (185 mL) and water (90 mL). Triethylamine (38.7 mL, 277.7 mmol) was then added, followed by the addition of Boc_2O (38.3 g, 166.5 mmol) in small portions. The resulting mixture was stirred overnight under open flask conditions to avoid building up pressure due to CO_2 evolution. The volatiles were removed under reduced pressure and the remaining oil was dissolved in EtOAc (250 mL). It was sequentially washed with aqueous HCl (0.5 M, 300 mL), aqueous saturated $NaHCO_3$ (300 mL) and brine (300 mL). It was dried over Na_2SO_4 and the solvent was removed under reduced pressure. Purification of the residue by flash chromatography (hexanes/EtOAc = 50/50) gave the title compound (33.0 g, 98%) as a colorless liquid. R_f = 0.4 (hexanes/EtOAc = 50/50), [$KMnO_4$]. $[\alpha]_D^{20}$ – 52.0 (*c* = 1.00, $CHCl_3$); IR (neat): ν_{max} = 3444, 2978, 1747, 1682, 1416, 1204, 1127 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 4.36 (1H, brs), 4.32 – 4.27 (1H, m), 3.84 – 3.82 (1H, m), 3.64 (3H, s), 3.50 – 3.43 (2H, m), 2.23 – 2.12 (1H, m), 1.96 – 1.90 (1H, m), 1.36 – 1.31 (9H, 2s); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.4, 173.1, 154.2, 153.6, 80.0, 79.8, 69.2, 68.5, 57.6, 57.1, 54.2, 54.1, 51.8, 51.6, 38.6, 37.9, 27.9, 27.8, 26.9; HRMS (ESIMS): calcd for $C_{11}H_{19}NO_5Na$ $[M+Na]^+$ 268.11554, found 268.11677. The analytical data are in complete agreement with that previously reported (*Chem Commun.* **2009**, 463 and references cited therein).

Methyl-3-keto-*N*-butoxycarbonbyl-L-prolinate (3.75)



The prolinol derivative **3.83** (4.8 g, 19.58 mmol) was dissolved in CH_2Cl_2 (20 mL), cooled to 0 ºC and treated with trichloroisocyanuric acid (4.55 g, 19.58 mmol) in small portions, then TEMPO (0.01 eq). The resulting mixture was stirred at r.t. for 20 min, until total consumption of the starting prolinol. The mixture was washed sequentially with aqueous saturated Na_2CO_3 (30 mL), HCl (0.5 M) and brine (30 mL). The organic layer was dried with Na_2SO_4 and the solvent was removed under reduced pressure. The clean intermediate (4.73 g, quant.) was obtained as a light pale yellow oil, which could be engaged in the next reaction without further purification. $R_f = 0.7$ (hexanes/EtOAc = 70/30), [$KMnO_4$], [CAM]. $[\alpha]_D^{20}$ +6.3 (*c* = 1.00, $CHCl_3$); IR (neat): ν_{max} = 2978, 1767, 1704, 1393, 1154 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 4.60 – 4.40 (1H, dd, *J* = 9.3 Hz), 4.18 – 4.08 (2H, m), 3.75 (3H, s), 2.97 – 2.91 (1H, m), 2.64 – 2.54 (1H, 2s), 1.50 – 1.44 (9H, 2s); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 208.0, 207.2, 171.8, 153.8, 153.1, 80.8, 55.8, 55.1, 53.1, 52.1, 52.0, 40.7, 40.3, 27.7; HRMS (ESIMS): calcd for $C_{11}H_{17}NO_5Na$ $[M+Na]^+$ 266,10044, found 266.10066. The analytical data are in complete agreement with the previously reported ones (*Bioorg. Med. Chem.* **2009**, *17*, 1557).

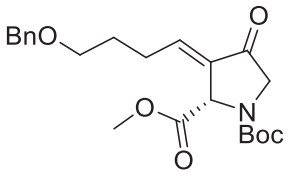
Enaminone (3.76)



The prolinone derivative **3.75** (5.2 g, 21.4 mmol) was dissolved in a mixture of toluene (43.0 mL) and *N,N*-dimethylformamide dimethyl acetal (8.52 mL, 64.2 mmol), and the resulting yellowish solution was heated under reflux at 105 °C for 6 h (until TLC analysis

indicated complete conversion of the starting material). The solvent of the resulting brownish-red solution was evaporated and the remaining red oil was purified by flash chromatography on silica (gradient hexanes/EtOAc = 10/90 to 0/100, then CH_2Cl_2/MeOH = 90/10). The desired enaminone (5.80 g, 91%) was isolated as a thick, red oil. R_f = 0.2 (100% EtOAc), [UV], [$KMnO_4$]. $[\alpha]_D^{20}$ +55.6 (*c* = 1.00, $CHCl_3$); IR (neat): ν_{max} = 3473, 2976, 1694, 1598, 1393, 1293, 1166, 1127 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), mixture of rotamers: δ = 5.39 – 5.29 (1H, 2s), 3.90 – 3.78 (2H, m), 3.63 (3H, s), 3.20 (6H, brs), 1.46 – 1.43 (9H, 2s); ^{13}C NMR (100 MHz, $CDCl_3$), mixture of rotamers: δ = 195.1, 194.5, 172.6, 172.3, 154.2, 153.2, 147.3, 147.1, 97.4, 80.3, 80.0, 60.5, 59.7, 52.6, 52.2, 52.0, 51.8, 27.9; HRMS (ESIMS): calcd for $C_{14}H_{23}N_2O_5$ $[M+H]^+$ 299.16070, found 299.16082.

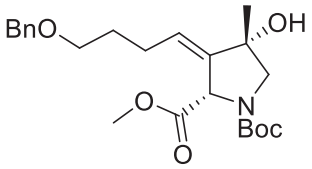
Enone (3.89)



Under argon and in a flame-dried flask, Mg-turnings (0.490 g, 20.1 mmol) and freshly prepared ((3-bromopropoxy)methyl)benzene (2.30 g, 10.1 mmol) were dissolved/placed in THF (10 mL). A mini-chip of iodine was added and the slightly yellow solution was stirred at room temperature under vigourous stirring. After the formation of the Grignard reagent had started (probed by disappearance of the yellow color) the reaction temperature was kept below 40 °C by cooling in a water bath. Once the temperature remained constant, the resulting grayish mixture was stirred at r.t. for an additional 1 h and then transferred dropwise to a -78 °C cold solution of the enaminone **3.76** (1.00 g, 3.35 mmol) in dry THF (60 mL). The resulting yellow-orange reaction solution was stirred at -78 °C for 1 h. The dry ice bath was removed and the reaction was allowed to warm to room temperature. It was stirred for 30 min at this temperature before aqueous saturated NH_4Cl solution (30 mL) was added slowly. The red biphasic mixture was separated and the aqueous phase was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (10 mL) and dried over Na_2SO_4, and the solvent was removed under reduced pressure. Purification of the residue by flash chromatography (hexanes/EtOAc = 90/10) gave the title compound (1.15 g, 2.85 mmol, 85%) as a colorless oil. Yields could be affected if the

bromoalkyl was overheated or overcooled during the Grignard reagent formation. R_f = 0.6 (hexanes/EtOAc = 75/25), [UV], [$KMnO_4$]. $[\alpha]_D^{20}$ +63.0 (*c* = 1.00, $CHCl_3$); IR (neat): ν_{max} = 2976, 1747, 1705, 1394, 1164 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), mixture of rotamers: δ = 7.29 – 7.22 (5H, m), 6.80 (1H, t, *J* = 1.4 Hz), 5.24 – 5.15 (1H, 2s), 4.44 (2H, m), 3.98 – 3.82 (2H, m), 3.63 (3H, s), 3.49 – 3.40 (2H, m), 2.52 – 2.34 (2H, m), 1.76 – 1.72 (2H, m), 1.46 – 1.42 (9H, 2s); ^{13}C NMR (100 MHz, $CDCl_3$), mixture of rotamers: δ = 196.6, 195.9, 171.0, 170.0, 153.9, 153.0, 142.0, 141.9, 138.0, 137.9, 131.5, 131.1, 128.0, 127.1, 80.7, 72.5, 68.8, 68.7, 59.8, 59.1, 52.9, 52.5, 52.1, 52.0, 27.8, 26.3, 26.1; HRMS (ESIMS): calcd for $C_{22}H_{29}NO_6Na$ $[M+Na]^+$ 426.18926, found 426.19095.

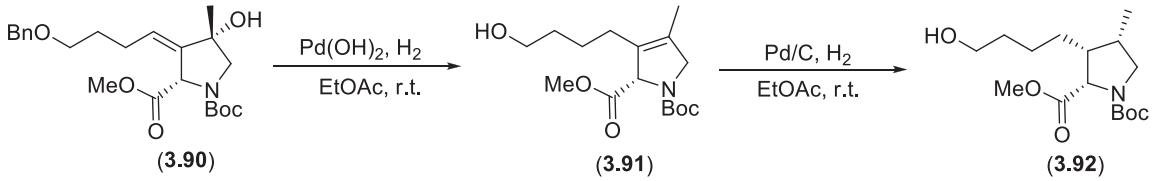
Allylic alcohol (3.90)



Under argon and in a flame-dried flask, the α,β-unsaturated ketone **3.89** (7.7 g, 19.1 mmol) was dissolved in dry THF (45 mL) and a commercial solution of $LaCl_3 \cdot 2LiCl$ (32.4 mL, 0.6 M, 19.1 mmol) was added at r.t. The mixture was allowed to stir as such for 1 h, then it was cooled to -78 °C and MeMgBr (9.7 mL, 3.0 M in Et_2O) was added dropwise. The resulting brownish solution was stirred at -78 °C for 1 h, then quenched at -78 °C with aqueous saturated NH_4Cl (30 mL). The biphasic mixture was separated and the aqueous phase was extracted with EtOAc (3 × 20 mL). The combined organic layers were extracted twice with 1 M HCl (2 × 100 mL), then added glycerol (20 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure. Purification of the residue by flash chromatography (hexanes/EtOAc = 80/20 to 60/40) gave the title compound (7.05 g, 88%) as a colorless oil. Warning: using more Grignard reagent or adding the latter too fast might entail formation of over-addition product (the methyl-ester being converted to the corresponding tertiary alcohol) in minor, yet non-neglectable yields. $[\alpha]_D^{20}$ +68.2 (*c* = 1.00, $CHCl_3$); IR (neat): ν_{max} = 3465, 2976, 1704, 1393, 1163, 1106 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), mixture of rotamers: δ = 7.35 – 7.29 (5H, m), 5.78 – 5.66 (1H, m), 4.92 – 4.86 (1H, 2s), 4.50 (2H, m), 4.15 – 3.93 (1H, 2s), 3.83 – 3.67 (1H, m), 3.81 (3H, 2s), 3.45 – 3.39

(2H, m), 3.26 (1H, d, J = 10.9 Hz), 2.40 – 2.16 (2H, m), 1.78 – 1.62 (2H, m), 1.47 – 1.43 (9H, 2s), 1.39 (3H, d, J = 4.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$), mixture of rotamers: δ = 173.6, 173.2, 170.7, 154.1, 153.2, 139.1, 138.3, 138.1, 138.0, 128.0, 127.4, 127.3, 127.2, 126.6, 126.4, 80.3, 75.3, 72.5, 69.0, 68.9, 60.7, 60.5, 60.2, 59.5, 52.6, 52.3, 28.7, 28.6, 28.0, 27.9, 25.3, 25.2, 20.8, 20.6; HRMS (ESIMS): calcd for $C_{23}H_{33}NO_6Na$ $[M+Na]^+$ 442.22001, found 442.22056.

Pyrrolidine alcohol (3.92)

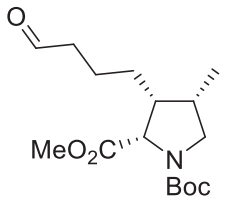


(**3.90**) (**3.91**) (**3.92**)

The allylic alcohol **3.90** (9.60 g, 22.9 mmol) was dissolved in EtOAc (110 mL) and $Pd(OH)_2$ (800 mg, 10 mol %) was added. The resulting mixture was purged with hydrogen and stirred overnight under an hydrogen atmosphere (until Ms-analysis indicated complete conversion to the corresponding tetra-substituted alkene). The mixture was filtered over Celite and the solvent was removed under reduced pressure. Purification of the residue by flash chromatography (hexanes/EtOAc = 70/30) gave the elimination product as a colorless oil (5.02 g, 70%) that was dissolved in EtOAc (30 mL). Pd on charcoal (2.45 g, 15 mol%) was then added and the reaction mixture was stirred under an hydrogen atmosphere for two days (until Ms-analysis indicated full conversion to the desired product). The mixture was filtered over Celite and the solvent was removed under reduced pressure. The title compound (5.04 g, quant.) was isolated as a colorless liquid and used without further purification. R_f = 0.4 (hexanes/EtOAc = 50/50), [$KMnO_4$], [CAM]. The complete sequence could be performed without purifying the tetra-substituted alkene; However, longer reactions times, as well as lower yields, then had to be expected (approximately four days).
For the transient tetra-substituted alkene (3.91): $[\alpha]_D^{20}$ –106.3 (c = 1.00, $CHCl_3$); IR (neat): ν_{max} = 3454, 2936, 1704, 1403, 1172 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), mixture of rotamers: δ = 4.92 – 4.80 (1H, 2brs), 4.17 – 4.09 (1H, m), 4.05 (1H, q, J = 14.6 Hz), 3.74 – 3.72 (3H, 2s), 3.66 – 3.63 (2H, m), 2.21 – 2.13 (1H, m), 2.04 (3H, m), 1.70 – 1.68

(3H, 2s), 1.53 (3H, m), 1.46 – 1.39 (9H, 2s); ^{13}C NMR (100 MHz, $CDCl_3$), mixture of rotamers: δ = 171.5, 171.4, 153.4, 152.9, 131.0, 128.9, 128.8, 79.7, 79.6, 68.1, 67.7, 62.0, 62.0, 56.9, 56.5, 51.7, 51.6, 31.8, 31.7, 28.0, 27.9, 24.5, 23.5, 23.4, 11.3, 11.2; HRMS (ESIMS): calcd for $C_{16}H_{27}NO_5Na$ $[M+Na]^+$ 336.17814, found 336.17894. **For the all-*syn* pyrrolidine derivative (3.92)**: $[\alpha]_D^{20}$ –0.4 (*c* = 1.00, $CHCl_3$); IR (neat): ν_{max} = 3458, 2936, 1698, 1403, 1178 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), mixture of rotamers: δ = 4.23 – 4.18 (1H, 2d, *J* = 9.4 Hz), 3.66 – 3.65 (3H, 2s), 3.60 (2H, t, *J* = 6.5 Hz), 3.49 – 3.45 (1H, 2d, *J* = 6.7 Hz), 3.37 – 3.25 (1H, 2dd, *J* = 10.7, 0.5 Hz), 2.44 – 2.32 (1H, m), 2.30 – 2.20 (2H, m), 1.53 – 1.47 (2H, m), 1.38 – 1.33 (9H, 2s), 1.38 – 1.33 (3H, m), 1.27 – 1.20 (1H, m), 0.94 (3H, d, *J* = 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$), mixture of rotamers: δ = 172.2, 172.0, 154.2, 153.6, 79.5, 79.4, 61.9, 61.8, 61.4, 53.4, 53.0, 51.3, 51.1, 45.0, 44.0, 34.4, 33.5, 32.3, 32.3, 28.0, 27.9, 25.7, 25.6, 23.9, 13.9, 13.7; HRMS (ESIMS): calcd for $C_{16}H_{29}NNaO_5$ $[M+Na]^+$ 338.19379, found 338.19399.

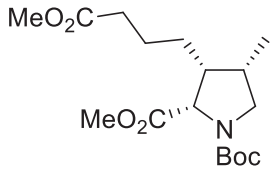
Pyrrolidine aldehyde (3.80)



The alcohol **3.92** (2.95 g, 9.35 mmol) was dissolved in DMSO (19 mL) and IBX (3.93 g, 14.0 mmol) was added. The resulting mixture was stirred for 4 h at r.t. (until TLC-analysis indicated full conversion). The mixture was diluted with CH_2Cl_2 (150 mL) and stirred for 30 min. It was filtered and the filter cake was washed with CH_2Cl_2 (3 × 40 mL). The organic phase was washed sequentially with aqueous saturated $NaHCO_3$ (60 mL) and brine (60 mL). The organic layer was dried with Na_2SO_4 and the solvent was removed under reduced pressure. Purification of the residue by flash chromatography (hexanes/EtOAc = 60/40) gave the title compound (2.46 g, 84 %) as a colorless oil. R_f = 0.5 (hexanes/EtOAc = 60/40), [UV], [$KMnO_4$]. $[\alpha]_D^{20}$ +7.2 (*c* = 1.00, $CHCl_3$); IR (neat): ν_{max} = 2939, 1698, 1398, 1177 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), mixture of rotamers: δ = 9.70 (1H, s), 4.24 – 4.15 (1H, 2d, *J* = 9.4 Hz), 3.64 – 3.63 (3H, 2s), 3.46 – 3.41 (1H, 2d, *J* = 6.7 Hz), 3.33 – 3.20 (1H, 2dd, *J* = 10.7, 1.6 Hz), 2.42 – 2.39 (3H, m), 2.29 – 2.22 (1H, m), 1.64 – 1.58 (2H, m), 1.37

– 1.32 (9H, 2s), 1.40 – 1.33 (1H, m), 1.25 – 1.18 (1H, m), 0.93 (3H, d, J = 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$), mixture of rotamers: δ = 201.5, 201.5, 172.0, 171.7, 154.1, 153.4, 79.4, 79.3, 61.6, 61.2, 53.3, 52.8, 51.2, 51.1, 44.8, 43.9, 43.4, 43.2, 34.3, 33.4, 27.9, 27.7, 25.6, 25.4, 20.2, 20.1, 13.8, 13.7; HRMS (ESIMS): calcd for $C_{16}H_{27}NNaO_5$ $[M+Na]^+$ 336.17814, found 336.17819.

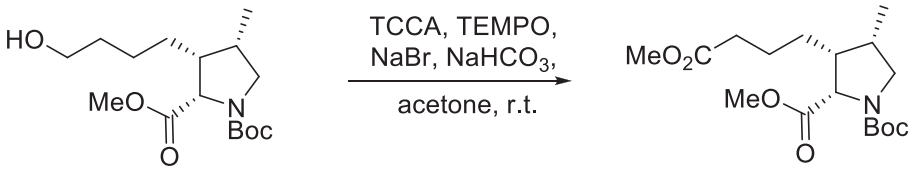
Pyrrolidine diester (3.81)



The aldehyde **3.80** (136 mg, 0.43 mmol) was dissolved in 4: 1 mixture of *tert*-butanol (8.6 mL) and 2-methyl-2-butene (2.2 mL), and solutions of NaH_2PO_4 (390 mg, 3.2 mmol) in water (2.2 mL) and $NaClO_2$ (363 mg, 3.2 mmol) in water (2.2 mL) were added. The biphasic mixture was stirred at room temperature for 1 h. The mixture was diluted with water (100 mL) and it was extracted with EtOAc (4 × 30 mL). The combined organic layers were washed with brine (30 mL) and dried over Na_2SO_4. Evaporation of the solvent gave the analytical pure carboxylic acid **3.93** that was used without further purification. This carboxylic acid (141 mg, 0.43 mmol), obtained from the latter procedure or from TEMPO oxidation described below, was dissolved in benzene: MeOH (3: 1, 4.4 mL). $TMSCHN_2$ (0.24 mL of 2.0M solution in diethyl ether) was added dropwise until the disappearance of the yellow color was not observed anymore. Water (10 mL) was added, and the mixture was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (15 mL) and dried over Na_2SO_4. The solvent was evaporated to give the analytical pure methyl ester **3.81** (147 mg, 100%) that was used without further purification. This intermediate doesn't stain with $KMnO_4$ (very feeble), CAM, iodine, cerium sulfate, vanillin, 2,4-DNP, *p*-anisaldehyde (very feeble) and phosphomolybdic acid (very feeble) and is not UV-active. $[\alpha]_D^{20}$ –5.0 (*c* = 1.00, $CHCl_3$); IR (neat): ν_{max} = 2951, 1732, 1704, 1402, 1177 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), mixture of rotamers: δ = 4.22 – 4.13 (1H, 2d, J = 9.4 Hz), 3.64 – 3.58 (6H, 2s), 3.44 – 3.40 (1H, 2d, J = 6.7 Hz), 3.32 – 3.18 (1H,

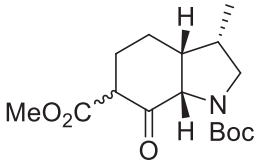
2dd, J = 10.7, 1.7 Hz), 2.44 – 2.33 (1H, m), 2.40 – 2.19 (3H, m), 1.62 – 1.56 (2H, m), 1.38 – 1.31 (9H, 2s), 1.40 – 1.31 (1H, m), 1.25 – 1.15 (1H, m), 0.92 (3H, d, J = 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$), mixture of rotamers: δ = 173.1, 173.1, 171.9, 171.7, 154.0, 153.3, 73.2, 79.1, 61.6, 61.2, 53.3, 52.8, 51.1, 50.9, 44.6, 43.7, 34.2, 33.5, 33.3, 27.9, 27.5, 25.4, 25.3, 22.9, 13.7, 13.5; HRMS (ESIMS): calcd for $C_{17}H_{30}NNaO_6$ $[M+Na]^+$ 344.20676, found 344.20740.

Carboxylic acid (3.93)



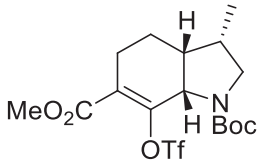
Alcohol **3.92** (1.00 g, 3.193 mmol,) was dissolved in acetone (32 mL) and cooled to 0 °C before adding a 15% solution of $NaHCO_3$ (15 mL). Then, NaBr (66 mg, 0.6386 mmol) and TEMPO (8 mg, 0.0639 mmol) were added to the mixture, after which trichloroisocyanuric acid (TCCA, 1.63 g, 7.024 mmol) was added in portions over 5 min. The mixture was allowed to warm up to r.t. and was stirred as such for 6 h. Isopropanol (1 eq.) was then added at r.t., and the mixture was treated with a saturated aqueous solution of Na_2CO_3 (3 mL), then reacidified with 1M HCl. The solid that had then formed was filtered on Celite, and the aqueous phase was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with brine (30 mL) and dried over Na_2SO_4. Evaporation of the solvent gave the analytical pure carboxylic acid that was esterified as described in the making of compound **3.81**, without further purification. This intermediate doesn't stain with $KMnO_4$ (feeble), CAM, iodine, cerium sulfate, vanillin, 2,4-DNP, *p*-anisaldehyde (feeble) and phosphomolybdic acid (feeble) and is not UV-active.

Bicyclic β-ketoester (3.82)



The diester **3.81** (750 mg, 2.18 mmol) was dissolved in THF (54 mL, 0.04 M) and cooled to -78 °C, then slowly treated with KHMDS (10.92 mL of 0.5 M solution in toluene, 5.46 mmol). The reaction mixture was stirred at -78 °C for 30 min, then left warming up slowly to r.t. for 20 min upon removal from the dry ice bath. It was then brought back to -78 °C and quenched with aqueous saturated NH_4Cl (40 mL), and the mixture was extracted with EtOAc (3 × 20 mL). The combined organic layers were dried over Na_2SO_4, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (hexanes/EtOAc = 80/20 to 60/40) to give the β-ketoester **3.82** (555 mg, 82%) as a colorless liquid. R_f = 0.5 (hexanes/EtOAc = 60/40), [UV], [$KMnO_4$]. $[\alpha]_D^{20}$ –4.6 (*c* = 1.00, $CHCl_3$); IR (neat): ν_{max} = 2953, 1698, 1397, 1168 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), mixture of diastereomers: δ = 3.85 (1H, d, *J* = 4.5 Hz), 3.67 (3H, s), 3.70 – 3.55 (2H, m), 3.11 (1H, t, *J* = 10.4 Hz), 2.46 – 2.37 (1H, m), 2.30 – 2.14 (2H, m), 1.91 (1H, dq, *J* = 13.3, 6.5 Hz), 1.70 – 1.63 (1H, m), 1.34 (9H, s), 1.52 – 1.38 (1H, m), 0.95 (3H, d, *J* = 7.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$), mixture of diastereomers: δ = 204.0, 169.7, 153.7, 81.0, 68.4, 51.7, 51.5, 50.7, 48.2, 35.0, 29.3, 27.3, 20.0, 12.1; HRMS (ESIMS): calcd for $C_{16}H_{26}NO_5Na$ $[M+Na]^+$ 334.16249, found 334.16280.

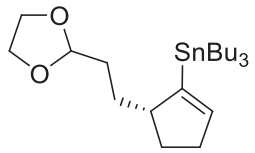
Enoltriflate (3.94)



The β-ketoester **3.82** (2.80 g, 9.00 mmol) was dissolved in THF (50 mL) and cooled to -78 °C, then slowly treated with KHMDS (21.6 mL of 0.5 M solution in hexanes, 10.8 mmol). The reaction mixture was stirred at -78 °C for 30 min, after which a solution of Comin's reagent (1.81 mL, 10.8 mmol) in dry THF (20 mL) was slowly added to the mixture. The reaction was then allowed to warm up to -40 °C, and stirred 4 h as such. Then, the reaction was stopped by slowly adding an aqueous saturated solution of NH_4Cl (20 mL). The two phases were separated, and the aqueous phase was extracted with EtOAc (3 × 20 mL). The combined organic layers were dried over Na_2SO_4, and the solvent was removed under

reduced pressure. The residue was purified by flash chromatography (hexanes/EtOAc = 90/10 to 80/20) to give the enoltriflate **3.94** (2.98 g, 75%) as a colorless liquid. R_f = 0.5 (hexanes/EtOAc = 70/30), [UV], [$KMnO_4$]. $[\alpha]_D^{20}$ –55.8 (*c* = 1.00, $CHCl_3$); IR (neat): ν_{max} = 3440, 2958, 1704, 1420, 1207 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 4.52 (1H, brs), 3.79 (3H, s), 3.77 (2H, dd, *J* = 7.4, 3.8 Hz), 2.83 (1H, t, *J* = 11.2 Hz), 2.58 – 2. 42 (3H, m), 2.32 – 2.23 (1H, m), 1.62 – 1.53 (1H, m), 1.46 (9H, s), 1.03 (3H, d, *J* = 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.9, 154.8, 149.2, 126.7, 119.5, 116.3, 80.4, 51.9, 51.7, 42.0, 35.4, 27.9, 25.0, 18.9, 12.0; HRMS (ESIMS): calcd for $C_{17}H_{24}F_3NNaO_7S$ $[M+Na]^+$ 466.11178, found 466.11286.

(R)-(5-(2-(1,3-dioxolan-2-yl)ethyl)cyclopent-1-enyl)tributylstannane (3.100)

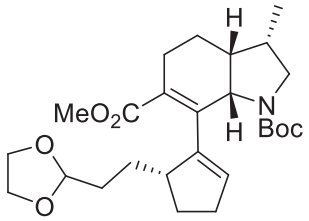


The known allylic iodide **3.99*** (270 mg, 0.153 mmol) was dissolved in Et_2O (2 mL) and cooled to -78 °C, then slowly treated with *n*BuLi (0.063 mL of 2.5 M solution in hexanes, 0.1575 mmol). The mixture was stirred for 30 min at -78 °C; The intermediate from the halogen-metal exchange (the quenched alkene) can be seen on TLC. Then, Bu_3SnCl (0.964 mL) was added slowly. The reaction was stirred approximately 2 h, then quenched with an aqueous saturated solution of NH_4Cl (10 mL). The biphasic system was then extracted with Et_2O (3 × 10 mL), dried over Na_2SO_4, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography by loading with hexanes (hexanes/EtOAc = 100/0 to 98/2) to give the stannane **3.100** (306 mg, 72%) as a colorless liquid. If the reaction was to be done in THF, the yield would go dramatically down (c.a. 30%) and wouldn't be complete. R_f = 0.4 (hexanes/EtOAc = 90/10), [$KMnO_4$]. $[\alpha]_D^{20}$ –3.5 (*c* = 1.00, $CHCl_3$); IR (neat): ν_{max} = 2925, 1463, 1139, 1040 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 5.87 (1H, m), 4.87 (1H, t, *J* = 4.5 Hz), 3.98 – 3.89 (2H, m), 3.86 – 3.78 (2H, m), 2.80 – 2.73 (1H, m), 2.44 – 2.26 (2H, m), 2.03 – 1.95 (1H, m), 1.72 – 1.64 (3H, m), 1.52 – 1.38 (7H, m), 1.32 – 1.27 (7H, m), 0.97 – 0.82 (15H, m); ^{13}C NMR (100 MHz,

$CDCl_3$): δ = 148.2, 140.7, 140.5, 104.4, 64.5, 51.1, 33.6, 31.6, 29.8, 28.9, 28.8, 27.0, 13.3, 9.2; HRMS (ESIMS): calcd for $C_{22}H_{42}NaO_5$[120Sn] $[M+Na]^+$ 481.20990, found 481.20990.

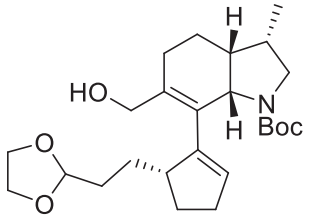
[*] Knochel, P. *et al*, *Org. Lett.*, **2003**, *5*, 1059.

Tricyclic ester (3.102)



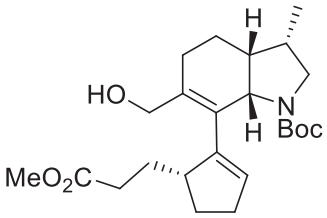
To a solution of the enoltriflate **3.94** (600 mg, 1.354 mmol,) and the tin reagent **3.100** (744 mg, 1.624 mmol) in degassed DMF (3.5 mL, 0.4 M) was added triphenyl arsine (62 mg, 0.2030 mmol, 20 mol %), lithium chloride (172 mg, 4.062 mmol) and $[Pd_2(dba)_3CHCl_3]\cdot MeCN$ (70 mg, 0.0677 mmol, 5 mol %) at r.t. The mixture was then heated up to 65 ºC and left stirring overnight (12 h) at that temperature. The reaction mixture was diluted with H_2O (10 mL) and extracted with Et_2O (3 × 10 mL). The combined organic layers were then dried over Na_2SO_4, and the solvent was removed *in vacuo*. (A biphasic extraction with hexanes and MeCN was attempted, but was not efficient due to solubility of both tin impurities and product in both solvents). The residue was purified by flash chromatography (hexanes/EtOAc = 80/20) to give the stable acetal **3.102** (518 mg, 89%) as a colorless liquid. R_f = 0.4 (hexanes/EtOAc = 70/30), [UV], [$KMnO_4$]. $[\alpha]_D^{20}$ – 115.5 (*c* = 1.00, $CHCl_3$); IR (neat): ν_{max} = 2929, 1698, 1391, 1365, 1159 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 5.39 (1H, m), 4.82 (1H, t, *J* = 4.7 Hz), 4.57 (1H, d, *J* = 7.9 Hz), 3.94 – 3.87 (2H, m), 3.82 – 3.75 (2H, m), 3.74 – 3.68 (1H, m), 3.59 (3H, s), 3.09 – 3.02 (1H, m), 2.53 (1H, t, *J* = 12.1 Hz), 2.41 – 2.33 (2H, m), 2.29 – 2.00 (6H, m), 1.74 – 1.46 (6H, m), 1.39 (9H, s), 0.98 (3H, d, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.0, 155.0, 145.2, 140.0, 130.6, 128.1, 104.6, 78.7, 64.4, 55.6, 51.7, 50.8, 46.2, 37.9, 35.7, 32.4, 31.0, 30.2, 28.1, 28.0, 24.5, 20.3, 12.8; HRMS (ESIMS): calcd for $C_{26}H_{40}NO_6Na$ $[M+Na]^+$ 484.26696, found 484.26836.

Tricyclic alcohol (3.114)



A solution of the ester **3.102** (100 mg, 0.2168 mmol) in dry CH_2Cl_2 (1.5 mL) was cooled to -78 ^oC and maintained under argon, and slowly treated with DIBAL-H (1.5 M in toluene, 363 μL, 0.5421 mmol). The reaction was achieved over 1 h, after which saturated solutions of NH_4Cl (5 mL) and Rochelle salt (5 mL) were added and left stirring over warming up of the mixture, until the organic and aqueous phases were separated. The aqueous phase was then exctrated with CH_2Cl_2 (3 × 5 mL). These combined organic layers were then dried over Na_2SO_4, and the solvent was removed *in vacuo*. The residue was purified by flash chromatography (hexanes/EtOAc = 60/40) to give the allylic alcohol **3.114** (96 mg, 98%) as a colorless liquid. R_f = 0.3 (hexanes/EtOAc = 60/40), [UV], [$KMnO_4$]. $[\alpha]_D^{20}$ –131.0 (*c* = 1.00, $CHCl_3$); IR (neat): ν_{max} = 3404, 2921, 1695, 1389, 1364, 1158 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 5.26 (1H, brs), 4.82 (1H, brs), 4.45 (1H, d, *J* = 7.0 Hz), 4.23 (1H, d, *J* = 11.3 Hz), 3.98 – 3.91 (2H, m), 3.88 (1H, m), 3.86 – 3.79 (2H, m), 3.77 – 3.68 (1H, m), 3.16 – 3.08 (1H, m), 2.66 (1H, t, *J* = 10.2 Hz), 2.42 – 2.26 (2H, m), 2.25 – 2.01 (6H, m), 1.77 – 1.67 (3H, m), 1.55 – 1.45 (2H, m), 1.41 (9H, s), 1.34 – 1.23 (2H, m), 1.00 (3H, d, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.3, 144.8, 136.3, 132.5, 128.3, 104.4, 78.4, 64.5, 64.0, 55.5, 51.6, 45.6, 38.3, 36.1, 31.6, 30.9, 30.1, 28.0, 27.9, 24.5, 20.3, 12.6; HRMS (ESIMS): calcd for $C_{25}H_{39}NO_5Na$ $[M+Na]^+$ 456.27204, found 456.27131.

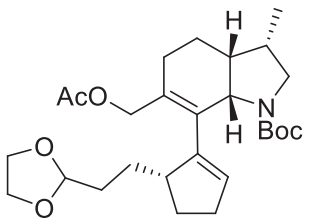
Allylic alcohol (3.118)



The allylic alcohol **3.114** (30 mg, 0.06924 mmol) was cooled to 0 ^oC and dissolved in 1 N HCl and THF (1: 1, 2 mL). The reaction mixture was allowed to warm up to r.t. and stirred

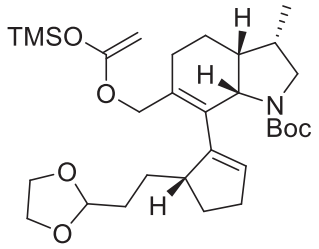
as such for 14 h, after which it was cooled back to 0 °C and slowly quenched upon addition of a saturated aqueous solution of $NaHCO_3$ (5 mL) The two phases were separated, and the aqueous phase was extracted with EtOAc (3 × 5 mL). The combined organic layers were dried over Na_2SO_4, and the solvent was removed under reduced pressure. The cruse residue was taken up in a 4: 1 mixture of *tert*-butanol (1.5 mL) and 2-methyl-2-butene (380 μL), after which solutions of NaH_2PO_4 (69 mg, 0.578 mmol) in water (380 μL) and $NaClO_2$ (51 mg, 0.578 mmol) in water (380 μL) were added. The biphasic mixture was stirred at room temperature for 2 h. The mixture was diluted with water and it was extracted with EtOAc (4 × 5 mL). The combined organic layers were washed with brine (15 mL) and dried over Na_2SO_4. The carboxylic acid thereby obtained was once again dissolved in benzene: MeOH (4: 1, 2.25 mL). $TMSCHN_2$ (2.0M solution in diethyl ether) was added dropwise until the disappearance of the yellow color was not observed anymore. Water (10 mL) was then added, and the mixture was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was evaporated and the residue was purified by flash chromatography (hexanes/EtOAc = 70/30) to give the methyl ester **3.118** (10 mg, 58%) as a colorless liquid. R_f = 0.2 (hexanes/EtOAc = 60/40), [UV], [$KMnO_4$]. $[\alpha]_D^{20}$ –65.9 (*c* = 1.00, $CHCl_3$); IR (neat): ν_{max} = 2939, 2363, 1702, 1368, 1163 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 5.34 (1H, brs), 4.46 (1H, d, *J* = 7.5 Hz), 4.07 (2H, m), 3.74 (1H, brs), 3.68 (3H, s), 3.16 – 3.03 (1H, m), 2.69 (1H, t, *J* = 10.5 Hz), 2.42 – 2.23 (6H, m), 2.26 – 2.05 (4H, m), 1.72 – 1.62 (2H, m), 1.55 – 1.35 (3H, m), 1.43 (9H, s), 1.01 (3H, d, *J* = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.5, 155.5, 144.5, 136.5, 132.4, 128.4, 78.5, 64.1, 55.6, 51.7, 51.3, 46.0, 38.5, 36.2, 32.4, 30.9, 29.6, 29.1, 28.0, 24.6, 20.3, 12.5; HRMS (ESIMS): calcd for $C_{24}H_{37}NO_5Na$ $[M+Na]^+$ 442.25639, found 442.25678.

Allylic acetate (3.121)



A solution of the allylic alcohol **3.114** (25 mg, 0.0577 mmol) in CH_2Cl_2 (1 mL) was cooled to 0 °C and treated with DMAP (cat.), NEt_3 (32 μL, 0.231 mmol), and Ac_2O (11 μL, 0.116 mmol). The reaction mixture was allowed to warm up to r.t. and stirred for 2 h, after which full conversion could be observed. The reaction mixture was then quenched with a 1 N HCl solution (5 mL), the aqueous and organic phases were separated and the aqueous phase was further extracted with EtOAc (3 × 10 mL). The residue was purified by flash chromatography (hexanes/EtOAc = 80/20) to give the acetate **3.121** (32 mg, 97%) as a colorless liquid. R_f = 0.6 (hexanes/EtOAc = 50/50), [UV], [$KMnO_4$]. $[\alpha]_D^{20}$ –176.5 (*c* = 1.00, $CHCl_3$); IR (neat): ν_{max} = 2931, 1738, 1698, 1365, 1235, 1158 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 5.26 (1H, brs), 4.82 (1H, t, *J* = 4.8 Hz), 4.55 (2H, q, *J* = 11.5 Hz), 4.46 (1H, d, *J* = 7.5 Hz), 3.89 – 3.81 (2H, m), 3.78 – 3.70 (2H, m), 3.66 – 3.58 (1H, m), 3.08 (1H, brs), 2.68 (1H, t, *J* = 10.7 Hz), 2.45 – 2.34 (2H, m), 2.27 – 1.97 (5H, m), 2.04 (3H, s), 1.77 – 1.46 (6H, m), 1.43 (9H, s), 1.12 – 1.00 (1H, m), 1.00 (3H, d, *J* = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.9, 155.3, 144.5, 135.6, 131.2, 128.3, 104.5, 78.5, 66.0, 64.4, 64.4, 55.4, 51.7, 46.3, 38.2, 36.0, 32.4, 30.8, 29.7, 28.0, 27.9, 24.7, 20.6, 20.0, 12.7; HRMS (ESIMS): calcd for $C_{27}H_{41}NO_6Na$ $[M+Na]^+$ 498.28261, found 498.28345.

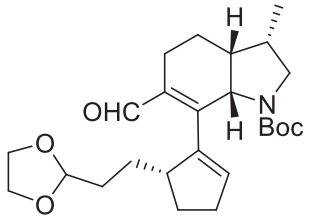
Silyl ketene acetal (3.122)



A solution of diisopropylamine (11 μL, 0.07574 mmol) in dry THF (0.5 mL) was maintained under argon, cooled to -78 °C, and slowly treated with *n*BuLi (28 μL, 0.06943 mmol). The reaction mixture was stirred 30 min as such, after which a solution of the allylic acetate **3.121** (30 mg, 0.06312 mmol) in dry THF (0.5 mL) was added drop-wisely. After stirring an additional 1 h, TMSCl (16 μL, 0.1265 mmol) was added slowly to the mixture. The reaction was left stirring at -78 °C for 1 h, and subsequently left warming up to r.t. for an additional 2 h. The reaction was then quenched upon addition of cold H_2O (5 mL), the aqueous and organic phases were separated. The aqueous phase was extracted further with

EtOAc (3 × 10 mL). The combined organic layers were then dried over Na_2SO_4, and the solvent was removed *in vacuo*. The residue was purified by flash chromatography (hexanes/EtOAc = 10/90 to 75/25 with 5% EtOAc increments) to give the silyl enol ether **3.122** (17 mg, 49%) as a colorless oil and some starting material (15 mg, 43%). R_f = 0.6 (hexanes/EtOAc = 70/30), [$KMnO_4$], [CAM]. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.26 (1H, brs), 4.82 (1H, t, *J* = 4.8 Hz), 4.56 (2H, q, *J* = 11.5 Hz), 4.46 (1H, d, *J* = 7.5 Hz), 3.96 – 3.92 (2H, m), 3.84 – 3.80 (2H, m), 3.79 – 3.72 (1H, m), 3.06 (1H, brs), 2.67 (1H, t, *J* = 10.7 Hz), 2.43 – 2.26 (2H, m), 2.25 – 1.97 (5H, m), 1.91 (2H, d, *J* = 4.3 Hz), 1.77 – 1.42 (6H, m), 1.43 (9H, s), 1.15 – 1.04 (1H, m), 1.00 (3H, d, *J* = 7.0 Hz), 0.12 (9H, s); ESIMS: calcd for $C_{30}H_{49}NNaO_6$ $[M+Na]^+$ 570.3, found 570.3.

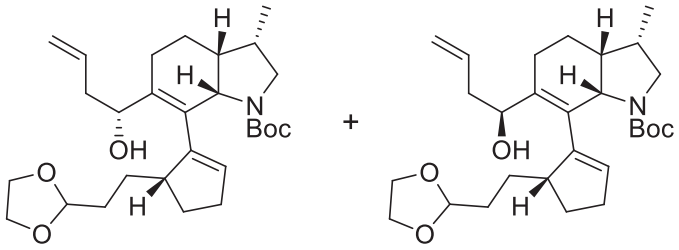
Unsaturated aldehyde



The primary allylic alcohol **3.114** (45 mg, 0.1039 mmol) was dissolved in wet CH_2Cl_2 (1 mL) and Dess-Martin periodinane (93 mg, 0.2181) was added at 0 °C. The mixture was allowed to stir as such for 1 h until complete transformation of the starting material, after which the reaction mixture was washed with saturated solutions of $Na_2S_2O_3$ (2 mL) and $NaHCO_3$ (2 mL). The aqueous phase was separated from the organic phase, and the former was washed with CH_2Cl_2 (3 × 5 mL). The solvent was removed under reduced pressure, and purification of the residue was achieved by flash chromatography (hexanes/Et_2O = 80/20) to give the title compound (37 mg, 83%) as a colorless oil. R_f = 0.7 (hexanes/EtOAc = 60/40), [UV], [$KMnO_4$]. $[\alpha]_D^{20}$ –162.2 (*c* = 1.00, $CHCl_3$); IR (neat): ν_{max} = 2925, 1697, 1672, 1364, 1157 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.81 (1H, s), 5.52 (1H, brs), 4.81 (1H, t, *J* = 4.8 Hz), 4.69 (1H, d, *J* = 7.5 Hz), 3.97 – 3.89 (2H, m), 3.86 – 3.78 (2H, m), 3.80 – 3.73 (1H, m), 3.25 (1H, brs), 2.63 (1H, t, *J* = 10.7 Hz), 2.55 – 2.36 (3H, m), 2.34 – 2.17 (3H, m), 2.02 – 1.91 (1H, m), 1.77 – 1.60 (3H, m), 1.60 – 1.47 (3H, m), 1.45 (9H, s), 1.21 – 1.11 (1H, m), 0.99 (3H, d, *J* = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 193.5, 155.5,

155.4, 142.3, 139.3, 133.0, 104.1, 79.0, 64.5, 64.4, 56.2, 52.0, 46.7, 38.8, 36.1, 32.3, 31.2, 29.9, 29.3, 29.0, 27.6, 19.7, 12.4; HRMS (ESIMS): calcd for $C_{25}H_{37}NO_5Na$ $[M+Na]^+$ 454.25639, found 454.25569.

Homoallylic alcohols (3.124)

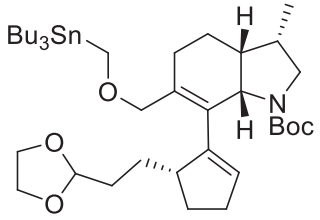


A solution of the above aldehyde (35 mg, 0.0812 mmol) in dry THF (1 mL) was cooled to -78 ^oC, maintained under argon and slowly added allylMgBr (100 μL, 0.0974 mmol). The mixture was stirred for 20 min at the latter temperature, and the reaction was quenched upon addition of a saturated solution of NH_4Cl (5 mL). The reaction mixture was diluted with H_2O (5 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were then dried over Na_2SO_4, and the solvent was removed *in vacuo*. The residue was purified by flash chromatography (hexanes/EtOAc = 10/90 to 60/40 with 10% EtOAc increments) to give two diastereomeric secondary allylic alcohols in a ratio of 4: 3 (33 mg, 86%) and as colorless liquids. The stereochemistry is arbitrary.

(*R*)-diastereomer: R_f = 0.4 (hexanes/EtOAc = 50/50), [UV], [$KMnO_4$]. $[\alpha]_D^{20}$ –117.6 (*c* = 1.00, $CHCl_3$); IR (neat): ν_{max} = 3466, 2924, 1700, 1389, 1365, 1158 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 5.84 – 5.76 (1H, m), 5.35 (1H, brs), 5.13 (1H, d, *J* = 17.4 Hz), 5.08 (1H, d, *J* = 10.2 Hz), 4.85 (1H, t, *J* = 4.8 Hz), 4.63 – 4.45 (1H, m), 4.43 (1H, d, *J* = 7.4 Hz), 3.99 – 3.91 (2H, m), 3.89 – 3.80 (2H, m), 3.72 (1H, brs), 3.10 (1H, brs), 2.70 (1H, t, *J* = 10.6 Hz), 2.43 – 2.24 (4H, m), 2.24 – 2.09 (4H, m), 1.95 – 1.40 (8H, m), 1.42 (9H, s), 1.18 – 1.11 (1H, m), 0.98 (3H, d, *J* = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.2, 145.6, 138.3, 135.5, 133.6, 117.1, 104.7, 78.8, 71.3, 64.8, 64.8, 56.1, 51.9, 47.2, 46.7, 39.7, 38.7, 36.9, 32.7, 31.2, 30.3, 28.7, 28.4, 21.2, 12.1; HRMS (ESIMS): calcd for $C_{28}H_{43}NO_5Na$ $[M+Na]^+$ 493.30334, found 496.30133.

(*S*)-diastereomer: R_f = 0.30 (hexanes/EtOAc = 50/50), [UV], [$KMnO_4$]. $[\alpha]_D^{20}$ –163.7 (*c* = 1.00, $CHCl_3$); IR (neat): ν_{max} = 3463, 2929, 1696, 1389, 1364, 1159 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 5.84 – 5.76 (1H, m), 5.35 (1H, brs), 5.13 (1H, d, *J* = 17.4 Hz), 5.08 (1H, d, *J* = 10.2 Hz), 4.85 (1H, t, *J* = 4.8 Hz), 4.63 – 4.45 (1H, m), 4.43 (1H, d, *J* = 7.4 Hz), 3.99 – 3.91 (2H, m), 3.89 – 3.80 (2H, m), 3.72 (1H, brs), 3.15 (1H, brs), 2.81 (1H, brs), 2.70 (1H, t, *J* = 10.6 Hz), 2.48 – 2.28 (3H, m), 2.24 – 1.96 (6H, m), 1.85 – 1.63 (4H, m), 1.59 – 1.40 (3H, m), 1.43 (9H, s), 1.01 (3H, d, *J* = 7.0 Hz), 0.92 – 0.84 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.3, 145.6, 138.3, 135.7, 133.7, 117.0, 104.7, 78.9, 71.3, 64.7, 64.7, 55.8, 52.0, 47.1, 46.5, 39.8, 38.7, 36.8, 32.7, 31.2, 30.2, 28.7, 28.3, 21.1, 12.0; HRMS (ESIMS): calcd for $C_{28}H_{43}NO_5Na$ $[M+Na]^+$ 493.30334, found 496.30136.

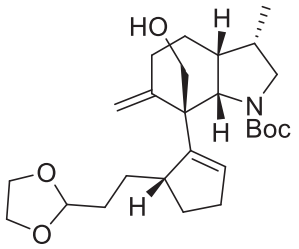
Tin ether (3.126)



To a suspension of KH in mineral oil (30%, 1 mL, 0.923 mmol) was slowly added a solution of the allylic alcohol **3.114** (86 mg, 0.199 mmol) in THF (2 mL) at r.t. under argon. After stirring for 1 h, the solution was cooled to 0 °C and quenched very carefully with water (15 mL). The organic and aqueous phases were then separated, and the aqueous phase was further extracted with Et_2O (3 × 5 mL). The combined organic layers were then dried over Na_2SO_4, and the solvent was removed *in vacuo*. The residue was purified by flash chromatography (hexanes/EtOAc = 100/0 to 80/20) to give the tin ether **3.126** (122 mg, 84%) as a very light colorless liquid. R_f = 0.65 (hexanes/EtOAc = 70/30), [UV] (feeble), [$KMnO_4$]. $[\alpha]_D^{20}$ –100.5 (*c* = 1.00, $CHCl_3$); IR (neat): ν_{max} = 2923, 1698, 1364, 1158, 1056 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 5.28 (1H, brs), 4.83 (1H, t, *J* = 4.8 Hz), 4.46 (1H, d, *J* = 7.7 Hz), 3.92 – 3.84 (2H, m), 3.81 – 3.73 (2H, m), 3.70 (2H, dd, *J* = 46.7, 10.6 Hz), 3.62 – 3.54 (1H, m), 3.55 (2H, dd, *J* = 11.1, 7.8 Hz), 3.06 (1H, brs), 2.66 (1H, t, *J* = 10.6 Hz), 2.43 – 2.30 (2H, m), 2.27 – 2.07 (4H, m), 1.96 – 1.84 (1H, m), 1.74 – 1.56 (3H, m), 1.54 – 1.45 (8H, m), 1.43 (9H, s), 1.33 – 1.22 (6H, m), 1.12 – 1.04 (1H, m), 1.00 (3H, d, *J*

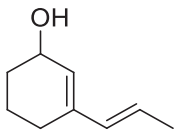
= 7.0 Hz), 1.43 – 1.32 (16H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.2, 144.8, 134.5, 132.8, 127.5, 104.6, 78.3, 64.5, 64.4, 60.5, 55.5, 51.3, 46.4, 38.3, 36.2, 32.6, 30.8, 29.8, 28.9, 28.8, 28.7, 28.0, 27.0, 24.3, 20.3, 13.4, 8.5; HRMS (ESIMS): calcd for $C_{38}H_{67}NSnO_5Na$ $[M+Na]^+$ 752.39597, found 752.39618.

Quaternary center (3.127)



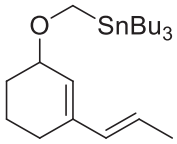
Typical procedure: a solution of the tin ether **3.126** (35 mg, 0.0474 mmol) in dry hexanes (1 mL) was cooled to -78 ºC, maintained under argon and slowly treated with *n*BuLi (2.5 M in hexanes, 190 μL, 0.475 mmol). The reaction mixture was stirred as such for 30 min, after which the reaction mixture was allowed to warm up to 20 ºC and stirred for 2 h. An aqueous saturated solution of NH_4Cl (5 mL) was then added, the mixture was allowed to warp up to r.t. The biphasic mixture was separated and the aqueous phase was extracted with Et_2O (3 × 5 mL). The solvent was removed under reduced pressure. Purification of the residue by flash chromatography (hexanes/EtOAc = 100/0 to 80/20 with 5% EtOAc increments) gave the intended [2,3]-rearrangement product **3.127** (5 mg, 25%) as a colorless oil. R_f = 0.6 (hexanes/EtOAc = 70/30), [UV], [$KMnO_4$]. $[\alpha]_D^{20}$ –3.0 (*c* = 1.00, $CHCl_3$); IR (neat): ν_{max} = 2923, 1671, 1391, 1161 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.52 (1H, brs), 5.24 (1H, s), 5.02 (1H, s), 4.98 (1H, brs), 4.83 (1H, t, *J* = 4.8 Hz), 4.46 (1H, d, *J* = 7.6 Hz), 3.99 – 3.94 (2H, m), 3.93 – 3.86 (1H, m), 3.85 – 3.80 (2H, m), 3.77 – 3.74 (1H, m), 3.65 – 3.58 (1H, m), 2.94 – 2.87 (1H, m), 2.81 – 2.73 (1H, m), 2.55 – 2.46 (1H, m), 2.24 – 2.03 (5H, m), 1.96 – 1.84 (1H, m), 1.79 – 1.74 (1H, m), 1.72 – 1.56 (2H, m), 1.43 (9H, s), 1.36 – 1.23 (4H, m), 0.97 (3H, d, *J* = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.0, 148.8, 146.9, 130.7, 110.8, 104.6, 79.9, 66.2, 64.4, 64.3, 60.8, 54.3, 52.7, 44.9, 41.2, 34.8, 31.7, 30.6, 29.3, 28.9, 28.0, 22.3, 18.8, 12.1; HRMS (ESIMS): calcd for $C_{26}H_{41}NO_5Na$ $[M+Na]^+$ 470.28769, found 470.28704.

(E)-3-(prop-1-enyl)cyclohex-2-enol (±)



A solution of the known cyclohexedione (200 mg, 1.470 mmol) in CH_2Cl_2: MeOH (1: 1, 10 mL) was cooled to 0 ºC and $CeCl_3 \cdot 7H_2O$ (725 mg, 0.2940 mmol), and $NaBH_4$ (67 mg, 1.763 mmol) were added in portions. After stirring for two hours, an aqueous saturated solution of NH_4Cl (15 mL) was added to the mixture, the biphasic mixture was separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The solvent was removed under reduced pressure without heating. Purification of the residue by flash chromatography (hexanes/Et_2O = 80/20) gave the title allylic alcohol (160 mg, 79%) as a colorless light oil. IR (neat): ν_{max} = 3294, 2930, 1448, 1034, 962 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 6.03 (1H, d, *J* = 15.6 Hz), 5.76 – 5.63 (1H, m), 5.61 (1H, s), 4.26 (1H, s), 2.20 – 2.01 (3H, m), 1.84 – 1.76 (2H, m), 1.76 (3H, d, *J* = 6.5 Hz), 1.65 – 1.48 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.0, 133.4, 127.8, 124.1, 65.8, 31.7, 24.1, 18.6, 17.9; HRMS (ESIMS): calcd for $C_9H_{14}ONa$ $[M+Na]^+$ 161.09369, found 161.09389.

Test dienyl tin ether (3.133)

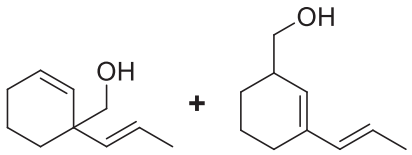


± (**3.133**)

To a suspension of KH in mineral oil (30%, 0.5 mL, 4.107 mmol) was slowly added a solution of the allylic alcohol reported above (85 mg, 0.616 mmol) in THF (3 mL) at r.t. under argon. After stirring for 1 h, the solution was cooled to 0 ºC and quenched very carefully with water (5 mL). The organic and aqueous phases were then separated, and the aqueous phase was further extracted with Et_2O (3 × 10 mL). The combined organic layers were then dried over Na_2SO_4, and the solvent was removed *in vacuo*. The residue was purified by flash chromatography (hexanes 100%) to give the tin ether (120 mg, 44%) as a

very light colorless liquid. R_f = 0.25 (hexanes), [$KMnO_4$]. IR (neat): ν_{max} = 2922, 1455, 1340, 1068, 962 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 6.08 (1H, d, *J* = 15.7 Hz), 5.73 – 5.66 (2H, m), 3.79 (2H, dd, *J* = 27.8, 10.0 Hz), 3.72 (1H, brs), 2.16 – 2.02 (2H, m), 1.88 – 1.79 (2H, m), 1.80 (3H, d, *J* = 6.4 Hz), 1.62 – 1.46 (8H, m), 1.41 – 1.27 (6H, m), 1.01 – 0.80 (15H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.8, 133.8, 126.3, 123.5, 77.6, 58.3, 28.8, 27.6, 27.0, 24.4, 19.0, 17.9, 13.4, 8.6; HRMS (ESIMS): calcd for $C_{22}H_{43}OSn$ $[M+H]^+$ 442.23359, found 442.23304.

Test dienyl [2,3] and [1,2] rearrangement product (3.134, 3.135)



± (**3.134**) ± (**3.135**)

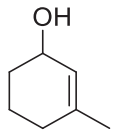
A solution of the tin ether **3.133** (45 mg, 0.1018 mmol) in dry THF (0.7 mL) was cooled to -78 ºC, maintained under argon and slowly treated with *n*BuLi (2.5 M in hexanes, 45 μL, 0.119 mmol). The reaction mixture was stirred as such for 4 h, after which an aqueous saturated solution of NH_4Cl (3 mL) was added, and the mixture was allowed to warp up to r.t. The biphasic mixture was separated and the aqueous phase was extracted with Et_2O (3 × 5 mL). The solvent was removed under reduced pressure without heating. Purification of the residue by flash chromatography (hexanes/Et_2O = 100/0 to 90/10 with 2.5% Et_2O increments) gave a mixture of the [2,3]-rearrangement product **3.134** (6 mg, 40%) and the [1,2]-rearrangement product **3.135** (5 mg, 33%), both as colorless oils.

[2,3]-rearrangement product (**3.134**): IR (neat): ν_{max} = 3294, 3014, 2930, 1447, 1032 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 5.89 – 5.80 (1H, m), 5.54 – 5.32 (3H, m), 3.50 – 3.37 (3H, m), 2.02 – 1.97 (1H, m), 1.63 (3H, d, *J* = 6.8 Hz), 1.59 – 1.49 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.4, 129.4, 129.3, 126.7, 69.6, 43.3, 30.6, 29.8, 25.1, 18.0; HRMS (ESIMS): calcd for $C_{10}H_{16}ONa$ $[M+Na]^+$ 175.10988, found 175.11047.

[1,2]-rearrangement product (**3.135**): IR (neat): ν_{max} = 3302, 2923, 2856, 1445, 1052 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 6.02 (1H, d, *J* = 15.6 Hz), 5.72 – 5.61 (1H, m), 5.53 (1H, s), 3.54 (2H, d, *J* = 6.3 Hz), 2.46 (1H, brs), 2.11 – 2.03 (2H, m), 1.82 – 1.73 (1H, m), 1.76

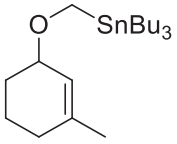
(3H, d, J = 6.5 Hz), 1.46 – 1.32 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.9, 134.3, 126.7, 122.6, 61.7, 38.9, 30.9, 25.6, 24.8, 18.2; HRMS (ESIMS): calcd for $C_{10}H_{16}ONa$ $[M+Na]^+$ 175.10988, found 175.10890.

3-methylcyclohex-2-enol (±)



A solution of the commercial 3-methylcyclohexenone (100 mg, 0.8922 mmol) in CH_2Cl_2: MeOH (1: 1, 8 mL) was cooled to 0 ºC and $CeCl_3 \cdot 7H_2O$ (440 mg, 1.817 mmol), and $NaBH_4$ (41 mg, 1.090 mmol) were added in portions. After stirring for two hours, an aqueous saturated solution of NH_4Cl (20 mL) was added to the mixture, the biphasic mixture was separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The solvent was removed under reduced pressure without heating. Purification of the residue by flash chromatography (hexanes/Et_2O = 80/20) gave the title allylic alcohol (96 mg, 96%) as a colorless light oil. R_f = 0.25 (hexanes/Et_2O = 80/20), [$KMnO_4$], not seen by UV. IR (neat): ν_{max} = 3294, 2930, 2860, 1448, 1034 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.47 (1H, s), 4.15 (1H, brs), 1.98 – 1.82 (3H, m), 1.76 – 1.66 (2H, m), 1.66 (3H, s), 1.59 – 1.51 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.0, 124.1, 65.8, 31.7, 24.1, 18.6, 17.9; HRMS (ESIMS): calcd for $C_9H_{14}ONa$ $[M+Na]^+$ 161.09369, found 161.09389.

Test tin ether (3.137)

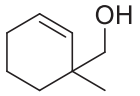


± (**3.137**)

A suspension of KH in mineral oil (30%, 1 mL) was slowly added a solution of the allylic alcohol reported above (100 mg, 0.8921 mmol) in 4 mL of THF at r.t. under argon. After stirring for 2 h, the solution was cooled to 0 ºC and quenched very carefully with water (10 mL). The organic and aqueous phases were then separated, and the aqueous phase was further extracted with Et_2O (3 × 10 mL). The combined organic layers were then dried over

Na_2SO_4, and the solvent was removed *in vacuo*. The residue was purified by flash chromatography (hexanes/EtOAc = 100/0 to 97.5/2.5) to give the tin ether **3.137** (250 mg, 68%) as a very light colorless liquid. R_f = 0.50 (hexanes), [$KMnO_4$], not seen by UV. IR (neat): ν_{max} = 2923, 2853, 1454, 1059 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 5.54 (1H, brs), 3.79 (2H, dd, *J* = 27.6, 10.0 Hz), 3.59 (1H, brs), 1.99 – 1.82 (2H, m), 1.77 – 1.67 (1H, m), 1.69 (3H, s), 1.65 – 1.42 (8H, m), 1.39 – 1.27 (6H, m), 1.01 – 0.83 (16H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.7, 122.2, 58.2, 30.0, 28.8, 27.1, 26.9, 26.5, 23.4, 19.1, 13.3, 8.6; HRMS (ESIMS): calcd for $C_{20}H_{40}ONa$ $[M+Na]^+$ 439.19934, found 439.19965.

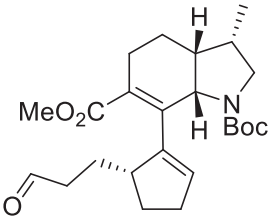
Test [2,3] rearrangement product (3.138)



± (**3.138**)

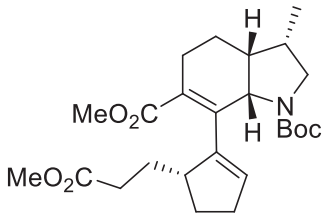
Typical procedure: a solution of the tin ether **3.137** (90 mg, 0.2162 mmol) in dry hexanes (1 mL) was cooled to -78 ºC, maintained under argon and slowly treated with *n*BuLi (2.5 M in hexanes, 105 μL). The reaction mixture was stirred as such for 30 min, after which the reaction mixture was allowed to warm up to -40 ºC and stirred for 8 h. An aqueous saturated solution of NH_4Cl (5 mL) was then added, the mixture was allowed to warp up to r.t. The biphasic mixture was separated and the aqueous phase was extracted with Et_2O (3 × 5 mL). The solvent was removed under reduced pressure without heating. Purification of the residue by flash chromatography (hexanes/Et_2O = 100/0 to 80/20 with 5% EtOAc increments) gave the intended [2,3]-rearrangement product **3.138** (13 mg, 48%) as a colorless oil. IR (neat): ν_{max} = 3343, 2929, 2865, 2351, 1674, 1461, 1041 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 5.85 – 5.77 (1H, m), 5.39 (1H, d, *J* = 10.0 Hz), 3.36 (2H, dd, *J* = 37.4, 10.5 Hz), 2.02 – 1.97 (2H, m), 1.77 – 1.56 (3H, m), 1.40 – 1.22 (2H, m), 0.96 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 132.4, 128.8, 71.1, 36.7, 31.2, 24.8, 23.9, 18.7; HRMS (ESIMS) could not be found due to the volatility of the product.

Tricyclic aldehyde (3.141)



The cyclic acetal **3.102** (390 mg, 0.846 mmol) was cooled to 0 ºC and dissolved in 1 N HCl and THF (1: 1, 8.5 mL). The reaction mixture was stirred as such for 14 h, after which it was cooled back to 0 ºC and slowly quenched upon addition of a saturated solution of $NaHCO_3$ (10 mL). The two phases were separated, and the aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (hexanes/EtOAc = 85/15) to give the stable aldehyde **3.141** (309 mg, 88%) as a colorless liquid. R_f = 0.5 (hexanes/EtOAc = 70/30), [UV], [$KMnO_4$], [CAM]. $[\alpha]_D^{20}$ –175.5 (*c* = 1.00, $CHCl_3$); IR (neat): ν_{max} = 3451, 2943, 1694, 1366, 1159 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 9.77 (1H, s), 5.45 (1H, brs), 4.59 (1H, d, *J* = 7.9 Hz), 3.74 – 3.68 (1H, m), 3.63 (3H, s), 3.14 – 3.06 (1H, m), 2.58 (1H, t, *J* = 12.1 Hz), 2.49 – 2.36 (4H, m), 2.31 – 2.03 (6H, m), 1.89 – 1.78 (1H, m), 1.77 – 1.67 (1H, m), 1.56 – 1.41 (2H, m), 1.41 (9H, s), 1.00 (3H, d, *J* = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 202.9, 170.0, 155.1, 144.8, 139.6, 134.0, 128.6, 78.8, 55.6, 51.8, 50.9, 45.8, 42.4, 38.0, 35.8, 31.0, 30.1, 28.0, 26.1, 24.3, 20.2, 12.8.; HRMS (ESIMS): calcd for $C_{24}H_{36}NO_5$ $[M+H]^+$ 418.25880, found 418.26082.

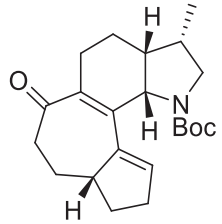
Tricyclic diester (3.142)



The protocol utilized herein is in all points similar to that used for the preparation of the diester **3.81**. The diester **3.142** was obtained in its pure form as a colorless oil (320 mg,

100% from 300 mg), without the need of chromatography. R_f = 0.6 (hexanes/EtOAc = 80/20), [UV], [$KMnO_4$]. $[\alpha]_D^{20}$ = -161.7 (*c* = 1.00, $CHCl_3$); IR (neat): ν_{max} = 2931, 1732, 1698, 1161 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 5.45 (1H, brs), 4.61 (1H, d, *J* = 7.8 Hz), 3.82 – 3.71 (1H, m), 3.67 (3H, s), 3.64 (3H, s), 3.14 – 3.05 (1H, m), 2.61 (1H, t, *J* = 12.1 Hz), 2.48 – 2.03 (10H, m), 1.90 – 1.80 (1H, m), 1.78 – 1.69 (1H, m), 1.58 – 1.41 (2H, m), 1.42 (9H, s), 1.02 (3H, d, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.2, 170.0, 155.1, 144.8, 139.8, 130.9, 128.4, 72.8, 55.6, 51.7, 51.1, 50.9, 46.0, 38.0, 35.8, 32.6, 31.0, 30.0, 29.0, 28.0, 24.5, 20.3, 12.7; HRMS (ESIMS): calcd for $C_{25}H_{37}NNaO_6$ $[M+Na]^+$ 470.25131, found 470.26264.

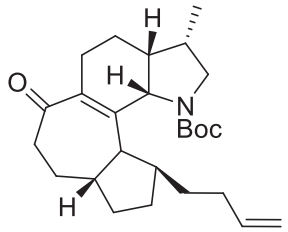
Tetracyclic enone (3.146)



The tricyclic diester **3.142** (90 mg, 0.2012 mmol) was dissolved in THF (20 mL, 0.01 M) and cooled to -78 °C, then slowly treated with NaHMDS (0.840 mL, 0.6M solution in toluene, 0.5030 mmol). The reaction mixture was stirred at -78 °C for 30 min, then left warming up slowly to r.t. for 20 min upon removal from the dry ice bath. It was then brought back to -78 °C and quenched with aqueous saturated NH_4Cl (10 mL), and the mixture was extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (hexanes/EtOAc = 80/20) to give the Dieckmann-product **3.146** as a colorless liquid. R_f = 0.6 (hexanes/EtOAc = 70/30), [UV], [$KMnO_4$]. Spectroscopic analysis suggests the product is obtained as a mixture of one major diastereomer, plus variable amounts of the enol tautomer. Without further purification, the tetracyclic β-ketoester was hence diluted in THF: H_2O (2: 1, 5 mL) and added KOH (112 mg, 2.012 mmol) at r.t. The reaction set was then equipped with a water condenser, and an overnight (12 h) reflux was carried on. The two phases were separated, and the aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, and the solvent was removed under reduced pressure. The residue was

purified by flash chromatography (hexanes/EtOAc = 90/10) to give the dienone **3.146** (40 mg, 62%, 2 steps) as a rather viscous colorless oil. R_f = 0.5 (hexanes/EtOAc = 80/20), [UV], [$KMnO_4$], [CAM] (feeble). $[\alpha]_D^{20}$ +115.0 (*c* = 1.00, $CHCl_3$); IR (neat): ν_{max} = 3459, 2931, 1694, 1391, 1162 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), δ = 5.89 (1H, brs), 4.45 (1H, d, *J* = 7.9 Hz), 3.63 (1H, brs), 3.04 (1H, brs), 2.95 (1H, dd, *J* = 10.9, 3.6 Hz), 2.62 – 2.40 (5H, m), 2.37 – 2.28 (2H, m), 2.18 – 2.09 (2H, m), 1.90 – 1.82 (1H, m), 1.70 – 1.61 (1H, m), 1.61 – 1.50 (2H, m), 1.40 (9H, s), 1.40 – 1.35 (1H, m), 0.96 (3H, d, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 203.5, 154.4, 142.6, 147.6, 137.8, 130.8, 78.9, 58.8, 53.4, 46.1, 44.5, 39.3, 36.4, 32.0, 30.2, 28.2, 27.3, 23.0, 20.0, 14.1; HRMS (ESIMS): calcd for $C_{22}H_{31}NO_3Na$ $[M+Na]^+$ 380.21961, found 380.22101.

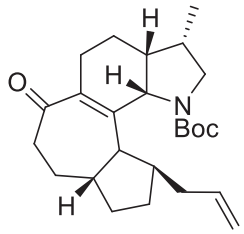
1,6-addition adduct (3.147)



The tetracyclic enone **3.146** (20 mg, 0.05590 mmol) was dissolved in THF (1 mL) and CuBr·DMS (3 mg, 0.0140 mmol) was added at r.t. The reaction mixture was stirred as such for 5 min, then cooled to -78 °C and slowly treated the yellowish solution with TMSCl (35 μL, 0.2795 mmol). After an additional 5 min, a solution of 3-butenyl-MgBr (0.5 M, 124 μL, 0.1120 mmol) was slowly added to the mixture to yield a bright orange-reddish solution. After 1 h, after which the reaction had turned green-grey, a saturated solution of NH_4Cl (5 mL) was added at -78 °C, and the mixture was extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (hexanes/EtOAc = 90/10) to give the 1,6-addition product **3.147** as a colorless liquid (13 mg, 64%). R_f = 0.6 (hexanes/EtOAc = 70/30), [UV], [$KMnO_4$], [CAM]. $[\alpha]_D^{20}$ +53.2 (*c* = 1.00, $CHCl_3$); IR (neat): ν_{max} = 3407, 2933, 1693, 1455, 1392 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), δ = 5.88 – 5.73 (1H, m), 5.05 (1H, d, *J* = 18.9 Hz), 5.00 (1H, d, *J* = 8.2 Hz), 4.37 (1H, d, *J* = 4.5 Hz), 3.71 (1H, brs), 3.13 (1H, t, *J* = 12.0 Hz), 3.03 – 2.89 (2H, m), 2.81

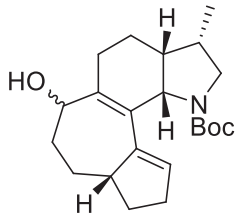
(1H, brs), 2.61 – 2.53 (1H, m), 2.34 – 2.10 (4H, m), 2.10 – 1.94 (2H, m), 1.92 – 1.82 (1H, m), 1.75 – 1.56 (6H, m), 1.47 (9H, s), 1.40 – 1.19 (4H, m), 0.96 (3H, d, J = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 203.9, 155.7, 143.4, 138.1, 129.2, 114.5, 79.1, 62.5, 54.4, 52.3, 45.6, 41.7, 37.3, 34.4, 33.3, 32.0, 31.8, 30.1, 29.3, 29.0, 27.1, 25.9, 21.8, 11.8; HRMS (ESIMS): calcd for $C_{26}H_{39}NO_3Na$ $[M+Na]^+$ 436.28358, found 436.28222.

Sakurai 1,6-addition adduct (3.151)



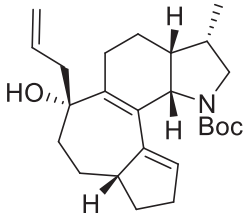
A solution of tetracyclic enone **3.146** (13 mg, 0.03359 mmol) in dry CH_2Cl_2 (0.7 mL) was maintained under argon, cooled to -78 °C and allyltrimethylsilane (10 μL, 0.05038 mmol) was added. The reaction mixture was stirred as such for 5 min, then added $TiCl_4$ (1.0 M in CH_2Cl_2, 44 μL) and stirred an additional 1 h at that temperature. Then, cold water was added to the mixture, and the aqeuous phase was extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (hexanes/EtOAc = 80/20) to give the 1,6-addition product **3.151** as a colorless liquid (11 mg, 82%). R_f = 0.4 (hexanes/EtOAc = 70/30), [UV], [$KMnO_4$], [CAM]. $[\alpha]_D^{20}$ +69.2 (c = 1.00, $CHCl_3$); IR (neat): ν_{max} = 2929, 1691, 1390, 1333, 1167, 1117 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.73 – 5.67 (1H, m), 4.96 (1H, s), 4.94 (1H, d, J = 12.0 Hz), 4.33 (1H, d, J = 4.0 Hz), 3.62 (1H, brs), 3.05 (1H, t, J = 8.0 Hz), 2.99 – 2.84 (2H, m), 2.72 (1H, brs), 2.53 – 2.37 (2H, m), 2.28 – 2.11 (3H, m), 2.00 – 1.85 (4H, m), 1.85 – 1.74 (1H, m), 1.67 – 1.52 (4H, m), 1.39 (9H, s), 1.26 – 1.14 (2H, m), 0.88 (3H, d, J = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 204.0, 154.6, 143.0, 137.2, 130.2, 116.0, 62.9, 54.8, 52.7, 42.2, 39.0, 37.8, 37.5, 34.8, 32.2, 31.6, 28.6, 27.5, 26.3, 22.7, 22.2, 14.5, 12.0; HRMS (ESIMS): calcd for $C_{25}H_{37}NO_3Na$ $[M+Na]^+$ 422.26657, found 422.26743.

Tetracyclic allylic alcohol (3.157)



Typical procedure: To a solution of the tetracyclic dienone **3.146** (20 mg, 0.0560 mmol) in MeOH: CH_2Cl_2 (1: 1, 1 mL) was added $CeCl_3 \cdot 7H_2O$ (28 mg, 0.1120 mmol), and, after cooling to -78 ºC, $NaBH_4$ (3 mg, 0.0672 mmol). After 2 h, the reaction mixture was added an aqueous saturated solution of NH_4Cl (10 mL) and the mixture was allowed to warp up to r.t. The biphasic mixture was separated and the aqueous phase was extracted with EtOAc (3 × 5 mL). The solvent was removed under reduced pressure, and the residue was purified by flash chromatography (hexanes/EtOAc = 70/30) to give the unseperable diastereomeric mixture of secondary alcohols **3.157** as a colorless liquid (17 mg, 84%). R_f = 0.3 (hexanes/EtOAc = 70/30), [UV], [$KMnO_4$], [CAM]. No optical measurements were recorded since dealing with a diastereomeric mixture; IR (neat): ν_{max} = 3371, 2932, 1686, 1395, 1165 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 5.53 (1H, brs), 4.32 (1H, brs), 4.30 (1H, d, *J* = 8.2 Hz), 4.06 (1H, brs), 3.71 (1H, brs), 2.81 (1H, m), 2.66 (1H, brs), 2.49 – 2.32 (2H, m), 2.31 – 2.14 (3H, m), 2.13 – 2.00 (2H, m), 1.81 – 1.46 (7H, m), 1.47 (9H, s), 1.02 (3H, d, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) was attempted, but doesn't allow clear interpretation due to the mixture of isomers, added to the usual presence of rotamers; HRMS (ESIMS): calcd for $C_{22}H_{33}NO_3Na$ $[M+Na]^+$ 382.23527, found 382.23600.

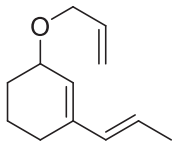
Triene (3.164)



Under argon and in a flame-dried flask, the α,β-unsaturated ketone **3.146** (17 mg, 0.04758 mmol) was dissolved in dry THF (1 mL) and a commercial solution of $LaCl_3 \cdot 2LiCl$ (0.6

M in THF, 80 μL, 0.04758 mmol) was added at r.t. The mixture was allowed to stir as such for 1 h, then it was cooled to -78 °C and added allylMgBr (1.0 M in Et_2O, 71 μL, 0.07134 mmol) dropwise. The resulting brownish solution was stirred at -78 °C for 1 h, then quenched at -78 °C with aqueous saturated NH_4Cl (5 mL). The biphasic mixture was separated slowly by adding brine, and the aqueous phase was extracted with EtOAc (3 × 5 mL). The solvent was removed under reduced pressure. Purification of the residue by flash chromatography (hexanes/EtOAc = 70/30) gave the title compound as a single diastereomer (17 mg, 89%) and as a colorless oil, very sensitive to acid (even to prolonged exposure to chloroform, neutralized or else). R_f = 0.3 (hexanes/EtOAc = 70/30), [UV], [$KMnO_4$], [CAM]. $[\alpha]_D^{20}$ +32.2 (*c* = 1.00, $CHCl_3$); IR (neat): ν_{max} = 3444, 2932, 1673, 1393, 1162 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 5.76 – 5.58 (1H, m), 5.29 (1H, brs), 5.13 – 4.89 (3H, m), 4.17 (1H, brs), 3.74 (2H, brs), 2.87 – 2.70 (2H, m), 2.51 – 2.21 (6H, m), 2.07 – 1.93 (1H, m), 1.89 – 1.66 (3H, m), 1.65 – 1.43 (4H, m), 1.37 (9H, s), 0.98 – 0.87 (1H, m), 0.89 (3H, d, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.1, 149.7, 136.9, 136.6, 131.2, 130.0, 113.7, 79.6, 71.5, 59.8, 53.0, 47.6, 43.1, 40.1, 38.4, 35.0, 34.8, 30.7, 27.7, 26.2, 20.4, 12.2; ESIMS: calcd for $C_{25}H_{37}NNaO_3$ $[M+Na]^+$ 422.2, found 422.2.

Test triene (3.177)

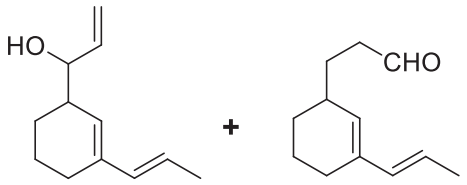


± (**3.177**)

A solution of corresponding allylic alcohol (75 mg, 0.5431 mmol) in THF (3 mL) was cooled to 0 °C and treated with KHMDS (0.5 M in toluene, 130 μL, 0.6517 mmol) under argon. After five minutes, allyl iode (75 μL, 0.8147 mmol) was added at the same temperature and the mixture was allowed to stir for two hours. The reaction mixture was quenched at 0 °C with a saturated solution of NH_4Cl (5 mL). The biphasic mixture was separated and the aqueous phase was extracted with Et_2O (3 × 20 mL). The solvent was removed under reduced pressure without heating. Purification of the residue by flash chromatography (hexanes/Et_2O = 100/0 to 95/5) gave the title compound (65 mg, 71%) as

a colorless light oil. R_f = 0.6 (hexanes/EtOAc = 95/5) [$KMnO_4$]. IR (neat): ν_{max} = 2930, 1645, 1374, 1339, 1076 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 6.05 (1H, d, *J* = 17.4 Hz), 6.00 – 5.85 (1H, m), 5.73 – 5.65 (2H, m), 5.28 (1H, d, *J* = 17.2 Hz), 5.14 (1H, d, *J* = 10.3 Hz), 4.05 – 3.96 (3H, m), 2.19 – 2.04 (2H, m), 1.86 – 1.75 (2H, m), 1.76 (3H, d, *J* = 6.4 Hz), 1.66 – 1.51 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.8, 135.5, 133.9, 126.0, 124.2, 116.5, 73.0, 69.1, 28.6, 24.7, 19.3, 18.3; HRMS (ESIMS) could not be found due to the volatility of the product.

Wittig-rearrangement products from test triene (3.178, 3.179)



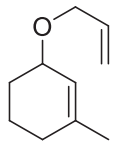
± (**3.178**) ± (**3.179**)

A solution of the bis-allylether **3.177** (30 mg, 0.1685 mmol) in dry THF (1 mL) was cooled to -78 ºC, maintained under argon and slowly treated with *n*BuLi (2.5 M in hexanes, 80 μL, 0.02021 mmol). The reaction mixture was stirred as such for 4 h, after which an aqueous saturated solution of NH_4Cl (5 mL) was added, and the mixture was allowed to warm up to r.t. The biphasic mixture was separated and the aqueous phase was extracted with Et_2O (3 × 5 mL). The solvent was removed under reduced pressure without heating. Purification of the residue by flash chromatography (hexanes/Et_2O = 100/0 to 90/10 with 2.5% EtOAc increments) gave a mixture of the [1,2]-rearrangement product **3.178** (14 mg, 45%) and the [1,4]-rearrangement product **3.179** (5 mg, 17%), both colorless oils.

[1,2]-rearrangement product (**3.178**): IR (neat): ν_{max} = 3359, 2928, 1447, 963 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 6.10 (1H, d, *J* = 15.4 Hz), 5.95 – 5.86 (1H, m), 5.69 – 5.60 (2H, m), 5.28 (1H, d, *J* = 17.2 Hz), 5.19 (1H, d, *J* = 10.5 Hz), 4.01 (1H, brs), 3.42 – 3.34 (1H, m), 2.24 – 2.00 (2H, m), 1.95 – 1.80 (1H, m), 1.77 (3H, d, *J* = 6.3 Hz), 1.66 – 1.48 (2H, m), 1.43 – 1.25 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.8, 138.4, 134.5, 125.6, 122.5, 115.3, 76.4, 41.9, 25.6, 24.7, 21.6, 18.2; HRMS (ESIMS): calcd for $C_{12}H_{18}ONa$ $[M+Na]^+$ 201.12499, found 201.12436.

[1,4]-rearrangement product (**3.179**): IR (neat): ν_{max} = 2927, 1724, 1447, 963 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 9.81 (1H, s), 6.05 (1H, d, *J* = 15.2 Hz), 5.53 – 5.54 (1H, m), 5.47 (1H, s), 2.50 (2H, t, *J* = 1.8 Hz), 2.24 – 2.01 (3H, m), 1.82 – 1.47 (6H, m), 1.76 (3H, d, *J* = 6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 202.4, 136.0, 134.0, 129.6, 122.0, 41.0, 34.8, 28.4, 27.8, 24.3, 21.0, 17.9; HRMS (ESIMS): calcd for $C_{12}H_{19}O$ $[M+H]^+$ 179.14304, found 179.14223.

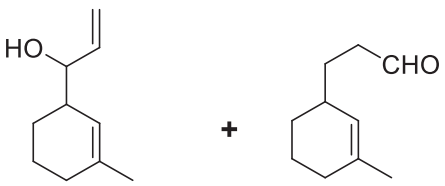
Test diene (3.180)



± (**3.180**)

A solution of corresponding allylic alcohol (100 mg, 0.8920 mmol) in THF (5 mL) was cooled to 0 °C and treated with portions of NaH (60% in mineral oil, 42 mg, 1.07 mmol) under argon. After five minutes, allyl iode (122 μL, 1.338 mmol) was added at the same temperature and the mixture was allowed to stir for two hours. The reaction was quenched at 0 °C with a saturated solution of NH_4Cl (5 mL). The biphasic mixture was separated and the aqueous phase was extracted with Et_2O (3 × 20 mL). The solvent was removed under reduced pressure without heating. Purification of the residue by flash chromatography (hexanes/Et_2O = 95/5) gave the title compound (110 mg, 82%) as a colorless light oil. IR (neat): ν_{max} = 2932, 2859, 1449, 1080 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 5.99 – 5.84 (1H, m), 5.53 (1H, s), 5.28 (1H, d, *J* = 17.2 Hz), 5.15 (1H, d, *J* = 11.3 Hz), 4.07 – 3.86 (2H, m), 3.87 (1H, brs), 2.00 – 1.80 (2H, m), 1.79 – 1.62 (3H, m), 1.74 (3H, s), 1.60 – 1.49 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.9, 135.6, 122.2, 116.3, 72.7, 69.1, 30.2, 28.0, 23.7, 19.3; HRMS (ESIMS) could not be found due to the volatility of the product.

Wittig-rearrangement products from test diene (3.181, 3.182)



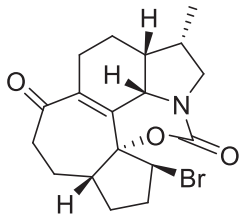
± (**3.181**) ± (**3.182**)

A solution of the bis-allylether **3.180** (40 mg, 0.2630 mmol) in dry THF (1.5 mL) was cooled to -78 °C, maintained under argon and slowly treated with *n*BuLi (2.5 M in hexanes, 125 μL, 0.3156 mmol). The reaction mixture was stirred as such for 4 h, after which an aqueous saturated solution of NH_4Cl (5 mL) was added, and the mixture was allowed to warp up to r.t. The biphasic mixture was separated and the aqueous phase was extracted with Et_2O (3 × 5 mL). The solvent was removed under reduced pressure without heating. Purification of the residue by flash chromatography (hexanes/Et_2O = 100/0 to 90/10 with 2.5% EtOAc increments) gave a mixture of the [1,2]-rearrangement product **3.181** (15 mg, 45%) and the [1,4]-rearrangement product **3.182** (4 mg, 12%), both colorless oils.

[1,2]-rearrangement product (**3.181**): IR (neat): ν_{max} = 3329, 2925, 2857, 1448, 916 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 5.96 – 5.86 (1H, m), 5.42 (1H, brs), 5.28 (1H, d, *J* = 17.2 Hz), 5.19 (1H, d, *J* = 10.5 Hz), 4.01 (1H, brs), 2.27 (1H, brs), 2.00 – 1.84 (2H, m), 1.84 – 1.70 (2H, m), 1.71 (3H, s), 1.66 – 1.48 (2H, m), 1.43 – 1.30 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.7, 137.4, 119.8, 114.6, 76.0, 41.0, 29.8, 25.1, 23.8, 21.6; HRMS (ESIMS): calcd for $C_{10}H_{17}O$ $[M+H]^+$ 153.12739, found 153.12689.

[1,4]-rearrangement product (**3.182**): ^1H NMR (400 MHz, $CDCl_3$): δ = 9.80 (1H, s), 5.26 (1H, s), 2.50 (2H, t, *J* = 1.8 Hz), 2.19 – 1.82 (3H, m), 1.77 – 1.47 (6H, m), 1.67 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 203.0, 135.1, 124.9, 41.5, 34.8, 30.1, 28.5, 28.5, 23.8, 21.7; HRMS (ESIMS): calcd for $C_{10}H_{16}ONa$ $[M+Na]^+$ 175.10934, found 175.11004.

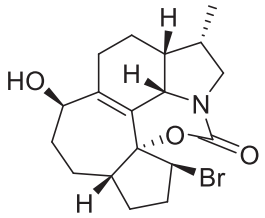
Pentacyclic bromocarbamate (3.183)



The tetracyclic enone **3.146** (14 mg, 0.0392 mmol) was dissolved in $CHCl_3$ (1 mL) and a standard solution of bromine in $CHCl_3$ (equivalent to 1.1 eq.) was added drop-wisely at -40 °C. The reaction mixture turned brownish almost instantaneously and was allowed to

stir for a further 20 min. Then, a saturated solution of NaS_2O_3 (5 mL) was added and the mixture was allowed to warm up to r.t. The phases were separated, and the aqueous phase was further extracted with EtOAc (3 × 5 mL). The combined organic layers were dried over Na_2SO_4, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (hexanes/EtOAc = 90/10) to give the pentacyclic bromocarbamate **3.183** as white crystals (13 mg, 88%). R_f = 0.3 (hexanes/EtOAc = 30/70), [UV] (feeble), [$KMnO_4$] (feeble), [CAM]. $[\alpha]_D^{20}$ –6.2 (*c* = 1.00, $CHCl_3$); IR (neat): ν_{max} = 3434, 2939, 1694, 1410 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 4.53 (1H, d, *J* = 6.7 Hz), 4.17 (1H, d, *J* = 4.7 Hz), 3.65 (1H, dd, *J* = 10.9, 8.6 Hz), 3.18 (1H, d, *J* = 11.1 Hz), 2.82 – 2.65 (4H, m), 2.64 – 2.55 (1H, m), 2.52 – 2.42 (1H, m), 2.34 – 2.10 (5H, m), 1.99 – 1.87 (1H, m), 1.81 – 1.70 (2H, m), 1.11 (3H, d, *J* = 6.9 Hz), 1.12 – 1.04 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 206.6, 154.9, 140.6, 128.0, 93.6, 55.5, 54.9, 51.6, 42.1, 41.4, 40.8, 33.5, 31.8, 27.5, 27.0, 22.3, 18.5, 17.3, 12.0; HRMS (ESIMS): calcd for $C_{18}H_{23}BrNO_3$ $[M+H]^+$ 380.08558, found 380.08411.

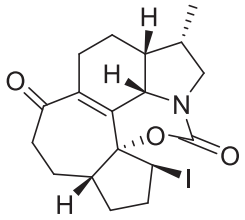
Bromohydrin (3.187)



A solution of the bromocarbamate **3.183** (5 mg, 0.0132 mmol) in THF (1 mL) was cooled to -78 °C, maintained under argon and slowly treated with Super-Hydride® (1.0 M in THF, 29μL, 0.0290 mmol). After 30 min, the reaction mixture was added an aqueous saturated solution of NH_4Cl (5 mL) and the mixture was allowed to warp up to r.t. The biphasic mixture was separated and the aqueous phase was extracted with EtOAc (3 × 5 mL). The solvent was removed under reduced pressure, and purification of the residue by flash chromatography (hexanes/Et_2O = 25/75) gave the allylic alcohol **3.187** as a single diastereomer and as a colorless oil (5 mg, 100%). R_f = 0.3 (hexanes/EtOAc = 20/80), [UV] (feeble), [$KMnO_4$], [CAM]. $[\alpha]_D^{20}$ +17.8 (*c* = 1.00, $CHCl_3$); IR (neat): ν_{max} = 3416, 2926,

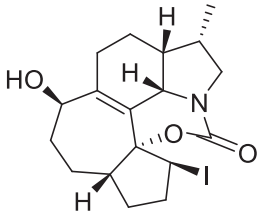
2348, 1683, 780 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 4.58 (1H, d, *J* = 6.8 Hz), 4.35 (1H, brs), 4.12 (1H, d, *J* = 5.9 Hz), 3.90 – 3.82 (1H, m), 3.60 (1H, dd, *J* = 10.9, 8.6 Hz), 3.16 (1H, t, *J* = 11.2 Hz), 2.78 – 2.66 (1H, m), 2.61 – 2.47 (2H, m), 2.29 – 2.00 (5H, m), 1.97 – 1.74 (5H, m), 1.71 – 1.62 (1H, m), 1.10 (3H, d, *J* = 6.9 Hz), 1.09 – 0.98 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.7, 144.1, 125.3, 94.6, 74.9, 56.5, 56.0, 51.4, 40.9, 38.0, 33.5, 32.7, 31.9, 29.1, 27.7, 19.9, 18.6, 12.2; HRMS (ESIMS): calcd for $C_{18}H_{24}BrNO_3Na$ $[M+Na]^+$ 404.08318, found 404.08314.

Iodocarbamate (3.190)



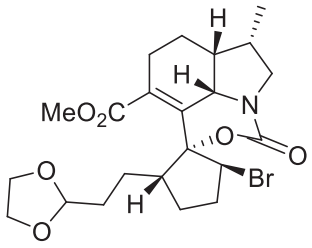
The tetracyclic enone **3.146** (20 mg, 0.05598 mmol) was dissolved in $CHCl_3$ (1 mL) and a standard solution of iodine in $CHCl_3$ (equivalent to 1.1 eq.) was added drop-wisely at -40 ºC. The reaction mixture was allowed to stir for a further 1 h. Then, a saturated solution of NaS_2O_3 (5 mL) was added and the mixture was allowed to warm up to r.t. The phases were separated, and the aqueous phase was further extracted with EtOAc (3 × 5 mL). The combined organic layers were dried over Na_2SO_4, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (hexanes/EtOAc = 90/10) to give the tetracyclic bromocarbamate **3.190** as a colorless oil (5 mg, 21%, 32% bsmr). R_f = 0.3 (hexanes/EtOAc = 70/30), [UV] (feeble), [$KMnO_4$], [CAM]. $[\alpha]_D^{20}$ +10.4 (*c* = 0.40, $CHCl_3$); IR (neat): ν_{max} = 2932, 1703, 1414, 1091 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 4.57 (1H, d, *J* = 6.9 Hz), 4.10 (1H, d, *J* = 6.0 Hz), 3.66 (1H, dd, *J* = 10.8, 8.6 Hz), 3.16 (1H, t, *J* = 11.1 Hz), 2.93 – 2.83 (2H, m), 2.79 – 2.62 (2H, m), 2.65 – 2.55 (1H, m), 2.54 – 2.43 (1H, m), 2.42 – 2.24 (3H, m), 2.22 – 2.10 (3H, m), 1.81 – 1.70 (2H, m), 1.11 (3H, d, *J* = 6.9 Hz), 1.12 – 1.00 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 206.5, 152.0, 140.3, 128.6, 93.9, 55.5, 51.6, 42.1, 41.6, 40.8, 33.5, 33.4, 29.3, 27.8, 26.9, 18.5, 17.7, 12.0; HRMS (ESIMS): calcd for $C_{18}H_{22}INO_3Na$ $[M+Na]^+$ 450.05366, found 450.05340.

Iodohydrin (3.191)



A solution of the iodocarbamate **3.190** (4 mg, 0.01120 mmol) in CH_2Cl_2 (1 mL) was cooled to -78 °C, maintained under argon and slowly treated with $NaBH_4$ (1 mg, 0.01345 mmol). After 30 min, the reaction mixture was added an aqueous saturated solution of NH_4Cl (10 mL) and the mixture was allowed to warp up to r.t. The biphasic mixture was separated and the aqueous phase was extracted with EtOAc (3 × 5 mL). The solvent was removed under reduced pressure, and purification of the residue by flash chromatography (hexanes/Et_2O = 25/75) gave the allylic alcohol **3.191** as a single diastereomer and as a colorless oil (4 mg, quant.). R_f = 0.3 (hexanes/EtOAc = 20/80), [UV] (feeble), [$KMnO_4$], [CAM]. $[\alpha]_D^{20}$ –16.8 (*c* = 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.62 (1H, d, *J* = 6.8 Hz), 4.36 (1H, brs), 4.08 (1H, d, *J* = 5.2 Hz), 4.05 – 3.96 (1H, m), 3.58 (1H, dd, *J* = 10.9, 8.6 Hz), 3.17 (1H, t, *J* = 11.2 Hz), 2.88 – 2.80 (1H, m), 2.63 – 2.49 (2H, m), 2.46 – 2.36 (1H, m), 2.23 – 2.02 (5H, m), 1.97 – 1.76 (4H, m), 1.71 – 1.62 (1H, m), 1.10 (3H, d, *J* = 6.9 Hz), 1.09 – 0.98 (1H, m); HRMS (ESIMS): calcd for $C_{18}H_{24}INNaO_3$ $[M+Na]^+$ 452.06931, found 452.06934.

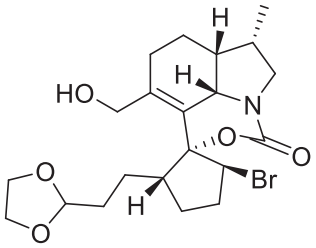
Tetracyclic bromocarbamate (3.195)



The tricyclic ester **3.102** (22 mg, 0.06504 mmol) was dissolved in $CHCl_3$ (1 mL) and a standard solution of bromine in $CHCl_3$ (equivalent to 1.1 eq.) was added drop-wisely at -40 °C. The reaction mixture turned brownish almost instantaneously and was allowed to stir for a further 20 min. Then, a saturated solution of NaS_2O_3 (5 mL) was added and the mixture was allowed to warm up to r.t. The phases were separated, and the aqueous phase

was further extracted with EtOAc (3 × 5 mL). The combined organic layers were dried over Na_2SO_4, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (hexanes/EtOAc = 20/80) to give the tetracyclic bromocarbamate **3.195** as a colorless oil (18 mg, 82%). R_f = 0.25 (hexanes/EtOAc = 30/70), [UV] (feeble), [$KMnO_4$] (feeble), [CAM]. $[\alpha]_D^{20}$ –12.6 (*c* = 1.00, $CHCl_3$); IR (neat): ν_{max} = 2927, 1708, 1413, 1259 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 4.81 (1H, t, *J* = 4.7 Hz), 4.52 (1H, d, *J* = 6.6 Hz), 4.07 (1H, d, *J* = 6.0 Hz), 4.00 – 3.91 (2H, m), 3.84 – 3.76 (2H, m), 3.83 (3H, s), 3.67 (1H, dd, *J* = 10.6, 8.3 Hz), 3.07 (1H, t, *J* = 11.0 Hz), 2.78 – 2.51 (4H, m), 2.30 – 2.14 (4H, m), 1.68 – 1.43 (6H, m), 1.17 – 1.06 (1H, m), 1.10 (3H, d, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.8, 151.3, 133.4, 126.2, 104.5, 96.5, 64.8, 57.9, 55.5, 52.5, 50.9, 41.7, 41.5, 34.0, 33.0, 32.5, 29.8, 28.3, 24.3, 18.4, 12.4; HRMS (ESIMS): calcd for $C_{22}H_{30}BrNO_6$ $[M+H]^+$ 506.11487, found 506.11504.

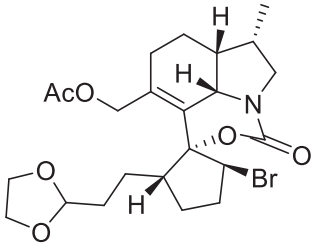
Tetracyclic bromohydrin (3.198)



A solution of the α,β-unsaturated ester **3.195** (19 mg, 0.03933 mmol) in dry CH_2Cl_2 (1 mL) was cooled to -78 °C and maintained under argon, and slowly treated with DIBAL-H (1.5 M in toluene, 80 μL, 0.1180 mmol). After 1 h, saturated aqueous solutions of NH_4Cl (5 mL) and Rochelle salt (5 mL) were added and left stirring over warming up of the mixture, until the organic and aqueous phases were separated. The aqueous phase was then exctrated with CH_2Cl_2 (3 × 5 mL). The combined organic layers were then dried over Na_2SO_4, and the solvent was removed *in vacuo*. The residue was purified by flash chromatography (EtOAc) to give the allylic alcohol **3.198** (14 mg, 79%) as a colorless liquid. R_f = 0.2 (EtOAc), [$KMnO_4$], [CAM]. $[\alpha]_D^{20}$ –42.0 (*c* = 1.00, $CHCl_3$); IR (neat): ν_{max} = 3409, 2349, 1694, 1427, 766 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 4.81 (1H, t, *J* = 4.7 Hz), 4.55 (1H, brs), 4.58 (1H, d, *J* = 6.8 Hz), 4.03 – 3.95 (2H, m), 3.92 (1H, brs), 3.91 – 3.83 (2H, m), 3.82 (1H, brs), 3.63 (1H, t, *J* = 6.1 Hz), 3.09 – 2.93 (3H, m), 2.84 – 2.76 (2H, m), 2.59 –

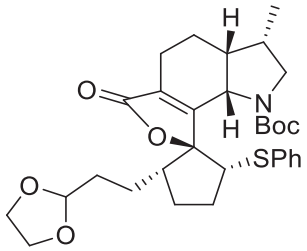
2.50 (1H, m), 2.24 – 2.16 (3H, m), 2.08 – 1.92 (2H, m), 1.84 – 1.57 (5H, m), 1.12 (3H, d, J = 6.8 Hz), 1.13 – 1.00 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.9, 141.0, 121.5, 104.0, 97.9, 64.9, 64.9, 60.5, 58.5, 56.5, 50.6, 43.8, 42.5, 34.3, 32.7, 32.1, 28.7, 27.9, 23.0, 18.6, 12.5; HRMS (ESIMS): calcd for $C_{21}H_{30}BrNNaO_5$ $[M+Na]^+$ 478.11996, found 478.12047.

Tricyclic bromo-acetate (3.203)



A solution of the allylic alcohol **3.198** (5 mg, 0.01318 mmol) in CH_2Cl_2 (0.5 mL) was cooled to 0 ºC and DMAP (cat.), NEt_3 (10 μL, 0.06590 mmol), and Ac_2O (4 μL, 0.03955 mmol) were added. The reaction mixture was allowed to warm up to r.t. and stirred for 1 h, after which full conversion could be observed. The reaction mixture was then quenched with a 1 N HCl solution (5 mL), the aqueous and organic phases were separated and the aqueous phase was further extracted with EtOAc (3 × 5 mL). The residue was purified by flash chromatography (hexanes/EtOAc = 20/80) to give the acetate **3.203** (4 mg, 74%) as a colorless liquid. R_f = 0.25 (hexanes/EtOAc = 20/80), [UV], [$KMnO_4$]. $[\alpha]_D^{20}$ –12.1 (c = 0.4, $CHCl_3$); IR (neat): ν_{max} = 2941, 1713, 1417, 1238 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.85 (1H, d, J = 8.6 Hz), 4.83 (1H, brs), 4.70 (1H, d, J = 12.6 Hz), 4.56 (1H, d, J = 6.4 Hz), 3.99 – 3.95 (1H, m), 3.97 – 3.92 (2H, m), 3.86 – 3.81 (2H, m), 3.68 (1H, dd, J = 10.7, 8.4 Hz), 3.06 (1H, t, J = 11.0 Hz), 2.97 – 2.85 (1H, m), 2.80 – 2.73 (1H, m), 2.59 – 2.50 (1H, m), 2.50 – 2.41 (1H, m), 2.27 – 2.17 (3H, m), 2.12 (3H, m), 1.85 – 1.71 (2H, m), 1.71 – 1.47 (5H, m), 1.10 (3H, d, J = 6.8 Hz), 1.13 – 1.02 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.6, 151.3, 135.1, 124.8, 103.9, 97.2, 64.4, 64.4, 62.7, 58.1, 56.1, 50.2, 43.5, 41.9, 33.8, 32.3, 31.9, 29.0, 27.7, 22.9, 20.5, 18.2, 12.1; HRMS (ESIMS): calcd for $C_{23}H_{32}[^{79}Br]NNaO_6$ $[M+Na]^+$ 520.13052, found 520.13040.

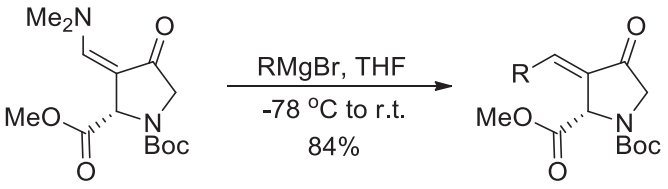
Tetracyclic lactone (3.206)



A freshly prepared solution of PhSCl in THF (1.0 M in CH_2Cl_2, 33 μL, 0.03252 mmol) was slowly added to the tricyclic ester **3.102** (15 mg, 0.03252 mmol) at -40 °C under argon. The conversion was found to be complete after only 20 min. Then, a saturated solution of NH_4Cl (5 mL) was added at that temperature and the mixture was allowed to warm up to r.t. The phases were separated, and the aqueous phase was further extracted with EtOAc (3 × 5 mL). The combined organic layers were dried over Na_2SO_4, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (hexanes/EtOAc = 90/10 to 75/25 with 5% EtOAc increments) to give the tetracyclic lactone **3.206** as a colorless oil (14 mg, 78%). R_f = 0.4 (hexanes/EtOAc = 30/70), [UV] (feeble), [$KMnO_4$] (feeble), [CAM]. $[\alpha]_D^{20}$ –119.4 (*c* = 1.00, $CHCl_3$); IR (neat): ν_{max} = 2932, 1757, 1687, 1390, 1159 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.49 (2H, d, *J* = 7.2 Hz), 7.24 (2H, t, *J* = 7.6 Hz), 7.19 – 7.14 (1H, m), 4.90 (1H, dd, *J* = 12.4, 6.4 Hz), 4.79 (1H, t, *J* = 4.0 Hz), 4.36 (1H, t, *J* = 6.0 Hz), 3.96 – 3.89 (2H, m), 3.84 – 3.76 (2H, m), 3.76 (1H, m), 2.66 (1H, t, *J* = 10.4 Hz), 2.54 – 2.48 (1H, m), 2.46 – 2.32 (2H, m), 2.14 – 2.05 (2H, m), 1.92 – 1.78 (4H, m), 1.73 – 1.60 (3H, m), 1.49 (9H, s), 1.46 – 1.34 (3H, m), 0.98 (3H, d, *J* = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.6, 160.5, 156.3, 135.2, 134.0, 131.6, 128.7, 126.6, 104.1, 99.4, 80.3, 64.9, 64.9, 54.6, 52.7, 50.6, 40.8, 37.2, 36.3, 33.0, 32.9, 39.9, 28.5, 24.9, 20.4, 19.7, 12.7; HRMS (ESIMS): calcd for $C_{31}H_{41}NNaO_6S$ $[M+Na]^+$ 578.125468, found 578.25508.

Annexe II – Partie expérimentale relative à la transposition allylique réductrice

Pyrrolidones (4.33a-i)



Typical procedures: under argon and in a flame-dried flask, a solution of the enaminone **3.76** (1.98 g, 6.75 mmol) in dry THF (40 mL) was cooled to -78 °C and treated with MeMgBr (3.37, 3.0 M in Et_2O, 10.12 mmol) dropwise. After stirring 1 h, the dry ice bath was removed and the reaction was allowed to warm to room temperature. It was stirred for 30 min at this temperature before a saturated aqueous solution of NH_4Cl (50 mL) was added slowly. The red biphasic mixture was separated and the aqueous phase was extracted with EtOAc (3 × 25 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure. Purification of the residue by flash chromatography (hexanes/EtOAc = 70/30) gave the desired enones (1.35g, 75%) as thick colorless oils.

For R = Me: $[\alpha]_D^{20}$ +80.1 (*c* = 1.00, $CHCl_3$); IR (neat): ν_{max} = 2978, 1747, 1705, 1394, 1167 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), mixture of rotamers: δ = 6.91 – 6.85 (1H, q, *J* = 7.2 Hz), 4.26 – 4.17 (1H, 2s), 4.03 – 3.88 (2H, m), 3.71 – 3.70 (3H, 2s), 1.99 – 1.97 (3H, d, *J* = 7.2 Hz), 1.44 – 1.42 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$), mixture of rotamers: δ = 196.5, 195.8, 169.9, 153.9, 153.0, 141.1, 137.7, 137.5, 132.4, 132.2, 80.8, 59.8, 59.1, 52.9, 52.5, 52.1, 52.0, 27.8, 15.0, 14.9; HRMS (ESIMS): calcd for $C_{13}H_{19}NO_5Na$ $[M+Na]^+$ 292.11652, found 292.11554.

For R = 4-OMe-phenyl: $[\alpha]_D^{20}$ +130.0 (*c* = 1.00, $CHCl_3$); IR (neat): ν_{max} = 1706, 1598, 1396, 1259, 1162 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), mixture of rotamers: δ = 7.77 (2H, d, *J* = 7.2 Hz), 7.48 (1H, d, *J* = 4.4 Hz), 6.98 – 6.89 (2H, m), 5.61 (1H, d, *J* = 53.6 Hz), 4.06 – 3.92 (2H, m), 3.82 (3H, s), 3.64 (3H, s), 1.47 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$), mixture of rotamers: δ = 198.0, 197.3, 169.8, 169.7, 161.9, 154.0, 153.1, 137.2, 136.9, 133.6, 126.6,

125.5, 125.2, 124.6, 114.1, 114.0, 81.0, 80.9, 67.5, 61.0, 60.2, 55.0, 52.1, 51.6, 27.9, 25.2; HRMS (ESIMS): calcd for $C_{19}H_{23}NO_6Na$ $[M+Na]^+$ 384.14176, found 384.14056.

For R = phenyl: $[\alpha]_D^{20}$ +143.8 (*c* = 1.00, $CHCl_3$); IR (neat): ν_{max} = 1707, 1629, 1396, 1162 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), mixture of rotamers: δ = 7.80 (2H, brs), 7.47 (1H, brs), 7.50 – 7.42 (3H, m), 5.69 (1H, d, *J* = 62.5 Hz), 4.06 – 3.99 (2H, m), 3.66 (3H, s), 1.50 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$), mixture of rotamers: δ = 198.2, 197.5, 169.7, 169.5, 153.9, 153.1, 137.4, 137.2, 132.0, 131.2, 131.0, 131.0, 128.6, 128.5, 128.4, 128.1, 81.2, 81.1, 60.8, 60.1, 52.2, 52.2, 52.0, 51.6, 36.2, 27.9, 27.8, 24.3; HRMS (ESIMS): calcd for $C_{18}H_{21}NO_5Na$ $[M+Na]^+$ 354.13119, found 354.13106.

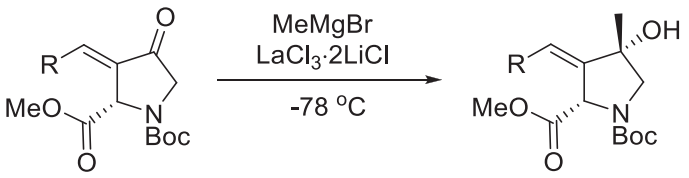
For R = 4-F-phenyl: $[\alpha]_D^{20}$ +238.4 (*c* = 1.00, $CHCl_3$); IR (neat): ν_{max} = 1742, 1703, 1395, 1238, 1160 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), mixture of rotamers: δ = 7.88 – 7.82 (2H, d, *J* = 7.2 Hz), 7.54 (1H, d, *J* = 4.4 Hz), 7.21 – 7.11 (2H, m), 5.63 (1H, d, *J* = 61.5 Hz), 4.06 – 3.99 (2H, m), 3.68 (3H, s), 1.51(9H, s). ^{13}C NMR (100 MHz, $CDCl_3$), mixture of rotamers: δ = 198.0, 197.4, 169.6, 169.5, 165.3, 162.7, 153.9, 153.0, 136.1, 135.8, 133.6, 133.5, 127.9, 127.6, 115.9, 115.8, 114.6, 114.4, 81.3, 81.1, 60.8, 60.0, 52.3, 52.3, 52.0, 51.6, 27.9; HRMS (ESIMS): calcd for $C_{18}H_{20}NFO_5Na$ $[M+Na]^+$ 372.12177, found 372.12254.

For R = nonyl: $[\alpha]_D^{20}$ +78.9 (*c* = 1.00, $CHCl_3$); IR (neat): ν_{max} = 2930, 1747, 1710, 1394, 1163 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), mixture of rotamers: δ = 6.81 (1H, brs), 5.20 (1H, d, *J* = 37.2 Hz), 4.02 – 3.92 (2H, m), 3.70 (3H, s), 2.38 – 2.30 (2H, m), 1.45 (11H, s), 1.24 (14H, brs), 0.85 (3H, brs); ^{13}C NMR (100 MHz, $CDCl_3$), mixture of rotamers: δ = 197.2, 196.5, 170.5, 154.3, 153.4, 143.3, 143.0, 131.6, 131.3, 81.2, 81.2, 60.3, 59.6, 53.3, 52.9, 52.5, 52.4, 31.8, 29.7, 29.6, 29.5, 29.4, 29.4, 29.2, 28.2, 28.1, 22.6, 14.0; HRMS (ESIMS): calcd for $C_{22}H_{37}NO_5Na$ $[M+Na]^+$ 418.25639, found 418.25722.

For R = phenethyl: $[\alpha]_D^{20}$ +70.5 (*c* = 1.00, $CHCl_3$); IR (neat): ν_{max} = 1745, 1703, 1395, 1161 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), mixture of rotamers: δ = 7.31 – 7.24 (2H, m), 7.24 – 7.16 (3H, m), 6.87 – 6.80 (1H, m), 5.24 – 5.12 (1H, 2s), 4.06 – 3.92 (2H, m), 2.74 – 2.67 (2H, m), 2.67 – 2.60 (2H, m), 3.63 (3H, s), 1.47 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$), mixture of rotamers: δ = 197.1, 196.4, 170.3, 154.3, 153.4, 1416, 141.4, 140.2, 132.2, 131.9, 128.6, 128.4, 128.3, 126.4, 81.3, 60.3, 59.6, 53.3, 52.8, 52.6, 52.5, 34.2, 31.4, 31.3,

28.3, 28.2; HRMS (ESIMS): calcd for $C_{20}H_{25}NO_5Na$ $[M+Na]^+$ 382.16249, found 382.16318.

Allylic alcohols (4.34a-i)



Typical procedures: under argon and in a flame-dried flask, the enone **4.33a** (1.102 g, 4.09 mmol) was dissolved in dry THF (20 mL) and commercial solution of $LaCl_3 \cdot 2LiCl$ (7.15 mL, 0.6 M, 4.29 mmol) was added at r.t. The mixture was allowed to stir as such for 1 h, then it was cooled to -78 °C and MeMgBr (2.05 mL, 3.0 M in Et_2O, 6.2 mmol) was added dropwise. The resulting brownish solution was stirred at -78 °C for 1 h, then quenched at -78 °C with aqueous saturated NH_4Cl (20 mL). The biphasic mixture was separated and the aqueous phase was extracted with Et_2O (3 × 20 mL). Special care was taken to avoid acidic wash (no HCl 1 M), as analogous intermediates had shown fast decomposition under such conditions. The solvent was removed under reduced pressure without heating. Purification of the residue by flash chromatography gave the title compounds as colorless oils (1.19 g, 80%).

For R = Me: $[\alpha]_D^{20}$ +67.8 (*c* = 1.00, $CHCl_3$); IR (neat): ν_{max} = 3464, 2928, 1707, 1398, 1170 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), mixture of rotamers: δ = 5.82 – 5.77 (1H, q, *J* = 7.2 Hz), 4.91 – 4.83 (1H, 2s), 4.10 – 3.88 (1H, 2s), 3.82 – 3.71 (1H, 2s), 3.79 – 3.77 (3H, 2s), 3.27 – 3.25 (1H, 2s), 1.76 – 1.74 (3H, d, *J* = 7.2 Hz), 1.44 – 1.41 (9H, 2s), 1.39 –1.36 (3H, 2s); ^{13}C NMR (100 MHz, $CDCl_3$), mixture of rotamers: δ = 173.5, 173.1, 154.1, 139.6, 138.9, 128.4, 125.9, 121.8, 80.3, 76.3, 76.1, 75.2, 60.5, 60.3, 60.0, 59.6, 52.6, 52.3, 29.6, 29.3, 28.0, 27.9, 20.7, 20.5, 14.0, 13.9; HRMS (ESIMS): calcd for $C_{14}H_{23}NO_5Na$ $[M+Na]^+$ 308.14627, found 308.14684.

For R = CD_3: ^1H NMR (400 MHz, $CDCl_3$): δ = 5.82 – 5.77 (1H, q, *J* = 7.2 Hz), 4.91 – 4.83 (1H, 2s), 4.09 – 3.86 (1H, 2s), 3.82 – 3.71 (1H, 2s), 3.79 – 3.77 (3H, 2s), 3.27 – 3.25 (1H,

2s), 1.76 – 1.74 (3H, d, J = 7.2 Hz), 1.44 – 1.41 (9H, 2s); HRMS (ESIMS): calcd for $C_{14}H_{20}NO_5Na$ $[M+Na]^+$ 311.16567, found 311.16594.

For R = 4-OMe-phenyl: $[\alpha]_D^{20}$ +192.6 (c = 1.00, $CHCl_3$); IR (neat): ν_{max} = 3437, 2983, 1694, 1397, 1254, 1161 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), mixture of rotamers: δ = 7.48 – 7.40 (2H, m), 6.94 – 6.84 (2H, m), 6.65 (1H, brs), 5.25 – 5.12 (1H, 2s), 4.53 – 4.30 (1H, 2s), 3.81 – 3.80 (3H, 2s), 3.75 – 3.72 (4H, brs), 3.30 (1H, dd, J = 11.3, 3.9 Hz), 1.53 (3H, s), 1.45 (9H, 2s); ^{13}C NMR (100 MHz, $CDCl_3$), mixture of rotamers: δ = 173.8, 173.4, 159.6, 154.3, 153.4, 137.1, 136.2, 130.4, 127.3, 126.3, 114.1, 80.8, 80.7, 61.3, 61.1, 59.9, 59.2, 55.2, 53.0, 52.7, 28.3, 22.2, 22.0; HRMS (ESIMS): calcd for $C_{20}H_{27}NO_6Na$ $[M+Na]^+$ 400.17306, found 400.17332.

For R = phenyl: $[\alpha]_D^{20}$ +234.9 (c = 1.00, $CHCl_3$); IR (neat): ν_{max} = 3430, 1694, 1396, 1160 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), mixture of rotamers: δ = 7.50 – 7.26 (5H, m), 6.75 (1H, brs), 5.26 – 5.13 (1H, 2s), 4.57 – 4.32 (1H, 2s), 3.77 – 3.73 (1H, m), 3.72 – 3.70 (3H, 2s), 3.37 (1H, dd, J = 11.2, 4.4 Hz), 1.56 (3H, s), 1.45 (9H, 2s); ^{13}C NMR (100 MHz, $CDCl_3$), mixture of rotamers: δ = 173.5, 173.0, 154.0, 153.0, 139.3, 138.4, 134.7, 134.5, 134.4, 128.5, 128.4, 128.1, 127.9, 127.8, 127.5, 126.5, 126.4, 80.5, 80.4, 60.8, 60.7, 59.5, 58.9, 52.7, 52.3, 27.9, 26.7, 21.8, 21.5; HRMS (ESIMS): calcd for $C_{19}H_{25}NO_5Na$ $[M+Na]^+$ 370.16249, found 370.16292.

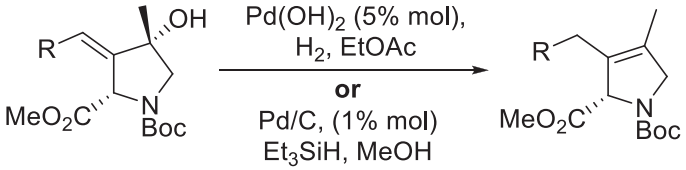
For R = 4-F-phenyl: $[\alpha]_D^{20}$ +174.6 (c = 1.00, $CHCl_3$); IR (neat): ν_{max} = 3440, 1697, 1396, 1225, 1160 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), mixture of rotamers: δ = 7.49 – 7.40 (2H, m), 7.09 – 7.02 (2H, m), 6.68 (1H, brs), 5.21 – 5.08 (1H, 2s), 4.44 – 4.21 (1H, 2s), 3.84 – 3.74 (1H, dd, J = 25.3, 11.3 Hz), 3.71 – 3.69 (3H, 2s), 3.39 – 3.33 (1H, 2brs), 1.54 (3H, s), 1.46 – 1.42 (9H, 2s). ^{13}C NMR (100 MHz, $CDCl_3$), mixture of rotamers: δ = 173.5, 173.0, 163.7, 161.2, 154.3, 153.3, 139.6, 138.7, 131.0, 130.7, 125.7, 125.6, 115.6, 115.4, 80.8, 61.1, 61.0, 59.8, 59.1, 53.0, 52.7, 28.3, 22.2, 22.0; HRMS (ESIMS): calcd for $C_{19}H_{24}NFO_5Na$ $[M+Na]^+$ 388.15307, found 388.15441.

For R = nonyl: $[\alpha]_D^{20}$ +99.1 (c = 1.00, $CHCl_3$); IR (neat): ν_{max} = 3480, 2932, 1711, 1398, 1173 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), mixture of rotamers: δ = 5.72 (1H, t, J = 7.7 Hz), 4.91 – 4.83 (1H, 2s), 3.84 – 3.74 (1H, m), 3.80 – 3.78 (3H, 2s), 3.30 – 3.27 (1H, 2s), 2.19 – 2.10 (2H, m), 1.46 – 1.43 (3H, 2s), 1.43 – 1.25 (17H, m), 1.26 (9H, s), 0.91 – 0.85 (3H,

m); ^{13}C NMR (100 MHz, $CDCl_3$), mixture of rotamers: δ = 174.0, 173.6, 154.5, 153.5, 138.8, 138.1, 127.9, 127.8, 80.6, 75.6, 661.0, 60.7, 60.0, 53.0, 52.6, 31.9, 29.6, 29.5, 29.3, 29.3, 29.0, 28.9, 28.3, 22.7, 21.2, 21.0, 14.1; HRMS (ESIMS): calcd for $C_{23}H_{41}NO_5Na$ $[M+Na]^+$ 434.28769, found 434.28790.

For R = phenethyl: $[\alpha]_D^{20}$ +72.4 (*c* = 1.00, $CHCl_3$); IR (neat): ν_{max} = 3454, 1703, 1395, 1155 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), mixture of rotamers: δ = 7.58 – 7.52 (2H, m), 7.29 – 7.20 (3H, m), 5.77 (1H, t, *J* = 7.7 Hz), 4.83 – 4.69 (1H, 2s), 4.14 – 3.89 (1H, 2s), 3.79 – 3.76 (3H, m), 3.80 – 3.72 (1H, m), 3.23 – 3.23 (1H, 2s), 2.74 – 2.65 (2H, m), 2.52 – 2.44 (2H, m), 1.47 (3H, s), 1.44 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$), mixture of rotamers: δ = 173.8, 173.4, 171.0, 154.4, 153.5, 141.3, 141.0, 139.8, 139.0, 128.4, 126.5, 126.3, 126.2, 126.1, 80.7, 60.9, 60.7, 60.5, 59.8, 53.0, 52.7, 35.2, 35.1, 30.7, 28.3, 21.3, 21.0; HRMS (ESIMS): calcd for $C_{21}H_{29}NO_5Na$ $[M+Na]^+$ 398.19379, found 398.19474.

Trisubstituted 3-pyrrolines



Typical procedure **A**: the allylic alcohol **4.10** (100 mg, 0.350 mmol) was dissolved in EtOAc (1.75 mL) and $Pd(OH)_2$ (800 mg, 10 mol %) was added. The resulting mixture was purged with hydrogen and stirred for 16 h under hydrogen atmosphere. The mixture was filtered over Celite and the solvent was removed under reduced pressure. Purification of the residue by flash chromatography (hexanes/EtOAc = 70/30) gave the elimination products as colorless oils. Typical procedure **B**: a solution of the allylic alcohol **4.10** (100 mg, 0.350 mmol) in MeOH (1.75 mL) was added Pd/C (2.8 mg, 0.0035 mmol), then Et_3SiH (85 μL, 0.700 mmol). The reaction mixture was stirred at r.t. for variable times, after which it was filtered through Celite with EtOAc washings. Similar purification methods as with procedure **A** were then employed.

For R = Me: $[\alpha]_D^{20}$ –141.8 (*c* = 1.00, $CHCl_3$); IR (neat): ν_{max} = 2922, 1759, 1400, 1163 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), mixture of rotamers: δ = 4.91 – 4.85 (1H, 2 brs), 4.20 – 4.11 (1H, m), 4.03 (1H, dd, *J* = 31.0, 15.4 Hz), 3.73 – 3.71 (3H, 2s), 2.23 – 2.15 (1H, s), 1.97 –

1.86 (1H, m), 1.69 – 1.67 (3H, 2s), 1.46 – 1.41 (9H, 2s), 1.48 – 1.42 (2H, m), 0.61 (3H, d, J = 6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$), mixture of rotamers: δ = 171.5, 171.3, 153.4, 152.9, 130.8, 130.6, 129.9, 129.8, 79.5, 77.9, 67.9, 67.4, 56.9, 56.6, 51.6, 51.5, 51.4, 28.0, 27.9, 18.1, 12.2, 11.0, 10.9; HRMS (ESIMS): calcd for $C_{14}H_{23}NO_4SNa$ $[M+Na]^+$ 292.15110, found 292.15193.

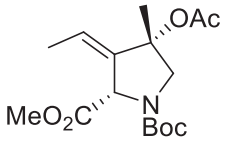
For R = 4-OMe-phenyl: $[\alpha]_D^{20}$ –19.4 (c = 1.00, $CHCl_3$); IR (neat): ν_{max} = 1699, 1394, 1246, 1174 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), mixture of rotamers: δ = 7.16 – 7.10 (2H, m), 6.88 – 6.82 (2H, m), 4.40 – 4.32 (1H, 2d, J = 8.7 Hz), 3.80 (3H, s), 3.70 – 3.68 (3H, 2s), 2.52 – 2.40 (2H, m), 2.91 – 2.83 (2H, m), 1.47 (3H, brs), 1.41 – 1.39 (9H, 2s); ^{13}C NMR (100 MHz, $CDCl_3$), mixture of rotamers: δ = 172.4, 172.1, 158.0, 154.6, 154.0, 131.6, 129.6, 129.4, 128.7, 113.9, 113.8, 79.9, 79.8, 68.4, 68.0, 62.1, 61.8, 57.3, 57.0, 55.2, 53.7, 53.2, 51.9, 51.7, 46.4, 45.5, 34.5, 33.7, 30.9, 28.4, 28.3, 14.5, 14.3; HRMS (ESIMS): calcd for $C_{20}H_{27}NO_5Na$ $[M+Na]^+$ 384.17814, found 384.17890.

For R = phenyl: $[\alpha]_D^{20}$ –56.7 (c = 1.00, $CHCl_3$); IR (neat): ν_{max} = 1702, 1393, 1170, 1115 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), mixture of rotamers: δ = 7.30 – 7.14 (5H, m), 4.80 – 4.72 (1H, 2brs), 4.27 – 4.22 (1H, m), 4.09 – 4.04 (1H, m), 3.56 (3H, brs), 3.34 – 3.28 (1H, m), 2.99 – 2.87 (1H, m), 1.47 (3H, brs), 1.42 – 1.39 (9H, 2s); ^{13}C NMR (100 MHz, $CDCl_3$), mixture of rotamers: δ = 172.3, 171.5, 153.2, 139.7, 139.5, 138.2, 132.6, 132.5, 128.7, 128.5, 128.4, 128.3, 126.4, 126.3, 80.1, 68.4, 68.0, 62.2, 61.9, 57.3, 57.0, 53.8, 53.2, 51.9, 51.7, 46.1, 45.3, 34.5, 33.7, 31.8, 31.5, 28.4, 28.3, 11.9, 11.8; HRMS (ESIMS): calcd for $C_{19}H_{25}NO_4Na$ $[M+Na]^+$ 354.16758, found 354.16756.

For R = nonyl: $[\alpha]_D^{20}$ –80.7 (c = 1.00, $CHCl_3$); IR (neat): ν_{max} = 2924, 1709, 1397, 1169 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), mixture of rotamers: δ = 4.93 – 4.85 (1H, 2brs), 4.19 (1H, m), 4.08 (1H, q, J = 15.7 Hz), 3.75 – 3.73 (3H, 2s), 2.22 – 2.13 (1H, m), 1.93 – 1.86 (1H, m), 1.71 – 1.69 (3H, 2s), 1.49 – 1.44 (9H, 2s), 1.33 – 1.24 (18H, m), 0.91 – 0.87 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$), mixture of rotamers: δ = 171.5, 171.4, 153.2, 152.9, 130.5, 129.6, 129.4, 79.6, 68.2, 67.7, 59.8, 59.6, 51.6, 51.5, 31.5, 29.3, 29.2, 29.0, 29.0, 28.0, 27.9, 27.4, 24.9, 22.3, 13.7, 11.2; HRMS (ESIMS): calcd for $C_{23}H_{41}NO_4Na$ $[M+Na]^+$ 418.29278, found 418.29227.

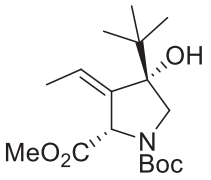
For R = phenetyl: $[\alpha]_D^{20}$ –93.6 (*c* = 1.00, $CHCl_3$); IR (neat): ν_{max} = 1707, 1398, 1172, 1119 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), mixture of rotamers: δ = 7.31 – 7.26 (2H, m), 7.22 – 7.18 (3H, m), 4.94 – 4.85 (1H, 2s), 4.19 (1H, m), 4.06 (1H, q, *J* = 15.4 Hz), 3.69 (3H, brs), 2.59 – 2.52 (2H, m), 2.24 – 2.20 (1H, m), 2.01 – 1.90 (2H, m), 1.71 – 1.65 (1H, m), 1.68 – 1.66 (3H, 2s), 1.47 – 1.44 (9H, 2s); ^{13}C NMR (100 MHz, $CDCl_3$), mixture of rotamers: δ = 171.8, 171.7, 153.8, 153.2, 141.8, 131.4, 129.4, 129.2, 128.4, 128.3, 125.9, 125.8, 80.0, 68.5, 68.1, 57.2, 57.0, 52.0, 51.9, 35.5, 35.4, 29.2, 29.1, 28.4, 28.3, 24.9, 11.7, 11.6; HRMS (ESIMS): calcd for $C_{21}H_{29}NO_4$ $[M+H]^+$ 382.19888, found 382.20035.

Allylic acetate (4.18)



A solution of the allylic alcohol **4.10** (148 mg, 0.500 mmol) in CH_2Cl_2 (2.5 mL) was cooled to 0 °C and DMAP (cat.), NEt_3 (88 μL, 0.600 mmol), and Ac_2O (60 μL, 0.600 mmol) were added. The reaction mixture was allowed to warm up to r.t. and stirred for 20 min, after which full conversion was observed. The reaction mixture was thus quenched with a 1 N HCl solution (5 mL), the aqueous and organic phases were separated and the aqueous phase was further extracted with EtOAc (3 × 5 mL). The residue was purified by flash chromatography (hexanes/EtOAc = 80/20) to give the allylic acetate **4.18** (170 mg, 99%) as a colorless liquid. R_f = 0.5 (hexanes/EtOAc = 70/30), [$KMnO_4$]. $[\alpha]_D^{20}$ +38.4 (*c* = 1.00, $CHCl_3$); IR (neat): ν_{max} = 2936, 1741, 1702, 1400, 1170 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), mixture of rotamers: δ = 5.95 – 5.79 (1H, m), 4.99 – 4.87 (1H, 2s), 4.02 – 3.95 (1H, 2d, *J* = 12 Hz), 3.67 (3H, s), 3.47 – 3.40 (1H, 2d, *J* = 12 Hz), 1.90 – 1.88 (3H, d, *J* = 7.2 Hz), 1.83 – 1.81 (3H, 2d, *J* = 6.8 Hz), 1.62 (3H, s), 1.42 – 1.39 (9H, 2s); ^{13}C NMR (100 MHz, $CDCl_3$), mixture of rotamers: δ = 170.9, 170.8, 170.7, 170.5, 154.7, 153.9, 137.1, 136.9, 126.9, 126.3, 84.5, 83.5, 80.8, 80.7, 77.7, 60.8, 60.2, 57.7, 57.6, 52.5, 52.3, 28.7, 28.6, 28.6, 22.4, 22.3, 21.8, 21.5, 15.3, 15.2; HRMS (ESIMS): calcd for $C_{14}H_{25}NO_6Na$ $[M+Na]^+$ 350.15621, found 350.15741.

Allylic alcohol *t*-butyl (4.20)



Typical protocol: under argon and in a flame-dried flask, the enone **4.9** (195 mg, 0.700 mmol) was dissolved in dry THF (3.5 mL) and a commercial solution of $LaCl_3 \cdot 2LiCl$ (1.17 mL, 0.6 M, 0.700 mmol) was added at r.t. The mixture was allowed to stir as such for 1 h, then it was cooled to -78 °C and added MeMgBr (350 μL, 3.0 M in Et_2O, 1.05 mmol) dropwise. The resulting brownish solution was stirred at -78 °C for 1 h, then quenched at -78 °C with aqueous saturated NH_4Cl (10 mL). The biphasic mixture was separated and the aqueous phase was extracted with Et_2O (3 × 10 mL). Special care was taken to avoid acidic wash (no HCl 1 M), as analogous intermediates had shown fast decomposition under such conditions. The solvent was removed under reduced pressure without heating. Purification of the residue by flash chromatography gave the title compound as colorless oil (118 mg, 48%). R_f = 0.4 (hexanes/EtOAc = 70/30), [$KMnO_4$]. $[\alpha]_D^{20}$ –4.7 (*c* = 1.00, $CHCl_3$); IR (neat): ν_{max} = 3463, 2963, 1700, 1393, 1165 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), mixture of rotamers: δ = 5.91 – 5.89 (1H, m), 4.90 – 4.81 (1H, 2s), 3.97 – 3.94 (1H, 2s), 3.88 – 3.83 (1H, 2d, *J* = 11.6 Hz), 3.78 – 3.76 (3H, 2s), 3.46 – 3.41 (1H, 2d, *J* = 11.2 Hz), 1.76 – 1.75 (3H, d, *J* = 4.0 Hz), 1.47 – 1.44 (9H, 2s), 0.99 – 0.98 (9H, 2s); ^{13}C NMR (100 MHz, $CDCl_3$), mixture of rotamers: δ = 173.1, 139.8, 139.3, 125.2, 83.4, 82.7, 81.0, 80.9, 65.1, 62.5, 62.0, 57.4, 56.6, 56.0, 52.9, 52.6, 37.5, 28.7, 28.6, 14.9, 14.8; HRMS (ESIMS): calcd for $C_{14}H_{25}NO_6Na$ $[M+Na]^+$ 350.19275, found 350.19379.

Annexe III – Rapports cristallographiques

Université de Montréal

CRYSTAL AND MOLECULAR STRUCTURE OF

C16 H21 N O3 S COMPOUND (bent71)

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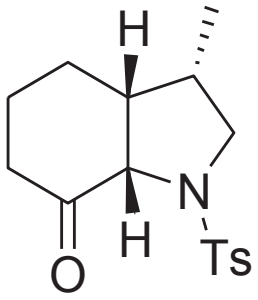


Racemic

Structure solved and refined in the laboratory of X-ray diffraction Université de Montréal by Benoît Deschênes Simard.

Table 1. Crystal data and structure refinement for C16 H21 N O3 S.

Identification code	bent71
Empirical formula	C16 H21 N O3 S
Formula weight	307.40
Temperature	200K
Wavelength	1.54178 Å
Crystal system	Monoclinic
Space group	P21/n
Unit cell dimensions	a = 10.3850(3) Å α = 90° b = 8.0285(2) Å β =99.513(2)° c = 18.6985(6) Å γ = 90°
Volume	1537.57(8)Å^3
Z	4
Density (calculated)	1.328 g/cm^3
Absorption coefficient	1.953 mm^{-1}
F(000)	656
Crystal size	0.29 x 0.14 x 0.13 mm
Theta range for data collection	4.58 to 72.11°
Index ranges	$-12 \le h \le 12$, $-9 \le k \le 9$, $20 \le \ell \le 22$
Reflections collected	15589
Independent reflections	2939 [R_{int} = 0.054]
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.7758 and 0.5654
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2939 / 78 / 225
Goodness-of-fit on F^2	1.050
Final R indices [I>2sigma(I)]	R_1 = 0.0413, wR_2 = 0.1097
R indices (all data)	R_1 = 0.0441, wR_2 = 0.1123
Extinction coefficient	0.0024(3)
Largest diff. peak and hole	0.319 and -0.465 e/Å^3

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for C16 H21 N O3 S.

U_{eq} is defined as one third of the trace of the orthogonalized Uij tensor.

	Occ.	x	y	z	U_{eq}
S(1A)	0.48	-1122(8)	3019(14)	8249(4)	34(1)
O(2A)	0.48	-650(20)	4520(30)	8609(14)	39(2)
O(3A)	0.48	-2483(14)	2640(30)	8136(14)	42(2)
N(1A)	0.48	-700(20)	3077(18)	7443(6)	34(1)
C(7A)	0.48	-159(16)	1660(30)	6402(8)	39(2)
C(8A)	0.48	-1147(12)	1711(18)	6926(6)	37(2)
C(9A)	0.48	-820(30)	1420(50)	5616(9)	62(3)
C(10A)	0.48	-191(8)	1408(10)	8728(3)	36(1)
C(11A)	0.48	-737(7)	-169(11)	8608(3)	36(1)
C(12A)	0.48	-102(10)	-1546(10)	8953(4)	40(1)
C(13A)	0.48	1079(9)	-1347(13)	9417(4)	41(1)
C(14A)	0.48	1625(8)	229(15)	9537(4)	35(1)
C(15A)	0.48	990(9)	1607(12)	9193(4)	35(1)
C(16A)	0.48	1738(17)	-2890(20)	9774(7)	49(1)
S(1B)	0.52	-988(8)	3134(13)	8316(4)	34(1)
O(2B)	0.52	-424(18)	4590(30)	8688(13)	39(2)
O(3B)	0.52	-2368(13)	2860(30)	8246(13)	42(2)
N(1B)	0.52	-670(20)	3238(17)	7494(5)	34(1)
C(7B)	0.52	-331(14)	1900(30)	6400(8)	39(2)
C(8B)	0.52	-1288(10)	2004(16)	6943(6)	37(2)
C(9B)	0.52	-980(30)	1540(40)	5631(8)	62(3)
C(10B)	0.52	-242(8)	1329(10)	8720(3)	36(1)
C(11B)	0.52	-862(7)	-216(10)	8732(3)	36(1)
C(12B)	0.52	-169(9)	-1543(10)	9068(4)	40(1)
C(13B)	0.52	1153(9)	-1385(13)	9396(4)	41(1)
C(14B)	0.52	1735(8)	190(14)	9374(4)	35(1)
C(15B)	0.52	1066(9)	1554(12)	9048(4)	35(1)
C(16B)	0.52	1940(15)	-2810(18)	9759(6)	49(1)
O(1)	1	2196(1)	5303(2)	8093(1)	54(1)
C(1)	1	678(1)	3530(2)	7376(1)	37(1)
C(2)	1	1186(2)	5224(2)	7661(1)	40(1)
C(3)	1	486(2)	6710(2)	7304(1)	44(1)
C(4)	1	463(2)	6591(2)	6485(1)	48(1)
C(5)	1	-147(2)	4957(2)	6179(1)	44(1)
C(6)	1	543(2)	3417(2)	6546(1)	41(1)

Table 3. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^2 x 10^3) for C16 H21 N O3 S.

	Occ.	x	y	z	U_{eq}
H(7AA)	0.48	485	744	6545	47
H(8AA)	0.48	-2036	1943	6661	44
H(8AB)	0.48	-1159	637	7185	44
H(9AA)	0.48	-1342	396	5576	93
H(9AB)	0.48	-153	1334	5303	93
H(9AC)	0.48	-1389	2373	5464	93
H(11A)	0.48	-1544	-305	8291	44
H(12A)	0.48	-475	-2624	8870	48
H(14A)	0.48	2432	365	9855	42
H(15A)	0.48	1363	2684	9275	42
H(16A)	0.48	1072	-3683	9874	74
H(16B)	0.48	2295	-2579	10230	74
H(16C)	0.48	2272	-3407	9449	74
H(7BA)	0.52	241	920	6553	47
H(8BA)	0.52	-2157	2394	6703	44
H(8BB)	0.52	-1385	906	7169	44
H(9BA)	0.52	-363	1736	5299	93
H(9BB)	0.52	-1740	2278	5503	93
H(9BC)	0.52	-1274	379	5595	93
H(11B)	0.52	-1748	-348	8512	44
H(12B)	0.52	-590	-2591	9079	48
H(14B)	0.52	2622	324	9592	42
H(15B)	0.52	1478	2610	9045	42
H(16D)	0.52	1449	-3361	10097	74
H(16E)	0.52	2767	-2388	10027	74
H(16F)	0.52	2117	-3610	9392	74
H(1)	1	1284	2639	7603	45
H(3A)	1	938	7743	7495	53
H(3B)	1	-418	6744	7408	53
H(4A)	1	-43	7536	6242	58
H(4B)	1	1366	6672	6382	58
H(5A)	1	-115	4911	5653	53
H(5B)	1	-1076	4934	6239	53
H(6)	1	1435	3341	6413	49

Table 4. Anisotropic parameters ($Å^2$ x 10^3) for C16 H21 N O3 S.

The anisotropic displacement factor exponent takes the form:

$$-2\pi^2 [h^2 a^{*2} U_{11} + ... + 2 h k a^* b^* U_{12}]$$

	U11	U22	U33	U23	U13	U12
S(1A)	24(1)	29(1)	50(1)	-2(1)	7(1)	-3(1)
O(2A)	36(5)	30(2)	52(4)	-5(2)	7(4)	-4(3)
O(3A)	26(2)	35(5)	64(6)	-3(3)	9(3)	-5(2)
N(1A)	26(1)	30(2)	47(1)	-3(1)	5(1)	-4(2)
C(7A)	29(3)	28(5)	58(1)	-6(2)	2(2)	5(3)
C(8A)	28(2)	26(4)	55(1)	-6(2)	2(1)	6(3)
C(9A)	64(5)	59(4)	62(1)	-18(1)	4(2)	0(5)
C(10A)	33(1)	32(1)	46(1)	0(1)	12(1)	-2(1)
C(11A)	33(1)	34(1)	46(1)	1(1)	17(1)	-4(1)
C(12A)	42(1)	33(1)	48(2)	1(1)	16(1)	-2(1)
C(13A)	45(1)	39(1)	43(1)	1(1)	15(1)	8(1)
C(14A)	36(1)	49(1)	24(3)	-2(2)	13(2)	2(1)
C(15A)	38(1)	38(1)	33(3)	-4(2)	13(2)	-4(1)
C(16A)	48(4)	47(2)	53(1)	7(1)	14(2)	10(2)
S(1B)	24(1)	29(1)	50(1)	-2(1)	7(1)	-3(1)
O(2B)	36(5)	30(2)	52(4)	-5(2)	7(4)	-4(3)
O(3B)	26(2)	35(5)	64(6)	-3(3)	9(3)	-5(2)
N(1B)	26(1)	30(2)	47(1)	-3(1)	5(1)	-4(2)
C(7B)	29(3)	28(5)	58(1)	-6(2)	2(2)	15(3)
C(8B)	28(2)	26(4)	55(1)	-6(2)	2(1)	6(3)
C(9B)	64(5)	59(4)	62(1)	-18(1)	4(2)	0(5)
C(10B)	33(1)	32(1)	46(1)	0(1)	12(1)	-2(1)
C(11B)	33(1)	34(1)	46(1)	1(1)	17(1)	-4(1)
C(12B)	42(1)	33(1)	48(2)	1(1)	16(1)	-2(1)
C(13B)	45(1)	39(1)	43(1)	1(1)	15(1)	8(1)
C(14B)	36(1)	49(1)	24(3)	-2(2)	13(2)	2(1)
C(15B)	38(1)	38(1)	33(3)	-4(2)	13(2)	-4(1)
C(16B)	48(4)	47(2)	53(1)	7(1)	14(2)	10(2)
O(1)	33(1)	60(1)	66(1)	-5(1)	-1(1)	-10(1)
C(1)	24(1)	37(1)	51(1)	1(1)	5(1)	1(1)
C(2)	28(1)	45(1)	48(1)	-2(1)	10(1)	-5(1)
C(3)	38(1)	37(1)	58(1)	-2(1)	11(1)	-5(1)
C(4)	46(1)	42(1)	59(1)	6(1)	13(1)	-2(1)
C(5)	40(1)	47(1)	45(1)	3(1)	8(1)	2(1)
C(6)	31(1)	42(1)	50(1)	-4(1)	9(1)	2(1)

Table 5. Bond lengths [Å] and angles [°] for C16 H21 N O3 S

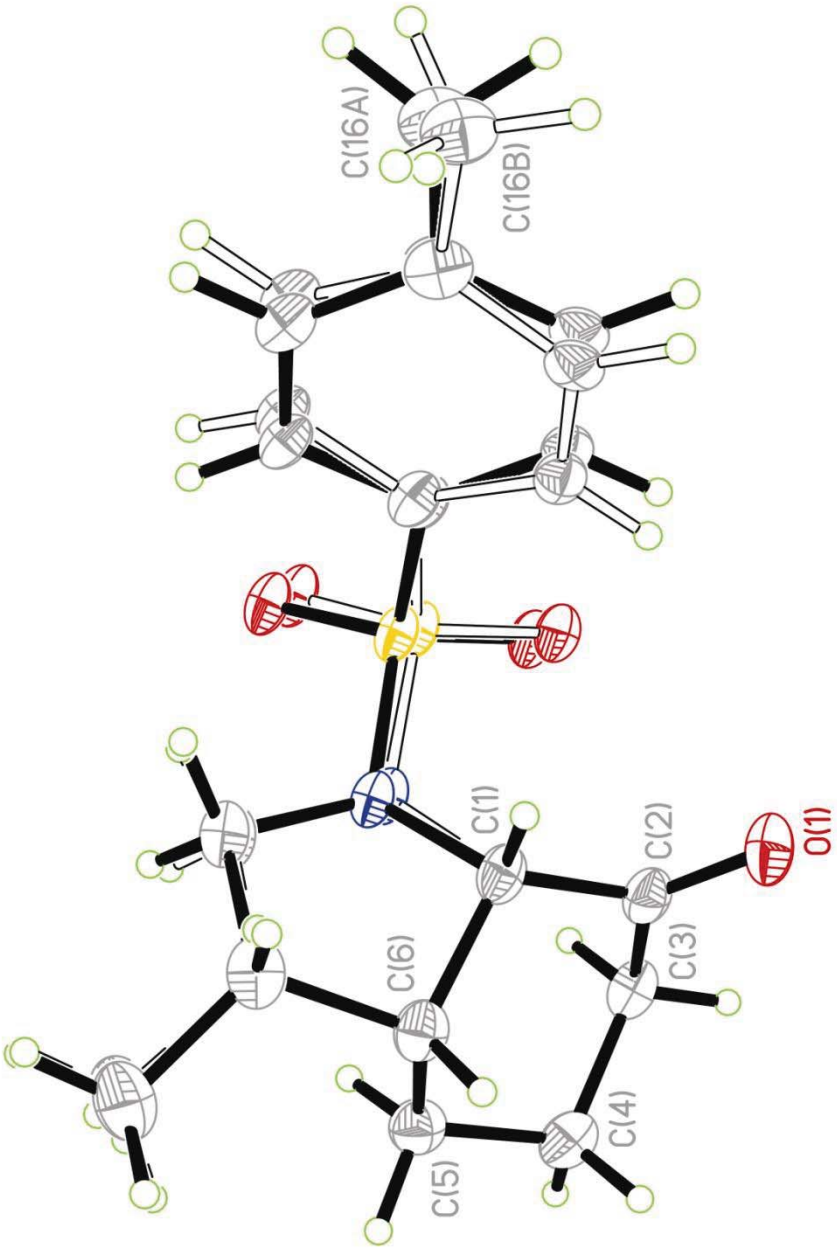
S(1a)-O(3a)	1.428(10)	C(12b)-C(13b)	1.414(5)
S(1a)-O(2a)	1.43(1)	C(13b)-C(14b)	1.405(5)
S(1a)-N(1a)	1.637(9)	C(13b)-C(16b)	1.502(9)
S(1a)-C(10a)	1.768(9)	C(14b)-C(15b)	1.383(5)
N(1a)-C(8a)	1.484(10)	O(1)-C(2)	1.214(2)
N(1a)-C(1)	1.50(2)	C(1)-C(2)	1.523(2)
C(7a)-C(9a)	1.528(11)	C(1)-C(6)	1.538(2)
C(7a)-C(8a)	1.532(11)	C(2)-C(3)	1.496(2)
C(7a)-C(6)	1.59(2)	C(3)-C(4)	1.530(3)
C(10a)-C(11a)	1.39	C(4)-C(5)	1.526(3)
C(10a)-C(15a)	1.39	C(5)-C(6)	1.533(2)
C(11a)-C(12a)	1.39		
C(12a)-C(13a)	1.39		
C(13a)-C(14a)	1.39	O(3A)-S(1A)-O(2A)	120.5(1)
C(13a)-C(16a)	1.516(9)	O(3A)-S(1A)-N(1A)	106.2(1)
C(14a)-C(15a)	1.39	O(2A)-S(1A)-N(1A)	106.6(11)
S(1b)-O(3b)	1.434(9)	O(3A)-S(1A)-C(10A)	111.2(14)
S(1b)-O(2b)	1.436(9)	O(2A)-S(1A)-C(10A)	105.2(13)
S(1b)-N(1b)	1.626(8)	N(1A)-S(1A)-C(10A)	106.3(7)
S(1b)-C(10b)	1.755(9)	C(8A)-N(1A)-C(1)	108.9(1)
N(1b)-C(1)	1.471(19)	C(8A)-N(1A)-S(1A)	118.4(9)
N(1b)-C(8b)	1.495(10)	C(1)-N(1A)-S(1A)	119.1(1)
C(7b)-C(9b)	1.513(10)	C(9A)-C(7A)-C(8A)	112.1(11)
C(7b)-C(6)	1.51(2)	C(9A)-C(7A)-C(6)	113.2(16)
C(7b)-C(8b)	1.536(9)	C(8A)-C(7A)-C(6)	101.8(9)
C(10b)-C(11b)	1.399(4)	N(1A)-C(8A)-C(7A)	105.4(9)
C(10b)-C(15b)	1.407(4)		
C(11b)-C(12b)	1.377(4)	C(11A)-C(10A)-C(15A)	120

```
    C(11A)-C(10A)-S(1A)
114.2(5)
    C(15A)-C(10A)-S(1A)
125.8(5)
    C(10A)-C(11A)-C(12A)   120
    C(13A)-C(12A)-C(11A)   120
    C(12A)-C(13A)-C(14A)   120
    C(12A)-C(13A)-C(16A)
117.9(8)
    C(14A)-C(13A)-C(16A)
122.1(8)
    C(13A)-C(14A)-C(15A)   120
    C(14A)-C(15A)-C(10A)   120
    O(3B)-S(1B)-O(2B)
119.3(9)
    O(3B)-S(1B)-N(1B)
106.2(1)
    O(2B)-S(1B)-N(1B)
106.6(11)
    O(3B)-S(1B)-C(10B)
106.1(13)
    O(2B)-S(1B)-C(10B)
110.4(12)
    N(1B)-S(1B)-C(10B)
107.7(7)
    C(1)-N(1B)-C(8B)
108.2(8)
    C(1)-N(1B)-S(1B)
119.8(1)
    C(8B)-N(1B)-S(1B)
119.1(8)
    C(9B)-C(7B)-C(6)
119.1(14)
    C(9B)-C(7B)-C(8B)
113.6(1)
    C(6)-C(7B)-C(8B)
105.8(9)
    N(1B)-C(8B)-C(7B)
103.8(8)
    C(11B)-C(10B)-C(15B)
121.3(3)
    C(11B)-C(10B)-S(1B)
124.6(5)
    C(15B)-C(10B)-S(1B)
114.0(5)
    C(12B)-C(11B)-C(10B)
119.1(3)
    C(11B)-C(12B)-C(13B)
121.7(3)
    C(14B)-C(13B)-C(12B)
117.4(3)
    C(14B)-C(13B)-C(16B)
119.6(8)
    C(12B)-C(13B)-C(16B)
123.0(8)
    C(15B)-C(14B)-C(13B)
122.5(3)
    C(14B)-C(15B)-C(10B)
118.0(3)
    N(1B)-C(1)-N(1A)
6.1(9)
    N(1B)-C(1)-C(2)
111.9(5)
    N(1A)-C(1)-C(2)
117.9(6)
    N(1B)-C(1)-C(6)
102.2(4)
    N(1A)-C(1)-C(6)
98.1(4)
    C(2)-C(1)-C(6)
111.96(14)
    O(1)-C(2)-C(3)
123.88(16)
    O(1)-C(2)-C(1)
119.38(15)
    C(3)-C(2)-C(1)
116.19(13)
    C(2)-C(3)-C(4)
108.83(14)
    C(5)-C(4)-C(3)
111.48(14)
    C(4)-C(5)-C(6)
113.01(14)
    C(7B)-C(6)-C(5)
110.2(7)
    C(7B)-C(6)-C(1)
100.4(5)
    C(5)-C(6)-C(1)
111.26(14)
    C(7B)-C(6)-C(7A)
9.3(11)
    C(5)-C(6)-C(7A)
118.2(7)
    C(1)-C(6)-C(7A)
100.7(6)
```

Table 6. Torsion angles [°] for C16 H21 N O3 S.

O(3A)-S(1A)-N(1A)-C(8A)	-46(2)
O(2A)-S(1A)-N(1A)-C(8A)	-175.9(18)
C(10A)-S(1A)-N(1A)-C(8A)	72.2(17)
O(3A)-S(1A)-N(1A)-C(1)	177.3(16)
O(2A)-S(1A)-N(1A)-C(1)	47.7(17)
C(10A)-S(1A)-N(1A)-C(1)	-64.2(11)
C(1)-N(1A)-C(8A)-C(7A)	-14.9(17)
S(1A)-N(1A)-C(8A)-C(7A)	-155.3(14)
C(9A)-C(7A)-C(8A)-N(1A)	-138(2)
C(6)-C(7A)-C(8A)-N(1A)	-16.5(16)
O(3A)-S(1A)-C(10A)-C(11A)	30(1)
O(2A)-S(1A)-C(10A)-C(11A)	162(1)
N(1A)-S(1A)-C(10A)-C(11A)	-85.1(7)
O(3A)-S(1A)-C(10A)-C(15A)	-150(1)
O(2A)-S(1A)-C(10A)-C(15A)	-18(1)
N(1A)-S(1A)-C(10A)-C(15A)	94.8(7)
C(15A)-C(10A)-C(11A)-C(12A)	0
S(1A)-C(10A)-C(11A)-C(12A)	179.94(7)
C(10A)-C(11A)-C(12A)-C(13A)	0
C(11A)-C(12A)-C(13A)-C(14A)	0
C(11A)-C(12A)-C(13A)-C(16A)	-179.5(2)
C(12A)-C(13A)-C(14A)-C(15A)	0
C(16A)-C(13A)-C(14A)-C(15A)	179.5(3)
C(13A)-C(14A)-C(15A)-C(10A)	0
C(11A)-C(10A)-C(15A)-C(14A)	0
S(1A)-C(10A)-C(15A)-C(14A)	-179.93(7)
O(3B)-S(1B)-N(1B)-C(1)	179.3(14)
O(2B)-S(1B)-N(1B)-C(1)	51.1(15)
C(10B)-S(1B)-N(1B)-C(1)	-67.4(1)
O(3B)-S(1B)-N(1B)-C(8B)	-43.7(18)
O(2B)-S(1B)-N(1B)-C(8B)	-171.9(16)
C(10B)-S(1B)-N(1B)-C(8B)	69.6(16)
C(1)-N(1B)-C(8B)-C(7B)	-12.2(15)
S(1B)-N(1B)-C(8B)-C(7B)	-153.7(13)
C(9B)-C(7B)-C(8B)-N(1B)	-148.6(19)
C(6)-C(7B)-C(8B)-N(1B)	-16.2(15)
O(3B)-S(1B)-C(10B)-C(11B)	19.4(8)
O(2B)-S(1B)-C(10B)-C(11B)	150(1)
N(1B)-S(1B)-C(10B)-C(11B)	-93.9(7)
O(3B)-S(1B)-C(10B)-C(15B)	-160.0(9)
O(2B)-S(1B)-C(10B)-C(15B)	-29.5(1)
N(1B)-S(1B)-C(10B)-C(15B)	86.6(7)
C(15B)-C(10B)-C(11B)-C(12B)	-0.5(3)
S(1B)-C(10B)-C(11B)-C(12B)	-179.9(2)
C(10B)-C(11B)-C(12B)-C(13B)	-0.4(3)
C(11B)-C(12B)-C(13B)-C(14B)	0.7(4)
C(11B)-C(12B)-C(13B)-C(16B)	-179.4(3)
C(12B)-C(13B)-C(14B)-C(15B)	-0.1(4)
C(16B)-C(13B)-C(14B)-C(15B)	180.0(3)
C(13B)-C(14B)-C(15B)-C(10B)	-0.8(4)
C(11B)-C(10B)-C(15B)-C(14B)	1.1(3)
S(1B)-C(10B)-C(15B)-C(14B)	-179.4(2)
C(8B)-N(1B)-C(1)-N(1A)	-12(10)

S(1B)-N(1B)-C(1)-N(1A) 129(11)
C(8B)-N(1B)-C(1)-C(2) 155.3(8)
S(1B)-N(1B)-C(1)-C(2) -63.6(1)
C(8B)-N(1B)-C(1)-C(6) 35.3(11)
S(1B)-N(1B)-C(1)-C(6) 176.4(8)
C(8A)-N(1A)-C(1)-N(1B) 174(11)
S(1A)-N(1A)-C(1)-N(1B) -46(10)
C(8A)-N(1A)-C(1)-C(2) 160.6(9)
S(1A)-N(1A)-C(1)-C(2) -59.3(12)
C(8A)-N(1A)-C(1)-C(6) 40.4(11)
S(1A)-N(1A)-C(1)-C(6) -179.5(9)
N(1B)-C(1)-C(2)-O(1) 125.0(6)
N(1A)-C(1)-C(2)-O(1) 126.5(6)
C(6)-C(1)-C(2)-O(1) -120.91(17)
N(1B)-C(1)-C(2)-C(3) -63.2(6)
N(1A)-C(1)-C(2)-C(3) -61.7(6)
C(6)-C(1)-C(2)-C(3) 50.90(18)
O(1)-C(2)-C(3)-C(4) 117.06(19)
C(1)-C(2)-C(3)-C(4) -54.34(18)
C(2)-C(3)-C(4)-C(5) 55.79(18)
C(3)-C(4)-C(5)-C(6) -56.72(19)
C(9B)-C(7B)-C(6)-C(5) 48.6(16)
C(8B)-C(7B)-C(6)-C(5) -80.7(11)
C(9B)-C(7B)-C(6)-C(1) 166(15)
C(8B)-C(7B)-C(6)-C(1) 36.7(11)
C(9B)-C(7B)-C(6)-C(7A) -101(7)
C(8B)-C(7B)-C(6)-C(7A) 129(8)
C(4)-C(5)-C(6)-C(7B) 162.0(5)
C(4)-C(5)-C(6)-C(1) 51.48(18)
C(4)-C(5)-C(6)-C(7A) 167.2(5)
N(1B)-C(1)-C(6)-C(7B) -43.6(8)
N(1A)-C(1)-C(6)-C(7B) -39.1(9)
C(2)-C(1)-C(6)-C(7B) -163.6(6)
N(1B)-C(1)-C(6)-C(5) 73.0(6)
N(1A)-C(1)-C(6)-C(5) 77.5(6)
C(2)-C(1)-C(6)-C(5) -46.96(17)
N(1B)-C(1)-C(6)-C(7A) -53.1(8)
N(1A)-C(1)-C(6)-C(7A) -48.6(8)
C(2)-C(1)-C(6)-C(7A) -173.1(6)
C(9A)-C(7A)-C(6)-C(7B) 72(7)
C(8A)-C(7A)-C(6)-C(7B) -48(6)
C(9A)-C(7A)-C(6)-C(5) 40.3(15)
C(8A)-C(7A)-C(6)-C(5) -80.3(11)
C(9A)-C(7A)-C(6)-C(1) 161.6(14)
C(8A)-C(7A)-C(6)-C(1) 41(11)



ORTEP view of the C16 H21 N O3 S compound with the numbering scheme adopted. Ellipsoids drawn at 30% probability level. Hydrogen atoms are represented by sphere of arbitrary size.

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Université de Montréal

CRYSTAL AND MOLECULAR STRUCTURE OF

C10 H17 N O3 S COMPOUND (bent75)

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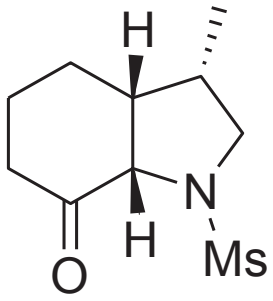


Racemic

Structure solved and refined in the laboratory of X-ray diffraction Université de Montréal by Benoît Deschênes Simard.

Table 1. Crystal data and structure refinement for C10 H17 N O3 S.

Identification code	bent75
Empirical formula	C10 H17 N O3 S
Formula weight	231.31
Temperature	200K
Wavelength	1.54178 Å
Crystal system	Monoclinic
Space group	Cc
Unit cell dimensions	a = 7.8369(1) Å α = 90° b = 19.2406(3) Å β = 115.624(1)° c = 8.2664(1) Å γ = 90°
Volume	1123.87(3)Å^3
Z	4
Density (calculated)	1.367 g/cm^3
Absorption coefficient	2.479 mm^{-1}
F(000)	496
Crystal size	0.22 x 0.18 x 0.09 mm
Theta range for data collection	4.60 to 72.03°
Index ranges	$-9 \le h \le 9$, $-23 \le k \le 23$, $-9 \le \ell \le 10$
Reflections collected	7112
Independent reflections	1834 [R_{int} = 0.037]
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.8000 and 0.6187
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1834 / 2 / 140
Goodness-of-fit on F^2	1.091
Final R indices [I>2sigma(I)]	R_1 = 0.0348, wR_2 = 0.0833
R indices (all data)	R_1 = 0.0348, wR_2 = 0.0833
Absolute structure parameter	0.162(16)
Extinction coefficient	0.0287(12)
Largest diff. peak and hole	0.199 and -0.322 e/Å^3

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for C10 H17 N O3 S.

U_{eq} is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U_{eq}
S(1)	1285(1)	1513(1)	11658(1)	33(1)
O(1)	5325(2)	2053(1)	10250(2)	45(1)
O(2)	3249(3)	1657(1)	12729(2)	52(1)
O(3)	337(3)	998(1)	12222(2)	49(1)
N(1)	1094(2)	1274(1)	9704(2)	29(1)
C(1)	2133(3)	1659(1)	8857(2)	26(1)
C(2)	4263(3)	1553(1)	9783(3)	29(1)
C(3)	4938(3)	829(1)	9798(3)	36(1)
C(4)	4209(3)	600(1)	7827(3)	39(1)
C(5)	2052(3)	624(1)	6888(3)	33(1)
C(6)	1260(3)	1348(1)	6943(2)	26(1)
C(7)	-847(3)	1343(1)	6558(3)	33(1)
C(8)	-789(3)	1063(1)	8313(3)	37(1)
C(9)	-2153(4)	927(2)	4919(3)	49(1)
C(10)	36(4)	2296(1)	11377(3)	41(1)

Table 3. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^2 x 10^3) for C10 H17 N O3 S.

	x	y	z	U_{eq}
H(1)	1830	2166	8804	31
H(3A)	4438	518	10447	43
H(3B)	6337	812	10401	43
H(4A)	4733	910	7199	47
H(4B)	4645	121	7778	47
H(5A)	1539	287	7468	39
H(5B)	1621	481	5621	39
H(6)	1470	1668	6092	31
H(7)	-1308	1834	6403	39
H(8A)	-1813	1269	8554	44
H(8B)	-923	550	8268	44
H(9A)	-1795	435	5100	74
H(9B)	-2038	1100	3855	74
H(9C)	-3464	979	4749	74
H(10A)	236	2477	12554	61
H(10B)	-1317	2212	10651	61
H(10C)	491	2635	10770	61

Table 4. Anisotropic parameters (Å^2 x 10^3) for C10 H17 N O3 S.

The anisotropic displacement factor exponent takes the form:

$$-2\,\pi^2\,[\,h^2\,a^{*2}\,U_{11} + \ldots + 2\,h\,k\,a^*\,b^*\,U_{12}\,]$$

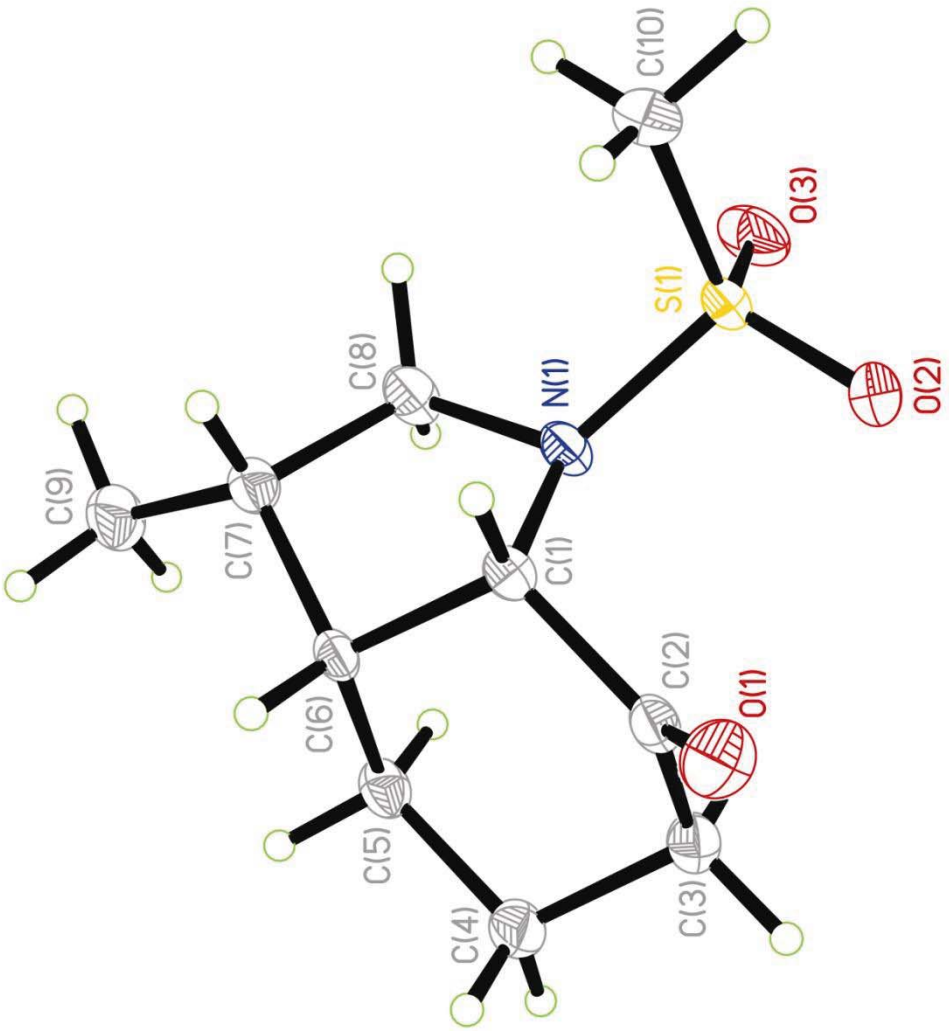
	U11	U22	U33	U23	U13	U12
S(1)	36(1)	42(1)	21(1)	0(1)	14(1)	8(1)
O(1)	36(1)	45(1)	49(1)	-8(1)	15(1)	-13(1)
O(2)	36(1)	86(1)	27(1)	-13(1)	6(1)	12(1)
O(3)	71(1)	48(1)	44(1)	13(1)	40(1)	12(1)
N(1)	33(1)	37(1)	23(1)	-4(1)	15(1)	-6(1)
C(1)	30(1)	25(1)	24(1)	-1(1)	13(1)	-3(1)
C(2)	31(1)	35(1)	20(1)	-3(1)	11(1)	-4(1)
C(3)	36(1)	40(1)	28(1)	2(1)	11(1)	6(1)
C(4)	42(1)	43(1)	30(1)	-4(1)	14(1)	11(1)
C(5)	40(1)	32(1)	25(1)	-5(1)	12(1)	-1(1)
C(6)	30(1)	32(1)	17(1)	2(1)	11(1)	0(1)
C(7)	30(1)	41(1)	26(1)	-3(1)	11(1)	-1(1)
C(8)	35(1)	50(1)	29(1)	-7(1)	16(1)	-13(1)
C(9)	36(1)	74(2)	30(1)	-12(1)	9(1)	-8(1)
C(10)	43(1)	42(1)	39(1)	-6(1)	21(1)	5(1)

Table 5. Bond lengths [Å] and angles [°] for C10 H17 N O3 S

		N(1)-S(1)-C(10)	107.81(10)
S(1)-O(2)	1.432(2)	C(1)-N(1)-C(8)	109.65(14)
S(1)-O(3)	1.4324(17)	C(1)-N(1)-S(1)	119.67(12)
S(1)-N(1)	1.6227(15)	C(8)-N(1)-S(1)	118.85(13)
S(1)-C(10)	1.756(2)	N(1)-C(1)-C(2)	113.74(15)
O(1)-C(2)	1.221(2)	N(1)-C(1)-C(6)	101.51(13)
N(1)-C(1)	1.482(2)	C(2)-C(1)-C(6)	111.50(15)
N(1)-C(8)	1.482(3)	O(1)-C(2)-C(3)	122.9(2)
C(1)-C(2)	1.520(3)	O(1)-C(2)-C(1)	120.25(17)
C(1)-C(6)	1.548(3)	C(3)-C(2)-C(1)	116.04(17)
C(2)-C(3)	1.488(3)	C(2)-C(3)-C(4)	106.98(17)
C(3)-C(4)	1.539(3)	C(5)-C(4)-C(3)	110.65(17)
C(4)-C(5)	1.525(3)	C(4)-C(5)-C(6)	112.72(16)
C(5)-C(6)	1.534(2)	C(5)-C(6)-C(7)	113.53(16)
C(6)-C(7)	1.541(3)	C(5)-C(6)-C(1)	112.12(15)
C(7)-C(9)	1.524(3)	C(7)-C(6)-C(1)	99.99(14)
C(7)-C(8)	1.529(3)	C(9)-C(7)-C(8)	113.08(18)
O(2)-S(1)-O(3)	120.17(12)	C(9)-C(7)-C(6)	115.74(18)
O(2)-S(1)-N(1)	106.42(10)	C(8)-C(7)-C(6)	102.52(16)
O(3)-S(1)-N(1)	106.86(9)	N(1)-C(8)-C(7)	104.53(15)
O(2)-S(1)-C(10)	107.73(12)		
O(3)-S(1)-C(10)	107.33(11)		

Table 6. Torsion angles [°] for C10 H17 N O3 S.

		C(3)-C(4)-C(5)-C(6)	57.9(2)
O(2)-S(1)-N(1)-C(1)	-43.24(18)	C(4)-C(5)-C(6)-C(7)	-161.77(16)
O(3)-S(1)-N(1)-C(1)	-172.79(15)	C(4)-C(5)-C(6)-C(1)	-49.4(2)
C(10)-S(1)-N(1)-C(1)	72.11(17)	N(1)-C(1)-C(6)-C(5)	-77.03(18)
O(2)-S(1)-N(1)-C(8)	177.68(17)	C(2)-C(1)-C(6)-C(5)	44.4(2)
O(3)-S(1)-N(1)-C(8)	48.13(18)	N(1)-C(1)-C(6)-C(7)	43.58(16)
C(10)-S(1)-N(1)-C(8)	-66.97(17)	C(2)-C(1)-C(6)-C(7)	165.03(15)
C(8)-N(1)-C(1)-C(2)	-147.46(17)	C(5)-C(6)-C(7)-C(9)	-48.1(2)
S(1)-N(1)-C(1)-C(2)	70.07(19)	C(1)-C(6)-C(7)-C(9)	-167.70(18)
C(8)-N(1)-C(1)-C(6)	-27.59(18)	C(5)-C(6)-C(7)-C(8)	75.45(19)
S(1)-N(1)-C(1)-C(6)	-170.06(13)	C(1)-C(6)-C(7)-C(8)	-44.14(17)
N(1)-C(1)-C(2)-O(1)	-127.50(19)	C(1)-N(1)-C(8)-C(7)	-0.1(2)
C(6)-C(1)-C(2)-O(1)	118.45(19)	S(1)-N(1)-C(8)-C(7)	142.74(14)
N(1)-C(1)-C(2)-C(3)	62.2(2)	C(9)-C(7)-C(8)-N(1)	153.29(18)
C(6)-C(1)-C(2)-C(3)	-51.8(2)	C(6)-C(7)-C(8)-N(1)	28.0(2)
O(1)-C(2)-C(3)-C(4)	-111.3(2)		
C(1)-C(2)-C(3)-C(4)	58.6(2)		
C(2)-C(3)-C(4)-C(5)	-60.0(2)		



ORTEP view of the C10 H17 N O3 S compound with the numbering scheme adopted. Ellipsoids drawn at 30% probability level. Hydrogen atoms are represented by sphere of arbitrary size.

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Université de Montréal

CRYSTAL AND MOLECULAR STRUCTURE OF

C16 H21 N O4 S COMPOUND (bent82)

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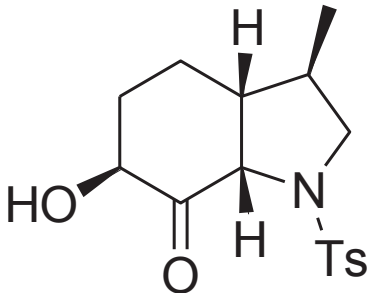


Racemic

Structure solved and refined in the laboratory of X-ray diffraction Université de Montréal by Benoît Deschênes Simard.

Table 1. Crystal data and structure refinement for C16 H21 N O4 S.

Identification code	bent82
Empirical formula	C16 H21 N O4 S
Formula weight	323.41
Temperature	200K
Wavelength	1.54178 Å
Crystal system	Triclinic
Space group	P-1
Unit cell dimensions	a = 7.7877(1) Å α = 111.412(1)° b = 10.2659(2) Å β = 99.237(1)° c = 11.5480(2) Å γ = 106.613(1)°
Volume	786.489(25)Å^3
Z	2
Density (calculated)	1.366 g/cm^3
Absorption coefficient	1.986 mm^{-1}
F(000)	344
Crystal size	0.15 x 0.14 x 0.09 mm
Theta range for data collection	4.31 to 72.66°
Index ranges	$-7 \le h \le 9$, $-12 \le k \le 12$, $-14 \le \ell \le 14$
Reflections collected	10498
Independent reflections	2995 [R_{int} = 0.027]
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.8363 and 0.7168
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2995 / 0 / 203
Goodness-of-fit on F^2	1.063
Final R indices [I>2sigma(I)]	R_1 = 0.0370, wR_2 = 0.1031
R indices (all data)	R_1 = 0.0382, wR_2 = 0.1046
Extinction coefficient	0.0192(13)
Largest diff. peak and hole	0.214 and -0.385 e/Å^3

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for C16 H21 N O4 S.

U_{eq} is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U_{eq}
S(1)	998(1)	1239(1)	7910(1)	30(1)
O(1)	4062(2)	1473(1)	11027(1)	44(1)
O(2)	5564(2)	4460(1)	12331(1)	55(1)
O(3)	261(2)	1694(1)	6970(1)	40(1)
O(4)	814(1)	1838(1)	9196(1)	36(1)
N(1)	3243(2)	1727(1)	8089(1)	30(1)
C(1)	4360(2)	1310(2)	8959(1)	29(1)
C(2)	4511(2)	2134(2)	10379(1)	32(1)
C(3)	5494(2)	3830(2)	11000(2)	39(1)
C(4)	7450(2)	4157(2)	10824(2)	47(1)
C(5)	7348(2)	3476(2)	9390(2)	41(1)
C(6)	6266(2)	1758(2)	8692(1)	33(1)
C(7)	5658(2)	1169(2)	7205(2)	37(1)
C(8)	3941(2)	1592(2)	6935(2)	38(1)
C(9)	5148(3)	-534(2)	6493(2)	44(1)
C(10)	1(2)	-745(2)	7260(1)	31(1)
C(11)	-555(2)	-1603(2)	5916(1)	39(1)
C(12)	-1368(2)	-3160(2)	5409(2)	48(1)
C(13)	-1632(2)	-3876(2)	6222(2)	47(1)
C(14)	-1047(2)	-2998(2)	7561(2)	43(1)
C(15)	-227(2)	-1433(2)	8088(1)	36(1)
C(16)	-2558(3)	-5574(2)	5660(2)	71(1)

Table 3. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for C16 H21 N O4 S.

	x	y	z	U_{eq}
H(2)	5092	3763	12538	82
H(1)	3817	195	8672	35
H(3)	4794	4258	10532	47
H(4A)	8143	5262	11215	56
H(4B)	8149	3735	11286	56
H(5A)	8638	3703	9316	49
H(5B)	6731	3959	8947	49
H(6)	7033	1226	8958	40
H(7)	6678	1711	6930	44
H(8A)	4305	2560	6865	46
H(8B)	2971	797	6121	46
H(9A)	6244	-777	6728	65
H(9B)	4755	-856	5551	65
H(9C)	4119	-1062	6744	65
H(11)	-378	-1126	5354	47
H(12)	-1753	-3749	4492	57
H(14)	-1211	-3474	8124	51
H(15)	173	-843	9005	43
H(16A)	-3848	-5850	5710	106
H(16B)	-1853	-5948	6159	106
H(16C)	-2572	-6025	4748	106

Table 4. Anisotropic parameters ($Å^2$ x 10^3) for C16 H21 N O4 S.

The anisotropic displacement factor exponent takes the form:

$$-2\pi^2 [h^2 a^{*2} U_{11} + ... + 2 h k a^* b^* U_{12}]$$

	U11	U22	U33	U23	U13	U12
S(1)	27(1)	33(1)	31(1)	14(1)	9(1)	13(1)
O(1)	55(1)	43(1)	39(1)	23(1)	15(1)	19(1)
O(2)	63(1)	43(1)	39(1)	5(1)	12(1)	10(1)
O(3)	37(1)	45(1)	43(1)	24(1)	9(1)	20(1)
O(4)	34(1)	39(1)	35(1)	12(1)	14(1)	15(1)
N(1)	27(1)	34(1)	33(1)	18(1)	10(1)	13(1)
C(1)	28(1)	26(1)	34(1)	14(1)	8(1)	10(1)
C(2)	30(1)	32(1)	36(1)	16(1)	7(1)	13(1)
C(3)	42(1)	31(1)	38(1)	11(1)	9(1)	12(1)
C(4)	36(1)	31(1)	55(1)	10(1)	5(1)	4(1)
C(5)	30(1)	30(1)	59(1)	17(1)	16(1)	8(1)
C(6)	27(1)	28(1)	44(1)	15(1)	12(1)	11(1)
C(7)	35(1)	37(1)	44(1)	20(1)	19(1)	15(1)
C(8)	40(1)	47(1)	40(1)	25(1)	20(1)	21(1)
C(9)	50(1)	40(1)	42(1)	15(1)	19(1)	20(1)
C(10)	25(1)	34(1)	30(1)	12(1)	7(1)	10(1)
C(11)	38(1)	43(1)	30(1)	13(1)	7(1)	12(1)
C(12)	44(1)	44(1)	35(1)	5(1)	8(1)	9(1)
C(13)	40(1)	36(1)	54(1)	12(1)	15(1)	9(1)
C(14)	41(1)	41(1)	49(1)	23(1)	17(1)	13(1)
C(15)	33(1)	40(1)	33(1)	15(1)	11(1)	11(1)
C(16)	72(1)	37(1)	83(2)	11(1)	27(1)	8(1)

Table 5. Bond lengths [Å] and angles [°] for C16 H21 N O4 S

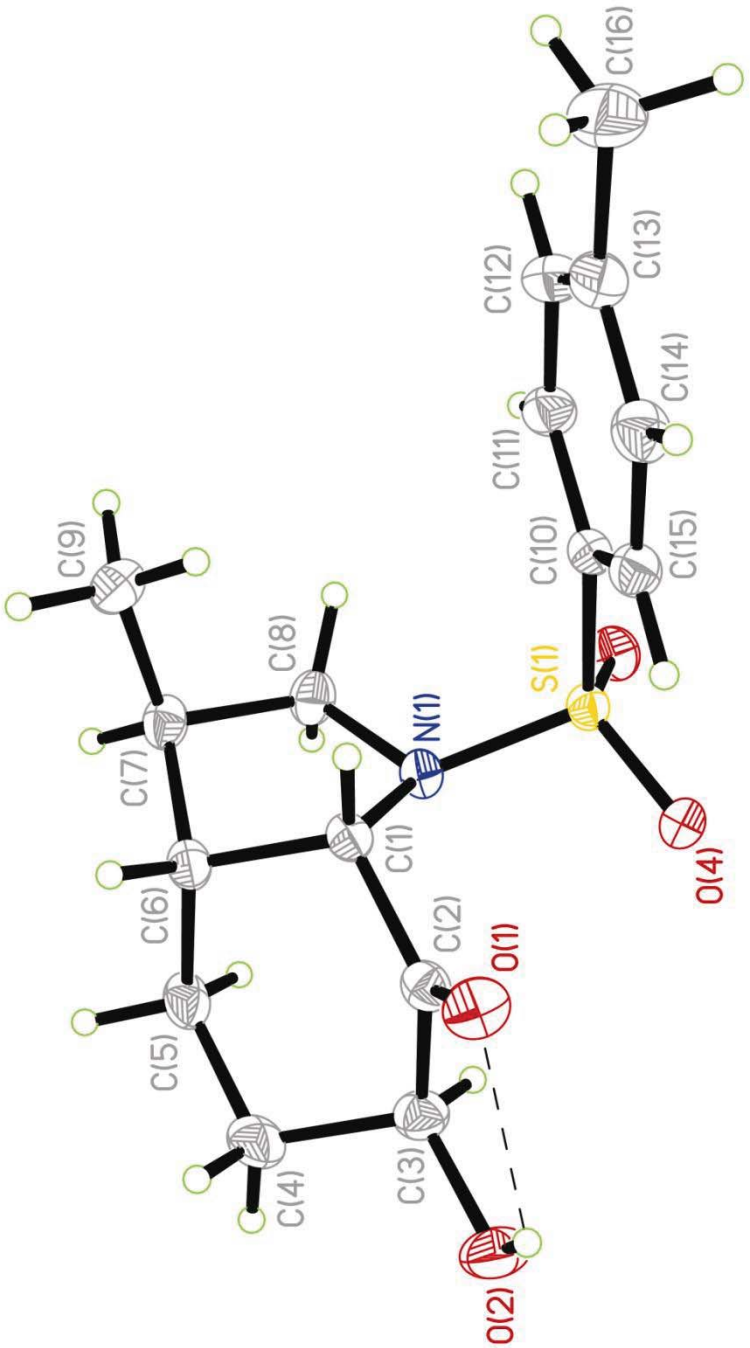
S(1)-O(3)	1.431(1)	C(1)-N(1)-S(1)	118.21(9)
S(1)-O(4)	1.4339(10)	C(8)-N(1)-S(1)	119.66(9)
S(1)-N(1)	1.6306(12)	N(1)-C(1)-C(2)	113.39(11)
S(1)-C(10)	1.7626(14)	N(1)-C(1)-C(6)	101.07(11)
O(1)-C(2)	1.2085(18)	C(2)-C(1)-C(6)	112.24(11)
O(2)-C(3)	1.4175(19)	O(1)-C(2)-C(3)	120.96(14)
N(1)-C(1)	1.4811(16)	O(1)-C(2)-C(1)	122.11(13)
N(1)-C(8)	1.4935(17)	C(3)-C(2)-C(1)	116.44(12)
C(1)-C(2)	1.5126(19)	O(2)-C(3)-C(2)	110.78(13)
C(1)-C(6)	1.5394(19)	O(2)-C(3)-C(4)	112.09(13)
C(2)-C(3)	1.5103(19)	C(2)-C(3)-C(4)	106.75(12)
C(3)-C(4)	1.527(2)	C(5)-C(4)-C(3)	111.35(13)
C(4)-C(5)	1.523(2)	C(4)-C(5)-C(6)	113.14(13)
C(5)-C(6)	1.5377(19)	C(7)-C(6)-C(5)	112.11(12)
C(6)-C(7)	1.534(2)	C(7)-C(6)-C(1)	101.56(11)
C(7)-C(9)	1.529(2)	C(5)-C(6)-C(1)	111.50(11)
C(7)-C(8)	1.540(2)	C(9)-C(7)-C(6)	112.64(12)
C(10)-C(15)	1.387(2)	C(9)-C(7)-C(8)	111.33(13)
C(10)-C(11)	1.393(2)	C(6)-C(7)-C(8)	103.30(12)
C(11)-C(12)	1.384(2)	N(1)-C(8)-C(7)	103.94(11)
C(12)-C(13)	1.394(3)	C(15)-C(10)-C(11)	120.77(14)
C(13)-C(14)	1.390(2)	C(15)-C(10)-S(1)	119.79(11)
C(13)-C(16)	1.512(2)	C(11)-C(10)-S(1)	119.44(11)
C(14)-C(15)	1.390(2)	C(12)-C(11)-C(10)	119.23(15)
O(3)-S(1)-O(4)	119.81(7)	C(11)-C(12)-C(13)	121.01(15)
O(3)-S(1)-N(1)	106.40(6)	C(14)-C(13)-C(12)	118.76(15)
O(4)-S(1)-N(1)	106.18(6)	C(14)-C(13)-C(16)	120.48(18)
O(3)-S(1)-C(10)	108.60(7)	C(12)-C(13)-C(16)	120.75(17)
O(4)-S(1)-C(10)	107.54(6)	C(15)-C(14)-C(13)	121.07(15)
N(1)-S(1)-C(10)	107.76(6)	C(10)-C(15)-C(14)	119.15(14)
C(1)-N(1)-C(8)	110.25(11)		

Table 6. Torsion angles [°] for C16 H21 N O4 S.

O(3)-S(1)-N(1)-C(1)	-176.49(9)	C(2)-C(1)-C(6)-C(5)	-44.41(16)
O(4)-S(1)-N(1)-C(1)	54.83(11)	C(5)-C(6)-C(7)-C(9)	161.97(13)
C(10)-S(1)-N(1)-C(1)	-60.17(11)	C(1)-C(6)-C(7)-C(9)	-78.89(14)
O(3)-S(1)-N(1)-C(8)	-37.25(12)	C(5)-C(6)-C(7)-C(8)	-77.79(15)
O(4)-S(1)-N(1)-C(8)	-165.94(10)	C(1)-C(6)-C(7)-C(8)	41.34(13)
C(10)-S(1)-N(1)-C(8)	79.07(11)	C(1)-N(1)-C(8)-C(7)	-3.82(15)
C(8)-N(1)-C(1)-C(2)	149.64(12)	S(1)-N(1)-C(8)-C(7)	-145.99(10)
S(1)-N(1)-C(1)-C(2)	-67.58(13)	C(9)-C(7)-C(8)-N(1)	97.58(14)
C(8)-N(1)-C(1)-C(6)	29.32(13)	C(6)-C(7)-C(8)-N(1)	-23.55(14)
S(1)-N(1)-C(1)-C(6)	172.11(9)	O(3)-S(1)-C(10)-C(15)	-151.20(12)
N(1)-C(1)-C(2)-O(1)	125.27(15)	O(4)-S(1)-C(10)-C(15)	-20.16(14)
C(6)-C(1)-C(2)-O(1)	-120.98(15)	N(1)-S(1)-C(10)-C(15)	93.93(13)
N(1)-C(1)-C(2)-C(3)	-62.71(16)	O(3)-S(1)-C(10)-C(11)	28.62(14)
C(6)-C(1)-C(2)-C(3)	51.05(16)	O(4)-S(1)-C(10)-C(11)	159.66(12)
O(1)-C(2)-C(3)-O(2)	-7.0(2)	N(1)-S(1)-C(10)-C(11)	-86.25(13)
C(1)-C(2)-C(3)-O(2)	-179.17(12)	C(15)-C(10)-C(11)-C(12)	1.0(2)
O(1)-C(2)-C(3)-C(4)	115.25(17)	S(1)-C(10)-C(11)-C(12)	-178.86(12)
C(1)-C(2)-C(3)-C(4)	-56.87(16)	C(10)-C(11)-C(12)-C(13)	-0.2(3)
O(2)-C(3)-C(4)-C(5)	-179.86(13)	C(11)-C(12)-C(13)-C(14)	-0.5(3)
C(2)-C(3)-C(4)-C(5)	58.67(17)	C(11)-C(12)-C(13)-C(16)	178.71(17)
C(3)-C(4)-C(5)-C(6)	-58.14(18)	C(12)-C(13)-C(14)-C(15)	0.5(3)
C(4)-C(5)-C(6)-C(7)	162.52(13)	C(16)-C(13)-C(14)-C(15)	-178.75(17)
C(4)-C(5)-C(6)-C(1)	49.40(17)	C(11)-C(10)-C(15)-C(14)	-1.0(2)
N(1)-C(1)-C(6)-C(7)	-42.86(12)	S(1)-C(10)-C(15)-C(14)	178.82(11)
C(2)-C(1)-C(6)-C(7)	-163.98(11)	C(13)-C(14)-C(15)-C(10)	0.3(2)
N(1)-C(1)-C(6)-C(5)	76.72(14)		

Table 7. Bond lengths [Å] and angles [°] related to the hydrogen bonding for C16 H21 N O4 S.

D-H	..A	d(D-H)	d(H..A)	d(D..A)	<DHA
O(2)-H(2)	O(1)	0.84	2.17	2.6547(17)	117



ORTEP view of the C16 H21 N O4 S compound with the numbering scheme adopted. Ellipsoids drawn at 30% probability level. Hydrogen atoms are represented by sphere of arbitrary size.

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Université de Montréal

CRYSTAL AND MOLECULAR STRUCTURE OF

C17 H20 N2 O3 S COMPOUND (bent86)

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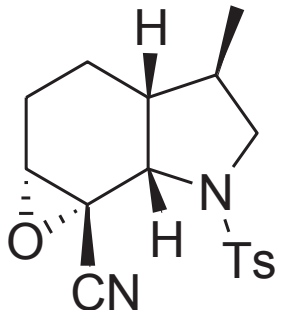


Recemic

Structure solved and refined in the laboratory of X-ray diffraction Université de Montréal by Benoît Deschênes Simard.

Table 1. Crystal data and structure refinement for C17 H20 N2 O3 S.

Identification code	bent86
Empirical formula	C17 H20 N2 O3 S
Formula weight	332.41
Temperature	200K
Wavelength	1.54178 Å
Crystal system	Monoclinic
Space group	P21/n
Unit cell dimensions	a = 9.9025(2) Å α = 90° b = 17.4833(3) Å β = 116.3860(10)° c = 10.5169(2) Å γ = 90°
Volume	1631.09(5)Å^3
Z	4
Density (calculated)	1.354 g/cm^3
Absorption coefficient	1.905 mm^{-1}
F(000)	704
Crystal size	0.20 x 0.19 x 0.18 mm
Theta range for data collection	5.06 to 72.58°
Index ranges	$-12 \le h \le 12$, $-21 \le k \le 21$, $-12 \le \ell \le 12$
Reflections collected	21270
Independent reflections	3205 [R_{int} = 0.035]
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.7097 and 0.5550
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3205 / 52 / 250
Goodness-of-fit on F^2	1.043
Final R indices [I>2sigma(I)]	R_1 = 0.0445, wR_2 = 0.1188
R indices (all data)	R_1 = 0.0459, wR_2 = 0.1201
Extinction coefficient	0.0122(8)
Largest diff. peak and hole	0.250 and -0.339 e/Å^3

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for C17 H20 N2 O3 S.

U_{eq} is defined as one third of the trace of the orthogonalized Uij tensor.

	Occ.	x	y	z	U_{eq}
S(11)	0.905(2)	4546(1)	7984(1)	7805(1)	40(1)
O(11)	0.905(2)	1220(1)	9815(1)	6904(1)	39(1)
O(12)	0.905(2)	3823(2)	7271(1)	7232(2)	58(1)
O(13)	0.905(2)	4930(2)	8188(1)	9242(2)	60(1)
N(11)	0.905(2)	3414(3)	8651(1)	6810(2)	34(1)
N(12)	0.905(2)	3392(3)	9496(1)	10405(2)	58(1)
C(12)	0.905(2)	2813(3)	9816(1)	7796(3)	35(1)
C(13)	0.905(2)	2000(3)	10548(1)	7232(2)	39(1)
C(14)	0.905(2)	2084(2)	10948(1)	6005(2)	42(1)
C(15)	0.905(2)	3428(2)	10693(1)	5766(2)	41(1)
C(17)	0.905(2)	2299(3)	9358(1)	4662(2)	34(1)
C(18)	0.905(2)	2696(2)	8545(1)	5245(2)	36(1)
C(19)	0.905(2)	3174(3)	9628(2)	9265(2)	41(1)
C(110)	0.905(2)	2125(7)	9442(2)	3150(2)	51(1)
C(111)	0.905(2)	6229(2)	8010(1)	7606(2)	34(1)
C(112)	0.905(2)	6386(2)	7523(1)	6635(1)	38(1)
C(113)	0.905(2)	7737(2)	7501(1)	6533(2)	41(1)
C(114)	0.905(2)	8932(2)	7965(2)	7403(3)	40(1)
C(115)	0.905(2)	8775(2)	8451(2)	8374(3)	43(1)
C(116)	0.905(2)	7423(2)	8474(1)	8476(2)	40(1)
C(117)	0.905(2)	10425(5)	7917(4)	7318(9)	56(1)
S(21)	0.095(2)	4851(7)	8158(3)	8305(8)	40(1)
O(21)	0.095(2)	1485(16)	10221(11)	6924(15)	39(1)
O(22)	0.095(2)	4197(19)	7408(7)	7990(20)	58(1)
O(23)	0.095(2)	5310(20)	8502(10)	9640(15)	60(1)
N(21)	0.095(2)	3560(30)	8669(7)	7025(15)	34(1)
N(22)	0.095(2)	2810(30)	9388(15)	10088(18)	58(1)
C(22)	0.095(2)	2930(30)	9895(9)	7810(20)	35(1)
C(23)	0.095(2)	2690(20)	10750(8)	7599(18)	39(1)
C(24)	0.095(2)	3230(20)	11134(7)	6614(17)	42(1)
C(25)	0.095(2)	3030(30)	10623(7)	5401(17)	41(1)
C(27)	0.095(2)	2380(30)	9204(9)	4749(15)	34(1)
C(28)	0.095(2)	3030(30)	8468(8)	5495(15)	36(1)
C(29)	0.095(2)	2820(40)	9590(30)	9070(30)	41(1)
C(210)	0.095(2)	2110(70)	9302(19)	3238(16)	51(1)
C(211)	0.095(2)	6410(17)	8089(11)	7890(20)	34(1)
C(212)	0.095(2)	6497(19)	7493(11)	7060(19)	38(1)
C(213)	0.095(2)	7760(20)	7419(13)	6820(20)	41(1)
C(214)	0.095(2)	8940(20)	7941(17)	7410(30)	40(1)
C(215)	0.095(2)	8850(20)	8537(17)	8240(30)	43(1)
C(216)	0.095(2)	7590(20)	8611(13)	8490(30)	40(1)
C(217)	0.095(2)	10400(50)	7820(40)	7290(90)	56(1)
C(1)	1	3817(2)	9466(1)	7196(2)	32(1)
C(6)	1	3590(2)	9823(1)	5781(2)	33(1)

Table 3. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for C17 H20 N2 O3 S.

	Occ.	x	y	z	U_{eq}
H(13)	0.905(2)	1836	10880	7925	47
H(14A)	0.905(2)	2153	11506	6179	51
H(14B)	0.905(2)	1144	10848	5132	51
H(15A)	0.905(2)	4361	10915	6517	49
H(15B)	0.905(2)	3309	10892	4841	49
H(17A)	0.905(2)	1333	9512	4675	41
H(18A)	0.905(2)	1779	8224	4930	43
H(18B)	0.905(2)	3403	8303	4935	43
H(11H)	0.905(2)	1276	9129	2503	77
H(11I)	0.905(2)	3051	9270	3117	77
H(11J)	0.905(2)	1938	9979	2860	77
H(11A)	0.905(2)	5569	7206	6041	46
H(11B)	0.905(2)	7845	7168	5869	49
H(11C)	0.905(2)	9591	8768	8969	51
H(11D)	0.905(2)	7316	8806	9140	48
H(11E)	0.905(2)	11225	7767	8245	84
H(11F)	0.905(2)	10665	8418	7051	84
H(11G)	0.905(2)	10347	7537	6604	84
H(23)	0.095(2)	2699	11059	8404	47
H(24A)	0.095(2)	2649	11612	6239	51
H(24B)	0.095(2)	4303	11270	7155	51
H(25A)	0.095(2)	1944	10603	4733	49
H(25B)	0.095(2)	3558	10859	4891	49
H(27A)	0.095(2)	1407	9293	4791	41
H(28A)	0.095(2)	3877	8296	5310	43
H(28B)	0.095(2)	2251	8062	5196	43
H(21H)	0.095(2)	1384	8917	2644	77
H(21I)	0.095(2)	3061	9239	3175	77
H(21J)	0.095(2)	1705	9815	2908	77
H(21A)	0.095(2)	5694	7136	6656	46
H(21B)	0.095(2)	7820	7012	6245	49
H(21C)	0.095(2)	9652	8894	8645	51
H(21D)	0.095(2)	7526	9018	9056	48
H(21E)	0.095(2)	11111	8228	7786	84
H(21F)	0.095(2)	10190	7818	6284	84
H(21G)	0.095(2)	10840	7323	7714	84
H(1)	1	4899	9508	7906	38
H(6)	1	4515	9709	5659	39

Table 4. Anisotropic parameters ($Å^2$ x 10^3) for C17 H20 N2 O3 S.

The anisotropic displacement factor exponent takes the form:

$$-2\pi^2 [h^2 a^{*2} U_{11} + ... + 2 h k a^* b^* U_{12}]$$

	U11	U22	U33	U23	U13	U12
S(11)	44(1)	35(1)	48(1)	16(1)	28(1)	10(1)
O(11)	32(1)	40(1)	46(1)	-5(1)	19(1)	-1(1)
O(12)	56(1)	29(1)	101(1)	18(1)	46(1)	2(1)
O(13)	66(1)	80(1)	44(1)	27(1)	35(1)	31(1)
N(11)	35(1)	29(1)	40(1)	5(1)	19(1)	2(1)
N(12)	71(2)	68(1)	39(1)	-8(1)	28(1)	-16(1)
C(12)	34(1)	39(1)	34(1)	-3(1)	17(1)	-2(1)
C(13)	41(1)	35(1)	46(1)	-8(1)	22(1)	0(1)
C(14)	51(1)	29(1)	51(1)	0(1)	26(1)	6(1)
C(15)	49(1)	28(1)	52(1)	2(1)	28(1)	-2(1)
C(17)	37(1)	30(1)	34(1)	2(1)	16(1)	6(1)
C(18)	36(1)	30(1)	40(1)	-2(1)	15(1)	0(1)
C(19)	42(2)	45(1)	39(1)	-9(1)	21(1)	-9(1)
C(110)	68(1)	50(2)	38(1)	1(1)	25(1)	8(2)
C(111)	37(1)	30(1)	36(1)	10(1)	17(1)	7(1)
C(112)	40(1)	32(1)	40(1)	1(1)	15(1)	1(1)
C(113)	46(1)	39(1)	42(1)	2(1)	23(1)	7(1)
C(114)	38(1)	40(1)	44(1)	12(1)	20(1)	7(1)
C(115)	39(1)	37(1)	46(1)	3(1)	13(1)	1(1)
C(116)	45(1)	35(1)	39(1)	0(1)	17(1)	7(1)
C(117)	43(1)	69(2)	62(1)	10(2)	29(1)	7(1)
S(21)	44(1)	35(1)	48(1)	16(1)	28(1)	10(1)
O(21)	32(1)	40(1)	46(1)	-5(1)	19(1)	-1(1)
O(22)	56(1)	29(1)	101(1)	18(1)	46(1)	2(1)
O(23)	66(1)	80(1)	44(1)	27(1)	35(1)	31(1)
N(21)	35(1)	29(1)	40(1)	5(1)	19(1)	2(1)
N(22)	71(2)	68(1)	39(1)	-8(1)	28(1)	-16(1)
C(22)	34(1)	39(1)	34(1)	-3(1)	17(1)	-2(1)
C(23)	41(1)	35(1)	46(1)	-8(1)	22(1)	0(1)
C(24)	51(1)	29(1)	51(1)	0(1)	26(1)	6(1)
C(25)	49(1)	28(1)	52(1)	2(1)	28(1)	-2(1)
C(27)	37(1)	30(1)	34(1)	2(1)	16(1)	6(1)
C(28)	36(1)	30(1)	40(1)	-2(1)	15(1)	0(1)
C(29)	42(2)	45(1)	39(1)	-9(1)	21(1)	-9(1)
C(210)	68(1)	50(2)	38(1)	1(1)	25(1)	8(2)
C(211)	37(1)	30(1)	36(1)	10(1)	17(1)	7(1)
C(212)	40(1)	32(1)	40(1)	1(1)	15(1)	1(1)
C(213)	46(1)	39(1)	42(1)	2(1)	23(1)	7(1)
C(214)	38(1)	40(1)	44(1)	12(1)	20(1)	7(1)
C(215)	39(1)	37(1)	46(1)	3(1)	13(1)	1(1)
C(216)	45(1)	35(1)	39(1)	0(1)	17(1)	7(1)
C(217)	43(1)	69(2)	62(1)	10(2)	29(1)	7(1)
C(1)	29(1)	32(1)	34(1)	1(1)	14(1)	1(1)
C(6)	36(1)	29(1)	39(1)	3(1)	22(1)	2(1)

Table 5. Bond lengths [Å] and angles [°] for C17 H20 N2 O3 S

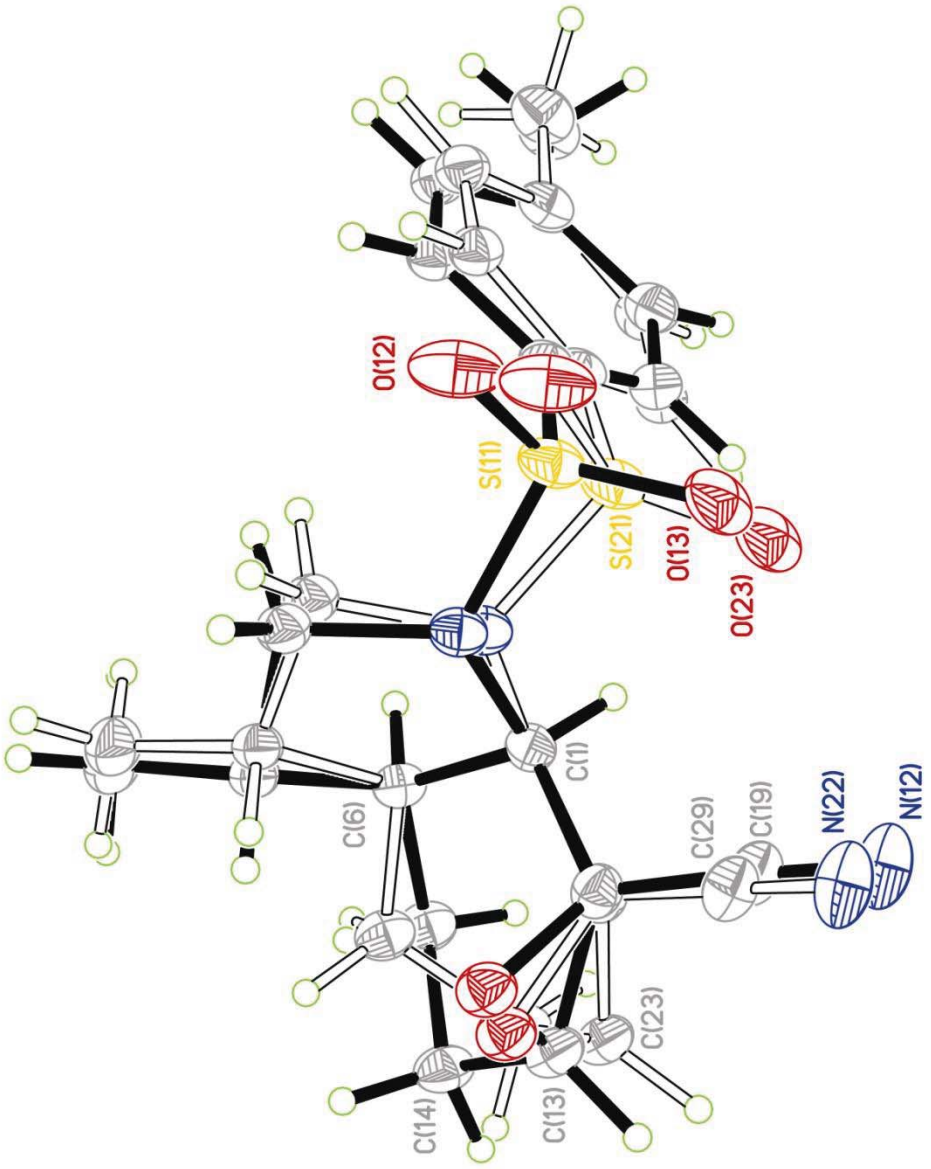
S(11)-O(12)	1.4307(17)	O(13)-S(11)-C(111)	107.25(9)
S(11)-O(13)	1.4307(17)	N(11)-S(11)-C(111)	108.70(11)
S(11)-N(11)	1.6335(17)	C(12)-O(11)-C(13)	61.98(11)
S(11)-C(111)	1.7688(12)	C(18)-N(11)-C(1)	111.11(14)
O(11)-C(12)	1.433(3)	C(18)-N(11)-S(11)	118.35(13)
O(11)-C(13)	1.456(2)	C(1)-N(11)-S(11)	119.01(14)
N(11)-C(18)	1.486(2)	O(11)-C(12)-C(19)	111.92(17)
N(11)-C(1)	1.487(2)	O(11)-C(12)-C(13)	59.78(13)
N(12)-C(19)	1.143(3)	C(19)-C(12)-C(13)	116.7(2)
C(12)-C(19)	1.460(3)	O(11)-C(12)-C(1)	117.36(17)
C(12)-C(13)	1.488(3)	C(19)-C(12)-C(1)	116.8(2)
C(12)-C(1)	1.523(2)	C(13)-C(12)-C(1)	121.16(16)
C(13)-C(14)	1.503(3)	O(11)-C(13)-C(12)	58.24(14)
C(14)-C(15)	1.527(3)	O(11)-C(13)-C(14)	115.58(18)
C(15)-C(6)	1.529(2)	C(12)-C(13)-C(14)	121.05(15)
C(17)-C(110)	1.528(3)	C(13)-C(14)-C(15)	112.98(15)
C(17)-C(18)	1.529(2)	C(14)-C(15)-C(6)	112.60(15)
C(17)-C(6)	1.530(2)	C(110)-C(17)-C(18)	113.40(18)
C(111)-C(112)	1.3900	C(110)-C(17)-C(6)	114.7(2)
C(111)-C(116)	1.3900	C(18)-C(17)-C(6)	101.96(14)
C(112)-C(113)	1.3900	N(11)-C(18)-C(17)	103.88(14)
C(113)-C(114)	1.3900	N(12)-C(19)-C(12)	176.7(3)
C(114)-C(115)	1.3900	C(112)-C(111)-C(116)	120.0
C(114)-C(117)	1.523(2)	C(112)-C(111)-S(11)	119.34(8)
C(115)-C(116)	1.3900	C(116)-C(111)-S(11)	120.53(8)
S(21)-O(23)	1.405(12)	C(113)-C(112)-C(111)	120.0
S(21)-O(22)	1.434(11)	C(114)-C(113)-C(112)	120.0
S(21)-N(21)	1.649(14)	C(113)-C(114)-C(115)	120.0
S(21)-C(211)	1.782(11)	C(113)-C(114)-C(117)	119.63(16)
O(21)-C(23)	1.424(16)	C(115)-C(114)-C(117)	120.34(17)
O(21)-C(22)	1.430(18)	C(116)-C(115)-C(114)	120.0
N(21)-C(1)	1.414(13)	C(115)-C(116)-C(111)	120.0
N(21)-C(28)	1.496(15)	O(23)-S(21)-O(22)	122.1(11)
N(22)-C(29)	1.135(14)	O(23)-S(21)-N(21)	111.8(10)
C(22)-C(29)	1.469(14)	O(22)-S(21)-N(21)	101.6(10)
C(22)-C(1)	1.506(13)	O(23)-S(21)-C(211)	109.9(10)
C(22)-C(23)	1.515(15)	O(22)-S(21)-C(211)	103.6(9)
C(23)-C(24)	1.515(15)	N(21)-S(21)-C(211)	106.3(12)
C(24)-C(25)	1.498(15)	C(23)-O(21)-C(22)	64.1(9)
C(25)-C(6)	1.492(13)	C(1)-N(21)-C(28)	108.9(10)
C(27)-C(28)	1.494(17)	C(1)-N(21)-S(21)	113.5(12)
C(27)-C(210)	1.498(18)	C(28)-N(21)-S(21)	121.6(12)
C(27)-C(6)	1.619(15)	O(21)-C(22)-C(29)	106(2)
C(211)-C(212)	1.3900	O(21)-C(22)-C(1)	121.5(15)
C(211)-C(216)	1.3900	C(29)-C(22)-C(1)	120(2)
C(212)-C(213)	1.3900	O(21)-C(22)-C(23)	57.7(8)
C(213)-C(214)	1.3900	C(29)-C(22)-C(23)	115(2)
C(214)-C(215)	1.3900	C(1)-C(22)-C(23)	120.7(11)
C(214)-C(217)	1.526(16)	O(21)-C(23)-C(22)	58.2(9)
C(215)-C(216)	1.3900	O(21)-C(23)-C(24)	114.7(14)
C(1)-C(6)	1.5347(19)	C(22)-C(23)-C(24)	117.3(10)
O(12)-S(11)-O(13)	120.71(11)	C(25)-C(24)-C(23)	111.5(11)
O(12)-S(11)-N(11)	106.24(10)	C(6)-C(25)-C(24)	116.0(11)
O(13)-S(11)-N(11)	106.44(10)	C(28)-C(27)-C(210)	119.3(19)
O(12)-S(11)-C(111)	107.09(8)	C(28)-C(27)-C(6)	102.0(12)

C(210)-C(27)-C(6)	111.5(17)	C(22)-C(1)-C(12)	6.6(9)
C(27)-C(28)-N(21)	103.1(11)	N(21)-C(1)-C(6)	109.7(6)
N(22)-C(29)-C(22)	176(4)	N(11)-C(1)-C(6)	102.64(12)
C(212)-C(211)-C(216)	120.0	C(22)-C(1)-C(6)	110.7(6)
C(212)-C(211)-S(21)	120.5(7)	C(12)-C(1)-C(6)	113.44(13)
C(216)-C(211)-S(21)	119.4(7)	C(25)-C(6)-C(15)	16.2(9)
C(211)-C(212)-C(213)	120.0	C(25)-C(6)-C(17)	102.0(9)
C(214)-C(213)-C(212)	120.0	C(15)-C(6)-C(17)	118.22(14)
C(213)-C(214)-C(215)	120.0	C(25)-C(6)-C(1)	121.2(6)
C(213)-C(214)-C(217)	120.5(9)	C(15)-C(6)-C(1)	112.54(13)
C(215)-C(214)-C(217)	119.2(9)	C(17)-C(6)-C(1)	104.03(13)
C(214)-C(215)-C(216)	120.0	C(25)-C(6)-C(27)	111.8(11)
C(215)-C(216)-C(211)	120.0	C(15)-C(6)-C(27)	128.0(8)
N(21)-C(1)-N(11)	7.8(6)	C(17)-C(6)-C(27)	9.8(7)
N(21)-C(1)-C(22)	115.9(10)	C(1)-C(6)-C(27)	97.2(7)
N(11)-C(1)-C(22)	117.2(9)		
N(21)-C(1)-C(12)	109.4(10)		
N(11)-C(1)-C(12)	110.64(14)		

Table 6. Torsion angles [°] for C17 H20 N2 O3 S.

O(12)-S(11)-N(11)-C(18) -43.6(2)	C(210)-C(27)-C(28)-N(21) 164(3)
O(13)-S(11)-N(11)-C(18) -173.44(19)	C(6)-C(27)-C(28)-N(21) 40(3)
C(111)-S(11)-N(11)-C(18) 71.3(2)	
O(12)-S(11)-N(11)-C(1) 176.29(16)	C(1)-N(21)-C(28)-C(27) -24(3)
O(13)-S(11)-N(11)-C(1) 46.5(2)	S(21)-N(21)-C(28)-C(27) -159(2)
C(111)-S(11)-N(11)-C(1) -68.77(18)	O(23)-S(21)-C(211)-C(212) 149.3(14)
C(13)-O(11)-C(12)-C(19) 109.1(2)	O(22)-S(21)-C(211)-C(212) 17.2(17)
C(13)-O(11)-C(12)-C(1) -111.89(18)	N(21)-S(21)-C(211)-C(212) -89.5(15)
C(12)-O(11)-C(13)-C(14) 112.09(18)	O(23)-S(21)-C(211)-C(216) -26.9(16)
C(19)-C(12)-C(13)-O(11) -101.0(2)	O(22)-S(21)-C(211)-C(216) -159.0(14)
C(1)-C(12)-C(13)-O(11) 105.6(2)	N(21)-S(21)-C(211)-C(216) 94.3(13)
O(11)-C(12)-C(13)-C(14) -102.7(2)	C(216)-C(211)-C(212)-C(213) 0.0
C(19)-C(12)-C(13)-C(14) 156.3(2)	S(21)-C(211)-C(212)-C(213) -176.2(18)
C(1)-C(12)-C(13)-C(14) 2.9(4)	C(211)-C(212)-C(213)-C(214) 0.0
O(11)-C(13)-C(14)-C(15) -86.1(2)	C(212)-C(213)-C(214)-C(215) 0.0
C(12)-C(13)-C(14)-C(15) -19.3(3)	C(212)-C(213)-C(214)-C(217) 173(5)
C(13)-C(14)-C(15)-C(6) 47.3(2)	C(213)-C(214)-C(215)-C(216) 0.0
C(1)-N(11)-C(18)-C(17) -14.2(3)	C(217)-C(214)-C(215)-C(216) -173(5)
S(11)-N(11)-C(18)-C(17) -157.21(19)	C(214)-C(215)-C(216)-C(211) 0.0
C(110)-C(17)-C(18)-N(11) 157.3(3)	C(212)-C(211)-C(216)-C(215) 0.0
C(6)-C(17)-C(18)-N(11) 33.4(2)	S(21)-C(211)-C(216)-C(215) 176.2(17)
O(12)-S(11)-C(111)-C(112) 18.98(15)	C(28)-N(21)-C(1)-N(11) 20(7)
O(13)-S(11)-C(111)-C(112) 149.89(12)	S(21)-N(21)-C(1)-N(11) 159(9)
N(11)-S(11)-C(111)-C(112) -95.41(12)	C(28)-N(21)-C(1)-C(22) 122(2)
O(12)-S(11)-C(111)-C(116) -156.79(12)	S(21)-N(21)-C(1)-C(22) -99.5(14)
O(13)-S(11)-C(111)-C(116) -25.88(13)	C(28)-N(21)-C(1)-C(12) 120.4(17)
N(11)-S(11)-C(111)-C(116) 88.82(12)	S(21)-N(21)-C(1)-C(12) -100.7(14)
C(116)-C(111)-C(112)-C(113) 0.0	C(28)-N(21)-C(1)-C(6) -5(2)
S(11)-C(111)-C(112)-C(113) -175.8(2)	S(21)-N(21)-C(1)-C(6) 134.3(10)
C(111)-C(112)-C(113)-C(114) 0.0	C(18)-N(11)-C(1)-N(21) -167(8)
C(112)-C(113)-C(114)-C(115) 0.0	S(11)-N(11)-C(1)-N(21) -25(8)
C(112)-C(113)-C(114)-C(117) 178.0(4)	C(18)-N(11)-C(1)-C(22) 110.4(9)
C(113)-C(114)-C(115)-C(116) 0.0	S(11)-N(11)-C(1)-C(22) -106.8(9)
C(117)-C(114)-C(115)-C(116) -178.0(4)	C(18)-N(11)-C(1)-C(12) 110.3(2)
C(114)-C(115)-C(116)-C(111) 0.0	S(11)-N(11)-C(1)-C(12) -106.94(18)
C(112)-C(111)-C(116)-C(115) 0.0	C(18)-N(11)-C(1)-C(6) -11.0(2)
S(11)-C(111)-C(116)-C(115) 175.73(15)	S(11)-N(11)-C(1)-C(6) 131.73(15)
O(23)-S(21)-N(21)-C(1) 39.4(19)	O(21)-C(22)-C(1)-N(21) -90.6(17)
O(22)-S(21)-N(21)-C(1) 171.3(14)	C(29)-C(22)-C(1)-N(21) 46(3)
C(211)-S(21)-N(21)-C(1) -80.6(14)	C(23)-C(22)-C(1)-N(21) -159.3(17)
O(23)-S(21)-N(21)-C(28) 172.6(19)	O(21)-C(22)-C(1)-N(11) -82.1(15)
O(22)-S(21)-N(21)-C(28) -56(2)	C(29)-C(22)-C(1)-N(11) 55(3)
C(211)-S(21)-N(21)-C(28) 53(2)	C(23)-C(22)-C(1)-N(11) -150.8(15)
C(23)-O(21)-C(22)-C(29) 110(2)	O(21)-C(22)-C(1)-C(12) -81(8)
C(23)-O(21)-C(22)-C(1) -108.8(16)	C(29)-C(22)-C(1)-C(12) 56(6)
C(22)-O(21)-C(23)-C(24) 107.9(13)	C(23)-C(22)-C(1)-C(12) -150(9)
C(29)-C(22)-C(23)-O(21) -94(2)	O(21)-C(22)-C(1)-C(6) 35(2)
C(1)-C(22)-C(23)-O(21) 110.1(19)	C(29)-C(22)-C(1)-C(6) 172(2)
O(21)-C(22)-C(23)-C(24) -103.4(18)	C(23)-C(22)-C(1)-C(6) -34(2)
C(29)-C(22)-C(23)-C(24) 162(2)	O(11)-C(12)-C(1)-N(21) -67.4(7)
C(1)-C(22)-C(23)-C(24) 7(3)	C(19)-C(12)-C(1)-N(21) 69.7(7)
O(21)-C(23)-C(24)-C(25) -31(2)	C(13)-C(12)-C(1)-N(21) -136.9(7)
C(22)-C(23)-C(24)-C(25) 35(2)	O(11)-C(12)-C(1)-N(11) -59.2(2)
C(23)-C(24)-C(25)-C(6) -48(2)	C(19)-C(12)-C(1)-N(11) 77.8(2)

C(13)-C(12)-C(1)-N(11)	-128.8(2)	C(22)-C(1)-C(6)-C(25)	19.9(16)
O(11)-C(12)-C(1)-C(22)	122(7)	C(12)-C(1)-C(6)-C(25)	26.3(12)
C(19)-C(12)-C(1)-C(22)	-101(7)	N(21)-C(1)-C(6)-C(15)	164.5(10)
C(13)-C(12)-C(1)-C(22)	52(7)	N(11)-C(1)-C(6)-C(15)	161.15(15)
O(11)-C(12)-C(1)-C(6)	55.5(2)	C(22)-C(1)-C(6)-C(15)	35.3(11)
C(19)-C(12)-C(1)-C(6)	-167.45(19)	C(12)-C(1)-C(6)-C(15)	41.8(2)
C(13)-C(12)-C(1)-C(6)	-14.1(3)	N(21)-C(1)-C(6)-C(17)	35.3(10)
C(24)-C(25)-C(6)-C(15)	-40.9(19)	N(11)-C(1)-C(6)-C(17)	31.99(18)
C(24)-C(25)-C(6)-C(17)	135.6(17)	C(22)-C(1)-C(6)-C(17)	-93.8(11)
C(24)-C(25)-C(6)-C(1)	21(2)	C(12)-C(1)-C(6)-C(17)	-87.41(18)
C(24)-C(25)-C(6)-C(27)	134(2)	N(21)-C(1)-C(6)-C(27)	28.1(16)
C(14)-C(15)-C(6)-C(25)	65(3)	N(11)-C(1)-C(6)-C(27)	24.8(12)
C(14)-C(15)-C(6)-C(17)	61.3(2)	C(22)-C(1)-C(6)-C(27)	-101.0(16)
C(14)-C(15)-C(6)-C(1)	-60.11(19)	C(12)-C(1)-C(6)-C(27)	-94.6(12)
C(14)-C(15)-C(6)-C(27)	59.6(14)	C(28)-C(27)-C(6)-C(25)	-169.1(18)
C(110)-C(17)-C(6)-C(25)	69.4(8)	C(210)-C(27)-C(6)-C(25)	63(3)
C(18)-C(17)-C(6)-C(25)	-167.6(8)	C(28)-C(27)-C(6)-C(15)	-167.4(13)
C(110)-C(17)-C(6)-C(15)	70.5(3)	C(210)-C(27)-C(6)-C(15)	64(3)
C(18)-C(17)-C(6)-C(15)	-166.47(18)	C(28)-C(27)-C(6)-C(17)	-176(9)
C(110)-C(17)-C(6)-C(1)	-163.8(2)	C(210)-C(27)-C(6)-C(17)	56(7)
C(18)-C(17)-C(6)-C(1)	-40.8(2)	C(28)-C(27)-C(6)-C(1)	-41(2)
C(110)-C(17)-C(6)-C(27)	-117(8)	C(210)-C(27)-C(6)-C(1)	-170(2)
C(18)-C(17)-C(6)-C(27)	6(7)		
N(21)-C(1)-C(6)-C(25)	149.0(16)		
N(11)-C(1)-C(6)-C(25)	145.7(12)		



ORTEP view of the C17 H20 N2 O3 S compound with the numbering scheme adopted. Ellipsoids drawn at 30% probability level. Hydrogen atoms are represented by sphere of arbitrary size.

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Université de Montréal

CRYSTAL AND MOLECULAR STRUCTURE OF

C16 H25 N O5 COMPOUND (bent94)

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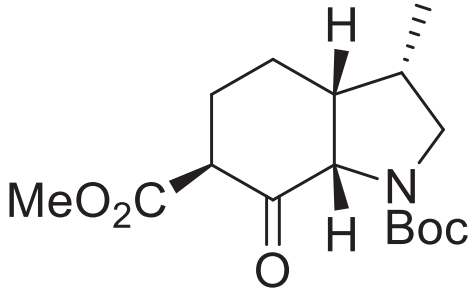


Structure solved and refined in the laboratory of X-ray diffraction Université de Montréal by Benoît Deschênes Simard.

Table 1. Crystal data and structure refinement for C16 H25 N O5.

Identification code	bent94
Empirical formula	C16 H25 N O5
Formula weight	311.37
Temperature	100K
Wavelength	1.54178 Å
Crystal system	Orthorhombic
Space group	P212121
Unit cell dimensions	a = 8.01610(10) Å α = 90° b = 12.04590(20) Å β = 90° c = 16.94970(30) Å γ = 90°
Volume	1636.68(3)Å^3
Z	4
Density (calculated)	1.264 g/cm^3
Absorption coefficient	0.769 mm^{-1}
F(000)	672
Crystal size	0.13 x 0.12 x 0.11 mm
Theta range for data collection	5.22 to 71.05°
Index ranges	$-9 \le h \le 9$, $-14 \le k \le 14$, $-20 \le \ell \le 20$
Reflections collected	42723
Independent reflections	3146 [R_{int} = 0.028]
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9189 and 0.8512
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3146 / 1 / 204
Goodness-of-fit on F^2	1.039
Final R indices [I>2sigma(I)]	R_1 = 0.0271, wR_2 = 0.0730
R indices (all data)	R_1 = 0.0277, wR_2 = 0.0735
Absolute structure parameter	-0.08(12)
Largest diff. peak and hole	0.224 and -0.152 e/Å^3

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for C16 H25 N O5.

U_{eq} is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U_{eq}
O(1)	-611(1)	1949(1)	2871(1)	22(1)
O(2)	-1829(1)	3698(1)	4461(1)	26(1)
O(3)	631(1)	3900(1)	3848(1)	24(1)
O(4)	5068(1)	493(1)	3695(1)	24(1)
O(5)	3173(1)	1504(1)	2982(1)	24(1)
N(1)	2280(1)	180(1)	3772(1)	19(1)
C(1)	572(1)	339(1)	3478(1)	18(1)
C(2)	-23(1)	1543(1)	3461(1)	17(1)
C(3)	-73(1)	2094(1)	4266(1)	18(1)
C(4)	-1331(1)	1418(1)	4760(1)	20(1)
C(5)	-704(2)	230(1)	4861(1)	20(1)
C(6)	-439(1)	-368(1)	4068(1)	20(1)
C(7)	722(1)	-1385(1)	4146(1)	21(1)
C(8)	2441(1)	-839(1)	4236(1)	20(1)
C(9)	300(2)	-2191(1)	4809(1)	27(1)
C(10)	-560(1)	3304(1)	4209(1)	20(1)
C(11)	288(2)	5074(1)	3793(1)	29(1)
C(12)	3651(1)	711(1)	3496(1)	19(1)
C(13)	4393(1)	2180(1)	2543(1)	22(1)
C(14)	5323(2)	2938(1)	3107(1)	28(1)
C(15)	5553(2)	1425(1)	2077(1)	27(1)
C(16)	3263(2)	2849(1)	2000(1)	28(1)

Table 3. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for C16 H25 N O5.

	x	y	z	U_{eq}
H(1)	472	11	2938	22
H(3)	1055	2038	4515	22
H(4A)	-1473	1769	5284	24
H(4B)	-2429	1412	4492	24
H(5A)	-1520	-193	5180	24
H(5B)	364	243	5154	24
H(6)	-1534	-590	3834	24
H(7)	703	-1802	3636	26
H(8A)	2685	-671	4796	24
H(8B)	3334	-1322	4024	24
H(9A)	1115	-2798	4813	40
H(9B)	-820	-2495	4724	40
H(9C)	335	-1799	5315	40
H(11A)	-778	5188	3522	44
H(11B)	1182	5438	3496	44
H(11C)	228	5392	4325	44
H(14A)	4523	3412	3386	43
H(14B)	6103	3404	2809	43
H(14C)	5943	2489	3489	43
H(15A)	6263	1008	2442	40
H(15B)	6253	1875	1727	40
H(15C)	4889	907	1760	40
H(16A)	2681	2345	1639	42
H(16B)	3936	3375	1695	42
H(16C)	2443	3257	2316	42

Table 4. Anisotropic parameters ($Å^2$ x 10^3) for C16 H25 N O5.

The anisotropic displacement factor exponent takes the form:

$$-2\pi^2 [h^2 a^{*2} U_{11} + ... + 2 h k a^* b^* U_{12}]$$

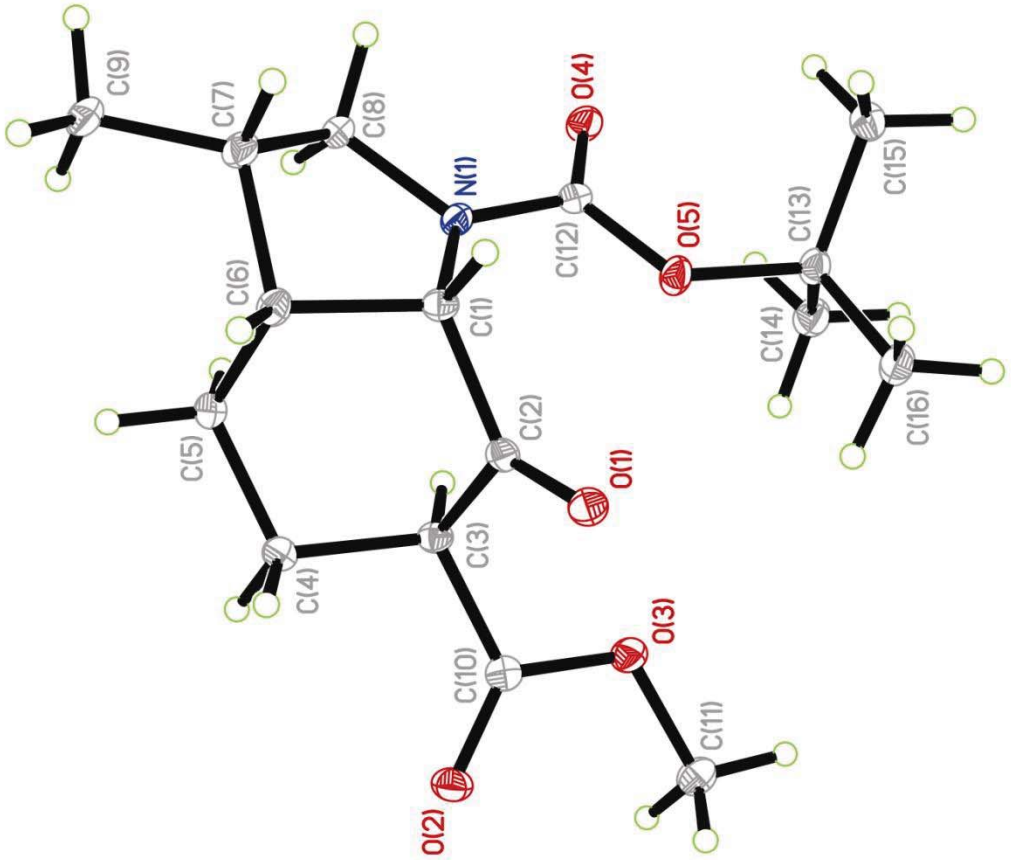
	U11	U22	U33	U23	U13	U12
O(1)	20(1)	24(1)	22(1)	2(1)	-2(1)	2(1)
O(2)	23(1)	21(1)	34(1)	-3(1)	5(1)	3(1)
O(3)	23(1)	18(1)	31(1)	1(1)	3(1)	-1(1)
O(4)	18(1)	24(1)	31(1)	6(1)	0(1)	3(1)
O(5)	17(1)	26(1)	31(1)	12(1)	2(1)	1(1)
N(1)	18(1)	17(1)	22(1)	4(1)	0(1)	2(1)
C(1)	18(1)	17(1)	19(1)	-2(1)	-1(1)	0(1)
C(2)	13(1)	18(1)	22(1)	0(1)	1(1)	-2(1)
C(3)	16(1)	17(1)	21(1)	-2(1)	-1(1)	1(1)
C(4)	19(1)	20(1)	21(1)	0(1)	2(1)	1(1)
C(5)	20(1)	19(1)	22(1)	2(1)	2(1)	-2(1)
C(6)	20(1)	17(1)	22(1)	0(1)	-1(1)	-4(1)
C(7)	25(1)	15(1)	24(1)	-1(1)	0(1)	-2(1)
C(8)	23(1)	15(1)	23(1)	3(1)	2(1)	1(1)
C(9)	30(1)	17(1)	33(1)	3(1)	1(1)	-3(1)
C(10)	20(1)	20(1)	19(1)	-3(1)	-3(1)	-1(1)
C(11)	35(1)	16(1)	37(1)	1(1)	3(1)	-1(1)
C(12)	20(1)	17(1)	22(1)	1(1)	2(1)	2(1)
C(13)	18(1)	23(1)	26(1)	7(1)	2(1)	-1(1)
C(14)	30(1)	25(1)	31(1)	3(1)	1(1)	-2(1)
C(15)	25(1)	28(1)	27(1)	4(1)	5(1)	2(1)
C(16)	22(1)	30(1)	32(1)	13(1)	2(1)	2(1)

Table 5. Bond lengths [Å] and angles [°] for C16 H25 N O5

		N(1)-C(1)-C(6)	101.33(8)
O(1)-C(2)	1.2081(13)	C(2)-C(1)-C(6)	111.88(9)
O(2)-C(10)	1.2004(14)	O(1)-C(2)-C(3)	123.72(9)
O(3)-C(10)	1.3418(14)	O(1)-C(2)-C(1)	121.52(9)
O(3)-C(11)	1.4430(13)	C(3)-C(2)-C(1)	114.01(8)
O(4)-C(12)	1.2141(14)	C(10)-C(3)-C(2)	111.80(8)
O(5)-C(12)	1.3496(13)	C(10)-C(3)-C(4)	111.99(9)
O(5)-C(13)	1.4739(12)	C(2)-C(3)-C(4)	105.88(8)
N(1)-C(12)	1.3548(14)	C(5)-C(4)-C(3)	109.91(9)
N(1)-C(8)	1.4639(13)	C(4)-C(5)-C(6)	112.74(9)
N(1)-C(1)	1.4698(14)	C(5)-C(6)-C(7)	112.36(9)
C(1)-C(2)	1.5263(13)	C(5)-C(6)-C(1)	112.31(8)
C(1)-C(6)	1.5442(14)	C(7)-C(6)-C(1)	100.19(8)
C(2)-C(3)	1.5185(14)	C(9)-C(7)-C(8)	113.51(9)
C(3)-C(10)	1.5116(14)	C(9)-C(7)-C(6)	115.77(10)
C(3)-C(4)	1.5431(15)	C(8)-C(7)-C(6)	102.10(8)
C(4)-C(5)	1.5264(14)	N(1)-C(8)-C(7)	103.08(9)
C(5)-C(6)	1.5390(15)	O(2)-C(10)-O(3)	123.60(10)
C(6)-C(7)	1.5441(15)	O(2)-C(10)-C(3)	125.23(10)
C(7)-C(9)	1.5228(15)	O(3)-C(10)-C(3)	111.16(9)
C(7)-C(8)	1.5346(15)	O(4)-C(12)-O(5)	126.74(10)
C(13)-C(14)	1.5171(16)	O(4)-C(12)-N(1)	124.17(10)
C(13)-C(15)	1.5221(15)	O(5)-C(12)-N(1)	109.09(9)
C(13)-C(16)	1.5221(15)	O(5)-C(13)-C(14)	109.95(9)
C(10)-O(3)-C(11)	114.72(9)	O(5)-C(13)-C(15)	109.70(9)
C(12)-O(5)-C(13)	121.92(8)	C(14)-C(13)-C(15)	112.75(10)
C(12)-N(1)-C(8)	120.64(9)	O(5)-C(13)-C(16)	101.66(9)
C(12)-N(1)-C(1)	125.23(9)	C(14)-C(13)-C(16)	110.78(9)
C(8)-N(1)-C(1)	111.98(9)	C(15)-C(13)-C(16)	111.43(10)
N(1)-C(1)-C(2)	114.92(8)		

Table 6. Torsion angles [°] for C16 H25 N O5.

C(12)-N(1)-C(1)-C(2)	-53.13(14)	C(5)-C(6)-C(7)-C(8)	-74.35(11)
C(8)-N(1)-C(1)-C(2)	143.56(9)	C(1)-C(6)-C(7)-C(8)	45.05(10)
C(12)-N(1)-C(1)-C(6)	-173.93(9)	C(12)-N(1)-C(8)-C(7)	-158.72(9)
C(8)-N(1)-C(1)-C(6)	22.76(11)	C(1)-N(1)-C(8)-C(7)	5.46(11)
N(1)-C(1)-C(2)-O(1)	128.04(10)	C(9)-C(7)-C(8)-N(1)	-156.85(9)
C(6)-C(1)-C(2)-O(1)	-117.12(11)	C(6)-C(7)-C(8)-N(1)	-31.52(10)
N(1)-C(1)-C(2)-C(3)	-61.53(12)	C(11)-O(3)-C(10)-O(2)	0.95(15)
C(6)-C(1)-C(2)-C(3)	53.30(12)	C(11)-O(3)-C(10)-C(3)	-177.98(9)
O(1)-C(2)-C(3)-C(10)	-13.56(15)	C(2)-C(3)-C(10)-O(2)	113.35(12)
C(1)-C(2)-C(3)-C(10)	176.26(8)	C(4)-C(3)-C(10)-O(2)	-5.30(15)
O(1)-C(2)-C(3)-C(4)	108.66(12)	C(2)-C(3)-C(10)-O(3)	-67.74(11)
C(1)-C(2)-C(3)-C(4)	-61.53(11)	C(4)-C(3)-C(10)-O(3)	173.61(9)
C(10)-C(3)-C(4)-C(5)	-174.96(8)	C(13)-O(5)-C(12)-O(4)	4.28(17)
C(2)-C(3)-C(4)-C(5)	62.95(11)	C(13)-O(5)-C(12)-N(1)	-176.17(9)
C(3)-C(4)-C(5)-C(6)	-58.90(12)	C(8)-N(1)-C(12)-O(4)	-10.80(16)
C(4)-C(5)-C(6)-C(7)	160.67(9)	C(1)-N(1)-C(12)-O(4)	-172.77(11)
C(4)-C(5)-C(6)-C(1)	48.61(13)	C(8)-N(1)-C(12)-O(5)	169.64(9)
N(1)-C(1)-C(6)-C(5)	78.47(10)	C(1)-N(1)-C(12)-O(5)	7.67(14)
C(2)-C(1)-C(6)-C(5)	-44.45(12)	C(12)-O(5)-C(13)-C(14)	-67.88(12)
N(1)-C(1)-C(6)-C(7)	-40.97(9)	C(12)-O(5)-C(13)-C(15)	56.66(13)
C(2)-C(1)-C(6)-C(7)	-163.89(8)	C(12)-O(5)-C(13)-C(16)	174.71(10)
C(5)-C(6)-C(7)-C(9)	49.47(13)		
C(1)-C(6)-C(7)-C(9)	168.87(9)		



ORTEP view of the C16 H25 N O5 compound with the numbering scheme adopted. Ellipsoids drawn at 30% probability level. Hydrogen atoms are represented by sphere of arbitrary size.

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Université de Montréal

CRYSTAL AND MOLECULAR STRUCTURE OF

C18 H22 Br N O3 COMPOUND (ben100)

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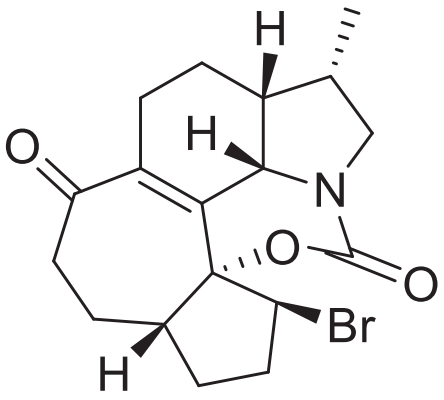


Structure solved and refined in the laboratory of X-ray diffraction Université de Montréal by Benoît Deschênes Simard.

Table 1. Crystal data and structure refinement for C18 H22 Br N O3.

Identification code	ben100
Empirical formula	C18 H22 Br N O3
Formula weight	380.28
Temperature	200K
Wavelength	1.54178 Å
Crystal system	Monoclinic
Space group	P21
Unit cell dimensions	a = 9.4918(2) Å α = 90° b = 7.8350(2) Å β = 95.981(1)° c = 11.3006(3) Å γ = 90°
Volume	835.83(4)Å^3
Z	2
Density (calculated)	1.511 g/cm^3
Absorption coefficient	3.474 mm^{-1}
F(000)	392
Crystal size	0.17 x 0.10 x 0.05 mm
Theta range for data collection	3.93 to 72.45°
Index ranges	$-11 \le h \le 11$, $-9 \le k \le 9$, $-13 \le \ell \le 13$
Reflections collected	10993
Independent reflections	3176 [R_{int} = 0.033]
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.8405 and 0.5962
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3176 / 2 / 210
Goodness-of-fit on F^2	1.038
Final R indices [I>2sigma(I)]	R_1 = 0.0361, wR_2 = 0.0914
R indices (all data)	R_1 = 0.0362, wR_2 = 0.0916
Absolute structure parameter	0.053(15)
Extinction coefficient	0.0204(11)
Largest diff. peak and hole	0.335 and -0.411 e/Å^3

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for C18 H22 Br N O3.

U_{eq} is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U_{eq}
Br(1)	-691(1)	10030(1)	8325(1)	46(1)
O(1)	3684(2)	10292(2)	8415(1)	33(1)
O(2)	5321(2)	11779(3)	7603(2)	47(1)
O(3)	1169(3)	4513(3)	7084(2)	57(1)
N(1)	3243(2)	11311(3)	6490(2)	29(1)
C(1)	1921(2)	10327(3)	6238(2)	25(1)
C(2)	2021(2)	8806(3)	7050(2)	25(1)
C(3)	2021(2)	7208(3)	6644(2)	30(1)
C(4)	1931(3)	6874(3)	5310(2)	38(1)
C(5)	2583(3)	8327(4)	4658(2)	36(1)
C(6)	1842(2)	9989(5)	4893(2)	29(1)
C(7)	2516(3)	11626(4)	4453(2)	35(1)
C(8)	3742(3)	11993(3)	5403(2)	36(1)
C(9)	2989(4)	11538(5)	3197(2)	53(1)
C(10)	2303(2)	9400(3)	8318(2)	28(1)
C(11)	1292(3)	10743(3)	8755(2)	32(1)
C(12)	1671(4)	10785(4)	10111(2)	48(1)
C(13)	2572(4)	9197(4)	10443(2)	42(1)
C(14)	2441(3)	8084(3)	9319(2)	33(1)
C(15)	3615(3)	6794(3)	9219(2)	41(1)
C(16)	3122(4)	5288(4)	8434(3)	49(1)
C(17)	2018(3)	5615(3)	7390(2)	36(1)
C(18)	4145(3)	11160(3)	7484(2)	32(1)

Table 3. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^2 x 10^3) for C18 H22 Br N O3.

	x	y	z	U_{eq}
H(1)	1099	11050	6410	29
H(4A)	2432	5798	5166	45
H(4B)	926	6737	4992	45
H(5A)	3605	8421	4934	43
H(5B)	2487	8090	3793	43
H(6)	828	9923	4554	34
H(7)	1811	12572	4468	42
H(8A)	4617	11407	5218	43
H(8B)	3928	13234	5475	43
H(9A)	3402	12634	2999	80
H(9B)	2169	11289	2622	80
H(9C)	3697	10633	3166	80
H(11)	1467	11884	8402	39
H(12A)	2210	11833	10348	57
H(12B)	799	10769	10522	57
H(13A)	2211	8582	11115	50
H(13B)	3572	9518	10672	50
H(14)	1526	7445	9290	39
H(15A)	3959	6372	10023	49
H(15B)	4417	7363	8885	49
H(16A)	3965	4788	8118	58
H(16B)	2740	4412	8945	58

Table 4. Anisotropic parameters ($Å^2$ x 10^3) for C18 H22 Br N O3.

The anisotropic displacement factor exponent takes the form:

$$-2\pi^2 [h^2 a^{*2} U_{11} + ... + 2 h k a^* b^* U_{12}]$$

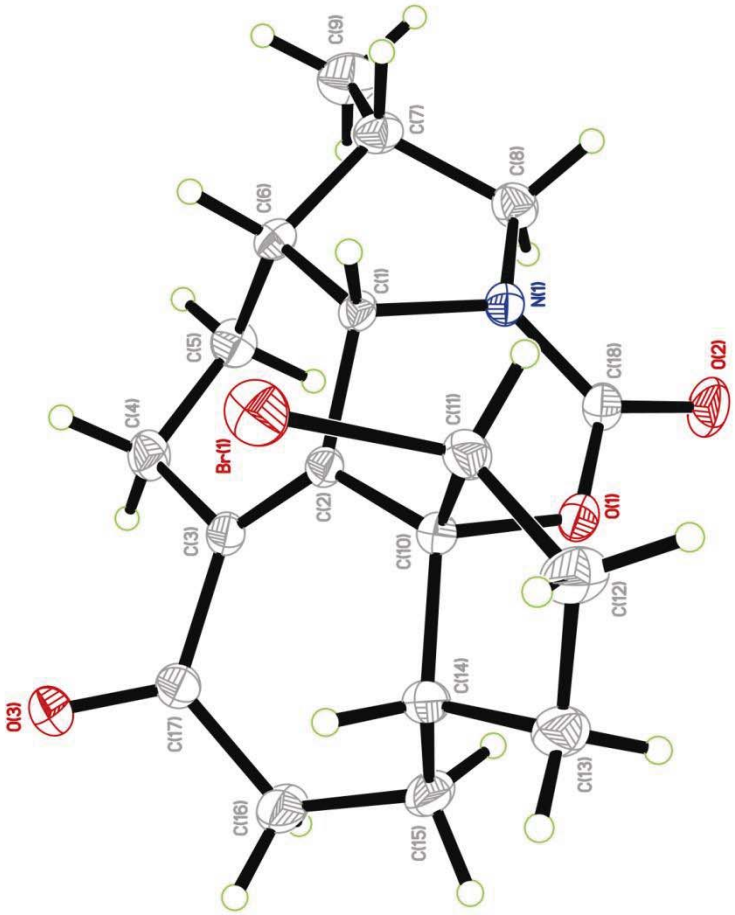
	U11	U22	U33	U23	U13	U12
Br(1)	36(1)	48(1)	56(1)	1(1)	13(1)	2(1)
O(1)	34(1)	36(1)	28(1)	-1(1)	-4(1)	-7(1)
O(2)	36(1)	60(1)	45(1)	-1(1)	-4(1)	-20(1)
O(3)	60(1)	33(1)	72(1)	12(1)	-24(1)	-15(1)
N(1)	29(1)	30(1)	29(1)	0(1)	0(1)	-5(1)
C(1)	21(1)	25(1)	27(1)	-2(1)	0(1)	2(1)
C(2)	22(1)	25(1)	27(1)	-1(1)	0(1)	0(1)
C(3)	27(1)	26(1)	35(1)	-2(1)	-4(1)	0(1)
C(4)	43(1)	32(1)	38(1)	-11(1)	0(1)	-2(1)
C(5)	38(1)	34(1)	36(1)	-9(1)	7(1)	5(1)
C(6)	28(1)	33(1)	24(1)	-1(1)	0(1)	2(1)
C(7)	41(1)	37(1)	26(1)	3(1)	3(1)	4(1)
C(8)	39(1)	34(1)	34(1)	2(1)	8(1)	-4(1)
C(9)	67(2)	63(2)	31(1)	8(1)	14(1)	2(2)
C(10)	30(1)	25(1)	27(1)	0(1)	-2(1)	-2(1)
C(11)	39(1)	28(1)	31(1)	-2(1)	3(1)	-1(1)
C(12)	71(2)	44(1)	28(1)	-5(1)	3(1)	12(1)
C(13)	59(2)	38(1)	28(1)	1(1)	1(1)	2(1)
C(14)	41(1)	28(1)	29(1)	2(1)	-2(1)	0(1)
C(15)	48(2)	33(1)	38(1)	-1(1)	-14(1)	9(1)
C(16)	59(2)	29(2)	53(1)	-3(1)	-19(1)	10(1)
C(17)	37(1)	25(1)	43(1)	-1(1)	-5(1)	2(1)
C(18)	31(1)	31(1)	32(1)	-4(1)	0(1)	-4(1)

Table 5. Bond lengths [Å] and angles [°] for C18 H22 Br N O3

Br(1)-C(11)	1.975(2)	C(1)-C(2)-C(10)	109.29(18)
O(1)-C(18)	1.363(3)	C(2)-C(3)-C(17)	125.8(2)
O(1)-C(10)	1.479(3)	C(2)-C(3)-C(4)	120.0(2)
O(2)-C(18)	1.212(3)	C(17)-C(3)-C(4)	114.1(2)
O(3)-C(17)	1.207(3)	C(5)-C(4)-C(3)	111.5(2)
N(1)-C(18)	1.345(3)	C(6)-C(5)-C(4)	109.7(2)
N(1)-C(8)	1.462(3)	C(5)-C(6)-C(1)	110.2(2)
N(1)-C(1)	1.476(3)	C(5)-C(6)-C(7)	116.31(18)
C(1)-C(2)	1.501(3)	C(1)-C(6)-C(7)	101.4(2)
C(1)-C(6)	1.536(2)	C(8)-C(7)-C(9)	112.6(2)
C(2)-C(3)	1.333(3)	C(8)-C(7)-C(6)	103.96(19)
C(2)-C(10)	1.504(3)	C(9)-C(7)-C(6)	115.7(2)
C(3)-C(17)	1.507(3)	N(1)-C(8)-C(7)	103.44(19)
C(3)-C(4)	1.523(3)	O(1)-C(10)-C(2)	106.59(17)
C(4)-C(5)	1.522(4)	O(1)-C(10)-C(14)	104.91(17)
C(5)-C(6)	1.516(5)	C(2)-C(10)-C(14)	119.32(19)
C(6)-C(7)	1.539(5)	O(1)-C(10)-C(11)	103.31(18)
C(7)-C(8)	1.526(4)	C(2)-C(10)-C(11)	117.53(19)
C(7)-C(9)	1.534(3)	C(14)-C(10)-C(11)	103.4(2)
C(10)-C(14)	1.526(3)	C(12)-C(11)-C(10)	104.2(2)
C(10)-C(11)	1.540(3)	C(12)-C(11)-BR1	111.6(2)
C(11)-C(12)	1.538(3)	C(10)-C(11)-BR1	109.72(16)
C(12)-C(13)	1.534(4)	C(13)-C(12)-C(11)	107.0(2)
C(13)-C(14)	1.535(3)	C(12)-C(13)-C(14)	105.3(2)
C(14)-C(15)	1.517(4)	C(15)-C(14)-C(10)	113.7(2)
C(15)-C(16)	1.521(4)	C(15)-C(14)-C(13)	116.3(2)
C(16)-C(17)	1.516(3)	C(10)-C(14)-C(13)	102.8(2)
C(18)-O(1)-C(10)	122.12(16)	C(14)-C(15)-C(16)	112.1(2)
C(18)-N(1)-C(8)	120.1(2)	C(17)-C(16)-C(15)	117.9(2)
C(18)-N(1)-C(1)	124.7(2)	O(3)-C(17)-C(3)	118.2(2)
C(8)-N(1)-C(1)	111.84(17)	O(3)-C(17)-C(16)	119.3(3)
N(1)-C(1)-C(2)	107.39(16)	C(3)-C(17)-C(16)	122.3(2)
N(1)-C(1)-C(6)	103.50(18)	O(2)-C(18)-N(1)	123.8(2)
C(2)-C(1)-C(6)	117.5(2)	O(2)-C(18)-O(1)	118.7(2)
C(3)-C(2)-C(1)	122.5(2)	N(1)-C(18)-O(1)	117.5(2)
C(3)-C(2)-C(10)	127.8(2)		

Table 6. Torsion angles [°] for C18 H22 Br N O3.

C(18)-N(1)-C(1)-C(2)	-18.2(3)
C(8)-N(1)-C(1)-C(2)	140.83(19)
C(18)-N(1)-C(1)-C(6)	-143.1(2)
C(8)-N(1)-C(1)-C(6)	15.9(3)
N(1)-C(1)-C(2)-C(3)	-117.1(2)
C(6)-C(1)-C(2)-C(3)	-1.1(3)
N(1)-C(1)-C(2)-C(10)	55.7(2)
C(6)-C(1)-C(2)-C(10)	171.70(18)
C(1)-C(2)-C(3)-C(17)	-175.6(2)
C(10)-C(2)-C(3)-C(17)	13.1(4)
C(1)-C(2)-C(3)-C(4)	0.6(3)
C(10)-C(2)-C(3)-C(4)	-170.8(2)
C(2)-C(3)-C(4)-C(5)	29.1(3)
C(17)-C(3)-C(4)-C(5)	-154.3(2)
C(3)-C(4)-C(5)-C(6)	-57.9(3)
C(4)-C(5)-C(6)-C(1)	56.6(3)
C(4)-C(5)-C(6)-C(7)	171.2(2)
N(1)-C(1)-C(6)-C(5)	90.1(2)
C(2)-C(1)-C(6)-C(5)	-28.0(3)
N(1)-C(1)-C(6)-C(7)	-33.7(2)
C(2)-C(1)-C(6)-C(7)	-151.8(2)
C(5)-C(6)-C(7)-C(8)	-79.7(2)
C(1)-C(6)-C(7)-C(8)	39.8(2)
C(5)-C(6)-C(7)-C(9)	44.2(3)
C(1)-C(6)-C(7)-C(9)	163.8(2)
C(18)-N(1)-C(8)-C(7)	169.2(2)
C(1)-N(1)-C(8)-C(7)	9.1(3)
C(9)-C(7)-C(8)-N(1)	-156.4(2)
C(6)-C(7)-C(8)-N(1)	-30.4(3)
C(18)-O(1)-C(10)-C(2)	31.3(3)
C(18)-O(1)-C(10)-C(14)	158.8(2)
C(18)-O(1)-C(10)-C(11)	-93.1(2)
C(3)-C(2)-C(10)-O(1)	110.3(3)
C(1)-C(2)-C(10)-O(1)	-62.0(2)
C(3)-C(2)-C(10)-C(14)	-8.1(4)
C(1)-C(2)-C(10)-C(14)	179.63(19)
C(3)-C(2)-C(10)-C(11)	-134.5(3)
C(1)-C(2)-C(10)-C(11)	53.2(3)
O(1)-C(10)-C(11)-C(12)	-74.4(2)
C(2)-C(10)-C(11)-C(12)	168.6(2)
C(14)-C(10)-C(11)-C(12)	34.8(3)
O(1)-C(10)-C(11)-BR1	165.92(13)
C(2)-C(10)-C(11)-BR1	48.9(2)
C(14)-C(10)-C(11)-BR1	-84.90(18)
C(10)-C(11)-C(12)-C(13)	-14.3(3)
BR1-C(11)-C(12)-C(13)	104.0(3)
C(11)-C(12)-C(13)-C(14)	-11.4(3)
O(1)-C(10)-C(14)-C(15)	-60.5(2)
C(2)-C(10)-C(14)-C(15)	58.7(3)
C(11)-C(10)-C(14)-C(15)	-168.5(2)
O(1)-C(10)-C(14)-C(13)	66.1(2)
C(2)-C(10)-C(14)-C(13)	-174.7(2)
C(11)-C(10)-C(14)-C(13)	-41.9(2)
C(12)-C(13)-C(14)-C(15)	157.8(3)
C(12)-C(13)-C(14)-C(10)	32.8(3)
C(10)-C(14)-C(15)-C(16)	-86.2(3)
C(13)-C(14)-C(15)-C(16)	154.6(3)
C(14)-C(15)-C(16)-C(17)	33.2(4)
C(2)-C(3)-C(17)-O(3)	131.1(3)
C(4)-C(3)-C(17)-O(3)	-45.3(4)
C(2)-C(3)-C(17)-C(16)	-54.6(4)
C(4)-C(3)-C(17)-C(16)	129.0(3)
C(15)-C(16)-C(17)-O(3)	-147.3(3)
C(15)-C(16)-C(17)-C(3)	38.4(4)
C(8)-N(1)-C(18)-O(2)	11.0(4)
C(1)-N(1)-C(18)-O(2)	168.5(2)
C(8)-N(1)-C(18)-O(1)	-170.6(2)
C(1)-N(1)-C(18)-O(1)	-13.1(3)
C(10)-O(1)-C(18)-O(2)	-175.8(2)
C(10)-O(1)-C(18)-N(1)	5.7(3)



ORTEP view of the C18 H22 Br N O3 compound with the numbering scheme adopted. Ellipsoids drawn at 30% probability level. Hydrogen atoms are represented by sphere of arbitrary size.

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Université de Montréal

CRYSTAL AND MOLECULAR STRUCTURE OF

C17 H19 Br F3 N O5 S2 COMPOUND (bent65)

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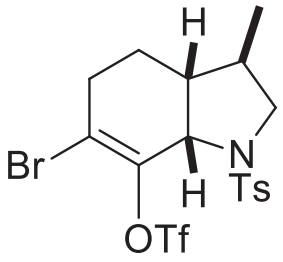


Structure solved and refined in the laboratory of X-ray diffraction Université de Montréal by Benoît Deschênes Simard.

Table 1. Crystal data and structure refinement for C17 H19 Br F3 N O5 S2.

Identification code	bent65
Empirical formula	C17 H19 Br F3 N O5 S2
Formula weight	518.36
Temperature	175K
Wavelength	1.54178 Å
Crystal system	Monoclinic
Space group	I2/a
Unit cell dimensions	a = 18.6581(5) Å α = 90° b = 9.0548(3) Å β = 97.989(1)° c = 24.7818(10) Å γ = 90°
Volume	4146.1(2)Å^3
Z	8
Density (calculated)	1.661 g/cm^3
Absorption coefficient	5.107 mm^{-1}
F(000)	2096
Crystal size	0.18 x 0.11 x 0.10 mm
Theta range for data collection	3.60 to 72.05°
Index ranges	$-22 \le h \le 22$, $-11 \le k \le 10$, $-30 \le \ell \le 30$
Reflections collected	26923
Independent reflections	4057 [R_{int} = 0.043]
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.6001 and 0.4910
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4057 / 261 / 409
Goodness-of-fit on F^2	1.087
Final R indices [I>2sigma(I)]	R_1 = 0.0416, wR_2 = 0.1157
R indices (all data)	R_1 = 0.0453, wR_2 = 0.1186
Extinction coefficient	0.00037(4)
Largest diff. peak and hole	0.756 and -0.971 e/Å^3

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for C17 H19 Br F3 N O5 S2.

U_{eq} is defined as one third of the trace of the orthogonalized Uij tensor.

	Occ.	x	y	z	U_{eq}
Br(1)	1	8699(1)	4147(1)	9336(1)	70(1)
S(1A)	0.25	8348(2)	7559(4)	9191(1)	51(1)
O(1A)	0.25	8683(2)	6968(7)	8666(2)	38(2)
O(2A)	0.25	7588(5)	7340(20)	9077(7)	84(4)
O(3A)	0.25	8737(8)	7202(15)	9693(4)	56(3)
C(10A)	0.25	8459(7)	9586(13)	9119(5)	64(3)
F(1A)	0.25	8017(7)	10235(14)	9422(6)	91(4)
F(2A)	0.25	8296(9)	9986(17)	8609(5)	88(5)
F(3A)	0.25	9130(6)	9990(13)	9305(7)	75(4)
S(1B)	0.50	8614(1)	8606(2)	9142(1)	54(1)
O(1B)	0.50	8724(1)	7146(4)	8792(2)	40(1)
O(2B)	0.50	8407(4)	9849(8)	8820(3)	72(2)
O(3B)	0.50	9170(2)	8652(6)	9592(2)	69(1)
C(10B)	0.50	7786(3)	8042(8)	9411(3)	70(2)
F(1B)	0.50	7920(2)	7086(6)	9807(2)	95(1)
F(2B)	0.50	7314(3)	7454(8)	9018(3)	91(2)
F(3B)	0.50	7493(3)	9237(5)	9600(3)	110(2)
S(1C)	0.25	8388(2)	7792(5)	9218(2)	51(1)
O(1C)	0.25	8762(3)	7277(8)	8701(2)	40(2)
O(2C)	0.25	7650(5)	7460(20)	9097(7)	78(3)
O(3C)	0.25	8793(8)	7537(15)	9724(4)	54(3)
C(10C)	0.25	8449(7)	9812(14)	9100(5)	64(3)
F(1C)	0.25	7939(7)	10467(14)	9337(6)	89(4)
F(2C)	0.25	8363(9)	10129(15)	8580(4)	65(3)
F(3C)	0.25	9089(6)	10311(13)	9332(6)	62(3)
S(2)	1	9948(1)	9881(1)	8145(1)	46(1)
O(4)	1	9352(1)	9402(2)	7758(1)	53(1)
O(5)	1	9932(1)	11296(2)	8403(1)	58(1)
N(1)	1	10042(1)	8661(2)	8642(1)	42(1)
C(1)	1	9960(1)	7077(3)	8505(1)	39(1)
C(2)	1	9397(1)	6371(3)	8806(1)	43(1)
C(3)	1	9481(1)	5072(3)	9055(1)	47(1)
C(4)	1	10179(2)	4233(3)	9138(1)	54(1)
C(5)	1	10701(2)	4750(3)	8753(1)	52(1)
C(6)	1	10711(1)	6424(3)	8692(1)	44(1)
C(7)	1	10963(1)	7300(3)	9213(1)	46(1)
C(8)	1	10678(1)	8873(3)	9074(1)	49(1)
C(9)	1	11779(2)	7256(4)	9393(1)	66(1)
C(11)	1	10736(1)	9833(3)	7826(1)	44(1)
C(12)	1	11287(2)	10859(3)	7963(1)	57(1)
C(13)	1	11904(2)	10768(4)	7716(1)	63(1)
C(14)	1	11993(1)	9678(4)	7331(1)	57(1)
C(15)	1	11432(1)	8661(3)	7199(1)	52(1)
C(16)	1	10808(1)	8734(3)	7441(1)	47(1)
C(17)	1	12665(2)	9601(5)	7059(2)	75(1)

Table 3. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for C17 H19 Br F3 N O5 S2.

	Occ.	x	y	z	U_{eq}
H(1)	1	9826	6946	8103	47
H(4A)	1	10077	3168	9077	65
H(4B)	1	10411	4360	9519	65
H(5A)	1	11195	4403	8893	63
H(5B)	1	10559	4298	8390	63
H(6)	1	11033	6679	8415	52
H(7)	1	10714	6899	9514	55
H(8A)	1	10529	9357	9399	59
H(8B)	1	11054	9485	8937	59
H(9A)	1	12030	7618	9097	99
H(9B)	1	11929	6238	9483	99
H(9C)	1	11902	7883	9715	99
H(12)	1	11239	11611	8224	68
H(13)	1	12280	11467	7810	76
H(15)	1	11480	7908	6940	62
H(16)	1	10430	8040	7346	57
H(17A)	1	12601	10217	6730	113
H(17B)	1	12750	8576	6958	113
H(17C)	1	13080	9960	7310	113

Table 4. Anisotropic parameters ($Å^2$ x 10^3) for C17 H19 Br F3 N O5 S2.

The anisotropic displacement factor exponent takes the form:

$$-2\pi^2 [h^2 a^{*2} U_{11} + ... + 2 h k a^* b^* U_{12}]$$

	U11	U22	U33	U23	U13	U12
Br(1)	64(1)	91(1)	54(1)	19(1)	2(1)	-26(1)
S(1A)	43(1)	64(1)	48(1)	-3(1)	9(1)	4(1)
O(1A)	30(2)	59(3)	22(3)	-7(2)	-6(2)	-8(2)
O(2A)	45(6)	126(8)	78(6)	-1(6)	3(6)	-3(6)
O(3A)	67(5)	59(6)	43(4)	-5(4)	7(4)	10(4)
C(10A)	71(5)	62(5)	64(5)	20(5)	27(5)	37(4)
F(1A)	100(6)	85(6)	99(7)	17(5)	50(6)	63(5)
F(2A)	75(8)	105(10)	82(9)	22(8)	6(8)	29(7)
F(3A)	79(6)	57(6)	91(7)	-30(5)	18(5)	10(5)
S(1B)	46(1)	64(1)	54(1)	-7(1)	8(1)	4(1)
O(1B)	32(2)	62(2)	24(2)	2(2)	-2(1)	-5(2)
O(2B)	67(4)	60(4)	93(7)	15(5)	22(5)	16(3)
O(3B)	62(2)	88(3)	56(2)	-25(2)	4(2)	5(2)
C(10B)	54(3)	86(5)	72(4)	-6(4)	21(3)	3(3)
F(1B)	97(3)	118(4)	79(3)	17(3)	46(2)	20(3)
F(2B)	54(3)	121(4)	98(4)	-2(3)	7(3)	-12(3)
F(3B)	90(3)	104(4)	147(5)	-20(3)	60(3)	22(3)
S(1C)	43(1)	63(1)	48(1)	-2(1)	9(1)	4(1)
O(1C)	34(3)	60(3)	25(3)	-1(2)	-3(2)	-4(3)
O(2C)	31(5)	127(7)	80(6)	6(6)	16(5)	-1(6)
O(3C)	66(5)	59(6)	37(4)	-13(4)	4(4)	10(5)
C(10C)	72(5)	62(6)	63(5)	19(5)	28(5)	30(5)
F(1C)	84(6)	87(7)	106(8)	27(6)	45(6)	46(5)
F(2C)	69(7)	67(6)	64(7)	26(5)	24(6)	17(5)
F(3C)	70(5)	47(5)	71(5)	-19(4)	13(4)	16(4)
S(2)	46(1)	48(1)	42(1)	5(1)	-1(1)	4(1)
O(4)	43(1)	65(1)	48(1)	9(1)	-7(1)	5(1)
O(5)	68(1)	48(1)	57(1)	2(1)	6(1)	9(1)
N(1)	41(1)	47(1)	36(1)	2(1)	-3(1)	1(1)
C(1)	36(1)	47(1)	33(1)	-1(1)	-1(1)	-1(1)
C(2)	35(1)	57(1)	36(1)	-2(1)	-2(1)	-3(1)
C(3)	47(1)	55(1)	38(1)	-2(1)	-2(1)	-10(1)
C(4)	65(2)	44(1)	50(1)	2(1)	-1(1)	-1(1)
C(5)	52(1)	51(1)	52(1)	1(1)	2(1)	8(1)
C(6)	37(1)	51(1)	42(1)	2(1)	1(1)	3(1)
C(7)	39(1)	54(1)	41(1)	6(1)	-6(1)	-2(1)
C(8)	50(1)	51(1)	41(1)	2(1)	-8(1)	-6(1)
C(9)	44(1)	83(2)	65(2)	7(2)	-13(1)	-2(1)
C(11)	46(1)	45(1)	40(1)	6(1)	-2(1)	-3(1)
C(12)	63(2)	52(2)	53(2)	0(1)	-1(1)	-14(1)
C(13)	56(2)	71(2)	60(2)	4(1)	-1(1)	-24(1)
C(14)	44(1)	74(2)	49(1)	18(1)	-1(1)	-3(1)
C(15)	50(1)	61(2)	42(1)	4(1)	3(1)	0(1)
C(16)	49(1)	50(1)	41(1)	2(1)	-1(1)	-7(1)
C(17)	46(2)	112(3)	67(2)	16(2)	6(1)	-3(2)

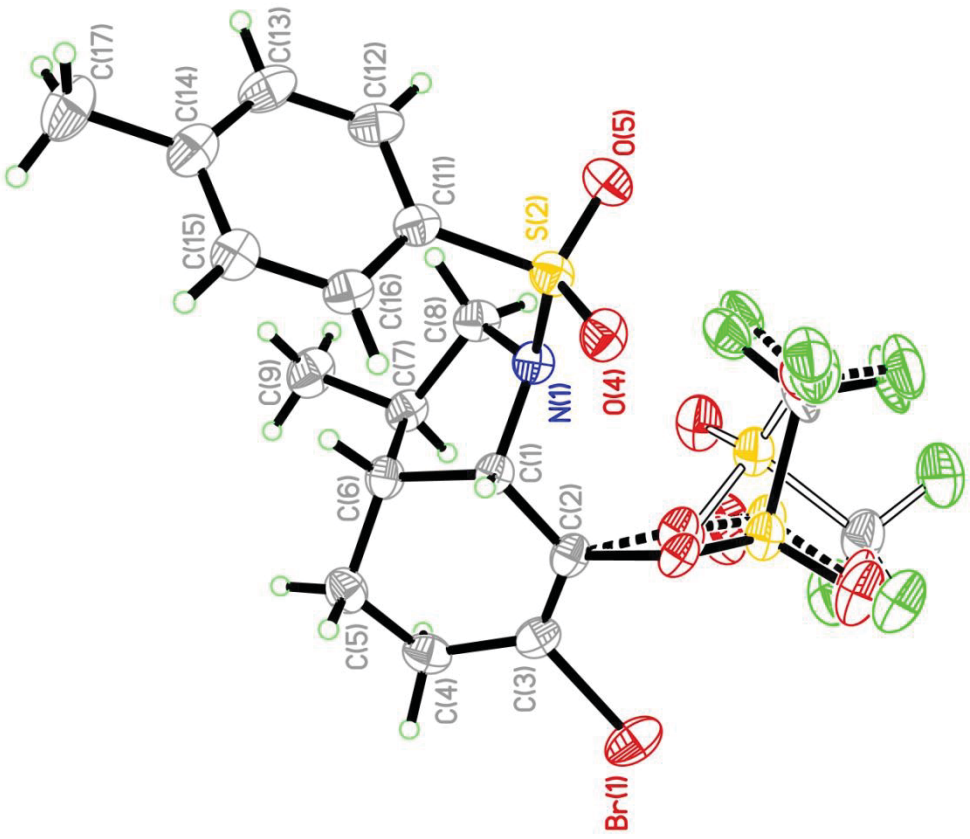
Table 5. Bond lengths [Å] and angles [°] for C17 H19 Br F3 N O5 S2

Br(1)-C(3)	1.897(3)	F(2A)-C(10A)-F(3A)	110.0(11)
S(1a)-O(3a)	1.390(8)	F(2A)-C(10A)-F(1A)	110.1(11)
S(1a)-O(2a)	1.420(9)	F(3A)-C(10A)-F(1A)	108.1(11)
S(1a)-O(1a)	1.610(3)	F(2A)-C(10A)-S(1A)	110.6(10)
S(1a)-C(10a)	1.858(12)	F(3A)-C(10A)-S(1A)	110.7(8)
O(1a)-C(2)	1.436(3)	F(1A)-C(10A)-S(1A)	107.2(9)
C(10a)-F(2a)	1.308(11)	O(2B)-S(1B)-O(3B)	122.6(4)
C(10a)-F(3a)	1.323(12)	O(2B)-S(1B)-O(1B)	113.4(4)
C(10a)-F(1a)	1.327(12)	O(3B)-S(1B)-O(1B)	108.3(2)
S(1b)-O(2b)	1.403(7)	O(2B)-S(1B)-C(10B)	104.5(4)
S(1b)-O(3b)	1.413(4)	O(3B)-S(1B)-C(10B)	106.6(3)
S(1b)-O(1b)	1.610(3)	O(1B)-S(1B)-C(10B)	98.3(3)
S(1b)-C(10b)	1.837(6)	C(2)-O(1B)-S(1B)	124.4(2)
O(1b)-C(2)	1.436(3)	F(1B)-C(10B)-F(3B)	108.7(6)
C(10b)-F(1b)	1.306(7)	F(1B)-C(10B)-F(2B)	108.8(6)
C(10b)-F(3b)	1.326(7)	F(3B)-C(10B)-F(2B)	108.8(6)
C(10b)-F(2b)	1.330(8)	F(1B)-C(10B)-S(1B)	111.9(4)
S(1c)-O(3c)	1.391(8)	F(3B)-C(10B)-S(1B)	108.0(5)
S(1c)-O(2c)	1.402(9)	F(2B)-C(10B)-S(1B)	110.5(5)
S(1c)-O(1c)	1.610(3)	O(3C)-S(1C)-O(2C)	123.5(8)
S(1c)-C(10c)	1.858(12)	O(3C)-S(1C)-O(1C)	115.4(6)
O(1c)-C(2)	1.436(3)	O(2C)-S(1C)-O(1C)	106.7(7)
C(10c)-F(2c)	1.310(12)	O(3C)-S(1C)-C(10C)	105.5(7)
C(10c)-F(1c)	1.325(12)	O(2C)-S(1C)-C(10C)	105.0(8)
C(10c)-F(3c)	1.330(12)	O(1C)-S(1C)-C(10C)	96.8(6)
S(2)-O(4)	1.4319(19)	C(2)-O(1C)-S(1C)	117.3(3)
S(2)-O(5)	1.434(2)	F(2C)-C(10C)-F(1C)	109.9(11)
S(2)-N(1)	1.645(2)	F(2C)-C(10C)-F(3C)	109.3(11)
S(2)-C(11)	1.764(3)	F(1C)-C(10C)-F(3C)	108.3(11)
N(1)-C(1)	1.477(3)	F(2C)-C(10C)-S(1C)	111.6(10)
N(1)-C(8)	1.497(3)	F(1C)-C(10C)-S(1C)	108.0(9)
C(1)-C(2)	1.513(3)	F(3C)-C(10C)-S(1C)	109.8(9)
C(1)-C(6)	1.532(3)	O(4)-S(2)-O(5)	120.41(12)
C(2)-C(3)	1.326(4)	O(4)-S(2)-N(1)	106.85(11)
C(3)-C(4)	1.497(4)	O(5)-S(2)-N(1)	105.88(11)
C(4)-C(5)	1.529(4)	O(4)-S(2)-C(11)	108.05(12)
C(5)-C(6)	1.523(4)	O(5)-S(2)-C(11)	106.99(13)
C(6)-C(7)	1.532(3)	N(1)-S(2)-C(11)	108.15(11)
C(7)-C(9)	1.526(3)	C(1)-N(1)-C(8)	109.61(18)
C(7)-C(8)	1.542(4)	C(1)-N(1)-S(2)	118.89(15)
C(11)-C(12)	1.393(4)	C(8)-N(1)-S(2)	116.13(16)
C(11)-C(16)	1.397(4)	N(1)-C(1)-C(2)	110.7(2)
C(12)-C(13)	1.380(5)	N(1)-C(1)-C(6)	104.14(18)
C(13)-C(14)	1.399(5)	C(2)-C(1)-C(6)	110.8(2)
C(14)-C(15)	1.398(4)	C(3)-C(2)-O(1A)	119.4(3)
C(14)-C(17)	1.505(4)	C(3)-C(2)-O(1C)	129.2(4)
C(15)-C(16)	1.383(4)	O(1A)-C(2)-O(1C)	12.9(5)
O(3A)-S(1A)-O(2A)	121.8(8)	C(3)-C(2)-O(1B)	119.4(3)
O(3A)-S(1A)-O(1A)	115.7(6)	O(1A)-C(2)-O(1B)	13.99(19)
O(2A)-S(1A)-O(1A)	106.5(7)	O(1C)-C(2)-O(1B)	10.9(4)
O(3A)-S(1A)-C(10A)	105.3(6)	C(3)-C(2)-C(1)	124.0(2)
O(2A)-S(1A)-C(10A)	103.9(8)	O(1A)-C(2)-C(1)	114.0(3)
O(1A)-S(1A)-C(10A)	101.0(5)	O(1C)-C(2)-C(1)	106.3(4)
C(2)-O(1A)-S(1A)	112.5(3)	O(1B)-C(2)-C(1)	116.5(3)
		C(2)-C(3)-C(4)	123.9(2)

C(2)-C(3)-BR1	121.0(2)	C(12)-C(11)-S(2)	120.4(2)
C(4)-C(3)-BR1	115.11(19)	C(16)-C(11)-S(2)	119.28(19)
C(3)-C(4)-C(5)	112.1(2)	C(13)-C(12)-C(11)	118.9(3)
C(6)-C(5)-C(4)	112.6(2)	C(12)-C(13)-C(14)	122.1(3)
C(5)-C(6)-C(1)	113.0(2)	C(15)-C(14)-C(13)	117.8(3)
C(5)-C(6)-C(7)	116.0(2)	C(15)-C(14)-C(17)	120.5(3)
C(1)-C(6)-C(7)	102.51(19)	C(13)-C(14)-C(17)	121.6(3)
C(9)-C(7)-C(6)	114.2(2)	C(16)-C(15)-C(14)	121.1(3)
C(9)-C(7)-C(8)	112.9(2)	C(15)-C(16)-C(11)	119.7(2)
C(6)-C(7)-C(8)	103.59(18)		
N(1)-C(8)-C(7)	104.79(19)		
C(12)-C(11)-C(16)	120.3(3)		

Table 6. Torsion angles [°] for C17 H19 Br F3 N O5 S2.

O(3A)-S(1A)-O(1A)-C(2)	-9.7(9)
O(2A)-S(1A)-O(1A)-C(2)	-148.5(9)
C(10A)-S(1A)-O(1A)-C(2)	103.3(6)
O(3A)-S(1A)-C(10A)-F(2A)	162.1(11)
O(2A)-S(1A)-C(10A)-F(2A)	-68.8(12)
O(1A)-S(1A)-C(10A)-F(2A)	41.4(11)
O(3A)-S(1A)-C(10A)-F(3A)	39.9(12)
O(2A)-S(1A)-C(10A)-F(3A)	169.0(11)
O(1A)-S(1A)-C(10A)-F(3A)	-80.8(10)
O(3A)-S(1A)-C(10A)-F(1A)	-77.8(11)
O(2A)-S(1A)-C(10A)-F(1A)	51.3(11)
O(1A)-S(1A)-C(10A)-F(1A)	161.5(8)
O(2B)-S(1B)-O(1B)-C(2)	117.7(5)
O(3B)-S(1B)-O(1B)-C(2)	-21.9(5)
C(10B)-S(1B)-O(1B)-C(2)	-132.5(4)
O(2B)-S(1B)-C(10B)-F(1B)	-166.9(6)
O(3B)-S(1B)-C(10B)-F(1B)	-35.8(6)
O(1B)-S(1B)-C(10B)-F(1B)	76.3(5)
O(2B)-S(1B)-C(10B)-F(3B)	-47.3(6)
O(3B)-S(1B)-C(10B)-F(3B)	83.8(5)
O(1B)-S(1B)-C(10B)-F(3B)	-164.1(5)
O(2B)-S(1B)-C(10B)-F(2B)	71.7(6)
O(3B)-S(1B)-C(10B)-F(2B)	-157.2(5)
O(1B)-S(1B)-C(10B)-F(2B)	-45.2(5)
O(3C)-S(1C)-O(1C)-C(2)	11.4(10)
O(2C)-S(1C)-O(1C)-C(2)	-129.9(9)
C(10C)-S(1C)-O(1C)-C(2)	122.2(7)
O(3C)-S(1C)-C(10C)-F(2C)	153.8(12)
O(2C)-S(1C)-C(10C)-F(2C)	-74.4(13)
O(1C)-S(1C)-C(10C)-F(2C)	35.0(11)
O(3C)-S(1C)-C(10C)-F(1C)	-85.4(11)
O(2C)-S(1C)-C(10C)-F(1C)	46.5(12)
O(1C)-S(1C)-C(10C)-F(1C)	155.8(9)
O(3C)-S(1C)-C(10C)-F(3C)	32.5(12)
O(2C)-S(1C)-C(10C)-F(3C)	164.3(11)
O(1C)-S(1C)-C(10C)-F(3C)	-86.3(9)
O(4)-S(2)-N(1)-C(1)	40.9(2)
O(5)-S(2)-N(1)-C(1)	170.36(18)
C(11)-S(2)-N(1)-C(1)	-75.24(19)
O(4)-S(2)-N(1)-C(8)	175.11(18)
O(5)-S(2)-N(1)-C(8)	-55.4(2)
C(11)-S(2)-N(1)-C(8)	59.0(2)
C(8)-N(1)-C(1)-C(2)	97.7(2)
S(2)-N(1)-C(1)-C(2)	-125.37(18)
C(8)-N(1)-C(1)-C(6)	-21.4(2)
S(2)-N(1)-C(1)-C(6)	115.53(18)
S(1A)-O(1A)-C(2)-C(3)	73.1(5)
S(1A)-O(1A)-C(2)-O(1C)	-68.7(13)
S(1A)-O(1A)-C(2)-O(1B)	-20.7(12)
S(1A)-O(1A)-C(2)-C(1)	-124.4(4)
S(1C)-O(1C)-C(2)-C(3)	57.8(8)
S(1C)-O(1C)-C(2)-O(1A)	101.8(16)
S(1C)-O(1C)-C(2)-O(1B)	29.9(14)
S(1C)-O(1C)-C(2)-C(1)	-130.0(5)
S(1B)-O(1B)-C(2)-C(3)	107.4(4)
S(1B)-O(1B)-C(2)-O(1A)	-158.5(18)
S(1B)-O(1B)-C(2)-O(1C)	-97(2)
S(1B)-O(1B)-C(2)-C(1)	-75.6(4)
N(1)-C(1)-C(2)-C(3)	-135.6(2)
C(6)-C(1)-C(2)-C(3)	-20.6(3)
N(1)-C(1)-C(2)-O(1A)	62.8(3)
C(6)-C(1)-C(2)-O(1A)	177.8(3)
N(1)-C(1)-C(2)-O(1C)	51.7(3)
C(6)-C(1)-C(2)-O(1C)	166.7(3)
N(1)-C(1)-C(2)-O(1B)	47.6(3)
C(6)-C(1)-C(2)-O(1B)	162.6(2)
O(1A)-C(2)-C(3)-C(4)	169.6(3)
O(1C)-C(2)-C(3)-C(4)	179.9(4)
O(1B)-C(2)-C(3)-C(4)	-174.3(2)
C(1)-C(2)-C(3)-C(4)	8.9(4)
O(1A)-C(2)-C(3)-BR1	-10.5(4)
O(1C)-C(2)-C(3)-BR1	-0.3(5)
O(1B)-C(2)-C(3)-BR1	5.6(3)
C(1)-C(2)-C(3)-BR1	-171.17(17)
C(2)-C(3)-C(4)-C(5)	-19.0(4)
BR1-C(3)-C(4)-C(5)	161.15(18)
C(3)-C(4)-C(5)-C(6)	41.5(3)
C(4)-C(5)-C(6)-C(1)	-55.8(3)
C(4)-C(5)-C(6)-C(7)	62.2(3)
N(1)-C(1)-C(6)-C(5)	162.3(2)
C(2)-C(1)-C(6)-C(5)	43.2(3)
N(1)-C(1)-C(6)-C(7)	36.6(2)
C(2)-C(1)-C(6)-C(7)	-82.4(2)
C(5)-C(6)-C(7)-C(9)	75.2(3)
C(1)-C(6)-C(7)-C(9)	-161.2(2)
C(5)-C(6)-C(7)-C(8)	-161.7(2)
C(1)-C(6)-C(7)-C(8)	-38.0(2)
C(1)-N(1)-C(8)-C(7)	-2.5(3)
S(2)-N(1)-C(8)-C(7)	-140.72(18)
C(9)-C(7)-C(8)-N(1)	149.3(2)
C(6)-C(7)-C(8)-N(1)	25.3(3)
O(4)-S(2)-C(11)-C(12)	147.0(2)
O(5)-S(2)-C(11)-C(12)	16.0(2)
N(1)-S(2)-C(11)-C(12)	-97.6(2)
O(4)-S(2)-C(11)-C(16)	-34.4(2)
O(5)-S(2)-C(11)-C(16)	-165.43(19)
N(1)-S(2)-C(11)-C(16)	80.9(2)
C(16)-C(11)-C(12)-C(13)	-0.3(4)
S(2)-C(11)-C(12)-C(13)	178.3(2)
C(11)-C(12)-C(13)-C(14)	0.1(4)
C(12)-C(13)-C(14)-C(15)	-0.1(4)
C(12)-C(13)-C(14)-C(17)	179.2(3)
C(13)-C(14)-C(15)-C(16)	0.2(4)
C(17)-C(14)-C(15)-C(16)	-179.1(3)
C(14)-C(15)-C(16)-C(11)	-0.4(4)
C(12)-C(11)-C(16)-C(15)	0.4(4)
S(2)-C(11)-C(16)-C(15)	-178.13(19)



ORTEP view of the C17 H19 Br F3 N O5 S2 compound with the numbering scheme adopted. Ellipsoids drawn at 30% probability level. Hydrogen atoms are represented by sphere of arbitrary size.

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Université de Montréal

CRYSTAL AND MOLECULAR STRUCTURE OF

C23 H27 N O3 S COMPOUND (HAN411)

mardi, juin 11, 2013

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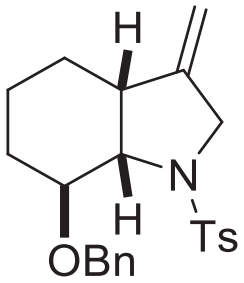


Structure solved and refined in the laboratory of X-ray diffraction Université de Montréal by Dr. Michel Simard.

Table 1. Crystal data and structure refinement for C23 H27 N O3 S.

Identification code	HAN411
Empirical formula	C23 H27 N O3 S
Formula weight	397.52
Temperature	293(2)K
Wavelength	1.54178 Å
Crystal system	Triclinic
Space group	P-1
Unit cell dimensions	a = 8.879(2) Å α = 82.55(2)° b = 10.452(3) Å β = 72.79(2)° c = 12.174(3) Å γ = 82.05(2)°
Volume	1064.1(5)Å^3
Z	2
Density (calculated)	1.241 Mg/m^3
Absorption coefficient	1.530 mm^{-1}
F(000)	424
Crystal size	0.53 x 0.38 x 0.15 mm
Theta range for data collection	3.82 to 69.92°
Index ranges	$-10 \le h \le 10$, $-12 \le k \le 12$, $-14 \le \ell \le 14$
Reflections collected	24660
Independent reflections	4035 [R_{int} = 0.037]
Absorption correction	Gaussian
Max. and min. transmission	0.8000 and 0.5000
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4035 / 16 / 253
Goodness-of-fit on F^2	1.001
Final R indices [I>2sigma(I)]	R_1 = 0.0476, wR_2 = 0.1358
R indices (all data)	R_1 = 0.0609, wR_2 = 0.1433
Extinction coefficient	0.0102(10)
Largest diff. peak and hole	0.406 and -0.364 e/Å^3

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for C23 H27 N O3 S.

U_{eq} is defined as one third of the trace of the orthogonalized Uij tensor.

	Occ.	x	y	z	U_{eq}
S(1)	1	10266(1)	2295(1)	6262(1)	67(1)
O(1)	1	9265(2)	2498(1)	3297(1)	67(1)
O(2)	1	11141(2)	1296(2)	5558(2)	79(1)
O(3)	1	11030(2)	3369(2)	6374(2)	92(1)
N(1)	1	8808(2)	2900(2)	5746(2)	57(1)
C(2)	1	7670(2)	3945(2)	6333(2)	65(1)
C(3)	1	6047(2)	3490(2)	6515(2)	57(1)
C(4)	1	6312(2)	2088(2)	6243(2)	55(1)
C(5)	1	5029(2)	1572(2)	5873(2)	69(1)
C(6)	1	4970(2)	2125(2)	4676(2)	70(1)
C(7)	1	6593(3)	1941(2)	3813(2)	68(1)
C(8)	1	7770(2)	2618(2)	4152(2)	56(1)
C(9)	1	7934(2)	2048(2)	5328(2)	52(1)
C(10)	1	4700(3)	4232(2)	6806(2)	74(1)
C(11)	1	9447(3)	1579(2)	7664(2)	67(1)
C(12)	1	9160(3)	2259(3)	8619(3)	86(1)
C(13)	1	8428(4)	1715(3)	9691(3)	98(1)
C(14)	1	7939(4)	490(3)	9870(2)	89(1)
C(15)	1	8259(4)	-193(2)	8904(2)	87(1)
C(16)	1	9002(3)	321(2)	7825(2)	73(1)
C(17)	1	7105(5)	-101(4)	11047(3)	125(1)
C(18)	0.520(3)	10305(7)	3479(6)	3201(5)	97(2)
C(19)	0.520(3)	11514(4)	3500(8)	2056(3)	61(1)
C(20)	0.520(3)	11114(3)	3831(8)	1027(4)	84(1)
C(21)	0.520(3)	12294(6)	3845(7)	-21(3)	100(2)
C(22)	0.520(3)	13873(5)	3528(6)	-39(3)	96(2)
C(23)	0.520(3)	14273(3)	3197(6)	990(4)	97(2)
C(24)	0.520(3)	13094(5)	3183(6)	2037(3)	81(1)
C(18')	0.48	9539(7)	3696(6)	2614(6)	97(2)
C(19')	0.48	11166(4)	3532(8)	1783(4)	61(1)
C(20')	0.48	11498(5)	3869(9)	599(4)	84(1)
C(21')	0.48	13059(7)	3778(8)	-92(3)	100(2)
C(22')	0.48	14288(4)	3349(7)	401(4)	96(2)
C(23')	0.48	13955(5)	3012(6)	1584(4)	97(2)
C(24')	0.48	12394(6)	3103(7)	2275(3)	81(1)

Table 3. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^2 x 10^3) for C23 H27 N O3 S.

	Occ.	x	y	z	U_{eq}
H(2A)	1	7771	4764	5855	78
H(2B)	1	7842	4048	7066	78
H(4)	1	6447	1545	6933	66
H(5A)	1	5225	634	5893	82
H(5B)	1	4006	1786	6419	82
H(6A)	1	4602	3043	4682	84
H(6B)	1	4225	1698	4445	84
H(7A)	1	6529	2294	3049	81
H(7B)	1	6950	1022	3788	81
H(8)	1	7384	3541	4190	68
H(9)	1	8469	1163	5295	62
H(10A)	1	3753	3905	6866	89
H(10B)	1	4692	5085	6953	89
H(12)	1	9467	3091	8530	103
H(13)	1	8253	2186	10324	117
H(15)	1	7957	-1027	8999	104
H(16)	1	9213	-163	7197	88
H(17A)	1	7445	239	11620	187
H(17B)	1	7357	-1026	11086	187
H(17C)	1	5981	106	11188	187
H(18A)	0.520(3)	10825	3295	3810	116
H(18B)	0.520(3)	9692	4322	3289	116
H(20)	0.520(3)	10057	4043	1039	101
H(21)	0.520(3)	12026	4066	-709	120
H(22)	0.520(3)	14662	3537	-740	115
H(23)	0.520(3)	15330	2985	978	116
H(24)	0.520(3)	13361	2961	2726	97
H(18C)	0.480(3)	9471	4377	3102	116
H(18D)	0.480(3)	8750	3931	2196	116
H(20')	0.480(3)	10676	4156	270	101
H(21')	0.480(3)	13282	4003	-883	120
H(22')	0.480(3)	15332	3288	-61	115
H(23')	0.480(3)	14777	2725	1914	116
H(24')	0.480(3)	12172	2878	3067	97

Table 4. Anisotropic parameters ($Å^2$ x 10^3) for C23 H27 N O3 S.

The anisotropic displacement factor exponent takes the form:

$$-2\pi^2 [h^2 a^{*2} U_{11} + ... + 2 h k a^* b^* U_{12}]$$

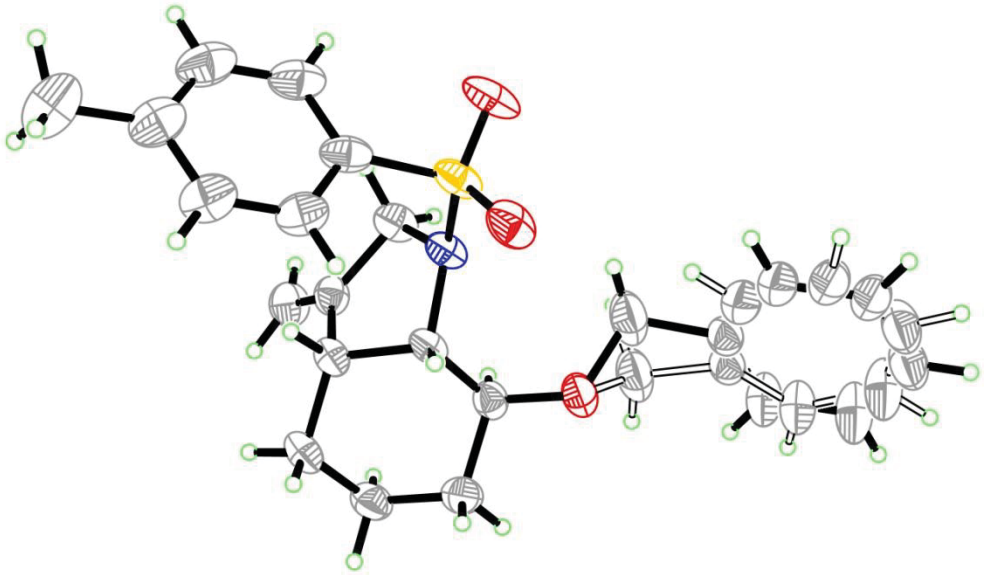
	U11	U22	U33	U23	U13	U12
S(1)	41(1)	60(1)	108(1)	-21(1)	-26(1)	-3(1)
O(1)	57(1)	55(1)	77(1)	-15(1)	4(1)	-13(1)
O(2)	44(1)	73(1)	115(1)	-28(1)	-15(1)	7(1)
O(3)	56(1)	77(1)	160(2)	-28(1)	-42(1)	-18(1)
N(1)	43(1)	47(1)	82(1)	-16(1)	-18(1)	-5(1)
C(2)	55(1)	52(1)	91(2)	-19(1)	-24(1)	2(1)
C(3)	49(1)	62(1)	56(1)	-3(1)	-12(1)	-1(1)
C(4)	46(1)	55(1)	62(1)	4(1)	-14(1)	-10(1)
C(5)	49(1)	73(1)	84(2)	2(1)	-15(1)	-20(1)
C(6)	55(1)	80(2)	81(2)	-7(1)	-25(1)	-15(1)
C(7)	65(1)	71(1)	73(1)	-15(1)	-22(1)	-12(1)
C(8)	49(1)	52(1)	62(1)	-10(1)	-4(1)	-6(1)
C(9)	41(1)	44(1)	72(1)	-9(1)	-15(1)	-8(1)
C(10)	57(1)	77(2)	81(2)	-11(1)	-12(1)	6(1)
C(11)	61(1)	59(1)	95(2)	-24(1)	-42(1)	7(1)
C(12)	89(2)	77(2)	108(2)	-35(2)	-45(2)	-2(1)
C(13)	112(2)	98(2)	98(2)	-45(2)	-45(2)	11(2)
C(14)	101(2)	87(2)	85(2)	-19(2)	-41(2)	16(2)
C(15)	115(2)	64(1)	89(2)	-11(1)	-45(2)	3(1)
C(16)	90(2)	57(1)	79(2)	-16(1)	-36(1)	4(1)
C(17)	155(3)	127(3)	83(2)	-11(2)	-33(2)	15(2)
C(18)	86(4)	82(2)	100(4)	-11(3)	18(2)	-31(3)
C(19)	61(2)	55(1)	63(2)	-9(2)	-6(2)	-16(2)
C(20)	68(3)	94(2)	69(4)	4(4)	3(3)	2(3)
C(21)	74(5)	120(3)	76(2)	20(2)	2(3)	8(5)
C(22)	56(3)	135(4)	85(4)	10(4)	-10(2)	-16(3)
C(23)	69(3)	160(4)	62(4)	-28(5)	-13(3)	-12(3)
C(24)	65(4)	108(3)	69(2)	-24(2)	-9(3)	-9(4)
C(18')	86(4)	82(2)	100(4)	-11(3)	18(2)	-31(3)
C(19')	61(2)	55(1)	63(2)	-9(2)	-6(2)	-16(2)
C(20')	68(3)	94(2)	69(4)	4(4)	3(3)	2(3)
C(21')	74(5)	120(3)	76(2)	20(2)	2(3)	8(5)
C(22')	56(3)	135(4)	85(4)	10(4)	-10(2)	-16(3)
C(23')	69(3)	160(4)	62(4)	-28(5)	-13(3)	-12(3)
C(24')	65(4)	108(3)	69(2)	-24(2)	-9(3)	-9(4)

Table 5. Bond lengths [Å] and angles [°] for C23 H27 N O3 S

		C(2)-N(1)-C(9)	108.93(14)
S(1)-O(2)	1.4288(16)	C(2)-N(1)-S(1)	118.60(14)
S(1)-O(3)	1.4293(16)	C(9)-N(1)-S(1)	120.63(12)
S(1)-N(1)	1.6196(17)	N(1)-C(2)-C(3)	104.33(16)
S(1)-C(11)	1.756(3)	C(10)-C(3)-C(4)	128.1(2)
O(1)-C(18')	1.418(6)	C(10)-C(3)-C(2)	124.3(2)
O(1)-C(8)	1.425(2)	C(4)-C(3)-C(2)	107.54(15)
O(1)-C(18)	1.444(5)	C(3)-C(4)-C(5)	117.66(17)
N(1)-C(2)	1.481(2)	C(3)-C(4)-C(9)	101.61(15)
N(1)-C(9)	1.481(2)	C(5)-C(4)-C(9)	114.03(17)
C(2)-C(3)	1.525(3)	C(6)-C(5)-C(4)	112.53(17)
C(3)-C(10)	1.312(3)	C(5)-C(6)-C(7)	110.85(19)
C(3)-C(4)	1.515(3)	C(6)-C(7)-C(8)	110.18(17)
C(4)-C(5)	1.526(3)	O(1)-C(8)-C(7)	109.41(16)
C(4)-C(9)	1.537(2)	O(1)-C(8)-C(9)	110.57(17)
C(5)-C(6)	1.510(3)	C(7)-C(8)-C(9)	110.59(16)
C(6)-C(7)	1.516(3)	N(1)-C(9)-C(8)	109.23(15)
C(7)-C(8)	1.517(3)	N(1)-C(9)-C(4)	103.15(15)
C(8)-C(9)	1.519(3)	C(8)-C(9)-C(4)	111.07(16)
C(11)-C(12)	1.383(3)	C(12)-C(11)-C(16)	118.7(3)
C(11)-C(16)	1.398(3)	C(12)-C(11)-S(1)	121.2(2)
C(12)-C(13)	1.363(4)	C(16)-C(11)-S(1)	119.97(18)
C(13)-C(14)	1.379(4)	C(13)-C(12)-C(11)	120.2(3)
C(14)-C(15)	1.391(4)	C(12)-C(13)-C(14)	122.2(3)
C(14)-C(17)	1.501(4)	C(13)-C(14)-C(15)	117.0(3)
C(15)-C(16)	1.361(4)	C(13)-C(14)-C(17)	122.3(3)
C(18)-C(19)	1.487(6)	C(15)-C(14)-C(17)	120.7(3)
C(19)-C(20)	1.39	C(16)-C(15)-C(14)	122.0(3)
C(19)-C(24)	1.39	C(15)-C(16)-C(11)	119.8(2)
C(20)-C(21)	1.39	O(1)-C(18)-C(19)	109.8(5)
C(21)-C(22)	1.39	C(20)-C(19)-C(24)	120
C(22)-C(23)	1.39	C(20)-C(19)-C(18)	122.3(4)
C(23)-C(24)	1.39	C(24)-C(19)-C(18)	117.7(4)
C(18')-C(19')	1.501(6)	C(21)-C(20)-C(19)	120
C(19')-C(20')	1.39	C(20)-C(21)-C(22)	120
C(19')-C(24')	1.39	C(23)-C(22)-C(21)	120
C(20')-C(21')	1.39	C(22)-C(23)-C(24)	120
C(21')-C(22')	1.39	C(23)-C(24)-C(19)	120
C(22')-C(23')	1.39	O(1)-C(18')-C(19')	107.8(5)
C(23')-C(24')	1.39	C(20')-C(19')-C(24')	120
O(2)-S(1)-O(3)	120.02(10)	C(20')-C(19')-C(18')	124.1(5)
O(2)-S(1)-N(1)	106.93(9)	C(24')-C(19')-C(18')	115.7(5)
O(3)-S(1)-N(1)	106.42(9)	C(19')-C(20')-C(21')	120
O(2)-S(1)-C(11)	108.43(10)	C(22')-C(21')-C(20')	120
O(3)-S(1)-C(11)	107.03(11)	C(23')-C(22')-C(21')	120
N(1)-S(1)-C(11)	107.42(10)	C(22')-C(23')-C(24')	120
C(18')-O(1)-C(8)	110.3(3)	C(23')-C(24')-C(19')	120
C(18')-O(1)-C(18)	45.5(3)		
C(8)-O(1)-C(18)	116.7(2)		

Table 6. Torsion angles [°] for C23 H27 N O3 S.

O(2)-S(1)-N(1)-C(2)	178.52(15)
O(3)-S(1)-N(1)-C(2)	-52.07(18)
C(11)-S(1)-N(1)-C(2)	62.30(16)
O(2)-S(1)-N(1)-C(9)	39.75(17)
O(3)-S(1)-N(1)-C(9)	169.16(15)
C(11)-S(1)-N(1)-C(9)	-76.47(16)
C(9)-N(1)-C(2)-C(3)	13.8(2)
S(1)-N(1)-C(2)-C(3)	-129.36(15)
N(1)-C(2)-C(3)-C(10)	-166.4(2)
N(1)-C(2)-C(3)-C(4)	11.0(2)
C(10)-C(3)-C(4)-C(5)	21.9(3)
C(2)-C(3)-C(4)-C(5)	-155.30(18)
C(10)-C(3)-C(4)-C(9)	147.2(2)
C(2)-C(3)-C(4)-C(9)	-30.1(2)
C(3)-C(4)-C(5)-C(6)	71.3(2)
C(9)-C(4)-C(5)-C(6)	-47.5(3)
C(4)-C(5)-C(6)-C(7)	52.7(3)
C(5)-C(6)-C(7)-C(8)	-59.8(2)
C(18')-O(1)-C(8)-C(7)	105.8(4)
C(18)-O(1)-C(8)-C(7)	155.3(4)
C(18')-O(1)-C(8)-C(9)	-132.2(4)
C(18)-O(1)-C(8)-C(9)	-82.7(4)
C(6)-C(7)-C(8)-O(1)	-176.69(17)
C(6)-C(7)-C(8)-C(9)	61.3(2)
C(2)-N(1)-C(9)-C(8)	85.48(19)
S(1)-N(1)-C(9)-C(8)	-132.23(15)
C(2)-N(1)-C(9)-C(4)	-32.7(2)
S(1)-N(1)-C(9)-C(4)	109.57(15)
O(1)-C(8)-C(9)-N(1)	70.74(18)
C(7)-C(8)-C(9)-N(1)	-167.92(15)
O(1)-C(8)-C(9)-C(4)	-176.15(15)
C(7)-C(8)-C(9)-C(4)	-54.8(2)
C(3)-C(4)-C(9)-N(1)	37.58(18)
C(5)-C(4)-C(9)-N(1)	165.21(16)
C(3)-C(4)-C(9)-C(8)	-79.32(18)
C(5)-C(4)-C(9)-C(8)	48.3(2)
O(2)-S(1)-C(11)-C(12)	151.16(19)
O(3)-S(1)-C(11)-C(12)	20.3(2)
N(1)-S(1)-C(11)-C(12)	-93.6(2)
O(2)-S(1)-C(11)-C(16)	-31.9(2)
O(3)-S(1)-C(11)-C(16)	-162.72(18)
N(1)-S(1)-C(11)-C(16)	83.33(19)
C(16)-C(11)-C(12)-C(13)	-1.3(4)
S(1)-C(11)-C(12)-C(13)	175.7(2)
C(11)-C(12)-C(13)-C(14)	-0.5(4)
C(12)-C(13)-C(14)-C(15)	1.6(4)
C(12)-C(13)-C(14)-C(17)	-178.8(3)
C(13)-C(14)-C(15)-C(16)	-0.9(4)
C(17)-C(14)-C(15)-C(16)	179.5(3)
C(14)-C(15)-C(16)-C(11)	-0.8(4)
C(12)-C(11)-C(16)-C(15)	1.9(4)
S(1)-C(11)-C(16)-C(15)	-175.06(18)
C(18')-O(1)-C(18)-C(19)	-67.6(6)
C(8)-O(1)-C(18)-C(19)	-160.4(4)
O(1)-C(18)-C(19)-C(20)	64.0(6)
O(1)-C(18)-C(19)-C(24)	-116.5(5)
C(24)-C(19)-C(20)-C(21)	0
C(18)-C(19)-C(20)-C(21)	179.5(6)
C(19)-C(20)-C(21)-C(22)	0
C(20)-C(21)-C(22)-C(23)	0
C(21)-C(22)-C(23)-C(24)	0
C(22)-C(23)-C(24)-C(19)	0
C(20)-C(19)-C(24)-C(23)	0
C(18)-C(19)-C(24)-C(23)	-179.5(6)
C(8)-O(1)-C(18')-C(19')	176.5(4)
C(18)-O(1)-C(18')-C(19')	68.6(6)
O(1)-C(18')-C(19')-C(20')	129.5(5)
O(1)-C(18')-C(19')-C(24')	-55.4(7)
C(24')-C(19')-C(20')-C(21')	0
C(18')-C(19')-C(20')-C(21')	174.9(7)
C(19')-C(20')-C(21')-C(22')	0
C(20')-C(21')-C(22')-C(23')	0
C(21')-C(22')-C(23')-C(24')	0
C(22')-C(23')-C(24')-C(19')	0
C(20')-C(19')-C(24')-C(23')	0
C(18')-C(19')-C(24')-C(23')	-175.3(7)



ORTEP view of the C23 H27 N O3 S compound with the numbering scheme adopted. Ellipsoids drawn at 30% probability level. Hydrogens represented by sphere of arbitrary size.

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Annexe IV

Articles 1, 2 et 3

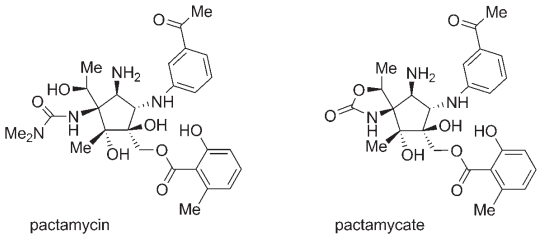
DOI: 10.1002/anie.201008079

Natural Product Synthesis

Total Synthesis of Pactamycin**

Stephen Hanessian, Ramkrishna Reddy Vakiti, Stéphane Dorich, Shyamapada Banerjee, Fabien Lecomte, Juan R. DelValle, Jianbin Zhang, and Benoît Deschênes-Simard*

Among the plethora of microbial secondary metabolites produced by the soil bacterium of the *Streptomyces* family is pactamycin, a structurally unique member of aminocyclopentitol-containing natural products (Scheme 1).



Scheme 1. Structures of pactamycin and pactamycate.

Pactamycin was isolated in 1961 from a fermentation broth of *Streptomyces pactum* var *pactum* by scientists at the former Upjohn Company.[1] It exhibits activity against Gram-positive and Gram-negative bacteria, in addition to potent in vitro and in vivo cytotoxic effects.[2] Its further development as a chemotherapeutic agent was curtailed owing to its toxicity. The potent protein synthesis inhibitory activity of pactamycin is attributed to the stage of translocation from the A and P sites to the P and E sites during formation of certain *m*-RNA-*t*-RNA complexes in prokaryotes as well as in eukaryotes.[3] Pioneering X-ray crystallographic studies[4] involving binding to the 30S site of *Thermus thermophilus* show unique interactions, whereby pactamycin adopts a spatial orientation so as to mimic an RNA nucleotide. The two aromatic moieties stack against each other like consecutive RNA bases, while the core cyclopentane motif mimics the RNA sugar-phosphate backbone, which results in an intricate network of hydrogen-bonded interactions within the 30S site of the ribosome. Recent elegant studies on the biosynthesis of pactamycin by Mahmud and coworkers[5a] revealed a gene cluster which also produced pactamycate, de-6-MSA-pactamycin and de-6-MSA-pactamycate, the natural congeners lacking the 6-methyl salicylic acid moiety.[5b–d]

A proposed structure of pactamycin was reported in 1970 by the Upjohn scientists as a result of seminal studies involving chemical degradation.[6] It was subsequently corrected in 1972 as a result of X-ray crystallographic studies, as shown in Scheme 1.[7] To the best of our knowledge, pactamycin is the most densely functionalized naturally occuring aminocyclopentitol.[8] In spite of its unique architecture and rich history in the realm of RNA structure and function,[3–5] efforts toward the synthesis of pactamycin and its congeners have been sparse. Knapp and Yu,[9] as well as Isobe and coworkers[10] recently reported conceptually different approaches toward the construction of the aminocyclopentane core motif. Herein, we communicate the first total synthesis of pactamycin and its naturally occurring congener, pactamycate (Scheme 1).

In considering a synthetic strategy, we were cognizant that the densely functionalized cyclopentane core harboring three contiguous tertiary centers would require a judicious choice of well-orchestrated bond-forming sequences. Furthermore, we wanted to adopt a modular approach for the introduction of substituents and appendages to allow for diversification to eventually prepare bioactive analogues while eliminating toxicity.

Analysis of the structure of pactamycin led to the choice of L-threonine as a partially hidden chiron, representing C1, C2, C7, and C8, and ensuring the configuration of the secondary hydroxy group in the hydroxyethyl appendage, as well as the position of the amine group at C1 (Scheme 2). The cyclopentenone core (**C**) would arise from a sequence of well-documented reactions culminating with an intramolecular aldol condensation. Systematic manipulation of the cyclopentenone (**C**) would then eventually lead to pactamycin. Straightforward as this plan may have been, its execution was met with several unexpected roadblocks particularly involving the elaboration of the *N*,*N*-dimethylurea group at C1, and the proximity of functional groups (see below).

A three-step sequence starting with L-threonine (**1**) led to the oxazoline derivative **2** (Scheme 3).[11,12] Formation of the enolate with LiHMDS, and condensation with O-TBDPS-2-hydroxymethyl acrolein, and subsequent protection with TESOTf afforded **3** as a single isomer. Reduction of the benzyl ester to the aldehyde, treatment with MeMgBr, and oxidation afforded the methyl ketone **4**. Ozonolytic cleavage of the exocyclic methylene group, followed by a highly stereoselective Mukaiyama-type intramolecular aldol condensation afforded **5** as a crystalline intermediate.[13] Upon treatment with trichloroacetyl chloride in pyridine, β-elimination took place to give the cyclopentenone **6**.

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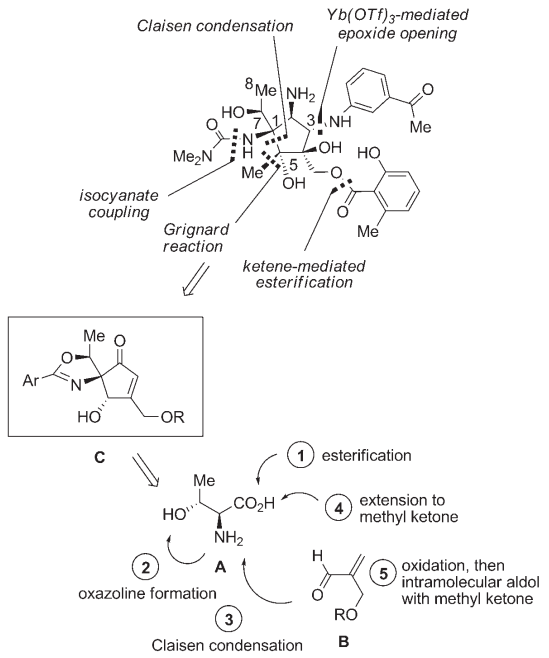
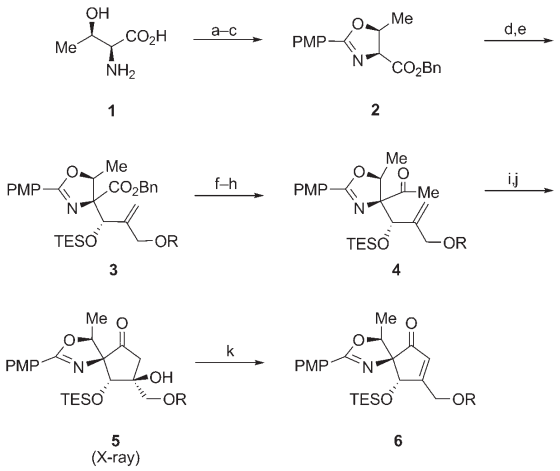
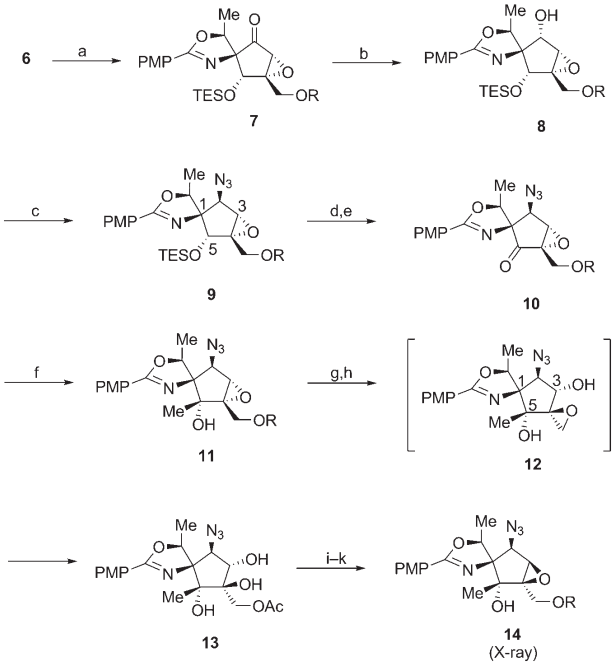


Scheme 2. Strategic bond disconnections and key transformations shown in their order of execution. **A** = L-threonine, **B** = oxygen-protected 2-hydroxymethyl acrolein, **C** = core cyclopentenone intermediate.



Scheme 3. Synthesis of the cyclopentenone intermediate **6**. Reagents and conditions: a) BnOH, PTSA, benzene, reflux, 67%; b) *p*-anisoyl chloride, TEA, CH_2Cl_2, RT, 64%; c) $SOCl_2$, MeCN, 0°C, 85%; d) LiHMDS, THF, −78°C, O-TBDPS-2-hydroxymethylacrolein; e) TESOTf, 2,6-lutidine, CH_2Cl_2, 0°C to RT, 67% (over 2 steps); f) DIBAL-H, CH_2Cl_2, −78°C; g) MeMgBr, Et_2O, 0°C, 87% (over 2 steps); h) $(COCl)_2$, DMSO, TEA, CH_2Cl_2, −78°C to RT, 91%; i) O_3, CH_2Cl_2, −78°C, then DMS, 84%; j) $TiCl_4$, CH_2Cl_2, DIPEA, TMSCl, 0°C, 85%; k) Cl_3CCOCl, py, CH_2Cl_2, RT, 89%. Bn = benzyl, DIBAL-H = diisobutylaluminum hydride, DIPEA = *N*,*N*-diisopropylethylamine, DMS = dimethyl sulfide, DMSO = dimethyl sulfoxide, HMDS = 1,1,1,3,3,3-hexamethyldisilazane, PMP = *p*-methoxyphenyl, PTSA = toluene-*p*-sulfonic acid, py = pyridine, R = TBDPS = *tert*-butyldiphenylsilyl, TEA = triethylamine, TES = triethylsilyl, Tf = trifluoromethanesulfonyl, THF = tetrahydrofuran.

From this point on, it was imperative to introduce the epoxide and hydroxy group in that order, while securing the desired configurations that would allow introduction of an azide group with inversion at C2, and the aniline moiety regioselectively at C3. In the event, base-induced epoxidation of **6** afforded epoxide **7**, which was stereoselectively reduced under Luche conditions to give **8** (Scheme 4). The formation



Scheme 4. Synthesis of the epoxide **14**. Reagents and conditions: a) H_2O_2 (30% w/w), 20% NaOH, MeOH/CH_2Cl_2 (7:1), 0°C, 75%, (88% bsmr); b) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH/CH_2Cl_2 (1:1), 0°C, 92%; c) Tf_2O, py, −78°C to 0°C, then Bu_4NN_3, toluene, RT, 87%; d) TFA/MeCN/H_2O (1:8:1), 0°C to RT, 93%; e) DMP, CH_2Cl_2, 0°C, 96%; f) MeMgBr, THF, −78°C; g) TBAF, THF, 0°C, 86% (over 2 steps); h) $Zn(OTf)_2$, AcOH, 80°C; i) K_2CO_3, MeOH, RT; j) TBDPSCl, TEA, DMAP, RT, 85% (over 3 steps); k) Tf_2O, py, CH_2Cl_2, −78°C to 0°C, 96%. DMAP = 4-dimethylaminopyridine, DMP = Dess–Martin periodinane, R = TBDPS, TBAF = tetra-*n*-butylammonium fluoride, TFA = trifluoroacetic acid.

of the α-oriented epoxide and secondary alcohol as in **8** was imperative, because the S_N2 azide displacement of the corresponding triflate in the diastereomeric β-epoxide in a related series was unsuccessful. Although the azide group could be easily introduced through the triflate ester of **8** to give **9**, it became necessary to "invert" the configuration of the epoxide to contemplate the stereo- and regioselective introduction of the aniline moiety by opening at C3. This operation was postponed in favor of the obligatory carbon-methyl branching at C5. Thus, selective cleavage of the TES ether and oxidation to the ketone gave **10**, which was treated with MeMgBr to give **11** as a single diastereomer. An X-ray structure of the phenyl oxazoline analogue of **10** confirmed its structure and absolute configuration.[12,13] The "inversion" of

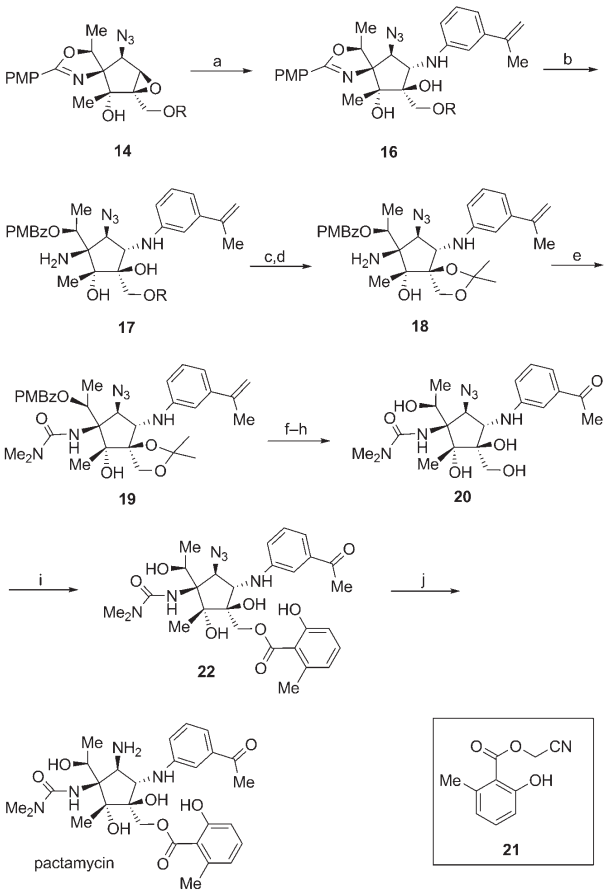
the epoxide in **11** was achieved by treatment of the corresponding primary alcohol with $Zn(OTf)_2$ in AcOH to give the triol **13** with C4 inversion. Presumably, this arose from the spiroepoxide **12** which underwent solvolysis to afford the primary acetate as in **13**. A two-step sequence restored the robust TBDPS ether group, and the resulting triol was converted in situ into the epoxide **14** through the secondary triflate (70% overall yield from **11**). An X-ray crystal structure validated the suggested sequence of inversions in going from **11** to **14**.[13]

Highly stereoselective epoxide opening at C3 with the aniline derivative **15** in the presence of $Yb(OTf)_3$[14] afforded the core structure **16** as the sole regioisomer (Scheme 5). Cleavage of the oxazoline moiety with aqueous HCl[15] led to the *p*-methoxybenzoyl ester, which was transformed into the acetonide **18** in straightforward manner.

Formation of an intermediate isocyanate in the presence of diphosgene,[16] then treatment with dimethylamine gave the urea **19** in excellent yield. Treatment of the ester with DIBAL-H, subsequent oxidative cleavage of the olefin to the methyl ketone, and hydrolysis of the acetonide function led to **20**. Esterification with the cyanomethyl ester **21**,[17] then reduction of the azide group in the presence of Lindlar's catalyst, afforded pactamycin which was purified by chromatography on silica gel. Synthetic pactamycin exhibited spectroscopic and chiroptical properties identical to the originally published data.[6,12] Furthermore, ^{1}H NMR data at 700 MHz, ^{13}C NMR data at 100 MHz, HPLC data, as well as single crystal X-ray structures of several intermediates provide hitherto unavailable characterization features for future synthetic endeavors.[12] Pactamycin is reported to be unstable in solution as evidenced by a change in optical rotation in different solvents, thus losing some of its biological activity with time.[6]

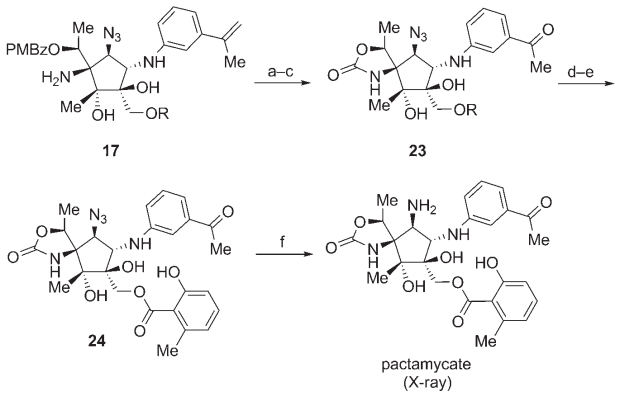
The synthesis of crystalline pactamycate,[6] a naturally occurring congener,[5a] is shown in Scheme 6. Treatment of **17** with DIBAL-H, then diphosgene,[16] resulted in the formation of the corresponding cyclic carbamate. Oxidative cleavage of the *exo*-methylene group in the latter afforded **23**, which was converted in two steps into the 2-azido precursor **24**. Hydrogenation in presence of Lindlar's catalyst gave crystalline pactamycate. An X-ray crystal structure confirmed the structure of pactamycin and the original assignment of its absolute configuration for the first time (Scheme 6).[7,12,13]

The successful and seemingly straightforward total synthesis of pactamycin described here underscores the importance (and frustrations) of many unwanted transformations caused by the proximity of reactive functional groups anchored on the cyclopentane core. For example, having introduced the primary amino group at C1 in intermediate **17** by acidic hydrolysis of the oxazoline **16**, there only remained to convert it into the *N*,*N*-dimethylurea, bringing us within a few steps from the intended target, pactamycin. In practice, various attempts at reaction of **17** with *N*,*N*-dimethylcarbamoyl chloride resulted in the formation of the precursor oxazoline **16** (Scheme 7 A). In fact, triethylamine and DMAP alone effected the same transformation into **16**. Attempted formation of the desired *N*,*N*-dimethylurea by treatment of **17** with diphosgene to give an intermediate isocyanate, then quenching with dimethylamine, formed the six-membered cyclic carbamate **25** in 91% yield even at −46 °C (Scheme 7 B)![13] This remarkably facile reaction, spanning a tertiary alcohol and a highly hindered amine, demonstrates the importance and unexpected consequences of spatial proximity in a confined architecture such as that found in **17**.

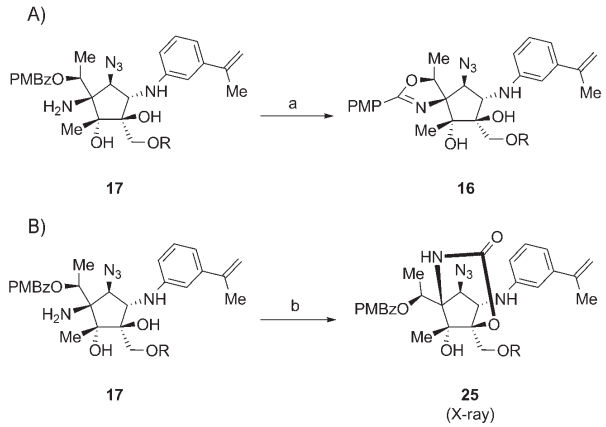


Scheme 5. Synthesis of pactamycin from the epoxide **14**. Reagents and conditions: a) 3-(prop-1-en-2-yl)aniline (**15**), $Yb(OTf)_3$, toluene, 80 °C, 81%, (91% brsm); b) 2 N HCl, THF, RT, 63%, (83% after two cycles); c) TASF, DMF, 0 °C to RT, 95%; d) 2,2-DMP/CH_2Cl_2 (1:5), CSA, 0 °C to RT, 86%; e) $Cl_3COCOCl$, activated charcoal, TEA, THF, −46 °C, then $HNMe_2$, −46 °C to RT, 86%; f) DIBAL-H, CH_2Cl_2, −78 °C, 90%; g) cat. OsO_4, THF/acetone/H_2O (5:5:1), NMO, then $NaIO_4$, THF/H_2O (1:1), RT, 80%; h) TFA/MeCN/H_2O (5:1:1), 0 °C to RT, 85%; i) **21**, K_2CO_3, DMA, RT, 96%; j) Lindlar's cat., H_2, MeOH/EtOH (1:1), 85%. brsm = based on recovered starting material, CSA = 10-camphorsulfonic acid, DMA = *N*,*N*-dimethylacetamide, DMF = *N*,*N*-dimethylformamide, 2,2-DMP = 2,2-dimethoxypropane, NMO = 4-methylmorpholine *N*-oxide, R = TBDPS, PMBz = *p*-methoxybenzoyl, TASF = tris(dimethylamino)sulfonium difluorotrimethylsilicate.

The total synthesis of pactamycin and pactamycate by the route described here was achieved in 29 linear steps and 3.0% overall yield starting with the known oxazoline **2** readily available from L-threonine.[11] The modular introduction of functional groups allows for a great deal of flexibility in the quest for the synthesis of less toxic congeners that maintain their antibacterial and cytotoxic activities.[18] Efforts toward



Scheme 6. Synthesis of pactamycate. Reagents and conditions: a) DIBAL-H, CH_2Cl_2, −78 °C, 89%; b) $Cl_3COCOCl$, activated charcoal, TEA, THF, −46 °C, 86%; c) cat. OsO_4, THF/acetone/H_2O (5:5:1), NMO, then $NaIO_4$, THF/H_2O (1:1), RT, 82%; d) TASF, DMF, 0 °C to RT, 93%; e) **21**, K_2CO_3, DMA, RT, 98%; f) Lindlar's cat., H_2, MeOH/EtOH (1:1), 83%. R = TBDPS.



Scheme 7. Unexpected results arising from the closeness of functional groups on the polysubstituted cyclopentane core structure. Reagents and conditions: a) *N*,*N*-dimethylcarbamoyl chloride, TEA, CH_2Cl_2, RT, 96%; b) $Cl_3COCOCl$, activated charcoal, TEA, THF, −46 °C, 91%. R = TBDPS.

these goals are presently being actively pursued in our laboratory.

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Keywords: natural products · pactamycate · pactamycin · polysubstituted cyclopentanes · total synthesis

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Total Synthesis of Pactamycin and Pactamycate: A Detailed Account

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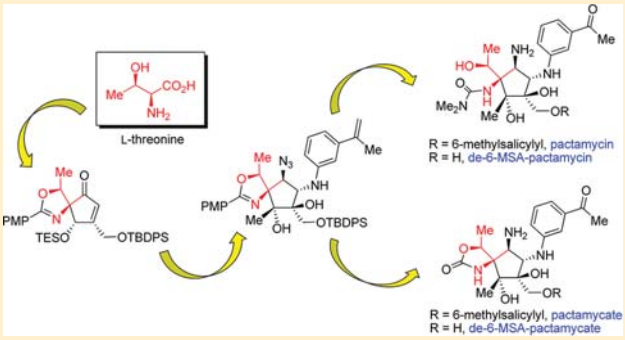
Supporting Information

ABSTRACT: This article describes synthetic studies that culminated in the first total synthesis of pactamycin and pactamycate and, in parallel, the two known congeners, de-6-MSA-pactamycin and de-6-MSA-pactamycate, lacking the 6-methylsalicylyl moiety. Starting with L-threonine as a *chiron*, a series of stereocontrolled condensations led to a key cyclopentenone harboring a spirocyclic oxazoline. A series of systematic functionalizations led initially to the incorrect cyclopentanone epoxide, which was "inverted" under solvolytic conditions. Installation of the remaining groups and manipulation of the oxazoline eventually led to pactamycin, pactamycate, and their desalicylyl analogues.



INTRODUCTION

The plethora of microbial secondary metabolites produced by the soil bacterium of the *Streptomyces* family comprise a family of highly substituted aminocyclopentitol-containing natural products.[1] Among these are pactamycin (**1**) and pactamycate (**2**), two structurally unique and functionally rich metabolites (Figure 1). Related cyclopentane core structures, albeit with simpler substitution patterns, are encountered in allosamizoline (**5**),[2] mannostatin A (**6**),[2] and trehazolamine (**7**).[3] Early studies on the biosynthesis of pactamycin were reported by Rinehart and co-workers in 1978.[4] More recently, Kudo and co-workers[5] cloned the biosynthetic gene cluster involved in the formation of the cyclopentane ring of pactamycin. Mahmud and co-workers[6] have shown pactamycin (**1**), pactamycate (**2**), de-6-MSA-pactamycin (**3**), and de-6-MSA-pactamycate (**4**) are produced from the same gene cluster.

Pactamycin was isolated in 1961 from a fermentation broth of *Streptomyces pactum var. pactum* by scientists at the former Upjohn Company.[7] Although it exhibited in vitro activity against certain Gram-positive and Gram-negative bacteria, as well as cytotoxicity toward cancer cell lines, its further development was curtailed due to its toxicity.[8] This can be attributed to its effect in arresting protein biosynthesis in eukaryotes as well as in prokaryotes.[9] Pioneering X-ray crystallographic studies by Ramakrishnan and co-workers[10] involving pactamycin bound to the 30S site of *Thermus thermophilus* showed unique interactions, whereby its two aromatic moieties are π-stacked against each other like consecutive RNA bases, while the core aminocyclopentitol motif mimics the RNA sugar−phosphate backbone. This results in an intricate network of H-bonded interactions with specific bases within the 30S site of the ribosome, as well as intramolecularly.

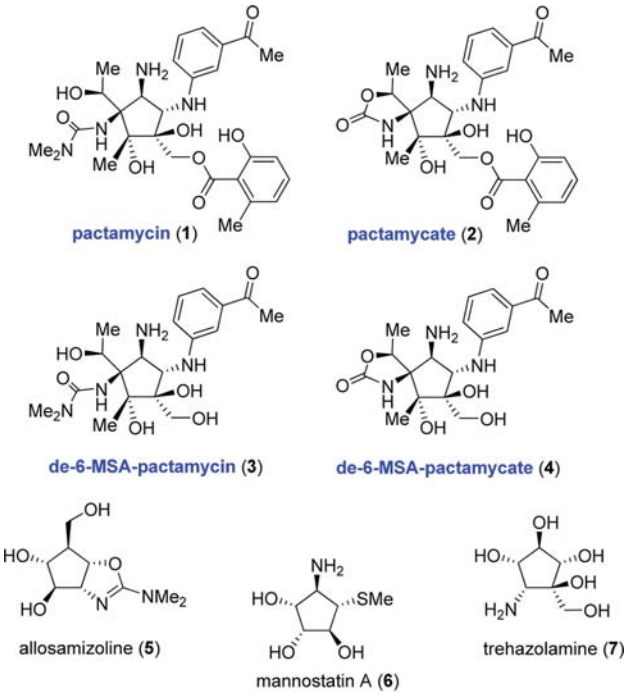


Figure 1. Structures of pactamycin, pactamycate, de-6-MSA-pactamycin, de-6-MSA-pactamycate, allosamizoline, mannostatin A, and trehazolamine.

An initially proposed structure for pactamycin by the Upjohn scientists in 1970 based on chemical degradation studies[11] was

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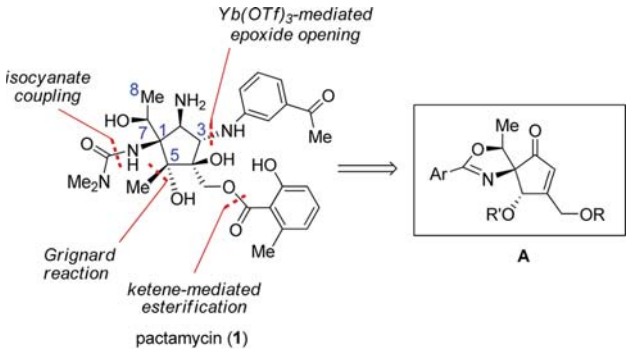
subsequently corrected in 1972 as a result of an X-ray crystal structure of a derivative.[12] To the best of our knowledge, pactamycin is the most densely functionalized naturally occurring aminocyclopentitol.[13] In spite of its unique architecture and rich history in the realm of other RNA-binding natural products, efforts toward its synthesis have been sparse. Conceptually different approaches toward the construction of the aminocyclopentitol core of pactamycin were reported by Isobe,[14] Knapp,[15] and more recently by Johnson,[16] Looper,[17] Nishikawa,[18] and their respective co-workers.

In a preliminary communication, we reported the first total synthesis of pactamycin (**1**) and pactamycate (**2**).[19] Herein, we provide a detailed account of our efforts, delineating initial studies that were met with a number of unexpected dead ends and road blocks, necessitating revisions of synthetic approaches. Analysis of the structure of pactamycin reveals a number of challenges, not the least of which are the presence of three contiguous tertiary centers at C4, C5, and C1 (Scheme 1). We

Scheme 1. Strategic Bond Disconnections to Key Intermediate Cyclopentenone A



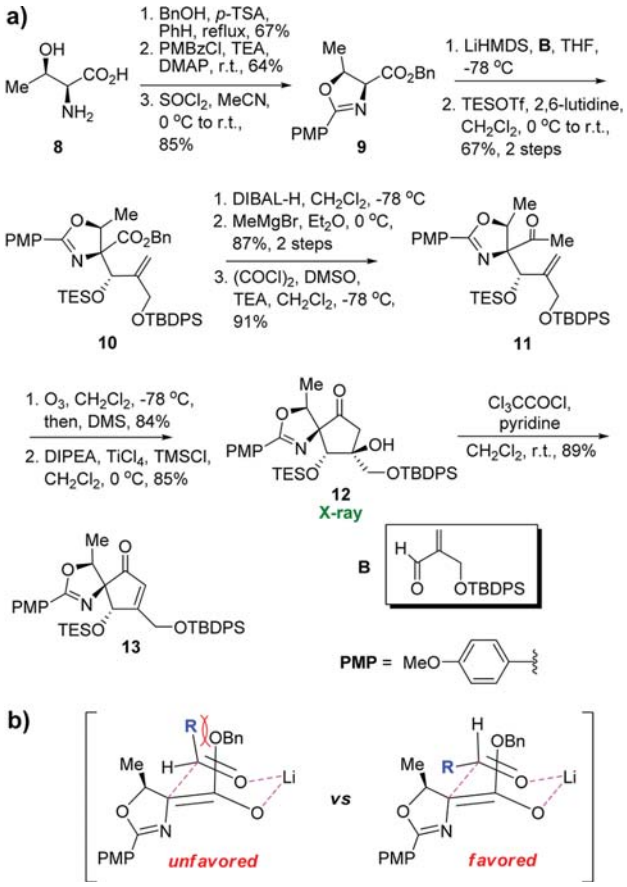
were cognizant that the densely functionalized core motif would require a judicious choice of carefully orchestrated bond-forming sequences, in which the order of execution would be crucial. On the basis of the existing functional groups and substituents on the cyclopentane core of pactamycin, a series of bond-forming sequences could be envisaged, as shown in Scheme 1.

Straightforward as this plan may have appeared to be at the outset, we were unaware of the potential difficulties associated with effecting seemingly routine transformations as new substituents and appendages were sequentially introduced on the cyclopentane core. Considering the nature and placement of the substituents, we chose to secure the aminoalcohol unit comprising C1 and extending toward C2 (or C5) that could be further elaborated into the cyclopentane core motif. With this initial objective in mind, we chose L-threonine as a suitable *chiron* that would provide a hydroxyethyl appendage with the desired absolute configuration and allowed further elaboration of the α-amino acid segment to introduce C-branching via enolate or Claisen condensation. Since the aminoalcohol portion of pactamycin was considered to be an inherent part of the molecule, we wanted to adopt a modular approach for the introduction of substituents around the cyclopentane core to allow for diversification in preparing potentially bioactive analogues and congeners with diminished toxicity. To this end, we chose the cyclopentenone core motif **A** as our initial objective for synthesis (Scheme 1).

RESULTS AND DISCUSSION

Cyclopentenone Core. A known three-step sequence starting with L-threonine (**8**) led to the PMP-oxazoline derivative **9** (Scheme 2a).[20] Formation of the enolate with

Scheme 2. (a) Synthesis of the Cyclopentenone Intermediate 13 and (b) Suggested Transition State for the Formation of 10



LiHMDS and condensation with O-TBDPS-2-hydroxymethyl acrolein (**B**), followed by protection with TESOTf, afforded **10** as a single isomer. The observed stereoselectivity can be rationalized based on a favored Zimmerman−Traxler transition state model (Scheme 2b). Reduction of the benzyl ester to the aldehyde, treatment with MeMgBr, and oxidation of the resulting alcohol afforded the methyl ketone **11**. Ozonolytic cleavage of the exocyclic methylene group, followed by a highly stereoselective Mukaiyama-type intramolecular aldol condensation, proceeding via a presumed Ti-coordinated Si-enol ether or the corresponding Ti-enolate, afforded **12** as a shelf-stable crystalline product which was fully characterized by X-ray crystallography.[21] Treatment of **12** with trichloroacetyl chloride in pyridine led to the corresponding ester, which underwent in situ β-elimination to give the intended cyclopentenone **13**.

Elaboration of the Cyclopentenone Core (Plan A). We started by exploring a sequence of reactions to introduce functional groups in a "clockwise manner" commencing with the carbonyl group at C2 in **13** (Scheme 3). Under a variety of conditions, reduction led almost exclusively to the (*R*)-allylic alcohol **14**. This result augured well for the introduction of an azide group at C2 (and eventually an amine), by an S_N2

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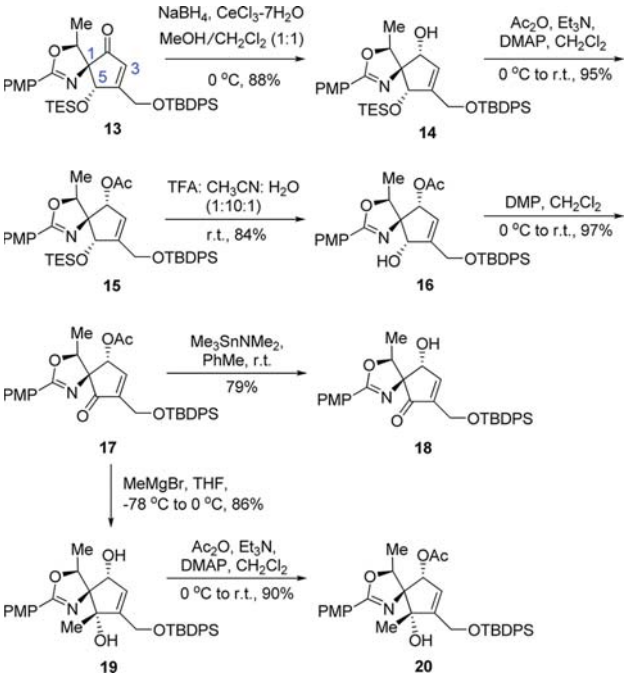
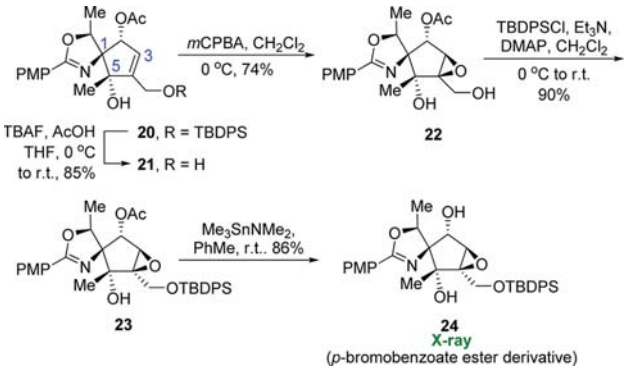
Scheme 3. Toward the Pactamycin Core, Plan A (Part 1)



reaction to secure the correct stereochemistry as found in pactamycin. Unfortunately, all attempts to prepare the triflate ester from **14** led to complex mixtures. Conversion to the acetate ester **15** and treatment of the latter with $Pd(PPh_3)_4$ and NaN_3 or $TMSN_3$ under classical Tsuji–Trost conditions[22] was also unsuccessful, as starting material remained intact and could be recovered. Selective deprotection of the TES ether in **15** gave **16**, which was oxidized under Dess–Martin conditions to give ketone **17**. Deacetylation to **18** with trimethylstannyl dimethylamine,[23] followed by attempted conversion to the triflate ester led to decomposition. However, treatment of **17** with MeMgBr afforded **19** as a single isomer with the required orientation as found in pactamycin. Unfortunately, formation of the corresponding triflate or mesylate esters also failed, giving a complex mixture of products.

We next decided to postpone the introduction of the azide group, in favor of the aniline moiety at C3. The acetate **20**, prepared from **19**, was transformed to the corresponding allylic alcohol **21**, which was treated with *m*CPBA to afford epoxide **22** (Scheme 4). Reprotection of the primary hydroxyl group as

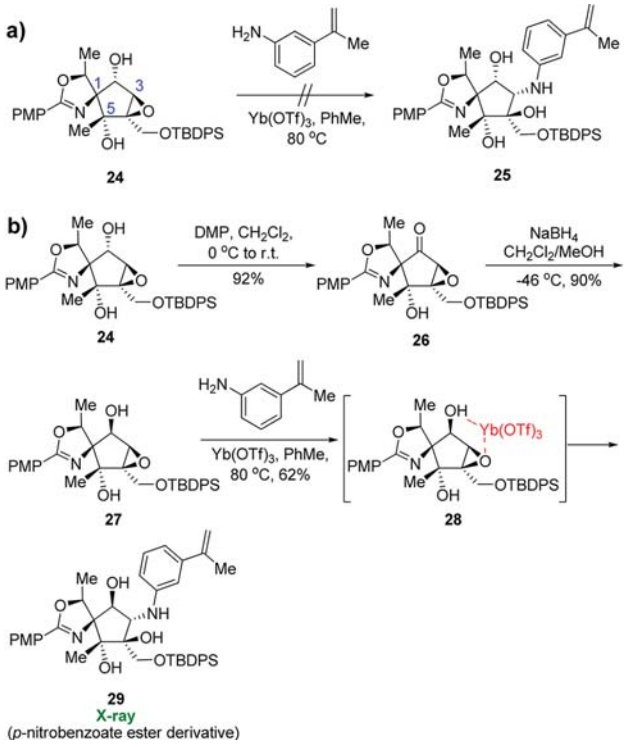
Scheme 4. Toward the Pactamycin Core, Plan A (Part 2)



in **23**, followed by deacetylation, led to **24**, whose structure was ascertained by X-ray crystallography of the corresponding *p*-bromobenzoate ester.[21] It is noteworthy that the direct epoxidation of **20** gave only trace amounts of **23** and mainly entailed slow decomposition. Disappointingly, attempts to prepare the C2 triflate ester of **24** led to a complex mixture of products.

Faced with yet another impasse in our attempts to functionalize C2, we proceeded to study conditions for the regioselective ring opening of the epoxide **24** with various anilines.[24] Preliminary model studies, to be discussed in a separate publication, with simple 1-hydroxy-2,3-epoxy-3-methyl cyclopentanes, with and without protecting groups utilizing various Lewis acids and anilines, resulted in exclusive opening at the tertiary carbon atom. Nevertheless, we hoped that the selectivity could be reversed due to the different topology, substitution pattern, and steric effects in **24**. However, treatment with 3-isopropenyl aniline in the presence of $Yb(OTf)_3$ in toluene at 80 °C did not lead to **25** but resulted in the formation of a complex mixture of products (Scheme 5a).

Scheme 5. Toward the Pactamycin Core, Plan A (Part 3): Introduction of the Aniline Moiety



Oxidation of **24** to the corresponding ketone **26** and reduction with $NaBH_4$ led to the C2 epimeric alcohol **27**. Much to our delight, treatment with 3-isopropenyl aniline in the presence of $Yb(OTf)_3$ now led to the expected aniline **29**. Definitive confirmation of structure and stereochemistry was obtained from a single X-ray crystal structure determination of a *p*-nitrobenzoate ester derivative.[21] The successful regio- and stereoselective opening of the *syn*-oriented epoxyalcohol **27** can be explained by a favorable Yb-coordinated complex (**28**),[24] which presumably was not formed in the case of **24** with an

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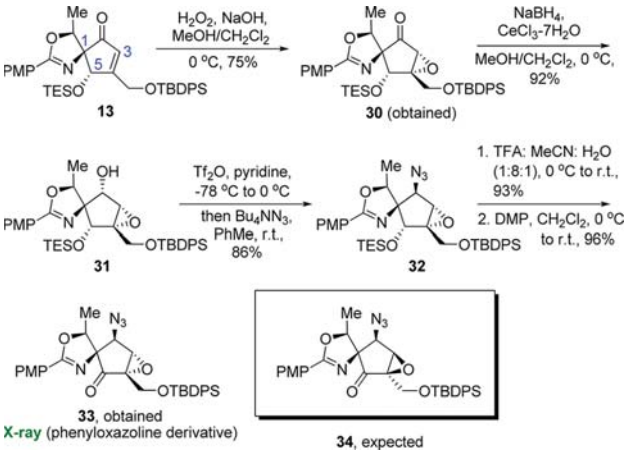
anti-orientation of the C2 alcohol compared to **27** (Scheme 5b).

Reassessing our options, it was clear that substantial progress had been made in reaching the advanced stage of intermediate **29**, which possessed all of the required functional appendages except at C2. Introduction of an azide group would require reinversion of the C2 hydroxyl group in order to attempt S_N2 substitution on the triflate ester. However, our prior negative experiences along those lines (vide supra) dissuaded us from continuing this approach.

Elaboration of the Cyclopentenone Core (Plan B). We returned to the cyclopentenone core motif **13** and considered a different sequence of funtionalizations. Treatment of **13** with H_2O_2 cleanly afforded a product which we believed to be the "*up*" epoxide analogue of **30** as observed for **21**, due to the orientation of the bulky O-TES group (Scheme 6). Reduction

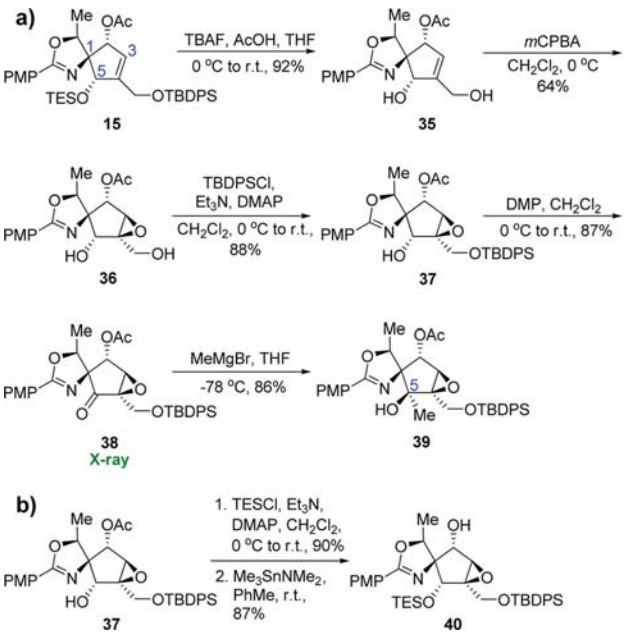
Scheme 6. Toward the Pactamycin Core, Plan B (Part 1): Introducing Azide on the Wrong Epoxide



of the ketone with $NaBH_4$ in the presence of $CeCl_3{\cdot}7H_2O$ gave a single alcohol at C2, which upon triflation and treatment with Bu_4NN_3 afforded a product containing the elusive azide group for the first time. However, not until the O-TES group was deprotected, and the resulting alcohol was oxidized, did we become aware that epoxidation had occurred from the *opposite face* of the enone in **13**, as evidenced from an X-ray structure.[21] Thus, epoxidation had led to **30**, which was reduced to **31**, and introduction of azide had led to **32** and **33** after silyl deprotection and oxidation, rather than the expected **34**. We presume that the combination of the spiro-oxazoline and the bulky O-TBDPS group may have disfavored the approach of the hydroperoxide ion from the same side, eventually leading to the wrong epoxide **30**.

We therefore once again changed our order of reactions, now starting with **15** (Scheme 7a). Deprotection of the silyl ethers led to **35**, which was smoothly epoxidized to **36** with *m*CPBA then reprotected to give **37**. Oxidation to **38** and X-ray analysis confirmed the required "*up*" orientation of the epoxide. However, deprotection of the acetate ester in **38** and attempted triflation led to decomposition. Having the ketone **38** in hand, we also attempted to introduce the methyl group at C5 using a Grignard reaction. In this case, however, attack occurred from the side *opposite* to the epoxide and the spiro-oxazoline to give the **39**, epimeric at C5 with **23**. Conversion of **37** to **40** (a

Scheme 7. Toward the Pactamycin Core, Plan B (Part 2): Introducing the Correct Epoxide



diastereomer of **31**) followed by attempted triflation led to yet another complex mixture (Scheme 7b).

Inverting the Epoxide (Plan C). From the various attempts to introduce an azide group at C2 with the correct stereochemistry, it was clear that a successful triflation and S_N2 azide displacement was possible only with a specific relative orientation of the epoxy alcohol as found in **31**. We were therefore faced with an "*epoxide inversion*" issue. Treatment of the ketone **33** with MeMgBr, then silyl ether deprotection, cleanly gave **41** (Scheme 8). For the "inversion" of the epoxide, we would rely on a regioselective solvolytic ring opening, followed by placing a leaving group at the resulting C3 alcohol, then treatment with an appropriate base to effect epoxide formation with the tertiary hydroxyl group at C4, acting as an internal nucleophile. A variety of conditions were tried to effect these transformations, but without success.[25] We then resorted to an activation of the epoxide with a Lewis acid in the presence of acetic acid as a nucleophile in the hope of obtaining the C4-inverted tertiary alcohol as the acetate ester. In the event, treatment of **41** with $Zn(OTf)_2$ in acetic acid[26] led directly to the primary acetate ester **44** in excellent yield.

Thus, configurational inversion at C3 and C4 had indeed been achieved, albeit by an alternative pathway than the one initially envisaged (vide supra). Presumably, solvolysis proceeded by initial activation of the epoxide by $Zn(OTf)_2$, as in **42**, followed by formation of a spiroepoxide **43** by intramolecular attack of the primary hydroxyl group with inversion of configuration of the tertiary C4 center. Subsequent regioselective ring opening with acetic acid at the primary carbon atom of the spiroepoxide, possibly activated by $Zn(OTf)_2$, led to **44** as the only product in good overall yield. A two-step sequence restored the TBDPS ether group, and the resulting triol was converted to the C3,C4-"inverted" epoxide **46** via the corresponding triflate (71% overall yield from **33**). An X-ray structure of **46** confirmed the structure of the latter intermediate. Highly regio- and stereoselective epoxide opening at C3 with 3-isopropenyl aniline in the

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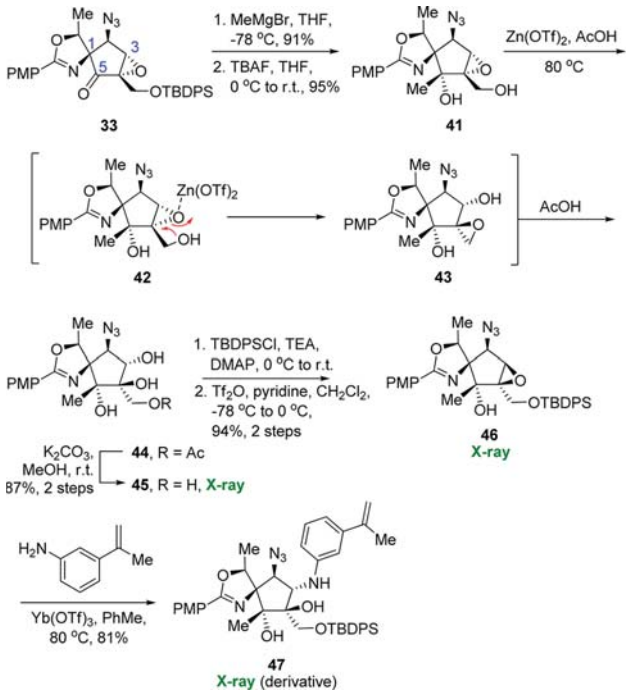
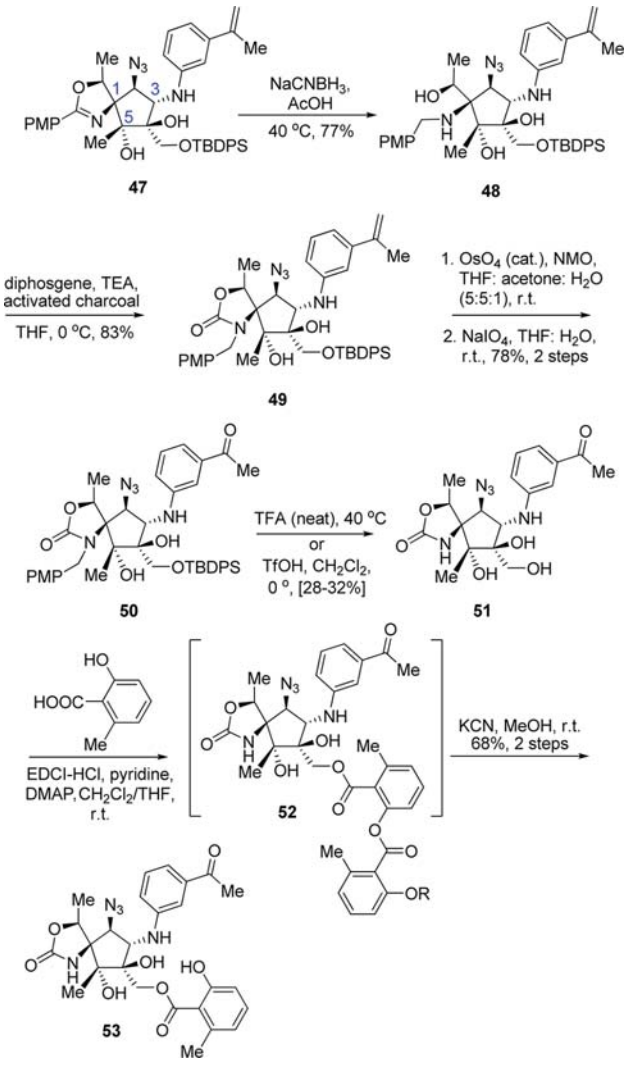
Scheme 8. Obtaining the Core Structure of Pactamycin



Scheme 9. Toward Pactamycate (First Approach)



presence of $Yb(OTf)_3$ afforded the advanced core structure **47** as the sole product.[21] It should be noted that activation of the epoxide **46** with $Yb(OTf)_3$ occurred in the absence of a coordinating hydroxyl group, and the regioselective opening with the aniline could be due to the inductive effect of the neighboring azido group and to steric effects.

Toward Pactamycate. Having secured the full complement of substituents directly attached to the cyclopentane core motif, we set our next objective toward the naturally occurring congener, pactamycate, previously obtained by acid treatment of pactamycin.[11] Studies by Mahmud and co-workers[6] on the biosynthesis of pactamycin led to the identification and isolation of pactamycate and its de-6-MSA-counterpart from the same gene cluster.

Our first steps toward pactamycate consisted of the conversion of **47** to the N-PMB derivative **48** by treatment with $NaCNBH_3$ in AcOH[20] (Scheme 9). Formation of the cyclic carbamate **49** using diphosgene in the presence of activated charcoal[27] was followed by an oxidative cleavage of the exocyclic methylene group to afford **50**. Treatment of **50** with ceric ammonium nitrate resulted in decomposition. However, treatment under strong acidic conditions removed the N-PMB group, albeit in modest yield, to furnish the 2-azido analog of de-6-MSA-pactamycate **51**. There remained to esterify the primary hydroxyl group and to reduce the azide group to reach pactamycate. Thus, treatment of **51** with 6-methylsalicylic acid in the presence of EDCI under standard conditions led to the formation of **52** as a mixture of oligomers containing two or more 6-MSA units as a result of multiple esterifications of the phenolic hydroxyl group in the initially formed 2-azido pactamycate. Treatment of **52** with KCN in MeOH[28] effected selective cleavage of the phenolic esters to afford the desired 2-azido pactamycate **53**.

In view of the modest yield of deprotection of the N-PMB group, coupled with the unwanted double esterification of **51**, we sought an alternative approach to pactamycate (Scheme 10). The oxazoline group in **47** was cleaved under acidic conditions to afford the *p*-methoxybenzoate ester **54**. Treatment with DIBAL-H led to **55**, which when treated with diphosgene in the presence of activated charcoal gave the cyclic carbamate **56**. Oxidative cleavage of the exocyclic methylene group, followed by cleavage of the OTBDPS group in the presence of TASF[29] afforded **51**, which had been obtained in lower yields by the earlier route (see Scheme 9). Esterification of **51** was successfully achieved using cyanomethyl 2-hydroxy-6-methylbenzoate (**57**) according to Porco and co-workers[30] to afford **53**. Reductive cleavage of the azido group in presence of Zn powder in aqueous NH_4Cl[31] gave crystalline pactamycate (**2**) whose structure and absolute stereochemistry was validated by X-ray crystallography for the first time. De-6-MSA-pactamycate (**4**) could be obtained by reductive cleavage of the azido group in **51**, adopting the same methods used for **53**.

Onward to Pactamycin. The advanced intermediates **54** and **55** were exquisitely poised for a straightforward completion of the total synthesis of pactamycin. All that would be required was the formation of the dimethylurea by suitable functionalization of the exposed primary amino group. The availability of N,N-dimethylcarbonyl chloride as a reagent would practically ensure access to the desired N,N-dimethylurea from one or

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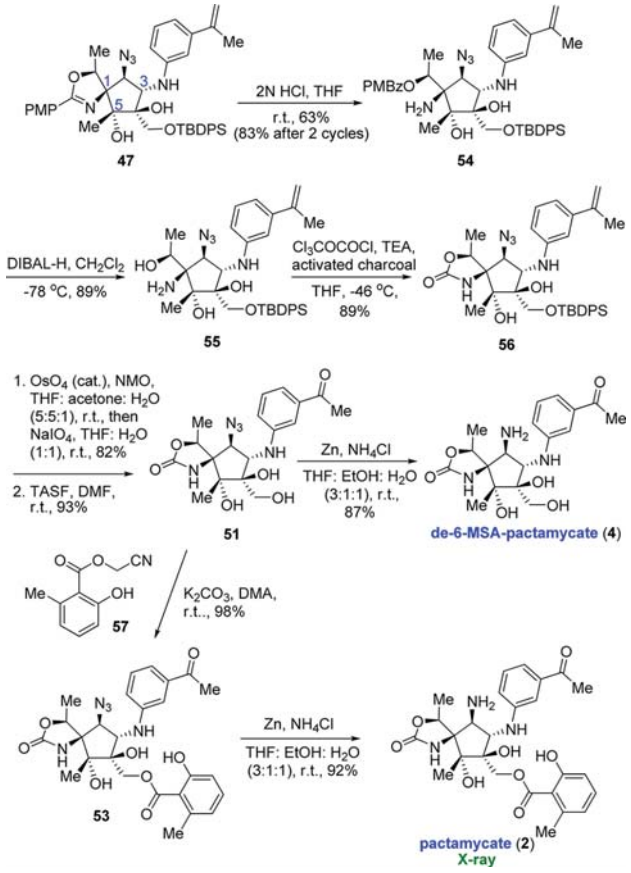
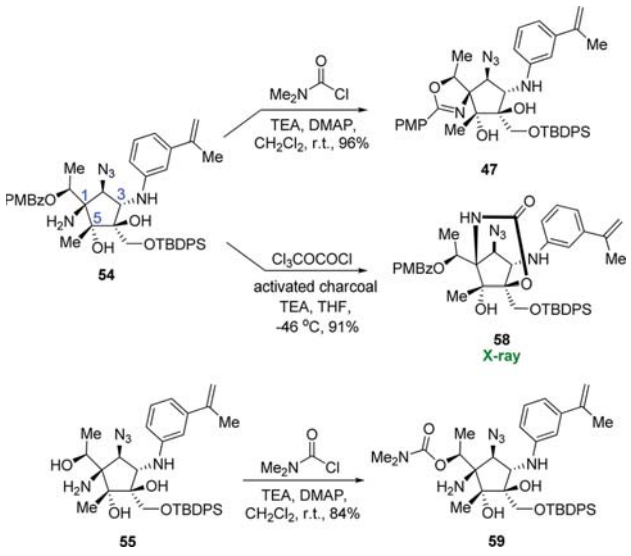
Scheme 10. Toward Pactamycate (Second Approach)



more of the aforementioned intermediates.[32] However, in practice, this turned out to be a frustrating experience and a reflection of the unexpected reactivities of an otherwise commonly reactive primary amino group in densely functionalized core motifs, such as **54** and **55** (Scheme 11). When **54** was treated with N,N-dimethylcarbamoyl chloride under a variety of conditions, none of the desired N,N-dimethylurea was observed. Instead, the oxazoline **47**, formed by an intramolecular attack of the amino group on the PMBz ester and elimination of water, was recovered. Under forcing conditions, using NaH, TBAI, and N,N-dimethylcarbamoyl chloride, only carbamoylation of **54** was observed. In an effort to obtain the intended urea via an intermediate isocyanate, we treated **54** with diphosgene in the presence of activated charcoal. Surprisingly, this led to the six-membered cyclic carbamate **58**, resulting from an intramolecular attack of the tertiary alcohol on the isocyanate group. The structure of **58** was ascertained by X-ray analysis. Treatment of the aminotriol **55** with N,N-dimethylcarbamoyl chloride led to the formation of the carbamate **59**, leaving the amino group unperturbed.

Scheme 11. Attempts To Form the Urea (Part 1)



We then reasoned that treatment of the cyclic carbamates **47**, **56**, and **58** with dimethylamine or trimethylstannyl dimethylamine (Me_3SnNMe_2) could result in the formation of the elusive N,N-dimethylurea via a direct attack on the carbonyl group of the carbamate or via a four-center activation mode with transfer of the dimethylamine group (Scheme 12). However, in the presence of Me_3SnNMe_2 in refluxing toluene, **56** was found to be completely stable, while **58** gave the O-PMBz deprotected carbamate **60**.

The unsuccessful attempts to prepare the N,N-dimethylurea derivative by selective acylation of the seemingly more nucleophilic primary amino group at C1 underscore the importance of proximity and steric effects in the densely functionalized cyclopentane core intermediates such as **54** and **55**. The extreme shielding of the amino group was further demonstrated in a last resort effort to achieve urea formation (Scheme 13). Thus, benzylation of the aminoester **54** in the presence of BnBr, NaH, and Bu_4NI in THF led unexpectedly to **62**, the structure of which was confirmed only after effecting two additional steps (vide infra). Realizing that benzylation had not occurred on the amino group from independent analysis, but as yet unaware of the exact placement of the two benzyl groups, we treated the product **62** with NaH, TBAI, and N,N-dimethylcarbamoyl chloride, which resulted in recovery of starting material. Then, the amine **62** was reduced with DIBAL-H to cleave the PMB ester, and the resulting amino alcohol **63** was treated with N,N-dimethylcarbamoyl chloride in the presence of NaH and Bu_4NI at rt. The product turned out to be the carbamate **64**, the structure of which was confirmed by X-ray analysis. Remarkably, and against all predictions, benzylation had spared the primary amino group and, instead, had occurred on two adjacent diols, albeit with an internal functional adjustment. Thus, the alkoxide initially formed from the tertiary alcohol at C4 of **54** had undergone an intramolecular silyl transfer reaction[33] via **61**, transposing the TBDPS group and exposing a primary alkoxide which was benzylated to give **62**!

In an alternative approach, benzylation of intermediate **63** under the same conditions as for **54** gave the tribenzyl ether **65** (Scheme 14). Treatment with diphosgene led to a chromatographically stable isocyanate **66** which was treated with neat dimethylamine to give the N,N-dimethylurea **67** for the first time. Oxidative cleavage of the exocyclic methylene group led to the ketone, which was desilylated to give the crystalline urea derivative **68**. Clearly, without X-ray crystallographic evidence, it would have been very difficult to interpret the results shown in Schemes 13 and 14, spectroscopically or otherwise.

Although we became aware of the inertness of the primary amino group toward acylation and alkylation, we also learned that in the absence of an interfering hydroxyl at C4, we could

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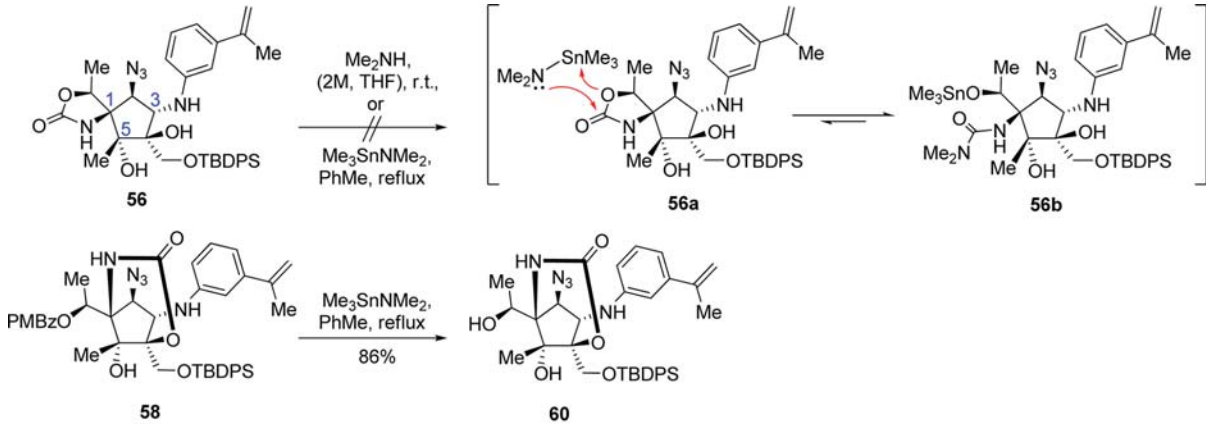
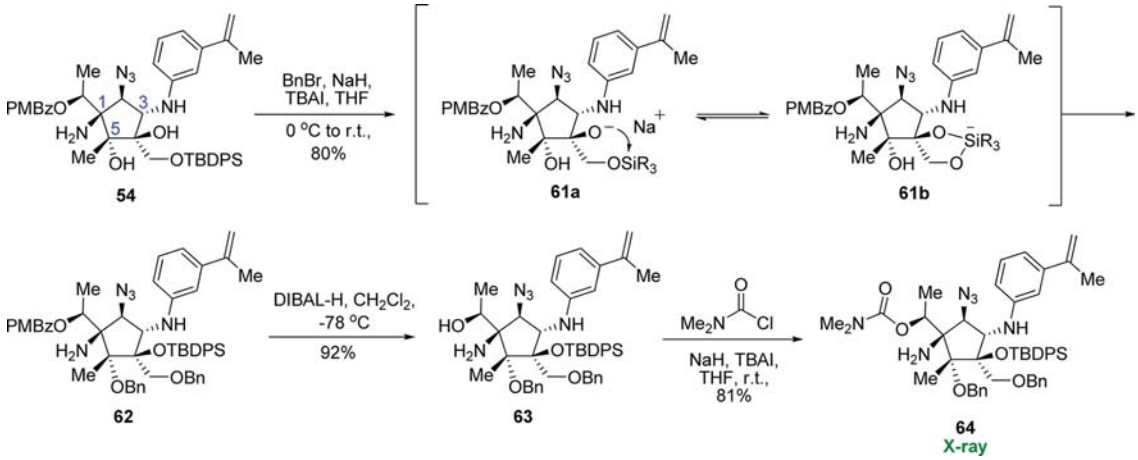
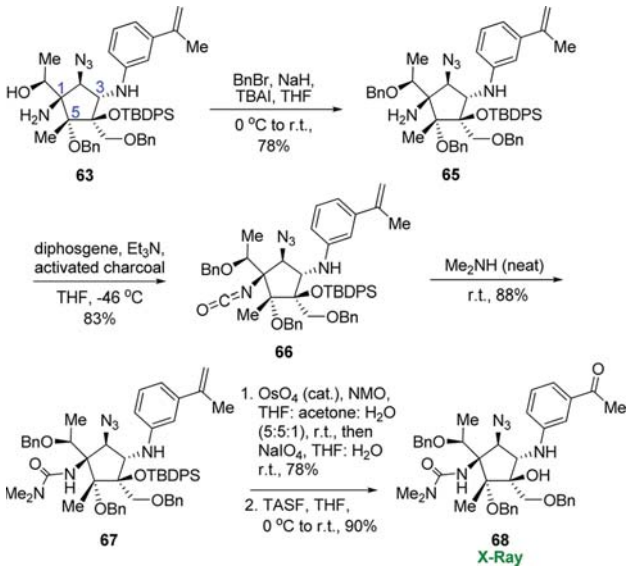
Scheme 12. Attempts To Form the Urea (Part 2)



Scheme 13. Attempts To Form the Urea (Part 3)



Scheme 14. Formation of the Urea via the Isocyanate



nevertheless form isocyanates and even the desired N,N-dimethylurea, as shown in Scheme 14. Rather than continuing with the fully protected intermediate **68**, we turned our attention instead to "neutralizing" the offending tertiary hydroxyl group at C4.

Deprotection of the TBDPS ether in **54** led to an aminotriol, which was converted to the acetonide **69** (Scheme 15). Formation of the isocyanate, then treatment with neat dimethylamine, afforded the N,N-dimethylurea derivative **70** in 86% yield. Reductive cleavage of the PMB ester followed by the oxidative cleavage of the methylene group, and finally, hydrolysis of the acetonide group gave **71**. Esterification as described for pactamycate (**2**), followed by reduction of the azido group, gave pactamycin (**1**) in excellent yield.[21] In parallel, reduction of the azide group in **71** led to de-6-MSA-pactamycin (**3**).

■ CONCLUSION

We described a detailed account of our efforts toward the total synthesis of pactamycin, pactamycate, and their de-esterified counterparts. Starting with L-threonine as the chiral cornerstone, we proceeded to construct the cyclopentenone core motif **A** (Scheme 1), which served as the pivotal scaffold upon which we attempted to introduce the required substituents in a systematic way. Initial failures and unexpected results forced us to explore alternative approaches to install functional groups in regio- and stereocontrolled reactions. At times, the difference between triumph and disaster hinged upon the judicious choice of methods and order of execution, such as the solvolytic

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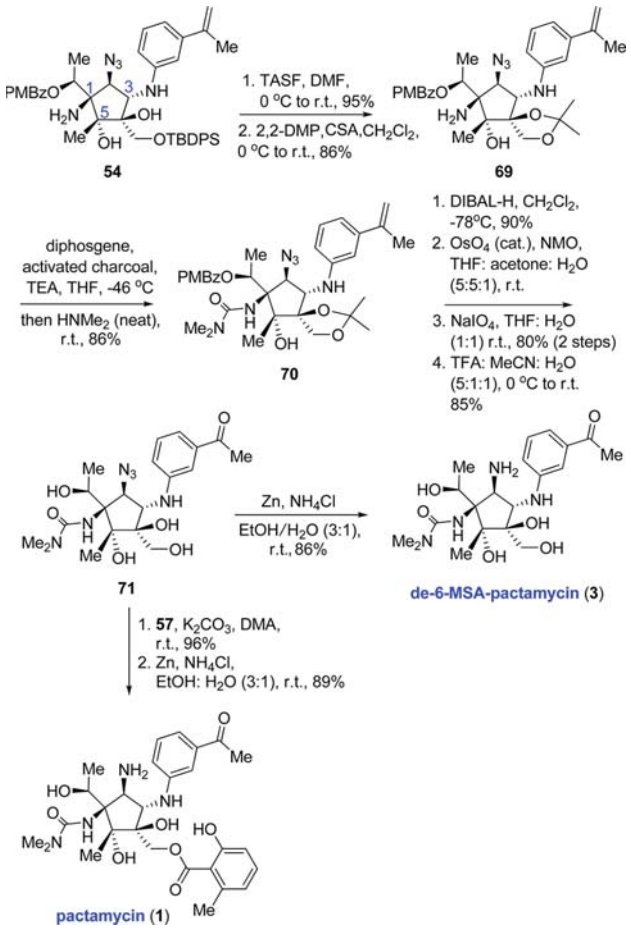
Scheme 15. Completion of the Total Synthesis of Pactamycin



"inversion" of the epoxide in presence of $Zn(OTf)_2$ and AcOH. The capricious S_N2 displacement of C2 triflate esters became cooperative when the substituents in the cyclopentanone ring provided a favored trajectory of approach for the azide ion. Epoxide opening with an aniline moiety was possible only when a neighboring hydroxy group had a *syn* relationship, favoring a coordination with the Lewis acid $Yb(OTf)_3$, or when an azide group was present, exerting an inductive effect. Finally, the importance of proximity effects and steric shielding became manifest in the numerous vain attempts to acylate or benzylate the presumably more basic and nucleophilic primary amino group in the presence of highly hindered tertiary hydroxyl groups. In spite of these humbling experiences, logic, deductive reasoning, and a strong resolve prevailed in the end. Pactamycin (**1**) and pactamycate (**2**) were synthesized in 29 steps (3.1%) and 26 steps (4.0%), respectively, starting with the known oxazoline **9**. With the recent reports on the antiprotozoal activities of pactamycin,[6] the study of this unique amino cyclopentitol and its analogues expands their scope as valuable biological probes to interact with RNAs of diverse sources. Studies relative to such objectives are in progress and will be reported in due course.

EXPERIMENTAL SECTION

Experimental procedures and characterization data for the preparation of compounds **1**, **2**, **8**−**13**, **30**−**33**, **41**−**47**, **51**, **53**−**56**, **58**, and **69**−**71** have been reported previously.[19]

(4*S*,5*R*,6*R*,9*S*)-8-((*tert*-Butyldiphenylsilyloxy)methyl)-2-(4-methoxyphenyl)-4-methyl-9-(tripropylsilyloxy)-3-oxa-1-azaspiro[4.4]nona-1,7-dien-6-ol (14). To a solution of cyclopentenone **13** (3.81 g, 5.81 mmol) in $MeOH/CH_2Cl_2$ (30 mL, 1:1) was added $CeCl_3·7H_2O$ (4.33 g, 11.63 mmol) at 0 °C under argon atmosphere, and the mixture was stirred for 10 min. Then, $NaBH_4$ (220 mg, 5.81 mmol) was added portionwise and stirred for 1 h at the same temperature. The reaction was then quenched with slow addition of a saturated aqueous NH_4Cl solution and extracted three times with EtOAc. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. Flash column chromatography using 25% EtOAc in hexanes eluent afforded the allylic alcohol **14** (3.37 g, 88%) as a viscous liquid: $[\alpha]_D^{20}$ −6.8 (*c* 1.00, acetone); IR (neat) ν_{max} 3178 (br, s), 3071, 2957, 2877, 1635, 1610, 1513, 1463, 1427, 1372, 1350, 1307, 1257, 1172, 1144, 1112, 1065, 1039, 1008, 974, 908, 875, 841, 741, 702, 611 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.86 (2H, d, J = 8.8 Hz), 7.75−7.72 (4H, m), 7.47−7.40 (6H, m), 6.90 (2H, d, J = 8.8 Hz), 6.30 (1H, d, J = 1.9 Hz), 5.10 (1H, q, J = 6.6 Hz), 4.72 (1H, s), 4.37−4.34 (3H, m), 3.86 (3H, s), 2.28 (1H, br s), 1.61 (3H, d, J = 6.6 Hz), 1.11 (9H, s), 0.85 (9H, t, J = 7.9 Hz), 0.56−0.49 (6H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.9, 162.0, 147.5, 135.6, 135.4, 133.5, 133.3, 130.1, 129.6, 129.2, 128.5, 127.6, 127.5, 120.4, 113.4, 86.0, 79.8, 78.9, 78.2, 61.3, 55.2, 26.7, 19.2, 16.6, 6.6, 4.7; HRMS-ESI (m/z) calcd for $C_{38}H_{52}NO_5Si_2$ $[M + H]^+$ 658.33785, found 658.33952.

(4*S*,5*S*,6*R*,9*S*)-8-((*tert*-Butyldiphenylsilyloxy)methyl)-2-(4-methoxyphenyl)-4-methyl-9-(tripropylsilyloxy)-3-oxa-1-azaspiro[4.4]nona-1,7-dien-6-yl acetate (15). To a solution of allylic alcohol **14** (3.12 g, 4.75 mmol) in CH_2Cl_2 (20 mL) were added Et_3N (3.31 mL, 23.73 mmol), Ac_2O (0.67 mL, 7.12 mmol), and DMAP (58.6 mg, 0.48 mmol) at 0 °C under argon atmosphere. The reaction mixture was stirred for 1 h at rt. The reaction was quenched with aqueous saturated NH_4Cl solution and extracted twice with CH_2Cl_2. The residue was purified by flash chromatography on silica gel using 15% EtOAc in hexanes to afford acetate **15** (3.16 g, 95%) as clear oil: $[\alpha]_D^{20}$ −22.4 (*c* 1.00, $CHCl_3$); IR (neat) ν_{max} 3072, 2957, 2935, 2877, 1743, 1640, 1610, 1513, 1462, 1427, 1369, 1306, 1254, 1238, 1169, 1145, 1112, 1071, 1034, 968, 911, 875, 841, 823, 741, 703, 613 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.92 (2H, d, J = 8.9 Hz), 7.73−7.71 (4H, m), 7.47−7.40 (6H, m), 6.93 (2H, d, J = 8.9 Hz), 6.04 (1H, s), 5.73 (1H, s), 5.13 (1H, q, J = 6.8 Hz), 4.65 (1H, s), 4.33 (2H, q, J = 6.8 Hz), 3.86 (3H, s), 2.07 (3H, s), 1.56 (3H, d, J = 6.8 Hz), 1.12 (9H, s), 0.82 (9H, t, J = 7.9 Hz), 0.54−0.48 (6H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 164.0, 162.0, 148.2, 135.5, 135.4, 133.3, 133.2, 129.9, 129.7, 127.7, 127.6, 124.1, 120.5, 113.5, 86.3, 80.7, 79.0, 77.8, 61.2, 55.3, 26.7, 21.2, 19.2, 16.5, 6.6, 4.7; HRMS-ESI (m/z) calcd for $C_{40}H_{54}NO_6Si_2$ $[M + H]^+$ 700.34842, found 700.34801.

(4*S*,5*S*,6*R*,9*S*)-8-((*tert*-Butyldiphenylsilyloxy)methyl)-9-hydroxy-2-(4-methoxyphenyl)-4-methyl-3-oxa-1-azaspiro[4.4]-nona-1,7-dien-6-yl acetate (16). The disilyl ether **15** (1.72 g, 2.46 mmol) was dissolved in a 1:10:1 mixture of TFA/MeCN/H_2O (18 mL) at rt and stirred for 3 h at the same temperature. The transformation was monitored on ESI-MS, and the reaction mixture was slowly quenched with a saturated solution of $NaHCO_3$ at 0 °C. The reaction mixture was extracted three times with EtOAc, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel using 20% EtOAc in hexanes to afford allylic alcohol **16** (1.21 g, 84%) as a colorless oil: $[\alpha]_D^{20}$ −65.1 (*c* 1.00, $CHCl_3$); IR (neat) ν_{max} 3072, 3014, 2959, 2933, 2857, 1739, 1632, 1610, 1513, 1462, 1427, 1371, 1307, 1255, 1236, 1171, 1112, 1031, 840, 823, 744, 703, 612 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.86 (2H, d, J = 8.9 Hz), 7.75−7.73 (4H, m), 7.47−7.42 (6H, m), 6.92 (2H, d, J = 8.9 Hz), 6.18 (1H, d, J = 1.9 Hz), 5.63 (1H, s), 5.19 (1H, q, J = 6.7 Hz), 4.50 (2H, s), 4.24 (1H, s), 3.86 (3H, s), 3.02 (1H, br s), 2.07 (3H, s), 1.44 (3H, d, J = 6.7 Hz), 1.12 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.7, 164.0, 162.2, 150.3, 135.5, 135.4, 133.1, 133.0, 130.1, 129.7, 127.7, 127.6, 126.2, 83.4, 81.0, 80.0, 77.7, 61.6, 55.3, 26.7, 21.2, 19.1, 16.0; HRMS (ESIMS) calcd for $C_{34}H_{40}NO_6Si$ $[M + H]^+$ 586.26194, found 586.26182.

(4*S*,5*S*,6*R*)-8-((*tert*-Butyldiphenylsilyloxy)methyl)-2-(4-methoxyphenyl)-4-methyl-9-oxo-3-oxa-1-azaspiro[4.4]nona-1,7-dien-6-yl acetate (17). To a stirred solution of allylic alcohol **16**

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(1.13 g, 1.93 mmol) in CH_2Cl_2 (20 mL) was added Dess−Martin periodinane (900 mg, 2.12 mmol) at 0 °C under argon atmosphere, and the reaction mixture was stirred at rt for 2 h. The reaction mixture was quenched with $Na_2S_2O_3$/$NaHCO_3$ (7:1) aqueous saturated solution (20 mL) at 0 °C. The mixture was stirred vigorously until the two layers were separated at rt. The crude product was extracted with ether (60 mL × 3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel using 15% EtOAc in hexanes afforded the enone **17** (1.09 g, 97%) as a colorless viscous foam: $[\alpha]_D^{20}$ −183.5 (*c* 1.00, $CHCl_3$); IR (neat) ν_{max} 2932, 1733, 1723, 1633, 1609, 1513, 1427, 1369, 1257, 1226, 1112, 1027, 839, 742, 703, 668 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.88 (2H, d, *J* = 8.9 Hz), 7.69−7.65 (5H, m), 7.47−7.39 (6H, m), 6.91 (2H, d, *J* = 8.9 Hz), 5.93 (1H, d, *J* = 1.9 Hz), 5.06 (1H, q, *J* = 6.7 Hz), 4.56−4.48 (2H, m), 3.86 (3H, s), 2.13 (3H, s), 1.50 (3H, d, *J* = 6.7 Hz), 1.12 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.9, 169.5, 165.5, 162.5, 150.7, 147.4, 135.5, 135.4, 132.9, 132.7, 130.4, 129.9, 129.8, 127.9, 127.8, 119.4, 113.6, 81.3, 79.4, 59.0, 55.4, 26.8, 21.1, 19.3, 16.1; HRMS-ESI (*m*/*z*) calcd for $C_{34}H_{38}NO_6Si$ $[M + H]^+$ 584.2463, found 584.2467.

(4*S*,5*R*,9*R*)-7-((*tert*-Butyldiphenylsilyloxy)methyl)-9-hydroxy-2-(4-methoxyphenyl)-4-methyl-3-oxa-1-azaspiro[4.4]nona-1,7-dien-6-one (18). To a solution of enone **17** (70 mg, 0.12 mmol) in toluene (3 mL) was added (dimethylamino)trimethyltin (0.1 mL, 0.60 mmol) dropwisely at rt under argon atmosphere and stirred for 3 h. Toluene was removed under reduced pressure, and the residue was purified by flash column chromatography on silica gel using 25% EtOAc in hexanes afforded the allylic alcohol **18** (51.4 mg, 79%) as colorless oil: $[\alpha]_D^{20}$ −147.9 (*c* 1.00, $CHCl_3$); IR (neat) ν_{max} 3222 (br s), 3072, 2958, 2932, 2858, 1715, 1626, 1609, 1513, 1462, 1427, 1360, 1307, 1258, 1172, 1113, 1030, 906, 868, 839, 823, 736, 702, 610 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.88 (2H, d, *J* = 8.9 Hz), 7.71−7.67 (4H, m), 7.65 (1H, d, *J* = 1.9 Hz), 7.47−7.41 (6H, m), 6.90 (2H, d, *J* = 8.9 Hz), 4.98 (1H, d, *J* = 1.9 Hz), 4.94 (1H, q, *J* = 6.7 Hz), 4.56−4.48 (2H, m), 3.85 (3H, s), 2.24 (1H, br s), 1.60 (3H, d, *J* = 6.7 Hz), 1.13 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.8, 165.7, 162.5, 154.4, 145.7, 135.5, 133.0, 132.8, 130.3, 129.9, 129.8, 127.9, 127.8, 119.6, 113.6, 83.2, 80.6, 76.4, 58.9, 55.3, 26.8, 19.2, 16.0; HRMS-ESI (*m*/*z*) calcd for $C_{32}H_{36}NO_5Si$ $[M + H]^+$ 542.23573, found 542.23740.

(4*S*,5*R*,6*S*,9*R*)-7-((*tert*-Butyldiphenylsilyloxy)methyl)-2-(4-methoxyphenyl)-4,6-dimethyl-3-oxa-1-azaspiro[4.4]nona-1,7-diene-6,9-diol (19). To a stirred solution of enone **17** (823 mg, 1.41 mmol) in dry THF (15 mL) was added MeMgBr (2.35 mL, 3.0 M solution in ether, 7.06 mmol) at −78 °C under argon atmosphere and stirred for 30 min. Then the temperature was raised to 0 °C and stirred for 20 min. The reaction mixture was quenched with saturated aqueous NH_4Cl solution and extracted with EtOAc (50 mL × 3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. Purification by column chromatography on silica gel using 35% EtOAc in hexanes afforded allylic alcohol **19** (676 mg, 86%) as a colorless liquid: $[\alpha]_D^{20}$ +29.4 (*c* 1.00, $CHCl_3$); IR (neat) ν_{max} 3402 (br), 3072, 2960, 2932, 2857, 1634, 1610, 1513, 1462, 1427, 1361, 1334, 1308, 1256, 1171, 1112, 1034, 996, 952, 912, 840, 824, 743, 702, 612 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.88 (2H, d, *J* = 8.9 Hz), 7.75−7.70 (4H, m), 7.49−7.43 (6H, m), 6.91 (2H, d, *J* = 8.9 Hz), 6.22 (1H, br s), 5.25 (1H, q, *J* = 6.6 Hz), 4.52 (1H, d, *J* = 8.0 Hz), 4.44 (2H, s), 3.86 (3H, s), 2.90 (1H, s), 2.07 (1H, d, *J* = 8.0 Hz), 1.63 (3H, d, *J* = 6.6 Hz), 1.21 (3H, s), 1.11 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.2, 162.1, 150.6, 135.6, 135.5, 132.8, 132.7, 131.7, 130.1, 130.0, 129.9, 127.8, 120.4, 113.6, 85.1, 83.9, 79.1, 77.7, 61.2, 55.3, 26.8, 19.1, 17.9, 17.2; HRMS-ESI (*m*/*z*) calcd for $C_{33}H_{40}NO_5Si$ $[M + H]^+$ 558.26703, found 558.26887.

(4*S*,5*S*,6*R*,9*S*)-8-((*tert*-Butyldiphenylsilyloxy)methyl)-9-hydroxy-2-(4-methoxyphenyl)-4,9-dimethyl-3-oxa-1-azaspiro-[4.4]nona-1,7-dien-6-yl acetate (20). To a solution of allylic alcohol **19** (658 mg, 1.18 mmol) in CH_2Cl_2 (20 mL) were added Et_3N (0.82 mL. 5.90 mmol), Ac_2O (0.17 mL, 1.77 mmol), and DMAP (14 mg, 0.12 mmol) at 0 °C under argon atmosphere. The reaction mixture was stirred for 1 h at rt. The reaction was quenched with aqueous saturated NH_4Cl solution and extracted twice with CH_2Cl_2. The residue was purified by flash chromatography on silica gel using 25% EtOAc in hexanes to afford acetate **20** (637 mg, 90%) as clear oil: $[\alpha]_D^{20}$ −37.0 (*c* 1.00, $CHCl_3$); IR (neat) ν_{max} 3220 (br), 2933, 2857, 1739, 1643, 1609, 1513, 1454, 1427, 1370, 1336, 1309, 1254, 1226, 1169, 1112, 1086, 1028, 950, 840, 824, 744, 703, 671, 612 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.88 (2H, d, *J* = 8.9 Hz), 7.74−7.70 (4H, m), 7.48−7.41 (6H, m), 6.92 (2H, d, *J* = 8.9 Hz), 6.30 (1H, d, *J* = 2.3 Hz), 5.60 (1H, d, *J* = 2.3 Hz), 5.23 (1H, q, *J* = 6.6 Hz), 4.45 (2H, s), 3.87 (3H, s), 2.11 (3H, s), 1.92 (1H, s), 1.43 (3H, d, *J* = 6.6 Hz), 1.11 (9H, s), 1.08 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 162.9, 162.2, 154.6, 135.6, 135.5, 133.2, 133.1. 130.1, 129.8, 129.7, 127.7, 127.6, 126.1, 84.9, 83.5, 80.9, 77.4, 60.4, 55.4, 26.8, 21.5, 19.2, 17.2, 17.1; HRMS-ESI (*m*/*z*) calcd for $C_{35}H_{42}NO_6Si$ $[M + H]^+$ 600.2776, found 600.2790.

(4*S*,5*S*,6*R*,9*S*)-9-Hydroxy-8-(hydroxymethyl)-2-(4-methoxyphenyl)-4,9-dimethyl-3-oxa-1-azaspiro[4.4]nona-1,7-dien-6-yl acetate (21). To a solution of silyl ether **20** (624 mg, 1.04 mmol) in THF (10 mL) were added AcOH (2 drops) and TBAF (1.15 mL, 1.0 M in THF, 1.15 mmol) at 0 °C under argon atmosphere. The reaction mixture was stirred at rt for 1 h, a saturated aqueous NH_4Cl solution was then added, and the aqueous phase was extracted three times with EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography on silica gel using 60% EtOAc in hexanes to afford allylic alcohol **21** (320 mg, 85%) as clear oil: $[\alpha]_D^{20}$ −56.5 (*c* 1.00, $CHCl_3$); IR (neat) ν_{max} 3401 (br), 2973, 2936, 2840, 1732, 1634, 1609, 1514, 1454, 1422, 1371, 1338, 1308, 1255, 1172, 1090, 1022, 953, 910, 842, 732 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.88 (2H, d, *J* = 8.9 Hz), 6.92 (2H, d, *J* = 8.9 Hz), 6.26 (1H, d, *J* = 2.2 Hz), 5.57 (1H, d, *J* = 2.2 Hz), 5.25 (1H, q, *J* = 6.6 Hz), 4.37 (2H, d, *J* = 9.7 Hz), 3.85 (3H, s), 3.21 (1H, br s), 2.08 (3H, s), 1.44 (3H, d, *J* = 6.6 Hz), 1.18 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 163.5, 162.4, 155.0, 130.2, 126.4, 119.7, 113.7, 84.7, 83.7, 77.5, 58.6, 55.4, 21.4, 17.2, 17.0; HRMS-ESI (*m*/*z*) calcd for $C_{19}H_{24}NO_6$ $[M + H]^+$ 362.15981, found 362.16011.

(1*R*,2*R*,3*S*,4*S*,5*R*,5′*S*)-2-Hydroxy-1-(hydroxymethyl)-2′-(4-methoxyphenyl)-2,5′-dimethyl-5′*H*-6-oxaspiro[bicyclo[3.1.0]-hexane-3,4′-oxazole]-4-yl acetate (22). To the solution of allylic alcohol **21** (316 mg, 0.875 mmol) in CH_2Cl_2 (15 mL) was added *m*CPBA (647 mg, 70% in water, 2.63 mmol) at 0 °C under argon atmosphere. The reaction mixture was stirred for 2 h at the same temperature. A saturated aqueous Na_2SO_3 solution was added to the reaction mixture at 0 °C and stirred for 30 min. The reaction mixture was then diluted with EtOAc and washed with a saturated aqueous $NaHCO_3$ solution. The aqueous phase was extracted two times with EtOAc, and the combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography on silica gel using 80% EtOAc in hexanes to afford epoxy alcohol **22** (244 mg, 74%) as a colorless oil: $[\alpha]_D^{20}$ −15.0 (*c* 1.00, $CHCl_3$); IR (neat) ν_{max} 3418 (br), 2937, 1738, 1634, 1610, 1514, 1455, 1422, 1372, 1308, 1255, 1226, 1172, 1092, 1030, 908, 841, 732 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.91 (2H, d, *J* = 8.9 Hz), 6.92 (2H, d, *J* = 8.9 Hz), 5.43 (1H, s), 5.24 (1H, q, *J* = 6.5 Hz), 4.17 (1H, d, *J* = 12.7 Hz), 4.07 (1H, d, *J* = 12.7 Hz), 3.86 (3H, s), 3.75 (1H, s), 2.44 (1H, s), 2.16 (3H, s), 1.33 (3H, d, *J* = 6.5 Hz), 1.22 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 163.0, 162.4, 130.4, 119.8, 113.6, 84.0, 81.0, 77.8, 67.7, 59.6, 58.0, 55.4, 21.2, 17.5, 16.7; HRMS-ESI (*m*/*z*) calcd for $C_{19}H_{24}NO_7$ $[M + H]^+$ 378.1547, found 378.1558.

(1*R*,2*R*,3*S*,4*S*,5*R*,5′*S*)-1-((*tert*-Butyldiphenylsilyloxy)methyl)-2-hydroxy-2′-(4-methoxyphenyl)-2,5′-dimethyl-5′*H*-6-oxaspiro[bicyclo[3.1.0]hexane-3,4′-oxazole]-4-yl acetate (23). To a solution of epoxy alcohol **22** (220 mg, 0.583 mmol) in CH_2Cl_2 (10 mL) were added Et_3N (0.2 mL. 1.46 mmol), TBDPSCl (0.16 mL, 0.64 mmol), and DMAP (7 mg, 0.06 mmol) at 0 °C under argon atmosphere. The reaction mixture was stirred for 4 h at rt, then quenched with aqueous saturated NH_4Cl solution and extracted twice with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography on silica gel using 25% EtOAc in hexanes to afford

silyl ether **23** (323 mg, 90%) as clear oil: $[\alpha]_D^{20}$ −11.6 (*c* 1.00, $CHCl_3$); IR (neat) ν_{max} 3486 (br), 3072, 2960, 2934, 2858, 1746, 1641, 1610, 1513, 1455, 1428, 1372, 1334, 1308, 1254, 1232, 1170, 1113, 1064, 1030, 910, 841, 823, 735, 703, 614 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.93 (2H, d, *J* = 8.9 Hz), 7.74−7.69 (4H, m), 7.48−7.42 (6H, m), 6.92 (2H, d, *J* = 8.9 Hz), 5.42 (1H, s), 5.30 (1H, q, *J* = 6.5 Hz), 4.25 (1H, d, *J* = 11.6 Hz), 3.90 (1H, d, *J* = 11.6 Hz), 3.86 (3H, s), 3.58 (1H, s), 3.21 (1H, s), 2.17 (3H, s), 1.35 (3H, d, *J* = 6.5 Hz), 1.24 (3H, s), 1.09 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 162.4, 161.9, 135.3, 135.2, 132.0, 131.9, 130.0, 129.7, 129.6, 127.5, 119.7, 113.2, 83.7, 80.6, 77.5, 76.5, 66.3, 61.1, 60.0, 55.0, 26.4, 20.9, 18.8, 17.3, 17.2; HRMS-ESI (*m*/*z*) calcd for $C_{35}H_{42}NO_7Si$ $[M + H]^+$ 616.2725, found 616.2733.

(1*R*,2*R*,3*R*,4*S*,5*R*,5′*S*)-1-((*tert*-Butyldiphenylsilyloxy)methyl)-2′-(4-methoxyphenyl)-2,5′-dimethyl-5′*H*-6-oxaspiro[bicyclo[3.1.0]hexane-3,4′-oxazole]-2,4-diol (24). To a solution of acetate **23** (270 mg, 0.44 mmol) in toluene (5 mL) was added (dimethylamino)trimethyltin (0.36 mL, 2.19 mmol) dropwisely at rt under argon atmosphere and stirred for 3 h. Toluene was removed under reduced pressure, and the residue was purified by flash column chromatography on silica gel using 50% EtOAc in hexanes afforded the epoxy alcohol **24** (216 mg, 86%) as colorless oil: $[\alpha]_D^{20}$ +4.4 (*c* 1.00, $CHCl_3$); IR (neat) ν_{max} 3326 (br), 2933, 2858, 1632, 1610, 1513, 1454, 1427, 1361, 1332, 1308, 1257, 1174, 1113, 1045, 944, 910, 841, 824, 735, 703, 614 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.92 (2H, d, *J* = 8.8 Hz), 7.73−7.70 (4H, m), 7.50−7.42 (6H, m), 6.91 (2H, d, *J* = 8.8 Hz), 5.27 (1H, q, *J* = 6.5 Hz), 4.43 (1H, br s), 4.33 (1H, d, *J* = 11.3 Hz), 4.32 (1H, s), 3.85 (3H, s), 3.80 (1H, d, *J* = 11.3 Hz), 3.55 (1H, s), 1.55 (3H, d, *J* = 6.5 Hz), 1.27 (3H, s), 1.11 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.4, 162.3, 135.5, 135.4, 131.8, 130.3, 130.2, 128.1, 128.0, 120.2, 113.5, 83.4, 81.7, 77.9, 74.8, 65.3, 63.1, 62.4, 55.3, 26.8, 19.1, 17.5, 17.2; HRMS-ESI (*m*/*z*) calcd for $C_{33}H_{40}NO_6Si$ $[M + H]^+$ 574.26194, found 574.26272.

(1*R*,2*R*,3*R*,5*S*,5′*S*)-1-((*tert*-Butyldiphenylsilyloxy)methyl)-2-hydroxy-2′-(4-methoxyphenyl)-2,5′-dimethyl-5′*H*-6-oxaspiro-[bicyclo[3.1.0]hexane-3,4′-oxazol]-4-one (26). To a stirred solution of epoxy alcohol **24** (125 mg, 0.218 mmol) in CH_2Cl_2 (5 mL) was added Dess−Martin periodinane (102 mg, 0.24 mmol) at 0 °C under argon atmosphere, and the reaction mixture was stirred at rt for 2 h. The reaction mixture was quenched with $Na_2S_2O_3$/$NaHCO_3$ (7:1) aqueous saturated solution (10 mL) at 0 °C. The mixture was stirred vigorously until the two layers were separated at rt. The crude product was extracted with Et_2O (20 mL × 3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel using 25% EtOAc in hexanes afforded the epoxy ketone **26** (115 mg, 92%) as a colorless oil: $[\alpha]_D^{20}$ +142.5 (*c* 1.00, $CHCl_3$); IR (neat) ν_{max} 3478 (br), 3072, 2933, 2858, 1753, 1627, 1610, 1513, 1462, 1427, 1362, 1306, 1257, 1170, 1113, 1033, 910, 840, 823, 800, 737, 703, 612 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.91 (2H, d, *J* = 9.0 Hz), 7.74−7.69 (4H, m), 7.52−7.46 (6H, m), 6.89 (2H, d, *J* = 9.0 Hz), 4.94 (1H, q, *J* = 6.6 Hz), 4.46 (1H, d, *J* = 11.8 Hz), 3.85 (3H, s), 3.82 (1H, d, *J* = 11.8 Hz), 3.20 (1H, s), 1.68 (3H, d, *J* = 6.6 Hz), 1.52 (3H, s), 1.11 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.0, 165.4, 162.3, 135.5, 131.6, 131.4, 130.5, 130.4, 128.1, 128.0, 119.9, 113.4, 82.7, 78.8, 78.5, 67.4, 61.9, 59.7, 55.3, 26.7, 19.4, 19.1, 16.4; HRMS-ESI (*m*/*z*) calcd for $C_{33}H_{38}NO_6Si$ $[M + H]^+$ 572.24629, found 572.24675.

(1*R*,2*R*,3*R*,4*R*,5*R*,5′*S*)-1-((*tert*-Butyldiphenylsilyloxy)methyl)-2′-(4-methoxyphenyl)-2,5′-dimethyl-5′*H*-6-oxaspiro[bicyclo[3.1.0]hexane-3,4′-oxazole]-2,4-diol (27). To a solution of epoxy ketone **26** (78 mg, 0.137 mmol) in MeOH/CH_2Cl_2 (1:1, 3 mL) was added $NaBH_4$ (5.2 mg, 0.137 mmol) at −46 °C under argon atmosphere and stirred for 1 h. The reaction was then quenched with slow addition of saturated aqueous NH_4Cl solution and extracted three times with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Flash column chromatography on silica gel using 35% EtOAc in hexanes eluent afforded the epoxy alcohol **27** (71 mg, 90%) as a colorless oil: $[\alpha]_D^{20}$ +31.0 (*c* 1.00, $CHCl_3$); IR (neat) ν_{max} 3474 (br), 2931, 1638, 1610, 1513, 1427, 1361, 1256, 1112, 1030, 840, 744, 702, 614 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.96 (2H, d, *J* = 8.9 Hz), 7.73−7.68 (4H, m), 7.51−7.43 (6H, m), 6.91 (2H, d, *J* = 8.9 Hz), 5.08 (1H, q, *J* = 6.5 Hz), 4.46 (1H, d, *J* = 8.0 Hz), 4.33 (1H, d, *J* = 11.5 Hz), 4.01 (1H, s), 3.86 (3H, s), 3.66 (1H, d, *J* = 11.5 Hz), 3.37 (1H, s), 2.66 (1H, d, *J* = 8.0 Hz), 1.52 (3H, d, *J* = 6.5 Hz), 1.30 (3H, s), 1.11 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.1, 162.3, 135.6, 135.5, 131.9, 131.7, 130.4, 130.3, 130.2, 128.0, 127.9, 120.0, 113.5, 81.5, 80.7, 78.4, 72.3, 64.3, 64.0, 62.8, 55.4, 26.8, 19.0, 18.8, 17.3; HRMS-ESI (*m*/*z*) calcd for $C_{33}H_{40}NO_6Si$ $[M + H]^+$ 574.26194, found 574.26343.

(4*S*,5*R*,6*R*,7*S*,8*S*,9*S*)-7-((*tert*-Butyldiphenylsilyloxy)methyl)-2-(4-methoxyphenyl)-4,6-dimethyl-8-(3-(prop-1-en-2-yl)-phenylamino)-3-oxa-1-azaspiro[4.4]non-1-ene-6,7,9-triol (29). To a stirred solution of epoxy alcohol **27** (56 mg, 0.098 mmol) in toluene (3 mL) were added the aniline derivative (130 mg, 0.98 mmol) and $Yb(OTf)_3$ (61 mg, 0.049 mmol) at rt under argon atmosphere. The reaction mixture was heated to 80 °C and stirred for 9 h, then cooled to rt, quenched with water (5 mL), and extracted with EtOAc (50 mL × 2). The combined organic layers were washed with 0.5 N HCl, saturated aqueous $NaHCO_3$ solution, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel using 40% EtOAc in hexanes to afford the aniline **29** (43 mg, 62%) as a pale yellow viscous liquid: $[\alpha]_D^{20}$ +20.5 (*c* 1.00, $CHCl_3$); IR (neat) ν_{max} 3421 (br), 2932, 1635, 1604, 1586, 1514, 1427, 1364, 1257, 1171, 1105, 1038, 822, 737, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.92−6.69 (18H, aromatic protons), 5.32 (1H, s), 5.07 (1H, q, *J* = 6.4 Hz), 5.03 (1H, s), 4.68−4.58 (2H, m), 4.40 (1H, dd, *J* = 11.2, 4.8 Hz), 4.17−4.12 (2H, m), 3.99 (1H, br s), 3.88 (3H, s), 3.83 (1H, d, *J* = 10.8 Hz), 2.25 (1H, d, *J* = 11.6 Hz), 2.10 (3H, s), 1.60 (3H, d, *J* = 6.4 Hz), 1.19 (3H, s), 1.12 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.2, 162.9, 147.8, 143.8, 142.3, 135.8, 135.6, 131.4, 131.3, 130.4, 130.2, 130.0, 129.1, 128.0, 127.9, 118.9, 114.9, 113.8, 112.4, 111.9, 111.0, 84.4, 83.6, 80.9, 80.3, 79.4, 72.8, 66.7, 55.5, 27.0, 21.9, 19.0, 17.3, 17.1; HRMS-ESI (*m*/*z*) calcd for $C_{42}H_{51}N_2O_6Si$ $[M + H]^+$ 707.35235, found 707.35109.

(4*S*,5*S*,6*R*,9*S*)-9-Hydroxy-8-(hydroxymethyl)-2-(4-methoxy-phenyl)-4-methyl-3-oxa-1-azaspiro[4.4]nona-1,7-dien-6-yl acetate (35). To the solution of silyl ether **15** (1.07g, 1.53 mmol) in THF (10 mL) was added TBAF (3.21 mL, 1.0 M in THF, 3.21 mmol) at 0 °C under argon atmosphere. The reaction mixture was stirred at rt for 1.5 h, a saturated aqueous NH_4Cl solution was then added, and the aqueous phase was extracted three times with EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography on silica gel using 80% EtOAc in hexanes to afford diol **35** (489 mg, 92%) as colorless viscous liquid: $[\alpha]_D^{20}$ −87.7 (*c* 1.00, $CHCl_3$); IR (neat) ν_{max} 3351 (br), 1733, 1631, 1514, 1422, 1372, 1308, 1255, 1173, 1028, 914, 841, 746 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.80 (2H, d, *J* = 8.9 Hz), 6.86 (2H, d, *J* = 8.9 Hz), 6.06 (1H, s), 5.54 (1H, s), 5.21 (1H, q, *J* = 6.7 Hz), 4.34 (3H, br s), 4.18 (1H, br s), 3.82 (3H, s), 2.03 (3H, s), 1.43 (3H, d, *J* = 6.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 164.7, 162.4, 150.6, 130.2, 126.7, 119.5, 113.6, 83.28, 80.89, 79.38, 78.17, 59.37, 55.32, 21.16, 16.11; HRMS-ESI (*m*/*z*) calcd for $C_{18}H_{22}NO_6$ $[M + H]^+$ 348.14416, found 348.14499.

(1*S*,2*R*,3*S*,4*S*,5*R*,5′*S*)-2-Hydroxy-1-(hydroxymethyl)-2′-(4-methoxyphenyl)-5′-methyl-5′*H*-6-oxaspiro[bicyclo[3.1.0]hexane-3,4′-oxazole]-4-yl acetate (36). To the solution of diol **35** (431 mg, 1.24 mmol) in CH_2Cl_2 (15 mL) was added *m*CPBA (918 mg, 70% in water, 3.73 mmol) at 0 °C under argon atmosphere. The reaction mixture was stirred for 2 h at the same temperature. A saturated aqueous Na_2SO_3 solution was added to the reaction mixture at 0 °C and stirred for 30 min. The reaction mixture was then diluted with EtOAc and washed with saturated aqueous $NaHCO_3$ solution. The aqueous phase was extracted two times with EtOAc, and the combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography on silica gel using 90% EtOAc in hexanes to afford epoxy diol **36** (286 mg, 64%) as a colorless oil: $[\alpha]_D^{20}$ −41.5 (*c* 1.00, $CHCl_3$); IR (neat) ν_{max} 3364 (br), 3008, 2937,

1746, 1633, 1610, 1514, 1455, 1422, 1373, 1334, 1308, 1256, 1230, 1173, 1088, 1029, 904, 842, 732, 688 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.84 (2H, d, J = 8.8 Hz), 6.85 (2H, d, J = 8.8 Hz), 5.30 (1H, s), 5.20 (1H, q, J = 6.5 Hz), 4.26 (1H, d, J = 12.7 Hz), 4.24 (1H, br s), 3.93 (1H, s), 3.82 (1H, d, J = 12.7 Hz), 3.80 (3H, s), 3.65 (1H, s), 2.11 (3H, s) 1.27 (3H, d, J = 6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.7, 163.5, 162.4, 130.4, 119.7, 113.6, 82.3, 78.4, 76.9, 76.3, 67.3, 60.5, 59.7, 55.3, 21.1, 16.4; HRMS-ESI (m/z) calcd for $C_{18}H_{22}NO_7$ $[M + H]^+$ 364.13908, found 364.13963.

(1*S*,2*R*,3*S*,4*S*,5*R*,5′*S*)-1-((*tert*-Butyldiphenylsilyloxy)methyl)-2-hydroxy-2′-(4-methoxyphenyl)-5′-methyl-5′*H*-6-oxaspiro-[bicyclo[3.1.0]hexane-3,4′-oxazole]-4-yl acetate (37). To a solution of epoxy alcohol **36** (269 mg, 0.74 mmol) in CH_2Cl_2 (10 mL) were added Et_3N (0.31 mL. 2.22 mmol), TBDPSCl (0.21 mL, 0.82 mmol) and DMAP (9 mg, 0.074 mmol) at 0 °C under argon atmosphere. The reaction mixture was stirred for 4 h at rt, then quenched with aqueous saturated NH_4Cl solution and extracted twice with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography on silica gel using 30% EtOAc in hexanes to afford silyl ether **37** (392 mg, 88%) as clear oil: $[\alpha]_D^{20}$ −28.7 (c 1.00, $CHCl_3$); IR (neat) ν_{max} 3466 (br), 3071, 3011, 2932, 2857, 1747, 1630, 1609, 1512, 1462, 1427, 1373, 1332, 1308, 1254, 1228, 1171, 1113, 1087, 1031, 841, 823, 744, 703, 612 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.92 (2H, d, J = 8.9 Hz), 7.72−7.68 (4H, m), 7.47−7.41 (6H, m), 6.90 (2H, d, J = 8.9 Hz), 5.39 (1H, s), 5.36 (1H, q, J = 6.5 Hz), 4.21 (1H, d, J = 11.6 Hz), 4.03 (1H, d, J = 11.6 Hz), 3.96 (1H, d, J = 3.1 Hz), 3.85 (3H, s), 3.58 (1H, s), 3.27 (1H, d, J = 3.1 Hz), 2.15 (3H, s), 1.31 (3H, d, J = 6.5 Hz), 1.09 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 163.1, 162.3, 135.5, 135.4, 132.3, 132.2, 130.3, 130.1, 130.0, 127.9, 120.1, 113.5, 82.5, 78.5, 77.9, 76.5, 65.3, 62.8, 60.6, 55.3, 26.7, 21.1, 19.1, 16.4; HRMS-ESI (m/z) calcd for $C_{34}H_{40}NO_7Si$ $[M + H]^+$ 602.25686, found 602.25821.

(1*R*,3*S*,4*S*,5*R*,5′*S*)-1-((*tert*-Butyldiphenylsilyloxy)methyl)-2′-(4-methoxyphenyl)-5′-methyl-2-oxo-5′*H*-6-oxaspiro[bicyclo-[3.1.0]hexane-3,4′-oxazole]-4-yl acetate (38). To a stirred solution of epoxy alcohol **37** (132 mg, 0.22 mmol) in CH_2Cl_2 (5 mL) was added Dess−Martin periodinane (140 mg, 0.33 mmol) at 0 °C under argon atmosphere, and the reaction mixture was stirred at rt for 2 h. The reaction mixture was quenched with $Na_2S_2O_3/NaHCO_3$ (7:1) aqueous saturated solution (5 mL) at 0 °C. The mixture was stirred vigorously until the two layers were separated at rt. The crude product was extracted with Et_2O (30 mL × 3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel using 25% EtOAc in hexanes to afford the epoxy ketone **38** (115 mg, 87%) as colorless crystals: mp 123−125 °C; $[\alpha]_D^{20}$ −136.4 (c 1.00, $CHCl_3$); IR (neat) ν_{max} 3072, 3010, 2959, 2933, 2858, 1754, 1723, 1631, 1609, 1513, 1463, 1427, 1372, 1353, 1309, 1257, 1220, 1170, 1113, 1086, 1058, 1030, 908, 864, 842, 739, 703, 616 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.91 (2H, d, J = 8.9 Hz), 7.71−7.67 (4H, m), 7.47−7.39 (6H, m), 6.90 (2H, d, J = 8.9 Hz), 5.57 (1H, s), 5.16 (1H, q, J = 6.5 Hz), 4.36 (1H, d, J = 12.4 Hz), 4.10 (1H, s), 4.03 (1H, d, J = 12.4 Hz), 3.86 (3H, s), 2.14 (3H, s), 1.37 (3H, d, J = 6.5 Hz), 1.09 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.8, 169.3, 164.7, 162.6, 135.6, 135.2, 132.9, 132.6, 130.6, 129.9, 129.8, 127.8, 127.7, 119.2, 113.6, 79.4, 79.1, 73.3, 61.2, 59.6, 57.2, 55.4, 26.7, 20.9, 19.3, 16.8; HRMS-ESI (m/z) calcd for $C_{34}H_{38}NO_7Si$ $[M + H]^+$ 600.24121, found 600.24208.

(1*R*,2*S*,3*S*,4*S*,5*R*,5′*S*)-1-((*tert*-Butyldiphenylsilyloxy)methyl)-2-hydroxy-2′-(4-methoxyphenyl)-2,5′-dimethyl-5′*H*-6-oxaspiro[bicyclo[3.1.0]hexane-3,4′-oxazole]-4-yl acetate (39). To a stirred solution of epoxy ketone **38** (66 mg, 0.11 mmol) in dry THF (3 mL) was added MeMgBr (0.07 mL, 3.0 M solution in ether, 0.22 mmol) at −78 °C under argon atmosphere and stirred for 1 h. The reaction mixture was quenched with saturated aqueous NH_4Cl solution and extracted with EtOAc (20 mL × 3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. Purification by column chromatography on silica gel using 30% EtOAc in hexanes afforded epoxy alcohol **39** (58 mg, 86%) as a colorless liquid: $[\alpha]_D^{20}$ −56.8 (c 1.00, $CHCl_3$); IR (neat) ν_{max} 3444 (br), 2957, 2932, 2857, 1745, 1636, 1609, 1513, 1462, 1427, 1373, 1337, 1309, 1255, 1236, 1171, 1113, 1080, 1049, 906, 841, 823, 741, 704, 687, 609 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.87 (2H, d, J = 8.9 Hz), 7.79−7.75 (4H, m), 7.45−7.41 (6H, m), 6.93 (2H, d, J = 8.9 Hz), 5.12 (1H, s), 5.11 (1H, q, J = 6.5 Hz), 4.49 (1H, d, J = 11.6 Hz), 4.33 (1H, s), 3.87 (3H, s), 3.71 (1H, d, J = 11.6 Hz), 2.15 (3H, s), 1.37 (3H, d, J = 6.5 Hz), 1.20 (3H, s), 1.09 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 163.4, 162.8, 135.7, 135.6, 133.2, 133.1, 130.4, 129.7, 129.6, 127.7, 127.6, 118.9, 113.8, 81.7, 78.9, 78.1, 75.3, 69.2, 68.9, 60.5, 55.4, 26.7, 21.3, 19.3, 17.1, 9.9; HRMS-ESI (m/z) calcd for $C_{35}H_{42}NO_7Si$ $[M + H]^+$ 616.27251, found 616.27303.

(1*R*,3*R*,4*S*,5*R*,5′*S*)-1-((*tert*-Butyldiphenylsilyloxy)methyl)-4-hydroxy-2′-(4-methoxyphenyl)-5′-methyl-5′*H*-6-oxaspiro-[bicyclo[3.1.0]hexane-3,4′-oxazol]-2-one (Alcohol of 38). To a solution of epoxy ketone **38** (40 mg, 0.067 mmol) in toluene (3 mL) was added (dimethylamino)trimethyltin (0.055 mL, 0.33 mmol) dropwisely at rt under argon atmosphere and stirred for 3 h. Toluene was removed under reduced pressure, and the residue was purified by flash column chromatography on silica gel using 35% EtOAc in hexanes afforded the epoxy alcohol (32.5 mg, 87%) as a colorless oil: $[\alpha]_D^{20}$ −93.7 (c 1.00, $CHCl_3$); IR (neat) ν_{max} 3230 (br), 3072, 2932, 2858, 1753, 1614, 1513, 1462, 1427, 1355, 1309, 1259, 1174, 1113, 1058, 1030, 996, 863, 841, 823, 798, 743, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.90 (2H, d, J = 8.8 Hz), 7.72−7.70 (4H, m), 7.46−7.39 (6H, m), 6.88 (2H, d, J = 8.8 Hz), 5.12 (1H, q, J = 6.5 Hz), 4.65 (1H, s), 4.35 (1H, d, J = 12.5 Hz), 4.09 (1H, d, J = 12.5 Hz), 4.08 (1H, s), 3.84 (3H, s), 2.85 (1H, br s), 1.50 (3H, d, J = 6.5 Hz), 1.06 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.4, 164.9, 162.6, 135.7, 135.6, 133.0, 132.6, 130.6, 129.9, 129.8, 127.8, 119.4, 113.6, 80.7, 79.7, 71.4, 62.4, 61.5, 57.4, 55.3, 26.7, 19.2, 17.0; HRMS-ESI (m/z) calcd for $C_{32}H_{36}NO_6Si$ $[M + H]^+$ 558.23064, found 558.23177.

(1*R*,2*R*,3*S*,4*S*,5*R*,5′*S*)-1-((*tert*-Butyldiphenylsilyloxy)methyl)-2′-(4-methoxyphenyl)-5′-methyl-2-(tripropylsilyloxy)-5′*H*-6-oxaspiro[bicyclo[3.1.0]hexane-3,4′-oxazole]-4-yl acetate (TES Ether of 37). To a solution of epoxy alcohol **37** (223 mg, 0.37 mmol) in CH_2Cl_2 (10 mL) were added Et_3N (0.1 mL. 0.74 mmol), TESCl (0.075 mL, 0.45 mmol), and DMAP (5 mg, 0.04 mmol) at 0 °C under argon atmosphere. The reaction mixture was stirred for 4 h at rt, then quenched with aqueous saturated NH_4Cl solution and extracted twice with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography on silica gel using 25% EtOAc in hexanes to afford silyl ether (239 mg, 90%) as clear oil: $[\alpha]_D^{20}$ −33.8 (c 1.00, $CHCl_3$); IR (neat) ν_{max} 3071, 3000, 2956, 2935, 2877, 1746, 1637, 1610, 1512, 1460, 1427, 1372, 1323, 1308, 1254, 1228, 1169, 1112, 1075, 1031, 1009, 901, 841, 740, 703, 613 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.94 (2H, d, J = 8.8 Hz), 7.74−7.72 (4H, m), 7.45−7.40 (6H, m), 6.93 (2H, d, J = 8.8 Hz), 5.31 (1H, s), 5.10 (1H, q, J = 6.5 Hz), 4.21 (1H, d, J = 12.0 Hz), 3.94 (1H, s), 3.90 (1H, d, J = 12.0 Hz), 3.87 (3H, s), 3.71 (1H, s), 2.09 (3H, s), 1.34 (3H, d, J = 6.5 Hz), 1.08 (9H, s), 0.90 (9H, t, J = 7.9 Hz), 0.65−0.61 (6H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.7, 162.9, 162.2, 135.8, 135.7, 133.2, 133.1, 130.3, 129.6, 127.6, 120.3, 113.5, 84.3, 78.5, 78.1, 76.2, 67.7, 60.0, 59.9, 55.3, 26.8, 21.0, 19.3, 16.3, 6.7, 4.8; HRMS-ESI (m/z) calcd for $C_{40}H_{54}NO_7Si_2$ $[M + H]^+$ 716.34333, found 716.34461.

(1*R*,2*R*,3*R*,4*S*,5*R*,5′*S*)-1-((*tert*-Butyldiphenylsilyloxy)methyl)-2′-(4-methoxyphenyl)-5′-methyl-2-(tripropylsilyloxy)-5′*H*-6-oxaspiro[bicyclo[3.1.0]hexane-3,4′-oxazol]-4-ol (40). To a solution of disilyl ether (186 mg, 0.26 mmol) in toluene (5 mL) was added (dimethylamino)trimethyltin (0.21 mL, 1.3 mmol) dropwise at rt under argon atmosphere and stirred for 3 h. Toluene was removed under reduced pressure, and the residue was purified by flash column chromatography on silica gel using 30% EtOAc in hexanes ot afford the epoxy alcohol **40** (152 mg, 87%) as a colorless oil: $[\alpha]_D^{20}$ −10.2 (c 1.00, $CHCl_3$); IR (neat) ν_{max} 3256, 2956, 1630, 1513, 1462, 1427, 1328, 1307, 1256, 1173, 1112, 841, 741, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.95 (2H, d, J = 8.9 Hz), 7.76−7.72 (4H, m), 7.45−7.38 (6H, m), 6.93 (2H, d, J = 8.9 Hz), 5.03 (1H, q, J = 6.5 Hz), 4.30 (1H, d, J = 11.8 Hz), 4.28 (1H, d, J = 11.7 Hz), 3.91 (1H, s), 3.87 (3H,

s), 3.86 (1H, d, J = 11.8 Hz), 3.73 (1H, s), 1.89 (1H, d, J = 11.8 Hz), 1.52 (3H, d, J = 6.5 Hz), 1.09 (9H, s), 0.92 (9H, t, J = 7.9 Hz), 0.70−0.63 (6H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.0, 162.2, 135.8, 135.7, 133.3, 133.0, 130.3, 129.7, 129.6, 127.6, 120.6, 113.5, 83.4, 78.7, 78.4, 74.6, 67.2, 61.0, 60.5, 55.4, 26.8, 19.3, 16.4, 6.8, 4.8; HRMS-ESI (m/z) calcd for $C_{38}H_{52}NO_6Si_2$ $[M + H]^+$ 674.33277, found 674.33367.

(1*S*,2*R*,3*R*,4*S*,5*S*)-4-Azido-1-((*tert*-butyldiphenylsilyloxy)-methyl)-3-((*S*)-1-hydroxyethyl)-3-(4-methoxybenzylamino)-2-methyl-5-(3-(prop-1-en-2-yl)phenylamino)cyclopentane-1,2-diol (48). To a stirred solution of oxazoline **47** (170 mg, 0.232 mmol) in dry AcOH (4 mL) was added $NaCNBH_3$ in portions (59 mg, 0.93 mmol) at rt under argon atmosphere. The reaction mixture was heated to 40 °C and stirred for 12 h. Then, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution and extracted with EtOAc (50 mL × 3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. Purification by column chromatography on silica gel using 30% EtOAc in hexanes afforded *N*-PMB amino alcohol **48** (132 mg, 77%) as a colorless liquid: $[\alpha]_D^{20}$ +60.8 (c 1.00, $CHCl_3$); IR (neat) ν_{max} 3413 (br), 2932, 2858, 2106, 1602, 1581, 1513, 1471, 1428, 1373, 1327, 1250, 1175, 1113, 1071, 1035, 890, 822, 738, 702 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64−6.58 (18H, aromatic protons), 5.30 (1H, s), 5.04 (1H, s), 5.01 (1H, s), 4.54 (1H, q, J = 6.7 Hz), 4.36 (1H, d, J = 10.1 Hz), 4.29 (1H, d, J = 6.5 Hz), 4.21 (1H, d, J = 10.1 Hz), 4.14 (1H, m), 4.04 (1H, d, J = 11.1 Hz), 3.98 (1H, d, J = 12.4 Hz), 3.81 (3H, s), 3.76 (1H, d, J = 11.1 Hz), 2.09 (3H, s), 1.62 (3H, s), 1.52 (3H, d, J = 6.7 Hz), 1.11 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.9, 146.8, 143.6, 142.5, 135.8, 135.6, 132.2, 131.1, 131.0, 130.3, 130.0, 129.3, 129.2, 128.0, 127.9, 115.4, 114.1, 112.2, 112.1, 111.0, 86.0, 80.4, 73.4, 69.7, 69.5, 66.0, 55.3, 47.5, 27.0, 21.9, 20.7, 19.5, 19.0; HRMS-ESI (m/z) calcd for $C_{42}H_{54}N_5O_5Si$ $[M + H]^+$ 736.38887, found 736.38914.

(4*S*,5*R*,6*R*,7*S*,8*S*,9*S*)-9-Azido-7-((*tert*-butyldiphenylsilyloxy)-methyl)-6,7-dihydroxy-1-(4-methoxybenzyl)-4,6-dimethyl-8-(3-(prop-1-en-2-yl)phenylamino)-3-oxa-1-azaspiro[4.4]nonan-2-one (49). To a stirred solution of *N*-PMB amino alcohol **48** (125 mg, 0.17 mmol) in dry THF (4 mL) were added activated charcoal (12 mg), Et_3N (0.17 mL, 1.19 mmol) and diphosgene (0.02 mL, 0.17 mmol) added slowly at 0 °C under argon atmosphere and stirred for 1 h. Then, the reaction was quenched by slow addition of a saturated aqueous $NaHCO_3$ solution and extracted with EtOAc (50 mL × 2). The combined organic layers were washed with brine, filtered, dried over anhydrous Na_2SO_4, and concentrated in vacuo. Flash column chromatography on silica gel using 25% EtOAc in hexanes eluted the cyclic carbamate **49** (108 mg, 83%) as a colorless liquid: $[\alpha]_D^{20}$ +5.8 (c 1.00, $CHCl_3$); IR (neat) ν_{max} 3366 (br), 2932, 2858, 2106, 1725, 1603, 1584, 1514, 1428, 1407, 1362, 1247, 1178, 1113, 1086, 1051, 908, 821, 782, 738, 702 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54−6.39 (18H, aromatic protons), 5.33 (1H, s), 5.09 (1H, s), 4.87 (1H, d, J = 15.8 Hz), 4.78 (1H, d, J = 15.8 Hz), 4.77 (1H, d, J = 12.4 Hz), 4.76 (1H, q, J = 6.2 Hz), 4.15 (1H, d, J = 10.9 Hz), 3.97 (1H, d, J = 10.9 Hz), 3.74 (3H, s), 3.71 (1H, s), 3.40 (1H, br s), 2.86 (1H, s), 2.78 (1H, s), 2.12 (3H, s), 1.54 (3H, d, J = 6.2 Hz), 1.44 (3H, s), 1.07 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3, 158.4, 146.2, 143.4, 142.1, 135.3, 131.8, 131.4, 130.2, 129.8, 129.1, 128.9, 128.0, 127.9, 115.9, 113.6, 112.7, 112.0, 110.8, 84.4, 81.9, 75.4, 74.6, 66.7, 66.2, 65.9, 55.1, 46.7, 26.9, 21.8, 19.8, 19.1, 17.2; HRMS-ESI (m/z) calcd for $C_{43}H_{52}N_5O_6Si$ $[M + H]^+$ 762.36814, found 762.36649.

(4*S*,5*R*,6*R*,7*S*,8*S*,9*S*)-8-(3-Acetylphenylamino)-9-azido-7-((*tert*-butyldiphenylsilyloxy)methyl)-6,7-dihydroxy-1-(4-methoxybenzyl)-4,6-dimethyl-3-oxa-1-azaspiro[4.4]nonan-2-one (50). To a stirred solution of olefin **49** (103 mg, 0.135 mmol) in THF (2 mL), acetone (2 mL), and H_2O (0.4 mL) were added NMO (79 mg, 0.677 mmol) and OsO_4 (0.1 mL, 4 wt % in H_2O) at 0 °C and stirred for 2 h at rt. A saturated aqueous sodium bisulfite solution was added to the reaction mixture and stirred for 30 min. The reaction mixture was extracted with EtOAc (50 mL × 3), and the combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. Flash column chromatography on silica gel using 70% EtOAc in hexanes eluted the tetrol as clear oil, which was directly used for the next reaction without characterization. To the stirred solution of above tetrol in THF (1.5 mL) and H_2O (1.5 mL) was added $NaIO_4$ (43 mg, 0.2 mmol) at rt and stirred for 3 h. The reaction mixture was extracted with EtOAc (50 mL × 3), and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. Flash column chromatography on silica gel using 30% EtOAc in hexanes eluted the methyl ketone **50** (81 mg, 78% in 2 steps) as a colorless liquid: $[\alpha]_D^{20}$ +7.5 (c 1.00, $CHCl_3$); IR (neat) ν_{max} 3365 (br), 2933, 2106, 1727, 1715, 1673, 1604, 1514, 1247, 1179, 1084, 909, 821, 735, 703 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54−7.14 (15H, aromatic protons), 6.80 (1H, d, J = 8.7 Hz), 6.65 (1H, m), 4.85 (1H, d, J = 23.1 Hz), 4.80 (1H, d, J = 23.1 Hz), 4.77 (1H, q, J = 6.4 Hz), 4.15 (1H, d, J = 10.8 Hz), 4.14 (1H, d, J = 11.0 Hz), 4.02 (1H, d, J = 10.8 Hz), 3.73 (3H, s), 3.70 (1H, s), 3.64 (1H, d, J = 11.0 Hz), 3.05 (1H, br s), 2.82 (1H, br s), 2.53 (3H, s), 1.54 (3H, d, J = 6.4 Hz), 1.44 (3H, s), 1.06 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.2, 159.2, 158.5, 146.4, 138.0, 135.4, 135.3, 131.6, 131.2, 130.4, 129.8, 129.3, 129.2, 128.1, 128.0, 118.7, 117.9, 113.6, 112.9, 84.5, 81.9, 75.3, 74.5, 66.8, 65.9, 65.7, 55.2, 46.7, 26.9, 26.7, 20.1, 19.1, 17.3; HRMS-ESI (m/z) calcd for $C_{42}H_{50}N_5O_7Si$ $[M + H]^+$ 764.3474, found 764.34611.

De-6-MSA-pactamycate (4). To a stirred solution of azide **51** (35 mg, 0.086 mmol) in THF/EtOH/H_2O (3:1:1, 2.5 mL) were added ammonium chloride (14 mg, 0.26 mmol) and zinc powder (8.5 mg, 0.13 mmol) at rt and stirred for 6 h. Then, the reaction mixture was quenched with aqueous ammonia (10 mL) and extracted with CH_2Cl_2 (50 mL × 2). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by flash column chromatography on silca gel using 8% MeOH in $CHCl_3$ to afford de-6-MSA-pactamycate **4** (28.5 mg, 87%) as a pale yellow solid: mp 93−95 °C; $[\alpha]_D^{20}$ −16.5 (c 1.00, MeOH); IR (neat) ν_{max} 3372 (br), 2939, 1732, 1674, 1602, 1385, 1359, 1335, 1267, 1063, 894, 777, 690 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 7.38 (1H, s), 7.21−7.18 (2H, m), 7.00 (1H, m), 4.82 (1H, q, J = 6.6 Hz), 3.91 (1H, d, J = 11.5 Hz), 3.53 (1H, d, J = 11.5 Hz), 3.52 (1H, d, J = 7.9 Hz), 3.49 (1H, d, J = 7.9 Hz), 2.54 (3H, s), 1.53 (3H, d, J = 6.6 Hz), 1.34 (3H, s); ^{13}C NMR (100 MHz, CD_3OD) δ 201.6, 161.1, 150.8, 139.1, 130.2, 119.2, 117.9, 113.2, 84.0, 83.0, 78.5, 72.6, 71.2, 63.8, 60.7, 26.9, 17.6, 17.2; HRMS-ESI (m/z) calcd for $C_{18}H_{26}N_3O_6$ $[M + H]^+$ 380.18161, found 380.18276.

(*S*)-1-((1*R*,2*R*,3*S*,4*S*,5*S*)-1-Amino-5-azido-3-((*tert*-butyldiphenylsilyloxy)methyl)-2,3-dihydroxy-2-methyl-4-(3-(prop-1-en-2-yl)phenylamino)cyclopentyl)ethyl dimethylcarbamate (59). To a solution of amino triol **55** (48 mg, 0.078 mmol) in CH_2Cl_2 (3 mL) were added Et_3N (0.065 mL. 0.47 mmol), *N*,*N*-dimethylcarbamoyl chloride (0.02 mL, 0.23 mmol), and DMAP (2 mg, 0.016 mmol) at rt under argon atmosphere and stirred for 12 h. The reaction was then quenched with aqueous saturated NH_4Cl solution and extracted twice with CH_2Cl_2. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel using 40% EtOAc in hexanes afforded carbamate **59** (45 mg, 84%) as a clear oil: $[\alpha]_D^{20}$ +86.2 (c 1.00, $CHCl_3$); IR (neat) ν_{max} 3385 (br), 2931, 2857, 2105, 1687, 1601, 1580, 1488, 1396, 1330, 1268, 1195, 1112, 887, 822, 738, 703 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63−6.56 (15H, aromatic protons and NH_2), 5.36 (1H, q, J = 6.5 Hz), 5.33 (1H, s), 5.04 (2H, s), 4.60 (1H, d, J = 11.2 Hz), 4.18 (1H, dd, J = 11.2, 3.6 Hz), 3.97 (1H, d, J = 10.9 Hz), 3.87 (1H, d, J = 10.9 Hz), 3.74 (1H, d, J = 11.2 Hz), 2.98 (3H, s), 2.96 (3H, s), 2.11 (3H, s), 1.29 (3H, d, J = 6.5 Hz), 1.26 (3H, s), 1.04 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.2, 146.4, 143.6, 142.5, 135.8, 135.6, 132.2, 132.0, 129.9, 129.7, 129.3, 127.8, 127.7, 115.3, 112.3, 112.1, 111.0, 83.8, 82.1, 74.2, 72.6, 69.4, 67.9, 64.4, 36.7, 35.9, 26.9, 21.9, 19.1, 17.9, 15.7; HRMS-ESI (m/z) calcd for $C_{37}H_{51}N_6O_5Si$ $[M + H]^+$ 687.36847, found 687.37043.

(1*S*,5*R*,6*S*,7*S*,8*R*)-6-Azido-1-((*tert*-butyldiphenylsilyloxy)-methyl)-8-hydroxy-5-((*S*)-1-hydroxyethyl)-8-methyl-7-(3-(prop-1-en-2-yl)phenylamino)-2-oxa-4-azabicyclo[3.2.1]octan-3-one (60). To a solution of cyclic carbamate **58** (47 mg, 0.06 mmol) in dry toluene (3 mL) was added (dimethylamino)trimethyltin (0.1 mL, 0.6 mmol) dropwise at rt under argon atmosphere, then the

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reaction mixture was heated to reflux and stirred for 3 h. Toluene was removed under reduced pressure, and the residue was purified by flash column chromatography on silica gel using 55% EtOAc in hexanes to afford diol **60** (33 mg, 86%) as a colorless oil: $[\alpha]_D^{20}$ +88.4 (*c* 1.00, $CHCl_3$); IR (neat) ν_{max} 3398 (br), 2931, 2857, 2107, 1699, 1602, 1582, 1390, 1326, 1263, 1113, 891, 822, 759, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.61−6.74 (15H, aromatic protons and OH), 6.18 (1H, s), 5.30 (1H, s), 5.06 (1H, t, *J* = 1.5 Hz), 4.85 (1H, s), 4.47 (1H, d, *J* = 5.1 Hz), 4.31 (1H, d, *J* = 11.0 Hz), 4.20 (1H, m), 4.19 (1H, d, *J* = 11.2 Hz), 4.01 (1H, m), 3.83 (1H, d, *J* = 11.2 Hz), 2.10 (3H, s), 1.52 (3H, d, *J* = 6.6 Hz), 1.30 (3H, s), 1.09 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.7, 145.7, 143.3, 143.0, 135.8, 135.5, 130.6, 130.4, 130.2, 129.6, 128.2, 128.0, 116.3, 112.6, 111.8, 110.9, 85.0, 78.5, 74.5, 67.1, 66.8, 65.9, 64.0, 27.0, 21.9, 20.7, 18.9, 16.8; HRMS-ESI (*m*/*z*) calcd for $C_{35}H_{44}N_5O_5Si$ $[M + H]^+$ 642.31062, found 642.31084.

(*S*)-1-((1*R*,2*R*,3*S*,4*S*,5*S*)-1-Amino-5-azido-2-(benzyloxy)-3-(benzyloxymethyl)-3-(*tert*-butyldiphenylsilyloxy)-2-methyl-4-(3-(prop-1-en-2-yl)phenylamino)cyclopentyl)ethyl 4-methoxybenzoate (62). To a solution of amino diol **54** (330 mg, 0.44 mmol) in THF (10 mL) were added NaH (88 mg, 60% dispersion in mineral oil, 2.2 mmol), benzyl bromide (0.13 mL, 1.1 mmol), and TBAI (81 mg, 0.22 mmol) at 0 °C. The reaction mixture was stirred for 2 h at rt, then quenched with aqueous saturated NH_4Cl solution and extracted with EtOAc (100 mL × 2). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel using 15% EtOAc in hexanes to afford the dibenzyl ether **62** (328 mg, 80%) as colorless viscous liquid: $[\alpha]_D^{20}$ +106.7 (*c* 1.00, $CHCl_3$); IR (neat) ν_{max} 3416 (br), 2934, 2858, 2098, 1707, 1604, 1580, 1511, 1318, 1276, 1257, 1168, 1103, 1029, 771, 738, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.16−6.66 (28H, aromatic protons), 5.78 (1H, s), 5.68 (1H, q, *J* = 6.4 Hz), 5.43 (1H, dd, *J* = 8.0, 1.8 Hz), 5.17(1H, s), 5.00 (1H, t, *J* = 1.4 Hz), 4.16 (1H, d, *J* = 8.9 Hz), 4.11 (1H, d, *J* = 8.9 Hz), 3.97 (1H, q, *J* = 11.6 Hz), 3.91 (3H, s), 3.71 (1H, d, *J* = 12.3 Hz), 3.62 (1H, d, *J* = 1.8 Hz), 3.53 (1H, d, *J* = 9.9 Hz), 3.43 (1H, d, *J* = 9.9 Hz), 3.26 (1H, d, *J* = 12.3 Hz), 2.01 (3H, s), 1.92 (3H, s), 1.39 (3H, d, *J* = 6.4 Hz), 1.13 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.2, 163.5, 145.7, 143.4, 141.9, 137.2, 136.8, 136.7, 135.7, 135.0, 134.1, 131.7, 129.7, 129.0, 128.9, 128.8, 128.7, 128.2, 128.0, 127.6, 127.3, 127.0, 122.9, 114.7, 113.8, 111.8, 111.3, 110.8, 91.9, 90.6, 76.9, 74.2, 71.9, 70.2, 67.7, 67.6, 66.6, 55.5, 27.6, 21.9, 20.0, 14.7, 13.5; HRMS-ESI (*m*/*z*) calcd for $C_{56}H_{64}N_5O_6Si$ $[M + H]^+$ 930.46204, found 930.45989.

(*S*)-1-((1*R*,2*R*,3*S*,4*S*,5*S*)-1-Amino-5-azido-2-(benzyloxy)-3-(benzyloxymethyl)-3-(*tert*-butyldiphenylsilyloxy)-2-methyl-4-(3-(prop-1-en-2-yl)phenylamino)cyclopentyl)ethanol (63). To a stirred solution of *p*-methoxy benzyl ester **62** (307 mg, 0.33 mmol) in dry CH_2Cl_2 (12 mL) was added DIBAL-H (1.65 mL, 1.0 M in toluene, 1.65 mmol) slowly at −78 °C under argon atmosphere and stirred for 1.5 h. The reaction mixture was then quenched with slow addition of MeOH and warmed to room temperature. A saturated aqueous potassium sodium tartrate solution was added to the reaction mixture and stirred for 1 h. The reaction mixture was extracted with CH_2Cl_2 (100 mL × 2), and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel using 35% EtOAc in hexanes afforded amino alcohol **63** (242 mg, 92%) as colorless liquid: $[\alpha]_D^{20}$ +27.8 (*c* 1.00, $CHCl_3$); IR (neat) ν_{max} 3399 (br), 3029, 2933, 2858, 2097, 1600, 1580, 1492, 1453, 1427, 1328, 1258, 1109, 1027, 975, 784, 739, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.92−6.65 (24H, aromatic protons), 5.93 (1H, t, *J* = 1.9 Hz), 5.42 (1H, dd, *J* = 8.0, 2.0 Hz), 5.19 (1H, s), 5.00 (1H, t, *J* = 1.5 Hz), 4.76 (1H, d, *J* = 9.7 Hz), 4.41 (1H, d, *J* = 9.7 Hz), 4.08 (1H, m), 4.05 (1H, d, *J* = 11.2 Hz), 3.98 (1H, d, *J* = 11.2 Hz), 3.61 (1H, d, *J* = 12.1 Hz), 3.55 (1H, d, *J* = 10.0 Hz), 3.47 (1H, d, *J* = 2.0 Hz), 3.46 (1H, d, *J* = 10.0 Hz), 2.02 (3H, s), 1.90 (3H, s), 1.12 (3H, d, *J* = 6.5 Hz), 1.09 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.8, 143.4, 141.9, 137.8, 137.3, 136.7, 135.6, 135.0, 134.0, 129.6, 129.1, 129.0, 128.4, 128.2, 128.0, 127.9, 127.6, 127.3, 127.0, 114.7, 111.8, 111.2, 111.0, 91.5, 90.7, 78.0, 71.9, 69.7, 69.4, 67.6, 67.3, 66.8, 27.6, 21.8, 20.0, 18.6, 13.7; HRMS-ESI (*m*/*z*) calcd for $C_{48}H_{58}N_5O_4Si$ $[M + H]^+$ 796.42526, found 796.42568.

(*S*)-1-((1*R*,2*R*,3*S*,4*S*,5*S*)-1-Amino-5-azido-2-(benzyloxy)-3-(benzyloxymethyl)-3-(*tert*-butyldiphenylsilyloxy)-2-methyl-4-(3-(prop-1-en-2-yl)phenylamino)cyclopentyl)ethyl dimethylcarbamate (64). To a solution of amino alcohol **63** (42 mg, 0.053 mmol) in dry THF (2 mL) were added NaH (8.5 mg, 60% dispersion in mineral oil, 0.21 mmol), *N*,*N*-dimethylcarbamoyl chloride (0.01 mL, 0.106 mmol), and TBAI (4 mg, 0.01 mmol) at rt under argon atmosphere and stirred for 6 h. The reaction was then quenched with aqueous saturated NH_4Cl solution and extracted twice with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel using 20% EtOAc in hexanes to afford carbamate **64** (37 mg, 81%) as pale yellow crystals: mp 153−155 °C; $[\alpha]_D^{20}$ +42.5 (*c* 1.00, $CHCl_3$); IR (neat) ν_{max} 3416 (br), 2933, 2099, 1698, 1600, 1493, 1393, 1270, 1187, 1109, 909, 736, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.98−6.67 (24H, aromatic protons), 5.78 (1H, s), 5.42 (1H, d, *J* = 8.0 Hz), 5.38 (1H, q, *J* = 6.4 Hz), 5.16 (1H, s), 4.99 (1H, s), 4.36 (1H, d, *J* = 8.7 Hz), 4.22 (1H, d, *J* = 8.7 Hz), 3.98 (1H, d, *J* = 11.2 Hz), 3.90 (1H, d, *J* = 11.2 Hz), 3.71 (1H, d, *J* = 12.3 Hz), 3.56 (1H, s), 3.55 (1H, d, *J* = 9.9 Hz), 3.42 (1H, d, *J* = 9.9 Hz), 3.29 (1H, d, *J* = 12.3 Hz), 3.07 (3H, s), 3.00 (3H, s), 2.00 (3H, s), 1.90 (3H, s), 1.31 (3H, d, *J* = 6.4 Hz), 1.11 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.4, 145.7, 143.4, 141.8, 137.3, 137.0, 136.7, 136.5, 135.7, 135.1, 134.1, 129.6, 129.1, 129.0, 128.9, 128.7, 128.2, 128.1, 128.0, 127.6, 127.3, 127.0, 114.6, 111.8, 111.2, 110.9, 91.7, 90.5, 76.6, 74.5, 71.9, 70.0, 67.7, 67.5, 66.6, 36.6, 36.1, 27.6, 21.8, 20.0, 15.4, 13.2; HRMS-ESI (*m*/*z*) calcd for $C_{51}H_{63}N_6O_5Si$ $[M + H]^+$ 867.46237, found 867.4628.

(1*S*,2*S*,3*R*,4*R*,5*S*)-2-Azido-4-(benzyloxy)-3-((*S*)-1-(benzyloxy)ethyl)-5-(benzyloxymethyl)-5-(*tert*-butyldiphenylsilyloxy)-4-methyl-N1-(3-(prop-1-en-2-yl)phenyl)cyclopentane-1,3-diamine (65). To a solution of amino alcohol **63** (186 mg, 0.234 mmol) in dry THF (5 mL) were added NaH (38 mg, 60% dispersion in mineral oil, 0.94 mmol), BnBr (0.04 mL, 0.35 mmol), and TBAI (9 mg, 0.02 mmol) at 0 °C under argon atmosphere and stirred for 3 h. The reaction was then quenched with aqueous saturated NH_4Cl solution and extracted twice with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel using 10% EtOAc in hexanes to afford amino tribenzyl ether **65** (162 mg, 78%) as clear oil: $[\alpha]_D^{20}$ +67.5 (*c* 1.00, $CHCl_3$); IR (neat) ν_{max} 3417 (br), 3029, 2933, 2858, 2098, 1600, 1579, 1494, 1453, 1427, 1329, 1266, 1109, 976, 909, 820, 784, 736, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.00−6.68 (29H, aromatic protons), 5.96 (1H, s), 5.53 (1H, dd, *J* = 8.0, 2.0 Hz), 5.22 (1H, s), 5.03 (1H, t, *J* = 1.4 Hz), 4.77 (1H, d, *J* = 11.4 Hz), 4.47 (1H, d, *J* = 9.9 Hz), 4.40 (1H, d, *J* = 11.4 Hz), 4.32 (1H, d, *J* = 9.9 Hz), 4.16 (1H, q, *J* = 6.3 Hz), 4.13 (1H, d, *J* = 11.7 Hz), 4.01 (1H, d, *J* = 11.7 Hz), 3.69 (1H, d, *J* = 12.2 Hz), 3.56 (1H, d, *J* = 2.1 Hz), 3.53 (1H, d, *J* = 9.9 Hz), 3.47 (1H, d, *J* = 9.9 Hz), 3.28 (1H, d, *J* = 12.2 Hz), 2.05 (3H, s), 1.96 (3H, s), 1.35 (3H, d, *J* = 6.3 Hz), 1.11 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.9, 143.4, 141.8, 138.6, 137.8, 137.3, 136.7, 135.6, 135.2, 134.8, 134.2, 129.5, 129.0, 128.9, 128.7, 128.4, 128.1, 127.9, 127.8, 127.7, 127.6, 127.5, 127.4, 127.2, 126.9, 114.5, 111.8, 111.1, 111.0, 92.5, 90.5, 78.4, 71.8, 70.9, 70.0, 67.7, 67.2, 66.3, 27.6, 21.9, 20.0, 13.8, 13.4; HRMS-ESI (*m*/*z*) calcd for $C_{55}H_{64}N_5O_4Si$ $[M + H]^+$ 886.47221, found 886.47332.

***N*-((1*S*,2*S*,3*R*,4*R*,5*S*)-5-Azido-3-(benzyloxy)-4-((*S*)-1-(benzyloxy)ethyl)-2-(benzyloxymethyl)-2-(*tert*-butyldiphenylsilyloxy)-4-isocyanato-3-methylcyclopentyl)-3-(prop-1-en-2-yl)aniline (66).** To a stirred solution of amine **65** (146 mg, 0.165 mmol) in dry THF (5 mL) were added activated charcoal (15 mg), Et_3N (0.07 mL, 0.49 mmol), and diphosgene (0.04 mL, 0.33 mmol) slowly at −46 °C under argon and stirred for 20 min. Then, the reaction was quenched with saturated aqueous $NaHCO_3$ solution and extracted with EtOAc (50 mL × 2). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. Flash column chromatography on silica gel using 8% EtOAc in hexanes eluted the stable isocyanate **66** (125 mg, 83%) as a colorless

liquid: $[\alpha]_D^{20}$ +49.5 (*c* 1.00, $CHCl_3$); IR (neat) ν_{max} 3417 (br), 3029, 2933, 2858, 2258, 2098, 1600, 1581, 1454, 1329, 1267, 1110, 909, 821, 737, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.93−6.73 (29H, aromatic protons), 6.07 (1H, s), 5.65 (1H, dd, *J* = 8.0, 1.9 Hz), 5.20 (1H, s), 5.02 (1H, s), 4.82 (1H, d, *J* = 11.5 Hz), 4.44 (1H, d, *J* = 10.3 Hz), 4.39 (1H, d, *J* = 11.5 Hz), 4.37 (1H, d, *J* = 10.3 Hz), 4.28 (1H, q, *J* = 6.2 Hz), 4.10 (1H, dd, *J* = 11.7, 4.0 Hz), 3.83 (1H, d, *J* = 11.7 Hz), 3.70 (1H, d, *J* = 12.0 Hz), 3.52 (1H, d, *J* = 4.0 Hz), 3.50 (1H, d, *J* = 9.9 Hz), 3.44 (1H, d, *J* = 12.0 Hz), 3.33 (1H, d, *J* = 9.9 Hz), 2.04 (3H, s), 1.96 (3H, s), 1.41 (3H, d, *J* = 6.2 Hz), 1.14 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.7, 143.3, 142.0, 137.9, 137.6, 137.4, 136.8, 136.0, 135.3, 134.6, 129.4, 129.1, 129.0, 128.7, 128.5, 128.1, 128.0, 127.6, 127.5, 127.4, 127.3, 127.1, 127.0, 125.4, 115.1, 112.0, 111.3, 111.1, 93.0, 88.3, 77.7, 75.6, 73.6, 72.1, 69.6, 68.7, 67.5, 66.8, 27.2, 21.8, 19.9, 14.8, 13.9.

3-((1*R*,2*R*,3*S*,4*S*,5*S*)-5-Azido-2-(benzyloxy)-1-((*S*)-1-(benzyloxy)ethyl)-3-(benzyloxymethyl)-3-(*tert*-butyldiphenylsilyloxy)-2-methyl-4-(3-(prop-1-en-2-yl)phenylamino)-cyclopentyl)-1,1-dimethylurea (67). To an isocyanate **66** (96 mg, 0.105 mmol) was added neat 0.2 mL of dimethyl amine (upon condensing the gas at −46 °C), and the reaction mixture was left warming to room temperature. It was directly subjected to flash column chromatography using 20% EtOAc in hexanes to afford urea **67** (89 mg, 88%) as a colorless oil: $[\alpha]_D^{20}$ +8.6 (*c* 1.00, $CHCl_3$); IR (neat) ν_{max} 3400 (br), 3030, 2931, 2857, 2100, 1666, 1602, 1581, 1524, 1496, 1454, 1361, 1334, 1243, 1172, 1108, 1028, 909, 821, 780, 733, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.68−6.41 (29H, aromatic protons), 5.58 (1H, s), 5.39 (1H, s), 5.08 (1H, s), 4.89 (1H, d, *J* = 11.8 Hz), 4.68 (1H, q, *J* = 6.1 Hz), 4.62 (1H, d, *J* = 11.8 Hz), 4.50 (1H, d, *J* = 11.0 Hz), 4.42 (1H, br s), 4.11−3.97 (4H, m), 3.87 (1H, d, *J* = 10.1 Hz), 3.64 (1H, d, *J* = 10.1 Hz), 2.90 (6H, s), 2.18 (3H, s), 1.91 (3H, s), 1.14 (3H, d, *J* = 6.1 Hz), 0.92 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.9, 147.2, 143.9, 141.5, 139.2, 139.0, 137.1, 136.2, 135.9, 135.3, 134.7, 129.2, 129.1, 128.6, 128.5, 128.3, 128.1, 128.0, 127.9, 127.2, 127.1, 127.0, 126.8, 126.7, 114.2, 111.7, 111.4, 110.7, 91.0, 86.1, 74.9, 72.9, 70.9, 70.4, 69.2, 67.2, 65.7, 62.3, 36.5, 27.5, 21.9, 19.9; HRMS-ESI (*m*/*z*) calcd for $C_{58}H_{69}N_6O_5Si$ $[M + H]^+$ 957.50932, found 957.5084.

3-((1*R*,2*R*,3*S*,4*S*,5*S*)-4-(3-Acetylphenylamino)-5-azido-2-(benzyloxy)-1-((*S*)-1-(benzyloxy)ethyl)-3-(benzyloxymethyl)-3-(*tert*-butyldiphenylsilyloxy)-2-methylcyclopentyl)-1,1-dimethylurea (methylketone of 67). To a stirred solution of olefin **67** (70 mg, 0.073 mmol) in THF (1 mL), acetone (1 mL), and H_2O (0.2 mL) were added NMO (60 mg, 0.51 mmol) and OsO_4 (0.05 mL, 4 wt % in H_2O) at 0 °C and stirred for 2 h at rt. A saturated aqueous sodium bisulfite solution was added to the reaction mixture and stirred for 30 min. The reaction mixture was extracted with EtOAc (30 mL × 3), and the combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. Flash column chromatography on silica gel using 70% EtOAc in hexanes eluted the diol as clear oil, which was directly used for the next reaction without characterization. To the stirred solution of the above diol in THF (1 mL) and H_2O (1 mL) was added $NaIO_4$ (24 mg, 0.11 mmol) at rt and stirred for 2 h. The reaction mixture was extracted with EtOAc (30 mL × 3), and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. Flash column chromatography on silica gel using 30% EtOAc in hexanes eluted the methyl ketone (55 mg, 78% in 2 steps) as a colorless liquid: $[\alpha]_D^{20}$ +23.2 (*c* 1.00, $CHCl_3$); IR (neat) ν_{max} 3434 (br), 2931, 2857, 2099, 1665, 1603, 1585, 1524, 1358, 1272, 1237, 1172, 1108, 910, 821, 733, 701, 607 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.62−7.08 (29H, aromatic protons), 6.62 (1H, br s), 6.38 (1H, s), 4.84 (1H, d, *J* = 8.0 Hz), 4.66 (1H, d, *J* = 12.1 Hz), 4.56 (1H, m), 4.45 (1H, d, *J* = 11.1 Hz), 4.19 (1H, m), 4.04−3.98 (2H, m), 3.92 (1H, d, *J* = 11.3 Hz), 3.86 (1H, d, *J* = 10.1 Hz), 3.59 (1H, d, *J* = 10.1 Hz), 2.94 (6H, s), 2.62 (3H, s), 1.89 (3H, s), 1.12 (3H, d, *J* = 6.4 Hz), 0.91 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.3, 158.6, 147.3, 139.3, 138.8, 137.6, 137.0, 136.1, 136.0, 135.1, 134.4, 129.3, 129.2, 128.8, 128.7, 128.4, 128.3, 128.1, 128.0, 127.2, 127.1, 126.9, 126.8, 126.5, 117.2, 116.7, 112.8, 90.9, 85.8, 73.0, 70.9, 68.9, 67.9, 65.7, 61.7, 36.6, 27.4, 26.8, 19.9.

3-((1*R*,2*R*,3*S*,4*S*,5*S*)-4-(3-Acetylphenylamino)-5-azido-2-(benzyloxy)-1-((*S*)-1-(benzyloxy)ethyl)-3-(benzyloxymethyl)-3-hydroxy-2-methylcyclopentyl)-1,1-dimethylurea (68). To a stirred solution of silyl ether (44 mg, 0.046 mmol) in dry DMF (2 mL) was added TASF (38 mg, 0.138 mmol) at 0 °C under argon and allowed to come to room temperature. After being stirred for 1 h at rt, the reaction mixture was cooled to 0 °C, quenched with a pH 7 phosphate buffer solution, and extracted with EtOAc (50 mL × 3). The combined organic layers were washed with water (30 mL × 3) and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel using 50% EtOAc in hexanes to afford the pure keto alcohol **68** (30 mg, 90%) as pale yellow crystals: mp 127−128 °C; $[\alpha]_D^{20}$ +53.1 (*c* 1.00, $CHCl_3$); IR (neat) ν_{max} 3385 (br), 2931, 2102, 1674, 1602, 1538, 1358, 1269, 1173, 1111, 910, 734, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37−7.15 (19H, aromatic protons), 6.92 (1H, d, *J* = 7.6 Hz), 6.32 (1H, s), 5.64 (1H, s), 4.81 (1H, q, *J* = 6.3 Hz), 4.68 (1H, d, *J* = 11.0 Hz), 4.66 (1H, d, *J* = 10.8 Hz), 4.59 (1H, d, *J* = 10.8 Hz), 4.52−4.49 (2H, m), 4.37 (1H, dd, *J* = 11.1, 4.3 Hz), 3.94 (1H, d, *J* = 10.0 Hz), 3.85 (1H, d, *J* = 7.1 Hz), 3.54 (1H, d, *J* = 10.0 Hz), 2.97 (6H, s), 2.56 (3H, s), 1.72 (3H, s), 1.40 (3H, d, *J* = 6.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.6, 158.4, 147.3, 138.5, 138.1, 138.0, 129.6, 128.6, 128.5, 128.2, 127.8, 127.7, 127.6, 127.5, 127.4, 118.0, 117.4, 113.0, 92.3, 82.4, 76.6, 74.0 72.4, 71.4, 71.2, 70.5, 68.5, 66.8, 36.7, 26.7, 14.9, 14.4; HRMS-ESI (*m*/*z*) calcd for $C_{41}H_{49}N_6O_6$ $[M + H]^+$ 721.37081, found 721.37077.

De-6-MSA-pactamycin (3). To a stirred solution of azide **71** (24 mg, 0.044 mmol) in EtOH/H_2O (3:1, 2 mL) were added NH_4Cl (7 mg, 0.133 mmol) and zinc powder (4.5 mg, 0.067 mmol) at rt and stirred for 6 h. Then, the reaction mixture was quenched with aqueous ammonia (10 mL) and extracted with CH_2Cl_2 (30 mL × 2). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by flash column chromatography on silca gel using 5% MeOH in $CHCl_3$ to afford de-6-MSA-pactamycin **3** (19.5 mg, 86%) as a pale yellow oil: $[\alpha]_D^{20}$ +32.5 (*c* 1.00, $CHCl_3$); IR (neat) ν_{max} 3383 (br), 2935, 1678, 1603, 1520, 1440, 1359, 1334, 1269, 1091, 1042, 912, 782, 732, 689 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.86 (1H, br s), 7.29−6.85 (5H, aromatic protons and NH_2), 5.56 (1H, br s), 5.48 (1H, d, *J* = 9.9 Hz), 4.13 (1H, d, *J* = 11.7 Hz), 3.93 (1H, m), 3.76 (1H, d, *J* = 9.9 Hz), 3.75 (1H, d, *J* = 11.7 Hz), 3.01 (6H, s), 2.97 (1H, s), 2.56 (3H, s), 1.47 (3H, s), 1.06 (3H, d, *J* = 6.4 Hz); ^1H NMR (400 MHz, $CDCl_3$+D_2O) δ = 7.29−6.85 (4H, aromatic protons), 4.14 (1H, d, *J* = 11.8 Hz), 3.92 (1H, q, *J* = 6.4 Hz), 3.75 (1H, s), 3.70 (1H, d, *J* = 11.8 Hz), 3.00 (6H, s), 2.93 (1H, s), 2.52 (3H, s), 1.45 (3H, s), 1.04 (3H, d, *J* = 6.4 Hz); ^1H NMR (400 MHz, CD_3OD) δ = 7.27−7.24 (3H, aromatic protons), 6.93 (1H, m), 4.07 (1H, q, *J* = 6.5 Hz), 3.94 (1H, d, *J* = 11.5 Hz), 3.74 (1H, d, *J* = 2.1 Hz), 3.68 (1H, d, *J* = 11.5 Hz), 3.01 (1H, d, *J* = 2.1 Hz), 2.98 (6H, s), 2.56 (3H, s), 1.42 (3H, s), 1.04 (3H, d, *J* = 6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 198.8, 159.3, 146.9, 138.1, 129.5, 119.1, 118.4, 110.6, 88.5, 84.9, 73.9, 71.7, 68.1, 62.9, 61.7, 36.9, 26.6, 21.3, 18.2; ^{13}C NMR (100 MHz, CD_3OD) δ 201.7, 161.2, 149.4, 139.5, 130.7, 119.7, 118.5, 113.3, 89.6, 85.6, 74.4, 72.9, 69.4, 64.1, 62.3, 37.3, 27.1, 22.0, 18.9; HRMS-ESI (*m*/*z*) calcd for $C_{20}H_{33}N_4O_6$ $[M + H]^+$ 425.23946, found 425.23998.

■ ASSOCIATED CONTENT

Supporting Information

Copies of the ^1H and ^{13}C NMR spectra of new compounds (PDF) and CIF files for compounds **2**, **12**, **24** (*p*-bromobenzoate ester derivative), **29** (*p*-nitrobenzoate ester derivative), **33** (phenyloxazoline derivative), **38**, **45**, **46**, **47** (derivative), **58**, **64**, and **68**. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Notes

The authors declare no competing financial interest.

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Probing functional diversity in pactamycin toward antibiotic, antitumor, and antiprotozoal activity

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ABSTRACT

A total of eight new analogs of pactamycin were prepared and tested alongside pactamycin and three of its natural congeners for antibacterial, anticancer, and antiprotozoal activities. The present study highlights the effects of changing the urea and aniline groups especially with regard to anticancer and antiprotozoal activities.

1. Introduction

Pactamycin represents a structurally unique natural product belonging to the aminocyclopentitol family[1] (Fig. 1). Its isolation in 1961 from a fermentation broth of *Streptomyces pactum* by the former Upjohn Company scientists,[2] was followed by its structure elucidation by chemical and spectroscopic methods,[3] and eventually as a derivative by X-ray crystallography.[4] Early studies by the Upjohn group have shown that pactamycin exhibited in vitro activity against a limited panel of Gram-positive and Gram-negative bacteria as well as cytotoxicity against some cancer cell lines.[5] However, further interest in pactamycin was curtailed because of its toxicity.

The highly functionalized and unique structure of pactamycin has generated interest in recent years on several fronts.[6] Pioneering X-ray crystallographic studies of a pactamycin-RNA complex from *Thermus thermophilus* by Ramakrishnan and co-workers[7] showed a unique mode of binding at the 30S site. Early studies on the biosynthesis of pactamycin were reported by Rinehart and co-workers.[8] More recently, Kudo and co-workers[9] cloned the biosynthetic gene cluster involved in the formation of the cyclopentane ring of pactamycin. Elegant studies by Mahmud and co-workers[10] on the biosynthesis of pactamycin have traced its components to small molecule precursors by isotopic labelling. Furthermore, they have identified the biosynthetic gene cluster that produces pactamycin (**1**), de-6-methylsalicylyl pactamycin (**2**), pactamycate (**3**), de-6-methylsalicylyl pactamycate (**4**), and 7-deoxypactamycin (**5a**) (Fig. 1).

Synthetic approaches toward the synthesis of the cyclopentane core of pactamycin were sparse except for preliminary reports from the Isobe[11] and Knapp[12] groups in 2005 and 2007, respectively. A total synthesis of pactamycin and pactamycate was reported in 2011 by our group.[13] More recently, conceptually different approaches to the substituted core structure of pactamycin were independently divulged by Johnson,[14] Looper,[15] and Nishikawa.[16]

In spite of the sustained interest in the mode of action of pactamycin as an inhibitor of protein biosynthesis in prokaryotes,[6] and the intriguing interactions with RNA's,[7] little was known regarding its activity beyond the limited testing done at the former Upjohn Company.[5] Recently, interest in pactamycin and its relatively few congeners available from biosynthetic studies in small amounts has been highlighted by the discovery of its antiprotozoal activity. Thus, Õmura and co-workers[17] reported that 7-deoxypactamycin (**5a**) exhibited activity against *Trypanosoma brucei* and *Plasmodium falciparum* at levels that were eightfold higher in potency compared to pactamycin. In a more recent report, Õmura and

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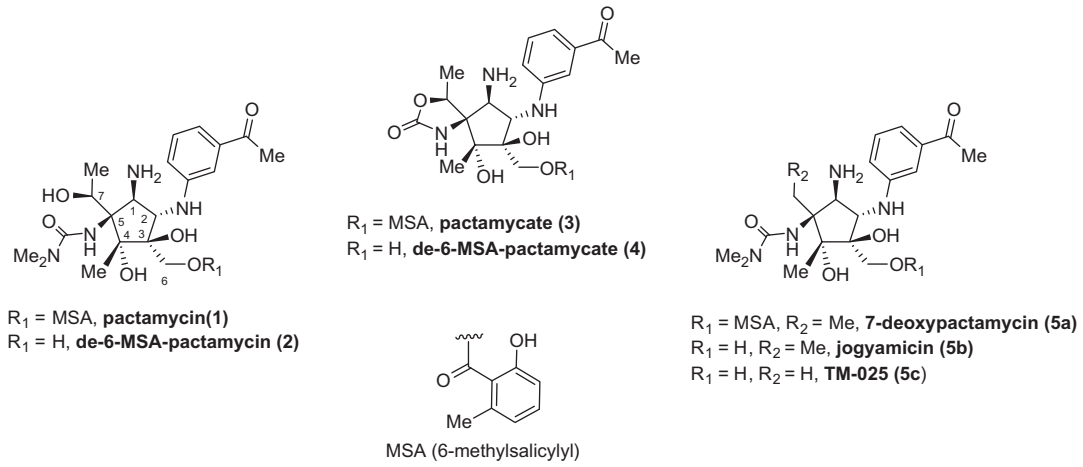


Figure 1. Structures of pactamycin, pactamycate, their de-6-methylsalicylyl analogs, jogyamicin, 7-deoxypactamycin, and TM-025.

co-workers[18] showed that jogyamycin (**5b**), the de-6-methylsalicylyl 7-deoxypactamycin congener, was also a potent antitrypanosomal agent and considerably better than pactamycin. Finally, superior activity of a new metabolite of pactamycin (**5c,** TM-025) against malaria parasites was recently divulged by Mahmud and co-workers.[19]

2. Results and discussion

2.1. Chemistry

Our synthesis plan toward pactamycin was conceived so as to allow the preparation of functionally modified analogs.[13] We were intrigued by the role that the unusual 6-methyl salicylyl ester (6-MSA) moiety in pactamycin could play in the in vitro activity as an antibiotic when our work began some years ago. Only within the past three years has it been demonstrated that de-6-methylsalicylyl pactamycin (**2**) and its 7-modified congeners were endowed with equal if not better antiprotozoal activity, but diminished antibacterial activity.[19] With this knowledge, we focussed on the synthesis of de-6-methylsalicylyl pactamycin analogs in which the aniline and urea moieties were modified, starting from appropriate advanced intermediates[13] (Fig. 2).

Maintaining the original aniline moiety with the *m*-acetyl group, we prepared a series of *N*,*N*-dialkyl ureas (**11a–11d**) varying the bulk of the substituents by treating the isocyanate **6**[13] with a series of amines. The resulting substituted ureas (**7a**–**7d**), were converted to the 7-hydroxy analog by treatment with DIBAL-H to give **8a**–**8d**. Subsequent oxidative transformation to the ketones **9a**–**9d**, cleavage of the acetal to **10a–10d,** and Zn-mediated reduction of the azide group led to the *N*,*N*-disubstituted urea analogs of de-6-methylsalicylyl pactamycin **11a–11d** (Scheme 1).

Next, keeping the *N*,*N*-dimethylurea group, we substituted the original *m*-acetyl-1-aniline moiety at C2 by aniline and *m*-substituted anilines (**19a–19d**) (Scheme 2). Thus $Yb(OTf)_3$ mediated cleavage of the epoxide group in **12**[13] in the presence of four different anilines gave the aniline analogs **13a–13d** as single diastereomers.[20] Acid-catalyzed cleavage of the oxazoline moiety afforded the aminoalcohols **14a–14d**, which were converted to the isocyanates **15a–15d**. Treatment with dimethylamine led to the *N*,*N*-dimethylurea derivatives **16a–16d**, which were eventually converted to **19a–19d** as described in Scheme 1.

2.2. Biological activity studies

The antibacterial activities of these and related derivatives against a panel of six representative microorganisms are shown in Table 1. Pactamycin and de-6-MSA pactamycin remained the most active against *Escherichia coli* and *Staphylococcus aureus*, closely followed by the *m*-fluoro, and *m*-trifluoromethyl aniline analogs. Modification of the urea group led to diminution or loss of activity showing its paramount importance.

The cytotoxicity of the same analogs against a panel of four cancer cell lines is shown in Table 2. Excellent activity was exhibited against a colorectal HCT116 cell lines by pactamycin (**1**) and de-6-MSA pactamycin (**2**). Among the modified urea analogs, the pyrrolidine urea **11b** appeared to be the best. Unfortunately, all other analogs were either inactive or weakly active against the other cell lines.

The most interesting results were obtained against *Plasmodium falciparum* (Table 3). A clear demarcation in the tolerance of *N*,*N*-dialkylurea groups was observed as the size increased. Thus, the threshold of activity was maintained up to the pyrrolidine urea (**11b**) (IC_{50} = 9 nM), but rapidly fell for the piperidine and morpholine analogs (**11c**, **11d**). Among the anilines, excellent activity was observed in the case of the *m*-fluoro and *m*-trifluoromethyl aniline analogs (**19b** and **19d**) against the D6 strain. In addition the same analogs were also highly active against chloroquine-resistant Dd2 and 7G8 strains.

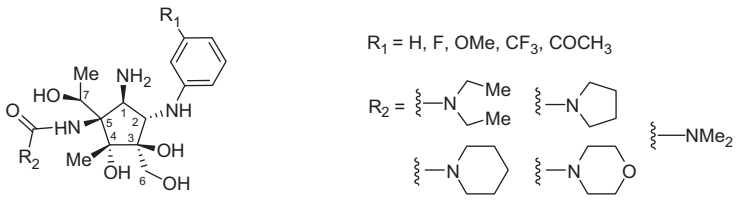
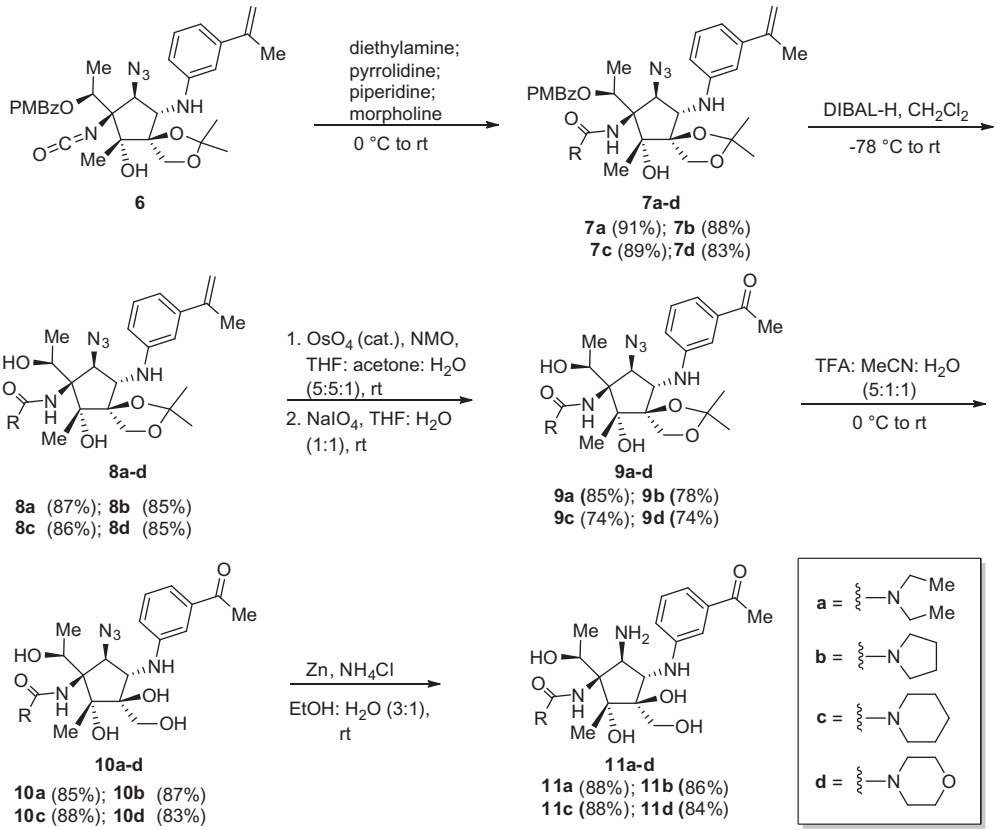


Figure 2. Two series of modifications toward the pactamycin analogs.



Scheme 1. Synthesis of disubstituted urea analogs of de-6-methylsalicylyl pactamycin.

3. Conclusion

In conclusion, we have prepared a series of modified urea and aniline analogs of de-6-MSA pactamycin and studied the influence of systematic modifications on the biological activities compared to pactamycin and de-6-MSA pactamycin. Antibacterial activity against *Escherichia coli* and *Staphylococcus aureus* was maintained only in the *m*-fluoro and *m*-trifluoromethyl aniline analogs. There appears to be a limit to steric tolerance in the antitumor activity of urea analogs against colorectal cancer cell line with the pyrrolidine analog of de-6MSA pactamycin being the most active. Variation in the *m*-position of the aniline resulted in excellent activity against *Plasmodium falciparum* indicating better tolerance compared to changes in the urea moiety. Moreover, equally high activity was observed against chloroquine-resistant strains by the *m*-fluoro and *m*-trifluoromethyl anline analogs. Further studies toward a better understanding of structure–activity relationships toward an extended panel of tumor cell lines and protozoal organisms will be reported in due course.

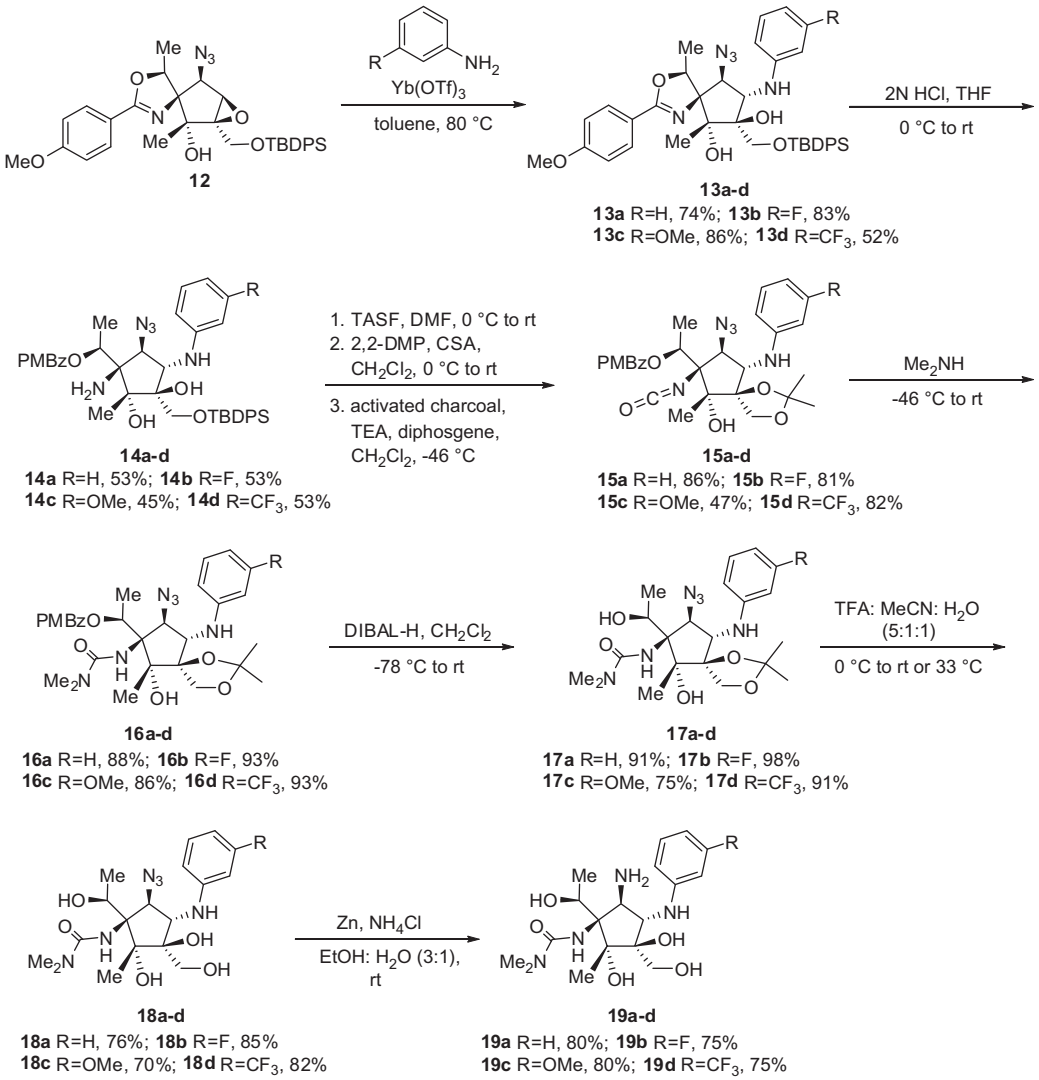
4. Experimental

4.1. General

All non-aqueous reactions were run in flame-dried glassware under a positive pressure of argon with exclusion of moisture from reagents and glassware using standard techniques for manipulating air-sensitive compounds. Anhydrous solvents were obtained using standard drying techniques. Unless stated otherwise, commercial grade reagents were used without further purification. Reactions were monitored by analytical thin-layer chromatography (TLC) performed on pre-coated, glass-backed silica gel plates. Visualization of the developed chromatogram was performed by UV absorbance, aqueous cerium ammonium molybdate, iodine, or aqueous potassium permanganate. Flash chromatography was performed on 230–400 mesh silica gel with the indicated solvent systems. Melting points are uncorrected. Infrared spectra were recorded on a FT-IR spectrometer and are reported in reciprocal centimeters (cm^{-1}). Routine nuclear magnetic resonance spectra were recorded either on AMX-300, AV-300, AV-400, or AV-700 spectrometer. Chemical shifts for ^{1}H NMR spectra are recorded in parts per million from tetramethylsilane with the solvent resonance as the internal standard ($CHCl_3$, δ 7.27 ppm). Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, m = multiplet and br = broad) and coupling constant in Hz. Chemical shifts for ^{13}C NMR spectra are recorded in parts per million from tetramethylsilane using the central peak of the solvent resonance as the internal standard ($CDCl_3$, δ 77.00 ppm). All spectra were obtained with complete proton decoupling. Optical rotations were determined at 589 nm at ambient temperature. Data are reported as follows: $[\alpha]_D$ concentration (*c* in g/100 mL), and solvent. High-resolution mass spectra were performed by the Centre régional de spectroscopie de masse de l'Université de Montréal using fast atom bombardment (FAB) or electrospray ionization (ESI) techniques. Low-resolution mass spectra were obtained using electrospray ionization (ESI).

4.1.1. General procedure for synthesis of compounds 7a–7d

To isocyanate **6** (49 mg, 0.085 mmol) was added 0.1 mL of secondary amines (neat) at 0 °C and the reaction mixture was left warming to room temperature. It was directly subjected to flash column chromatography using [40–50]% ethyl acetate in hexanes to afford **7a–7d** as colorless oils.



Scheme 2. Synthesis of de-6-methylsalicylyl aniline analogs of pactamycin.

4.1.1.1. (*S*)-1-((5*S*,6*R*,7*R*,8*S*,9*S*)-8-Azido-7-(3,3-diethylureido)-6-hydroxy-2,2,6-trimethyl-9-((3-(prop-1-en-2-yl)phenyl)amino)-1,3-dioxaspiro[4.4]nonan-7-yl)ethyl 4-methoxybenzoate (7a). Yield: 91% (50 mg from 49 mg); $[\alpha]_D^{20}$ +90.9 (*c* 1.00, $CHCl_3$); IR (neat): ν_{max} 3403, 2977, 2107, 1708, 1644, 1605, 1582, 1511, 1257, 1168, 1032, 849, 769 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.98 (2H, d, *J* = 8.9 Hz), 7.17 (1H, t, *J* = 8.0 Hz), 6.94 (2H, d, *J* = 8.9 Hz), 6.89–6.85 (2H, m), 6.69 (1H, dd, *J* = 8.0, 1.8 Hz), 6.57 (1H, q, *J* = 6.6 Hz), 5.66 (1H, s), 5.33 (1H, s), 5.06 (1H, t, *J* = 1.4 Hz), 4.42 (1H, d, *J* = 9.8 Hz), 4.25–4.20 (3H, m), 3.97 (2H, s), 3.88 (3H, s), 3.34–3.20 (4H, m), 2.13 (3H, s), 1.58 (1H, d, *J* = 6.6 Hz), 1.57 (3H, s), 1.43 (3H, s), 1.35 (3H, s), 1.15 (6H, t, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.5, 163.5, 156.7, 147.2, 143.5, 142.6, 131.6, 129.2, 122.3, 116.0, 113.8, 112.5, 112.2, 111.1, 109.9, 90.2, 83.0, 71.9, 70.6, 68.1, 65.9, 65.2, 55.4, 41.7, 26.0, 25.7, 22.4, 21.8, 17.2, 13.9; HRMS-ESI (*m*/*z*): calcd for $C_{34}H_{47}N_6O_7$ $[M+H]^+$ 651.35007, found 651.35183.

4.1.1.2. (*S*)-1-((5*S*,6*R*,7*R*,8*S*,9*S*)-8-Azido-6-hydroxy-2,2,6-trimethyl-9-((3-(prop-1-en-2-yl)phenyl)amino)-7-(pyrrolidine-1-carboxamido)-1,3-dioxaspiro[4.4]nonan-7-yl)ethyl 4-methoxybenzoate (7b). Yield: 88% (66 mg from 67 mg); $[\alpha]_D^{20}$ +88.8 (*c* 1.00, $CHCl_3$); IR (neat): ν_{max} 3388, 2979, 2107, 1709, 1649, 1605,

Table 1
Antibacterial activities (minimum inhibitory concentration) for compounds **1–4**, **11a–d** and **19a–d**

Compound	*E. coli* (mg/L)	*S. aureus* (mg/L)	*K. pneumoniae* (mg/L)	*A. baumanii* (mg/L)	*P. aeruginosa* (mg/L)	*E. faecalis* (mg/L)
1	16	0.12	32	16	128	128
2	4	2	8	128	128	64
2[a]	8	8	16	128	>128	>128
3	>128	>128	>128	>128	>128	>128
4	>128	>128	>128	>128	>128	>128
4[a]	>128	>128	>128	>128	>128	>128
11a	>128	4	>128	>128	>128	128
11b	64	8	128	>128	>128	128
11b[a]	64	8	128	>128	>128	128
11c	>128	>128	>128	>128	>128	>128
11d	>128	>128	>128	>128	>128	>128
19a	32	64	64	>128	>128	>128
19b	8	4	32	64	>128	128
19c	64	16	>128	128	>128	>128
19d	16	2	128	64	>128	64
19d[a]	32	2	128	64	>128	128

[a] Compounds tested after 24 h storage at 0 °C.

Table 2
Cytotoxicity values for compounds **1–4**, **11a–d** and **19a–d**

Compound	HCT116 (colorectal) IC_{50} (μM)	PC3 (prostate) IC_{50} (μM)	WI-38 (lung) IC_{50} (μM)	MDA-231 (breast) IC_{50} (μM)
1	0.07	0.24	>1	0.5
2	0.07	0.31	>1	0.26
3	>1	>1	>1	>1
4	>1	>1	>1	>1
11a	0.23	0.40	>1	0.44
11b	0.09	0.15	>1	0.12
11c	>1	>1	>1	>1
11d	>1	>1	>1	>1
19a	0.81	>1	>1	>1
19b	0.19	>1 (35%)	>1 (34%)	>1
19c	0.39	>1	>1	>1
19d	0.10	0.75	>1 (42%)	0.38

Table 3
Typical antimalarial activity for compounds **1–4**, **11a–d** and **19a–d**[21]

Compound	D6 IC_{50} (nM)	Dd2 IC_{50} (nM)	7G8 IC_{50} (nM)
1	<2.5	<2.5	2.5
2	<2.5	<2.5	2.5
3	>2500	>2500	>2500
4	>2500	>2500	>2500
11a	29	40	42
11b	9	9	10
11c	>2500	2003	1596
11d	>2500	>2500	>2500
19a	14.6	13.9	18.5
19b	6.5	7.4	<2.5
19c	13.7	11.5	19.8
19d	6.7	3.5	<2.5

1511, 1382, 1257, 1168, 849, 757 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.99 (2H, d, J = 8.9 Hz), 7.14 (1H, t, J = 7.9 Hz), 6.95 (2H, d, J = 8.9 Hz), 6.87 (1H, d, J = 14.1 Hz), 6.86 (1H, d, J = 1.9 Hz), 6.69 (1H, dd, J = 7.9, 1.9 Hz), 6.47 (1H, q, J = 6.6 Hz), 5.56 (1H, s), 5.33 (1H, s), 5.06 (1H, s), 4.42 (1H, d, J = 9.8 Hz), 4.29–4.19 (3H, m), 4.01–3.93 (2H, m), 3.88 (3H, s), 3.41–3.21 (4H, m), 2.13 (3H, s), 1.91 (1H, br s), 1.93–1.87 (4H, m), 1.43 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.6, 163.5, 156.4, 147.2, 143.6, 142.6, 131.6, 129.2, 122.3, 116.0, 113.8, 112.5, 112.2, 111.1, 109.8, 90.2, 82.8, 71.9, 70.6, 68.3, 65.9, 65.2, 55.4, 45.7, 26.0, 25.7, 25.6, 22.4, 21.8, 17.2; HRMS-ESI (m/z): calcd for $C_{34}H_{45}N_6O_7$ $[M+H]^+$ 649.33442, found 649.33597.

4.1.1.3. (*S*)-1-((5*S*,6*R*,7*R*,8*S*,9*S*)-8-Azido-6-hydroxy-2,2,6-trimethyl-7-(piperidine-1-carboxamido)-9-((3-(prop-1-en-2-yl)phenyl)amino)-1,3-dioxaspiro[4.4]nonan-7-yl)ethyl 4-methoxybenzoate (7c). Yield: 89% (72 mg from 70 mg); $[\alpha]_D^{20}$ +85.7 (c 1.00, $CHCl_3$); IR (neat): ν_{max} 3406, 2937, 2108, 1708, 1643, 1605, 1581, 1511, 1382, 1326, 1256, 1168, 1101, 1031, 850, 769 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.99 (2H, d, J = 8.9 Hz), 7.17 (1H, t, J = 7.9 Hz), 6.95 (2H, d, J = 8.9 Hz), 6.87 (1H, d, J = 7.7 Hz), 6.86 (1H, d, J = 2.0 Hz), 6.69 (1H, dd, J = 7.8, 1.9 Hz), 6.51 (1H, q, J = 6.6 Hz), 5.80 (1H, s), 5.33 (1H, s), 5.06 (1H, t, J = 1.4 Hz), 4.41 (1H, d, J = 9.8 Hz), 4.26–4.20 (3H, m), 3.99–3.97 (2H, m), 3.88 (3H, s), 3.42–3.38 (2H, m), 3.33–3.28 (2H, m), 2.13 (3H, s), 1.62–1.51 (12H, m), 1.43 (3H, s), 1.28 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.6, 163.6, 157.0, 147.1, 143.5, 142.6, 131.6, 129.2, 122.3, 116.0, 114.0, 113.8, 112.5, 112.2, 111.1, 109.8, 90.2, 82.9, 71.9, 70.7, 68.1, 66.0, 65.2, 60.4, 55.4, 45.5, 25.9, 25.7, 25.5, 24.5, 22.3, 21.8, 17.2; HRMS-ESI (m/z): calcd for $C_{35}H_{47}N_6O_7$ $[M+H]^+$ 663.35007, found 663.3517.

4.1.1.4. (*S*)-1-((5*S*,6*R*,7*R*,8*S*,9*S*)-8-Azido-6-hydroxy-2,2,6-trimethyl-7-(morpholine-4-carboxamido)-9-((3-(prop-1-en-2-yl)phenyl)amino)-1,3-dioxaspiro[4.4]nonan-7-yl)ethyl 4-methoxybenzoate (7d). Yield: 83% (59 mg from 62 mg); $[\alpha]_D^{20}$ +81.9 (c 1.00, $CHCl_3$); IR (neat): ν_{max} 3406, 2984, 2109, 1708, 1605, 1581, 1511, 1382, 1257, 1168, 1116, 1030, 849, 768 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.00 (2H, d, J = 8.9 Hz), 7.15 (1H, t, J = 7.8 Hz), 6.95 (2H, d, J = 8.9 Hz), 6.88 (1H, d, J = 7.8 Hz), 6.84 (1H, d, J = 1.9 Hz), 6.69 (1H, dd, J = 7.9, 1.9 Hz), 6.44 (1H, q, J = 6.6 Hz), 5.77 (1H, s), 5.33 (1H, s), 5.06 (1H, t, J = 1.4 Hz), 4.40 (1H, d, J = 9.9 Hz), 4.28 (1H, d, J = 9.2 Hz), 4.22 (1H, d, J = 9.9 Hz), 4.11 (1H, s), 4.00–3.94 (2H, m), 3.88 (3H, s), 3.71–3.60 (4H, m), 3.42–3.28 (4H, m), 2.13 (3H, s), 1.57 (3H, d, J = 6.6 Hz), 1.55 (3H, s), 1.42 (3H, s), 1.35 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.7, 163.7, 157.2, 147.0, 143.5, 142.6, 131.6, 129.2, 122.1, 116.1, 113.9, 112.5, 112.3, 111.1, 109.9, 90.2, 82.8, 71.6, 70.6, 68.2, 66.4, 66.1, 65.2, 55.4, 44.3, 25.9, 25.7, 22.2, 21.8, 17.2; HRMS-ESI (m/z): calcd for $C_{34}H_{45}N_6O_8$ $[M+H]^+$ 665.32934, found 665.33075.

4.1.2. General procedure for synthesis of 8a–8d

To a stirred solution of **7a–7d** (49 mg, 0.075 mmol) in dry CH_2Cl_2 (3 mL), DIBAL-H (0.26 mL, 1.5 M in toluene, 0.385 mmol) was added slowly at −78 °C under argon and the mixture was stirred for 1.5 h. The reaction mixture was then quenched by slow addition of methanol and warmed to room temperature. A saturated aqueous potassium sodium tartrate solution was added, the reaction mixture stirred for 1 h, then extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Flash column chromatography using [20–25]% ethyl acetate in hexanes gave compounds **8a–8d** as colorless liquids.

4.1.2.1. 3-((5*S*,6*R*,7*R*,8*S*,9*S*)-8-Azido-6-hydroxy-7-((*S*)-1-hydroxyethyl)-2,2,6-trimethyl-9-((3-(prop-1-en-2-yl)phenyl)amino)-1,3-dioxaspiro[4.4]nonan-7-yl)-1,1-diethylurea (8a). Yield: 87% (34 mg from 49 mg); $[\alpha]_D^{20}$ +19.3 (c 1.00, $CHCl_3$); IR (neat): ν_{max} 3424, 2983, 2935, 2104, 1635, 1602, 1580, 1528, 1489, 1455, 1407, 1374, 1287, 1259, 1216, 1118, 1057, 890, 855, 784 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.67 (1H, d, J = 11.2 Hz), 7.23 (1H, t, J = 7.9 Hz), 6.92 (1H, d, J = 7.7 Hz), 6.73 (1H, s), 6.57 (1H, dd, J = 8.0, 2.0 Hz), 5.39 (1H, s), 5.38 (1H, s), 5.29 (1H, d, J = 11.2 Hz), 5.10 (1H, s), 4.85 (1H, s), 4.30 (1H, d, J = 9.9 Hz), 4.26 (1H, d, J = 9.9 Hz), 3.98–3.88 (2H, m), 3.69 (1H, s), 3.35 (2H, q, J = 7.1 Hz), 2.16 (3H, s), 1.47 (3H, s), 1.44 (3H, s), 1.43 (3H, s), 1.24 (6H, t, J = 7.1 Hz), 1.20 (3H, d, J = 6.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.3, 145.8, 143.4, 143.0, 129.6, 115.8, 112.6, 112.1, 110.6, 110.5, 91.4, 88.7, 73.9, 73.5, 72.8, 66.3, 65.5, 42.3, 26.3, 25.9, 21.9, 21.0, 17.8, 13.8; HRMS-ESI (m/z): calcd for $C_{26}H_{41}FN_6O_5$ $[M+H]^+$ 517.31329, found 517.31392.

4.1.2.2. *N*-((5*S*,6*R*,7*R*,8*S*,9*S*)-8-Azido-6-hydroxy-7-((*S*)-1-hydroxyethyl)-2,2,6-trimethyl-9-((3-(prop-1-en-2-yl)phenyl)amino)-1,3-dioxaspiro[4.4]nonan-7-yl)pyrrolidine-1-carboxamide (8b). Yield: 85% (52 mg from 65 mg); $[\alpha]_D^{20}$ +30.0 (c 1.00, $CHCl_3$); IR (neat): ν_{max} 3408, 2984, 2104, 1634, 1602, 1581, 1531, 1487, 1396, 1325, 1258, 1212, 1146, 1060, 856, 784, 730 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.54 (1H, d, J = 11.4 Hz), 7.23 (1H, t, J = 7.9 Hz), 6.92 (1H, d, J = 7.9 Hz), 6.73 (1H, s), 6.57 (1H, dd, J = 8.0, 2.0 Hz), 5.38 (1H, s), 5.24 (1H, s), 5.23 (1H, d, J = 11.0 Hz), 5.11 (1H, t, J = 1.3 Hz), 4.67 (1H, s), 4.27 (2H, s), 4.01–3.91 (2H, m), 3.69 (1H, s), 3.49–3.37 (4H, m), 2.16 (3H, s), 2.02–1.98 (4H, m), 1.46 (6H, s), 1.43 (3H, s), 1.24 (3H, d, J = 6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.8, 145.8, 143.4, 142.9, 129.6, 115.8, 112.6, 112.1, 110.6, 110.5, 91.4, 88.4, 73.8, 73.1, 72.9, 66.6, 65.4,

45.9, 26.3, 25.6, 21.9, 20.8, 17.8; HRMS-ESI (*m/z*): calcd for $C_{26}H_{39}FN_6O_5$ $[M+H]^+$ 515.29764, found 515.29897.

4.1.2.3. *N*-((5*S*,6*R*,7*R*,8*S*,9*S*)-8-Azido-6-hydroxy-7-((*S*)-1-hydroxyethyl)-2,2,6-trimethyl-9-((3-(prop-1-en-2-yl)phenyl)amino)-1,3-dioxaspiro[4.4]nonan-7-yl)piperidine-1-carboxamide (8c). Yield: 86% (48 mg from 70 mg); $[\alpha]_D^{20}$ +29.6 (***c*** 1.00, $CHCl_3$); IR (neat): ν_{max} 3374, 2986, 2935, 2855, 2104, 1631, 1602, 1579, 1528, 1374, 1258, 1209, 1120, 1059, 890, 855, 784, 730 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.52 (1H, d, ***J*** = 11.3 Hz), 7.23 (1H, t, ***J*** = 7.9 Hz), 6.92 (1H, d, ***J*** = 7.6 Hz), 6.73 (1H, s), 6.57 (1H, dd, ***J*** = 8.1, 2.0 Hz), 5.51 (1H, s), 5.38 (1H, s), 5.25 (1H, d, ***J*** = 11.3 Hz), 5.10 (1H, s), 4.67 (1H, s), 4.28 (2H, s), 4.39–3.91 (2H, m), 3.69 (1H, s), 3.51–3.47 (2H, m), 3.40–3.35 (2H, m), 2.16 (3H, s), 1.70–1.60 (6H, m), 1.59 (3H, s), 1.46 (3H, s), 1.45 (3H, s), 1.43 (3H, s), 1.21(3H, d, ***J*** = 6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.4, 145.8, 143.4, 143.0, 129.6, 115.9, 112.6, 112.1, 110.6, 91.3, 88.5, 74.1, 73.2, 72.6, 66.7, 65.5, 45.7, 29.7, 26.4, 25.9, 25.6, 24.4, 21.9, 20.8, 17.8; HRMS-ESI (***m/z***): calcd for $C_{27}H_{41}N_6O_5$ $[M+H]^+$ 529.31329, found 529.31370.

4.1.2.4. *N*-((5*S*,6*R*,7*R*,8*S*,9*S*)-8-Azido-6-hydroxy-7-((*S*)-1-hydroxyethyl)-2,2,6-trimethyl-9-((3-(prop-1-en-2-yl)phenyl)amino)-1,3-dioxaspiro[4.4]nonan-7-yl)morpholine-4-carboxamide (8d). Yield: 85% (39 mg from 58 mg); $[\alpha]_D^{20}$ +39.7 (***c*** 1.00, $CHCl_3$); IR (neat): ν_{max} 3377, 2986, 2106, 1640, 1602, 1580, 1538, 1373, 1263, 1210, 1119, 1059, 855, 730 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.25–7.21 (2H, m), 6.92 (1H, d, ***J*** = 7.8 Hz), 6.73 (1H, s), 6.57 (1H, dd, ***J*** = 8.0, 1.9 Hz), 5.51 (1H, s), 5.38 (1H, s), 5.21 (1H, d, ***J*** = 11.4 Hz), 5.10 (1H, s), 4.57 (1H, s), 4.28 (2H, ABq, ***J*** = 9.9 Hz), 4.02–3.92 (2H, m), 3.77–3.74 (4H, m), 3.70 (1H, s), 3.54–3.50 (2H, m), 3.41–3.37 (2H, m), 2.16 (3H, s), 1.46 (3H, s), 1.45 (3H, s), 1.42 (3H, s), 1.21 (3H, d, ***J*** = 6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.2, 145.4, 143.0, 142.7, 129.3, 115.6, 112.3, 111.8, 110.3, 110.2, 91.0, 88.1, 73.7, 72.8, 72.2, 66.5, 66.2, 65.1, 44.1, 26.0, 25.2, 21.5, 20.4, 17.5; HRMS-ESI (***m/z***): calcd for $C_{26}H_{39}FN_6O_6$ $[M+H]^+$ 531.29256, found 531.29410.

4.1.3. General procedure for synthesis of 9a–9d

To a stirred solution of **8a–8d** (34 mg, 0.066 mmol) in THF (1 mL), acetone (1 mL) and H_2O (0.2 mL) were added NMO (54 mg, 0.46 mmol) and a catalytic amount of OsO_4 (0.1 mL, 4% wt in H_2O) at 0 °C. After stirring for 2 h at rt, a saturated aqueous sodium bisulfite solution was added, the reaction mixture stirred for 30 min, then extracted with ethyl acetate. The combined organic layers were washed with water, brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Flash column chromatography using 80% ethyl acetate in hexanes gave the tetrol as clear oil, which was directly used for the next reaction without characterisation. To the stirred solution of above tetrol in THF (1 mL) and H_2O (1 mL) was added $NaIO_4$ (28 mg, 0.13 mmol) at rt and stirred for 3 h. The reaction mixture was extracted with ethyl acetate and the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Flash column chromatography using [40–50]% ethyl acetate in hexanes gave compounds **9a–9d** as colorless liquids.

4.1.3.1. 3-((5*S*,6*R*,7*R*,8*S*,9*S*)-9-((3-Acetylphenyl)amino)-8-azido-6-hydroxy-7-((*S*)-1-hydroxyethyl)-2,2,6-trimethyl-1,3-dioxaspiro[4.4]nonan-7-yl)-1,1-diethylurea (9a). Yield: 85% in two steps (29 mg from 34 mg); $[\alpha]_D^{20}$ +30.5 (*c* 1.00, $CHCl_3$); IR (neat): ν_{max} 3373, 2985, 2935, 2105, 1682, 1634, 1603, 1531, 1436, 1374, 1358, 1288, 1119, 1057, 855, 783, 688 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.66 (1H, d, *J* = 11.2 Hz), 7.39–7.31 (2H, m), 7.23 (1H, s), 6.83 (1H, d, *J* = 7.6 Hz), 5.42 (1H, d, *J* = 11.1 Hz), 5.37 (1H, s), 4.82 (1H, s), 4.25 (2H, ABq, *J* = 11.0 Hz), 3.96 (1H, d, *J* = 11.1 Hz), 3.90 (1H, m), 3.64 (1H, s), 3.34 (4H, q, *J* = 7.2 Hz), 2.61 (3H, s), 1.47 (3H, s), 1.43 (6H, s), 1.24 (6H, t, *J* = 7.2 Hz), 1.19 (3H, d, *J* = 6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.2, 157.2, 146.2, 138.6, 129.9, 118.5, 117.9, 111.8, 110.8, 91.3, 88.6, 74.2, 73.4, 72.8, 66.4, 65.5, 42.3, 26.7, 26.3, 26.0, 20.9, 17.7, 13.8; HRMS-ESI (*m/z*): calcd for $C_{25}H_{39}N_6O_6$ $[M+H]^+$ 519.29256, found 519.29356.

4.1.3.2. *N*-((5*S*,6*R*,7*R*,8*S*,9*S*)-9-((3-Acetylphenyl)amino)-8-azido-6-hydroxy-7-((*S*)-1-hydroxyethyl)-2,2,6-trimethyl-1,3-dioxaspiro[4.4]nonan-7-yl)pyrrolidine-1-carboxamide (9b). Yield: 78% in two steps (39 mg from 50 mg); $[\alpha]_D^{20}$ +37.4 (***c*** 1.00, $CHCl_3$); IR (neat): ν_{max} 3184, 2984, 2104, 1681, 1637, 1602, 1534, 1487, 1398, 1357, 1324, 1263, 1146, 1060, 914, 855, 781, 731, 688 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.52 (1H, d, ***J*** = 11.4 Hz), 7.37–7.32 (2H, m), 7.22 (1H, s), 6.83 (1H, m), 5.37 (1H, d, ***J*** = 11.1 Hz), 5.22 (1H, s), 4.66 (1H, s), 4.24 (2H, ABq, ***J*** = 9.9 Hz), 3.95 (1H, m), 3.93 (1H, d, ***J*** = 11.1 Hz), 3.63 (1H, s), 3.50–3.38 (4H, m), 2.60 (3H, s), 2.07–1.97 (4H, m), 1.46 (3H, s), 1.45 (3H, s), 1.45 (3H, s), 1.23 (3H, d, ***J*** = 6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.2, 156.7, 146.2, 138.6, 129.9, 118.5, 117.9, 111.9, 110.7, 91.3, 88.4, 74.0, 73.0, 72.9, 66.7, 65.4, 45.9, 26.7, 26.3, 25.7, 25.6, 20.7, 17.8; HRMS-ESI (***m/z***): calcd for $C_{25}H_{37}N_6O_6$ $[M+H]^+$ 517.27691, found 517.27822.

4.1.3.3. *N*-((5*S*,6*R*,7*R*,8*S*,9*S*)-9-((3-Acetylphenyl)amino)-8-azido-6-hydroxy-7-((*S*)-1-hydroxyethyl)-2,2,6-trimethyl-1,3-dioxaspiro[4.4]nonan-7-yl)piperidine-1-carboxamide (9c). Yield: 74% in two steps (34 mg from 46 mg); $[\alpha]_D^{20}$ +38.8 (***c*** 1.00, $CHCl_3$); IR (neat): ν_{max} 3371, 2988, 2937, 2857, 2106, 1682, 1603, 1532, 1487, 1438, 1373, 1357, 1323, 1270, 1233, 1209, 1125, 1059, 1023, 913, 854, 781, 732, 688 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.49 (1H, d, ***J*** = 11.3 Hz), 7.38–7.35 (2H, m), 7.31 (1H, s), 6.83 (1H, m), 5.49 (1H, s), 5.65 (1H, d, ***J*** = 11.2 Hz), 4.65 (1H, s), 4.25 (2H, ABq, ***J*** = 9.9 Hz), 3.98–3.90 (2H, m), 3.64 (1H, s), 3.52–3.46 (2H, m), 3.40–3.34 (2H, m), 2.60 (3H, s), 2.19 (1H, s), 1.68–1.60 (6H, m), 1.47 (3H, s), 1.45 (3H, s), 1.43 (3H, s), 1.19 (3H, d, ***J*** = 6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.2, 157.4, 146.2, 138.6, 129.9, 118.6, 117.9, 111.8, 110.7, 91.3, 88.5, 74.3, 73.2, 72.6, 66.7, 65.4, 45.7, 26.7, 26.3, 25.7, 24.4, 20.7, 17.8; HRMS-ESI (***m/z***): calcd for $C_{26}H_{39}N_6O_6$ $[M+H]^+$ 531.29256, found 531.29356.

4.1.3.4. *N*-((5*S*,6*R*,7*R*,8*S*,9*S*)-9-((3-Acetylphenyl)amino)-8-azido-6-hydroxy-7-((*S*)-1-hydroxyethyl)-2,2,6-trimethyl-1,3-dioxaspiro[4.4]nonan-7-yl)morpholine-4-carboxamide (9d). Yield: 74% in two steps (29 mg from 39 mg); $[\alpha]_D^{20}$ +43.6 (***c*** 1.00, $CHCl_3$); IR (neat): ν_{max} 3378, 2987, 2935, 2858, 2107, 1682, 1637, 1602, 1537, 1437, 1374, 1304, 1265, 1119, 1060, 1021, 914, 854, 781, 732 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.36–7.34 (2H, m), 7.28–7.19 (2H, m), 6.83 (1H, m), 5.49 (1H, s), 5.34 (1H, d, ***J*** = 11.2 Hz), 4.56 (1H, s), 4.25 (1H, ABq, ***J*** = 10.0 Hz), 3.96 (1H, m), 3.93 (1H, d, ***J*** = 11.2 Hz), 3.80–3.70 (4H, m), 3.65 (1H, s), 3.55–3.49 (2H, m), 3.41–3.36 (2H, m), 2.60 (3H, s), 2.19 (3H, s), 1.46 (3H, s), 1.44 (3H, s), 1.42 (3H, s), 1.20 (3H, d, ***J*** = 6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.2, 157.5, 146.1, 138.6, 129.9, 118.7, 117.9, 111.8, 110.7, 91.3, 88.4, 74.4, 73.1, 72.6, 66.9, 66.7, 65.4, 44.5, 26.7, 26.3, 25.6, 20.6, 17.8; HRMS-ESI (***m/z***): calcd for $C_{25}H_{37}N_6O_7$ $[M+H]^+$ 533.27182, found 533.27306.

4.1.4. General procedure for synthesis of 10a–10d

To the stirred solution of **9a–9d** (29 mg, 0.056 mmol) in acetonitrile (0.2 mL) and H_2O (0.2 mL), TFA (1 mL) was added at 0 °C and stirred for 45 min at rt, then the reaction mixture was cooled to 0 °C and quenched very slowly with a saturated aqueous $NaHCO_3$ solution and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Flash column chromatography using [83–95]% ethyl acetate in hexanes gave compounds **10a–10d** as colorless liquids.

4.1.4.1. 3-((1*R*,2*R*,3*S*,4*S*,5*S*)-4-((3-Acetylphenyl)amino)-5-azido-2,3-dihydroxy-1-((*S*)-1-hydroxyethyl)-3-(hydroxymethyl)-2-methylcyclopentyl)-1,1-diethylurea (10a). Yield: 87% (23 mg from 29 mg); $[\alpha]_D^{20}$ +31.6 (***c*** 1.00, $CHCl_3$); IR (neat): ν_{max} 3418, 2977, 2934, 2103, 1681, 1633, 1603, 1531, 1439, 1358, 1302, 1113, 1056, 917, 783, 757, 688 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.64 (1H, d, ***J*** = 11.2 Hz), 7.38–7.30 (2H, m), 7.25 (1H, s), 6.87 (1H, d, ***J*** = 7.2 Hz), 5.47 (1H, s), 5.38 (1H, d, ***J*** = 11.2 Hz), 4.70 (1H, s), 4.17 (1H, d, ***J*** = 11.6 Hz), 3.97 (1H, m), 3.91 (1H, d, ***J*** = 11.2 Hz), 3.66 (1H, d, ***J*** = 11.6 Hz), 3.63 (1H, s), 3.41–3.25 (4H, m), 3.22 (1H, s), 2.57 (3H, s), 2.23 (1H, br s), 1.44 (3H, s), 1.25–1.20 (9H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.8, 157.9, 146.6, 138.9, 130.3, 119.3, 119.0, 112.7, 89.0, 84.8, 74.7, 74.2, 73.7, 67.0, 61.6, 42.7, 27.1, 21.1, 18.2, 14.2; HRMS-ESI (***m/z***): calcd for $C_{22}H_{35}N_6O_6$ $[M+H]^+$ 479.26126, found 479.26241.

4.1.4.2. *N*-((1*R*,2*R*,3*S*,4*S*,5*S*)-4-((3-Acetylphenyl)amino)-5-azido-2,3-dihydroxy-1-((*S*)-1-hydroxyethyl)-3-(hydroxymethyl)-2-methylcyclopentyl)pyrrolidine-1-carboxamide (10b). Yield: 87% (26 mg from 32 mg); $[\alpha]_D^{20}$ +22.2 (***c*** 1.00, $CHCl_3$); IR (neat): ν_{max} 3396 (br), 2978, 2937, 2937, 2875, 2103, 1681, 1633, 1603, 1531, 1487, 1402, 1326, 1234, 1136, 755, 689 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.56 (1H, d, ***J*** = 11.2 Hz), 7.34–7.23 (2H, m), 6.86 (1H, d, ***J*** = 7.2 Hz), 5.35 (1H, s), 5.34 (1H, d, ***J*** = 11.6 Hz), 4.59 (1H, s), 4.15 (1H, d, ***J*** = 11.2 Hz), 3.98 (1H, m), 3.94 (1H, d, ***J*** = 11.2 Hz), 3.66 (1H, d, ***J*** = 11.6 Hz), 3.62 (1H, s), 3.42 (4H, br s), 3.33 (1H, s), 1.99 (4H, br s), 1.45 (3H, s), 1.24 (3H, d, ***J*** = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.4, 157.0, 146.2, 138.4, 129.9, 118.8, 118.6, 112.3, 88.4, 84.4, 73.9, 73.0, 66.6, 61.2, 46.0, 26.6, 25.6, 20.6, 17.8; HRMS-ESI (***m/z***): calcd for $C_{22}H_{33}N_6O_6$ $[M+H]^+$ 477.24561, found 477.24459.

4.1.4.3. *N*-((1*R*,2*R*,3*S*,4*S*,5*S*)-4-((3-Acetylphenyl)amino)-5-azido-2,3-dihydroxy-1-((*S*)-1-hydroxyethyl)-3-(hydroxymethyl)-2-methylcyclopentyl)piperidine-1-carboxamide (10c). Yield: 88% (21 mg from 26 mg); $[\alpha]_D^{20}$ +26.8 (***c*** 1.00, $CHCl_3$); IR (neat): ν_{max} 3381, 2937, 2856, 2103, 1681, 1627, 1603, 1531, 1487, 1442, 1325, 1270, 1114, 1060, 912, 732 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.55 (1H, d, ***J*** = 11.2 Hz), 7.37–7.31 (2H, m), 7.26 (1H, s), 6.87 (1H, d, ***J*** = 7.2 Hz), 5.60 (1H, s), 5.35 (1H, d, ***J*** = 11.2 Hz), 4.62 (1H, s), 4.16 (1H, d, ***J*** = 11.6 Hz), 3.99 (1H, m), 3.91 (1H, d, ***J*** = 11.2 Hz), 3.67 (1H, d, ***J*** = 11.6 Hz), 3.63 (1H, s), 3.49–3.36 (4H, m), 3.20 (1H, s), 2.58 (3H, s), 1.66–1.60 (6H, m), 1.46 (3H, s), 1.22 (3H, d, ***J*** = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.3, 157.6, 146.2, 138.5, 129.9, 118.9, 118.5, 112.4, 88.4, 84.4, 74.3, 73.7, 73.2, 66.7, 61.2, 45.9, 26.7, 25.8, 24.4, 20.6, 17.8; HRMS-ESI (***m/z***): calcd for $C_{23}H_{35}N_6O_6$ $[M+H]^+$ 491.26126, found 491.26460.

4.1.4.4. *N*-((1*R*,2*R*,3*S*,4*S*,5*S*)-4-((3-Acetylphenyl)amino)-5-azido-2,3-dihydroxy-1-((*S*)-1-hydroxyethyl)-3-(hydroxymethyl)-2-methylcyclopentyl)morpholine-4-carboxamide (10d). Yield: 83% (22 mg from 28 mg); $[\alpha]_D^{20}$ +35.6 (***c*** 1.00, $CHCl_3$); IR (neat): ν_{max} 3378, 2977, 2921, 2859, 2104, 1675, 1627, 1603, 1537, 1434, 1395, 1359, 1333, 1304, 1260, 1118, 1077, 1003, 916, 786, 730, 686 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.38–7.32 (2H, m), 7.26–7.23 (2H, m), 6.87 (1H, d, ***J*** = 7.2 Hz), 5.61 (1H, s), 5.34 (1H, d, ***J*** = 11.6 Hz), 4.52 (1H, s), 4.17 (1H, d, ***J*** = 11.6 Hz), 4.01 (1H, m), 3.92 (1H, d, ***J*** = 11.6 Hz), 3.76–3.73 (4H, m), 3.65 (1H, d, ***J*** = 11.6 Hz), 3.63 (1H, s), 3.51–3.46 (2H, m), 3.43–3.38 (2H, m), 3.23 (1H, s), 2.58 (3H, s), 2.12 (1H, s), 1.45 (3H, s), 1.22 (3H, d, ***J*** = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.3, 157.8, 146.1, 138.5, 130.0, 119.1, 118.6, 112.3, 88.4, 84.5, 74.3, 73.7, 73.1, 66.8, 66.5, 61.1, 44.6, 26.7, 20.5, 17.8; HRMS-ESI (***m/z***): calcd for $C_{22}H_{33}N_6O_7$ $[M+H]^+$ 493.24052, found 493.24255.

4.1.5. General procedure for synthesis of 11a–11d

To a stirred solution of **10a–10d** (10 mg, 0.021 mmol) in EtOH/H_2O (3:1, 2 mL) were added ammonium chloride (33 mg, 0.62 mmol), zinc powder (20 mg, 0.31 mmol) at rt and stirred for 6 h. The reaction mixture was quenched with aqueous ammonia (2 mL) and extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography using [5–8]% methanol in chloroform to give compounds **11a–11d**.

4.1.5.1. 3-((1*R*,2*R*,3*S*,4*S*,5*S*)-4-((3-Acetylphenyl)amino)-5-amino-2,3-dihydroxy-1-((*S*)-1-hydroxyethyl)-3-(hydroxymethyl)-2-methylcyclopentyl)-1,1-diethylurea (11a). Pale yellow oil, yield: 88% (8.4 mg from 10 mg); $[\alpha]_D^{20}$ +41.2 (***c*** 0.33, $CHCl_3$); IR (neat): ν_{max} 3381, 2976, 2931, 1679, 1603, 1515, 1359, 1298, 1081, 1056, 913, 784, 732 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.05 (1H, d, ***J*** = 10.0 Hz), 7.28–7.21 (2H, m), 7.05 (1H, s), 6.84 (1H, m), 5.68 (1H, s), 5.50 (1H, d, ***J*** = 10.4 Hz), 4.13 (1H, d, ***J*** = 11.6 Hz), 3.92 (1H, m), 3.76 (1H, d, ***J*** = 11.6 Hz), 3.42–3.29 (4H, m), 2.96 (1H, s), 2.57 (3H, s), 2.10–1.82 (4H, m), 1.48 (3H, s), 1.37–1.13 (6H, m), 1.05 (3H, d, ***J*** = 6.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.6, 158.2, 146.9, 138.3, 129.6, 118.9, 118.4, 110.9, 88.7, 84.7, 74.2, 71.5, 68.2, 62.6, 61.8, 42.2, 26.7, 21.5, 18.2, 13.8; HRMS-ESI (***m/z***): calcd for $C_{22}H_{37}N_4O_6$ $[M+H]^+$ 453.27076, found 453.26901.

4.1.5.2. *N*-((1*R*,2*R*,3*S*,4*S*,5*S*)-4-((3-Acetylphenyl)amino)-5-amino-2,3-dihydroxy-1-((*S*)-1-hydroxyethyl)-3-(hydroxymethyl)-2-methylcyclopentyl)pyrrolidine-1-carboxamide (11b). Pale yellow solid, yield: 86% (9.8 mg from 12 mg); $[\alpha]_D^{20}$ +29.5 (***c*** 1.00, $CHCl_3$); IR (neat): ν_{max} 3381, 2977, 2918, 2875, 1679, 1603, 1519, 1486, 1398, 1357, 1337, 1235, 1136, 1072, 911, 781, 731, 689 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.89 (1H, d, ***J*** = 10.8 Hz), 7.28–7.24 (2H, m), 7.19 (1H, s), 6.84 (1H, d, ***J*** = 3.2 Hz), 6.74 (1H, s), 5.49 (1H, s) 5.46 (1H, d, ***J*** = 10.8 Hz), 4.13 (1H, d, ***J*** = 11.6 Hz), 3.94 (1H, m), 3.77–3.72 (2H, m), 3.43 (4H, br s), 2.96 (1H, s), 2.55 (3H, s), 1.97 (4H, br s), 1.49 (3H, s), 1.08 (3H, d, ***J*** = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.7, 157.8, 146.9, 138.2, 129.6, 119.0, 118.4, 110.8, 88.6, 84.8, 73.9, 71.7, 68.0, 62.6, 61.8, 46.0, 29.7, 26.7, 25.6, 21.5, 18.2; HRMS-ESI (***m/z***): calcd for $C_{22}H_{35}N_4O_6$ $[M+H]^+$ 451.25511, found 451.25380.

4.1.5.3. *N*-((1*R*,2*R*,3*S*,4*S*,5*S*)-4-((3-Acetylphenyl)amino)-5-amino-2,3-dihydroxy-1-((*S*)-1-hydroxyethyl)-3-(hydroxymethyl)-2-methylcyclopentyl)piperidine-1-carboxamide (11c). Pale yellow solid, yield: 88% (7.5 mg from 9 mg); $[\alpha]_D^{20}$ +24.2 (***c*** 0.45, $CHCl_3$); IR (neat): ν_{max} 3379, 2935, 2850, 1678, 1602, 1515, 1442, 1273, 1060, 910, 731, 688 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.93 (1H, d, ***J*** = 10.4 Hz), 7.28–7.20 (3H, m), 6.85 (1H, d, ***J*** = 6.8 Hz), 5.63 (1H, s), 5.47 (1H, d, ***J*** = 10.0 Hz), 4.11 (1H, d, ***J*** = 11.6 Hz), 3.94 (1H, m), 3.78–3.73 (2H, m), 3.49–3.39 (4H, m), 3.08 (1H, s), 2.58 (3H, s), 1.66–1.60 (6H, m), 1.49 (3H, s), 1.06 (3H, d, ***J*** = 6.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.6, 158.6, 146.9, 138.3, 129.7, 118.9, 118.4, 111.0, 88.6, 84.7, 74.1, 71.3, 68.3, 62.7, 61.8, 45.9, 26.7, 25.8, 24.5, 21.5, 18.2; HRMS-ESI (***m/z***): calcd for $C_{23}H_{37}N_4O_6$ $[M+H]^+$ 465.27076, found 465.27025.

4.1.5.4. *N*-((1*R*,2*R*,3*S*,4*S*,5*S*)-4-((3-Acetylphenyl)amino)-5-amino-2,3-dihydroxy-1-((*S*)-1-hydroxyethyl)-3-(hydroxymethyl)-2-methylcyclopentyl)morpholine-4-carboxamide (11d). Pale yellow solid, yield: 84% (8.8 mg from 11 mg); $[\alpha]_D^{20}$ +29.3 (***c*** 0.75, $CHCl_3$); IR (neat): ν_{max} 3381, 2917, 2850, 1678, 1603, 1515, 1440, 1359, 1335, 1303, 1269, 1118, 1072, 909, 732 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.65 (1H, d, ***J*** = 10.4 Hz), 7.35–7.28 (2H, m), 7.20 (1H, s), 6.84 (1H, d, ***J*** = 3.2 Hz), 5.55 (1H, s), 5.50 (1H, d, ***J*** = 10.4 Hz), 4.13 (1H, d, ***J*** = 11.6 Hz), 3.94 (1H, m), 3.78 (5H, br s), 3.53–3.40 (4H, m), 2.95 (1H, s), 2.57 (3H, s), 1.47 (3H, s), 1.05 (3H, d, ***J*** = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.7, 158.8, 146.8, 138.3, 129.7, 118.9, 118.5, 110.8, 88.6, 84.8, 74.0, 71.4, 68.4, 66.6, 62.7, 61.6, 44.7, 26.7,

21.3, 18.2; HRMS-ESI (***m/z***): calcd for $C_{22}H_{35}N_4O_7$ $[M+H]^+$ 467.25003, found 467.24941.

4.1.6. General procedure for synthesis of 13a–13d

To a stirred solution of **12** (130 mg, 0.217 mmol) in toluene (4 mL), the anilines (0.2 mL, 2.173 mmol) and $Yb(OTf)_3$ (67.5 mg, 0.108 mmol) were added at rt and heated at 80 °C and stirred for 9–26 h at the same temperature. The reaction mixture was cooled to rt, then quenched with water and extracted with ethyl acetate. The combined organic layers were washed with 0.5 N HCl, saturated aqueous $NaHCO_3$ solution, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography using 10% ethyl acetate in hexanes to afford compounds **13a–13d** as pale yellow viscous liquids. Further elution at 12% EtOAc in hexanes recovered the unreacted epoxide.

4.1.6.1. (4*S*,5*R*,6*R*,7*S*,8*S*,9*S*)-9-Azido-7-(((tert-butyldiphenylsilyl)oxy)methyl)-2-(4-methoxyphenyl)-4,6-dimethyl-8-(phenylamino)-3-oxa-1-azaspiro[4.4]non-1-ene-6,7-diol (13a). Yield: 74% (110 mg from 130 mg); $[\alpha]_D^{20}$ +6.56 (***c*** 1.00, $CHCl_3$); IR (neat): ν_{max} 3409, 2938, 3864, 2102, 1642, 1606, 1516, 1466, 1430, 1366, 1349, 1312, 1259, 1173, 1153, 1108, 1059, 1033, 842, 824, 746, 703, 616 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.87 (2H, d, ***J*** = 9.0 Hz), 7.64 (1H, d, ***J*** = 1.4 Hz), 7.62 (1H, d, ***J*** = 1.6 Hz), 7.49–7.37 (6H, m), 7.27–7.13 (4H, m), 6.91 (2H, d, ***J*** = 9.0 Hz), 6.75 (1H, tt, ***J*** = 1.0, 7.3 Hz), 6.69 (2H, dd, ***J*** = 1, 7.6 Hz), 5.58 (1H, s), 4.95 (1H, q, ***J*** = 6.6 Hz), 4.85 (1H, s), 4.38–4.30 (2H, m), 4.13 (1H, d, ***J*** = 11.1 Hz), 3.97–3.89 (1H, m), 3.83 (3H, s), 3.80 (1H, d, ***J*** = 11.1 Hz), 1.59 (3H, d, ***J*** = 6.6 Hz), 1.17 (3H, s), 1.08 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.0, 162.7, 147.0, 135.8, 135.5, 131.1, 131.0, 130.4, 130.2, 129.4, 127.8, 118.9, 117.7, 113.1, 84.5, 84.4, 80.1, 78.6, 71.0, 68.1, 66.4, 55.3, 26.9, 18.9, 17.3, 17.0; HRMS (ESIMS): calcd for $C_{39}H_{46}N_5O_5Si$ $[M+H]^+$ 692.3263, found 692.3268.

4.1.6.2. (4*S*,5*R*,6*R*,7*S*,8*S*,9*S*)-9-Azido-7-(((tert-butyldiphenylsilyl)oxy)methyl)-8-((3-fluorophenyl)amino)-2-(4-methoxyphenyl)-4,6-dimethyl-3-oxa-1-azaspiro[4.4]non-1-ene-6,7-diol (13b). Yield: 83% (98 mg from 110 mg); $[\alpha]_D^{20}$ +2.3 (***c*** 1.00, $CHCl_3$); IR (neat): ν_{max} 3392, 2933, 2107, 1704, 1606, 1512, 1259, 1168, 1104, 1073, 822, 770, 738, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.80 (2H, d, ***J*** = 8.9 Hz), 7.55 (2H, dd, ***J*** = 1.2, 7.9 Hz), 7.40 (2H, dd, ***J*** = 1.2, 7.9 Hz), 7.40–7.26 (4H, m), 7.21–7.17 (2H, m), 7.03–6.96 (1H, m), 6.83 (2H, d, ***J*** = 8.9 Hz), 6.39–6.26 (4H, m), 5.48 (1H, s), 4.88 (1H, q, ***J*** = 6.6 Hz), 4.71 (1H, s), 4.73 (1H, d, ***J*** = 9.7 Hz), 4.19 (1H, dd, ***J*** = 6.8, 9.7 Hz), 4.00 (1H, d, ***J*** = 11.1 Hz), 3.85 (1H,d, ***J*** = 6.8 Hz), 3.76 (3H, s), 3.72 (1H, d, ***J*** = 11.1 Hz), 1.51 (3H, d, ***J*** = 6.6 Hz), 1.11 (3H, s), 1.01 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.3, 164.1, 162.9, 162.7, 148.9, 148.8, 135.8, 135.5, 131.1, 130.9, 130.5, 130.4, 130.4, 130.3, 130.1, 129.7, 127.9, 127.8, 127.7, 118.8, 113.7, 108.7, 104.3, 104.1, 100.0, 99.7, 84.5, 84.4, 84.3, 80.1, 78.6, 70.8, 68.2, 66.3, 55.3, 26.9, 18.9, 17.4, 17.0; HRMS (ESIMS): calcd for $C_{39}H_{45}FN_5O_5Si$ $[M+H]^+$ 710.31685, found 710.31712.

4.1.6.3. (4*S*,5*R*,6*R*,7*S*,8*S*,9*S*)-9-Azido-7-(((tert-butyldiphenylsilyl)oxy)methyl)-2-(4-methoxyphenyl)-8-((3-methoxyphenyl)amino)-4,6-dimethyl-3-oxa-1-azaspiro[4.4]non-1-ene-6,7-diol (13c). Yield: 86% (140 mg from 150 mg); $[\alpha]_D^{20}$ +5.14 (***c*** 1.00, $CHCl_3$); IR (neat): ν_{max} 3418, 2934, 2099, 1641, 1610, 1514, 1496, 1463, 1455, 1427, 1364, 1345, 1305, 1258, 1213, 1170, 1113, 1055, 1037, 908, 840, 822, 794, 739, 702 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.87 (2H, d, ***J*** = 8.9 Hz), 7.64 (2H, dd, ***J*** = 1.4, 8.0 Hz), 7.48 (2H, dd, ***J*** = 1.4, 8.0 Hz), 7.44–7.30 (4H, m), 7.29–7.21 (2H, m), 7.06 (1H, t, ***J*** = 8.0 Hz), 6.90 (2H, d, ***J*** = 8.9 Hz), 6.35–6.24 (3H, m), 5.56 (1H, br s), 4.94 (1H, q, ***J*** = 6.6 Hz), 4.81 (1H, s), 4.46–4.36 (1H, m), 4.35–4.26 (1H, m), 4.13 (1H, d, ***J*** = 11.0 Hz), 3.91 (1H, d, ***J*** = 6. Hz), 3.82 (3H, s), 3.80 (1H, d, ***J*** = 11.0 Hz), 3.71 (3H, s), 1.58 (3H, d, ***J*** = 6.6 Hz), 1.16 (3H, s), 1.08 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.0, 162.7, 160.9, 148.4, 135.7, 135.5, 131.1, 130.4, 130.2, 130.1, 127.9, 127.8, 118.9, 113.7, 105.9, 103.7, 98.7, 84.5, 80.0, 78.6, 70.9, 68.1, 66.4, 55.3, 54.9, 26.9, 18.9, 17.3, 17.0; HRMS (ESIMS): calcd for $C_{40}H_{48}N_5O_6Si$ $[M+H]^+$ 722.3368, found 722.3369.

4.1.6.4. (4*S*,5*R*,6*R*,7*S*,8*S*,9*S*)-9-Azido-7-(((tert-butyldiphenylsilyl)oxy)methyl)-2-(4-methoxyphenyl)-4,6-dimethyl-8-((3-(trifluoromethyl)phenyl)amino)-3-oxa-1-azaspiro[4.4]non-1-ene-6,7-diol (13d). Yield: 52% (122 mg from 200 mg); 20 equiv of ***m***-trifluoromethyl aniline was required; $[\alpha]_D^{20}$ +2.4 (***c*** 1.00, $CHCl_3$); IR (neat): ν_{max} 3415, 2934, 2098, 1639, 1611, 1514, 1427, 1344, 1258, 1167, 1115, 1068, 743, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.90 (2H, d, ***J*** = 8.9 Hz), 7.62 (2H, d, ***J*** = 6.8 Hz), 7.47–7.34 (6H, m), 7.28–7.22 (4H, m), 6.98 (1H, d, ***J*** = 7.7 Hz), 6.94 (2H, d, ***J*** = 8.9 Hz), 6.85–6.80 (2H, m), 5.61 (1H, s), 4.98 (1H, q, ***J*** = 6.6 Hz), 4.78 (1H, s), 4.60 (1H, d, ***J*** = 9.6 Hz), 4.33 (1H, dd, ***J*** = 6.8, 9.6 Hz), 4.07 (1H, d, ***J*** = 11.2 Hz), 3.94 (1H, d, ***J*** = 6.8 Hz), 3.85–3.82 (4H, m), 1.61 (3H, d, ***J*** = 6.6 Hz), 1.21 (3H, s), 1.10 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.2, 162.8, 147.2, 135.7, 135.4, 131.0, 130.9, 130.5, 130.3, 130.1, 129.9, 128.0, 127.9, 118.9, 115.4, 114.2, 114.1, 113.8, 109.8, 109.6, 84.5, 84.4, 80.1, 78.6, 70.9, 68.1, 66.4, 55.4, 26.9, 19.0, 17.4, 17.0; HRMS (ESIMS): calcd for $C_{40}H_{45}F_3N_5O_5Si$ $[M+H]^+$ 760.31366, found 760.31417.

4.1.7. General procedure for synthesis of 14a–14d

To a stirred solution of **13a–13d** (56 mg, 0.081 mmol) in THF (1.4 mL) was added 2.0 N HCl (0.6 mL) at 0 °C and the solution was allowed to warm up to room temperature. After being stirred for 18 h at rt, the reaction mixture was cooled to 0 °C, quenched with a saturated aqueous $NaHCO_3$ solution and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification by column chromatography using 10% EtOAc in hexanes gave the starting oxazoline (33–39%). Elution with [10–25]% EtOAc in hexanes afforded compounds **14a–14d** as pale yellow viscous liquids.

4.1.7.1. (*S*)-1-((1*R*,2*R*,3*S*,4*S*,5*S*)-1-Amino-5-azido-3-(((tert-butyldiphenylsilyl)oxy)methyl)-2,3-dihydroxy-2-methyl-4-(phenylamino)cyclopentyl)ethyl 4-methoxybenzoate (14a). Yield: 53% (30 mg from 56 mg); $[\alpha]_D^{20}$ +96.8 (***c*** 1.00, $CHCl_3$); IR (neat): ν_{max} 3391, 2934, 2170, 1704, 1604, 1511, 1463, 1382, 1316, 1259, 1168, 1104, 1072, 1029, 846, 821, 747, 701, 504 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.02 (2H, d, ***J*** = 8.9 Hz), 7.59 (2H, d, ***J*** = 6.8 Hz), 7.48 (2H, d, ***J*** = 6.8 Hz), 7.44–7.26 (4H, m), 7.26–7.17 (4H, m), 6.95 (2H, d, ***J*** = 8.9 Hz), 6.76 (1H, t, ***J*** = 7.3 Hz), 6.66 (2H, d, ***J*** = 7.8 Hz), 5.76 (1H, q, ***J*** = 6.5 Hz), 4.86 (1H, s), 4.47 (1H, d, ***J*** = 11.2 Hz), 4.23 (1H, dd, ***J*** = 4.6, 11.1 Hz), 4.04 (1H, d, ***J*** = 11.0 Hz), 3.92 (1H, d, ***J*** = 4.6 Hz), 3.88 (3H, s), 3.73 (1H, d, ***J*** = 11.0 Hz), 1.34 (3H, d, ***J*** = 6.5 Hz), 1.26 (3H, s), 1.04 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.0, 163.6, 146.5, 135.7, 135.6, 131.6, 131.3, 131.3, 130.0, 129.8, 129.5, 127.7, 122.3, 117.8, 113.8, 113.3, 83.7, 80.8, 74.0, 70.8, 70.5, 66.8, 65.4, 55.4, 26.9, 18.9, 18.1, 15.1; HRMS (ESIMS): calcd for $C_{39}H_{48}N_5O_6Si$ $[M+H]^+$ 710.3368, found 710.3371.

4.1.7.2. (*S*)-1-((1*R*,2*R*,3*S*,4*S*,5*S*)-1-Amino-5-azido-3-(((tert-butyldiphenylsilyl)oxy)methyl)-4-((3-fluorophenyl)amino)-2,3-dihydroxy-2-methylcyclopentyl)ethyl 4-methoxybenzoate (14b). Yield: 53% (30 mg from 55 mg); $[\alpha]_D^{20}$ +105.6 (***c*** 1.00, $CHCl_3$); IR (neat): ν_{max} 3418, 2935, 2100, 1640, 1621, 1614, 1515, 1495,1427, 1365, 1346, 1258, 1171, 1152, 1114, 1057, 1033, 840, 823, 740, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.92 (2H, d, ***J*** = 8.9 Hz), 7.49 (2H, d, ***J*** = 6.7 Hz), 7.41 (2H, d, ***J*** = 6.7 Hz), 7.30 (2H, q,

J = 7.3 Hz), 7.27–7.15 (4H, m), 7.02 (1H, m), 6.89 (2H, d, *J* = 8.9 Hz), 6.34 (1H, dt, *J* = 1.8, 8.4 Hz), 6.28 (1H, dd, *J* = 1.8, 8.1 Hz), 6.22 (2H, td, *J* = 2.2, 11.5 Hz), 5.67 (1H, q, *J* = 6.5 Hz), 4.73 (1H, s), 4.51 (1H, d, *J* = 11.0 Hz), 4.07 (1H, dd, *J* = 4.6, 11.0 Hz), 3.88–3.80 (5H, m), 3.68 (1H, d, *J* = 11.0 Hz), 1.28 (3H, d, *J* = 6.5 Hz), 1.17 (3H, s), 0.96 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.1, 163.7, 148.3, 135.7, 135.5, 131.6, 131.3, 131.3, 131.1, 130.6, 130.5, 130.1, 129.9, 127.7, 127.8, 122.3, 113.8, 109.0, 104.4, 100.1, 99.9, 83.7, 80.8, 74.1, 70.8, 70.6, 66.8, 65.4, 55.5, 26.9, 18.9, 18.1, 15.2; HRMS (ESIMS): calcd for $C_{39}H_{47}FN_5O_6Si$ $[M+H]^+$ 728.3274, found 728.3286.

4.1.7.3. (*S*)-1-((1*R*,2*R*,3*S*,4*S*,5*S*)-1-Amino-5-azido-3-(((tert-butyldiphenylsilyl)oxy)methyl)-2,3-dihydroxy-4-((3-methoxyphenyl)amino)-2-methylcyclopentyl)ethyl 4-methoxybenzoate (14c). Yield: 45% (65 mg from 140 mg); $[\alpha]_D^{20}$ +99.2 (***c*** 1.00, $CHCl_3$); IR (neat): ν_{max} 3395, 3072, 2934, 2858, 2107, 1704, 1605, 1512, 1496, 1463, 1428, 1259, 1212, 1168, 1104, 1073, 1030, 822, 770, 737, 702 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.00 (2H, d, *J* = 9.0 Hz), 7.58 (2H, dd, *J* = 1.4, 8.0 Hz), 7.50 (2H, d, *J* = 1.4, 8.0 Hz), 7.43–7.20 (7H, m), 7.08 (1H, d, *J* = 8.0 Hz), 6.96 (2H, d, *J* = 9.0 Hz), 6.33 (1H, dd, *J* = 2.2, 8.1 Hz), 6.24 (1H, dd, *J* = 2.0, 8.0 Hz), 6.20 (1H, t, *J* = 2.2 Hz), 5.74 (1H, q, *J* = 6.5 Hz), 4.82 (1H, s), 4.52 (1H, d, *J* = 11.2 Hz), 4.18 (1H, dd, *J* = 2.7, 11.2 Hz), 3.98 (1H, d, *J* = 10.9 Hz), 3.90 (1H, d, *J* = 4.5 Hz), 3.88 (3H, s), 3.74 (1H, d, *J* = 10.9 Hz), 3.72 (3H, s), 1.36 (3H, d, *J* = 6.5 Hz), 1.24 (3H, s), 1.04 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.1, 163.6, 160.9, 147.9, 135.8, 135.6, 131.6, 131.4, 131.3, 130.2, 130.1, 129.8, 127.8, 127.7, 122.4, 113.8, 106.1, 103.8, 99.0, 83.8, 80.8, 74.1, 70.9, 70.5, 66.9, 65.4, 55.0, 26.9, 18.9, 18.1, 15.1; HRMS (ESIMS): calcd for $C_{40}H_{50}N_5O_7Si$ $[M+H]^+$ 740.3474, found 740.34816.

4.1.7.4. (*S*)-1-((1*R*,2*R*,3*S*,4*S*,5*S*)-1-Amino-5-azido-3-(((tert-butyldiphenylsilyl)oxy)methyl)-2,3-dihydroxy-2-methyl-4-((3-(trifluoromethyl)phenyl)amino)cyclopentyl)ethyl 4-methoxybenzoate (14d). Yield: 53% (124 mg from 230 mg); $[\alpha]_D^{20}$ +102.4 (***c*** 1.00, $CHCl_3$); IR (neat): ν_{max} 3392, 2934, 2107, 1698, 1606, 1512, 1423, 1344, 1259, 1167, 1114, 1069, 1030, 847, 821, 770, 699 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 (2H, d, *J* =8.7 Hz), 7.55 (2H, d, *J* = 7.4 Hz), 7.47 (2H, d, *J* = 7.4 Hz), 7.39 (2H, q, *J* = 7.7 Hz), 7.31–7.21 (6H, m), 6.97 (3H, d, *J* = 8.7 Hz), 6.81 (1H, s), 6.75 (1H, d, *J* = 8.2 Hz), 5.80–5.73 (1H, m), 4.79 (1H, s), 4.73 (1H, d, *J* = 10.9 Hz), 4.20 (1H, dd, *J* = 4.5, 10.9 Hz), 3.93 (1H, d, *J* = 4.5 Hz), 3.92–3.88 (4H, m), 3.79 (1H, d, *J* = 11.0 Hz), 1.35 (3H, d, *J* = 6.5 Hz), 1.27 (3H, s), 1.04 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.1, 163.7, 146.7, 135.7, 135.6, 131.6, 131.3, 130.1, 129.9, 129.9, 127.8, 127.7, 122.3, 115.7, 114.1, 114.1, 113.8, 109.5, 109.5, 83.7, 80.8, 74.1, 70.8, 70.3, 66.9, 65.3, 55.4, 26.8, 18.9, 18.0, 15.1; HRMS (ESIMS): calcd for $C_{40}H_{47}F_3N_5O_6Si$ $[M+H]^+$ 778.32422, found 778.32531.

4.1.8. General procedure for synthesis 15a–15d

To a stirred solution of **14a–14d** (94 mg, 0.134 mmol) in dry DMF (3 mL) was added TAS-F (110 mg, 0.401 mmol) at 0 °C under argon and allowed to room temperature. After being stirred for 1 h at rt, the reaction mixture was cooled to 0 °C, quenched with a pH 7 phosphate buffer solution and extracted with ethyl acetate. The combined organic layers were washed with water, brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure.

To a stirred solution of crude amino triol in dry DCM (2 mL), CSA (37.3 mg, 0.16 mmol) and 2,2-dimethoxypropane (0.4 mL) were added sequentially at 0 °C under argon and warm up to room temperature. After being stirred for 2 h at rt, the reaction mixture was cooled to 0 °C, quenched with saturated aqueous $NaHCO_3$ solution and extracted with DCM. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure.

To a stirred solution of crude acetonide in dry THF (2 mL), activated charcoal (10 mg), Et_3N (0.037 mL, 0.266 mmol) and diphosgene (0.024 mL, 0.199 mmol) were added slowly at −46 °C under argon and the reaction mixture was stirred for 60 min. The reaction was quenched with saturated aqueous $NaHCO_3$ solution and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Flash column chromatography using [22–26]% ethyl acetate in hexanes gave compounds **15a–15d** as colorless liquids.

4.1.8.1. (*S*)-1-((1*R*,2*R*,3*S*,4*S*,5*S*)-1-Amino-5-azido-2,3-dihydroxy-3-(hydroxymethyl)-2-methyl-4-(phenylamino)cyclopentyl)ethyl 4-methoxybenzoate (15a). Yield: 86% (63 mg from 94 mg); $[\alpha]_D^{20}$ +14.27 (***c*** 1.00, $CHCl_3$); IR (neat): ν_{max} 3390, 2989, 2934, 2271, 2105, 1688, 1604, 1511, 1455, 1382, 1317, 1260, 1169, 1065, 1029, 848, 771, 750, 694 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02 (2H, d, *J* = 8.9 Hz), 7.24 (2H, d, *J* = 7.4 Hz), 6.97 (2H, d, *J* = 8.9 Hz), 6.78 (1H, t, *J* = 7.4 Hz), 6.69 (2H, d, *J* = 7.7 Hz), 5.48 (1H, q, *J* = 6.4 Hz), 4.52 (1H, br s), 4.35 (1H, br s), 4.31 (1H, d, *J* = 10.1 Hz), 4.21 (1H, d, *J* = 10.1 Hz), 4.12 (1H, br s), 3.89 (3H, s), 3.46 (1H, d, *J* = 2.6 Hz), 1.45–1.40 (9H, m), 1.24 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.9, 164.0, 132.3, 129.7, 124.0, 121.1, 118.5, 114.0, 113.5, 111.3, 90.8, 85.6, 75.5, 73.8, 72.4, 67.0, 65.9, 55.5, 26.0, 25.1, 18.0, 16.1; HRMS (ESIMS): calcd for $C_{27}H_{32}N_5O_7$ $[M+H]^+$ 538.2296, found 538.2308.

4.1.8.2. (*S*)-1-((1*R*,2*R*,3*S*,4*S*,5*S*)-1-Amino-5-azido-4-((3-fluorophenyl)amino)-2,3-dihydroxy-3-(hydroxymethyl)-2-methylcyclopentyl)ethyl 4-methoxybenzoate (15b). Yield: 81% (45 mg from 70 mg); $[\alpha]_D^{20}$ +11.79 (***c*** 1.00, $CHCl_3$); IR (neat): ν_{max} 3398, 2988, 2939, 2272, 2104, 1687, 1606, 1512, 1496, 1382, 1261, 1169, 1070, 1029, 851, 771 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05 (2H, d, *J* = 8.9 Hz), 7.17 (1H, ABq, *J* = 8.1 Hz), 6.97 (2H, d, *J* = 8.9 Hz), 6.50–6.36 (3H, m), 5.48 (1H, q, *J* = 6.3 Hz), 4.67 (1H, d, *J* = 11.5 Hz), 4.42 (1H, s), 4.27 (1H, d, *J* = 10.1 Hz), 4.18 (1H, d, *J* = 10.1 Hz), 4.06 (1H, dd, *J* = 2.6, 11.5 Hz), 3.89 (3H, s), 3.43 (1H, d, *J* = 2.6 Hz), 1.44–1.41 (9H, m), 1.24 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.8, 165.3, 164.4, 162.9, 147.9, 147.8, 132.3, 130.9, 130.8, 124.0, 121.0, 114.0, 111.5, 109.0, 109.0, 105.1, 104.9, 100.5, 100.2, 90.6, 85.5, 75.5, 73.7, 72.3, 67.0, 65.8, 55.5, 26.0, 25.2, 17.9, 16.1; HRMS (ESIMS): calcd for $C_{27}H_{31}FN_5O_7$ $[M+H]^+$ 556.2202, found 556.2220.

4.1.8.3. (*S*)-1-((1*R*,2*R*,3*S*,4*S*,5*S*)-1-Amino-5-azido-2,3-dihydroxy-3-(hydroxymethyl)-4-((3-methoxyphenyl)amino)-2-methylcyclopentyl)ethyl 4-methoxybenzoate (15c). Yield: 47% (39 mg from 110 mg); $[\alpha]_D^{20}$ +11.2 (***c*** 1.00, $CHCl_3$); IR (neat): ν_{max} 3389, 2990, 2938, 2271, 2104, 1688, 1606, 1512, 1496, 1383, 1318, 1261, 1212, 1169, 1103, 1064, 1030, 909, 854, 733, 689 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05 (2H, d, *J* = 8.9 Hz), 7.14 (1H, t, *J* = 8.1 Hz), 6.97 (2H, d, *J* = 8.9 Hz), 6.34 (1H, dd, *J* = 2.2, 7.7 Hz), 6.30 (1H, dd, *J* = 1.7, 8.0 Hz), 6.24 (1H, t, *J* = 2.2 Hz), 5.48 (1H, q, *J* = 6.3 Hz), 4.53 (1H, d, *J* = 11.6 Hz), 4.38 (1H, s), 4.28 (1H, d, *J* = 10.1 Hz), 4.20 (1H, d, *J* = 10.1 Hz), 4.10 (1H, dd, *J* = 2.6, 11.6 Hz), 3.88 (3H, s), 3.79 (3H, s), 3.47 (1H, d, *J* = 2.6 Hz), 1.45 (3H, s), 1.43 (3H, d, *J* = 6.3 Hz), 1.42 (3H, s), 1.25 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.8, 164.3, 161.0, 147.5, 132.3, 130.4, 124.0, 121.1, 114.0, 111.3, 106.2, 103.9, 99.4, 90.7, 85.5, 75.5, 73.7, 72.4, 66.9, 65.9, 55.5, 55.1, 26.0, 25.1, 18.0, 16.1; HRMS (ESIMS): calcd for $C_{28}H_{34}N_5O_8$ $[M+H]^+$ 568.24019, found 568.24056.

4.1.8.4. (*S*)-1-((1*R*,2*R*,3*S*,4*S*,5*S*)-1-Amino-5-azido-2,3-dihydroxy-3-(hydroxymethyl)-2-methyl-4-((3-(trifluoromethyl)phenyl)amino)cyclopentyl)ethyl 4-methoxybenzoate (15d). Yield: 82% (54 mg from 80 mg); $[\alpha]_D^{20}$ +19.0 (***c*** 1.00, $CHCl_3$); IR (neat***):*** ν_{max} 3382, 2969, 2104, 1687, 1605, 1513, 1342, 1317, 1261, 1168, 1124, 1069, 852, 771, 697 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05 (2H, d,

J = 8.9 Hz), 7.33 (1H, t, *J* = 7.8 Hz), 7.02 (1H, d, *J* = 7.8 Hz), 6.97 (2H, d, *J* = 8.9 Hz), 6.78 (1H, t, *J* = 7.4 Hz), 6.89 (1H, s), 6.85 (1H, d, *J* = 8.1 Hz), 5.49 (1H, q, *J* = 6.3 Hz), 4.75 (1H, d, *J* = 11.5 Hz), 4.47 (1H, s), 4.35 (1H, br s), 4.24 (2H, ABq, *J* = 10.1 Hz), 4.15–4.09 (1H, m), 3.88 (3H, s), 3.47 (1H, d, *J* = 2.7 Hz), 2.04 (1H, s), 1.45–1.43 (9H, m), 1.26 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 167.9, 164.4, 146.3, 132.3, 130.1, 125.4, 124.1, 122.7, 121.0, 115.8, 114.9, 114.0, 111.5, 110.0, 110.0, 90.6, 85.6, 75.4, 73.8, 72.3, 66.9, 66.9, 65.8, 55.5, 25.9, 25.2, 17.9, 16.1; HRMS (ESIMS): calcd for $C_{28}H_{31}F_3N_5O_7$ $[M+H]^+$ 606.21701, found 606.21775.

4.1.9. General procedure for synthesis of 16a–16d

To **15a–15d** (82 mg, 0.152 mmol) was added neat 0.5 mL dimethylamine (upon condensing the gas at −46 °C) and the reaction mixture was left warming to room temperature. It was directly subjected to flash column chromatography using [32–40]% ethyl acetate in hexanes to afford compounds **16a–16d** as colorless liquids.

4.1.9.1. (*S*)-1-((5*S*,6*R*,7*R*,8*S*,9*S*)-8-Azido-7-(3,3-dimethylureido)-6-hydroxy-2,2,6-trimethyl-9-(phenylamino)-1,3-dioxaspiro[4.4]nonan-7-yl)ethyl 4-methoxybenzoate (16a). Yield: 88% (78 mg from 82 mg); $[\alpha]_D^{20}$ +96.8 (***c*** 1.00, $CHCl_3$); IR (neat): ν_{max} 3401, 2987, 2937, 2109, 1711, 1652, 1605, 1512, 1372, 1317, 1258, 1168, 1101, 1057, 1030, 848, 732, 694 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 7.98 (2H, d, *J* = 9.0 Hz), 7.18 (2H, t, *J* = 7.6 Hz), 6.94 (2H, d, *J* = 9.0 Hz), 6.79–6.69 (3H, m), 6.44 (1H, q, *J* = 6.5 Hz), 5.70 (1H, s), 4.39 (1H, d, *J* = 9.8 Hz), 4.15 (1H, d, *J* = 9.8 Hz), 4.15–4.09 (1H, m), 3.99–3.89 (2H, m), 3.86 (3H, s), 2.90 (6H, s), 1.54–1.52 (6H, m), 1.39 (3H, s), 1.30 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 164.5, 163.3, 157.9, 147.2, 131.6, 129.4, 122.2, 118.4, 113.8, 113.5, 109.8, 90.1, 82.8, 72.0, 70.6, 68.0, 65.9, 65.1, 55.4, 36.5, 29.6, 25.6, 22.4, 17.0; HRMS (ESIMS): calcd for $C_{29}H_{39}N_6O_7$ $[M+H]^+$ 583.28747, found 583.28885.

4.1.9.2. (*S*)-1-((5*S*,6*R*,7*R*,8*S*,9*S*)-8-Azido-7-(3,3-dimethylureido)-9-((3-fluorophenyl)amino)-6-hydroxy-2,2,6-trimethyl-1,3-dioxaspiro[4.4]nonan-7-yl)ethyl 4-methoxybenzoate (16b). Yield: 93% (12 mg from 12 mg); $[\alpha]_D^{20}$ +78.0 (***c*** 1.00, $CHCl_3$); IR (neat): ν_{max} 3405, 2932, 2109, 1709, 1650, 1607, 1513, 1495, 1372, 1317, 1258, 1168, 1102, 1058, 1031, 848, 768, 733 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.97 (2H, d, *J* = 8.9 Hz), 7.14–7.06 (1H, m), 6.94 (2H, d, *J* = 8.9 Hz), 6.53–6.38 (4H, m), 5.67 (1H,s), 4.39 (1H, d, *J* = 9.8 Hz), 4.29 (1H, d, *J* = 8.4 Hz), 4.10 (2H, d, *J* = 9.8 Hz), 3.93–3.86 (5H, m), 2.89 (6H, s), 1.54 (3H, m), 1.52 (3H, d, *J* = 6.6 Hz), 1.39 (3H, s), 1.31 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 165.7, 164.5, 163.6, 162.4, 157.9, 149.1, 149.0, 131.6, 130.6, 130.4, 122.1, 113.8, 109.8, 109.3, 105.0, 104.8, 100.4, 100.0, 89.8, 82.6, 72.0, 70.1, 67.8, 65.8, 65.1, 55.4, 36.5, 25.6, 22.4, 17.0; HRMS (ESIMS): calcd for $C_{29}H_{38}FN_6O_7$ $[M+H]^+$ 601.2781, found 601.2804.

4.1.9.3. (*S*)-1-((5*S*,6*R*,7*R*,8*S*,9*S*)-8-Azido-7-(3,3-dimethylureido)-6-hydroxy-9-((3-methoxyphenyl)amino)-2,2,6-trimethyl-1,3-dioxaspiro[4.4]nonan-7-yl)ethyl 4-methoxybenzoate (16c). Yield: 86% (36 mg from 39 mg); $[\alpha]_D^{20}$ +90.9 (***c*** 1.00, $CHCl_3$); IR (neat): ν_{max} 3397, 2988, 2937, 2109, 1710, 1658, 1606, 1512, 1496, 1463, 1372, 1258, 1213, 1167, 1102, 1054, 1031, 849, 732 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 7.97 (2H, d, *J* = 9.0 Hz), 7.08 (1H, t, *J* = 8.7 Hz), 6.94 (2H, d, *J* = 9.0 Hz), 6.44 (1H, q, *J* = 6.5 Hz), 6.38–6.27 (3H, m), 5.70 (1H, s), 4.38 (1H, d, *J* = 9.8 Hz), 4.24–4.09 (3H, m), 3.95–3.89 (2H, m), 3.86 (3H, s), 3.75 (3H, s), 2.89 (6H, s), 1.53 (3H, s), 1.53 (3H, d, *J* = 6.5 Hz), 1.39 (3H, s), 1.33 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 164.6, 163.5, 160.8, 157.9, 148.6, 131.6, 130.1, 122.2, 113.8, 109.8, 106.5, 103.4, 99.6, 90.0, 82.8, 72.0, 70.6, 68.0, 65.9, 65.1, 55.4, 55.0, 36.5, 26.0, 25.7, 22.3, 17.0; HRMS (ESIMS): calcd for $C_{30}H_{41}N_6O_8$ $[M+H]^+$ 613.29804, found 613.29907.

4.1.9.4. (*S*)-1-((5*S*,6*R*,7*R*,8*S*,9*S*)-8-Azido-7-(3,3-dimethylureido)-6-hydroxy-2,2,6-trimethyl-9-((3-(trifluoromethyl)phenyl)amino)-1,3-dioxaspiro[4.4]nonan-7-yl)ethyl 4-methoxybenzoate (16d). Yield: 93% (54 mg from 54 mg); $[\alpha]_D^{20}$ +101.07 (***c*** 1.00, $CHCl_3$); IR (neat): ν_{max} 3403, 2938, 2109, 1708, 1651, 1606, 1512, 1452, 1343, 1258, 1167, 1122, 1068, 1031, 849, 766, 697 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.97 (2H, d, *J* = 8.9 Hz), 7.31–7.24 (2H, m), 7.00–6.85 (5H, m), 6.47 (1H, q, *J* = 6.5 Hz), 5.70 (1H, s), 4.48–4.44 (1H, m), 4.39 (1H, d, *J* = 9.9 Hz), 4.23 (1H, s), 4.16 (1H, d, *J* = 9.9 Hz), 3.97–3.93 (2H, m), 3.85 (3H, s), 2.89 (6H, s), 1.56–1.54 (6H, m), 1.39 (3H, s), 1.30 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 164.5, 163.6, 157.9, 147.4, 131.5, 128.2, 125.5, 122.8, 12212, 116.3, 114.7, 114.7, 113.8, 109.9, 109.7, 109.6, 90.0, 82.7, 71.7, 7036, 68.0, 65.7, 65.1, 55.4, 36.5, 36.5, 25.9, 25.6, 22.2, 17.1; HRMS (ESIMS): calcd for $C_{30}H_{38}F_3N_6O_7$ $[M+H]^+$ 651.27486, found 651.27541.

4.1.10. General procedure for synthesis of 17a–17d

To a stirred solution of **16a–16d** (74 mg, 0.127 mmol) in dry DCM (3.5 mL), DIBAL-H (0.34 mL, 1.5 M in toluene, 0.51 mmol) was added slowly at −78 °C under argon and stirred for 1.5 h. The reaction mixture was then quenched with slow addition of methanol and warmed to room temperature. A saturated aqueous potassium sodium tartrate solution was added to the reaction mixture and stirred for 1 h, extracted with ethyl acetate, the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Flash column chromatography using [24–28]% ethyl acetate in hexanes gave compounds **17a–17d** as colorless liquids.

4.1.10.1. 3-((5*S*,6*R*,7*R*,8*S*,9*S*)-8-Azido-6-hydroxy-7-((*S*)-1-hydroxyethyl)-2,2,6-trimethyl-9-(phenylamino)-1,3-dioxaspiro[4.4]nonan-7-yl)-1,1-dimethylurea (17a). Yield: 91% (52 mg from 74 mg); $[\alpha]_D^{20}$ +40.9 (***c*** 1.00, $CHCl_3$); IR (neat): ν_{max} 3419, 2988, 2935, 2106, 1644, 1602, 1538, 1505, 1372, 1311, 1260, 1139, 1117, 1061, 1047, 860, 750, 693, 532 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 7.44 (1H, d, *J* = 11.4 Hz), 7.24 (1H, t, *J* = 8.6 Hz), 6.77 (1H, t, *J* = 7.3 Hz), 6.61 (2H, d, *J* = 8.6 Hz), 5.41 (1H, s), 5.18 (1H, d, *J* = 11.2 Hz), 4.60 (1H, s), 4.24 (2H, s), 4.00–3.84 (2H, m), 3.65 (1H, s), 3.00 (6H, s), 1.44 (3H, s), 1.43 (3H, s), 1.39 (3H, s), 1.17 (3H, d, *J* = 6.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 158.3, 145.8, 129.7, 118.2, 113.1, 110.5, 97.3, 83.3, 74.0, 73.1, 72.7, 66.7, 65.4, 36.7, 26.3, 25.6, 20.7, 17.7; HRMS (ESIMS): calcd for $C_{21}H_{33}N_6O_5$ $[M+H]^+$ 449.25069, found 449.25239.

4.1.10.2. 3-((5*S*,6*R*,7*R*,8*S*,9*S*)-8-Azido-9-((3-fluorophenyl)amino)-6-hydroxy-7-((*S*)-1-hydroxyethyl)-2,2,6-trimethyl-1,3-dioxaspiro[4.4]nonan-7-yl)-1,1-dimethylurea (17b). Yield: 98% (43 mg from 56 mg); $[\alpha]_D^{20}$ +41.8 (***c*** 1.00, $CHCl_3$); IR (neat): ν_{max} 3380, 2995, 2933, 2108, 1737, 1622, 1593, 1536, 1515, 1498, 1375, 1339, 1260, 1214, 1181, 1156, 1062, 1049, 967, 941, 857, 757, 685 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 7.45 (1H, d, *J* = 11.4 Hz), 7.24–7.21 (1H, m), 6.54 (1H, ddt, *J* = 0.8, 2.3, 8.5 Hz), 6.37 (1H, ddd, *J* = 0.8, 2.3, 8.1 Hz), 6.30 (1H, td, *J* = 2.3, 11.4 Hz), 5.39 (1H, s), 5.31 (1H, d, *J* = 11.2 Hz), 4.62 (1H, s), 4.21 (2H, ABq, J = 9.9 Hz), 3.98–3.85 (1H, m), 3.80 (1H, d, *J* = 11.2 Hz), 3.62 (1H, s), 2.99 (6H, s), 1.43 (6H, s), 1.38 (3H, s), 1.21 (3H, d, *J* = 6.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 165.4, 163.0, 158.2, 147.8, 147.7, 130.9, 130.8, 110.7, 108.9, 108.9, 104.8, 104.6, 100.0, 99.8, 91.2, 88.3, 74.2, 73.0, 72.8, 66.7, 65.3, 36.7, 26.3, 25.6, 20.6, 17.7; HRMS (ESIMS): calcd for $C_{21}H_{31}FN_6NaO_5$ $[M+Na]^+$ 489.2232, found 489.2254.

4.1.10.3. 3-((5*S*,6*R*,7*R*,8*S*,9*S*)-8-Azido-6-hydroxy-7-((*S*)-1-hydroxyethyl)-9-((3-methoxyphenyl)amino)-2,2,6-trimethyl-1,3-dioxaspiro[4.4]nonan-7-yl)-1,1-dimethylurea (17c). Yield: 75% (36 mg from 62 mg); $[\alpha]_D^{20}$ +47.5 (***c*** 1.00, $CHCl_3$); IR (neat): ν_{max} 3418, 2988, 2936, 2106, 1643, 1614, 1538, 1495, 1373, 1308, 1259, 1212, 1164, 1139, 1061, 1046, 856, 761, 733, 689 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): *δ*

7.47 (1H, d, J = 11.3 Hz), 7.13 (1H, t, J = 8.1 Hz), 6.34 (1H, dd, J = 2.2, 8.1 Hz), 6.22 (1H, dd, J = 1.7, 8.1 Hz), 6.16 (1H, t, J = 2.2 Hz), 5.41 (1H, s), 5.22 (1H, d, J = 11.3 Hz), 4.63 (1H, s), 4.23 (2H, s), 3.93 (1H, sept, J = 6.5 Hz), 3.84 (1H, d, J = 11.3 Hz), 3.78 (3H, s), 3.65 (1H, s), 2.99 (6H, s), 1.43 (3H, s), 1.42 (3H, s), 1.38 (3H, s), 1.18 (3H, d, J = 6.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.1, 158.3, 147.2, 130.5, 110.5, 106.0, 103.6, 99.0, 91.3, 83.3, 74.0, 73.1, 72.7, 66.6, 65.3, 55.1, 36.7, 26.3, 25.5, 20.7, 17.7; HRMS (ESIMS): calcd for $C_{22}H_{35}N_6O6$ $[M+H]^+$ 479.26126, found 479.26244.

4.1.10.4. 3-((5*S*,6*R*,7*R*,8*S*,9*S*)-8-Azido-6-hydroxy-7-((*S*)-1-hydroxyethyl)-2,2,6-trimethyl-9-((3-(trifluoromethyl)phenyl)amino)-1,3-dioxaspiro[4.4]nonan-7-yl)-1,1-dimethylurea (17d). Yield: 91% (110 mg from 130 mg); $[\alpha]_D^{20}$ +44.0 (***c*** 1.00, $CHCl_3$); IR (neat): ν_{max} 3377, 2988, 2936, 2105, 1641, 1535, 1148, 1373, 1343, 1281, 1163, 1122, 1062, 855, 785, 693 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46 (1H, d, J = 11.3 Hz), 7.31 (1H, t, J = 7.9 Hz), 7.00 (1H, d, J = 7.6 Hz), 6.82 (1H, s), 6.77 (1H, d, J = 8.2 Hz), 5.42 (2H, d, J = 11.3 Hz), 4.67 (1H, s), 4.22 (2H, ABq, J = 9.9 Hz), 3.96–3.87 (1H, s), 3.85 (1H, d, J = 11.3 Hz), 3.6 (1H, s), 2.99 (6H, s), 1.43 (3H, s), 1.43 (6H, s), 1.39 (3H, s), 1.21 (3H, d, J = 6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.2, 146.1, 130.1, 125.4, 122.7, 116.0, 114.6, 114.5, 110.7, 109.3, 109.2, 91.2, 88.2, 74.9, 72.8, 66.6, 65.3, 41.9, 36.6, 26.2, 25.6, 20.5, 17.7; HRMS (ESIMS): calcd for $C_{22}H_{32}F_3N_6O_5$ $[M+H]^+$ 517.23808, found 517.23916.

4.1.11. General procedure for synthesis of 18a–18d

To the stirred solution of **17a–17d** (13 mg, 0.029 mmol) in acetonitrile (0.1 mL) and H_2O (0.1 mL); TFA (0.5 mL) was added at 0 °C and the solution was stirred at 33 °C for variable times (90 min for **17a**, 75 min for **17b** and 60 min for **17c**, rt for 90 min in the case of **17d**), cooled to 0 °C, quenched very slowly with saturated aqueous $NaHCO_3$ solution and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Flash column chromatography using [70–80]% ethyl acetate in hexanes gave compounds **18a–18d** as colorless liquids.

4.1.11.1. 3-((1*R*,2*R*,3*S*,4*S*,5*S*)-5-Azido-2,3-dihydroxy-1-((*S*)-1-hydroxyethyl)-3-(hydroxymethyl)-2-methyl-4-(phenylamino)cyclopentyl)-1,1-dimethylurea (18a). Yield: 76% (9 mg from 13 mg); $[\alpha]_D^{20}$ +13.5 (***c*** 1.00, $CHCl_3$); IR (neat): ν_{max} 3412, 2928, 2104, 1634, 1602, 1537, 1506, 1374, 1307, 1249, 1110, 1036, 912, 752, 734, 694 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 (1H, d, J = 11.4 Hz), 7.30–7.21 (2H, m), 6.80 (1H, t, J = 7.3 Hz), 6.67 (2H, d, J = 7.8 Hz), 5.51 (1H, s), 5.13 (1H, d, J = 10.7 Hz), 4.53 (1H, s), 4.17 (2H, d, J = 11.8 Hz), 4.03–3.91 (1H, m), 3.81 (1H, d, J = 8.9 Hz), 3.64 (1H, s), 3.62 (1H, d, J = 11.8 Hz), 3.00 (6H, s), 2.15 (1H, br s), 1.74 (1H, br s), 1.41 (3H, s), 1.21 (3H, d, J = 6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.5, 145.7, 129.7, 118.7, 113.9, 88.2, 84.6, 73.9, 73.8, 72.9, 66.8, 61.4, 36.7, 20.4, 17.7; HRMS (ESIMS): calcd for $C_{18}H_{29}N_6O5$ $[M+H]^+$ 409.21939, found 409.22051.

4.1.11.2. 3-((1*R*,2*R*,3*S*,4*S*,5*S*)-5-Azido-4-((3-fluorophenyl)amino)-2,3-dihydroxy-1-((*S*)-1-hydroxyethyl)-3-(hydroxymethyl)-2-methylcyclopentyl)-1,1-dimethylurea (18b). Yield: 85% (10 mg from 12.5 mg); $[\alpha]_D^{20}$ +18.9 (***c*** 1.00, $CHCl_3$); IR (neat): ν_{max} 3408, 2931, 2104, 1622, 1590, 1538, 1374, 1334, 1248, 1180, 1152, 1110, 1037, 763, 733 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 (1H, d, J = 11.3 Hz), 7.20–7.13 (1H, m), 6.47 (1H, dt, J = 2.0, 8.4 Hz), 6.41 (1H, dd, J = 1.8, 8.2 Hz), 6.35 (1H, td, J = 2.2, 11.3 Hz), 5.50 (1H, s), 5.29 (1H, d, J = 11.3 Hz), 4.56 (1H, s), 4.10 (1H, d, J = 11.6 Hz), 4.00–3.91 (1H, m), 3.77 (1H, d, J = 11.3 Hz), 3.65–3.60 (2H, m), 3.17 (1H, s), 2.99 (6H, s), 2.07 (1H, br s), 1.73 (1H, br s), 1.40 (3H, s), 1.22 (3H, d, J = 6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.4, 163.0, 158.5, 147.7, 147.6, 130.9, 130.8, 109.4, 109.4, 105.3, 105.0, 100.7, 100.4, 88.3, 84.4, 74.0, 73.8, 73.0, 66.7, 61.2, 36.7, 36.6, 20.4, 17.7; HRMS (ESIMS): calcd for $C_{18}H_{28}FN_6O_5$ $[M+H]^+$ 427.20997, found 427.21009.

4.1.11.3. 3-((1*R*,2*R*,3*S*,4*S*,5*S*)-5-Azido-2,3-dihydroxy-1-((*S*)-1-hydroxyethyl)-3-(hydroxymethyl)-4-((3-methoxyphenyl)amino)-2-methylcyclopentyl)-1,1-dimethylurea (18c). Yield: 70% (9 mg from 14 mg); $[\alpha]_D^{20}$ +16.9 (***c*** 1.00, $CHCl_3$); IR (neat): ν_{max} 3413, 2929, 2104, 1615, 1537, 1514, 1374, 1305, 1261, 1212, 1164, 1110, 1038, 913, 762, 733 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 (1H, d, J = 11.3 Hz), 7.14 (1H, t, J = 8.1 Hz), 6.37 (1H, dd, J = 1.7, 8.1 Hz), 6.26 (1H, dd, J = 1.2, 8.1 Hz), 6.22 (1H, t, J = 1.7 Hz), 5.50 (1H, s), 5.14 (1H, d, J = 11.7 Hz), 4.54 (1H, s), 4.17 (1H, d, J = 11.7 Hz), 4.02–3.91 (1H, m), 3.84–3.76 (4H, m), 3.65 (1H, s), 3.59 (1H, d, J = 11.7 Hz), 2.99 (6H, s), 1.81 (1H, br s), 1.61 (2H, br s), 1.41 (3H, s), 1.20 (3H, d, J = 6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.1, 158.5, 147.1, 130.6, 106.5, 104.2, 99.7, 88.2, 84.6, 73.9, 73.8, 73.0, 66.8, 61.4, 55.1, 36.7, 20.5, 17.7; HRMS (ESIMS): calcd for $C_{19}H_{30}N_6O_6$ $[M+H]^+$ 439.22996, found 439.23098.

4.1.11.4. 3-((1*R*,2*R*,3*S*,4*S*,5*S*)-5-Azido-2,3-dihydroxy-1-((*S*)-1-hydroxyethyl)-3-(hydroxymethyl)-2-methyl-4-((3-(trifluoromethyl)phenyl)amino)cyclopentyl)-1,1-dimethylurea (18d). Yield: 82% (14 mg from 18 mg); $[\alpha]_D^{20}$ +26.9 (***c*** 1.00, $CHCl_3$); IR (neat): ν_{max} 3408, 2934, 2104, 1633, 1538, 1488, 1375, 1342, 1284, 1164, 1122, 1068, 908, 787, 735, 699 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$: δ 7.48 (1H, d, J = 11.3 Hz), 7.33 (1H, t, J = 7.8 Hz), 7.03 (1H, d, J = 7.8 Hz), 6.87 (1H, s), 6.81 (1H, d, J = 8.2 Hz), 5.50 (1H, s), 5.40 (1H, d, J = 11.3 Hz), 4.58 (1H, s), 4.13 (1H, d, J = 11.6 Hz), 4.02–3.92 (1H, m), 3.84 (1H, d, J = 11.1 Hz), 3.63 (1H, d, J = 11.6 Hz), 3.60 (1H, s), 3.15 (1H, s), 2.99 (6H, s), 2.05 (1H, br s), 1.69 (1H, br s), 1.42 (3H, s), 1.23 (3H, d, J = 6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.4, 146.1, 132.2, 131.9, 130.2, 116.6, 115.0, 114.9, 109.8, 109.8, 88.3, 84.1, 74.1, 73.8, 73.8, 73.0, 66.5, 61.1, 36.7, 20.4, 17.7; HRMS (ESIMS): calcd for $C_{19}H_{28}F_3N_6O_5$ $[M+H]^+$ 477.20678, found 477.20767.

4.1.12. General procedure for synthesis of 19a–19d

To a stirred solution of **18a–18d** (9 mg, 0.022 mmol) in EtOH/H_2O (3:1, 1.4 mL) were added ammonium chloride (35 mg, 0.662 mmol), zinc powder (22 mg, 0.331 mmol) at rt and the mixture was stirred for 8 h. The reaction mixture was quenched with aqueous ammonia (2 mL) and extracted with CH_2Cl_2, the combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography using [4–5]% methanol in chloroform to give **19a–19d** as a pale yellow oils.

4.1.12.1. 3-((1*R*,2*R*,3*S*,4*S*,5*S*)-5-Amino-2,3-dihydroxy-1-((*S*)-1-hydroxyethyl)-3-(hydroxymethyl)-2-methyl-4-(phenylamino)cyclopentyl)-1,1-dimethylurea (19a). Yield: 80% (7 mg from 9 mg); $[\alpha]_D^{20}$ +29.3 (***c*** 1.00, $CHCl_3$); IR (neat): ν_{max} 3382, 2927, 2724, 1603, 1505, 1373, 1297, 1089, 1041, 912, 750 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85 (1H, d, J = 10.5 Hz), 7.20 (2H, t, J = 7.8 Hz), 7.05 (1H, s), 6.73 (1H, t, J = 7.3 Hz), 6.64 (2H, d, J = 7.8 Hz), 5.56 (1H, s), 5.20 (1H, d, J = 10.9 Hz), 4.11 (1H, d, J = 11.7 Hz), 3.99–3.87 (1H, m), 3.72 (1H, d, J = 11.7 Hz), 3.67 (1H, d, J = 10.5 Hz), 2.99 (6H, s), 1.79 (5H, br s), 1.45 (3H, s), 1.05 (3H, d, J = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.4, 146.6, 129.6, 117.9, 113.4, 88.4, 84.8, 74.0, 71.3, 68.6, 62.4, 61.9, 36.8, 21.5, 18.2; HRMS (ESIMS): calcd for $C_{18}H_{31}N_4O_5$ $[M+H]^+$ 383.2289, found 383.22804.

4.1.12.2. 3-((1*R*,2*R*,3*S*,4*S*,5*S*)-5-Amino-4-((3-fluorophenyl)amino)-2,3-dihydroxy-1-((*S*)-1-hydroxyethyl)-3-(hydroxymethyl)-2-methylcyclopentyl)-1,1-dimethylurea (19b). Yield: 75% (7.6 mg from

10 mg); $[\alpha]_D^{20}$ +33.2 (***c*** 1.00, $CHCl_3$); IR (neat): ν_{max} 3382, 2927, 1719, 1621, 1515, 1455, 1374, 1337, 1180, 1150, 1088, 1041, 918, 759 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.86 (1H, d, J = 10.8 Hz), 7.17–7.03 (2H, m), 6.46–6.28 (3H, m), 5.62 (1H, s), 5.39 (1H, d, J = 10.5 Hz), 4.06 (1H, d, J = 11.6 Hz), 3.97–3.84 (1H, m), 3.73 (1H, d, J = 11.6 Hz), 3.60 (1H, dd, J = 1.4, 10.5 Hz), 2.99 (6H, s), 2.95 (1H, s), 1.77 (1H, br s), 1.45 (3H, s), 1.04 (3H, d, J = 6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.4, 162.9, 159.3, 148.3, 130.6, 109.5, 109.4, 104.3, 104.1, 99.9, 99.6, 88.4, 84.6, 73.9, 71.3, 68.4, 62.4, 61.7, 36.8, 21.4, 18.2; HRMS (ESIMS): calcd for $C_{18}H_{30}FN_4O_5$ $[M+H]^+$ 401.21947, found 401.2182.

4.1.12.3. 3-((1R,2*R*,3*S*,4*S*,5*S*)-5-Amino-2,3-dihydroxy-1-((*S*)-1-hydroxyethyl)-3-(hydroxymethyl)-4-((3-methoxyphenyl)amino)-2-methylcyclopentyl)-1,1-dimethylurea (19c). Yield: 80% (7 mg from 9 mg); $[\alpha]_D^{20}$ +36.3 (***c*** 1.00, $CHCl_3$); IR (neat): ν_{max} 3385, 2934, 1614, 1515, 1455, 1374, 1212, 1162, 1090, 1041, 912, 823, 762, 732, 690 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.86 (1H, d, J = 10.7 Hz), 7.15–7.02 (2H, m), 6.28 (1H, d, J = 8.2 Hz), 6.25 (1H, d, J = 8.2 Hz), 6.17 (1H, s), 5.56 (1H, s) 5.25 (1H, d, J = 10.7 Hz), 4.08 (1H, d, J = 11.7 Hz), 3.98–3.87 (1H, m), 3.77 (3H,s), 3.69 (1H, d, J = 11.7 Hz), 3.60 (1H, d, J = 10.7 Hz), 3.05–2.91 (7H, s), 1.81 (2H, s), 1.44 (3H, s), 1.05 (3H, d, J = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.0, 159.4, 148.0, 130.0, 106.4, 102.8, 99.4, 88.4, 84.7, 71.3, 68.6, 62.4, 61.9, 55.1, 36.8, 21.5, 18.2; HRMS (ESIMS): calcd for $C_{19}H_{33}N_4O_6$ $[M+H]^+$ 413.23946, found 413.23835.

4.1.12.4. 3-((1*R*,2*R*,3*S*,4*S*,5*S*)-5-Amino-2,3-dihydroxy-1-((*S*)-1-hydroxyethyl)-3-(hydroxymethyl)-2-methyl-4-((3-(trifluoromethyl) phenyl)amino)cyclopentyl)-1,1-dimethylurea (19d). Yield: 75% (10 mg from 14 mg); $[\alpha]_D^{20}$ +32.7 (***c*** 1.00, $CHCl_3$); IR (neat): ν_{max} 3381, 2933, 1614, 1520, 1449, 1374, 1346, 1283, 1164, 1122, 1068, 909, 787, 733, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.88 (1H, d, J = 10.7 Hz), 7.32–7.20 (1H, m), 7.06 (1H, s), 6.96 (1H, d, J = 7.6 Hz), 6.81 (1H, s), 6.77 (1H, d, J = 8.0 Hz), 5.62 (1H, s), 5.48 (1H, d, J = 10.3 Hz), 4.06 (1H, d, J = 11.5 Hz), 3.97–3.84 (1H, m), 3.73 (1H, d, J = 11.5 Hz), 3.67 (1H, d, J = 10.3 Hz), 2.99 (6H, s), 2.93 (1H, s), 1.86 (3H, br s), 1.45 (3H, s), 1.04 (3H, d, J = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.3, 146.8, 131.9, 131.6, 129.9, 125.5, 122.8, 116.4, 114.1, 114.1, 109.1, 109.1, 88.4, 84.5, 74.0, 73.9, 71.3, 68.6, 62.4, 61.5, 36.8, 21.4, 18.2; HRMS (ESIMS): calcd. for $C_{19}H_{30}F_3N_4O_5$ $[M+H]^+$ 451.21628, found 451.21758.

4.1.13. In vitro antimalarial activity

In vitro antimalarial activity was determined by the malaria SYBR Green-based fluorescence (MSF) assay described previously[22] with slight modification.[21] Stock solutions of each test drug were prepared in sterile distilled water at a concentration of 10 mM. The drug solutions were serially diluted with culture medium and distributed to asynchronous parasite cultures on 96-well plates in quadruplicate in a total volume of 100 μL to achieve 0.2% parasitemia with a 2% hematocrit in a total volume of 100 μL. Automated pipetting and dilution were carried out with a programmable Precision 2000 robotic station (Bio-Tek, Winooski, VT). The Plates were then incubated for 72 h at 37 °C. After incubation, 100 μL of lysis buffer with 0.2 μL/ml SYBR Green I (54, 66) was added to each well. The plates were incubated at room temperature for an hour in the dark and then placed in a 96-well fluorescence plate reader (Spectramax Gemini-EM; Molecular Diagnostics) with excitation and emission wavelengths at 497 nm and 520 nm, respectively, for measurement of fluorescence. The 50% inhibitory concentration (IC50) was determined by nonlinear regression analysis of logistic dose-response curves (GraphPad Prism software).

4.1.14. In vitro antibacterial activity

Minimum inhibitory concentrations (MIC) were measured by a standard broth microdilution method following the Clinical Laboratory Standard Institute recommendations.[23] Isolates tested were *Escherichia coli* ATCC 25922, *Staphylococcus aureus* ATCC 25923, *Klebsiella pneumoniae* ATCC 700603, a clinical isolate of *Acinetobacter baumanii, Pseudomonas aeruginosa* ATCC 27853 and *Enterococcus faecalis* ATCC 29212. Plates were read after an incubation period of 20 h.

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