Université de Montréal

Étude de la cyclisation de lactones à 9 membres par réaction de métathèse et formation catalytique de liens benzyliques asymétriques

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Résumé

Préalablement, une synthèse de l'aliskiren, un inhibiteur de la rénine développé pour le traitement de l'hypertension, a été réalisée auprès du groupe Hanessian. Durant cette synthèse, une réaction clé de cyclisation par métathèse, menant à la formation de lactone à neuf membres, a été réalisée. Durant cette réaction, nous avons observé une différence de réactivité entre les diastéréomères, menant à la formation de monolactones et de dilactones, générant ainsi de l'intérêt pour l'étude des facteurs en cause. Le présent mémoire rapporte et détaille les résultats de cette analyse quant à la formation de monomères versus celle de dimères par cyclisation à l'aide de catalyseurs de Grubbs et l'impact de différentes conditions réactionnelles et la diastéréochimie relative sur la réaction.

Un intérêt pour la formation de liens benzyliques nous a incité à approfondir notre compréhension d'une méthodologie de substitution nucléophile diastéréosélective catalysée par des acides. Le rationnel mit de l'avant par les groupes Bach et Olah a procuré une compréhension du mécanisme réactionnel sur lequel nous avons basé nos observations subséquentes. Nous avons porté notre attention sur l'alkylation d'arènes, de phénols et de sulfonamides. Diverses régiosélectivités et diastéréosélectivités ont pu être observées en présence de substrats dérivés de la synthèse de l'aliskiren, de nitroalcools ainsi que de azidoalcools en utilisant plusieurs acides de Lewis et de Brønsted.

Mots-clés : aliskiren, lactone à neuf membres, macrocycle, dimèrisation, métathèse par fermeture de cycle, catalyse acide, carbocation benzylique, diaryles, alkylation diastéréosélective, éther benzylique, sulfonamide, empilement π – π.

Abstract

Previously, a synthesis of aliskiren, a renin inhibitor developed for the treatment of hypertension, was developed in the Hanessian group. As part of that synthesis, they used a ring-closing metathesis which led to the formation of a nine-membered lactone, a key intermediate of the synthesis. During the reaction, we observed a difference in reactivity between the various diastereoisomers leading to the formation of mono- and dilactones, inciting us to study the various factors involved. The present master's thesis reports and details the results of the study of monomers versus dimers formation by cyclization using Grubbs's catalysts and the effect of various reaction conditions and relative configuration on the reaction.

An interest for the formation of benzylic bonds drove us to deepen our comprehension of a methodology of diastereselective nucleophilic substitution catalysed by acids. The rational brought forth by the Bach and Olah groups served as a basis for our understanding of the mechanism involved upon which we based our following observations. We focused our attention on the alkylation of arenes, phenols and sulfonamides. Various regioselectivities and diastereoselectivities were observed on substrates derived from the aliskiren's synthesis, nitroaocohols and azidoalcohols while using various Lewis and Brønsted acids.

Keywords: aliskiren, nine-membered ring lactone, macrocycle, dimerization, ring-closing metathesis, acid catalysts, benzylic carbocation, diaryls, diastereoselective alkylation, benzylic ethers, sulfonamides, $\pi - \pi$ stacking.

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Liste des abréviations

Ac acétyle

Ar groupement aromatique

BHT hydroxytoluène butylé

Bn benzyle

Boc *tert*-butyloxycarbonyle

Bu butyle

Bz benzoyle

CCM chromatographie sur couche mince

DCE 1,2-dichloroéthane

DCM dichlorométhane

DCN 1,4-dicyanonaphthalene

dba acétone dibenzylidène

DIPEA diisopropyléthylamine

DMAP diméthylaminopyridine

DMF diméthylformamide

dr ratio diastéréomérique

ee excès énantiomérique

Et éthyle

h heure

IC50 concentration inhibitrice à 50%

IR infra-rouge

M molaire

***m*-CPBA** acide *méta*-chloroperbenzoïque

Me méthyle

Mes mésitylène

MHz mégahertz

min minute(s)

NaHMDS *N,N*-bis(triméthylsilyl)amidure de sodium

NBS *N*-bromosuccinimide

Nu nucléophile

NOE effet nucléaire d'Overhauser

PCy tricyclohexylphosphine

Ph phényle

$PhCH_3$ toluène

Pr propyle

Pyr pyridine

RMN résonance magnétique nucléaire

ta température ambiante

Tf triflyle

TFA acide trifluoroacétique

THF tétrahydrofurane

TMS tétraméthylsilane

Ts tosyle

À mes parents, Mylène et Marc.

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En premier lieu, j'aimerais remercier le professeur Hanessian pour m'avoir accepté auprès de son groupe pour mes études graduées. Mon séjour en votre compagnie a été une expérience grandement enrichissante pour moi et je serai toujours reconnaissant de la patience et du support continuel que j'ai eu la chance de recevoir durant toutes ces années.

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Chapitre 1 : Formation de lactones à 9 membres par réaction de cyclisation par métathèse

1.1 Origine du projet

L'hypertension a depuis longtemps été un sujet d'importance dans le domaine médical. Celle-ci est responsable de 49% des cas de maladie cardiaque ainsi que 62% des infarctus du myocarde.[1] Le système rénine-angiotensine-aldostérone (SRAA) est connu pour avoir un rôle clé dans la régulation de la pression artérielle.[2] Ainsi, le développement de plusieurs types de traitements, affectant le SRAA à divers stages, a permis de réguler la pression artérielle. Notamment, les inhibiteurs de l'ECA, les inhibiteurs du récepteur AT_1, les β-bloquants et les antagonistes du récepteur de l'aldostérone sont parmi les traitements conventionnels.[3]

À l'époque, il n'y avait aucun inhibiteur de la rénine commercialement disponible pour cibler le SRAA rendant le développement de ceux-ci une cible d'intérêt pour l'industrie. La préparation de plusieurs composés peptidomimétiques ayant une bonne activité, mais aussi une faible biodisponibilité[4] mena à une période où le domaine est resté silencieux. Des efforts au sein de la compagnie Novartis ont renouvelé l'intérêt suite à une réévaluation du site actif de l'enzyme. Ainsi, une combinaison de modélisation moléculaire et de co-cristallisation avec la rénine[5] a mené à l'optimisation de composés ayant une plus grande affinité avec les sites actifs. Cela a permis l'élaboration d'une classe de composés non peptidiques possédant une forte activité inhibitrice (*Figure 1.1*).[6] Issue de celle-ci fut l'aliskiren (**1.1**), un inhibiteur non peptidique de la rénine pouvant inhiber ~40-80% de son activité.[7] Le produit est présentement commercialisé sous le nom de Tekturna™. Plusieurs brevets décrivent des procédés visant la synthèse de l'aliskiren à l'échelle de production industrielle.[8,9]

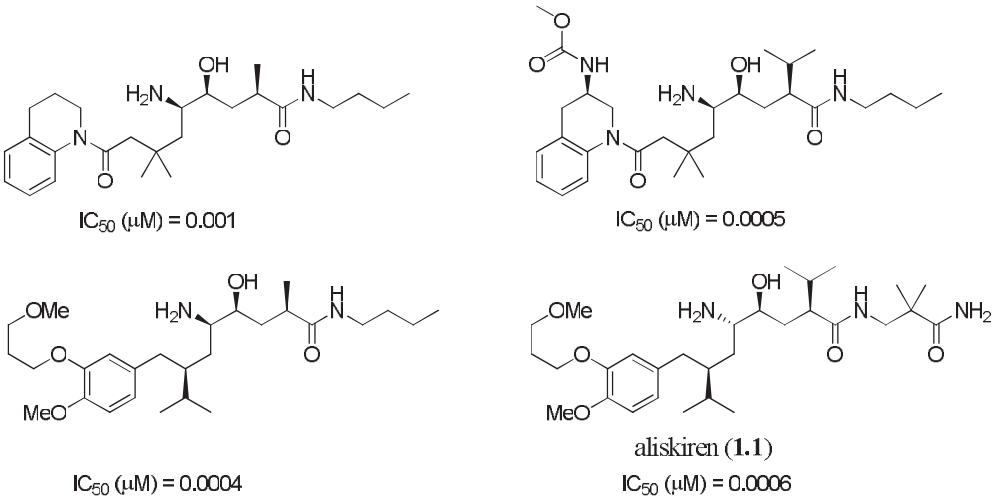

Figure 1.1 : Activité biologique d'inhibiteurs non peptidiques de la rénine sur la rénine humaine purifiée

Préalablement à mon arrivée, plusieurs projets liés à l'aliskiren ont été réalisés au sein du groupe de Hanessian,[10] dont une synthèse totale de l'aliskiren qui a été publiée en 2010 par les Dr Étienne Chénard et Sébastien Guesné.[11] Cette synthèse utilise une route macrocyclique exploitant le caractère symétrique de la chaîne octyle (illustré en rouge, *Schéma 1.1*). À partir du protocole catalytique de MacMillan[12], le (2*S*)-2-isopropyl-4-pentanal (**1.4**) et son dérivé acide carboxylique (**1.6**) ont été préparés pour introduire deux des quatre stéréocentres de la molécule. Une estérification de Yamaguchi a permis de coupler **1.5** et **1.6** afin d'obtenir le diène **1.7** avec un ratio de 8:1. Une métathèse de fermeture de cycle forme l'intermédiaire macrocyclique clé **1.8** comme seul produit tandis que le diastéréoisomère mineur ne réagit pas. Par la suite, une azidiration de Du Bois[13] a permis d'introduire l'amine sous forme d'aziridine de façon diastéréocontrolée. Cette assignation a été basée sur le résultat d'une hydroxylation diastéréosélective d'un substrat test. Une élégante ouverture de cycle suivi d'une contraction de cycle de **1.9** en présence de TFA ont permis d'obtenir le bicycle **1.10** et de fixer les deux stéréocentres manquants grâce à l'aziridine. Un mécanisme passant par un carbocation benzylique suivi d'une ouverture de l'aziridine installe l'oxygène avec une stéréochimie inverse

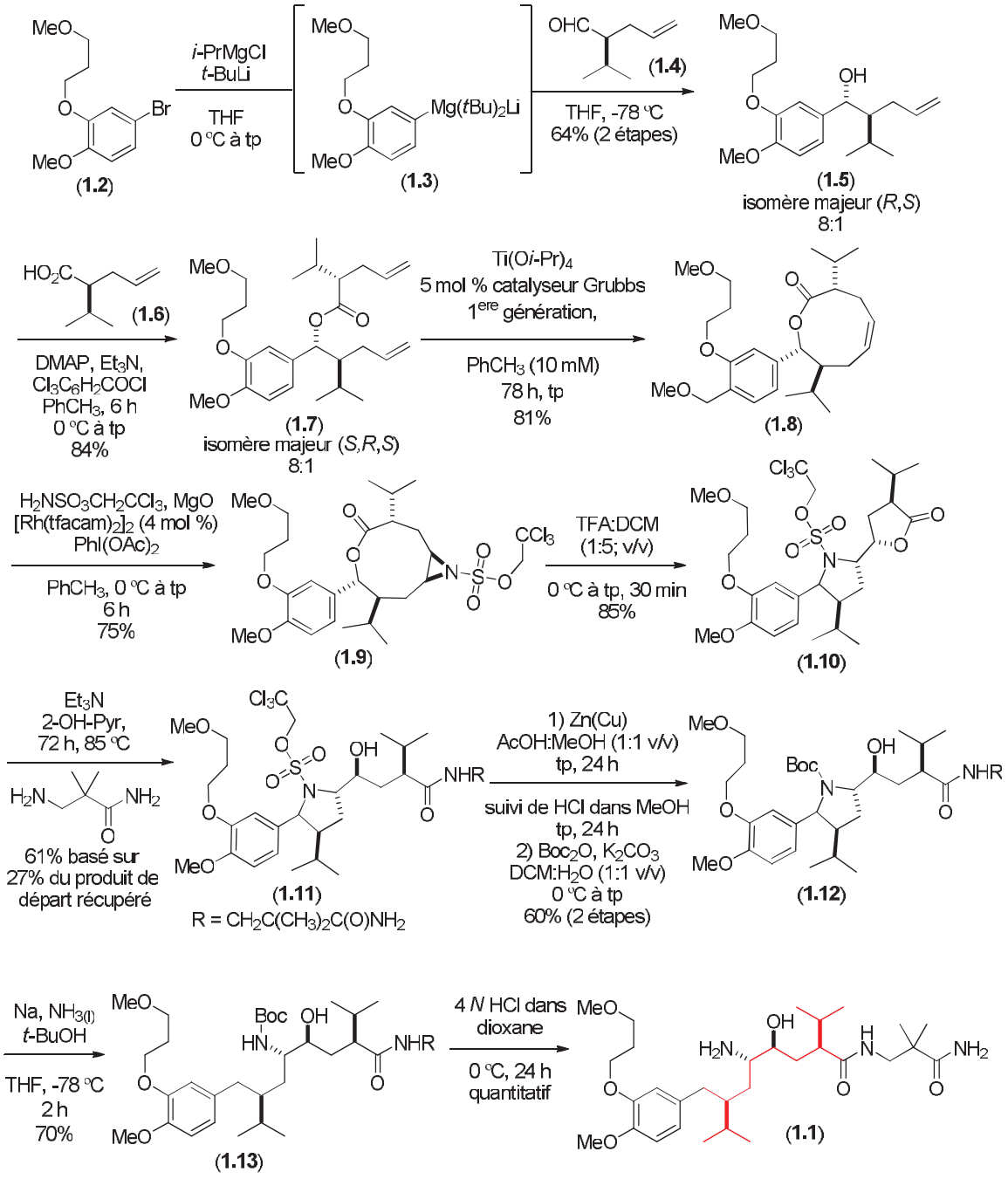

Schéma 1.1 : Synthèse totale de l'aliskiren

et d'une attaque de l'azote sur la position benzylique a expliqué l'obtention de la stéréochimie voulue (*Schéma 1.2*). La synthèse totale de l'aliskiren décrite ici utilise une approche imaginative passant par une contraction de cycle pour obtenir un rendement global de 7% en seulement onze étapes.

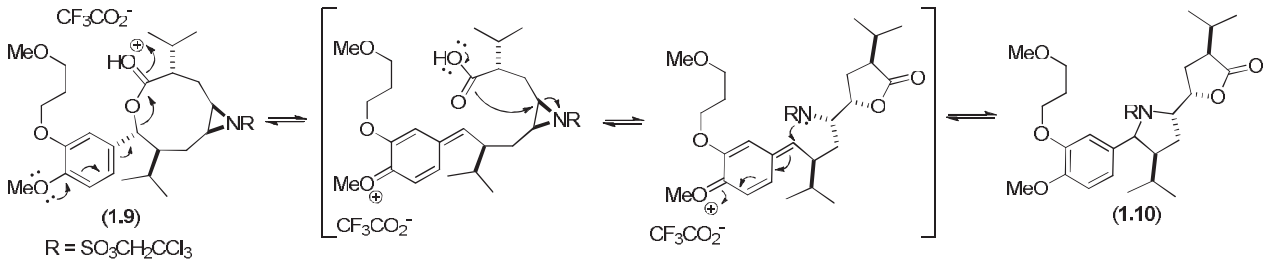

Schéma 1.2 : Mécanisme proposé pour la contraction de cycle

La formation exclusive du diastéréoisomère **1.8** lors de la métathèse de fermeture de cycle a été un résultat d'intérêt demandant une étude supplémentaire. En effet, le diastéréoisomère mineur (*S*,*S*,*S*) du diène (*S*,*R*,*S*) **1.7** était récupéré intacte après la réaction. Des tests initiaux ont ainsi été réalisés par le Dr Étienne Chénard pour tenter la formation du macrocycle à partir des diènes analogues **1.14**. Le mélange de diastéréoisomères en présence du catalyseur de Grubbs de 1^{ere} génération (**G1**) a résulté en la même absence de cyclisation de la part du diène (*S*,*S*,*S*) (*Schéma 1.3*). En utilisant le catalyseur Hoveyda-Grubbs de 2^{e} génération (**G2**), un mélange complexe de produits semblant contenir le composé attendu a été observé par CCM. Cependant, la structure du composé obtenue par rayon X a montré que le produit était en réalité une dilactone macrocyclique à dix-huit membres faisant partie d'un mélange des dimères **1.15** et **1.16**.

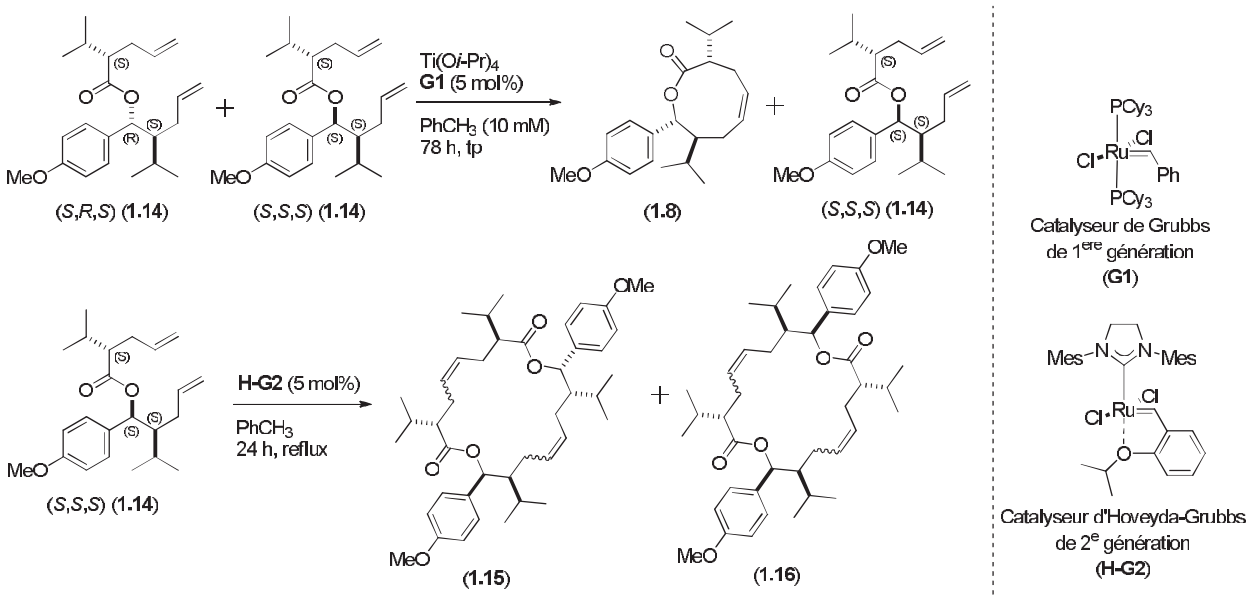

Schéma 1.3 : Formation des dilactones **1.15** et **1.16**

Ce résultat inattendu a stimulé un intérêt pour déterminer les facteurs en cause lors de la réaction. L'exploration de diverses conditions expliquant la formation de la lactone versus la dilactone ainsi que la possibilité d'obtenir la monolactone correspondante à partir du diène (*S*,*S*,*S*) **1.14** pour ensuite former l'aziridine correspondante et ainsi compléter la synthèse ont été déterminés comme étant les objectifs principaux.

1.2 Métathèse d'oléfines et formation de macrolactones

La formation de liens C-C catalysée par des métaux de transitions compte parmis les réactions les plus importantes de la chimie organique. Parmis celles-ci, se trouve la métathèse d'oléfines qui possède un vaste rayon d'applications. Sa contribution au monde de la chimie a été reconnue en 2005 par le prix Nobel de chimie attribué aux professeurs Yves Chauvin, Robert H. Grubbs et Richard R. Schrock pour leurs travaux quant au développement de la métathèse en chimie organique. La grande variété de catalyseurs pouvant être utilisés dans des conditions douces ainsi que la possibilité de former des oléfines hautement fonctionnalisées et encombrées résulte en une réaction hautement versatile.[14]

Le mécanisme de la métathèse d'oléfines en présence de catalyseurs de ruthénium a été étudié en profondeur par plusieurs groupes dans le but de mieux comprendre les paramètres qui influencent cette réaction (*Schéma 1.4*).[15, 16] L'étape d'initialisation qui débute le cycle catalytique est la dissociation du ligand phosphine pour former un complexe à 14 électrons qui peut ensuite se relier au ligand phosphine ou se lier à une oléfine. Le groupe Grubbs a rapporté que la nature du ligand phosphine affecte la vitesse de la réaction.[16f] L'alcène réagit ensuite avec le métallocarbène pour former un intermédiaire métallacyclobutane. Par la suite, il y a formation d'un nouveau carbène qui réagit avec un deuxième alcène et libère une oléfine croisée. Il est important de noter que chaque étape du cycle catalytique est réversible et la libération d'éthylène contribue à pousser la réaction à complétion. Des groupes ont étudié le mécanisme pour tenter de déterminer si l'alcène est inséré en position *trans* au ligand NHC ou en position *cis* avec un déplacement d'un groupement halogène vers la position *trans*, mais aucun consensus n'a été atteint en ce moment dû à des observations pointant aux deux mécanismes.[17] Les ligands présents sur le catalyseur à base de ruthénium jouent un rôle important, car dans le cas du benzilydène, il réduit la vitesse de décomposition du ligand comparé au méthylidène qui est l'intermédiaire présent dans la réaction après le premier cycle catalytique. L'addition de phosphine augmente la stabilité des complexes benzylidènes mais la réactivité du catalyseur est réduite par le même fait. L'utilisation d'un carbène N-hétérocyclique saturé 1,3-bis(2,4,6-triméthylphényl)imidazolidine comme ligand pour remplacer un des ligands phosphine permet d'augmenter la stabilité du catalyseur à haute température. Ces ligands permettent ainsi d'utiliser la réaction de métathèse pour des composés difficiles à former, comme dans le cas de la métathèse de fermeture de cycle de plusieurs macrocycles, qui nécessitent des températures élévées et des temps de réaction prolongés.

Il existe plusieurs applications de la métathèse d'oléfines permettant d'obtenir une vaste gamme d'oléfines. Les 4 principales sont: la réaction de métathèse croisée (CM), la métathèse de fermeture de cycle (RCM), la métathèse de polymérisation par ouverture de cycle (ROMP) et la métathèse de polymérisation de diènes acycliques (ADMET). Parmis celles-ci, la réaction de métathèse croisée d'oléfine dépend fortement de la réactivité des deux oléfines de départ. Les oléfines peuvent ainsi être réparties en plusieurs catégories selon leur susceptibilité à

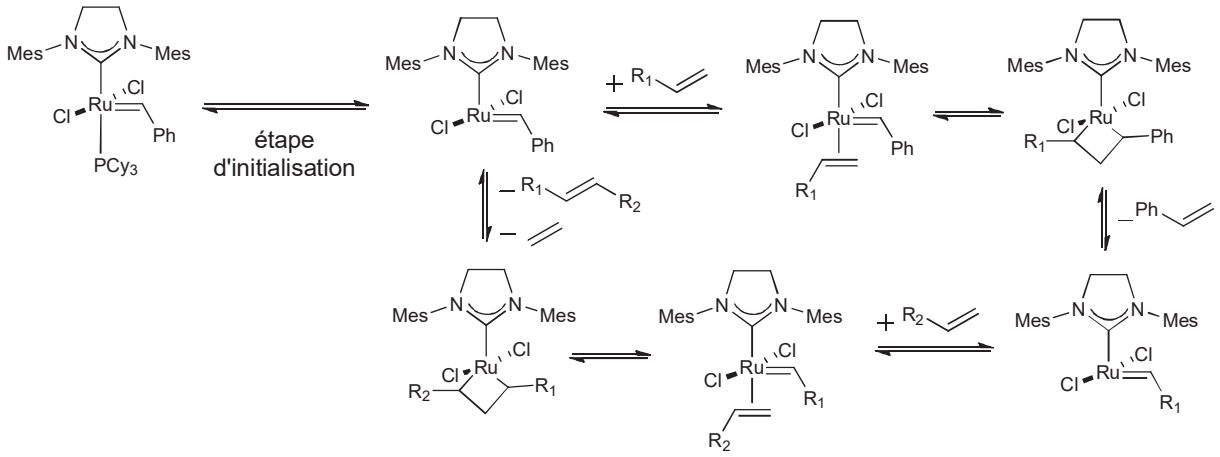

Schéma 1.4 : Mécanisme général de la métathèse d'oléfine en présence d'un catalyseur de Grubbs de 2^{e} génération

homodimèriser. Les oléfines de type 1 réagissent rapidement pour former un homodimère mais celles-ci peuvent réagir à leur tour. Une métathèse croisée impliquant deux oléfines de type 1 donne des produits croisés selon une répartition statistique et un ratio élevé entre les produits de départ est nécessaire pour favoriser le produit croisé mixte (*Schéma 1.5*). Les oléfines qui sont lentes à homodimèriser sont dites de type 2 tandis que celles qui ne peuvent réagir avec elle-mêmes ou sont inertes dans la réaction de métathèse sont de type 3 et 4 respectivement. Si deux oléfines qui ne sont pas de type 1 réagissent ensemble, la réaction de métathèse croisée est non-sélective. Pour mieux contrôler le produit obtenu, il est préférable de faire réagir une oléfine de type 1 avec une oléfine de type 2 ou 3 qui sont moins réactives. La réaction obtenue est ainsi sélective et favorise la formation du produit croisé (*Schéma 1.5*). Le produit *trans* est favorisé lors de ces réactions pour diminuer l'encombrement stérique.[18] Une des principales caractéristiques de la réaction de métathèse croisée est sa réversibilité due à la réactivité des produits. Il est possible pour le produit obtenu de réagir à nouveau avec le catalyseur métallique pour reformer les oléfines de départ.

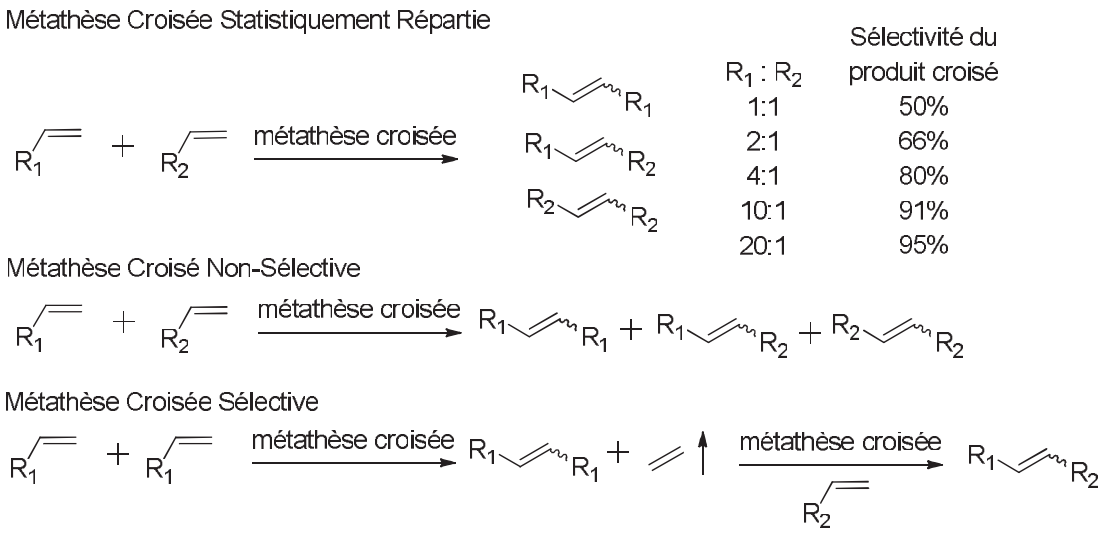

Schéma 1.5 : Règles de sélectivité pour la métathèse croisée

De nouveaux catalyseurs à base de ruthénium ont permis récemment de favoriser la formation des oléfines *Z*. Le ratio entre les oléfines *E* et *Z* réflecte habituellement la différence d'énergie thermodynamique entre les deux isomères, qui se situent aux alentours de 9:1, *E*:*Z*. Afin d'inverser ce ratio, il a été nécessaire de modifier le catalyste utilisé. Le remplacement de certains ligands afin d'optimiser l'encombrement stérique combiné avec des effets électroniques ont menés à la modification de la sélectivité observée (*Schéma 1.6*).[19]

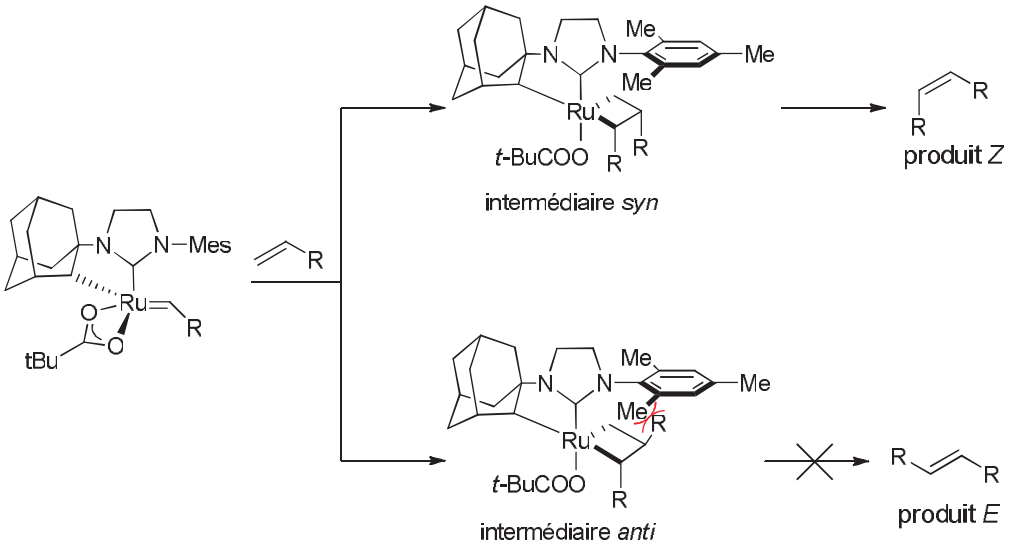

Schéma 1.6 : Mécamisme favorisant la formation d'oléfine *Z*

Les macrolactones sont présentes dans plusieurs composés et ont attiré l'attention grâce aux nombreuses activités biologiques dont elles font preuve. Elles sont ainsi présentes dans plusieurs médicaments.[20] La cyclisation de macrolactones est généralement faite par estérification intramoléculaire ou métathèse de fermeture de cycle. Plusieurs exemples existent pour la formation de cycles à douze membres dans la littérature.[21] Parmi ceux-ci, on retrouve l'isomigrastatine et le salicylihalamide A qui sont respectivement un inhibiteur de migration cellulaire et un inhibiteur de la V-ATPase. Dans les deux cas, l'étape clé de cyclisation est réalisée par une réaction de métathèse de fermeture de cycle. Alternativement, la synthèse de la carolactone est réalisée par une macrolactonisation de Shiina.

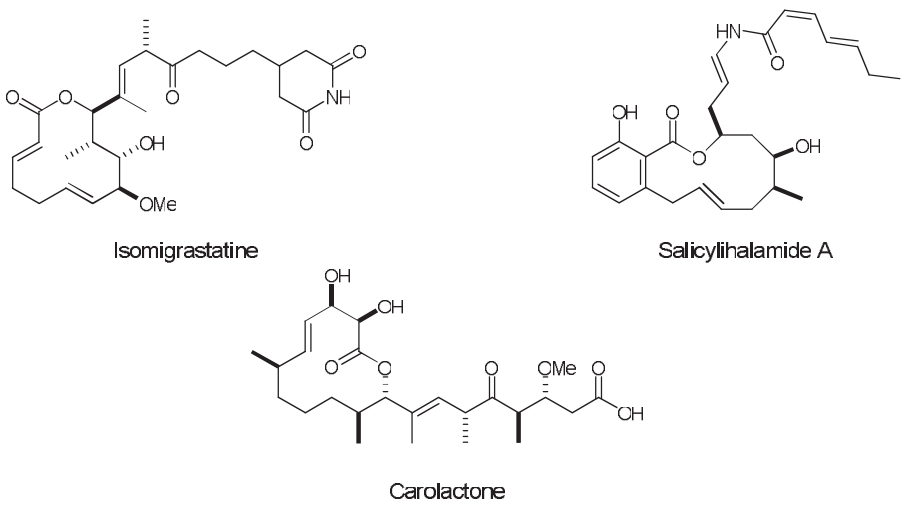

Figure 1.2 : Sélection de macrolactones à douze membres

Les lactones de taille moyenne contenant huit à onze membres sont aussi des cibles d'intérêt de par leur activité biologique.[22] Cependant, la formation de celles-ci s'avère difficile et est donc peu souvent rapportée dans la littérature. Le groupe de Illuminati a étudié la formation de lactones allant de trois à vingt-trois chaînons en comparant les constantes de vitesse de la cyclisation intramoléculaire d'une espèce bifonctionnelle versus le couplage de deux chaînes monofonctionnelles ressemblant à l'espèce bifonctionnelle.[23] Ils ont observé une

importante chute de la constante pour les cycles de huit et neuf membres avec une amélioration graduelle jusqu'au cycle à treize membres à partir duquel la constante de vitesse resta stable (*Figure 1.3*). Ils en ont conclu que la formation de cycles de taille moyenne est rendue difficile en raison de facteurs enthalpiques et entropiques.[24]

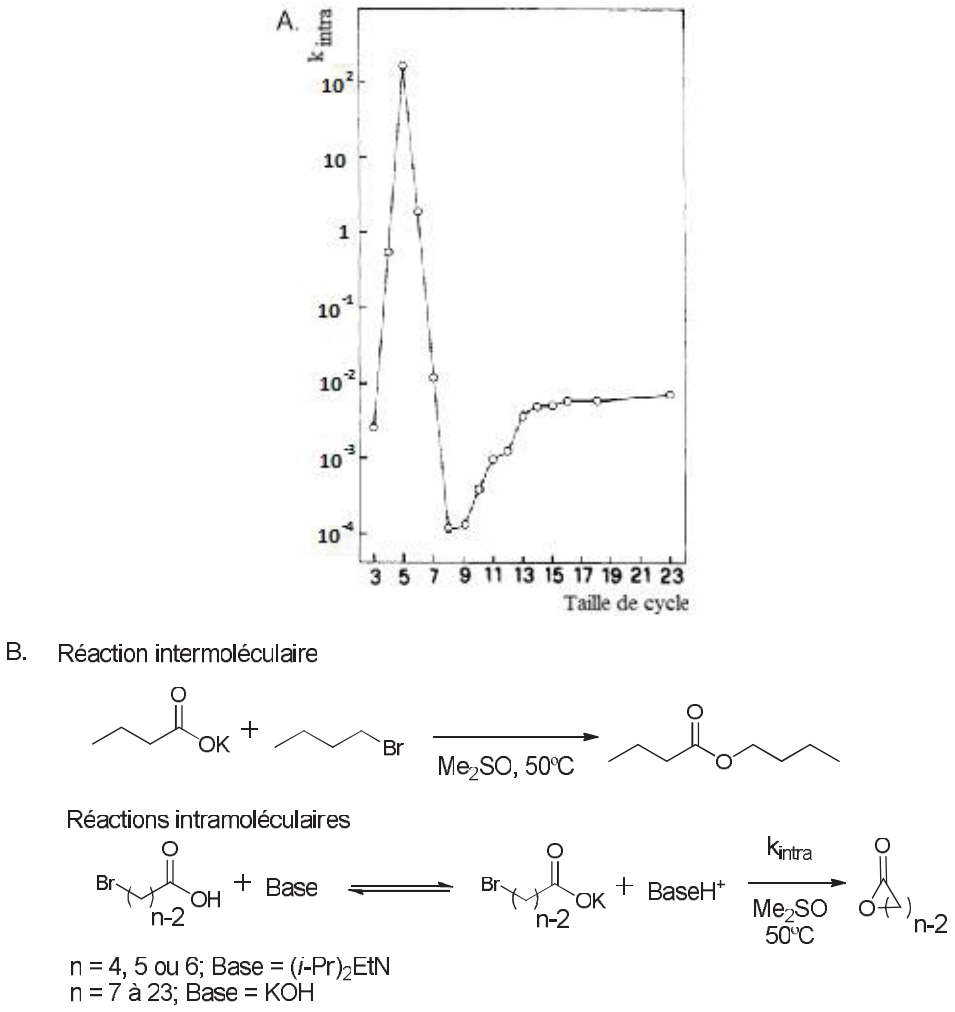

Figure 1.3 : A. Constantes réactionnelles pour la formation de lactones intramoléculaires à partir de ω-bromoacides $Br(CH_2)_{n-2}CO_2H$ [23b] B. Réactions intra- et intermoléculaire étudiées

La formation de macrolactones est affectée par la tension de cycle et celle-ci peut être réduite par des facteurs stéréoélectroniques. Les lactones peuvent prendre deux conformations, soit, les formes *cis* (*Z*) et *anti* (*E*) (*Figure 1.4*). Le groupement fonctionnel ester des lactones

comptant sept à neuf membres ont tendance à être forcés en conformation *trans* malgré que la forme *cis* soit généralement la plus stable par 2-8 kcal/mole. À partir des cycles à dix membres, la forme *cis* redevient plus accessible. [25]

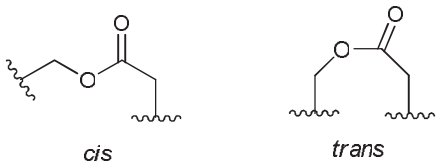

Figure 1.4 : Conformations possibles d'un groupement lactone

La formation de macrolactones par métathèse de fermeture de cycle est un sujet qui a généré beaucoup d'intérêt car il permet l'obtention de macrocycles efficacement. Une étude par le groupe Grubbs a identifié des facteurs clés pour favoriser la cyclisation de diènes versus leur polymérisation.[26] La concentration du substrat en solution affecte grandement le produit obtenu et une dillution du milieu réactionnel permet favoriser la monocyclisation en réduisant la probabilité de rencontres intermoléculaires. La tension de cycle fait des cycles à huits membres des cibles difficiles en favorisant leur réactivité dans des réactions de métathèse de polymérisation par ouverture de cycle. Pour contrer cela, il a été proposé que la présence de contraintes conformationelles rendent leur formation possible.[27] Parmis celles-ci, l'effet Thorpe-Ingold permet de contrer la tendance des diènes à polimériser en introduisant des groupements qui modifient la conformation du produit de départ pour rapprocher les groupements impliqués dans la cyclisation.[28]

Le groupe Fürstner a rapporté la formation de macrolactones par métathèse de fermeture de cycle à partir de substrats sans aucune contrainte conformationelle.[29] Afin d'obtenir ces composés (*Schéma 1.7*), ils ont utilisé une addition lente d'une solution des réactifs au mélange réactionnel contenant le catalyseur permettant ainsi de contrôler la concentration de réactif présent pour former le produit désiré avec un bon rendement comme illustré par la macrolactone **1.19**. Lors de la synthèse du produit **1.23**, ils ont obtenu **1.22** avec un rendement extrêmement

bas (10%) tandis que la cyclisation à partir de **1.24** procède de façon attendue. Deux explications ont été avancées pour justifier le manque de réactivité de **1.21,** soit l'effet stérique du groupement méthyle et/ou la coordination de l'ester et de l'intermédiaire carbène ruthénium.[30]

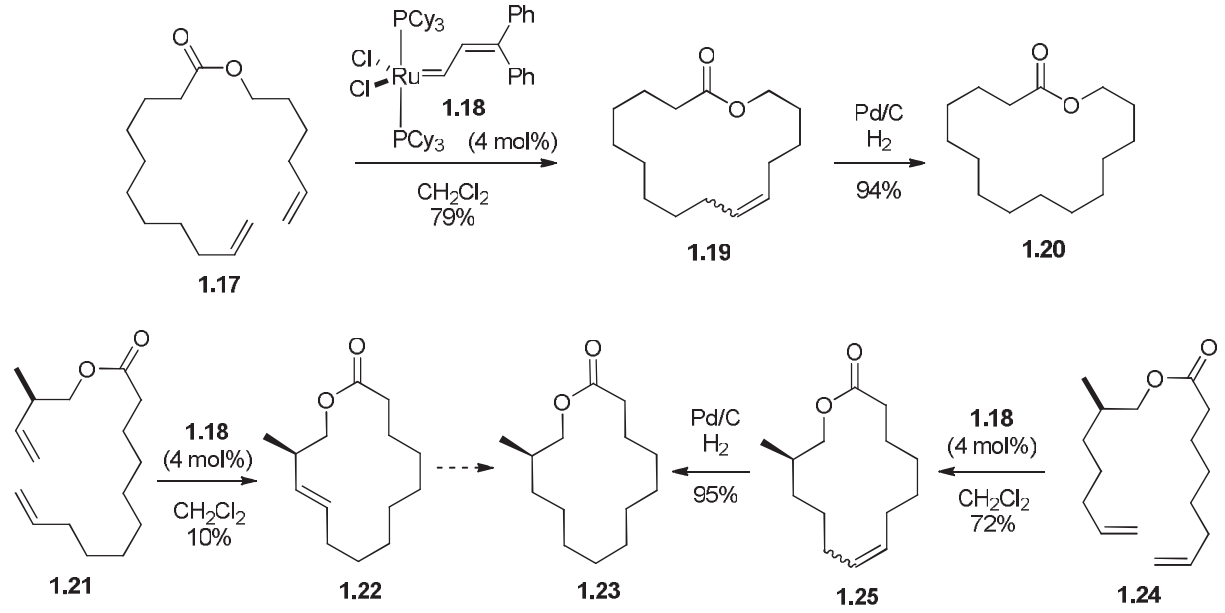

Schéma 1.7 : Macrocyclisation de diènes par Fürstner *et al.*

Plusieurs autres groupes ont utilisé la métathèse de fermeture de cycle dans le cadre de macrocyclisations pour la synthèse totale de molécules complexes (*Figure 1.5*).[31] Les groupes Danishefsky et Horwitz ont rapportés la formation de l'épothilone A (**1.26**) en utilisant une réaction de métathèse comme étape clé dans la fermeture d'un cycle à 16 membres.[32] Ils ont observés que la permutation de fonctionnalités et la stéréochimie peuvent affecter le site de la métathèse malgré la grande distance entre ceux-ci. Le groupe Smith a quant à lui fait la synthèse du (-)-cylindrocyclophane F (**1.27**) en utilisant la même réaction.[33] Ils ont utilisé des conditions dilués (0.004 M dans le CH_2Cl_2) pour obtenir le macrocycle désiré avec 88% de rendement et ils n'ont observé que l'isomère *E*. La synthèse énantiosélective de la manzamine A (**1.28**) par le groupe Martin utilise la réaction de cyclisation à deux reprises pour former les cycles à huit et

treize membres.[34] Il est intéressant de noter que la formation du cycle à treize membres à été réalisée avec un meilleur rendement (67% versus 26%) comparé à la lactame à huit membres.

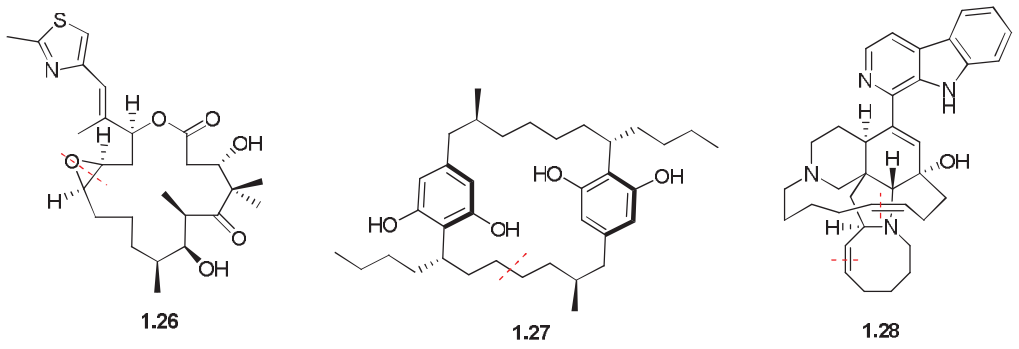

Figure 1.5 : Exemples de macrocyclisations par métathèse dans la synthèse totale de molécules complexes

Certains groupes ont étudié l'effet de substituants lors de la fermeture de cycle par métathèse pour synthétiser des lactones de taille moyenne.[35] Le groupe de Hernández-Galán s'est intéressé aux effets des divers substituants porté par les chaînes oléfiniques lors de la

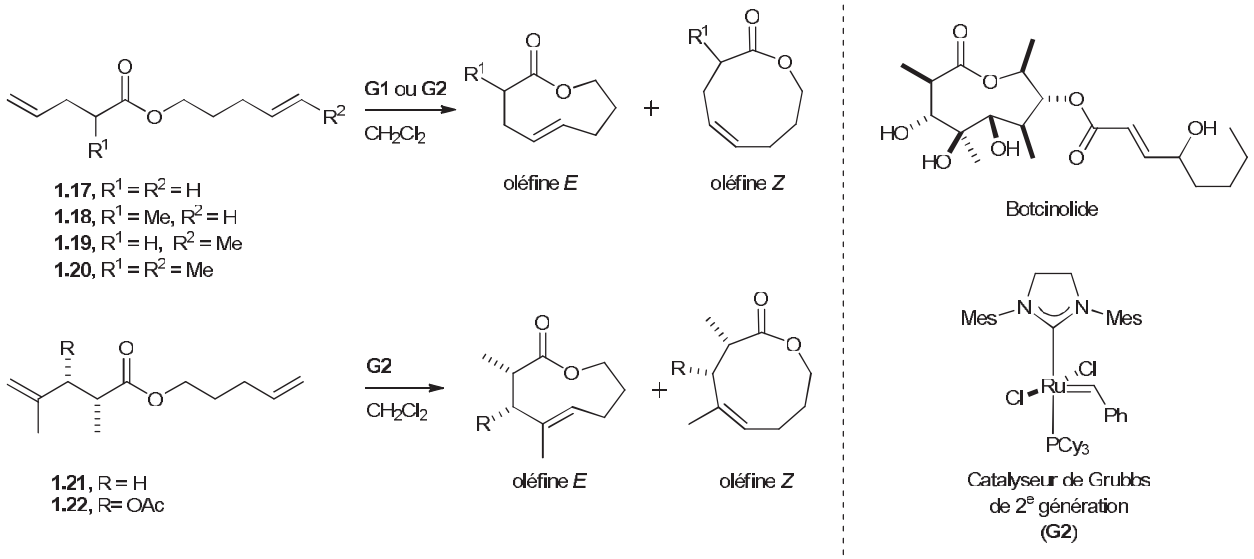

Schéma 1.8 : Étude par Hernández-Galán *et al.*

cyclisation de la lactone à neuf membres.[36] Ils ont observé que le traitement des diènes **1.17** à **1.20** en présence du catalyseur de Grubbs de 2^{e} génération (**G2**) dans le dichlorométhane durant 12 heures donne un mélange 1:1 entre les isomères *E* et *Z* (*Schéma 1.8*). Par la suite, les composés **1.21** et **1.22** ont été soumis aux mêmes conditions pour obtenir seulement les oléfines *E* et *Z* respectivement. Les différences de sélectivité ont été attribuées aux substituants et aucune mention de la présence de dimères n'a été faite.

Le groupe de Banwell s'est également intéressé à la synthèse d'une lactone de taille moyenne, la (-)-cladospolide B.[37] L'étape clé de la synthèse est une cyclisation par métathèse de fermeture de cycle pour obtenir l'intermédiaire cyclique à huit membres **1.24** (*Schéma 1.9*). En présence du catalyseur **G2**, ils ont obtenu 18% de l'isomère *Z* de **1.24** et un rendement combiné de 62% de dimères **1.25** et **1.26**. En remplaçant le catalyseur par **G1**, le rendement de **1.24** a été amélioré jusqu'à 66% tandis que le rendement de dimères a été de 5%. Par contre, ils ont rapporté que la monolactone a été obtenue sous forme de mélange inséparable 1.3:1 des isomères *E* et *Z* qui est par la suite hydrogéné vers le produit saturé.

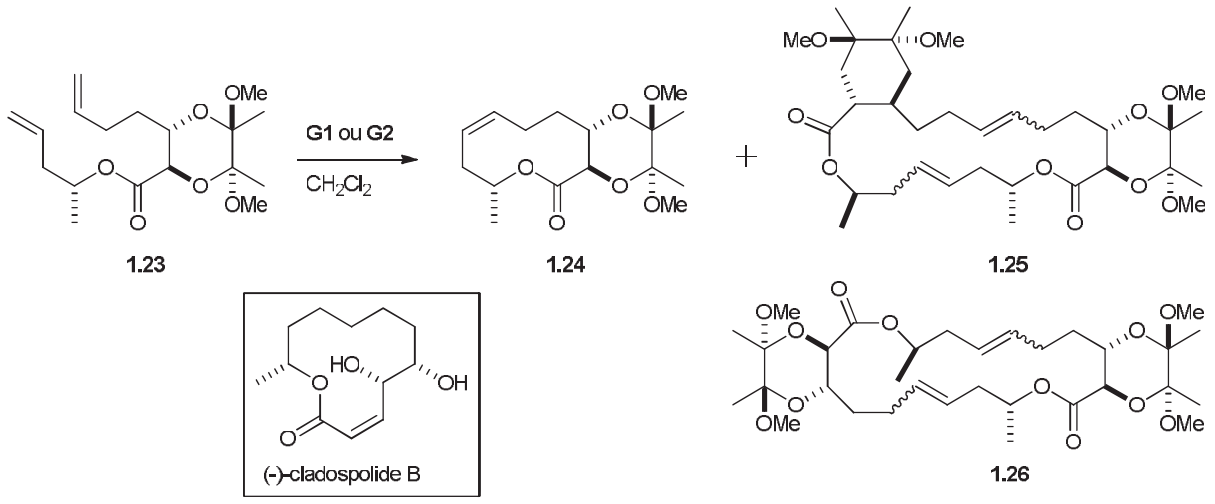

Schéma 1.9 : Cyclisation clé par Banwell *et al.*

En se basant sur le travail préliminaire du Dr Étienne Chénard sur la formation des dimères mentionnés préalablement (*Schéma 1.3)* et dans les articles 1 et 2, qui ont permis l'idetification des dimères observés, j'ai travaillé sur l'analyse des effets des substituants, de la température, de solvant employé et plusieurs variantes du catalyseur de Grubbs afin de comprendre les facteurs favorisant la formation des cycles à neuf et dix-huit membres. J'ai ensuite étudié la formation des monolactones ainsi que leur stabilité pour finalement appliquer l'aziridination à la lactone (*S*,*S*,*S*) et démontrer l'obtention du même produit de réarrangement de la synthèse de l'aliskiren. Le Dr Étienne Chénard et le Dr Sébastien Guesné ont effectué les travaux d'optimisation des diverses étapes de la synthèse incluant l'étude des divers réarrangements contenus dans l'article 2.

1.3 Article 1

On the importance of the relative stereochemistry of substituents in the formation of 9-membered lactones by ring-closing metathesis

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Synthesis **2015**, *47*, 1317.

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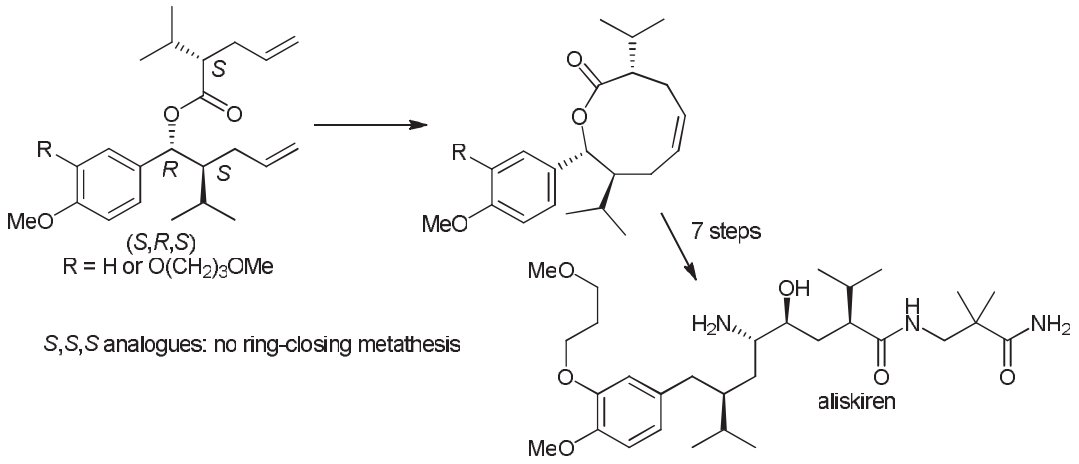
Abstract: The effects of isopropyl substituents and molar concentration of diastereomeric esters toward the formation of 9-membered unsaturated lactones, in the context of the synthesis of the intermediate of the antihypertensive drug aliskiren, have been studied.

Keywords lactone, metathesis, cyclization, macrocycle, dimerization.

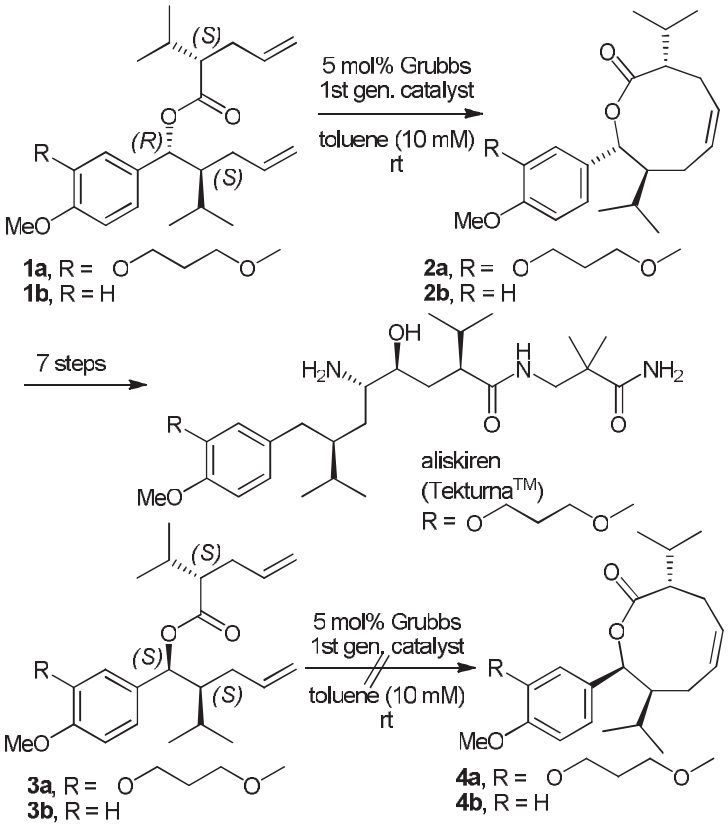


The now-venerable Grubbs olefin metathesis reaction[1] and its many recent variants[2] is an exceedingly useful and versatile method to construct internally unsaturated compounds of varying ring sizes.[3] Among these, the synthesis of nine-membered unsaturated lactones[4] and ethers[5] is of particular interest because of their limited occurrence in nature and their interesting biological activity.[6]

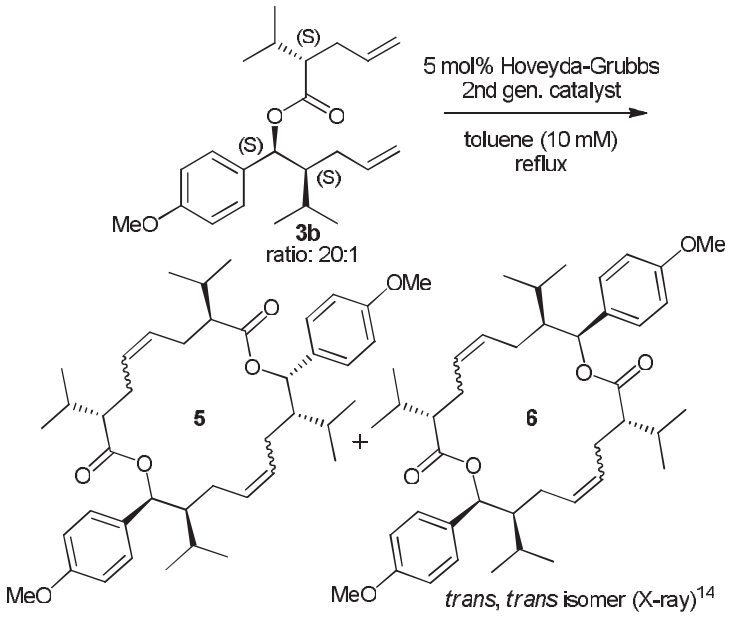
In a recent paper[7] on the total synthesis of the marketed antihypertensive drug aliskiren (Tekturna™)[8] we utilized a ring-closing metathesis reaction with the ester **1a** using Grubbs' 1st generation catalyst (**G1**)[9] to obtain a critical nine-membered unsaturated lactone intermediate **2a** that harbored two isopropyl groups in strategically pre-defined positions on an 8-aryloctanoic acid core unit (*Scheme 1.10*). The lactone **2a** was further elaborated to provide aliskiren in seven steps and 7% overall yield from readily available starting materials.[7] Compared to recent syntheses,[10] and a plethora of published patents,[11] our synthesis proved to be the shortest to date.

During the ring-closing metathesis reaction of a mixture of esters **1a** and diastereomeric **3a** with **G1** catalyst in refluxing toluene at a concentration of 10 mM, we observed that only the (*S*,*R*,*S*)-ester **1a** was converted into the lactone **2a**. The same observation was made with the (*S*,*R*,*S*)-ester of the corresponding *p*-methoxyphenyl analogue **1b**. The diastereomeric ester **3b** did not give the expected lactone **4b** and remained unchanged. Further studies with Grubbs

second-generation (**G2**)[12] and Hoveyda–Grubbs second generation (**H-G2**)[2b] catalysts with a 4:1 diastereomeric mixture of *p*-methoxyphenyl analogue **1b** led to the lactone **2b** in excellent yield and in much shorter time. Under these conditions, the diastereomeric (*S*,*S*,*S*)-ester **3b**, obtained independently from a stereoselective reduction of the corresponding ketone[13] led to an approximately 1:1 mixture of head-to-head and head-to-tail 18-membered dilactone dimers **5** and **6** as an inseparable mixture of olefin isomers. The structure of the C_2-symmetrical dilactone **6** was ascertained by X-ray crystallography (*Scheme 1.11*).[14]



Scheme 1.10 : Synthetic route to aliskiren via a 9-membered lactone



Scheme 1.11 : Formation of dilactone dimers from ester **3b**

In view of the continuing interest to develop viable synthetic routes to aliskiren, we focused on the key ring-closing metathesis step in our original synthesis.[7] In this paper, we report our qualitative observations pertaining to the reaction of the *p*-methoxyphenyl analogues **1b** and **3b** as well as their mono- and disubstituted diastereomeric esters in the presence of a variety of catalysts, in order to determine the influence of the isopropyl and vicinal aryl substituents and their relative stereochemistry on the nature of the products (*Figure 1.6*).

In the absence of any substituents, a mixture of racemic esters **7a** led to an inseparable mixture of dilactones **8a** and **9a** in excellent yield in presence of the **G1**, **G2**, and **H-G2** catalysts (*Scheme 1.12*, Table 1.1, entries 1–4). Compared to the **G1** catalyst, the dilactones were formed much faster with the **G2** catalyst. The reaction rate was slower in presence of **H-G2** catalyst in dichloromethane (entries 1–3). However, complete conversion occurred in refluxing toluene within 30 minutes (entry 4). No reaction occurred with the **G1** catalyst even in the presence of titanium(IV) isopropoxide[15] at room temperature in toluene. Hydrogenation of the double bonds was followed by treatment with triethylsilane/trifluoroacetic acid to give **11a** and **12a** in a quasi

1:1 ratio, which mirrored the amounts of the respective original dilactones **8a** and **9a** in the mixture (entries 1–4). The octanedioic acid was not isolated.

Treatment of the benzylic (*R*)-ester of **7b** with the **G1** catalyst resulted in the formation of the lactone **10b** in 33% yield, but only in the presence of titanium(IV) isopropoxide[15] and after repeated addition of catalyst (entry 5). In addition, dilactones **8b** and **9b** were formed in equal amounts as an inseparable mixture. The reaction rate was accelerated in the presence of the **G2** and **H-G2** catalysts (entries 6 and 7), but the yields were not improved. After completion of the reaction, lactone **10b** was isolated by chromatography and the mixture of the remaining dilactones was submitted to hydrogenation then reductive cleavage of the benzylic ester functioned to give the corresponding products **11b** and **12b** (*Scheme 1.12*).

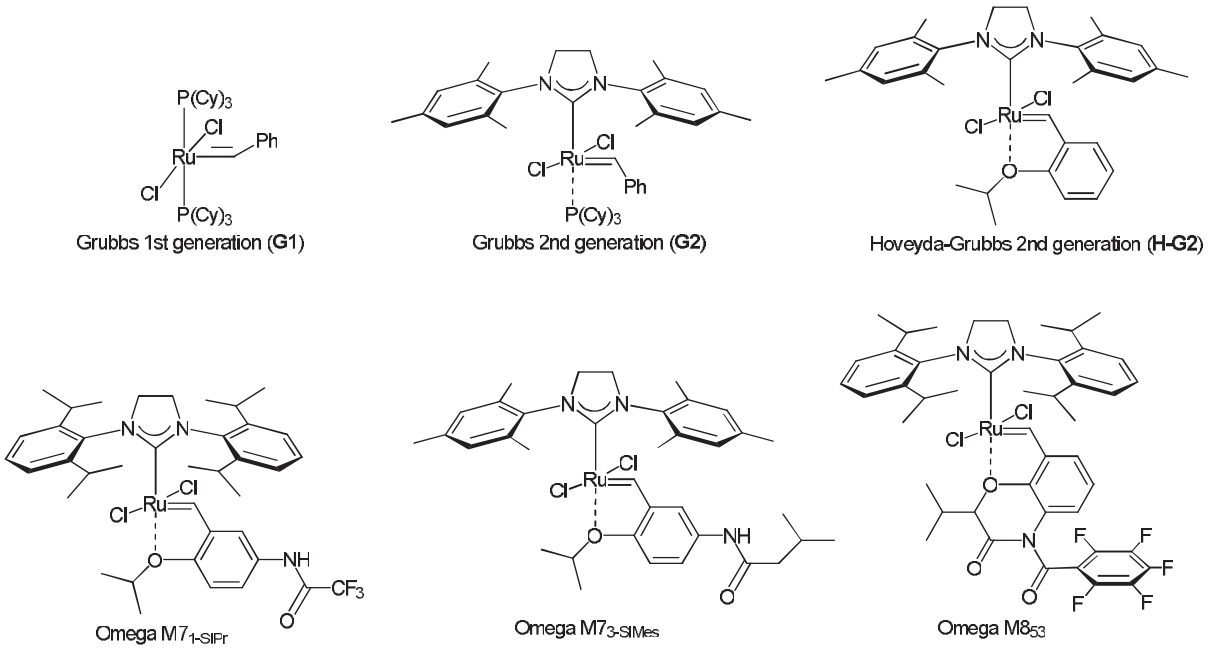


Figure 1.6 : Structures of catalysts used for the ring-closing metathesis. (M7$_{1\text{-SIPr}}$, M7$_{3\text{-SIMes}}$ and M8$_{53}$)[16]

In contrast, reaction of the benzylic (*S*)-ester of **7b** with the **G2** and **H-G2** catalysts led only to a mixture of the dilactones **8b** and **9b** which were converted into a 1:1 mixture of **11b** and **12b** as described above (entries 8 and 9). No reaction was observed with the **G1** catalyst.

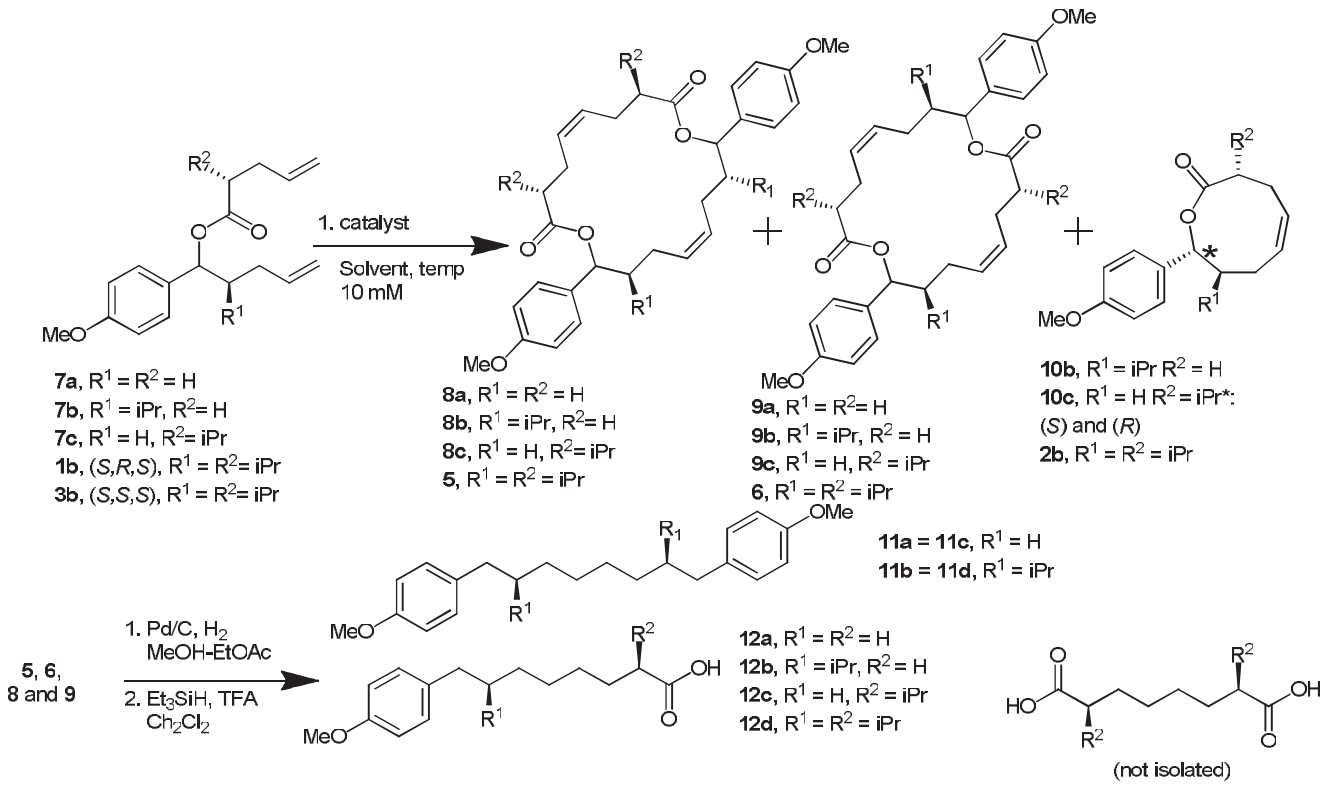
Treatment of **7c** (as a mixture of benzylic ester diastereomers) with **G1**, **G2**, and **H-G2** gave dilactones **8c** and **9c** in a quasi 1:1 ratio with a distinct preference for the latter catalyst with regard to time. Hydrogenation and reductive cleavage led to **11c** and **12c** (entries 9–11). Trace amounts of the corresponding lactone **10c** were observed by MS. We then returned to the original disubstituted model (*S*,*R*,*S*)-ester **1b**, and studied the reaction in the presence of **G2** and then **H-G2** catalysts and the newer generation catalysts (*Figure 1.6*).[16] Using 5 mol% catalyst in refluxing toluene led to the nine-membered lactone **2b** in good yield, although the reaction was 2–3 times slower with the new generation catalysts (entries 13–17). Finally, the (*S*,*S*,*S*)-ester **3b** was subjected to the same reactions conditions, leading solely to the dilactones **5** and **6** as previously observed with the **G2** and **H-G2** catalysts (entries 18–22).[14] Hydrogenation of the double bonds and reductive cleavage in the presence of triethylsilane/trifluoroacetic acid led to **11d** and **12d** in a 1:1 ratio; 2,7-diisopropyloctanedioic acid was not isolated.

Table 1.1 : Formation of Dilactones, Products from Cleavage Reactions, Reaction Parameters, and Ratio of Products with Different Catalysts (*Scheme 1.12*)

Entry	Ester	Ratio	Catalyst[a]	Solvent[b]	Temp (°C)	Time	Yield (%)		
							11	**12**	**2/10**
1	**7a** (*R*/*S*)	*Rac*	**G1**	CH_2Cl_2	50	24 h	47	49	-
2	**7a** (*R*/*S*)	*Rac*	**G2**	CH_2Cl_2	50		34	45	-
3	**7a** (*R*/*S*)	*Rac*	**H-G2**	CH_2Cl_2	50	24 h	39	44	-
4	**7a** (*R*/*S*)	*Rac*	**H-G2**	Toluene	110	30 min	31	38	-
5	**7b** (*R*)	4:1	**G1**[c,d]	Toluene	r.t.	5 d	17	20	33
6	**7b** (*R*)	4:1	**G2**[e]	Toluene	110	40 min	16	17	30

7	**7b** (*R*)	4:1	**H-G2**	Toluene	110	20 min	19	19	32
8	**7b** (*S*)	20:1	**G2**[e]	Toluene	110	45 min	32	36	-
9	**7b** (*S*)	20:1	**H-G2**	Toluene	110	45 min	36	37	-
10	**7c** (*R*/*S*)	*Rac*	**G1**[c,d]	Toluene	r.t.	5 d	40	35	-
11	**7c** (*R*/*S*)	*Rac*	**G2**[e]	Toluene	110	40 min	46	45	-
12	**7c** (*R*/*S*)	*Rac*	**H-G2**	Toluene	110	20 min	44	41	-
13	**1b** (*R*)	4:1	**G2**[e]	Toluene	110	40 min	-	-	67
14	**1b** (*R*)	4:1	**H-G2**	Toluene	110	20 min	-	-	64
15	**1b** (*R*)	4:1	$M7_{1\text{-SIPr}}$[e]	Toluene	110	1 h	-	-	66
16	**1b** (*R*)	4:1	$M7_{3\text{-SIMes}}$[e]	Toluene	110	1 h	-	-	63
17	**1b** (*R*)	4:1	$M8_{53}$[e]	Toluene	110	1 h	-	-	61
18	**3b** (*S*)	20:1	**G2**[e]	Toluene	110	40 min	39	40	-
19	**3b** (*S*)	20:1	**H-G2**	Toluene	110	40 min	40	43	-
20	**3b** (*S*)	20:1	$M7_{1\text{-SIPr}}$[e]	Toluene	110	1 h	37	38	-
21	**3b** (*S*)	20:1	$M7_{3\text{-SIMes}}$[e]	Toluene	110	1 h	39	36	-
22	**3b** (*S*)	20:1	$M8_{53}$[e]	toluene	110	1 h	38	38	-

[a] Unless otherwise stated, 0.05 equiv (5 mol%).
[b] 0.01 M.
[c] Ti(O*i*-Pr)4 (1 equiv).
[d] Catalyst (5 mol%) was added every day.
[e] Catalyst (5 mol%) was added after 30 min.



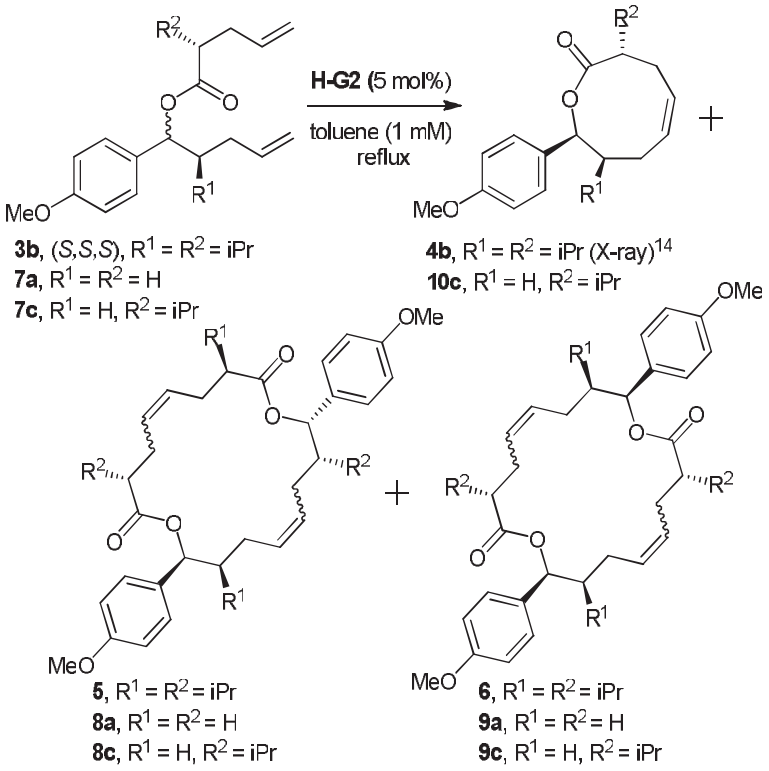
Scheme 1.12 : Formation of dilactones and products from cleavage reactions (Table 1.1)

Table 1.2 : Ring-Closing Metathesis of Diastereomeric Esters at 1 mM (*Scheme 1.13*)

Entry	Ester	Ratio	Time	Yield (%)	
				Monomer	Dimers
1	**7a** (*R*/*S*)	*Rac*	Overnight	-	81
2	**7c** (*R*/*S*)	*Rac*	Overnight	42	37
3	**3b** (*S*)	20:1	Overnight	46	32
4	**3b** (*S*)	20:1	7h	53	24

Since the formation of dilactone dimers prevailed in the case of the (*S*,*S*,*S*)-esters **3a** and **3b** (as well as other esters shown in Table 1.1), we considered running the reaction at higher dilution. Surprisingly, upon changing the concentration from 10 mM to 1 mM in refluxing toluene, ester **3b** gave the elusive lactone **4b** in 53% isolated yield, accompanied by 24% of the

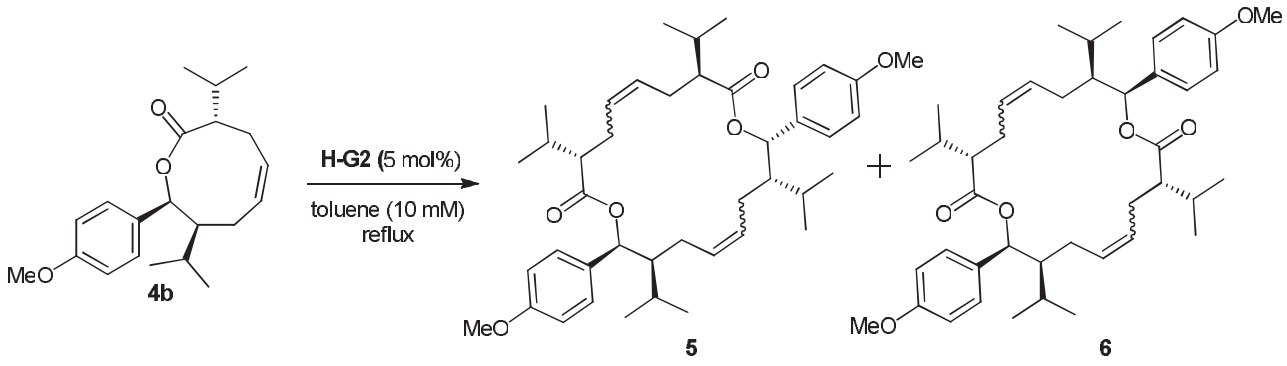
dimers **5** and **6** (*Scheme 1.13*, Table 1.2, entry 4). Extending the reaction time reduced the yield of lactone **4b** while favoring dilactone formation (entry 3). In contrast, dilution did not affect dilactone formation in the case of the unsubstituted ester **7a**, since no monolactone was observed. The monosubstituted ester **7c** afforded 42% of the corresponding lactone **10c** and 37% yield of dilactones (entry 2). This was an improvement compared to the traces observed in 10 mM solution (Table 1.1, entries 10–12).



Scheme 1.13 : Ring-closing metathesis of diastereomeric esters at 1 mM (Table 1.2)

The somewhat diminished yield of nine-membered (*S*,*S*,*S*)-lactone **4b** when the reaction was run overnight as a 1 mM solution, led us to question whether once formed, it could undergo cycloreversion via alkylidene–ruthenium intermediates to the dilactones **5** and **6**. Indeed, submitting lactone **4b** to the reaction conditions at the original concentration of 10 mM in presence of **H-G2** catalyst yielded the corresponding dilactones **5** and **6** (*Scheme 1.14*). When a

1:1 mixture of (*S*,*S*,*S*)-lactones **4b** and **10c** was subjected to the ring-closing metathesis with the **H-G2** catalyst in 10 mM solution, a mixture of all possible dilactones, including cross-over products was obtained, indicating that cycloreversion was possible in each case.

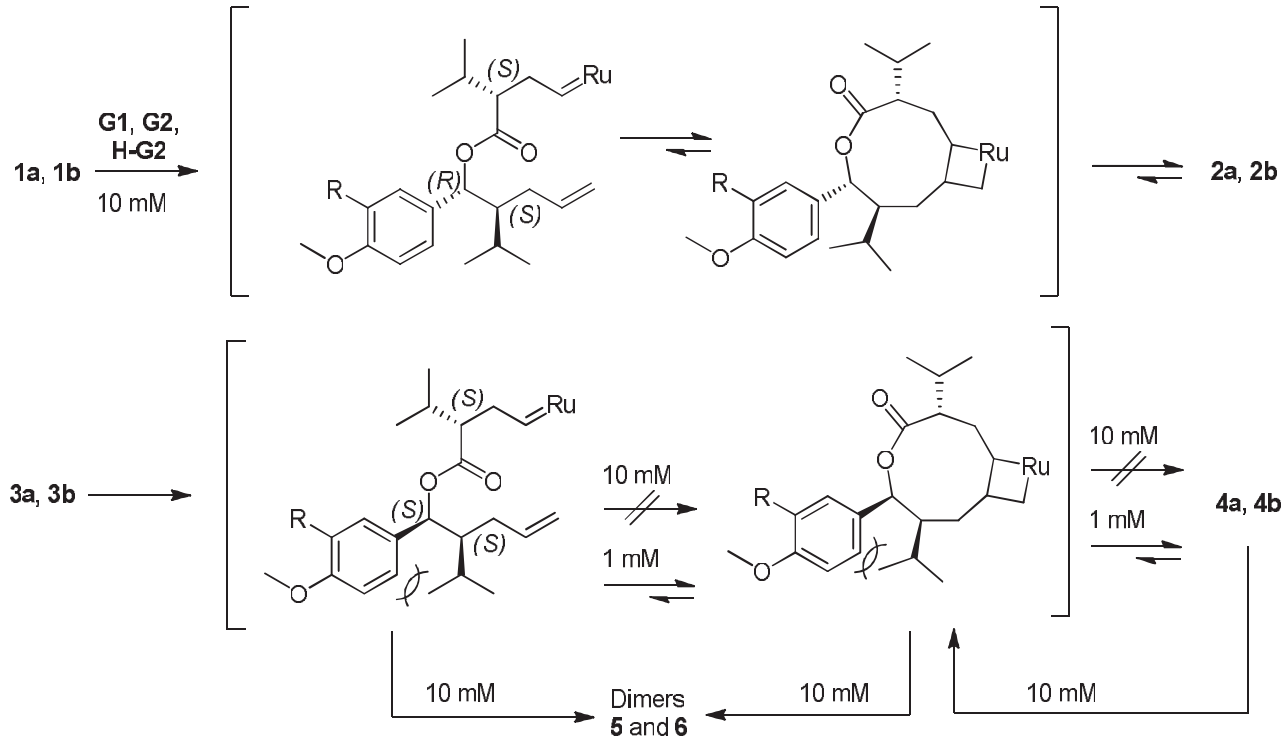


Scheme 1.14 : Cycloreversion via ring-opening metathesis and cross-coupling reactions

The existence of multiple coordination sites within each series of esters presents a major challenge with regard to the identity of the actual reactive intermediates and a preferred pathway. The outcome of ring-closing metathesis reactions leading to medium-sized rings is difficult to predict due to many intervening factors. For example, the nature of the catalyst, the solvent, the molarity, combined with conformational pre-organization, steric factors, as well as substituent and polar effects can have dramatic influences on the nature of the products (and byproducts) in a given reaction.[17] Nevertheless, it is clear that the ratio of nine-membered lactone formation compared to dilactones depends on the relative stereochemistry of the C7 isopropyl group and the adjacent C8 aryl moiety, and the concentration in the case of **1b** and **3b** (*Scheme 1.12*, Table 1.1, entries 14 and 19). This is evident from the results of reactions comprising the diastereomeric ester pairs (*S*,*R*,*S*)-**1b** and (*S*,*S*,*S*)-**3b**, and (*S*,*R*)-**7b** and (*S*,*S*)-**7b** (*Scheme 1.12*, Table 1.1, entries 13 and 18).

From our qualitative observations, it appears that the (*S*,*R*,*S*)-ester **1b** offers a less encumbered path to the ruthenium metallocycle, and eventually to the observed lactone **2b**

(*Scheme 1.15*). A combination of stereochemical, conformational, and possibly stereoelectronic effects associated with a transoid ester configuration combine to favor the cyclization to give **2a** and **2b** as thermodynamically favored products. Reports concerned with the formation of nine-membered lactones using ring-closing metathesis are scarce. For example, cyclization of functionalized esters harboring terminal olefinic appendages, led to nine-membered unsaturated lactones with *cis*- and *trans*-geometries depending on the substituents.[18] However, no dimeric dilactones were reported or discussed in this study. The key steps in the total synthesis of the nine-membered unsaturated marine metabolite helicolactone, involved a ring-closing metathesis step achieved in the presence of **G1** catalyst in excellent yields.[4] The effect of substituents in the cyclization of larger rings has been reported.[18,19]



Scheme 1.15 : Ring-closing metathesis in 10 mM and 1 mM solutions; only one of the two possible alkylidene–ruthenium intermediates is shown

It can be presumed that the (*S*,*S*,*S*)-esters **3a** and **3b** experience substantial steric clash between the C7 isopropyl and the C8 aryl moiety so as to interfere with the proper alignment of the alkylidene–ruthenium intermediates en route to the ruthenium metallocycles. Thus, competitive intermolecular cross-coupling reactions predominate to give the corresponding dilactones irreversibly (*Scheme 1.15*). At lower molar concentration, the steric effect is overcome by the low rate of interactions of the alkylidene–ruthenium intermediates. This is reflected by the fact that the lactone **4b** may be kinetically formed at 10 mM concentrations, but rapidly undergoes cycloreversion to form the stable dilactones **5** and **6**. Although there appears to be a cooperative beneficial effect of having the two isopropyl groups present in addition to a stereochemical preference for the (*S*,*R*,*S*)-esters **1a** and **1b**, it is not clear why the monosubstituted or the unsubstituted substrates such as **7a** and **7c** have a preference for macrocyclic dilactone formation.

In earlier reports, Smith and co-workers[20] have discussed the potentially reversible nature of the metathesis reaction, while Fürstner and co-workers[21] exploited the reversibility of olefin metathesis in the formation of macrocyclic dilactones related to (–)-(*R*,*R*)-pyrenophorin.[22]

In conclusion, we have reported our observations regarding the effect of vicinal isopropyl and aryl substituents in diastereomeric esters with regard to their preference to give nine-membered unsaturated lactones. These have been recently utilized in the total synthesis of the antihypertensive drug aliskiren.[7]

Unfortunately, the involvement of multiple ruthenium coordinated species and the dynamic nature of the ring closing metathesis process do not allow a more detailed analysis beyond the qualitative observations reported in this paper. Further studies in this area are in progress.

General Information. All reactions were performed in oven-dried glassware under an argon atmosphere using anhydrous, deoxygenated solvents. CH_2Cl_2 and toluene were dried by passage through an activated alumina column under argon [Solvent Drying System (SDS)]. Reagents were purchased and used without further purification. Reactions were monitored by analytical TLC carried out on 0.25-mm silica plates that were visualized under a UV lamp (254 nm) and developed by staining with ceric ammonium molybdate, *p*-anisaldehyde, and/or potassium permanganate solution. Flash column chromatography was performed using silica (particle size 40–63 μm, 230–400 mesh) at increased pressure. NMR spectra (^1H, ^{13}C) were recorded using Bruker AV- 300, AV-400, or AV-500 with MHz relative to TMS ($\delta = 0.00$) with the solvent resonance as the internal standard ($CHCl_3$, $\delta = 7.26$); ^{13}C NMR spectra are recorded using the central peak of $CDCl_3$ ($\delta = 77.16$) as the internal standard. Optical rotations were determined with a polarimeter at 589 nm, using a 1-dm cell at r.t. and are reported in units of $deg \cdot cm^3 \cdot g^{-1} \cdot dm^{-1}$.

Experimental procedures.

1-(4-Methoxyphenyl)pent-4-enyl Pent-4-enoate (7a); Typical Procedure

To a solution of pent-4-enoic acid (52 mg, 0.52 mmol, 1.0 equiv) in anhydrous toluene (4 mL) at 0 °C, Et_3N (0.09 mL, 0.62 mmol, 1.2 equiv), 2,4,6-trichlorobenzoyl chloride (0.1 mL, 0.62 mmol, 1.2 equiv), and DMAP (76 mg, 0.62 mmol, 1.2 equiv) were added. The resulting white slurry was stirred at 0 °C for 10 min. In a second dry round-bottomed flask a solution of 1-(4-methoxyphenyl)pent-4-en-1-ol (100 mg, 0.52 mmol, 1.0 equiv) in a minimum amount of anhydrous toluene was transferred to the reaction vessel containing the slurry in a dropwise manner at 0 °C then the reaction media was allowed to warm to r.t. The reaction was stirred at r.t. until TLC monitoring indicated no starting material remained. The volatiles were removed and the resulting residue was taken up in EtOAc (10 mL) and H_2O (10 mL). The aqueous layer was separated and extracted with EtOAc (3 × 10 mL). The combined organic layers were successively washed with 10% aq citric acid (10 mL) and sat. aq $NaHCO_3$ (10 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated to afford a yellow oil. The residue was purified by flash chromatography (silica gel, 1.5 cm × 20 cm; CH_2Cl_2–hexanes, 3:7) to yield **7a**

(134 mg, 94%) as a pale yellow oil; R_f= 0.55 (Et_2O–hexanes, 1:9). IR (neat): 3077, 2979, 2935, 2837, 1735, 1641, 1613, 1515, 1253, 1169, 1035 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.28–7.23 (m, 2 H), 6.89–6.84 (m, 2 H), 5.85–5.69 (m, 3 H), 5.06–4.95 (m, 4 H), 3.80 (s, 3 H), 2.45–2.31 (m, 4 H), 2.11–1.96 (m, 3 H), 1.89–1.79 (m, 1 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 172.5, 159.4, 137.6, 136.8, 132.8, 128.1, 115.6, 115.3, 114.0, 75.4, 55.4, 35.4, 34.0, 29.9, 29.0. HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{17}H_{22}NaO_3$: 297.1461; found: 297.1468.

(*S*)-2-Isopropyl-1-(4-methoxyphenyl)pent-4-enyl Pent-4-enoate (7b)

After following the representative procedure for **7a** using (2S)-2-isopropyl-1-(4-methoxyphenyl)pent-4-en-1-ol and pent-4-enoic acid, flash chromatography (silica gel, 2.5 cm × 20 cm; EtOAc–hexanes, 1:9) gave **7b** (236 mg, 75%) as a pale yellow oil; R_f= 0.57 (EtOAc–hexanes, 1:9); $[\alpha]_D^{20}$ +37 (*c* 0.5, $CDCl_3$). IR (neat): 3077, 2958, 2874, 2837, 1736, 1640, 1612, 1514, 1464, 1369, 1250, 1171, 1036 cm_{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.24–7.20 (m, 2 H), 6.87–6.82 (m, 2 H), 5.84–5.73 (m, 1 H), 5.69–5.66 (m, 1 H), 5.57–5.46 (m, 1 H), 5.05–4.94 (m, 2 H), 4.85 (s, 1 H), 4.81 (dd, *J* = 6.5, 1.8 Hz, 1 H), 3.79 (s, 3 H), 2.44–2.31 (m, 4 H), 2.04–1.93 (m, 2 H), 1.90–1.79 (m, 2 H), 0.93 (m, 6 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.2, 159.2, 138.1, 136.8, 132.4, 128.6, 128.2, 115.6, 115.6, 113.7, 55.4, 48.8, 34.0, 31.1, 29.0, 27.3, 21.2, 18.4. HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{20}H_{28}NaO_3$: 339.1919; found: 339.1931.

1-(4-Methoxyphenyl)pent-4-enyl (*S*)-2-Isopropylpent-4-enoate (7c)

After following the representative procedure for **7a** using 1-(4-methoxyphenyl)pent-4-en-1-ol and (S)-2-isopropylpent-4-enoic acid, flash chromatography (silica gel, 2.5 cm × 20 cm; EtOAc–hexanes, 1:9) gave **7c** (771 mg, 94%) as a pale yellow oil; R_f= 0.57 (EtOAc–hexanes, 1:9). IR (neat): 3077, 2960, 2926, 2875, 1735, 1640, 1613, 1514, 1465, 1248, 1167, 1107, 1035 cm_{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.28–7.23 (m, 2 H), 6.87–6.83 (m, 2 H), 5.83–5.56 (m, 3 H), 5.03–4.95 (m, 3 H), 4.90 (ddd, *J* = 11.9, 8.7, 1.7 Hz, 1 H), 3.80 (s, 3 H), 2.35–2.17 (m, 3 H), 2.10–1.96 (m, 3 H), 1.91–1.78 (m, 2 H), 0.94 (d, *J* = 6.8 Hz, 1.5 H), 0.87 (d, *J* = 6.7 Hz, 1.5 H), 0.87 (d, *J* = 6.8 Hz, 1.5 H), 0.80 (d, *J* = 6.7 Hz, 1.5 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 174.5, 174.5, 159.3, 137.7, 137.7, 136.1, 135.9, 132.9, 132.8, 128.3, 116.56, 116.47, 115.31,

115.28, 113.79, 75.17, 75.13, 55.38, 52.72, 52.63, 35.40, 35.37, 34.12, 33.99, 30.54, 30.31, 29.92, 20.50, 20.33, 20.23. HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{20}H_{28}NaO_3$: 339.1918; found: 339.1935.

(8*S*,9*R*)-8-Isopropyl-9-(4-methoxyphenyl)-4,7,8,9-tetrahydrooxonin-2(3*H*)-one (10b)

Hoveyda–Grubbs 2nd generation catalyst (5 mg, 0.008 mmol, 0.05 equiv) was added to a solution of diene **7b** (50 mg, 0.16 mmol, 1.0 equiv) in anhydrous toluene (16 mL) and the mixture was stirred at reflux for 20 min. The mixture was cooled to r.t., treated with excess of ethyl vinyl ether and evaporated at r.t. carefully. The residue was purified by flash chromatography (silica gel, 1.5 cm diameter × 20.0 cm height, EtOAc– hexanes, 1:50) to yield **10b** (17 mg, 38%) as a clear oil; R_f = 0.55 (EtOAc–hexanes, 1:9); $[\alpha]_D^{20}$+37 (*c* 0.5, $CDCl_3$). IR (neat): 2955, 2925, 2872, 1722, 1612, 1514, 1460, 1245, 1173, 1138, 1035 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.30 (m, 2 H), 6.91–6.85 (m, 2 H), 5.84 (d, *J* = 10.6 Hz, 1 H), 5.72–5.63 (m, 1 H), 5.63–5.54 (m, 1 H), 3.80 (s, 3 H), 2.48 (dd, *J* = 20.3, 10.7 Hz, 1 H), 2.40–2.27 (m, 2 H), 2.17–2.08 (m, 1 H), 2.07–1.89 (m, 3 H), 1.47 (dtd, *J* = 13.7, 6.9, 2.4 Hz, 1 H), 0.86 (d, *J* = 6.9 Hz, 3 H), 0.86 (d, *J* = 6.8 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.9, 159.6, 135.7, 132.1, 129.3, 125.5, 114.0, 79.8, 55.4, 52.6, 33.9, 27.8, 25.1, 24.8, 22.0, 16.3. HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{18}H_{24}NaO_3$: 311.3765; found: 311.2605.

(3*S*,9*R*)-3-Isopropyl-9-(4-methoxyphenyl)-4,7,8,9-tetrahydrooxonin-2(3*H*)-one (10c)

Aftrer fllowing the representative procedure for **10b** using diene **7c** (30 mg, 0.095 mmol, 1.0 equiv) and heated at reflux overnight, residue was purified by flash chromatography (silica gel, 1.5 cm diameter × 20.0 cm height, EtOAc–hexanes, 1:50) to yield **10c** (12 mg, 42%) as a clear oil; R_f = 0.55 (EtOAc–hexanes, 1:9); $[\alpha]_D^{20}$ –32 (*c* 0.5, $CDCl_3$). IR (neat): 2954, 2928, 2865, 1702, 1513, 1459, 1247, 1173, 1159, 1037 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.27–7.24 (m, 2 H), 6.90–6.85 (m, 2 H), 5.84–5.73 (m, 1 H), 5.71–5.61 (m, 1 H), 5.61–5.51 (m, 1 H), 3.80 (s, 3 H), 2.62–2.50 (m, 2 H), 2.33–2.24 (m, 1 H), 2.21–2.09 (m, 2 H), 2.06– 1.92 (m, 3 H), 0.99 (d, *J* = 6.6 Hz, 3 H), 0.95 (d, *J* = 6.6 Hz, 3 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 177.1, 164.8, 159.3, 137.5, 135.9, 135.1, 133.1, 131.0, 128.6, 127.9, 126.0, 114.0, 55.4, 51.5, 36.9, 29.9, 28.4, 23.8, 21.5, 19.8. HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{18}H_{24}NaO_3$: 311.3766; found: 311.3772.

1,8-Bis(4-methoxyphenyl)octane (11a) and 8-(4-Methoxyphenyl)octanoic Acid (12a); Representative Procedure

Hoveyda–Grubbs 2nd generation catalyst (4 mg, 0.006 mmol, 0.05 equiv) was added to a solution of **7a** (30 mg, 0.11 mmol, 1.0 equiv) in anhydrous toluene (11 mL) and the mixture was stirred and heated at reflux for 30 min. The mixture was cooled to r.t., treated with excess of ethyl vinyl ether, evaporated slowly and filtered through Celite^{TM} to yield a crude mixture of dilactones 8a and **9a**. Pd/C (cat.) was added to a solution of dilactones **8a** and **9a** in MeOH (3 mL) and EtOAc (3 mL). The mixture was purged with H_2 and the mixture was stirred under a H_2 atmosphere (H_2 balloon). The reaction was monitored by LR-MS. When the reaction was complete, the mixture was filtered through Celite and concentrated to afford the crude dilactones.

TFA (3 drops) was added to a solution of the crude dilactones and Et_3SiH (0.1 mL) in CH_2Cl_2 (1 mL). The solution was stirred at r.t. for 10 min. Volatiles were removed under vacuum with a rotary evaporator and the residue was purified by flash chromatography [silica gel, 1.5 cm diameter × 20 cm height, hexanes (150 mL) then EtOAc–hexanes, 1:19] to yield alkane **11a** (6 mg, 31%) and acid **12a** (11 mg, 38%), both as clear oils.

Alkane 11a

R_f= 0.68 (EtOAc–hexanes, 1:4). IR (neat): 2921, 2849, 1512, 1464, 1245, 1177, 1033 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.09 (d, *J* = 8.3 Hz, 4 H), 6.82 (d, *J* = 8.5 Hz, 4 H), 3.79 (s, 6 H), 2.59–2.48 (m, 4 H), 1.61–1.52 (m, 4 H), 1.36– 1.28 (m, 8 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.7, 135.2, 129.4, 113.8, 55.4, 35.2, 31.9, 29.6, 29.4. HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{22}H_{31}O_2$: 327.2319; found: 327.2328.

Acid 12a

R_f= 0.17 (EtOAc–hexanes, 1:4). IR (neat): 2923, 2853, 1709, 1512, 1465, 1245, 1177, 1054, 1033 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.12–7.05 (m, 2 H), 6.85–6.79 (m, 2 H), 3.79 (s, 3 H), 2.61–2.48 (m, 2 H), 2.34 (t, *J* = 7.5 Hz, 2 H), 1.71–1.51 (m, 4 H), 1.35–1.29 (m, 6 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 179.9, 157.7, 135.0, 129.4, 113.8, 55.4, 35.1, 34.1, 31.8, 29.2, 29.1, 29.1, 24.8. HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{15}H_{22}NaO_3$: 273.1461; found: 273.1472.

(3*R*,8*R*)-3,8-Bis(4-methoxybenzyl)-2,9-dimethyldecane (11b) and (*R*)-7-(4-Methoxybenzyl)-8-methylnonanoic Acid (12b)

The representative procedure used to obtain **11a** and **12a** was applied to diene **7b** to give **11b** (7 mg, 36%) and **12b** (10 mg, 37%), both as clear oils.

Alkane 11b

R_f= 0.64 (EtOAc–hexanes, 1:9); $[\alpha]_D^{20}$ +21 (*c* 1.0, $CHCl_3$). IR (neat): 2924, 2861, 1512, 1246, 1055, 1464, 1033 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.08–7.01 (m, 4 H), 6.84–6.78 (m, 4 H), 3.79 (s, 6 H), 2.49 (dd, *J* = 13.7, 6.8 Hz, 2 H), 2.35 (dd, *J* = 13.8, 7.6 Hz, 2 H), 1.67 (dtd, *J* = 13.7, 6.9, 3.5 Hz, 2 H), 1.44–1.33 (m, 2 H), 1.23–1.02 (m, 8 H), 0.86 (d, *J* = 13.9 Hz, 6 H), 0.83 (d, *J* = 13.9 Hz, 6 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.6, 134.5, 130.1, 113.6, 55.4, 46.1, 36.3, 29.7, 28.4, 28.0, 19.3, 18.8. HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{28}H_{43}O_2$: 411.3258; found: 411.3277.

Acid 12b

R_f= 0.12 (EtOAc–hexanes, 1:9); $[\alpha]_D^{20}$ +11 (*c* 1.0, $CHCl_3$). IR (neat): 2938, 2866, 1709, 1512, 1455, 1346, 1321, 1059, 1016 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.05 (d, *J* = 8.6 Hz, 2 H), 6.84–6.78 (m, 2 H), 3.79 (s, 3 H), 2.53 (dt, *J* = 12.0, 5.6 Hz, 1 H), 2.38–2.34 (m, 1 H), 2.34–2.28 (m, 2 H), 1.74–1.65 (m, 1 H), 1.62–1.53 (m, 2 H), 1.46–1.38 (m, 1 H), 1.31–1.22 (m, 6 H), 1.14 (dd, *J* = 18.5, 11.4 Hz, 1 H), 0.89 (d, *J* = 6.9 Hz, 3 H), 0.84 (d, *J* = 6.9 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 179.2, 157.7, 134.4, 130.0, 113.7, 55.4, 46.1, 36.3, 34.0, 29.6, 29.5, 28.6, 27.4, 24.8, 19.3, 18.9. HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{18}H_{28}NaO_3$: 411.3258; found: 411.3277.

2-Isopropyl-8-(4-methoxybenzyl)octanoic Acid (12c)

The representative procedure used to obtain **11a** and **12a** was applied to diene **7c** to give **12c** (19 mg, 41%) as a clear oil; R_f= 0.11 (EtOAc–hexanes, 1:9); $[\alpha]_D^{20}$ –5 (*c* 1.0, $CHCl_3$). IR (neat): 2926, 2854, 1700, 1511, 1464, 1298, 1176, 1116, 1037 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.13–7.06 (m, 2 H), 6.86–6.79 (m, 2 H), 3.79 (s, 3 H), 2.58–2.50 (m, 2 H), 2.17–2.07 (m, 1 H), 1.88 (dq, *J* = 13.7, 6.7 Hz, 1 H), 1.67–1.45 (m, 4 H), 1.44–1.19 (m, 7 H), 0.97 (d, *J* = 6.7 Hz, 6 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 182.4, 157.7, 135.0, 129.4, 113.8, 55.4, 52.7, 35.1, 31.8,

30.6, 29.6, 29.4, 29.2, 27.9, 20.6, 20.2. HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{18}H_{28}NaO_3$: 411.3258; found: 411.3113.

2-Isopropyl-7-(4-methoxybenzyl)-8-methylnonanoic Acid (12d)

The representative procedure used to obtain **11a** and **12a** was applied to diene **3b** to give gave **12d** (11 mg, 40%). R_f = 0.12 (EtOAc–hexanes, 1:9) as a clear oil; $[\alpha]_D^{20}$ +16 (*c* 0.3, $CDCl_3$). IR (neat): 2925, 2860, 1704, 1511, 1461, 1375, 1245, 1178, 1038 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 10.59 (s, 1 H), 7.05 (d, *J* = 8.4 Hz, 2 H), 6.81 (d, *J* = 8.5 Hz, 2 H), 3.78 (s, 3 H), 2.51 (dd, *J* = 13.7, 6.6 Hz, 1 H), 2.36 (dd, *J* = 13.7, 7.8 Hz, 1 H), 2.13–2.05 (m, 1 H), 1.85 (dq, *J* = 13.7, 6.9 Hz, 1 H), 1.74–1.63 (m, 1 H), 1.60–1.49 (m, 1 H), 1.48–1.36 (m, 2 H), 1.29–1.14 (m, 6 H), 0.96–0.92 (m, 6 H), 0.88 (d, *J* = 6.8 Hz, 3 H), 0.84 (d, *J* = 6.9 Hz, 3 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 181.5, 157.7, 134.4, 130.1, 113.7, 55.4, 52.6, 46.1, 36.3, 30.6, 29.5, 29.4, 28.6, 28.2, 27.7, 20.6, 20.2, 19.3, 18.8. HRMS (ESI–): *m*/*z* $[M - H]^-$ calcd for $C_{21}H_{33}O_3$: 333.2435; found: 333.2440.

Acknowledgment

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1380130.

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1.4 Article 2

Conception and Evolution of Stereocontrolled Strategies toward Functionalized 8-Aryloctanoic Acids Related to the Total Synthesis of Aliskiren

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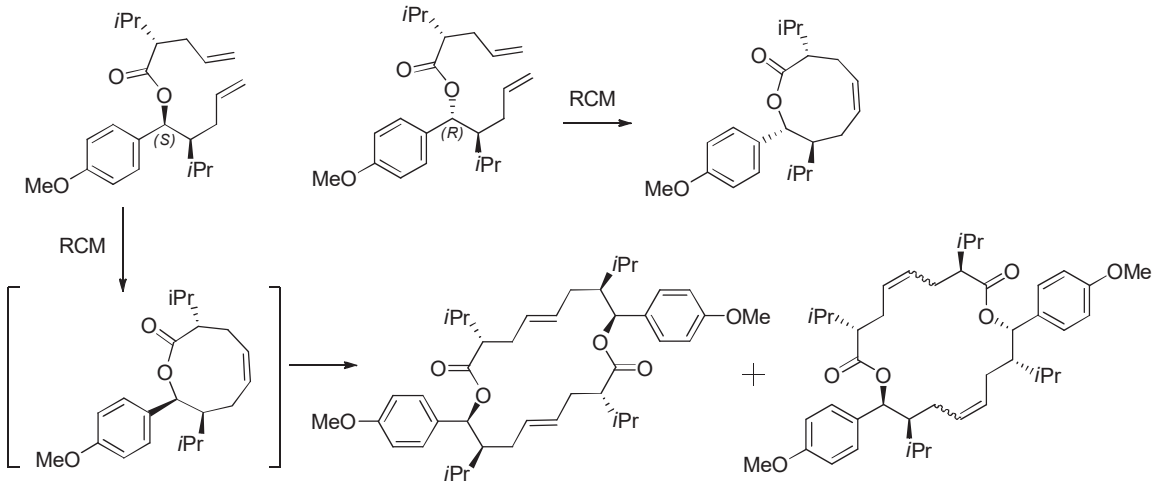
Abstract: A detailed account is given describing the approaches used toward the total synthesis of aliskiren. In particular, ring-closing metathesis with the Hoveyda−Grubbs catalyst accelerates the formation of a 9-membered lactone from an (R)-ester. The diastereomeric (S)-ester leads to the formation of dimeric dilactones, which were characterized by X-ray analysis and chemical conversions.



Introduction

The regulation of arterial blood pressure is a complex physiological process with important implications in the pathogenesis of cardiovascular diseases.[1] Among these,

hypertension is considered to be a high risk factor and associated with incidences of stroke and kidney failure. A natural substance produced by the kidney, named renin, was known to have a hypertensive effect in experimental animals as far back as 1898.[2] Since then, pioneering efforts in cardiovascular medicine have advanced the frontiers of antihypertensive research, culminating with the availability of drugs to control the disease.[3] The aspartyl protease renin is part of the renin angiotensin system (RAS), known to be a regulator of blood pressure and electrolyte balance.[4] Stimulation of the RAS leads to the release of renin from the kidney, whereupon a series of proteolytic events take place ultimately forming vasoconstricting peptides.[5] Thus, renin cleaves a Leu-Val peptide linkage in its endogenous substrate angiotensinogen, releasing the decapeptide angiotensin I (*Figure 1.7A*). A second enzyme in the RAS, angiotensin-converting enzyme (ACE), then cleaves two amino acids from angiotensin I to give the vasoconstricting octapeptide angiotensin II. On the basis of these observations, the inhibition of renin as the first and rate-limiting step in the RAS cycle was considered to be a viable and attractive strategy in the quest toward discovery of novel antihypertensives working by a unique mechanism.[6] Indeed, major advances toward this goal have been made during the past three decades.[7] Unfortunately, and in spite of achieving highly effective in vivo inhibition of renin with beneficial antihypertensive action, such activities had to be terminated in a number of pharmaceutical companies primarily due to issues dealing with cost of production and bioavailability. Nevertheless, the synthesis of minimally peptidic potent inhibitors, such as CGP-38960 (*Figure 1.7B*), was admirably guided by structure-based design relying on valuable information gleaned from cocrystal structures with human recombinant renin.[8] Although active investigations toward the synthesis of new renin inhibitors had somewhat waned, a new class of nonpeptidic 8-aryloctanoic acid amides was found to have highly promising activity.[9] Further refinement in this series by scientists at Ciba-Geigy (Pharma) in Basel led to aliskiren (**1**), which is presently marketed by Novartis for the treatment of hypertension under the trade name Tekturna (*Figure 1.7C*).[10] The cocrystal structure analysis of aliskiren in complex with renin revealed the characteristic interactions of the hydroxyethylene segment with aspartic acid residue and unique binding interactions of the hydrophobic moieties.[11] Of particular significance in optimizing the inhibitory activity was the truncation of segments corresponding to the P2 and P4 site in the original inhibitors such as CGP-38560 by directly linking P1 and P3 (*Figure 1.7*). Compared to the previous generation of renin inhibitors, often possessing heterocyclic

appendages near the hydroxyethylene subunit,[10] aliskiren represents a structurally simple ω-aryloctanoic acid amide harboring four stereogenic carbon atoms (*Figure 1.7*). Further SAR studies also demonstrated an improvement of the affinity at the P2′ site when the n-butylamide was exchanged for a 3-amino-2,2-dimethylpropionamide unit.[12] Already, considerable interest has been generated in the clinical aspects of aliskiren, a first-in-class, orally active antihypertensive.[13]

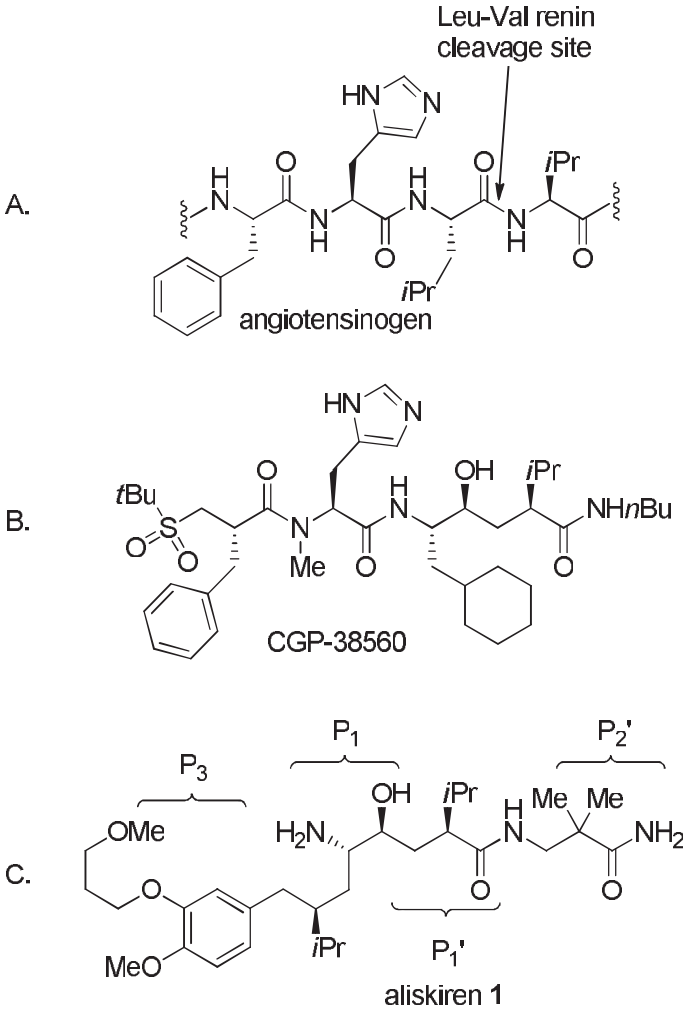
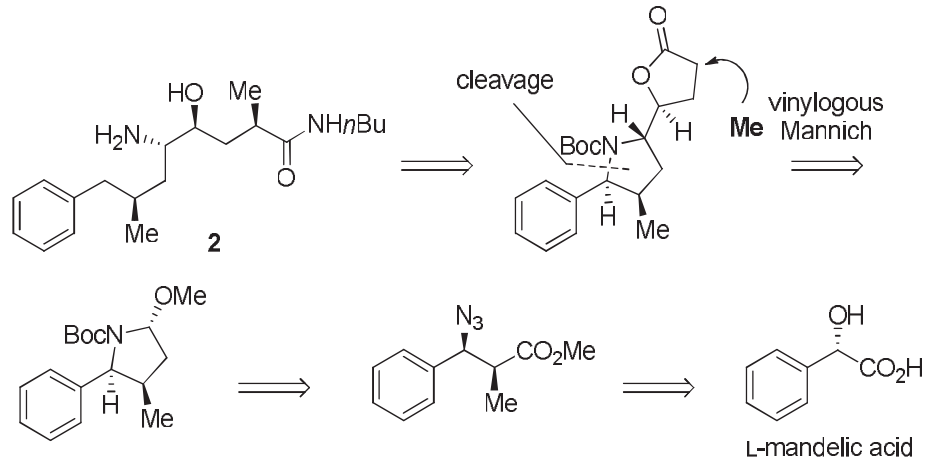


Figure 1.7 : (A) Scissile Leu-Val bond in angiotensinogen by the enzyme renin. (B) First-generation peptidic inhibitor. (C) Structure of aliskiren

Background

Among the many research collaborations with pharmaceutical companies, none are more challenging than when an academic is asked to contribute to an active project with the prospects of developing a viable synthesis of a molecule of interest.[14] Encouraged by such an opportunity, we first explored a stereocontrolled approach to a bioactive prototype of aliskiren, starting with L-mandelic acid (*Figure 1.8A*).[15] In the following years, we were motivated to devise strategies avoiding the use of azide as a source of the C-5 nitrogen atom (aliskiren numbering) for safety considerations in an eventual scale-up operation. Further consideration to our mandate was to avoid the use of chiral auxiliaries to create stereogenic carbon atoms with required substituents for cost and possibly IP reasons. Faced with these restrictions, we devised two stereocontrolled approaches to 2,7-dialkyl-4-hydroxy-5-amino-8-aryloctanoic acids exemplified by **3**, starting with the readily available L-pyroglutamic acid as a chiron[16] (*Figure 1.8B* and *1.8C*). In addition to providing the source of the nitrogen atom, the inherent stereochemistry in the starting chiron served to control the sequential stereocontrolled introduction of appropriate functionality.

A.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H2N
NHnBu
O
Me
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O
O
H
BocN
H
H
Me
Me
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Mannich
OMe
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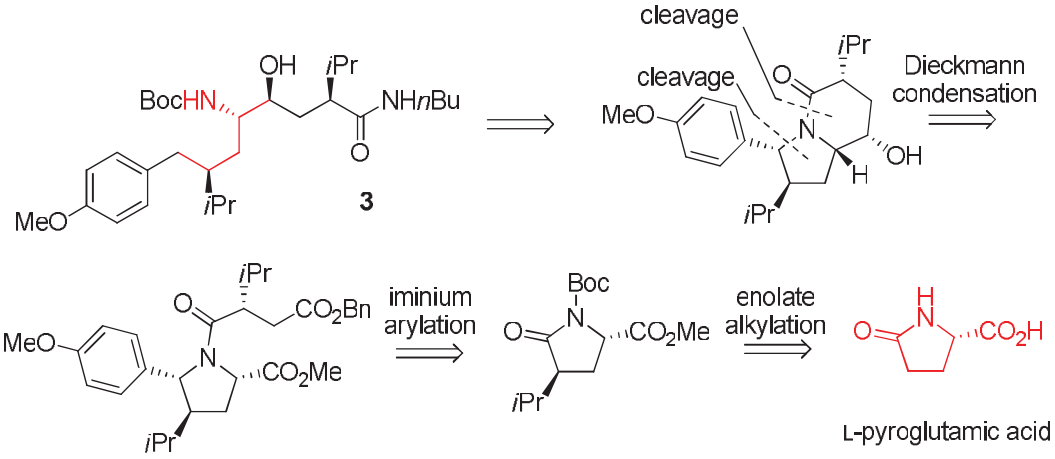
H
Me
N3
CO2Me
Me
OH
CO2H
L-mandelic acid

B.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NHnBu
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iPr
O
MeO
N
OH
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Dieckmann
condensation
iPr
O
CO2Bn
MeO
N
CO2Me
iPr
iminium
arylation
Boc
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alkylation
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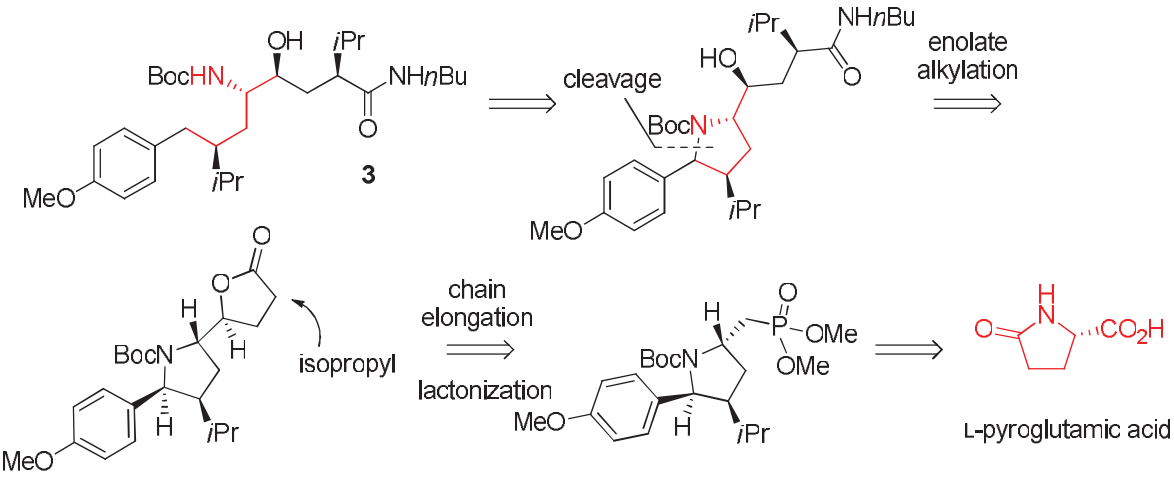
N
O
CO2H
L-pyroglutamic acid

C.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MeO
enolate
alkylation
O
H
BocN
H
H
iPr
MeO
isopropyl
chain
elongation
lactonization
O
H
P
OMe
BocN
OMe
MeO
H
iPr
H
N
O
CO2H
L-pyroglutamic acid

Figure 1.8 : Early prototypes of renin inhibitors: (A) L-mandelic acid as starting chiron; (B and C) L-pyroglutamic acid as starting chiron and source of nitrogen (Dieckmann and phosphate extension routes)

Since our initial efforts towards the stereocontrolled synthesis of aliskiren,[15,16] there has been a plethora of reports particularly in the patent literature[17] describing a variety of approaches to intermediates and analogs. In a brief overview, we shall distinguish those involving approaches[18] or formal syntheses,[19] from those pertaining to actual total syntheses[20] of aliskiren.[21] In the majority of these syntheses, extensive use was made of the Evans,[22] and Schöllkopf[23] chiral auxiliaries to secure the C-2/C-7 isopropyl and C-4/C-5 amino alcohol groups respectively, in high enantio- or diastereoselectivity. Alternative approaches are described in several patents.[17,24] For example, the key building blocks used in the Speedel process[25] for the synthesis of aliskiren are shown in *Figure 1.9*. Intermediate **A** was obtained by an asymmetric catalytic hydrogenation of an α,β-unsaturated precursor in >95% ee starting from a racemic dialkoxyphenyl propionate precursor (total 7 steps). The enantiopure chlorovinyl intermediate **B** was prepared from the racemic ester via pig liver esterase resolution in 47% yield, after distillation. The undesired enantiomeric carboxylic acid was recycled by epimerization, esterification and repeated enzyme treatment (total 3 steps to **B** from methyl isobutyrate in one pass). Intermediate **C** was prepared from acid **A**, in three steps. Coupling of **C** and **B** was accomplished via the corresponding Grignard reagent derived from **B** in the presence of Fe^{III} acetylacetonate to give **D** in 75% yield. Subsequent steps involving hydrolysis to the acid, bromolactonization, epoxide formation, lactonization, mesylation and azide displacement to give the azidolactone precursor **E**. Condensation with 3-amino-2,2-dimethylpropionamide, followed by hydrogenation and crystallization gave aliskiren fumarate (total 10 steps from **D**). Improvements in the bromolactonization step have also been reported.[24]

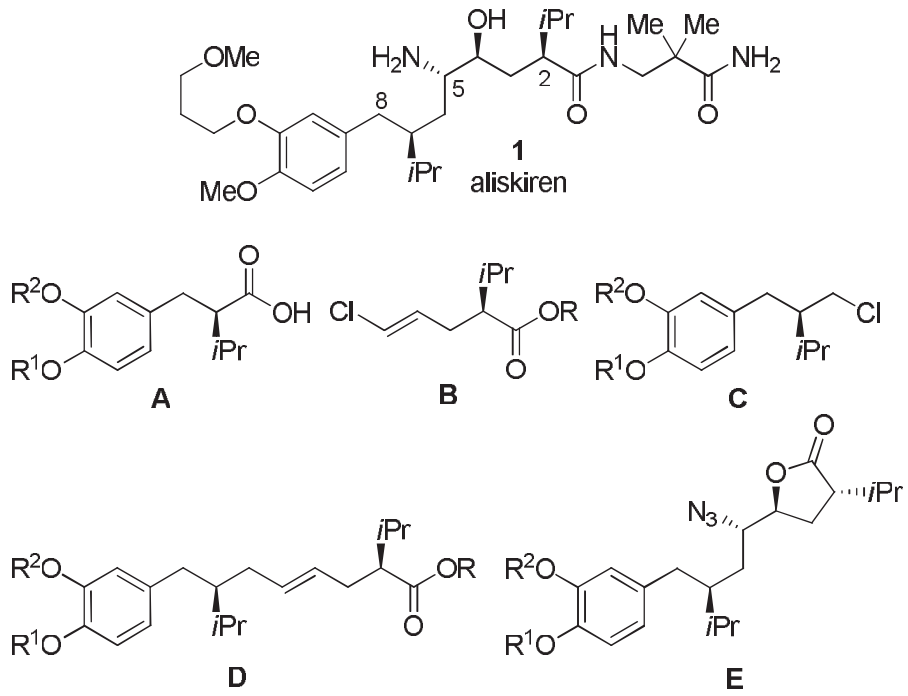
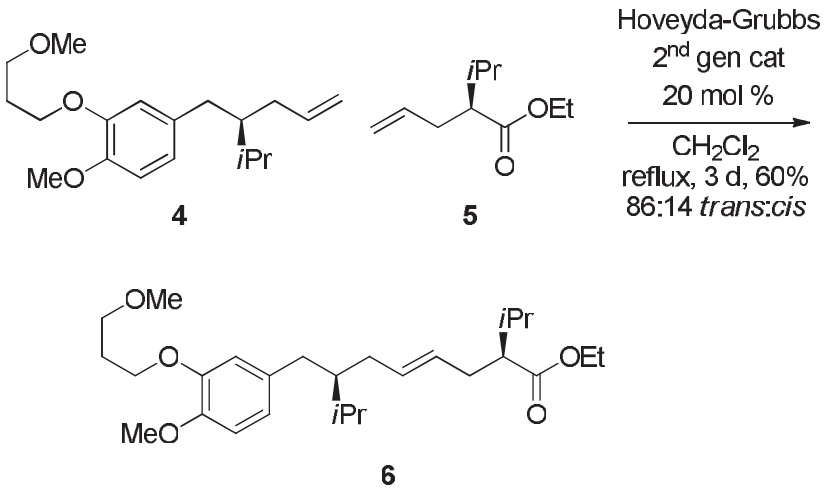


Figure 1.9 : Key building blocks in the Speedel process toward aliskiren

In the past, chiral auxiliaries were used to access intermediates such as **C** and **D** (*Figure 1.9*).[18-20,22] In spite of this invaluable method, all of the reported syntheses comprise numerous steps to access the building blocks individually, and prior to engaging them in a stepwise assembly. Furthermore, except for some of the patented processes, none of the published papers provide experimental details leading to aliskiren.

Recently, we reported on an efficient synthesis of intermediate **4** adopting an extension of the Stoltz[26] catalytic asymmetric transposition of an allylic enolcarbonate derived from the corresponding aryl ketone precursor followed by reduction at the benzylic carbon (*Scheme 1.16*). [27] A cross metathesis reaction with ester **5,** led to the advanced Speedel intermediate **6** in five linear steps and 38% overall yield from 4-methoxy-3-methoxypropoxy-1-bromobenzene.



Scheme 1.16 : Shorter route to an advanced intermediate in the Speedel process

Nine-membered lactone route towards aliskiren

As is clear from the preceding section, a major challenge in devising synthetic approaches to aliskiren is the introduction of the C-2/C-7 isopropyl groups, and the C-4/C-5 amino alcohol subunit in the 8-aryloctanoic acid framework with high stereocontrol (*Figure 1.7C*). Added to this, is the desire to devise a relatively shorter route compared to existing reports, including those in the patent literature. We recently reported an 11-step total synthesis of aliskiren starting with a single chiral progenitor (*Figure 1.10*).[28] Thus, (2*S*)-2-isopropyl-4-pentenal **8**, easily prepared from the acid **7**,[28] was converted to a 6:1 mixture of diastereomeric benzylic alcohols **H**, which was used to assemble the ester **G**. Ring-closing metathesis in the presence of the Grubbs I catalyst[29,30] gave the 9-membered lactone **F** (*Figure 1.10*). Regio- and stereoselective introduction of an amino and an alcohol group provided the entirely functionalized 8-aryloctanoic acid framework of aliskiren and of selected amide variants. In this paper, we wish to elaborate on various aspects of this synthesis, particularly with regard to the preparation and functionalization of the 9-membered lactones using a ring-closing metathesis en route toward aliskiren.

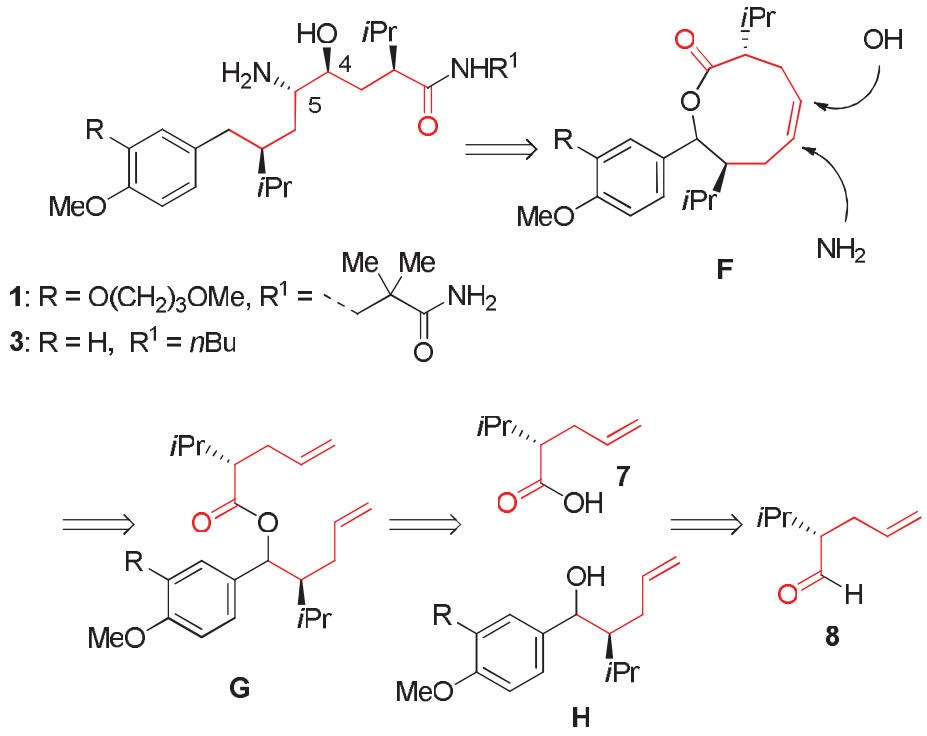
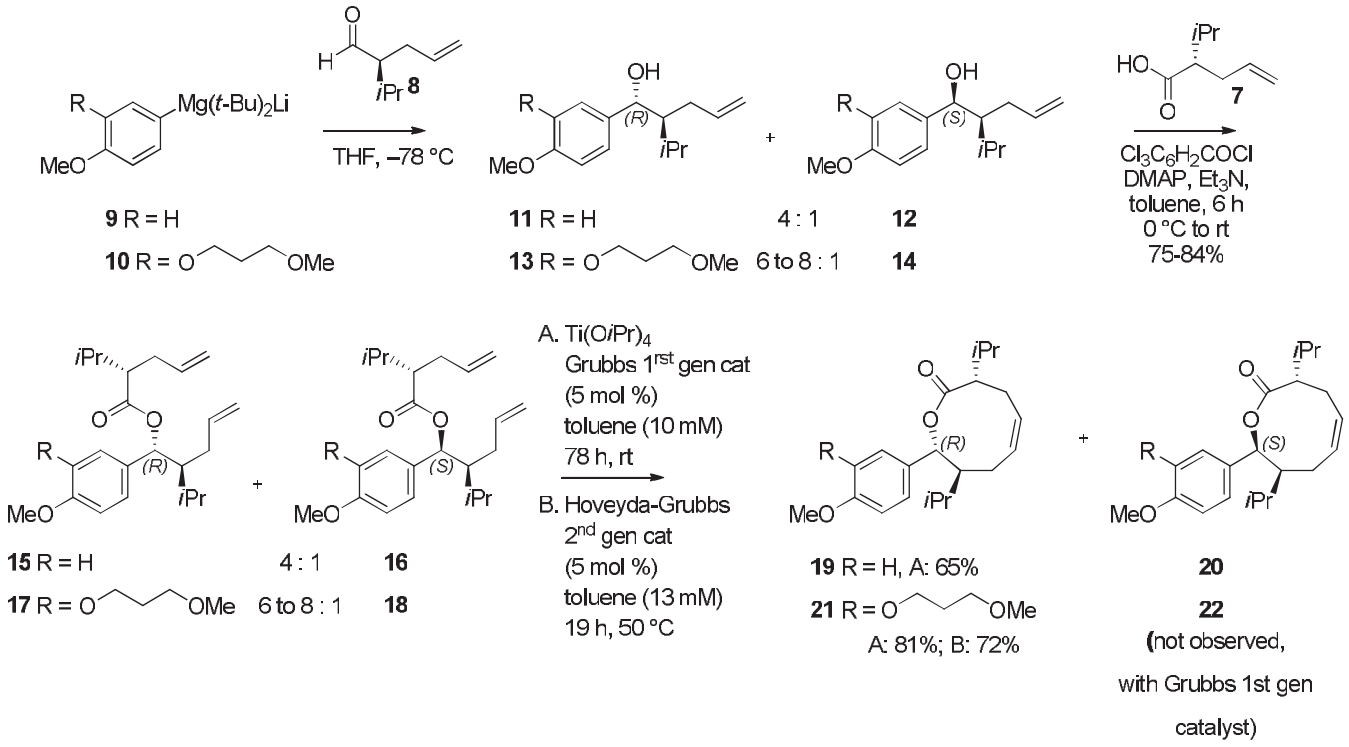


Figure 1.10 : The 9-membered lactone route to aliskiren from a common chiron

Result and discussion

Synthesis of the 9-membered lactone.

Initially, we focused on the 4-methoxy analog (**3**, *Figure 1.10*) in order to explore aspects of stereoselectivity and conditions for the ring-closing metathesis. As will become evident, it was important to attempt the ring-closing metathesis reaction with a higher proportion of the (*R*)-ester derived from alcohol diastereomer **11** (*Scheme 1.17*).[31]

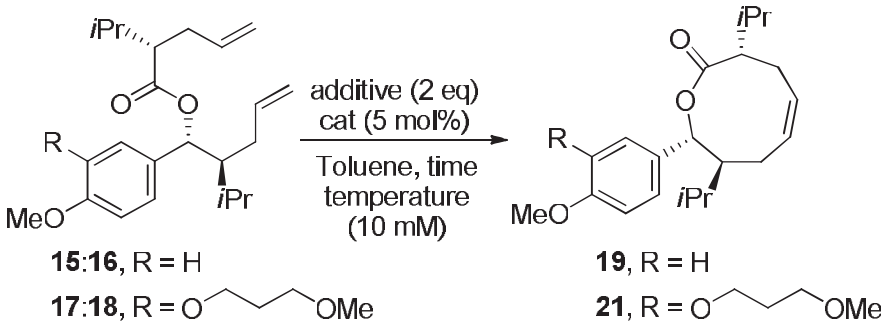


Scheme 1.17 : Synthesis of the 9-membered lactones

Attempts to add various organometallic derivatives of **9** (X = Br; M = Mg(*n*-Bu); TMEDA; Mg(*n*-Bu) inverse addition; Mg(*n*-Bu), $CeCl_3$; Li, $CeCl_3$; Et_2ZnLi; Mg(*n*-Bu)$_2$Li) to the aldehyde **8** resulted in modest to low yields and unsatisfactory ratios. After extensive trials, the best ratio of inseparable diastereomers **11** and **12** favoring the (R)-lactone was obtained with a mixed Mg/Li Grignard reagent described by Inoue[32] in 68% yield. Application of the same protocol to the aliskiren aryl moiety **10** led to a better ratio of **13** and **14** (6-8:1) of diastereomers. Esterification by the Yamaguchi method[33] afforded the diastereomeric mixture of esters **15**:**16** and **17**:**18**, maintaining the same ratios respectively. In our original report, we had utilized the Grubbs 1st generation catalyst due to its availability at time. A 5 mol% loading in a 10 mM solution of the esters **15**:**16** or **17**:**18** in toluene led, after 78 h at room temperature, to the intended lactones **19** and **21**, in 65% and 81% yield respectively. In this process, the mixture of esters was first stirred with Ti(Oi-Pr)$_4$ for 24 h before adding the catalyst. Then, to ensure complete conversion of the (*R*)-esters **15** and **17**, an additional 5-10 mol% of the first generation Grubbs catalyst was added every 24 h. In the absence of Ti(Oi-Pr)$_4$, the low yield of the

cyclization was attributed to the coordination of the Ru catalyst to the proximal ester carbonyl group.[34] The results of the cyclization of different batches of diastereomeric esters, under different conditions and catalysts are shown in *Table 1.1*. Starting with an ester mixture enriched in the (*R*)-isomer, we obtained the (*R*)-lactone in 71% yield in the presence of the 1st generation Grubbs catalyst (**G1**) at room temperature (*Table 1.1*, entry 9). Using a 4:1 mixture of esters **15** and **16** in the presence of the 2nd generation Hoveyda-Grubbs catalyst (**H-G2**) at reflux, resulted in the formation of **19** within 20 minutes in 64% yield (*Table 1.1*, entry 8). Ultimately, utilizing the 2nd generation Hoveyda-Grubbs catalyst and a 6:1 mixture of **17** and **18**,[35] the cyclization was completed within 19 h at 50 °C, to give **21** in 72% yield (*Table 1.1*, entry 13). We were at first intrigued by the observation of that only the (*R*)-esters **15** and **17** were transformed to the corresponding lactones **19** and **21**, respectively. At the time of execution, reports of the formation of 9-membered functionalized lactones by ring closing metathesis were sparse.[36,37]

Table 1.3 : Formation of the 9-membered lactones **19** and **21**



entry	ester dr	R	cat	add	time	temp	**yield**[a]
1	3:1	H	**G2**	---	1 d	rt	**0**
2	3:1	H	**G2**	Ti(O*i*Pr)$_4$	2 d	rt	**43%**
3	3:1	H	**G1**	Ti(O*i*Pr)$_4$	2 d	rt	**57%**
4	3:1	H	**G1**	Ti(O*i*Pr)$_4$	3 d	rt	**58%**

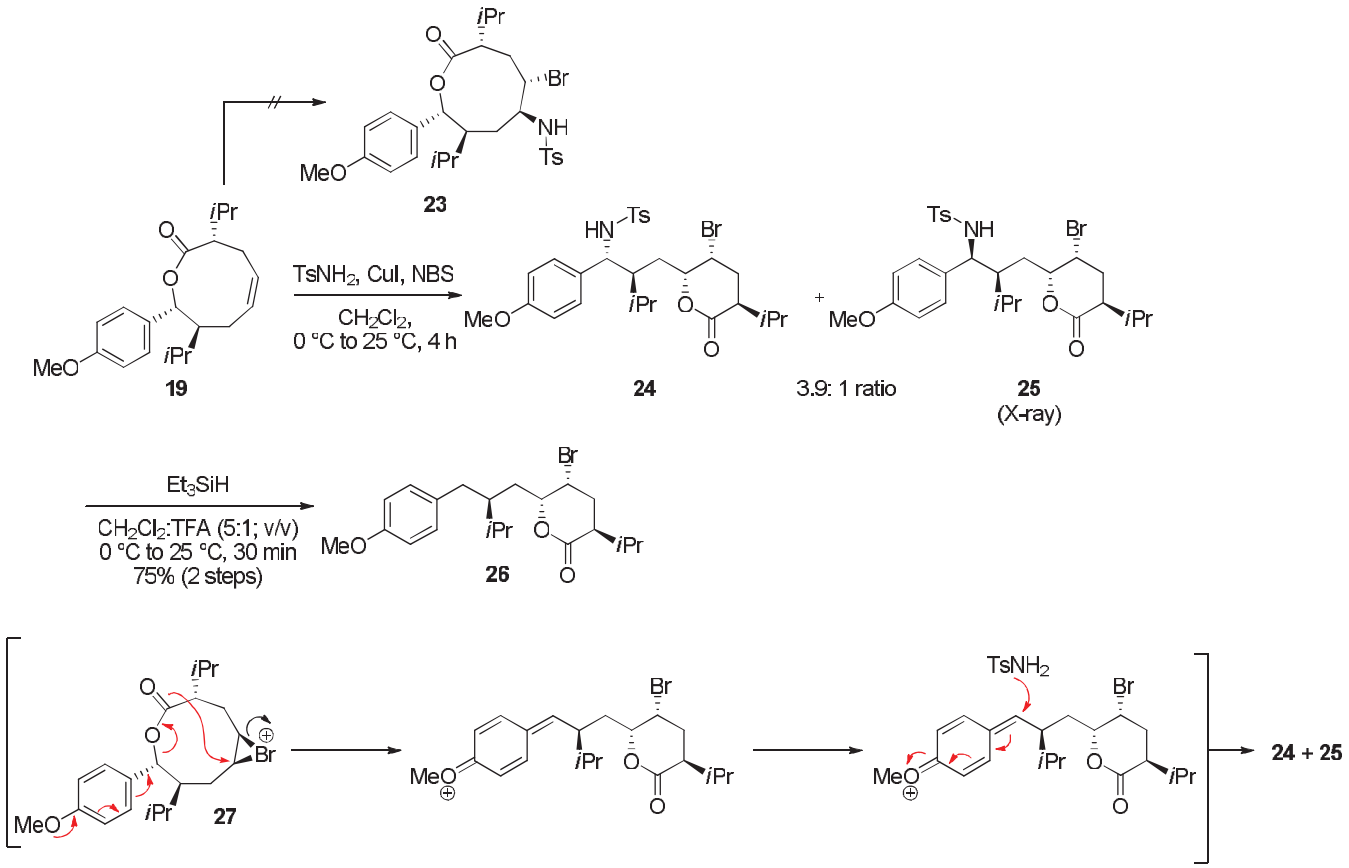
5	2:1	H	**G1**	Ti(O*i*Pr)$_4$	3 d	rt	**49%**
6	4:1	H	**G1**	Ti(O*i*Pr)$_4$	3 d	rt	**65%**
7	4:1	H	**G2**	---	40 min	reflux	**67%**
8	4:1	H		---	20 min	reflux	**64%**
9	7:1	H	**G1**	Ti(O*i*Pr)$_4$	3 d	rt	**71%**
10	2:1	H	**H-G2**	---	20 h[b]	reflux	**44%**
11	8:1	$O(CH_2)_3OCH_3$	**G1**	Ti(O*i*Pr)$_4$	3 d	rt	**65%**
12	8:1	$O(CH_2)_3OCH_3$	**G1**	Ti(O*i*Pr)$_4$	3-4 d	rt	**81%**
13	5:1	$O(CH_2)_3OCH_3$	**H-G2**	---	16 h	50 °C	**72%**

[a]isolated yield. [b]conversion was completed within 20 h. [c]extra 5 mol % of the catalyst was added if no further progress was noticed by TLC. **G1**, **G2**, and **H-G2** refer to Grubbs 1st generation, Grubbs 2nd generation, and Hoveyda-Grubbs 2nd generation catalyst.

Functionalization of the 9-membered lactone.

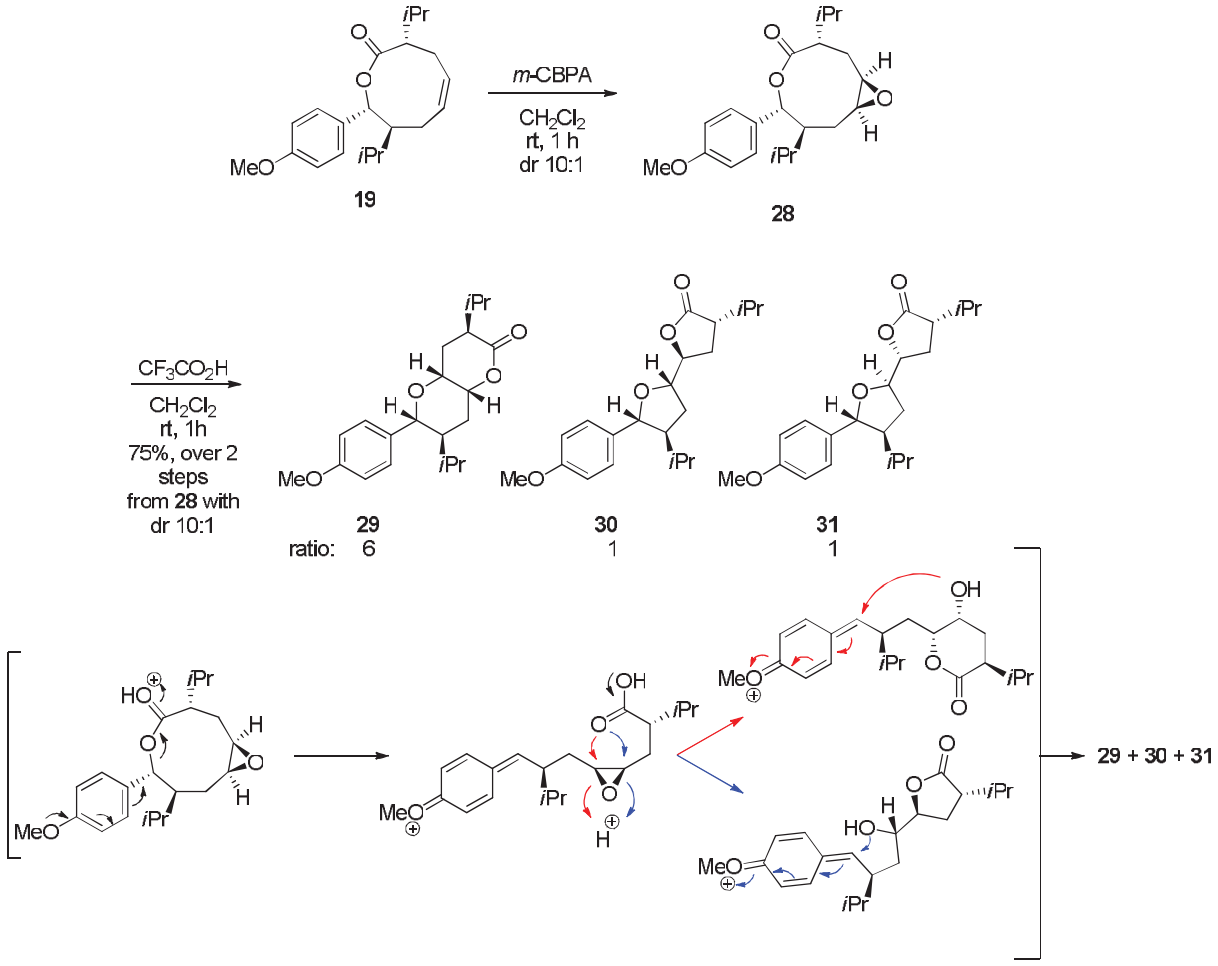
Our next task was to explore methods for the regio- and stereoselective introduction of an amino alcohol unit on the double bond of lactones **19** and **21**. We surmised that in the presence of NBS, CuI and $TsNH_2$,[38] a bromonium ion (**27**) would be attacked to give the corresponding vicinally substituted 9-membered lactone **23** (arbitrary regio and stereochemistry, *Scheme 1.18*). Instead, the products formed with a good conversion, were found to be the bromolactones **24** and **25** in a ratio of 3.9:1 arising from an intramolecular attack of the carboxylate released by concomitant formation of quinonoid intermediates followed by an anti-attack of $TsNH_2$ relative to the bulky isopropyl group. The structures of **24** and **25** were assigned by detailed NMR studies. The bromolactone structure (**25**) was also confirmed by X-ray crystallography. Reductive cleavage of the benzylic sulfonamide group in the mixture of **24**

and **25** with Et_3SiH and trifluoroacetic acid, gave the bromolactone **26** in a good overall yield from **19**.



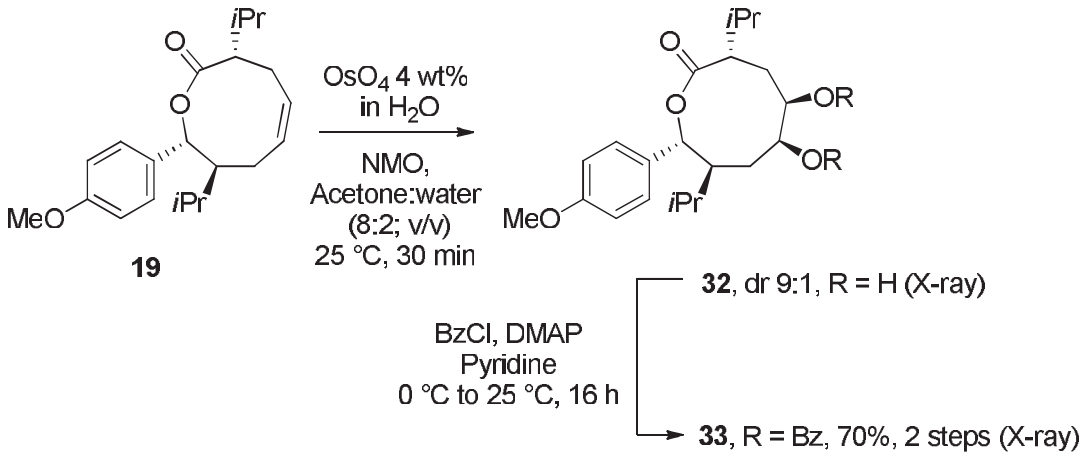
Scheme 1.18 : Attempted bromoamination of the macrocyclic lactone **19**

Next, we converted the 9-membered lactone **19** into the corresponding epoxide **28** (*Scheme 1.19*). The major product with the designated stereochemistry as shown was formed in excellent yield at 0 °C or room temperature. Surprisingly, treatment with NaN_3-NH_4Cl in methoxyethanol or Bu_4NN_3 in refluxing toluene gave back starting epoxide. Upon treatment with Et_3SiH and trifluoroacetic acid, it was expected that the benzylic carbon oxygen bond would be cleaved. Instead, a mixture of the three products **29**, **30**, and **31** (6:1:1 ratio) was obtained, the structures of which are proposed based on detailed NOE studies.[31] A plausible mechanism is shown in *Scheme 1.19*.



Scheme 1.19 : Epoxidation of the lactone **19** and further transformations

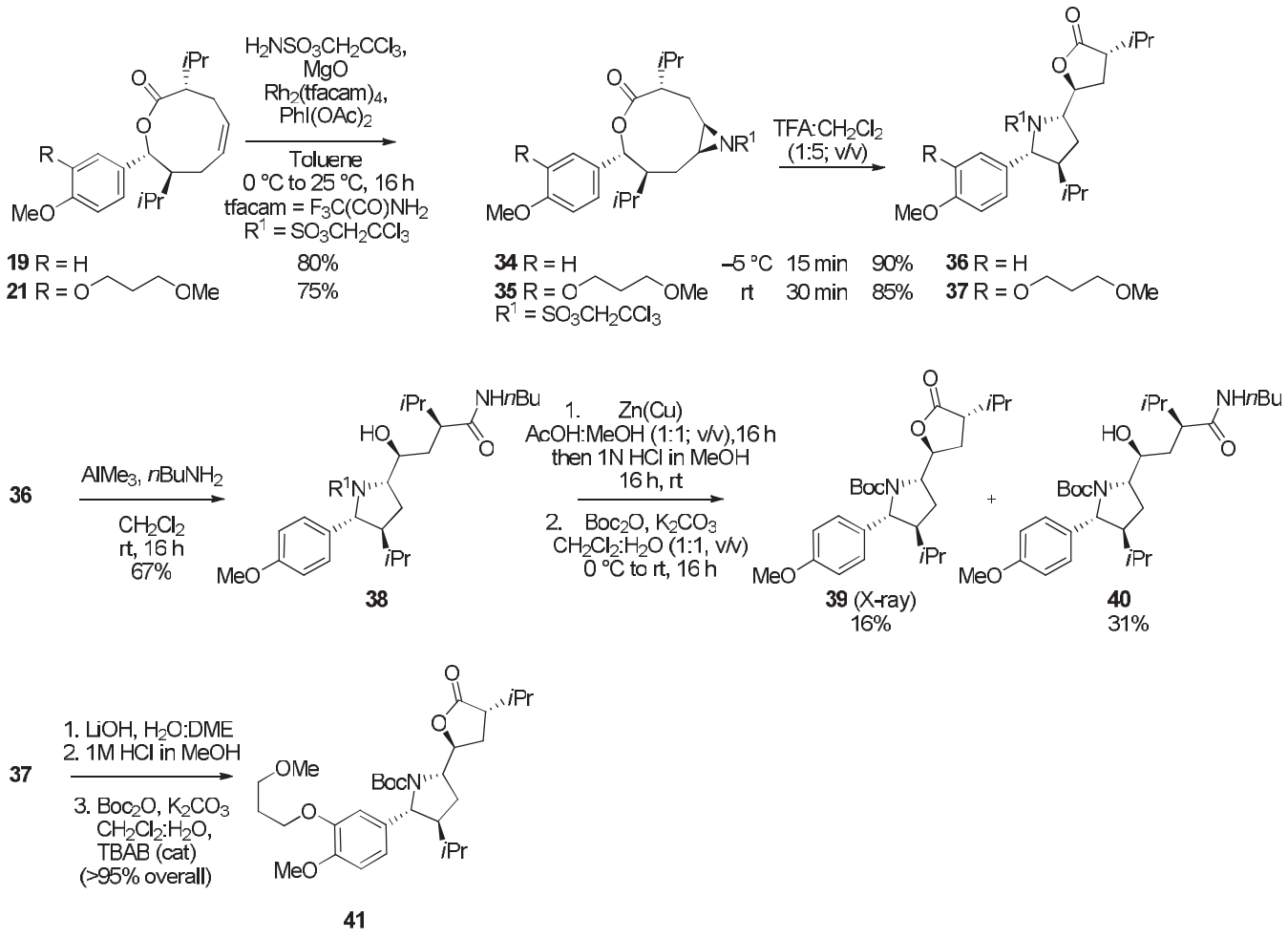
Dihydroxylation of **19** under standard conditions led to the dihydroxy lactone **32** and the dibenzoate **33** after benzoylation,[28] the structures and stereochemistry of which were confirmed by X-ray analysis,[31] validating a trajectory of approach that would be opposed to the orientation of the resident C-8 4-methoxyphenyl group (*Scheme 1.20*).[28] Although this stereochemical outcome could not be predicted a priori in a quasi C_2-symmetrical 9-membered lactone with respect to the orientation of the isopropyl groups at C-2 and C-7 such as in **19**, it became clear that C-8 aryl group may have exerted a steric influence in the dihydroxylation step.



Scheme 1.20 : Diastereoselective dihydroxylation of lactone **19**[28]

Encouraged by this result, we attempted a Du Bois aziridination reaction,[39] expecting to obtain the aziridine with the "up" orientation. We would then attempt a solvolysis with an appropriate carboxylic acid, hoping for a regioselective opening at the C-4 position, thereby generating the vicinal *trans*-amino alcohol (*Scheme 1.21*).

In the event, treatment of **19** and **21** individually with trichloroethylsulfamate in the presence of $Rh_2(tfacam)_4$ and $PhI(OAc)_2$ according to Du Bois[39] led to the desired aziridines **34** and **35** in excellent yields (*Scheme 1.21*). Suspecting the need for a strong acid to activate the *N*-trichloroethylsulfamoyl group in the solvolysis, aziridines **34** and **35** were treated with a dilute solution of trifluoroacetic acid in CH_2Cl_2. Remarkably, in both cases, a double ring contraction occurred to give the pyrrolidine lactones **36** and **37** respectively in excellent yields (*Scheme 1.21*).[28] It should be noted that this simple solvolytic reaction produced the desired (4*S*, 5*S*) amino alcohol with exquisite regio- and stereocontrol. Confirmation of the structure and stereochemistry of **36** (hence **37**) was obtained from the X-ray crystal structure of the amide **38**. Treatment of **36** with $AlMe_3$ and *n*-butylamine gave the amide **38** which was converted to the *N*-Boc analog **40**, accompanied by the lactone **39**, the structure of which was ascertained by X-ray crystallography.[31] Alternatively, alkaline hydrolysis of the sulfamate group in **37** followed by acidification and *N*-protection led to the known *N*-Boc lactone **41** (*Scheme 1.21*).[16b,40]

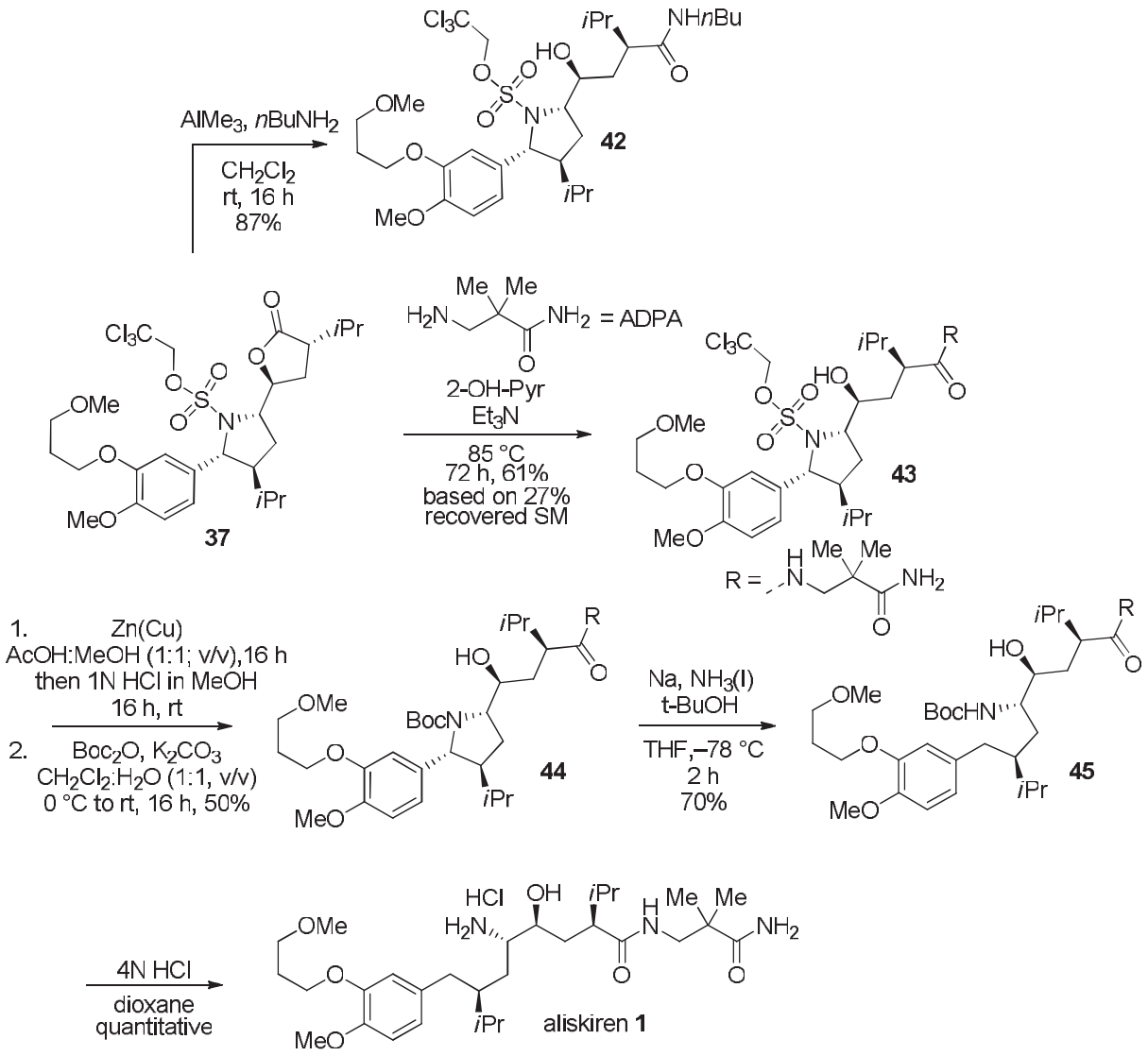


Scheme 1.21 : Elaboration of 9-membered lactones via aziridination and ring contraction

Completion of the total synthesis of aliskiren.

To test the compatibility of the sulfamate group under amide forming conditions from the lactone **37**, we were pleased that treatment with *n*-butylamine in the presence of $AlMe_3$ gave an excellent yield of the *n*-butylamine derivative **42** (*Scheme 1.22*). However, the same conditions to form an amide failed with the sterically demanding neopentylic 3-amino-2,2-dimethylpropionamide (ADPA). The utility of 2-hydroxypyridine as an activator in amide formation is well documented.[41] In fact, this method is claimed to work in high yield in a number of patents describing aliskiren.[25,42] In our hands, the methods described for the *N*-Boc derivative

corresponding to the *N*-sulfamate **37** resulted in low yields. Prolonged heating of lactone **37** with ADPA in neat Et_3N at 85 °C led to a 61% yield of the desired amide **43**, with recovery of starting lactone. We then decided to convert the *N*-sulfamoyl group in **43** into an *N*-Boc group to give **44** in good overall yield. There remained to cleave the benzylic amine bond and the *N*-Boc group to complete the total synthesis of aliskiren. Cleavage of the benzylic pyrrolidine bond of **44** with Na in liquid ammonia in the presence of *t*-BuOH followed by acid treatment to remove the *N*-Boc group gave aliskiren (**1**). Overall, our linear synthesis comprised 11 steps and a 7% unoptimized yield starting from aldehyde **8**.[28] After completion of this work, Foley and Jamison described a conceptually innovative method for an acid-promoted aminolysis of lactones that has since been applied toward the synthesis of aliskiren.[22b, 43, 44]

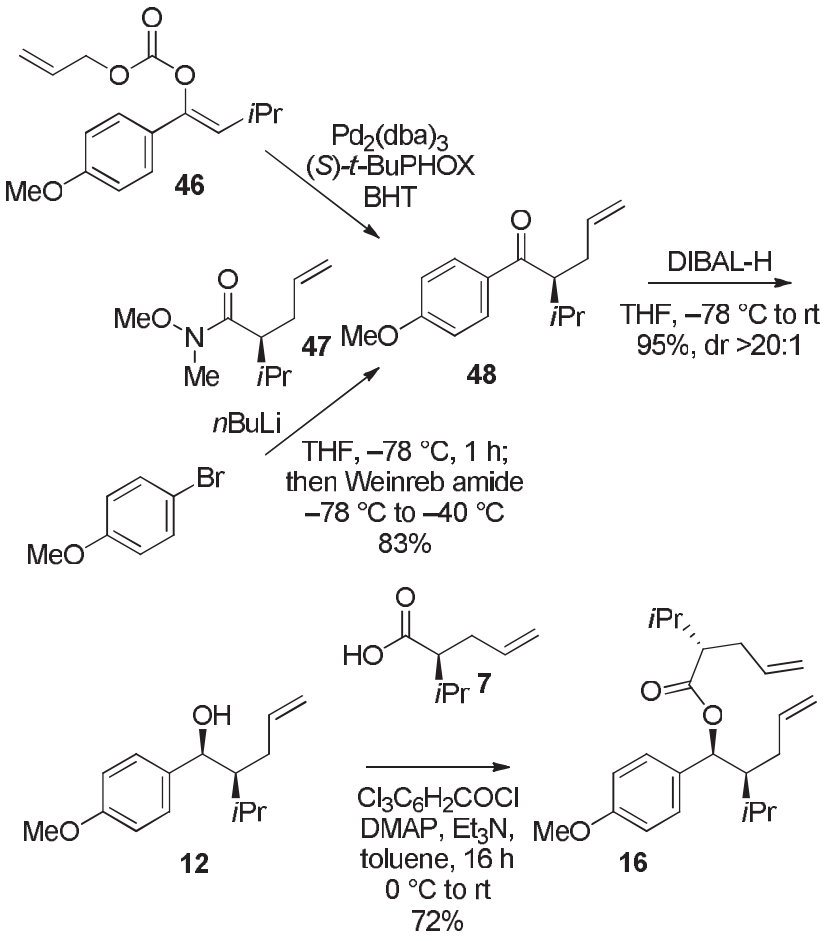


Scheme 1.22 : Completion of the synthesis of aliskiren **1**

What about the (*S*)-lactones 20 and 22?

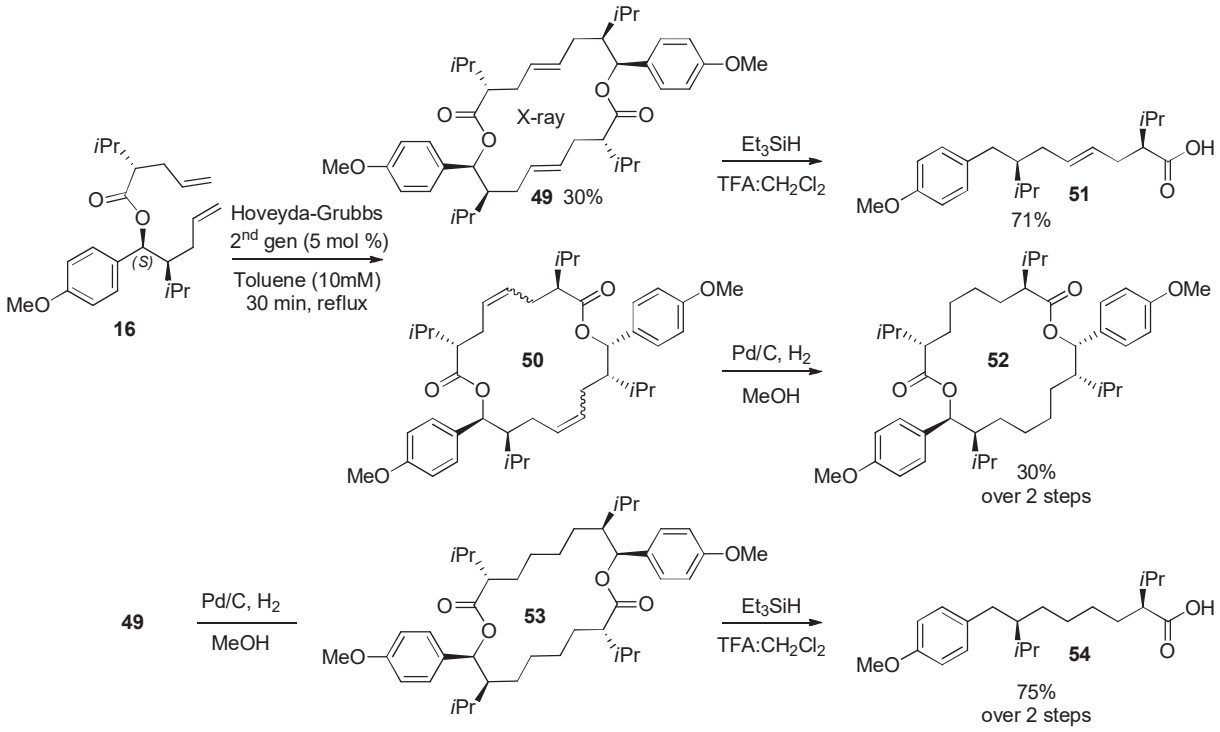
Earlier we commented on the exquisite selectivity of the Grubbs metathesis reaction with the first generation catalyst. In fact, using an inseparable mixture of the diastereomeric esters **15** and **16** (as well as **17** and **18**) led to a single diastereomer in each case involving the cyclization of the (*R*)-esters to give the 9-membered lactones **19** and **21**, respectively (*Scheme 1.17*). The other diastereomeric esters **16** (and **18**) were recovered in poor yield and contaminated with some other metathesis side-products. To further study the fate of the (*S*)-ester **16**, we prepared

it in a stereoselective manner (*Scheme 1.23*). Thus, allylic transposition of allyl enolcarbonate **46** in the presence of $Pd_2(dba)_3$ catalyst, (*S*)-*t*-BuPHOX ligand[26,45] and BHT as additive,[27] led to the ketone **48**, in good yield and acceptable enantiomeric excess (average of 90% yield, and 88 to 91% ee). The same ketone was also prepared by arylation of the Weinreb amide derivative **47** of (2*S*)-isopropylbuta-4-enoic acid **7** independently prepared via an Evans[22] or MacMillan[28,46] asymmetric allylation. Reduction with a slow addition of DIBAL-H, keeping the temperature at −78 °C, led quantitatively to the (*S*)-alcohol **12**, with a diastereomeric ratio of >20:1. Esterification with the acid **7** using the Yamaguchi method[33] led to **16**.



Scheme 1.23 : Catalytic asymmetric synthesis of (*S*)-ester **16**

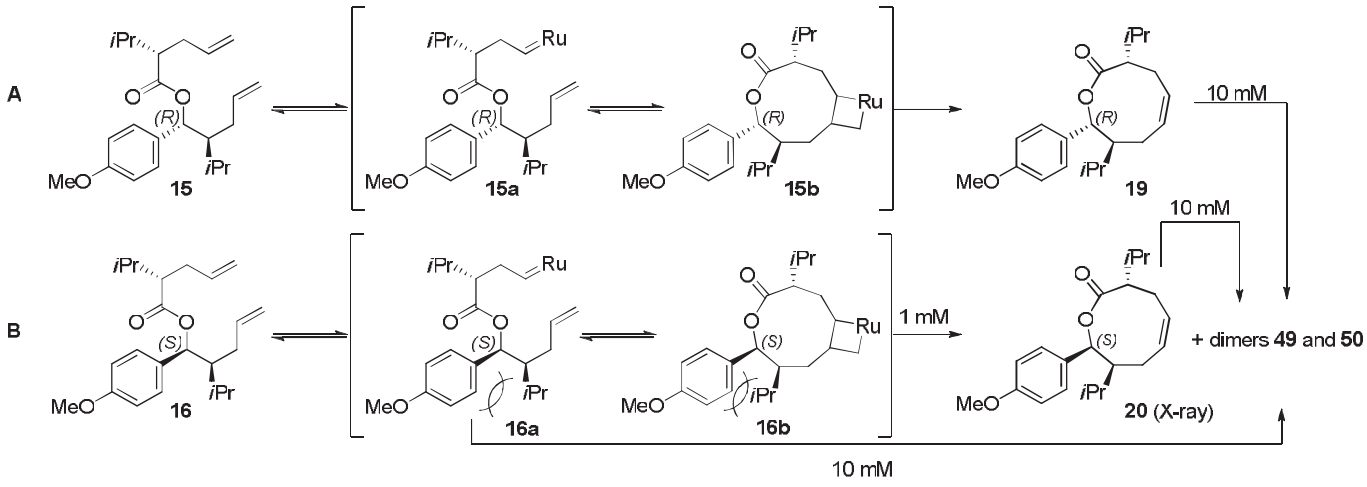
In the presence of 5 mol % of the 2nd generation Hoveyda-Grubbs catalyst (at 10 mM in toluene at reflux), the (*S*)-ester **16** yielded 31% of the C_2-symmetrical trans-trans bis-unsaturated dilactone **49** and a mixture of non-symmetric dilactones as double bond isomers **50** (*Scheme 1.24*). The structure of **49** was also confirmed by single crystal X-ray analysis. Reductive cleavage of the benzylic ester bonds in **49** led to the acid **51** which is a known intermediate in the Speedel process for the synthesis of aliskiren.[24,25] Controlled catalytic hydrogenation of the double bonds in **49** led to the saturated dilactone **53**, which upon reductive cleavage in acidic media yielded acid **54**. Alternatively, hydrogenation of the mixture of isomers corresponding to dilactones **50** afforded the head-to-head dilactone **52** (*Scheme 1.24*).



Scheme 1.24 : Cross metathesis reaction of the (*S*)-ester **16** and reductive cleavage of macrocyclic dilactones

Judging from the results using Grubbs 1st generation catalyst (**G1**) with the (*R*)-esters **15** and **17** (10 mol % catalyst, 72 h, rt, toluene at 10 mM concentration), we speculate that the

formation of the corresponding 9-membered lactones **19** (and **21**) can be attributed to the contribution of cooperative stereochemical, stereoelectronic and conformational effects leading first to the alkylidene Ru-complexes intermediates (exemplified by the structure **15a** as one of the two possible intermediates). Presumably the olefinic termini are favorably aligned with minimal steric interaction to lead to a ruthenium-alkylidene complex en route to the Ru-metallocycle **15b**, and eventually collapse to the intended lactones **19** (*Scheme 1.25* A). In contrast, the transition states starting with the (*S*)-ester **16** will be subject to a significant steric clash between the isopropyl and aromatic moieties, thereby slowing down the reaction (*Scheme 1.25* B) and the same conclusion would also apply in the case of ester **18**. Dimerization during ring-closing metathesis has been previously reported.[47]



Scheme 1.25 : Possible Ru-metallacyclic intermediates

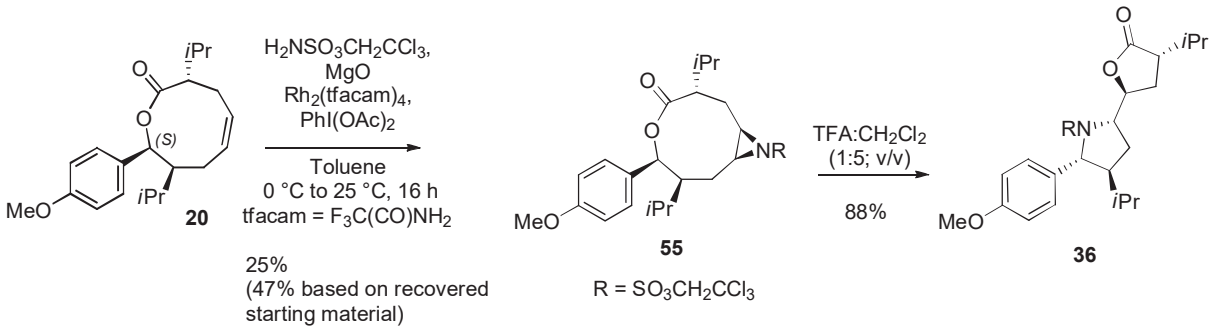
A. 1st generation Grubbs (**G1**) and 2nd generation Hoveyda-Grubbs (**H-G2**) catalyst at 10 mM (72 h at rt and 20 min at toluene reflux, respectively) B. **H-G2** catalyst at 1mM and 10mM (20 min at toluene reflux). Only one alkylidene Ru-intermediate is shown.

In the presence of the more robust 2nd generation Hoveyda-Grubbs (**H-G2**) catalyst (5 mol %, at a concentration of 10 mM in toluene at 110 °C for 20 min), the (*R*)-ester **15** in a mixture containing the (*S*)-ester **16** as the minor isomer is converted to lactone **19** in 64% yield.

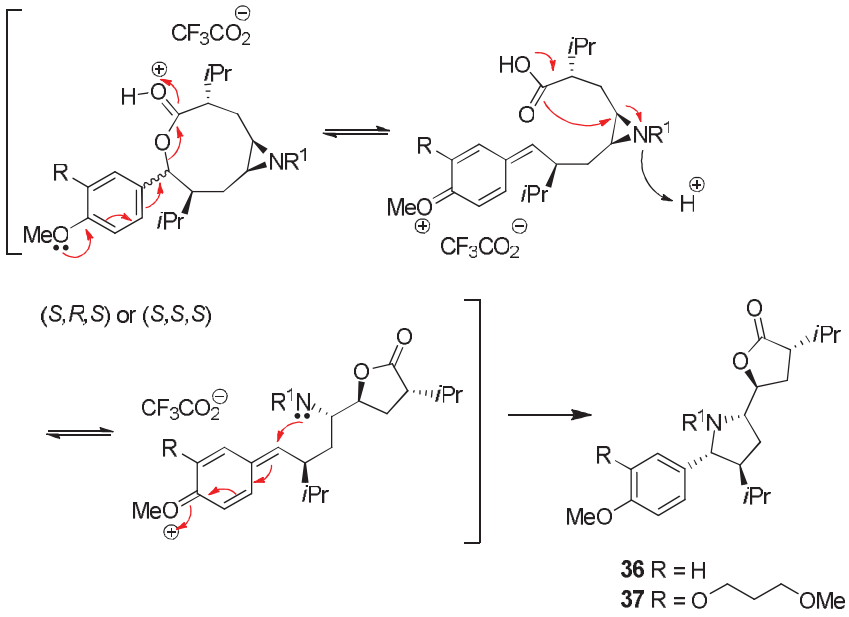
Under the same conditions the minor (*S*)-ester **16** undergoes direct dimerization to the macrocyclic dilactones **49** and **50**, which were not reverted to starting material under these conditions (*Scheme 1.25* B). This was corroborated with the enantioenriched (*S*)-ester **16** (*Scheme 1.24*). Surprisingly, when the reaction was performed at a concentration of 1 mM instead of 10 mM, in refluxing toluene for 6h, the (*S*)-ester **16** led to the elusive (*S*)-lactone **20** in 53% yield, accompanied by the usual dimers **49** and **50** (~ 24%). The structure of **20** was confirmed by X-ray crystallography.[31] When heated at reflux temperature in 10 mM in toluene for 24h in the presence of the 2nd generation Hoveyda-Grubbs catalyst, the (*S*)-lactone was rapidly converted to the lactones **49** and **50**.

Intrigued by this observation, we subjected the (*R*)-lactone **19** to the same reaction conditions, only to find that dimerization to **49** and **50** had also taken place. We can conclude that depending on the concentration, the catalyst and temperature, the (*R*)-lactone **19** and (*S*)-lactone **20** are the kinetic products. At a concentration of 1mM, a diastereomeric mixture of **15** and **16** led to the corresponding lactones **19** and **20** respectively, accompanied by the dimers **49** and **50**.

Finally, we subjected the (*S*)-lactone **20** to an aziridination reaction to give **55** in 25% yield with recovery of starting material. TFA-induced double ring contractions as for the (*R*)-lactone **19** (*Scheme 1.21*) gave the known lactone **36** in 88% yield (*Scheme 1.26*). Presumably, the activation of the *N*-sulfamoyl aziridine lactone in either 9-membered lactones engendered participation by the electron rich aryl moiety to give a quinonoid oxocarbenium ion which underwent regioselective intramolecular attack liberating the sulfamate group (*Scheme 1.27*). The latter would attack the quinonoid benzylic carbon atom with high anti-selectivity with regard to the C-7 isopropyl substituent leading to the observed pyrrolidine lactones **36**.[28]



Scheme 1.26 : Aziridination and double ring contraction of the (*S*)-lactone **20**



Scheme 1.27 : Proposed double ring contraction mechanism[28]

Conclusion.

In conclusion, we have provided a detailed account of various approaches leading to the total synthesis of the antihypertensive marketed drug aliskiren. Ring closing metathesis using the Grubbs (**G1** and **G2**) and Hoveyda-Grubbs (**H-G2**) catalysts with stereochemically distinct esters carrying terminal allyl moieties led to 9-membered lactones which were further elaborated to aliskiren and its *p*-methoxyphenyl congener. The formation of 9-membered lactones from

diastereomeric (*R*)- and (*S*)-esters **15** and **16** were found to be concentration dependent and favored at a concentration of 1mM in toluene using **H-G2** catalyst. At higher concentrations, the (*R*)-ester **15** afforded the expected 9-membered lactone, while the (*S*)-ester **16** led to a mixture of macrocyclic dilactones. Further studies focusing on the nature and stereochemistry of substituents in related cyclizations by ring-closing metathesis are in progress and will be reported in due course.

Experimental section

General procedure. All reactions were performed in oven dried glassware under an argon atmosphere using dry, deoxygenated solvents. Dichloromethane and toluene were dried by passage through an activated alumina column under argon (Solvent Drying System (SDS)). Reagents were purchased and used without further purification. Reactions were monitored by analytical thin-layer chromatography (TLC) carried out on 0.25 mm silica plates that were visualized under a UV lamp (254nm) and developed by staining with ceric ammonium molybdate, *p*-anisaldehyde and/or potassium permanganate solution. Flash columns chromatography were performed using silica (particle size 40-63 μm, 230-400 mesh) at increased pressure. FTIR are reported in reciprocal centimeters (cm^{-1}). NMR spectra (^{1}H, ^{13}C, DEPT 135, COSY, HMQC, NOESY) were recorded at either 300, 400, 500 or 700 MHz. Chemical shifts for ^{1}H NMR spectra are recorded in parts per million relative to trimethylsilane (TMS, $\delta = 0.00$ ppm) with the solvent resonance as the internal standard (CH_3Cl, $\delta = 7.26$ ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, h = hextet, m = multiplet and br = broad), coupling constant in Hertz (Hz), integration (xH). Chemical shifts for ^{13}C NMR spectra are recorded in parts per million using the central peak of $CDCl_3$ ($\delta = 77.16$ ppm) as the internal standard. Optical rotations were determined with a polarimeter at 589 nm, using a 1 dm cell at ambient temperature and are reported in units of $deg \bullet cm^3 \bullet g^{-1} \bullet dm^{-1}$. Melting points are given as ranges and are reported in °C.

(**1*S*,2*S*)-2-Isopropyl-1-(4-methoxyphenyl)pent-4-en-1-ol (12)**: A solution of 1.5 M of DIBAL-H in toluene (1.8 mL, 2.7 mmol, 1.5 equiv) was added in a slow dropwise manner to a

solution of ketone **48** (0.42 g, 1.8 mmol, 1.0 equiv) in THF (10mL) at −78 °C. The solution was kept at −78 °C for at least 3 h, then allowed to slowly warm to room temperature. Silica gel was added until the reaction mixture stopped to generate bubbles. The mixture was filtered on a silica pad (silica gel, 2.5 cm diameter × 4.0 cm height; 5V diethyl ether, then 2V ethyl acetate) to yield alcohol **12** (0.40 g, 95%, dr >20:1) as a colorless oil. R_f = 0.11 (1:9, diethyl ether:hexanes); $[\alpha]_D^{20}$ −12 (*c* 3.0, $CDCl_3$) (from ketone **48** with 83% ee, prepared with the PdAAA protocol[27]); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 – 7.23 (m, 2H), 6.89 – 6.85 (m, 2H), 5.53 (ddt, *J* = 17.1, 10.1, 7.1 Hz, 1H), 4.88 – 4.79 (m, 2H), 4.58 (dd, *J* = 7.7, 3.3 Hz, 1H), 3.81 (s, 3H), 2.16 – 2.04 (m, 1H), 2.04 – 1.95 (m, 1H), 1.92 – 1.83 (m, 1H), 1.74 – 1.68 (m, 1H), 1.67 (dd, *J* = 3.4, 0.4 Hz, 1H), 0.98 – 0.93 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.2, 138.9, 136.5, 128.1, 115.1, 113.9, 75.9, 55.4, 50.6, 31.3, 27.2, 21.5, 18.4; IR (neat) 3454, 3005, 2962, 2940, 2880, 2845, 1615, 1515, 1468, 1248, 1177, 1038 cm^{-1}; HRMS (ESI-TOF) m/z: calcd for $C_{15}H_{22}NaO_2$ $[M+Na]^+$ 257.1512, found $[M+Na]^+$ 257.1516.

(*S*)-(1*S*,2*S*)-2-Isopropyl-1-(4-methoxyphenyl)pent-4-en-1-yl-2-isopropylpent-4-enoate (ester 16): Triethylamine (70 μL, 0.51 mmol, 1.2 equiv), 2,4,6-trichlorobenzoyl chloride (80 μL, 0.51 mmol, 1.2 equiv) and 4-dimethylaminopyridine (62 mg, 0.51 mmol, 1.2 equiv) were successively added to a solution of acid **7** (64 mg, 0.45 mmol, 1.05 equiv) in dry toluene (3 mL) at 0 °C. The resulting white slurry was stirred at 0 °C for 10 min during which time the white slurry turned yellow. A solution of alcohol **12** (0.10 g, 0.43 mmol, 1.0 equiv) in dry toluene (1 mL) was added to the reaction vessel containing the yellow slurry in a dropwise manner at 0 °C. The flask that contained alcohol **12** was rinsed three times with dry toluene (1 mL) and the reaction mixture was allowed to warm to room temperature and monitored by TLC analysis until no more starting material was observed (Around 4 h at room temperature). The solvent was removed and the resulting yellow solid was taken up in ethyl acetate (10 mL) and H_2O (10 mL). The aqueous layer was separated and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were successively washed with a 10 % aqueous solution of acid citric (10 mL) and a saturated aqueous solution of sodium bicarbonate (10 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated. The residue was purified by flash chromatography (silica gel, 2.5 cm × 14.0 cm; 1:19 diethyl ether:hexanes) to yield ester

16 (110 mg, 72%) as an oil. R_f = 0.53 (1:9 diethyl ether:hexanes); $[\alpha]_D^{20}$ − 58 (*c* 2.0, $CDCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 – 7.21 (m, 2H), 6.87 – 6.77 (m, 2H), 5.79 – 5.58 (m, 2H), 5.57 – 5.37 (m, 1H), 5.05 – 4.91 (m, 2H), 4.87 – 4.73 (m, 2H), 3.79 (s, 3H), 2.39 – 2.14 (m, 3H), 2.12 – 1.71 (m, 5H), 0.96 – 0.89 (m, 6H), 0.84 (d, *J* = 6.8 Hz, 3H), 0.74 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.4, 159.1, 138.3, 136.2, 132.4, 129.1, 116.6, 115.4, 113.5, 77.1, 55.3, 52.8, 48.7, 34.0, 30.9, 30.7, 27.2, 21.2, 20.5, 20.3, 18.0; IR (neat) 3075, 2957, 2931, 2873, 2837, 1728, 1612, 1513, 1249, 1169, 1035 cm^{-1}; HRMS (ESI-TOF) m/z: calcd for $C_{23}H_{34}NaO_3$ $[M+Na]^+$ 381.2400, found $[M+Na]^+$381.2400.

Lactone 20: Hoveyda-Grubbs second generation catalyst (3 mg, 0.048 mmol, 0.06 equiv) was added to a solution of **16** (30 mg, 0.084 mmol, 1.0 equiv, dr 20:1) in dry toluene (84 mL) and the mixture was stirred at reflux for 6 h. The reaction mixture was cooled to room temperature then an excess of ethyl vinyl ether was added and the resulting solution was evaporated slowly at rt. The residue was purified by flash chromatography (silica gel, 1.5 cm diameter × 20.0 cm height, 1:50 ethyl acetate:hexanes) to yield **20** (16 mg, 53%) as pure white crystals. m.p. 89-91 °C; R_f = 0.55 (1:9 diethyl ether:hexanes); $[\alpha]_D^{20}$- 119 (*c* 0.5, $CDCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, *J* = 8.7 Hz, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 5.74 – 5.64 (m, 2H), 5.55 (ddd, *J* = 11.0, 10.9, 6.1 Hz, 1H), 3.80 (s, 3H), 3.10 – 3.00 (m, 1H), 2.87 – 2.77 (m, 1H), 2.48 (ddd, *J* = 8.4, 7.0, 1.5 Hz, 1H), 2.23 – 2.10 (m, 2H), 2.00 (dq, *J* = 13.5, 6.7 Hz, 1H), 1.90 – 1.81 (m, 1H), 1.48 (dq, *J* = 13.2, 6.6 Hz, 1H), 1.00 (d, *J* = 6.7 Hz, 6H), 0.84 – 0.79 (m, *J* = 7.2 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.9, 159.1, 133.5, 131.0, 128.4 (2H), 126.2, 113.9 (2H), 78.2, 55.4, 50.7, 49.5, 28.8, 26.9, 26.5, 23.4, 22.4, 21.9, 20.3, 19.0; IR (neat) 3008, 2956, 2871, 2836, 1735, 1612, 1513, 1463, 1386, 1367, 1247, 1158, 1112, 1030 cm^{-1}; HRMS (ESI-TOF) m/z: cacld $C_{21}H_{31}O_3$ $[M+H]^+$ 331.2268, found $[M+H]^+$ 331.2259.

Lactone 21: See reference 28, Also prepared from adding Hoveyda-Grubbs second generation catalyst (4 mg, 0.0064 mmol, 0.06 equiv) to a solution of esters **17:18** (52 mg, 0.11 mmol, 1.0 equiv, dr 5:1) in dry toluene (9 mL) and stirred at 50˚C for 2 h. The reaction mixture was cooled to room temperature, filtered on silica and Fluorisil pad then eluted using 50%

AcOEt/Hexanes. The residue was purified by flash chromatography (silica gel, 1.5 cm diameter × 20.0 cm height, 1:9 ethyl acetate: hexanes) to yield **21** (33 mg, 72%).

Lactones 24 and 25: A solution of NBS (29 mg, 0.16 mmol, 1.1 equiv) in dichloromethane (3ml) was added in a dropwise manner to a mixture of lactone **19** (47 mg, 0.14 mmol, 1 equiv), copper(I) iodide (3 mg, 0.015, 0.11 equiv), and p-toluenesulfonamide (26 mg, 0.15 mmol, 1.1 equiv) in dichloromethane (3 mL). The mixture was stirred at room temperature for 4 h, then H_2O (4 mL) was added to the round bottom flask which was covered with aluminum foil. The mixture was diluted with ethyl acetate (15 mL) and stirred for a few min, then layers were separated. The aqueous layer was back-extracted with ethyl acetate (5 mL) and the organic layers were combined, washed with brine (10 mL), dried over sodium sulfate and concentrated. A diastereomeric ratio of 3.9:1 was observed by ^{1}H NMR of the crude mixture. The residue was purified by flash chromatography (silica gel, 1.5 cm diameter × 21 cm height, 1:9 to 1:4 ethyl acetate: hexanes) to yield the lactone **24** (42 mg, 52%) as a white solid along with impure fractions of **25**, which could be obtained as a pure white solid by recrystallization in methanol. Also, starting from 63 mg (0.19 mmol, 1 equiv) of lactone **19**, 14 mg (13%) of lactone **25** could be obtained pure by flash chromatography (silica gel, 2.5 cm × 20 cm, 0 to 1:19 ethyl acetate: hexanes) and 64 mg of impure lactone **24** which was re-purified by flash chromatography (silica gel, 1.5 cm diameter × 20 cm height, 1:4 ethyl acetate: hexanes) to yield the pure lactone **24** (40 mg, 36%).

Lactone 24: R_f = 0.29 (1:4 ethyl acetate:hexanes); (recrystallized from isopropanol) m.p. 113-115 °C; $[\alpha]_D^{20}$ +49 (*c* 0.5, $CHCl_3$); ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.42 – 7.39 (m, 2H), 7.03 (d, *J* = 8.0 Hz, 2H), 6.91 – 6.88 (m, 2H), 6.63 – 6.60 (m, 2H), 5.34 (d, *J* = 7.7 Hz, 1H), 4.45 – 4.43 (m, 1H), 4.20 (dd, *J* = 9.2, 8.1 Hz, 1H), 4.16 (ddd, *J* = 9.0, 4.4, 1.5 Hz, 1H), 3.73 (s, 3H), 2.96 (ddd, *J* = 11.3, 7.6, 3.8 Hz, 1H), 2.58 – 2.51 (m, 1H), 2.31 (s, 3H), 2.31 – 2.27 (m, 1H), 2.11 (ddd, *J* = 14.4, 11.2, 3.1 Hz, 1H), 2.03 (ddd, *J* = 14.7, 9.2, 5.4 Hz, 1H), 1.81 – 1.77 (m, 1H), 1.69 (ddd, *J* = 14.9, 4.4 Hz, 1H), 1.47 – 1.42 (m, 1H), 0.97 (d, *J* = 7.0 Hz, 3H), 0.95 (d, *J* = 6.9 Hz, 3H), 0.82 (d, *J* = 7.0 Hz, 3H), 0.71 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (176 MHz, $CDCl_3$)

δ 170.9, 158.8, 142.6, 138.2, 132.5, 129.2 (2C), 128.1 (2C), 127.1 (2C), 113.8 (2C), 81.1, 60.5, 55.4, 50.0, 45.7, 42.9, 32.0, 30.2, 29.2, 28.1, 21.7, 21.6, 19.7, 18.5, 16.2; IR (neat) 3252, 2958, 2923, 2852, 1732, 1704, 1612, 1514, 1463, 1443, 1325, 1248, 1218, 1179, 1160,1093, 1046 cm^{-1}; HRMS (ESI-TOF) m/z: calcd for $C_{28}H_{38}{}^{79}BrNNaO_5S$ $[M+Na]^+$ 602.1546, found $[M+Na]^+$ 602.1517.

Lactone 25: R_f = 0.21 (1:4 ethyl acetate:hexanes); (gradual dec.) (recrystallized from ethanol) m.p. 151 to 167 °C; $[\alpha]_D^{20}$ −56 (*c* 0.5, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.48 – 7.44 (m, 2H), 7.07 – 7.03 (m, 2H), 6.92 – 6.86 (m, 2H), 6.65 – 6.59 (m, 2H), 5.30 (d, *J* = 8.5 Hz, 1H), 4.19 – 4.16 (m, 1H), 4.12 – 4.07 (m, 1H), 3.69 (s, 3H), 2.76 – 2.66 (m, 2H), 2.40 – 2.29 (m, 4H), 2.29 – 2.21 (m, 1H), 2.07 (ddd, *J* = 14.6, 8.2, 3.4 Hz, 1H), 1.66 (ddd, *J* = 14.4, 9.4, 1.5 Hz, 1H), 1.63 – 1.55 (m, 1H), 1.50 – 1.43 (m, 1H), 1.40 (ddd, *J* = 14.4, 9.3, 5.0 Hz, 1H), 1.00 (d, *J* = 7.0 Hz, 3H), 0.81 (d, *J* = 7.0 Hz, 3H), 0.79 (d, *J* = 6.8 Hz, 3H), 0.69 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 171.3, 159.3, 143.1, 137.5, 132.3, 129.3 (2C), 128.3 (2C), 127.3 (2C), 114.0 (2C), 78.8, 60.4, 55.3, 49.0, 45.7, 42.9, 31.7, 30.3, 29.5, 28.1, 22.0, 21.6, 19.5, 18.1, 16.0; IR (neat) 3273, 2966, 2930, 2860, 2880, 1740, 1727, 1667, 1615, 1518, 1467, 1449 1329, 1256, 1183, 1161, 1052, 1041 cm^{-1}; HRMS (ESI-TOF) m/z: calcd for $C_{28}H_{38}{}^{79}BrNNaO_5S$ $[M+Na]^+$ 602.1546, found $[M+Na]^+$ 602.1535.

Lactone 26: Starting from the lactone **19** (66 mg, 0.20 mmol, 1.0 equiv), the bromosulfonamidation protocol was followed and the crude mixture of the bromosulfonamides **24**:**25** (dr 3.9:1) was dissolved in dichloromethane and cooled to 0°C. Triethylsilane (0.16 mL, 1.0 mmol, 5.0 equiv) was added to the solution followed by TFA (0.1 mL). The solution was allowed to slowly reach room temperature and the progress of the reaction was monitored by TLC. Volatiles were removed under vacuum with a rotary evaporator and the residue was purified by flash chromatography (silica gel, 2.0 cm diameter × 20 cm height, 1:9 ethyl acetate:hexanes) to yield bromolactone **26** (62 mg, 75%, 2 steps) as an oil. R_f = 0.43 (1:4, ethyl acetate:hexanes); $[\alpha]_D^{20}$ +11 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.15 – 7.01 (m, 2H), 6.89 – 6.75 (m, 2H), 4.26 – 4.20 (m, 1H), 3.77 (s, 3H), 3.70 (ddd, *J* = 6.8, 5.2, 1.0 Hz, 1H), 2.79

(ddd, J = 11.3, 7.8, 3.9 Hz, 1H), 2.71 (dd, J = 13.8, 5.2 Hz, 1H), 2.54 – 2.33 (m, 2H), 2.13 (ddd, J = 14.6, 7.8, 3.4 Hz, 1H), 1.85 – 1.53 (m, 5H), 0.96 – 0.91 (m, 6H), 0.88 (d, J = 7.0 Hz, 3H), 0.83 (d, J = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.5, 158.2, 133.4, 129.9 (2C), 114.1 (2C), 79.3, 55.4, 49.9, 42.8, 41.7, 37.8, 36.2, 31.21, 30.23, 29.3, 19.7, 19.6, 18.4, 18.3; IR (neat) 2966, 2940, 2879, 1736, 1615, 1515, 1468, 1249, 1226, 1209, 1180, 1069, 1041 cm^{-1}; HRMS (ESI-TOF) m/z: calcd for $C_{21}H_{31}{}^{79}BrNaO_3$ $[M+Na]^+$ 433.1349, found $[M+Na]^+$ 433.1340.

Epoxide 28: *m*-CPBA (77% purity) (65 mg, 0.29 mmol, 1.9 equiv) was added to a solution of lactone **19** (51 mg, 0.15 mmol, 1.0 equiv) in dichloromethane (1 mL) and the reaction mixture was stirred for 1 h at room temperature. The solution was diluted with diethyl ether (5 mL) and washed with a saturated aqueous solution of sodium bicarbonate (2 × 10 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated to yield 47 mg of the crude epoxide **28** (dr 10:1) as a gel. R_f = 0.52 (1:4, ethyl acetate:hexanes). Only signals for the major diastereomer is reported. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 – 7.27 (m, 2H), 6.92 – 6.85 (m, 2H), 5.75 (d, J = 11.1 Hz, 1H), 3.81 (s, 3H), 3.29 – 3.20 (m, 1H), 3.04 (ddd, J = 10.7, 3.7, 1.8 Hz, 1H), 2.60 – 2.50 (m, 1H), 2.25 (ddd, J = 11.4, 5.2, 1.9 Hz, 1H), 2.21 – 2.07 (m, 1H), 2.07 – 1.93 (m, 2H), 1.58 – 1.38 (m, 2H), 1.03 (d, J = 6.5 Hz, 3H), 0.99 – 0.92 (m, 1H), 0.89 (d, J = 6.9 Hz, 3H), 0.84 (d, J = 6.9 Hz, 3H), 0.79 (d, J = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.7, 159.6, 131.7, 128.9 (2C), 114.0 (2C), 78.0, 61.0, 55.4, 55.4, 52.7, 48.6, 28.5, 27.0, 26.5, 25.0, 22.0, 21.8, 19.7, 15.9; IR (neat) 3004, 2967, 2947, 2936, 2929, 2880, 1733, 1519, 1466, 1393, 1375, 1277, 1252, 1204, 1179, 1122, 1117, 1038 cm^{-1}; HRMS (ESI-TOF) m/z: calcd for $C_{21}H_{31}O_4$ $[M+H]^+$ 347.2217, found $[M+H]^+$ 347.2204 and calcd for $C_{21}H_{30}NaO_4$ $[M+Na]^+$ 369.2036, found $[M+Na]^+$ 369.2029.

Lactones 29, 30, and **31:** To a solution of the crude epoxide **28** (47 mg) in dichloromethane (1 mL) was added trifluoroacetic acid (60 μL). The solution was stirred for 10 min then the reaction was stopped by adding a saturated aqueous solution of sodium bicarbonate (5 mL) followed by ethyl acetate (10 mL). The organic layer was washed with a saturated aqueous solution of sodium bicarbonate (5 mL), dried over magnesium sulfate, filtered and

concentrated. A ratio of 6:1:1 was observed in the ^{1}H NMR of the crude mixture. The residue was purified by flash chromatography (silica gel, 2.0 cm diameter × 20.0 cm height, 1:19 ethyl acetate:hexanes) to yield lactones **29** (15 mg, 29%), **30** (4 mg, 8%), **31** (4 mg, 8%) and 7 mg of mixed fractions. All lactones produced from this reaction were clear oils.

Lactone 29: R_f = 0.41 (1:4 ethyl acetate:hexanes); $[\alpha]_D^{20}$ +14 (*c* 1.5, $CHCl_3$);^{1}H NMR (700 MHz, $CDCl_3$) δ 7.24 – 7.21 (m, 2H), 6.89 – 6.86 (m, 2H), 4.53 – 4.43 (m, 1H), 4.25 (d, *J* = 10.5 Hz, 1H), 3.89 – 3.87 (m, 1H), 3.80 (s, 3H), 2.81 (ddd, *J* = 11.5, 7.3, 3.8 Hz, 1H), 2.59 – 2.52 (m, 1H), 2.17 – 2.11 (m, 1H), 2.08 (ddd, *J* = 14.0, 7.3, 3.9 Hz, 1H), 2.00 – 1.93 (m, 1H), 1.74 (ddd, *J* = 14.3, 12.5, 2.3 Hz, 1H), 1.64 (ddd, *J* = 14.4, 12.9, 2.8 Hz, 1H), 1.43 – 1.36 (m, 1H), 0.93 – 0.90 (m, 6H), 0.78 (d, *J* = 7.0 Hz, 3H), 0.74 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 173.9, 159.6, 132.7, 128.6 (2C), 114.1 (2C), 83.2, 76.1, 70.5, 55.4, 41.0, 39.7, 29.0, 28.3, 26.4, 25.8, 20.9, 19.8, 17.9, 15.9; IR (neat) 3018, 3003, 2965, 2954, 2941, 2935, 2923, 2913, 2905, 2881, 2844, 1724, 1617, 1590, 1518, 1469, 1446, 1391, 1373, 1367, 1350, 1248, 1226, 1175, 1157, 1129, 1082, 1056, 1030, 1007 cm^{-1}; HRMS (ESI-TOF) m/z: calcd for $C_{21}H_{30}O_4$ $[M+H]^+$ 347.2217, found $[M+H]^+$ 347.2225 and calcd for $C_{21}H_{30}NaO_4$ $[M+Na]^+$ 369.2036, found $[M+Na]^+$ 369.2044.

Lactone 30: R_f = 0.46 (1:4 ethyl acetate:hexanes); $[\alpha]_D^{20}$ +39 (*c* 0.4, $CHCl_3$); ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.24 – 7.21 (m, 2H), 6.88 – 6.85 (m, 2H), 4.50 (ddd, *J* = 9.3, 3.2, 2.1 Hz, 1H), 4.41 (d, *J* = 9.3 Hz, 1H), 4.08 (ddd, *J* = 9.2, 5.0, 2.0 Hz, 1H), 3.79 (s, 3H), 2.70 (ddd, *J* = 9.8, 9.3, 5.0 Hz, 1H), 2.22 (ddd, *J* = 13.1, 10.0, 3.3 Hz, 1H), 2.20 – 2.13 (m, 2H), 2.13 – 2.06 (m, 2H), 1.92 (ddd, *J* = 12.4, 9.3 Hz, 1H), 1.60 – 1.53 (m, 1H), 0.96 (d, *J* = 6.9 Hz, 3H), 0.90 (d, *J* = 6.1 Hz, 3H), 0.89 (d, *J* = 6.0 Hz, 3H), 0.71 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 179.8, 159.6, 133.2, 128.7 (2C), 114.0 (2C), 85.8, 79.6, 79.4, 55.4, 52.4, 45.4, 31.7, 29.0, 28.6, 26.3, 22.0, 20.6, 19.6, 18.1; IR (neat) 3000, 2967, 2931, 2907, 2899, 2889, 2878, 2859, 1771, 1619, 1519, 1471, 1374, 1251, 1178, 1110, 1093, 1036 cm^{-1}; HRMS (ESI-TOF) m/z: calcd for $C_{21}H_{31}O_4$ $[M+H]^+$ 347.2217, found $[M+H]^+$ 347.2220 and calcd for $C_{21}H_{30}NaO_4$ $[M+Na]^+$ 369.2036, found $[M+Na]^+$ 369.2042.

Lactone 31: R_f = 0.31 (1:4 ethyl acetate:hexanes); $[\alpha]_D^{20}$ −2 (*c* 0.4, $CHCl_3$); ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.26 – 7.23 (m, 2H), 6.87 – 6.84 (m, 2H), 4.57 (d, *J* = 9.3 Hz, 1H), 4.36 – 4.32 (m, 1H), 4.25 – 4.20 (m, 1H), 3.79 (s, 3H), 2.61 – 2.56 (m, 1H), 2.21 – 2.15 (m, 2H), 2.15 – 2.12 (m, 1H), 2.12 – 2.07 (m, 1H), 2.05 – 1.95 (m, 1H), 1.84 – 1.77 (m, 1H), 1.71 – 1.64 (m, 1H), 1.03 (d, *J* = 6.9 Hz, 3H), 0.93 (d, *J* = 6.7 Hz, 3H), 0.90 (d, *J* = 6.8 Hz, 3H), 0.75 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 178.0, 159.3, 134.3, 128.5 (2C), 113.9 (2C), 85.0, 79.9, 78.7, 55.4, 54.1, 46.9, 31.8, 28.9, 27.9, 26.3, 22.4, 20.8, 19.6, 18.5; IR (neat) 3006, 2966, 2928, 2906, 2897, 2878, 2864, 2858, 2834, 2818, 1770, 1618, 1518, 1469, 1251, 1177, 1038, 1001, 981, 828, 763 cm^{-1}; HRMS (ESI-TOF) m/z: calcd for $C_{21}H_{31}O_4$ $[M+H]^+$ 347.2217, found $[M+H]^+$ 347.2223 and calcd for $C_{21}H_{30}NaO_4$ $[M+Na]^+$ 369.2036 and $[M+Na]^+$ 369.2044.

Lactone diol 32: *N*-Methylmorpholine-*N*-oxide (53 mg, 0.45 mmol, 1.5 equiv) was added to a solution of lactone **15** (0.1 g, 0.3 mmol, 1 equiv) in acetone (2.4 mL) and distilled water (0.6 mL) at 0°C, then a 2.5 weight% solution of osmium tetroxide in *tert*-butanol (0.2 mL, 0.02 mmol, 0.05 equiv) was added and the reaction mixture was allowed to warm up to room temperature. After 1 h of stirring, the reaction media was poured into a cold solution of ethyl acetate (2 mL) and saturated aqueous solution of sodium thiosulfate (2 mL). The aqueous layer was separated and back-extracted with ethyl acetate (3 × 2 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated to leave 102 mg of a black oil which was purified by flash chromatography (silica gel, 1.5 cm × 20 cm; 2:3 ethyl acetate: hexanes) to yield diol **32** (89 mg, 81%, dr 9:1) as a colorless oil.

Diol **32** was also prepared using the same protocol, with a 4 weight% solution of osmium tetroxide in H_2O in 91% yield and an estimated dr of 6:1 ascertamed by NMR spectroscopy. The oil was recrystallized from ethyl acetate:hexanes (1:4) to give white needles with an estimated dr of 7:1; m.p. 96 to 106 °C; R_f = 0.2 (2:3 ethyl acetate:hexanes) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 – 7.26 (m, 0.27H), 7.26 – 7.20 (m, estimated to ~1.6H), 6.88 – 6.82 (m, 2H), 5.68 (d, *J* = 11.0 Hz, 1H), 4.50 (d, *J* = 6.5 Hz, 1H), 3.84 – 3.69 (m, 4H), 2.47 (s, 2H), 2.29 (ddd, *J* =

15.9, 6.8, 2.7 Hz, 1H), 2.24 – 2.01 (m, 2H), 1.92 – 1.58 (m, 3H), 1.55 – 1.45 (m, 0.21H), 1.45 – 1.30 (m, 1H), 1.24 – 1.08 (m, 1H), 0.98 (d, J = 6.1 Hz, 3H), 0.92 – 0.71 (m, 9H).Only the signlas for major diastereomer is reported for the ^{13}C NMR. ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.1, 159.7, 131.0, 128.7, 114.1, 78.8, 77.9, 69.0, 55.4, 53.2, 48.4, 31.6, 30.1, 27.5, 26.9, 21.5, 21.3, 20.2, 15.3; IR (neat) 3394, 2867, 2945, 2881, 1730, 1617, 1519, 1467, 1253, 1179, 1052, 1036 cm^{-1}; HRMS (ESI-TOF) m/z: calcd for $C_{21}H_{32}NaO_5$ $[M+Na]^+$ 387.2142, found $[M+Na]^+$ 387.2126.

Pyrrolidine lactone 36: A dry round-bottomed flask was charged with 8 mg (0.014 mmol, 1.0 eq.) of **55** and a magnetic stirrer and 0.5 mL of dry dichloromethane ([**55**] = 0.028 M) were introduced via a glass syringe followed by 5 drops of trifluoroacetic acid. The solution was stirred and monitored by TLC analysis (20:80 ethyl acetate-hexanes, CAM). After 10 minutes, when TLC analysis showed no more starting material, the volatiles were first removed under reduced pressure at room temperature to leave yellow oil which was purified by flash column chromatography (silica gel, 1.5 cm × 20 cm; 1:19 ethyl acetate-hexanes) to yield 7 mg (0.0123 mmol, 88%) of lactone **36** as a yellow oil. R_f = 0.44 (1:9 ethyl acetate:hexanes); $[\alpha]_D$ +21 (*c* 0.7, $CDCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7-31 (m, 2H), 6.89-6.86 (m, 2H), 4.57-4.52 (m, 2H), 4.34 (d, J = 11.2 Hz, 2H), 4.23 (dd, 5.2 and 8.4 Hz, 1H), 3.78 (s, 3H), 2.64 (ddd, J = 5.6, 7.6, 10.0 Hz, 1H), 2.56-2.47 (m, 1H), 2.41-2.34 (m, 1H), 2.21-2.05 (m, 3H), 1.95 (dd, J = 6.4, 12.8 Hz, 1H), 1.71-1-62 (m, 1H), 1.04 (d, J = 6.4 Hz, 3H), 0.97 (d, J = 6.8 Hz, 3H), 0.91 (d, J = 6.8 Hz, 3H), 0.79 (d, J = 6.4 Hz, 3H).

Lactone 39: Zn(Cu) (0.18 g, 2.8 mmol, 5.0 equiv) was added to a solution of amide **38** (0.36 g, 0.56 mmol, 1.0 equiv) in MeOH:AcOH (1 mL, 1:1 v/v) and stirred at room temperature. The reaction was monitored by MS. The mixture was filtered on Celite®, eluted with a minimal amount of MeOH, and concentrated. The resulting solid was dissolved in dry MeOH (5 mL), cooled to 0 °C, and treated with AcCl (0.36 mL). The solution was allowed to reach room temperature and stirred for 24 h. The volatiles were removed under vacuum with a rotary evaporator and the resulting white solid was dissolved in CH_2Cl_2 (2 mL). To the latter, H_2O (2 mL), Boc_2O (0.16 g, 0.73 mmol, 1.3 equiv), K_2CO_3 (0.39 g, 2.8 mmol, 5.0 equiv) and TBAB

(43 mg, 0.11 mmol, 0.2 equiv) were added. The mixture was stirred at room temperature and monitored by TLC. An excess of imidazole was added to the mixture which was acidified to pH = 3-4, using a 10% solution of citric acid. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The organic layers were combined, dried over sodium sulfate, filtered, and concentrated. The residue was purified by flash chromatography (silica gel, 1:4 ethyl acetate:hexanes) to yield the known amide **40**[28] (90 mg, 31%) (R_f = 0.57, 2:3 ethyl acetate:hexanes) as a colorless oil and lactone **39** (40 mg, 16%) (R_f = 0.37, 2:3 ethyl acetate:hexanes) as a white solid, which was recrystallized by diffusing hexanes to a solution of lactone **39** in a minimal amount of ethyl acetate. m.p. 140 to 143 °C; $[\alpha]_D$ +14 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (d, *J* = 8.4 Hz, 2H), 6.84 (d, *J* = 8.4 Hz, 2H), 4.60 – 4.25 (m, 2H), 4.20 – 4.05 (m, 1H), 3.79 (s, 1H), 4.70 – 4.55 (m, 1H), 2.40 – 2.10 (m, 4H), 2.00 – 1.80 (m, 1H), 1.73 (br s, 2H), 1.50 – 1.10 (br m, 9H), 1.04 (d, *J* = 6.8 Hz, 3H), 0.97 – 0.90 (m, 6H), 0.82 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.1, 158.4, 136.0, 127.9, 113.7, 80.3, 65.7, 60.0, 55.3, 52.5, 45.1, 29.2, 28.3, 28.2, 27.8, 27.4, 22.2, 20.7, 18.6, 17.8; IR (neat) 2959, 2930, 2874, 2837, 1772, 1690, 1613, 1513, 1466, 1386, 1366, 1245, 1170, 1101, 1033 cm^{-1}; HRMS (ESI-TOF) m/z: calcd for $C_{26}H_{40}NO_5$ $[M+H]^+$ 446.2901, found $[M+H]^+$ 446.2891 and calcd for $C_{26}H_{39}NNaO_5$ $[M+Na]^+$ 468.2720, found $[M+Na]^+$ 468.2729.

Lactone 41: An aqueous 1 M solution of LiOH (1.4 mL, 1.4 mmol, 10 equiv) was added to a solution of lactone **37** (88 mg, 0.14 mmol, 1.0 equiv) in DME (1.4 mL) at 0 °C. The reaction mixture was allowed to reach room temperature and monitored by TLC and MS. The mixture was then acidified with a 1M HCl solution in MeOH to pH = 3-4 and volatiles were removed under vacuum with a rotary evaporator to give 312 mg of the crude mixture.

Boc_2O (0.10 g, 0.48 mmol, 2.4 equiv) was added to a mixture of the crude deprotected intermediate (0.18 g, estimated to 0.20 mmol, 1.0 equiv) in CH_2Cl_2 (1 mL) and H_2O (1 mL) at 0 °C. K_2CO_3 (0.26 g, 1.9 mmol, 10 equiv) and TBAB (24 mg, 74 μmol, 0.37 equiv) were added and the mixture was allowed to reach room temperature. The mixture was stirred for 16 h at room temperature then the layers were separated. The aqueous layer was extracted with CH_2Cl_2

(3 × 2 mL). The organic layers were combined, dried over sodium sulfate, filtered and concentrated. The residue was purified via flash chromatography (silica gel, 1:9 ethyl acetate:hexanes) to yield Boc protected lactone **41** (105 mg, >95%) as a colorless oil; $[\alpha]_D^{20}$ −70 (*c* 0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.01 (s, 1H), 6.85 – 6.72 (m, 2H), 4.82 (s, 1H), 4.35 – 3.95 (m, 4H), 3.83 (s, 3H), 3.62 – 3.48 (m, 2H), 3.36 – 3.28 (m, 3H), 2.66 – 2.53 (m, 1H), 2.35 – 2.02 (m, 5H), 1.99 – 1.56 (m, 4H), 1.35 – 1.10 (m, 9H), 1.04 (d, *J* = 6.9 Hz, 3H), 0.93 (d, *J* = 6.8 Hz, 3H), 0.88 (d, *J* = 6.7 Hz, 3H), 0.80 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.6, 155.4, 148.3, 148.2, 119.9, 111.9, 111.2, 80.1, 79.2, 69.7, 66.32, 66.29, 61.1, 58.8, 56.1, 46.9, 29.6, 28.6, 28.3, 27.9, 27.7, 21.9, 20.7, 18.4, 18.3; IR (NaCl) 2961, 2874, 2835, 1770, 1682, 1515, 1469, 1391, 1260, 1143, 1028 cm^{-1}; HRMS (ESI-TOF) m/z: calcd for $C_{30}H_{47}NNaO_7$ $[M+Na]^+$ 556.3245, found $[M+Na]^+$ 556.3241.

Amide 42: A 2 M solution of $AlMe_3$ in toluene (0.1 mL, 0.2 mmol, 5 equiv) was added to a solution of *n*-butylamine (20 μL, 0.20 mmol, 5.0 equiv) in CH_2Cl_2 (1 mL) and the mixture was stirred at room temperature for 5 min. The resulting solution was transferred to a solution of lactone **37** (25 mg, 40 μmol, 1.0 equiv) in CH_2Cl_2 (1 mL) and the solution was stirred at room temperature overnight then quenched with a saturated solution of ammonium chloride (10 mL). The organic phase was separated. The aqueous phase was extracted with dichloromethane (3 × 10 mL). The combined organic extracts were dried over sodium sulfate, filtered, and concentrated. The residue was purified by flash chromatography (silica gel, 1:4 ethyl acetate:hexanes) to yield amide **42** (25 mg, 87%) as a colorless oil; R_f = (0.31, 2:3 ethyl acetate:hexanes); $[\alpha]_D^{20}$ + 11 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.07 (d, *J* = 2.0 Hz, 1H), 6.86 (dd, *J* = 8.3, 2.0 Hz, 1H), 6.79 (d, *J* = 8.3 Hz, 1H), 5.94 (t, *J* = 5.7 Hz, 1H), 4.55 (d, *J* = 9.2 Hz, 1H), 4.44 (q, *J* = 10.8 Hz, 2H), 4.16 – 4.07 (m, 2H), 4.00 – 3.93 (m, 1H), 3.83 (s, 3H), 3.65 – 3.57 (m, 3H), 3.37 (s, 3H), 3.34 – 3.24 (m, 1H), 3.23 – 3.13 (m, 1H), 2.34 – 2.25 (m, 1H), 2.17 – 2.07 (m, 3H), 2.00 – 1.83 (m, 4H), 1.75 – 1.67 (m, 1H), 1.60 (ddd, *J* = 13.5, 10.4, 2.8 Hz, 1H), 1.51 – 1.44 (m, 2H), 1.38 – 1.28 (m, 3H), 0.97 – 0.86 (m, 12H), 0.83 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.4, 149.2, 148.7, 134.2, 120.1, 112.6, 111.6, 93.9, 77.6, 71.4, 69.9, 69.7, 67.7, 66.2, 58.8, 56.1, 53.4, 51.5, 39.3, 35.1, 32.0, 30.6, 30.4, 29.6, 28.7, 22.1, 21.3, 20.6, 20.3, 18.5, 13.9; IR (NaCl) 3330, 3012, 2960, 2931, 2874, 1634, 1516, 1464, 1373, 1261,

1183, 1000 cm^{-1}; HRMS (ESI-TOF) m/z: calcd for $C_{31}H_{52}Cl_3N_2O_8S$ $[M+H]^+$ 717.2505, found $[M+H]^+$ 717.2524 and calcd for $C_{31}H_{51}Cl_3N_2NaO_8S$ $[M+Na]^+$ 739.2324, found $[M+Na]^+$ 739.2341.

(*S*)-2-Isopropyl-*N*-methoxy-*N*-methylpent-4-enamide (47): EDC (0.71 g, 3.7 mmol, 1.1 equiv) was added to a solution of acid **7** (0.50 g, 3.5 mmol, 1 equiv) in dichloromethane (15 mL) at 0 °C, followed by triethylamine (0.59 mL, 4.2 mmol, 1.2 equiv), *N*,*O*-dimethylhydroxylamine hydrochloride, and a small chip of DMAP. The reaction mixture was allowed to slowly reach room temperature and stirred for 16 h. Volatiles were removed under vacuum with a rotary evaporator and the resulting residue was partitioned between ethyl acetate (10 mL) and H_2O (10 mL). The aqueous layer was back-extracted twice with ethyl acetate (2 × 10 mL). The organic layers were combined, washed with a saturated aqueous solution of sodium bicarbonate (3 × 10 mL), dried over sodium sulfate and concentrated. The residue was purified by flash chromatography (silica gel, 2.5 cm diameter × 20 cm height, 1:4 ethyl acetate:hexanes) to yield amide **47** (0.46 g, 70%) as an oil. R_f = 0.7 (3:7, ethyl acetate:hexanes) $[\alpha]_D^{20}$ +8 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 5.74 (ddt, *J* = 17.2, 10.2, 7.1 Hz, 1H), 5.05 (ddt, *J* = 17.0, 1.8, 1.2 Hz, 1H), 5.00 – 4.90 (m, 1H), 3.66 (s, 3H), 3.18 (s, 3H), 2.69 (br s, 1H), 2.43 – 2.23 (m, 2H), 1.96 – 1.82 (m, 1H), 0.96 (d, *J* = 6.8 Hz, 3H), 0.91 (d, *J* = 6.7 Hz, 3H); (residual chloroform signal was set at 77.9 ppm)^{13}C NMR (75 MHz, $CDCl_3$) δ 177.6, 137.3, 117.0, 62.1, 48.2, 35.1, 32.8, 31.4, 21.9, 21.8; IR (neat) 3077, 2961, 2873, 2820, 1661, 1464, 1440, 1416, 1385, 1337, 1321, 1177, 1116, 1085; HRMS (ESI-TOF) m/z: calcd for $C_{10}H_{20}NO_2$ $[M+H]^+$ 186.1489, found $[M+H]^+$ 186.1482.

(*S*)-2-Isopropyl-1-(4-methoxyphenyl)pent-4-en-1-one (48):[27] A solution of 1.6 *M* of *n*BuLi in hexane (1.35 mL, 2.16 mmol, 1.03 equiv) was added to a solution of 4-bromoanisole (0.26 mL, 2.1 mmol, 1.0 equiv) in THF (8 mL) at −78 °C. The solution was stirred at −78 °C for 40 to 60 min, then treated dropwise with a solution of amide **47** (0.46 g, 2.5 mmol, 1.2 equiv) in THF (2-3 mL) was added in a dropwise manner. The reaction mixture was allowed to warm to room temperature and stirred for 1h then quenched with water (10 mL). The organic layer

was separated from the aqueous layer. The aqueous layer was extracted with diethyl ether (2 × 10 mL). The organic phases were combined, washed with brine (2 ×10 mL), dried over magnesium sulfate, filtered and concentrated. The residue was purified by flash chromatography (silica gel, 2.5 cm diameter × 13 cm height; 1:9 diethyl ether: hexanes) to yield ketone **48** (0.40 g, 83%) as a clear oil; R_f = 0.47 (1:4 ethyl acetate:hexanes); $[\alpha]_D^{20}$ +38 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 (d, *J* = 8.8 Hz, 2H), 6.93 (d, *J* = 8.8 Hz, 2H), 5.69 (ddt, *J* = 17.0, 10.1, 7.0 Hz, 1H), 4.99 (d, *J* = 17.0 Hz, 1H), 4.89 (d, *J* = 10.1 Hz, 1H), 3.87 (s, 3H), 3.29 (ddd, *J* = 10.2, 6.8, 3.9 Hz, 1H), 2.64 – 2.45 (m, 1H), 2.38 – 2.21 (m, 1H), 2.16 – 1.91 (m, *J* = 6.7 Hz, 1H), 0.98 – 0.88 (m, 6H);^{13}C NMR (75 MHz, $CDCl_3$) δ 202.4, 163.4, 136.6, 131.5, 130.6 (2C), 116.3, 113.8 (2C), 55.6, 52.0, 33.4, 30.8, 21.4, 19.7; IR (neat) 3076, 2960, 2934, 2872, 2840, 1670, 1640, 1599, 1576, 1509, 1463, 1439, 1419, 1388, 1370, 1308, 1259, 1211, 1170, 1114, 1031 cm^{-1}; HRMS (ESI-TOF) m/z: calcd for $C_{15}H_{21}O_2$ $[M+H]^+$ 233.1536, found $[M+H]^+$ 233.1530 and calcd for $C_{15}H_{20}NaO_2$ $[M+Na]^+$ 255.1356, found $[M+Na]^+$ 255.1345.

Dilactone 49: Hoveyda-Grubbs' second generation catalyst (6 mg, 0.01 mmol, 0.05 equiv) was added to a solution of ester **16** (70 mg, 0.20, 1.0 equiv) in toluene (20 mL) and the mixture was heated to a reflux for 24 h. The solution was concentrated by blowing air in the flask. The residue was purified by flash chromatography (silica gel, 2.0 cm diameter × 20 cm height, 0:100 to 3:97 ethyl acetate:hexanes) to yield dilactone **49** (20 mg, 30%) R_f = 0.2 (1:9 ethyl acetate:hexanes); Recrystallization from MeOH gave white crystals. m.p. 191 to 198 °C; $[\alpha]_D$ −48 (*c* 0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22 – 7.13 (m, 4H), 6.91 – 6.78 (m, 4H), 6.14 (d, *J* = 2.7 Hz, 2H), 5.75 – 5.60 (m, 2H), 5.54 – 5.35 (m, 2H), 3.80 (s, 6H), 2.54 – 2.27 (m, 4H), 2.21 (ddd, *J* = 11.2, 7.9, 3.6 Hz, 2H), 2.14 – 1.94 (m, 4H), 1.94 – 1.70 (m, 4H), 1.52 – 1.42 (m, 2H), 0.98 (d, *J* = 6.7 Hz, 6H), 0.94 (d, *J* = 6.9 Hz, 6H), 0.90 (d, *J* = 6.6 Hz, 6H), 0.78 (d, *J* = 6.9 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.8, 158.6, 132.8, 131.4, 130.0, 127.3, 113.5, 75.3, 55.4, 54.4, 50.1, 34.5, 31.5, 28.2, 25.7, 23.3, 21.2, 20.6, 18.0; IR (neat) 2956, 2932, 2873, 1733, 1513, 1465, 1248, 1148, 1035 cm^{-1}; HRMS (ESI-TOF) m/z: calcd for $C_{42}H_{64}NO_6$ $[M+NH_4]^+$ 678.4728, found $[M+NH_4]^+$ 678.4721.

Other fractions were combined to give 28 mg of mixture of head-to-head isomers **50**

(2*S*,7*R*,*E*)-2-Isopropyl-7-(4-methoxybenzyl)-8-methylnon-4-enoic acid (Acid 51): TFA (3 drops) was added to a solution of dilactone **49** (17 mg, 0.026 mmol, 1.0 equiv) and triethylsilane (0.10 mL, 0.63 mmol, 24 equiv) in dichloromethane (1 mL). The solution was stirred at room temperature for 10 min. The volatiles were removed under vacuum with a rotary evaporator and the residue was purified by flash chromatography (silica gel, 1.5 cm diameter × 20 cm height, 100 mL of hexanes then 1:19 ethyl acetate:hexanes) to yield acid **51** (12 mg, 71%) as a clear oil. R_f = 0.14 (1:9 ethyl acetate:hexanes); $[\alpha]_D$ +27 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.74 (s, 1H), 7.07 – 7.02 (m, 2H), 6.83 – 6.78 (m, 2H), 5.47 – 5.29 (m, 2H), 3.78 (s, 3H), 2.50 (dd, *J* = 13.8, 6.6 Hz, 1H), 2.36 (dd, *J* = 13.8, 8.0 Hz, 1H), 2.31 – 2.12 (m, 3H), 2.00 – 1.80 (m, 3H), 1.76 – 1.62 (m, 1H), 1.53 – 1.40 (m, 1H), 1.00 – 0.92 (m, 6H), 0.88 (d, *J* = 6.9 Hz, 3H), 0.85 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.6, 157.7, 134.2, 132.0, 130.1, 128.3, 113.7, 55.4, 52.7, 46.4, 35.7, 33.0, 32.7, 30.1, 28.3, 20.4 , 20.3, 19.3, 19.0; IR (neat) 2956, 2925, 2871, 1703, 1511, 1244, 1176, 1038 cm^{-1}; HRMS (ESI-TOF) m/z: calcd for $C_{21}H_{36}NO_3$ $[M+NH_4]^+$ 350.2690, found $[M+NH_4]^+$ 350.2688 and calcd for $C_{21}H_{32}NaO_3$ $[M+Na]^+$ 355.2244, found $[M+Na]^+$ 355.2248.

Dilactone 52: Pd/C (cat, spatula tip) was added to a solution of the mixture of isomers **50** (28 mg) in methanol:ethyl acetate (6 mL, 1:1). The suspension was purged with H_2 and stirred for 24 h. The mixture was then filtered on Celite® and concentrated to afford a residue which was purified by flash chromatography (silica gel, 1.5 cm diameter × 20 cm height, 1:9 ethyl acetate:hexanes) to yield dilactone **52** (20 mg, 30% over 2 steps) as a clear oil. R_f = 0.33 (1:9 ethyl acetate:hexanes); $[\alpha]_D^{20}$ −64 (*c* 0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.19 – 7.11 (m, 4H), 6.90 – 6.83 (m, 4H), 6.05 (d, *J* = 1.5 Hz, 2H), 3.79 (s, 6H), 2.22 (td, *J* = 8.7, 2.8 Hz, 2H), 2.00 – 1.82 (m, 2H), 1.82 – 1.27 (m, 20H), 0.96 – 0.84 (m, 18H), 0.81 (d, *J* = 6.9 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.3, 158.7, 132.4, 127.5, 113.6, 76.2, 55.3, 52.7, 50.3, 30.3, 29.7, 29.5, 27.0, 26.9, 25.8, 23.0, 21.5, 20.0, 18.6; IR (neat) 2953, 2934, 2868, 1730, 1608, 1507, 1461, 1379, 1295, 1250, 1172, 1118, 1035 cm^{-1}; HRMS (ESI-TOF) m/z: calcd for $C_{42}H_{64}NaO_6$ $[M+Na]^+$ 687.4595, found $[M+Na]^+$ 687.4580.

(2*S*,7*R*)-2-Isopropyl-7-(4-methoxybenzyl)-8-methylnonanoic acid (Acid 54): Pd/C (cat) was added to a solution of dilactone **49** (4 mg, 0.006 mmol, 1 equiv) in MeOH (0.5 mL) and EtOAc (0.05 mL). The suspension was purged with H_2 and the reaction was stirred under H_2 atmosphere (H_2 balloon). The reaction was monitored by TLC: R_f = 0.31 (1:9 ethyl acetate:hexanes). When completed, the mixture was filtered through Celite® and concentrated to afford 4 mg of the crude dilactone **53**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18 – 7.09 (m, 4H), 6.88 – 6.75 (m, 4H), 6.14 (d, *J* = 1.8 Hz, 2H), 3.77 (s, 6H), 2.15 – 2.03 (m, 2H), 1.91 – 1.10 (m, 22H), 0.92 (d, *J* = 6.7 Hz, 12H), 0.83 (d, *J* = 6.6 Hz, 6H), 0.74 (d, *J* = 7.0 Hz, 6H); HRMS (ESI-TOF) m/z: calcd for $C_{42}H_{64}NaO_6$ $[M+Na]^+$ 687.4595, found $[M+Na]^+$ 687.4576.

TFA (3 drops) was added to a solution of the crude dilactone **53** (4 mg, 0.006 mmol, 1 equiv) and triethylsilane (0.1 mL, 0.63 mmol, 100 equiv) in dichloromethane (1 mL). The solution was stirred at room temperature for 10 min. The volatiles were removed under vacuum with a rotary evaporator and the residue was purified by flash chromatography (silica gel, 1.5 cm diameter × 20 cm height, 100 mL of hexanes then 1:19 ethyl acetate:hexanes) to yield acid **54** (3 mg, 75%). $[\alpha]_D^{20}$ +16 (*c* 0.3, $CDCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.45 (s, 1H), 7.10 – 7.02 (m, 2H), 6.84 – 6.76 (m, 2H), 3.78 (s, 3H), 2.51 (dd, *J* = 13.7, 6.7 Hz, 1H), 2.35 (dd, *J* = 13.7, 7.8 Hz, 1H), 2.17 – 2.03 (m, 1H), 1.94 – 1.79 (m, 1H), 1.75 – 1.62 (m, 1H), 1.62 – 1.49 (m, 2H), 1.49 – 1.36 (m, 2H), 1.36 – 1.08 (m, 5H), 0.96 – 0.92 (m, 6H), 0.88 (d, *J* = 6.9 Hz, 3H), 0.84 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 179.6, 157.7, 134.5, 130.1, 113.7, 55.4, 52.4, 46.1, 36.3, 30.6, 29.6, 29.5, 28.6, 28.4, 27.7, 20.6, 20.3, 19.3, 16.9; ^{13}C NMR (101 MHz, $CDCl_3$) δ 181.5, 157.7, 134.4, 130.1, 113.7, 55.4, 52.6, 46.1, 36.3, 30.6, 29.5, 29.4, 28.6, 28.2, 27.7, 20.6, 20.2, 19.3, 18.8; IR (neat) 2925, 2860, 1704, 1511, 1461, 1375, 1245, 1178, 1038 cm^{-1}; HRMS (ESI_NEG) calcd for $C_{21}H_{33}O_3$ $[M-H]^-$ 333.2435, found $[M-H]^-$ 333.2440.

Lactone 55: 2,2,2-trichloroethylsulfamate (14 mg, 0.061 mmol, 1.1 equiv) was added to a solution of lactone **20** (18 mg, 0.055 mmol, 1.0 equiv) in toluene (0.3 ml) followed by magnesium oxide (6 mg, 0.15 mmol, 2.7 equiv) and rhodium acetamide dimer (2 mg, 0.003

mmol, 0.04 equiv). The resulting pale blue slurry was cooled down to 0 °C then (diacetoxy)iodobenzene (27 mg 0.083 mmol, 1.5 eq.) was added and the reaction was slowly warmed to room temperature. The progress of the reaction was monitored by TLC analysis (30:70 ethyl acetate-hexanes, CAM). After 20 h of stirring at room temperature TLC analysis showed no more conversion. The reaction mixture was diluted with dichloromethane and filtered through a pad of Celite, then washed with dichloromethane (3 x 10ml). The solvent was removed under reduced pressure to leave a brown oil which was purified by flash column chromatography (silica gel, 1.5 cm diameter × 20.0 cm height, 1:19 ethyl acetate:hexanes) to yield compound **55** (8 mg, 0.014 mmol, global yield: 25%) and starting material **20** (8 mg, 0.024 mmol, yield based on recovered starting material: 47%); R_f = 0.27 (1:9 ethyl acetate: hexanes); $[\alpha]_D^{20}$- 19 (*c* 0.8, $CDCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, *J* = 8.7 Hz, 1H), 6.89 (d, *J* = 8.7 Hz, 1H), 5.85 (d, *J* = 6.3 Hz, 1H), 4.80 (s, 1H), 3.81 (s, 1H), 2.94 (ddd, *J* = 12.2, 6.8, 2.6 Hz, 1H), 2.81 (ddd, *J* = 10.1, 6.8, 3.0 Hz, 1H), 2.48 – 2.39 (m, 1H), 2.32 – 2.25 (m, 1H), 2.21 – 1.99 (m, 1H), 1.97 – 1.87 (m, *J* = 14.6, 11.3, 6.2 Hz, 1H), 1.51 – 1.41 (m, 1H), 1.03 (t, *J* = 6.8 Hz, 3H), 0.88 (d, *J* = 6.6 Hz, 2H), 0.77 (d, *J* = 6.6 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.2, 159.8, 129.2, 128.9, 114.1, 93.1, 79.5, 77.1, 55.4, 49.1, 48.1, 44.1, 43.6, 29.6, 26.9, 26.0, 23.4, 22.6, 21.7, 20.2, 19.7; IR (neat) 2959, 2931, 2873, 2839, 1733, 1612, 1515, 1464, 1369, 1250, 1178, 1118 cm^{-1}; HRMS (ESI-TOF) m/z: calcd for $C_{23}H_{33}NO_6SCl_3$ $[M+H]^+$ 556.1089, found $[M+H]^+$ 556.1075.

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Supporting Information

^{1}H and ^{13}C NMR spectra of new compounds, as well as X-ray crystallography reports and CIF files for compounds 20, 25, 32, 33, 39 and 49 are available free of charge via the internet at http://pubs.acs.org.

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1.5 Conclusions et perspectives

Dans le cadre de ce projet, l'étude des facteurs affectant la cyclisation par métathèse par fermeture de cycle d'ester en lactone comme le solvant et la nature du catalyseur utilisé, par exemple, ont permis de mieux comprendre la complexité de la réaction. La stéréochimie des substituants a d'ailleurs été identifiée comme étant un facteur clé de la cyclisation intramoléculaire étudiée. Le ratio de monolactone, obtenu à faible concentration, a aussi suggéré qu'un effet Thorpe-Ingold influence le produit obtenu sans toutefois qu'on puisse confirmer l'hypothèse. Le nombre de variables en jeu, les divers sites de coordination possibles pour le catalyseur ainsi que la réversibilité de la réaction ont empêché de tirer des conclusions définitives pour en rester à des observations quantitatives. Par contre, l'obtention de la monolactone (*S*,*S*,*S*) **1.8** préalablement inaccessible a donné l'occasion d'améliorer la synthèse de l'aliskiren en éliminant le problème de cyclisation originalement observé.

Chapitre 2 : Formation de liens benzyliques par substitution nucléophilique diastéréosélective catalysée par des acides

2.1 Introduction

La formation de liens stéréosélectifs en position benzylique est un sujet qui a suscité l'intérêt de plusieurs groupes de recherches importants au fil des ans.[38] Parmi ceux-ci, les groupes des Pr. Olah et Bach ont porté leur attention sur une alkylation de type Friedel-Crafts diastéréosélective permettant l'accès à des alcools benzyliques.[39] Cette réaction passe par un intermédiaire benzylique carbocationique et leur a permis d'obtenir un bon stéréocontrôle de la réaction (*Schéma 2.1*). De semblables réactivités ont déjà été rapportées, les carbocations benzyliques étant connus pour être stables[40] tout en fixant la conformation grâce à la tension allylique 1,3 ($A^{1,3}$).[41]

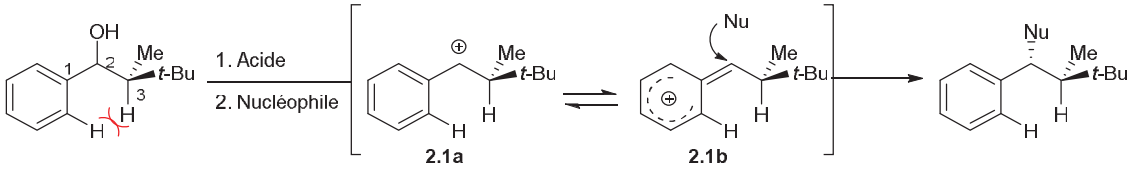


*Schéma 2.*1: Mécanisme expliquant la différenciation des faces du carbocation

Le concept de tension allylique 1,3 correspond aux interactions stériques entre les substituants des carbones C1 et C3 du système allylique (*Schéma 2.2*).[40] La conformation **2.2b** constitue un maximum énergétique qui est déstabilisé par la tension allylique 1,3 et représente ainsi la barrière d'énergie rotationnelle à franchir tandis que la conformation **2.2a** est fortement favorisée par l'effet stabilisateur de celle-ci. Malgré que la conformation **2.2c** soit un minimum, elle peut être ignorée de l'équilibre conformationnel de par le fait qu'elle soit supérieure en énergie de 3.44 kcal / mole par rapport à **2.2a**. La conformation de **2.2** n'est cependant pas rigide et il est possible d'obtenir une rotation de C3 de ± 30º pour moins de 1 kcal / mole.

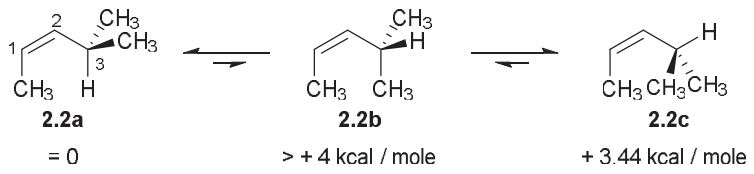


Schéma 2.2 : Différentes conformations de la tension allylique

En remplaçant les substituants méthyles du carbone C3 par des groupements alkyles différents l'environnement des faces *Si* et *Ré* deviennent différents du leur encombrement stérique (*Schéma 2.1*). De plus, il peut être avancé que la nature prochirale du groupement allylique permette l'obtention d'un seul diastéréoisomère favorisé selon la taille relative des substituants. La sélectivité de la réaction de type Friedel-Crafts étudiée par le Pr Olah et le Pr Bach[39] provient ainsi de l'intermédiaire **2.1b** stabilisé par résonance et de sa conformation favorisée par la réduction de la tension allylique 1,3 (*Schéma 2.1*). L'espèce quinonoïdale clé est obtenue par la protonation d'un alcool benzylique. Par la suite, l'addition du nucléophile se fait par la face moins encombrée, la face *Ré* dans la structure **2.1b** du *Schéma 2.1*, pour générer un produit diastéréoriquement enrichi.

Les travaux réalisés par le Pr Olah et le Pr Bach se sont concentrés sur la substitution de groupements aryles.[39] Ils ont permis d'établir un répertoire varié de nucléophiles (*Schéma 2.3*) ainsi qu'une règle générale. Celle-ci prédit une meilleure diastéréosélectivité lorsque la différence entre les valeurs A[42] des groupements fonctionnels du carbone C3 (*Schéma 2.2*) est grande.

Au cours de ses études doctorales auprès du groupe Hanessian, le Dr Étienne Chénard a eu l'occasion de travailler sur le même type de réaction de Friedel-Crafts. En s'inspirant des travaux de Bach, il avait prédit qu'une différentiation faciale liée aux valeurs A des substituants isopropyle et allyle permettrait l'obtention d'une diastéréosélectivité à partir d'un analogue de l'intermédiaire **1.5** de la synthèse de l'aliskiren présentée au chapitre 1. Cependant, seule une faible sélectivité a pu être observée lors de la réaction. Cela a mené à étudier l'influence de

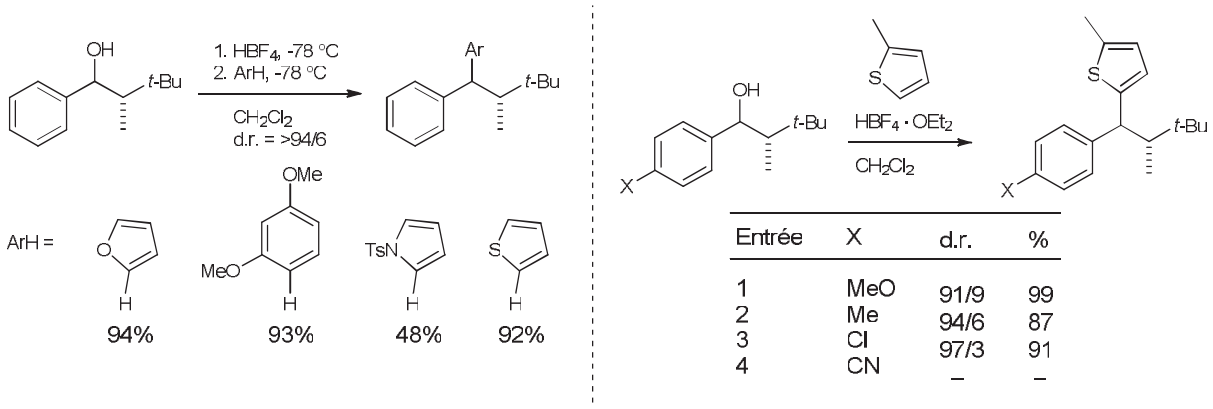
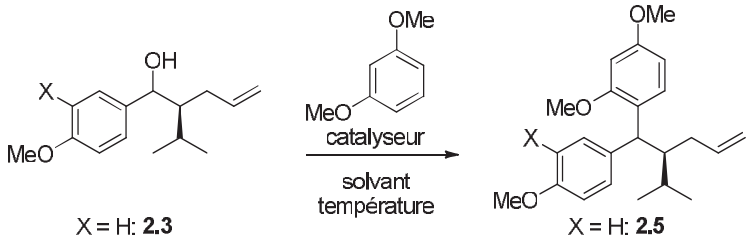


Schéma 2.3 : Sélection d'alkylations de type Friedel-Crafts réalisées par Bach et Olah

Tableau 2.1 : Étude de solvants et de catalyseurs réalisée par le Dr Étienne Chénard



X = H: **2.3**
X = OMe: **2.4**

X = H: **2.5**
X = OMe: **2.6**

entrée	X	catalyseur	solvant	température	mole %	temps[a]	dr[b]
1	H et OMe	$FeCl_3$•$6H_2O$	CH_2Cl_2 ou 1,2-DCE	ta	0.1	15 min	~1:1
2	H et OMe	$FeCl_3$•$6H_2O$	1,2-DCE	0 °C	0.1	1 h	1.3:1
3	H et OMe	*p*-TsOH•H_2O	CH_2Cl_2	ta	0.2	60 min	1.2:1
4	H	*p*-TsOH•H_2O	CH_2Cl_2	ta	0.2	16 h	1.5:1
5	H	(–)-TADDOL	CH_2Cl_2	ta	0.1	15 min	1.5:1
6	H	$Bi(OTf)_3$	CH_2Cl_2	ta	0.1	5 min	1.5:1
7	H	$Yb(OTf)_3$	CH_2Cl_2	ta	0.1	24 h	1.5:1[c]
8	H	$AgSbF_6$	CH_2Cl_2	ta	0.4	16 h	1.5:1
9	OMe	$AuCl_3$	CH_2Cl_2	ta	0.1	15 min	1.3:1
10	OMe	*p*-TsOH•H_2O	$[BMIM]BF_4$	ta	0.2	4 h	1.4:1
11	OMe	*p*-TsOH•H_2O	*t*-BuOH	ta	0.2	24 h	aucune conversion
12	OMe	*p*-TsOH•H_2O	Hexane	ta	0.2	48 h	1.4:1
13	OMe	*p*-TsOH•H_2O	PhMe	ta	0.2	72 h	1.4:1
14	OMe	$AlCl_3$	CH_2Cl_2	–78 °C	1	5 min	1.7:1
15	OMe	$AlCl_3$	PhMe	–78 °C	1	3 h	1.4:1

a) La conversion complète a été observée par CCM. b) Le ratio diastéréosélectif a été calculé par RMN ^{1}H.

nombreux solvants et de multiples acides de Lewis et de Brønsted afin de mieux comprendre les facteurs influençant la diastéréosélectivité de cette réaction (*Tableau 2.1*). Cependant, aucune de ces conditions n'a permis l'obtention d'un meilleur ratio.

Par la suite, il s'est intéressé à différents nucléophiles aryles pour déterminer leur effet sur la sélectivité (*Schéma 2.4*). L'acide *p*-TsOH hydraté s'est avéré utile pour simplifier la purification des réactions. La variation observée lors de cette étude s'est avérée négligeable et les ratios diastéréoisomériques quasi inexistants malgré les bons rendements obtenus avec plusieurs nucléophiles.

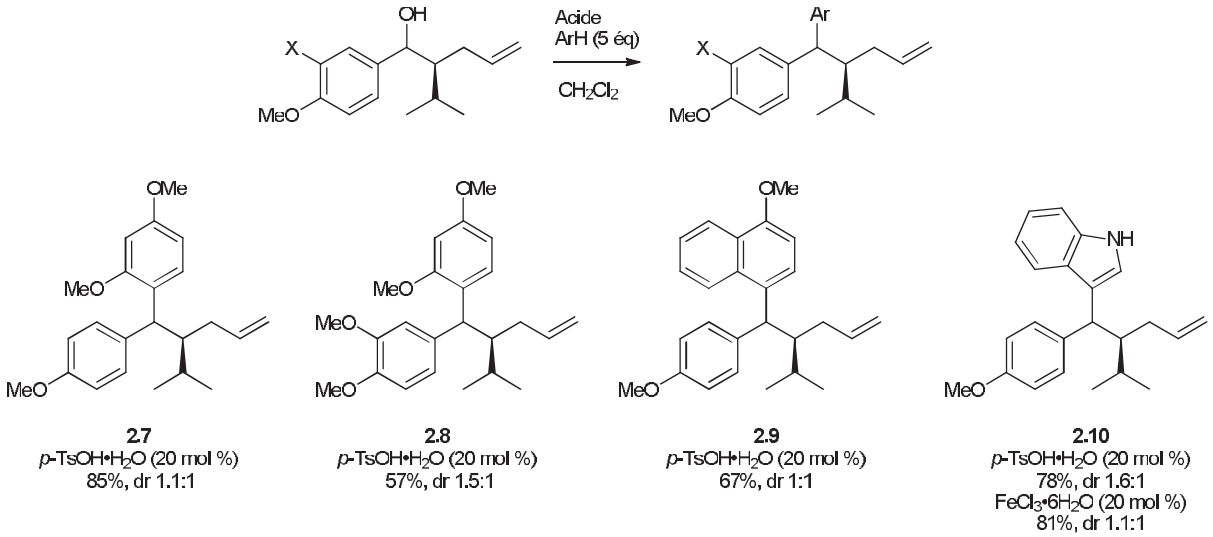


Schéma 2.4 : Étude de substituants aryles par le Dr Étienne Chénard

2.2 Formation de diaryles par réaction de type Friedel-Crafts

Lorsque j'ai pris en main le projet d'alkylation diastéréosélective catalysée par des acides, il a été suggéré de voir si la stéréosélectivité du motif allylalkyle pouvait être améliorée. La différence de valeur A entre les groupements fonctionnels isopropyle (A = 2.15) et allyle (A ~ 1.7) avait laissé croire qu'un certain contrôle sur l'attaque nucléophile aurait du avoir lieu. Or,

il a été observé par la suite que la différentiation faciale générée par l'encombrement stérique n'était pas suffisante. La première idée a été de remplacer le groupement isopropyle par des groupements alkyles de différentes tailles ayant pour but d'augmenter le ratio diastéréomérique (*Schéma 2.5*). Il a été constaté que l'acide *p*-TsOH hydraté en quantité catalytique (10 mol%) a donné de bons rendements, mais la sélectivité est restée inchangée. Le 1,3-diméthoxybenzène et le 1-méthoxynaphtalène ont été de bons nucléophiles que nous avons réutilisés avec les différents substrats au cours de notre étude. Il a été possible de déterminer, par des études NOE, la stéréochimie relative *syn* des produits **2.11** et **2.13** qui semblent restreints dans une seule conformation par leurs substituants, malgré leur structure acyclique. Celle-ci a été corrélée par la sélectivité prédite par les travaux de Bach. L'utilisation de groupements alkyles a été mise de côté suite à ses résultats pour favoriser d'autres groupements fonctionnels.

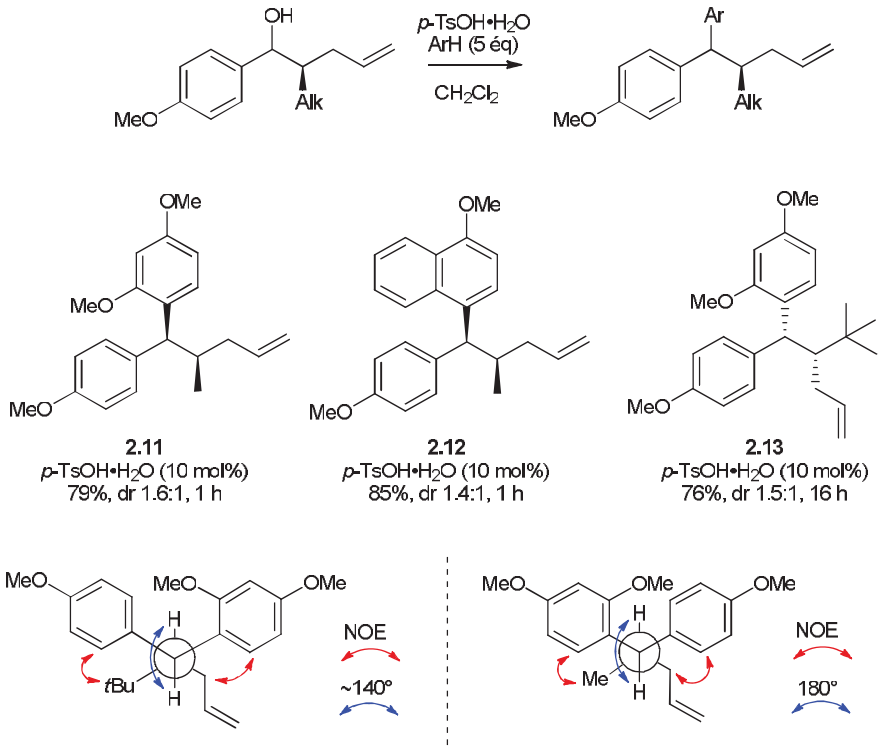


Schéma 2.5 : Formation de diarylallylalkanes et étude NOE

Les groupements phényles et benzyles ont été proposés comme alternative aux alcanes. L'encombrement stérique combiné à leurs propriétés électroniques nous a poussés à explorer cette option. Le triaryle **2.16** a montré une sélectivité faible qui a été attribuée à la distance entre le cycle aromatique et le carbocation dans l'état de transition, causant un encombrement semblable des deux faces (*Schéma 2.6A*). Nous avons été heureux d'obtenir le produit **2.14** avec un d.r. de 20 : 1 pour ainsi confirmer nos attentes quant à l'efficacité du groupement phényle. En voulant comprendre l'origine de cette soudaine amélioration de la sélectivité, nous avons fait une étude NOE. Le même encombrement stérique observé plus tôt semble avoir restreint la

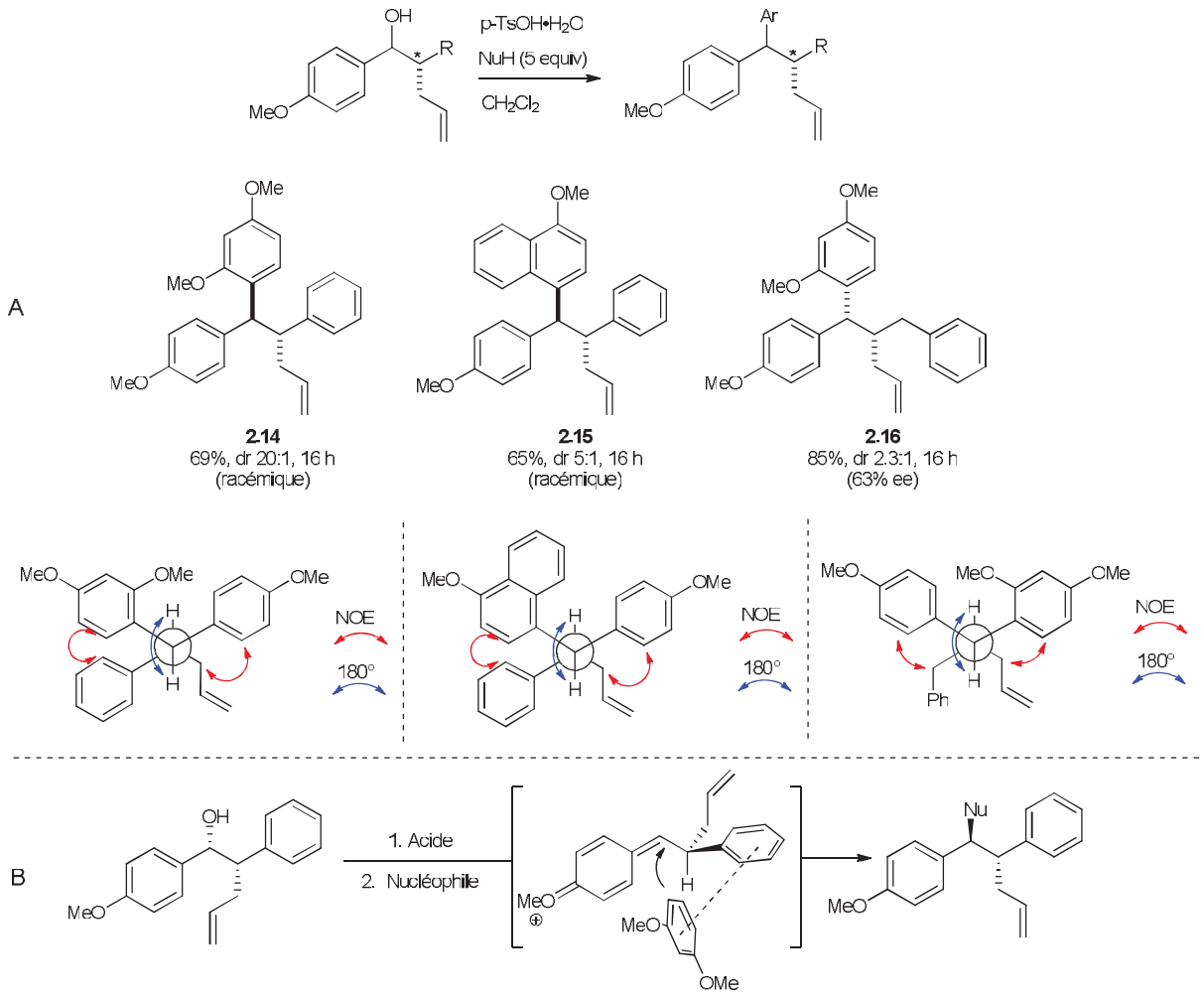
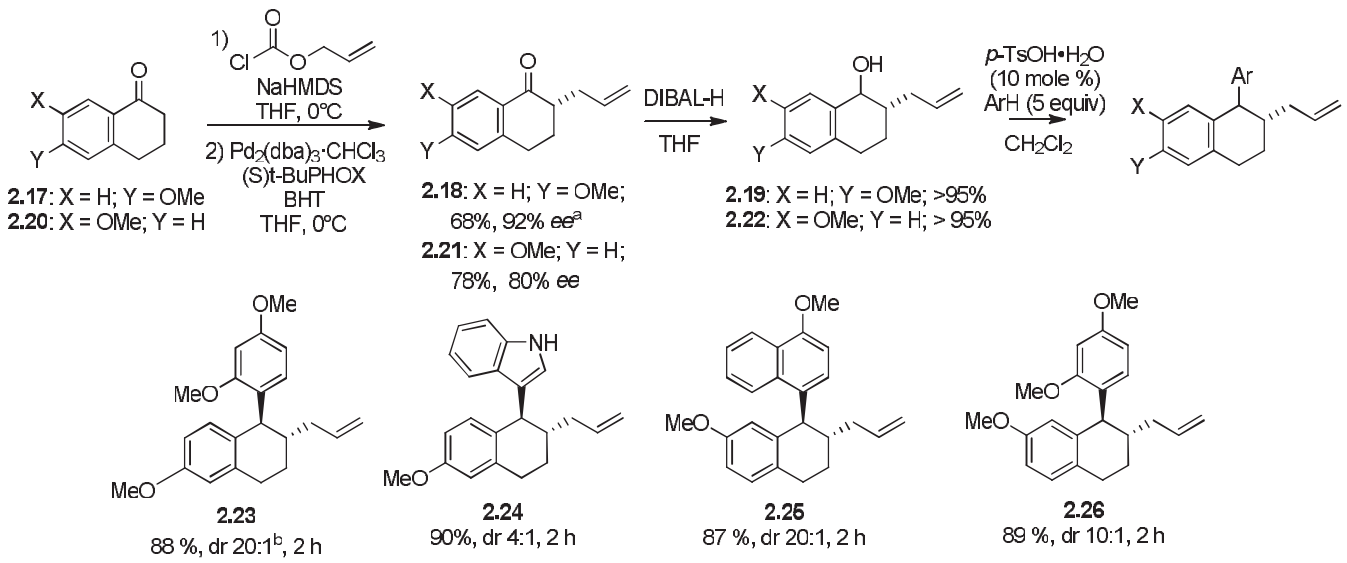


Schéma 2.6 : A. Alkylation d'arylallyles et étude NOE B. Mécanisme proposé pour la formation des composés *anti*

rotation libre autour du lien carbone-carbone dans la représentation de Newman. Nous avons réalisé qu'alors que nous pensions que le diastéréoisomère majeur avait une conformation *syn*, il possédait en fait une conformation *anti*. Pour rationaliser ce résultat, nous avons supposé quel nucléophile aromatique était guidé par un empilement π - π avec le groupement phényle (*Schéma 2.6B*). Cette interaction pouvait expliquer la meilleure sélectivité obtenue malgré la valeur A du groupement phényle inférieure à celle du groupement *tert*-butyle, suggérant que l'effet dominant contrôlant l'attaque du nucléophile n'est pas de nature stérique. Une étude réalisée dans les laboratoires de Merck a proposé la même explication pour expliquer des résultats obtenus avec la même sélectivité sur des substrats similaires.[43]

Parallèlement aux travaux réalisés ci-dessus, nous avons travaillé sur la formation asymétrique de 2-allyltetrahydronaphthalènes. Le but était de substituer la stabilisation de l'intermédiaire carbocationique amenée par la tension allylique 1,3 à l'aide d'une structure bicyclique rigide (*Schéma 2.7*). En utilisant l'allylation asymétrique de Stoltz en présence d'un ligand PHOX chirale[44], nous avons préparé les composés **2.19** et **2.22** avec un bon excès énantiomérique. Cette procédure avait été largement optimisée par le Dr Étienne Chénard lors de la synthèse asymétrique de composés hydroxyallyles. Les produits **2.23** à **2.26** ont été formés avec d'excellents ratios sauf dans le cas de l'indole où la sélectivité a été plus faible. Cette différenciation des deux faces contenant respectivement un groupement allylique et un hydrogène provient du squelette bicyclique forçant le maintien de cette conformation durant l'attaque du nucléophile. L'utilisation du squelette rigide offre une nouvelle approche pour la formation de diaryles allylés qui ont démontrés une diastéréosélectivité minimale comparé aux exemples utilisant des substrats dialkanes dans la littérature.[38, 39]



a) L'exces énatiomérique (ee) a été calculé par séparation HPLC chirale b) Le d.r. a été déterminé à partir de l'analyse des spectres RMN ^{1}H

Schéma 2.7 : Formation de 1,1'-diaryl-2-allylalkanes à partir de tétrahydronaphthalènes

2.3 Synthèse d'éthers benzyliques par substitution nucléophile sur des motifs aminés

La formation d'éthers benzyliques a aussi été le focus de plusieurs études. Diverses méthodes ont été utilisées pour former ce type de lien. Mukaiyama a étudié la formation d'éthers à partir de deux alcools par une réaction de condensation oxydoréductive en présence de chlorotriphénylphosphine et de quinone comme oxidant permettant de transformer le groupement phosphine en groupe partant (*Schéma 2.8*).[45] Lorsque la réaction est faite en utilisant au moins un alcool chiral, cette méthode permet de conserver la configuration de cet alcool en formant l'espèce intermédiaire alkoxydiphénylphosphine à partir de l'autre alcool. À l'opposé, en commençant avec l'alcool chiral, il devient possible d'inverser la configuration. Cette réaction permet d'utiliser une grande variété d'alkyle- et arylalcools, mais requiert un produit de départ énantiopure.

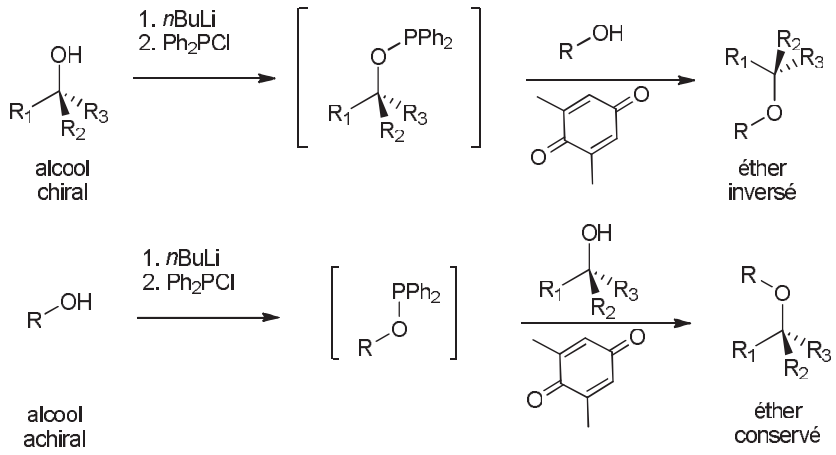


Schéma 2.8 : Inversion et conservation de configuration d'éthers par Mukaiyama

Certains groupes ont publié des réactions de C-H activation récemment pour former des éthers benzyliques. Le groupe de Pandey a démontré l'utilisation de systèmes catalytiques photoredox pour parvenir à former des éthers cycliques (*Schéma 2.9*).[46] La réaction intramoléculaire utilise le 1,4-dicyanonaphthalène (DCN) en présence de lumière UV. Le mécanisme proposé est initié par un transfert monoélectronique de la forme excitée de l'arylalcool vers le DCN suivi par l'élimination spontanée d'un proton. Un second transfert permet de générer l'espèce carbocationique, qui cyclise spontanément pour donner le produit.

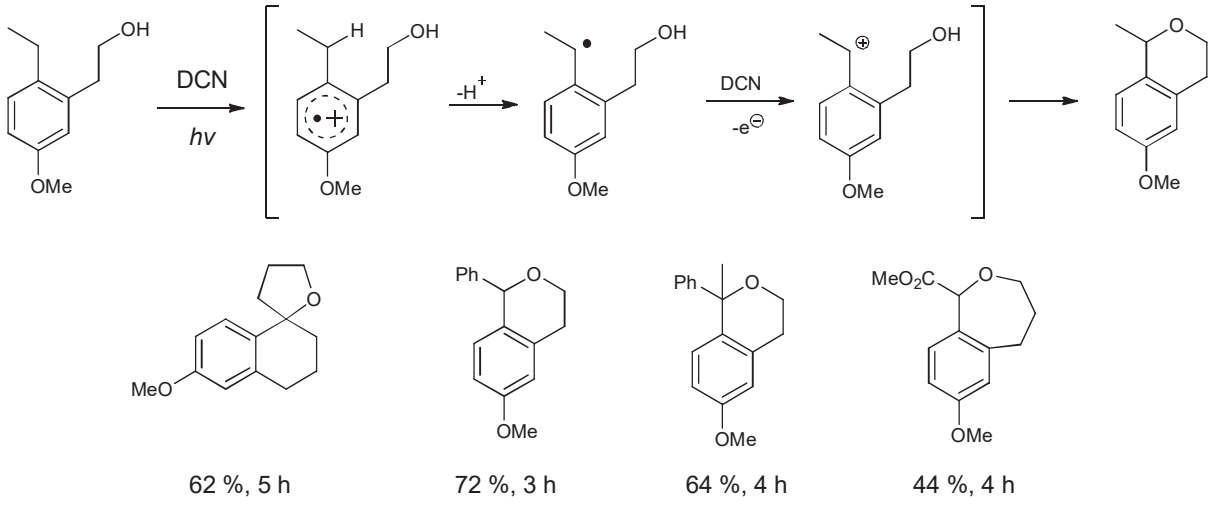


Schéma 2.9 : C-H activation benzylique par Pandey

Récemment, le groupe de Carreira a travaillé sur la synthèse énantiosélective d'éthers allyliques.[47] Préalablement à leur étude, il était nécessaire d'utiliser un électrophile allylique activé (carbonates, éthers et chlorures) ou d'activer un alcool par la formation de l'alkoxyde correspondant pour la formation d'éthers catalysés par des métaux de transition. Par contre, leur travaux ont documenté une méthode ne requiérant qu'un alcool allylique en tant qu'électrophile et un alcool aliphatique comme nucleophile. Ils ont utilisé un catalyseur à base d'iridium pour former énantiosélectivement les produits par un procédé de résolution cinétique et ont rapporté que la réaction est possible sous atmosphère ambiante sans perte significative d'énantiosélectivité.

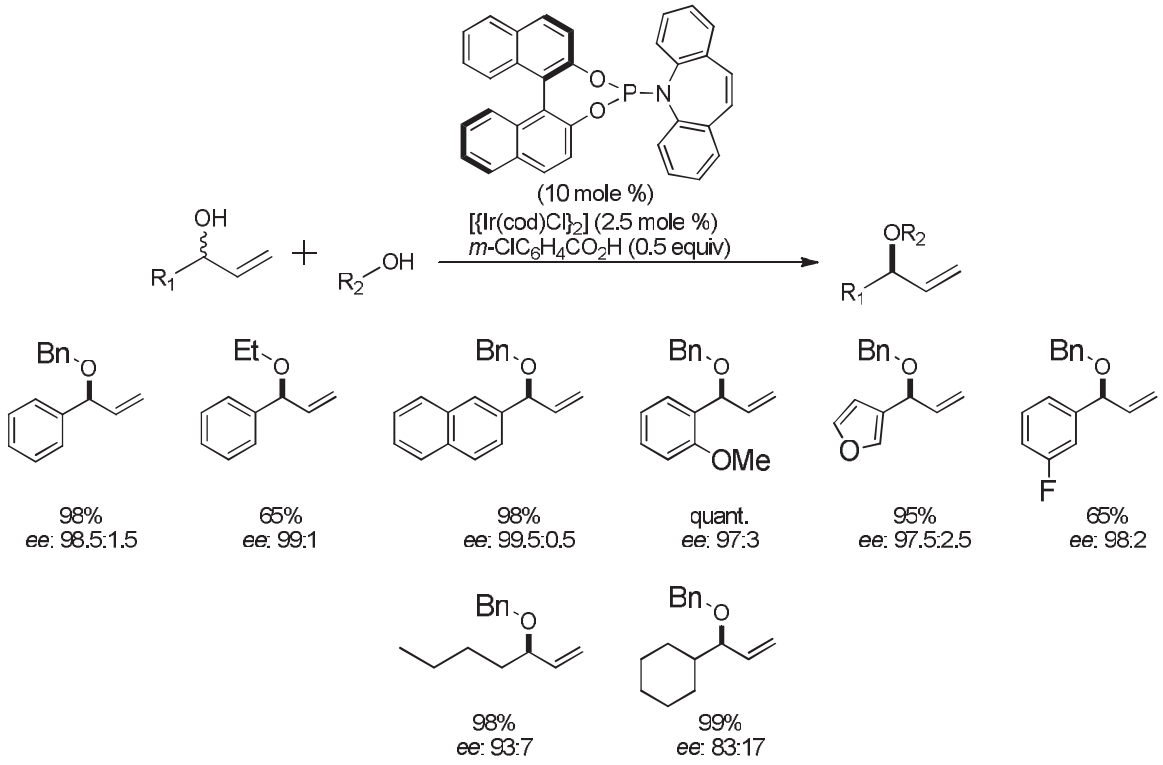


Schéma 2.10: Sélection d'étherifications allyliques énantiosélectives par Carreira

Le groupe de Sun a publié des travaux quant à la formation d'éthers benzyliques sur des motifs *o*-quinone.[48] Leur approche utilise la formation d'une "quinone methide" in situ pour ensuite effectuer une addition conjuguée énantiosélective d'un alcool (*Schéma 2.11*). Le catalyseur d'acide phosphorique chirale employé a permis de rapporter d'excellente sélectivité sur des substrats phénoliques. L'optimisation de la réaction a indiqué que l'utilisation de tamis moléculaires augmente le rendement ainsi que l'énantiosélectivité de la réaction. L'étude faite par le groupe Sun a montré une bonne compatibilité avec plusieurs alcools, mais l'utilisation d'alcools aromatiques n'a pas été rapportée.

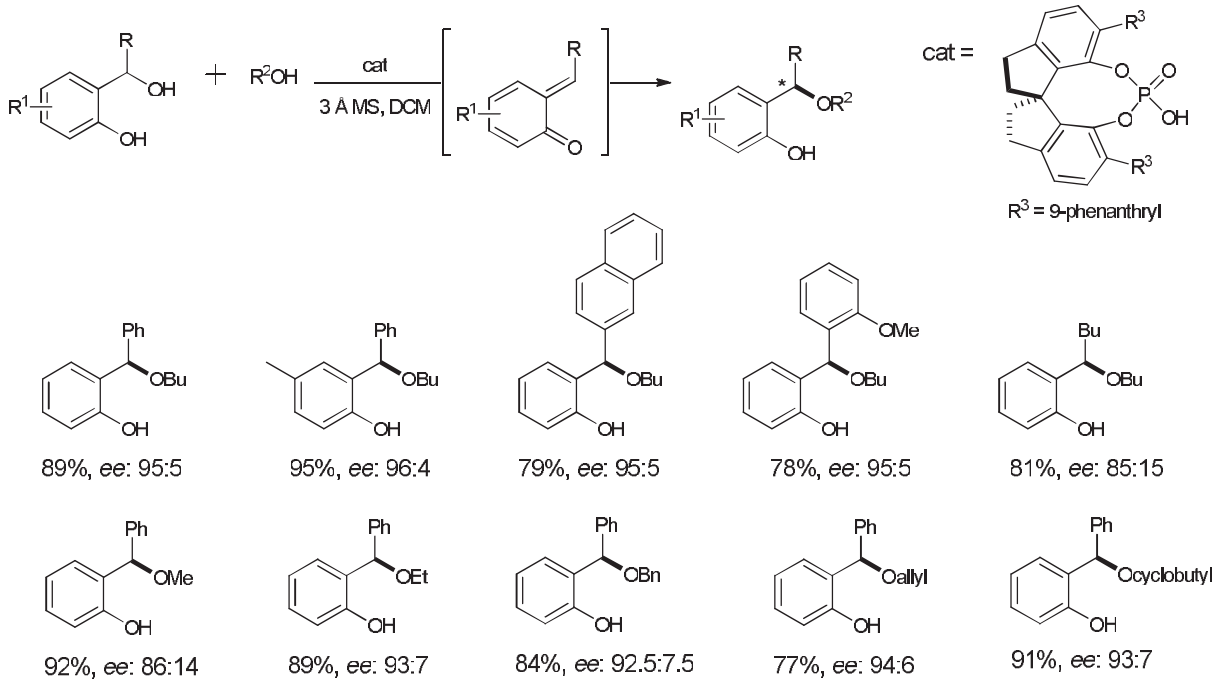


Schéma 2.11 : Addition nucléophilique sur des motifs *o*-quinone par le groupe Sun

Durant ses travaux avec les nucléophiles aryles, le Dr Étienne Chénard a effectué plusieurs tests avec des nucléophiles phénoliques visant la formation de liens carbone-carbone en position *ortho* et *para* en utilisant le $AuCl_3$ et *p*-TsOH•H_2O comme catalyseur. Cependant, des éthers benzyliques ont été formés avec une variété de d'alcools incluant le *p*-anisole (*Schéma 2.12*). De bons rendements ainsi qu'une bonne sélectivité ont été obtenus avec des substrats de

type nitroalcools benzylique. À l'opposé, les composés **2.31** et **2.32** ont été formés avec une mauvaise diastérosélectivité. Le produit allylique **2.32** a démontré le même manque de sélectivité que démontré auparavant.

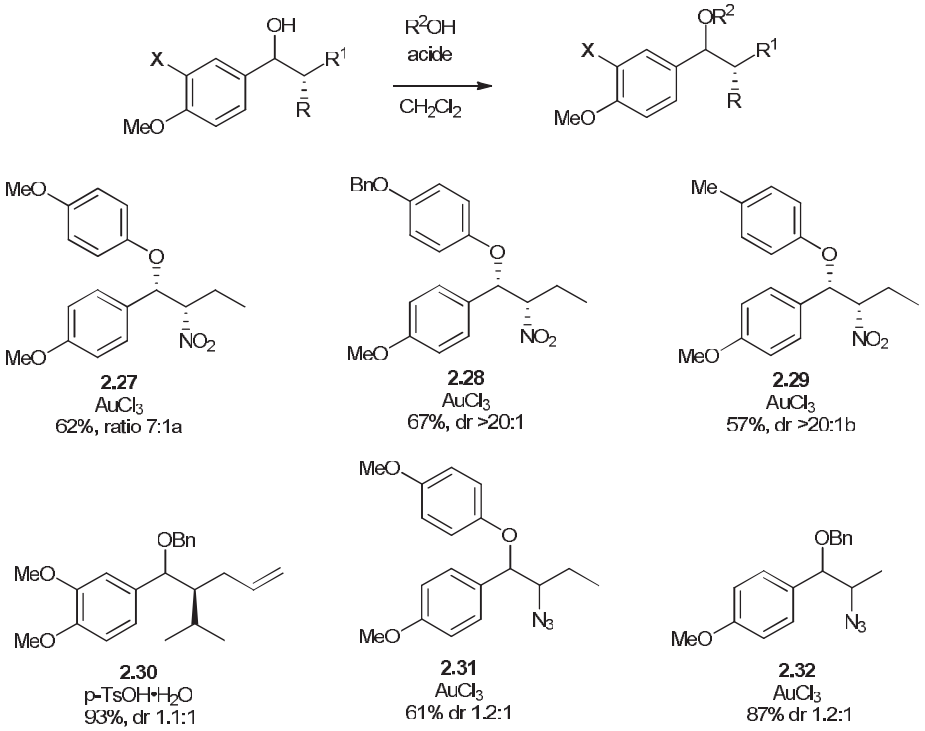
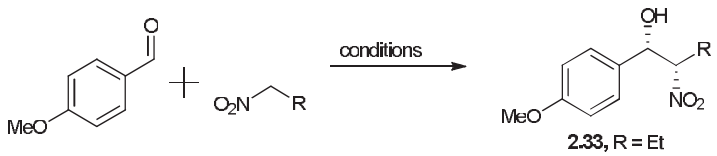


Schéma 2.12 : Étude de substituants phényles par le Dr Étienne Chénard

En nous basant sur ces résultats préliminaires, nous avons décidé d'étudier les phénols pour déterminer leur viabilité quant à la formation d'éthers benzyliques en présence d'un catalyseur acide. Nous avons choisi les nitroalcools comme substrat dû à la diastéréosélectivité des premiers résultats. Le groupe de Bach a aussi rapporté d'excellentes diastéréosélectivités lors de l'alkylation de nitroalcools ainsi que d'autres espèces aminées.[49] L'intérêt de ces structures réside dans la possibilité de fonctionnaliser le groupement nitro pour différents produits d'intérêt pharmaceutique.

Les nitroalcools ont été synthétisés par une réaction de Henry dont les conditions avaient été optimisées au préalable par le Dr Étienne Chénard. Il avait déterminé que les conditions optimales étaient l'utilisation de la base de Hünig et de LiBr en présence du *p*-anisaldéhyde et d'un nitroalkane (*Tableau 2.2*). Dans le but de tester des conditions alternatives, l'alumine[50] et l'Amberlyst A21[51] ont également été testés pour catalyser la réaction, bien qu'amenant des résultats plus modestes. Bien que simples d'utilisation, l'absence de bromure de lithium et de base semble affecter le rendement de la réaction. De plus, celles-ci n'ont pas été agitée durant un lapse de temps similaire aux conditions optimales.

Tableau 2.2 : Étude de conditions réactionnelles pour la réaction de Henry



2.33, R = Et
2.34, R = Allyl

entrée	conditions[a]	temps	rendement[b], dr[c]
1	DIPEA[d] (2 éq), LiBr (0.2 éq),(aldéhyde 1 éq, nitropropane 3 éq)	5 d	50%, 4:1
2	DIPEA (2 éq), LiBr (0.2 éq),(aldéhyde 1 éq, 4-nitrobutène 3 éq)	5 d	53%. 2.2:1
3	Alumina (aldéhyde 1 éq, nitropropane 1 éq)	1 d	9%, 3.3:1
4	Amberlyst A21 (aldéhyde 1 éq, nitropropane 1 éq)	1 d	18%, 3.3:1

a) Les réactions ont été réalisées sans solvant. b) Rendement isolé. c) Les dr ont été calculé sur le produit pur.
d) DIPEA = *N*,*N*-diisopropyléthylamine = *base de* Hünig

Dans le but d'agrandir la banque de substrats éthérés, il a été décidé d'essayer le 4-méthoxyphénol, le 4-méthylphénol et le benzylalcool sur le substrat **2.34** (*Schéma 2.13*). Nous avons utilisé $AuCl_3$ comme acide de Lewis ainsi que le dichlorométhane dû à leur efficacité observée préalablement comme catalyseur et solvant. Les phénols ont offert une bonne régiosélectivité en raison de leur activation par les groupements électrodonneurs en position *para*. La bonne diastéréosélectivité favorisant le produit *syn* a été attribuée à la différence de taille entre les groupements nitro et alkyles utilisés.

Il est important de noter que la formation de dimères éthérés à partir des substrats de départ n'a pas constitué un produit secondaire majeur dans la formation d'éthers asymétriques que nous avons étudié dans ce projet. L'utilisation de cinq équivalents du nucléophile a constitué un excès suffisant pour favoriser les produits désirés. La stéréochimie des produits a été assumé en ce basant sur la sélectivité observée en présence de nucléophiles aromatiques, les rayons X des 1,1-diaryles présentés au *Schéma 2.16* ainsi que le mécanisme proposé par le Pr. Bach présenté au *Schéma 2.1*.

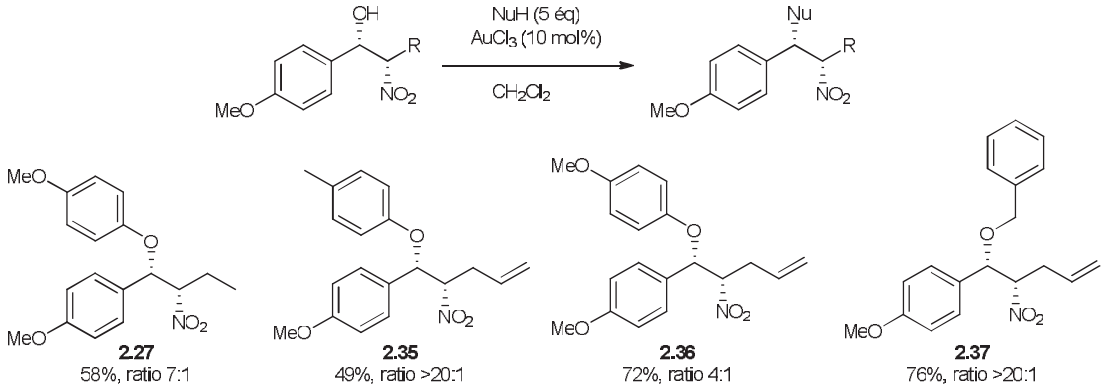


Schéma 2.13 : Formation diastéréosélective d'éthers benzyliques en présence de $AuCl_3$

Parallèlement, des substrats α-azidoalcools ont été préparés afin d'étudier si une bonne diastéréosélectivité comme celle observée pour les séries nitro du *Schéma 2.13*. Les α-azidoalcools ont ainsi été synthétisés. Les composés **2.38**, **2.39** et **2.40** ont été formés grâce à une bromation de leurs cétones correspondantes. Une substitution nucléophile subséquente en présence de l'azoture de sodium a donné les produits **2.41**, **2.42** et **2.43**, et ce avec des rendements acceptables. La réduction de la cétone à l'aide de borohydrure de sodium a résulté en un mélange légèrement diastéréoenrichi des produits **2.44**, **2.45** et **2.46** ainsi qu'un bon rendement.

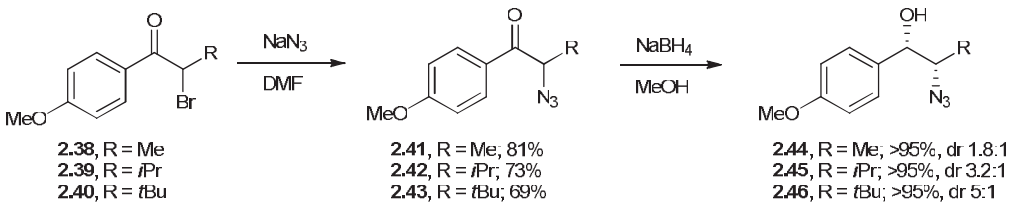


Schéma 2.14: Préparation des azidoalcools à partir des α-bromocétones correspondantes

La réaction de substitution nucléophile diastéréosélective a été réalisée sur les composés **2.44** et **2.46** (*Schéma 2.15*). Nous avons observé des rendements acceptables en utilisant des nucléophiles électroniquement enrichis comme le 4-méthoxyphénol, le 4-méthylphénol et le 4-benzyloxyanisole. Un faible ratio diastéréomérique a été obtenu pour **2.47** et **2.48** malgré la grande différence entre la taille des groupements fonctionnels méthyle et azido qui ont respectivement des valeurs A de 1.70 et 0.62.[42] Cela porte à croire que la diastéréosélectivité ne dépend pas seulement de l'encombrement stérique. Dans le but de renforcer cette théorie, nous avons substitué le groupement alkyle pour un *tert*-butyle pour ensuite obtenir **2.49** avec un ratio diastéréomérique semblable au reste de la série azido.

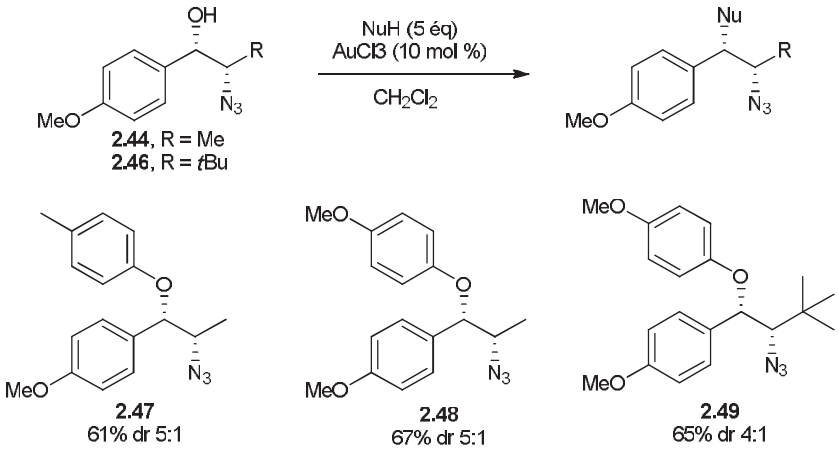


Schéma 2.15 : Étude de la réaction de substitution nucléophilique diastéréosélective sur les composés azido

La baisse marquée en diastéréosélectivité entre les séries nitro et azido ayant suggéré la présence d'autres effets de nature électronique, le Dr Étienne Chénard avait proposé une hypothèse mettant en avant une minimisation des effets dipôle-dipôle, d'hyperconjugaison et d'encombrement stérique afin de justifier la stéréochimie obtenue. Se basant sur cette théorie, il peut être avancé que la diastérésélectivité observée résulterait d'une interaction des otbitales *p* du carbocation avec les différents groupements fonctionnels (*Figure 2.1*). Dans le cas des états de transition carbocationiques de la série azido, les conformations **B** et **C** résultent d'un hyperconjugaison entre le lien carbone-carbone et le carbocation pour stabiliser celui-ci et favorisent la formation de l'isomère *syn* (flèche bleue). La conformation **D** favorise elle aussi un produit *syn* en se basant sur la minimisation de la tension allylique 1,3 qui est préconisée dans les composés dialkyles selon la littérature [39]. À l'opposé, le conformère **A** suppose la

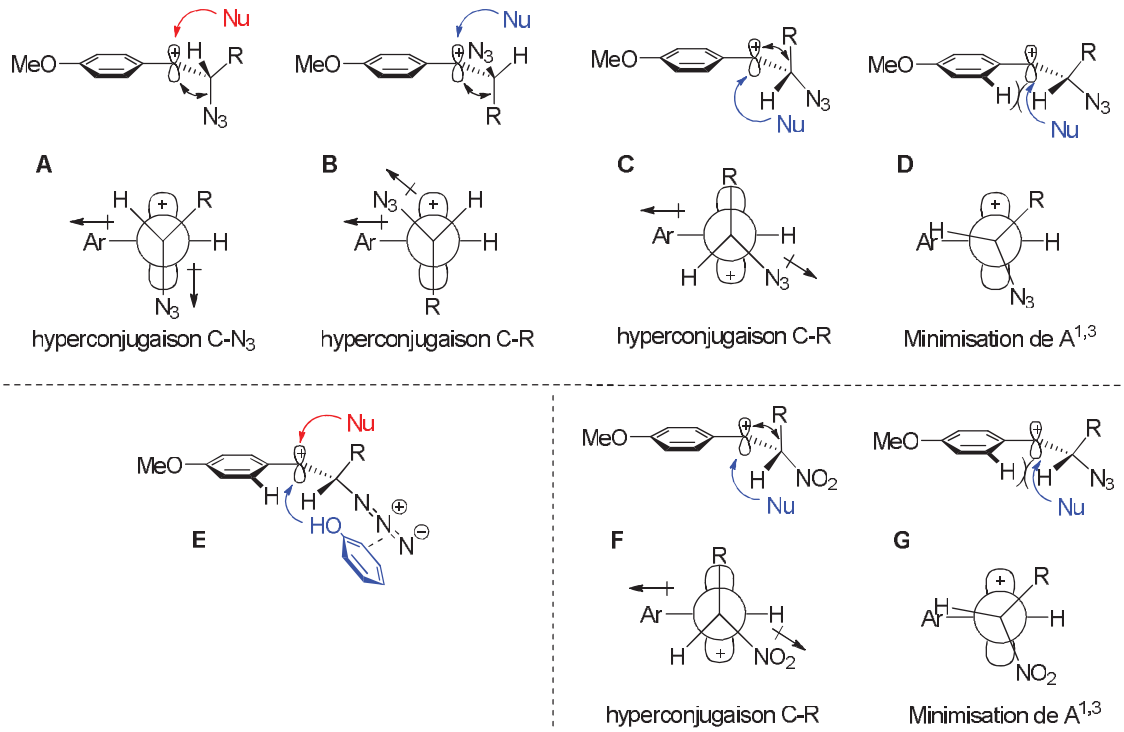


Figure 2.1 : Conformations principales expliquant les interactions et leur impact sur la diastéréosélectivité

formation d'un ion aziridinium et force la formation du conformère *trans* (flèche rouge) qui explique la faible sélectivité observée. Une autre explication possible est un empilement π - π entre le phénol et le groupement azido illustré par **E**. Ce type d'empilement a été proposé par Mascal et Armstrong à l'aide de calculs théoriques.[52] Cependant, la formation de deux isomères pourrait être expliquée par cette approche. Il pourrait être assumé que l'empilement π – π guide le nucléophile vers le centre carbocationique similairement aux substrats phényliques mentionnés au préalable (*Schéma 2.6*), mais le ratio observé ne reflète pas cela. Contrairement, le nucléophile présent en excès, pourrait bloquer davantage la face d'approche pour favoriser le produit *trans*. En ce qui concerne la série nitro, la minimisation de la tension allylique du conformère **G** ainsi que l'hyperconjugaison du conformère **F** démontrent que l'isomère *syn* est favorisé. L'effet du catalyseur d'or sur la sélectivité observé n'a pas été étudié mais les résultats similaires observé en présence de $AuCl_3$ et de *p*-TsOH•H_2O comme catalyseur sur des substrats azido dans la section 2.5 (*Schéma 2.22*) laissent croire que celui-ci n'a pas impact visible sur la sélectivité de la réaction.

2.4 Formation de 1,1-diaryles par substitution nucléophile sur des chaînes portant des groupements nitro et azido

Lors de notre étude sur les nucléophiles phénoliques, la capacité des phénols *para* substitués à former des éthers benzyliques n'a pas été observée pour des composés phénoliques portant des substituants sur des positions différentes. Cependant, la formation des 1,1'-diaryles a été observée avec des substrats nitro et azido (*Schéma 2.16)*. Le premier essai a été le 2,4-diméthylphénol qui a formé le diaryle **2.53** via une alkylation de Friedel-Crafts diastéréosélective contrairement à ce qui était prédit. Cette régiosélectivité a été expliquée par une activation du cycle aryle par les deux groupements méthyles qui ont ensuite dirigé l'attaque de l'intermédiaire carbocationique. Le 2,6-diméthylphénol, le 2-méthylphénol et le

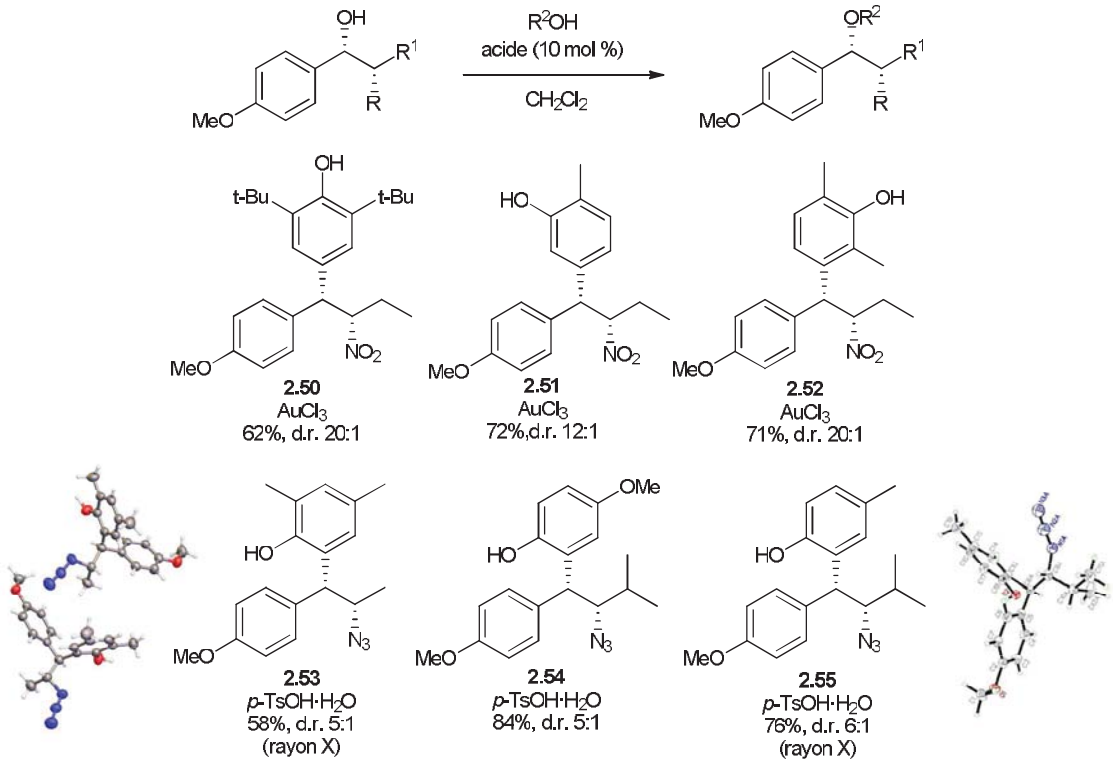


Schéma 2.16 : Étude de l'alkylation diastéréosélective de phénols catalysés par acide

2,6-di-*tert*-butylphénol ont été testés dans le but d'observer si des substituants en position ortho donnent des éthers benzyliques grâce à une activation de différentes positions tout en activant le groupement phénol. Les produits **2.50**, **2.51** et **2.52** ont plutôt confirmé la nécessité d'utiliser un nucléophile *para*-substitué pour obtenir des éthers benzyliques. La régiosélectivité des produits **2.54** et **2.55** n'a pas pu être expliquée en se basant sur notre compréhension de la réaction. La stéréochimie des produits 1,1-diaryle a été déterminé en ce basant sur les rayons X des composés **2.53** et **2.55**.

Nous nous sommes intéressés à la régiosélectivité des diaryles obtenus avec des phénols monosubstitués comme le produit **2.51**. Cela nous a menés à essayer les différents isomères de l'anisole et du crésol sur le substrat **2.33** (*Schéma 2.17*). Les résultats obtenus montrent une différence de sélectivité entre les isomères *para* qui forment des produits éthérés versus les

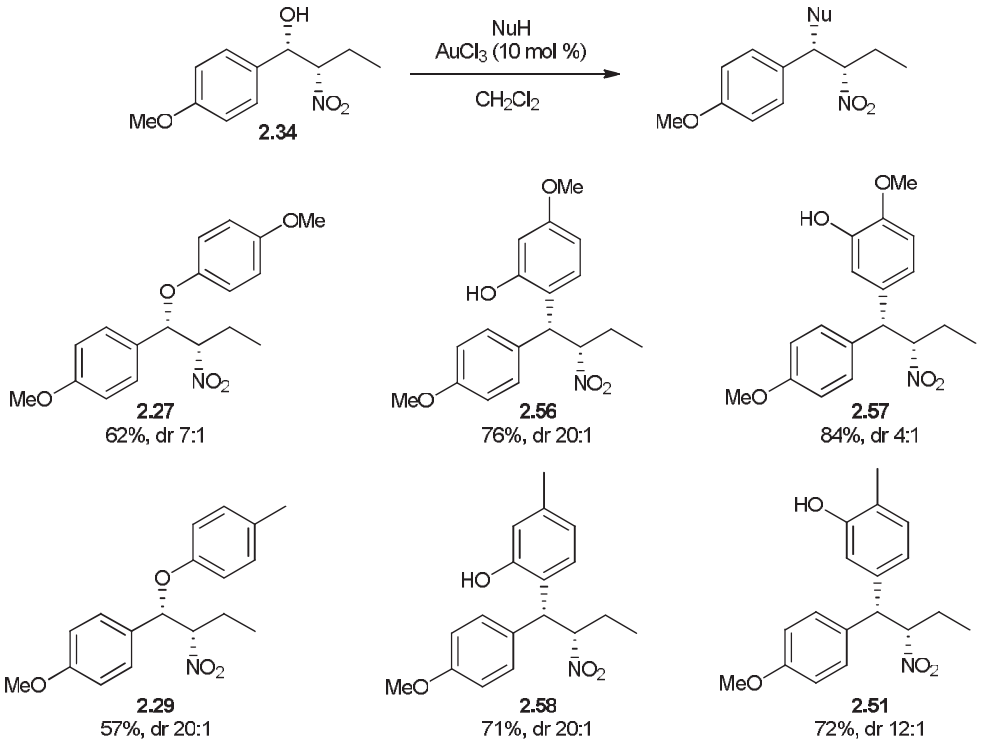


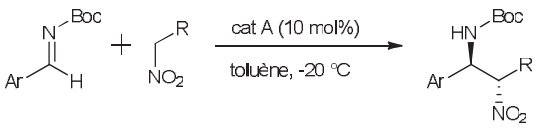
Schéma 2.17 : Étude de la régiosélectivité des isomères de l'anisole et du crésol

isomères *ortho* et *méta*. Dans le cas de ces derniers, la formation des diaryles a été guidée par les substituants méthoxy et méthyles. Les groupements phénol et méthoxy sont de forts groupements électrodonneurs tandis que le méthyle est considéré comme un donneur faible. Cela devrait donc diriger l'alkylation en position *para* de l'hydroxyle pour les produits **2.58** et **2.51**. En effet, des calculs de modélisation moléculaire ont démontré une densité légèrement plus haute aux positions activées par le groupement hydroxyle. Nous croyons donc qu'un effet d'encombrement stérique force l'éloignement des groupements méthoxylé et méthyle du site carbocationique pour former les produits observés.

2.5 Formation de sulfonamides benzylique vers des diamines vicinales

Durant l'étude de la formation d'éthers benzyliques, nous avons été intéressés par la formation de diamines vicinales. Ainsi, l'application de la substitution unimoléculaire diastéréosélective a été envisagée à cet effet. Préalablement, plusieurs groupes ont travaillé sur la formation de ces diamines.[53] La littérature contient de multiples exemples de réactions de aza-Henry énantiosélectives utilisant une grande variété de catalyseurs. Parmi ceux-ci, le groupe de Johnston a utilisé comme catalyseur un acide de Brønsted chiral en présence de différents nitroalkanes et d'un partenaire imine (*Schéma 2.18 A*).[54] Ils ont rapporté une augmentation de la vitesse de réaction et du stéréocontrôle de la réaction grâce à une augmentation de la basicité

A



entrée	Ar	R	dr (*anti*/*syn*)	*ee* (%)	rendement (%)
1	*p*ClC$_6$H$_4$	Me	18:1	91	87
2	*p*MeOC$_6$H$_4$	Me	24:1	88	84
3	*p*MeC$_6$H$_4$	Me	28:1	89	100
4	*p*ClC$_6$H$_4$	Et	20:1	91	86
5	*p*ClC$_6$H$_4$	*n*Pr	23:1	89	89

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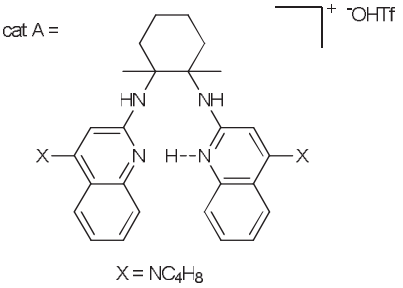
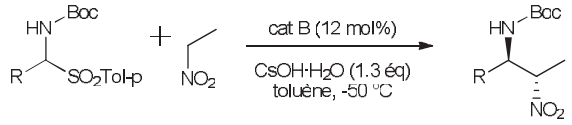


B



entrée	R	dr (*anti*/*syn*)	*ee* (%)	rendement (%)
1	Ph	93:7	94	88
2	*p*ClC$_6$H$_4$	82:18	98	70
3	*p*MeOC$_6$H$_4$	95:5	90	87
4	*p*MeC$_6$H$_4$	92:8	90	93
5	CH_3CH_2	94:6	>90	90

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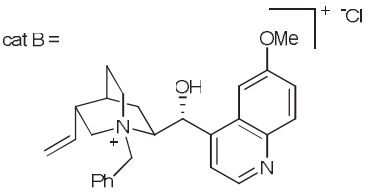
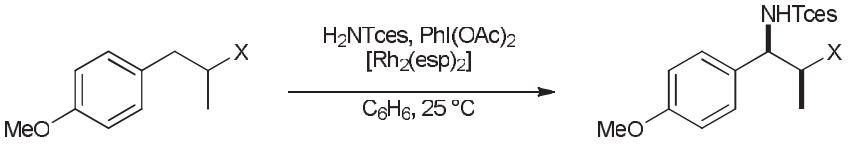


Schéma 2.18 : A. Sélection de réactions de aza-Henry par le groupe Johnston B. Sélection des travaux réalisés par le groupe Palomo

de Brønsted du catalyseur *bis*(amidine) chiral. Similairement, le groupe de Palomo a également travaillé sur des réactions de aza-Henry asymétriques (*Schéma 2.18 B*).[55] Ils ont concentré leurs efforts sur l'utilisation de sels d'ammoniums quaternaires en présence d'hydroxyde de césium hydraté. Ils ont pu déterminer que la réaction est sensible à la présence d'eau et que l'utilisation de solvants polaires réduit l'énantiosélectivité ainsi que le ratio diastéréomérique.

Similairement à la formation de diarylalkanes par une alkylation de Friedel-Crafts, le groupe de Bach a été intéressé par la formation d'amines benzyliques.[56] Cette fois-ci, ils ont étudié une C-H benzylamination diastéréosélective (*Schéma 2.19*). Une courte étude a démontré la possibilité de former des amines benzyliques avec une bonne diastéréosélectivité. La réaction supporte une variété de groupements fonctionnels comme les groupements nitro, acétate et cyano. La taille du substituant (X) n'a pas eu d'effet notable sur la direction de la sélectivité car ils ont noté que les groupements avec une valeur A supérieure au groupement méthyle tout comme ceux ayant une valeur inférieure ont formé le produit *syn* majoritairement. Le mécanisme n'a pas été rapporté, mais ils ont établi qu'un centre stéréogénique en position *bêta* ne peut être racémisé.



entrée	X	dr (*syn*/*anti*)	rendement (%)
1	COOMe	82:18	81
2	$PO(OEt)_2$	>95:5	65
3	SO_2Ph	>95:5	56
4	NO_2	91:9	63
5	CN	80:20	86
6	OAc	86:14	40

Tces = trichloroéthoxysulfonyl-

Schéma 2.19 : Étude de réactions de C-H benzylamination par le groupe de Bach

Une réaction de photo-Ritter a été rapportée par le groupe Song pour la formation d'amides benzyliques (*Schéma 2.20*).[57] Les produits ont été obtenus avec des rendements moyens en quelques heures. Ils ont performé la réaction à l'aide d'une lampe au xénon en se basant sur la bande d'absorption des réactifs qui est situé dans l'ultraviolet. L'utilisation de solvant anhydre a offert de meilleurs rendements, car la présence d'eau peut mener à la formation du produit d'hydrolyse. La baisse de rendement sur l'intermédiaire carbocationique secondaire est quant à lui expliquée par une réaction secondaire d'élimination.

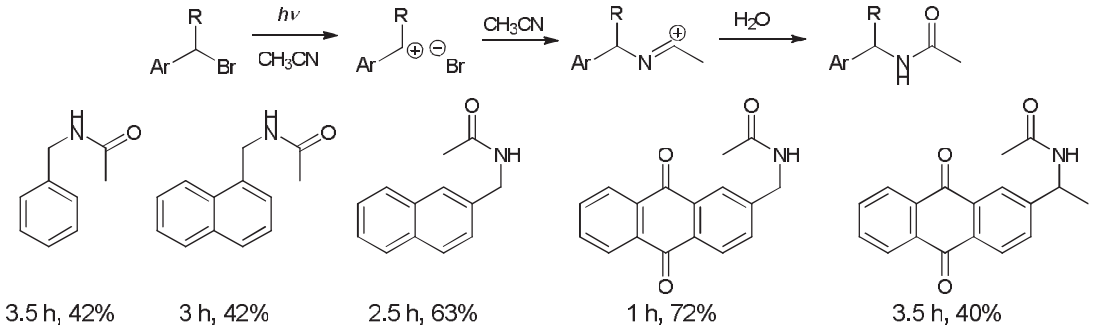


Schéma 2.20 : Formation d'amides benzyliques par réaction de photo-Ritter

Pour débuter notre étude sur la formation de diamines benzyliques, nous avons testé plusieurs substrats utilisés précédemment pour la synthèse d'éthers benzyliques (*Schéma 2.21*). Les acides $AuCl_3$ et *p*-TsOH•H_2O ont été choisis en fonction de leur efficacité précédente et aucune différence de sélectivité notable n'a pu être observée au cours de l'étude. Le produit **2.63** a été formé avec un bon ratio diastéréomérique en comparaison à la faible sélectivité typique des composés allyles présentés à la section 2.2. La série de composés azido (**2.59**, **2.60**, et **2.61**) a montré des ratios supérieurs comparés aux éthers benzyliques du *Schéma 2.15*. En particulier, le *tert*-butylazidosulfonamide **2.61** a été formé avec un dr de 20:1 probablement en raison de la grande différence d'encombrement entre les deux faces d'attaque possibles. La cause exacte de cette amélioration des résultats reste inconnue, cependant il semble probable que la taille du

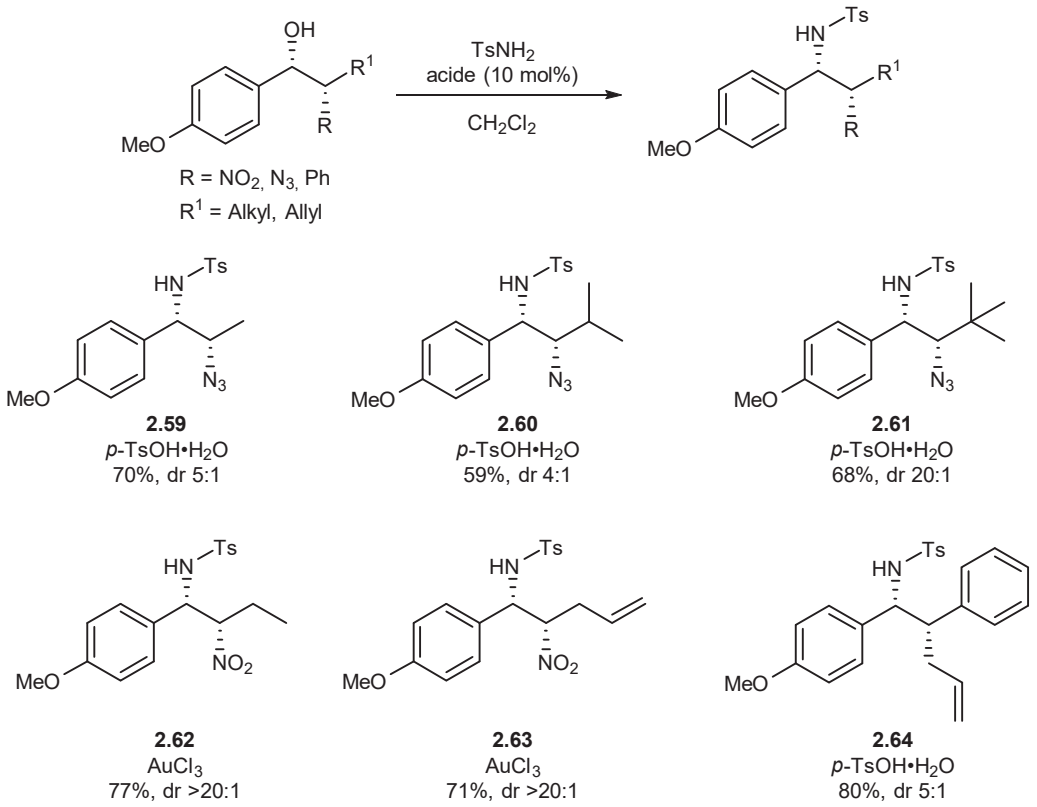


Schéma 2.21 : Étude de la formation de diamine vicinale par une réaction de substitution d'alcools benzyliques

nucléophile affecte la diastéréosélectivité de par son interraction avec les substituants. Les composés **2.62** et **2.63** ont eux aussi un excellent ratio diastéréomérique typique des composés nitroalkanes jusque là étudiés. Ces premiers résultats ont été encourageants pour la formation de pharmacophores diaminés. Ils montrent aussi la possibilité d'utiliser cette réaction comme une alternative aux multiples exemples de réaction d'aza-Henry rapportée dans la littérature[54, 55, 58] en focussant sur la formation d'un lien C-N.

La bonne diastéréosélectivité observée lors de nos premiers essais nous a convaincus de l'efficacité des sulfonamides dans la réaction. Nous avons ensuite décidé de tester quelques dérivés du toluènesulfonamide sur l'azidoalcool **2.44** en espérant pouvoir observer toute

variation possible du ratio diastéréomérique. Les produits d'alkylation **2.65** et **2.66** ont montré une sélectivité similaire au **2.59**, ce qui indique l'absence d'effet directeur des substituants sur la réaction. De plus, le tosylsulfonamide **2.59** a été obtenu avec le même rendement et ratio en présence des acides $AuCl_3$ et *p*-TsOH•H_2O (*Schéma 2.22*). Les alcools benzyliques utilisés ainsi que les produits éthérés sont généralement des huiles tandis que les produits d'alkylation avec les divers sulfonamides ont donné des solides. Nous avons pu ainsi effectuer plusieurs analyses par rayons X afin de confirmer les diastéosélectivités que nous avions prévu selon le mécanisme proposé par Bach[39]. Nous avons assumé la stéréochimie des composés 1,2-diamines en ce basant

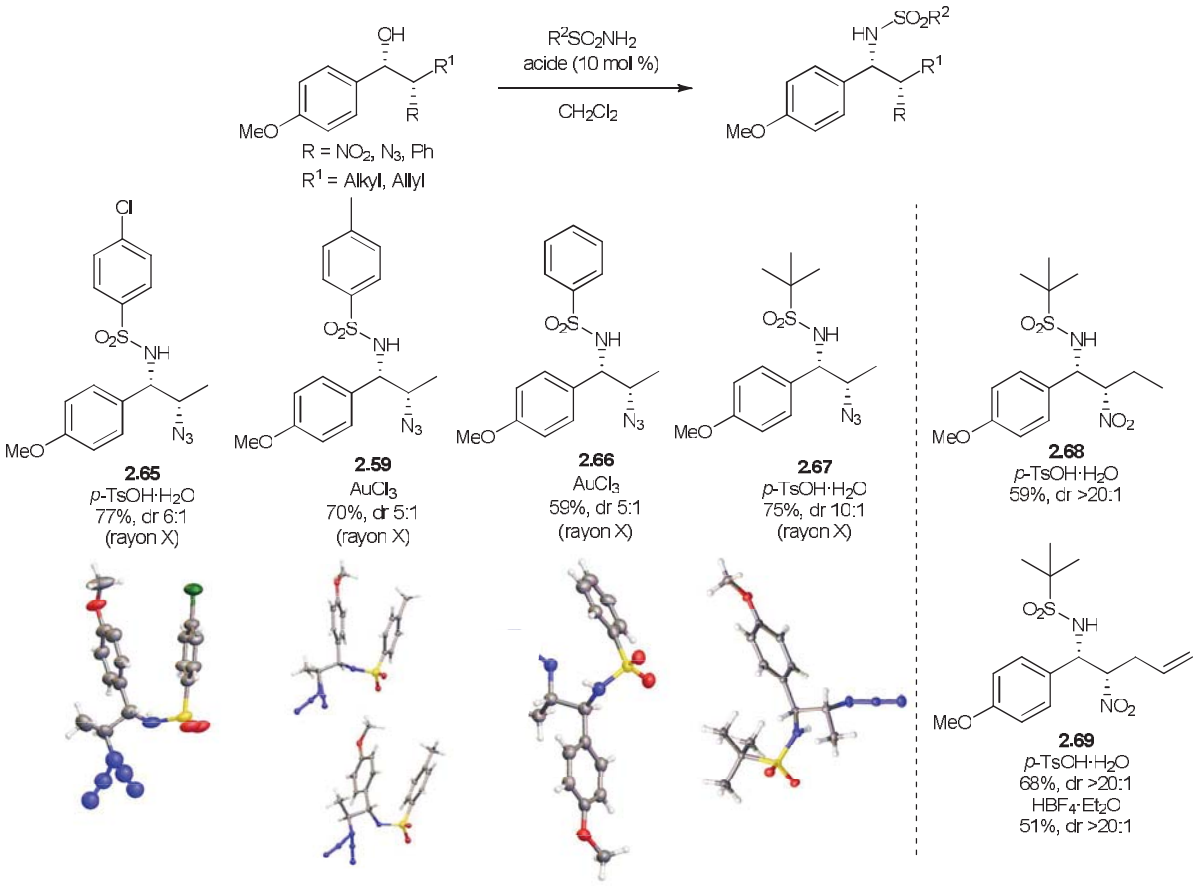


Schéma 2.22 : Alkylation d'une série de sulfonamides et confirmation de leur sélectivité

sur ses analyses rayon X. La similitude de la diastéréosélectivité des dérivés du tosylsulfonamide suggère de favoriser l'utilisation du meilleur nucléophile parmi ceux-ci pour améliorer le rendement sans affecter la sélectivité. Le groupement *tert*-butylsulfonamide a été considéré en raison des conditions de déprotection relativement douces utilisées pour obtenir l'amine libre.[59] Le produit **2.67** ayant été formé avec un bon ratio diastéréomérique supérieur aux autres sulfonamides avançant une fois encore l'hypothèse d'une amélioration de la diastéréosélectivité due à l'encombrement stérique. Nous avons ensuite testé le *tert*-butylsulfonamide avec des substrats nitro afin de confirmer leur tendance à former des produits diastéréomériquement plus enrichis. Les produits **2.68** et **2.69** ont tous deux étés obtenus avec des ratios supérieurs à 20:1 bien qu'avec des rendements plus modestes.

Lors de nos travaux sur les sulfonamides, nous avons décidé d'essayer le BF_3•DMF comme acide de Lewis doux. Connaissant la capacité de coordination du BF_3 lors de la synthèse de glycosides,[60] nous étions curieux de voir son effet sur la réaction de substitution unimoléculaire. Lors des cas précédents, le produit *syn*-**2.61** a été synthétisé avec une excellente sélectivité (*Schéma 2.23 A*). Par contre, l'utilisation de BF_3•DMF a donné un mélange de produits racémiques avec un rendement similaire. Intrigué par ce résultat, nous avons tenté la réaction en présence de *p*-TsOH•H_2O (10 mol%) et de DMF (1.0 eq) pour constater que nous formions majoritairement le produit anti-**2.61** avec un léger excès diastéréomérique de 3:1. Une comparaison du diastéréomère majeur avec *syn*-**2.61** par RMN a confirmé la nouvelle sélectivité observée. Une hypothèse a été avancée pour le mécanisme afin d'expliquer ce résultat (*Schéma 2.23 B*). Nous pensons que l'intermédiaire carbocationique **H** est premièrement formé par l'acide et habituellement la réaction aurait dû procéder par une attaque du centre cationique, démontré par **I**, et ensuite formé le produit *syn*. Nous pensons que ce mécanisme est encore

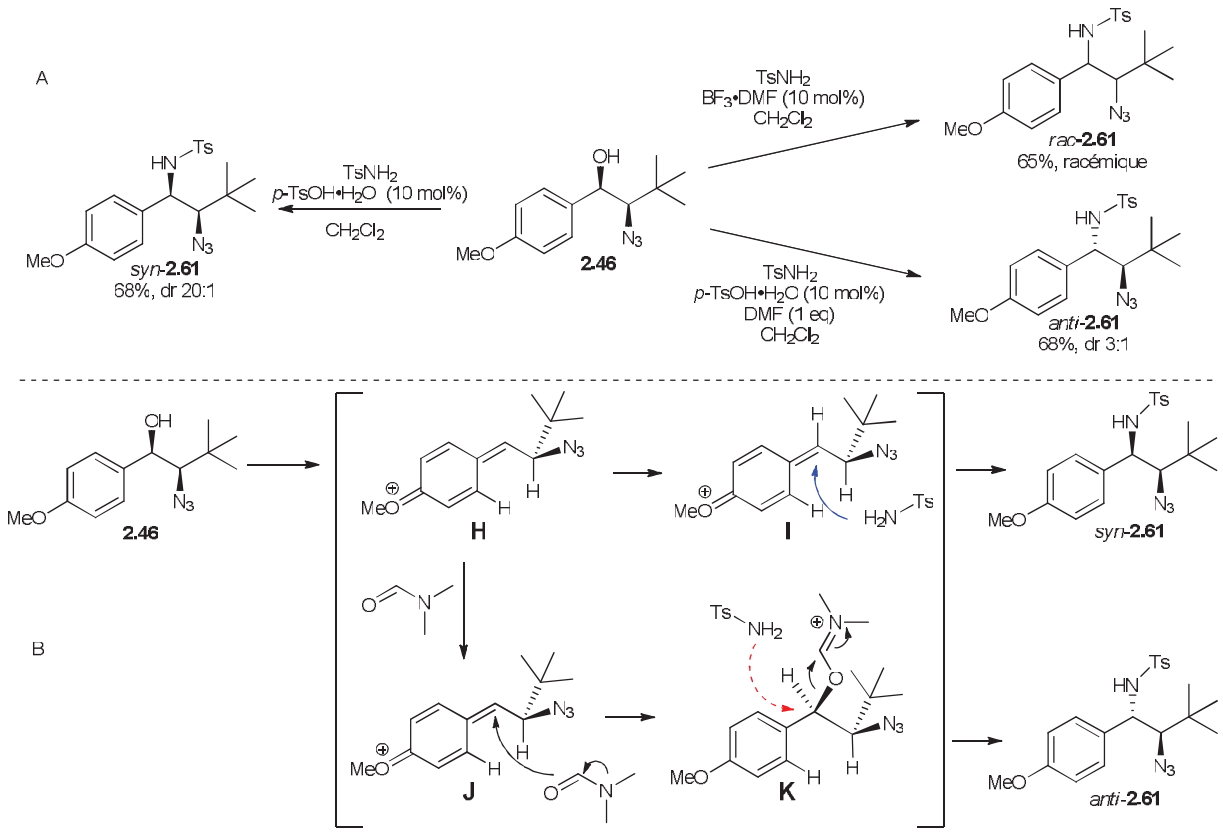


Schéma 2.23 : A. Étude de l'effet du DMF sur la sélectivité de l'alkylation B. Mécanisme proposé pour expliquer les différentes sélectivités

possible durant la transformation, mais il est maintenant en compétition avec une attaque du diméthylformamide (DMF) comme dans l'état de transition **J**. Celui-ci favoriserait ensuite une attaque du sulfonamide par la face moins encombrée contenant l'hydrogène pour relâcher le diméthylformamide et former le composé *anti* selon **K**. La faible sélectivité de la réaction en présence de DMF montre que la méthode n'est pas optimale pour former le produit *anti* de façon majoritaire.

Nous avons par la suite travaillé sur la déprotection du groupement sulfonamide et la réduction orthogonale de la fonctionnalité nitro. Notre premier essai a été de déprotéger le groupement *tert*-butylsulfonamide en présence d'acide triflique et d'anisole, qui a pour rôle de

capter les carbocations, comme décrit dans la littérature.[59] Nous avons cependant obtenu le produit **2.71** qui suggère une substitution du sulfonamide devenu protoné, qui est facilement déplaçable, par l'anisole présent en excès. En conséquence, la réaction a été retentée sans anisole pour obtenir **2.70** qui résulte d'une élimination du groupement sulfonamide (*Schéma 2.24*). Nous avons supposé qu'une fois la sulfonamide protonnée, l'élimination causée par l'acidité du

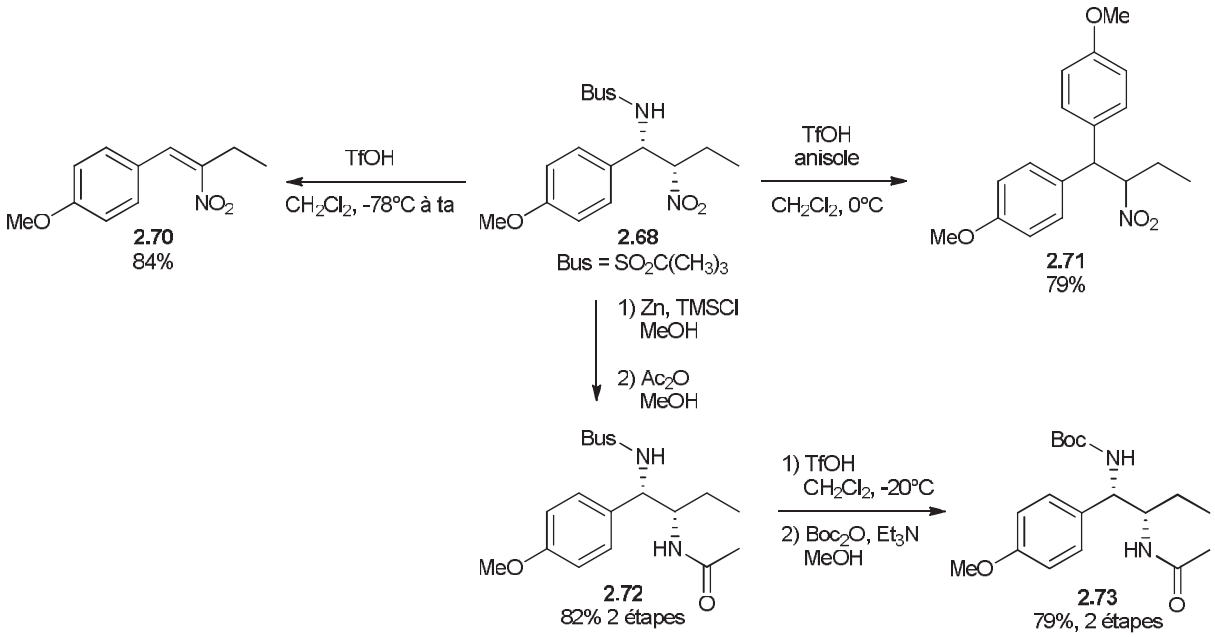


Schéma 2.24 : Déprotection des groupements sulfonamide et nitro du composé **2.68**

proton géminal au groupement nitro est favorisée face à la perte du cation *tert*-butylique et la libération de SO_2 sous forme gazeuse. Nous avons contourné ce problème à l'aide de zinc, de chlorure de triméthylsilane et de méthanol, permettant la réduction chimiosélective du groupement nitro. La déprotection du *tert*-butylsulfonamide a été possible après réduction et acétylation du groupement nitro (**2.72**) à l'aide des conditions de déprotection usuelles pour obtenir le produit **2.73**.

La dérivation des composés diaminés nous a intéressé pour la formation de composés bicycliques semblables à **2.77** (*Schéma 2.25*). Nous avons donc réduit le groupement nitro comme décrit précédemment pour former l'amine **2.74** et ensuite synthétiser l'isocyanate **2.75** en présence de triphosgène. Le produit brut de celui-ci a pu être directement soumis à des conditions réactionnelles de type Friedel-Crafts utilisant du chlorure d'aluminium. Contrairement à nos attentes, l'urée cyclique **2.76** a été formée avec un bon rendement et une conservation du ratio diastéréomérique. En nous basant sur des travaux antérieurs réalisés au sein du groupe, nous avions prévu synthétiser la lactame **2.77.**[61] La formation de ces urées cyclique reste à explorer mais ce résultat ouvre la porte vers la formation d'hétérocycles diastéréoenrichies. Ainsi, il semble que la réactivité du *tert*-butylsulfonamide soit en cause pour expliquer le composé obtenu. Nous pensons que la présence d'un second groupement méthoxy en position *ortho* du premier ou un sulfonamide plus robuste seraient capables de favoriser la formation du bicycle.

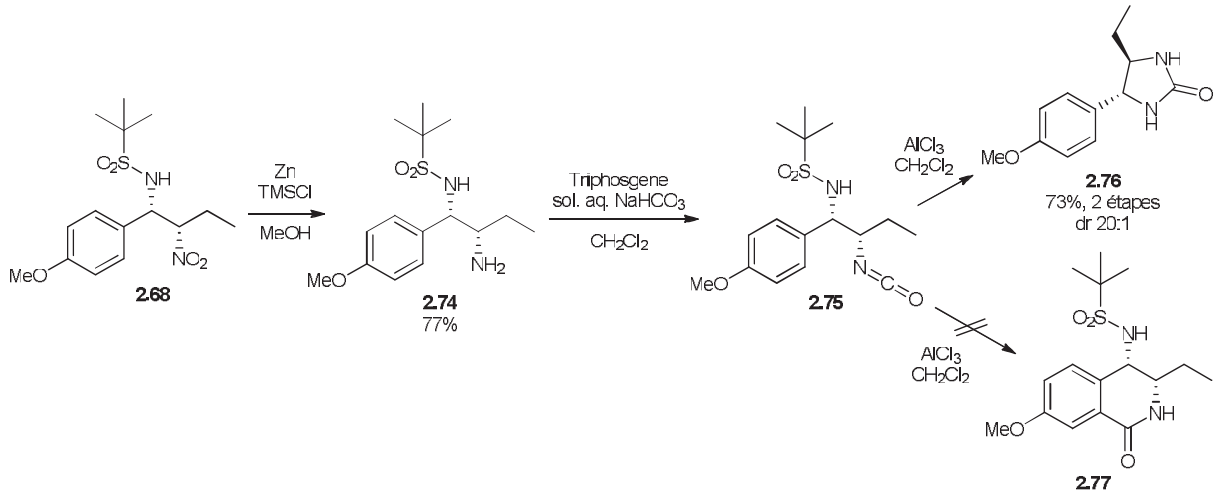


Schéma 2.25 : Formation diastéréosélective d'une urée cyclique en présence d'$AlCl_3$

2.6 Conclusion

Cette étude de la réaction de substitution nucléophile diastéréosélective a permis de former une large gamme de composés. La formation de triaryles et l'utilisation de structures rigides ont été d'excellentes solutions pour augmenter la sélectivité observée sur les composés allyliques. Les nucléophiles phénoliques ont démontré une régiosélectivité variable permettant la synthèse d'éthers benzyliques ainsi que de diaryles. La plus grande susceptibilité des substrats contenant un groupement nitro à favoriser une attaque diastéréosélective lorsque comparé à ceux contenant un groupement azido a pu être constaté à plusieurs reprises, faisant de ces substrats des intermédiaires de choix pour contrôler la sélectivité de la réaction. Les sulfonamides ont démontré une bonne sélectivité sur une grande variété de substrats, surpassant souvent les phénols. Malgré les difficultés observées afin d'agir sélectivement sur les groupements nitro ou sulfonamide, des conditions menant à leur réduction et déprotection respectives ont été établies. La formation d'urée cyclique diastéréoenrichiee constitue un résultat intéressant et pourrait être étudiée de façon plus approfondie.

Partie expérimentale

Instrumentation

L'acquisition de spectres de résonance magnétique nucléaire de proton (RMN ^{1}H) et de carbone (RMN ^{13}C) ont été effectué en utilisant des apprareils de type Bruker AV-300, Bruker AV-400 et Bruker AV-500. 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 ont été exprimées en Hertz (Hz) et la multiplicité a été rapportée selon le code suivant : singulet (s), doublet (d), triplet (t), quadruplet (q), quintuplet (p), 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 analyses en séparation SFC et en spectrométrie de masse de haute résolution ont été expertisées par l'équipe du Centre régionale de spectrométrie de masse de l'Université de Montréal.

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

Les traces HPLC ont été faites sur appareil Agilent 1100 Series HPLC avec les colonnes chiralpak AD-H et chiralcel OD. Toutes les colonnes avaient les dimensions suivantes: 4.6 mm de diamètre x 250 mm de long, et ont été acheté chez Daicel Chemical Industries Ltd. Les chromatogrammes HPLC ont été obtenus par détection UV, avec les longueurs d'onde à 254 et/ou 210 nm.

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. Lorsque mentionné, les solvants anhydres (tétrahydrofurane, éther diéthylique, dichlorométhane et le toluène) ont été séchés à partir d'un système SDS (*Solvent Delivery System*).

Les chromatographies sur couche mince (CCM) ont été réalisée à l'aide de support de verre couvert d'une couche uniforme de silice (0.25 mm, 60Å, indicateur de fluorescence F254) pour le suivit des réactions.

Notes

Lorsque nécessaire, les réactions en conditions anhydres ont été réalisée à l'aide de verreries séchée à la flamme et ensuite le montage est maintenu sous argon. Le sulfate de sodium a été utilisé comme agent de séchage par défaut. Les réactions d'alkylation diastéréosélective catalysée par acide réalisée au chapitre 2 sont réalisée sans précausions pour préserver le milieu anhydre. Tel que permis dans 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.

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Annexes

Annexe 1 – Partie relative à la formation de liens benzylique par substitution nucléophilique

Representative protocol for the synthesis of allyl enol carbonates

The formation of allyl enol carbonate **2.13a** is used as a representative protocol. To a solution of the aryl ketone (200 mg, 0.97 mmol, 1.0 equiv.) in tetrahydrofuran (5 ml, 0.2 M), a solution of 1 M KHMDS in toluene (1.16 ml, 1.2 equiv.) was added at −78 °C. The solution was stirred for 60 minutes at −78 °C, and then allyl chloroformate (0.12 ml, 1.16 mmol, 1.2 equiv.) was added. The solution was allowed to slowly reach room temperature, then was partitioned between diethyl ether (10 ml) and an aqueous solution saturated with ammonium chloride (10 ml). The layers were separated and the organic phase was washed twice with an aqueous solution saturated with ammonium chloride, dried over sodium sulfate, filtered and concentrated under reduced pressure.

Preparation of the palladium-ligand solution

The preparation of the catalyst solution for the formation of ketone **2.13b** is used as a representative protocol. A flask was charged with tris(dibenzylideneacetone) dipalladium(0) ($Pd_2(dba)_3$) (21 mg, 0.02 mmol, 0.025 equiv.) and (*S*)- or (*R*)-t-BuPHOX (20 mg, 0.05 mmol, 0.063 equiv.) (ratio 1 $Pd_2(dba)_3$: 2.5 Ligand). The flask containing the solids was purged with an argon stream for 15 minutes, and the solids were then dissolved in tetrahydrofuran (6 ml, $[Pd_2(dba)_3]$ = 0.0034 M) using sonication, for 15 minutes.

Representative protocol for palladium-catalyzed asymmetric allylation

The formation of ketone **2.13b** is used as a representative protocol. An oven dried flask cooled under argon was charged with the starting allyl aryl enol carbonate **2.13a** (234 mg, 0.81 mmol, 1.0 equiv.) and BHT (178 mg, 0.81 mmol, 1.0 equiv.) then the solids were dissolved in dry tetrahydrofuran (0.8 ml, 1 M). The solution was cooled to 0 ºC. A freshly prepared solution of the palladium-ligand solution (which corresponds to $Pd_2(dba)_3$ (2.5

mol%) and (*S*)-t-BuPHOX (6.3 mol%)) was added ([allyl enol carbonate] in tetrahydrofuran = 0.01 M). The progress of the reaction was monitored by TLC. The solution was concentrated at room temperature under reduced pressure.

Representative protocol for the synthesis of benzylic alcohols

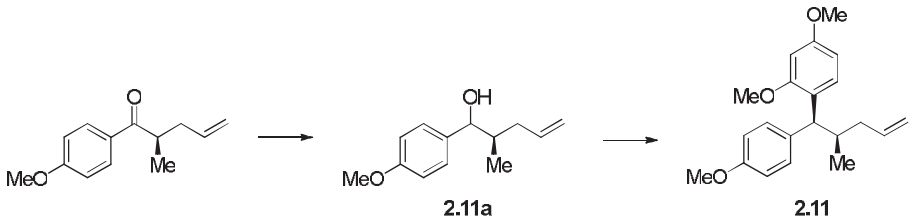
The formation of alcohol **2.13c** is used as a representative protocol. A solution of DIBAL-H in toluene (0.89 ml, 0.89 mmol, 1.5 equiv) was added over 3 min to a solution of the starting ketone **2.13b** (146 mg, 0.59 mmol, 1.0 equiv) in dry THF (2.4 ml, 0.25 M), at −78 °C under argon, stirred at −78 °C for 3 h and, allowed to slowly reach room temperature. The conversion was monitored by TLC. Silica gel was added after full conversion.

Representative protocol for the acid catalyzed arylation of allylalcohols

The formation of 1,1'-diaryl **2.13** is used as a representative protocol. *p*-TsOH•H_2O (acid) (2.7 mg, 0.0089 mmol, 10 mol%) was added to a solution of starting benzylic alcohol **2.13c** (22 mg, 0.089 mmol, 1.0 equiv) and 1,3-dimethoxybenzene (nucleophile) (0.06 ml, 0.445 mmol, 5.0 equiv) in dichloromethane (0.9 ml, ~0.1M). The solution was stirred at room temperature and progress was monitored by TLC.

Arylation of allylalcohols and precursors

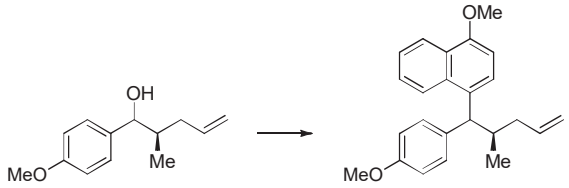
Arylation product **2.11**



After following the representative protocol for benzylic alcohol preparation using the starting ketone (110 mg), the reaction mixture was filtered through a silica pad (silica gel, 2.5 cm × 4.0 cm; 4V diethyl ether, then 2V ethyl acetate) to yield alcohol **2.11a** (110 mg, >95%) as colorless oil; R_f = 0.37 (1:9, ethyl acetate:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$, mixture of diastereoisomeres) δ 7.25 – 7.22 (m, 2H), 6.89 – 6.86 (m, 2H), 5.92 – 5.72 (m, 1H), 5.10 – 4.96 (m, 2H), 4.50 (dd, *J* = 5.7, 3.4 Hz, 0.5H), 4.38 (dd, *J* = 7.4, 3.0 Hz, 0.5H), 3.81 (s, 3H), 2.45 – 2.39 (m, 0.5H), 2.17 – 2.11 (m, 0.5H), 2.02 – 1.94 (m, 0.5H), 1.94 – 1.77 (m, 2.5H), 0.94 (d, *J* = 6.6 Hz, 1.5H), 0.72 (d, *J* = 6.7 Hz, 1.5H); ^{13}C NMR (126 MHz, $CDCl_3$, mixture of diastereoisomeres) δ 159.2, 159.0, 137.4, 137.3, 135.8, 135.7, 130.7, 128.0, 127.7, 116.3, 116.2, 113.8, 113.7, 78.4, 77.5, 55.4, 40.3, 40.1, 37.8, 37.4, 15.8, 14.5; IR (neat) 3414, 3073, 2958, 2927, 2836, 1610, 1511, 1460, 1244, 1173, 1034 cm^{-1}; HRMS (ESI) calcd for $C_{13}H_{18}O_2$ $[M+H]^+$ 207.1385, found $[M+H]^+$ 207.1522 and calcd for $C_{13}H_{18}O_2$ $[M+Na]^+$ 229.1205, found $[M+Na]^+$ 229.1175.

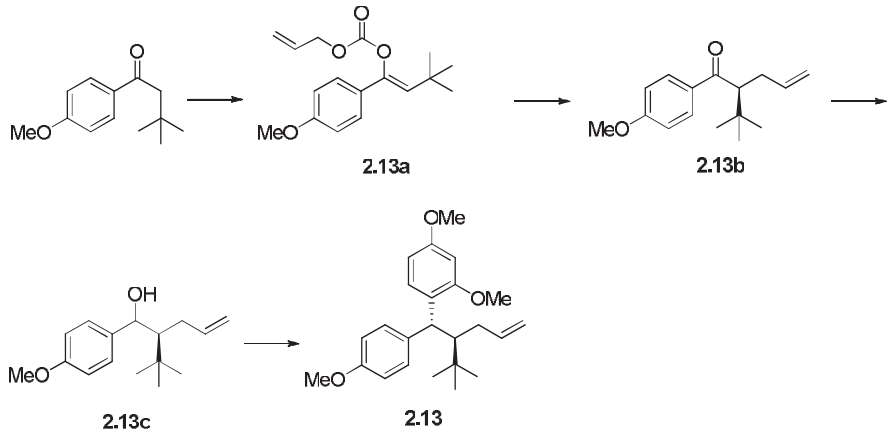
After following the representative protocol for the acid catalyzed arylation of benzylic alcohols using starting alcohol **2.11a** (30 mg, 0.14 mmol) and *p*-TsOH•H_2O as the catalyst. The reaction mixture was stirred 1h, then th residue was purified by flash chromatography (silica gel, 1.5 cm × 20.0 cm; 1:19, diethyl ether:hexanes) to yield **2.11** (37 mg, 79%, dr 1.6:1) as a clear oil; R_f = 0.43 (1:9, ethyl acetate:hexanes) ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.25 – 7.18 (m, 2H), 6.80 – 6.76 (m, 2H), 6.46 (m, 1H), 6.40 (m, 1H), 5.83 – 5.75 (m, 1H), 4.99 – 4.89 (m, 1H), 3.98 (d, *J* = 11.3 Hz, 0.6H), 3.95 (d, *J* = 11.4 Hz, 0.4H), 3.78 (s, 1.8H), 3.77 (s, 1.2H), 3.77 (s, 1.2H), 3.76 (s, 1.8H), 3.75 (s, 1.8H), 3.75 (s, 1.2H), 2.38 (m, 1H), 2.17 (m, 1H), 1.76 (m, 1H), 0.84 (d, *J* = 6.5 Hz, 1.8H), 0.82 (d, *J* = 6.5 Hz, 1.2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.9, 158.8, 158.1, 157.64, 157.61, 137.6, 137.3, 137.2, 129.33, 129.30, 128.2, 128.0, 126.1, 126.0, 115.9, 115.8, 113.7, 113.63, 104.58, 104.52, 98.9, 98.8, 55.6, 55.4, 55.3, 48.51, 48.50, 39.7, 39.4, 36.2, 18.4, 17.9; IR (neat) 3071, 2997, 2954, 2928, 2834, 1608, 1585, 1505, 1462, 1291, 1246, 1207, 1177, 1036 cm^{-1}; HRMS (ESI) calcd for $C_{21}H_{26}O_3$ $[M+H]^+$ 327.160, found $[M+H]^+$ 327.1481 and calcd for $C21H_{26}O_3$ $[M+Na]^+$ 349.1420, found $[M+Na]^+$ 349.1327.

Diaryl **2.12**



After following the representative protocol for the acid catalyzed arylation of benzylic alcohols using starting alcohol **2.11a** (30 mg, 0.14 mmol) and *p*-TsOH•H_2O as the catalyst, the reaction mixture was stirred 1h. The residue was purified by flash chromatography (silica gel, 1.5 cm × 20.0 cm; 1:19, diethyl ether:hexanes) to yield **2.12** (43 mg, 85%, dr 1.4:1) as a clear oil; R_f = 0.51 (1:9, ethyl acetate:hexanes); ^{1}H NMR (700 MHz, $CDCl_3$) δ 8.29 (d, *J* = 8.4 Hz, 1H), 8.21 (d, *J* = 8.5 Hz, 0.6H), 8.17 (d, *J* = 8.6 Hz, 0.4H), 7.55 (d, *J* = 8.0 Hz, 0.4H), 7.52 – 7.47 (m, 1.6H), 7.45 – 7.42 (m, 1H), 7.30 – 7.27 (m, 1H), 7.27 – 7.24 (m, 1H), 6.86 (d, *J* = 8.0 Hz, 1H), 6.84 (d, *J* = 8.0 Hz, 1H), 6.79 – 6.76 (m, 2H), 5.89 – 5.76 (m, 1H), 5.04 (d, *J* = 10.2 Hz, 0.6H), 5.00 (d, *J* = 17.2 Hz, 0.6H), 4.96 (d, *J* = 10.0 Hz, 0.4H), 4.88 (d, *J* = 18.5 Hz, 0.4H), 4.33 (d, *J* = 10.7 Hz, 1H), 4.30 (d, *J* = 10.5 Hz, 1H), 4.00 (s, 1H), 3.99 (s, 2H), 3.73 (s, 2H), 3.72 (s, 1H), 2.57 – 2.50 (m, 1H), 2.31 – 2.23 (m, 1H), 1.87 (dt, *J* = 13.9, 8.6 Hz, 1H), 0.93 – 0.90 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.79, 157.76, 154.0, 153.9, 137.4, 137.3, 136.79, 136.76, 133.23, 133.20, 132.7, 132.4, 129.31, 129.29, 126.5, 126.4, 126.2, 126.1, 124.73, 124.70, 124.0, 123.7, 123.41, 123.40, 122.72, 122.70, 116.2, 116.1, 113.8, 113.7, 103.65, 103.60, 55.6, 55.3, 50.8, 50.7, 39.8, 39.7, 37.4, 37.3, 18.6, 18.4; IR (neat) 3072, 2954, 2927, 2835, 1608, 1585, 1509, 1461, 1388, 1248, 1177, 1094, 1034 cm^{-1}; HRMS (ESI) calcd for $C_{24}H_{26}O_2$ $[M+H]^+$ 347.2011, found $[M+H]^+$ 347.2078 and calcd for $C_{24}H_{26}O_2$ $[M+Na]^+$ 369.1831, found $[M+Na]^+$ 369.2015.

Diaryl **2.13** and precursors



After following the representative protocol for the synthesis of allyl enol carbonates using the aryl ketone (200 mg, 0.97 mmol), the reaction mixture was stirred for 16h. The residue was purified by flash chromatography (silica gel, 1.5 cm × 20.0 cm; 1:19, diethyl ether:hexanes) to yield allyl enol carbonate **2.13a** (237 mg, 84%) as a clear oil; R_f = 0.32 (1:9, ethyl acetate:hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.31 (m, 2H), 6.87 – 6.82 (m, 2H), 5.92 (ddd, *J* = 16.3, 11.0, 5.8 Hz, 1H), 5.49 (s, 1H), 5.36 (dd, *J* = 17.2, 1.3 Hz, 1H), 5.27 (dd, *J* = 10.4, 1.0 Hz, 1H), 4.65 (d, *J* = 5.7 Hz, 2H), 3.80 (s, 3H), 1.19 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.7, 153.1, 145.2, 131.5, 129.1, 126.2, 126.1, 119.3, 114.1, 69.0, 55.4, 32.6, 30.4; IR (neat) 3054, 2954, 2932, 2848, 1672, 1655, 1611, 1581, 1514, 1463, 1447, 1422, 1367, 1340, 1314, 1280, 1236, 1177, 1116, 1078, 1032 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{22}O_4$ $[M+H]^+$ 291.1596, found $[M+H]^+$ 291.1462 and calcd for $C_{17}H_{22}O_4$ $[M+Na]^+$ 313.1416, found $[M+Na]^+$ 313.1524.

After following the representative protocol for the synthesis of palladium-catalyzed asymmetric allylation using allyl enol carbonate **2.13a** (234 mg, 0.81 mmol), the solution was stirred 16h. The residue was purified by flash chromatography (silica gel-silver nitrate[1], 1.5 cm × 20.0 cm; 1:19, diethyl ether:hexanes) to yield ketone **2.13b** (146 mg, 73%) as an oil; R_f = 0.45 (1:9, ethyl acetate:hexanes); $[\alpha]_D$ +35.4° (*c* 0.8, $CDCl_3$, optical rotation was measured from a sample with 84% *ee*); (the enantiomeric excess was determined by analytical chiral HPLC method); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 – 7.90

(m, 2H), 6.94 – 6.89 (m, 2H), 5.70 – 5.57 (m, 1H), 4.99 (dd, J = 17.0, 1.6 Hz, 1H), 4.86 – 4.81 (m, 1H), 3.86 (s, 3H), 3.38 (dd, J = 11.5, 2.9 Hz, 1H), 2.67 – 2.57 (m, 1H), 2.34 – 2.27 (m, 1H), 0.96 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.1, 163.3, 137.0, 133.3, 130.6, 116.3, 113.8, 55.6, 54.2, 34.3, 33.4, 28.5; IR (neat) 3012, 2953, 2943, 2874, 2839, 1664, 1643, 1625, 1577, 1511, 1467, 1431, 1389, 1342, 1257, 1244, 1199, 1139, 1134, 1035 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{22}O_2$ $[M+H]^+$ 247.1698, found $[M+H]^+$ 247.1644 and calcd for $C_{16}H_{22}O_2$ $[M+Na]^+$ 269.1518, found $[M+Na]^+$ 269.1375.

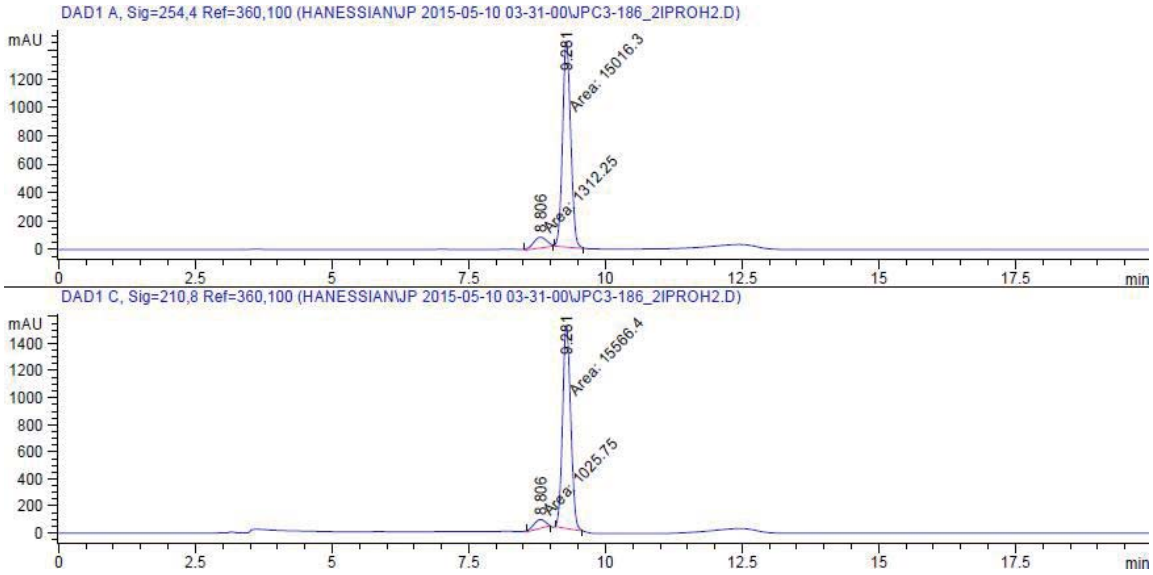
After following the representative protocol for benzylic alcohols preparation using ketone **2.13b** (146 mg, 0.59 mmol), the reaction mixture was filtered on silica pad (silica gel, 2.5 cm × 4.0 cm; 5V diethyl ether, then 2V ethyl acetate) to yield alcohol **2.13c** (146 mg, >95%) as a yellow oil; R_f = 0.45 (1:9, ethyl acetate:hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.26 (m, 2H), 6.88 – 6.84 (m, 2H), 5.68 (ddt, J = 17.1, 10.3, 7.0 Hz, 1H), 4.86 – 4.76 (m, 3H), 3.80 (s, 3H), 2.07 – 2.01 (m, 2H), 1.77 – 1.71 (m, 1H), 1.00 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.0, 139.8, 137.1, 128.5, 114.7, 113.7, 76.2, 55.4, 54.3, 34.4, 32.8, 29.5; IR (neat) 3449, 3062, 3019, 2995, 2924, 2832, 1611, 1582, 1513, 1440, 1371, 1302, 1247, 1207, 1172, 1092, 1033 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{24}O_2$ $[M+H]^+$ 249.1854, found $[M+H]^+$ 249.1926 and calcd for $C_{16}H_{24}O_2$ $[M+Na]^+$ 271.1674, found $[M+Na]^+$ 271.1385.

After following the representative protocol for the acid catalyzed arylation of alkylalcohols using starting alcohol **2.13c** (22 mg, 0.089 mmol) and p-TsOH•H_2O as the catalyst. The reaction mixture was stirred for 16h. The residue was purified by flash chromatography (silica gel, 1.5 cm × 20.0 cm; 1:19, diethyl ether:hexanes) to yield diaryl **2.13** (25 mg, 76%, dr 1.5:1) as a clear oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 – 7.21 (m, 1H), 7.19 – 7.15 (m, 1H), 7.11 – 7.08 (m, 0.4H), 6.78 – 6.72 (m, 2H), 6.43 (dd, J = 8.5, 2.5 Hz, 0.6H), 6.39 – 6.36 (m, 1.4H), 5.64 – 5.52 (m, 1H), 4.74 – 4.70 (m, 1H), 4.69 – 4.63 (m, 1H), 4.54 (d, J = 8.8 Hz, 0.4H), 4.50 (d, J = 7.8 Hz, 0.6H), 3.79 (s, 1.2H), 3.78 (s, 1.8H), 3.76 (s, 1.8H), 3.75 (s, 3H), 3.75 (s, 1.2H), 2.24 – 2.13 (m, 2H), 2.12 – 2.06 (m, 0.6H), 2.03 – 1.96 (m, 0.4H), 0.84 (s, 5.4H), 0.83 (s, 3.5H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.79, 157.76, 157.6, 157.5,

157.2, 141.2, 141.1, 139.3, 137.1, 130.9, 130.6, 129.9, 129.7, 128.2, 126.5, 113.7, 113.6, 113.5, 113.3, 104.1, 104.0, 98.8, 98.5, 55.6, 55.43, 55.36, 55.26, 51.9, 51.6, 44.1, 35.87, 35.85, 34.2, 34.0, 29.6, 29.2; HRMS (ESI) calcd for $C_{24}H_{32}O_3$ $[M+H]^+$ 369.2429, found $[M+H]^+$ 369.2192 and calcd for $C_{24}H_{32}O_3$ $[M+Na]^+$ 391.4989, found $[M+Na]^+$ 391.4989.

Chiral HPLC separation of ketone **2.13b** for *ee*:

Method info: 2% IPA/Hex, chiralpak AD-H, 1ml/min, 20min



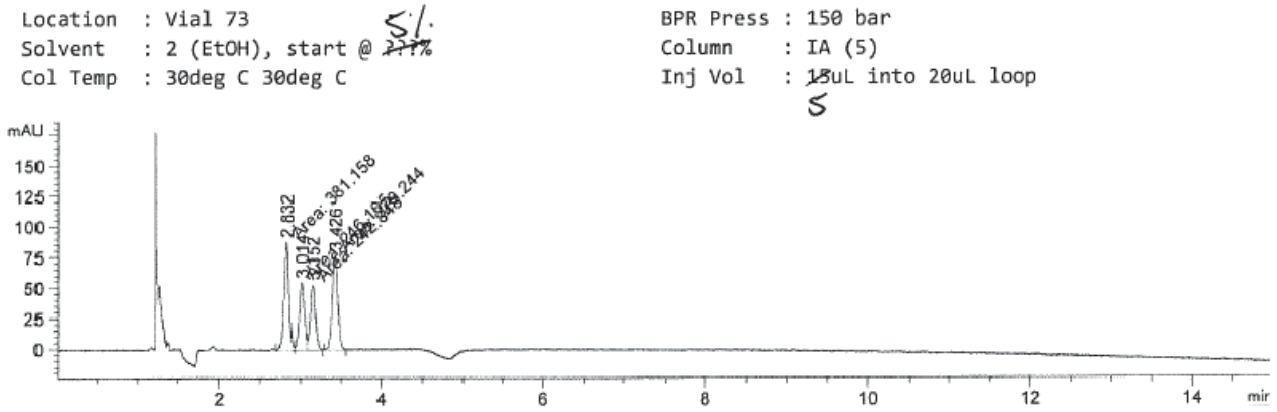
Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.806	MM	0.2865	1312.24634	76.33271	8.0365
2	9.281	MM	0.1729	1.50163e4	1447.63342	91.9635
Totals :				1.63285e4	1523.96613	

Signal 2: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.806	MM	0.2527	1025.74634	67.66221	6.1821
2	9.281	MM	0.1726	1.55664e4	1503.22949	93.8179
Totals :				1.65921e4	1570.89170	

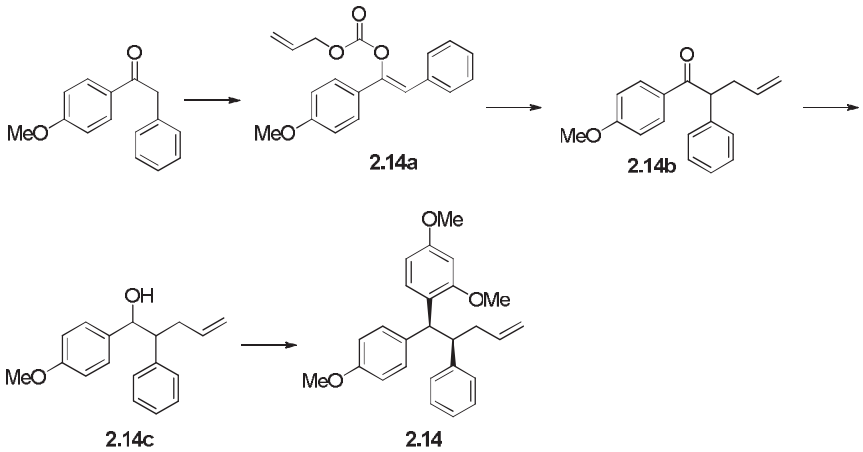
SFC separation of racemic diaryl **2.13** after flash column: d.r. 1.5:1



Signal 1: DAD1 A, Sig=210,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.832	MF	0.0718	381.15802	88.49593	30.5084
2	3.014	MF	0.0741	246.10544	55.33797	19.6986
3	3.152	FM	0.0762	242.84799	53.13820	19.4379
4	3.426	MM	0.0822	379.24387	76.89584	30.3552
Totals :				1249.35532	273.86793	

Diaryl **2.14** and precursors



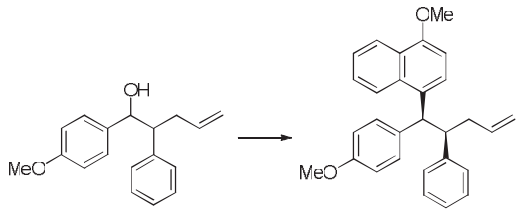
After following the representative protocol for the synthesis of allyl enol carbonates using starting ketone (340 mg), the mixture was stirred for 16h. The residue was purified by flash chromatography (silica gel, 1.5 cm × 20.0 cm; 1:19, diethyl ether:hexanes) to yield **2.14a** (0.4 g, 85%) as a clear oil; R_f = 0.36 (1:9, ethyl acetate:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 – 7.53 (m, 2H), 7.53 – 7.50 (m, 2H), 7.38 – 7.33 (m, 2H), 7.28 – 7.23 (m, 1H), 6.95 – 6.90 (m, 2H), 6.55 (s, 1H), 5.95 – 5.85 (m, 1H), 5.35 (dd, *J* = 17.2, 1.3 Hz, 1H), 5.27 (dd, *J* = 10.5, 0.9 Hz, 1H), 4.65 (dd, *J* = 5.7, 1.1 Hz, 2H), 3.84 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.3, 152.5, 146.6, 134.3, 131.3, 128.9, 128.7, 128.0, 127.6, 126.4, 119.3, 115.2, 114.3, 69.3, 55.5; IR (neat) 3055, 3039, 2957, 2934, 2847, 1671, 1652, 1612, 1578, 1512, 1465, 1446, 1421, 1364, 1341, 1314, 1281, 1234, 1179, 1115, 1105, 1077, 1034 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{18}O_4$ $[M+H]^+$ 311.1283, found $[M+H]^+$ 311.1304 and calcd for $C_{19}H_{18}O_4$ $[M+Na]^+$ 333.1103, found $[M+Na]^+$ 333.1117.

After following the representative protocol for the synthesis of palladium-catalyzed asymmetric allylation using allyl enol carbonate **2.14a** (320 mg), the reaction mixture was stirred for 16h. The residue was purified by flash chromatography (silica gel-silver nitrate, 1.5 cm × 20.0 cm; 1:19, diethyl ether:hexanes) to yield ketone **2.14b** (224 mg, 82%) as a clear oil; R_f = 0.45 (1:9, ethyl acetate:hexanes); (the product obtained was determined to be racemic by analytical chiral HPLC method); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 – 7.93 (m, 2H), 7.33 – 7.27 (m, 4H), 7.22 – 7.17 (m, 1H), 6.89 – 6.84 (m, 2H), 5.75 (ddt, *J* = 17.1, 10.2, 6.9 Hz, 1H), 5.03 (dd, *J* = 17.1, 1.5 Hz, 1H), 4.96 (dd, *J* = 10.2, 0.7 Hz, 1H), 4.58 (t, *J* = 7.3 Hz, 1H), 3.82 (s, 3H), 2.94 (dt, *J* = 14.5, 7.3 Hz, 1H), 2.55 (dt, *J* = 14.1, 6.9 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.9, 163.5, 139.7, 136.4, 131.2, 129.9, 129.0, 128.3, 127.2, 116.7, 113.9, 55.6, 53.4, 38.4; IR (neat) 3014, 2952, 2942, 2875, 2841, 1668, 1641, 1624, 1579, 1511, 1464, 1427, 1389, 1371, 1342, 1264, 1248, 1197, 1144, 1133, 1035 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{18}O_2$ $[M+H]^+$ 267.1385, found $[M+H]^+$ 267.1362 and calcd for $C_{18}H_{18}O_2$ $[M+Na]^+$ 289.1205, found $[M+Na]^+$ 289.1311.

After following the representative protocol for benzylic alcohols preparation using ketone **2.14b** (200 mg), the mixture was filtered on silica pad (silica gel, 2.5 cm × 4.0 cm; 4V diethyl ether, then 2V ethyl acetate) to yield alcohol **2.14c** (0.2 g, >95%, dr 1:1) of a colorless oil; R_f = 0.45 (1:9, ethyl acetate:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 – 7.31 (m, 2H), 7.28 – 7.25 (m, 1H), 7.24 – 7.21 (m, 4H), 6.90 – 6.86 (m, 2H), 5.49 (ddt, *J* = 17.1, 10.2, 6.9 Hz, 1H), 4.86 – 4.80 (m, 2H), 4.74 (d, *J* = 2.7 Hz, 0.5H), 4.73 (d, *J* = 2.7 Hz, 0.5H), 3.82 (s, 3H), 2.93 (ddd, *J* = 10.1, 8.1, 5.0 Hz, 1H), 2.34 – 2.20 (m, 2H), 1.76 (d, *J* = 2.8 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.4, 140.8, 136.4, 134.7, 129.1, 128.7, 128.2, 127.1, 116.3, 113.9, 77.8, 55.4, 54.3, 36.7; IR (neat) 3431, 3062, 3027, 2998, 2922, 2851, 1610, 1585, 1511, 1441, 1301, 1246, 1174, 1034 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{20}O_2$ $[M+H]^+$ 269.1541, found $[M+H]^+$ 269.1705 and calcd for $C_{18}H_{20}O_2$ $[M+Na]^+$ 291.1361, found $[M+Na]^+$ 291.1274.

After following the representative protocol for the acid catalyzed arylation of benzylic alcohols using alcohol **2.14c** (30 mg) and *p*-TsOH•H_2O as the catalyst. The mixture was stirred for 2h. The residue was purified by flash chromatography (silica gel, 1.5 cm × 20.0 cm; 1:19, diethyl ether:hexanes) to yield diaryl **2.14** (30 mg, 69%, dr 20:1) as an oil; R_f = 0.27 (1:9, ethyl acetate:hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.32 (m, 2H), 7.14 – 7.10 (m, 5H), 7.06 – 6.98 (m, 1H), 6.86 – 6.81 (m, 2H), 6.25 (dd, *J* = 8.5, 2.4 Hz, 1H), 6.16 (d, *J* = 2.4 Hz, 1H), 5.51 (ddt, *J* = 17.2, 10.2, 7.1 Hz, 1H), 4.83 – 4.78 (m, 1H), 4.78 – 4.72 (m, 1H), 4.61 (d, *J* = 12.0 Hz, 1H), 3.78 (s, 3H), 3.66 (s, 3H), 3.64 (s, 3H), 3.49 (ddd, *J* = 12.1, 10.2, 3.5 Hz, 1H), 2.42 – 2.34 (m, *J* = 13.7, 6.9, 3.4 Hz, 1H), 2.25 – 2.15 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.5, 157.9, 157.6, 143.5, 136.9, 136.6, 129.5, 128.64, 128.58, 127.8, 125.8, 125.5, 115.8, 113.9, 104.2, 98.6, 55.5, 55.3, 55.2, 49.8, 47.3, 40.0; IR (neat) 3026, 2995, 2948, 2926, 2834, 1732, 1609, 1585, 1505, 1462, 1439, 1418, 1289, 1250, 1208, 1176, 1119, 1035 cm^{-1}; HRMS (ESI) calcd for $C_{26}H_{28}O_3$ $[M+H]^+$ 389.2116, found $[M+H]^+$ 389.2194 and calcd for $C_{26}H_{28}O_3$ $[M+Na]^+$ 411.1936, found $[M+Na]^+$ 411.1786.

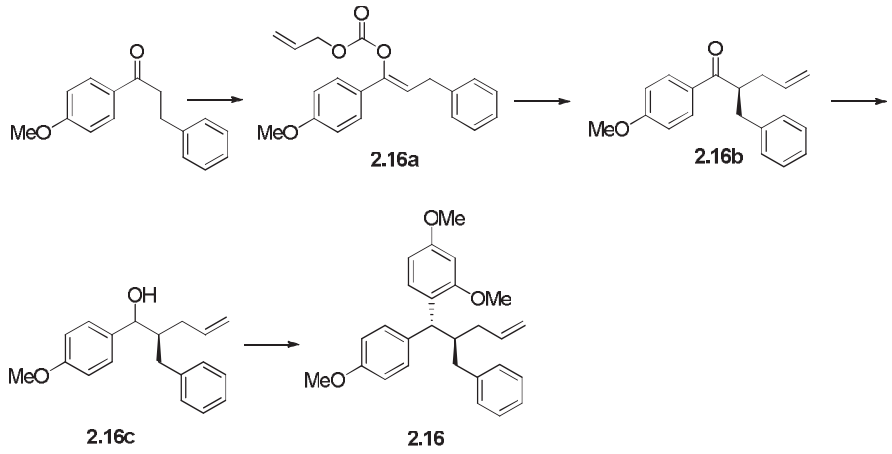
Diaryl **2.15**



2.14c **2.15**

After following the representative protocol for the acid catalyzed arylation of benzylic alcohols using alcohol **2.14c** (30 mg) and *p*-TsOH•H_2O as the catalyst. The solution was stirred for 2h. The residue was purified by flash chromatography (silica gel, 1.5 cm × 20.0 cm; 1:19, diethyl ether:hexanes) to yield diaryl **2.15** (29 mg, 65%, dr 5:1) as an oil; R_f = 0.24 (1:9, ethyl acetate:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.33 (dd, *J* = 8.3, 1.2 Hz, 0.15H), 8.24 (d, *J* = 8.5 Hz, 0.15H), 8.21 – 8.16 (m, 1.7H), 7.66 (d, *J* = 8.1 Hz, 0.15H), 7.53 (ddd, *J* = 8.4, 6.8, 1.4 Hz, 0.15H), 7.48 – 7.44 (m, 1.85H), 7.41 – 7.34 (m, 2.55H), 7.22 – 7.15 (m, 2.3H), 7.12 – 7.07 (m, 1.85H), 7.01 – 6.96 (m, 1.15H), 6.92 (d, *J* = 8.1 Hz, 0.15H), 6.84 – 6.80 (m, 1.7H), 6.65 (d, *J* = 8.1 Hz, 0.85H), 6.55 – 6.52 (m, 0.3H), 5.55 (ddt, *J* = 17.1, 10.1, 7.1 Hz, 1H), 4.99 (d, *J* = 11.3 Hz, 0.85H), 4.91 – 4.76 (m, 2.15H), 4.02 (s, 0.45H), 3.87 (s, 2.55H), 3.75 (s, 2.55H), 3.68 – 3.63 (m, 0.85H), 3.61 (s, 0.45H), 2.62 – 2.55 (m, 0.15H), 2.47 – 2.41 (m, 0.85H), 2.39 – 2.33 (m, 0.15H), 2.33 – 2.25 (m, 0.85H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.79, 157.76, 157.6, 157.5, 157.2, 141.2, 141.1, 139.3, 137.1, 130.9, 130.6, 129.9, 129.7, 128.2, 126.5, 113.7, 113.6, 113.5, 113.3, 104.1, 104.0, 98.8, 98.5, 55.6, 55.43, 55.36, 55.3, 51.9, 51.6, 44.1, 35.87, 35.85, 34.2, 34.0, 29.9, 29.6, 29.2; IR (neat): 3072, 3026, 3001, 2929, 2835, 1585, 1509, 1461, 1387, 1246, 1176, 1110, 1033, 913 cm^{-1}; HRMS (ESI) calcd for $C_{29}H_{28}O_2$ $[M+H]^+$ 409.2167, found $[M+H]^+$ 409.2042 and calcd for $C_{29}H_{28}O_2$ $[M+Na]^+$ 431.1987, found $[M+Na]^+$ 431.1734.

Diaryl **2.16** and precursors



After following the representative protocol for the synthesis of allyl enol carbonates using the starting ketone (200 mg), the solution was stirred for 16h. The residue was purified by flash chromatography (silica gel, 1.5 cm × 20.0 cm; 1:19, diethyl ether:hexanes) to yield **2.16a** (216 mg, 80%) as a clear oil; R_f = 0.34 (1:9, ethyl acetate:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 – 7.38 (m, 2H), 7.32 – 7.25 (m, 4H), 7.24 – 7.19 (m, 1H), 6.88 – 6.85 (m, 2H), 6.00 – 5.88 (m, 1H), 5.81 (t, *J* = 7.5 Hz, 1H), 5.39 (dq, *J* = 17.2, 1.4 Hz, 1H), 5.32 – 5.28 (m, 1H), 4.69 (dt, *J* = 5.8, 1.3 Hz, 2H), 3.81 (s, 3H), 3.54 (d, *J* = 7.5 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.0, 153.1, 146.9, 139.8, 131.4, 128.7, 128.7, 127.4, 126.4, 126.2, 119.4, 115.3, 114.1, 69.2, 55.5, 32.3; IR (neat) 3052, 3039, 2951, 2936, 2848, 1668, 1652, 1614, 1575, 1510, 1457, 1452, 1423, 1361, 1342, 1316, 1282, 1236, 1177, 1124, 1102, 1074, 1033 cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{20}O_4$ $[M+H]^+$ 325.1440, found $[M+H]^+$ 325.1455 and calcd for $C_{20}H_{20}O_4$ $[M+Na]^+$ 347.1260, found $[M+Na]^+$ 347.1019.

After following the representative protocol for the synthesis of palladium-catalyzed asymmetric allylation using allyl enol carbonate **2.16a** (215 mg), the solution was stirred for 16h. The residue was purified by flash chromatography (silica gel-silver nitrate, 1.5 cm × 20.0 cm; 1:19, diethyl ether:hexanes) to yield **2.16b** (147 mg, 79%) as an oil; R_f = 0.42 (1:9, ethyl acetate:hexanes); $[\alpha]_D$ +22.3° (*c* 1.1, $CDCl_3$, optical rotation was measured from a sample with 63% *ee*); (the enantiomeric excess was determined by analytical chiral HPLC method); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 – 7.83 (m, 2H), 7.24 – 7.12 (m, 5H), 6.90 –

6.86 (m, 2H), 5.73 (ddt, *J* = 17.1, 10.2, 7.0 Hz, 1H), 5.05 – 4.99 (m, 1H), 4.99 – 4.96 (m, 1H), 3.84 (s, 3H), 3.77 – 3.71 (m, 1H), 3.09 (dd, *J* = 13.7, 7.7 Hz, 1H), 2.80 (dd, *J* = 13.7, 6.5 Hz, 1H), 2.56 – 2.49 (m, 1H), 2.32 – 2.25 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 201.5, 163.5, 140.0, 135.6, 130.7, 130.4, 129.2, 128.5, 126.3, 117.1, 113.9, 55.6, 47.7, 38.0, 36.6; IR (neat) 3013, 2954, 2940, 2876, 2838, 1669, 1642, 1624, 1576, 1512, 1467, 1434, 1385, 1372, 1340, 1258, 1245, 1198, 1142, 1131, 1034 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{20}O_2$ $[M+H]^+$ 325.1440, found $[M+H]^+$ 325.1455 and calcd for $C_{19}H_{20}O_2$ $[M+Na]^+$ 347.1260, found $[M+Na]^+$ 347.1019.

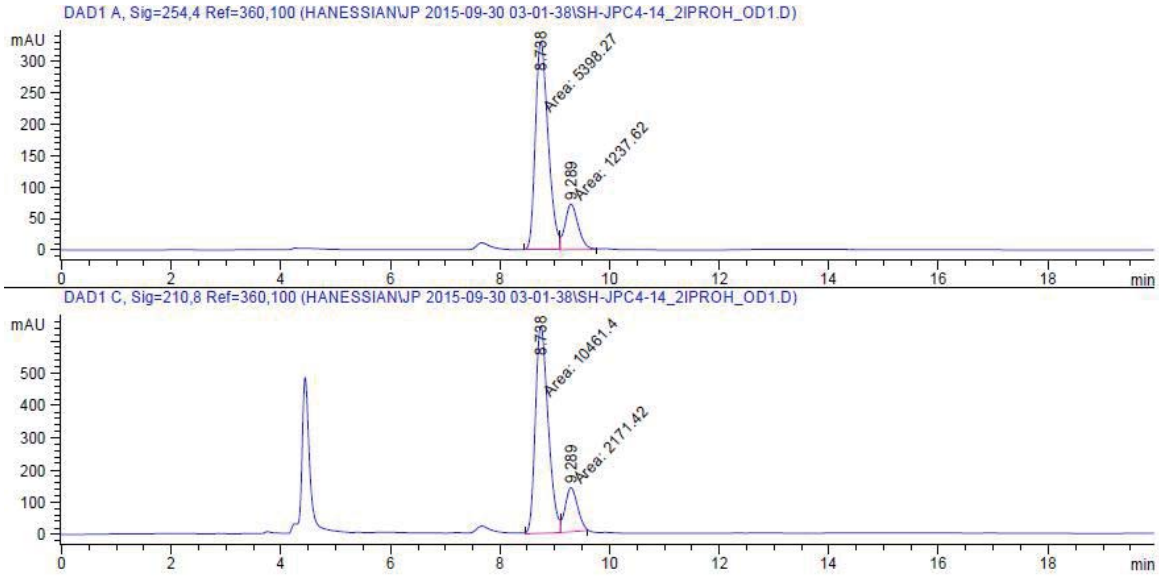
After following the representative protocol for alkylalcohols preparation using ketone **2.16b** (147 mg), the mixture was filtered on silica pad (silica gel, 2.5 cm × 4.0 cm; 5V diethyl ether, then 2V ethyl acetate) to yield alcohol **2.16c** (147 mg, >95%, dr 4:1) of a colorless oil; R_f = 0.42 (1:9, ethyl acetate:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 – 7.21 (m, 4H), 7.20 – 7.12 (m, 3H), 6.91 – 6.86 (m, 2H), 5.88 – 5.72 (m, 1H), 5.08 – 4.96 (m, 2H), 4.69 (dd, *J* = 5.3, 3.5 Hz, 1H), 4.63 (dd, *J* = 4.9, 3.9 Hz, 1H), 3.82 (s, 0.6H), 3.81 (s, 2.4H), 2.67 – 2.58 (m, 1H), 2.49 (dd, *J* = 13.7, 7.8 Hz, 1H), 2.24 – 2.17 (m, 1H), 2.15 – 2.05 (m, 2H), 1.79 (d, *J* = 3.7 Hz, 0.8H), 1.76 (d, *J* = 3.5 Hz, 0.2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.0, 141.1, 137.2, 137.0, 135.6, 129.5, 129.3, 128.5, 128.4, 127.7, 127.6, 126.0, 125.9, 116.9, 113.84, 113.81, 74.7, 55.4, 47.3, 47.1, 36.2, 34.6, 34.0, 32.8; IR (neat) 3454, 3063, 2999, 2923, 2835, 1609, 1584, 1509, 1440, 1300, 1246, 1175, 1093, 1034 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{22}O_2$ $[M+H]^+$ 283.1698, found $[M+H]^+$ 283.1542 and calcd for $C_{19}H_{22}O_2$ $[M+Na]^+$ 305.1518, found $[M+Na]^+$ 305.1762.

After following the representative protocol for the acid catalyzed arylation of benzylic alcohols using alcohol **2.16c** (30 mg) and *p*-TsOH•H_2O as the catalyst. The reaction was stirred 1h. The residue was purified by flash chromatography (silica gel, 1.5 cm × 20.0 cm; 1:19, diethyl ether:hexanes) to yield diaryl **2.16** (36 mg, 85%, dr 2.3:1) as a clear oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (d, *J* = 8.6 Hz, 0.5H), 7.31 (d, *J* = 8.7 Hz, 1.2H), 7.27 – 7.22 (m, 3H), 7.18 – 7.13 (m, 1H), 7.10 (d, *J* = 7.5 Hz, 2H), 6.84 – 6.80 (m, 1.4H), 6.79 – 6.76 (m, 0.6H), 6.49 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.45 (dd, *J* = 8.5, 2.4 Hz, 1H), 6.41 (d, *J* =

2.4 Hz, 1H), 6.40 (d, J = 2.4 Hz, 1H), 5.85 – 5.69 (m, 1H), 5.04 – 4.97 (m, 1H), 4.88 – 4.78 (m, 1H), 4.23 – 4.17 (m, 1H), 3.80 (s, 1H), 3.78 (s, 2H), 3.77 (s, 1H), 3.76 (s, 2H), 3.76 (s, 2H), 3.75 (s, 1H), 2.76 – 2.70 (m, 1H), 2.70 – 2.62 (m, 1H), 2.46 (dd, J = 13.7, 9.5 Hz, 0.3H), 2.39 (dd, J = 13.7, 10.3 Hz, 0.7H), 2.04 – 1.91 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.02, 158.95, 158.2, 158.0, 157.8, 157.7, 141.9, 141.6, 137.0, 136.5, 135.8, 135.6, 129.49, 129.44, 129.38, 129.34, 128.4, 128.2, 128.1, 125.8, 125.7, 125.3, 117.12, 117.09, 113.9, 113.7, 104.7, 104.6, 98.92, 98.90, 55.60, 55.56, 55.41, 55.38, 55.32, 55.28, 45.7, 43.0, 42.8, 37.2, 36.7, 33.8, 33.7; IR (neat) 3061, 3025, 2998, 2928, 2834, 1607, 1584, 1503, 1439, 1417, 1288, 1246, 1206, 1175, 1156, 1117, 1034 cm^{-1}; HRMS (ESI) calcd for $C_{27}H_{30}O_3$ $[M+H]^+$ 403.2273, found $[M+H]^+$ 403.2146 and calcd for $C_{27}H_{30}O_3$ $[M+Na]^+$ 425.1995, found $[M+Na]^+$ 425.1864.

Chiral HPLC separation of ketone **2.16b** for *ee*:

Method info: 2% IPA/Hex, chiralcel OD, 1ml/min, 20min



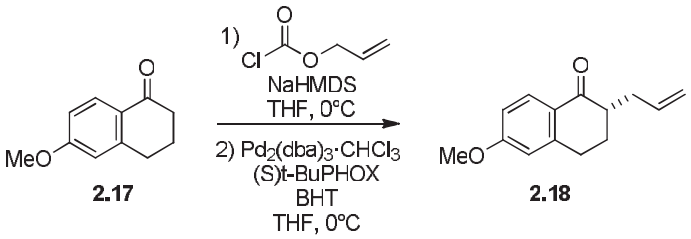
Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.738	MM	0.2705	5398.27148	332.59793	81.3496
2	9.289	MM	0.2816	1237.62158	73.25723	18.6504
Totals :				6635.89307	405.85516	

Signal 2: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.738	MM	0.2708	1.04614e4	643.84332	82.8113
2	9.289	MM	0.2630	2171.42188	137.59880	17.1887
Totals :				1.26328e4	781.44212	

Allylketone **2.18**



2.17 **2.18**

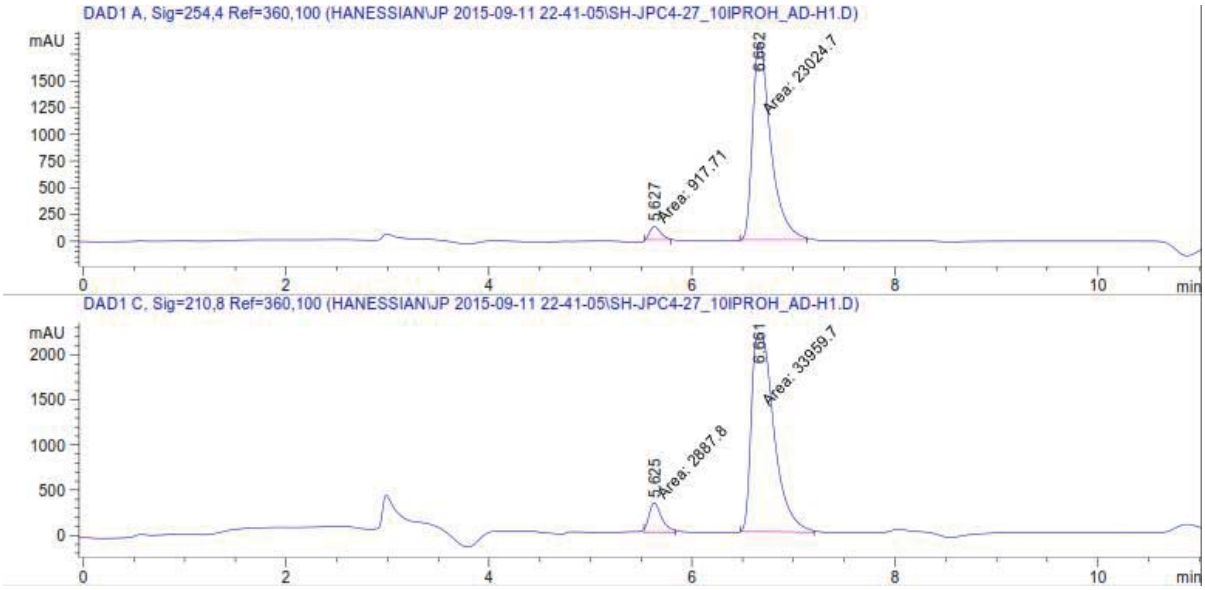
After following the representative protocol for the synthesis of allyl enol carbonates using ketone **2.17** (690 mg), the solution was stirred for 16h. The residue was purified by flash chromatography (silica gel, 1.5 cm × 20.0 cm; 1:19, diethyl ether:hexanes) to yield the enol carbonate (610mg, 60%) as a clear oil which was used directly for the following step; R_f = 0.52 (1:9, ethyl acetate:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.12 (d, J = 8.1 Hz, 1H), 6.73 – 6.69 (m, 2H), 5.99 (ddt, J = 16.3, 10.5, 5.8 Hz, 1H), 5.67 (t, J = 4.7 Hz, 1H), 5.41

(dq, J = 17.2, 1.4 Hz, 1H), 5.32 (dd, J = 10.4, 1.2 Hz, 1H), 4.70 (dt, J = 5.8, 1.3 Hz, 2H), 3.80 (s, 3H), 2.84 (t, J = 8.1 Hz, 2H), 2.45 – 2.40 (m, 2H).

After following the representative protocol for the synthesis of palladium-catalyzed asymmetric allylation using the allyl enol carbonate made from **2.17** (610 mg), the solution was stirred for 16h. The residue was purified by flash chromatography (1:9, diethyl ether:hexanes) to yield **2.18** (396 mg, 78%) as an oil; R_f = 0.59 (1:9, ethyl acetate:hexanes); $[\alpha]_D$ -37.1° (*c* 1.0, $CDCl_3$, optical rotation was measured from a sample with 92% *ee*); (the enantiomeric excess was determined by analytical chiral HPLC method); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 (d, J = 8.8 Hz, 0.9H), 7.75 (d, J = 16.0 Hz, 0.2H), 6.82 (dd, J = 8.7, 2.6 Hz, 1H), 6.68 (d, J = 2.5 Hz, 1H), 6.06 – 5.92 (m, 0.1H), 5.92 – 5.76 (m, 0.9H), 5.36 (ddq, J = 25.6, 10.4, 1.3 Hz, 0.2H), 5.14 – 5.02 (m, 1.8H), 3.85 (s, 2.7H), 3.79 (s, 0.3H), 2.95 (dd, J = 7.6, 4.6 Hz, 2H), 2.81 – 2.70 (m, 1H), 2.56 – 2.38 (m, 1H), 2.31 – 2.17 (m, 2H), 1.92 – 1.77 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.4, 163.6, 146.7, 143.5, 136.6, 130.1, 129.1, 128.5, 126.3, 125.6, 116.8, 113.3, 112.6, 55.6, 47.0, 34.3, 29.1, 28.1; IR (neat) , 2924, 2843, 1632, 1564, 1443, 1252, 1032 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{16}NaO_2$ $[M+H]^+$ 239.1048, found $[M+H]^+$ 239.1065.

Chiral HPLC separation of ketone **2.18** for *ee*:

Method info: 10% IPA/Hex, chiralpak AD-H, 1ml/min, 10min



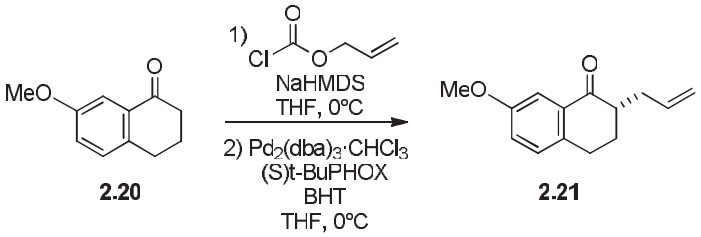
Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.627	MM	0.1229	917.71008	124.41824	3.8330
2	6.662	MM	0.2071	2.30247e4	1852.91418	96.1670
Totals :				2.39424e4	1977.33243	

Signal 2: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.625	MM	0.1456	2887.80273	330.50104	7.8372
2	6.661	MM	0.2578	3.39597e4	2195.14819	92.1628
Totals :				3.68475e4	2525.64923	

Allylketone **2.21**

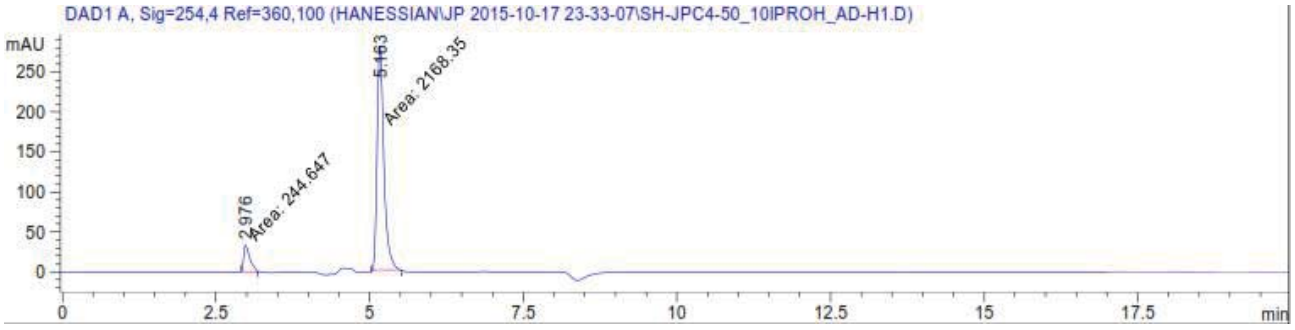


After following the representative protocol for the synthesis of allyl enol carbonates using ketone **2.20** (1 g), the solution was stirred for 16h. The residue was purified by flash chromatography (silica gel, 1.5 cm × 20.0 cm; 1:19, diethyl ether:hexanes) to yield the enol carbonate (1.12g, 76%) as a clear oil which was used directly for the following step; R_f = 0.50 (1:9, ethyl acetate:hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06 (d, *J* = 8.2 Hz, 1H), 6.79 – 6.70 (m, 2H), 5.99 (ddt, *J* = 22.1, 10.5, 5.8 Hz, 1H), 5.83 (t, *J* = 4.7 Hz, 1H), 5.42 (ddd, *J* = 17.2, 2.8, 1.4 Hz, 1H), 5.32 (dd, *J* = 10.4, 1.2 Hz, 1H), 4.73 – 4.69 (m, 2H), 3.78 (s, 3H), 2.79 (t, *J* = 8.1 Hz, 2H), 2.43 (td, *J* = 8.1, 4.7 Hz, 2H).

After following the representative protocol for the synthesis of palladium-catalyzed asymmetric allylation using the allyl enol carbonate made from **2.20** (1.12 g), the solution was stirred for 16h. The residue was purified by flash chromatography (1:9, diethyl ether:hexanes) to yield **2.18** (396 mg, 78%) as an oil; R_f = 0.63 (1:9, ethyl acetate:hexanes); $[\alpha]_D$ -30.1° (*c* 1.1, $CDCl_3$, optical rotation was measured from a sample with 80% *ee*); (the enantiomeric excess was determined by analytical chiral HPLC method); ^1H NMR (500 MHz, $CDCl_3$) δ 7.52 (d, *J* = 2.8 Hz, 1H), 7.15 (d, *J* = 8.4 Hz, 1H), 7.05 (dd, *J* = 8.4, 2.8 Hz, 1H), 5.89 – 5.80 (m, 1H), 5.13 – 5.05 (m, 2H), 3.83 (s, 3H), 2.94 – 2.90 (m, 2H), 2.78 – 2.71 (m, 1H), 2.53 (ddd, *J* = 12.8, 8.7, 4.5 Hz, 1H), 2.31 – 2.18 (m, 2H), 1.85 (dddd, *J* = 13.3, 11.7, 8.6, 6.8 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 199.6, 158.5, 136.8, 136.4, 133.4, 130.1, 121.8, 117.0, 109.5, 55.6, 47.2, 34.2, 28.3, 27.9; IR (neat) 2928, 2834, 1631, 1556, 1431, 1327, 1255, 1022 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{16}NaO_2$ $[M+H]^+$ 239.1048, found $[M+H]^+$ 239.1065.

Chiral HPLC separation of ketone **2.21** for *ee*:

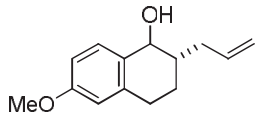
Method info: 10% IPA/Hex, chiralpak AD-H, 1ml/min, 20min



Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.976	MM	0.1220	244.64706	33.43341	10.1387
2	5.163	MM	0.1285	2168.34741	281.16669	89.8613
Totals :				2412.99448	314.60010	

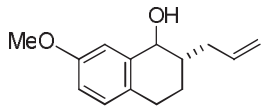
Allylalcohol **2.19**



2.19

After following the representative protocol for alkylalcohols preparation using ketone **2.18** (200 mg), the mixture was filtered on silica pad (silica gel, 2.5 cm × 4.0 cm; 5V diethyl ether) to yield alcohol **2.19** (200 mg, >95%, dr 2:1) of a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8.7 Hz, 0.66H), 7.15 (d, *J* = 8.5 Hz, 0.33H), 6.82 (dd, *J* = 8.7, 2.5 Hz, 0.66H), 6.73 (dd, *J* = 8.4, 2.6 Hz, 0.33H), 6.68 (d, *J* = 2.4 Hz, 0.66H), 6.58 (d, *J* = 2.5 Hz, 0.33H), 5.91 – 5.79 (m, 1H), 5.13 – 4.97 (m, 2H), 3.85 (s, 2H), 3.76 (s, 1H), 2.95 (dd, *J* = 7.5, 4.7 Hz, 1H), 2.80 – 2.64 (m, 1.33H), 2.50 (ddt, *J* = 11.4, 8.7, 4.5 Hz, 0.66H), 2.31 – 2.16 (m, 2H), 1.97 (t, *J* = 7.4 Hz, 1H), 1.85 (ddt, *J* = 13.3, 11.4, 7.6 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.4, 163.6, 159.0, 146.7, 138.7, 137.3, 136.6, 132.4, 130.1, 128.0, 126.3, 116.8, 116.3,113.24, 113.20, 112.68, 112.61, 55.6, 55.3, 47.0, 36.2, 34.6, 34.3, 29.9, 29.1, 28.1, 25.0, 22.6, 21.6; IR (neat) 3402, 2920, 2853, 1665, 1638, 1577, 1453, 1254, 1153, 1036 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{18}NaO_2$ $[M+H]^+$ 219.1385, found $[M+Na]^+$ 219.1347.

Allylalcohol **2.22**

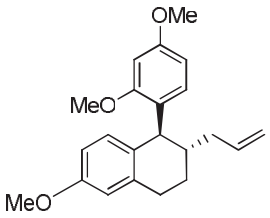


2.22

After following the representative protocol for alkylalcohols preparation using ketone **2.21** (240 mg), the mixture was filtered on silica pad (silica gel, 2.0 cm × 4.0 cm; 5V diethyl ether) to yield alcohol **2.22** (240 mg, >95%, dr 4:1) of a colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.07 (d, *J* = 8.4 Hz, 0.8H), 7.03 (d, *J* = 8.5 Hz, 00.2H), 6.91 (d, *J* = 2.6 Hz, 1H), 6.83 (dd, *J* = 8.4, 2.7 Hz, 0.8H), 6.80 (dd, *J* = 8.4, 2.6 Hz, 0.2H), 5.95 (ddt, *J* = 17.2, 10.1, 7.2 Hz, 1H), 5.20 – 5.09 (m, 2H), 4.64 (dd, *J* = 5.9, 3.0 Hz, 1H3.82 (s, 3H), 2.87 – 2.80 (m,

1H), 2.76 – 2.67 (m, 1H), 2.52 – 2.38 (m, 1H), 2.24 – 2.09 (m, 1H), 1.88 – 1.79 (m, 1H), 1.76 (ddd, J = 9.8, 7.4, 3.9 Hz, 2H), 1.54 (d, J = 6.1 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.0, 139.5, 137.3, 130.2, 129.1, 116.4, 114.9 114.1, 70.2, 55.5, 39.7, 36.2, 28.4, 23.1; IR (neat) 3427, 2874, 2824, 1621, 1604, 1589, 1457, 1251, 1126, 1087 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{18}NaO_2$ $[M+H]^+$ 219.1385, found $[M+Na]^+$ 219.1317.

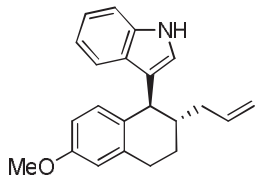
Diaryl **2.23**



2.23

After following the representative protocol for the acid catalyzed arylation of alkylalcohols using alcohol **2.19** (30 mg) and *p*-TsOH•H_2O as the catalyst, the reaction mixture was stirred for 2h. The residue was purified by flash chromatography (silica gel, 1.5 cm × 20.0 cm; 1:19, diethyl ether:hexanes) to yield diaryl **2.23** (42 mg, 88%, dr 20:1) as a clear oil; R_f = 0.47 (1:9, ethyl acetate:hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.69 (s, 1H), 6.67 (s, 1H), 6.64 (d, J = 2.5 Hz, 1H), 6.59 (dd, J = 8.5, 2.7 Hz, 1H), 6.49 (d, J = 2.4 Hz, 1H), 6.38 (dd, J = 8.4, 2.4 Hz, 1H), 5.87 – 5.76 (m, 1H), 5.01 – 4.95 (m, 2H), 4.14 (d, J = 6.1 Hz, 1H), 3.80 (s, 3H), 3.79 (s, 3H), 3.77 (s, 3H), 2.87 – 2.80 (m, 2H), 2.21 – 2.12 (m, 1H), 1.95 (dt, J = 8.3, 4.9 Hz, 3H), 1.50 (dd, J = 13.5, 6.1 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.1, 158.5, 157.4, 138.5, 137.8, 132.1, 131.4, 130.7, 128.0, 115.8, 112.9, 112.3, 104,3, 98.5, 55.6, 55.4, 55.3, 42.5, 40.0, 38.0, 29.8, 28.3, 25.6; IR (neat) 2922, 2840, 1671, 1638, 1598, 1492, 1458, 1249, 1028 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{26}NaO_3$ $[M+Na]^+$ 361.1780, found $[M+Na]^+$ 361.1795.

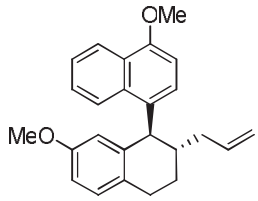
Diaryl **2.24**



2.24

After following the representative protocol for the acid catalyzed arylation of alkylalcohols using alcool **2.19** (30 mg) and *p*-TsOH•H_2O as the catalyst, the reaction mixture was stirred for 2h. The residue was purified by flash chromatography (silica gel, 1.5 cm × 20.0 cm; 1:19, diethyl ether:hexanes) to yield diaryl **2.24** (40 mg, 90%, dr 4:1) as a clear oil; R_f = 0.22 (1:19, diethyl ether:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99 (s, 0.25H), 7.95 (s, 0.75H), 7.55 (d, *J* = 8.0 Hz, 0.2H), 7.39 – 7.31 (m, 1.8H), 7.21 – 7.14 (m, 1H), (ddd, *J* = 8.0, 7.1, 1.0 Hz, 0.2H), (ddd, *J* = 8.0, 7.03, 1.0 Hz, 0.8H), 6.95 (d, *J* = 8.5 Hz, 0.2H), 6.89 (d, *J* = 8.6 Hz, 0.8H), 6.78 (d, *J* = 2.3 Hz, 0.8H), 6.71 (d, *J* = 2.3 Hz, 0.2H),, 6.69 (d, *J* = 2.7 Hz, 0.8H), 6.66 (d, *J* = 2.3 Hz, 0.2H), 6.61 (dd, *J* = 8.5, 2.7 Hz, 0.2H), 6.58 (dd, *J* = 8.5, 2.8 Hz, 0.8H), 5.90 – 5.77 (m, 1.6H), 5.06 – 4.99 (m, 0.4H), 4.99 – 4.91 (m, 2H), 4.48 (d, *J* = 4.9 Hz, 0.2H), 4.03 (d, *J* = 7.5 Hz, 0.8H), 3.79 (s, 0.75H), 3.78 (s, 2.25H), 2.93 – 2.87 (m, 2H), 2.31 – 2.23 (m, 1H), 2.22 – 2.14 (m, 1H), 2.08 – 1.97 (m, 2H), 1.68 – 1.60 (m, 0.2H), 1.55 (dtd, *J* = 14.1, 8.4, 5.9 Hz, 0.8H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.5, 138.1, 137.9, 137.5, 136.8, 131.5, 131.5, 126.7, 124.2, 123.5, 121.9, 121.7, 121.3, 119.9, 119.4, 119.2, 116.3, 115.8, 113.0, 112.3, 112.2, 111.3, 111.1, 55.3, 41.5, 40.1, 39.4, 39.2, 38.3, 38.1, 29.5, 28.5, 26.1, 23.5; IR (neat) 2884, 2835, 1629, 1612, 1546, 1499, 1448, 1252, 1033 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{23}NNaO$ $[M+Na]^+$ 340.1678, found $[M+Na]^+$ 340.1641.

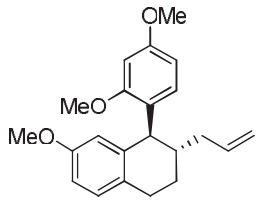
Diaryl **2.25**



2.25

After following the representative protocol for the acid catalyzed arylation of alkylalcohols using alcohol **2.22** (30 mg) and *p*-TsOH•H_2O as the catalyst, the reaction mixture was stirred for 2h. The residue was purified by flash chromatography (silica gel, 1.5 cm × 20.0 cm; 1:19, diethyl ether:hexanes) to yield diaryl **2.25** (43 mg, 87%, dr 20:1) as a clear oil; R_f = 0.45 (1:9, diethyl ether:hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 – 8.30 (m, 1H), 8.05 – 7.92 (m, 1H), 7.52 – 7.43 (m, 2H), 7.10 (d, *J* = 8.4 Hz, 1H), 6.95 – 6.83 (m, 1H), 6.75 – 6.66 (m, 2H), 6.35 (d, *J* = 2.6 Hz, 1H), 5.89 – 5.76 (m, 1H), 5.09 – 4.96 (m, 2H), 4.52 – 4.40 (m, 1H), 4.01 (s, 0.15H), 3.97 (s, 2.85H), 3.60 (s, 0.15H), 3.57 (s, 2.85H), 2.87 (t, *J* = 6.0 Hz, 2H), 2.28 – 2.15 (m, 2H), 2.08 – 1.96 (m, 2H), 1.62 – 1.51 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.9, 154.3, 137.3, 129.6, 129.4, 128.0, 126.4, 124.8, 122.8, 116.6., 115.2, 112.5, 103.4, 55.6, 55.2, 39.4, 32.1, 30.2, 29.9, 22.9, 14.3; IR (neat) 2921, 2851, 1735, 1720, 1637, 1608, 1500, 1461, 1388, 1263, 1159,1037 cm^{-1}; HRMS (ESI) calcd for $C_{25}H_{26}NaO_2$ $[M+Na]^+$ 381.1831, found $[M+Na]^+$ 381.1867.

Diaryl **2.26**

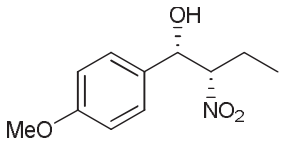


2.26

After following the representative protocol for the acid catalyzed arylation of alkylalcohols using alcohol **2.22** (26 mg) and *p*-TsOH•H_2O as the catalyst, the reaction mixture was stirred for 2h. The residue was purified by flash chromatography (silica gel, 1.5 cm × 20.0 cm; 1:19, diethyl ether:hexanes) to yield diaryl **2.26** (41 mg, 89%, dr 10:1) as a clear oil;

R_f = 0.41 (1:9, diethyl ether:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.15 (d, *J* = 8.8 Hz, 0.1H), 7.01 (d, *J* = 8.4 Hz, 0.9H), 6.72 – 6.62 (m, 2H), 6.47 (t, *J* = 2.8 Hz, 1H), 6.42 (dd, *J* = 15.8, 2.7 Hz, 0.1H), 6.37 (dd, *J* = 8.4, 2.4 Hz, 0.9H), 6.33 (d, *J* = 2.5 Hz, 0.1H), 6.30 (d, *J* = 2.7 Hz, 0.9H), 5.86 – 5.76 (m, 1H), 5.01 – 4.98 (m, 1H), 4.98 – 4.94 (m, 1H), 4.14 (d, *J* = 6.3 Hz, 1H), 3.79 (s, 2.7H), 3.78 (s, 2.7H), 3.77 (s, 0.6H), 3.66 (s, 0.3H), 3.63 (s, 2.7H), 2.78 (t, *J* = 6.4 Hz, 2H), 1.98 – 1.92 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.1, 158.4, 157.7, 141.1, 137.8, 130.8, 129.8, 129.4, 127.5, 115.8, 115.2, 111.8, 104.4, 98.5, 55.6, 55.4, 55.3, 39.7, 38.1, 27.2, 25.8; IR (neat) 2930, 2873, 2831, 1624, 1616, 1573, 1542, 1445, 1322, 1256, 1032 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{26}NaO_3$ $[M+Na]^+$ 361.178, found $[M+Na]^+$ 361.1628.

Nitroalcohol **2.33**



2.33

N,N-diisopropylethylamine (8.5 mL, 0.049 mol, 2.0 equiv) and LiBr (0.42 g, 4.8 mmol, 0.20 equiv) were added sequentially to a solution of *p*-anisaldehyde (3.0 mL, 0.025 mol, 1.0 equiv) and 1-nitropropane (11 mL, 0.12 mol, 5.0 equiv). The mixture was stirred at room temperature for 3 days, then diluted with ethyl acetate (50 mL), and washed with a saturated aqueous solution of sodium thiosulfate (3 × 50 mL). The organic layer was dried over sodium sulfate, filtered, and concentrated. The residue was purified by flash column chromatography (silica gel, 3.5 cm × 30 cm; 1:19 to 1:9 ethyl acetate:hexanes) to yield nitroalcohol **2.33** (2.9 g, 50%, dr 4:1) as a light yellow oil. Rf = 0.31 (1:4 ethyl acetate:hexanes); ^{1}H NMR (300 MHz, CDCl3) d 7.31 – 7.24 (m, 2H), 6.96 – 6.85 (m, 2H), 5.09 (d, *J* = 5.4 Hz, 0.2H), 4.98 (d, *J* = 9.1 Hz, 0.8H), 4.63 – 4.51 (m, 1H), 3.82 (s, 2.3H), 3.80 (s, 0.6H), 2.57 (br s, 0.2H), 2.40 (br s, 0.8H), 2.14 (ddq, *J* = 14.6, 10.7, 7.3 Hz, 0.2H), 2.04 – 1.72 (m, 1H), 1.40 (dqd, *J* = 14.8, 7.5, 3.5 Hz, 0.84H), 0.94 (t, *J* = 7.4 Hz,0.57H), 0.86 (t, *J* = 7.4 Hz, 2.43H); Major diastereomer (*syn*) ^{13}C NMR (75 MHz, $CDCl_3$) d 160.3, 130.8, 128.3, 114.6, 95.5, 75.3, 55.5, 24.1,10.2; Minor diastereomer (*anti*) ^{13}C NMR (75

MHz, CD) d 160.0, 130.8, 127.7, 114.3,94.9, 74.2, 55.4, 21.9, 10.5; IR (neat) 3456, 2981, 2947, 2848, 1615, 1552, 1517, 1464,1376, 1308, 1251, 1180, 1033 cm^{-1}; HRMS (ESI) calcd for $C_{11}H_{15}NNaO_4$ $[M+Na]^+$ 248.08933, found $[M+Na]^+$ 248.08874.

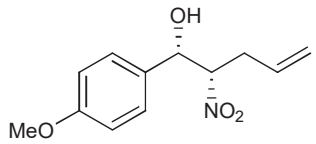
The original procedure for the reactions in presence of alumina and Amberlyst A21 are described in the following references:

-Alumina: Rosini, G.; Ballini, R.; Sorrenti, P. *Synthesis* **1983**, *1983*, 1014.
-Amberlyst A21: Ballini, R.; Bosica, G.; Forconi, P. *Tetrahedron* **1996**, *52*, 1677.

Anisaldehyde (0.61 ml, 5 mmol, 1 equiv.) and nitropropane (0.45 ml, 5 mmol, 1 equiv.) were added to a round bottom flask and stirred for 10 min. Alumina (4g) was added to the solution and stirred 1h then the mixture was left to rest for 23h then the reaction was stopped. The alumina was extracted with EtOAc (3 x 50 ml) then volatiles of the organic phase were evaporated. The residue was purified by flash column chromatography (silica gel, 3.5 cm × 20 cm; 1:19 to 1:9 ethyl acetate:hexanes) to yield nitroalcohol **2.33** (100 mg, 9%, dr 4:1) as a light yellow oil.

Anisaldehyde (3 ml, 24.68 mmol, 1 equiv.) and nitropropane (2.2 ml, 234.68 mmol, 1 equiv.) were added to a round bottom flask and stirred for 10 min. Amberlyst A21 (5g) was added to the solution and stirred 1h then the mixture was left to rest for 23h then the reaction was stopped. The Amberlyst A21 was extracted with EtOAc (3 x 100 ml) then volatiles of the organic phase were evaporated. The residue was purified by flash column chromatography (silica gel, 3.5 cm × 20 cm; 1:19 to 1:9 ethyl acetate:hexanes) to yield nitroalcohol **2.33** (950 mg, 18%, dr 4:1) as a light yellow oil.

Nitroalcohol **2.34**



2.34

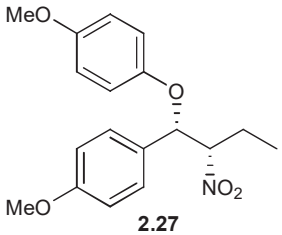
N,N-diisopropylethylamine (1.2 mL, 6.7 mmol, 2.0 equiv) and LiBr (57 mg, 0.66 mmol, 0.20 equiv) were added sequentially to a solution of *p*-anisaldehyde (0.40 mL, 3.3 mmol, 1.0 equiv) and 4-nitrobutene (1.0 g, 9.9 mmol, 3.0 equiv). The mixture was stirred at room temperature for 3 days, then diluted with ethyl acetate (50 mL), and washed with a saturated aqueous solution of sodium bisulfite (3 × 20 mL). The organic layer was dried over sodium sulfate, filtered, and concentrated. The residue was purified by flash column chromatography (silica gel, 2.5 cm × 20 cm; 1:19 to 1:9 ethyl acetate:hexanes) to yield nitroalcohol **2.34** (0.48 g, 61%, dr 2.8:1 *syn*:*anti*) as a light yellow oil; Rf = 0.29 (1:4 ethyl acetate:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) d 7.33 – 7.28 (m, 2H), 6.95 – 6.89 (m, 2H), 5.70 (dddd, *J* = 16.9, 10.2, 7.9, 6.1 Hz, 0.28H), 5.65 – 5.55 (m, 0.73H), 5.19 – 4.97 (m, 3H), 4.77 – 4.63 (m, 1H), 3.82 (s, 2.14H), 3.81 (s, 0.74H), 2.88 – 2.81 (m, 0.28H), 2.70 – 2.62 (m,0.28H), 2.56 – 2.46 (m, 1H), 2.38 – 2.36 (m, 0.71H), 2.20 – 2.13 (m, 0.76H); Major diastereomer: ^{13}C NMR (126 MHz, CD_3NO_2) d 161.6, 133.3, 132.5, 129.8, 119.7, 115.4, 95.0, 76.3, 56.1, 36.1; Minor diastereomer: ^{13}C NMR (126 MHz, CD_3NO_2) d 161.4, 134.0, 132.8, 129.3, 119.5, 115.1, 94.2, 75.3, 56.0, 34.9; IR (neat) 3445, 3013, 2962, 2942, 851, 1615, 1550, 1517, 1374, 1308, 1251, 1179, 1035 cm^{-1}; HRMS (ESI) calcd for $C_{12}H_{19}N_2O_4$ $[M+NH_4]^+$ 255.13393, found $[M+NH4]^+$ 255.13336 and calcd for $C_{12}H_{15}NNaO_4$ $[M+Na]^+$ 260.08933, found $[M+Na]^+$ 260.08859.

Representative protocol for the acid catalyzed alkylation of nitroalcohols and azidoalcohols

The formation of benzylic ether **2.27** is used as a representative protocol. *p*-TsOH•H_2O (acid) (6.3 mg, 0.021mmol, 10 mol%) was added to a solution of starting benzylic alcohol **2.33** (48 mg, 0.21 mmol, 1.0 equiv) and 4-methoxyphenol (nucleophile) (13 mg, 0.105

mmol, 5.0 equiv) in dichloromethane (2.1 ml, ~0.1M). The solution was stirred at room temperature and progress was monitored by TLC then diluted with dichloromethane (~10 mL), and washed with a saturated aqueous solution of sodium bicarbonate (~10 mL). The organic layer was dried over sodium sulfate, filtered, and concentrated.

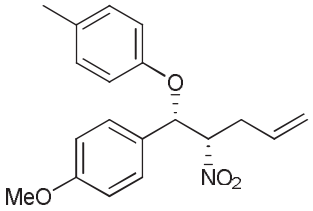
Ether **2.27**



2.27

After following the representative protocol for alkylation of nitroalcohols using alcohol **2.33** (48 mg) and gold(III) chloride as the catalyst, the solution was stirred at room temperature for 2 h. The residue was purified by flash chromatography (silica gel, 1.5 cm diameter × 20 cm height; 1:9 diethyl ether:hexanes) to yield ether **2.27** (41 mg, 58%, dr 7:1) of a light yellow oil. Rf = 0.40 (1:9 ethyl acetate:hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) d 7.35 – 7.27 (m, 2H), 6.95 – 6.87 (m, 2H), 6.75 – 6.64 (m, 4H), 5.25 (d, *J* = 9.6 Hz, 1H), 4.76 (td, *J* = 11.0, 3.3 Hz, 1H), 3.80 (s, 3H), 3.69 (s, 3H), 1.83 (ddq, *J* = 14.4, 11.1, 7.2 Hz, 1H), 1.42 (dqd, *J* = 14.9, 7.5, 3.4 Hz, 1H), 0.89 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (101MHz, $CDCl_3$) d 160.4, 154.9, 151.3, 128.9, 128.2, 118.5, 114.6 , 114.5, 94.4, 82.9, 55.7, 55.4, 23.8, 10.3; IR (neat) 3041, 2997, 2931, 2837, 1611, 1551, 1504, 1461, 1250, 1213, 1175, 1033 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{21}NNaO_5$ $[M+Na]^+$ 354.13119, found $[M+Na]^+$ 354.13118.

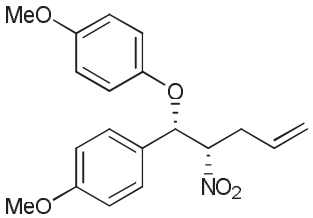
Ether **2.35**



2.35

After following the representative protocol for alkylation of nitroalcohols using alcohol **2.34** (50 mg) and gold(III) chloride as the catalyst, the solution was stirred at room temperature for 16 h. The residue was purified by flash chromatography (silica gel, 1.5 cm diameter × 20 cm height; 1:9 diethyl ether:hexanes) to yield ether **2.35** (34 mg, 49%, dr 11:1) of a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, J = 8.7 Hz, 2H), 6.94 (d, J = 8.2 Hz, 2H), 6.91 (d, J = 8.7 Hz, 2H), 6.69 (d, J = 8.6 Hz, 2H), 5.62 (dddd, J = 16.5, 10.3, 8.2, 5.8 Hz, 1H), 5.42 (d, J = 7.2 Hz, 0.02H), 5.37 (d, J = 9.5 Hz, 0.98H), 5.12 – 5.04 (m, 2H), 4.89 (ddd, J = 10.7, 9.6, 3.5 Hz, 1H), 3.80 (s, 2.88H), 3.78 (s, 0.12H), 2.52 (ddd, J = 14.8, 10.7, 8.3 Hz, 1H), 2.23 – 2.15 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.4, 155.1, 131.5, 130.8, 129.9, 128.9, 127.8, 120.0, 116.8, 114.7, 92.3, 81.4, 55.4, 34.7, 20.6; IR (neat) 2902, 2825, 1651, 1611, 1513, 1327, 1250, 1031; HRMS (ESI) calcd for $C_{19}H_{21}NNaO_4$ $[M+Na]^+$ 350.1369, found $[M+Na]^+$ 350.1417.

Ether **2.36**

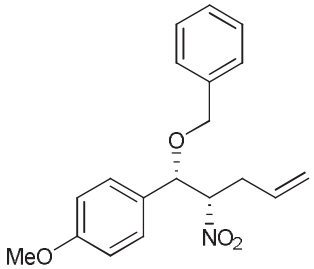


2.36

After following the representative protocol for alkylation of nitroalcohols using alcohol **2.34** (50 mg) and gold(III) chloride as the catalyst, the solution was stirred at room temperature for 16 h. The residue was purified by flash chromatography (silica gel, 1.5 cm diameter × 20 cm height; 1:9 diethyl ether:hexanes) to yield ether **2.36** (52 mg, 72%, dr 20:1) of a light yellow oil. Rf = 0.36 (1:9 ethyl acetate:hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.26 (m, 2H), 6.93 – 6.89 (m, 1.6H), 6.89 – 6.85 (m, 0.4H), 6.75 – 6.65

(m, J = 9.4, 6.7, 4.5 Hz, 4H), 5.76 (dddd, J = 16.2, 10.2, 8.2, 5.8 Hz, 0.2H), 5.61 (dddd, J = 16.2, 10.2, 8.2, 5.8 Hz, 0.8H), 5.35 (d, J = 7.2 Hz, 0.2H), 5.27 (d, J = 9.6 Hz, 0.8H), 5.20 – 5.12 (m, 0.4H), 5.07 (dd, J = 20.4, 5.0 Hz, 1.6H), 4.92 – 4.85 (m, 0.8H), 4.81 (ddd, J = 10.3, 7.2, 3.4 Hz, 0.2H), 3.80 (s, 2.4H), 3.78 (s, 0.6H), 3.71 (s, 0.6H), 3.69 (s, 2.4H), 2.55 – 2.45 (m, 1H), 2.20 – 2.13 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.5, 155.0, 151.3, 131.7, 130.8, 129.0, 128.4, 128.2, 127.8, 120.0, 119.7, 118.5, 117.6, 114.7, 114.7, 114.6, 114.5, 92.4, 82.6, 80.8, 55.7, 55.7, 55.4, 55.4, 34.7, 33.9; IR (neat) 2901, 2850, 1681, 1600, 1572, 1510, 1421, 1312, 1118; HRMS (ESI) calcd for $C_{19}H_{21}NNaO_5$ $[M+Na]^+$ 366.1318, found $[M+Na]^+$ 366.1375.

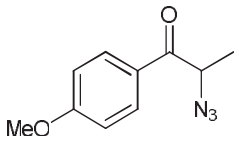
Ether **2.37**



2.37

After following the representative protocol for alkylation of nitroalcohols using alcohol **2.34** (50 mg) and gold(III) chloride as the catalyst, the solution was stirred at room temperature for 16 h. The residue was purified by flash chromatography (silica gel, 1.5 cm diameter × 20 cm height; 1:9 diethyl ether:hexanes) to yield ether **2.37** (52 mg, 76%, dr 20:1) of a light yellow oil. Rf = 0.39 (1:9 ethyl acetate:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 – 7.26 (m, 5H), 7.18 – 7.15 (m, 2H), 6.97 – 6.94 (m, 2H), 5.56 (dddd, J = 16.8, 10.2, 8.2, 5.8 Hz, 1H), 5.07 – 4.98 (m, 2H), 4.74 (ddd, J = 10.8, 9.7, 3.3 Hz, 1H), 4.66 (d, J = 9.7 Hz, 1H), 4.42 (d, J = 11.7 Hz, 1H), 4.20 (d, J = 11.7 Hz, 1H), 3.85 (s, 3H), 2.41 (ddd, J = 14.9, 10.8, 8.3 Hz, 1H), 2.04 (dddd, J = 14.9, 7.2, 3.1, 1.5 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.5, 137.2, 131.0, 129.3, 128.5, 128.0, 127.8, 119.7, 114.7, 92.5, 81.2, 70.5, 55.5, 34.8, 29.9; IR (neat) 2923, 2852, 1609, 1555, 1512, 1455, 1250, 1174; HRMS (ESI) calcd for $C_{19}H_{21}NNaO_4$ $[M+Na]^+$ 350.1369, found $[M+Na]^+$ 350.1296.

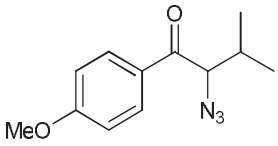
Azidoketone **2.41**



2.41

Sodium azide (1.6 g, 25 mmol, 3.0 equiv) was added to a solution of bromoketone **2.38** (2.0 g, 8.2 mmol, 1.0 equiv) in dry DMF (30 mL), at room temperature, and under argon atmosphere. The solution was stirred at this temperature for 2 h and then partitioned between diethyl ether (50 mL) and brine (30 mL). The organic layer was separated, washed with brine (5 × 20 mL), dried over magnesium sulfate, filtered, and concentrated. The residue was purified by flash column chromatography (silica gel, 3.5 ×20 cm; 1:4 ethyl acetate:hexanes) to yield azidoketone **2.41** (1.49 g, 89%); Rf = 0.43 (1:4 ethyl acetate:hexanes); ^{1}H NMR spectrum correspond to literature data.[2] ^{1}H NMR (400 MHz, CDCl3) d 7.99 – 7.87 (m, 2H), 7.03 – 6.91 (m, 2H), 4.65 (q, *J* = 7.0 Hz, 1H), 3.88 (s, 3H), 1.56 (d, *J* = 7.0 Hz, 3H); IR (neat) 2982, 2841, 2093, 1679, 1595, 1573, 1255, 1221, 1171, 1029 cm^{-1}.

Azidoketone **2.42**

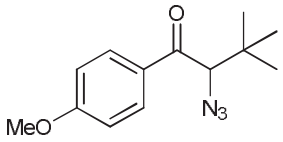


2.42

Sodium azide (0.52 g, 8.0 mmol, 2.5 equiv) was added to a solution of bromoketone **2.39** (estimated to be 3.25 mmol, 1.0 equiv) in dry DMF (30 mL), under argon atmosphere. The solution was stirred for 2-3 h and then partitioned between diethyl ether (50 mL) and brine (30 mL). The organic layer was separated, washed with brine (5 × 20 mL), dried over magnesium sulfate, filtered, and concentrated. The residue was purified by flash column chromatography (silica gel, 3.5 cm × 30 cm, 1:19 ethyl acetate:hexanes) to yield azidoketone **2.42** (0.58 g, 76% over 2 steps) as clear oil; Rf = 0.42 (1:9 ethyl acetate:hexanes); ^{1}H NMR (500 MHz, CDCl3) d 7.95 – 7.89 (m, 2H), 6.98 – 6.93 (m, 2H),

4.33 (d, J = 7.2 Hz, 1H), 3.87 (s, 3H), 2.37 – 2.26 (m, 1H), 1.03 (d, J = 6.7 Hz, 3H), 0.98 (d, J = 6.7 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) d 195.3, 164.2, 131.1, 128.5, 114.2, 68.8, 55.7, 31.1, 20.0, 18.4; IR (neat) 2957, 2928, 2861, 2849, 2098, 1676, 1600, 1578, 1514, 1472, 1265, 1220, 1173, 1031 cm^{-1}; HRMS (ESI) calcd for$C_{12}H_{16}N_3O_2$ $[M+H]^+$ 234.1237, found $[M+H]^+$ 234.122797 and calcd for $C_{12}H_{15}N_3NaO_2$ $[M+Na]^+$ 256.10565, found $[M+Na]^+$ 256.10577.

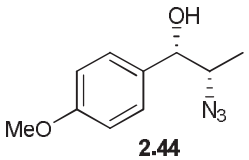
Azidoketone **2.43**



2.43

Sodium azide (1.6 g, 24.75 mmol, 3 equiv) was added to a solution of bromoketone **2.40** (estimated to be 8.25 mmol, 1.0 equiv) in dry DMF (33 mL), under argon atmosphere. The solution was stirred for 4 h and then partitioned between diethyl ether (50 mL) and brine (30 mL). The organic layer was separated, washed with brine (5 × 20 mL), dried over magnesium sulfate, filtered, and concentrated. The residue was purified by flash column chromatography (silica gel, 3.5 cm × 30 cm, 1:19 ethyl acetate:hexanes) to yield azidoketone **2.43** (1.4 g, 69%) as clear oil; Rf = 0.40 (1:9 ethyl acetate:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 – 7.95 (m, 2H), 6.97 – 6.93 (m, 2H), 5.10 (s, 1H), 3.88 (s, 3H), 1.21 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 193.0, 164.0, 131.1, 129.1, 114.1, 57.8, 55.7, 35.3, 27.6; IR (neat) 2957, 2932, 2868, 2100, 1671, 1597, 1509, 1365, 1307, 1171, 1089 cm^{-1}; HRMS (ESI) calcd for $C_{13}H_{17}N_3NaO_2$ $[M+Na]^+$ 270.1219, found $[M+Na]^+$ 270.1311.

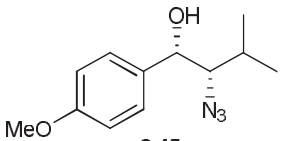
Azidoalcohol **2.44**



2.44

$NaBH_4$ (0.31 g, 8.2 mmol, 1.1equiv) was added to a solution of azidoketone **2.41** (1.5 g, 7.3 mmol, 1 equiv) in MeOH (30 mL) at room temperature. The solution was stirred at room temperature for 30 min. H_2O (30 mL) was slowly added and the methanol was removed under vacuum with a rotary evaporator. The aqueous mixture was extracted with diethyl ether (30 mL) then the layers were separated. The organic solution was washed with brine (2 × 15 mL), dried over sodium sulfate, filtered, and concentrated. The residue was filtered on a short pad (silica gel, 2.5 cm × 2 cm, 5V diethyl ether) to yield azidoalcohol **2.44** (1.5 g, 99%, dr 1.8:1 *syn*:*anti*) as an oil. Rf = 0.5 (3:7, ethyl acetate:hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.21 (m, 2H), 6.93 – 6.85 (m, 2H), 4.71 – 4.62 (m, 0.36H), 4.40 (dd, J = 7.6, 2.9 Hz, 0.64H), 3.80 (s, 3H), 3.74 – 3.57 (m, 1H), 2.42 (d, J = 2.9 Hz, 0.61H), 2.10 (d, J = 3.3 Hz, 0.34H), 1.18 (d, J = 6.7 Hz, 1.05H), 1.08 (d, J = 6.7 Hz, 1.95H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.81, 159.60, 132.51, 132.37, 128.11, 127.85, 114.14, 113.99, 77.92, 76.33, 63.80, 62.59, 55.43, 16.06, 13.98; IR (neat) 3409, 2963, 2935, 2902, 2839, 2101, 1611, 1586, 1552, 1512, 1463, 1443, 1246, 1175, 1032 cm^{-1}; HRMS (ESI) calcd for $C_{10}H_{13}N_3O_2$ $[M+Na]^+$ 230.09000, found $[M+Na]^+$ 230.09088.

Azidoalcohol **2.45**

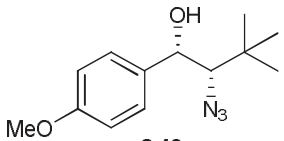


2.45

$NaBH_4$ (36 mg, 0.95 mmol, 1.1equiv) was added to a solution of azidoketone **2.42** (0.2 g, 0.86 mmol, 1 equiv) in MeOH (3 mL) at room temperature. The solution was stirred at room temperature for 30 min. H_2O (3 mL) was slowly added and the methanol was removed under vacuum with a rotary evaporator. The aqueous mixture was extracted with diethyl ether (5 mL) then the layers were separated. The organic solution was washed with brine (2 × 5 mL), dried over sodium sulfate, filtered, and concentrated. The residue was filtered on a short pad (silica gel, 2.5 cm × 2 cm, 5V diethyl ether) to yield azidoalcohol **2.45** (186 mg, 92%, dr 3.2:1 *syn*:*anti*) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$) d 7.40 – 7.31 (m, 1.5H), 7.30 – 7.24 (m,~0.5H), 6.95 – 6.84 (m, 2H), 4.68 – 4.61 (m, 1H), 3.81 (s, 2.21H),

3.81 (s, 0.7H), 3.41 (dd, J = 7.3, 4.9 Hz, 0.74H), 3.33 (dd, J = 7.3, 4.2 Hz, 0.23H), 2.31 (s, 0.2H), 2.09 – 1.93 (m, 1.46H), 1.68 – 1.57 (m, 0.5H), 1.05 (d, J = 6.8 Hz, 2.29H), 0.99 (d, J = 6.8 Hz, 0.73H), 0.96 (d, J = 6.7 Hz, 0.23H), 0.91 (d, J = 6.7 Hz, 0.7H); ^{13}C NMR (101 MHz, $CDCl_3$) d 159.8, 159.7, 133.4, 133.3, 128.5, 127.9, 114.24, 14.15, 75.19, 75.16, 74.4, 74.1, 55.4, 29.4, 29.2, 21.1, 20.8, 17.0, 16.8; IR (neat) 3418, 2982, 2964, 2937, 2104, 1615, 1589, 1517, 1389, 1370, 1342, 1302, 1249, 1178, 1035 cm^{-1}; HRMS (ESI) calcd for $C_{12}H_{17}N_3NaO_2$ $[M+Na]^+$ 258.1213, found $[M+Na]^+$ 258.12067.

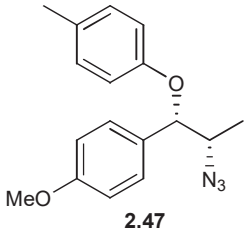
Azidoalcohol **2.46**



2.46

$NaBH_4$ (45 mg, 1.17 mmol, 1.1equiv) was added to a solution of azidoketone **2.43** (290 mg, 1.17 mmol, 1 equiv) in MeOH (5 mL) at room temperature. The solution was stirred at room temperature for 30 min. H_2O (3 mL) was slowly added and the methanol was removed under vacuum with a rotary evaporator. The aqueous mixture was extracted with diethyl ether (5 mL) then the layers were separated. The organic solution was washed with brine (2 × 5 mL), dried over sodium sulfate, filtered, and concentrated. The residue was filtered on a short pad (silica gel, 2.5 cm × 2 cm, 5V diethyl ether) to yield azidoalcohol **2.46** (277 mg, 95%, dr 6:1 *syn*:*anti*) as an oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 – 7.34 (m, 2H), 6.92 – 6.88 (m, 2H), 4.90 (dd, J = 7.4, 2.9 Hz, 0.16H), 4.78 (dd, J = 5.9, 3.2 Hz, 0.84H), 3.82 (s, 2.5H), 3.80 (s, 0.5H), 3.46 (d, J = 5.9 Hz, 1H), 0.97 (s, 1.5H), 0.93 (s, 7.5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.8, 134.1, 129.2, 127.2, 127.1, 114.2, 114.0, 114.0, 77.4, 77.3, 75.1, 55.4, 35.4, 30.3, 27.5, 27.4; IR (neat) 3417, 2956, 2866, 2839, 2107, 1677, 1598, 1574, 1509, 1462, 1419, 1395, 1313, 1171, 1029 cm^{-1}; HRMS (ESI) calcd for $C_{13}H_{19}N_3NaO_2$ $[M+Na]^+$ 272.1375, found $[M+Na]^+$ 272.1504.

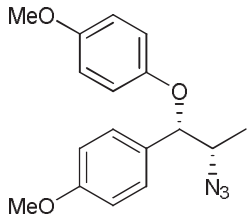
Ether **2.47**



2.47

After following the representative protocol for alkylation of azidoalcohols using alcohol **2.44** (50 mg) and gold(III) chloride as the catalyst, the solution was stirred at room temperature for 16 h. The residue was purified by flash chromatography (silica gel, 1.5 cm diameter × 20 cm height; 1:9 diethyl ether:hexanes) to yield ether **2.47** (43 mg, 61%, dr 5:1) of a light yellow oil. Rf = 0.23 (1:9 diethyl ethher:hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 – 7.29 (m, 0.33H), 7.24 – 7.19 (m, 1.67H), 7.06 – 7.01 (m, 1H), 6.95 – 6.90 (m, 1H), 6.88 – 6.81 (m, 2.5H), 6.74 (d, *J* = 2.1 Hz, 0.3H), 6.69 (d, *J* = 8.1 Hz, 0.85H), 6.61 (d, *J* = 8.1 Hz, 0.15H), 5.43 (s, 1H), 4.40 – 4.28 (m, 1H), 4.18 (d, *J* = 9.1 Hz, 0.15H), 4.12 (d, *J* = 9.1 Hz, 0.85H), 3.78 (s, 0.5H), 3.78 (s, 2.5H), 2.28 (s, 2.5H), 2.25 (s, 0.5H), 1.31 (dd, *J* = 6.4, 4.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.5, 153.4, 151.5, 150.9, 133.3, 133.1, 130.4, 130.2, 130.1, 129.8, 129.6, 129.5, 128.7, 128.6, 128.4, 127.6, 116.9, 116.2, 115.2, 114.2, 114.0, 60.6, 60.2, 55.4, 51.3, 50.3, 20.9, 20.6, 18.8, 18.5; IR (neat) 2914, 2858, 2100, 1615, 1542, 1504, 1437, 1241, 1188, 1033 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{19}N_3NaO_3$ M+Na]$^+$ 320.1375, found [M+Na]$^+$ 320.1321.

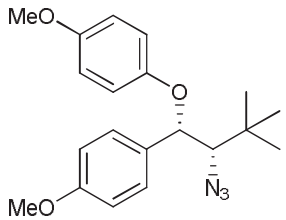
Ether **2.48**



2.48

After following the representative protocol for alkylation of azidoalcohols using alcohol **2.44** (50 mg) and gold(III) chloride as the catalyst, the solution was stirred at room temperature for 16 h. The residue was purified by flash chromatography (silica gel, 1.5 cm diameter × 20 cm height; 1:9 diethyl ether:hexanes) to yield ether **2.48** (50 mg, 67%, dr 1.2:1) of a colorless oil. Rf = 0.21 (1:9 diethyl ethher:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 – 7.28 (m, 0.4H), 7.22 – 7.18 (m, 1.6H), 6.86 – 6.81 (m, 3H), 6.67 (dd, *J* = 8.7, 3.0 Hz, 1H), 4.33 – 4.25 (m, 1H), 4.19 (d, *J* = 8.8 Hz, 0.0.15H), 4.12 (d, *J* = 9.2 Hz, 0.85H), 3.78 (s, 0.5H), 3.77 (s, 2.5H), 3.75 (s, 2.5H), 3.73 (s, 0.5H), 1.32 (d, *J* = 6.4 Hz, 0.5H), 1.30 (d, *J* = 6.4 Hz, 2.5H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.6, 154.0, 153.9, 147.7, 147.2, 132.8, 132.7, 129.8, 129.5, 129.4, 117.7, 116.9, 116.2, 115.7, 115.4, 115.0, 114.2, 114.1, 112.5, 112.1, 60.8, 60.1, 55.8, 55.4, 51.0, 50.2, 29.8, 18.8, 18.5; IR (neat) 2928, 2835, 2102, 1608, 1554, 1508, 1431, 1246, 1178, 1033 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{19}N3NaO_3$ M+Na]$^{+}$ 336.1324, found [M+Na]$^{+}$ 336.1273.

Ether **2.49**

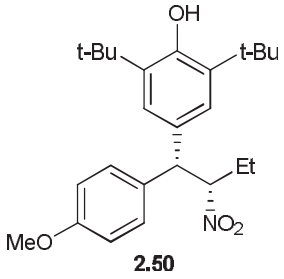


2.49

After following the representative protocol for alkylation of azidoalcohols using alcohol **2.46** (30 mg) and gold(III) chloride as the catalyst, the solution was stirred at room temperature for 16 h. The residue was purified by flash chromatography (silica gel, 1.5 cm diameter × 10 cm height; 1:19 diethyl ether:hexanes) to yield ether **2.49** (28 mg, 65%, dr 5:1) of a colorless oil. Rf = 0.20 (1:9 diethyl ethher:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$)

δ 7.41 – 7.38 (m, 0.4H), 7.35 – 7.32 (m, 1.6H), 6.94 – 6.90 (m, 1.6H), 6.89 – 6.86 (m, 0.4H), 6.79 – 6.73 (m, 4H), 5.30 (d, *J* = 2.7 Hz, 0.8H), 5.07 (d, *J* = 6.7 Hz, 0.2H), 3.82 (s, 2.4H), 3.82 (s, 0.6H), 3.73 (s, 2.4H), 3.73 (s, 0.6H), 3.59 (d, *J* = 6.7 Hz, 0.2H), 3.20 (d, *J* = 2.7 Hz, 0.8H), 1.10 (s, 7.2H), 1.02 (s, 1.8H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.6, 159.5, 154.1, 151.6, 131.9, 131.0, 130.7, 129.4, 127.8, 117.1, 116.6, 114.69 (s), 114.66, 114.3, 114.02, 114.00, 80.6, 79.6, 77.6, 55.8, 55.4, 55.3, 42.5, 36.6, 35.6, 29.8, 29.0, 27.9, 27.5, 26.6; IR (neat) 2998, 2922, 2113, 1638, 1610, 1584, 1440, 1300, 1109, 1033 cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{25}N_3NaO_3$ M+Na]$^+$ 378.1794, found [M+Na]$^+$ 378.1752.

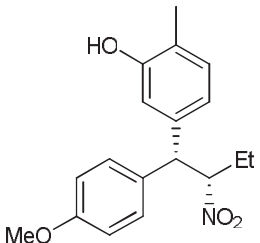
Diaryl **2.50**



2.50

After following the representative protocol for alkylation of nitroalcohols using alcohol **2.33** (50 mg) and gold(III) chloride as the catalyst, the solution was stirred at room temperature for 16 h. The residue was purified by flash chromatography (silica gel, 1.5 cm diameter × 20 cm height; 1:9 ethyl acetate:hexanes) to yield diaryl **2.50** (52 mg, 62%, dr 20:1) of a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (d, *J* = 8.7 Hz, 2H), 7.06 (s, 2H), 6.85 (d, *J* = 8.7 Hz, 2H), 5.12 (td, *J* = 11.0, 3.0 Hz, 1H), 4.27 (d, *J* = 11.5 Hz, 1H), 3.83 (s, 0.16H), 3.77 (s, 2.84H), 1.86(m, 1H), 1.67 (m, 1H), 1.41 (s, 0.7H), 1.39 (s, 17.3H), 0.92 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.8, 153.0, 136.0, 132.7, 130.7, 129.1, 124.0, 114.5, 94.1, 55.4, 54.9, 34.5, 30.4, 26.7, 10.6; IR (neat) 3406, 2854, 2832, 2814, 1638, 1610, 1580, 1454, 1357, 1225, 1124 cm^{-1}; HRMS (ESI) calcd for $C_{25}H_{35}NNaO_4$ M+Na]$^+$ 436.2464, found [M+Na]$^+$ 436.2479.

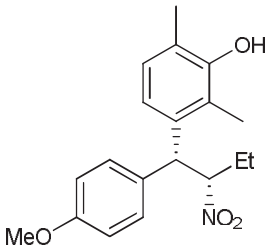
Diaryl **2.51**



2.51

After following the representative protocol for alkylation of nitroalcohols using alcohol **2.33** (50 mg) and gold(III) chloride as the catalyst, the solution was stirred at room temperature for 16 h. The residue was purified by flash chromatography (silica gel, 1.5 cm diameter × 20 cm height; 1:9 ethyl acetate:hexanes) to yield diaryl **2.51** (55 mg, 72%, dr 12:1) of a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 – 7.21 (m, 0.05H), 7.20 – 7.16 (m, 1.95H), 7.04 – 7.00 (m, 2H), 6.88 – 6.84 (m, 1.93H), 6.83 – 6.79 (m, 0.07H), 6.67 (d, J = 8.2 Hz, 0.06H), 6.61 (t, J = 5.3 Hz, 0.94H), 5.13 (td, J = 10.8, 3.1 Hz, 1H), 5.00 (s, 1H), 4.41 (d, J = 11.6 Hz, 0.01H), 4.28 (d, J = 11.5 Hz, 0.99H), 3.77 (s, 2.9H), 3.74 (s, 0.1H), 2.21 (s, 0.1H), 2.16 (s, 2.9H), 1.93 – 1.81 (m, 1H), 1.78 – 1.68 (m, 1H), 0.99 (t, J = 7.4 Hz, 0.03H), 0.93 (t, J = 7.4 Hz, 2.97H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.8, 153.2, 132.2, 132.2, 130.3, 129.0, 125.7, 124.4, 115.3, 114.6, 94.0, 55.4, 54.1, 26.5, 16.0, 10.5; IR (neat) 3433, 2972, 2934, 2879, 2837, 1608, 1584, 1545, 1508, 1249, 1178, 1030; HRMS (ESI) calcd for $C_{18}H_{21}NNaO_4$ $[M+Na]^+$ 338.1369, found $[M+Na]^+$ 338.1395.

Diaryl **2.52**

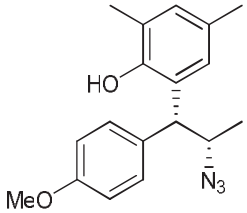


2.52

After following the representative protocol for alkylation of nitroalcohols using alcohol **2.33** (50 mg) and gold(III) chloride as the catalyst, the solution was stirred at room temperature for 16 h. The residue was purified by flash chromatography (silica gel, 1.5 cm diameter × 20 cm height; 1:9 ethyl acetate:hexanes) to yield diaryl **2.52** (51 mg, 71%, dr

20:1) of a white oil. Rf = 0.15 (1:9 ethyl acetate:hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 – 7.18 (m, 2H), 6.92 (d, *J* = 8.6 Hz, 1H), 6.85 – 6.77 (m, 2H), 6.60 (d, *J* = 8.6 Hz, 1H), 5.45 (s, 0.8H), 5.19 (ddd, *J* = 11.7, 10.6, 3.1 Hz, 1H), 4.79 (d, *J* = 11.8 Hz, 1H), 3.83 (s, 3H), 3.80 (s, 3H), 3.75 (s, 3H), 1.89 (ddq, *J* = 14.5, 10.4, 7.2 Hz, 1H), 1.73 (dqd, *J* = 14.9, 7.5, 3.2 Hz, 1H), 0.93 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.8, 147.1, 145.0, 139.0, 131.9, 129.6, 126.8, 116.3, 114.4, 106.2, 92.8, 60.5, 56.2, 55.4, 47.3, 26.7, 10.6; IR (neat) 3491, 2936, 2838, 1609, 1548, 1511, 1496, 1319, 1247, 1088; HRMS (ESI) calcd for $C_{19}H_{23}NNaO_4$ $[M+Na]^+$ 352.1525, found $[M+Na]^+$ 258.12067.

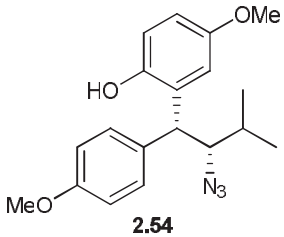
Diaryl **2.53**



2.53

After following the representative protocol for alkylation of azidoalcohols using alcohol **2.44** (50 mg) and *p*-TsOH•H_2O as the catalyst, the solution was stirred at room temperature for 16 h. The residue was purified by flash chromatography (silica gel, 1.5 cm diameter × 20 cm height; 1:9 ethyl acetate:hexanes) to yield diaryl **2.53** (43 mg, 58%, dr 6:1) of a colorless oil. Rf = 0.12 (1:9 ethyl acetate:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 – 7.27 (m, 0.33H), 7.23 – 7.17 (m, 1.67H), 6.90 (d, *J* = 1.6 Hz, 0.85H), 6.88 – 6.80 (m, 3.15H), 5.25 (s, 0.8H), 4.35 – 4.26 (m, 1H), 4.18 (d, *J* = 8.8 Hz, 0.15H), 4.12 (d, *J* = 9.1 Hz, 0.85H), 3.78 (s, 0.5H), 3.78 (s, 2.5H), 2.25 (s, 2.5H), 2.23 (s, 0.5H), 2.19 (s, 2.5H), 2.17 (s, 0.5H), 1.32 – 1.28 (m, *J* = 9.5, 6.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.5, 149.9, 133.1, 130.3, 123.0, 129.8, 129.6, 129.5, 127.6, 127.4, 127.1, 124.6, 114.2, 114.1, 60.7, 60.2, 55.3, 51.1, 50.3, 20.9, 18.8, 18.6, 16.3, 16.1; IR (neat) 3423, 2925, 2100, 1685, 1607, 1582, 1509, 1482, 1454, 1377, 1301, 1245, 1178, 1123, 1033 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{21}N_3NaO_2$ $[M+Na]^+$ 334.1532, found $[M+Na]^+$ 334.1689.

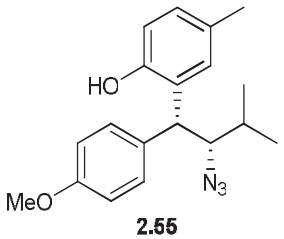
Diaryl **2.54**



2.54

After following the representative protocol for alkylation of azidoalcohols using alcohol **2.45** (50 mg) and *p*-TsOH•H_2O as the catalyst, the solution was stirred at room temperature for 16 h. The residue was purified by flash chromatography (silica gel, 1.5 cm diameter × 20 cm height; 1:9 ethyl acetate:hexanes) to yield diaryl **2.54** (60 mg, 84%, dr 5:1) of a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 – 7.38 (m, 0.33H), 7.24 (dd, *J* = 6.8, 5.0 Hz, 1.67H), 6.90 (d, *J* = 2.7 Hz, 0.8H), 6.87 – 6.83 (m, 2H), 6.80 (d, *J* = 2.4 Hz, 0.2H), 6.75 (s, 0.3H), 6.73 (s, 0.5H), 6.67 (d, *J* = 3.0 Hz, 0.5H), 6.66 (d, *J* = 3.0 Hz, 0.3H), 5.59 (s, 0.8H), 4.40 (d, *J* = 9.7 Hz, 1H), 4.05 (dd, *J* = 9.7, 3.8 Hz, 0.2H), 3.97 (dd, *J* = 9.6, 4.1 Hz, 0.8H), 3.77 (s, 2.5H), 3.76 (s, 0.5H), 3.75 (s, 2.5H), 3.74 (s, 0.5H), 1.91 – 1.76 (m, 1H), 1.07 – 1.03 (m, 3H), 0.97 (d, *J* = 6.7 Hz, 2.5H), 0.93 (d, *J* = 6.7 Hz, 0.5H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.5, 153.9, 147.7, 147.0, 133.5, 132.9, 130.0, 129.9, 129.5, 129.5, 117.7, 116.6, 116.2, 115.6, 115.0, 114.3, 114.1, 112.7, 111.9, 73.1, 72.0, 66.0, 56.2, 55.3, 47.5, 47.3, 30.9, 30.7, 21.3, 21.1, 16.3, 16.1, 15.3; IR (neat) 3418, 2895, 2807, 2102, 1673, 1640, 1587, 1499, 1482, 1454, 1357, 1318, 1267, 1178, 1124, 1033 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{23}N_3NaO_3$ $[M+Na]^+$ 364.1637, found $[M+Na]^+$ 364.1704.

Diaryl **2.55**

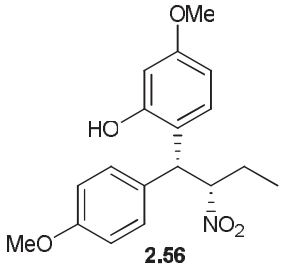


2.55

After following the representative protocol for alkylation of azidoalcohols using alcohol **2.45** (50 mg) and *p*-TsOH•H_2O as the catalyst, the solution was stirred at room temperature

for 16 h. The residue was purified by flash chromatography (silica gel, 1.5 cm diameter × 20 cm height; 1:9 ethyl acetate:hexanes) to yield diaryl **2.55** (52 mg, 76%, dr 7:1) of a white solid. m.p.: 112 to 113 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 – 7.37 (m, 3H), 7.26 – 7.22 (m, 1.7H), 7.09 (d, *J* = 1.8 Hz, 0.85H), 7.01 (d, *J* = 1.9 Hz, 0.15H), 6.91 (dd, *J* = 8.1, 2.1 Hz, 0.85H), 6.87 – 6.83 (m, 2.15H), 6.70 (d, *J* = 8.1 Hz, 0.85H), 6.58 (d, *J* = 8.1 Hz, 0.15H), 5.66 (s, 0.6H), 4.37 (dd, *J* = 9.7, 4.0 Hz, 1H), 4.09 (dd, *J* = 9.9, 3.7 Hz, 0.15H), 3.98 (dd, *J* = 9.4, 4.6 Hz, 0.85H), 3.78 (s, 0.5H), 3.78 (s, 2.5H), 2.27 (s, 2.5H), 2.26 (s, 0.5H), 1.89 – 1.83 (m, 0.15H), 1.83 – 1.72 (m, 0.85H), 1.08 – 1.02 (m, 3H), 0.98 (d, *J* = 6.7 Hz, 2.5H), 0.91 (d, *J* = 6.7 Hz, 0.5H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.5, 151.5, 150.6, 133.9, 133.2, 130.4, 130.3, 129.9, 129.7, 129.5, 128.7, 128.5, 128.2, 127.6, 116.9, 116.0, 114.3, 114.1, 73.0, 72.0, 66.0, 55.4, 48.1, 47.5, 30.9, 30.7, 29.8, 21.3, 21.1, 20.9, 16.6, 16.0, 15.4; IR (neat) 3402, 2963, 2930, 2873, 2096, 1670, 1573, 1541, 1462, 1482, 1454, 1357, 1388, 1225, 1141, 1135, 1028 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{23}N_3NaO_2$ $[M+Na]^+$ 348.1688, found $[M+Na]^+$ 348.1651.

Diaryl **2.56**

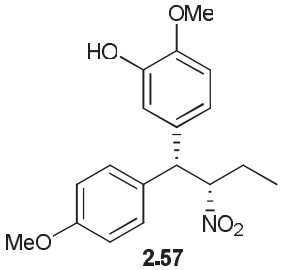


2.56

After following the representative protocol for alkylation of nitroalcohols using alcohol **2.33** (30 mg) and gold(III) chloride as the catalyst, the solution was stirred at room temperature for 5 h. The residue was purified by flash chromatography (silica gel, 1.5 cm diameter × 15 cm height; 1:9 diethyl ether:hexanes) to yield diaryl **2.56** (37 mg, 76%, dr 20:1) of a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 – 7.17 (m, 3H), 6.85 – 6.76 (m, 2H), 6.46 – 6.21 (m, 2H), 5.30 (ddd, *J* = 24.7, 12.4, 2.7 Hz, 1H), 4.70 (dd, *J* = 11.6, 3.5 Hz, 1H), 3.76 (s, 3H), 3.73 (s, 1.5H), 3.67 (s, 1.5H), 1.87 (dtt, *J* = 21.4, 14.5, 7.3 Hz, 1H), 1.78 – 1.65 (m, 1H), 0.92 (q, *J* = 7.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.7, 158.8,

158.6, 158.1, 156.1, 154.1, 149.0, 132.0, 131.8, 129.60, 129.57, 129.0, 128.3, 127.8, 124.4, 121.0, 119.6, 114.4, 114.2, 114.2, 107.2, 106.5, 106.4, 102.9, 102.8, 99.9, 93.6, 92.66, 92.64, 55.7 , 55.38, 55.36, 55.3, 48.0, 47.9, 31.7, 30.2, 29.8, 26.7, 26.3, 14.3, 10.59, 10.54; IR (neat) 3428, 2924, 2918, 1637, 1611, 1559, 1495, 1457, 1374, 1305, 1157, 1117, 1033 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{22}NO_5$ $[M+H]^+$ 332.1498, found $[M+H]^+$ 332.1425.

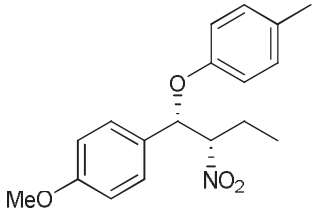
Diaryl **2.57**



2.57

After following the representative protocol for alkylation of nitroalcohols using alcohol **2.33** (30 mg) and gold(III) chloride as the catalyst, the solution was stirred at room temperature for 5 h. The residue was purified by flash chromatography (silica gel, 1.5 cm diameter × 15 cm height; 1:9 diethyl ether:hexanes) to yield diaryl **2.57** (37 mg, 84%, dr 4:1) of a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.19 – 7.16 (m, 2H), 6.88 – 6.73 (m, 5H), 5.56 (s, 0.25H), 5.51 (s, 0.75H), 5.15 – 5.07 (m, 1H), 4.29 (dd, *J* = 16.4, 8.0 Hz, 1H), 3.84 (s, 2.4H), 3.81 (s, 0.6H), 3.77 (s, 2.4H), 3.76 (s, 0.6H), 1.94 – 1.81 (m, 1H), 1.72 (dqd, *J* = 14.9, 7.5, 3.0 Hz, 1H), 0.95 – 0.90 (m, *J* = 7.4, 2.8 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.9, 158.9, 146.7, 145.88, 145.85, 145.0, 133.5, 132.2, 132.04, 131.98, 129.1, 128.5, 119.9, 118.9, 114.8, 114.6, 114.4, 113.8, 110.9, 110.4, 93.9, 93.8, 56.02, 55.97, 55.4, 54.5, 54.3, 26.6, 26.5, 10.5; IR (neat) 3421, 2929, 2905, 1618, 1571, 1499, 1456, 1417, 1314, 1129, 1102, 1031 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{22}NO_5$ $[M+H]^+$ 332.1498, found $[M+H]^+$ 332.1466.

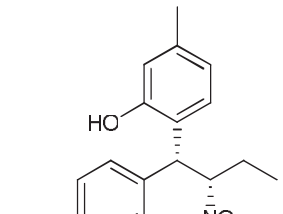
Ether **2.29**



2.29

After following the representative protocol for alkylation using alcohol **2.33** (30 mg) and gold(III) chloride as the catalyst, the solution was stirred at room temperature for 4 h. The residue was purified by flash chromatography (silica gel, 1.5 cm diameter × 20 cm height; 1:9 diethyl ether:hexanes) to yield ether **2.29** (16 mg, 57%, dr >20:1) of a colorless oil. R_f = 0.52 (1:4 diethyl ether:hexanes); ^{1}HNMR (300 MHz, $CDCl_3$) d 7.36 – 7.29 (m, 2H), 6.97 – 6.92 (m, 2H), 6.92 – 6.87 (m, 2H), 6.75 – 6.61 (m, 2H), 5.34 (d, *J* = 9.6 Hz, 1H), 4.76 (ddd, *J* = 11.1, 9.6, 3.4 Hz, 1H), 3.79 (s, 3H), 2.20 (s, 3H), 1.85 (ddq, *J* = 14.4, 11.0, 7.2 Hz, 1H), 1.43 (dqd, *J* = 14.7, 7.4, 3.4 Hz, 1H), 0.89 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) d 160.3, 155.1, 131.4, 129.9, 128.8, 128.1, 116.8, 114.6, 94.4, 81.7, 55.4, 23.8, 20.6, 10.3; IR (neat) 2980, 2932, 2846, 1615, 1556, 1513, 1255, 1232, 1178, 1035 cm^{-1} ; HRMS (ESI) calcd for $C_{18}H_{25}N_2O_4$ $[M+NH_4]^+$ 333.18088, found $[M+NH_4]^+$ 333.18044 and calcd for $C_{18}H_{21}NNaO_4$ $[M+Na]^+$ 338.13628, found $[M+Na]^+$ 338.13592.

Diaryl **2.58**

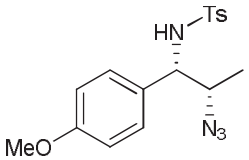


2.58

After following the representative protocol for alkylation of nitroalcohols using alcohol **2.33** (40 mg) and gold(III) chloride as the catalyst, the solution was stirred at room temperature for 5 h. The residue was purified by flash chromatography (silica gel, 1.5 cm diameter × 15 cm height; 1:9 diethyl ether:hexanes) to yield diaryl **2.58** (42 mg, 71%, dr

20:1) of a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (d, J = 8.4 Hz, 1H), 7.17 (d, J = 8.6 Hz, 2H), 6.83 (d, J = 8.6 Hz, 2H), 6.63 (dd, J = 8.4, 2.4 Hz, 1H), 6.55 (d, J = 2.3 Hz, 1H), 5.14 (td, J = 11.0, 3.0 Hz, 1H), 4.56 (d, J = 11.4 Hz, 1H), 3.76 (s, 2.9H), 3.73 (s, 0.1H), 2.32 (s, 0.1H), 2.25 (s, 2.9H), 1.87 (ddq, J = 14.5, 10.5, 7.3 Hz, 1H), 1.69 (dqd, J = 14.8, 7.4, 3.1 Hz, 1H), 0.92 (t, J = 7.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.8, 154.5, 138.2, 131.1, 130.7, 129.7, 126.3, 118.1, 114.5, 113.1, 93.4, 55.4, 49.3, 26.8, 19.9, 10.5; IR (neat) 3405, 2975, 2944, 2861, 1635, 1540, 1456, 1249, 1216, 1136, 1033 cm^{-1} ; HRMS (ESI) calcd for $C_{18}H_{25}N_2O_4$ $[M+NH_4]^+$ 333.1809, found $[M+NH_4]^+$ 333.1783 and calcd for $C_{18}H_{21}NNaO_4$ $[M+Na]^+$ 338.13628, found $[M+Na]^+$ 338.13654.

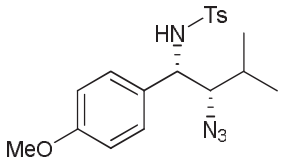
Azidosulfonamide **2.59**



2.59

After following the representative protocol for alkylation of azidoalcohols using alcohol **2.44** (30 mg) and *p*-TsOH•H_2O (20 mol%) as the catalyst, the solution was stirred at room temperature for 3 days. The residue was purified by flash chromatography (silica gel, 1.5 cm diameter × 20 cm height; 1:4 to 3:7 ethyl acetate:hexanes) to yield sulfonamide **2.59** (26mg, 70%, dr 5:1) of a white solid. m.p.: 98 to 100 °C; R_f = 0.35 (3:7 ethyl acetate:hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) d 7.55 – 7.44 (m, 2H), 7.09 (d, J = 8.0 Hz, 2H), 6.99 – 6.89 (m, 2H), 6.71 – 6.63 (m, 2H), 5.53 (d, J = 8.4 Hz, 0.18H), 5.46 (d, J = 6.8 Hz, 0.81H), 4.23 (dd, J = 8.4, 4.8 Hz, 0.18H), 4.16 (dd, J = 6.3 Hz, 0.82H), 3.79 – 3.56 (m, 4H), 2.34 (s, 3H), 1.19 (d, J = 6.6 Hz, 2.5H), 1.10 (d, J = 6.7 Hz, 0.59H). ^{13}C NMR (75 MHz, $CDCl_3$) d 159.41, 159.36, 143.24, 143.18, 137.44, 137.42, 129.9, 129.8, 129.43, 129.37, 129.0, 128.4, 128.1, 127.2, 127.1, 113.9, 113.8, 62.1, 61.5, 61.2, 60.9, 55.4, 21.6, 16.7, 16.1; IR (neat) 3282, 2928, 2859, 2113, 1616, 1517, 1444, 1326, 1253, 1161, 1094, 1035 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{20}N_4NaO_3S$ $[M+Na]^+$ 383.11483, found $[M+Na]^+$ 383.11623.

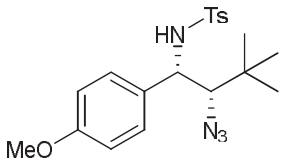
Azidosulfonamide **2.60**



2.60

After following the representative protocol for alkylation of azidoalcohols using alcohol **2.45** (57 mg) and *p*-TsOH•H_2O (20 mol%) as the catalyst, the solution was stirred at room temperature for 16 h. The residue was purified by flash chromatography (silica gel, 1.5 cm diameter × 20 cm height; 3:17 ethyl acetate:hexanes) to yield sulfonamide **2.60** (56mg, 59%, dr 3.5:1) of a white oil. R_f = 0.20 (3:17 ethyl acetate:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (d, *J* = 8.3 Hz, 0.5H), 7.47 (d, *J* = 8.3 Hz, 1.5H), 7.09 (d, *J* = 8.1 Hz, 0.5H), 7.05 (d, *J* = 8.1 Hz, 1.5H), 6.96 (d, *J* = 8.7 Hz, 0.5H), 6.92 (d, *J* = 8.7 Hz, 1.5H), 6.68 – 6.62 (m, 2H), 5.44 (d, *J* = 8.9 Hz, 0.2H), 5.37 (d, *J* = 8.7 Hz, 0.8H), 4.53 (dd, *J* = 8.7, 4.7 Hz, 0.8H), 4.36 (dd, *J* = 8.9, 5.9 Hz, 0.2H), 3.73 (s, 2.4H), 3.73 (s, 0.6H), 3.35 (dd, *J* = 7.1, 6.0 Hz, 0.2H), 3.15 (dd, *J* = 7.1, 4.7 Hz, 0.8H), 2.34 (s, 0.6H), 2.32 (s, 2.4H), 1.77 (td, *J* = 13.7, 6.9 Hz, 0.8H), 1.69 (td, *J* = 13.7, 6.9 Hz, 0.2H), 1.00 (d, *J* = 6.7 Hz, 2.4H), 0.97 – 0.94 (m, 3H), 0.92 (d, *J* = 6.6 Hz, 0.6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.4, 159.2, 143.2, 143.0, 137.8, 137.5, 130.5, 129.5, 129.3, 129.1, 129.0, 128.0, 127.2, 127.1, 114.0, 113.9, 75.3, 73.8, 58.4, 58.3, 55.4, 55.3, 30.5, 30.2, 29.8, 21.5, 20.2, 20.1, 18.4, 18.2; IR (neat) 3257, 2901, 2857,2112, 1617, 1539, 1467, 1324, 1165, 1053 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{24}N_4NaO_3S$ $[M+Na]^+$ 411.1467, found $[M+Na]^+$ 411.1429.

Azidosulfonamide **2.61**

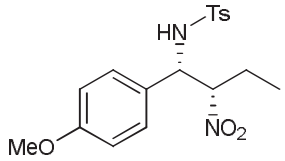


2.61

After following the representative protocol for alkylation of azidoalcohols using alcohol **2.46** (50 mg) and *p*-TsOH•H_2O (20 mol%) as the catalyst, the solution was stirred at room temperature for 16 h. The residue was purified by flash chromatography (silica gel, 1.5 cm

diameter × 20 cm height; 3:17 ethyl acetate:hexanes) to yield sulfonamide **2.61** (55mg, 68%, dr 20:1) of a white oil. R_f = 0.40 (3:7 ethyl acetate:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.3 Hz, 2H), 7.16 (d, *J* = 7.9 Hz, 2H), 7.01 (d, *J* = 8.8 Hz, 2H), 6.65 (d, *J* = 8.8 Hz, 2H), 4.89 (d, *J* = 7.9 Hz, 1H), 4.44 (dd, *J* = 7.8, 3.6 Hz, 1H), 3.74 (s, 3H), 3.62 (d, *J* = 3.5 Hz, 1H), 2.38 (s, 3H), 0.75 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.5, 143.4, 137.4, 129.9, 129.8, 129.6, 127.3, 113.9, 58.2, 55.3, 36.4, 27.2, 21.6; IR (neat) 3267, 2915, 2879, 2106, 1624, 1549, 1462, 1307, 1252, 1033 cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{26}N_4NaO_3S$ $[M+Na]^+$ 425.1624, found $[M+Na]^+$ 425.1602.

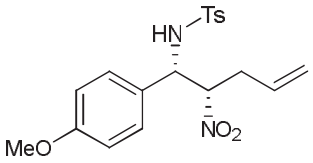
Nitrosulfonamide **2.62**



2.62

After following the representative protocol for alkylation of nitroalcohols using alcohol **2.33** (50 mg) and gold(III) chloride as the catalyst, the solution was stirred at room temperature for 16 h. The residue was purified by flash chromatography (silica gel, 1.5 cm diameter × 20 cm height; 1:4 ethyl acetate:hexanes) to yield sulfonamide **2.62** (64mg, 77%, dr 20:1) of a white oil. R_f = 0.42 (3:7 ethyl acetate:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 (d, *J* = 8.3 Hz, 2H), 7.10 (d, *J* = 8.0 Hz, 2H), 6.91 – 6.86 (m, 2H), 6.71 – 6.67 (m, 2H), 5.62 (d, *J* = 9.3 Hz, 1H), 4.74 (dd, *J* = 9.6, 6.9 Hz, 1H), 4.60 – 4.54 (m, 1H), 3.74 (s, 2.85H), 3.73 (s, 0.15H), 2.36 (s, 2.85H), 2.34 (s, 0.15H), 0.93 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.5, 137.4, 129.5, 127.8, 127.1, 114.5, 94.2, 58.9, 55.4, 25.0, 21.6, 10.3; IR (neat) 3264, 2922, 2849,1611, 1555, 1515, 1456, 1373, 1324, 1162, 1032 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{33}N_2NaO_5S$ $[M+Na]^+$ 401.1147, found $[M+Na]^+$ 401.1237.

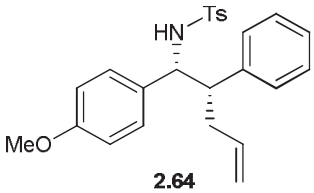
Nitrosulfonamide **2.63**



2.63

After following the representative protocol for alkylation of nitroalcohols using alcohol **2.34** (30 mg) and gold(III) chloride as the catalyst, the solution was stirred at room temperature for 16 h. The residue was purified by flash chromatography (silica gel, 1.5 cm diameter × 20 cm height; 1:4 ethyl acetate:hexanes) to yield sulfonamide **2.63** (36mg, 71%, dr 20:1) of a white oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (d, J = 8.4 Hz, 2H), 7.09 (d, J = 8.1 Hz, 2H), 6.93 – 6.86 (m, 2H), 6.70 – 6.63 (m, 2H), 5.86 (d, J = 9.4 Hz, 1H), 5.70 – 5.54 (m, 1H), 5.13 (s, 1H), 5.08 (d, J = 5.9 Hz, 1H), 4.80 – 4.65 (m, 2H), 3.73 (s, 3H), 2.73 – 2.59 (m, 1H), 2.44 – 2.31 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.8, 143.5, 137.2, 130.6, 129.5, 127.9, 127.5, 127.2, 120.5, 114.5, 92.0, 59.0, 55.4, 35.6, 21.6; IR (neat) 3241, 3027, 2922,1638,1614, 1510, 1440, 1246, 1174, 1034 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{22}N_2NaO_5S$ $[M+Na]^+$ 413.1147, found $[M+Na]^+$ 413.1162.

Phenylsulfonamide **2.64**

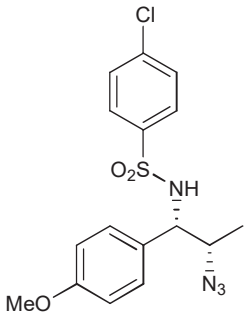


2.64

After following the representative protocol for alkylation of nitroalcohols with sulfonamide using alcohol **2.14c** (22 mg) and *p*-TsOH•H_2O as the catalyst, the solution was stirred at room temperature for 16 h. The residue was purified by flash chromatography (silica gel, 1.5 cm diameter × 20 cm height; 1:9 ethyl acetate:hexanes) to yield sulfonamide **2.64** (29mg, 80%, dr 5:1) of a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 – 7.40 (m, 0.33H), 7.33 – 7.29 (m, 1.7H), 7.25 – 7.22 (m, 2H), 7.15 (dd, J = 5.0, 1.8 Hz, 0.33H), 7.05 – 7.01 (m, 2H), 6.97 – 6.94 (m, 1.67H), 6.87 – 6.83 (m, 2H), 6.68 – 6.64 (m, 2H), 6.50 (s,

1H), 5.64 – 5.55 (m, 0.15H), 5.45 (ddt, *J* = 17.2, 10.3, 7.0 Hz, 0.85H), 5.02 – 4.92 (m, 0.3H), 4.86 – 4.78 (m, 1.7H), 4.55 (d, *J* = 5.6 Hz, 0.85H), 4.50 (dd, *J* = 8.9, 6.7 Hz, 0.15H), 4.38 (dd, *J* = 7.7, 5.7 Hz, 0.85H), 3.76 (s, 2.5H), 3.69 (s, 0.5H), 3.06 (dt, *J* = 9.4, 6.3 Hz, 0.15H), 2.82 (td, *J* = 8.5, 5.8 Hz, 0.85H), 2.59 (dt, *J* = 13.5, 6.7 Hz, 0.15H), 2.34 (s, 2.5H), 2.31 (s, 0.5H), 2.29 – 2.17 (m, 1.85H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.02, 142.93, 142.86, 139.1, 137.3, 136.2, 135.7, 131.7, 129.4, 129.3, 129.2, 128.9, 128.8, 128.7, 128.2, 127.5, 127.3, 127.13, 127.06, 117.1, 113.6, 113.1, 61.3, 61.1, 55.35, 55.27, 52.5, 51.6, 36.8, 36.4, 21.6; IR (neat) 3274, 2924, 2836, 1611, 1513, 1438, 1417, 1321, 1248, 1157, 1033 cm^{-1}; HRMS (ESI) calcd for $C_{25}H_{27}NNaO_3S$ $[M+Na]^+$ 444.1610, found $[M+Na]^+$ 444.1524.

Azidosulfonamide **2.65**

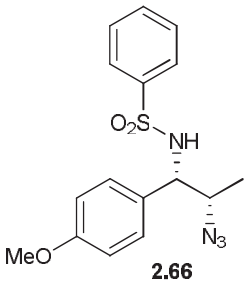


2.65

After following the representative protocol for alkylation of azidoalcohols using alcohol **2.44** (50 mg) and gold(III) chloride as the catalyst, the solution was stirred at room temperature for 16 h. The residue was purified by flash chromatography (silica gel, 1.5 cm diameter × 20 cm height; 1:9 ethyl acetate:hexanes) to yield sulfonamide **2.65** (70mg, 77%, dr 6:1) of a colorless oil. R_f = 0.15 (1:9 ethyl acetate:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 – 7.51 (m, 2H), 7.27 – 7.23 (m, *J* = 8.7, 2.2 Hz, 2H), 6.95 – 6.91 (m, 2H), 6.70 – 6.67 (m, 2H), 5.76 (d, *J* = 8.7 Hz, 0.15H), 5.67 (d, *J* = 6.1 Hz, 0.85H), 4.30 (dd, *J* = 7.9, 4.6 Hz, 0.15H), 4.22 (t, *J* = 5.7 Hz, 0.85H), 3.93 – 3.89 (m, 0.15H), 3.77 (s, 3H), 3.69 (p, *J* = 6.5 Hz, 0.85H), 1.24 (d, *J* = 6.6 Hz, 2.5H), 1.14 (d, *J* = 6.7 Hz, 0.5H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.6, 159.5, 139.1, 139.0, 138.80, 138.76, 129.3, 129.1, 129.0, 128.9, 128.6, 128.52, 128.46, 127.5, 114.0, 113.8, 62.0, 61.8, 61.1, 61.0, 55.4, 16.8, 16.1; IR (neat)

3271, 2932, 2837, 2108, 1610, 1585, 1439, 1250, 1161, 1089, 1031 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{17}ClN_4NaO_3S$ $[M+Na]^+$ 403.0608, found $[M+Na]^+$ 403.0529.

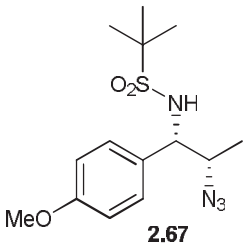
Azidosulfonamide **2.66**



2.66

After following the representative protocol for alkylation of azidoalcohols using alcohol **2.44** (50 mg) and gold(III) chloride as the catalyst, the solution was stirred at room temperature for 16 h. The residue was purified by flash chromatography (silica gel, 1.5 cm diameter × 20 cm height; 1:9 ethyl acetate:hexanes) to yield sulfonamide **2.66** (49mg, 59%, dr 5:1) of a colorless oil. R_f = 0.10 (1:9 ethyl acetate:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 – 7.60 (m, 2H), 7.42 (t, *J* = 7.5 Hz, 1H), 7.30 (t, *J* = 7.9 Hz, 2H), 6.96 – 6.91 (m, 2H), 6.68 – 6.64 (m, 2H), 5.47 (d, *J* = 8.6 Hz, 0.15H), 5.41 (d, *J* = 6.9 Hz, 0.85H), 4.27 (dd, *J* = 8.6, 4.7 Hz, 0.15H), 4.22 – 4.18 (m, 0.85H), 3.89 – 3.85 (m, 0.15H), 3.74 (s, 3H), 3.67 (m, 0.85H), 1.21 (d, *J* = 6.6 Hz, 2.5H), 1.11 (d, *J* = 6.7 Hz, 0.5H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.4, 140.5, 132.4, 129.7, 129.0, 128.9, 128.8, 128.4, 127.13, 127.06, 114.0, 113.9, 62.1, 61.6, 61.3, 60.9, 55.4, 16.8, 16.1; IR (neat) 3275, 3063, 2930, 2837, 2106, 1611, 1585, 1513, 1446, 1380, 1322, 1249, 1178, 1159, 1091, 1030 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{18}N_4NaO_3S$ $[M+Na]^+$ 369.0998, found $[M+Na]^+$ 369.0944.

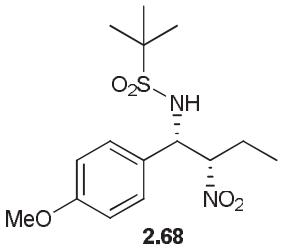
Azidosulfonamide **2.67**



2.67

After following the representative protocol for alkylation of azidoalcohols using alcohol **2.44** (50 mg) and *p*-TsOH•H_2O as the catalyst, the solution was stirred at room temperature for 16 h. The residue was purified by flash chromatography (silica gel, 1.5 cm diameter × 20 cm height; 1:9 ethyl acetate:hexanes) to yield sulfonamide **2.67** (57mg, 75%, dr 10:1) of a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20 – 7.16 (m, 2H), 6.92 – 6.88 (m, 2H), 4.84 (d, *J* = 9.5 Hz, 0.05H), 4.66 (d, *J* = 9.2 Hz, 0.95H), 4.44 (dd, *J* = 9.2, 3.6 Hz, 0.95H), 4.38 (dd, *J* = 9.7, 4.4 Hz, 0.05H), 3.81 (s, 3H), 3.78 (dd, *J* = 6.6, 3.6 Hz, 1H), 1.43 (d, *J* = 6.6 Hz, 3H), 1.25 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.4, 132.2, 129.2, 128.0, 114.3, 114.1, 63.7, 61.3, 60.1, 55.4, 24.3, 17.6; IR (neat) 3231, 2895, 2877, 2111, 1632, 1522, 1489, 1453, 1378, 1300, 1156, 1034 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{22}N_4NaO_3S$ $[M+Na]^+$ 349.1311, found $[M+Na]^+$ 349.1341.

Azidosulfonamide **2.68**

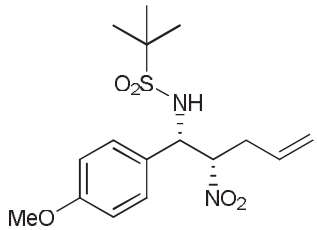


2.68

After following the representative protocol for alkylation of nitroalcohols using alcohol **2.33** (200 mg) and *p*-TsOH•H_2O as the catalyst, the solution was stirred at room temperature for 16 h. The residue was purified by flash chromatography (silica gel, 1.5 cm diameter × 20 cm height; 1:19 to 3:17 ethyl acetate:hexanes) to yield sulfonamide **2.68** (180mg, 59%, dr >20:1) of a colorless oil. R_f = 0.41 (1:9 ethyl acetate:hexanes); ^{1}H NMR

(500 MHz, $CDCl_3$) δ 7.19 – 7.14 (m, 2H), 6.97 – 6.89 (m, 2H), 5.29 (d, *J* = 10.0 Hz, 1H), 4.84 (dd, *J* = 10.0, 5.7 Hz, 1H), 4.62 (ddd, *J* = 10.1, 5.7, 4.1 Hz, 1H), 3.83 (s, 3H), 2.21 (ddq, *J* = 14.5, 10.4, 7.2 Hz, 1H), 1.95 (dqd, *J* = 15.0, 7.6, 4.0 Hz, 1H), 1.29 (s, 9H), 1.03 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.1, 129.8, 127.9, 115.0, 95.2, 60.7, 59.5, 55.7, 25.7, 24.5, 10.7; IR (neat) 3231, 2895, 2877,1632, 1522, 1489, 1453, 1378, 1300, 1156, 1034 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{22}N_4NaO_3S$ [M+Na]+ 401.1147, found [M+Na]+ 401.1237; IR (neat) 3231, 2895, 2877,1632, 1522, 1489, 1453, 1378, 1300, 1156, 1034 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{22}N_4NaO_3S$ $[M+Na]^+$ 349.1311, found $[M+Na]^+$ 349.1341.

Azidosulfonamide **2.69**

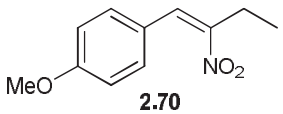


2.69

After following the representative protocol for alkylation of nitroalcohols using alcohol **2.34** (300 mg) and *p*-TsOH•H_2O as the catalyst, the solution was stirred at room temperature for 3 days. The residue was purified by flash chromatography (silica gel, 1.5 cm diameter × 20 cm height; 1:19 to 3:17 ethyl acetate:hexanes) to yield sulfonamide **2.69** (307mg, 68%, dr >20:1) of a colorless oil. R_f = 0.38 (1:9 ethyl acetate:hexanes). ^1H NMR (400 MHz, $CDCl_3$) δ 7.16 (d, *J* = 8.6 Hz, 2H), 6.89 (d, *J* = 8.6 Hz, 2H), 5.70 (dtd, *J* = 10.0, 7.9, 6.2 Hz, 1H), 5.39 (d, *J* = 10.0 Hz, 1H), 5.20 – 5.11 (m, *J* = 13.1, 10.2 Hz, 2H), 4.84 (dd, *J* = 10.0, 6.1 Hz, 1H), 4.73 (ddd, *J* = 10.1, 5.9, 3.9 Hz, 1H), 3.80 (s, 3H), 2.88 – 2.75 (m, 1H), 2.63 – 2.52 (m, *J* = 10.2, 4.7 Hz, 1H), 1.26 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.9, 130.7, 129.3, 127.7, 120.4, 114.8, 92.7, 60.5, 59.4, 55.4, 36.1, 24.2; IR (neat) 3271, 2934, 2837,1611, 1585, 1513, 1439, 1453, 1396, 1250, 1161, 1013 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{24}N_2NaO_5S$ $[M+Na]^+$ 379.1304, found $[M+Na]^+$ 379.1322.

When using HBF_4•Et_2O as catalyst in dichloromethane, the reaction was stirred for 16h. The mixture was purified as above to yield sulfonamide **2.69** (27mg, 51%, dr >20:1) of a colorless oil.

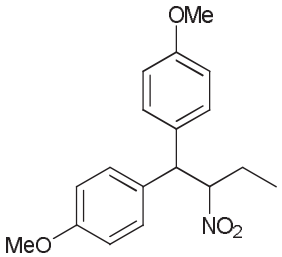
Nitroalkene **2.70**



2.70

A solution of triflic acid (0.05 ml, 0.516 mmol, 6 equiv) in DCM (3 ml) was added slowly to a solution of sulfonamide **2.68** (30 mg, 0.086 mmol, 1 equiv) in DCM (3 ml) at -78°C. The solution was stirred for 45 minutes while left to warm up to room temperature and monitered by TLC. After full conversion, the mixture was quenched with a 10% NaOH solution in water then extracted with DCM (2 x 10ml). The organic solution was dried over magnesium sulfate, filtered, and concentrated. The residue was purified by flash chromatography (silica gel, 1.5 cm diameter × 10 cm height; 3:17 ethyl acetate:hexanes) to yield nitroalkene **2.70** (15mg, 84%) of a colorless oil. R_f = 0.38 (1:9 ethyl acetate:hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 (s, 0..67H), 7.43 – 7.39 (m, 1.33H), 7.21 – 7.18 (m, 0.67H), 7.00 – 6.95 (m, 1.33H), 6.87 – 6.83 (m, 0.67H), 6.29 (s, 0.33H), 3.86 (s, 2H), 3.81 (s, 1H), 2.90 (q, *J* = 7.4 Hz, 1.33H), 2.67 (qd, *J* = 7.4, 1.3 Hz, 0.67H), 1.29 (t, *J* = 7.4 Hz, 2H), 1.20 (t, *J* = 7.4 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.3, 160.3, 151.4, 150.8, 133.4, 132.0, 130.8, 129.9, 124.8, 124.4, 122.9, 114.7, 114.3, 113.8, 55.6, 55.4, 29.9, 27.5, 21.0, 12.5, 11.7; IR (neat) 2954, 2923, 2852, 1693, 1647, 1509, 1299, 1254, 1175, 1022 cm^{-1}; HRMS (ESI) calcd for $C_{11}H_{13}NNaO_3$ $[M+Na]^+$ 230.0793, found $[M+Na]^+$ 230.0751.

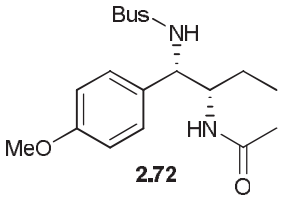
Diaryl **2.71**



2.71

A solution of triflic acid (0.015 ml, 0.168 mmol, 6 equiv) in DCM (0.9 ml) was added slowly to a solution of sulfonamide **2.68** (10 mg, 0.028 mmol, 1 equiv) and anisole (0.06 ml, 0.56 mmol, 20 equiv) in DCM (0.9 ml) at 0°C. The solution was stirred for 3 h. After full conversion, the mixture was quenched with a 10% NaOH solution in water then extracted with DCM (2 x 5ml). The organic solution was dried over sodium sulfate, filtered, and concentrated. The residue was purified by flash chromatography (silica gel, 1.5 cm diameter × 5 cm height; 1:9 diethyl ether:hexanes) to yield diaryl **2.71** (7mg, 79%) of a colorless oil. R_f = 0.55 (1:4 ethyl acetate:hexanes); ^{1}HNMR (300 MHz, $CDCl_3$) d 7.26 – 7.09 (m, 4H), 6.89 – 6.76 (m, 4H), 5.18 – 5.07 (m, 1H), 4.32 (d, *J* = 11.5 Hz, 1H), 3.77 (s, 3H), 3.74 (s, 3H), 1.89 (ddq, *J* = 14.5, 10.5, 7.3 Hz, 1H), 1.73 (dqd, *J* = 14.8, 7.5, 3.2 Hz, 1H), 0.93 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) d 158.9, 158.8, 132.3, 132.1, 129.1, 128.5, 114.6, 114.4, 94.0, 55.4, 55.3, 54.1, 26.5, 10.5; IR (neat) 3011, 2981, 2966, 2941, 2868, 1613, 1552, 1514, 1466, 1377, 1306, 1253, 1181, 1035 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{21}NNaO_4$ $[M+Na]^+$ 338.13628, found $[M+Na]^+$ 338.13595.

Amide **2.72**



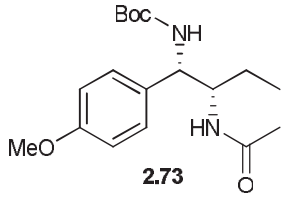
2.72

To a solution of **2.68** (30mg, 0.086 mmol, 1 equiv) in MeOH (0.8 ml) was added TMSCl (0.3 ml, 2.58 mmol, 30 equiv) then zinc powder (112 mg, 1.72 mmol, 20 equiv) slowly, be careful of high gas production. The mixture was stirred 5 minutes then after full conversion

the reaction was quenched with a saturated aqueous solution of $NaHCO_3$. It was then extracted with DCM (1 x 10 ml) and dried over sodium sulfate, filtered, and concentrated.

The crude was directly used and dissolved in MeOH (1 ml) and acetic anhydride (0.02 ml, 0.196 mmol, 2.25 equiv) was added. The solution was stirred overnight and washed with DCM (2 x 5ml) then dried over sodium sulfate, filtered, and concentrated. The residue was purified by flash chromatography (silica gel, 0.5 cm diameter × 5 cm height; 1:19 ethyl acetate:hexanes) to yield amide **2.72** (25mg, 82% over 2 steps) of a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 – 7.18 (m, 2H), 6.87 (d, J = 8.2 Hz, 2H), 6.66 – 6.54 (m, 0.65H), 5.77 (d, J = 8.0 Hz, 1H), 4.28 (t, J = 8.8 Hz, 1H), 4.17 – 4.01 (m, 1H), 3.80 (s, 3H), 2.11 (s, 3H), 1.49 – 1.42 (m, J = 9.4 Hz, 2H), 1.18 (s, 9H), 0.85 (t, J = 7.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.2, 159.3, 133.7, 132.4, 128.6, 114.9, 114.3, 63.0, 59.4, 57.0, 55.4, 25.0, 24.2, 24.1, 23.2, 10.6; IR (neat) 3223, 2906, 2864, 2877,1632, 1510, 1440, 1379, 1301, 1174, 1033 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{28}N2NaO_4S$ $[M+Na]^+$ 379.1668, found $[M+Na]^+$ 379.1642.

Amide **2.73**

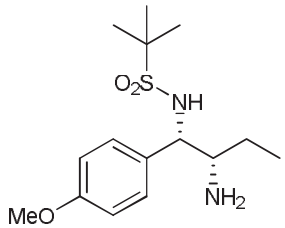


2.73

A solution of triflic acid (0.07 ml, 0.79 mmol, 6 equiv) in DCM (4 ml) was added slowly to a solution of sulfonamide **2.72** (47 mg, 0.13 mmol, 1 equiv) in DCM (4 ml) at -20°C. The solution was stirred for 30 minutes while left to warm up to room temperature and monitered by TLC. After full conversion, the mixture was quenched with a 10% NaOH solution in water then extracted with DCM (2 x 10ml). The organic solution was dried over magnesium sulfate, filtered, and concentrated.

The crude was directly used and dissolved in DCM (1,3 ml) and Boc_2O (43 mg, 0.195 mmol, 1.5 equiv) was added. The solution was stirred overnight and washed with DCM (2 x 5ml) then dried over sodium sulfate, filtered, and concentrated. The residue was purified by flash chromatography (silica gel, 1.5 cm diameter × 10 cm height; 1:9 ethyl acetate:hexanes) to yield amide **2.73** (32 mg, 73% over 2 steps) of a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (t, J = 4.2 Hz, 2H), 6.89 – 6.84 (m, 2H), 5.67 (d, J = 6.7 Hz, 1H), 4.47 (d, J = 9.8 Hz, 1H), 3.93 – 3.84 (m, 1H), 3.79 (s, 3H), 2.07 (s, 3H), 1.49 (d, J = 5.3 Hz, 1H), 1.40 (s, 9H), 1.34 – 1.30 (m, 1H), 0.91 (t, J = 7.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.5, 159.6, 155.9, 130.2, 128.5, 114.0, 79.3, 56.1, 55.4, 28.5, 25.0, 21.3, 10.3; HRMS (ESI) calcd for $C_{17}H_{28}N2NaO_4$ $[M+Na]^+$ 359.1947, found $[M+Na]^+$ 359.1889.

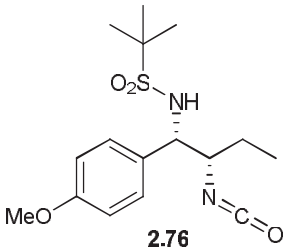
Amine **2.74**



2.74

To a solution of **2.68** (30mg, 0.086 mmol, 1 equiv) in MeOH (0.8 ml) was added TMSCl (0.3 ml, 2.58 mmol, 30 equiv) then zinc powder (112 mg, 1.72 mmol, 20 equiv) slowly, be careful of high gas production. The mixture was stirred 5 minutes then after full conversion the reaction was quenched with a saturated aqueous solution of $NaHCO_3$. It was then extracted with DCM (1 x 10 ml) and dried over sodium sulfate, filtered, and concentrated. The residue was purified by flash chromatography (silica gel, 0.5 cm diameter × 5 cm height; 3:97 MeOH:DCM) to yield amide **2.74** (21 mg, 77%) of a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 (d, J = 8.4 Hz, 2H), 6.89 (d, J = 8.2 Hz, 2H), 4.50 (d, J = 3.9 Hz, 1H), 3.80 (s, 3H), 3.15 – 3.09 (m, 1H), 1.75 – 1.66 (m, 1H), 1.54 – 1.44 (m, 1H), 1.21 (s, 9H), 1.02 (t, J = 7.3 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.1, 133.1, 128.3, 114.3, 60.1, 59.7, 58.7, 55.4, 29.8, 24.3, 10.5; HRMS (ESI) calcd for $C_{15}H_{26}N_2NaO_3S$ $[M+Na]^+$ 337.1562, found $[M+Na]^+$ 337.1527.

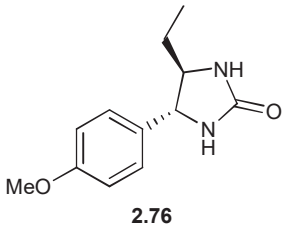
Isocyanate **2.75**



2.76

Amine **2.74** (13 mg) was dissolved in a saturated aqueous solution of $NaHCO_3$ (0.2 ml) and DCM (0.1 ml) at 0°C then triphosgene (4.1 mg) was added. The reaction was stirred 1 h then diluted in AcOEt and washed rapidly with water (pH 3). The aqueous layer was extracted with AcOEt and the combined organic phases washed rapidly with a saturated aqueous NaHCO solution, brine, then dried over Na2SO, filtered and concentrated to give isocyanate **2.75** (16 mg) as a brown oil which was used without purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, *J* = 8.6 Hz, 2H), 6.89 (d, *J* = 8.6 Hz, 2H), 5.98 (s, 1H), 4.94 (d, *J* = 2.9 Hz, 1H), 3.81 (s, 3H), 3.51 (td, *J* = 6.3, 3.1 Hz, 1H), 1.75 – 1.66 (m, 2H), 1.22 (s, 9H), 0.98 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.9, 156.0, 133.5, 128.6, 114.4, 65.3, 63.2, 60.4, 55.5, 29.8, 29.3, 24.6, 24.3, 9.4; IR (neat) 3245, 2871, 2837, 2264,1601, 1581, 1436, 1304, 1172, 1034 cm^{-1}.

Urea **2.76**



2.76

To **2.75** (16 mg crude) dissolved in dry DCM (0.2 ml) at 0°C was added Aluminium (III) chloride (16 mg, 0.118 mmol). The mixture was stirred for 40 min. then quenched using water (5 ml). The mixture was extracted with DCM (1 x 10 ml) and dried over sodium sulfate, filtered, and concentrated. The residue was purified by flash chromatography

(silica gel, 0.5 cm diameter × 5 cm height; 1:9 ethyl acetate:hexanes) to yield urea **2.76** (6 mg, 73%) of a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (d, *J* = 8.6 Hz, 2H), 6.90 (d, *J* = 8.7 Hz, 2H), 4.98 (s, 1H), 4.85 (s, 1H), 4.35 (d, *J* = 6.8 Hz, 1H), 3.81 (s, 3H), 3.46 (dd, *J* = 12.3, 7.0 Hz, 1H), 1.74 – 1.52 (m, 2H), 0.94 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.6, 159.8, 133.4, 127.9, 114.4, 63.7, 62.2, 55.5, 27.8, 10.1; IR (neat) 3234, 2960, 2924, 2851, 1701, 1610, 1512, 1459, 1373, 1247, 1176, 1033 cm^{-1}; HRMS (ESI) calcd for $C_{12}H_{16}N_2NaO_2$ $[M+H]^+$ 221.1290, found $[M+H]^+$ 221.1317.

Reference

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[1] (a) Williams, C. M.; de Meijere, A. *J. Chem. Soc., Perkin Trans. 1*, **1998**, 3699. (b) L. J. Morris, *Chem. Ind.*, **1962**, 1239; silica gel (200 g) was suspended in acetonitrile (~400 ml) to which was added a solution of silver nitrate (40 g) in acetonitrile (~50 ml). The solvent was then slowly evaporated (1 Torr) and the silica gel placed in an oven (80 8C) or in an evacuated flask (0.01 Torr) for 24 h.

[2]Ghosh, U.; Ganessunker, D.; Sattigeri, V. J.; Carlson, K. E.; Mortensen, D. J.; Katzenellenbogen, B. S.; Katzenellenbogen, J. A. *Bioorg. Med. Chem.* **2003**, *11*, 629.

Annexe 2 - Rapports cristallographiques

Article 1, Lactone **4b** / Article 2, Lactone **20**

Université de Montréal

CRYSTAL AND MOLECULAR STRUCTURE OF

C21 H30 O3 COMPOUND (ROBE48)

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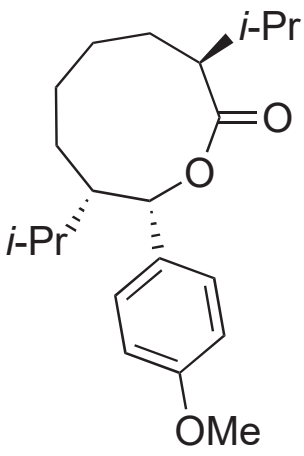


Structure solved and refined in the laboratory of X-ray diffraction Université de Montréal by Robert D. Giacometti.

Table 1. Crystal data and structure refinement for C21 H30 O3.

Identification code	ROBE48
Empirical formula	$C_{21}H_{30}O_3$
Formula weight	330.45
Temperature/K	100
Crystal system	monoclinic
Space group	$P2_1$
a/Å	9.63600(9)
b/Å	9.33460(9)
c/Å	10.49330(10)
α/°	90
β/°	100.0230(3)
γ/°	90
Volume/Å^3	929.448(15)
Z	2
ρ_{calc}g/cm^3	1.181
μ/mm^{-1}	0.607
F(000)	360.0
Crystal size/mm^3	0.16 × 0.11 × 0.1
Radiation	CuKα (λ = 1.54178)
2Θ range for data collection/°	8.556 to 143.38
Index ranges	-11 ≤ h ≤ 11, -11 ≤ k ≤ 11, -12 ≤ l ≤ 12
Reflections collected	19284
Independent reflections	3466 [R_{int} = 0.0177, R_{sigma} = 0.0130]
Data/restraints/parameters	3466/1/222
Goodness-of-fit on F^2	1.038
Final R indexes [I>=2σ (I)]	R_1 = 0.0276, wR_2 = 0.0729
Final R indexes [all data]	R_1 = 0.0278, wR_2 = 0.0731
Largest diff. peak/hole / e Å^{-3}	0.19/-0.15
Flack parameter	0.06(3)

Table 2. Fractional atomic coordinates (× 10^4) and equivalent isotropic displacement parameters (Å^2 x 10^3) for C21 H30 O3.

U_{eq} is defined as one third of the trace of the orthogonalized Uij tensor.

Atom	*x*	*y*	*z*	U(eq)
C1	9570.4(15)	3317.6(17)	928.7(14)	15.3(3)
C2	9651.1(16)	2748.3(17)	-415.7(14)	17.8(3)
C3	8102.9(17)	2605(2)	-1141.8(15)	23.1(3)
C4	7316.3(17)	4001(2)	-1201.8(15)	25.4(4)
C5	6498.0(17)	4443(2)	-380.0(16)	25.0(4)
C6	6170.4(16)	3626(2)	772.2(15)	22.6(3)
C7	7083.3(15)	4149.7(17)	2075.2(15)	18.1(3)
C8	8216.7(15)	3033.9(16)	2631.7(14)	15.7(3)
C9	7751.5(15)	1787.9(17)	3371.0(14)	16.2(3)
C10	8570.3(16)	1388.7(17)	4541.8(15)	17.6(3)
C11	8189.4(16)	269.0(18)	5291.2(14)	18.2(3)
C12	6952.9(15)	-487.1(18)	4848.3(14)	17.1(3)
C13	6117.1(16)	-109.6(18)	3672.7(15)	18.8(3)
C14	6508.7(16)	1012.4(18)	2953.5(14)	18.2(3)
C15	10604.2(16)	3683.1(17)	-1115.7(14)	18.7(3)
C16	10484.3(18)	3246(2)	-2536.3(15)	24.5(4)
C17	12141.9(17)	3566(2)	-448.8(15)	25.1(4)
C18	6199.6(17)	4647.5(19)	3089.0(17)	22.8(3)
C19	7122.4(19)	5074(2)	4371.3(17)	27.9(4)
C20	5272(2)	5922(2)	2571(2)	33.2(4)
C21	7274.0(18)	-2023.6(19)	6685.1(16)	25.2(4)
O1	8804.6(11)	2421.6(12)	1546.7(10)	16.3(2)
O2	10060.0(11)	4429.2(12)	1390.2(10)	18.3(2)
O3	6460.2(11)	-1608.7(13)	5477(1)	20.6(2)

Table 3. Hydrogen atom coordinates (× 10^4) and isotropic displacement parameters (Å^2 x 10^3) for C21 H30 O3.

U_{eq} is defined as one third of the trace of the orthogonalized Uij tensor.

Atom	*x*	*y*	*z*	U(eq)
H2	10069	1766	-315	21
H3A	8108	2260	-2033	28
H3B	7606	1883	-696	28
H4	7413	4629	-1894	30
H5	6080	5363	-534	30
H6A	6347	2593	656	27
H6B	5160	3744	820	27
H7	7608	5014	1854	22
H8	8991	3546	3214	19
H10	9419	1896	4842	21
H11	8765	26	6092	22
H13	5276	-626	3366	23
H14	5924	1264	2160	22
H15	10300	4704	-1080	22
H16A	10636	2211	-2591	37
H16B	11197	3757	-2923	37
H16C	9543	3489	-3005	37
H17A	12228	3878	453	38
H17B	12730	4176	-898	38
H17C	12454	2568	-474	38
H18	5574	3840	3257	27
H19A	7640	4233	4760	42
H19B	6525	5446	4962	42
H19C	7792	5815	4213	42

Table 4. Anisotropic displacement parameters ($Å^2$ x 10^3) for C21 H30 O3.

The anisotropic displacement factor exponent takes the form:
$-2\pi^2[h^2a^{*2}U_{11} + ... + 2hka^*b^*U_{12}]$

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
C1	13.1(6)	15.3(7)	17.0(7)	1.7(6)	0.7(5)	1.7(5)
C2	22.3(7)	15.5(8)	15.7(7)	-0.6(6)	3.8(6)	-1.6(6)
C3	25.6(8)	27.5(9)	15.5(7)	-1.5(7)	1.5(6)	-8.3(7)
C4	22.3(8)	32.7(10)	18.1(7)	7.1(7)	-5.4(6)	-4.9(7)
C5	19.7(7)	27.3(9)	24.3(8)	7.1(7)	-6.6(6)	1.0(7)
C6	15.4(7)	27.7(9)	22.9(7)	3.4(7)	-1.1(5)	0.8(6)
C7	15.2(7)	17.9(8)	21.2(7)	1.2(6)	3.1(6)	0.2(6)
C8	14.8(6)	17.6(8)	14.9(6)	-2.8(6)	2.9(5)	-0.3(5)
C9	15.4(7)	18.5(8)	15.2(7)	-2.2(6)	4.1(6)	1.1(6)
C10	15.3(7)	20.1(8)	17.1(7)	-3.9(6)	2.1(5)	-0.7(6)
C11	17.8(7)	22.0(8)	14.3(7)	-0.5(6)	1.4(5)	1.9(6)
C12	18.5(7)	17.6(7)	16.6(7)	-1.5(6)	7.0(5)	0.3(6)
C13	14.9(7)	21.5(8)	19.6(7)	-1.3(6)	2.3(6)	-1.5(6)
C14	17.1(7)	21.0(8)	15.8(7)	-0.6(6)	0.6(5)	0.1(6)
C15	23.1(8)	16.4(8)	17.0(7)	0.6(6)	4.7(5)	-1.2(6)
C16	30.6(8)	26.8(9)	17.0(7)	-0.2(6)	6.6(6)	-5.6(7)
C17	22.3(8)	33.9(10)	19.9(7)	1.9(7)	6.1(6)	-1.2(7)
C18	19.9(7)	20.3(8)	29.9(8)	0.5(7)	9.2(6)	1.8(6)
C19	31.5(9)	25.9(9)	28.6(9)	-4.9(7)	11.8(7)	4.1(7)
C20	27.2(9)	28.7(10)	45.5(11)	2.0(9)	11.5(8)	9.2(8)
C21	26.7(8)	28.2(9)	20.4(8)	6.9(7)	3.3(6)	-1.3(7)
O1	17.9(5)	16.8(6)	14.6(5)	-1.2(4)	4.3(4)	-0.4(4)
O2	19.1(5)	17.5(6)	18.0(5)	-1.8(4)	2.8(4)	-2.4(4)
O3	21.5(5)	22.2(6)	18.3(5)	2.8(5)	3.8(4)	-3.1(5)

Table 5. Bond lengths [Å] for C21 H30 O3.

Atom	Atom	Length/Å	Atom	Atom	Length/Å
C1	C2	1.522(2)	C9	C10	1.390(2)
C1	O1	1.3531(18)	C9	C14	1.403(2)
C1	O2	1.2060(19)	C10	C11	1.395(2)
C2	C3	1.558(2)	C11	C12	1.393(2)
C2	C15	1.543(2)	C12	C13	1.396(2)
C3	C4	1.503(3)	C12	O3	1.3659(19)
C4	C5	1.331(3)	C13	C14	1.381(2)
C5	C6	1.509(2)	C15	C16	1.530(2)
C6	C7	1.570(2)	C15	C17	1.528(2)
C7	C8	1.548(2)	C18	C19	1.531(2)
C7	C18	1.545(2)	C18	C20	1.530(2)
C8	C9	1.509(2)	C21	O3	1.4234(19)
C8	O1	1.4725(17)			

Table 6. Bond angles [Å] for C21 H30 O3.

Atom	Atom	Atom	Angle/˚	Atom	Atom	Atom	Angle/˚
O1	C1	C2	110.39(13)	C10	C9	C14	117.39(14)
O2	C1	C2	126.37(14)	C14	C9	C8	123.44(14)
O2	C1	O1	123.18(13)	C9	C10	C11	122.30(15)
C1	C2	C3	106.51(12)	C12	C11	C10	119.03(14)
C1	C2	C15	112.00(13)	C11	C12	C13	119.68(14)
C15	C2	C3	114.48(12)	O3	C12	C11	125.18(13)
C4	C3	C2	112.27(14)	O3	C12	C13	115.13(13)
C5	C4	C3	126.35(16)	C14	C13	C12	120.25(14)
C4	C5	C6	126.33(17)	C13	C14	C9	121.35(14)
C5	C6	C7	112.14(14)	C16	C15	C2	111.26(13)
C8	C7	C6	111.75(12)	C17	C15	C2	110.58(13)
C18	C7	C6	113.63(12)	C17	C15	C16	109.25(13)
C18	C7	C8	112.31(13)	C19	C18	C7	112.21(13)
C9	C8	C7	117.34(12)	C20	C18	C7	110.32(14)
O1	C8	C7	108.10(12)	C20	C18	C19	108.90(15)
O1	C8	C9	106.68(12)	C1	O1	C8	116.48(12)
C10	C9	C8	119.16(13)	C12	O3	C21	117.05(12)

Table 7. Torsion angles [°] for C21 H30 O3.

A	B	C	D	Angle/˚	A	B	C	D	Angle/˚
C1	C2	C3	C4	57.39(16)	C9	C8	O1	C1	-165.59(12)
C1	C2	C15	C16	-170.69(13)	C9	C10	C11	C12	0.6(2)
C1	C2	C15	C17	67.72(17)	C10	C9	C14	C13	-0.4(2)
C2	C1	O1	C8	-159.39(11)	C10	C11	C12	C13	-0.3(2)
C2	C3	C4	C5	-94.36(19)	C10	C11	C12	O3	179.56(14)
C3	C2	C15	C16	-49.31(18)	C11	C12	C13	C14	-0.3(2)
C3	C2	C15	C17	-170.90(14)	C11	C12	O3	C21	0.6(2)
C3	C4	C5	C6	-1.0(3)	C12	C13	C14	C9	0.7(2)
C4	C5	C6	C7	100.2(2)	C13	C12	O3	C21	-179.54(13)
C5	C6	C7	C8	-108.33(16)	C14	C9	C10	C11	-0.3(2)
C5	C6	C7	C18	123.29(15)	C15	C2	C3	C4	-66.96(17)
C6	C7	C8	C9	-80.64(16)	C18	C7	C8	C9	48.43(18)
C6	C7	C8	O1	39.95(16)	C18	C7	C8	O1	169.02(12)
C6	C7	C18	C19	176.91(14)	O1	C1	C2	C3	58.23(16)
C6	C7	C18	C20	-61.47(19)	O1	C1	C2	C15	-175.91(12)
C7	C8	C9	C10	-134.57(15)	O1	C8	C9	C10	104.10(14)
C7	C8	C9	C14	44.2(2)	O1	C8	C9	C14	-77.17(17)
C7	C8	O1	C1	67.37(15)	O2	C1	C2	C3	-119.15(16)
C8	C7	C18	C19	48.82(19)	O2	C1	C2	C15	6.7(2)
C8	C7	C18	C20	170.44(14)	O2	C1	O1	C8	18.1(2)
C8	C9	C10	C11	178.54(14)	O3	C12	C13	C14	179.79(13)
C8	C9	C14	C13	-179.14(14)					

Experimental

Single crystals of $C_{21}H_{30}O_3$ [ROBE481] were obtained by slow recrystallized from diethyl ether. A suitable crystal was selected and mounted on a loop fiber on a Bruker APEX-II CCD diffractometer. The crystal was kept at 100 K during data collection. Using Olex2 [1], the structure was solved with the XT [2] structure solution program using Direct Methods and refined with the ShelXL [2] refinement package using Least Squares minimization.

1. Dolomanov, O.V., Bourhis, L.J., Gildea, R.J, Howard, J.A.K. & Puschmann, H. (2009), J. Appl. Cryst. 42, 339-341.
2. Sheldrick, G.M. (2008). Acta Cryst. A64, 112-122.
3. APEX2 (2008), Bruker AXS Inc., Madison, WI 53719-1173.
4. SAINT (2013) V8.34A, Bruker AXS Inc., Madison, WI 53719-1173.
5. XPREP (2013); X-ray data Preparation and Reciprocal space Exploration Program. Bruker AXS Inc., Madison, WI 53719-1173.

Crystal structure determination of ROBE481:

Crystal Data for $C_{21}H_{30}O_3$ (M =330.45 g/mol): monoclinic, space group $P2_1$ (no. 4), a = 9.63600(9) Å, b = 9.33460(9) Å, c = 10.49330(10) Å, β = 100.0230(3)°, V = 929.448(15) Å^3, Z = 2, T = 100 K, μ(CuKα) = 0.607 mm^{-1}, *Dcalc* = 1.181 g/cm^3, 19284 reflections measured (8.556° ≤ 2Θ ≤ 143.38°), 3466 unique (R_{int} = 0.0177, R_{sigma} = 0.0130) which were used in all calculations. The final R_1 was 0.0276 (I > 2σ(I)) and wR_2 was 0.0731 (all data).

Refinement model description

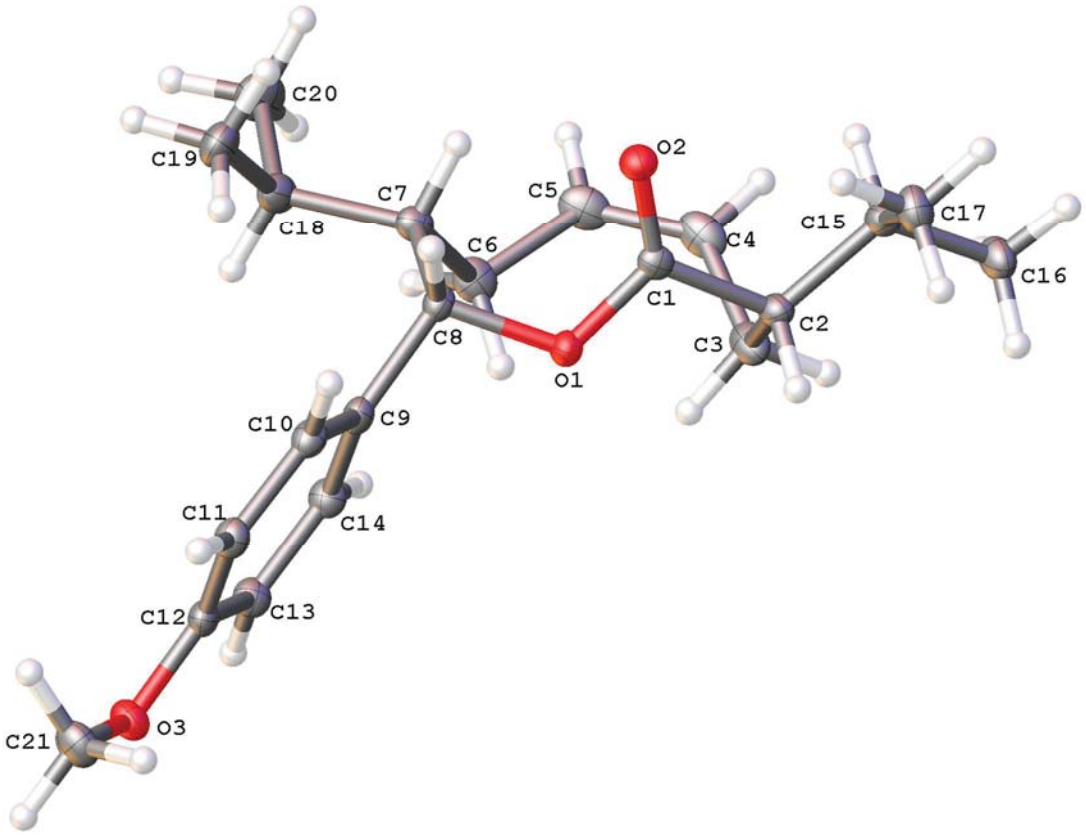
Number of restraints - 1, number of constraints - unknown.
Details:
1. Fixed Uiso
 At 1.2 times of:
  All C(H) groups, All C(H,H) groups
 At 1.5 times of:
  All C(H,H,H) groups
2.a Ternary CH refined with riding coordinates:
 C2(H2), C7(H7), C8(H8), C15(H15), C18(H18)
2.b Secondary CH2 refined with riding coordinates:
 C3(H3A,H3B), C6(H6A,H6B)
2.c Aromatic/amide H refined with riding coordinates:

C4(H4), C5(H5), C10(H10), C11(H11), C13(H13), C14(H14)

2.d Idealized Me refined as rotating group:

C16(H16A,H16B,H16C), C17(H17A,H17B,H17C), C19(H19A,H19B,H19C), C20(H20A,H20B,

H20C), C21(H21A,H21B,H21C)



ORTEP view of the C21 H30 O3 compound with the numbering scheme adopted. Ellipsoids are drawn at the 50% probability level. Hydrogen atoms are represented by spheres of arbitrary size.

Article 2, Bromolactone **25**

Université de Montréal

CRYSTAL AND MOLECULAR STRUCTURE OF

C28 H38 Br N O5 S COMPOUND (rober7)

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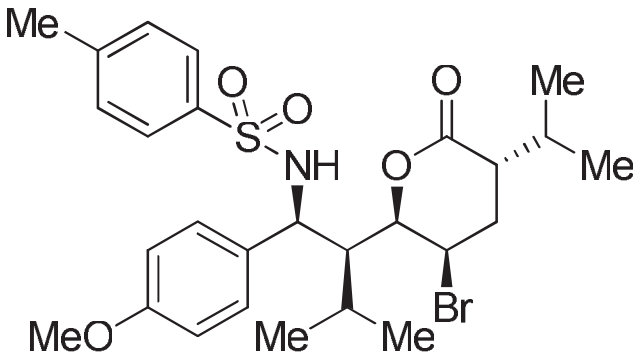


Structure solved and refined in the laboratory of X-ray diffraction
Université de Montréal by Robert D. Giacometti.

Table 1. Crystal data and structure refinement for C28 H38 Br N O5 S.

Identification code	rober7
Empirical formula	C28 H38 Br N O5 S
Formula weight	580.56
Temperature	150K
Wavelength	1.54178 Å
Crystal system	Orthorhombic
Space group	P212121
Unit cell dimensions	a = 8.2272(4) Å α = 90° b = 18.3055(8) Å β = 90° c = 18.5334(9) Å γ = 90°
Volume	2791.2(2)Å^3
Z	4
Density (calculated)	1.382 g/cm^3
Absorption coefficient	3.010 mm^{-1}
F(000)	1216
Crystal size	0.20 x 0.05 x 0.05 mm
Theta range for data collection	3.39 to 69.75°
Index ranges	$-9 \le h \le 9$, $-22 \le k \le 20$, $-22 \le l \le 22$
Reflections collected	56291
Independent reflections	5227 [R_{int} = 0.049]
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.8603 and 0.6653
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5227 / 0 / 332

Goodness-of-fit on F^2	1.041
Final R indices [I>2sigma(I)]	R_1 = 0.0276, wR_2 = 0.0743
R indices (all data)	R_1 = 0.0281, wR_2 = 0.0747
Absolute structure parameter	-0.023(12)
Extinction coefficient	0.00119(11)
Largest diff. peak and hole	0.386 and -0.317 e/Å^3

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for C28 H38 Br N O5 S.

U_{eq} is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U_{eq}
Br(1)	3977(1)	2598(1)	9671(1)	49(1)
S(1)	10004(1)	5154(1)	7447(1)	29(1)
O(1)	2396(2)	4064(1)	9050(1)	29(1)
O(2)	-53(2)	4069(1)	9483(1)	34(1)
O(3)	9317(2)	5001(1)	6754(1)	37(1)
O(4)	11707(2)	5032(1)	7571(1)	37(1)
O(5)	4739(2)	6831(1)	10008(1)	41(1)
N(1)	9057(2)	4677(1)	8042(1)	28(1)
C(1)	1396(2)	4049(1)	9617(1)	27(1)
C(2)	2017(2)	3998(1)	10381(1)	31(1)
C(3)	3880(3)	3945(1)	10447(1)	38(1)
C(4)	4651(3)	3625(1)	9779(1)	35(1)
C(5)	4157(2)	4078(1)	9134(1)	26(1)
C(6)	4832(2)	3866(1)	8403(1)	26(1)
C(7)	6703(2)	3903(1)	8336(1)	24(1)
C(8)	7270(2)	4675(1)	8097(1)	25(1)
C(9)	6637(2)	5281(1)	8586(1)	26(1)
C(10)	5435(3)	5750(1)	8351(1)	31(1)
C(11)	4765(3)	6281(1)	8807(1)	35(1)
C(12)	5316(3)	6334(1)	9510(1)	31(1)
C(13)	6530(3)	5867(1)	9757(1)	32(1)
C(14)	7184(3)	5348(1)	9297(1)	29(1)
C(15)	3356(4)	7247(2)	9813(2)	63(1)
C(16)	1345(3)	4621(2)	10858(1)	46(1)
C(17)	1525(4)	5366(2)	10496(2)	67(1)
C(18)	-400(3)	4485(2)	11102(2)	59(1)
C(19)	7375(3)	3303(1)	7828(1)	29(1)
C(20)	7135(3)	2537(1)	8137(1)	41(1)
C(21)	6704(3)	3346(1)	7064(1)	42(1)
C(22)	9577(2)	6081(1)	7631(1)	29(1)
C(23)	8698(3)	6493(1)	7146(1)	33(1)
C(24)	8354(3)	7223(1)	7306(1)	35(1)
C(25)	8873(3)	7531(1)	7950(1)	33(1)
C(26)	9768(3)	7102(1)	8428(1)	34(1)
C(27)	10126(3)	6381(1)	8274(1)	34(1)
C(28)	8465(3)	8309(1)	8139(2)	45(1)

Table 3. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for C28 H38 Br N O5 S.

	x	y	z	U_{eq}
H(1)	9624	4408	8344	34
H(2)	1572	3533	10584	37
H(3A)	4331	4439	10532	46
H(3B)	4157	3637	10868	46
H(4)	5860	3645	9831	42
H(5)	4485	4595	9231	32
H(6A)	4351	4192	8033	31
H(6B)	4478	3362	8292	31
H(7)	7164	3811	8827	29
H(8)	6826	4765	7603	30
H(10)	5053	5711	7869	37
H(11)	3942	6601	8635	42
H(13)	6910	5905	10239	38
H(14)	8017	5033	9467	35
H(15A)	2484	6918	9657	94
H(15B)	3638	7578	9417	94
H(15C)	2988	7532	10229	94
H(16)	2029	4634	11304	55
H(17A)	835	5385	10065	100
H(17B)	2662	5441	10356	100
H(17C)	1194	5751	10833	100
H(18A)	-460	4017	11357	89
H(18B)	-1117	4472	10680	89
H(18C)	-744	4879	11427	89
H(19)	8575	3384	7792	35
H(20A)	7690	2181	7829	61
H(20B)	5972	2424	8155	61
H(20C)	7590	2516	8625	61
H(21A)	5517	3301	7078	63
H(21B)	7159	2948	6774	63
H(21C)	7002	3816	6848	63
H(23)	8328	6283	6708	40
H(24)	7761	7511	6970	42
H(26)	10139	7309	8869	41
H(27)	10739	6095	8603	40
H(28A)	7504	8318	8452	67
H(28B)	8238	8584	7697	67
H(28C)	9385	8532	8392	67

Table 4. Anisotropic parameters ($Å^2$ x 10^3) for C28 H38 Br N O5 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
Br(1)	56(1)	36(1)	56(1)	15(1)	21(1)	14(1)
S(1)	31(1)	25(1)	32(1)	1(1)	5(1)	-1(1)
O(1)	23(1)	37(1)	27(1)	5(1)	0(1)	3(1)
O(2)	24(1)	42(1)	35(1)	0(1)	0(1)	5(1)
O(3)	48(1)	34(1)	31(1)	0(1)	4(1)	-4(1)
O(4)	29(1)	32(1)	49(1)	3(1)	8(1)	1(1)
O(5)	48(1)	38(1)	38(1)	-11(1)	-4(1)	17(1)
N(1)	27(1)	26(1)	33(1)	5(1)	3(1)	0(1)
C(1)	28(1)	23(1)	30(1)	0(1)	2(1)	1(1)
C(2)	28(1)	37(1)	27(1)	0(1)	1(1)	-3(1)
C(3)	29(1)	59(1)	27(1)	-2(1)	-1(1)	-5(1)
C(4)	26(1)	50(1)	30(1)	6(1)	-1(1)	3(1)
C(5)	20(1)	32(1)	27(1)	0(1)	0(1)	-1(1)
C(6)	23(1)	27(1)	27(1)	-2(1)	1(1)	-3(1)
C(7)	25(1)	22(1)	26(1)	1(1)	2(1)	-4(1)
C(8)	26(1)	23(1)	28(1)	1(1)	1(1)	-1(1)
C(9)	28(1)	21(1)	29(1)	1(1)	1(1)	-3(1)
C(10)	35(1)	29(1)	29(1)	0(1)	-1(1)	3(1)
C(11)	39(1)	31(1)	35(1)	0(1)	-3(1)	11(1)
C(12)	35(1)	25(1)	34(1)	-4(1)	1(1)	4(1)
C(13)	33(1)	30(1)	33(1)	-5(1)	-6(1)	1(1)
C(14)	28(1)	27(1)	33(1)	-2(1)	-3(1)	2(1)
C(15)	75(2)	65(2)	48(2)	-18(1)	-14(1)	46(2)
C(16)	40(1)	59(2)	37(1)	-18(1)	5(1)	-1(1)
C(17)	74(2)	40(1)	86(2)	-28(2)	6(2)	-6(1)
C(18)	45(2)	90(2)	44(1)	-14(2)	10(1)	9(1)
C(19)	30(1)	23(1)	35(1)	-2(1)	6(1)	0(1)
C(20)	46(1)	24(1)	52(1)	1(1)	12(1)	0(1)
C(21)	52(1)	41(1)	34(1)	-9(1)	2(1)	5(1)
C(22)	28(1)	22(1)	36(1)	2(1)	5(1)	-3(1)
C(23)	31(1)	34(1)	34(1)	-2(1)	0(1)	-2(1)
C(24)	33(1)	29(1)	44(1)	4(1)	-1(1)	5(1)
C(25)	31(1)	26(1)	44(1)	0(1)	5(1)	0(1)
C(26)	37(1)	30(1)	37(1)	-2(1)	2(1)	-4(1)

C(27)	39(1)	28(1)	34(1)	4(1)	0(1)	1(1)
C(28)	45(1)	29(1)	60(2)	-5(1)	4(1)	4(1)

Table 5. Bond lengths [Å] and angles [°] for C28 H38 Br N O5 S

Br(1)-C(4)	1.969(2)
S(1)-O(3)	1.4306(16)
S(1)-O(4)	1.4370(16)
S(1)-N(1)	1.6080(16)
S(1)-C(22)	1.766(2)
O(1)-C(1)	1.336(2)
O(1)-C(5)	1.457(2)
O(2)-C(1)	1.218(3)
O(5)-C(12)	1.380(3)
O(5)-C(15)	1.416(3)
N(1)-C(8)	1.473(3)
C(1)-C(2)	1.508(3)
C(2)-C(3)	1.540(3)
C(2)-C(16)	1.546(3)
C(3)-C(4)	1.510(3)
C(4)-C(5)	1.512(3)
C(5)-C(6)	1.515(3)
C(6)-C(7)	1.545(3)
C(7)-C(19)	1.547(3)
C(7)-C(8)	1.553(3)
C(8)-C(9)	1.523(3)
C(9)-C(10)	1.380(3)
C(9)-C(14)	1.398(3)
C(10)-C(11)	1.402(3)
C(11)-C(12)	1.383(3)
C(12)-C(13)	1.391(3)
C(13)-C(14)	1.386(3)
C(16)-C(18)	1.526(4)
C(16)-C(17)	1.527(4)
C(19)-C(21)	1.523(3)
C(19)-C(20)	1.527(3)
C(22)-C(23)	1.378(3)
C(22)-C(27)	1.388(3)
C(23)-C(24)	1.397(3)
C(24)-C(25)	1.387(3)
C(25)-C(26)	1.395(3)
C(25)-C(28)	1.505(3)
C(26)-C(27)	1.381(3)
O(3)-S(1)-O(4)	119.86(10)
O(3)-S(1)-N(1)	108.50(9)
O(4)-S(1)-N(1)	106.20(10)
O(3)-S(1)-C(22)	106.39(10)
O(4)-S(1)-C(22)	108.24(10)

N(1)-S(1)-C(22)	107.06(9)
C(1)-O(1)-C(5)	121.92(16)
C(12)-O(5)-C(15)	117.40(18)
C(8)-N(1)-S(1)	122.19(14)
O(2)-C(1)-O(1)	116.23(18)
O(2)-C(1)-C(2)	121.66(18)
O(1)-C(1)-C(2)	122.11(17)
C(1)-C(2)-C(3)	114.58(18)
C(1)-C(2)-C(16)	111.78(19)
C(3)-C(2)-C(16)	110.91(19)
C(4)-C(3)-C(2)	112.18(18)
C(3)-C(4)-C(5)	108.78(18)
C(3)-C(4)-BR1	109.61(16)
C(5)-C(4)-BR1	111.60(15)
O(1)-C(5)-C(4)	110.02(16)
O(1)-C(5)-C(6)	105.34(15)
C(4)-C(5)-C(6)	117.88(17)
C(5)-C(6)-C(7)	115.22(16)
C(6)-C(7)-C(19)	111.98(16)
C(6)-C(7)-C(8)	111.22(16)
C(19)-C(7)-C(8)	111.42(16)
N(1)-C(8)-C(9)	112.41(16)
N(1)-C(8)-C(7)	108.77(15)
C(9)-C(8)-C(7)	112.98(16)
C(10)-C(9)-C(14)	118.24(19)
C(10)-C(9)-C(8)	120.68(19)
C(14)-C(9)-C(8)	120.96(18)
C(9)-C(10)-C(11)	121.6(2)
C(12)-C(11)-C(10)	119.1(2)
O(5)-C(12)-C(11)	124.26(19)
O(5)-C(12)-C(13)	115.59(18)
C(11)-C(12)-C(13)	120.16(19)
C(14)-C(13)-C(12)	119.8(2)
C(13)-C(14)-C(9)	121.02(19)
C(18)-C(16)-C(17)	111.6(3)
C(18)-C(16)-C(2)	112.7(2)
C(17)-C(16)-C(2)	111.8(2)
C(21)-C(19)-C(20)	110.41(19)
C(21)-C(19)-C(7)	113.52(18)
C(20)-C(19)-C(7)	112.17(17)
C(23)-C(22)-C(27)	120.91(19)
C(23)-C(22)-S(1)	120.32(17)
C(27)-C(22)-S(1)	118.77(16)
C(22)-C(23)-C(24)	119.5(2)
C(25)-C(24)-C(23)	120.5(2)
C(24)-C(25)-C(26)	118.72(19)
C(24)-C(25)-C(28)	121.1(2)
C(26)-C(25)-C(28)	120.2(2)

C(27)-C(26)-C(25)	121.2(2)
C(26)-C(27)-C(22)	119.1(2)

Table 6. Torsion angles [°] for C28 H38 Br N O5 S.

O(3)-S(1)-N(1)-C(8)	-51.38(18)
O(4)-S(1)-N(1)-C(8)	178.54(15)
C(22)-S(1)-N(1)-C(8)	63.06(18)
C(5)-O(1)-C(1)-O(2)	176.98(18)
C(5)-O(1)-C(1)-C(2)	-3.8(3)
O(2)-C(1)-C(2)-C(3)	177.5(2)
O(1)-C(1)-C(2)-C(3)	-1.6(3)
O(2)-C(1)-C(2)-C(16)	-55.2(3)
O(1)-C(1)-C(2)-C(16)	125.6(2)
C(1)-C(2)-C(3)-C(4)	-25.4(3)
C(16)-C(2)-C(3)-C(4)	-153.1(2)
C(2)-C(3)-C(4)-C(5)	56.3(3)
C(2)-C(3)-C(4)-BR1	-66.0(2)
C(1)-O(1)-C(5)-C(4)	35.5(2)
C(1)-O(1)-C(5)-C(6)	163.49(17)
C(3)-C(4)-C(5)-O(1)	-60.8(2)
BR1-C(4)-C(5)-O(1)	60.22(19)
C(3)-C(4)-C(5)-C(6)	178.42(18)
BR1-C(4)-C(5)-C(6)	-60.5(2)
O(1)-C(5)-C(6)-C(7)	175.22(16)
C(4)-C(5)-C(6)-C(7)	-61.6(2)
C(5)-C(6)-C(7)-C(19)	146.17(17)
C(5)-C(6)-C(7)-C(8)	-88.4(2)
S(1)-N(1)-C(8)-C(9)	-88.15(19)
S(1)-N(1)-C(8)-C(7)	145.97(14)
C(6)-C(7)-C(8)-N(1)	-179.92(16)
C(19)-C(7)-C(8)-N(1)	-54.2(2)
C(6)-C(7)-C(8)-C(9)	54.5(2)
C(19)-C(7)-C(8)-C(9)	-179.78(17)
N(1)-C(8)-C(9)-C(10)	128.7(2)
C(7)-C(8)-C(9)-C(10)	-107.7(2)
N(1)-C(8)-C(9)-C(14)	-55.3(2)
C(7)-C(8)-C(9)-C(14)	68.3(2)
C(14)-C(9)-C(10)-C(11)	-0.2(3)
C(8)-C(9)-C(10)-C(11)	176.0(2)
C(9)-C(10)-C(11)-C(12)	-0.4(3)
C(15)-O(5)-C(12)-C(11)	8.6(4)
C(15)-O(5)-C(12)-C(13)	-171.5(2)
C(10)-C(11)-C(12)-O(5)	-179.6(2)
C(10)-C(11)-C(12)-C(13)	0.6(3)
O(5)-C(12)-C(13)-C(14)	179.9(2)
C(11)-C(12)-C(13)-C(14)	-0.2(3)
C(12)-C(13)-C(14)-C(9)	-0.4(3)
C(10)-C(9)-C(14)-C(13)	0.5(3)

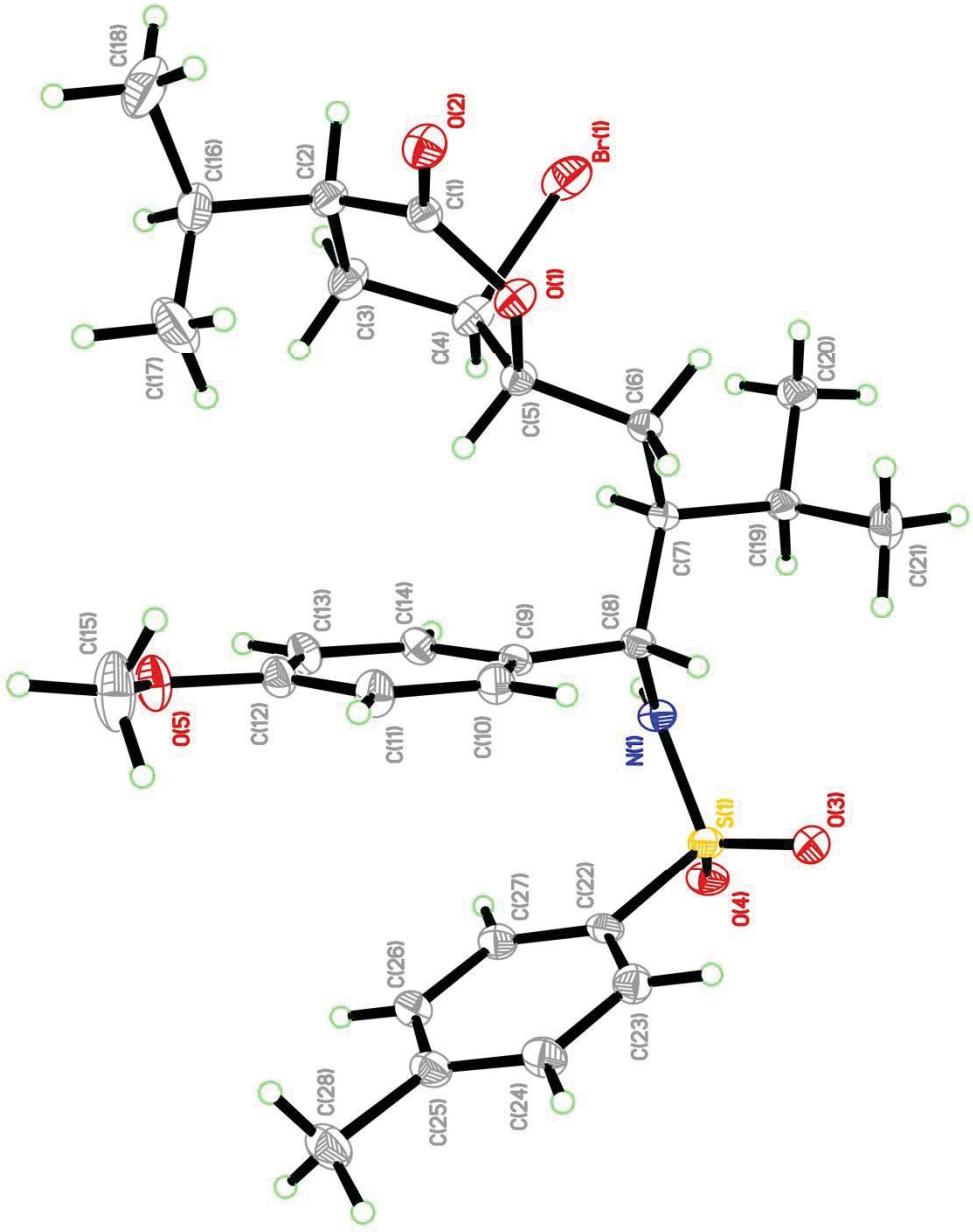
C(8)-C(9)-C(14)-C(13)	-175.61(19)
C(1)-C(2)-C(16)-C(18)	78.3(3)
C(3)-C(2)-C(16)-C(18)	-152.5(2)
C(1)-C(2)-C(16)-C(17)	-48.4(3)
C(3)-C(2)-C(16)-C(17)	80.8(3)
C(6)-C(7)-C(19)-C(21)	59.3(2)
C(8)-C(7)-C(19)-C(21)	-65.9(2)
C(6)-C(7)-C(19)-C(20)	-66.7(2)
C(8)-C(7)-C(19)-C(20)	168.05(18)
O(3)-S(1)-C(22)-C(23)	1.4(2)
O(4)-S(1)-C(22)-C(23)	131.46(17)
N(1)-S(1)-C(22)-C(23)	-114.44(18)
O(3)-S(1)-C(22)-C(27)	-179.33(17)
O(4)-S(1)-C(22)-C(27)	-49.3(2)
N(1)-S(1)-C(22)-C(27)	64.81(19)
C(27)-C(22)-C(23)-C(24)	0.0(3)
S(1)-C(22)-C(23)-C(24)	179.19(16)
C(22)-C(23)-C(24)-C(25)	-0.8(3)
C(23)-C(24)-C(25)-C(26)	1.2(3)
C(23)-C(24)-C(25)-C(28)	-178.0(2)
C(24)-C(25)-C(26)-C(27)	-0.7(3)
C(28)-C(25)-C(26)-C(27)	178.5(2)
C(25)-C(26)-C(27)-C(22)	-0.2(3)
C(23)-C(22)-C(27)-C(26)	0.6(3)
S(1)-C(22)-C(27)-C(26)	-178.70(17)

Table 7. Bond lengths [Å] and angles [°] related to the hydrogen bonding for C28 H38 Br N O5 S.

D-H	..A	d(D-H)	d(H..A)	d(D..A)	<DHA
N(1)-H(1)	O(2)#1	0.88	2.22	2.985(2)	145.8

Symmetry transformations used to generate equivalent atoms:

#1 x+1,y,z


C(18)
C(16)
C(2)
O(2)
C(1)
Br(1)
C(17)
C(3)
C(4)
O(1)
C(5)
C(6)
C(20)
C(7)
C(19)
C(21)
C(15)
C(13)
C(14)
C(9)
C(8)
O(5)
C(12)
C(11)
C(10)
N(1)
Si(1)
O(3)
O(4)
C(27)
C(22)
C(26)
C(23)
C(28)
C(25)
C(24)

ORTEP view of the C28 H38 Br N O5 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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Article 2, Lactone diol **32**

Université de Montréal

CRYSTAL AND MOLECULAR STRUCTURE OF

C21 H32 O5 COMPOUND (robe17)

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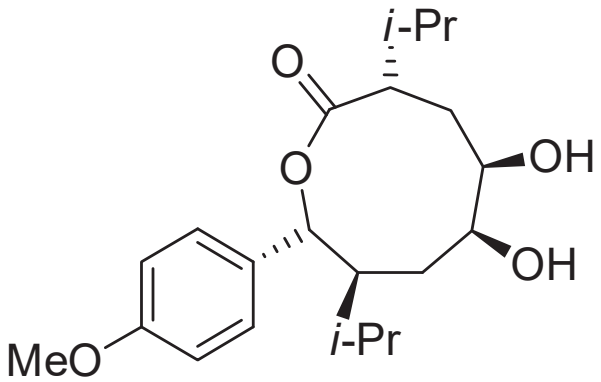


As Ether or Hexane Solvate (Solvent Squeezed Out)

Structure solved and refined in the laboratory of X-ray diffraction
Université de Montréal by Robert D. Giacometti.

Table 1. Crystal data and structure refinement for C21 H32 O5.

Identification code	robe17
Empirical formula	C21 H32 O5 (after squeeze)
Formula weight	364.47 (after squeeze)
Temperature	150K
Wavelength	1.54178 Å
Crystal system	Trigonal
Space group	P32
Unit cell dimensions	a = 25.5016(5) Å α = 90° b = 25.5016(5) Å β = 90° c = 5.8826(1) Å γ = 120°
Volume	3313.10(11)Å^3
Z	6
Density (calculated)	1.096 g/cm^3 (after squeeze)
Absorption coefficient	0.621 mm^{-1} (after squeeze)
F(000)	1188 (after squeeze)
Crystal size	0.21 x 0.06 x 0.02 mm
Theta range for data collection	2.00 to 71.18°
Index ranges	$-31 \leq h \leq 31$, $-30 \leq k \leq 29$, $-7 \leq l \leq 7$
Reflections collected	44115
Independent reflections	8463 [R_{int} = 0.059]
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9877 and 0.8428
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	8463 / 583 / 782

Goodness-of-fit on F^2	1.075
Final R indices [I>2sigma(I)]	R_1 = 0.0477, wR_2 = 0.1379
R indices (all data)	R_1 = 0.0512, wR_2 = 0.1421
Absolute structure parameter	0.09(17)
Largest diff. peak and hole	0.241 and -0.151 e/Å^3

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for C21 H32 O5.

U_{eq} is defined as one third of the trace of the orthogonalized Uij tensor.

	Occ.	x	y	z	U_{eq}
C(12)	1	8035(1)	7995(1)	2709(4)	51(1)
C(17)	1	9700(1)	7982(1)	2264(4)	43(1)
C(18)	1	9111(1)	7440(1)	3189(4)	44(1)
C(22)	1	3372(1)	4703(1)	6038(4)	51(1)
C(27)	1	5051(1)	6368(1)	5599(4)	44(1)
C(28)	1	5004(1)	5777(1)	6521(4)	43(1)
C(115)	1	7609(1)	7600(1)	811(4)	52(1)
C(116)	1	7117(1)	7005(1)	1790(6)	72(1)
C(117)	1	7335(2)	7924(2)	-491(6)	76(1)
C(118)	1	10259(1)	7955(1)	3137(4)	48(1)
C(119)	1	10833(1)	8404(1)	1870(5)	61(1)
C(120)	1	10352(1)	8064(2)	5688(5)	62(1)
C(215)	1	3342(1)	4275(1)	4142(4)	51(1)
C(216)	1	3440(2)	3783(1)	5121(6)	72(1)
C(217)	1	2743(2)	4003(2)	2853(6)	77(1)
C(218)	1	5636(1)	6927(1)	6469(4)	48(1)
C(219)	1	5764(1)	7499(1)	5196(5)	62(1)
C(220)	1	5623(1)	7020(1)	9022(5)	63(1)
O(11)	0.740(6)	8642(2)	7554(2)	2360(6)	33(1)
O(12)	0.740(6)	8297(2)	7535(2)	5914(5)	67(1)
O(13)	0.740(6)	8947(2)	8958(2)	-1975(7)	70(1)
O(14)	0.740(6)	9839(2)	9535(1)	1340(10)	65(1)
O(15)	0.740(6)	8786(2)	5214(2)	-11(8)	74(1)
O(21)	0.740(6)	4420(1)	5309(3)	5692(6)	34(1)
O(22)	0.740(6)	4096(2)	4961(2)	9247(5)	67(1)
O(23)	0.740(6)	3319(2)	5615(1)	1364(7)	69(1)
O(24)	0.740(6)	3638(2)	6507(2)	4696(9)	65(1)
O(25)	0.740(6)	6856(2)	5386(3)	3122(11)	89(2)
C(11)	0.740(6)	8333(2)	7678(2)	3926(6)	51(1)
C(13)	0.740(6)	8543(2)	8610(2)	1843(9)	57(1)
C(14)	0.740(6)	8968(2)	8627(2)	-22(8)	49(1)
C(15)	0.740(6)	9634(2)	8916(2)	711(8)	50(1)
C(16)	0.740(6)	9767(2)	8615(2)	2725(7)	45(1)
C(19)	0.740(6)	8998(1)	6846(2)	2366(7)	45(1)
C(110)	0.740(6)	8757(2)	6611(2)	243(9)	51(1)
C(111)	0.740(6)	8690(2)	6064(2)	-452(9)	55(1)
C(112)	0.740(6)	8861(2)	5740(2)	921(9)	55(1)
C(113)	0.740(6)	9087(3)	5955(2)	3022(9)	57(1)

C(114)	0.740(6)	9156(3)	6508(2)	3754(8)	54(1)
C(121)	0.740(6)	8986(3)	4877(2)	1256(12)	86(1)
C(21)	0.740(6)	3989(2)	5001(2)	7260(6)	52(1)
C(23)	0.740(6)	3263(2)	5207(2)	5177(9)	58(1)
C(24)	0.740(6)	3677(2)	5636(2)	3313(8)	49(1)
C(25)	0.740(6)	4049(2)	6298(2)	4065(9)	48(1)
C(26)	0.740(6)	4487(2)	6430(2)	6046(7)	46(1)
C(29)	0.740(6)	5482(1)	5642(1)	5643(8)	43(1)
C(210)	0.740(6)	5451(2)	5395(2)	3519(8)	45(1)
C(211)	0.740(6)	5915(2)	5310(3)	2762(9)	54(1)
C(212)	0.740(6)	6416(2)	5470(3)	4073(10)	61(1)
C(213)	0.740(6)	6452(2)	5705(3)	6203(10)	63(1)
C(214)	0.740(6)	5985(2)	5786(3)	6959(9)	55(1)
C(221)	0.740(6)	7404(3)	5585(4)	4351(14)	96(2)
O(31)	0.260(6)	8562(7)	7447(7)	2493(18)	58(5)
O(32)	0.260(6)	8470(5)	7857(5)	5785(13)	59(2)
O(33)	0.260(6)	9056(6)	9177(7)	-1320(20)	93(4)
O(34)	0.260(6)	9896(6)	9548(4)	2090(30)	71(4)
O(35)	0.260(6)	8583(6)	5147(4)	-570(20)	92(3)
O(41)	0.260(6)	4448(3)	5222(9)	5828(18)	54(6)
O(42)	0.260(6)	3945(4)	5133(5)	9116(13)	57(2)
O(43)	0.260(6)	3208(5)	5734(5)	2035(19)	91(4)
O(44)	0.260(6)	3682(6)	6573(6)	5450(30)	86(5)
O(45)	0.260(6)	6966(4)	5523(7)	3570(20)	69(2)
C(31)	0.260(6)	8338(5)	7722(5)	3810(13)	51(1)
C(33)	0.260(6)	8546(5)	8705(5)	2230(20)	54(2)
C(34)	0.260(6)	8989(4)	8745(4)	400(19)	63(4)
C(35)	0.260(6)	9628(4)	8935(4)	1279(18)	51(3)
C(36)	0.260(6)	9671(6)	8549(6)	3200(20)	48(2)
C(39)	0.260(6)	8978(3)	6794(3)	2320(17)	43(3)
C(310)	0.260(6)	8722(5)	6613(4)	177(18)	44(3)
C(311)	0.260(6)	8598(6)	6061(4)	-698(18)	55(4)
C(312)	0.260(6)	8726(5)	5678(4)	511(19)	63(4)
C(313)	0.260(6)	8972(7)	5843(5)	2620(20)	73(5)
C(314)	0.260(6)	9100(7)	6402(5)	3532(18)	50(3)
C(321)	0.260(6)	8722(9)	4739(6)	520(30)	92(4)
C(41)	0.260(6)	3950(3)	5005(5)	7135(13)	52(1)
C(43)	0.260(6)	3174(5)	5216(5)	5560(20)	54(2)
C(44)	0.260(6)	3582(4)	5667(4)	3739(19)	68(4)
C(45)	0.260(6)	4024(4)	6300(4)	4643(19)	67(5)
C(46)	0.260(6)	4455(5)	6344(7)	6530(20)	45(2)
C(49)	0.260(6)	5529(3)	5709(3)	5807(17)	41(3)
C(410)	0.260(6)	5530(4)	5475(6)	3686(19)	49(3)
C(411)	0.260(6)	6017(4)	5418(7)	3008(19)	56(4)
C(412)	0.260(6)	6504(4)	5589(6)	4407(19)	50(3)
C(413)	0.260(6)	6512(5)	5820(8)	6520(20)	54(3)
C(414)	0.260(6)	6024(5)	5876(7)	7194(18)	44(2)
C(421)	0.260(6)	7500(5)	5753(8)	4920(30)	76(3)

Table 3. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for C21 H32 O5.

	Occ.	x	y	z	U_{eq}
H(12)	1	7791	8072	3850	62
H(17)	1	9692	7933	576	52
H(18)	1	9116	7446	4889	53
H(22)	1	3051	4458	7180	61
H(27)	1	5092	6359	3911	53
H(28)	1	5006	5781	8221	52
H(115)	1	7851	7507	-286	62
H(11A)	1	7303	6813	2661	108
H(11B)	1	6875	6737	550	108
H(11C)	1	6856	7082	2792	108
H(11D)	1	7118	8045	570	113
H(11E)	1	7052	7651	-1640	113
H(11F)	1	7659	8285	-1238	113
H(118)	1	10188	7539	2826	58
H(11G)	1	10923	8818	2190	92
H(11H)	1	10772	8327	232	92
H(11I)	1	11172	8354	2373	92
H(12A)	1	10722	8067	6147	93
H(12B)	1	10005	7741	6498	93
H(12C)	1	10387	8455	6061	93
H(215)	1	3676	4515	3041	61
H(21A)	1	3106	3530	6151	108
H(21B)	1	3823	3968	5963	108
H(21C)	1	3455	3533	3885	108
H(21D)	1	2407	3787	3920	115
H(21E)	1	2731	3719	1701	115
H(21F)	1	2706	4327	2111	115
H(218)	1	5980	6854	6157	58
H(21G)	1	5439	7589	5500	92
H(21H)	1	5784	7439	3560	92
H(21I)	1	6151	7839	5709	92
H(22A)	1	5999	7383	9484	94
H(22B)	1	5585	6667	9830	94
H(22C)	1	5277	7072	9394	94
H(13)	0.740(6)	9263	9300	-2017	106
H(14)	0.740(6)	10127	9768	490	98
H(23)	0.740(6)	3326	5946	1244	103
H(24)	0.740(6)	3680	6781	3798	97
H(13A)	0.740(6)	8351	8840	1287	69
H(13B)	0.740(6)	8796	8833	3167	69

H(14A)	0.740(6) 8827	8201	-507	59
H(15)	0.740(6) 9877	8916	-625	60
H(16A)	0.740(6) 9492	8572	3988	54
H(16B)	0.740(6)10186	8891	3247	54
H(110)	0.740(6) 8638	6828	-739	61
H(111)	0.740(6) 8523	5908	-1907	66
H(113)	0.740(6) 9198	5729	3997	68
H(114)	0.740(6) 9315	6655	5226	64
H(12D)	0.740(6) 9416	5135	1626	129
H(12E)	0.740(6) 8931	4530	357	129
H(12F)	0.740(6) 8751	4734	2664	129
H(23A)	0.740(6) 3288	5458	6501	69
H(23B)	0.740(6) 2842	5013	4606	69
H(24A)	0.740(6) 3963	5496	2823	58
H(25)	0.740(6) 4290	6541	2728	58
H(26A)	0.740(6) 4256	6156	7313	55
H(26B)	0.740(6) 4628	6849	6570	55
H(210)	0.740(6) 5108	5283	2579	55
H(211)	0.740(6) 5886	5138	1304	65
H(213)	0.740(6) 6794	5810	7144	76
H(214)	0.740(6) 6010	5946	8439	66
H(22D)	0.740(6) 7585	6018	4694	144
H(22E)	0.740(6) 7686	5519	3433	144
H(22F)	0.740(6) 7317	5356	5773	144
H(33)	0.260(6) 9190	9520	-725	140
H(34)	0.260(6) 9739	9552	3342	107
H(43)	0.260(6) 3117	5991	2477	136
H(44)	0.260(6) 3335	6300	5846	129
H(33A)	0.260(6) 8343	8930	1726	65
H(33B)	0.260(6) 8769	8893	3650	65
H(34A)	0.260(6) 8820	8338	-334	75
H(35)	0.260(6) 9875	8929	-33	61
H(36A)	0.260(6) 9315	8407	4208	57
H(36B)	0.260(6) 10038	8804	4116	57
H(310)	0.260(6) 8631	6871	-694	53
H(311)	0.260(6) 8422	5943	-2165	66
H(313)	0.260(6) 9057	5579	3478	87
H(314)	0.260(6) 9273	6514	5006	60
H(12G)	0.260(6) 8382	4463	1484	138
H(12H)	0.260(6) 9086	4965	1453	138
H(12I)	0.260(6) 8796	4505	-631	138
H(43A)	0.260(6) 2747	5015	5054	65
H(43B)	0.260(6) 3208	5436	6991	65
H(44A)	0.260(6) 3820	5501	2988	81
H(45)	0.260(6) 4276	6548	3334	80
H(46A)	0.260(6) 4241	5990	7550	54
H(46B)	0.260(6) 4571	6712	7442	54
H(410)	0.260(6) 5194	5353	2695	59
H(411)	0.260(6) 6013	5257	1548	67
H(413)	0.260(6) 6848	5939	7507	64

H(414)	0.260(6)	6029	6036	8659	53
H(42D)	0.260(6)	7396	5561	6418	113
H(42E)	0.260(6)	7680	6192	5086	113
H(42F)	0.260(6)	7790	5664	4173	113

Table 4. Anisotropic parameters ($Å^2$ x 10^3) for C21 H32 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
C(12)	41(1)	55(1)	63(1)	-11(1)	4(1)	28(1)
C(17)	39(1)	49(1)	42(1)	-4(1)	-5(1)	22(1)
C(18)	44(1)	57(1)	36(1)	0(1)	-1(1)	29(1)
C(22)	40(1)	42(1)	61(1)	2(1)	14(1)	13(1)
C(27)	45(1)	40(1)	42(1)	-5(1)	-1(1)	17(1)
C(28)	43(1)	41(1)	36(1)	-1(1)	-1(1)	13(1)
C(115)	46(1)	53(1)	59(1)	-3(1)	-2(1)	27(1)
C(116)	54(1)	60(2)	88(2)	3(1)	-9(1)	17(1)
C(117)	64(2)	75(2)	91(2)	7(2)	-8(1)	38(1)
C(118)	42(1)	58(1)	48(1)	-9(1)	-7(1)	27(1)
C(119)	40(1)	78(2)	62(1)	-7(1)	-4(1)	26(1)
C(120)	55(1)	82(2)	50(1)	-9(1)	-12(1)	35(1)
C(215)	46(1)	45(1)	57(1)	-1(1)	2(1)	19(1)
C(216)	75(2)	53(1)	89(2)	-8(1)	-10(1)	33(1)
C(217)	63(2)	62(2)	92(2)	-6(1)	-15(2)	22(1)
C(218)	44(1)	43(1)	47(1)	-7(1)	4(1)	14(1)
C(219)	64(2)	41(1)	63(1)	-4(1)	4(1)	14(1)
C(220)	66(2)	57(1)	51(1)	-13(1)	-3(1)	21(1)
O(11)	29(1)	37(1)	35(2)	-4(1)	0(1)	17(1)
O(12)	78(2)	96(3)	44(1)	12(2)	17(1)	57(2)
O(13)	55(2)	58(2)	97(2)	30(2)	6(1)	27(1)
O(14)	63(2)	42(1)	85(4)	-1(1)	25(2)	21(1)
O(15)	83(3)	57(2)	99(2)	-5(1)	6(2)	47(2)
O(21)	32(2)	30(1)	36(2)	2(1)	4(1)	13(1)
O(22)	58(2)	80(2)	44(1)	18(1)	6(1)	21(2)
O(23)	58(2)	55(1)	95(2)	5(1)	-25(1)	29(1)
O(24)	61(2)	60(2)	87(3)	26(2)	27(2)	41(2)
O(25)	59(2)	100(4)	108(3)	12(2)	14(2)	40(2)
C(11)	45(1)	67(2)	44(1)	-9(1)	3(1)	30(1)
C(13)	46(1)	41(2)	93(3)	-14(2)	4(2)	28(1)
C(14)	47(2)	37(2)	66(2)	3(2)	10(1)	22(1)
C(15)	49(2)	45(2)	55(2)	3(1)	16(1)	23(1)
C(16)	32(2)	48(2)	48(2)	-2(1)	11(1)	14(1)

C(19)	38(2)	50(2)	46(2)	9(2)	4(2)	23(2)
C(110)	53(2)	51(2)	49(2)	3(2)	2(2)	27(2)
C(111)	59(2)	54(2)	56(2)	-3(2)	8(2)	30(2)
C(112)	48(2)	44(2)	78(3)	9(2)	13(2)	26(2)
C(113)	53(2)	53(2)	74(2)	16(2)	6(2)	34(2)
C(114)	56(2)	53(2)	54(2)	8(1)	1(2)	28(2)
C(121)	101(3)	71(2)	112(3)	1(2)	4(2)	62(2)
C(21)	52(1)	45(1)	45(1)	3(1)	13(1)	14(1)
C(23)	32(2)	45(1)	95(3)	4(2)	20(2)	19(1)
C(24)	37(2)	48(2)	66(2)	9(1)	5(2)	25(1)
C(25)	44(2)	48(2)	57(2)	14(1)	11(1)	27(2)
C(26)	50(1)	33(2)	48(2)	12(1)	14(1)	16(1)
C(29)	38(2)	35(2)	46(2)	5(1)	-4(1)	10(1)
C(210)	40(2)	48(2)	44(2)	0(1)	-1(1)	18(2)
C(211)	51(2)	52(2)	57(2)	8(2)	9(2)	24(2)
C(212)	39(2)	55(3)	84(3)	19(2)	14(2)	21(2)
C(213)	41(2)	54(3)	81(3)	7(2)	-14(2)	13(2)
C(214)	52(2)	47(2)	57(2)	-2(2)	-8(2)	17(2)
C(221)	68(2)	114(3)	113(3)	6(2)	3(2)	51(2)
O(31)	55(8)	66(9)	48(6)	15(5)	8(4)	27(6)
O(32)	66(5)	76(6)	38(4)	6(4)	9(3)	39(5)
O(33)	87(6)	85(6)	111(6)	1(4)	-7(4)	47(4)
O(34)	65(5)	63(5)	80(9)	1(4)	12(5)	28(4)
O(35)	92(6)	79(4)	107(5)	-4(4)	-1(5)	45(4)
O(41)	61(7)	51(8)	45(5)	5(4)	-5(4)	23(5)
O(42)	59(5)	70(5)	38(4)	9(3)	5(3)	28(4)
O(43)	82(5)	84(5)	108(6)	-11(4)	-4(4)	42(4)
O(44)	75(6)	74(6)	98(10)	10(5)	10(6)	31(5)
O(45)	38(3)	82(5)	101(5)	6(4)	8(3)	41(4)
C(31)	45(1)	67(2)	44(1)	-9(1)	3(1)	30(1)
C(33)	46(3)	35(3)	91(4)	-20(3)	6(3)	27(2)
C(34)	66(6)	30(5)	98(8)	-7(5)	-5(6)	28(4)
C(35)	42(3)	51(4)	65(5)	-2(4)	14(3)	28(3)
C(36)	31(3)	51(2)	50(3)	-3(2)	9(2)	12(2)
C(39)	37(4)	48(4)	49(4)	5(4)	15(4)	26(3)
C(310)	50(4)	49(4)	44(4)	-3(4)	8(4)	32(3)
C(311)	47(5)	62(6)	61(6)	7(5)	2(4)	30(4)
C(312)	46(6)	65(7)	75(7)	-8(5)	13(5)	27(5)
C(313)	55(7)	65(7)	96(9)	11(6)	7(6)	29(5)
C(314)	45(4)	59(5)	57(4)	11(4)	4(3)	35(4)
C(321)	94(5)	88(5)	99(5)	-2(3)	-1(3)	50(3)
C(41)	52(1)	45(1)	45(1)	3(1)	13(1)	14(1)
C(43)	30(2)	44(2)	94(3)	2(2)	23(2)	23(2)
C(44)	44(5)	66(6)	106(9)	-1(6)	12(5)	37(4)
C(45)	56(6)	46(6)	82(8)	10(5)	24(5)	13(5)
C(46)	52(2)	30(2)	50(3)	9(2)	14(2)	18(2)
C(49)	40(4)	35(4)	41(4)	-1(3)	1(4)	13(3)
C(410)	47(4)	46(4)	53(4)	1(4)	-5(4)	20(4)
C(411)	49(6)	53(6)	60(6)	2(5)	6(5)	22(5)
C(412)	35(5)	42(5)	68(6)	3(4)	-14(4)	16(4)

C(413)	37(4)	50(5)	70(4)	-5(4)	-15(3)	18(4)
C(414)	38(3)	48(4)	49(4)	-7(3)	-14(3)	23(3)
C(421)	67(4)	82(4)	84(4)	-3(3)	-2(3)	41(3)

Table 5. Bond lengths [Å] and angles [°] for C21 H32 O5

C(12)-C(31)	1.429(7)
C(12)-C(115)	1.532(3)
C(12)-C(11)	1.535(4)
C(12)-C(13)	1.538(5)
C(12)-C(33)	1.642(10)
C(17)-C(18)	1.546(3)
C(17)-C(118)	1.549(3)
C(17)-C(16)	1.557(5)
C(17)-C(36)	1.583(13)
C(18)-O(11)	1.448(3)
C(18)-O(31)	1.468(11)
C(18)-C(19)	1.476(4)
C(18)-C(39)	1.591(7)
C(22)-C(41)	1.430(7)
C(22)-C(23)	1.531(5)
C(22)-C(215)	1.536(3)
C(22)-C(21)	1.540(4)
C(22)-C(43)	1.644(10)
C(27)-C(218)	1.547(3)
C(27)-C(28)	1.547(3)
C(27)-C(26)	1.548(5)
C(27)-C(46)	1.588(12)
C(28)-O(21)	1.450(4)
C(28)-O(41)	1.475(13)
C(28)-C(49)	1.494(7)
C(28)-C(29)	1.515(4)
C(115)-C(116)	1.517(4)
C(115)-C(117)	1.529(4)
C(118)-C(120)	1.523(3)
C(118)-C(119)	1.527(4)
C(215)-C(216)	1.509(4)
C(215)-C(217)	1.526(4)
C(218)-C(220)	1.524(3)
C(218)-C(219)	1.525(4)
O(11)-C(11)	1.349(3)
O(12)-C(11)	1.214(4)
O(13)-C(14)	1.443(4)
O(14)-C(15)	1.441(4)
O(15)-C(112)	1.370(4)
O(15)-C(121)	1.412(6)
O(21)-C(21)	1.347(3)
O(22)-C(21)	1.216(4)
O(23)-C(24)	1.451(4)
O(24)-C(25)	1.442(4)

O(25)-C(212)	1.361(4)
O(25)-C(221)	1.422(7)
C(13)-C(14)	1.527(5)
C(14)-C(15)	1.538(4)
C(15)-C(16)	1.539(5)
C(19)-C(114)	1.385(4)
C(19)-C(110)	1.388(4)
C(110)-C(111)	1.380(4)
C(111)-C(112)	1.372(6)
C(112)-C(113)	1.358(7)
C(113)-C(114)	1.400(6)
C(23)-C(24)	1.536(5)
C(24)-C(25)	1.531(5)
C(25)-C(26)	1.529(5)
C(29)-C(214)	1.381(4)
C(29)-C(210)	1.383(4)
C(210)-C(211)	1.380(4)
C(211)-C(212)	1.369(6)
C(212)-C(213)	1.372(7)
C(213)-C(214)	1.381(5)
O(31)-C(31)	1.346(3)
O(32)-C(31)	1.211(4)
O(33)-C(34)	1.444(4)
O(34)-C(35)	1.441(5)
O(35)-C(312)	1.369(5)
O(35)-C(321)	1.411(6)
O(41)-C(41)	1.344(3)
O(42)-C(41)	1.213(4)
O(43)-C(44)	1.452(4)
O(44)-C(45)	1.441(5)
O(45)-C(412)	1.362(5)
O(45)-C(421)	1.425(7)
C(33)-C(34)	1.527(6)
C(34)-C(35)	1.537(5)
C(35)-C(36)	1.538(5)
C(39)-C(314)	1.384(4)
C(39)-C(310)	1.389(4)
C(310)-C(311)	1.380(4)
C(311)-C(312)	1.372(6)
C(312)-C(313)	1.358(7)
C(313)-C(314)	1.400(6)
C(43)-C(44)	1.536(5)
C(44)-C(45)	1.530(5)
C(45)-C(46)	1.528(5)
C(49)-C(414)	1.380(4)
C(49)-C(410)	1.383(4)
C(410)-C(411)	1.380(4)
C(411)-C(412)	1.368(6)
C(412)-C(413)	1.372(7)

C(413)-C(414) 1.381(5)

C(31)-C(12)-C(115) 112.9(4)
C(31)-C(12)-C(11) 2.6(6)
C(115)-C(12)-C(11) 111.6(2)
C(31)-C(12)-C(13) 105.2(6)
C(115)-C(12)-C(13) 112.8(3)
C(11)-C(12)-C(13) 107.8(3)
C(31)-C(12)-C(33) 107.0(5)
C(115)-C(12)-C(33) 120.7(6)
C(11)-C(12)-C(33) 109.5(5)
C(13)-C(12)-C(33) 11.3(5)
C(18)-C(17)-C(118) 110.42(18)
C(18)-C(17)-C(16) 114.8(2)
C(118)-C(17)-C(16) 111.2(2)
C(18)-C(17)-C(36) 103.1(6)
C(118)-C(17)-C(36) 113.0(5)
C(16)-C(17)-C(36) 12.9(5)
O(11)-C(18)-O(31) 10.1(8)
O(11)-C(18)-C(19) 109.8(2)
O(31)-C(18)-C(19) 102.9(6)
O(11)-C(18)-C(17) 103.5(3)

O(31)-C(18)-C(17) 113.5(7)
C(19)-C(18)-C(17) 113.95(18)
O(11)-C(18)-C(39) 109.2(4)
O(31)-C(18)-C(39) 102.3(5)
C(19)-C(18)-C(39) 1.0(3)
C(17)-C(18)-C(39) 114.9(2)
C(41)-C(22)-C(23) 105.6(6)
C(41)-C(22)-C(215) 112.5(4)
C(23)-C(22)-C(215) 113.0(3)
C(41)-C(22)-C(21) 2.5(6)
C(23)-C(22)-C(21) 108.1(3)
C(215)-C(22)-C(21) 111.5(2)
C(41)-C(22)-C(43) 107.0(5)
C(23)-C(22)-C(43) 11.2(5)
C(215)-C(22)-C(43) 121.1(6)
C(21)-C(22)-C(43) 109.3(5)
C(218)-C(27)-C(28) 110.49(18)
C(218)-C(27)-C(26) 111.5(2)
C(28)-C(27)-C(26) 114.7(2)
C(218)-C(27)-C(46) 112.7(5)
C(28)-C(27)-C(46) 103.6(6)
C(26)-C(27)-C(46) 12.5(6)
O(21)-C(28)-O(41) 10.8(10)
O(21)-C(28)-C(49) 114.8(5)
O(41)-C(28)-C(49) 107.3(7)
O(21)-C(28)-C(29) 108.0(3)
O(41)-C(28)-C(29) 100.6(7)

C(49)-C(28)-C(29) 6.8(5)
O(21)-C(28)-C(27) 103.4(3)
O(41)-C(28)-C(27) 114.0(8)
C(49)-C(28)-C(27) 112.2(3)
C(29)-C(28)-C(27) 115.00(18)
C(116)-C(115)-C(117) 111.0(2)
C(116)-C(115)-C(12) 109.9(2)
C(117)-C(115)-C(12) 112.1(2)
C(120)-C(118)-C(119) 110.0(2)
C(120)-C(118)-C(17) 112.34(18)
C(119)-C(118)-C(17) 111.3(2)
C(216)-C(215)-C(217) 110.8(2)
C(216)-C(215)-C(22) 110.0(2)
C(217)-C(215)-C(22) 111.6(2)
C(220)-C(218)-C(219) 110.1(2)
C(220)-C(218)-C(27) 112.56(19)
C(219)-C(218)-C(27) 111.5(2)
C(11)-O(11)-C(18) 117.1(2)
C(112)-O(15)-C(121) 117.9(4)
C(21)-O(21)-C(28) 116.9(2)
C(212)-O(25)-C(221) 118.3(5)
O(12)-C(11)-O(11) 123.6(3)
O(12)-C(11)-C(12) 128.6(3)
O(11)-C(11)-C(12) 107.8(3)
C(14)-C(13)-C(12) 119.4(4)
O(13)-C(14)-C(13) 110.8(3)
O(13)-C(14)-C(15) 107.3(3)
C(13)-C(14)-C(15) 114.2(4)
O(14)-C(15)-C(14) 107.8(3)
O(14)-C(15)-C(16) 107.4(3)
C(14)-C(15)-C(16) 116.3(3)
C(15)-C(16)-C(17) 116.4(3)
C(114)-C(19)-C(110) 117.7(3)
C(114)-C(19)-C(18) 118.5(3)
C(110)-C(19)-C(18) 123.8(3)
C(111)-C(110)-C(19) 120.5(3)
C(112)-C(111)-C(110) 121.2(4)
C(113)-C(112)-O(15) 125.6(4)
C(113)-C(112)-C(111) 119.4(3)
O(15)-C(112)-C(111) 115.0(4)
C(112)-C(113)-C(114) 120.1(3)
C(19)-C(114)-C(113) 121.1(3)
O(22)-C(21)-O(21) 123.7(3)
O(22)-C(21)-C(22) 128.6(3)
O(21)-C(21)-C(22) 107.6(3)
C(22)-C(23)-C(24) 119.0(4)
O(23)-C(24)-C(25) 107.5(3)
O(23)-C(24)-C(23) 109.9(3)
C(25)-C(24)-C(23) 113.9(4)
O(24)-C(25)-C(26) 107.8(4)

O(24)-C(25)-C(24) 108.5(3)
C(26)-C(25)-C(24) 116.4(3)
C(25)-C(26)-C(27) 117.4(3)
C(214)-C(29)-C(210) 117.6(3)
C(214)-C(29)-C(28) 119.7(3)
C(210)-C(29)-C(28) 122.8(3)
C(211)-C(210)-C(29) 120.2(3)
C(212)-C(211)-C(210) 121.3(4)
O(25)-C(212)-C(211) 116.2(5)
O(25)-C(212)-C(213) 124.3(4)
C(211)-C(212)-C(213) 119.5(3)
C(212)-C(213)-C(214) 119.0(3)
C(29)-C(214)-C(213) 122.4(4)
C(31)-O(31)-C(18) 120.0(7)
C(312)-O(35)-C(321) 118.5(6)
C(41)-O(41)-C(28) 119.6(8)
C(412)-O(45)-C(421) 116.9(6)
O(32)-C(31)-O(31) 124.9(5)
O(32)-C(31)-C(12) 115.8(6)
O(31)-C(31)-C(12) 117.7(6)
C(34)-C(33)-C(12) 110.3(8)
O(33)-C(34)-C(33) 110.2(4)
O(33)-C(34)-C(35) 107.1(4)
C(33)-C(34)-C(35) 114.7(5)
O(34)-C(35)-C(34) 107.9(4)
O(34)-C(35)-C(36) 107.6(4)
C(34)-C(35)-C(36) 116.7(4)
C(35)-C(36)-C(17) 112.3(8)
C(314)-C(39)-C(310) 117.7(4)
C(314)-C(39)-C(18) 125.1(6)
C(310)-C(39)-C(18) 117.2(6)
C(311)-C(310)-C(39) 120.5(4)
C(312)-C(311)-C(310) 121.3(4)
C(313)-C(312)-O(35) 125.8(5)
C(313)-C(312)-C(311) 119.3(4)
O(35)-C(312)-C(311) 114.9(5)
C(312)-C(313)-C(314) 120.1(4)
C(39)-C(314)-C(313) 121.1(4)
O(42)-C(41)-O(41) 125.1(5)
O(42)-C(41)-C(22) 115.5(6)
O(41)-C(41)-C(22) 118.1(5)
C(44)-C(43)-C(22) 110.6(8)
O(43)-C(44)-C(45) 107.2(4)
O(43)-C(44)-C(43) 109.3(4)
C(45)-C(44)-C(43) 114.4(5)
O(44)-C(45)-C(46) 108.2(5)
O(44)-C(45)-C(44) 108.7(4)
C(46)-C(45)-C(44) 116.9(4)
C(45)-C(46)-C(27) 113.1(8)
C(414)-C(49)-C(410) 118.0(3)

C(414)-C(49)-C(28)	122.1(6)
C(410)-C(49)-C(28)	119.9(6)
C(411)-C(410)-C(49)	120.1(4)
C(412)-C(411)-C(410)	121.0(4)
O(45)-C(412)-C(411)	116.4(5)
O(45)-C(412)-C(413)	123.7(5)
C(411)-C(412)-C(413)	119.9(4)
C(412)-C(413)-C(414)	119.0(4)
C(49)-C(414)-C(413)	122.1(4)

Table 6. Torsion angles [°] for C21 H32 O5.

C(118)-C(17)-C(18)-O(11)	176.24(18)
C(16)-C(17)-C(18)-O(11)	49.6(3)
C(36)-C(17)-C(18)-O(11)	55.3(4)
C(118)-C(17)-C(18)-O(31)	178.0(4)
C(16)-C(17)-C(18)-O(31)	51.4(5)
C(36)-C(17)-C(18)-O(31)	57.1(6)
C(118)-C(17)-C(18)-C(19)	-64.6(3)
C(16)-C(17)-C(18)-C(19)	168.8(3)
C(36)-C(17)-C(18)-C(19)	174.5(4)
C(118)-C(17)-C(18)-C(39)	-64.7(5)
C(16)-C(17)-C(18)-C(39)	168.6(5)
C(36)-C(17)-C(18)-C(39)	174.3(6)
C(218)-C(27)-C(28)-O(21)	176.18(19)
C(26)-C(27)-C(28)-O(21)	49.1(3)
C(46)-C(27)-C(28)-O(21)	55.3(4)
C(218)-C(27)-C(28)-O(41)	178.2(4)
C(26)-C(27)-C(28)-O(41)	51.1(5)
C(46)-C(27)-C(28)-O(41)	57.4(6)
C(218)-C(27)-C(28)-C(49)	-59.6(5)
C(26)-C(27)-C(28)-C(49)	173.3(5)
C(46)-C(27)-C(28)-C(49)	179.5(6)
C(218)-C(27)-C(28)-C(29)	-66.3(3)
C(26)-C(27)-C(28)-C(29)	166.6(3)
C(46)-C(27)-C(28)-C(29)	172.8(4)
C(31)-C(12)-C(115)-C(116)	61.5(5)
C(11)-C(12)-C(115)-C(116)	59.0(3)
C(13)-C(12)-C(115)-C(116)	-179.4(3)
C(33)-C(12)-C(115)-C(116)	-170.3(5)
C(31)-C(12)-C(115)-C(117)	-174.6(5)
C(11)-C(12)-C(115)-C(117)	-177.1(3)
C(13)-C(12)-C(115)-C(117)	-55.6(3)
C(33)-C(12)-C(115)-C(117)	-46.4(5)
C(18)-C(17)-C(118)-C(120)	-68.1(3)
C(16)-C(17)-C(118)-C(120)	60.5(3)
C(36)-C(17)-C(118)-C(120)	46.7(6)
C(18)-C(17)-C(118)-C(119)	168.06(19)
C(16)-C(17)-C(118)-C(119)	-63.3(3)
C(36)-C(17)-C(118)-C(119)	-77.1(6)
C(41)-C(22)-C(215)-C(216)	61.8(5)
C(23)-C(22)-C(215)-C(216)	-178.8(2)
C(21)-C(22)-C(215)-C(216)	59.3(3)
C(43)-C(22)-C(215)-C(216)	-170.0(5)
C(41)-C(22)-C(215)-C(217)	-174.8(5)

C(23)-C(22)-C(215)-C(217) -55.3(3)
C(21)-C(22)-C(215)-C(217) -177.2(3)
C(43)-C(22)-C(215)-C(217) -46.6(5)
C(28)-C(27)-C(218)-C(220) -68.0(3)
C(26)-C(27)-C(218)-C(220) 60.8(3)
C(46)-C(27)-C(218)-C(220) 47.3(6)
C(28)-C(27)-C(218)-C(219) 167.66(19)
C(26)-C(27)-C(218)-C(219) -63.5(3)
C(46)-C(27)-C(218)-C(219) -77.0(6)
O(31)-C(18)-O(11)-C(11) 76(2)
C(19)-C(18)-O(11)-C(11) 124.4(4)
C(17)-C(18)-O(11)-C(11) -113.6(4)
C(39)-C(18)-O(11)-C(11) 123.6(5)
O(41)-C(28)-O(21)-C(21) 77(2)

C(49)-C(28)-O(21)-C(21) 124.0(6)
C(29)-C(28)-O(21)-C(21) 124.2(5)
C(27)-C(28)-O(21)-C(21) -113.5(5)
C(18)-O(11)-C(11)-O(12) -21.7(7)
C(18)-O(11)-C(11)-C(12) 160.3(4)
C(31)-C(12)-C(11)-O(12) 122(10)
C(115)-C(12)-C(11)-O(12)-119.1(5)
C(13)-C(12)-C(11)-O(12) 116.5(6)
C(33)-C(12)-C(11)-O(12) 104.7(8)
C(31)-C(12)-C(11)-O(11) -60(9)
C(115)-C(12)-C(11)-O(11) 58.8(4)
C(13)-C(12)-C(11)-O(11) -65.6(5)
C(33)-C(12)-C(11)-O(11) -77.4(6)
C(31)-C(12)-C(13)-C(14) 66.3(5)
C(115)-C(12)-C(13)-C(14) -57.2(4)
C(11)-C(12)-C(13)-C(14) 66.5(4)
C(33)-C(12)-C(13)-C(14) 167(3)
C(12)-C(13)-C(14)-O(13) 121.7(4)
C(12)-C(13)-C(14)-C(15) -116.9(4)
O(13)-C(14)-C(15)-O(14) 61.9(5)
C(13)-C(14)-C(15)-O(14) -61.4(4)
O(13)-C(14)-C(15)-C(16) -177.5(4)
C(13)-C(14)-C(15)-C(16) 59.2(5)
O(14)-C(15)-C(16)-C(17) -168.5(3)
C(14)-C(15)-C(16)-C(17) 70.7(4)
C(18)-C(17)-C(16)-C(15) -102.2(3)
C(118)-C(17)-C(16)-C(15) 131.5(2)
C(36)-C(17)-C(16)-C(15) -128(2)
O(11)-C(18)-C(19)-C(114) -146.3(4)
O(31)-C(18)-C(19)-C(114) -138.6(6)
C(17)-C(18)-C(19)-C(114) 98.2(3)
C(39)-C(18)-C(19)-C(114) -90(32)
O(11)-C(18)-C(19)-C(110) 35.7(4)
O(31)-C(18)-C(19)-C(110) 43.4(7)
C(17)-C(18)-C(19)-C(110) -79.9(3)

C(39)-C(18)-C(19)-C(110) 91(32)
C(114)-C(19)-C(110)-C(111) -1.0(2)
C(18)-C(19)-C(110)-C(111) 177.0(2)
C(19)-C(110)-C(111)-C(112) -0.3(2)
C(121)-O(15)-C(112)-C(113) -3.3(6)
C(121)-O(15)-C(112)-C(111) 176.3(4)
C(110)-C(111)-C(112)-C(113) 1.5(5)
C(110)-C(111)-C(112)-O(15) -178.1(2)
O(15)-C(112)-C(113)-C(114) 178.2(4)
C(111)-C(112)-C(113)-C(114) -1.4(6)
C(110)-C(19)-C(114)-C(113) 1.2(4)
C(18)-C(19)-C(114)-C(113) -177.0(3)
C(112)-C(113)-C(114)-C(19) 0.0(6)
C(28)-O(21)-C(21)-O(22) -22.3(8)
C(28)-O(21)-C(21)-C(22) 160.4(5)
C(41)-C(22)-C(21)-O(22) 128(11)
C(23)-C(22)-C(21)-O(22) 117.1(6)
C(215)-C(22)-C(21)-O(22) -118.2(5)
C(43)-C(22)-C(21)-O(22) 105.3(8)
C(41)-C(22)-C(21)-O(21) -55(10)
C(23)-C(22)-C(21)-O(21) -65.8(5)
C(215)-C(22)-C(21)-O(21) 58.9(4)
C(43)-C(22)-C(21)-O(21) -77.5(7)
C(41)-C(22)-C(23)-C(24)   65.5(5)
C(215)-C(22)-C(23)-C(24) -57.8(4)
C(21)-C(22)-C(23)-C(24)   66.0(4)
C(43)-C(22)-C(23)-C(24) 164(3)
C(22)-C(23)-C(24)-O(23) 122.5(4)
C(22)-C(23)-C(24)-C(25) -116.8(4)
O(23)-C(24)-C(25)-O(24)   60.9(5)
C(23)-C(24)-C(25)-O(24) -61.1(5)
O(23)-C(24)-C(25)-C(26) -177.3(4)
C(23)-C(24)-C(25)-C(26)   60.7(5)
O(24)-C(25)-C(26)-C(27) -167.9(3)
C(24)-C(25)-C(26)-C(27)   69.9(5)
C(218)-C(27)-C(26)-C(25) 131.5(3)
C(28)-C(27)-C(26)-C(25) -101.9(3)
C(46)-C(27)-C(26)-C(25) -131(3)
O(21)-C(28)-C(29)-C(214)-146.4(4)
O(41)-C(28)-C(29)-C(214)-138.3(7)
C(49)-C(28)-C(29)-C(214) 32(3)
C(27)-C(28)-C(29)-C(214) 98.7(3)
O(21)-C(28)-C(29)-C(210) 35.7(4)
O(41)-C(28)-C(29)-C(210) 43.8(7)
C(49)-C(28)-C(29)-C(210)-146(4)
C(27)-C(28)-C(29)-C(210) -79.2(3)
C(214)-C(29)-C(210)-C(211) -1.3(2)
C(28)-C(29)-C(210)-C(211) 176.7(2)
C(29)-C(210)-C(211)-C(212) -0.3(2)
C(221)-O(25)-C(212)-C(211) 175.6(6)

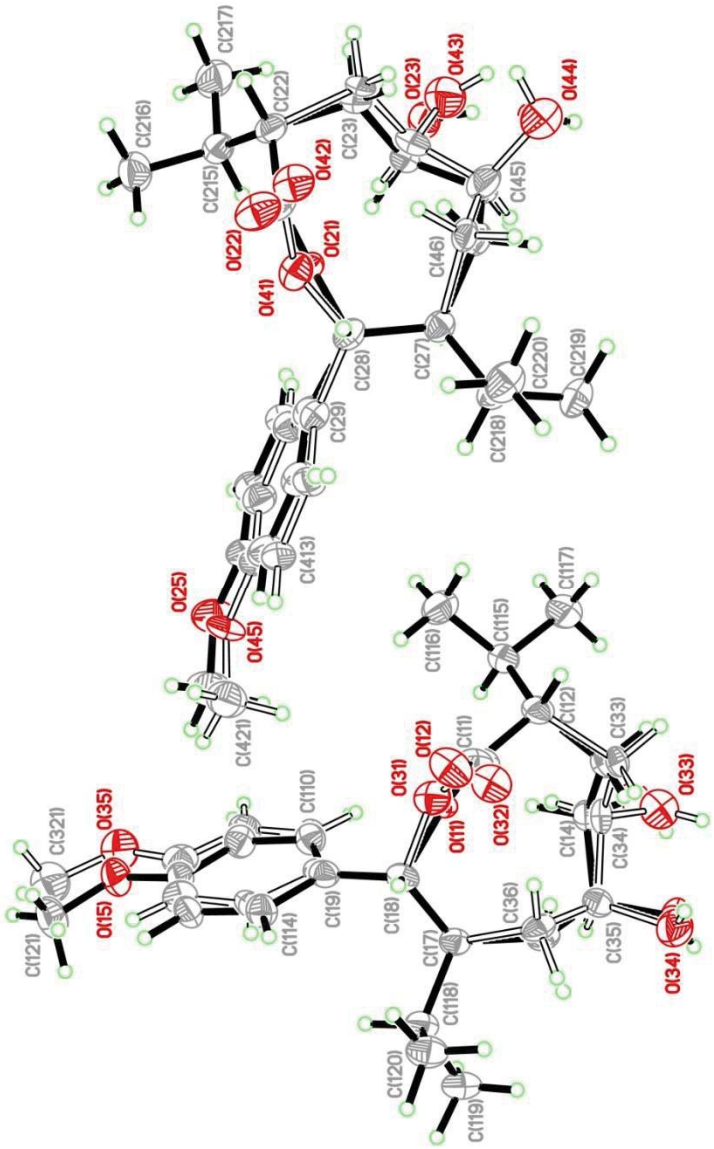
C(221)-O(25)-C(212)-C(213) -3.7(8)
C(210)-C(211)-C(212)-O(25) -177.7(3)
C(210)-C(211)-C(212)-C(213) 1.6(5)
O(25)-C(212)-C(213)-C(214) 178.0(4)
C(211)-C(212)-C(213)-C(214) -1.2(6)
C(210)-C(29)-C(214)-C(213) 1.7(4)
C(28)-C(29)-C(214)-C(213) -176.3(3)
C(212)-C(213)-C(214)-C(29) -0.4(6)
O(11)-C(18)-O(31)-C(31) -81(3)
C(19)-C(18)-O(31)-C(31) 145.4(11)
C(17)-C(18)-O(31)-C(31) -91.0(11)
C(39)-C(18)-O(31)-C(31) 144.6(10)
O(21)-C(28)-O(41)-C(41) -79(3)
C(49)-C(28)-O(41)-C(41) 145.3(12)
C(29)-C(28)-O(41)-C(41) 146.5(13)
C(27)-C(28)-O(41)-C(41) -89.9(13)
C(18)-O(31)-C(31)-O(32) -16.8(17)
C(18)-O(31)-C(31)-C(12) 148.3(11)
C(115)-C(12)-C(31)-O(32) -150.5(8)
C(11)-C(12)-C(31)-O(32) -88(10)
C(13)-C(12)-C(31)-O(32) 86.1(9)
C(33)-C(12)-C(31)-O(32) 74.5(10)
C(115)-C(12)-C(31)-O(31) 43.0(10)
C(11)-C(12)-C(31)-O(31) 105(10)
C(13)-C(12)-C(31)-O(31) -80.4(10)
C(33)-C(12)-C(31)-O(31) -92.0(11)
C(31)-C(12)-C(33)-C(34) 69.5(8)
C(115)-C(12)-C(33)-C(34) -61.2(7)
C(11)-C(12)-C(33)-C(34) 70.3(7)
C(13)-C(12)-C(33)-C(34) -13(2)
C(12)-C(33)-C(34)-O(33) 130.3(9)
C(12)-C(33)-C(34)-C(35) -108.9(8)
O(33)-C(34)-C(35)-O(34) 56.9(9)
C(33)-C(34)-C(35)-O(34) -65.7(9)
O(33)-C(34)-C(35)-C(36) 178.1(9)
C(33)-C(34)-C(35)-C(36) 55.6(9)
O(34)-C(35)-C(36)-C(17) -152.0(9)
C(34)-C(35)-C(36)-C(17) 86.6(10)
C(18)-C(17)-C(36)-C(35) -116.0(6)
C(118)-C(17)-C(36)-C(35) 124.8(5)
C(16)-C(17)-C(36)-C(35) 40(2)
O(11)-C(18)-C(39)-C(314) -145.3(7)
O(31)-C(18)-C(39)-C(314) -137.6(9)
C(19)-C(18)-C(39)-C(314) 90(32)
C(17)-C(18)-C(39)-C(314) 99.0(7)
O(11)-C(18)-C(39)-C(310) 35.0(7)
O(31)-C(18)-C(39)-C(310) 42.6(8)
C(19)-C(18)-C(39)-C(310) -89(32)
C(17)-C(18)-C(39)-C(310) -80.8(7)
C(314)-C(39)-C(310)-C(311) -0.3(3)

C(18)-C(39)-C(310)-C(311) 179.4(3)
C(39)-C(310)-C(311)-C(312) -0.3(3)
C(321)-O(35)-C(312)-C(313) -3.1(16)
C(321)-O(35)-C(312)-C(311) 177.5(13)
C(310)-C(311)-C(312)-C(313) 0.8(7)
C(310)-C(311)-C(312)-O(35) -179.7(4)
O(35)-C(312)-C(313)-C(314) 179.7(6)
C(311)-C(312)-C(313)-C(314) -0.8(9)
C(310)-C(39)-C(314)-C(313) 0.3(7)
C(18)-C(39)-C(314)-C(313) -179.4(5)
C(312)-C(313)-C(314)-C(39) 0.3(9)
C(28)-O(41)-C(41)-O(42) -18.8(19)
C(28)-O(41)-C(41)-C(22) 147.4(13)
C(23)-C(22)-C(41)-O(42) 86.3(10)
C(215)-C(22)-C(41)-O(42) -150.0(8)
C(21)-C(22)-C(41)-O(42) -83(10)
C(43)-C(22)-C(41)-O(42) 74.8(11)
C(23)-C(22)-C(41)-O(41) -81.1(11)
C(215)-C(22)-C(41)-O(41) 42.6(11)
C(21)-C(22)-C(41)-O(41) 109(11)
C(43)-C(22)-C(41)-O(41) -92.7(12)
C(41)-C(22)-C(43)-C(44) 69.0(7)
C(23)-C(22)-C(43)-C(44) -16(2)
C(215)-C(22)-C(43)-C(44) -61.5(7)
C(21)-C(22)-C(43)-C(44) 70.0(7)
C(22)-C(43)-C(44)-O(43) 130.6(9)
C(22)-C(43)-C(44)-C(45) -109.1(8)
O(43)-C(44)-C(45)-O(44) 55.2(9)
C(43)-C(44)-C(45)-O(44) -66.2(9)
O(43)-C(44)-C(45)-C(46) 178.0(9)
C(43)-C(44)-C(45)-C(46) 56.6(9)
O(44)-C(45)-C(46)-C(27) -152.0(9)
C(44)-C(45)-C(46)-C(27) 84.9(10)
C(218)-C(27)-C(46)-C(45) 124.8(5)
C(28)-C(27)-C(46)-C(45) -115.8(6)
C(26)-C(27)-C(46)-C(45) 37(2)
O(21)-C(28)-C(49)-C(414) -145.6(8)
O(41)-C(28)-C(49)-C(414) -137.3(10)
C(29)-C(28)-C(49)-C(414) -147(4)
C(27)-C(28)-C(49)-C(414) 96.7(8)
O(21)-C(28)-C(49)-C(410) 34.8(8)
O(41)-C(28)-C(49)-C(410) 43.1(10)
C(29)-C(28)-C(49)-C(410) 33(3)
C(27)-C(28)-C(49)-C(410) -82.8(7)
C(414)-C(49)-C(410)-C(411) -0.4(3)
C(28)-C(49)-C(410)-C(411) 179.2(3)
C(49)-C(410)-C(411)-C(412) 0.1(3)
C(421)-O(45)-C(412)-C(411) 174.2(14)
C(421)-O(45)-C(412)-C(413) -5.1(16)
C(410)-C(411)-C(412)-O(45) -179.1(4)

C(410)-C(411)-C(412)-C(413) 0.2(7)
O(45)-C(412)-C(413)-C(414) 179.0(6)
C(411)-C(412)-C(413)-C(414) -0.2(9)
C(410)-C(49)-C(414)-C(413) 0.4(7)
C(28)-C(49)-C(414)-C(413) -179.2(5)
C(412)-C(413)-C(414)-C(49) -0.1(10)

Table 7. Bond lengths [Å] and angles [°] related to the hydrogen bonding for C21 H32 O5.

D-H	..A	d(D-H)	d(H..A)	d(D..A)	<DHA
O(13)-H(13)	O(14)	0.84	2.35	2.792(6)	113.1
O(23)-H(23)	O(24)	0.84	2.38	2.797(6)	111.4
O(33)-H(33)	O(34)	0.84	2.42	2.739(12)	103.1
O(43)-H(43)	O(44)	0.84	2.28	2.738(12)	114.5



ORTEP view of the C21 H32 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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Article 2, Lactone dibenzoate **33**

Université de Montréal

CRYSTAL AND MOLECULAR STRUCTURE OF

C35 H40 O7 COMPOUND (12)

Friday, October 23, 2009

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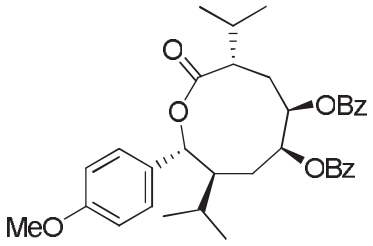


12
$C_{35}H_{40}O_7$
MW 572.69

Structure solved and refined in the laboratory of X-ray diffraction

Université de Montréal by Michel Simard.

Table 1. Crystal data and structure refinement for C35 H40 O7.

Identification code	12
Empirical formula	C35 H40 O7
Formula weight	572.67
Temperature	100(2)K
Wavelength	1.54178 Å
Crystal system	Monoclinic
Space group	$P2R_1$
Unit cell dimensions	a = 12.6491(2) Å α = 90° b = 7.4042(1) Å β = 101.056(1)° c = 16.8171(3) Å γ = 90°
Volume	1545.80(4)ÅP^{3P}
Z	2
Density (calculated)	1.230 g/cm^3
Absorption coefficient	0.686 mmP^{-1P}
F(000)	612
Crystal size	0.28 x 0.20 x 0.04 mm
Theta range for data collection	2.68 to 67.77°
Index ranges	$-15 \leq h \leq 15$, $-7 \leq k \leq 8$, $-20 \leq l \leq 20$
Reflections collected	24377
Independent reflections	5122 [R_{int} = 0.031]
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9800 and 0.6400
Refinement method	Full-matrix least-squares on FP^{2P}
Data / restraints / parameters	5122 / 1 / 385
Goodness-of-fit on FP^{2P}	1.069

Final R indices [I>2sigma(I)] RR_{1R} = 0.0263, wRR_{2R} = 0.0665

R indices (all data) RR_{1R} = 0.0271, wRR_{2R} = 0.0673

Absolute structure parameter 0.06(10)

Extinction coefficient 0.0026(2)

Largest diff. peak and hole 0.150 and -0.133 e/ÅP^{3P}

Table 2. Atomic coordinates (x $10P^{4P}$) and equivalent isotropic displacement parameters (ÅP^{2P} x $10P^{3P}$) for C35 H40 O7.

U_{eq} is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U_{eq}
O(1)	5833(1)	6624(1)	7372(1)	25(1)
O(2)	6113(1)	5077(2)	6272(1)	35(1)
O(3)	2547(1)	8121(1)	7060(1)	27(1)
O(4)	3129(1)	9397(2)	8280(1)	43(1)
O(5)	2515(1)	4416(1)	7018(1)	27(1)
O(6)	1344(1)	5232(2)	7817(1)	31(1)
O(7)	10007(1)	8167(1)	9873(1)	30(1)
C(1)	5696(1)	6303(2)	6570(1)	25(1)
C(2)	4869(1)	7603(2)	6118(1)	26(1)
C(3)	3760(1)	6944(2)	6258(1)	27(1)
C(4)	3558(1)	7123(2)	7128(1)	25(1)
C(5)	3398(1)	5340(2)	7546(1)	25(1)
C(6)	4342(1)	4027(2)	7692(1)	26(1)
C(7)	5314(1)	4659(2)	8344(1)	25(1)
C(8)	6258(1)	5171(2)	7940(1)	24(1)
C(9)	5123(1)	9592(2)	6324(1)	29(1)
C(10)	6214(1)	10098(2)	6124(1)	40(1)
C(11)	4237(1)	10827(2)	5873(1)	34(1)
C(12)	5648(1)	3281(2)	9034(1)	28(1)
C(13)	4735(1)	2936(2)	9494(1)	34(1)
C(14)	6056(1)	1499(2)	8751(1)	38(1)
C(15)	2409(1)	9101(2)	7712(1)	28(1)
C(16)	1278(1)	9707(2)	7648(1)	29(1)
C(17)	461(1)	9130(2)	7022(1)	32(1)
C(18)	-597(1)	9605(2)	7026(1)	37(1)
C(19)	-841(1)	10651(2)	7650(1)	41(1)
C(20)	-30(1)	11256(2)	8263(1)	41(1)
C(21)	1030(1)	10793(2)	8263(1)	34(1)
C(22)	1518(1)	4600(2)	7193(1)	26(1)
C(23)	669(1)	3944(2)	6516(1)	27(1)
C(24)	908(1)	2940(2)	5875(1)	31(1)
C(25)	85(1)	2344(2)	5268(1)	39(1)
C(26)	-973(1)	2754(3)	5297(1)	43(1)
C(27)	-1221(1)	3771(3)	5925(1)	41(1)
C(28)	-396(1)	4367(2)	6538(1)	33(1)
C(29)	7260(1)	5891(2)	8482(1)	24(1)
C(30)	7216(1)	7019(2)	9134(1)	27(1)
C(31)	8149(1)	7724(2)	9593(1)	28(1)
C(32)	9147(1)	7337(2)	9397(1)	26(1)

C(33)	9208(1)	6196(2)	8755(1)	27(1)
C(34)	8262(1)	5479(2)	8309(1)	27(1)
C(35)	11059(1)	7624(2)	9782(1)	33(1)

Table 3. Hydrogen coordinates (x $10P^{4P}$) and isotropic displacement parameters ($ÅP^{2P}$ x $10P^{3P}$) for C35 H40 O7.

	x	y	z	U_{eq}
H(2)	4872	7450	5527	31
H(3A)	3193	7630	5893	33
H(3B)	3677	5657	6098	33
H(4)	4158	7822	7465	30
H(5)	3180	5605	8074	30
H(6A)	4592	3838	7175	31
H(6B)	4087	2849	7860	31
H(7)	5085	5783	8594	29
H(8)	6454	4112	7629	29
H(9)	5163	9760	6919	35
H(10A)	6774	9321	6431	60
H(10B)	6376	11363	6271	60
H(10C)	6191	9935	5543	60
H(11A)	4474	12088	5939	52
H(11B)	3580	10669	6094	52
H(11C)	4089	10516	5296	52
H(12)	6257	3830	9427	34
H(13A)	4165	2236	9152	51
H(13B)	4441	4093	9634	51
H(13C)	5014	2259	9991	51
H(14A)	6302	717	9220	57
H(14B)	6657	1736	8474	57
H(14C)	5472	900	8376	57
H(17)	628	8414	6594	38
H(18)	-1156	9212	6601	45
H(19)	-1569	10955	7655	49
H(20)	-201	11991	8684	49
H(21)	1587	11215	8683	41
H(24)	1635	2663	5853	37
H(25)	246	1652	4831	47
H(26)	-1535	2333	4880	52
H(27)	-1949	4059	5938	49
H(28)	-560	5065	6973	40
H(30)	6539	7309	9266	32
H(31)	8109	8477	10043	34
H(33)	9885	5909	8621	33
H(34)	8303	4683	7873	32
H(35A)	11169	6349	9932	50
H(35B)	11598	8362	10135	50
H(35C)	11133	7789	9217	50

Table 4. Anisotropic parameters (ÅP^{2P} x 10P^{3P}) for C35 H40 O7.

The anisotropic displacement factor exponent takes the form:

$$-2\,\pi^{2P}\,[\,h^{2P}\,a^{*2P}\,U_{11R} + \ldots + 2\,h\,k\,a^{*}\,b^{*}\,U_{12R}\,]$$

	U11	U22	U33	U23	U13	U12
O(1)	26(1)	26(1)	22(1)	1(1)	1(1)	2(1)
O(2)	40(1)	36(1)	29(1)	0(1)	9(1)	10(1)
O(3)	24(1)	29(1)	26(1)	-3(1)	3(1)	3(1)
O(4)	35(1)	50(1)	41(1)	-18(1)	-3(1)	5(1)
O(5)	21(1)	30(1)	30(1)	-6(1)	3(1)	-4(1)
O(6)	29(1)	35(1)	31(1)	-4(1)	8(1)	-2(1)
O(7)	25(1)	31(1)	33(1)	-5(1)	0(1)	-3(1)
C(1)	25(1)	28(1)	24(1)	1(1)	5(1)	-3(1)
C(2)	27(1)	30(1)	21(1)	0(1)	3(1)	2(1)
C(3)	26(1)	30(1)	25(1)	-2(1)	2(1)	1(1)
C(4)	21(1)	27(1)	27(1)	-3(1)	2(1)	0(1)
C(5)	21(1)	27(1)	26(1)	-3(1)	1(1)	-3(1)
C(6)	26(1)	24(1)	28(1)	-2(1)	3(1)	-2(1)
C(7)	24(1)	24(1)	25(1)	0(1)	3(1)	0(1)
C(8)	24(1)	22(1)	24(1)	1(1)	2(1)	2(1)
C(9)	33(1)	31(1)	22(1)	1(1)	2(1)	-1(1)
C(10)	36(1)	36(1)	47(1)	6(1)	5(1)	-5(1)
C(11)	39(1)	33(1)	30(1)	2(1)	6(1)	5(1)
C(12)	29(1)	28(1)	28(1)	2(1)	4(1)	-1(1)
C(13)	40(1)	30(1)	34(1)	3(1)	11(1)	-1(1)
C(14)	43(1)	33(1)	41(1)	8(1)	13(1)	9(1)
C(15)	31(1)	24(1)	29(1)	-3(1)	4(1)	0(1)
C(16)	32(1)	24(1)	31(1)	2(1)	7(1)	4(1)
C(17)	31(1)	28(1)	35(1)	-1(1)	5(1)	3(1)
C(18)	30(1)	34(1)	47(1)	2(1)	5(1)	3(1)
C(19)	35(1)	39(1)	52(1)	8(1)	15(1)	12(1)
C(20)	51(1)	37(1)	39(1)	4(1)	19(1)	17(1)
C(21)	42(1)	29(1)	30(1)	0(1)	7(1)	7(1)
C(22)	23(1)	23(1)	31(1)	3(1)	5(1)	0(1)
C(23)	24(1)	26(1)	30(1)	3(1)	2(1)	-3(1)
C(24)	29(1)	27(1)	35(1)	0(1)	1(1)	1(1)
C(25)	41(1)	35(1)	37(1)	-3(1)	-5(1)	0(1)
C(26)	34(1)	46(1)	43(1)	1(1)	-10(1)	-8(1)
C(27)	24(1)	49(1)	47(1)	10(1)	-1(1)	-3(1)
C(28)	28(1)	36(1)	36(1)	5(1)	7(1)	0(1)

C(29)	24(1)	23(1)	24(1)	2(1)	1(1)	1(1)
C(30)	24(1)	26(1)	31(1)	-2(1)	6(1)	1(1)
C(31)	30(1)	25(1)	29(1)	-3(1)	5(1)	0(1)
C(32)	26(1)	23(1)	26(1)	3(1)	0(1)	-2(1)
C(33)	23(1)	30(1)	29(1)	1(1)	5(1)	1(1)
C(34)	28(1)	28(1)	23(1)	-1(1)	5(1)	2(1)
C(35)	24(1)	33(1)	40(1)	1(1)	0(1)	-1(1)

Table 5. Bond lengths [Å] and angles [°] for C35 H40 O7

O(1)-C(1)	1.3472(14)
O(1)-C(8)	1.4707(16)
O(2)-C(1)	1.2063(17)
O(3)-C(15)	1.3529(16)
O(3)-C(4)	1.4627(15)
O(4)-C(15)	1.2069(16)
O(5)-C(22)	1.3562(14)
O(5)-C(5)	1.4570(14)
O(6)-C(22)	1.2070(16)
O(7)-C(32)	1.3656(15)
O(7)-C(35)	1.4261(16)
C(1)-C(2)	1.5146(18)
C(2)-C(9)	1.533(2)
C(2)-C(3)	1.5460(17)
C(3)-C(4)	1.5375(16)
C(4)-C(5)	1.527(2)
C(5)-C(6)	1.5229(18)
C(6)-C(7)	1.5540(16)
C(7)-C(8)	1.5315(16)
C(7)-C(12)	1.5418(18)
C(8)-C(29)	1.5090(16)
C(9)-C(10)	1.5281(19)
C(9)-C(11)	1.5301(19)
C(12)-C(14)	1.526(2)
C(12)-C(13)	1.5300(18)
C(15)-C(16)	1.4831(18)
C(16)-C(21)	1.3929(19)
C(16)-C(17)	1.3941(19)
C(17)-C(18)	1.3847(19)
C(18)-C(19)	1.385(2)
C(19)-C(20)	1.382(2)
C(20)-C(21)	1.384(2)
C(22)-C(23)	1.4881(17)
C(23)-C(24)	1.390(2)
C(23)-C(28)	1.3907(17)
C(24)-C(25)	1.3826(19)
C(25)-C(26)	1.381(2)
C(26)-C(27)	1.382(2)
C(27)-C(28)	1.3910(19)
C(29)-C(34)	1.3875(17)
C(29)-C(30)	1.3881(18)
C(30)-C(31)	1.3822(18)
C(31)-C(32)	1.3944(18)
C(32)-C(33)	1.3853(19)
C(33)-C(34)	1.3902(18)

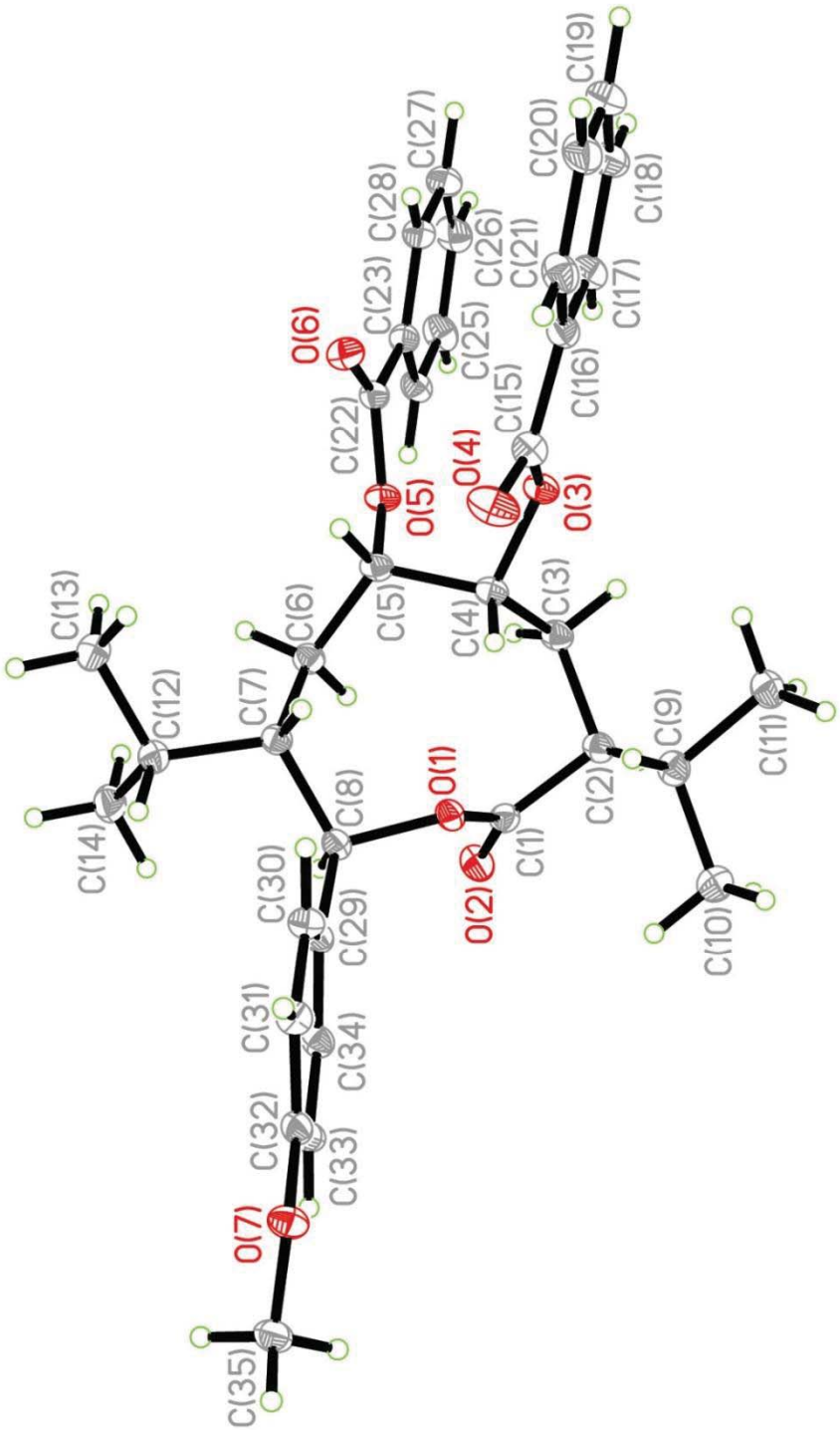
C(1)-O(1)-C(8)	118.80(11)
C(15)-O(3)-C(4)	117.05(9)
C(22)-O(5)-C(5)	117.23(9)
C(32)-O(7)-C(35)	117.73(10)
O(2)-C(1)-O(1)	124.50(12)
O(2)-C(1)-C(2)	125.74(11)
O(1)-C(1)-C(2)	109.55(11)
C(1)-C(2)-C(9)	113.73(10)
C(1)-C(2)-C(3)	106.39(11)
C(9)-C(2)-C(3)	115.19(11)
C(4)-C(3)-C(2)	116.04(10)
O(3)-C(4)-C(5)	106.33(9)
O(3)-C(4)-C(3)	105.79(9)
C(5)-C(4)-C(3)	115.06(12)
O(5)-C(5)-C(6)	106.55(11)
O(5)-C(5)-C(4)	106.23(9)
C(6)-C(5)-C(4)	117.21(10)
C(5)-C(6)-C(7)	114.31(11)
C(8)-C(7)-C(12)	111.92(10)
C(8)-C(7)-C(6)	109.86(9)
C(12)-C(7)-C(6)	113.43(11)
O(1)-C(8)-C(29)	107.12(11)
O(1)-C(8)-C(7)	104.48(9)
C(29)-C(8)-C(7)	117.09(10)
C(10)-C(9)-C(11)	110.54(12)
C(10)-C(9)-C(2)	110.16(12)
C(11)-C(9)-C(2)	111.13(11)
C(14)-C(12)-C(13)	110.30(13)
C(14)-C(12)-C(7)	113.42(11)
C(13)-C(12)-C(7)	111.49(11)
O(4)-C(15)-O(3)	122.95(12)
O(4)-C(15)-C(16)	124.97(12)
O(3)-C(15)-C(16)	112.06(10)
C(21)-C(16)-C(17)	119.83(12)
C(21)-C(16)-C(15)	118.21(12)
C(17)-C(16)-C(15)	121.84(12)
C(18)-C(17)-C(16)	119.69(13)
C(17)-C(18)-C(19)	120.16(14)
C(20)-C(19)-C(18)	120.30(13)
C(19)-C(20)-C(21)	119.99(14)
C(20)-C(21)-C(16)	119.99(14)
O(6)-C(22)-O(5)	124.00(11)
O(6)-C(22)-C(23)	124.53(11)
O(5)-C(22)-C(23)	111.46(10)
C(24)-C(23)-C(28)	119.81(12)
C(24)-C(23)-C(22)	122.41(11)
C(28)-C(23)-C(22)	117.78(12)
C(25)-C(24)-C(23)	119.89(12)

C(26)-C(25)-C(24)	120.08(14)
C(25)-C(26)-C(27)	120.67(13)
C(26)-C(27)-C(28)	119.44(13)
C(23)-C(28)-C(27)	120.10(14)
C(34)-C(29)-C(30)	118.32(11)
C(34)-C(29)-C(8)	119.39(11)
C(30)-C(29)-C(8)	122.24(11)
C(31)-C(30)-C(29)	120.59(11)
C(30)-C(31)-C(32)	120.39(12)
O(7)-C(32)-C(33)	125.01(11)
O(7)-C(32)-C(31)	115.17(11)
C(33)-C(32)-C(31)	119.82(11)
C(32)-C(33)-C(34)	118.87(11)
C(29)-C(34)-C(33)	121.98(12)

Table 6. Torsion angles [°] for C35 H40 O7.

C(8)-O(1)-C(1)-O(2)	-17.70(18)
C(8)-O(1)-C(1)-C(2)	157.25(10)
O(2)-C(1)-C(2)-C(9)	-131.52(14)
O(1)-C(1)-C(2)-C(9)	53.61(13)
O(2)-C(1)-C(2)-C(3)	100.61(15)
O(1)-C(1)-C(2)-C(3)	-74.26(13)
C(1)-C(2)-C(3)-C(4)	68.04(15)
C(9)-C(2)-C(3)-C(4)	-58.96(15)
C(15)-O(3)-C(4)-C(5)	84.22(13)
C(15)-O(3)-C(4)-C(3)	-152.99(11)
C(2)-C(3)-C(4)-O(3)	126.57(12)
C(2)-C(3)-C(4)-C(5)	-116.37(13)
C(22)-O(5)-C(5)-C(6)	137.84(11)
C(22)-O(5)-C(5)-C(4)	-96.47(12)
O(3)-C(4)-C(5)-O(5)	61.08(11)
C(3)-C(4)-C(5)-O(5)	-55.67(12)
O(3)-C(4)-C(5)-C(6)	179.98(10)
C(3)-C(4)-C(5)-C(6)	63.23(14)
O(5)-C(5)-C(6)-C(7)	-171.5(1)
C(4)-C(5)-C(6)-C(7)	69.77(14)
C(5)-C(6)-C(7)-C(8)	-109.40(13)
C(5)-C(6)-C(7)-C(12)	124.52(12)
C(1)-O(1)-C(8)-C(29)	123.07(11)
C(1)-O(1)-C(8)-C(7)	-112.06(11)
C(12)-C(7)-C(8)-O(1)	-173.74(10)
C(6)-C(7)-C(8)-O(1)	59.32(13)
C(12)-C(7)-C(8)-C(29)	-55.48(16)
C(6)-C(7)-C(8)-C(29)	177.58(12)
C(1)-C(2)-C(9)-C(10)	59.33(13)
C(3)-C(2)-C(9)-C(10)	-177.49(11)
C(1)-C(2)-C(9)-C(11)	-177.81(10)
C(3)-C(2)-C(9)-C(11)	-54.62(13)
C(8)-C(7)-C(12)-C(14)	-61.03(15)
C(6)-C(7)-C(12)-C(14)	63.95(14)
C(8)-C(7)-C(12)-C(13)	173.74(11)
C(6)-C(7)-C(12)-C(13)	-61.27(15)
C(4)-O(3)-C(15)-O(4)	11.4(2)
C(4)-O(3)-C(15)-C(16)	-167.08(11)
O(4)-C(15)-C(16)-C(21)	4.1(2)
O(3)-C(15)-C(16)-C(21)	-177.43(13)
O(4)-C(15)-C(16)-C(17)	-171.90(15)
O(3)-C(15)-C(16)-C(17)	6.6(2)
C(21)-C(16)-C(17)-C(18)	-1.6(2)
C(15)-C(16)-C(17)-C(18)	174.38(14)

C(16)-C(17)-C(18)-C(19) 0.1(2)
C(17)-C(18)-C(19)-C(20) 1.2(3)
C(18)-C(19)-C(20)-C(21) -1.1(3)
C(19)-C(20)-C(21)-C(16) -0.4(2)
C(17)-C(16)-C(21)-C(20) 1.7(2)
C(15)-C(16)-C(21)-C(20) -174.37(14)
C(5)-O(5)-C(22)-O(6) -11.88(19)
C(5)-O(5)-C(22)-C(23) 167.45(11)
O(6)-C(22)-C(23)-C(24) -168.30(14)
O(5)-C(22)-C(23)-C(24) 12.37(19)
O(6)-C(22)-C(23)-C(28) 11.7(2)
O(5)-C(22)-C(23)-C(28) -167.61(12)
C(28)-C(23)-C(24)-C(25) -0.9(2)
C(22)-C(23)-C(24)-C(25) 179.08(14)
C(23)-C(24)-C(25)-C(26) 0.3(2)
C(24)-C(25)-C(26)-C(27) 0.5(3)
C(25)-C(26)-C(27)-C(28) -0.7(3)
C(24)-C(23)-C(28)-C(27) 0.7(2)
C(22)-C(23)-C(28)-C(27) -179.30(13)
C(26)-C(27)-C(28)-C(23) 0.1(2)
O(1)-C(8)-C(29)-C(34) -97.97(14)
C(7)-C(8)-C(29)-C(34) 145.19(13)
O(1)-C(8)-C(29)-C(30) 79.38(14)
C(7)-C(8)-C(29)-C(30) -37.46(19)
C(34)-C(29)-C(30)-C(31) 0.6(2)
C(8)-C(29)-C(30)-C(31) -176.74(13)
C(29)-C(30)-C(31)-C(32) 1.1(2)
C(35)-O(7)-C(32)-C(33) -9.68(19)
C(35)-O(7)-C(32)-C(31) 170.99(12)
C(30)-C(31)-C(32)-O(7) 177.46(13)
C(30)-C(31)-C(32)-C(33) -1.9(2)
O(7)-C(32)-C(33)-C(34) -178.38(13)
C(31)-C(32)-C(33)-C(34) 0.9(2)
C(30)-C(29)-C(34)-C(33) -1.6(2)
C(8)-C(29)-C(34)-C(33) 175.81(13)
C(32)-C(33)-C(34)-C(29) 0.9(2)



ORTEP view of the C35 H40 O7 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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Article 2, Lactone **39**

Université de Montréal

CRYSTAL AND MOLECULAR STRUCTURE OF

C26 H39 N O5 COMPOUND (bent38)

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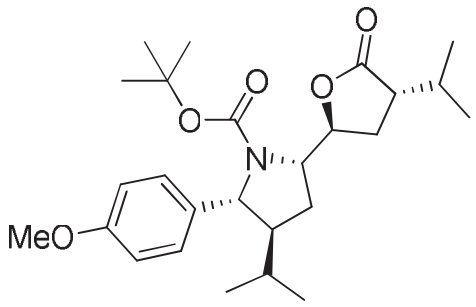


Structure solved and refined in the laboratory of X-ray diffraction
Université de Montréal by Benoît Deschênes Simard.

Table 1. Crystal data and structure refinement for C26 H39 N O5.

Identification code	bent38
Empirical formula	C26 H39 N O5
Formula weight	445.58
Temperature	175K
Wavelength	1.54178 Å
Crystal system	Orthorhombic
Space group	P212121
Unit cell dimensions	a = 10.2176(1) Å α = 90° b = 10.2887(1) Å β = 90° c = 24.2502(3) Å γ = 90°
Volume	2549.32(5)Å^3
Z	4
Density (calculated)	1.161 g/cm^3
Absorption coefficient	0.636 mm^{-1}
F(000)	968
Crystal size	0.22 x 0.20 x 0.18 mm
Theta range for data collection	3.65 to 72.43°
Index ranges	$-12 \leq h \leq 12$, $-12 \leq k \leq 12$, $-29 \leq l \leq 28$
Reflections collected	33232
Independent reflections	4996 [R_{int} = 0.035]
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.8918 and 0.8079
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4996 / 54 / 349

Goodness-of-fit on F^2	1.070
Final R indices [I>2sigma(I)]	R_1 = 0.0376, wR_2 = 0.0945
R indices (all data)	R_1 = 0.0381, wR_2 = 0.0953
Absolute structure parameter	0.02(15)
Extinction coefficient	0.0220(6)
Largest diff. peak and hole	0.182 and -0.221 e/Å^3

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^2 x 10^3) for C26 H39 N O5.

U_{eq} is defined as one third of the trace of the orthogonalized Uij tensor.

	Occ.	x	y	z	U_{eq}
O(4)	1	7813(1)	4192(1)	7683(1)	39(1)
O(5)	1	7281(1)	4370(1)	6772(1)	36(1)
N(1)	1	9056(1)	5364(1)	7086(1)	33(1)
C(1)	1	9373(1)	5782(1)	6517(1)	32(1)
C(2)	1	10731(1)	6419(1)	6595(1)	33(1)
C(3)	1	11321(1)	5652(1)	7080(1)	36(1)
C(4)	1	10153(1)	5490(1)	7469(1)	34(1)
C(5)	1	10032(1)	6655(1)	7864(1)	38(1)
C(15)	1	11561(1)	6518(1)	6068(1)	40(1)
C(16)	1	11870(2)	5208(2)	5805(1)	57(1)
C(17)	1	12809(2)	7278(2)	6175(1)	52(1)
C(21)	1	8014(1)	4609(1)	7220(1)	32(1)
C(22)	1	5931(1)	3882(1)	6820(1)	37(1)
C(23)	1	5477(2)	3900(2)	6226(1)	51(1)
C(24)	1	5915(1)	2517(2)	7050(1)	52(1)
C(25)	1	5142(2)	4815(2)	7170(1)	60(1)
O(1A)	0.75	7189(2)	6731(3)	8635(1)	60(1)
O(2A)	0.75	8690(2)	7015(3)	7983(1)	39(1)
O(3A)	0.75	5542(2)	8966(2)	5488(1)	49(1)
C(6A)	0.75	10580(2)	6283(2)	8449(1)	38(1)
C(7A)	0.75	9368(2)	5728(2)	8732(1)	40(1)
C(8A)	0.75	8274(2)	6512(4)	8467(1)	43(1)
C(9A)	0.75	8349(1)	6650(2)	6260(1)	32(1)
C(10A)	0.75	7997(2)	6485(2)	5708(1)	36(1)
C(11A)	0.75	7063(2)	7275(2)	5464(1)	39(1)
C(12A)	0.75	6453(2)	8243(2)	5768(1)	38(1)
C(13A)	0.75	6785(2)	8416(3)	6320(1)	40(1)
C(14A)	0.75	7732(2)	7618(2)	6558(1)	37(1)
C(18A)	0.75	9330(2)	5700(2)	9368(1)	50(1)
C(19A)	0.75	9336(4)	7038(3)	9620(1)	86(1)
C(20A)	0.75	10418(2)	4853(3)	9594(1)	60(1)
C(26A)	0.75	4955(3)	10020(2)	5770(2)	59(1)
O(1B)	0.25	7204(6)	6498(13)	8603(4)	60(1)
O(2B)	0.25	8633(6)	6912(9)	7937(3)	39(1)
O(3B)	0.25	5740(6)	9173(6)	5491(3)	49(1)
C(6B)	0.25	10647(5)	6594(9)	8389(3)	38(1)
C(7B)	0.25	9550(5)	6008(8)	8739(2)	40(1)
C(8B)	0.25	8322(5)	6483(12)	8448(3)	43(1)
C(9B)	0.25	8387(3)	6721(4)	6280(2)	32(1)

C(10B)	0.25	8179(5)	6679(5)	5711(2)	36(1)
C(11B)	0.25	7289(6)	7509(6)	5461(2)	39(1)
C(12B)	0.25	6596(5)	8396(6)	5776(2)	38(1)
C(13B)	0.25	6787(7)	8449(7)	6345(2)	40(1)
C(14B)	0.25	7686(7)	7608(7)	6589(3)	37(1)
C(18B)	0.25	9609(5)	6362(7)	9358(2)	50(1)
C(19B)	0.25	8487(7)	5755(8)	9672(3)	86(1)
C(20B)	0.25	10944(6)	6000(8)	9581(2)	60(1)
C(26B)	0.25	5208(11)	10248(9)	5780(6)	59(1)

Table 3. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for C26 H39 N O5.

	Occ.	x	y	z	U_{eq}
H(1)	1	9478	4991	6282	38
H(2)	1	10577	7326	6729	39
H(3A)	1	11660	4799	6957	43
H(3B)	1	12037	6145	7259	43
H(4)	1	10252	4670	7687	40
H(5)	1	10520	7418	7713	45
H(15)	1	11038	7025	5794	48
H(16A)	1	12352	4667	6068	85
H(16B)	1	12404	5343	5474	85
H(16C)	1	11052	4773	5703	85
H(17A)	1	13271	7419	5826	78
H(17B)	1	13372	6786	6427	78
H(17C)	1	12591	8119	6341	78
H(23A)	1	5511	4792	6085	76
H(23B)	1	4576	3576	6205	76
H(23C)	1	6050	3344	6004	76
H(24A)	1	6173	2536	7439	78
H(24B)	1	6530	1974	6842	78
H(24C)	1	5031	2156	7017	78
H(25A)	1	5211	5693	7016	91
H(25B)	1	5481	4812	7548	91
H(25C)	1	4222	4544	7172	91
H(6A)	0.75	11285	5626	8422	45
H(6B)	0.75	10916	7057	8647	45
H(7A)	0.75	9269	4810	8603	48
H(10A)	0.75	8405	5821	5496	43
H(11A)	0.75	6840	7153	5087	47
H(13A)	0.75	6369	9072	6533	48
H(14A)	0.75	7959	7743	6934	44
H(18A)	0.75	8485	5281	9475	60
H(19A)	0.75	8638	7563	9454	129
H(19B)	0.75	10183	7453	9552	129
H(19C)	0.75	9188	6969	10018	129
H(20A)	0.75	10295	4735	9991	89
H(20B)	0.75	11264	5273	9526	89
H(20C)	0.75	10399	4005	9410	89
H(26A)	0.75	4455	9692	6085	88
H(26B)	0.75	4366	10484	5519	88
H(26C)	0.75	5637	10615	5901	88
H(6C)	0.25	10899	7469	8522	45
H(6D)	0.25	11429	6026	8382	45

H(7B)	0.25	9591	5040	8704	48
H(10B)	0.25	8654	6074	5492	43
H(11B)	0.25	7155	7469	5074	47
H(13B)	0.25	6310	9052	6563	48
H(14B)	0.25	7820	7646	6976	44
H(18B)	0.25	9518	7327	9389	60
H(19D)	0.25	8626	4815	9701	129
H(19E)	0.25	7665	5923	9477	129
H(19F)	0.25	8443	6133	10043	129
H(20D)	0.25	11605	6584	9425	89
H(20E)	0.25	11149	5102	9478	89
H(20F)	0.25	10942	6080	9983	89
H(26D)	0.25	4754	9938	6111	88
H(26E)	0.25	4588	10709	5542	88
H(26F)	0.25	5915	10839	5888	88

Table 4. Anisotropic parameters (Å^2 x 10^3) for C26 H39 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(4)	41(1)	42(1)	35(1)	8(1)	-4(1)	-7(1)
O(5)	34(1)	41(1)	35(1)	1(1)	-5(1)	-7(1)
N(1)	33(1)	36(1)	29(1)	4(1)	-5(1)	-4(1)
C(1)	34(1)	33(1)	29(1)	1(1)	-1(1)	1(1)
C(2)	30(1)	36(1)	33(1)	1(1)	-1(1)	0(1)
C(3)	32(1)	42(1)	35(1)	1(1)	-4(1)	0(1)
C(4)	33(1)	36(1)	32(1)	3(1)	-5(1)	-3(1)
C(5)	37(1)	40(1)	36(1)	0(1)	-1(1)	-8(1)
C(15)	34(1)	52(1)	33(1)	3(1)	3(1)	4(1)
C(16)	52(1)	69(1)	51(1)	-14(1)	10(1)	8(1)
C(17)	38(1)	69(1)	48(1)	2(1)	11(1)	-6(1)
C(21)	33(1)	30(1)	33(1)	1(1)	-4(1)	0(1)
C(22)	28(1)	39(1)	42(1)	4(1)	-6(1)	-1(1)
C(23)	43(1)	62(1)	47(1)	5(1)	-15(1)	-12(1)
C(24)	43(1)	45(1)	68(1)	13(1)	-16(1)	-13(1)
C(25)	45(1)	76(1)	61(1)	-5(1)	-1(1)	17(1)
O(1A)	42(1)	77(2)	63(1)	2(1)	7(1)	16(1)
O(2A)	42(1)	39(1)	37(1)	-1(1)	-5(1)	5(1)
O(3A)	41(1)	53(1)	54(1)	10(1)	-10(1)	7(1)
C(6A)	36(1)	43(1)	34(1)	-2(1)	-6(1)	-4(1)
C(7A)	38(1)	50(1)	33(1)	2(1)	0(1)	5(1)
C(8A)	40(1)	49(1)	40(1)	1(1)	1(1)	6(1)
C(9A)	30(1)	36(1)	30(1)	3(1)	-2(1)	-3(1)
C(10A)	37(1)	39(1)	32(1)	-1(1)	-3(1)	-2(1)
C(11A)	39(1)	47(1)	33(1)	4(1)	-8(1)	-5(1)
C(12A)	31(1)	40(1)	43(1)	9(1)	-5(1)	-3(1)
C(13A)	38(1)	41(1)	41(1)	2(1)	2(1)	4(1)
C(14A)	39(1)	41(1)	30(1)	2(1)	-1(1)	1(1)
C(18A)	59(1)	58(1)	33(1)	8(1)	6(1)	13(1)
C(19A)	146(3)	72(2)	41(1)	-2(1)	8(2)	28(2)
C(20A)	64(1)	79(1)	37(1)	9(1)	-5(1)	16(1)
C(26A)	49(2)	46(1)	80(1)	7(1)	-16(1)	10(1)
O(1B)	42(1)	77(2)	63(1)	2(1)	7(1)	16(1)
O(2B)	42(1)	39(1)	37(1)	-1(1)	-5(1)	5(1)
O(3B)	41(1)	53(1)	54(1)	10(1)	-10(1)	7(1)

C(6B)	36(1)	43(1)	34(1)	-2(1)	-6(1)	-4(1)
C(7B)	38(1)	50(1)	33(1)	2(1)	0(1)	5(1)
C(8B)	40(1)	49(1)	40(1)	1(1)	1(1)	6(1)
C(9B)	30(1)	36(1)	30(1)	3(1)	-2(1)	-3(1)
C(10B)	37(1)	39(1)	32(1)	-1(1)	-3(1)	-2(1)
C(11B)	39(1)	47(1)	33(1)	4(1)	-8(1)	-5(1)
C(12B)	31(1)	40(1)	43(1)	9(1)	-5(1)	-3(1)
C(13B)	38(1)	41(1)	41(1)	2(1)	2(1)	4(1)
C(14B)	39(1)	41(1)	30(1)	2(1)	-1(1)	1(1)
C(18B)	59(1)	58(1)	33(1)	8(1)	6(1)	13(1)
C(19B)	146(3)	72(2)	41(1)	-2(1)	8(2)	28(2)
C(20B)	64(1)	79(1)	37(1)	9(1)	-5(1)	16(1)
C(26B)	49(2)	46(1)	80(1)	7(1)	-16(1)	10(1)

Table 5. Bond lengths [Å] and angles [°] for C26 H39 N O5

O(4)-C(21)	1.2191(15)
O(5)-C(21)	1.3420(14)
O(5)-C(22)	1.4726(15)
N(1)-C(21)	1.3576(16)
N(1)-C(4)	1.4628(15)
N(1)-C(1)	1.4794(14)
C(1)-C(9a)	1.511(2)
C(1)-C(9b)	1.511(4)
C(1)-C(2)	1.5457(16)
C(2)-C(15)	1.5376(17)
C(2)-C(3)	1.5378(17)
C(3)-C(4)	1.5314(17)
C(4)-C(5)	1.5384(18)
C(5)-C(6b)	1.421(7)
C(5)-O(2a)	1.449(3)
C(5)-O(2b)	1.465(7)
C(5)-C(6a)	1.573(2)
C(15)-C(17)	1.519(2)
C(15)-C(16)	1.524(2)
C(22)-C(24)	1.5106(19)
C(22)-C(25)	1.514(2)
C(22)-C(23)	1.5146(19)
O(1a)-C(8a)	1.203(2)
O(2a)-C(8a)	1.352(2)
O(3a)-C(12a)	1.3712(19)
O(3a)-C(26a)	1.416(2)
C(6a)-C(7a)	1.527(2)
C(7a)-C(8a)	1.521(2)
C(7a)-C(18a)	1.542(2)
C(9a)-C(14a)	1.382(2)
C(9a)-C(10a)	1.398(2)
C(10a)-C(11a)	1.386(2)
C(11a)-C(12a)	1.386(2)
C(12a)-C(13a)	1.393(2)
C(13a)-C(14a)	1.394(2)
C(18a)-C(19a)	1.507(3)
C(18a)-C(20a)	1.515(3)
O(1b)-C(8b)	1.202(4)
O(2b)-C(8b)	1.353(4)
O(3b)-C(12b)	1.372(4)
O(3b)-C(26b)	1.418(5)
C(6b)-C(7b)	1.529(5)
C(7b)-C(8b)	1.520(4)
C(7b)-C(18b)	1.547(4)
C(9b)-C(14b)	1.381(4)

C(9b)-C(10b)	1.396(4)
C(10b)-C(11b)	1.387(4)
C(11b)-C(12b)	1.385(4)
C(12b)-C(13b)	1.393(4)
C(13b)-C(14b)	1.394(4)
C(18b)-C(19b)	1.512(5)
C(18b)-C(20b)	1.513(5)

C(21)-O(5)-C(22)	121.40(10)
C(21)-N(1)-C(4)	119.91(10)
C(21)-N(1)-C(1)	124.19(9)
C(4)-N(1)-C(1)	113.52(9)

N(1)-C(1)-C(9A)	113.83(10)
N(1)-C(1)-C(9B)	113.3(2)
C(9A)-C(1)-C(9B)	3.6(2)
N(1)-C(1)-C(2)	101.88(9)
C(9A)-C(1)-C(2)	114.95(8)
C(9B)-C(1)-C(2)	111.99(10)
C(15)-C(2)-C(3)	116.95(10)
C(15)-C(2)-C(1)	114.90(10)
C(3)-C(2)-C(1)	103.19(9)
C(4)-C(3)-C(2)	102.80(9)
N(1)-C(4)-C(3)	102.37(9)
N(1)-C(4)-C(5)	113.81(10)
C(3)-C(4)-C(5)	111.19(10)
C(6B)-C(5)-O(2A)	104.6(3)
C(6B)-C(5)-O(2B)	109.3(4)
O(2A)-C(5)-O(2B)	6.4(5)
C(6B)-C(5)-C(4)	119.2(4)
O(2A)-C(5)-C(4)	113.48(14)
O(2B)-C(5)-C(4)	107.1(4)
C(6B)-C(5)-C(6A)	12.5(4)
O(2A)-C(5)-C(6A)	102.72(13)
O(2B)-C(5)-C(6A)	106.4(2)
C(4)-C(5)-C(6A)	110.10(13)
C(17)-C(15)-C(16)	110.65(12)
C(17)-C(15)-C(2)	110.84(11)
C(16)-C(15)-C(2)	113.82(12)
O(4)-C(21)-O(5)	125.91(11)
O(4)-C(21)-N(1)	123.69(11)
O(5)-C(21)-N(1)	110.37(10)
O(5)-C(22)-C(24)	110.88(10)
O(5)-C(22)-C(25)	109.11(11)
C(24)-C(22)-C(25)	112.18(13)
O(5)-C(22)-C(23)	101.96(10)
C(24)-C(22)-C(23)	111.02(12)
C(25)-C(22)-C(23)	111.22(12)
C(8A)-O(2A)-C(5)	111.84(16)
C(12A)-O(3A)-C(26A)	117.7(2)

C(7A)-C(6A)-C(5) 101.95(14)
C(8A)-C(7A)-C(6A) 101.99(15)
C(8A)-C(7A)-C(18A) 114.48(17)
C(6A)-C(7A)-C(18A) 118.45(17)
O(1A)-C(8A)-O(2A) 120.8(2)
O(1A)-C(8A)-C(7A) 129.3(2)
O(2A)-C(8A)-C(7A) 109.85(16)
C(14A)-C(9A)-C(10A) 118.11(16)
C(14A)-C(9A)-C(1) 121.79(17)
C(10A)-C(9A)-C(1) 120.09(16)
C(11A)-C(10A)-C(9A) 120.91(17)
C(12A)-C(11A)-C(10A) 120.34(17)
O(3A)-C(12A)-C(11A) 115.62(17)
O(3A)-C(12A)-C(13A) 124.84(18)
C(11A)-C(12A)-C(13A) 119.54(16)
C(12A)-C(13A)-C(14A) 119.41(18)
C(9A)-C(14A)-C(13A) 121.68(18)
C(19A)-C(18A)-C(20A) 112.0(2)
C(19A)-C(18A)-C(7A) 112.85(18)
C(20A)-C(18A)-C(7A) 110.75(16)
C(8B)-O(2B)-C(5) 106.3(4)
C(12B)-O(3B)-C(26B) 116.6(6)
C(5)-C(6B)-C(7B) 101.0(4)
C(8B)-C(7B)-C(6B) 102.7(4)
C(8B)-C(7B)-C(18B) 114.0(5)
C(6B)-C(7B)-C(18B) 114.7(5)
O(1B)-C(8B)-O(2B) 120.3(5)
O(1B)-C(8B)-C(7B) 130.1(5)
O(2B)-C(8B)-C(7B) 109.6(4)
C(14B)-C(9B)-C(10B) 118.6(4)
C(14B)-C(9B)-C(1) 124.1(4)
C(10B)-C(9B)-C(1) 117.3(4)
C(11B)-C(10B)-C(9B) 120.8(4)
C(12B)-C(11B)-C(10B) 120.1(4)
O(3B)-C(12B)-C(11B) 115.6(4)
O(3B)-C(12B)-C(13B) 124.4(4)
C(11B)-C(12B)-C(13B) 120.0(4)
C(12B)-C(13B)-C(14B) 119.2(4)
C(9B)-C(14B)-C(13B) 121.4(4)
C(19B)-C(18B)-C(20B) 113.7(5)
C(19B)-C(18B)-C(7B) 111.3(4)
C(20B)-C(18B)-C(7B) 108.9(4)

Table 6. Torsion angles [°] for C26 H39 N O5.

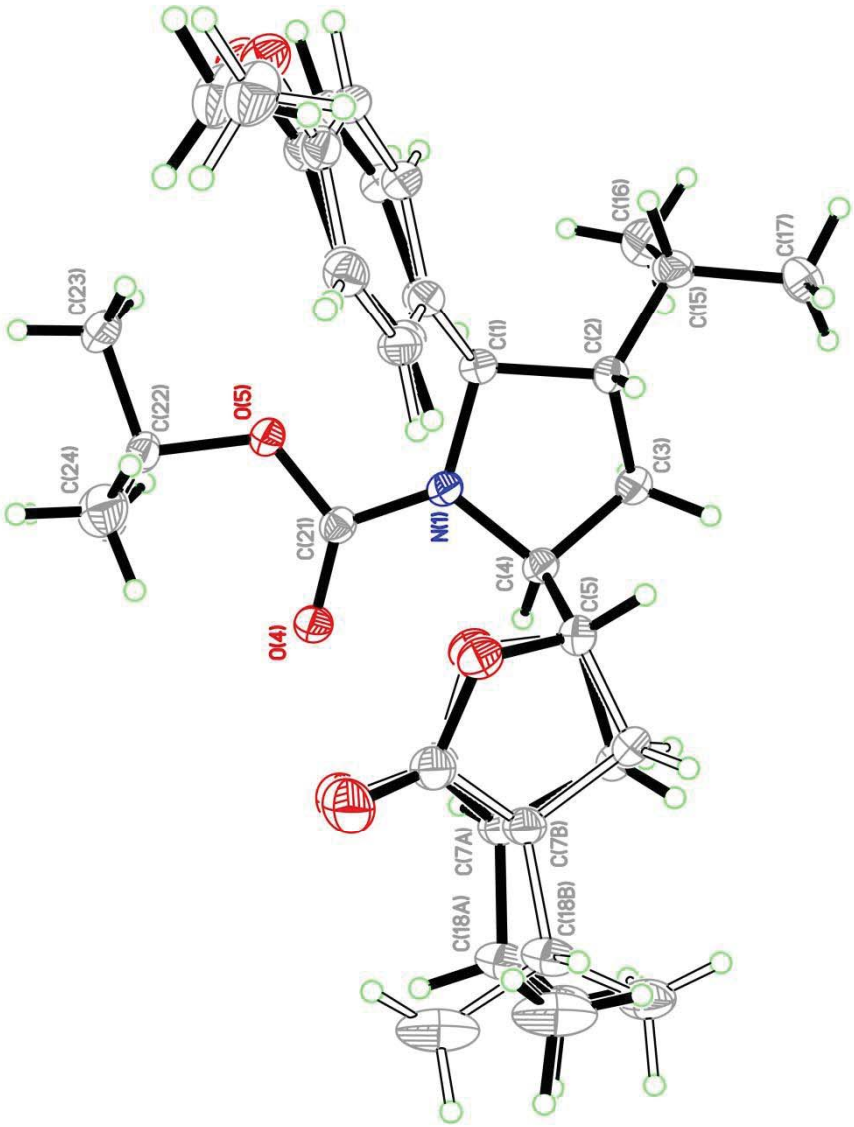
C(21)-N(1)-C(1)-C(9A)	63.88(15)
C(4)-N(1)-C(1)-C(9A)	-133.73(11)
C(21)-N(1)-C(1)-C(9B)	67.78(19)
C(4)-N(1)-C(1)-C(9B)	-129.84(17)
C(21)-N(1)-C(1)-C(2)	-171.77(11)
C(4)-N(1)-C(1)-C(2)	-9.38(12)
N(1)-C(1)-C(2)-C(15)	158.90(10)
C(9A)-C(1)-C(2)-C(15)	-77.50(15)
C(9B)-C(1)-C(2)-C(15)	-79.8(3)
N(1)-C(1)-C(2)-C(3)	30.44(11)
C(9A)-C(1)-C(2)-C(3)	154.03(12)
C(9B)-C(1)-C(2)-C(3)	151.8(3)
C(15)-C(2)-C(3)-C(4)	-167.80(11)
C(1)-C(2)-C(3)-C(4)	-40.62(11)
C(21)-N(1)-C(4)-C(3)	147.61(11)
C(1)-N(1)-C(4)-C(3)	-15.61(13)
C(21)-N(1)-C(4)-C(5)	-92.31(13)
C(1)-N(1)-C(4)-C(5)	104.48(12)
C(2)-C(3)-C(4)-N(1)	34.12(12)
C(2)-C(3)-C(4)-C(5)	-87.77(11)
N(1)-C(4)-C(5)-C(6B)	152.5(3)
C(3)-C(4)-C(5)-C(6B)	-92.6(3)
N(1)-C(4)-C(5)-O(2A)	28.60(16)
C(3)-C(4)-C(5)-O(2A)	143.57(13)
N(1)-C(4)-C(5)-O(2B)	27.8(3)
C(3)-C(4)-C(5)-O(2B)	142.7(3)
N(1)-C(4)-C(5)-C(6A)	143.09(12)
C(3)-C(4)-C(5)-C(6A)	-101.94(13)
C(3)-C(2)-C(15)-C(17)	-64.63(16)
C(1)-C(2)-C(15)-C(17)	174.15(11)
C(3)-C(2)-C(15)-C(16)	60.85(16)
C(1)-C(2)-C(15)-C(16)	-60.36(15)
C(22)-O(5)-C(21)-O(4)	18.28(18)
C(22)-O(5)-C(21)-N(1)	-163.50(10)
C(4)-N(1)-C(21)-O(4)	13.15(18)
C(1)-N(1)-C(21)-O(4)	174.48(11)
C(4)-N(1)-C(21)-O(5)	-165.11(10)
C(1)-N(1)-C(21)-O(5)	-3.78(16)
C(21)-O(5)-C(22)-C(24)	-67.36(15)
C(21)-O(5)-C(22)-C(25)	56.69(15)
C(21)-O(5)-C(22)-C(23)	174.39(11)
C(6B)-C(5)-O(2A)-C(8A)	-33.5(5)
O(2B)-C(5)-O(2A)-C(8A)	105(3)
C(4)-C(5)-O(2A)-C(8A)	98.1(3)

C(6A)-C(5)-O(2A)-C(8A) -20.8(3)
C(6B)-C(5)-C(6A)-C(7A) 132.3(16)
O(2A)-C(5)-C(6A)-C(7A) 32.3(2)
O(2B)-C(5)-C(6A)-C(7A) 26.9(4)
C(4)-C(5)-C(6A)-C(7A) -88.89(16)
C(5)-C(6A)-C(7A)-C(8A) -31.6(2)

C(5)-C(6A)-C(7A)-C(18A) -158.23(17)
C(5)-O(2A)-C(8A)-O(1A) 178.7(3)
C(5)-O(2A)-C(8A)-C(7A) 0.2(4)
C(6A)-C(7A)-C(8A)-O(1A) -157.3(4)
C(18A)-C(7A)-C(8A)-O(1A) -28.1(5)
C(6A)-C(7A)-C(8A)-O(2A) 21.0(3)

C(18A)-C(7A)-C(8A)-O(2A) 150.2(3)
N(1)-C(1)-C(9A)-C(14A) 40.68(15)
C(9B)-C(1)-C(9A)-C(14A) -41(3)
C(2)-C(1)-C(9A)-C(14A) -76.30(16)
N(1)-C(1)-C(9A)-C(10A) -139.15(13)
C(9B)-C(1)-C(9A)-C(10A) 139(3)
C(2)-C(1)-C(9A)-C(10A) 103.86(14)
C(14A)-C(9A)-C(10A)-C(11A) 0.42(19)
C(1)-C(9A)-C(10A)-C(11A) -179.74(12)
C(9A)-C(10A)-C(11A)-C(12A) -0.4(2)
C(26A)-O(3A)-C(12A)-C(11A) -175.9(2)
C(26A)-O(3A)-C(12A)-C(13A) 4.3(3)
C(10A)-C(11A)-C(12A)-O(3A) -179.80(16)
C(10A)-C(11A)-C(12A)-C(13A) 0.0(3)
O(3A)-C(12A)-C(13A)-C(14A) -179.83(19)
C(11A)-C(12A)-C(13A)-C(14A) 0.4(3)
C(10A)-C(9A)-C(14A)-C(13A) 0.0(2)
C(1)-C(9A)-C(14A)-C(13A) -179.86(15)
C(12A)-C(13A)-C(14A)-C(9A) -0.4(3)
C(8A)-C(7A)-C(18A)-C(19A) -55.8(3)
C(6A)-C(7A)-C(18A)-C(19A) 64.6(3)
C(8A)-C(7A)-C(18A)-C(20A) 177.6(2)
C(6A)-C(7A)-C(18A)-C(20A) -62.0(3)
C(6B)-C(5)-O(2B)-C(8B) -24.5(9)
O(2A)-C(5)-O(2B)-C(8B) -67(3)
C(4)-C(5)-O(2B)-C(8B) 105.9(7)
C(6A)-C(5)-O(2B)-C(8B) -11.8(8)
O(2A)-C(5)-C(6B)-C(7B) 37.8(6)
O(2B)-C(5)-C(6B)-C(7B) 33.4(7)
C(4)-C(5)-C(6B)-C(7B) -90.3(5)
C(6A)-C(5)-C(6B)-C(7B) -45.1(12)
C(5)-C(6B)-C(7B)-C(8B) -29.1(7)
C(5)-C(6B)-C(7B)-C(18B) -153.4(5)
C(5)-O(2B)-C(8B)-O(1B) -175.1(11)
C(5)-O(2B)-C(8B)-C(7B) 3.7(10)
C(6B)-C(7B)-C(8B)-O(1B) -165.3(13)

C(18B)-C(7B)-C(8B)-O(1B) -40.6(15)
C(6B)-C(7B)-C(8B)-O(2B) 16.1(10)
C(18B)-C(7B)-C(8B)-O(2B) 140.8(8)
N(1)-C(1)-C(9B)-C(14B) 31.4(3)
C(9A)-C(1)-C(9B)-C(14B) 131(3)
C(2)-C(1)-C(9B)-C(14B) -83.1(4)
N(1)-C(1)-C(9B)-C(10B) -148.6(3)
C(9A)-C(1)-C(9B)-C(10B) -49(3)
C(2)-C(1)-C(9B)-C(10B) 96.9(3)
C(14B)-C(9B)-C(10B)-C(11B) 0.0(4)
C(1)-C(9B)-C(10B)-C(11B) 180.0(2)
C(9B)-C(10B)-C(11B)-C(12B) 0.2(5)
C(26B)-O(3B)-C(12B)-C(11B) -168.2(8)
C(26B)-O(3B)-C(12B)-C(13B) 12.1(10)
C(10B)-C(11B)-C(12B)-O(3B) 180.0(4)
C(10B)-C(11B)-C(12B)-C(13B) -0.3(7)
O(3B)-C(12B)-C(13B)-C(14B) -180.0(5)
C(11B)-C(12B)-C(13B)-C(14B) 0.4(7)
C(10B)-C(9B)-C(14B)-C(13B) 0.0(5)
C(1)-C(9B)-C(14B)-C(13B) -179.9(3)
C(12B)-C(13B)-C(14B)-C(9B) -0.2(7)
C(8B)-C(7B)-C(18B)-C(19B) 61.5(8)
C(6B)-C(7B)-C(18B)-C(19B) 179.5(6)
C(8B)-C(7B)-C(18B)-C(20B) -172.5(6)
C(6B)-C(7B)-C(18B)-C(20B) -54.4(8)


C(16)
C(17)
C(15)
C(23)
C(1)
C(2)
O(5)
C(22)
C(3)
C(24)
N(1)
C(21)
C(4)
C(5)
O(4)
C(7A)
C(7B)
C(18A)
C(18B)

ORTEP view of the C26 H39 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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Article 2, Dilactone **49**

Université de Montréal

CRYSTAL AND MOLECULAR STRUCTURE OF

C42 H60 O6 COMPOUND (bent69)

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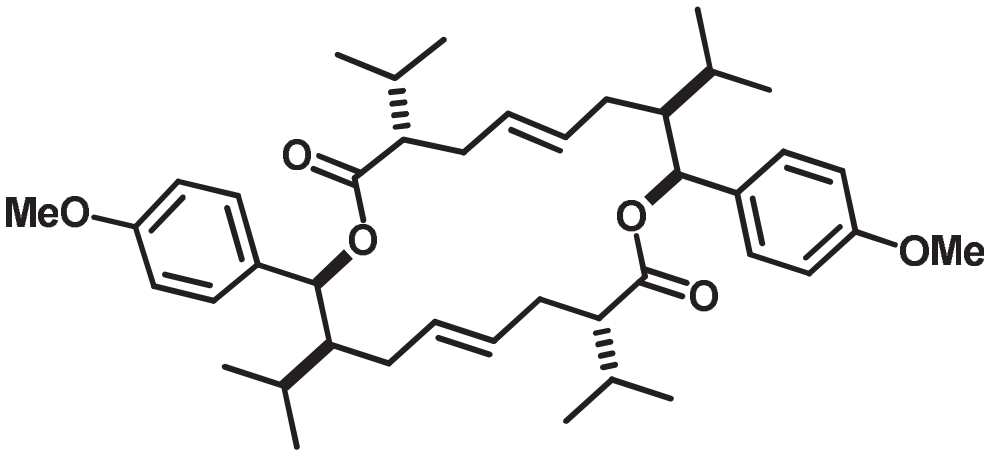


Structure solved and refined in the laboratory of X-ray diffraction Université de Montréal by Benoît Deschênes Simard.

Table 1. Crystal data and structure refinement for C42 H60 O6.

Identification code	bent69
Empirical formula	C42 H60 O6
Formula weight	660.90
Temperature	200K
Wavelength	1.54178 Å
Crystal system	Orthorhombic
Space group	P212121
Unit cell dimensions	a = 8.2377(2) Å α = 90° b = 12.7351(4) Å β = 90° c = 38.5075(10) Å γ = 90°
Volume	4039.74(19)Å^3
Z	4
Density (calculated)	1.087 g/cm^3
Absorption coefficient	0.558 mm^{-1}
F(000)	1440
Crystal size	0.18 x 0.16 x 0.07 mm
Theta range for data collection	2.29 to 56.09°
Index ranges	$-8 \le h \le 8$, $-13 \le k \le 13$, $-40 \le l \le 41$
Reflections collected	53912
Independent reflections	5254 [R_{int} = 0.056]
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9617 and 0.7039
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5254 / 126 / 531
Goodness-of-fit on F^2	0.913

Final R indices [I>2sigma(I)]	R_1 = 0.0455, wR_2 = 0.1130
R indices (all data)	R_1 = 0.0849, wR_2 = 0.1238
Absolute structure parameter	0.0(3)
Largest diff. peak and hole	0.170 and -0.158 e/Å^3

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for C42 H60 O6.

U_{eq} is defined as one third of the trace of the orthogonalized Uij tensor.

	Occ.	x	y	z	U_{eq}
O(12)	1	7863(3)	1278(2)	8220(1)	79(1)
O(13)	1	8990(4)	7183(2)	10672(1)	111(1)
O(11)	0.683(4)	6127(8)	2294(5)	8521(2)	108(2)
C(11)	0.683(4)	6908(10)	1503(6)	8495(2)	87(2)
C(12)	0.683(4)	6871(11)	624(6)	8757(2)	85(1)
C(13)	0.683(4)	7183(8)	1064(4)	9126(2)	89(2)
C(14)	0.683(4)	8838(8)	1518(4)	9168(1)	88(2)
C(15)	0.683(4)	9153(9)	2542(4)	9167(2)	78(2)
C(16)	0.683(4)	10858(9)	2960(8)	9202(4)	84(1)
C(17)	0.683(4)	11073(10)	3702(5)	9514(3)	77(1)
C(115)	0.683(4)	5285(15)	-18(9)	8741(2)	94(2)
C(116)	0.683(4)	5110(20)	-543(14)	8393(3)	116(4)
C(117)	0.683(4)	3765(16)	595(19)	8830(5)	115(5)
C(118)	0.683(4)	12873(10)	3930(9)	9587(3)	82(2)
C(119)	0.683(4)	13641(18)	3037(13)	9783(3)	105(4)
C(120)	0.683(4)	13851(15)	4172(17)	9264(4)	103(4)
C(22)	0.683(4)	10046(11)	6345(5)	8687(2)	76(1)
C(23)	0.683(4)	9560(20)	5831(7)	8345(2)	96(2)
C(24)	0.683(4)	10398(7)	4815(5)	8289(2)	89(2)
C(25)	0.683(4)	9625(7)	3899(5)	8285(2)	92(2)
C(26)	0.683(4)	10450(11)	2838(5)	8205(3)	93(2)
C(27)	0.683(4)	9743(5)	2339(6)	7872(2)	86(1)
C(215)	0.683(4)	9391(18)	7477(5)	8710(3)	97(2)
C(216)	0.683(4)	9910(30)	8011(10)	9046(3)	125(5)
C(217)	0.683(4)	9889(13)	8127(9)	8400(4)	131(5)
C(218)	0.683(4)	10831(8)	1517(5)	7705(3)	83(2)
C(219)	0.683(4)	12365(10)	1983(6)	7554(3)	117(3)
C(220)	0.683(4)	11245(19)	596(10)	7930(4)	113(3)
O(31)	0.317(4)	5659(18)	2106(12)	8379(4)	108(2)
C(31)	0.317(4)	6648(19)	1448(12)	8451(3)	87(2)
C(32)	0.317(4)	6770(20)	794(11)	8778(3)	85(1)
C(33)	0.317(4)	7009(17)	1575(11)	9082(3)	89(2)
C(34)	0.317(4)	8436(13)	2281(10)	9032(3)	88(2)
C(35)	0.317(4)	9704(19)	2257(11)	9245(5)	78(2)
C(36)	0.317(4)	11123(19)	3002(17)	9227(8)	84(1)
C(37)	0.317(4)	11155(19)	3764(10)	9537(5)	77(1)
C(315)	0.317(4)	5280(40)	80(20)	8826(5)	94(2)
C(316)	0.317(4)	5010(50)	-580(30)	8510(9)	116(4)

C(317)	0.317(4)	3740(30)	640(40)	8935(15)	115(5)
C(318)	0.317(4)	12880(20)	4041(19)	9654(8)	82(2)
C(319)	0.317(4)	13590(40)	3200(30)	9880(10)	105(4)
C(320)	0.317(4)	14030(30)	4290(40)	9359(11)	103(4)
C(42)	0.317(4)	10060(20)	6250(11)	8668(4)	76(1)
C(43)	0.317(4)	9470(50)	5682(14)	8343(4)	96(2)
C(44)	0.317(4)	9660(20)	4518(12)	8365(4)	89(2)
C(45)	0.317(4)	10483(15)	3987(10)	8125(4)	92(2)
C(46)	0.317(4)	10660(20)	2782(11)	8146(7)	93(2)
C(47)	0.317(4)	9783(7)	2177(11)	7857(4)	86(1)
C(415)	0.317(4)	9510(40)	7408(10)	8689(6)	97(2)
C(416)	0.317(4)	9610(90)	7790(20)	9066(7)	125(5)
C(417)	0.317(4)	10520(40)	8110(20)	8460(10)	131(5)
C(418)	0.317(4)	10691(19)	1182(13)	7743(6)	83(2)
C(419)	0.317(4)	12280(20)	1444(14)	7566(7)	117(3)
C(420)	0.317(4)	10950(50)	390(20)	8025(11)	113(3)
C(18)	1	9950(5)	4654(3)	9477(1)	77(1)
C(19)	1	9754(5)	5371(3)	9786(1)	72(1)
C(110)	1	8500(5)	5175(3)	10015(1)	83(1)
C(111)	1	8287(5)	5802(3)	10308(1)	94(1)
C(112)	1	9314(6)	6620(3)	10372(1)	87(1)
C(113)	1	10569(5)	6842(3)	10146(1)	91(1)
C(114)	1	10766(5)	6211(3)	9855(1)	89(1)
C(121)	1	10122(6)	7986(3)	10766(1)	122(2)
O(21)	1	7932(4)	5565(2)	9024(1)	94(1)
O(22)	1	10521(3)	5271(2)	9179(1)	72(1)
O(23)	1	5111(3)	629(2)	6677(1)	105(1)
C(21)	1	9390(6)	5682(3)	8973(1)	74(1)
C(28)	1	7975(4)	2017(3)	7931(1)	77(1)
C(29)	1	7134(4)	1586(3)	7618(1)	68(1)
C(210)	1	6725(5)	2285(3)	7353(1)	87(1)
C(211)	1	6067(5)	1952(4)	7053(1)	96(1)
C(212)	1	5787(4)	902(4)	7000(1)	80(1)
C(213)	1	6111(4)	164(3)	7255(1)	81(1)
C(214)	1	6811(4)	539(3)	7565(1)	80(1)
C(221)	1	4821(5)	-452(3)	6621(1)	118(2)

Table 3. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for C42 H60 O6.

	Occ.	x	y	z	U_{eq}
H(12D)	0.683(4)	7785	136	8701	102
H(13A)	0.683(4)	6368	1614	9177	106
H(13B)	0.683(4)	7037	493	9298	106
H(14A)	0.683(4)	9723	1048	9196	106
H(15A)	0.683(4)	8279	3025	9145	93
H(16A)	0.683(4)	11149	3340	8986	101
H(16B)	0.683(4)	11616	2361	9226	101
H(17A)	0.683(4)	10667	3305	9720	92
H(11A)	0.683(4)	5384	-590	8918	112
H(11B)	0.683(4)	6090	-952	8343	174
H(11C)	0.683(4)	4959	-8	8213	174
H(11D)	0.683(4)	4166	-1011	8397	174
H(11E)	0.683(4)	2831	118	8834	172
H(11F)	0.683(4)	3589	1141	8655	172
H(11G)	0.683(4)	3892	921	9059	172
H(11H)	0.683(4)	12921	4564	9740	98
H(11I)	0.683(4)	13074	2937	10004	157
H(11J)	0.683(4)	14785	3199	9828	157
H(11K)	0.683(4)	13565	2393	9645	157
H(12E)	0.683(4)	14940	4406	9331	155
H(12F)	0.683(4)	13310	4729	9132	155
H(12G)	0.683(4)	13934	3539	9121	155
H(22D)	0.683(4)	11257	6361	8704	91
H(23A)	0.683(4)	8368	5713	8344	115
H(23B)	0.683(4)	9818	6312	8151	115
H(24A)	0.683(4)	11539	4819	8254	107
H(25A)	0.683(4)	8496	3897	8335	110
H(26A)	0.683(4)	11631	2948	8175	112
H(26B)	0.683(4)	10289	2353	8403	112
H(27A)	0.683(4)	9692	2926	7700	103
H(21A)	0.683(4)	8179	7437	8711	117
H(21B)	0.683(4)	9510	8735	9049	188
H(21C)	0.683(4)	11100	8014	9062	188
H(21D)	0.683(4)	9462	7627	9245	188
H(21E)	0.683(4)	9413	8830	8419	197
H(21F)	0.683(4)	9503	7789	8187	197
H(21G)	0.683(4)	11075	8184	8393	197
H(21H)	0.683(4)	10206	1228	7504	99
H(21I)	0.683(4)	12833	1492	7385	175
H(21J)	0.683(4)	13148	2111	7741	175
H(21K)	0.683(4)	12108	2647	7438	175

H(22E)	0.683(4)12035	149	7810	170
H(22F)	0.683(4)10259	191	7978	170
H(22G)	0.683(4)11712	846	8149	170
H(32A)	0.317(4) 7760	341	8761	102
H(33A)	0.317(4) 6018	2008	9106	106
H(33B)	0.317(4) 7153	1174	9300	106
H(34A)	0.317(4) 8438	2760	8842	106
H(35A)	0.317(4) 9717	1734	9421	93
H(36A)	0.317(4)11058	3411	9008	101
H(36B)	0.317(4)12145	2593	9222	101
H(37A)	0.317(4)10689	3352	9735	92
H(31A)	0.317(4) 5554	-415	9019	112
H(31B)	0.317(4) 5973	-1021	8469	174
H(31C)	0.317(4) 4828	-129	8309	174
H(31D)	0.317(4) 4064	-1034	8546	174
H(31E)	0.317(4) 3903	966	9163	172
H(31F)	0.317(4) 2844	139	8947	172
H(31G)	0.317(4) 3481	1189	8764	172
H(31H)	0.317(4)12800	4690	9800	98
H(31I)	0.317(4)14245	3518	10064	157
H(31J)	0.317(4)14281	2736	9739	157
H(31K)	0.317(4)12714	2783	9985	157
H(32B)	0.317(4)15013	4620	9451	155
H(32C)	0.317(4)13501	4761	9194	155
H(32D)	0.317(4)14329	3633	9240	155
H(42A)	0.317(4)11270	6220	8676	91
H(43A)	0.317(4) 8309	5849	8305	115
H(43B)	0.317(4)10084	5945	8140	115
H(44A)	0.317(4) 9194	4150	8554	107
H(45A)	0.317(4)10965	4355	7936	110
H(46A)	0.317(4)11833	2604	8138	112
H(46B)	0.317(4)10240	2543	8374	112
H(47A)	0.317(4) 9820	2653	7650	103
H(41A)	0.317(4) 8355	7453	8611	117
H(41B)	0.317(4) 9038	8465	9087	188
H(41C)	0.317(4)10752	7889	9131	188
H(41D)	0.317(4) 9109	7275	9220	188
H(41E)	0.317(4)10506	7839	8222	197
H(41F)	0.317(4)11641	8121	8546	197
H(41G)	0.317(4)10074	8821	8464	197
H(41H)	0.317(4) 9995	835	7564	99
H(41I)	0.317(4)12792	796	7482	175
H(41J)	0.317(4)13011	1789	7732	175
H(41K)	0.317(4)12081	1915	7369	175
H(42B)	0.317(4) 9894	174	8120	170
H(42C)	0.317(4)11605	702	8211	170
H(42D)	0.317(4)11511	-224	7930	170
H(18)	1	8847	4381	9417	92
H(110)	1	7778	4608	9973	100
H(111)	1	7421	5659	10463	112

H(113)	1	11281	7415	10188	109
H(114)	1	11626	6361	9699	107
H(12A)	1	10061	8561	10598	184
H(12B)	1	11223	7694	10767	184
H(12C)	1	9857	8252	10998	184
H(28)	1	7372	2664	8001	92
H(210)	1	6918	3014	7385	105
H(211)	1	5795	2445	6878	115
H(213)	1	5874	-559	7222	97
H(214)	1	7068	52	7744	95
H(22A)	1	4300	-754	6827	177
H(22B)	1	5854	-812	6578	177
H(22C)	1	4108	-541	6420	177

Table 4. Anisotropic parameters ($Å^2$ x 10^3) for C42 H60 O6.

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(12)	84(2)	70(2)	82(2)	-9(2)	9(2)	6(1)
O(13)	111(2)	107(2)	114(2)	-38(2)	-3(2)	6(2)
O(11)	137(4)	64(3)	124(6)	-7(3)	49(4)	10(3)
C(11)	95(4)	52(3)	114(4)	-17(3)	18(3)	-6(3)
C(12)	93(3)	71(3)	90(3)	-8(3)	9(2)	-4(3)
C(13)	136(4)	48(5)	82(4)	1(4)	9(3)	-20(4)
C(14)	113(5)	78(3)	74(4)	3(3)	-15(3)	-20(4)
C(15)	82(6)	85(4)	67(5)	-11(3)	-18(4)	-2(4)
C(16)	99(4)	73(2)	80(3)	-14(2)	0(4)	-18(3)
C(17)	104(4)	57(2)	69(3)	0(2)	0(2)	-8(2)
C(115)	108(3)	75(4)	98(5)	-8(4)	18(4)	-12(3)
C(116)	117(4)	97(3)	134(10)	-33(7)	29(7)	-33(3)
C(117)	122(4)	123(4)	99(14)	-10(8)	25(5)	-10(4)
C(118)	95(3)	67(3)	84(5)	-10(3)	-17(3)	6(3)
C(119)	136(4)	101(6)	77(9)	-1(6)	-20(5)	28(4)
C(120)	85(4)	97(6)	129(11)	19(8)	-21(5)	-6(4)
C(22)	70(2)	67(3)	90(3)	2(2)	2(2)	-6(2)
C(23)	112(4)	82(4)	94(3)	13(3)	4(3)	15(4)
C(24)	77(6)	94(5)	95(5)	-4(4)	3(4)	1(4)
C(25)	58(5)	92(4)	126(6)	4(4)	-16(4)	-7(4)
C(26)	90(4)	84(3)	106(5)	-17(3)	-13(4)	-4(3)
C(27)	79(3)	78(3)	102(3)	-5(3)	-7(2)	-11(2)
C(215)	107(4)	57(2)	127(4)	13(3)	2(3)	7(2)
C(216)	135(12)	69(6)	173(5)	-31(4)	-42(5)	-2(8)
C(217)	102(12)	107(4)	185(8)	37(4)	28(8)	8(5)
C(218)	58(3)	83(5)	108(4)	-1(4)	10(3)	-18(3)
C(219)	76(4)	119(8)	155(5)	14(8)	19(3)	-22(6)
C(220)	117(7)	94(6)	129(11)	26(5)	47(5)	35(6)
O(31)	137(4)	64(3)	124(6)	-7(3)	49(4)	10(3)
C(31)	95(4)	52(3)	114(4)	-17(3)	18(3)	-6(3)
C(32)	93(3)	71(3)	90(3)	-8(3)	9(2)	-4(3)
C(33)	136(4)	48(5)	82(4)	1(4)	9(3)	-20(4)
C(34)	113(5)	78(3)	74(4)	3(3)	-15(3)	-20(4)
C(35)	82(6)	85(4)	67(5)	-11(3)	-18(4)	-2(4)

C(36)	99(4)	73(2)	80(3)	-14(2)	0(4)	-18(3)
C(37)	104(4)	57(2)	69(3)	0(2)	0(2)	-8(2)
C(315)	108(3)	75(4)	98(5)	-8(4)	18(4)	-12(3)
C(316)	117(4)	97(3)	134(10)	-33(7)	29(7)	-33(3)
C(317)	122(4)	123(4)	99(14)	-10(8)	25(5)	-10(4)
C(318)	95(3)	67(3)	84(5)	-10(3)	-17(3)	6(3)
C(319)	136(4)	101(6)	77(9)	-1(6)	-20(5)	28(4)
C(320)	85(4)	97(6)	129(11)	19(8)	-21(5)	-6(4)
C(42)	70(2)	67(3)	90(3)	2(2)	2(2)	-6(2)
C(43)	112(4)	82(4)	94(3)	13(3)	4(3)	15(4)
C(44)	77(6)	94(5)	95(5)	-4(4)	3(4)	1(4)
C(45)	58(5)	92(4)	126(6)	4(4)	-16(4)	-7(4)
C(46)	90(4)	84(3)	106(5)	-17(3)	-13(4)	-4(3)
C(47)	79(3)	78(3)	102(3)	-5(3)	-7(2)	-11(2)
C(415)	107(4)	57(2)	127(4)	13(3)	2(3)	7(2)
C(416)	135(12)	69(6)	173(5)	-31(4)	-42(5)	-2(8)
C(417)	102(12)	107(4)	185(8)	37(4)	28(8)	8(5)
C(418)	58(3)	83(5)	108(4)	-1(4)	10(3)	-18(3)
C(419)	76(4)	119(8)	155(5)	14(8)	19(3)	-22(6)
C(420)	117(7)	94(6)	129(11)	26(5)	47(5)	35(6)
C(18)	85(3)	68(2)	78(3)	-4(2)	-7(2)	-5(2)
C(19)	73(3)	64(2)	79(3)	0(2)	-4(2)	-2(2)
C(110)	91(3)	75(2)	83(3)	-6(2)	1(3)	-11(2)
C(111)	94(3)	94(3)	93(3)	-10(3)	11(2)	-5(3)
C(112)	96(4)	77(3)	86(3)	-13(3)	-6(3)	4(3)
C(113)	87(3)	75(3)	111(3)	-10(3)	-2(3)	-11(2)
C(114)	88(3)	87(3)	91(3)	-20(2)	5(2)	-16(3)
C(121)	129(4)	95(3)	143(4)	-44(3)	-27(3)	0(3)
O(21)	72(2)	101(2)	108(2)	10(2)	-5(2)	-1(2)
O(22)	68(2)	73(2)	76(2)	8(1)	-7(1)	-4(1)
O(23)	102(2)	101(2)	113(2)	9(2)	-10(2)	-7(2)
C(21)	65(3)	70(2)	89(3)	-12(2)	-1(3)	1(2)
C(28)	69(3)	65(2)	95(3)	-6(2)	15(2)	-3(2)
C(29)	57(2)	64(3)	85(3)	-1(2)	5(2)	6(2)
C(210)	76(3)	82(3)	105(3)	1(3)	-5(2)	-11(2)
C(211)	78(3)	93(3)	116(4)	16(3)	-7(3)	-8(3)
C(212)	60(2)	87(3)	93(3)	-1(3)	7(2)	-1(2)
C(213)	70(2)	64(2)	107(3)	-12(3)	16(2)	1(2)
C(214)	72(3)	73(3)	94(3)	-15(2)	6(2)	16(2)
C(221)	84(3)	96(2)	175(4)	-34(3)	-6(3)	1(2)

Table 5. Bond lengths [Å] and angles [°] for C42 H60 O6

O(12)-C(11)	1.349(6)
O(12)-C(31)	1.357(11)
O(12)-C(28)	1.461(4)
O(13)-C(112)	1.385(4)
O(13)-C(121)	1.431(5)
O(11)-C(11)	1.199(6)
C(11)-C(12)	1.510(6)
C(12)-C(115)	1.542(6)
C(12)-C(13)	1.548(6)
C(13)-C(14)	1.489(7)
C(14)-C(15)	1.3299(8)
C(15)-C(16)	1.507(7)
C(16)-C(17)	1.540(5)
C(17)-C(18)	1.531(7)
C(17)-C(118)	1.537(6)
C(115)-C(116)	1.505(6)
C(115)-C(117)	1.514(7)
C(118)-C(119)	1.504(6)
C(118)-C(120)	1.514(6)
C(22)-C(21)	1.489(6)
C(22)-C(23)	1.528(6)
C(22)-C(215)	1.541(6)
C(23)-C(24)	1.484(8)
C(24)-C(25)	1.3284(8)
C(25)-C(26)	1.544(7)
C(26)-C(27)	1.544(6)
C(27)-C(218)	1.521(6)
C(27)-C(28)	1.530(5)
C(215)-C(217)	1.509(7)
C(215)-C(216)	1.526(8)
C(218)-C(220)	1.497(7)
C(218)-C(219)	1.512(6)
O(31)-C(31)	1.200(9)
C(31)-C(32)	1.513(8)
C(32)-C(315)	1.540(9)
C(32)-C(33)	1.548(8)
C(33)-C(34)	1.493(9)
C(34)-C(35)	1.3296(8)
C(35)-C(36)	1.507(9)
C(36)-C(37)	1.540(8)
C(37)-C(18)	1.525(11)
C(37)-C(318)	1.532(9)
C(315)-C(316)	1.496(9)
C(315)-C(317)	1.516(9)
C(318)-C(319)	1.503(9)

C(318)-C(320)	1.514(9)
C(42)-C(21)	1.485(10)
C(42)-C(43)	1.525(8)
C(42)-C(415)	1.544(9)
C(43)-C(44)	1.493(10)
C(44)-C(45)	1.3294(8)
C(45)-C(46)	1.544(9)
C(46)-C(47)	1.538(8)
C(47)-C(28)	1.530(5)
C(47)-C(418)	1.535(9)
C(415)-C(417)	1.504(11)
C(415)-C(416)	1.535(9)
C(418)-C(420)	1.499(10)
C(418)-C(419)	1.517(10)
C(18)-O(22)	1.470(4)
C(18)-C(19)	1.508(5)
C(19)-C(110)	1.381(5)
C(19)-C(114)	1.382(5)
C(110)-C(111)	1.390(5)
C(111)-C(112)	1.365(5)
C(112)-C(113)	1.381(5)
C(113)-C(114)	1.387(5)
O(21)-C(21)	1.226(4)
O(22)-C(21)	1.330(4)
O(23)-C(212)	1.408(4)
O(23)-C(221)	1.413(5)
C(28)-C(29)	1.494(5)
C(29)-C(214)	1.374(5)
C(29)-C(210)	1.396(5)
C(210)-C(211)	1.342(5)
C(211)-C(212)	1.373(5)
C(212)-C(213)	1.384(5)
C(213)-C(214)	1.410(5)

C(11)-O(12)-C(31)	11.9(11)
C(11)-O(12)-C(28)	119.8(4)
C(31)-O(12)-C(28)	116.3(6)
C(112)-O(13)-C(121)	117.1(4)
O(11)-C(11)-O(12)	123.9(5)
O(11)-C(11)-C(12)	123.8(6)
O(12)-C(11)-C(12)	112.3(5)
C(11)-C(12)-C(115)	112.5(5)
C(11)-C(12)-C(13)	110.0(5)
C(115)-C(12)-C(13)	111.7(5)
C(14)-C(13)-C(12)	113.0(5)
C(15)-C(14)-C(13)	124.0(5)
C(14)-C(15)-C(16)	121.8(7)
C(15)-C(16)-C(17)	113.1(5)

C(18)-C(17)-C(118) 116.8(5)
C(18)-C(17)-C(16) 110.2(6)
C(118)-C(17)-C(16) 111.8(5)
C(116)-C(115)-C(117) 110.5(6)
C(116)-C(115)-C(12) 110.6(5)
C(117)-C(115)-C(12) 114.8(6)
C(119)-C(118)-C(120) 110.0(6)
C(119)-C(118)-C(17) 110.8(6)
C(120)-C(118)-C(17) 113.6(5)
C(21)-C(22)-C(23) 107.4(6)
C(21)-C(22)-C(215) 111.2(5)
C(23)-C(22)-C(215) 110.9(5)
C(24)-C(23)-C(22) 112.1(7)
C(25)-C(24)-C(23) 122.9(10)
C(24)-C(25)-C(26) 124.0(7)
C(27)-C(26)-C(25) 111.2(5)
C(218)-C(27)-C(28) 116.0(5)
C(218)-C(27)-C(26) 114.3(5)
C(28)-C(27)-C(26) 110.3(5)
C(217)-C(215)-C(216) 110.5(6)
C(217)-C(215)-C(22) 111.9(6)
C(216)-C(215)-C(22) 111.5(6)
C(220)-C(218)-C(219) 109.8(6)
C(220)-C(218)-C(27) 115.3(5)
C(219)-C(218)-C(27) 112.7(5)
O(31)-C(31)-O(12) 117.5(10)
O(31)-C(31)-C(32) 128.5(12)
O(12)-C(31)-C(32) 114.0(10)
C(31)-C(32)-C(315) 111.8(10)
C(31)-C(32)-C(33) 106.5(9)
C(315)-C(32)-C(33) 112.9(10)
C(34)-C(33)-C(32) 112.9(10)
C(35)-C(34)-C(33) 121.7(11)
C(34)-C(35)-C(36) 124.5(15)
C(35)-C(36)-C(37) 112.0(11)
C(18)-C(37)-C(318) 118.5(10)
C(18)-C(37)-C(36) 109.8(11)
C(318)-C(37)-C(36) 112.9(10)
C(316)-C(315)-C(317) 111.7(12)
C(316)-C(315)-C(32) 110.7(11)
C(317)-C(315)-C(32) 114.9(12)
C(319)-C(318)-C(320) 109.8(12)
C(319)-C(318)-C(37) 111.5(12)
C(320)-C(318)-C(37) 114.1(12)
C(21)-C(42)-C(43) 107.5(11)
C(21)-C(42)-C(415) 108.4(10)
C(43)-C(42)-C(415) 113.8(10)
C(44)-C(43)-C(42) 112.9(10)
C(45)-C(44)-C(43) 121.3(15)
C(44)-C(45)-C(46) 121.1(13)

C(47)-C(46)-C(45) 114.4(11)
C(28)-C(47)-C(418) 114.7(9)
C(28)-C(47)-C(46) 113.0(10)
C(418)-C(47)-C(46) 113.0(9)
C(417)-C(415)-C(416) 109.4(12)
C(417)-C(415)-C(42) 112.0(12)
C(416)-C(415)-C(42) 109.9(11)
C(420)-C(418)-C(419) 110.6(11)
C(420)-C(418)-C(47) 114.7(12)
C(419)-C(418)-C(47) 111.7(11)
O(22)-C(18)-C(19) 109.1(3)
O(22)-C(18)-C(37) 107.9(8)
C(19)-C(18)-C(37) 113.6(7)
O(22)-C(18)-C(17) 107.5(5)
C(19)-C(18)-C(17) 118.2(4)
C(37)-C(18)-C(17) 5.2(9)
C(110)-C(19)-C(114) 117.9(4)
C(110)-C(19)-C(18) 118.3(3)
C(114)-C(19)-C(18) 123.8(4)
C(19)-C(110)-C(111) 120.5(4)
C(112)-C(111)-C(110) 120.4(4)
C(111)-C(112)-C(113) 120.4(4)
C(111)-C(112)-O(13) 115.3(4)
C(113)-C(112)-O(13) 124.4(4)
C(112)-C(113)-C(114) 118.5(4)
C(19)-C(114)-C(113) 122.2(4)
C(21)-O(22)-C(18) 116.9(3)
C(212)-O(23)-C(221) 116.2(3)
O(21)-C(21)-O(22) 122.9(4)
O(21)-C(21)-C(42) 123.2(8)
O(22)-C(21)-C(42) 113.8(8)
O(21)-C(21)-C(22) 122.8(5)
O(22)-C(21)-C(22) 114.2(5)
C(42)-C(21)-C(22) 5.5(9)
O(12)-C(28)-C(29) 110.4(3)
O(12)-C(28)-C(27) 110.2(4)
C(29)-C(28)-C(27) 114.9(4)
O(12)-C(28)-C(47) 106.8(7)
C(29)-C(28)-C(47) 110.5(6)
C(27)-C(28)-C(47) 8.2(7)
C(214)-C(29)-C(210) 117.6(4)
C(214)-C(29)-C(28) 124.4(4)
C(210)-C(29)-C(28) 117.9(4)
C(211)-C(210)-C(29) 121.7(4)
C(210)-C(211)-C(212) 120.2(4)
C(211)-C(212)-C(213) 121.5(4)
C(211)-C(212)-O(23) 116.0(4)
C(213)-C(212)-O(23) 122.4(4)
C(212)-C(213)-C(214) 116.7(4)
C(29)-C(214)-C(213) 122.2(4)

Table 6. Torsion angles [°] for C42 H60 O6.

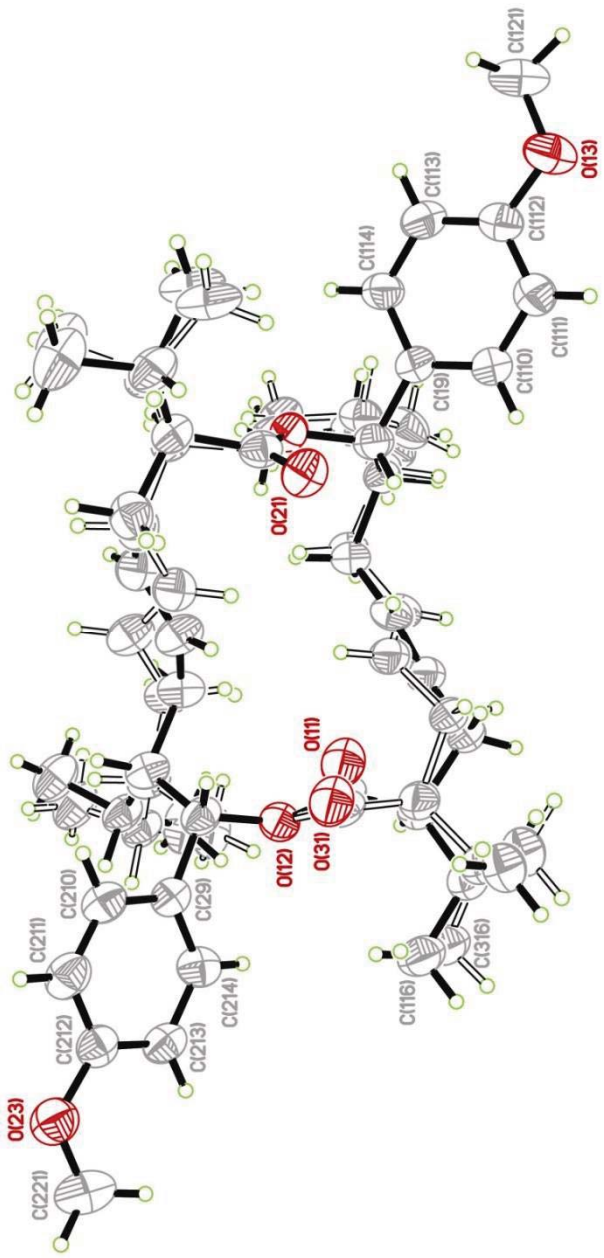
..C(31)-O(12)-C(11)-O(11)	-77(3)
C(28)-O(12)-C(11)-O(11)	-0.6(11)
C(31)-O(12)-C(11)-C(12)	101(4)
C(28)-O(12)-C(11)-C(12)	176.7(4)
O(11)-C(11)-C(12)-C(115)	73.4(10)
O(12)-C(11)-C(12)-C(115)	-103.9(7)
O(11)-C(11)-C(12)-C(13)	-51.8(10)
O(12)-C(11)-C(12)-C(13)	130.9(7)
C(11)-C(12)-C(13)-C(14)	-64.8(8)
C(115)-C(12)-C(13)-C(14)	169.5(7)
C(12)-C(13)-C(14)-C(15)	102.7(8)
C(13)-C(14)-C(15)-C(16)	-178.5(7)
C(14)-C(15)-C(16)-C(17)	-122.3(10)
C(15)-C(16)-C(17)-C(18)	-60.3(11)
C(15)-C(16)-C(17)-C(118)	168.1(9)
C(11)-C(12)-C(115)-C(116)	62.4(11)
C(13)-C(12)-C(115)-C(116)	-173.3(10)
C(11)-C(12)-C(115)-C(117)	-63.4(11)
C(13)-C(12)-C(115)-C(117)	60.9(10)
C(18)-C(17)-C(118)-C(119)	152.2(9)
C(16)-C(17)-C(118)-C(119)	-79.6(11)
C(18)-C(17)-C(118)-C(120)	-83.3(11)
C(16)-C(17)-C(118)-C(120)	44.9(12)
C(21)-C(22)-C(23)-C(24)	-68.0(13)
C(215)-C(22)-C(23)-C(24)	170.2(11)
C(22)-C(23)-C(24)-C(25)	113.3(11)
C(23)-C(24)-C(25)-C(26)	175.9(7)
C(24)-C(25)-C(26)-C(27)	-116.8(8)
C(25)-C(26)-C(27)-C(218)	159.9(7)
C(25)-C(26)-C(27)-C(28)	-67.2(9)
C(21)-C(22)-C(215)-C(217)	-173.5(9)
C(23)-C(22)-C(215)-C(217)	-54.0(13)
C(21)-C(22)-C(215)-C(216)	62.1(10)
C(23)-C(22)-C(215)-C(216)	-178.4(11)
C(28)-C(27)-C(218)-C(220)	-70.9(10)
C(26)-C(27)-C(218)-C(220)	59.3(10)
C(28)-C(27)-C(218)-C(219)	161.9(8)
C(26)-C(27)-C(218)-C(219)	-67.9(10)
C(11)-O(12)-C(31)-O(31)	119(5)
C(28)-O(12)-C(31)-O(31)	8.5(19)
C(11)-O(12)-C(31)-C(32)	-59(3)
C(28)-O(12)-C(31)-C(32)	-169.2(8)
O(31)-C(31)-C(32)-C(315)	63(2)
O(12)-C(31)-C(32)-C(315)	-119.8(15)
O(31)-C(31)-C(32)-C(33)	-61(2)

O(12)-C(31)-C(32)-C(33) 116.4(14)
C(31)-C(32)-C(33)-C(34) -55.8(16)
C(315)-C(32)-C(33)-C(34) -178.8(15)
C(32)-C(33)-C(34)-C(35) -116.3(18)
C(33)-C(34)-C(35)-C(36) -175.0(13)
C(34)-C(35)-C(36)-C(37) 110(2)
C(35)-C(36)-C(37)-C(18) -80(2)
C(35)-C(36)-C(37)-C(318) 145.7(19)
C(31)-C(32)-C(315)-C(316) 54(3)
C(33)-C(32)-C(315)-C(316) 174(2)
C(31)-C(32)-C(315)-C(317) -73(3)
C(33)-C(32)-C(315)-C(317) 47(3)

C(18)-C(37)-C(318)-C(319) 149(2)
C(36)-C(37)-C(318)-C(319) -81(3)
C(18)-C(37)-C(318)-C(320) -86(2)
C(36)-C(37)-C(318)-C(320) 44(3)
C(21)-C(42)-C(43)-C(44) -46(3)
C(415)-C(42)-C(43)-C(44) -166(2)
C(42)-C(43)-C(44)-C(45) -125(3)
C(43)-C(44)-C(45)-C(46) -179.3(18)
C(44)-C(45)-C(46)-C(47) 113(2)
C(45)-C(46)-C(47)-C(28) -82(2)
C(45)-C(46)-C(47)-C(418) 145.4(15)
C(21)-C(42)-C(415)-C(417) 162(2)
C(43)-C(42)-C(415)-C(417) -78(3)
C(21)-C(42)-C(415)-C(416) 40(2)
C(43)-C(42)-C(415)-C(416) 160(3)
C(28)-C(47)-C(418)-C(420) -72(2)
C(46)-C(47)-C(418)-C(420) 60(2)
C(28)-C(47)-C(418)-C(419) 161.6(18)
C(46)-C(47)-C(418)-C(419) -67(2)
C(318)-C(37)-C(18)-O(22) 66.2(14)
C(36)-C(37)-C(18)-O(22) -65.6(13)
C(318)-C(37)-C(18)-C(19) -54.9(14)
C(36)-C(37)-C(18)-C(19) 173.3(10)
C(318)-C(37)-C(18)-C(17) 153(13)
C(36)-C(37)-C(18)-C(17)   21(12)
C(118)-C(17)-C(18)-O(22) 61.9(7)
C(16)-C(17)-C(18)-O(22) -67.0(7)
C(118)-C(17)-C(18)-C(19) -62.0(7)
C(16)-C(17)-C(18)-C(19) 169.0(5)
C(118)-C(17)-C(18)-C(37) -33(13)
C(16)-C(17)-C(18)-C(37) -162(13)
O(22)-C(18)-C(19)-C(110) 144.8(3)
C(37)-C(18)-C(19)-C(110) -94.7(8)
C(17)-C(18)-C(19)-C(110) -92.0(5)
O(22)-C(18)-C(19)-C(114) -35.7(4)
C(37)-C(18)-C(19)-C(114) 84.8(9)
C(17)-C(18)-C(19)-C(114) 87.5(6)

C(114)-C(19)-C(110)-C(111) -0.8(5)
C(18)-C(19)-C(110)-C(111) 178.8(3)
C(19)-C(110)-C(111)-C(112) 0.1(6)
C(110)-C(111)-C(112)-C(113) 0.6(6)
C(110)-C(111)-C(112)-O(13) -179.5(3)
C(121)-O(13)-C(112)-C(111) 174.4(3)
C(121)-O(13)-C(112)-C(113) -5.7(6)
C(111)-C(112)-C(113)-C(114) -0.6(6)
O(13)-C(112)-C(113)-C(114) 179.6(3)
C(110)-C(19)-C(114)-C(113) 0.8(5)
C(18)-C(19)-C(114)-C(113) -178.7(3)
C(112)-C(113)-C(114)-C(19) -0.1(6)
C(19)-C(18)-O(22)-C(21) -90.6(3)
C(37)-C(18)-O(22)-C(21) 145.5(7)
C(17)-C(18)-O(22)-C(21) 140.1(4)
C(18)-O(22)-C(21)-O(21) 0.0(5)
C(18)-O(22)-C(21)-C(42) -177.2(7)
C(18)-O(22)-C(21)-C(22) 176.8(4)
C(43)-C(42)-C(21)-O(21) -59.6(17)
C(415)-C(42)-C(21)-O(21) 63.8(15)
C(43)-C(42)-C(21)-O(22) 117.5(12)
C(415)-C(42)-C(21)-O(22) -119.1(12)
C(43)-C(42)-C(21)-C(22) -147(11)
C(415)-C(42)-C(21)-C(22) -24(11)
C(23)-C(22)-C(21)-O(21) -65.3(9)
C(215)-C(22)-C(21)-O(21) 56.3(8)
C(23)-C(22)-C(21)-O(22) 117.9(6)
C(215)-C(22)-C(21)-O(22) -120.5(6)
C(23)-C(22)-C(21)-C(42) 30(11)
C(215)-C(22)-C(21)-C(42) 152(11)
C(11)-O(12)-C(28)-C(29) -109.1(5)
C(31)-O(12)-C(28)-C(29) -96.1(9)
C(11)-O(12)-C(28)-C(27) 122.9(6)
C(31)-O(12)-C(28)-C(27) 135.8(10)
C(11)-O(12)-C(28)-C(47) 130.7(7)
C(31)-O(12)-C(28)-C(47) 143.7(10)
C(218)-C(27)-C(28)-O(12) 73.9(6)
C(26)-C(27)-C(28)-O(12) -58.2(6)
C(218)-C(27)-C(28)-C(29) -51.6(7)
C(26)-C(27)-C(28)-C(29) 176.3(4)
C(218)-C(27)-C(28)-C(47) 7(6)
C(26)-C(27)-C(28)-C(47) -125(7)
C(418)-C(47)-C(28)-O(12) 62.4(11)
C(46)-C(47)-C(28)-O(12) -69.1(11)
C(418)-C(47)-C(28)-C(29) -57.8(12)
C(46)-C(47)-C(28)-C(29) 170.7(9)
C(418)-C(47)-C(28)-C(27) 178(10)
C(46)-C(47)-C(28)-C(27) 47(6)
O(12)-C(28)-C(29)-C(214) -21.1(5)
C(27)-C(28)-C(29)-C(214) 104.2(5)

C(47)-C(28)-C(29)-C(214) 96.8(7)
O(12)-C(28)-C(29)-C(210) 162.5(3)
C(27)-C(28)-C(29)-C(210) -72.1(5)
C(47)-C(28)-C(29)-C(210) -79.6(7)
C(214)-C(29)-C(210)-C(211) -1.2(6)
C(28)-C(29)-C(210)-C(211) 175.5(3)
C(29)-C(210)-C(211)-C(212) -0.4(6)
C(210)-C(211)-C(212)-C(213) 2.5(6)
C(210)-C(211)-C(212)-O(23) -179.3(3)
C(221)-O(23)-C(212)-C(211) -180.0(4)
C(221)-O(23)-C(212)-C(213) -1.7(5)
C(211)-C(212)-C(213)-C(214) -2.8(5)
O(23)-C(212)-C(213)-C(214) 179.1(3)
C(210)-C(29)-C(214)-C(213) 0.7(5)
C(28)-C(29)-C(214)-C(213) -175.6(3)
C(212)-C(213)-C(214)-C(29) 1.2(5)



ORTEP view of the C42 H60 O6 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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Diaryl **2.53**

Université de Montréal

CRYSTAL AND MOLECULAR STRUCTURE OF

C18 H21 N3 O2 COMPOUND (han503)

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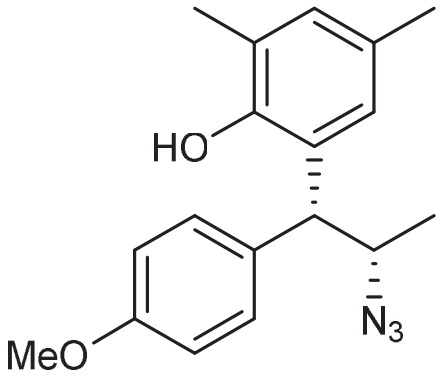


Structure solved and refined in the laboratory of X-ray diffraction
Université de Montréal by Michel Simard.

Table 1 Crystal data and structure refinement for han503.

Identification code	han503
Empirical formula	$C_{18}H_{21}N_3O_2$
Formula weight	311.38
Temperature/K	100
Crystal system	monoclinic
Space group	$P2_1/n$
a/Å	17.8748(15)
b/Å	9.6303(8)
c/Å	21.1356(17)
α/°	90
β/°	113.245(4)
γ/°	90
Volume/Å^3	3342.9(5)
Z	8
ρ_{calc}g/cm^3	1.237
μ/mm^{-1}	0.424
F(000)	1328.0
Crystal size/mm^3	0.24 × 0.12 × 0.07
Radiation	GaKα (λ = 1.34139)
2Θ range for data collection/°	4.792 to 121.48
Index ranges	$-23 \leq h \leq 23$, $-12 \leq k \leq 12$, $-20 \leq l \leq 27$
Reflections collected	53076
Independent reflections	7681 [R_{int} = 0.0559, R_{sigma} = 0.0404]
Data/restraints/parameters	7681/13/433

Goodness-of-fit on F^2	1.016
Final R indexes [I>=2σ (I)]	R_1 = 0.0556, wR_2 = 0.1518
Final R indexes [all data]	R_1 = 0.0698, wR_2 = 0.1621
Largest diff. peak/hole / e $Å^{-3}$	0.48/-0.25

Table 2 Fractional Atomic Coordinates (×10^4) and Equivalent Isotropic Displacement Parameters ($Å^2$×10^3) for han503. U_{eq} is defined as 1/3 of of the trace of the orthogonalised U_{IJ} tensor.

Atom	*x*	*y*	*z*	U(eq)
O11	6646.2(8)	7820.2(12)	4371.7(6)	39.8(3)
O12A	6827.9(8)	437.0(15)	3823.9(8)	44.5(4)
O12B	7826(10)	3814(15)	2598(8)	44.5(4)
N11	6205.5(11)	1394.1(17)	1914.6(8)	47.8(4)
N12	5974.4(10)	1265.5(17)	1291.7(9)	47.0(4)
N13	5774.3(13)	1021(2)	724.1(10)	62.4(5)
C11	6402.0(11)	7856(2)	4941.2(9)	41.7(4)
C12	6588.5(9)	6562.7(16)	4046.5(8)	31.8(3)
C13	6792.3(10)	6568.2(17)	3475.0(9)	35.3(4)
C14	6741.3(10)	5356.0(17)	3108.1(8)	33.2(3)
C15	6477.4(9)	4117.3(16)	3294.9(8)	29.6(3)
C16	6271.7(9)	4144.9(17)	3864.0(8)	31.5(3)
C17	6331.7(9)	5345.0(17)	4245.8(8)	31.4(3)
C18	6465.0(9)	2734.5(16)	2943.5(8)	32.0(3)
C19	6122.8(10)	2834.3(17)	2158.8(8)	35.6(4)
C110	5239.5(11)	3302(2)	1860.9(10)	45.7(4)
C111	7319.2(10)	2103.5(17)	3248.6(8)	32.4(3)

C112	7476.6(10)	971.3(17)	3692.1(8)	35.2(4)
C113	8270.1(11)	443.8(19)	4021.3(9)	41.5(4)
C114	8887.5(11)	1074(2)	3881(1)	45.1(5)
C115	8753.5(11)	2197(2)	3436(1)	44.8(4)
C116	7963.5(10)	2705.1(19)	3126.8(9)	38.4(4)
C117	8448.0(14)	-700(2)	4543.1(11)	58.5(6)
C118	9438.0(13)	2857(3)	3293.7(14)	62.6(6)
O21	6778.0(8)	-1382.1(13)	9395.6(6)	41.9(3)
O22A	7014.1(8)	6030.2(14)	8917.0(7)	41.9(3)
O22B	7992(9)	2819(15)	7660(7)	41.9(3)
N21	6330.9(9)	5161.3(17)	7016.9(8)	43.4(4)
N22	6022(1)	5322.9(17)	6391.4(8)	45.7(4)
N23	5750.0(12)	5600(2)	5822.6(9)	61.3(5)
C21	6561.3(12)	-1421(2)	9980.8(9)	43.6(4)
C22	6742.9(10)	-114.5(17)	9085.7(8)	33.1(3)
C23	6905.1(11)	-112.5(18)	8493.9(9)	39.0(4)
C24	6881.8(10)	1118.2(18)	8147.9(8)	36.1(4)
C25	6687.5(9)	2369.1(17)	8377.4(8)	31.3(3)
C26	6526.4(10)	2337.1(17)	8969.4(8)	33.6(3)
C27	6556.8(10)	1119.1(18)	9327.8(8)	33.6(3)
C28	6668.0(9)	3768.7(17)	8037.1(8)	32.2(3)
C29	6308.2(10)	3692.0(17)	7251.9(8)	34.1(3)
C210	5440.2(10)	3154.5(18)	6969.6(9)	37.5(4)
C211	7520.6(9)	4414.1(16)	8335.1(8)	30.8(3)
C212	7667.8(10)	5540.3(17)	8780.3(8)	32.3(3)
C213	8451.7(10)	6094.5(17)	9107.3(8)	35.0(4)
C214	9078.1(10)	5508.3(18)	8964.2(9)	36.7(4)
C215	8951.2(10)	4398.4(18)	8511.6(9)	37.9(4)

C216	8166.2(10)	3857.1(17)	8209.8(8)	34.8(3)
C217	8612.8(13)	7248(2)	9626.7(11)	51.7(5)
C218	9633.4(12)	3821(2)	8335.6(12)	53.4(5)

Table 3 Anisotropic Displacement Parameters ($Å^2 \times 10^3$) for han503. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+\ldots]$.

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O11	50.6(7)	32.0(6)	37.0(6)	-4.4(5)	17.6(5)	3.4(5)
O12A	43.3(8)	37.8(7)	54.9(8)	11.9(6)	22.0(6)	8.0(6)
O12B	43.3(8)	37.8(7)	54.9(8)	11.9(6)	22.0(6)	8.0(6)
N11	60.5(10)	42.3(9)	36.8(8)	-7.6(7)	15.2(7)	3.0(7)
N12	46.4(9)	46.1(9)	46.6(9)	-9.7(7)	16.3(7)	-2.8(7)
N13	76.5(13)	64.3(12)	46.9(10)	-12.8(9)	24.8(9)	-3.1(10)
C11	40.6(9)	46.6(10)	35.7(9)	-9.8(8)	12.6(7)	5.2(8)
C12	29.8(7)	30.6(8)	30.2(7)	-2.8(6)	6.8(6)	4.3(6)
C13	39.1(9)	29.8(8)	38.3(8)	1.7(7)	16.7(7)	-1.0(6)
C14	35.0(8)	34.3(8)	33.2(8)	-0.8(6)	16.6(7)	0.1(6)
C15	26.3(7)	30.1(7)	29.4(7)	-0.7(6)	7.7(6)	2.4(6)
C16	30.4(8)	31.2(8)	30.6(7)	4.1(6)	9.6(6)	1.4(6)
C17	29.7(7)	36.7(8)	26.3(7)	1.4(6)	9.7(6)	4.0(6)
C18	30.1(8)	30.6(8)	33.3(8)	-2.2(6)	10.4(6)	0.2(6)
C19	37.8(9)	33.5(8)	34.8(8)	-3.0(7)	13.7(7)	-1.2(7)
C110	37.1(9)	51.8(11)	40.1(9)	1.2(8)	6.4(7)	4.0(8)
C111	31.1(8)	32.9(8)	30.6(8)	-7.5(6)	9.6(6)	2.0(6)
C112	36.0(8)	33.7(8)	33.7(8)	-6.2(7)	11.2(7)	5.2(6)
C113	39.7(9)	40.2(9)	36.2(9)	-8.2(7)	6.0(7)	9.8(7)
C114	32.2(9)	49.2(10)	43.9(10)	-17.9(8)	4.4(7)	10.5(7)
C115	33.8(9)	48.3(10)	51.1(10)	-18.0(9)	15.6(8)	-0.1(7)

C116	35.7(9)	37.9(9)	40.4(9)	-8.3(7)	13.8(7)	0.7(7)
C117	55.7(12)	52.8(12)	53.9(12)	6.7(10)	7.6(10)	20(1)
C118	37.5(10)	65.7(14)	87.5(17)	-18.0(12)	27.9(11)	-3.6(10)
O21	55.1(8)	32.7(6)	43.4(7)	7.0(5)	25.4(6)	1.7(5)
O22A	39.7(7)	38.6(7)	52.7(8)	-12.5(6)	23.9(6)	-6.5(6)
O22B	39.7(7)	38.6(7)	52.7(8)	-12.5(6)	23.9(6)	-6.5(6)
N21	44.0(8)	43.7(8)	36.0(8)	8.6(6)	8.8(6)	-2.5(6)
N22	44.2(9)	45.4(9)	44.4(9)	8.4(7)	14.0(7)	1.1(7)
N23	69.5(12)	64.6(12)	42.9(10)	10.0(9)	14.8(9)	-3.5(9)
C21	46.6(10)	45.6(10)	41.8(9)	12.6(8)	21.0(8)	1.7(8)
C22	31.5(8)	32.5(8)	33.3(8)	4.0(7)	10.8(6)	-1.6(6)
C23	48.3(10)	34.1(8)	38.0(9)	-0.4(7)	20.8(7)	3.3(7)
C24	40.4(9)	39.1(9)	30.7(8)	0.8(7)	16.1(7)	-1.3(7)
C25	26.0(7)	33.6(8)	28.5(7)	1.4(6)	4.7(6)	-3.1(6)
C26	34.0(8)	32.6(8)	31.1(8)	-2.4(6)	9.6(6)	-0.7(6)
C27	31.7(8)	39.5(9)	28.2(7)	1.5(7)	10.4(6)	-0.9(6)
C28	29.8(8)	33.5(8)	30.3(8)	0.2(6)	8.6(6)	-0.8(6)
C29	33.8(8)	34.6(8)	31.6(8)	1.9(6)	10.3(6)	2.9(6)
C210	30.0(8)	40.1(9)	34.9(8)	1.5(7)	4.8(6)	0.7(7)
C211	32.5(8)	30.7(8)	25.1(7)	4.2(6)	7.0(6)	-1.9(6)
C212	33.8(8)	31.6(8)	30.9(8)	3.1(6)	12.1(6)	-1.9(6)
C213	38.9(9)	31.5(8)	31.0(8)	2.2(6)	9.8(7)	-6.7(6)
C214	30.4(8)	37.3(9)	36.7(8)	8.3(7)	7.2(6)	-5.2(6)
C215	34.6(8)	37.3(9)	40.7(9)	7.4(7)	13.7(7)	4.1(7)
C216	38.3(8)	31.7(8)	31.9(8)	1.4(6)	11.1(7)	1.0(6)
C217	52.3(11)	46.7(11)	51.8(11)	-14.5(9)	16.1(9)	-15.2(9)
C218	37.8(10)	51.2(11)	72.3(14)	1.3(10)	22.6(9)	5.0(8)

Table 4 Bond Lengths for han503.

Atom	Atom	Length/Å	Atom	Atom	Length/Å
O11	C11	1.434(2)	O21	C21	1.435(2)
O11	C12	1.3760(19)	O21	C22	1.3750(19)
O12A	C112	1.393(2)	O22A	C212	1.392(2)
O12B	C116	1.495(11)	O22B	C216	1.471(11)
N11	N12	1.221(2)	N21	N22	1.225(2)
N11	C19	1.507(2)	N21	C29	1.505(2)
N12	N13	1.133(2)	N22	N23	1.136(2)
C12	C13	1.392(2)	C22	C23	1.391(2)
C12	C17	1.384(2)	C22	C27	1.385(2)
C13	C14	1.384(2)	C23	C24	1.385(2)
C14	C15	1.396(2)	C24	C25	1.393(2)
C15	C16	1.390(2)	C25	C26	1.391(2)
C15	C18	1.521(2)	C25	C28	1.522(2)
C16	C17	1.389(2)	C26	C27	1.386(2)
C18	C19	1.527(2)	C28	C29	1.527(2)
C18	C111	1.530(2)	C28	C211	1.532(2)
C19	C110	1.519(2)	C29	C210	1.517(2)
C111	C112	1.392(2)	C211	C212	1.391(2)
C111	C116	1.401(2)	C211	C216	1.389(2)
C112	C113	1.405(2)	C212	C213	1.401(2)
C113	C114	1.390(3)	C213	C214	1.390(2)
C113	C117	1.502(3)	C213	C217	1.508(2)
C114	C115	1.391(3)	C214	C215	1.392(3)
C115	C116	1.390(2)	C215	C216	1.393(2)
C115	C118	1.511(3)	C215	C218	1.514(2)

Table 5 Bond Angles for han503.

Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
C12	O11	C11	116.95(13)	C22	O21	C21	117.16(13)
N12	N11	C19	115.18(16)	N22	N21	C29	114.59(15)
N13	N12	N11	173.8(2)	N23	N22	N21	173.7(2)
O11	C12	C13	115.87(14)	O21	C22	C23	116.30(15)
O11	C12	C17	124.20(14)	O21	C22	C27	123.92(14)
C17	C12	C13	119.93(15)	C27	C22	C23	119.78(15)
C14	C13	C12	120.05(15)	C24	C23	C22	120.18(16)
C13	C14	C15	121.14(14)	C23	C24	C25	121.06(15)
C14	C15	C18	123.48(14)	C24	C25	C28	124.32(14)
C16	C15	C14	117.56(14)	C26	C25	C24	117.57(15)
C16	C15	C18	118.79(14)	C26	C25	C28	118.08(14)
C17	C16	C15	122.17(15)	C27	C26	C25	122.22(15)
C12	C17	C16	119.14(14)	C22	C27	C26	119.18(15)
C15	C18	C19	113.43(13)	C25	C28	C29	113.09(13)
C15	C18	C111	108.80(12)	C25	C28	C211	109.36(12)
C19	C18	C111	112.84(13)	C29	C28	C211	112.98(13)
N11	C19	C18	105.22(13)	N21	C29	C28	104.98(13)
N11	C19	C110	110.94(14)	N21	C29	C210	110.33(13)
C110	C19	C18	111.96(14)	C210	C29	C28	111.77(14)
C112	C111	C18	119.85(14)	C212	C211	C28	119.09(14)
C112	C111	C116	119.04(15)	C216	C211	C28	122.08(14)
C116	C111	C18	120.96(15)	C216	C211	C212	118.70(15)
O12A	C112	C113	121.63(16)	O22A	C212	C213	121.78(15)
C111	C112	O12A	117.44(14)	C211	C212	O22A	117.03(14)
C111	C112	C113	120.83(16)	C211	C212	C213	121.08(15)
C112	C113	C117	120.57(18)	C212	C213	C217	120.44(16)

C114	C113	C112	117.89(17)	C214	C213	C212	118.22(15)
C114	C113	C117	121.40(17)	C214	C213	C217	121.27(16)
C113	C114	C115	122.98(16)	C213	C214	C215	122.32(15)
C114	C115	C118	121.66(18)	C214	C215	C216	117.61(16)
C116	C115	C114	117.63(17)	C214	C215	C218	121.49(16)
C116	C115	C118	120.7(2)	C216	C215	C218	120.88(17)
C111	C116	O12B	121.9(6)	C211	C216	O22B	118.7(6)
C115	C116	O12B	116.1(6)	C211	C216	C215	122.04(16)
C115	C116	C111	121.62(18)	C215	C216	O22B	118.5(6)

Table 6 Hydrogen Bonds for han503.

D	H	A	d(D-H)/Å	d(H-A)/Å	d(D-A)/Å	D-H-A/°
O12A	H12A	O11[1]	0.82	2.10	2.8450(18)	150.4
O12B	H12B	N11[2]	0.82	2.16	2.971(16)	168.9
O22A	H22A	O21[3]	0.82	2.04	2.7838(18)	150.9
O22B	H22B	N21[4]	0.82	2.06	2.798(16)	149.3
O22B	H22B	N22[4]	0.82	2.44	3.180(17)	149.9

[1]+X,-1+Y,+Z; [2]3/2-X,1/2+Y,1/2-Z; [3]+X,1+Y,+Z; [4]3/2-X,-1/2+Y,3/2-Z

Table 7 Hydrogen Atom Coordinates (Å×10^4) and Isotropic Displacement Parameters (Å^2×10^3) for han503.

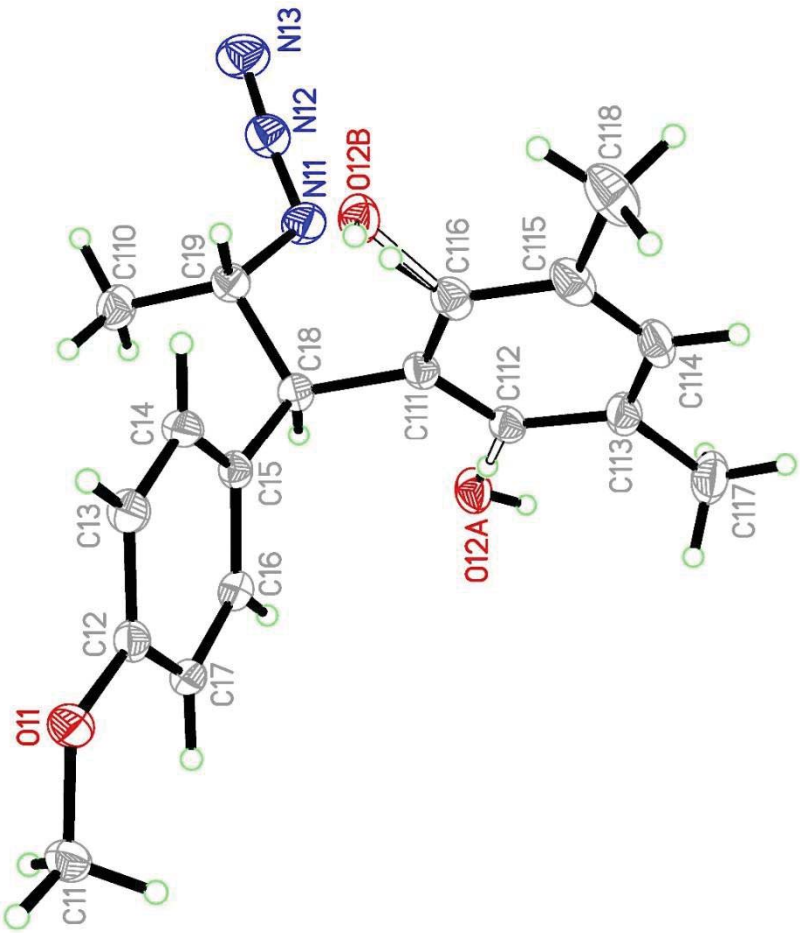
Atom	*x*	*y*	*z*	U(eq)
H12A	6958	-314	4020	79(9)
H12B	8083	4511	2782	67
H11A	5848	7546	4792	63
H11B	6445	8789	5112	63
H11C	6749	7258	5300	63

H13	6963	7387	3340	42
H14	6885	5367	2731	40
H16	6088	3333	3993	38
H17	6201	5330	4630	38
H18	6106	2113	3062	38
H19	6452	3485	2020	43
H11D	5045	3340	1368	69
H11E	5199	4207	2036	69
H11F	4916	2656	1991	69
H112	7051	559	3772	42
H114	9414	728	4094	54
H116	7860	3463	2832	46
H11G	8282	-418	4904	88
H11H	9021	-894	4735	88
H11I	8154	-1521	4324	88
H11J	9808	3305	3703	94
H11K	9218	3530	2932	94
H11L	9723	2154	3155	94
H22A	7122	6804	9091	66(8)
H22B	8068	2038	7828	63
H21A	6014	-1088	9850	65
H21B	6927	-842	10339	65
H21C	6597	-2358	10145	65
H23	7029	-940	8330	47
H24	6998	1109	7756	43
H26	6394	3161	9130	40
H27	6454	1130	9726	40
H28	6312	4376	8167	39

H29	6647	3096	7097	41
H21D	5108	3757	7113	56
H21E	5431	2235	7142	56
H21F	5232	3132	6476	56
H212	7239	5931	8862	39
H214	9601	5870	9178	44
H216	8071	3100	7915	42
H21G	8335	8074	9399	77
H21H	9187	7425	9839	77
H21I	8419	6980	9972	77
H21J	9630	4269	7929	80
H21K	9557	2840	8255	80
H21L	10146	3986	8712	80

Table 8 Atomic Occupancy for han503.

Atom	***Occupancy***	**Atom**	***Occupancy***	**Atom**	***Occupancy***
O12A	0.9190(19)	H12A	0.9190(19)	O12B	0.0810(19)
H12B	0.0810(19)	H112	0.0810(19)	H116	0.9190(19)
O22A	0.9190(19)	H22A	0.9190(19)	O22B	0.0810(19)
H22B	0.0810(19)	H212	0.0810(19)	H216	0.9190(19)



ORTEP view of the C18 H21 N3 O2 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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Diaryl **2.55**

Université de Montréal

CRYSTAL AND MOLECULAR STRUCTURE OF

C19 H23 N3 O2 COMPOUND (han497)

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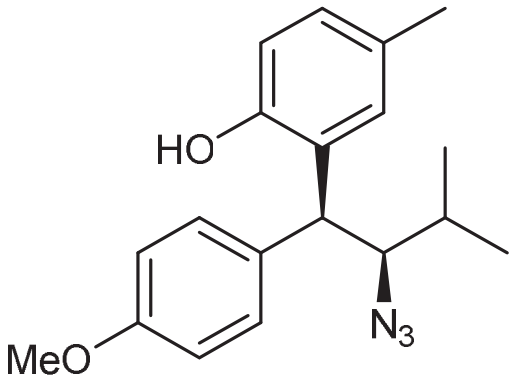


Structure solved and refined in the laboratory of X-ray diffraction
Université de Montréal by Michel Simard.

Table 1 Crystal data and structure refinement for han497.

Identification code	han497
Empirical formula	$C_{19}H_{23}N_3O_2$
Formula weight	325.40
Temperature/K	100
Crystal system	monoclinic
Space group	$P2_1/n$
a/Å	14.1416(11)
b/Å	6.8552(5)
c/Å	18.0683(14)
α/°	90
β/°	92.663(4)
γ/°	90
Volume/Å^3	1749.7(2)
Z	4
ρ_{calc}g/cm^3	1.235
μ/mm^{-1}	0.419
F(000)	696.0
Crystal size/mm^3	0.32 × 0.02 × 0.02
Radiation	GaKα (λ = 1.34139)
2Θ range for data collection/°	6.756 to 114.268
Index ranges	-17 ≤ h ≤ 16, -8 ≤ k ≤ 8, -22 ≤ l ≤ 22
Reflections collected	21128
Independent reflections	3583 [R_{int} = 0.0743, R_{sigma} = 0.0576]
Data/restraints/parameters	3583/12/247
Goodness-of-fit on F^2	1.054
Final R indexes [I>=2σ (I)]	R_1 = 0.0754, wR_2 = 0.1849
Final R indexes [all data]	R_1 = 0.0984, wR_2 = 0.1977
Largest diff. peak/hole / e Å^{-3}	0.30/-0.28

Table 2 Fractional Atomic Coordinates (×10^4) and Equivalent Isotropic Displacement Parameters (Å^2×10^3) for han497. U_{eq} is defined as 1/3 of of the trace of the orthogonalised U_{IJ} tensor.

Atom	*x*	*y*	*z*	U(eq)
O1	4151.9(13)	485(3)	3832.3(10)	46.9(5)
O2	7084.4(16)	7110(3)	5362.9(12)	59.1(6)
C8A	7695(4)	4248(7)	4500(3)	42.9(10)
C9A	8525(3)	3487(7)	4054(2)	49.9(9)

C10A	8371(5)	3791(9)	3220(4)	53.1(13)
C11A	9079(4)	2596(11)	2789(3)	77.2(15)
C12A	8433(10)	5894(15)	2980(5)	100(2)
C8B	7851(9)	3437(15)	4550(7)	42.9(10)
C9B	8180(6)	5067(14)	4064(4)	49.9(9)
C10B	8190(12)	4540(20)	3221(9)	53.1(13)
C11B	8816(11)	2810(30)	3087(8)	77.2(15)
C12B	8560(20)	6350(40)	2780(12)	100(2)
C1	4063(2)	-1596(4)	3797.8(16)	49.7(7)
C2	5043.4(18)	1233(4)	3995.7(13)	41.4(6)
C3	5136(2)	3234(4)	3942.9(16)	49.6(7)
C4	6005(2)	4104(4)	4098.8(16)	53.2(7)
C5	6799(2)	3027(4)	4313.3(14)	48.6(7)
C6	6690(2)	1034(4)	4365.0(15)	50.6(7)
C7	5826(2)	124(4)	4211.8(14)	46.8(6)
C13	7912.2(18)	4110(4)	5353.1(14)	45.5(6)
C14	8394.9(19)	2653(4)	5745.1(16)	50.3(7)
C15	8549(2)	2698(4)	6507.5(17)	53.1(7)
C16	8217(2)	4287(4)	6882.9(15)	52.2(7)
C17	7725(2)	5765(4)	6510.5(15)	50.5(7)
C18	7569.2(19)	5672(4)	5750.0(15)	46.5(6)
C19	9068(3)	1050(6)	6904(2)	78.3(11)
N1A	9484(5)	4073(11)	4333(5)	54.3(11)
N2A	10049(6)	2779(13)	4583(5)	75(2)
N3A	10622(7)	1862(13)	4798(5)	66.8(14)
N1B	9181(6)	5565(17)	4331(5)	54.3(11)
N2B	9264(8)	7129(18)	4682(7)	73(3)
N3B	9364(7)	8499(14)	4907(6)	66.8(14)
N1C	9375(6)	4783(13)	4259(5)	54.3(11)
N2C	9259(6)	6521(16)	4439(6)	55(2)
N3C	9221(7)	8112(14)	4562(6)	66.8(14)

Table 3 Anisotropic Displacement Parameters ($Å^2 \times 10^3$) for han497. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+\ldots]$.

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O1	50.6(11)	37.1(10)	52.6(11)	0.6(8)	-2.3(8)	-2.3(8)
O2	63.3(13)	52.6(12)	61.8(13)	14.9(10)	6.6(10)	6.8(10)
C8A	49(2)	40(3)	40.0(17)	3(3)	3.7(16)	3(2)
C9A	45(2)	59(2)	45.6(19)	1.3(19)	5.6(16)	-1.3(17)
C10A	48(3)	67(5)	45.3(17)	7(3)	8(2)	18(3)

C11A	67(4)	103(4)	62(4)	7(4)	17(3)	23(3)
C12A	152(6)	82(7)	66(6)	31(4)	24(5)	6(5)
C8B	49(2)	40(3)	40.0(17)	3(3)	3.7(16)	3(2)
C9B	45(2)	59(2)	45.6(19)	1.3(19)	5.6(16)	-1.3(17)
C10B	48(3)	67(5)	45.3(17)	7(3)	8(2)	18(3)
C11B	67(4)	103(4)	62(4)	7(4)	17(3)	23(3)
C12B	152(6)	82(7)	66(6)	31(4)	24(5)	6(5)
C1	59.6(17)	36.5(14)	53.3(16)	-0.6(12)	6.7(13)	-7.7(12)
C2	48.0(15)	38.4(13)	38.0(13)	0.0(11)	2.9(11)	-0.6(11)
C3	51.7(16)	35.3(14)	61.5(17)	1.1(12)	-1.0(13)	2.8(12)
C4	61.9(18)	39.2(15)	58.6(17)	-5.6(13)	5.2(14)	-7.0(13)
C5	50.8(16)	61.4(18)	33.9(13)	-1.4(12)	6.0(11)	-5.4(13)
C6	48.3(16)	59.8(18)	43.8(14)	9.9(13)	2.3(12)	7.6(13)
C7	58.5(17)	36.9(14)	45.1(14)	7.0(11)	3.5(12)	3.9(12)
C13	41.3(14)	52.2(16)	43.3(14)	-5.6(12)	6.3(11)	-9.0(12)
C14	46.5(15)	47.1(16)	57.6(17)	-7.5(13)	6.5(12)	-1.4(12)
C15	45.3(15)	52.1(17)	61.7(18)	5.7(14)	0.6(13)	-1.9(13)
C16	58.4(17)	56.3(17)	41.7(14)	-0.5(13)	-0.2(12)	-11.7(14)
C17	59.5(17)	43.2(15)	49.3(15)	-7.7(12)	8.5(13)	-8.0(13)
C18	49.5(15)	42.5(15)	47.8(15)	4.4(12)	4.6(12)	-4.3(12)
C19	66(2)	76(2)	92(3)	21(2)	-6.6(19)	11.7(18)

Table 4 Bond Lengths for han497.

Atom	Atom	Length/Å	Atom	Atom	Length/Å
O1	C1	1.434(3)	C2	C7	1.384(4)
O1	C2	1.380(3)	C3	C4	1.383(4)
O2	C18	1.374(3)	C4	C5	1.385(4)
C8A	C9A	1.545(6)	C5	C6	1.378(4)
C8A	C5	1.542(6)	C6	C7	1.389(4)
C8A	C13	1.561(6)	C13	C14	1.386(4)
C9A	C10A	1.526(8)	C13	C18	1.388(4)
C9A	N1A	1.481(8)	C14	C15	1.385(4)
C9A	N1C	1.528(8)	C15	C16	1.378(4)
C10A	C11A	1.535(7)	C15	C19	1.510(4)
C10A	C12A	1.510(10)	C16	C17	1.385(4)
C8B	C9B	1.507(14)	C17	C18	1.383(4)
C8B	C5	1.554(13)	N1A	N2A	1.262(9)
C8B	C13	1.522(13)	N2A	N3A	1.084(9)
C9B	C10B	1.567(18)	N1B	N2B	1.248(11)
C9B	N1B	1.514(10)	N2B	N3B	1.030(11)

C10B	C11B	1.507(16)	N1C	N2C	1.247(10)	
C10B	C12B	1.58(2)	N2C	N3C	1.115(12)	
C2	C3	1.382(4)				

Table 5 Bond Angles for han497.

Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
C2	O1	C1	117.1(2)	C4	C5	C8B	137.2(4)
C9A	C8A	C13	112.0(3)	C6	C5	C8A	128.1(3)
C5	C8A	C9A	109.8(4)	C6	C5	C8B	105.6(4)
C5	C8A	C13	107.8(3)	C6	C5	C4	117.1(3)
C10A	C9A	C8A	113.0(4)	C5	C6	C7	122.1(3)
N1A	C9A	C8A	115.9(5)	C2	C7	C6	119.6(3)
N1A	C9A	C10A	112.7(5)	C14	C13	C8A	128.2(3)
C9A	C10A	C11A	111.2(5)	C14	C13	C8B	105.9(4)
C12A	C10A	C9A	114.0(7)	C14	C13	C18	117.9(2)
C12A	C10A	C11A	108.4(7)	C18	C13	C8A	113.9(3)
C9B	C8B	C5	106.9(7)	C18	C13	C8B	136.1(4)
C9B	C8B	C13	109.0(8)	C15	C14	C13	122.9(3)
C13	C8B	C5	109.1(8)	C14	C15	C19	120.4(3)
C8B	C9B	C10B	114.3(10)	C16	C15	C14	117.8(3)
C8B	C9B	N1B	106.9(8)	C16	C15	C19	121.8(3)
N1B	C9B	C10B	108.1(9)	C15	C16	C17	120.9(3)
C9B	C10B	C12B	109.1(15)	C18	C17	C16	120.1(3)
C11B	C10B	C9B	111.8(12)	O2	C18	C13	117.9(2)
C11B	C10B	C12B	109.3(18)	O2	C18	C17	121.7(3)
O1	C2	C3	116.3(2)	C17	C18	C13	120.4(3)
O1	C2	C7	124.6(2)	N2A	N1A	C9A	119.0(7)
C3	C2	C7	119.2(3)	N3A	N2A	N1A	170.3(11)
C2	C3	C4	120.0(3)	N2B	N1B	C9B	114.8(9)
C3	C4	C5	121.9(3)	N3B	N2B	N1B	172.3(14)
C4	C5	C8A	114.8(3)	N3C	N2C	N1C	173.8(11)

Table 6 Hydrogen Bonds for han497.

D	H	A	d(D-H)/Å	d(H-A)/Å	d(D-A)/Å	D-H-A/°
O2	H2	O1[1]	0.94(5)	1.92(5)	2.850(3)	170(5)

[1]1-X,1-Y,1-Z

Table 7 Torsion Angles for han497.

A	B	C	D	Angle/°	A	B	C	D	Angle/°
O1	C2	C3	C4	179.8(2)	C4	C5	C6	C7	-0.1(4)
O1	C2	C7	C6	-179.8(2)	C5	C8A	C9A	C10A	66.0(5)
C8A	C9A	C10A	C11A	-166.3(5)	C5	C8A	C9A	N1A	-161.7(5)
C8A	C9A	C10A	C12A	70.8(8)	C5	C8A	C13	C14	83.2(4)
C8A	C9A	N1A	N2A	114.1(8)	C5	C8A	C13	C18	-96.9(3)
C8A	C5	C6	C7	176.8(3)	C5	C8B	C9B	C10B	-64.4(11)
C8A	C13	C14	C15	179.6(3)	C5	C8B	C9B	N1B	176.0(7)
C8A	C13	C18	O2	0.6(4)	C5	C8B	C13	C14	113.5(5)
C8A	C13	C18	C17	-178.7(3)	C5	C8B	C13	C18	-62.0(9)
C9A	C8A	C5	C4	-127.4(3)	C5	C6	C7	C2	0.4(4)
C9A	C8A	C5	C6	55.6(5)	C7	C2	C3	C4	0.6(4)
C9A	C8A	C13	C14	-37.6(5)	C13	C8A	C9A	C10A	-174.3(4)
C9A	C8A	C13	C18	142.2(3)	C13	C8A	C9A	N1A	-42.1(6)
C10A	C9A	N1A	N2A	-113.5(8)	C13	C8A	C5	C4	110.4(3)
C8B	C9B	C10B	C11B	-58.4(16)	C13	C8A	C5	C6	-66.6(4)
C8B	C9B	C10B	C12B	179.4(16)	C13	C8B	C9B	C10B	177.8(8)
C8B	C9B	N1B	N2B	106.3(11)	C13	C8B	C9B	N1B	58.2(10)
C8B	C5	C6	C7	178.4(5)	C13	C8B	C5	C4	78.7(8)
C8B	C13	C14	C15	-176.7(6)	C13	C8B	C5	C6	-99.4(5)
C8B	C13	C18	O2	-4.4(8)	C13	C14	C15	C16	-1.1(4)
C8B	C13	C18	C17	176.2(7)	C13	C14	C15	C19	179.1(3)
C9B	C8B	C5	C4	-39.1(11)	C14	C13	C18	O2	-179.5(2)
C9B	C8B	C5	C6	142.8(6)	C14	C13	C18	C17	1.1(4)
C9B	C8B	C13	C14	-130.0(7)	C14	C15	C16	C17	1.5(4)
C9B	C8B	C13	C18	54.4(11)	C15	C16	C17	C18	-0.7(4)
C10B	C9B	N1B	N2B	130.2(10)	C16	C17	C18	O2	180.0(3)
C1	O1	C2	C3	172.8(2)	C16	C17	C18	C13	-0.7(4)
C1	O1	C2	C7	-8.0(4)	C18	C13	C14	C15	-0.2(4)
C2	C3	C4	C5	-0.3(4)	C19	C15	C16	C17	-178.6(3)
C3	C2	C7	C6	-0.6(4)	N1A	C9A	C10A	C11A	59.9(7)
C3	C4	C5	C8A	-177.3(3)	N1A	C9A	C10A	C12A	-63.0(8)
C3	C4	C5	C8B	-177.8(7)	N1B	C9B	C10B	C11B	60.5(16)
C3	C4	C5	C6	0.1(4)	N1B	C9B	C10B	C12B	-60.5(18)

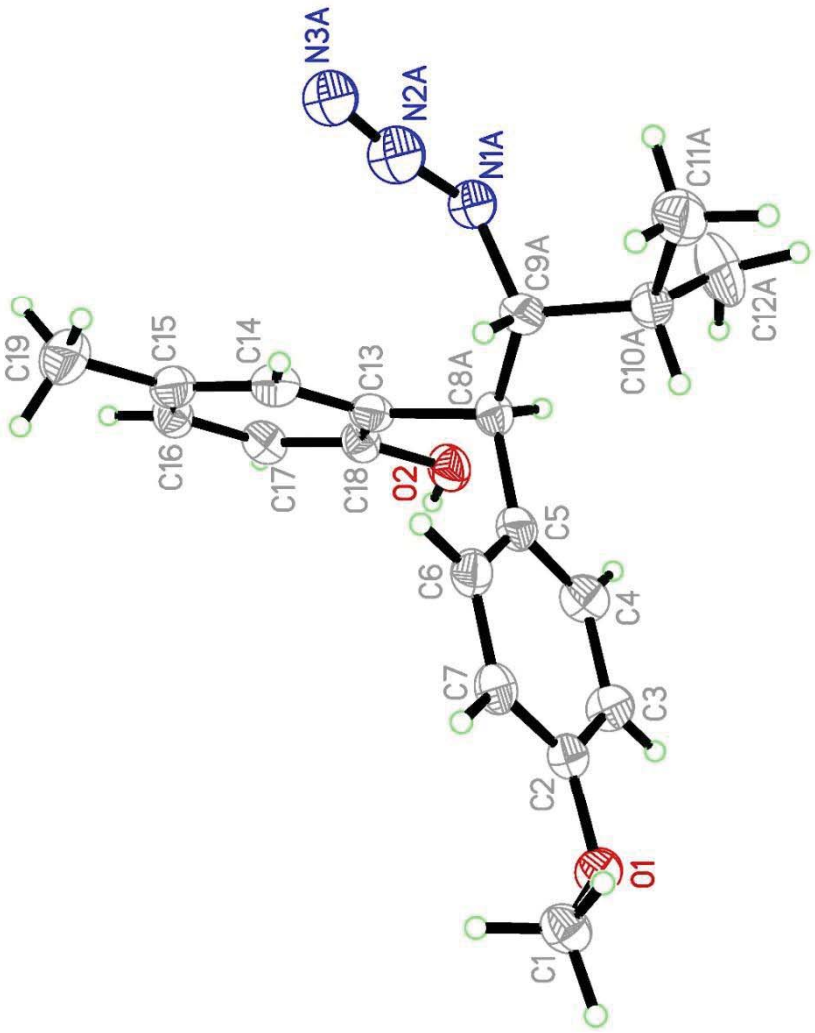
Table 8 Hydrogen Atom Coordinates (Å×10^4) and Isotropic Displacement Parameters (Å^2×10^3) for han497.

Atom	*x*	*y*	*z*	U(eq)
H2	6730(30)	7900(70)	5680(30)	128(18)
H8A	7567	5640	4363	51
H9A	8510	2039	4121	60
H9AA	8690	2110	4190	60
H10A	7721	3311	3074	64
H11A	9723	3052	2915	116
H11B	8941	2759	2256	116
H11C	9025	1215	2920	116
H12A	7884	6613	3147	149
H12B	8442	5957	2438	149
H12C	9015	6478	3198	149
H8B	8245	2243	4486	51
H9B	7765	6232	4127	60
H10B	7530	4224	3036	64
H11D	9479	3168	3190	116
H11E	8728	2389	2569	116
H11F	8647	1732	3414	116
H12D	8308	7552	2992	149
H12E	8337	6248	2258	149
H12F	9249	6377	2815	149
H1A	4479	-2110	3425	75
H1B	3405	-1944	3662	75
H1C	4244	-2158	4283	75
H3	4603	4012	3799	60
H4	6058	5481	4057	64
H6	7224	258	4510	61
H7	5772	-1252	4255	56
H14	8630	1576	5479	60
H16	8326	4371	7405	63
H17	7495	6845	6778	61
H19A	8616	256	7168	118
H19B	9543	1587	7260	118
H19C	9381	236	6543	118

Table 9 Atomic Occupancy for han497.

Atom	*Occupancy*	Atom	*Occupancy*	Atom	*Occupancy*
C8A	0.67	H8A	0.67	C9A	0.67

H9A	0.34	H9AA	0.33	C10A	0.67		
H10A	0.67	C11A	0.67	H11A	0.67		
H11B	0.67	H11C	0.67	C12A	0.67		
H12A	0.67	H12B	0.67	H12C	0.67		
C8B	0.33	H8B	0.33	C9B	0.33		
H9B	0.33	C10B	0.33	H10B	0.33		
C11B	0.33	H11D	0.33	H11E	0.33		
H11F	0.33	C12B	0.33	H12D	0.33		
H12E	0.33	H12F	0.33	N1A	0.34		
N2A	0.34	N3A	0.34	N1B	0.33		
N2B	0.33	N3B	0.33	N1C	0.33		
N2C	0.33	N3C	0.33				



ORTEP view of the C19 H23 N3 O2 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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Sulfonamide **2.65**

Université de Montréal

CRYSTAL AND MOLECULAR STRUCTURE OF

C16 H17 Cl N4 O3 S COMPOUND (han502)

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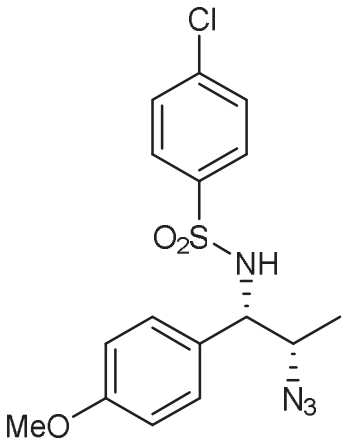


Structure solved and refined in the laboratory of X-ray diffraction

Table 1 Crystal data and structure refinement for han502.

Identification code	han502
Empirical formula	$C_{16}H_{17}ClN_4O_3S$
Formula weight	380.84
Temperature/K	100
Crystal system	monoclinic
Space group	$P2_1/n$
a/Å	13.0736(8)
b/Å	9.5713(6)
c/Å	15.0403(10)
α/°	90
β/°	107.872(3)
γ/°	90
Volume/Å^3	1791.2(2)
Z	4
ρ_{calc}g/cm^3	1.412
μ/mm^{-1}	2.091
F(000)	792.0
Crystal size/mm^3	0.24 × 0.2 × 0.1
Radiation	GaKα (λ = 1.34139)
2Θ range for data collection/°	9.67 to 121.812
Index ranges	-16 ≤ h ≤ 16, -11 ≤ k ≤ 12, -19 ≤ l ≤ 19
Reflections collected	35215
Independent reflections	4093 [R_{int} = 0.0538, R_{sigma} = 0.0333]
Data/restraints/parameters	4093/1/254
Goodness-of-fit on F^2	1.083
Final R indexes [I>=2σ (I)]	R_1 = 0.0662, wR_2 = 0.1967
Final R indexes [all data]	R_1 = 0.0706, wR_2 = 0.2012
Largest diff. peak/hole / e Å^{-3}	0.85/-0.41

Table 2 Fractional Atomic Coordinates (×10^4) and Equivalent Isotropic Displacement Parameters (Å^2×10^3) for han502. U_{eq} is defined as 1/3 of of the trace of the orthogonalised U_{IJ} tensor.

Atom	*x*	*y*	*z*	U(eq)
Cl1	9854.8(6)	2357.7(11)	4602.4(7)	84.2(3)
S1	5412.6(5)	2295.8(7)	5325.9(5)	54.7(2)
O1A	7210(60)	1260(80)	1470(60)	72(3)

C1A	7990(30)	2180(30)	1210(30)	92(4)
O1B	7310(30)	1420(30)	1520(30)	72(3)
C1B	8224(14)	2266(14)	1607(17)	92(4)
O2	5235.3(18)	3622(2)	5660.2(16)	70.9(6)
O3	5326.0(18)	1073(2)	5851.6(16)	69.1(6)
N1	4535.8(19)	2007(3)	4298.2(18)	62.7(6)
N2A	2641(3)	3673(5)	3469(3)	70.8(11)
N3A	2317(4)	2699(5)	3882(4)	80.5(13)
N4A	1983(4)	1982(6)	4295(5)	117(2)
C9A	3336(8)	3234(6)	2924(7)	60.9(16)
C10A	3256(8)	4410(10)	2195(5)	73.9(17)
N2B	2503(12)	3051(17)	3612(12)	70.8(11)
N3B	1670(9)	3033(12)	3257(10)	80.5(13)
N4B	761(11)	3106(15)	2979(13)	117(2)
C9B	3230(20)	2830(20)	2940(20)	60.9(16)
C10B	3220(30)	4160(30)	2453(16)	73.9(17)
C2	6622(2)	1825(3)	1991(2)	59.5(7)
C3	5827(2)	896(3)	2040.6(19)	57.5(6)
C4	5131(2)	1267(3)	2538.0(19)	58.1(6)
C5	5223(2)	2571(3)	2980.5(19)	57.7(6)
C6	6006(2)	3477(3)	2909(2)	60.6(6)
C7	6715(2)	3123(3)	2424(2)	63.2(7)
C8	4493(2)	2998(3)	3549(2)	61.9(7)
C11	6691(2)	2301(3)	5159.1(18)	52.7(6)
C12	7284(2)	3521(3)	5306.9(19)	59.2(6)
C13	8270(2)	3538(3)	5133(2)	64.8(7)
C14	8624(2)	2339(4)	4824(2)	64.2(7)
C15	8033(2)	1117(3)	4667(2)	64.7(7)
C16	7051(2)	1098(3)	4836(2)	59.2(6)

Table 3 Anisotropic Displacement Parameters ($Å^2 \times 10^3$) for han502. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+\ldots]$.

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
Cl1	54.7(4)	114.0(7)	98.0(6)	18.1(5)	44.3(4)	1.0(4)
S1	57.0(4)	63.9(4)	57.7(4)	-8.1(3)	38.9(3)	-4.7(3)
O1A	82(6)	63(7)	100(4)	10(4)	70(5)	8(5)
C1A	113(7)	73(3)	135(10)	15(6)	102(8)	4(4)
O1B	82(6)	63(7)	100(4)	10(4)	70(5)	8(5)
C1B	113(7)	73(3)	135(10)	15(6)	102(8)	4(4)
O2	82.3(14)	65.5(12)	87.5(14)	-15.5(10)	59.4(12)	-5.7(10)

O3	79.8(13)	65.8(12)	84.1(14)	-7.7(10)	58.2(11)	-9.4(10)
N1	57.1(12)	69.9(14)	74.8(15)	-13.7(12)	40.5(12)	-4.6(11)
N2A	62.6(19)	63(3)	101(3)	-22(2)	46.7(17)	-5.4(19)
N3A	63(2)	76(3)	123(4)	3(2)	57(2)	6.3(18)
N4A	100(3)	98(3)	198(6)	14(3)	111(4)	11(2)
C9A	55(3)	60(4)	73.7(19)	-23(4)	28.3(17)	4(3)
C10A	71(2)	82(4)	66(4)	-1(3)	17(3)	25(3)
N2B	62.6(19)	63(3)	101(3)	-22(2)	46.7(17)	-5.4(19)
N3B	63(2)	76(3)	123(4)	3(2)	57(2)	6.3(18)
N4B	100(3)	98(3)	198(6)	14(3)	111(4)	11(2)
C9B	55(3)	60(4)	73.7(19)	-23(4)	28.3(17)	4(3)
C10B	71(2)	82(4)	66(4)	-1(3)	17(3)	25(3)
C2	65.8(16)	61.3(15)	65.8(15)	7.7(12)	41.6(13)	12.1(12)
C3	65.5(15)	58.4(14)	60.7(14)	-2.9(11)	37.5(12)	5.4(11)
C4	55.3(14)	68.2(16)	61.0(14)	-4.1(12)	33.0(12)	2.5(11)
C5	57.2(15)	69.1(16)	53.8(14)	-4.7(11)	27.3(12)	13.7(11)
C6	62.4(15)	59.6(15)	64.2(15)	-3.3(12)	26.0(12)	6.9(12)
C7	66.0(16)	60.1(15)	73.1(17)	8.6(13)	35.8(14)	6.0(13)
C8	57.5(15)	69.3(17)	67.4(16)	-12.0(13)	31.6(13)	5.1(12)
C11	50.7(13)	64.7(15)	51.8(13)	-3.8(10)	29.3(11)	-3.8(10)
C12	61.7(15)	68.5(16)	55.9(13)	-8.4(12)	30.7(12)	-9.4(12)
C13	58.9(15)	79.4(19)	63.3(15)	-2.0(14)	29.3(12)	-15.2(13)
C14	48.7(14)	88(2)	63.9(16)	7.8(14)	28.7(12)	-2.6(12)
C15	59.7(15)	73.8(18)	73.3(17)	1.0(14)	39.3(13)	5.3(13)
C16	56.9(14)	63.6(15)	68.1(15)	-5.7(12)	35.3(12)	-2.2(12)

Table 4 Bond Lengths for han502.

Atom	Atom	Length/Å	Atom	Atom	Length/Å
Cl1	C14	1.740(3)	N3B	N4B	1.134(18)
S1	O2	1.410(2)	C9B	C10B	1.47(3)
S1	O3	1.436(2)	C9B	C8	1.63(3)
S1	N1	1.641(3)	C2	C3	1.388(4)
S1	C11	1.764(3)	C2	C7	1.391(4)
O1A	C1A	1.49(7)	C3	C4	1.391(3)
O1A	C2	1.368(15)	C4	C5	1.402(4)
O1B	C1B	1.42(3)	C5	C6	1.371(4)
O1B	C2	1.361(8)	C5	C8	1.521(3)
N1	C8	1.460(4)	C6	C7	1.386(4)
N2A	N3A	1.262(7)	C11	C12	1.382(4)
N2A	C9A	1.461(10)	C11	C16	1.388(4)

N3A	N4A	1.103(7)	C12	C13	1.392(4)
C9A	C10A	1.553(10)	C13	C14	1.371(4)
C9A	C8	1.532(11)	C14	C15	1.382(4)
N2B	N3B	1.057(19)	C15	C16	1.382(4)
N2B	C9B	1.60(3)			

Table 5 Bond Angles for han502.

Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
O2	S1	O3	119.20(12)	C3	C2	C7	120.4(2)
O2	S1	N1	110.09(14)	C2	C3	C4	119.4(3)
O2	S1	C11	108.35(13)	C3	C4	C5	120.5(3)
O3	S1	N1	103.37(14)	C4	C5	C8	121.9(3)
O3	S1	C11	108.58(13)	C6	C5	C4	118.9(2)
N1	S1	C11	106.55(12)	C6	C5	C8	119.2(3)
C2	O1A	C1A	118(5)	C5	C6	C7	121.5(3)
C2	O1B	C1B	117.5(18)	C6	C7	C2	119.2(3)
C8	N1	S1	117.9(2)	N1	C8	C9A	111.5(4)
N3A	N2A	C9A	115.0(5)	N1	C8	C9B	99.2(11)
N4A	N3A	N2A	170.9(5)	N1	C8	C5	112.2(2)
N2A	C9A	C10A	105.6(6)	C5	C8	C9A	111.5(4)
N2A	C9A	C8	111.4(7)	C5	C8	C9B	111.2(11)
C8	C9A	C10A	112.4(6)	C12	C11	S1	119.3(2)
N3B	N2B	C9B	113.7(19)	C12	C11	C16	121.6(2)
N2B	N3B	N4B	170.6(18)	C16	C11	S1	119.1(2)
N2B	C9B	C8	109(2)	C11	C12	C13	119.1(3)
C10B	C9B	N2B	106(2)	C14	C13	C12	118.9(3)
C10B	C9B	C8	92.7(18)	C13	C14	Cl1	119.0(2)
O1A	C2	C3	110(3)	C13	C14	C15	122.5(3)
O1A	C2	C7	130(3)	C15	C14	Cl1	118.5(2)
O1B	C2	C3	118.1(13)	C14	C15	C16	118.8(3)
O1B	C2	C7	121.5(13)	C15	C16	C11	119.2(3)

Table 6 Hydrogen Bonds for han502.

D	H	A	d(D-H)/Å	d(H-A)/Å	d(D-A)/Å	D-H-A/°
N1	H1	O3[1]	0.88	2.16	2.966(3)	151.0

[1]1-X,-Y,1-Z

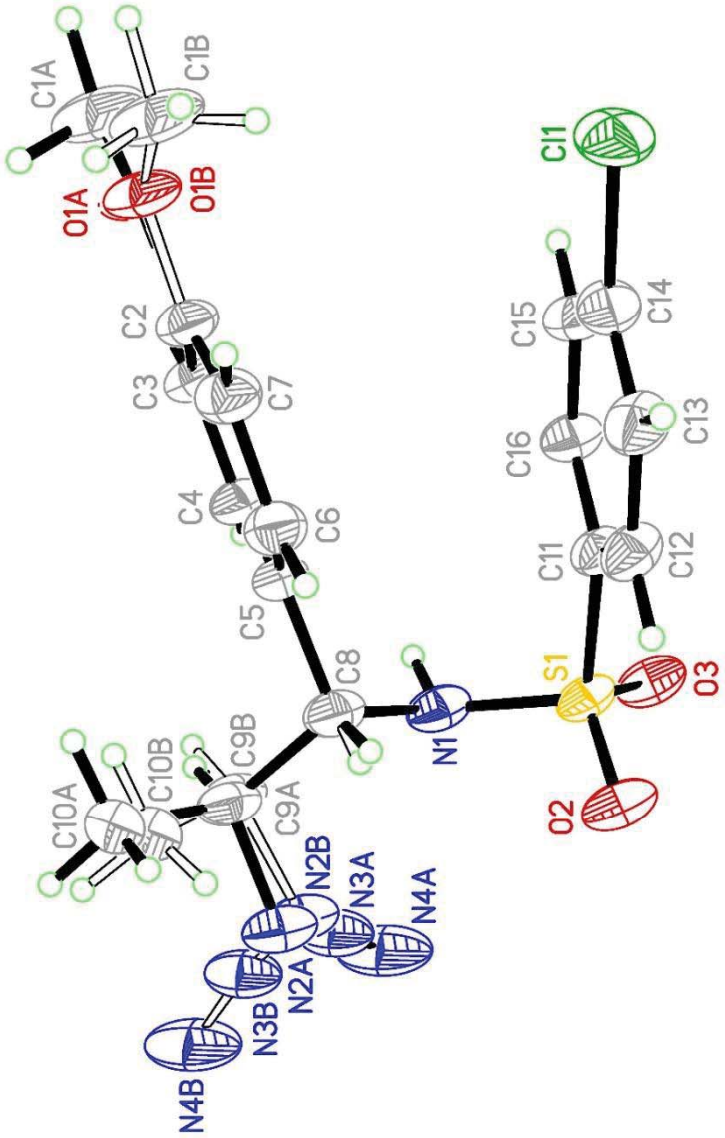
Table 7 Hydrogen Atom Coordinates (Å×10^4) and Isotropic Displacement Parameters (Å^2×10^3) for han502.

Atom	*x*	*y*	*z*	U(eq)
H1AA	8392	1627	875	138
H1AB	8496	2578	1774	138
H1AC	7605	2932	803	138
H1BA	7996	3183	1325	138
H1BB	8687	1816	1288	138
H1BC	8623	2384	2270	138
H1	4511	1177	4040	75
H9A	3052	2345	2590	73
H10A	2506	4518	1809	111
H10B	3698	4164	1796	111
H10C	3514	5290	2519	111
H9B	3055	1984	2534	73
H10D	2496	4341	2031	111
H10E	3728	4116	2091	111
H10F	3430	4923	2910	111
H3	5759	14	1738	69
H4	4588	632	2578	70
H6	6064	4368	3198	73
H7	7258	3760	2387	76
H8A	4763	3913	3851	74
H8B	4654	3969	3797	74
H12	7023	4338	5524	71
H13	8691	4366	5227	78
H15	8296	304	4447	78
H16	6629	271	4731	71

Table 8 Atomic Occupancy for han502.

Atom	*Occupancy*	Atom	*Occupancy*	Atom	*Occupancy*
O1A	0.31(4)	C1A	0.31(4)	H1AA	0.31(4)
H1AB	0.31(4)	H1AC	0.31(4)	O1B	0.69(4)
C1B	0.69(4)	H1BA	0.69(4)	H1BB	0.69(4)
H1BC	0.69(4)	N2A	0.728(4)	N3A	0.728(4)
N4A	0.728(4)	C9A	0.728(4)	H9A	0.728(4)
C10A	0.728(4)	H10A	0.728(4)	H10B	0.728(4)
H10C	0.728(4)	N2B	0.272(4)	N3B	0.272(4)

N4B	0.272(4)	C9B	0.272(4)	H9B	0.272(4)
C10B	0.272(4)	H10D	0.272(4)	H10E	0.272(4)
H10F	0.272(4)	H8A	0.728(4)	H8B	0.272(4)



ORTEP view of the C16 H17 Cl N4 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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Sulfonamide **2.59**

Université de Montréal

CRYSTAL AND MOLECULAR STRUCTURE OF

C17 H20 N4 O3 S COMPOUND (han500)

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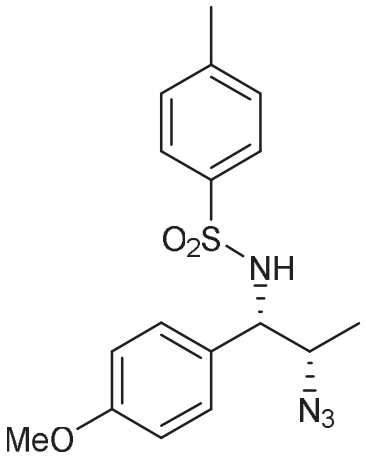


Structure solved and refined in the laboratory of X-ray diffraction
Université de Montréal by Michel Simard.

Table 1 Crystal data and structure refinement for han500.

Identification code	han500
Empirical formula	$C_{17}H_{20}N_4O_3S$
Formula weight	360.43
Temperature/K	100
Crystal system	monoclinic
Space group	$P2_1/n$
a/Å	13.2777(9)
b/Å	9.5699(7)
c/Å	14.8692(10)
α/°	90
β/°	106.071(3)
γ/°	90
Volume/Å^3	1815.5(2)
Z	4
ρ_{calc}g/cm^3	1.319
μ/mm^{-1}	1.159
F(000)	760.0
Crystal size/mm^3	0.24 × 0.16 × 0.06
Radiation	GaKα (λ = 1.34139)
2Θ range for data collection/°	9.678 to 121.882
Index ranges	-17 ≤ h ≤ 16, -12 ≤ k ≤ 12, -17 ≤ l ≤ 19
Reflections collected	19373
Independent reflections	4145 [R_{int} = 0.0636, R_{sigma} = 0.0548]
Data/restraints/parameters	4145/8/265
Goodness-of-fit on F^2	1.058
Final R indexes [I>=2σ (I)]	R_1 = 0.0725, wR_2 = 0.2020
Final R indexes [all data]	R_1 = 0.0863, wR_2 = 0.2117
Largest diff. peak/hole / e Å^{-3}	0.44/-0.31

Table 2 Fractional Atomic Coordinates (×10^4) and Equivalent Isotropic Displacement Parameters (Å^2×10^3) for han500. U_{eq} is defined as 1/3 of of the trace of the orthogonalised U_{IJ} tensor.

Atom	*x*	*y*	*z*	U(eq)
S1	4577.1(6)	2317.0(8)	4633.3(5)	59.9(3)
O1	2722.0(19)	1425(2)	8530.1(18)	77.0(7)
O2A	4655(3)	1072(4)	4070(2)	70.2(10)
O3A	4764(3)	3631(3)	4313(2)	68.5(9)

N1A	5428(2)	1984(3)	5636(2)	56.2(7)
N2A	7320(8)	3029(12)	6250(10)	89(3)
N3A	8251(6)	3007(8)	6633(5)	84.3(19)
N4A	9132(6)	3012(11)	6882(6)	126(3)
C8A	5500(3)	2986(4)	6412(2)	55.2(8)
O2B	4919(18)	1170(20)	4440(12)	70.2(10)
O3B	4492(16)	3607(19)	3912(10)	68.5(9)
N1B	5342(10)	3092(14)	5563(9)	56.2(7)
N2B	7345(9)	3645(11)	6505(11)	89(3)
N3B	7720(8)	2647(9)	6185(9)	114(4)
N4B	8100(8)	1945(10)	5781(9)	138(4)
C8B	5685(13)	2254(19)	6418(12)	55.2(8)
C1	1874(4)	2316(5)	8554(5)	117(2)
C2	3368(2)	1860(3)	8019(2)	58.6(7)
C3	4140(2)	914(3)	7953(2)	59.0(7)
C4	4829(2)	1257(3)	7448(2)	59.7(7)
C5	4779(2)	2550(3)	7000(2)	58.4(7)
C6	4021(2)	3480(3)	7081(2)	61.6(7)
C7	3314(2)	3146(3)	7586(2)	62.7(7)
C9	6660(3)	3021(5)	7011(3)	80.3(11)
C10	6740(3)	4258(5)	7687(3)	109.2(16)
C11	3319(2)	2293(3)	4817(2)	56.0(7)
C12	2719(3)	3496(3)	4666(2)	62.6(7)
C13	1737(3)	3474(4)	4824(2)	68.6(8)
C14	1366(3)	2288(4)	5151(2)	69.7(9)
C15	1997(3)	1099(4)	5316(2)	69.2(8)
C16	2972(2)	1095(3)	5151(2)	61.6(7)
C17	296(3)	2269(5)	5316(3)	89.9(12)

Table 3 Anisotropic Displacement Parameters ($Å^2 \times 10^3$) for han500. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+\ldots]$.

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
S1	68.5(5)	65.4(5)	57.7(4)	6.7(3)	37.7(4)	7.5(3)
O1	79.8(15)	76.7(14)	95.8(16)	-10.8(12)	59.9(13)	-11.8(11)
O2A	91(3)	64.3(14)	71(2)	0.0(18)	49(2)	8.8(15)
O3A	89(2)	64.4(14)	66.6(19)	15.4(18)	46(2)	12.7(14)
N1A	57.8(16)	54.6(15)	67.7(17)	12.7(13)	36.9(14)	9.2(13)
N2A	66(2)	102(8)	105(8)	30(6)	33(4)	-7(5)
N3A	63(4)	108(5)	94(5)	6(4)	42(4)	-4(4)
N4A	74(5)	199(9)	120(6)	-20(6)	56(4)	-15(5)

C8A	52.9(18)	56(2)	62.2(18)	14.1(17)	25.8(15)	3.0(16)
O2B	91(3)	64.3(14)	71(2)	0.0(18)	49(2)	8.8(15)
O3B	89(2)	64.4(14)	66.6(19)	15.4(18)	46(2)	12.7(14)
N1B	57.8(16)	54.6(15)	67.7(17)	12.7(13)	36.9(14)	9.2(13)
N2B	66(2)	102(8)	105(8)	30(6)	33(4)	-7(5)
N3B	45(5)	91(6)	207(13)	-2(6)	38(6)	18(4)
N4B	110(6)	98(6)	249(13)	-14(7)	120(8)	-5(5)
C8B	52.9(18)	56(2)	62.2(18)	14.1(17)	25.8(15)	3.0(16)
C1	107(3)	94(3)	190(5)	-47(3)	110(4)	-22(2)
C2	60.4(16)	60.6(16)	63.3(16)	-7.3(13)	31.5(14)	-9.1(13)
C3	63.9(17)	60.0(16)	59.4(15)	2.1(13)	27.5(14)	-1.8(13)
C4	55.9(16)	67.8(17)	61.1(16)	1.5(13)	26.1(13)	5.2(13)
C5	51.6(15)	74.6(19)	52.5(14)	5.2(13)	20.4(12)	-9.5(13)
C6	60.8(17)	61.3(17)	62.0(16)	6.9(13)	15.8(14)	-5.0(13)
C7	57.5(16)	63.3(17)	70.5(18)	-11.9(14)	22.8(14)	-0.7(13)
C9	54.7(18)	113(3)	76(2)	28(2)	23.9(16)	-13.4(18)
C10	86(3)	113(3)	110(3)	29(3)	-5(2)	-44(2)
C11	59.0(16)	63.9(16)	50.2(14)	2.3(12)	23.3(12)	7.8(12)
C12	70.2(18)	63.8(17)	57.4(16)	8.6(13)	23.6(14)	11.0(14)
C13	68.9(19)	75(2)	63.0(17)	4.4(15)	20.0(15)	20.3(16)
C14	51.8(17)	95(2)	61.3(17)	-5.9(16)	14.6(14)	8.4(15)
C15	61.6(18)	76(2)	74(2)	4.6(16)	25.1(15)	-3.3(15)
C16	60.2(17)	62.6(17)	67.5(17)	5.0(14)	26.9(14)	4.8(13)
C17	59(2)	115(3)	98(3)	-5(2)	27(2)	6.8(19)

Table 4 Bond Lengths for han500.

Atom	Atom	Length/Å	Atom	Atom	Length/Å
S1	O2A	1.477(3)	N3B	N4B	1.111(11)
S1	O3A	1.391(3)	C8B	C5	1.690(17)
S1	N1A	1.633(3)	C8B	C9	1.537(18)
S1	O2B	1.253(19)	C2	C3	1.391(4)
S1	O3B	1.618(16)	C2	C7	1.382(5)
S1	N1B	1.648(14)	C3	C4	1.373(4)
S1	C11	1.765(3)	C4	C5	1.398(4)
O1	C1	1.421(5)	C5	C6	1.374(4)
O1	C2	1.360(3)	C6	C7	1.391(4)
N1A	C8A	1.484(5)	C9	C10	1.537(6)
N2A	N3A	1.210(11)	C11	C12	1.383(4)
N2A	C9	1.613(13)	C11	C16	1.379(4)
N3A	N4A	1.124(9)	C12	C13	1.388(4)

C8A	C5	1.523(4)	C13	C14	1.378(5)
C8A	C9	1.551(5)	C14	C15	1.393(5)
N1B	C8B	1.465(15)	C14	C17	1.507(5)
N2B	N3B	1.232(11)	C15	C16	1.383(4)
N2B	C9	1.459(14)			

Table 5 Bond Angles for han500.

Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
O2A	S1	N1A	102.75(18)	C7	C2	C3	119.4(2)
O2A	S1	C11	107.17(19)	C4	C3	C2	119.8(3)
O3A	S1	O2A	119.22(18)	C3	C4	C5	121.4(3)
O3A	S1	N1A	110.18(19)	C4	C5	C8A	124.2(3)
O3A	S1	C11	109.31(17)	C4	C5	C8B	98.6(6)
N1A	S1	C11	107.54(13)	C6	C5	C8A	117.7(3)
O2B	S1	O3B	118.7(10)	C6	C5	C8B	142.8(6)
O2B	S1	N1B	114.2(10)	C6	C5	C4	118.1(3)
O2B	S1	C11	116.2(11)	C5	C6	C7	121.2(3)
O3B	S1	N1B	97.2(8)	C2	C7	C6	120.0(3)
O3B	S1	C11	102.5(7)	C8A	C9	N2A	104.1(5)
N1B	S1	C11	105.4(4)	N2B	C9	C8B	116.5(8)
C2	O1	C1	117.2(3)	N2B	C9	C10	94.7(5)
C8A	N1A	S1	117.6(2)	C8B	C9	C10	129.7(8)
N3A	N2A	C9	110.6(10)	C10	C9	N2A	120.2(5)
N4A	N3A	N2A	171.5(10)	C10	C9	C8A	105.6(3)
N1A	C8A	C5	110.7(3)	C12	C11	S1	119.5(2)
N1A	C8A	C9	107.5(3)	C16	C11	S1	119.5(2)
C5	C8A	C9	111.0(3)	C16	C11	C12	121.0(3)
C8B	N1B	S1	116.9(12)	C11	C12	C13	119.1(3)
N3B	N2B	C9	105.0(10)	C14	C13	C12	121.1(3)
N4B	N3B	N2B	166.0(15)	C13	C14	C15	118.6(3)
N1B	C8B	C5	105.0(11)	C13	C14	C17	120.8(3)
N1B	C8B	C9	104.3(11)	C15	C14	C17	120.6(3)
C9	C8B	C5	103.4(11)	C16	C15	C14	121.2(3)
O1	C2	C3	115.6(3)	C11	C16	C15	119.0(3)
O1	C2	C7	125.0(3)				

Table 6 Hydrogen Bonds for han500.

D	H	A	d(D-H)/Å	d(H-A)/Å	d(D-A)/Å	D-H-A/°

N1A H1A O2A[1]	0.88	2.13	2.963(5)	157.1
N1B H1B O3B[2]	0.88	2.50	3.25(2)	142.9

[1]1-X,-Y,1-Z; [2]1-X,1-Y,1-Z

Table 7 Torsion Angles for han500.

A	B	C	D	Angle/°	A	B	C	D	Angle/°
S1	N1A	C8A	C5	91.9(3)	N1B	C8B	C9	C10	85.1(12)
S1	N1A	C8A	C9	-146.7(2)	N3B	N2B	C9	C8B	-66.7(15)
S1	N1B	C8B	C5	-91.9(12)	N3B	N2B	C9	C10	154.2(11)
S1	N1B	C8B	C9	159.8(9)	C8B	C5	C6	C7	168.9(11)
S1	C11	C12	C13	-179.1(2)	C1	O1	C2	C3	-175.2(4)
S1	C11	C16	C15	178.3(2)	C1	O1	C2	C7	5.6(5)
O1	C2	C3	C4	179.8(3)	C2	C3	C4	C5	0.5(5)
O1	C2	C7	C6	179.8(3)	C3	C2	C7	C6	0.7(5)
O2A	S1	N1A	C8A	-175.3(3)	C3	C4	C5	C8A	-178.6(3)
O2A	S1	C11	C12	-132.6(3)	C3	C4	C5	C8B	-173.3(7)
O2A	S1	C11	C16	50.6(3)	C3	C4	C5	C6	0.3(5)
O3A	S1	N1A	C8A	56.7(3)	C4	C5	C6	C7	-0.6(5)
O3A	S1	C11	C12	-2.0(3)	C5	C8A	C9	N2A	163.4(5)
O3A	S1	C11	C16	-178.9(3)	C5	C8A	C9	C10	-69.2(4)
N1A	S1	C11	C12	117.6(3)	C5	C8B	C9	N2B	-146.5(7)
N1A	S1	C11	C16	-59.3(3)	C5	C8B	C9	C10	-24.5(11)
N1A	C8A	C5	C4	57.5(4)	C5	C6	C7	C2	0.1(5)
N1A	C8A	C5	C6	-121.3(3)	C7	C2	C3	C4	-1.0(5)
N1A	C8A	C9	N2A	42.1(5)	C9	C8A	C5	C4	-61.9(4)
N1A	C8A	C9	C10	169.6(3)	C9	C8A	C5	C6	119.3(4)
N3A	N2A	C9	C8A	-177.7(8)	C9	N2B	N3B	N4B	161(5)
N3A	N2A	C9	C10	64.5(11)	C9	C8B	C5	C4	-101.6(8)
C8A	C5	C6	C7	178.3(3)	C9	C8B	C5	C6	87.8(11)
O2B	S1	N1B	C8B	-51.0(15)	C11	S1	N1A	C8A	-62.4(3)
O2B	S1	C11	C12	-154.5(9)	C11	S1	N1B	C8B	77.8(11)
O2B	S1	C11	C16	28.6(10)	C11	C12	C13	C14	1.8(5)
O3B	S1	N1B	C8B	177.0(12)	C12	C11	C16	C15	1.4(5)
O3B	S1	C11	C12	-23.3(7)	C12	C13	C14	C15	-0.4(5)
O3B	S1	C11	C16	159.8(7)	C12	C13	C14	C17	-179.7(3)
N1B	S1	C11	C12	77.9(5)	C13	C14	C15	C16	-0.5(5)
N1B	S1	C11	C16	-99.0(5)	C14	C15	C16	C11	0.0(5)
N1B	C8B	C5	C4	149.4(11)	C16	C11	C12	C13	-2.3(5)

N1B	C8B	C5	C6	-21.2(19)	C17	C14	C15	C16	178.8(3)
N1B	C8B	C9	N2B	-37.0(15)					

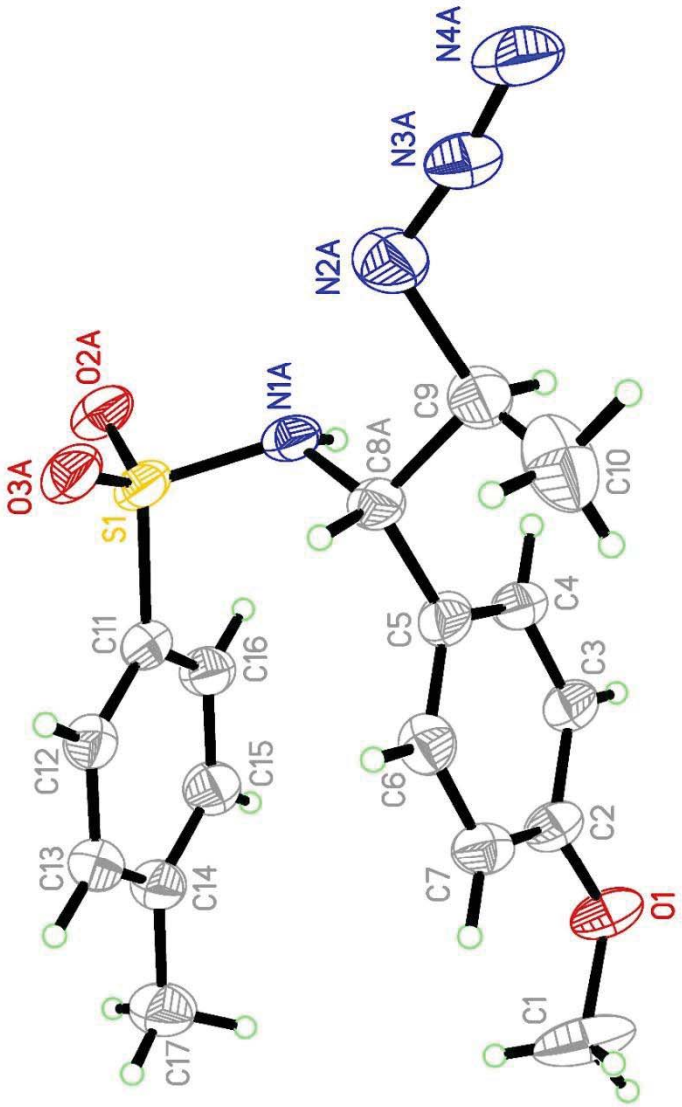
Table 8 Hydrogen Atom Coordinates (Å×10^4) and Isotropic Displacement Parameters (Å^2×10^3) for han500.

Atom	*x*	*y*	*z*	U(eq)
H1A	5389	1153	5879	67
H8A	5293	3937	6146	66
H1B	5091	3872	5734	67
H8B	5802	1243	6307	66
H1C	1412	2432	7919	175
H1D	2146	3229	8806	175
H1E	1478	1900	8954	175
H3	4191	32	8256	71
H4	5350	602	7402	72
H6	3978	4367	6787	74
H7	2794	3802	7633	75
H9A	6817	2138	7384	96
H9B	7095	2271	7402	96
H10A	7472	4386	8048	164
H10B	6311	4069	8114	164
H10C	6487	5109	7328	164
H12	2975	4326	4457	75
H13	1313	4289	4704	82
H15	1753	278	5546	83
H16	3396	279	5266	74
H17A	16	3222	5268	135
H17B	351	1897	5942	135
H17C	-174	1676	4845	135

Table 9 Atomic Occupancy for han500.

Atom	*Occupancy*	Atom	*Occupancy*	Atom	*Occupancy*
O2A	0.822(4)	O3A	0.822(4)	N1A	0.822(4)
H1A	0.822(4)	N2A	0.52	N3A	0.52
N4A	0.52	C8A	0.822(4)	H8A	0.822(4)
O2B	0.178(4)	O3B	0.178(4)	N1B	0.178(4)
H1B	0.178(4)	N2B	0.48	N3B	0.48
N4B	0.48	C8B	0.178(4)	H8B	0.178(4)

H9A 0.822(4) H9B 0.178(4)



ORTEP view of the C17 H20 N4 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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Sulfonamide **2.66**

Université de Montréal

CRYSTAL AND MOLECULAR STRUCTURE OF

C16 H18 N4 O3 S COMPOUND (han501)

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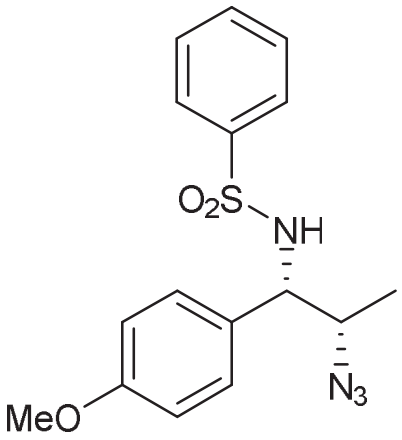


Structure solved and refined in the laboratory of X-ray diffraction
Université de Montréal by Michel Simard.

Table 1 Crystal data and structure refinement for han501.

Identification code	han501
Empirical formula	$C_{16}H_{18}N_4O_3S$
Formula weight	346.40
Temperature/K	100
Crystal system	orthorhombic
Space group	$Pca2_1$
a/Å	10.0504(6)
b/Å	22.0996(14)
c/Å	7.5565(5)
α/°	90
β/°	90
γ/°	90
Volume/Å^3	1678.37(18)
Z	4
ρ_{calc}g/cm^3	1.371
μ/mm^{-1}	1.240
F(000)	728.0
Crystal size/mm^3	0.3 × 0.04 × 0.03
Radiation	GaKα (λ = 1.34139)
2Θ range for data collection/°	6.96 to 121.522
Index ranges	-13 ≤ h ≤ 13, -28 ≤ k ≤ 28, -9 ≤ l ≤ 9
Reflections collected	17510
Independent reflections	3812 [R_{int} = 0.0548, R_{sigma} = 0.0466]
Data/restraints/parameters	3812/1/223
Goodness-of-fit on F^2	1.044
Final R indexes [I>=2σ (I)]	R_1 = 0.0384, wR_2 = 0.1002
Final R indexes [all data]	R_1 = 0.0412, wR_2 = 0.1023
Largest diff. peak/hole / e Å^{-3}	0.26/-0.41
Flack parameter	0.004(16)

Table 2 Fractional Atomic Coordinates (×10^4) and Equivalent Isotropic Displacement Parameters (Å^2×10^3) for han501. U_{eq} is defined as 1/3 of of the trace of the orthogonalised U_{IJ} tensor.

Atom	*x*	*y*	*z*	U(eq)
S1	4147.4(6)	7932.1(3)	7499.4(8)	32.27(17)
O1	3314(2)	4752.2(9)	3904(3)	41.4(5)
O2	5040(2)	7592.9(9)	8597(3)	41.9(5)

O3	2835(2)	8082.3(9)	8153(3)	40.5(4)
N1	3878(2)	7549.8(10)	5713(3)	32.4(5)
N2	5634(2)	8120.9(11)	3233(3)	39.7(5)
N3	5025(2)	8466.7(11)	2233(3)	37.8(5)
N4	4542(3)	8828.9(12)	1391(4)	48.2(6)
C1	3973(4)	4283.4(14)	4845(4)	53.3(8)
C2	3768(3)	5331.1(12)	4180(3)	33.5(5)
C3	3010(3)	5789.6(13)	3410(4)	36.5(5)
C4	3378(3)	6388.6(12)	3635(4)	35.9(6)
C5	4510(3)	6542.8(12)	4624(3)	32.9(5)
C6	5245(3)	6081.2(13)	5371(3)	34.5(6)
C7	4890(3)	5476.7(13)	5163(3)	36.4(6)
C8	4945(3)	7199.2(12)	4839(3)	33.2(5)
C9	5308(3)	7468.6(12)	3008(4)	35.5(5)
C10	6543(3)	7156.5(13)	2260(4)	39.5(6)
C11	4929(3)	8623.6(12)	6970(3)	31.4(5)
C12	6253(3)	8721.0(13)	7408(4)	37.8(5)
C13	6851(3)	9262.9(14)	6926(4)	43.9(7)
C14	6131(3)	9699.8(14)	6020(5)	45.6(7)
C15	4804(3)	9603.0(14)	5592(4)	43.6(7)
C16	4184(3)	9064.0(13)	6073(4)	36.0(6)

Table 3 Anisotropic Displacement Parameters ($Å^2×10^3$) for han501. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+\ldots]$.

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
S1	36.4(3)	36.9(3)	23.5(3)	1.7(2)	2.6(2)	-0.4(2)
O1	54.0(12)	34.7(10)	35.4(9)	-1.5(8)	5.3(9)	-9.5(9)
O2	49.4(12)	44.9(11)	31.2(9)	4.8(8)	-2.4(8)	1.8(9)
O3	41.3(10)	46.5(10)	33.7(9)	-0.4(8)	9.7(8)	-0.9(8)
N1	33.4(11)	36.3(11)	27.5(10)	1.5(9)	-0.6(9)	0.6(9)
N2	47.2(13)	39.6(12)	32.4(11)	-0.4(10)	3.8(10)	-5(1)
N3	44.4(12)	36.7(11)	32.4(12)	-1.9(10)	6.3(9)	-4.1(10)
N4	61.8(16)	40.8(14)	42.1(13)	1.4(11)	-2.3(13)	1.4(13)
C1	88(3)	34.7(15)	36.7(15)	4.6(12)	8.0(16)	-7.3(15)
C2	41.3(13)	34.4(13)	24.8(11)	-1.8(10)	6(1)	-6.4(11)
C3	35.1(13)	43.7(14)	30.5(12)	-1.5(10)	-2.5(10)	-5.4(11)
C4	35.4(13)	37.0(13)	35.4(12)	2.2(10)	-2.5(10)	0.7(11)
C5	35.8(12)	37.1(14)	25.9(11)	-0.6(9)	3.9(10)	-2.1(10)
C6	34.9(13)	41.1(14)	27.5(12)	1.2(10)	-2.6(9)	-3.5(11)
C7	42.4(15)	38.3(14)	28.5(12)	6.4(10)	0(1)	-1.0(11)

C8	33.6(12)	38.3(13)	27.6(12)	-0.7(10)	1.0(9)	-1(1)
C9	39.1(13)	36.3(13)	31.0(12)	1.4(10)	3.1(11)	-2(1)
C10	42.5(14)	43.4(14)	32.7(14)	-2.6(11)	5.3(12)	0.6(11)
C11	35.2(12)	34.7(13)	24.2(11)	-3.1(9)	2.7(8)	0.4(10)
C12	35.6(12)	42.3(14)	35.5(12)	-5.4(12)	-1.7(12)	3.2(10)
C13	35.8(14)	44.0(15)	51.9(16)	-10.9(12)	2.8(12)	-2.9(12)
C14	46.9(16)	37.5(15)	52.4(18)	-8.2(13)	11.6(13)	-7.3(12)
C15	49.2(17)	37.5(14)	44.2(15)	0.1(12)	4.2(13)	3.4(13)
C16	34.6(13)	36.8(14)	36.4(14)	-0.6(11)	0.5(10)	2.8(11)

Table 4 Bond Lengths for han501.

Atom	Atom	Length/Å	Atom	Atom	Length/Å
S1	O2	1.433(2)	C4	C5	1.403(4)
S1	O3	1.447(2)	C5	C6	1.381(4)
S1	N1	1.615(2)	C5	C8	1.524(4)
S1	C11	1.764(3)	C6	C7	1.392(4)
O1	C1	1.420(4)	C8	C9	1.550(4)
O1	C2	1.374(3)	C9	C10	1.528(4)
N1	C8	1.479(3)	C11	C12	1.388(4)
N2	N3	1.237(4)	C11	C16	1.403(4)
N2	C9	1.488(4)	C12	C13	1.388(4)
N3	N4	1.132(4)	C13	C14	1.387(5)
C2	C3	1.394(4)	C14	C15	1.389(5)
C2	C7	1.388(4)	C15	C16	1.392(4)
C3	C4	1.385(4)			

Table 5 Bond Angles for han501.

Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
O2	S1	O3	119.51(13)	C6	C5	C8	120.4(2)
O2	S1	N1	108.35(12)	C5	C6	C7	121.7(3)
O2	S1	C11	107.81(13)	C2	C7	C6	119.4(3)
O3	S1	N1	104.64(12)	N1	C8	C5	109.8(2)
O3	S1	C11	106.53(12)	N1	C8	C9	111.6(2)
N1	S1	C11	109.76(12)	C5	C8	C9	109.7(2)
C2	O1	C1	116.7(2)	N2	C9	C8	108.8(2)
C8	N1	S1	121.72(19)	N2	C9	C10	107.5(2)
N3	N2	C9	114.8(2)	C10	C9	C8	110.4(2)
N4	N3	N2	173.1(3)	C12	C11	S1	120.5(2)

O1	C2	C3	115.6(2)	C12	C11	C16	121.3(3)
O1	C2	C7	124.5(3)	C16	C11	S1	118.2(2)
C7	C2	C3	119.9(2)	C11	C12	C13	119.1(3)
C4	C3	C2	119.8(2)	C14	C13	C12	120.3(3)
C3	C4	C5	120.9(3)	C13	C14	C15	120.6(3)
C4	C5	C8	121.4(2)	C14	C15	C16	120.0(3)
C6	C5	C4	118.2(3)	C15	C16	C11	118.7(3)

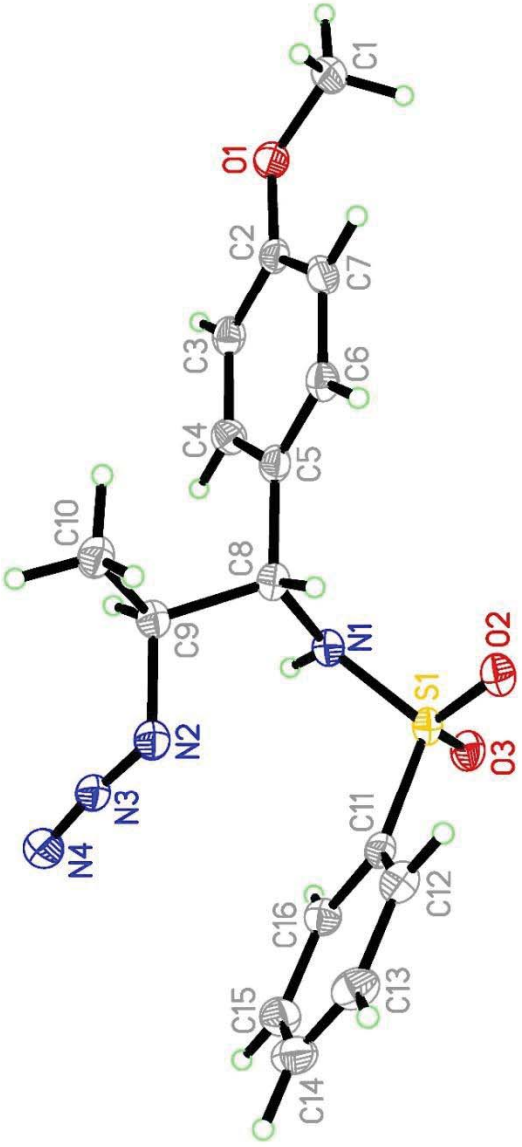
Table 6 Hydrogen Bonds for han501.

D	H	A	d(D-H)/Å	d(H-A)/Å	d(D-A)/Å	D-H-A/°
N1	H1	O3[1]	0.86(3)	1.99(3)	2.845(3)	168(3)

[1]1/2-X,+Y,-1/2+Z

Table 7 Hydrogen Atom Coordinates (Å×10^4) and Isotropic Displacement Parameters (Å^2×10^3) for han501.

Atom	*x*	*y*	*z*	U(eq)
H1A	4902	4260	4459	80
H1B	3529	3897	4609	80
H1C	3941	4370	6116	80
H3	2244	5691	2733	44
H4	2856	6699	3113	43
H6	6014	6179	6046	41
H7	5411	5166	5689	44
H8	5755	7210	5608	40
H9	4544	7421	2173	43
H10A	6724	7311	1069	59
H10B	6389	6719	2203	59
H10C	7307	7239	3028	59
H12	6743	8421	8030	45
H13	7756	9335	7218	53
H14	6549	10068	5690	55
H15	4319	9905	4971	52
H16	3274	8996	5798	43
H1	3260(30)	7693(13)	5030(40)	29(7)



ORTEP view of the C16 H18 N4 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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Exploration Program. Bruker AXS Inc., Madison, WI 53719-1173.

Sulfonamide **2.67**

Université de Montréal

CRYSTAL AND MOLECULAR STRUCTURE OF

C14 H22 N4 O3 S COMPOUND (han504)

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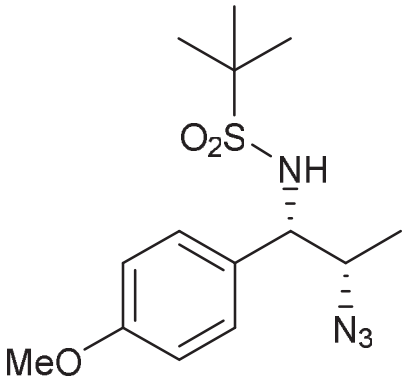


Structure solved and refined in the laboratory of X-ray diffraction
Université de Montréal by Michel Simard.

Table 1 Crystal data and structure refinement for han504.

Identification code	han504
Empirical formula	$C_{14}H_{22}N_4O_3S$
Formula weight	326.41
Temperature/K	100
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	11.1383(9)
b/Å	14.0920(11)
c/Å	11.7874(9)
α/°	90
β/°	114.813(3)
γ/°	90
Volume/Å^3	1679.4(2)
Z	4
ρ_{calc}g/cm^3	1.291
μ/mm^{-1}	1.212
F(000)	696.0
Crystal size/mm^3	0.22 × 0.16 × 0.12
Radiation	GaKα (λ = 1.34139)
2Θ range for data collection/°	9.028 to 121.424
Index ranges	$-14 \leq h \leq 14$, $-17 \leq k \leq 18$, $-15 \leq l \leq 15$
Reflections collected	32475
Independent reflections	3840 [R_{int} = 0.0366, R_{sigma} = 0.0208]
Data/restraints/parameters	3840/0/208
Goodness-of-fit on F^2	1.043
Final R indexes [I>=2σ (I)]	R_1 = 0.0311, wR_2 = 0.0828
Final R indexes [all data]	R_1 = 0.0318, wR_2 = 0.0833
Largest diff. peak/hole / e Å^{-3}	0.35/-0.34

Table 2 Fractional Atomic Coordinates (×10^4) and Equivalent Isotropic Displacement Parameters (Å^2×10^3) for han504. U_{eq} is defined as 1/3 of of the trace of the orthogonalised U_{IJ} tensor.

Atom	*x*	*y*	*z*	U(eq)
S1	11157.4(2)	934.9(2)	4226.1(2)	17.25(8)
O1	5759.4(8)	4495.8(5)	3118.9(8)	24.87(17)

O2	11488.4(8)	30.6(5)	4866.6(7)	21.67(17)
O3	11679.3(8)	1152.7(6)	3326.0(7)	23.23(17)
N1	9566.2(9)	971.6(6)	3521.5(8)	19.05(18)
N2	7182.3(10)	266.6(7)	1740.7(9)	24.8(2)
N3	6547.4(9)	-370.4(7)	1011.4(9)	24.0(2)
N4	5931.9(11)	-984.6(7)	437(1)	31.8(2)
C1	5629.6(13)	5381.9(8)	2484.5(12)	30.0(3)
C2	6472.5(10)	3798.4(7)	2870.1(10)	20.1(2)
C3	6498.6(10)	2917.7(8)	3427.2(10)	20.5(2)
C4	7253(1)	2180.2(7)	3289.8(9)	19.6(2)
C5	7978.9(10)	2302.1(7)	2576.0(9)	18.6(2)
C6	7903.9(11)	3174.4(8)	1997.4(10)	22.3(2)
C7	7163.9(11)	3926.9(8)	2137.3(11)	23.3(2)
C8	8819.8(10)	1524.1(7)	2386.8(9)	18.6(2)
C9	8012.9(11)	858.2(7)	1299.3(10)	21.3(2)
C10	8882.2(12)	270.8(8)	864.1(11)	28.0(2)
C11	11705.2(10)	1851.0(7)	5410.3(10)	20.4(2)
C12	11033.2(13)	1700.8(8)	6291.0(11)	28.1(2)
C13	11326.0(12)	2818.1(8)	4775.6(11)	26.6(2)
C14	13207.0(12)	1755.1(10)	6108.4(12)	33.3(3)

Table 3 Anisotropic Displacement Parameters ($Å^2×10^3$) for han504. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+2hka^*b^*U_{12}+\ldots]$.

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
S1	19.60(13)	13.84(13)	20.10(13)	1.51(8)	10.09(10)	1.58(8)
O1	27.0(4)	19.2(4)	32.3(4)	-1.4(3)	16.2(3)	2.4(3)
O2	25.3(4)	15.1(4)	26.0(4)	3.8(3)	12.2(3)	3.5(3)
O3	26.1(4)	22.9(4)	26.1(4)	2.4(3)	16.4(3)	1.4(3)
N1	19.7(4)	18.2(4)	19.8(4)	4.0(3)	8.9(4)	-0.6(3)
N2	26.8(5)	25.0(5)	22.1(4)	-3.9(4)	9.6(4)	-5.4(4)
N3	23.5(4)	23.0(5)	25.5(4)	-0.4(4)	10.3(4)	1.2(4)
N4	32.2(5)	28.4(5)	36.2(6)	-8.0(4)	15.7(5)	-5.4(4)
C1	33.2(6)	19.5(5)	40.4(6)	2.2(5)	18.4(5)	5.7(4)
C2	18.9(5)	17.8(5)	22.5(5)	-3.3(4)	7.4(4)	-0.4(4)
C3	21.3(5)	21.1(5)	20.1(5)	-2.2(4)	9.8(4)	-3.6(4)
C4	22.6(5)	16.9(5)	18.9(5)	0.4(4)	8.2(4)	-2.5(4)
C5	20.0(5)	16.8(5)	18.4(4)	-0.3(4)	7.6(4)	0.0(4)
C6	25.1(5)	20.0(5)	25.6(5)	3.8(4)	14.5(4)	1.4(4)
C7	25.8(5)	17.4(5)	28.6(5)	3.8(4)	13.2(4)	1.2(4)
C8	22.2(5)	15.8(5)	18.5(5)	2.2(4)	9.4(4)	1.3(4)

C9	27.3(5)	17.9(5)	19.0(5)	0.8(4)	10.1(4)	0.7(4)
C10	35.0(6)	22.4(6)	31.2(6)	-5.6(4)	18.5(5)	-0.9(4)
C11	22.5(5)	15.9(5)	21.5(5)	-0.3(4)	8.2(4)	-1.0(4)
C12	39.9(6)	23.2(5)	25.3(5)	-3.7(4)	17.9(5)	-3.0(5)
C13	32.8(6)	15.7(5)	27.7(5)	0.6(4)	9.3(5)	-2.5(4)
C14	22.9(5)	33.4(6)	35.4(6)	-3.0(5)	4.2(5)	0.0(5)

Table 4 Bond Lengths for han504.

Atom	Atom	Length/Å	Atom	Atom	Length/Å
S1	O2	1.4478(7)	C2	C7	1.3893(15)
S1	O3	1.4406(8)	C3	C4	1.3880(15)
S1	N1	1.6118(9)	C4	C5	1.4008(14)
S1	C11	1.8091(11)	C5	C6	1.3911(14)
O1	C1	1.4313(14)	C5	C8	1.5179(14)
O1	C2	1.3705(13)	C6	C7	1.3947(15)
N1	C8	1.4674(13)	C8	C9	1.5378(14)
N2	N3	1.2388(13)	C9	C10	1.5175(15)
N2	C9	1.4919(14)	C11	C12	1.5280(15)
N3	N4	1.1349(14)	C11	C13	1.5266(14)
C2	C3	1.3987(15)	C11	C14	1.5292(15)

Table 5 Bond Angles for han504.

Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
O2	S1	N1	106.34(5)	C6	C5	C4	118.15(9)
O2	S1	C11	107.22(5)	C6	C5	C8	118.69(9)
O3	S1	O2	118.58(5)	C5	C6	C7	122.06(10)
O3	S1	N1	108.06(5)	C2	C7	C6	118.93(10)
O3	S1	C11	107.85(5)	N1	C8	C5	113.44(8)
N1	S1	C11	108.45(5)	N1	C8	C9	110.20(8)
C2	O1	C1	117.02(9)	C5	C8	C9	112.48(8)
C8	N1	S1	124.51(7)	N2	C9	C8	106.34(8)
N3	N2	C9	114.82(9)	N2	C9	C10	112.97(9)
N4	N3	N2	173.04(12)	C10	C9	C8	112.46(9)
O1	C2	C3	115.82(9)	C12	C11	S1	108.82(7)
O1	C2	C7	124.18(10)	C12	C11	C14	111.06(10)
C7	C2	C3	119.99(10)	C13	C11	S1	108.94(7)
C4	C3	C2	120.26(10)	C13	C11	C12	110.06(9)
C3	C4	C5	120.56(10)	C13	C11	C14	110.97(9)

C4	C5	C8	123.15(9)	C14	C11	S1	106.90(8)

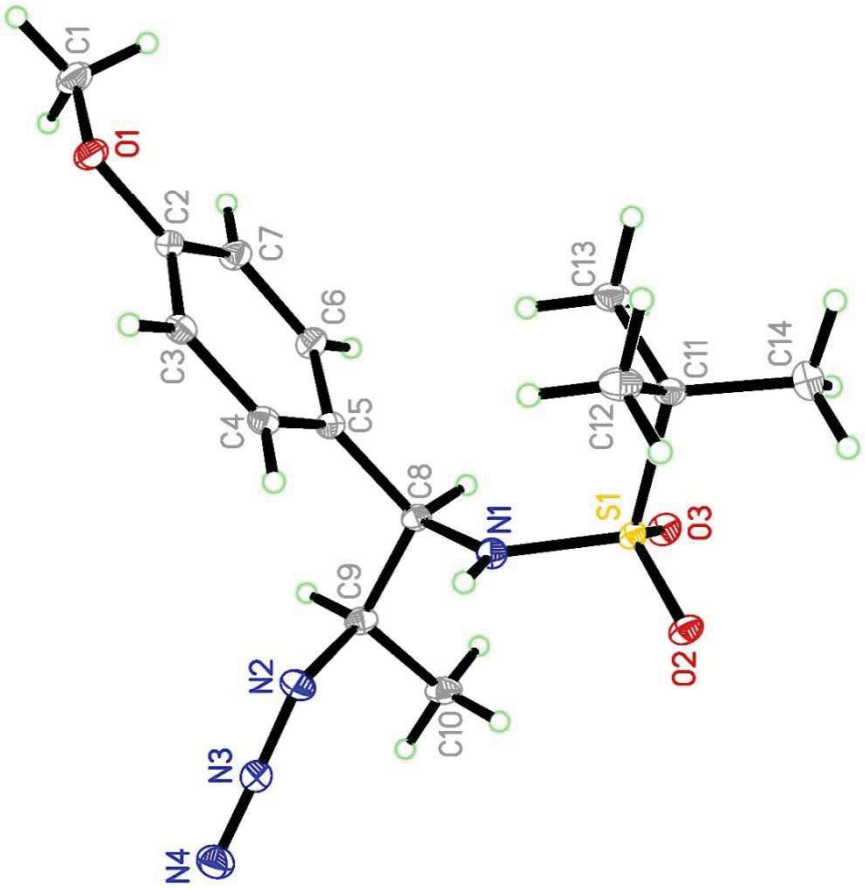
Table 6 Hydrogen Bonds for han504.

D	H	A	d(D-H)/Å	d(H-A)/Å	d(D-A)/Å	D-H-A/°
N1	H1	O2[1]	0.805(16)	2.185(16)	2.9762(12)	167.4(14)

[1]2-X,-Y,1-Z

Table 7 Hydrogen Atom Coordinates (Å×10^4) and Isotropic Displacement Parameters (Å^2×10^3) for han504.

Atom	*x*	*y*	*z*	U(eq)
H1A	5190	5278	1580	45
H1B	6509	5654	2704	45
H1C	5101	5820	2736	45
H3	5998	2824	3901	25
H4	7277	1588	3683	24
H6	8371	3260	1491	27
H7	7133	4518	1738	28
H8	9485	1845	2154	22
H9	7412	1254	582	26
H10A	9464	-134	1550	42
H10B	9419	694	605	42
H10C	8325	-126	156	42
H12A	10072	1739	5816	42
H12B	11326	2193	6938	42
H12C	11271	1075	6684	42
H13A	11742	2901	4196	40
H13B	11630	3319	5410	40
H13C	10363	2855	4313	40
H14A	13427	1120	6477	50
H14B	13543	2233	6772	50
H14C	13613	1850	5523	50
H1	9180(15)	681(11)	3854(14)	27(4)



ORTEP view of the C14 H22 N4 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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Annexe 3 – Articles 1 et 2

Synthesis J.-P. Cusson et al. Paper

On the Importance of the Relative Stereochemistry of Substituents in the Formation of Nine-Membered Lactones by Ring-Closing Metathesis

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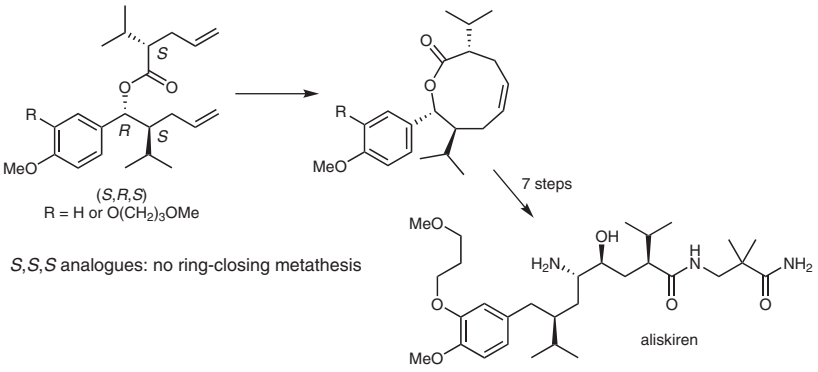

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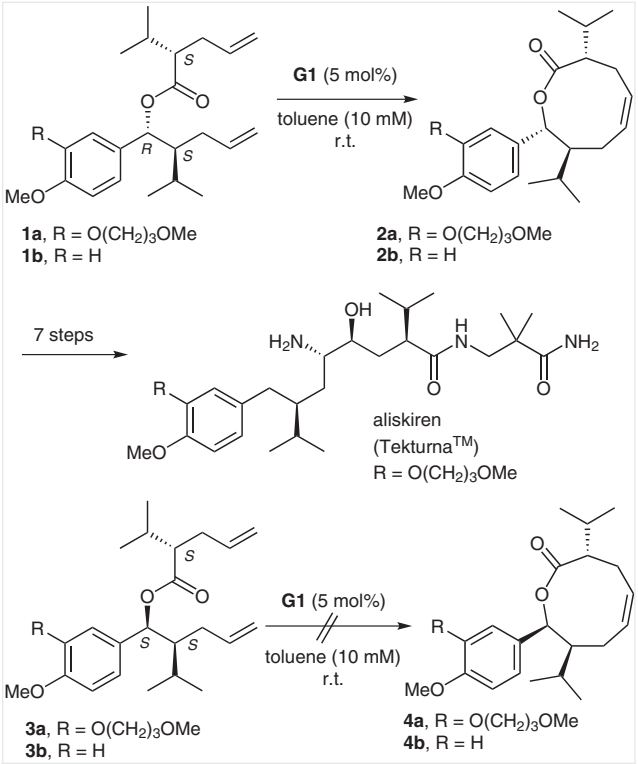
Abstract The effects of isopropyl substituents and molar concentration of diastereomeric esters toward the formation of nine-membered unsaturated lactones, in the context of the synthesis of the intermediates of the antihypertensive drug aliskiren, have been studied.

Key words lactone, metathesis, cyclization, macrocycle, dimerization

The now-venerable Grubbs olefin metathesis reaction[1] and its many recent variants[2] is an exceedingly useful and versatile method to construct internally unsaturated compounds of varying ring sizes.[3] Among these, the synthesis of nine-membered unsaturated lactones[4] and ethers[5] is of particular interest because of their limited occurrence in nature and their interesting biological activity.[6]

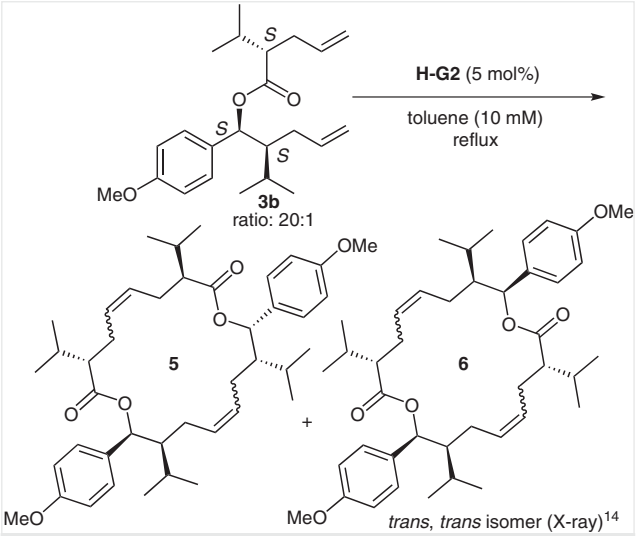
In a recent paper[7] on the total synthesis of the marketed antihypertensive drug aliskiren (Tekturna™)[8] we utilized a ring-closing metathesis reaction with the ester **1a** using Grubbs' 1st generation catalyst (**G1**)[9] to obtain a critical nine-membered unsaturated lactone intermediate **2a** that harbored two isopropyl groups in strategically pre-defined positions on an 8-aryloctanoic acid core unit (Scheme 1). The lactone **2a** was further elaborated to provide aliskiren in seven steps and 7% overall yield from readily available starting materials.[7] Compared to recent syntheses,[10] and a plethora of published patents,[11] our synthesis proved to be the shortest to date.

During the ring-closing metathesis reaction of a mixture of esters **1a** and diastereomeric **3a** with **G1** catalyst in refluxing toluene at a concentration of 10 mM, we observed that only the (*S*,*R*,*S*)-ester **1a** was converted into the lactone **2a**. The same observation was made with the (*S*,*R*,*S*)-ester of the corresponding *p*-methoxyphenyl analogue **1b**. The



Scheme 1 Synthetic route to aliskiren via a nine-membered lactone

diastereomeric ester **3b** did not give the expected lactone **4b** and remained unchanged. Further studies with Grubbs second-generation (**G2**)[12] and Hoveyda–Grubbs second-generation (**H-G2**)[2b] catalysts with a 4:1 diastereomeric mixture of *p*-methoxyphenyl analogue **1b** led to the lactone **2b** in excellent yield and in much shorter time. Under these conditions, the diastereomeric (*S*,*S*,*S*)-ester **3b**, obtained independently from a stereoselective reduction of the corre-



Scheme 2 Formation of dilactone dimers from ester **3b**

sponding ketone[13] led to an approximately 1:1 mixture of head-to-head and head-to-tail 18-membered dilactone dimers **5** and **6** as an inseparable mixture of olefin isomers. The structure of the C_2-symmetrical dilactone **6** was ascertained by X-ray crystallography (Scheme 2).[14]

In view of the continuing interest to develop viable synthetic routes to aliskiren, we focused on the key ring-closing metathesis step in our original synthesis.[7] In this paper, we report our qualitative observations pertaining to the reaction of the *p*-methoxyphenyl analogues **1b** and **3b** as well as their mono- and disubstituted diastereomeric esters in the presence of a variety of catalysts, in order to determine the influence of the isopropyl and vicinal aryl substituents and their relative stereochemistry on the nature of the products (Figure 1).

In the absence of any substituents, a mixture of racemic esters **7a** led to an inseparable mixture of dilactones **8a** and **9a** in excellent yield in presence of the **G1**, **G2**, and **H-G2** catalysts (Scheme 3, Table 1, entries 1–4). Compared to the **G1** catalyst, the dilactones were formed much faster with the **G2** catalyst. The reaction rate was slower in presence of **H-G2** catalyst in dichloromethane (entries 1–3). However, complete conversion occurred in refluxing toluene within 30 minutes (entry 4). No reaction occurred with the **G1** catalyst even in the presence of titanium(IV) isopropoxide[15] at room temperature in toluene. Hydrogenation of the double bonds was followed by treatment with triethylsilane/trifluoroacetic acid to give **11a** and **12a** in a quasi 1:1 ratio, which mirrored the amounts of the respective original dilactones **8a** and **9a** in the mixture (entries 1–4). The octanedioic acid was not isolated.

Treatment of the benzylic (*R*)-ester of **7b** with the **G1** catalyst resulted in the formation of the lactone **10b** in 33% yield, but only in the presence of titanium(IV) isopropoxide[15] and after repeated addition of catalyst (entry 5). In addition, dilactones **8b** and **9b** were formed in equal amounts as an inseparable mixture. The reaction rate was accelerated in the presence of the **G2** and **H-G2** catalysts (entries 6 and 7), but the yields were not improved. After completion of the reaction, lactone **10b** was isolated by chromatography and the mixture of the remaining dilactones was sub-

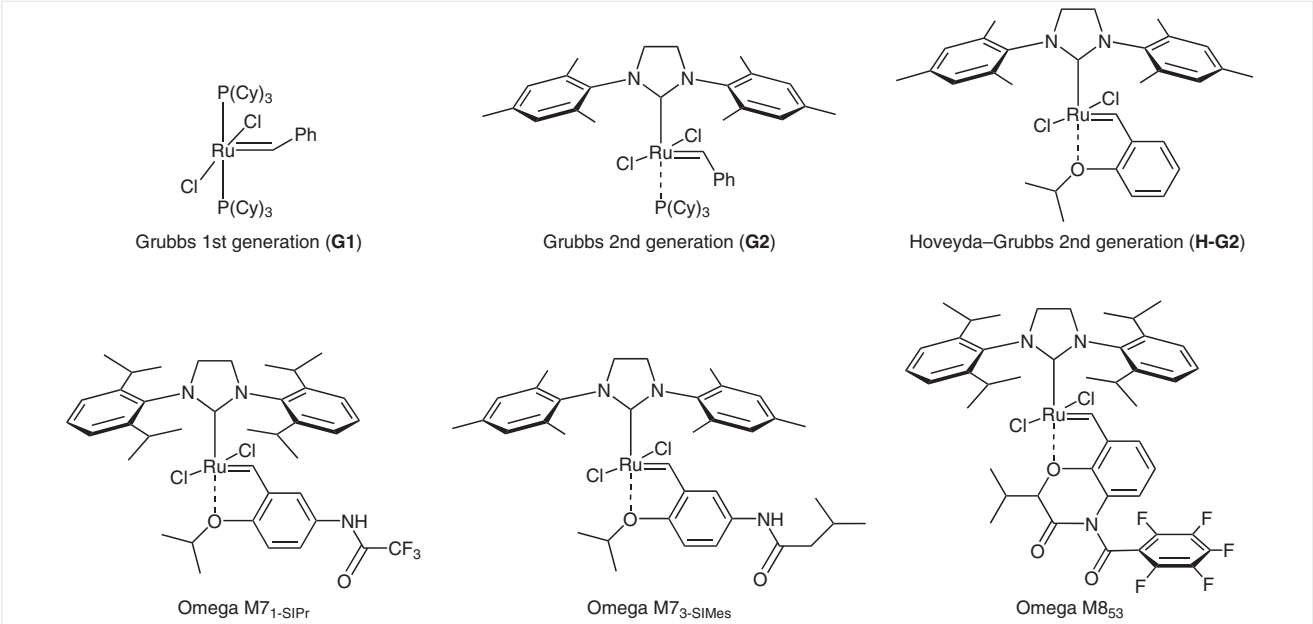


Figure 1 Structures of catalysts used for the ring-closing metathesis ($M7_{1\text{-SIPr}}$, $M7_{3\text{-SIMes}}$, and $M8_{53}$)[16]

mitted to hydrogenation then reductive cleavage of the benzylic ester functions to give the corresponding products **11b** and **12b** (Scheme 3).

In contrast, reaction of the benzylic (*S*)-ester of **7b** with the **G2** and **H-G2** catalysts led only to a mixture of the dilactones **8b** and **9b** which were converted into a 1:1 mixture of **11b** and **12b** as described above (entries 8 and 9). No reaction was observed with the **G1** catalyst.

Treatment of **7c** (as a mixture of benzylic ester diastereomers) with **G1**, **G2**, and **H-G2** gave dilactones **8c** and **9c** in a quasi 1:1 ratio with a distinct preference for the latter catalyst with regard to time. Hydrogenation and reductive cleavage led to **11c** and **12c** (entries 9–11). Trace amounts of the corresponding lactone **10c** were observed by MS.

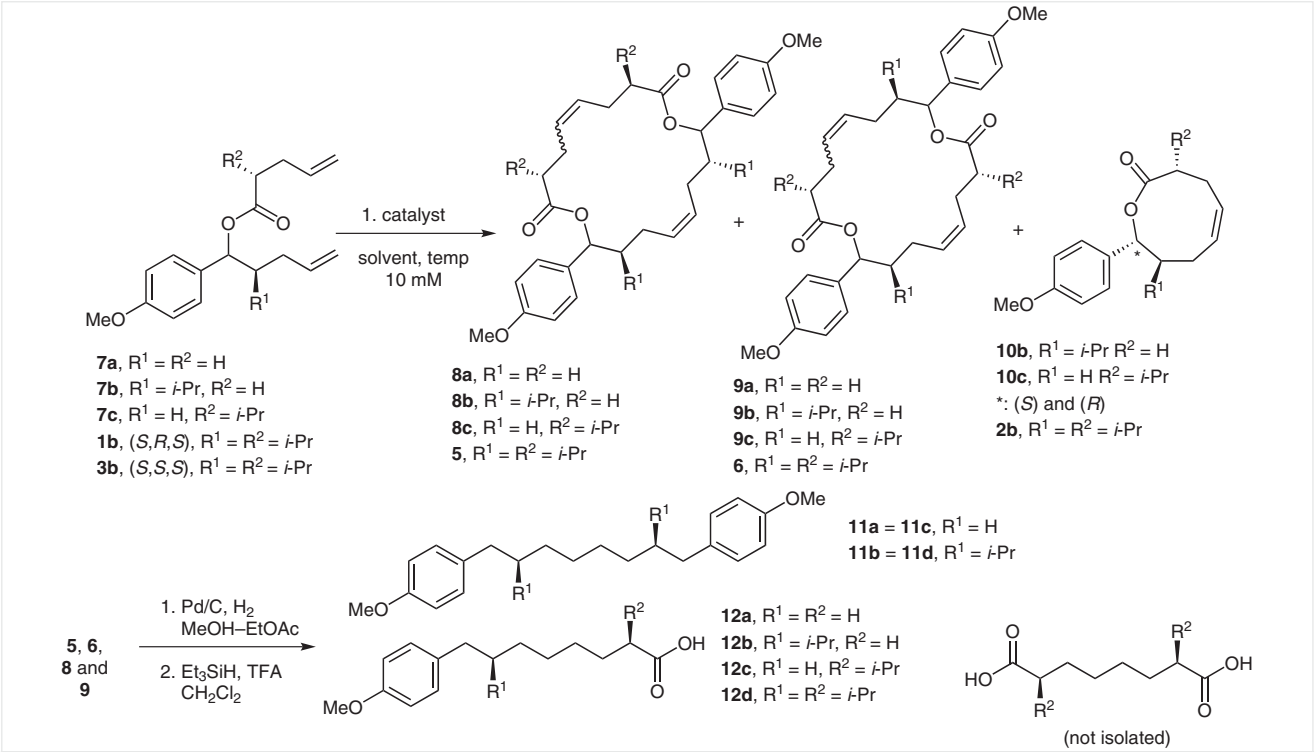
We then returned to the original disubstituted model (*S*,*R*,*S*)-ester **1b**, and studied the reaction in the presence of **G2** and then **H-G2** catalysts and the newer generation catalysts (Figure 1).[16] Using 5 mol% catalyst in refluxing toluene led to the nine-membered lactone **2b** in good yield, although the reaction was 2–3 times slower with the new generation catalysts (entries 13–17). Finally, the (*S*,*S*,*S*)-ester **3b** was subjected to the same reactions conditions, leading solely to the dilactones **5** and **6** as previously observed with the **G2** and **H-G2** catalysts (entries 18–22).[14] Hydrogenation of the double bonds and reductive cleavage in the presence of triethylsilane/trifluoroacetic acid led to **11d** and **12d** in a 1:1 ratio; 2,7-diisopropyloctanedioic acid was not isolated.

Since the formation of dilactone dimers prevailed in the case of the (*S*,*S*,*S*)-esters **3a** and **3b** (as well as other esters shown in Table 1), we considered running the reaction at higher dilution. Surprisingly, upon changing the concentration from 10 mM to 1 mM in refluxing toluene, ester **3b** gave the elusive lactone **4b** in 53% isolated yield, accompanied by 24% of the dimers **5** and **6** (Scheme 4, Table 2, entry 4). Extending the reaction time reduced the yield of lactone **4b** while favoring dilactone formation (entry 3). In contrast, dilution did not affect dilactone formation in the case of the

Table 1 Formation of Dilactones, Products from Cleavage Reactions, Reaction Parameters, and Ratio of Products with Different Catalyst (Scheme 3)

Entry	Ester	Ratio	Catalyst[a]	Solvent[b]	Temp (°C)	Time	Yield (%)		
							11	**12**	**2**/**10**
1	**7a** (*R*/*S*)	*rac*	**G1**	CH_2Cl_2	50	24 h	47	49	–
2	**7a** (*R*/*S*)	*rac*	**G2**	CH_2Cl_2	50	75 min	34	45	–
3	**7a** (*R*/*S*)	*rac*	**H-G2**	CH_2Cl_2	50	24 h	39	44	–
4	**7a** (*R*/*S*)	*rac*	**H-G2**	toluene	110	30 min	31	38	–
5	**7b** (*R*)	4:1	**G1**[c,d]	toluene	r.t.	5 d	17	20	33
6	**7b** (*R*)	4:1	**G2**[e]	toluene	110	40 min	16	17	30
7	**7b** (*R*)	4:1	**H-G2**	toluene	110	20 min	19	19	32
8	**7b** (*S*)	20:1	**G2**[e]	toluene	110	45 min	32	36	–
9	**7b** (*S*)	20:1	**H-G2**	toluene	110	45 min	36	37	–
10	**7c** (*R*/*S*)	*rac*	**G1**[c,d]	toluene	r.t.	5 d	40	35	–
11	**7c** (*R*/*S*)	*rac*	**G2**[e]	toluene	110	40 min	46	45	–
12	**7c** (*R*/*S*)	*rac*	**H-G2**	toluene	110	20 min	44	41	–
13	**1b** (*R*)	4:1	**G2**[e]	toluene	110	40 min	–	–	67
14	**1b** (*R*)	4:1	**H-G2**	toluene	110	20 min	–	–	64
15	**1b** (*R*)	4:1	$M7_{1\text{-SIPr}}$[e]	toluene	110	1 h	–	–	66
16	**1b** (*R*)	4:1	$M7_{3\text{-SIMes}}$[e]	toluene	110	1 h	–	–	63
17	**1b** (*R*)	4:1	$M8_{53}$[e]	toluene	110	1 h	–	–	61
18	**3b** (*S*)	20:1	**G2**[e]	toluene	110	40 min	39	40	–
19	**3b** (*S*)	20:1	**H-G2**	toluene	110	40 min	40	43	–
20	**3b** (*S*)	20:1	$M7_{1\text{-SIPr}}$[e]	toluene	110	1 h	37	38	–
21	**3b** (*S*)	20:1	$M7_{3\text{-SIMes}}$[e]	toluene	110	1 h	39	36	–
22	**3b** (*S*)	20:1	$M8_{53}$[e]	toluene	110	1 h	38	38	–

[a] Unless otherwise stated, 0.05 equiv (5 mol%).
[b] 0.01 M.
[c] $Ti(O\text{-}i\text{-}Pr)_4$ (1 equiv).
[d] Catalyst (5 mol%) was added every day.
[e] Catalyst (5 mol%) was added after 30 min.



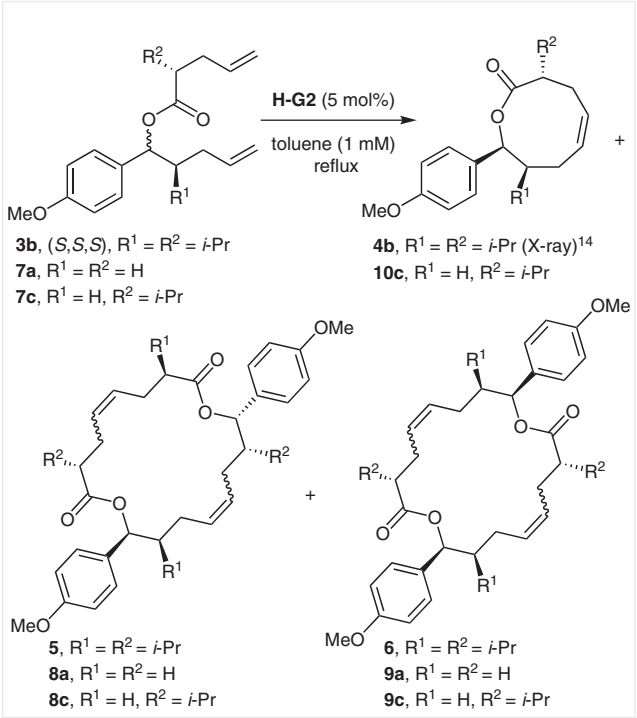
Scheme 3 Formation of dilactones and products from cleavage reactions (Table 1)

unsubstituted ester **7a**, since no monolactone was observed. The monosubstituted ester **7c** afforded 42% of the corresponding lactone **10c** and 37% yield of dilactones (entry 2). This was an improvement compared to the traces observed in 10 mM solution (Table 1, entries 10–12).

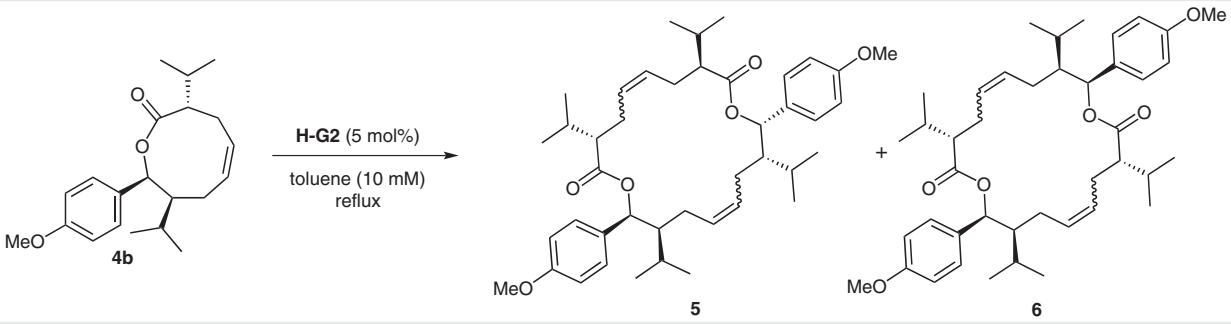
Table 2 Ring-Closing Metathesis of Diastereomeric Esters at 1 mM (Scheme 4)

Entry	Ester	Ratio	Time	Yield (%)	
				Monomer	Dimers
1	**7a** (*R*/*S*)	*rac*	overnight	–	81
2	**7c** (*R*/*S*)	*rac*	overnight	42	37
3	**3b** (*S*)	20:1	overnight	46	32
4	**3b** (*S*)	20:1	7 h	53	24

The somewhat diminished yield of nine-membered (*S*,*S*,*S*)-lactone **4b** when the reaction was run overnight as a 1 mM solution, led us to question whether once formed, it could undergo cycloreversion via alkylidene–ruthenium intermediates to the dilactones **5** and **6**. Indeed, submitting lactone **4b** to the reaction conditions at the original concentration of 10 mM in presence of **H-G2** catalyst yielded the corresponding dilactones **5** and **6** (Scheme 5). When a 1:1 mixture of (*S*,*S*,*S*)-lactones **4b** and **10c** was subjected to the ring-closing metathesis with the **H-G2** catalyst in 10 mM



Scheme 4 Ring-closing metathesis of diastereomeric esters at 1 mM (Table 2)

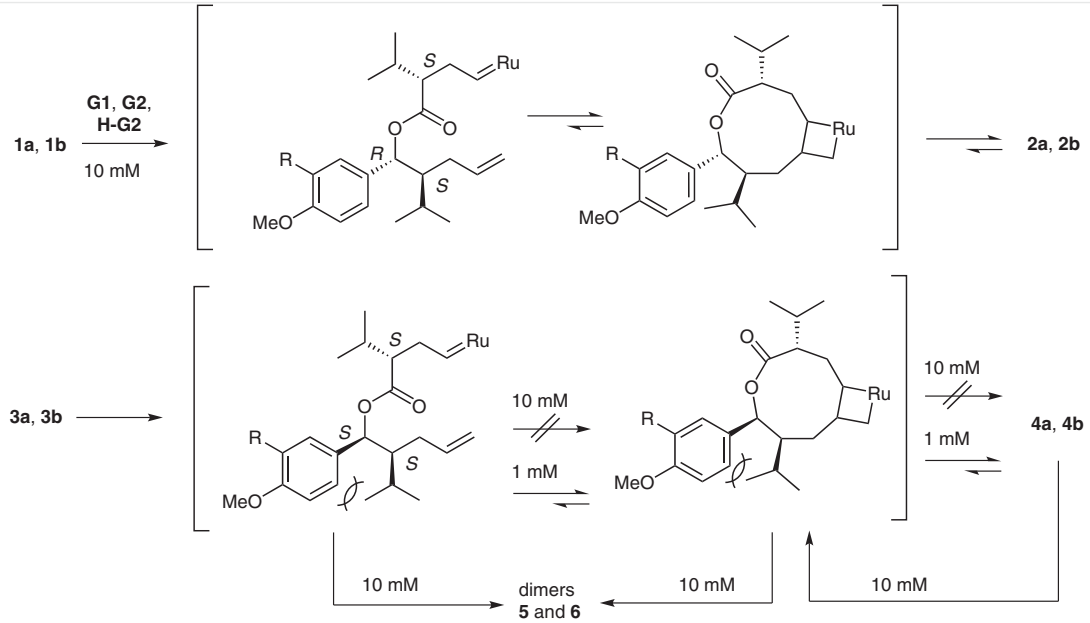


Scheme 5 Cycloreversion via ring-opening metathesis and cross-coupling reactions

solution, a mixture of all possible dilactones, including cross-over products was obtained, indicating that cycloreversion was possible in each case.

The existence of multiple coordination sites within each series of esters presents a major challenge with regard to the identity of the actual reactive intermediates and a preferred pathway. The outcome of ring-closing metathesis reactions leading to medium-sized rings is difficult to predict due to many intervening factors. For example, the nature of the catalyst, the solvent, the molarity, combined with conformational pre-organization, steric factors, as well as substituent and polar effects can have dramatic influences on the nature of the products (and byproducts) in a given reaction.[17] Nevertheless, it is clear that the ratio of nine-membered lactone formation compared to dilactones depends on the relative stereochemistry of the C7 isopropyl group and the adjacent C8 aryl moiety, and the concentration in the case of **1b** and **3b** (Scheme 3, Table 1, entries 14 and 19). This is evident from the results of reactions comprising the diastereomeric ester pairs (*S*,*R*,*S*)-**1b** and (*S*,*S*,*S*)-**3b**, and (*S*,*R*)-**7b** and (*S*,*S*)-**7b** (Scheme 3, Table 1, entries 13 and 18).

From our qualitative observations, it appears that the (*S*,*R*,*S*)-ester **1b** offers a less encumbered path to the ruthenium metallocycle, and eventually to the observed lactone **2b** (Scheme 6). A combination of stereochemical, conformational, and possibly stereoelectronic effects associated with a transoid ester configuration combine to favor the cyclization to give **2a** and **2b** as thermodynamically favored products. Reports concerned with the formation of nine-membered lactones using ring-closing metathesis are scarce. For example, cyclization of functionalized esters harboring terminal olefinic appendages, led to nine-membered unsaturated lactones with *cis*- and *trans*-geometries depending on the substituents.[18] However, no dimeric dilactones were reported or discussed in this study. The key steps in the total synthesis of the nine-membered unsaturated marine me-



Scheme 6 Ring-closing metathesis in 10 mM and 1 mM solutions; only one of the two possible alkylidene–ruthenium intermediates is shown

tabolite helicolactone, involved a ring-closing metathesis step achieved in the presence of **G1** catalyst in excellent yields.[4] The effect of substituents in the cyclization of larger rings has been reported.[18,19]

It can be presumed that the (*S*,*S*,*S*)-esters **3a** and **3b** experience substantial steric clash between the C7 isopropyl and the C8 aryl moiety so as to interfere with the proper alignment of the alkylidene–ruthenium intermediates en route to the ruthenium metallocycles. Thus, competitive intermolecular cross-coupling reactions predominate to give the corresponding dilactones irreversibly (Scheme 6). At lower molar concentration, the steric effect is overcome by the low rate of interactions of the alkylidene–ruthenium intermediates. This is reflected by the fact that the lactone **4b** may be kinetically formed at 10 mM concentrations, but rapidly undergoes cycloreversion to form the stable dilactones **5** and **6**. Although there appears to be a cooperative beneficial effect of having the two isopropyl groups present in addition to a stereochemical preference for the (*S*,*R*,*S*)-esters **1a** and **1b**, it is not clear why the monosubstituted or the unsubstituted substrates such as **7a** and **7c** have a preference for macrocyclic dilactone formation.

In earlier reports, Smith and co-workers[20] have discussed the potentially reversible nature of the metathesis reaction, while Fürstner and co-workers[21] exploited the reversibility of olefin metathesis in the formation of macrocyclic dilactones related to (–)-(*R*,*R*)-pyrenophorin.[22]

In conclusion, we have reported our observations regarding the effect of vicinal isopropyl and aryl substituents in diastereomeric esters with regard to their preference to give nine-membered unsaturated lactones. These have been recently utilized in the total synthesis of the antihypertensive drug aliskiren.[7]

Unfortunately, the involvement of multiple ruthenium-coordinated species and the dynamic nature of the ring-closing metathesis process do not allow a more detailed analysis beyond the qualitative observations reported in this paper. Further studies in this area are in progress.

All reactions were performed in oven-dried glassware under an argon atmosphere using anhydrous, deoxygenated solvents. CH_2Cl_2 and toluene were dried by passage through an activated alumina column under argon [Solvent Drying System (SDS)]. Reagents were purchased and used without further purification. Reactions were monitored by analytical TLC carried out on 0.25-mm silica plates that were visualized under a UV lamp (254 nm) and developed by staining with ceric ammonium molybdate, *p*-anisaldehyde, and/or potassium permanganate solution. Flash column chromatography was performed using silica (particle size 40–63 µm, 230–400 mesh) at increased pressure. NMR spectra (^1H, ^{13}C) were recorded at either 300, 400, or 500 MHz relative to TMS (δ = 0.00) with the solvent resonance as the internal standard ($CHCl_3$, δ = 7.26); ^{13}C NMR spectra are recorded using the central peak of $CDCl_3$ (δ = 77.16) as the internal standard. Optical rotations were determined with a polarimeter at 589 nm, using a 1-dm cell at r.t. and are reported in units of deg·cm^3·g^{-1}·dm^{-1}.

1-(4-Methoxyphenyl)pent-4-enyl Pent-4-enoate (7a); Typical Procedure

To a solution of the corresponding allylic acid (52 mg, 0.52 mmol, 1.0 equiv) in anhydrous toluene (4 mL) at 0 °C was added Et_3N (0.09 mL, 0.62 mmol, 1.2 equiv), 2,4,6-trichlorobenzoyl chloride (0.1 mL, 0.62 mmol, 1.2 equiv), and DMAP (76 mg, 0.62 mmol, 1.2 equiv). The resulting white slurry was stirred at 0 °C for 10 min. In a second dry round-bottomed flask a solution of corresponding benzylic alcohol (100 mg, 0.52 mmol, 1.0 equiv) in a minimum amount of anhydrous toluene was transferred to the reaction vessel containing the slurry in a dropwise manner at 0 °C then the reaction media was allowed to warm to r.t. The reaction was stirred at r.t. until TLC monitoring indicated no starting material remained. The solvent was removed and the resulting crude was taken up in EtOAc (10 mL) and H_2O (10 mL). The aqueous layer was separated and extracted with EtOAc (3 × 10 mL). The combined organic layers were successively washed with 10% aq citric acid (10 mL) and sat. aq $NaHCO_3$ (10 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated to afford a yellow oil. The residue was purified by flash chromatography (silica gel, 1.5 cm × 20 cm; CH_2Cl_2–hexanes, 3:7) to yield **7a** (134 mg, 94%) as a pale yellow oil; R_f = 0.55 (Et_2O–hexanes, 1:9).

IR (neat): 3077, 2979, 2935, 2837, 1735, 1641, 1613, 1515, 1253, 1169, 1035 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.28–7.23 (m, 2 H), 6.89–6.84 (m, 2 H), 5.85–5.69 (m, 3 H), 5.06–4.95 (m, 4 H), 3.80 (s, 3 H), 2.45–2.31 (m, 4 H), 2.11–1.96 (m, 3 H), 1.89–1.79 (m, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 172.5, 159.4, 137.6, 136.8, 132.8, 128.1, 115.6, 115.3, 114.0, 75.4, 55.4, 35.4, 34.0, 29.9, 29.0.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{22}NaO_3$: 297.1461; found: 297.1468.

(*S*)-2-Isopropyl-1-(4-methoxyphenyl)pent-4-enyl Pent-4-enoate (7b)

Following the typical procedure for **7a**; chromatography (silica gel, 2.5 cm × 20 cm; EtOAc–hexanes, 1:9) gave **7b** (236 mg, 75%) as a pale yellow oil; R_f = 0.57 (EtOAc–hexanes, 1:9); $[\alpha]_D^{20}$ +37 (*c* 0.5, $CDCl_3$).

IR (neat): 3077, 2958, 2874, 2837, 1736, 1640, 1612, 1514, 1464, 1369, 1250, 1171, 1036 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.24–7.20 (m, 2 H), 6.87–6.82 (m, 2 H), 5.84–5.73 (m, 1 H), 5.69–5.66 (m, 1 H), 5.57–5.46 (m, 1 H), 5.05–4.94 (m, 2 H), 4.85 (s, 1 H), 4.81 (dd, *J* = 6.5, 1.8 Hz, 1 H), 3.79 (s, 3 H), 2.44–2.31 (m, 4 H), 2.04–1.93 (m, 2 H), 1.90–1.79 (m, 2 H), 0.93 (m, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.2, 159.2, 138.1, 136.8, 132.4, 128.6, 128.2, 115.6, 115.6, 113.7, 55.4, 48.8, 34.0, 31.1, 29.0, 27.3, 21.2, 18.4.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{20}H_{28}NaO_3$: 339.1919; found: 339.1931.

1-(4-Methoxyphenyl)pent-4-enyl (*S*)-2-Isopropylpent-4-enoate (7c)

Following the typical procedure for **7a**; chromatography (silica gel, 2.5 cm × 20 cm; EtOAc–hexanes, 1:9) gave **7c** (771 mg, 94%) as a pale yellow oil; R_f = 0.57 (EtOAc–hexanes, 1:9).

IR (neat): 3077, 2960, 2926, 2875, 1735, 1640, 1613, 1514, 1465, 1248, 1167, 1107, 1035 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.28–7.23 (m, 2 H), 6.87–6.83 (m, 2 H), 5.83–5.56 (m, 3 H), 5.03–4.95 (m, 3 H), 4.90 (ddd, *J* = 11.9, 8.7, 1.7 Hz, 1 H), 3.80 (s, 3 H), 2.35–2.17 (m, 3 H), 2.10–1.96 (m, 3 H), 1.91–1.78 (m, 2 H), 0.94 (d, *J* = 6.8 Hz, 1.5 H), 0.87 (d, *J* = 6.7 Hz, 1.5 H), 0.87 (d, *J* = 6.8 Hz, 1.5 H), 0.80 (d, *J* = 6.7 Hz, 1.5 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 174.5, 174.5, 159.3, 137.7, 137.7, 136.1, 135.9, 132.9, 132.8, 128.3, 116.56, 116.47, 115.31, 115.28, 113.79, 75.17, 75.13, 55.38, 52.72, 52.63, 35.40, 35.37, 34.12, 33.99, 30.54, 30.31, 29.92, 20.50, 20.33, 20.23.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{20}H_{28}NaO_3$: 339.1918; found: 339.1935.

(8*S*,9*R*)-8-Isopropyl-9-(4-methoxyphenyl)-4,7,8,9-tetrahydro-oxonin-2(3*H*)-one (10b)

Hoveyda–Grubbs 2nd generation catalyst (5 mg, 0.008 mmol, 0.05 equiv) was added to a solution of **7b** (50 mg, 0.16 mmol, 1.0 equiv) in anhydrous toluene (16 mL) and the mixture was stirred at reflux for 20 min. The mixture was cooled to r.t. then excess of ethyl vinyl ether was added and gently evaporated. The residue was purified by flash chromatography (silica gel, 1.5 cm diameter × 20.0 cm height, EtOAc–hexanes, 1:50) to yield **10b** (17 mg, 38%) as a clear oil; R_f = 0.55 (EtOAc–hexanes, 1:9); $[\alpha]_D^{20}$ +37 (*c* 0.5, $CDCl_3$).

IR (neat): 2955, 2925, 2872, 1722, 1612, 1514, 1460, 1245, 1173, 1138, 1035 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.30 (m, 2 H), 6.91–6.85 (m, 2 H), 5.84 (d, *J* = 10.6 Hz, 1 H), 5.72–5.63 (m, 1 H), 5.63–5.54 (m, 1 H), 3.80 (s, 3 H), 2.48 (dd, *J* = 20.3, 10.7 Hz, 1 H), 2.40–2.27 (m, 2 H), 2.17–2.08 (m, 1 H), 2.07–1.89 (m, 3 H), 1.47 (dtd, *J* = 13.7, 6.9, 2.4 Hz, 1 H), 0.86 (d, *J* = 6.9 Hz, 3 H), 0.86 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.9, 159.6, 135.7, 132.1, 129.3, 125.5, 114.0, 79.8, 55.4, 52.6, 33.9, 27.8, 25.1, 24.8, 22.0, 16.3.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{24}NaO_3$: 311.3765; found: 311.2605.

(3*S*,9*R*)-3-Isopropyl-9-(4-methoxyphenyl)-4,7,8,9-tetrahydro-oxonin-2(3*H*)-one (10c)

Hoveyda–Grubbs 2nd generation catalyst (3 mg, 0.005 mmol, 0.05 equiv) was added to a solution of **7c** (30 mg, 0.095 mmol, 1.0 equiv) in anhydrous toluene (95 mL) and the mixture was stirred at reflux overnight. The mixture was cooled to r.t. then excess of ethyl vinyl ether was added and gently evaporated. The residue was purified by flash chromatography (silica gel, 1.5 cm diameter × 20.0 cm height, EtOAc–hexanes, 1:50) to yield **10c** (12 mg, 42%) as a clear oil; R_f = 0.55 (EtOAc–hexanes, 1:9); $[\alpha]_D^{20}$ –32 (*c* 0.5, $CDCl_3$).

IR (neat): 2954, 2928, 2865, 1702, 1513, 1459, 1247, 1173, 1159, 1037 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.27–7.24 (m, 2 H), 6.90–6.85 (m, 2 H), 5.84–5.73 (m, 1 H), 5.71–5.61 (m, 1 H), 5.61–5.51 (m, 1 H), 3.80 (s, 3 H), 2.62–2.50 (m, 2 H), 2.33–2.24 (m, 1 H), 2.21–2.09 (m, 2 H), 2.06–1.92 (m, 3 H), 0.99 (d, *J* = 6.6 Hz, 3 H), 0.95 (d, *J* = 6.6 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 177.1, 164.8, 159.3, 137.5, 135.9, 135.1, 133.1, 131.0, 128.6, 127.9, 126.0, 114.0, 55.4, 51.5, 36.9, 29.9, 28.4, 23.8, 21.5, 19.8.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{24}NaO_3$: 311.3766; found: 311.3772.

1,8-Bis(4-methoxyphenyl)octane (11a) and 8-(4-Methoxyphenyl)octanoic Acid (12a); Typical Procedure

Hoveyda–Grubbs 2nd generation catalyst (4 mg, 0.006 mmol, 0.05 equiv) was added to a solution of **7a** (30 mg, 0.11 mmol, 1.0 equiv) in anhydrous toluene (11 mL) and the mixture was stirred at reflux for 30 min. The mixture was cooled to r.t. then excess of ethyl vinyl ether was added and gently evaporated and the mixture was filtered through Celite to yield a crude mixture of dilactones **8a** and **9a**.

Pd/C (cat.) was added to a solution of dilactones **8a** and **9a** in MeOH (3 mL) and EtOAc (3 mL). The mixture was purged with H_2 and the mixture was stirred under a H_2 atmosphere (H_2 balloon). The reaction was monitored by LR-MS. When the reaction was complete, the mixture was filtered through Celite and concentrated to afford the crude dilactones.

TFA (3 drops) was added to a solution of the crude dilactones and Et_3SiH (0.1 mL) in CH_2Cl_2 (1 mL). The solution was stirred at r.t. for 10 min. Volatiles were removed under vacuum with a rotary evaporator and the residue was purified by flash chromatography [silica gel, 1.5 cm diameter × 20 cm height, hexanes (150 mL) then EtOAc–hexanes, 1:19] to yield alkane **11a** (6 mg, 31%) and acid **12a** (11 mg, 38%), both as clear oils.

Alkane 11a

R_f = 0.68 (EtOAc–hexanes, 1:4).

IR (neat): 2921, 2849, 1512, 1464, 1245, 1177, 1033 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.09 (d, *J* = 8.3 Hz, 4 H), 6.82 (d, *J* = 8.5 Hz, 4 H), 3.79 (s, 6 H), 2.59–2.48 (m, 4 H), 1.61–1.52 (m, 4 H), 1.36–1.28 (m, 8 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.7, 135.2, 129.4, 113.8, 55.4, 35.2, 31.9, 29.6, 29.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{31}O_2$: 327.2319; found: 327.2328.

Acid 12a

R_f = 0.17 (EtOAc–hexanes, 1:4).

IR (neat): 2923, 2853, 1709, 1512, 1465, 1245, 1177, 1054, 1033 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.12–7.05 (m, 2 H), 6.85–6.79 (m, 2 H), 3.79 (s, 3 H), 2.61–2.48 (m, 2 H), 2.34 (t, *J* = 7.5 Hz, 2 H), 1.71–1.51 (m, 4 H), 1.35–1.29 (m, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 179.9, 157.7, 135.0, 129.4, 113.8, 55.4, 35.1, 34.1, 31.8, 29.2, 29.1, 29.1, 24.8.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{22}NaO_3$: 273.1461; found: 273.1472.

(3*R*,8*R*)-3,8-Bis(4-methoxybenzyl)-2,9-dimethyldecane (11b) and (*R*)-7-(4-Methoxybenzyl)-8-methylnonanoic Acid (12b)

Following the typical procedure for **11a** and **12a** gave **11b** (7 mg, 36%) and **12b** (10 mg, 37%), both as clear oils.

Alkane 11b

R_f = 0.64 (EtOAc–hexanes, 1:9); $[\alpha]_D^{20}$ +21 (*c* 1.0, $CHCl_3$).

IR (neat): 2924, 2861, 1512, 1246, 1055, 1464, 1033 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.08–7.01 (m, 4 H), 6.84–6.78 (m, 4 H), 3.79 (s, 6 H), 2.49 (dd, *J* = 13.7, 6.8 Hz, 2 H), 2.35 (dd, *J* = 13.8, 7.6 Hz, 2 H), 1.67 (dtd, *J* = 13.7, 6.9, 3.5 Hz, 2 H), 1.44–1.33 (m, 2 H), 1.23–1.02 (m, 8 H), 0.86 (d, *J* = 13.9 Hz, 6 H), 0.83 (d, *J* = 13.9 Hz, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.6, 134.5, 130.1, 113.6, 55.4, 46.1, 36.3, 29.7, 28.4, 28.0, 19.3, 18.8.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{28}H_{43}O_2$: 411.3258; found: 411.3277.

Acid 12b

R_f = 0.12 (EtOAc–hexanes, 1:9); $[\alpha]_D^{20}$ +11 (*c* 1.0, $CHCl_3$).

IR (neat): 2938, 2866, 1709, 1512, 1455, 1346, 1321, 1059, 1016 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.05 (d, *J* = 8.6 Hz, 2 H), 6.84–6.78 (m, 2 H), 3.79 (s, 3 H), 2.53 (dt, *J* = 12.0, 5.6 Hz, 1 H), 2.38–2.34 (m, 1 H), 2.34–2.28 (m, 2 H), 1.74–1.65 (m, 1 H), 1.62–1.53 (m, 2 H), 1.46–1.38 (m, 1 H), 1.31–1.22 (m, 6 H), 1.14 (dd, *J* = 18.5, 11.4 Hz, 1 H), 0.89 (d, *J* = 6.9 Hz, 3 H), 0.84 (d, *J* = 6.9 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 179.2, 157.7, 134.4, 130.0, 113.7, 55.4, 46.1, 36.3, 34.0, 29.6, 29.5, 28.6, 27.4, 24.8, 19.3, 18.9.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{28}NaO_3$: 411.3258; found: 411.3277.

2-Isopropyl-8-(4-methoxybenzyl)octanoic Acid (12c)

Following the typical procedure for **11a** and **12a** gave **12c** (19 mg, 41%) as a clear oil; R_f = 0.11 (EtOAc–hexanes, 1:9); $[\alpha]_D^{20}$ –5 (*c* 1.0, $CHCl_3$).

IR (neat): 2926, 2854, 1700, 1511, 1464, 1298, 1176, 1116, 1037 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.13–7.06 (m, 2 H), 6.86–6.79 (m, 2 H), 3.79 (s, 3 H), 2.58–2.50 (m, 2 H), 2.17–2.07 (m, 1 H), 1.88 (dq, *J* = 13.7, 6.7 Hz, 1 H), 1.67–1.45 (m, 4 H), 1.44–1.19 (m, 7 H), 0.97 (d, *J* = 6.7 Hz, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 182.4, 157.7, 135.0, 129.4, 113.8, 55.4, 52.7, 35.1, 31.8, 30.6, 29.6, 29.4, 29.2, 27.9, 20.6, 20.2.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{28}NaO_3$: 411.3258; found: 411.3113.

2-Isopropyl-7-(4-methoxybenzyl)-8-methylnonanoic Acid (12d)

Following the typical procedure for **11a** and **12a** gave **12d** (11 mg, 40%). R_f = 0.12 (EtOAc–hexanes, 1:9) as a clear oil; $[\alpha]_D^{20}$ +16 (*c* 0.3, $CDCl_3$).

IR (neat): 2925, 2860, 1704, 1511, 1461, 1375, 1245, 1178, 1038 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.59 (s, 1 H), 7.05 (d, *J* = 8.4 Hz, 2 H), 6.81 (d, *J* = 8.5 Hz, 2 H), 3.78 (s, 3 H), 2.51 (dd, *J* = 13.7, 6.6 Hz, 1 H), 2.36 (dd, *J* = 13.7, 7.8 Hz, 1 H), 2.13–2.05 (m, 1 H), 1.85 (dq, *J* = 13.7, 6.9 Hz, 1 H), 1.74–1.63 (m, 1 H), 1.60–1.49 (m, 1 H), 1.48–1.36 (m, 2 H), 1.29–1.14 (m, 6 H), 0.96–0.92 (m, 6 H), 0.88 (d, *J* = 6.8 Hz, 3 H), 0.84 (d, *J* = 6.9 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 181.5, 157.7, 134.4, 130.1, 113.7, 55.4, 52.6, 46.1, 36.3, 30.6, 29.5, 29.4, 28.6, 28.2, 27.7, 20.6, 20.2, 19.3, 18.8.

HRMS (ESI–): *m*/*z* [M – H]$^-$ calcd for $C_{21}H_{33}O_3$: 333.2435; found: 333.2440.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1380130.

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Conception and Evolution of Stereocontrolled Strategies toward Functionalized 8-Aryloctanoic Acids Related to the Total Synthesis of Aliskiren

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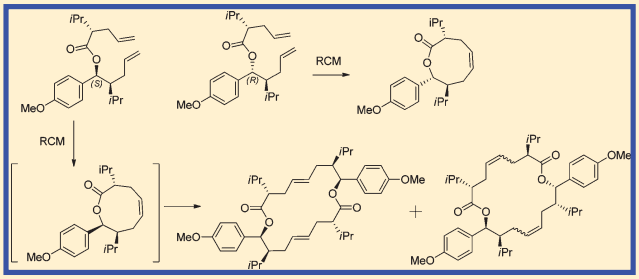
Supporting Information

ABSTRACT: A detailed account is given describing the approaches used toward the total synthesis of aliskiren. In particular, ring-closing metathesis with the Hoveyda−Grubbs catalyst accelerates the formation of a 9-membered lactone from an (*R*)-ester. The diastereomeric (*S*)-ester leads to the formation of dimeric dilactones, which were characterized by X-ray analysis and chemical conversions.



INTRODUCTION

The regulation of arterial blood pressure is a complex physiological process with important implications in the pathogenesis of cardiovascular diseases.[1] Among these, hypertension is considered to be a high risk factor and associated with incidences of stroke and kidney failure. A natural substance produced by the kidney, named renin, was known to have a hypertensive effect in experimental animals as far back as 1898.[2] Since then, pioneering efforts in cardiovascular medicine have advanced the frontiers of antihypertensive research, culminating with the availability of drugs to control the disease.[3] The aspartyl protease renin is part of the renin angiotensin system (RAS), known to be a regulator of blood pressure and electrolyte balance.[4] Stimulation of the RAS leads to the release of renin from the kidney, whereupon a series of proteolytic events take place ultimately forming vasoconstricting peptides.[5] Thus, renin cleaves a Leu-Val peptide linkage in its endogenous substrate angiotensinogen, releasing the decapeptide angiotensin I (Figure 1A). A second enzyme in the RAS, angiotensin-converting enzyme (ACE), then cleaves two amino acids from angiotensin I to give the vasoconstricting octapeptide angiotensin II. On the basis of these observations, the inhibition of renin as the first and rate-limiting step in the RAS cycle was considered to be a viable and attractive strategy in the quest toward discovery of novel antihypertensives working by a unique mechanism.[6] Indeed, major advances toward this goal have been made during the past three decades.[7] Unfortunately, and in spite of achieving highly effective in vivo inhibition of renin with beneficial antihypertensive action, such activities had to be terminated in a number of pharmaceutical companies primarily due to issues dealing with cost of production and bioavailability. Nevertheless, the synthesis of minimally peptidic potent inhibitors, such as CGP-38960 (Figure 1B), was admirably guided by structure-based design relying on valuable information gleaned from cocrystal structures

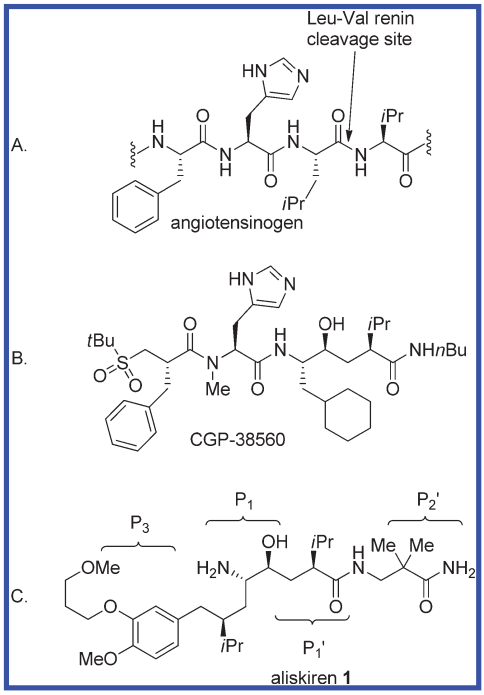


Figure 1. (A) Scissile Leu-Val bond in angiotensinogen by the enzyme renin. (B) First-generation peptidic inhibitor. (C) Structure of aliskiren.

with human recombinant renin.[8] Although active investigations toward the synthesis of new renin inhibitors had somewhat waned, a new class of nonpeptidic 8-aryloctanoic acid amides was

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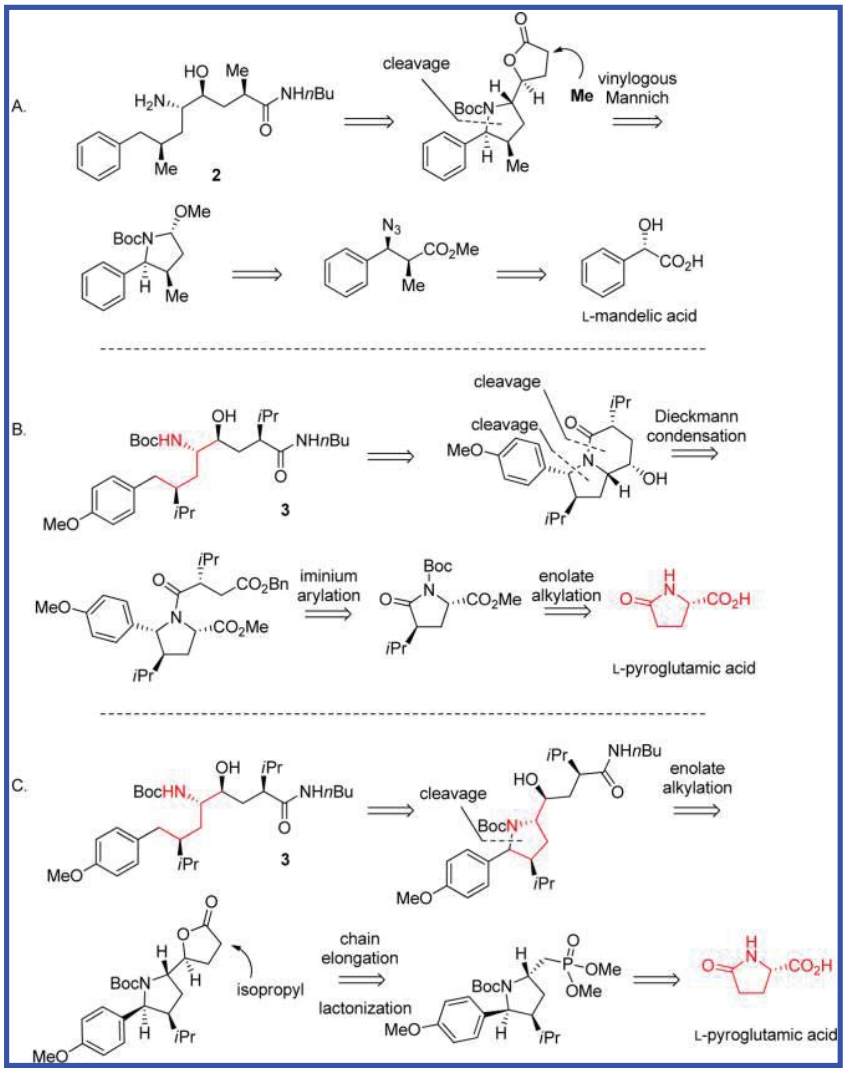

Figure 2. Early prototypes of renin inhibitors: (A) L-mandelic acid as starting chiron; (B and C) L-pyroglutamic acid as starting chiron and source of nitrogen (Dieckmann and phosphate extension routes).

found to have highly promising activity.[9] Further refinement in this series by scientists at Ciba-Geigy (Pharma) in Basel led to aliskiren (**1**), which is presently marketed by Novartis for the treatment of hypertension under the trade name Tekturna (Figure 1C).[10] The cocrystal structure analysis of aliskiren in complex with renin revealed the characteristic interactions of the hydroxyethylene segment with aspartic acid residue and unique binding interactions of the hydrophobic moieties.[11] Of particular significance in optimizing the inhibitory activity was the truncation of segments corresponding to the P_2 and P_4 site in the original inhibitors such as CGP-38560 by directly linking P_1 and P_3 (Figure 1). Compared to the previous generation of renin inhibitors, often possessing heterocyclic appendages near the hydroxyethylene subunit,[10] aliskiren represents a structurally simple ω-aryloctanoic acid amide harboring four stereogenic carbon atoms (Figure 1). Further SAR studies also demonstrated an improvement of the affinity at the P_2' site when the *n*-butylamide was exchanged for a 3-amino-2,2-dimethylpropionamide unit.[12] Already, considerable interest has been generated in the clinical aspects of aliskiren, a first-in-class, orally active antihypertensive.[13]

BACKGROUND

Among the many research collaborations with pharmaceutical companies, none are more challenging than when an academic is asked to contribute to an active project with the prospects of developing a viable synthesis of a molecule of interest.[14] Encouraged by such an opportunity, we first explored a stereocontrolled approach to a bioactive prototype of aliskiren, starting with L-mandelic acid (Figure 2A).[15] In the following years, we were motivated to devise strategies avoiding the use of azide as a source of the C-5 nitrogen atom (aliskiren numbering) for safety considerations in an eventual scale-up operation. Further consideration to our mandate was to avoid the use of chiral auxiliaries to create stereogenic carbon atoms with required substituents for cost and possibly IP reasons. Faced with these restrictions, we devised two stereocontrolled approaches to 2,7-dialkyl-4-hydroxy-5-amino-8-aryloctanoic acids exemplified by **3**, starting with the readily available L-pyroglutamic acid as a chiron[16] (Figure 2B and 2C). In addition to providing the source of the nitrogen atom, the inherent stereochemistry in the starting chiron served to control the sequential stereocontrolled introduction of appropriate functionality.

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Since our initial efforts toward the stereocontrolled synthesis of aliskiren,[15,16] there has been a plethora of reports particularly in the patent literature[17] describing a variety of approaches to intermediates and analogues. In a brief overview, we shall distinguish those involving approaches[18] or formal syntheses[19] from those pertaining to actual total syntheses[20] of aliskiren.[21] In the majority of these syntheses, extensive use was made of the Evans[22] and Schöllkopf[23] chiral auxiliaries to secure the C-2/C-7 isopropyl and C-4/C-5 amino alcohol groups, respectively, in high enantio- or diastereoselectivity. Alternative approaches are described in several patents.[17,24] For example, the key building blocks used in the Speedel process[25] for the synthesis of aliskiren are shown in Figure 3. Intermediate **A** was obtained by an

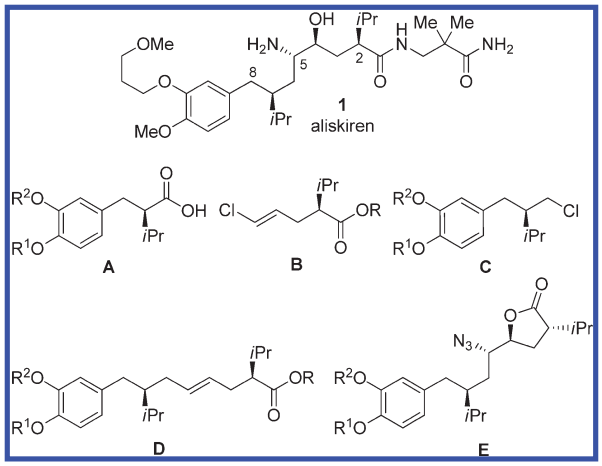


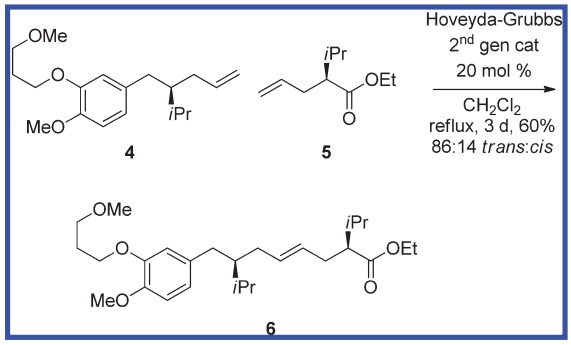
Figure 3. Key building blocks in the Speedel process toward aliskiren.

asymmetric catalytic hydrogenation of an α,β-unsaturated precursor in >95% ee starting from a racemic dialkoxyphenyl propionate precursor (total of seven steps). The enantiopure chlorovinyl intermediate **B** was prepared from the racemic ester via pig liver esterase resolution in 47% yield, after distillation. The undesired enantiomeric carboxylic acid was recycled by epimerization, esterification, and repeated enzyme treatment (total three steps to **B** from methyl isobutyrate in one pass). Intermediate **C** was prepared from acid **A** in three steps. Coupling of **C** and **B** was accomplished via the corresponding Grignard reagent derived from **B** in the presence of Fe^{III} acetylacetonate to give **D** in 75% yield. Subsequent steps involving hydrolysis to the acid, bromolactonization, epoxide formation, lactonization, mesylation, and azide displacement gave the azidolactone precursor **E**. Condensation with 3-amino-2,2-dimethylpropionamide, followed by hydrogenation and crystallization, gave aliskiren fumarate (total of 10 steps from **D**). Improvements in the bromolactonization step have also been reported.[24]

In the past, chiral auxiliaries were used to access intermediates such as **C** and **D** (Figure 3).[18−20,22] In spite of this invaluable method, all of the reported syntheses comprise numerous steps to access the building blocks individually and prior to engaging them in a stepwise assembly. Furthermore, except for some of the patented processes, none of the published papers provide experimental details leading to aliskiren.

Recently, we reported on an efficient synthesis of intermediate **4** adopting an extension of the Stoltz[26] catalytic asymmetric transposition of an allylic enolcarbonate derived from the corresponding aryl ketone precursor followed by reduction at the

Scheme 1. Shorter Route to an Advanced Intermediate in the Speedel Process



benzylic carbon (Scheme 1).[27] A cross-metathesis reaction with ester **5** led to the advanced Speedel intermediate **6** in five linear steps and 38% overall yield from 4-methoxy-3-(methoxypropoxy)-1-bromobenzene.

Nine-Membered Lactone Route toward Aliskiren. As is clear from the preceding section, a major challenge in devising synthetic approaches to aliskiren is the introduction of the C-2/C-7 isopropyl groups and the C-4/C-5 amino alcohol subunit in the 8-aryloctanoic acid framework with high stereocontrol (Figure 1C). Added to this is the desire to devise a relatively shorter route compared to existing reports, including those in the patent literature. We recently reported an 11-step total synthesis of aliskiren starting with a single chiral progenitor (Figure 4).[28]

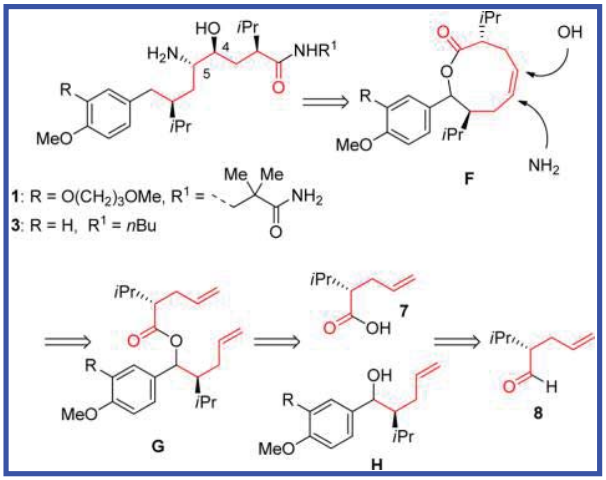


Figure 4. Nine-membered lactone route to aliskiren from a common chiron.

Thus, (2*S*)-2-isopropyl-4-pentenal **8**, easily prepared from the acid **7**,[28] was converted to a 6:1 mixture of diastereomeric benzylic alcohols **H**, which was used to assemble the ester **G**. Ring-closing metathesis in the presence of the Grubbs I catalyst[29,30] gave the 9-membered lactone **F** (Figure 4). Regio- and stereoselective introduction of an amino and an alcohol group provided the entirely functionalized 8-aryloctanoic acid framework of aliskiren and of selected amide variants. In this paper, we elaborate on various aspects of this synthesis, particularly with regard to the preparation and functionalization of the 9-membered lactones using a ring-closing metathesis en route toward aliskiren.

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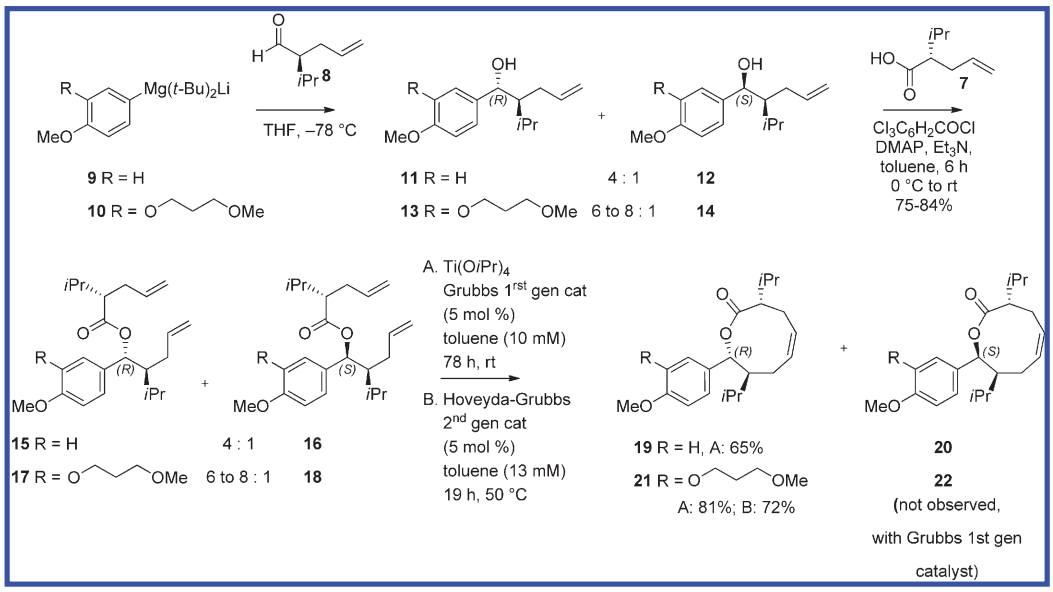
Scheme 2. Synthesis of the 9-Membered Lactones



RESULTS AND DISCUSSION

Synthesis of the 9-Membered Lactone. Initially, we focused on the 4-methoxy analogue (**3**, Figure 4) in order to explore aspects of stereoselectivity and conditions for the ring-closing metathesis. As will become evident, it was important to attempt the ring-closing metathesis reaction with a higher proportion of the (*R*)-ester derived from alcohol diastereomer **11** (Scheme 2).[31]

Attempts to add various organometallic derivatives of **9** (X = Br; M = Mg-*n*-Bu; TMEDA; Mg-*n*-Bu inverse addition; Mg-*n*-Bu, $CeCl_3$; Li, $CeCl_3$; Et_2ZnLi; $Mg(n\text{-}Bu)_2Li$) to the aldehyde **8** resulted in modest to low yields and unsatisfactory ratios. After extensive trials, the best ratio of inseparable diastereomers **11** and **12** favoring the (*R*)-lactone was obtained with a mixed Mg/Li Grignard reagent described by Inoue[32] in 68% yield. Application of the same protocol to the aliskiren aryl moiety **10** led to a better ratio of **13** and **14** (5−8:1) of diastereomers. Esterification by the Yamaguchi method[33] afforded the diastereomeric mixture of esters **15**:**16** and **17**:**18**, maintaining the same ratios, respectively. In our original report, we had utilized the Grubbs first-generation catalyst due to its availability at time. A 5 mol % loading in a 10 mM solution of the esters **15**:**16** or **17**:**18** in toluene led, after 78 h at room temperature, to the intended lactones **19** and **21**, in 65% and 81% yield, respectively. In this process, the mixture of esters was first stirred with $Ti(O\text{-}i\text{-}Pr)_4$ for 24 h before adding the catalyst. Then, to ensure complete conversion of the (*R*)-esters **15** and **17**, an additional 5−10 mol % of the first generation Grubbs catalyst was added every 24 h. In the absence of $Ti(O\text{-}i\text{-}Pr)_4$, the low yield of the cyclization was attributed to the coordination of the Ru catalyst to the proximal ester carbonyl group.[34] The results of the cyclization of different batches of diastereomeric esters under different conditions and catalysts are shown in Table 1. Starting with an ester mixture enriched in the (*R*)-isomer, we obtained the (*R*)-lactone in 71% yield in the presence of the first-generation Grubbs catalyst (**G1**) at room temperature (Table 1, entry 9). Using a 4:1 mixture of esters **15** and **16** in the presence of the second-generation Hoveyda−Grubbs catalyst (**H−G2**)[35] at reflux resulted in the formation of **19** within 20 min in 64% yield (Table 1, entry 8). Ultimately, utilizing the second-generation Hoveyda−Grubbs catalyst and a 6:1 mixture of **17** and **18**, the cyclization was completed within 19 h at 50 °C to give **21** in 72% yield (Table 1, entry 13). We were at first intrigued by the observation that only the (*R*)-esters **15** and **17** were transformed to the corresponding lactones **19** and **21**, respectively. At the time of execution, reports of the formation of 9-membered functionalized lactones by ring-closing metathesis were sparse.[36,37]

Functionalization of the 9-Membered Lactone. Our next task was to explore methods for the regio- and stereoselective introduction of an amino alcohol unit on the double bond of lactones **19** and **21**. We surmised that in the presence of NBS, CuI, and $TsNH_2$[38] a bromonium ion (**27**) would be attacked to give the corresponding vicinally substituted 9-membered lactone **23** (arbitrary regio- and stereochemistry, Scheme 3). Instead, the products formed with a good conversion were found to be the bromolactones **24** and **25** in a ratio of 3.9:1 arising from an intramolecular attack of the carboxylate released by concomitant formation of quinonoid intermediates followed by an *anti* attack of $TsNH_2$ relative to the bulky isopropyl group. The structures of **24** and **25** were assigned by detailed NMR studies. The bromolactone structure (**25**) was also confirmed by X-ray crystallography. Reductive cleavage of the benzylic sulfonamide group in the mixture of **24** and **25** with Et_3SiH and trifluoroacetic acid gave the bromolactone **26** in a good overall yield from **19**.

Next, we converted the 9-membered lactone **19** into the corresponding epoxide **28** (Scheme 4). The major product with the designated stereochemistry as shown was formed in excellent yield at 0 °C or room temperature. Surprisingly, treatment with NaN_3-NH_4Cl in methoxyethanol or Bu_4NN_3 in refluxing toluene gave back starting epoxide. Upon treatment with Et_3SiH and trifluoroacetic acid, it was expected that the benzylic carbon oxygen bond would be cleaved. Instead, a mixture of the three products **29**, **30**, and **31** (6:1:1 ratio) was obtained whose structures are proposed on the basis of detailed NOE studies.[31] A plausible mechanism is shown in Scheme 4.

Dihydroxylation of **19** under standard conditions led to the dihydroxy lactone **32** and the dibenzoate **33** after benzoylation,[28] whose structures and stereochemistry was confirmed by X-ray analysis,[31] validating a trajectory of approach that would be opposed

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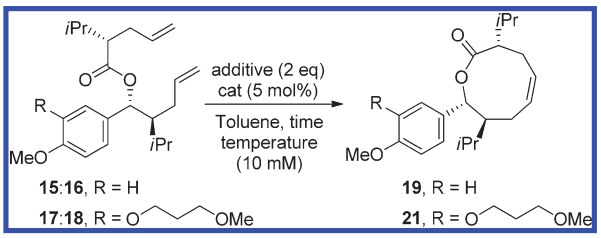
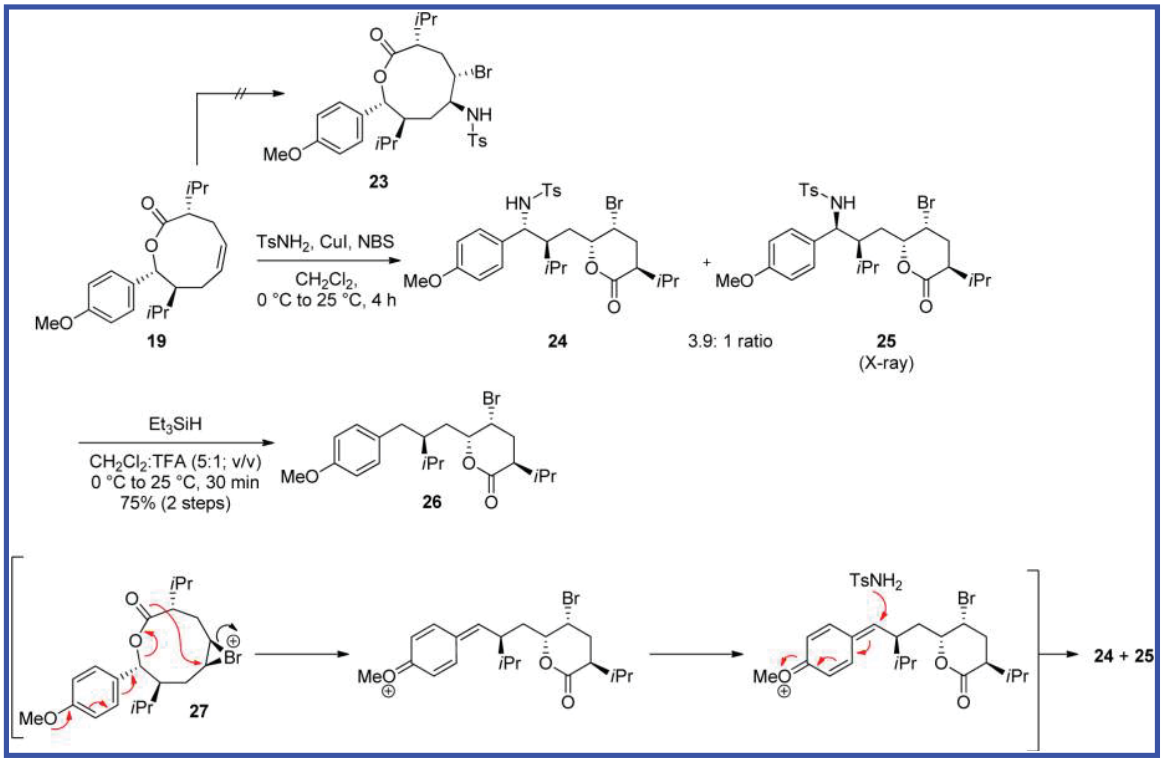
Table 1. Formation of the 9-Membered Lactones 19 and 21



entry	ester dr	R	cat.	add.	time	temp (°C)	yield[a] (%)
1	3:1	H	**G2**		1 d	rt	0
2	3:1	H	**G2**	$Ti(O\text{-}i\text{-}Pr)_4$	2 d	rt	43
3	3:1	H	**G1**	$Ti(O\text{-}i\text{-}Pr)_4$	2 d	rt	57
4	3:1	H	**G1**	$Ti(O\text{-}i\text{-}Pr)_4$	3 d	rt	58
5	2:1	H	**G1**	$Ti(O\text{-}i\text{-}Pr)_4$	3 d	rt	49
6	4:1	H	**G1**	$Ti(O\text{-}i\text{-}Pr)_4$	3 d	rt	65
7	4:1	H	**G2**		40 min	reflux	67
8	4:1	H	**H−G2**		20 min	reflux	64
9	7:1	H	**G1**	$Ti(O\text{-}i\text{-}Pr)_4$	3 d	rt	71
10	2:1	H	**H−G2**		20 h[b]	reflux	44
11	8:1	$O(CH_2)_3OCH_3$	**G1**	$Ti(O\text{-}i\text{-}Pr)_4$	3 d	rt	65
12	8:1	$O(CH_2)_3OCH_3$	**G1**	$Ti(O\text{-}i\text{-}Pr)_4$	3−4 d	rt	81[c]
13	5:1	$O(CH_2)_3OCH_3$	**H−G2**		16 h	50	72

[a]Isolated yield. [b]Conversion was completed within 20 h. [c]An extra 5 mol % of the catalyst was added if no further progress was noticed by TLC. **G1**, **G2**, and **H−G2** refer to Grubbs first generation, Grubbs second generation, and Hoveyda−Grubbs 2nd generation catalyst.

Scheme 3. Attempted Bromoamination of the Macrocyclic Lactone 19



to the orientation of the resident C-8 4-methoxyphenyl group (Scheme 5).[28] Although this stereochemical outcome could not be predicted a priori in a quasi C_2-symmetrical 9-membered lactone with respect to the orientation of the isopropyl groups at C-2 and C-7 such as in **19**, it became clear that C-8 aryl group may have exerted a steric influence in the dihydroxylation step.

Encouraged by this result, we attempted a Du Bois aziridination reaction,[39] expecting to obtain the aziridine with the "up" orientation. We would then attempt a solvolysis with an appropriate carboxylic acid, hoping for a regioselective opening at the C-4 position, thereby generating the vicinal *trans*-amino alcohol (Scheme 6).

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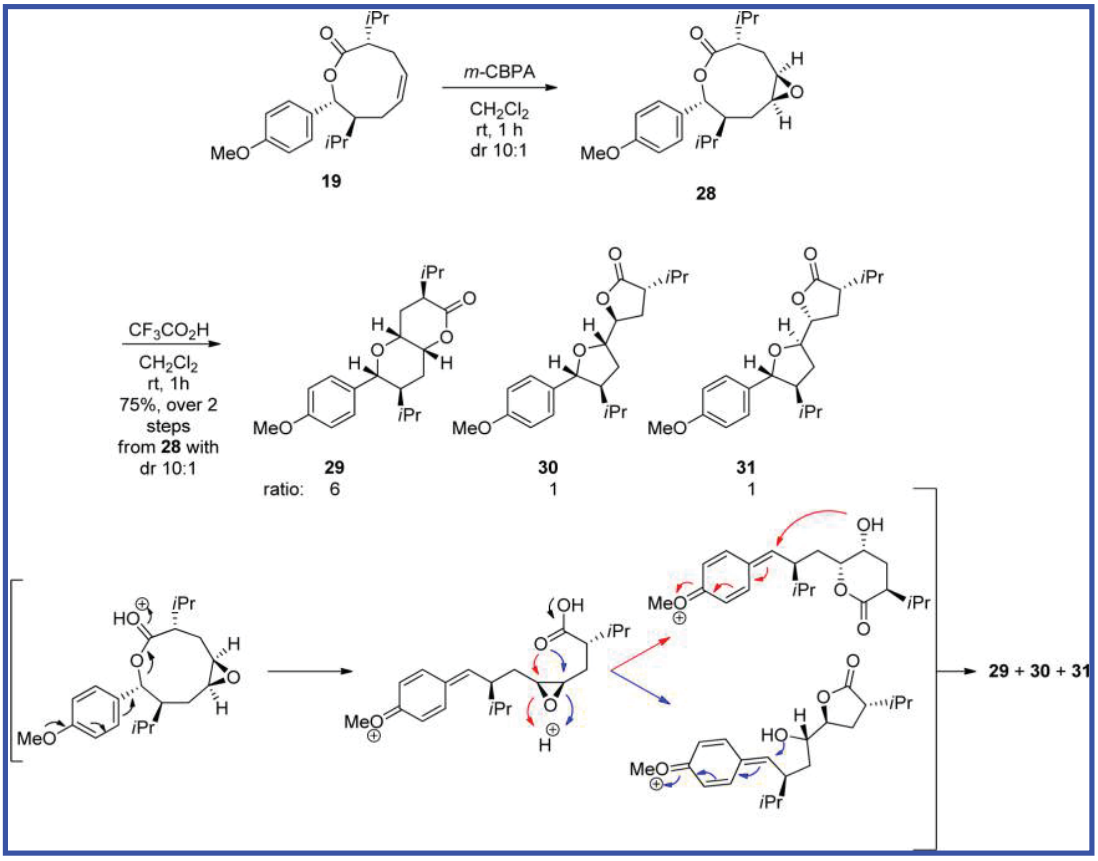
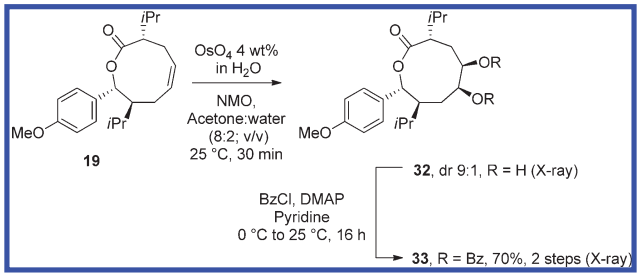
Scheme 4. Epoxidation of the Lactone 19 and Further Transformations



Scheme 5. Diastereoselective Dihydroxylation of Lactone 19[28]



In the event, treatment of **19** and **21** individually with trichloroethylsulfamate in the presence of $Rh_2(tfacam)_4$ and $PhI(OAc)_2$ according to Du Bois[39] led to the desired aziridines **34** and **35** in excellent yields (Scheme 6). Suspecting the need for a strong acid to activate the *N*-(trichloroethyl)sulfamoyl group in the solvolysis, aziridines **34** and **35** were treated with a dilute solution of trifluoroacetic acid in CH_2Cl_2. Remarkably, in both cases, a double-ring contraction occurred to give the pyrrolidine lactones **36** and **37**, respectively, in excellent yields (Scheme 6).[28] It should be noted that this simple solvolytic reaction produced the desired (4*S*,5*S*) amino alcohol with exquisite regio- and stereocontrol. Confirmation of the structure and stereochemistry of **36** (hence **37**) was obtained from the X-ray crystal structure of the amide **38**. Treatment of **36** with $AlMe_3$ and *n*-butylamine gave the amide **38** which was converted to the *N*-Boc analogue **40**, accompanied by the lactone **39**, the structure of which was ascertained by X-ray crystallography.[31] Alternatively, alkaline hydrolysis of the sulfamate group in **37** followed by acidification and *N*-protection led to the known *N*-Boc lactone **41** (Scheme 6).[16b,40]

Completion of the Total Synthesis of Aliskiren. To test the compatibility of the sulfamate group under amide forming conditions from the lactone **37**, we were pleased that treatment with *n*-butylamine in the presence of $AlMe_3$ gave an excellent yield of the *n*-butylamine derivative **42** (Scheme 7). However, the same conditions to form an amide failed with the sterically demanding neopentylic 3-amino-2,2-dimethylpropionamide (ADPA). The utility of 2-hydroxypyridine as an activator in amide formation is well documented.[41] In fact, this method is claimed to work in high yield in a number of patents describing aliskiren.[25,42] In our hands, the methods described for the *N*-Boc derivative corresponding to the lactone **37** resulted in low yields. Prolonged heating of **37** with ADPA in neat Et_3N at 85 °C led to a 61% yield of the desired amide **43**, with recovery of starting lactone. We then decided to convert the *N*-sulfamoyl group in **43** into an *N*-Boc group to give **44** in good overall yield. There remained to cleave the benzylic amine bond and the *N*-Boc group to complete the total synthesis of aliskiren. Thus, treatment of **44** with Na in liquid ammonia in the presence of *t*-BuOH followed by acid cleavage of the *N*-Boc group gave aliskiren (**1**). Overall, our linear synthesis comprised 11 steps and a 7% unoptimized yield starting from aldehyde **8**.[28] After completion of this work, Foley and Jamieson described a conceptually innovative method for an acid-promoted aminolysis of lactones that has since been applied toward the synthesis of aliskiren.[43,44]

What about the (*S*)-Lactones 20 and 22? We previously commented on the exquisite selectivity of the Grubbs metathesis reaction with the first-generation catalyst. In fact, using an

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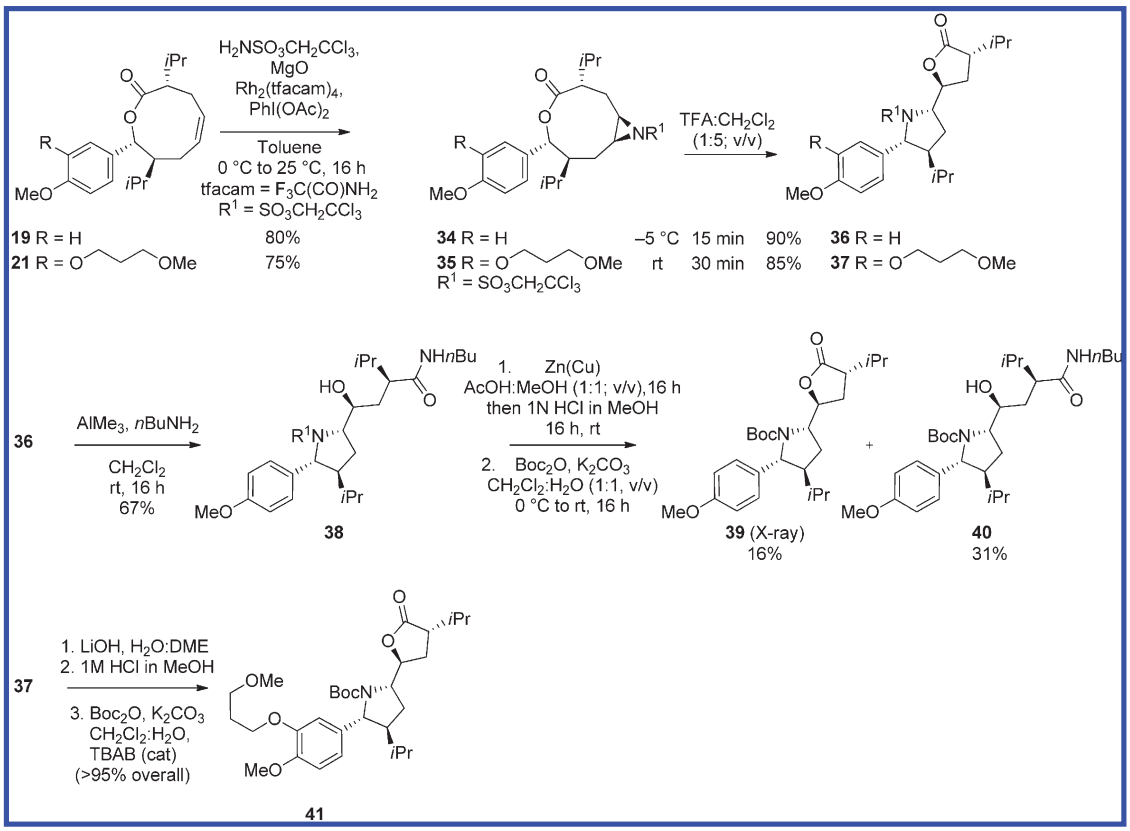
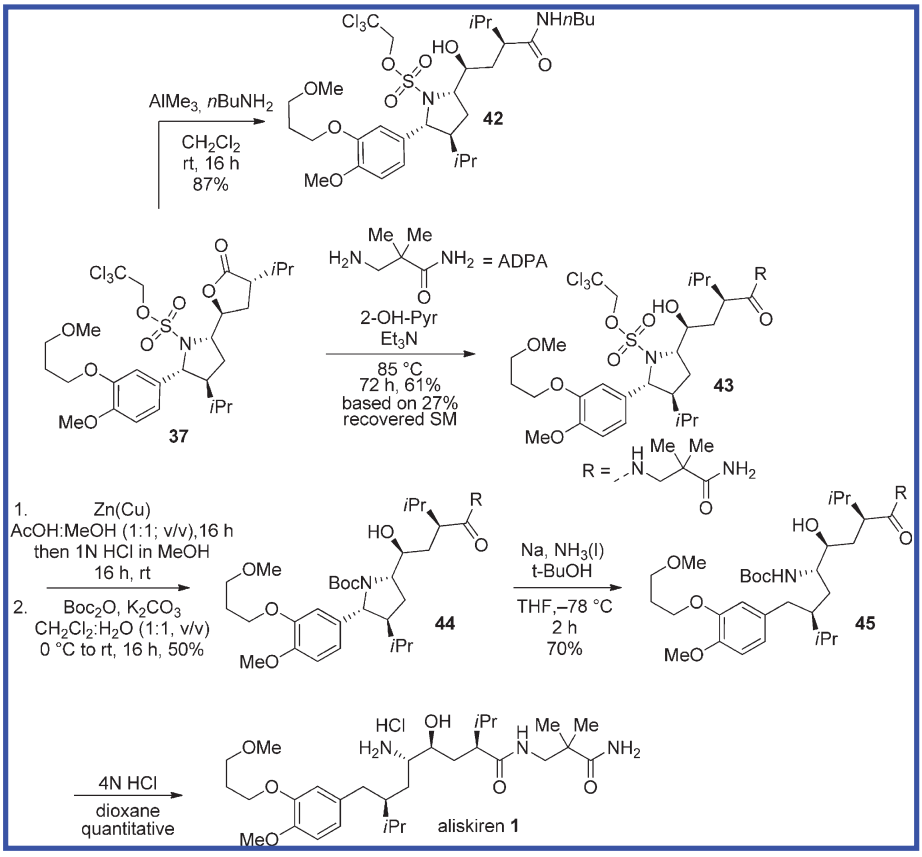
Scheme 6. Elaboration of 9-Membered Lactones via Aziridination and Ring Contraction



Scheme 7. Completion of the Synthesis of Aliskiren (1)



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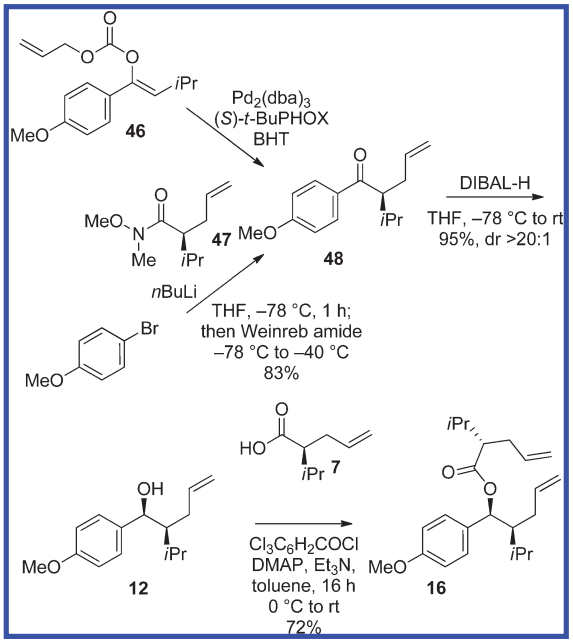
inseparable mixture of the diastereomeric esters **15** and **16** (as well as **17** and **18**) led to a single diastereomer in each case involving the cyclization of the (*R*)-esters to give the 9-membered lactones **19** and **21**, respectively (Scheme 2). The other diastereomeric esters **16** (and **18**) were recovered in poor yield and contaminated with some other metathesis side products. To further study the fate of the (*S*)-ester **16**, we prepared it in a stereoselective manner (Scheme 8). Thus, allylic transposition of allyl enolcarbonate **46** in the presence of $Pd_2(dba)_3$ catalyst, (*S*)-*t*-BuPHOX ligand,[26,45] and BHT as additive[27] led to the ketone **48** in good yield and acceptable enantiomeric excess (average of 90% yield and 88 to 91% ee).

Scheme 8. Catalytic Asymmetric Synthesis of (*S*)-Ester 16

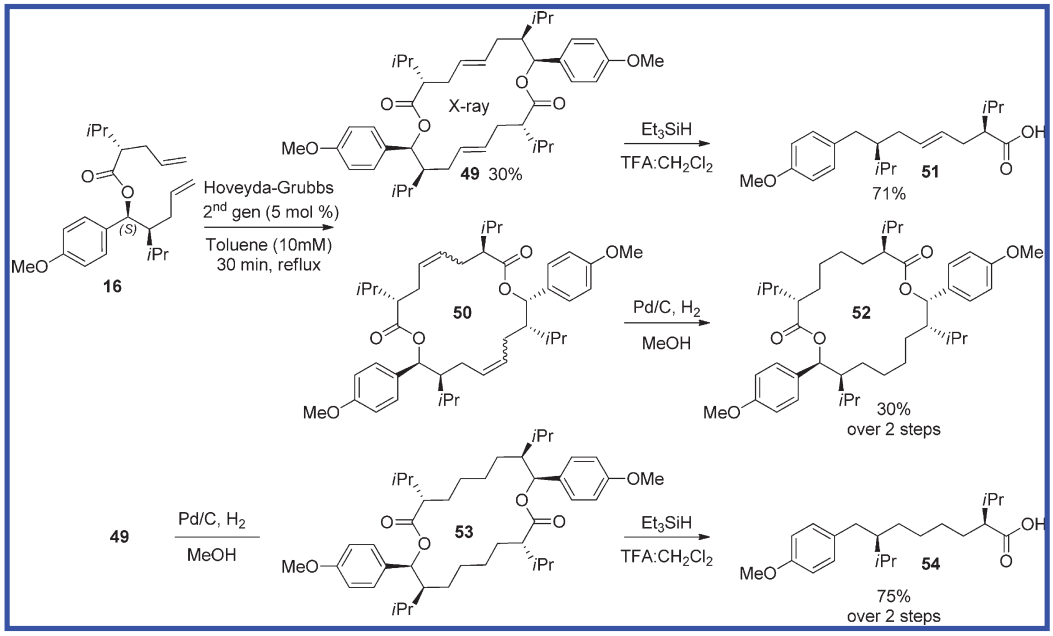


The same ketone was also prepared by arylation of the Weinreb amide derivative **47** of (2*S*)-isopropylbuta-4-enoic acid **7** independently prepared via an Evans[22] or MacMillan[28,46] asymmetric allylation. Reduction with a slow addition of DIBAL-H, keeping the temperature at −78 °C, led quantitatively to the (*S*)-alcohol **12** with a diastereomeric ratio of >20:1. Esterification with the acid **7** using the Yamaguchi method[33] led to **16**.

In the presence of 5 mol % of the second-generation Hoveyda−Grubbs catalyst (**H-G2**) at 10 mM in refluxing toluene, the (*S*)-ester **16** yielded 30% of the C_2-symmetrical *trans*−*trans* bis-unsaturated dilactone **49** and a mixture of non-symmetric dilactones as double-bond isomers **50** (Scheme 9). The structure of **49** was also confirmed by single-crystal X-ray analysis. Reductive cleavage of the benzylic ester bonds in **49** led to the acid **51**, which is a known intermediate in the Speedel process for the synthesis of aliskiren.[24,25] Controlled catalytic hydrogenation of the double bonds in **49** led to the saturated dilactone **53**, which upon reductive cleavage in acidic media yielded acid **54**. Alternatively, hydrogenation of the mixture of isomers corresponding to dilactones **50** afforded the head-to-head dilactone **52** (Scheme 9).

Judging from the results using the Grubbs first-generation catalyst (**G1**) with the (*R*)-esters **15** and **17** (10 mol % catalyst, 72 h, rt, toluene at 10 mM concentration), we speculate that the formation of the corresponding 9-membered lactones **19** (and **21**) can be attributed to the contribution of cooperative stereochemical, stereoelectronic, and conformational effects leading first to alkylidene Ru complexes (exemplified by the structure **15a** as one of the two possible intermediates). Presumably, the olefinic termini are favorably aligned with minimal steric interaction to lead to the Ru-metallacycle **15b**, which eventually collapses to the intended lactone **19** (Scheme 10A). In contrast, the transition state starting with the (*S*)-ester **16** will be subject to a significant steric clash between the isopropyl and aromatic moieties, thereby slowing

Scheme 9. Cross-Metathesis Reaction of the (*S*)-Ester 16 and Reductive Cleavage of Macrocylic Dilactones



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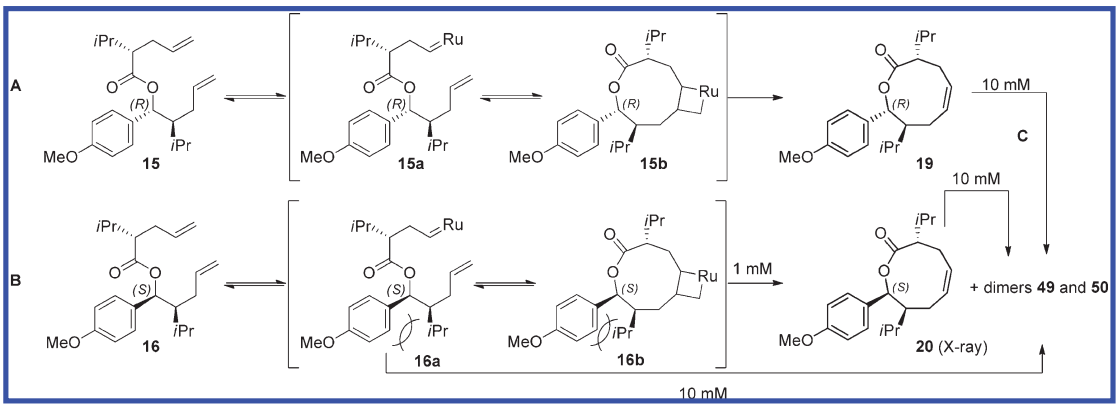
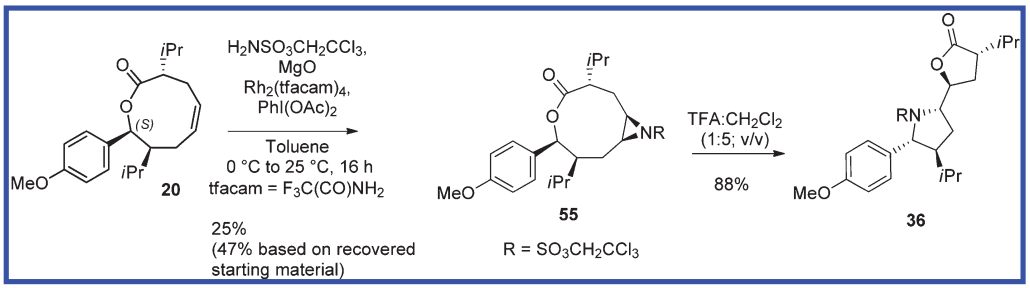
Scheme 10. Possible Ru-Metallacyclic Intermediates[a]



[a](A) First-generation Grubbs (**G1**) and second-generation Hoveyda–Grubbs (**H–G2**) catalysts at 10 mM (72 h at rt and 20 min, toluene reflux, respectively). (B) **H–G2** catalyst at 1 mM (6 h, toluene reflux) and 10 mM (24 h, toluene reflux). (C) **H–G2** catalyst at 10 mM (24 h, toluene reflux). Only one alkylidene Ru-intermediate is shown.

Scheme 11. Aziridination and Double-Ring Contraction of the (*S*)-Lactone 20



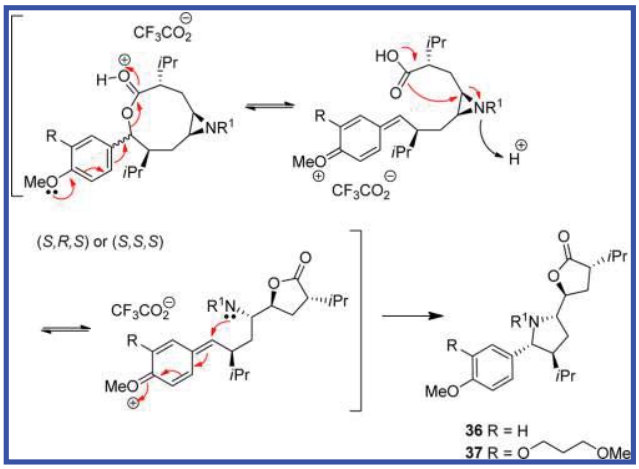
down the reaction (Scheme 10B). The same conclusion would also apply in the case of ester **18**.

In the presence of the more robust second-generation Hoveyda–Grubbs catalyst (**H–G2** 5 mol %, at a concentration of 10 mM in toluene at 110 °C for 20 min), the (*R*)-ester **15** in a mixture containing the (*S*)-ester **16** as the minor isomer is converted to lactone **19** in 64% yield. Under the same conditions, the minor (*S*)-ester **16** undergoes direct dimerization to the macrocyclic dilactones **49** and **50**, which were not reverted to starting material under these conditions (Scheme 10B). This was corroborated with the enantioenriched (*S*)-ester **16** (Scheme 9). Surprisingly, when the reaction was performed at a concentration of 1 mM instead of 10 mM, in refluxing toluene for 6 h, the (*S*)-ester **16** led to the elusive (*S*)-lactone **20** in 53% yield, accompanied by the usual dimers **49** and **50** (~24%) (Scheme 10B). The structure of **20** was confirmed by X-ray crystallography.[31] When heated at reflux temperature in 10 mM in toluene for 24 h in the presence of the second-generation Hoveyda–Grubbs catalyst (**H–G2**), the (*S*)-lactone **20** was rapidly converted to the lactones **49** and **50**. At a concentration of 1 mM, a diastereomeric mixture of **15** and **16** led to the corresponding lactones **19** and **20** respectively, accompanied by the dimers **49** and **50**.

Intrigued by this observation, we subjected the (*R*)-lactone **19** to the same reaction conditions, only to find that dimerization to **49** and **50** had also taken place (Scheme 10A). We can conclude that, depending on the concentration, the catalyst, and temperature, the (*R*)-lactone **19** and (*S*)-lactone **20** are the kinetic products. Dimerization during ring-closing metathesis has been previously reported.[47]

Finally, we subjected the (*S*)-lactone **20** to an aziridination reaction to give **55** in 25% yield with recovery of starting material (Scheme 11). TFA-induced double-ring contraction as for the (*R*)-lactone **19** (Scheme 6) gave the known lactone **36** in 88% yield. Presumably, the activation of the *N*-sulfamoyl aziridine lactone in either 9-membered lactones engendered participation by the electron-rich aryl moiety to give a quinonoid oxocarbenium ion which underwent regioselective intramolecular attack liberating the sulfamate group (Scheme 12). The latter would attack the quinonoid benzylic carbon atom with high antiselectivity with regard to

Scheme 12. Proposed Double-Ring Contraction Mechanism[28]



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the C-7 isopropyl substituent leading to the observed pyrrolidine lactone **36**.[28]

CONCLUSION

In conclusion, we have provided a detailed account of various approaches leading to the total synthesis of the antihypertensive marketed drug aliskiren. Ring-closing metathesis using the Grubbs (**G1** and **G2**) and Hoveyda−Grubbs (**H−G2**) catalysts with stereochemically distinct esters carrying terminal allyl moieties led to 9-membered lactones which were further elaborated to aliskiren and its *p*-methoxyphenyl congener. The formation of 9-membered lactones from diastereomeric (*R*)- and (*S*)-esters **15** and **16** were found to be concentration dependent and favored at a concentration of 1 mM in toluene using the Hoveyda−Grubbs second-generation catalyst (**H−G2**). At higher concentrations, the (*R*)-ester **15** afforded the expected 9-membered lactone, while the (*S*)-ester **16** led to a mixture of macrocyclic dilactones. Further studies focusing on the nature and stereochemistry of substituents in related cyclizations by ring-closing metathesis are in progress and will be reported in due course.

EXPERIMENTAL SECTION

General Procedure. All reactions were performed in oven-dried glassware under an argon atmosphere using dry, deoxygenated solvents. Dichloromethane and toluene were dried by passage through an activated alumina column under argon (solvent drying system (SDS)). Reagents were purchased and used without further purification. Reactions were monitored by analytical thin-layer chromatography (TLC) carried out on 0.25 mm silica plates that were visualized under a UV lamp (254 nm) and developed by staining with ceric ammonium molybdate, *p*-anisaldehyde, and/or potassium permanganate solution. Flash column chromatography was performed using silica (particle size 40−63 μm, 230−400 mesh) at increased pressure. FTIR are reported in reciprocal centimeters (cm^{-1}). NMR spectra (^1H, ^{13}C, DEPT 135, COSY, HMQC, NOESY) were recorded at either 300, 400, 500, or 700 MHz. Chemical shifts for ^1H NMR spectra are recorded in parts per million relative to trimethylsilane (TMS, δ = 0.00 ppm) with the solvent resonance as the internal standard (CH_3Cl, δ = 7.26 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, h = hextet, m = multiplet, and br = broad), coupling constants in hertz (Hz), integration (*x*H). Chemical shifts for ^{13}C NMR spectra are recorded in parts per million using the central peak of $CDCl_3$ (δ = 77.16 ppm) as the internal standard. Optical rotations were determined with a polarimeter at 589 nm using a 1 dm cell at ambient temperature and are reported in units of $deg{\cdot}cm^3{\cdot}g^{-1}{\cdot}dm^{-1}$. Melting points are given as ranges and are reported in °C.

(1*S*,2*S*)-2-Isopropyl-1-(4-methoxyphenyl)pent-4-en-1-ol (12). A solution of 1.5 M of DIBAL-H in toluene (1.8 mL, 2.7 mmol, 1.5 equiv) was added in a slow dropwise manner to a solution of ketone **48** (0.42 g, 1.8 mmol, 1.0 equiv) in THF (10 mL) at −78 °C. The solution was kept at −78 °C for at least 3 h and then allowed to slowly warm to room temperature. Silica gel was added until the reaction mixture stopped to generate bubbles. The mixture was filtered on a silica pad (silica gel, 2.5 cm diameter ×4.0 cm height; 5 V diethyl ether, then 2 V ethyl acetate) to yield alcohol **12** (0.40 g, 95%, dr >20:1) as a colorless oil: R_f = 0.11 (1:9, diethyl ether:hexanes); $[\alpha]_D^{20}$ −12 (*c* 3.0, $CDCl_3$) (from ketone **48** with 83% ee, prepared with the PdAAA protocol[27]); ^1H NMR (400 MHz, $CDCl_3$) δ 7.28−7.23 (m, 2H), 6.89−6.85 (m, 2H), 5.53 (ddt, *J* = 17.1, 10.1, 7.1 Hz, 1H), 4.88−4.79 (m, 2H), 4.58 (dd, *J* = 7.7, 3.3 Hz, 1H), 3.81 (s, 3H), 2.16−2.04 (m, 1H), 2.04−1.95 (m, 1H), 1.92−1.83 (m, 1H), 1.74−1.68 (m, 1H), 1.67 (dd, *J* = 3.4, 0.4 Hz, 1H), 0.98−0.93 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.2, 138.9, 136.5, 128.1, 115.1, 113.9, 75.9, 55.4, 50.6, 31.3, 27.2, 21.5, 18.4; IR (neat) 3454, 3005, 2962, 2940, 2880, 2845, 1615, 1515, 1468, 1248, 1177, 1038 cm^{-1}; HRMS (ESI-TOF) *m*/*z* calcd for $C_{15}H_{22}NaO_2$ $[M + Na]^+$ 257.1512, found $[M + Na]^+$ 257.1516.

(*S*)-(1*S*,2*S*)-2-Isopropyl-1-(4-methoxyphenyl)pent-4-en-1-yl-2-isopropylpent-4-enoate (Ester 16). Triethylamine (70 μL, 0.51 mmol, 1.2 equiv), 2,4,6-trichlorobenzoyl chloride (80 μL, 0.51 mmol, 1.2 equiv), and 4-(dimethylamino)pyridine (62 mg, 0.51 mmol, 1.2 equiv) were successively added to a solution of acid **7** (64 mg, 0.45 mmol, 1.05 equiv) in dry toluene (3 mL) at 0 °C. The resulting white slurry was stirred at 0 °C for 10 min during which the white slurry turned yellow. A solution of alcohol **12** (0.10 g, 0.43 mmol, 1.0 equiv) in dry toluene (1 mL) was added to the reaction vessel containing the yellow slurry in a dropwise manner at 0 °C. The flask that contained alcohol **12** was rinsed three times with dry toluene (1 mL), and the reaction mixture was allowed to warm to room temperature and monitored by TLC analysis until no more starting material was observed (Around 4 h at room temperature). The solvent was removed, and the resulting yellow solid was taken up in ethyl acetate (10 mL) and H_2O (10 mL). The aqueous layer was separated and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were successively washed with a 10% aqueous solution of acid citric (10 mL) and a saturated aqueous solution of sodium bicarbonate (10 mL). The organic layer was dried over magnesium sulfate, filtered, and concentrated. The residue was purified by flash chromatography (silica gel, 2.5 cm × 14.0 cm; 1:19 diethyl ether/hexanes) to yield ester **16** (110 mg, 72%) as an oil: R_f = 0.53 (1:9 diethyl ether/hexanes); $[\alpha]_D^{20}$ − 58 (*c* 2.0, $CDCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.26−7.21 (m, 2H), 6.87−6.77 (m, 2H), 5.79−5.58 (m, 2H), 5.57−5.37 (m, 1H), 5.05−4.91 (m, 2H), 4.87−4.73 (m, 2H), 3.79 (s, 3H), 2.39−2.14 (m, 3H), 2.12−1.71 (m, 5H), 0.96−0.89 (m, 6H), 0.84 (d, *J* = 6.8 Hz, 3H), 0.74 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.4, 159.1, 138.3, 136.2, 132.4, 129.1, 116.6, 115.4, 113.5, 77.1, 55.3, 52.8, 48.7, 34.0, 30.9, 30.7, 27.2, 21.2, 20.5, 20.3, 18.0; IR (neat) 3075, 2957, 2931, 2873, 2837, 1728, 1612, 1513, 1249, 1169, 1035 cm^{-1}; HRMS (ESI-TOF) *m*/*z* calcd for $C_{23}H_{34}NaO_3$ $[M + Na]^+$ 381.2400, found $[M + Na]^+$381.2400.

Lactone 20. Hoveyda−Grubbs second-generation catalyst (3 mg, 0.048 mmol, 0.06 equiv) was added to a solution of **16** (30 mg, 0.084 mmol, 1.0 equiv, dr 20:1) in dry toluene (84 mL), and the mixture was stirred at reflux for 6 h. The reaction mixture was cooled to room temperature, then an excess of ethyl vinyl ether was added and gently evaporated. The residue was purified by flash chromatography (silica gel, 1.5 cm diameter ×20.0 cm height, 1:50 ethyl acetate/hexanes) to yield **20** (16 mg, 53%) as pure white crystals: mp 89−91 °C; R_f = 0.55 (1:9 diethyl ether/hexanes); $[\alpha]^{20}{}_D$ −119 (*c* 0.5, $CDCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, *J* = 8.7 Hz, 1H), 6.88 (d, *J* = 8.6 Hz, 1H), 5.74−5.64 (m, 1H), 5.55 (ddd, *J* = 11.0, 10.9, 6.1 Hz, 1H), 3.80 (s, 2H), 3.10−3.00 (m, 1H), 2.87−2.77 (m, 1H), 2.48 (ddd, *J* = 8.4, 7.0, 1.5 Hz, 1H), 2.23−2.10 (m, 1H), 2.00 (dq, *J* = 13.5, 6.7 Hz, 1H), 1.90−1.81 (m, 1H), 1.48 (dq, *J* = 13.2, 6.6 Hz, 1H), 1.00 (d, *J* = 6.7 Hz, 3H), 0.84−0.79 (m, *J* = 7.2 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.9, 159.1, 133.5, 131.0, 128.4 (2H), 126.2, 113.9 (2H), 78.2, 55.4, 50.7, 49.5, 28.8, 26.9, 26.5, 23.4, 22.4, 21.9, 20.3, 19.0; IR (neat) 3008, 2956, 2871, 2836, 1735, 1612, 1513, 1463, 1386, 1367, 1247, 1158, 1112, 1030 cm^{-1}; HRMS (ESI-TOF) *m*/*z* calcd $C_{21}H_{31}O_3$ $[M + H]^+$ 331.2268, found $[M + H]^+$ 331.2259.

Lactone 21. See ref 28. Also prepared from addition of Hoveyda−Grubbs second-generation catalyst (4 mg, 0.0064 mmol, 0.06 equiv) to a solution of esters **17**:**18** (52 mg, 0.11 mmol, 1.0 equiv, dr 5:1) in dry toluene (9 mL) with stirring at 50 °C for 2 h. The reaction mixture was cooled to room temperature, filtered on silica and a Fluorisil pad, and then rinsed using 50% ethyl acetate/hexanes. The residue was purified by flash chromatography (silica gel, 1.5 cm diameter × 20.0 cm height, 1:9 ethyl acetate/hexanes) to yield **21** (33 mg, 72%).

Lactones 24 and 25. A solution of NBS (29 mg, 0.16 mmol, 1.1 equiv) was added in a dropwise manner to a mixture of lactone **19** (47 mg, 0.14 mmol, 1 equiv), copper(I) iodide (3 mg, 0.015, 0.11 equiv), and *p*-toluenesulfonamide (26 mg, 0.15 mmol, 1.1 equiv) in dichloromethane (3 mL). The mixture was stirred at room temperature for 4 h, and then H_2O (4 mL) was added in a round-bottom flask covered with aluminum foil. The mixture was diluted with ethyl acetate (15 mL) and stirred for a few minutes, and then layers were separated.

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The aqueous layer was back-extracted with ethyl acetate (5 mL), and the organic layers were combined, washed with brine (10 mL), dried over sodium sulfate, and concentrated. A diastereomeric ratio of 3.9:1 was observed by ^{1}H NMR of the crude mixture. The residue was purified by flash chromatography (silica gel, 1.5 cm diameter ×21 cm height, 1:9 to 1:4 ethyl acetate/hexanes) to yield the lactone **24** (42 mg, 52%) as a white solid along with impure fractions of **25**, which could be obtained as a pure white solid by recrystallization in methanol. Also, starting from 63 mg (0.19 mmol, 1 equiv) of lactone **19**, 14 mg (13%) of lactone **25** could be obtained pure by flash chromatography (silica gel, 2.5 cm × 20 cm, 0 to 1:19 ethyl acetate/hexanes) and 64 mg of impure lactone **24** which was repurified by flash chromatography (silica gel, 1.5 cm diameter × 20 cm height, 1:4 ethyl acetate/hexanes) to yield the pure lactone **24** (40 mg, 36%).

Lactone 24: R_f = 0.29 (1:4 ethyl acetate/hexanes); (recrystallized from 2-propanol) mp 113−115 °C; $[\alpha]_D^{20}$ +49 (*c* 0.5, $CHCl_3$); ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.42−7.39 (m, 2H), 7.03 (d, *J* = 8.0 Hz, 2H), 6.91−6.88 (m, 2H), 6.63−6.60 (m, 2H), 5.34 (d, *J* = 7.7 Hz, 1H), 4.45−4.43 (m, 1H), 4.20 (dd, *J* = 9.2, 8.1 Hz, 1H), 4.16 (ddd, *J* = 9.0, 4.4, 1.5 Hz, 1H), 3.73 (s, 3H), 2.96 (ddd, *J* = 11.3, 7.6, 3.8 Hz, 1H), 2.58−2.51 (m, 1H), 2.31 (s, 3H), 2.31−2.27 (m, 1H), 2.11 (ddd, *J* = 14.4, 11.2, 3.1 Hz, 1H), 2.03 (ddd, *J* = 14.7, 9.2, 5.4 Hz, 1H), 1.81−1.77 (m, 1H), 1.69 (ddd, *J* = 14.9, 4.4 Hz, 1H), 1.47−1.42 (m, 1H), 0.97 (d, *J* = 7.0 Hz, 3H), 0.95 (d, *J* = 6.9 Hz, 3H), 0.82 (d, *J* = 7.0 Hz, 3H), 0.71 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 170.9, 158.8, 142.6, 138.2, 132.5, 129.2 (2C), 128.1 (2C), 127.1 (2C), 113.8 (2C), 81.1, 60.5, 55.4, 50.0, 45.7, 42.9, 32.0, 30.2, 29.2, 28.1, 21.7, 21.6, 19.7, 18.5, 16.2; IR (neat) 3252, 2958, 2923, 2852, 1732, 1704, 1612, 1514, 1463, 1443, 1325, 1248, 1218, 1179, 1160, 1093, 1046 cm^{-1}; HRMS (ESI-TOF) *m*/*z*
calcd for $C_{28}H_{38}{}^{79}BrNNaO_5S$ $[M + Na]^+$ 602.1546, found $[M + Na]^+$ 602.1517.

Lactone 25: R_f = 0.21 (1:4 ethyl acetate/hexanes); (gradual dec) (recrystallized from ethanol) mp 151−167 °C; $[\alpha]_D^{20}$ −56 (*c* 0.5, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48−7.44 (m, 2H), 7.07−7.03 (m, 2H), 6.92−6.86 (m, 2H), 6.65−6.59 (m, 2H), 5.30 (d, *J* = 8.5 Hz, 1H), 4.19−4.16 (m, 1H), 4.12−4.07 (m, 1H), 3.69 (s, 3H), 2.76−2.66 (m, 2H), 2.40−2.29 (m, 4H), 2.29−2.21 (m, 1H), 2.07 (ddd, *J* = 14.6, 8.2, 3.4 Hz, 1H), 1.66 (ddd, *J* = 14.4, 9.4, 1.5 Hz, 1H), 1.63−1.55 (m, 1H), 1.50−1.43 (m, 1H), 1.40 (ddd, *J* = 14.4, 9.3, 5.0 Hz, 1H), 1.00 (d, *J* = 7.0 Hz, 3H), 0.81 (d, *J* = 7.0 Hz, 3H), 0.79 (d, *J* = 6.8 Hz, 3H), 0.69 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 171.3, 159.3, 143.1, 137.5, 132.3, 129.3 (2C), 128.3 (2C), 127.3 (2C), 114.0 (2C), 78.8, 60.4, 55.3, 49.0, 45.7, 42.9, 31.7, 30.3, 29.5, 28.1, 22.0, 21.6, 19.5, 18.1, 16.0; IR (neat) 3273, 2966, 2930, 2860, 2880, 1740, 1727, 1667, 1615, 1518, 1467, 1449 1329, 1256, 1183, 1161, 1052, 1041 cm^{-1}; HRMS (ESI-TOF) *m*/*z* calcd for $C_{28}H_{38}{}^{79}BrNNaO_5S$ $[M + Na]^+$ 602.1546, found $[M + Na]^+$ 602.1535.

Lactone 26. Starting from the lactone **19** (66 mg, 0.20 mmol, 1.0 equiv), the bromosulfonamidation protocol was followed and the crude mixture of the bromosulfonamides **24**:**25** (dr 3.9:1) was dissolved in dichloromethane and cooled to 0 °C. Triethylsilane (0.16 mL, 1.0 mmol, 5.0 equiv) was added to the solution followed by TFA (0.1 mL). The solution was allowed to slowly reach room temperature, and the progress of the reaction was monitored by TLC. Volatiles were removed under vacuum with a rotary evaporator, and the residue was purified by flash chromatography (silica gel, 2.0 cm diameter ×20 cm height, 1:9 ethyl acetate/hexanes) to yield bromolactone **26** (62 mg, 75%, 2 steps) as an oil: R_f = 0.43 (1:4, ethyl acetate/hexanes); $[\alpha]_D^{20}$ +11 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15−7.01 (m, 2H), 6.89−6.75 (m, 2H), 4.26−4.20 (m, 1H), 3.77 (s, 3H), 3.70 (ddd, *J* = 6.8, 5.2, 1.0 Hz, 1H), 2.79 (ddd, *J* = 11.3, 7.8, 3.9 Hz, 1H), 2.71 (dd, *J* = 13.8, 5.2 Hz, 1H), 2.54−2.33 (m, 2H), 2.13 (ddd, *J* = 14.6, 7.8, 3.4 Hz, 1H), 1.85−1.53 (m, 5H), 0.96−0.91 (m, 6H), 0.88 (d, *J* = 7.0 Hz, 3H), 0.83 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.5, 158.2, 133.4, 129.9 (2C), 114.1 (2C), 79.3, 55.4, 49.9, 42.8, 41.7, 37.8, 36.2, 31.21, 30.23, 29.3, 19.7, 19.6, 18.4, 18.3; IR (neat) 2966, 2940, 2879, 1736, 1615, 1515, 1468, 1249, 1226, 1209, 1180, 1069, 1041 cm^{-1}; HRMS (ESI-TOF) *m*/*z* calcd for $C_{21}H_{31}{}^{79}BrNaO_3$ $[M + Na]^+$ 433.1349, found $[M + Na]^+$ 433.1340.

Epoxide 28. *m*-CPBA (77%) (65 mg, 0.29 mmol, 1.9 equiv) was added to a solution of lactone **19** (51 mg, 0.15 mmol, 1.0 equiv) in dichloromethane (1 mL), and the reaction mixture was stirred for 1 h at room temperature. The solution was diluted with diethyl ether (5 mL) and washed with a saturated aqueous solution of sodium bicarbonate (2 × 10 mL). The organic layer was dried over magnesium sulfate, filtered, and concentrated to yield 47 mg of the crude epoxide **28** (dr 10:1) as a gel: R_f = 0.52 (1:4, ethyl acetate/hexanes). Only the major diastereomer is reported: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33−7.27 (m, 2H), 6.92−6.85 (m, 2H), 5.75 (d, *J* = 11.1 Hz, 1H), 3.81 (s, 3H), 3.29−3.20 (m, 1H), 3.04 (ddd, *J* = 10.7, 3.7, 1.8 Hz, 1H), 2.60−2.50 (m, 1H), 2.25 (ddd, *J* = 11.4, 5.2, 1.9 Hz, 1H), 2.21−2.07 (m, 1H), 2.07−1.93 (m, 2H), 1.58−1.38 (m, 2H), 1.03 (d, *J* = 6.5 Hz, 3H), 0.99−0.92 (m, 1H), 0.89 (d, *J* = 6.9 Hz, 3H), 0.84 (d, *J* = 6.9 Hz, 3H), 0.79 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.7, 159.6, 131.7, 128.9 (2C), 114.0 (2C), 78.0, 61.0, 55.4, 55.4, 52.7, 48.6, 28.5, 27.0, 26.5, 25.0, 22.0, 21.8, 19.7, 15.9; IR (neat) 3004, 2967, 2947, 2936, 2929, 2880, 1733, 1519, 1466, 1393, 1375, 1277, 1252, 1204, 1179, 1122, 1117, 1038 cm^{-1}; HRMS (ESI-TOF) *m*/*z* calcd for $C_{21}H_{31}O_4$ $[M + H]^+$ 347.2217, found $[M + H]^+$ 347.2204 and calcd for $C_{21}H_{30}NaO_4$ $[M + Na]^+$ 369.2036, found $[M + Na]^+$ 369.2029.

Lactones 29, 30, and 31. To a solution of the crude epoxide **28** (47 mg) in dichloromethane (1 mL) was added trifluoroacetic acid (60 μL). The solution was stirred 10 min,a nd then the reaction was stopped by adding a saturated aqueous solution of sodium bicarbonate (5 mL) followed by ethyl acetate (10 mL). The organic layer was washed with a saturated aqueous solution of sodium bicarbonate (5 mL), dried over magnesium sulfate, filtered, and concentrated. A ratio of 6:1:1 was observed in the ^{1}H NMR spectrum of the crude mixture. The residue was purified by flash chromatography (silica gel, 2.0 cm diameter × 20.0 cm height, 1:19 ethyl acetate:hexanes) to yield lactones **29** (15 mg, 29%) + **30** (4 mg, 8%) + **31** (4 mg, 8%) + 7 mg of mixed fractions. All lactones produced from this reaction were clear oils.

Lactone 29: R_f = 0.41 (1:4 ethyl acetate/hexanes); $[\alpha]_D^{20}$ +14 (*c* 1.5, $CHCl_3$); ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.24−7.21 (m, 2H), 6.89−6.86 (m, 2H), 4.53−4.43 (m, 1H), 4.25 (d, *J* = 10.5 Hz, 1H), 3.89−3.87 (m, 1H), 3.80 (s, 3H), 2.81 (ddd, *J* = 11.5, 7.3, 3.8 Hz, 1H), 2.59−2.52 (m, 1H), 2.17−2.11 (m, 1H), 2.08 (ddd, *J* = 14.0, 7.3, 3.9 Hz, 1H), 2.00−1.93 (m, 1H), 1.74 (ddd, *J* = 14.3, 12.5, 2.3 Hz, 1H), 1.64 (ddd, *J* = 14.4, 12.9, 2.8 Hz, 1H), 1.43−1.36 (m, 1H), 0.93−0.90 (m, 6H), 0.78 (d, *J* = 7.0 Hz, 3H), 0.74 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 173.9, 159.6, 132.7, 128.6 (2C), 114.1 (2C), 83.2, 76.1, 70.5, 55.4, 41.0, 39.7, 29.0, 28.3, 26.4, 25.8, 20.9, 19.8, 17.9, 15.9; IR (neat) 3018, 3003, 2965, 2954, 2941, 2935, 2923, 2913, 2905, 2881, 2844, 1724, 1617, 1590, 1518, 1469, 1446, 1391, 1373, 1367, 1350, 1248, 1226, 1175, 1157, 1129, 1082, 1056, 1030, 1007 cm^{-1}; HRMS (ESI-TOF) *m*/*z* calcd for $C_{21}H_{30}O_4$ $[M + H]^+$ 347.2217, found $[M + H]^+$ 347.2225 and calcd for $C_{21}H_{30}NaO_4$ $[M + Na]^+$ 369.2036, found $[M + Na]^+$ 369.2044.

Lactone 30: R_f = 0.46 (1:4 ethyl acetate/hexanes); $[\alpha]_D^{20}$ +39 (*c* 0.4, $CHCl_3$); ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.24−7.21 (m, 2H), 6.88−6.85 (m, 2H), 4.50 (ddd, *J* = 9.3, 3.2, 2.1 Hz, 1H), 4.41 (d, *J* = 9.3 Hz, 1H), 4.08 (ddd, *J* = 9.2, 5.0, 2.0 Hz, 1H), 3.79 (s, 3H), 2.70 (ddd, *J* = 9.8, 9.3, 5.0 Hz, 1H), 2.22 (ddd, *J* = 13.1, 10.0, 3.3 Hz, 1H), 2.20−2.13 (m, 2H), 2.13−2.06 (m, 2H), 1.92 (ddd, *J* = 12.4, 9.3 Hz, 1H), 1.60−1.53 (m, 1H), 0.96 (d, *J* = 6.9 Hz, 3H), 0.90 (d, *J* = 6.1 Hz, 3H), 0.89 (d, *J* = 6.0 Hz, 3H), 0.71 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 179.8, 159.6, 133.2, 128.7 (2C), 114.0 (2C), 85.8, 79.6, 79.4, 55.4, 52.4, 45.4, 31.7, 29.0, 28.6, 26.3, 22.0, 20.6, 19.6, 18.1; IR (neat) 3000, 2967, 2931, 2907, 2899, 2889, 2878, 2859, 1771, 1619, 1519, 1471, 1374, 1251, 1178, 1110, 1093, 1036 cm^{-1}; HRMS (ESI-TOF) *m*/*z* calcd for $C_{21}H_{31}O_4$ $[M + H]^+$ 347.2217, found $[M + H]^+$ 347.2220 and calcd for $C_{21}H_{30}NaO_4$ $[M + Na]^+$ 369.2036, found $[M + Na]^+$ 369.2042.

Lactone 31: R_f = 0.31 (1:4 ethyl acetate/hexanes); $[\alpha]_D^{20}$ −2 (*c* 0.4, $CHCl_3$); ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.26−7.23 (m, 2H), 6.87−6.84 (m, 2H), 4.57 (d, *J* = 9.3 Hz, 1H), 4.36−4.32 (m, 1H), 4.25−4.20 (m, 1H), 3.79 (s, 3H), 2.61−2.56 (m, 1H), 2.21−2.15 (m, 2H), 2.15−2.12 (m, 1H), 2.12−2.07 (m, 1H), 2.05−1.95 (m, 1H), 1.84−1.77 (m, 1H), 1.71−1.64 (m, 1H), 1.03 (d, *J* = 6.9 Hz, 3H), 0.93 (d, *J* = 6.7 Hz, 3H), 0.90 (d, *J* = 6.8 Hz, 3H), 0.75 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (176 MHz, $CDCl_3$) δ 178.0, 159.3, 134.3, 128.5 (2C), 113.9 (2C), 85.0, 79.9, 78.7,

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55.4, 54.1, 46.9, 31.8, 28.9, 27.9, 26.3, 22.4, 20.8, 19.6, 18.5; IR (neat) 3006, 2966, 2928, 2906, 2897, 2878, 2864, 2858, 2834, 2818, 1770, 1618, 1518, 1469, 1251, 1177, 1038, 1001, 981, 828, 763 cm^{-1}; HRMS (ESI-TOF) m/z calcd for $C_{21}H_{31}O_4$ $[M + H]^+$ 347.2217, found $[M + H]^+$ 347.2223 and calcd for $C_{21}H_{30}NaO_4$ $[M + Na]^+$ 369.2036 and $[M + Na]^+$ 369.2044.

Lactone Diol 32. *N*-Methylmorpholine *N*-oxide (53 mg, 0.45 mmol, 1.5 equiv) was added to a solution of lactone **15** (0.1 g, 0.3 mmol, 1 equiv) in acetone (2.4 mL) and distilled water (0.6 mL) at 0 °C, a 2.5 wt % solution of osmium tetra oxide in 2-methyl-2-propanol (0.2 mL, 0.02 mmol, 0.05 equiv) was added, and the reaction mixture was allowed to warm to room temperature. After 1 h of stirring, the reaction media was poured into a cold solution of ethyl acetate (2 mL) and a saturated aqueous solution of sodium thiosulfate (2 mL). The aqueous layer was separated and back-extracted with ethyl acetate (3 × 2 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated to leave 102 mg of a black oil which was purified by flash chromatography (silica gel, 1.5 cm × 20 cm; 2:3 ethyl acetate/hexanes) to yield diol **32** (89 mg, 81%, dr 9:1) as a colorless oil.

Diol **32** was also prepared using the same protocol, with 4 wt % solution of osmium tetraoxide in H_2O in 91% yield and an estimated dr of 6:1 by NMR. The oil was recrystallized from ethyl acetate:hexanes (1:4) to give white needles with an estimated dr of 7:1; mp 96 to 106 °C; R_f = 0.2 (2:3 ethyl acetate/hexanes): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32−7.26 (m, 0.27H), 7.26−7.20 (m, estimated to ∼1.6H), 6.88−6.82 (m, 2H), 5.68 (d, J = 11.0 Hz, 1H), 4.50 (d, J = 6.5 Hz, 1H), 3.84−3.69 (m, 4H), 2.47 (s, 2H), 2.29 (ddd, J = 15.9, 6.8, 2.7 Hz, 1H), 2.24−2.01 (m, 2H), 1.92−1.58 (m, 3H), 1.55−1.45 (m, 0.21H), 1.45−1.30 (m, 1H), 1.24−1.08 (m, 1H), 0.98 (d, J = 6.1 Hz, 3H), 0.92−0.71 (m, 9H).Only the major diastereomer is reported for the ^{13}C NMR. ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.1, 159.7, 131.0, 128.7, 114.1, 78.8, 77.9, 69.0, 55.4, 53.2, 48.4, 31.6, 30.1, 27.5, 26.9, 21.5, 21.3, 20.2, 15.3; IR (neat) 3394, 2867, 2945, 2881, 1730, 1617, 1519, 1467, 1253, 1179, 1052, 1036 cm^{-1}; HRMS (ESI-TOF) m/z calcd for $C_{21}H_{32}NaO_5$ $[M + Na]^+$ 387.2142, found $[M + Na]^+$ 387.2126.

Pyrrolidine Lactone 36. A dry round-bottomed flask was charged with 8 mg (0.014 mmol, 1.0 equiv) of **55**, a magnetic stirrer and 0.5 mL of dry dichloromethane ([**55**] = 0.028 M) were introduced via a glass syringe then added 5 drops of trifluoroacetic acid. The solution was stirred and monitored by TLC analysis (20:80 ethyl acetate−hexanes, CAM). After 10 min, when TLC analysis showed no more starting material, the trifluoroacetic acid and dichloromethane were first removed under reduced pressure at room temperature to leave yellow oil which was purified by flash column chromatography (silica gel, 1.5 cm × 20 cm; 1:19 ethyl acetate−hexanes) to yield 7 mg (0.0123 mmol, 88%) of the titled compound **36** as a yellow oil: R_f = 0.44 (1:9 ethyl acetate:hexanes); $[\alpha]_D^{20}$ +21 (c 0.7, $CDCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33−7−31 (m, 2H), 6.89−6.86 (m, 2H), 4.57−4.52 (m, 2H), 4.34 (d, J = 11.2 Hz, 2H), 4.23 (dd, 5.2 and 8.4 Hz, 1H), 3.78 (s, 3H), 2.64 (ddd, J = 5.6, 7.6, 10.0 Hz, 1H), 2.56−2.47 (m, 1H), 2.41−2.34 (m, 1H), 2.21−2.05 (m, 3H), 1.95 (dd, J = 6.4, 12.8 Hz, 1H), 1.71−1.62 (m, 1H), 1.04 (d, J = 6.4 Hz, 3H), 0.97 (d, J = 6.8 Hz, 3H), 0.91 (d, J = 6.8 Hz, 3H), 0.79 (d, J = 6.4 Hz, 3H).

Lactone 39. Zn(Cu) (0.18 g, 2.8 mmol, 5.0 equiv) was added to a solution of amide **38** (0.36 g, 0.56 mmol, 1.0 equiv) in methanol/ethyl acetate (1 mL, 1:1 v/v) and stirred at room temperature. The reaction was monitored by MS. The mixture was filtered on Celite, rinsed with a minimal amount of MeOH, and concentrated. The resulting solid was dissolved in dry MeOH (5 mL) and cooled to 0 °C, and AcCl (0.36 mL) was added. The solution was allowed to reach room temperature and stirred 24 h. The solvent was removed under vacuum with a rotary evaporator, and the resulting white solid was dissolved in CH_2Cl_2 (2 mL). To this last were added H_2O (2 mL), Boc_2O (0.16 g, 0.73 mmol, 1.3 equiv), K_2CO_3 (0.39 g, 2.8 mmol, 5.0 equiv), and TBAB (43 mg, 0.11 mmol, 0.2 equiv). The mixture was stirred at room temperature and monitored by TLC. An excess of imidazole was added, and then the mixture was acidified to a pH = 3−4, with a 10% solution of citric acid. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The organic layers were combined, dried over sodium sulfate, filtered, and concentrated. The residue was purified by flash chromatography (silica gel, 1:4 ethyl acetate/hexanes) to yield the known amide **40**[28] (90 mg, 31%) (R_f = 0.57, 2:3 ethyl acetate/hexanes) as a colorless oil and lactone **39** (40 mg, 16%) (R_f = 0.37, 2:3 ethyl acetate/hexanes) as a white solid, which was recrystallized from diffusing hexanes to a solution of lactone **39** in a minimal amount of ethyl acetate: mp 140 to 143 °C; $[\alpha]_D^{20}$ +14 (c 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (d, J = 8.4 Hz, 2H), 6.84 (d, J = 8.4 Hz, 2H), 4.60−4.25 (m, 2H), 4.20−4.05 (m, 1H), 3.79 (s, 1H), 4.70−4.55 (m, 1H), 2.40−2.10 (m, 4H), 2.00−1.80 (m, 1H), 1.73 (br s, 2H), 1.50−1.10 (br m, 9H), 1.04 (d, J = 6.8 Hz, 3H), 0.97−0.90 (m, 6H), 0.82 (d, J = 6.8 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.1, 158.4, 136.0, 127.9, 113.7, 80.3, 65.7, 60.0, 55.3, 52.5, 45.1, 29.2, 28.3, 28.2, 27.8, 27.4, 22.2, 20.7, 18.6, 17.8; IR (neat) 2959, 2930, 2874, 2837, 1772, 1690, 1613, 1513, 1466, 1386, 1366, 1245, 1170, 1101, 1033 cm^{-1}; HRMS (ESI-TOF) m/z calcd for $C_{26}H_{40}NO_5$ $[M + H]^+$ 446.2901, found $[M + H]^+$ 446.2891 and calcd for $C_{26}H_{39}NNaO_5$ $[M + Na]^+$ 468.2720, found $[M + Na]^+$ 468.2729.

Lactone 41. An aqueous 1 M solution of LiOH (1.4 mL, 1.4 mmol, 10 equiv) was added to a solution of lactone **37** (88 mg, 0.14 mmol, 1.0 equiv) in DME (1.4 mL) at 0 °C. The reaction mixture was allowed to reach room temperature and monitored by TLC and MS. The mixture was then acidified with a 1 M HCl solution in MeOH to pH = 3−4, and volatiles were removed under vacuum with a rotary evaporator to give 312 mg of the crude mixture.

Boc_2O (0.10 g, 0.48 mmol, 2.4 equiv) was added to a mixture of the crude deprotected intermediate (0.18 g, estimated to 0.20 mmol, 1.0 equiv) in dichloromethane (1 mL) and H_2O (1 mL) at 0 °C. K_2CO_3 (0.26 g, 1.9 mmol, 10 equiv) and TBAB (24 mg, 74 μmol, 0.37 equiv) were added, and the mixture was allowed to reach room temperature. The mixture was stirred for 16 h at room temperature, and then the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 2 mL), and the organic layers were combined, dried over sodium sulfate, filtered, and concentrated. The residue was purified via flash chromatography (silica gel, 1:9 ethyl acetate:hexanes) to yield Boc-protected lactone **41** (105 mg, >95%) as a colorless oil: $[\alpha]_D^{20}$ −70 (c 0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.01 (s, 1H), 6.85−6.72 (m, 2H), 4.82 (s, 1H), 4.35−3.95 (m, 4H), 3.83 (s, 3H), 3.62−3.48 (m, 2H), 3.36−3.28 (m, 3H), 2.66−2.53 (m, 1H), 2.35−2.02 (m, 5H), 1.99−1.56 (m, 4H), 1.35−1.10 (m, 9H), 1.04 (d, J = 6.9 Hz, 3H), 0.93 (d, J = 6.8 Hz, 3H), 0.88 (d, J = 6.7 Hz, 3H), 0.80 (d, J = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.64, 155.42, 148.26, 148.15, 119.86, 111.86, 111.19, 80.12, 79.22, 69.73, 66.32, 66.29, 61.11, 58.76, 56.14, 46.86, 29.60, 28.59, 28.31, 27.90, 27.66, 21.88, 20.72, 18.36, 18.28; IR (NaCl) 2961, 2874, 2835, 1770, 1682, 1515, 1469, 1391, 1260, 1143, 1028 cm^{-1}; HRMS (ESI-TOF) m/z calcd for $C_{30}H_{47}NNaO_7$ $[M + Na]^+$ 556.3245, found $[M + Na]^+$ 556.3241.

Amide 42. A 2 M solution of $AlMe_3$ in toluene (0.1 mL, 0.2 mmol, 5 equiv) was added to a solution of *n*-butylamine (20 μL, 0.20 mmol, 5.0 equiv) in dichloromethane (1 mL), and the mixture was stirred at room temperature for 5 min. The resulting solution was transferred to a solution of lactone **37** (25 mg, 40 μmol, 1.0 equiv) in dichloromethane (1 mL), and the solution was stirred at room temperature overnight and then quenched with a saturated solution of ammonium chloride (10 mL). The organic phase was separated, and the aqueous phase was extracted with dichloromethane (3 × 10 mL). The combined organic extracts were dried over sodium sulfate, filtered, and concentrated. The residue was purified by flash chromatography (silica gel, 1:4 ethyl acetate/hexanes) to yield amide **42** (25 mg, 87%) as a colorless oil: R_f = (0.31, 2:3 ethyl acetate/hexanes); $[\alpha]_D^{20}$ + 11 (c 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.07 (d, J = 2.0 Hz, 1H), 6.86 (dd, J = 8.3, 2.0 Hz, 1H), 6.79 (d, J = 8.3 Hz, 1H), 5.94 (t, J = 5.7 Hz, 1H), 4.55 (d, J = 9.2 Hz, 1H), 4.44 (q, J = 10.8 Hz, 2H), 4.16−4.07 (m, 2H), 4.00−3.93 (m, 1H), 3.83 (s, 3H), 3.65−3.57 (m, 3H), 3.37 (s, 3H), 3.34−3.24 (m, 1H), 3.23−3.13 (m, 1H), 2.34−2.25 (m, 1H), 2.17−2.07 (m, 3H), 2.00−1.83 (m, 4H), 1.75−1.67 (m, 1H), 1.60 (ddd, J = 13.5, 10.4, 2.8 Hz, 1H), 1.51−1.44 (m, 2H), 1.38−1.28 (m, 3H), 0.97−0.86 (m, 12H), 0.83 (d, J = 6.8 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.4, 149.2, 148.7, 134.2, 120.1, 112.6, 111.6, 93.9, 77.6, 71.4, 69.9, 69.7, 67.7, 66.2, 58.8, 56.1, 53.4, 51.5, 39.3, 35.1, 32.0, 30.6, 30.4, 29.6, 28.7, 22.1, 21.3, 20.6, 20.3, 18.5, 13.9; IR (NaCl) 3330, 3012, 2960, 2931, 2874, 1634, 1516,

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1464, 1373, 1261, 1183, 1000 cm^{-1}; HRMS (ESI-TOF) m/z calcd for $C_{31}H_{52}Cl_3N_2O_8S$ $[M + H]^+$ 717.2505, found $[M + H]^+$ 717.2524 and calcd for $C_{31}H_{51}Cl_3N_2NaO_8S$ $[M + Na]^+$ 739.2324, found $[M + Na]^+$ 739.2341.

(*S*)-2-Isopropyl-*N*-methoxy-*N*-methylpent-4-enamide (47). EDC (0.71 g, 3.7 mmol, 1.1 equiv) was added to a solution of acid **7** (0.50 g, 3.5 mmol, 1 equiv) in dichloromethane (15 mL) at 0 °C, followed by triethylamine (0.59 mL, 4.2 mmol, 1.2 equiv), *N*,*O*-dimethylhydroxylamine hydrochloride, and a small chip of DMAP. The reaction mixture was allowed to slowly reach room temperature and stirred for 16 h. Volatiles were removed under vacuum with a rotary evaporator, and the resulting residue was partitioned between ethyl acetate (10 mL) and H_2O (10 mL). The aqueous layer was back-extracted twice with ethyl acetate (2 × 10 mL), and the organic layers were combined, washed with a saturated aqueous solution of sodium bicarbonate (3 × 10 mL), dried over sodium sulfate, and concentrated. The residue was purified by flash chromatography (silica gel, 2.5 cm diameter × 20 cm height, 1:4 ethyl acetate/hexanes) to yield **47** (0.46 g, 70%) as an oil: R_f = 0.7 (3:7, ethyl acetate/hexanes) $[\alpha]_D^{20}$ +8 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 5.74 (ddt, *J* = 17.2, 10.2, 7.1 Hz, 1H), 5.05 (ddt, *J* = 17.0, 1.8, 1.2 Hz, 1H), 5.00−4.90 (m, 1H), 3.66 (s, 3H), 3.18 (s, 3H), 2.69 (br s, 1H), 2.43−2.23 (m, 2H), 1.96−1.82 (m, 1H), 0.96 (d, *J* = 6.8 Hz, 3H), 0.91 (d, *J* = 6.7 Hz, 3H); (residual chloroform signal was set at 77.9 ppm); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.6, 137.3, 117.0, 62.1, 48.2, 35.1, 32.8, 31.4, 21.9, 21.8; IR (neat) 3077, 2961, 2873, 2820, 1661, 1464, 1440, 1416, 1385, 1337, 1321, 1177, 1116, 1085; HRMS (ESI-TOF) m/z calcd for $C_{10}H_{20}NO_2$ $[M + H]^+$ 186.1489, found $[M + H]^+$ 186.1482.

(*S*)-2-Isopropyl-1-(4-methoxyphenyl)pent-4-en-1-one (48).[27] A solution of 1.6 M *n*-BuLi in hexane (1.35 mL, 2.16 mmol, 1.03 equiv) was added to a solution of 4-bromoanisole (0.26 mL, 2.1 mmol, 1.0 equiv) in tetrahydrofuran (8 mL) at −78 °C. The solution was stirred at −78 °C for 40−60 min, and then a solution of **47** (0.46 g, 2.5 mmol, 1.2 equiv) in tetrahydrofuran (2−3 mL) was added in a dropwise manner. The reaction mixture was allowed to warm to room temperature, stirred for 1 h, and then quenched with water (10 mL). The organic layer was separated from the aqueous layer. The aqueous layer was extracted with diethyl ether (2 × 10 mL). Organic solutions were combined, washed with brine (2 × 10 mL), dried over magnesium sulfate, filtered, and concentrated. The residue was purified by flash chromatography (silica gel, 2.5 cm diameter × 13 cm height; 1:9 diethyl ether/hexanes) to yield ketone **48** (0.40 g, 83%) as a clear oil: R_f = 0.47 (1:4 ethyl acetate/hexanes); $[\alpha]_D^{20}$ +38 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.93 (d, *J* = 8.8 Hz, 2H), 6.93 (d, *J* = 8.8 Hz, 2H), 5.69 (ddt, *J* = 17.0, 10.1, 7.0 Hz, 1H), 4.99 (d, *J* = 17.0 Hz, 1H), 4.89 (d, *J* = 10.1 Hz, 1H), 3.87 (s, 3H), 3.29 (ddd, *J* = 10.2, 6.8, 3.9 Hz, 1H), 2.64−2.45 (m, 1H), 2.38−2.21 (m, 1H), 2.16−1.91 (m, *J* = 6.7 Hz, 1H), 0.98−0.88 (m, 6H);^{13}C NMR (75 MHz, $CDCl_3$) δ 202.4, 163.4, 136.6, 131.5, 130.6 (2C), 116.3, 113.8 (2C), 55.6, 52.0, 33.4, 30.8, 21.4, 19.7; IR (neat) 3076, 2960, 2934, 2872, 2840, 1670, 1640, 1599, 1576, 1509, 1463, 1439, 1419, 1388, 1370, 1308, 1259, 1211, 1170, 1114, 1031 cm^{-1}; HRMS (ESI-TOF) m/z calcd for $C_{15}H_{21}O_2$ $[M + H]^+$ 233.1536, found $[M + H]^+$ 233.1530 and calcd for $C_{15}H_{20}NaO_2$ $[M + Na]^+$ 255.1356, found $[M + Na]^+$ 255.1345.

Dilactone 49. Hoveyda−Grubbs' second-generation catalyst (6 mg, 0.01 mmol, 0.05 equiv) was added to a solution of ester **16** (70 mg, 0.20, 1.0 equiv) in toluene (20 mL), and the mixture was heated to reflux for 24 h. The solution was concentrated by blowing air in the flask. The residue was purified by flash chromatography (silica gel, 2.0 cm diameter × 20 cm height, 0:100 to 3:97 ethyl acetate/hexanes) to yield the dilactone **49** (20 mg, 30%): R_f = 0.2 (1:9 ethyl acetate/hexanes); recrystallization from methanol gave white crystals; mp 191−198 °C; $[\alpha]_D^{20}$ −48 (*c* 0.5, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.22−7.13 (m, 4H), 6.91−6.78 (m, 4H), 6.14 (d, *J* = 2.7 Hz, 2H), 5.75−5.60 (m, 2H), 5.54−5.35 (m, 2H), 3.80 (s, 6H), 2.54−2.27 (m, 4H), 2.21 (ddd, *J* = 11.2, 7.9, 3.6 Hz, 2H), 2.14−1.94 (m, 4H), 1.94−1.70 (m, 4H), 1.52−1.42 (m, 2H), 0.98 (d, *J* = 6.7 Hz, 6H), 0.94 (d, *J* = 6.9 Hz, 6H), 0.90 (d, *J* = 6.6 Hz, 6H), 0.78 (d, *J* = 6.9 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.8, 158.6, 132.8, 131.4, 130.0, 127.3, 113.5, 75.3, 55.4, 54.4, 50.1, 34.5, 31.5, 28.2, 25.7, 23.3, 21.2, 20.6, 18.0; IR (neat) 2956, 2932, 2873, 1733, 1513, 1465, 1248, 1148, 1035 cm^{-1}; HRMS (ESI-TOF) m/z calcd for $C_{42}H_{64}NO_6$ $[M + NH_4]^+$ 678.4728, found $[M + NH_4]^+$ 678.4721.

Other fractions were combined to give 28 mg of mixture of head-to-head isomers **50**.

(2*S*,7*R*,*E*)-2-Isopropyl-7-(4-methoxybenzyl)-8-methylnon-4-enoic Acid (Acid 51). TFA (3 drops) was added to a solution of dilactone **49** (17 mg, 0.026 mmol, 1.0 equiv) and triethylsilane (0.10 mL, 0.63 mmol, 24 equiv) in dichloromethane (1 mL). The solution was stirred at room temperature for 10 min. Volatiles were removed under vacuum with a rotary evaporator, and the residue was purified by flash chromatography (silica gel, 1.5 cm diameter × 20 cm height, 100 mL of hexanes then 1:19 ethyl acetate/hexanes) to yield acid **51** (12 mg, 71%) as a clear oil: R_f = 0.14 (1:9 ethyl acetate/hexanes); $[\alpha]_D^{20}$ +27 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 10.74 (s, 1H), 7.07−7.02 (m, 2H), 6.83−6.78 (m, 2H), 5.47−5.29 (m, 2H), 3.78 (s, 3H), 2.50 (dd, *J* = 13.8, 6.6 Hz, 1H), 2.36 (dd, *J* = 13.8, 8.0 Hz, 1H), 2.31−2.12 (m, 3H), 2.00−1.80 (m, 3H), 1.76−1.62 (m, 1H), 1.53−1.40 (m, 1H), 1.00−0.92 (m, 6H), 0.88 (d, *J* = 6.9 Hz, 3H), 0.85 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.6, 157.7, 134.2, 132.0, 130.1, 128.3, 113.7, 55.4, 52.7, 46.4, 35.7, 33.0, 32.7, 30.1, 28.3, 20.4, 20.3, 19.3, 19.0; IR (neat) 2956, 2925, 2871, 1703, 1511, 1244, 1176, 1038 cm^{-1}; HRMS (ESI-TOF) m/z calcd for $C_{21}H_{36}NO_3$ $[M + NH_4]^+$ 350.2690, found $[M + NH_4]^+$ 350.2688 and calcd for $C_{21}H_{32}NaO_3$ $[M + Na]^+$ 355.2244, found $[M + Na]^+$ 355.2248.

Dilactone 52. Pd/C (cat) was added to a solution of the mixture of isomers **50** (28 mg) in methanol/ethyl acetate (6 mL, 1:1). The suspension was purged with H_2 and stirred 24 h. The mixture was then filtered on Celite and concentrated to afford a residue which was purified by flash chromatography (silica gel, 1.5 cm diameter × 20 cm height, 1:9 ethyl acetate/hexanes) to yield dilactone **52** (20 mg, 30% over two steps) as a clear oil: R_f = 0.33 (1:9 ethyl acetate/hexanes); $[\alpha]_D^{20}$ −64 (*c* 0.5, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.19−7.11 (m, 4H), 6.90−6.83 (m, 4H), 6.05 (d, *J* = 1.5 Hz, 2H), 3.79 (s, 6H), 2.22 (td, *J* = 8.7, 2.8 Hz, 2H), 2.00−1.82 (m, 2H), 1.82−1.27 (m, 20H), 0.96−0.84 (m, 18H), 0.81 (d, *J* = 6.9 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.3, 158.7, 132.4, 127.5, 113.6, 76.2, 55.3, 52.7, 50.3, 30.3, 29.7, 29.5, 27.0, 26.9, 25.8, 23.0, 21.5, 20.0, 18.6; IR (neat) 2953, 2934, 2868, 1730, 1608, 1507, 1461, 1379, 1295, 1250, 1172, 1118, 1035 cm^{-1}; HRMS (ESI-TOF) m/z calcd for $C_{42}H_{64}NaO_6$ $[M + Na]^+$ 687.4595, found $[M + Na]^+$ 687.4580.

(2*S*,7*R*)-2-Isopropyl-7-(4-methoxybenzyl)-8-methylnonanoic Acid (Acid 54). Pd/C (cat) was added to a solution of dilactone **49** (4 mg, 0.006 mmol, 1 equiv) in methanol (0.5 mL) and ethyl acetate (0.05 mL). The suspension was purged with H_2, and the reaction was stirred under H_2 atmosphere (H_2 balloon). The reaction was monitored by TLC: R_f = 0.31 (1:9 ethyl acetate/hexanes). When completed, the mixture was filtered through Celite and concentrated to afford 4 mg of the crude dilactone **53**: ^1H NMR (300 MHz, $CDCl_3$) δ 7.18−7.09 (m, 2H), 6.88−6.75 (m, 2H), 6.14 (d, *J* = 1.8 Hz, 1H), 3.77 (s, 3H), 2.15−2.03 (m, 1H), 1.91−1.10 (m, 11H), 0.92 (d, *J* = 6.7 Hz, 6H), 0.83 (d, *J* = 6.6 Hz, 3H), 0.74 (d, *J* = 7.0 Hz, 3H); HRMS (ESI-TOF) m/z calcd for $C_{42}H_{64}NaO_6$ $[M + Na]^+$ 687.4595, found $[M + Na]^+$ 687.4576.

TFA (3 drops) was added to a solution of the crude dilactone **53** (4 mg, 0.006 mmol, 1 equiv) and triethylsilane (0.1 mL, 0.63 mmol, 100 equiv) in dichloromethane (1 mL). The solution was stirred at room temperature for 10 min. Volatiles were removed under vacuum with a rotary evaporator, and the residue was purified by flash chromatography (silica gel, 1.5 cm diameter × 20 cm height, 100 mL of hexanes then 1:19 ethyl acetate:hexanes) to yield acid **54** (3 mg, 75%): $[\alpha]_D^{20}$ +16 (*c* 0.3, $CDCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 9.45 (s, 1H), 7.10−7.02 (m, 2H), 6.84−6.76 (m, 2H), 3.78 (s, 3H), 2.51 (dd, *J* = 13.7, 6.7 Hz, 1H), 2.35 (dd, *J* = 13.7, 7.8 Hz, 1H), 2.17−2.03 (m, 1H), 1.94−1.79 (m, 1H), 1.75−1.62 (m, 1H), 1.62−1.49 (m, 2H), 1.49−1.36 (m, 2H), 1.36−1.08 (m, 5H), 0.96−0.92 (m, 6H), 0.88 (d, *J* = 6.9 Hz, 3H), 0.84 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 179.6, 157.7, 134.5, 130.1, 113.7, 55.4, 52.4, 46.1, 36.3, 30.6, 29.6, 29.5, 28.6, 28.4, 27.7, 20.6, 20.3, 19.3, 16.9; ^{13}C NMR (101 MHz, $CDCl_3$) δ 181.5, 157.7, 134.4, 130.1, 113.7, 55.4, 52.6, 46.1, 36.3, 30.6, 29.5, 29.4, 28.6, 28.2, 27.7, 20.6, 20.2, 19.3, 18.8; IR (neat) 2925, 2860, 1704, 1511, 1461, 1375, 1245,

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1178, 1038 cm^{-1}; HRMS (ESI_NEG) calcd for $C_{21}H_{33}O_3$ $[M - H]^-$ 333.2435, found $[M-H]^-$ 333.2440.

Lactone 55. 2,2,2-Trichloroethylsulfamate (14 mg, 0.061 mmol, 1.1 equiv) was added to a solution of lactone **20** (18 mg, 0.055 mmol, 1.0 equiv) in toluene (0.3 mL) followed by magnesium oxide (6 mg, 0.15 mmol, 2.7 equiv) and rhodium trifluoroacetamide dimer (2 mg, 0.003 mmol, 0.04 equiv). The resulting pale blue slurry was cooled to 0 °C, diacetoxyiodobenzene (27 mg 0.083 mmol, 1.5 equiv) was added, and the reaction was slowly warmed to room temperature. The progress of the reaction was monitored by TLC analysis (30:70 ethyl acetate−hexanes, CAM). After 20 h of stirring at room temperature, TLC analysis showed no more conversion. The reaction mixture was diluted with dichloromethane, filtered through a pad of Celite, and then washed with dichloromethane (3 × 10 mL). The solvent was removed under reduced pressure to leave a brown oil which was purified by flash column chromatography (silica gel, 1.5 cm diameter ×20.0 cm height, 1:19 ethyl acetate/hexanes) to yield compound **55** (8 mg, 0.014 mmol; 25%) and starting material **20** (8 mg, 0.024 mmol, yield based on recovered starting material: 47%): R_f = 0.27 (1:9 ethyl acetate/hexanes); $[\alpha]_D^{20}$ −19 (*c* 0.8, $CDCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, *J* = 8.7 Hz, 1H), 6.89 (d, *J* = 8.7 Hz, 1H), 5.85 (d, *J* = 6.3 Hz, 1H), 4.80 (s, 1H), 3.81 (s, 1H), 2.94 (ddd, *J* = 12.2, 6.8, 2.6 Hz, 1H), 2.81 (ddd, *J* = 10.1, 6.8, 3.0 Hz, 1H), 2.48−2.39 (m, 1H), 2.32−2.25 (m, 1H), 2.21−1.99 (m, 1H), 1.97−1.87 (m, *J* = 14.6, 11.3, 6.2 Hz, 1H), 1.51−1.41 (m, 1H), 1.03 (t, *J* = 6.8 Hz, 3H), 0.88 (d, *J* = 6.6 Hz, 2H), 0.77 (d, *J* = 6.6 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.2, 159.8, 129.2, 128.9, 114.1, 93.1, 79.5, 77.1, 55.4, 49.1, 48.1, 44.1, 43.6, 29.6, 26.9, 26.0, 23.4, 22.6, 21.7, 20.2, 19.7; IR (neat) 2959, 2931, 2873, 2839, 1733, 1612, 1515, 1464, 1369, 1250, 1178, 1118 cm^{-1}; HRMS (ESI-TOF) *m*/*z* calcd for $C_{23}H_{33}NO_6SCl_3$ $[M + H]^+$ 556.1089, found $[M + H]^+$ 556.1075.

■ ASSOCIATED CONTENT

Supporting Information

^1H and ^{13}C NMR spectra of new compounds as well as X-ray crystallography reports and CIF files for compounds **20**, **25**, **32**, **33**, **39**, and **49**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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