Université de Montréal

Ring-opening of Cycloalkane Epoxides and Aziridines with Aromatic Amines - Toward the Total Synthesis of Pactamycin

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Abbreviations

$[\alpha]_D$	specific rotation
Ac	acetyl
Bn	benzyl
Boc	*tert*-butoxylcarbonyl
δ	chemical shift in ppm
COSY	correlation spectroscopy
^oC	degrees Celsius
dd	doublet of doublets
d	doublet
DCM	dichloromethane
DEPBT	3-(diethoxyphosphoryloxy)-1,2,3-benzotriazin-4(3H)-one
DMAP	dimethylaminopyridine
2,2-DMP	2,2-dimethoxypropane
DMSO	dimethyl sulfoxide, methyl sulfoxide
dt	doublet of triplets
Et	ethyl
eq (equiv.)	equivalent
ESI/MS	electrospray ionisation-mass spectrometry
g	gram
h	hour(s)
HRMS	high resolution mass spectrum
Hz	hertz
IR	infrared
J	coupling constant
m	multiplet

μ	micro (10^{-6})
μL	microliter
m-CPBA	*meta*-chloroperoxybenzoic acid
Me	methyl
mg	milligram
min.	minute
MHz	megahertz
mL	milliliter
mmol	millimole
Ms	mesyl
MS	molecular sieves
Ph	phenyl
PMB	*para*-methoxybenzyl
PMBTCA	*para*-methoxybenzyl trichloroacetimidate
PTSA	*para*-toluenesulfonic acid
ppm	parts per million
Py.	pyridine
q	quartet
rt	room temperature
s	singlet
sec	second(s)
t	triplet
TBAF	tetrabutylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
t-Bu	*tert*-butyl
TEA (NEt_3)	triethylamine

tert	tertiary
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
Ts	tosyl

Abstract

Ring-opening reactions of epoxides and aziridines have been extensively studied. The influence of different protecting groups on the hydroxyl group in the ring-opening reactions of *cis*- and *trans*- 3-hydroxy-1,2-cycloalkane epoxides with aromatic amines was studied. It was shown that $Yb(OTf)_3$ in toluene was a mild catalyst for regioselective ring-opening, to give β-anilino cycloalkanols in good yields. Heating the reaction mixture accelerated the rate of the reaction, albeit at the expense of yield. The aniline moiety was regioselectively added at the carbon furthest from the hydroxyl or ether group to yield a single regioisomer. The same trend was also observed with 3-azidocyclohex-1-ene epoxides and the corresponding 3-carbamates. The reaction time became shorter when acetonitrile was used as solvent, possibly due to the homogeneous medium.

Ytterbium(III) triflate has also been used as the catalyst for the regioselective ring-opening of unactivated aziridines in cyclohexanes having an azide or benzyl ether substituent. Azide ion or aniline forms the corresponding *trans*-products giving access to vicinal diamines in good yields.

A racemic ω-alkoxy *p*-methoxy benzyl ether HDAC inhibitor has been prepared in 8 synthetic steps (26% overall yield) from 1-((*tert*-butyldiphenylsilyl)oxy)hept-6-en-2-ol. This is an improvement over the published method (9 steps, 16% overall yield). The cross-metathesis method proved to be efficient and practical in this strategy, and alkylation using *p*-methoxybenzyl trichloroacetimidate in the presence of $Sc(OTf)_3$ improved the overall yield of the synthesis.

An amino alcohol that contains all the core carbons, functional groups and the required stereochemistry present in pactamycin was obtained starting from L-threonine over 27 steps. The methodology described in this thesis allows for a synthesis of this key intermediate on a multigram scale.

Key words: epoxide, aziridine, $Yb(OTf)_3$, *p*-methoxybenzyl trichloroacetimidate, HDAC inhibitor, pactamycin, L-threonine

Résumé

Cette thèse consiste en trois thèmes résumés dans les paragraphes ci-dessous. L'influence de différents groupements protecteurs du groupe hydroxyle lors des réactions d'ouverture des *cis*- et *trans*- 3-hydroxy-1,2-époxycycloalcanes a été étudiée. Il a été montré que $Yb(OTf)_3$ constituait un catalyseur doux pour l'ouverture régiosélective de cycles afin d'obtenir les β-anilino cycloalcanols correspondants avec de bons rendements. Le chauffage du milieu réactionnel dans le toluène comme solvant a permis d'augmenter la cinétique de la réaction, au dépend du rendement. La partie aniline a été régiosélectivement introduite en position vicinale du groupe hydroxyle ou éther afin d'obtenir un unique régioisomère. La même tendance a été observée avec les époxydes du 3-azidocyclohex-1-ène et du 3-carbamate correspondant. Le temps de réaction a été réduit lorsque $Yb(OTf)_3$ a été dissous dans l'acétonitrile. Le triflate d'ytterbium (III) a également été utilisé comme catalyseur pour l'ouverture de cycle régiosélective d'aziridines non-activées sur des cyclohexanes portant des substituants azotures ou éthers de benzyle. L'ion azoture ou l'aniline forment les produits *trans* correspondants, donnant alors accès à des diamines vicinales avec de bons rendements.

Un éther ω-alcoxy *p*-méthoxybenzylique racémique, inhibiteur de HDAC, a été ainsi préparé en huit étapes synthétiques (rendement total de 26%) à partir du 1-((*tert*-butyldiphénylsilyl)oxy)hept-6-èn-2-ol. Ceci représente un progrès par rapport à la précédente méthode (9 étapes, rendement total de 16%). La métathèse croisée se montre particulièrement efficace et pratique dans cette stratégie et l'alkylation par le trichloroacétimidate de *p*-méthoxybenzyle en présence de $Sc(OTf)_3$ améliore le rendement global de la synthèse.

Un aminoalcool présent dans la pactamycine et contenant le squelette carboné, les groupements fonctionnels et la stéréochimie requise a été synthétisé en 27 étapes à partir de la L-thréonine. La méthodologie décrite dans cette thèse permet la synthèse de cet

intermédiaire clé à l'échelle multigramme.

Mots clés: époxyde, aziridine, $Yb(OTf)_3$, trichloroacétimidate de *p*-méthoxybenzyle, inhibiteur de HDAC, pactamycine, L-thréonine

Chapter One

Ring-opening of
Cycloalkane Epoxides and Aziridines with Aromatic Amines

1.1 Ring-opening of cycloalkane epoxides with aromatic amines

1.1.1 Introduction

Epoxides are among the most versatile intermediates in organic synthesis. In addition, a number of biologically significant molecules contain epoxides within their structures[1]. Ring-opening reactions of epoxides have been extensively studied with a large number of nucleophiles[2], such as halides, alkoxides, thioalkoxides, azides, etc as well as carbon-based nucleophiles leading to β-substituted alcohols.

β-Amino alcohols are important intermediates as unnatural amino acids[3] and as chiral auxiliaries[4] in asymmetric processes. The aminolysis of epoxides is one of the most common practical methods for the preparation of β-amino alcohols [5].

1.1.2 Epoxide formation

A classical method to prepare epoxides is the peroxidation of an olefin, also known as the Prilezhaev reaction[6]. In 1959, Henbest and Wilson observed that upon treatment with perbenzoic acid, 2-cyclohexen-1-ol affords the *syn*-epoxy alcohol as the predominant product. The stereochemical outcome of this transformation was rationalized based on a transition structure largely involving the "butterfly mechanism"[7] as shown in Figure 1.1. The interaction of the nucleophilic alkene with the electrophilic peracid was postulated relying on the formation of a hydrogen bond formed between the hydroxyl group and one of the peracid oxygens leading to delivery of the reagent to the olefin face *syn* to the hydroxyl group.

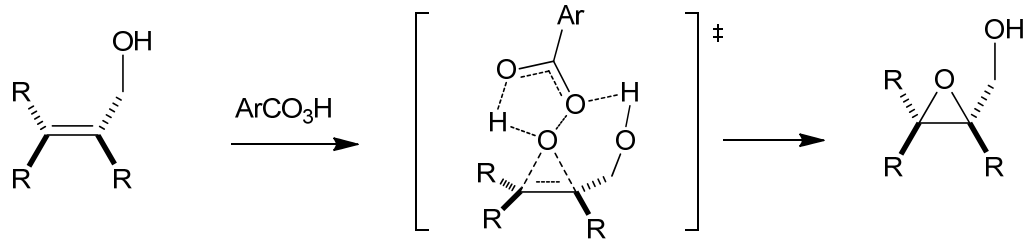


Figure 1.1 Butterfly Mechanism

In the case of allylic ethers, no such interaction is available with common peracids, and *anti* epoxidation is mainly observed. However, epoxidation with trifluoroperacetic acid (TFPA)[8] or perbenzimidic acid [Ph-C(=NH)OOH], generated *in situ* from PhCN and H_2O_2 (Payne reaction)[9], usually lead to the *syn* epoxides[10]. The transition state models for both cases are shown in Figure 1.2.

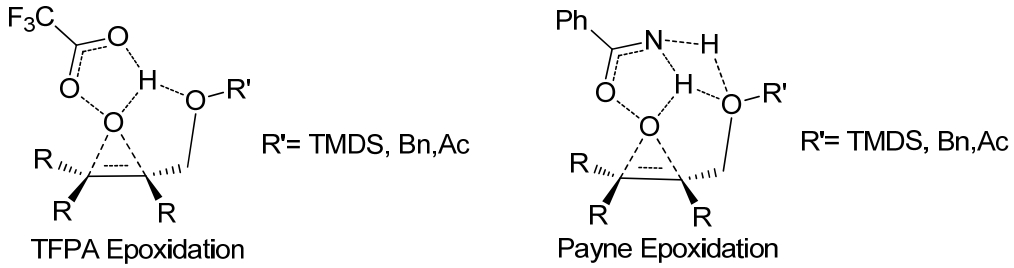


Figure 1.2 Transition state of epoxidation

1.1.3 Epoxide opening reactions

The nucleophilic opening of epoxides has been studied extensively since it provides a suitable route to the formation of C-C, C-N, C-O or C-S σ-bonds[1]. The ring-opening of epoxides by amines can form *β*-amino alcohols, a useful building block in the synthesis of natural products. Despite many studies on regio- and stereoselectivity in epoxide opening reactions[11], the opening of epoxy alcohols and the corresponding ethers with aromatic anilines[12] has received less attention[13].

The classical method for the preparing of *β*-amino alcohols is direct aminolysis of epoxides at elevated temperature with excess of amine[14], which is not only detrimental to other functional groups, but also to the control of regioselectivities. Several catalysts have been used in order to overcome these problems. These include the use of: 1) metal salts[15] (lithium, sodium, magnesium and calcium), 2) metal amides[16] (lithium, magnesium, lead, tin, and amide cuprate), 3) metal alkoxides[17] (DIPAT, Ti(O*i*Pr)$_4$, 4) metal triflates[18] (lithium, copper, Ph_4SbOTf), 5) alumina[19], 6) microwave assisted solvent-free montmorillonite clay[20], 7) transition metal halides[21] ($TaCl_5$, $ZrCl_4$, VCl_3, $ZnCl_2$), 8) rare earth metal halides[22] ($SmI_2(THF)_2$, $CeCl_3.7H_2O$), 9) transition metal salts

under solvent-free conditions[23], 10) ionic liquids[24], and 11) $Bi(OTf)_3$ and $Bi(TFA)_3$ under microwave irradiation[25] and 12) hetero poly acids[26]. Some of these methods suffer from one or more limitations such as the use of costly chemicals, refluxing temperatures, inert atmosphere conditions, low regioselectivity, side reactions, etc.

The growing popularity of lanthanide salts in organic synthesis stems from their ease of handling, robustness towards moisture and air, as well as unique reactivity and selectivity. Over the past few years, lanthanide trifluoromethanesulfonates (triflates), $Ln(OTf)_3$ have been used as Lewis acid to activate a variety of reactions[27] including epoxide opening reactions.

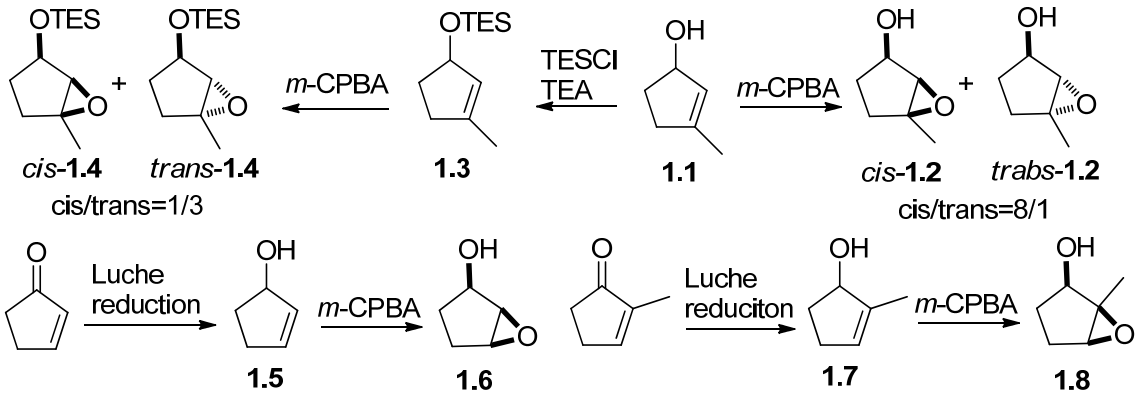
Research objective: In conjunction with an ongoing project toward the total synthesis of pactamycin (see Chapter 3), we explored the opening of an epoxide in a model cyclopentane ring with a variety of anilines. We were therefore led to study the reaction in five and six-membered ring model compounds as outlined in this Chapter.

1.1.4 Results and discussion

1.1.4.1 Synthesis of model epoxides

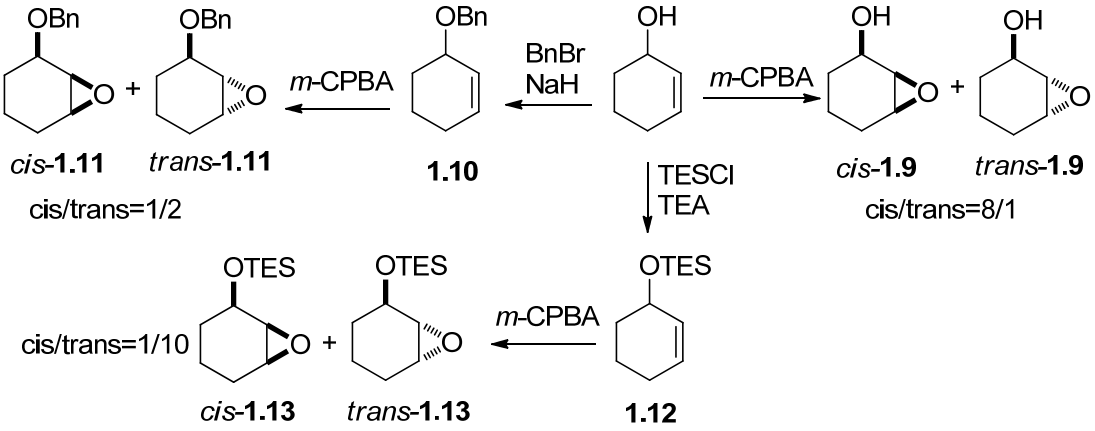
The model epoxides were formed by oxidizing the unsaturated alcohols with *m*-chloroperbenzoic acid (*m*-CPBA)[28], one of the most commonly used, commercially available oxidants in the epoxidation of simple alkenes. The *trans*- and *cis*-isomers were separated by flash column chromatography. All epoxides used in this study were racemic.

The *m*-CPBA oxidation of the unsaturated alcohol **1.1**, which was obtained by Luche reduction[29] of 3-methylcyclopent-2-enone, afforded an 8:1 mixture of *cis*-**1.2** and *trans*-**1.2** epoxy alcohols. When *m*-CPBA oxidation was performed on the TES protected unsaturated alcohol **1.3**, an 1:3 mixture of epoxides *cis*-**1.4** and *trans*-**1.4** could be separated by flash chromatography. Epoxides **1.6** and **1.8** were obtained by the same manner as for **1.2** (Scheme 1.1).



Scheme 1.1 Five-membered ring epoxide formation

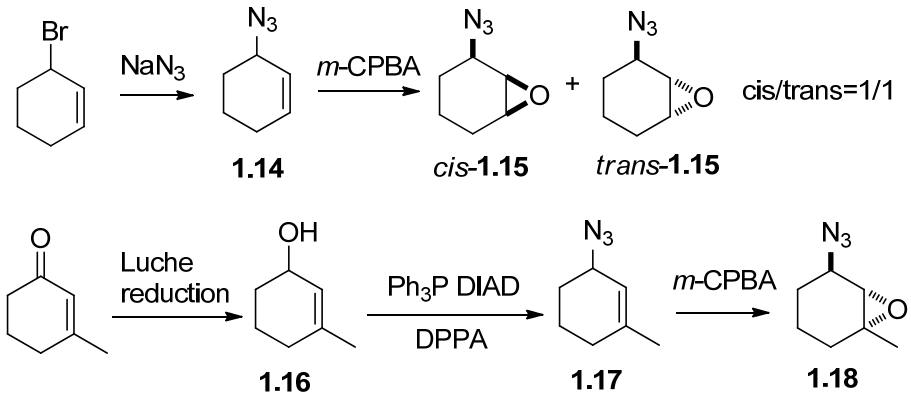
Epoxides *cis*-**1.9** and *trans*-**1.9** were obtained in a ratio of 8:1 *cis/trams* respectively by directed oxidation of 2-cyclohexenol with *m*-CPBA. Treatment of 2-cyclohexenol with BnBr/NaH afforded the allylic benzyl ether **1.10**, which was oxidized with *m*-CPBA to give an 1:2 mixture of the benzylated *cis*-**1.11** and *trans*-**1.11** epoxides. 2-Cyclohexenol was protected by TES group to give **1.12**, which was oxidized with *m*-CPBA to afford an 1:10 mixture of *cis*-**1.13** and *trans*-**1.13** epoxy alcohol ethers (Scheme 1.2).



Scheme 1.2 Six-membered ring epoxide formation

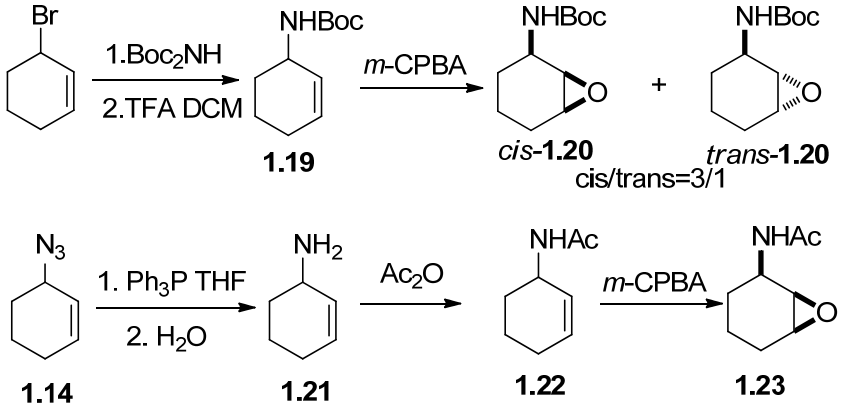
3-Bromocyclohexene was treated with sodium azide to form 3-azido cyclohexene[30] **1.14**, which was oxidized with *m*-CPBA to give *cis*-**1.15** and *trans*-**1.15** epoxy azides as an 1:1 separable mixture. Treatment of 3-methylcyclohexenone under Luche reduction conditions afforded 3-methylcyclohexenol **1.16**, which was treated with

diphenylphosphoryl azide (DPPA), diisopropyl azodicarboxylate (DIAD) and PPh_3 (Mitsunobu reaction[31]) to form the 3-azido-1-methylcyclohexene **1.17**. Oxidation with *m*-CPBA gave epoxy azide **1.18** (Scheme 1.3).



Scheme 1.3 Azido cyclohexane epoxide formation

The *N*-Boc-protected allylic amine **1.19**, prepared from 3-bromocyclohexene with di-*tert*-butyl imidodicarbonate (Boc_2NH) [32], was oxidized to the corresponding epoxides *cis*-**1.20** and *trans*-**1.20** with *m*-CPBA in a ratio of 3:1. Treatment of **1.14** with PPh_3 and H_2O (Staudinger reaction[33]) afforded allylic amine **1.21**, which was acetylated to give **1.22**, then oxidized with *m*-CPBA to afford **1.23** (Scheme 1.4)**.**



Scheme 1.4 NHBoc and NHAc epoxide formation

1.1.4.2 Epoxide opening reactions with anilines

1.1.4.2.1 Five-membered ring epoxide opening with anilines

Reaction of five-membered ring *cis*-epoxy alcohols and the corresponding TES ethers in the presence of 10 mol% $Yb(OTf)_3$ were studied. In each case, attack took place at the epoxide carbon atom furthest from the substituent to give *trans*-1,2-anilino cycloalkane alcohols as shown in Table 1.1. The introduction of anilines occurred with inversion of configuration at C-3 (The numbers in the structures are for simplification). Reaction media were heterogeneous in toluene, see p21.

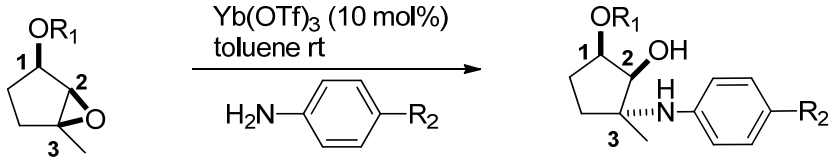


Table 1.1 Five-membered ring *cis*-epoxy alcohol/TES ether opening reactions

Entry	Epoxide	R_1	R_2	Product	Time (day)	Yield (%)[a]
1	*cis*-**1.2**	H	H	**1.24a**	2	76
2	*cis*-**1.2**	H	Cl	**1.24b**	3	74
3	*cis*-**1.2**	H	Br	**1.24c**	3	73
4	*cis*-**1.2**	H	OMe	**1.24d**	1.5	72
5	*cis*-**1.4**	TES	H	**1.25a**	8	70
6	*cis*-**1.4**	TES	Cl	**1.25b**	11	69
7	*cis*-**1.4**	TES	Br	**1.25c**	11	68
8	*cis*-**1.4**	TES	OMe	**1.25d**	5	71

a. Yields are for isolated compounds.

In Table 1.2 are listed the results for the opening of five-membered ring *trans*-epoxy alcohols and the corresponding TES ethers.

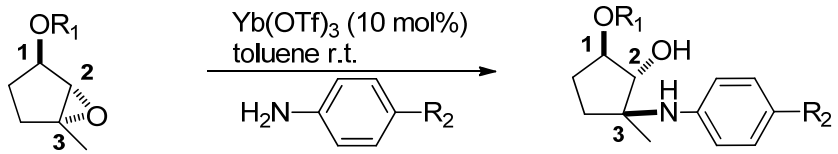


Table 1.2 Five-membered ring *trans*-epoxy alcohol/TES ether opening reactions

Entry	Epoxide	R_1	R_2	Product	Time (day)	Yield (%)[a]
1	*trans*-**1.2**	H	H	**1.26a**	2	75
2	*trans*-**1.2**	H	Cl	**1.26b**	3	71
3	*trans*-**1.2**	H	Br	**1.26c**	3	74
4	*trans*-**1.2**	H	OMe	**1.26d**	2	73
5	*trans*-**1.4**	TES	H	**1.27a**	3	72
6	*trans*-**1.4**	TES	Cl	**1.27b**	4	75
7	*trans*-**1.4**	TES	Br	**1.27c**	4	70
8	*trans*-**1.4**	TES	OMe	**1.27d**	2	74

a. Yields are for isolated compounds.

Usually, unsymmetrical epoxides undergo regioselective addition of the nucleophiles to the less substituted carbon[15]. However, all the anilines were added to the more substituted position in the case of five-membered ring epoxy alcohols and ethers (Tables 1.1, 1.2). An X-ray structure confirmed the regioselectivity of addition for **1.26d** (Figure 1.3).

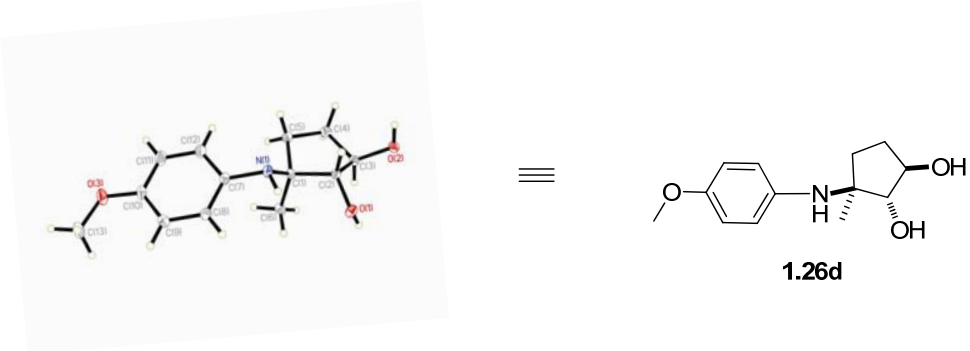
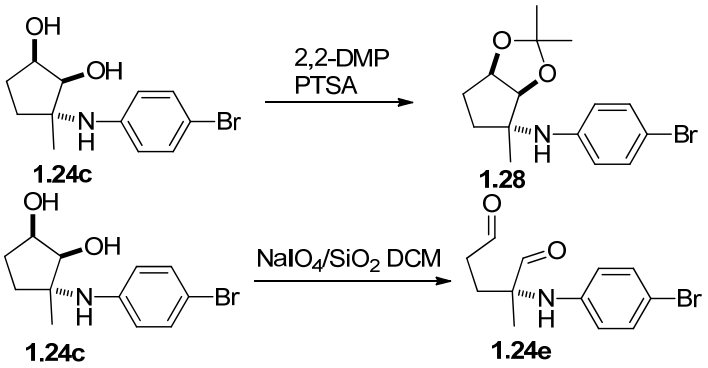


Figure 1.3 X-ray of **1.26d**

We therefore assumed that the other analogues gave the same regioselectivity. For the *trans*-epoxy TES ether **1.27d**, cleavage of the TES group gave **1.26d**, thus confirming the regioselectivity in the epoxy alcohols series as well (Tables 1.1, 1.2, entries 1-4).

For the products of the *cis*-epoxy alcohols, exemplified by **1.24c,** treatment with 2,2-dimethoxypropane and a catalytic amount PTSA afforded the protected diol **1.28.** Diol **1.24c** could be cleaved with silica gel supported $NaIO_4$[34] to the dialdehyde **1.24e** (Scheme 1.5).



Scheme 1.5 The regioselectivity of the opening reactions of *cis*-epoxy alcohols

It is thought that this type of epoxide opening reaction is a borderline S_N2 reaction[35], in which the nucleophile is further away than usual from the site of attack. The driving force of the reaction is provided more by transfer of electrons from carbon to oxygen than from nucleophile to carbon. In the presence of a Lewis acid, it is supposed that the C-2 carbon carries a fractional positive charge in the transition state, in which bond breaking is more important than bond making (Figure 1.4). Therefore electron donating substituents stabilize the positive charge and facilitate the bond breaking. Conversely, electron withdrawing substituents inhibit the bond breaking.

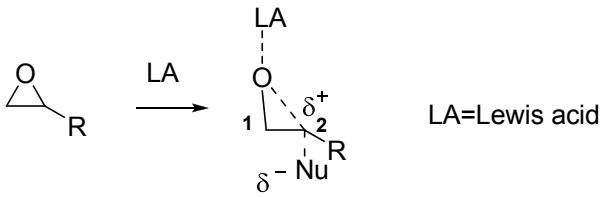
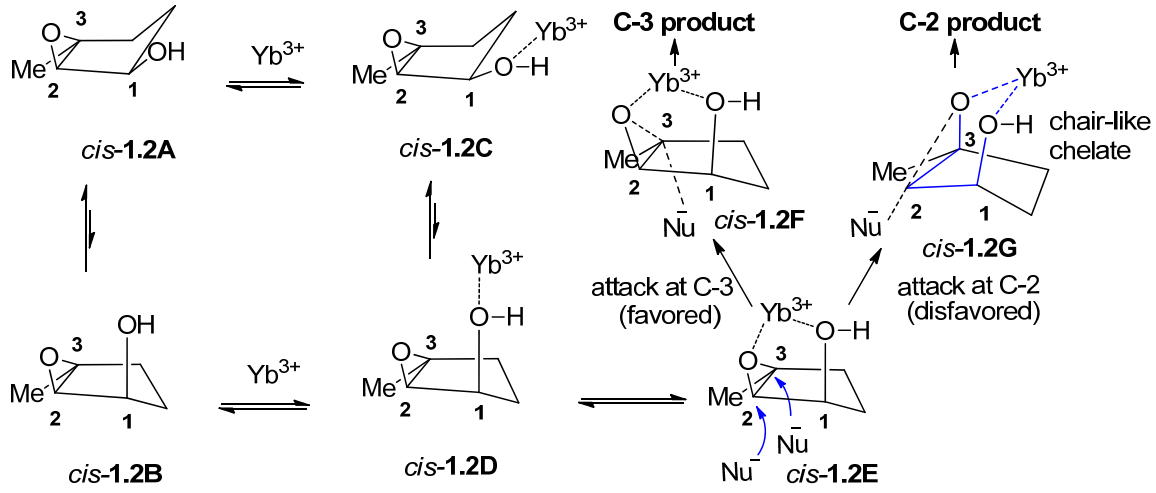


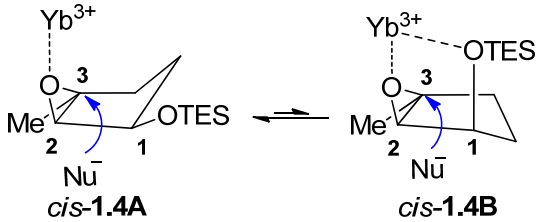
Figure 1.4 The borderline S_N2 mechanism of epoxide opening reaction

Among the two conformations of *cis*-**1.2** (*cis*-**1.2A** and *cis*-**1.2B)**, the latter can also engage the Lewis acid $Yb(OTf)_3$ and the epoxide oxygen in bidentate fashion (*cis*-**1.2D** to *cis*-**1.2E**). Nucleophilic attack at C-3 of *cis*-**1.2F** in a chair-like six-membered ring in a borderline S_N2 type modality may also be enhanced by the inductive effect of the methyl group in the bond-breaking step (Scheme 1.6). As a result, the C-3 regioselectivity was observed in all cases.



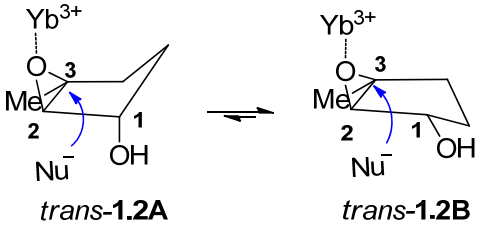
Scheme 1.6 Possible mechanism for the regioselectivity for epoxy alcohol *cis*-**1.2**

In the case of the silyl ethers (Table 1.1, entries 5-8), S_N2 attack of the anilines also takes place at C-3, possibly by activation of the epoxide oxygen atom. Conformations related to *cis*-**1.4B** may be less favored for OTES ether due to the steric bulk of the silyl group[36]. The epoxide opening reaction of the *cis*-epoxy TES ether took much longer time than the corresponding hydroxyl isomers. This may be due to the ineffective coordination to the $Yb(OTf)_3$ as in *cis*-**1.4B** due to the bulk of the TES ether (Scheme 1.7).



Scheme 1.7 The regioselectivity of epoxide opening of *cis*-**1.4**

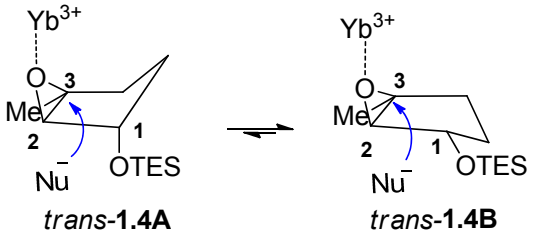
The corresponding *trans*-epoxy alcohol, exemplified by *trans*-**1.2** (Table 1.2, entries 1-4) reacted at a similar rate compared to the *cis*-isomers, which indicates that activation of the epoxide oxygen without a bidentate chelation is equally effective for the cleavage reaction (Scheme 1.8).



trans-**1.2A** *trans*-**1.2B**

Scheme 1.8 The regioselectivity of epoxide opening for epoxy alcohol *trans*-**1.2**

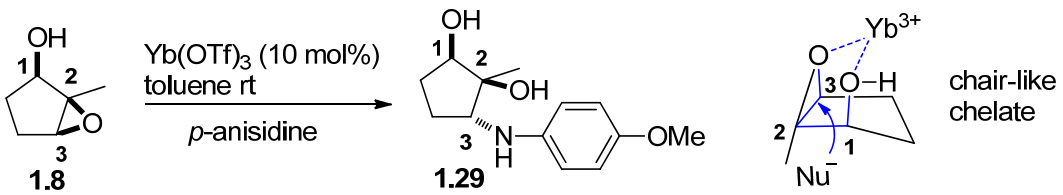
In the OTES *trans*-series (Table 1.2, entries 5-8), the pseudo equatorial ether orientations *trans*-**1.4B** is favored. Coordination occurs mostly on the epoxide oxygen and attack is favored at C-3 (Scheme 1.9) for the reasons discussed above in conjunction with the presence of the methyl branch.



trans-**1.4A** *trans*-**1.4B**

Scheme 1.9 The regioselectivity of epoxide opening for epoxy TES ether *trans*-**1.4**

We then studied the epoxide opening of a regioisomer having the methyl group at C-2. Opening still occurred at C-3 (Scheme 1.10). The regioisomeric C-2 ring-opening product would have given a symmetrical molecule, easily distinguished by ^{1}H and ^{13}C NMR. The reason for this selectivity remains to be explained.

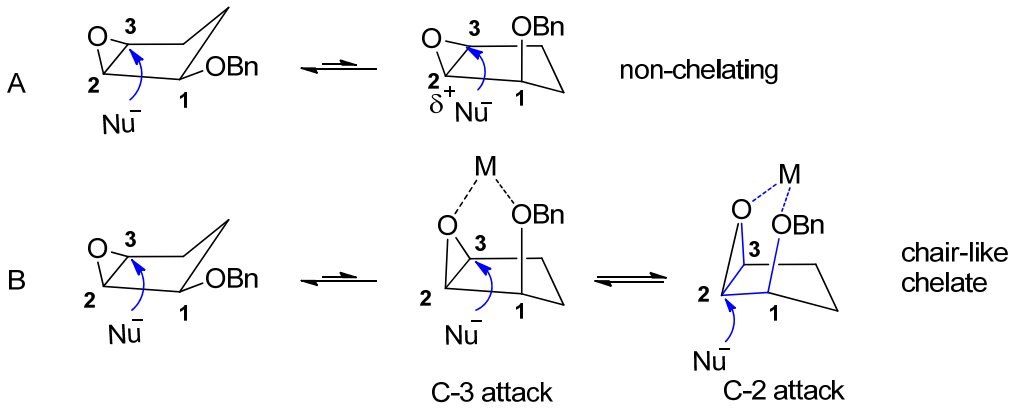


1.8 **1.29**

Scheme 1.10 Epoxide opening reaction of **1.8** with *p*-anisidine

From Tables 1.1 and 1.2, we could see that when there was an electron withdrawing group (Cl, Br) on the *para* position of the aniline, the epoxide opening reactions time became longer. Conversely an electron donating group (OMe) led to shorter reaction time. However, the reaction time of the *trans*-epoxy TES ether (Table 1.2, entries 5-8) was much less than the *cis*-isomer, possibly due to a more efficient coordination of $Yb(OTf)_3$ with the epoxide oxygen than the corresponding *cis*-isomer.

It has been reported that the opening of 1-(benzyloxy)-cyclopentane 2,3-epoxides with various nucleophiles can be subject to variable results depending on the nature of the nucleophile and the presence or absence of chelating agents[37]. For example, Crotti and coworkers reported that in the absence of a chelating agent, attack is favored mostly at C-3, the carbon furthest away from the electronegative ether substituent. While in the presence of a chelating agent, C-2 is preferentially attacked (Scheme 1.11).



Scheme 1.11 Regioselectivity of epoxide opening under chelation or non-chelating conditions

It has been postulated that the electron-withdrawing nature of the ether group cannot stabilize the epoxide carbon atom as the bond-breaking event is in progress and the nucleophile attacks at the distal carbon C-3 carbon atom (Scheme 1.11, A). When chelation takes place, a chair-like chelate can be attacked at the stereoelectronically more favored C-2, overriding the inductive effect of the ether substituent.

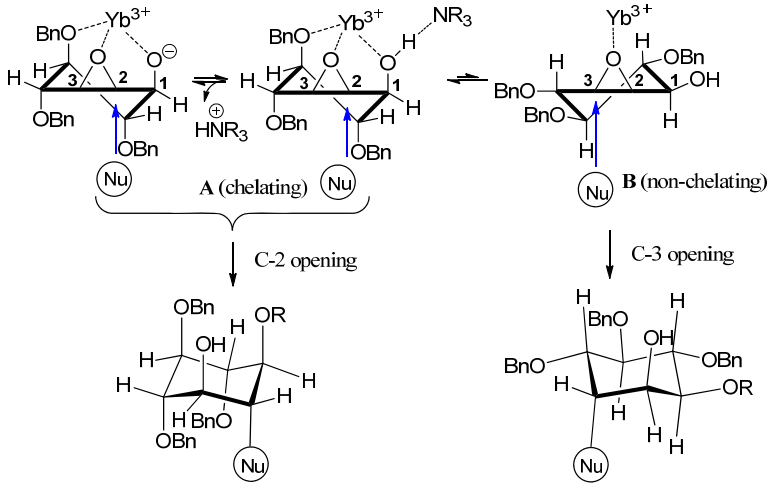
The exclusive epoxide ring-opening at C-3 in our C-3 methyl substituted analogues in the presence of $Yb(OTf)_3$ can be rationalized based on the electron-withdrawing hydroxyl or ether group and the stabilizing effect of the C-3 methyl group on the developing positive charge as the bond breaking event is in progress. Consequently a borderline S_N2 type reaction results with the aniline attacking at the more substituted carbon extremity of the epoxide (Scheme 1.6).

These results are contrary to those reported by Crotti, where chelation through a chair-like intermediate (Scheme 1.11, B) favors attack at C-2. Evidently, in our case, the electrondonating ability of the C-3 methyl group overrides other factors. This means to hold true whether or not the hydroxyl group is free or substituted.

Attack at C-3 in the case of the C-2 methyl epoxide **1.8** may be guided by a stereoelectronically more favorable trajectory in a chair-like chelate (Scheme 1.10).

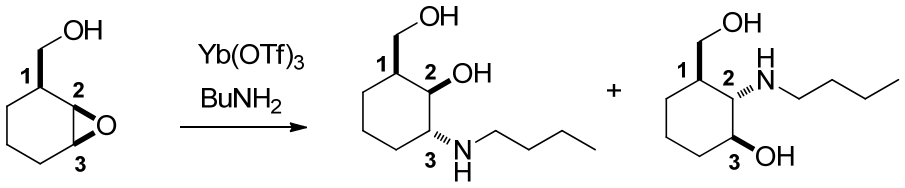
1.1.4.2.2 Six-membered ring epoxide opening with anilines

Recently, a chelation-controlled aminolysis of cyclitol epoxide with $Yb(OTf)_3$ was reported by Serrano[12b], regioselective attack at C-2 was interpreted as a result of a stereocontrolled *trans*-diaxial opening[38] of **A** through an "all-axial" conformation stabilized by lanthanide chelation (Scheme 1.12).



Scheme 1.12 All-axial conformation that stabilized by $Yb(OTf)_3$ chelation

A simplified model by the same author indicated that at least three coordination sites were needed for an effective chelation-controlled $Yb(OTf)_3$ catalysis to give the C-2 regioselectivity (Scheme 1.13).



Scheme 1.13 Regioselectivity under chelation conditions in the presence of $Yb(OTf)_3$

We studied the opening of *cis*- and *trans*- six-membered ring epoxides with different anilines as shown in Tables 1.3 and 1.4.

In this case, we studied the effect of an alcohol, TES and benzyl ethers on the regioselectivity of epoxide opening with anilines in the presence of $Yb(OTf)_3$.

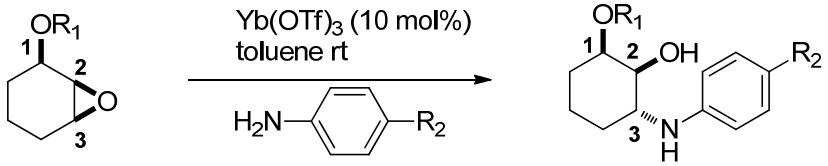


Table 1.3 Six-membered ring *cis*-epoxide opening reactions with aromatic amines

Entry	Epoxide	R_1	R_2	Product	Time (day)	Yield (%)[a]
1	*cis*-**1.9**	H	H	**1.30a**	1.5	79
2	*cis*-**1.9**	H	Cl	**1.30b**	2	74
3	*cis*-**1.9**	H	Br	**1.30c**	2	74
4	*cis*-**1.9**	H	OMe	**1.30d**	1	75
5	*cis*-**1.9**	H	F	**1.30e**	2	73
6	*cis*-**1.11**	OBn	H	**1.31a**	2	71
7	*cis*-**1.11**	OBn	Cl	**1.31b**	2	70
8	*cis*-**1.11**	OBn	Br	**1.31c**	2	69

9	*cis*-**1.11**	OBn	OMe	**1.31d**	1	72
10	*cis*-**1.13**	TES	H	**1.32a**	3	74
11	*cis*-**1.13**	TES	Cl	**1.32b**	3	70
12	*cis*-**1.13**	TES	Br	**1.32c**	3	70
13	*cis*-**1.13**	TES	OMe	**1.32d**	2	73

a. Yields are for isolated compounds.

Results for the *trans*-epoxide are shown in Table 1.4.

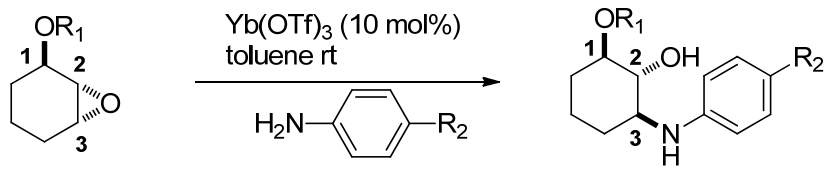


Table 1.4 Six-membered ring *trans*-epoxide opening reactions with aromatic amines

Entry	Epoxide	R_1	R_2	Product	Time (day)	Yield (%)[a]
1	*trans*-**1.9**	H	H	**1.33a**	1.5	72
2	*trans*-**1.9**	H	Cl	**1.33b**	2	73
3	*trans*-**1.9**	H	Br	**1.33c**	2	77
4	*trans*-**1.9**	H	OMe	**1.33d**	1	77
5	*trans*-**1.9**	H	F	**1.33e**	2	75
6	*trans*-**1.11**	Bn	H	**1.34a**	3	72
7	*trans*-**1.11**	Bn	Cl	**1.34b**	3	68
8	*trans*-**1.11**	Bn	Br	**1.34c**	3	69
9	*trans*-**1.11**	Bn	OMe	**1.34d**	2	70
10	*trans*-**1.13**	TES	H	**1.35a**	4	71
11	*trans*-**1.13**	TES	Cl	**1.35b**	4	72
12	*trans*-**1.13**	TES	Br	**1.35c**	4	70

13	*trans*-**1.13**	TES	OMe	**1.35d**	3	73

a. Yields are for isolated compounds.

In all cases, the aniline moiety was introduced at C-3 to give the *trans*-products in good yields. In general, electron donating groups on the anilines led to relatively shorter reaction times (Table 1.3, entries 4, 9, 13). An X-ray crystal study of **1.34b** confirmed the relative stereochemical assignment (Figure 1.5). After cleavage of the benzyl group of **1.34b** by hydrogenation on Pd/C, and the cleavage of the TES group of **1.35b** with TBAF, the NMR data of the obtained epoxy alcohols were identical to **1.33b**. For the *cis*-epoxy alcohol, the C-3 regioselectivity could be determined by NMR analysis. The products arising from a C-2 opening could have been easily distinguished from their C-3 opening regioisomers, since both ^{1}H and ^{13}C NMR would have been simplified due to the symmetry of the molecule. The same trends were found in the case of the *trans*-six-membered epoxy alcohols and ethers. Reaction times for the TES ethers were longer compared to the *cis*-series (Table 1.4, entries 10-13).

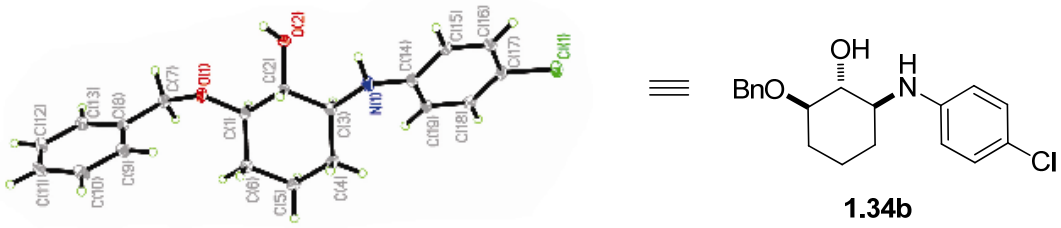
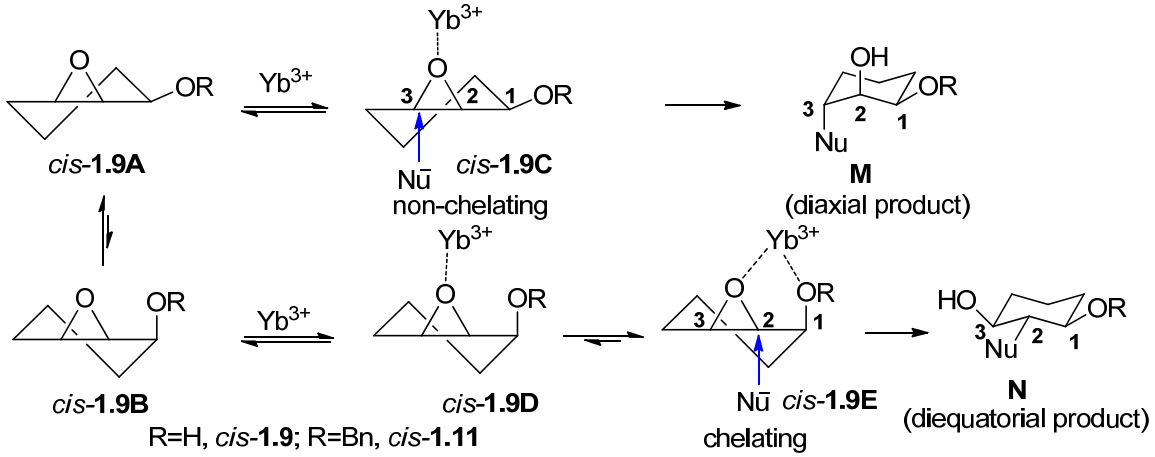


Figure 1.5 X-ray of **1.34b**

The reason of the C-3 regioselectivity of the *cis*-epoxy alcohols and benzyl ethers could be rationalized on conformational grounds exemplified by *cis*-**1.9** and *cis*-**1.11** (Scheme 1.14). In accordance with the Fürst-Plattner rule[39], the attack of the nucleophile on the chelate structure *cis*-**1.9C** should occur at the C-3 carbon to yield the initially formed diaxial product **M**. For chelate structure *cis*-**1.9E**, attack should occur at the C-2 carbon to yield the diequatorial product **N**. Crotti and coworkers have found that the C-2

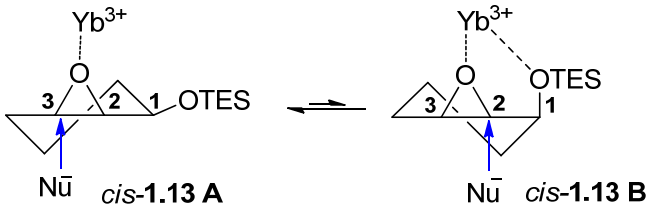
selectivity depended largely on the type of the nucleophile. When strong nucleophile, such as PhSH, H^- were used, the C-2 selectivity was increased[40]. For aniline, resonance of the N lone pair with the adjacent JI system decreases the availability of the lone pair and makes it a poorer nucleophile. Complete C-3 regioselectivity was observed.



Scheme 1.14 Mechanism of the regioselectivity of *cis*- six-membered epoxy alcohols/benzyl ethers

The C-3 regioselectivity of the *cis*-epoxy TES ethers could be explained due to 1,3-non bonded diaxial strain effect in the trajectory of attack of the aniline. Complete C-3 regioselectivity was observed.

The ring-opening reaction time of *cis*-epoxy TES ethers *cis*-**1.13** was a little longer than the corresponding free hydroxyl isomer *cis*-**1.9**, possible due to the inefficient coordination of the epoxide and the $Yb(OTf)_3$ and the steric bulk of the adjacent TES ether. However, the epoxide opening reaction time of the epoxy benzyl ether *cis*-**1.11** were almost the same as their corresponding hydroxyl isomers, possibly because OBn and OH both could easily coordinate with $Yb(OTf)_3$ (Scheme 1.15).



Scheme 1.15 The coordination of the *cis*-epoxy TES ethers

1.1.4.2.3 Effect of ring size

A comparative study was done in the epoxide ring-opening of *cis*-five and six-membered ring epoxides with aniline and *p*-anisidine (Table 1.5). In general, reactions were a little faster in the six-membered series (Table 1.5, entries 3, 4). As expected, reactions with the electron donating aniline analogue were relatively faster.

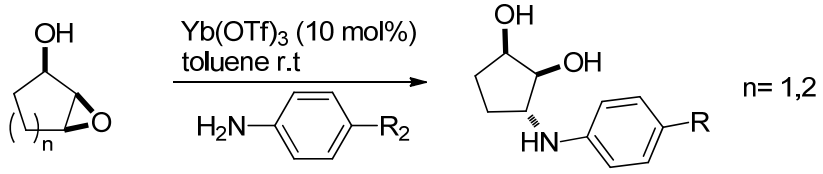


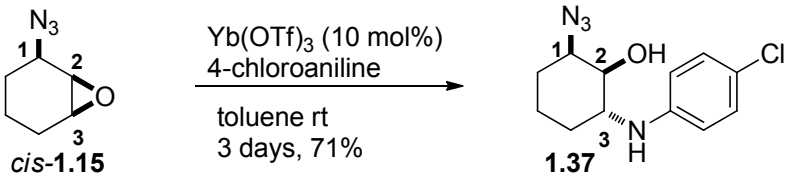
Table 1.5 Effect of ring size

Entry	n	R	Compound	Yield (%)[a]	Time (day)
1	1	H	**1.36a**	70	2
2	1	OMe	**1.36b**	72	1.5
3	2	H	**1.30a**	79	1.5
4	2	OMe	**1.30d**	75	1

a. Yields are for isolated compounds.

1.1.4.2.4 Six-membered ring-opening of azide epoxides with anilines

In order to diversity the effect of substituent, we explored the opening of 3-azido-1,2-cyclohexane epoxides. Treatment with various anilines afforded good yields of the *trans*-opening products with the previously observed regioselectivity. In general, reactions were slower, requiring 2-4 days for completion at rt (Table 1.6).



Regioselective opening at C-3 was observed based on an X-ray analysis as shown in Figure 1.6.

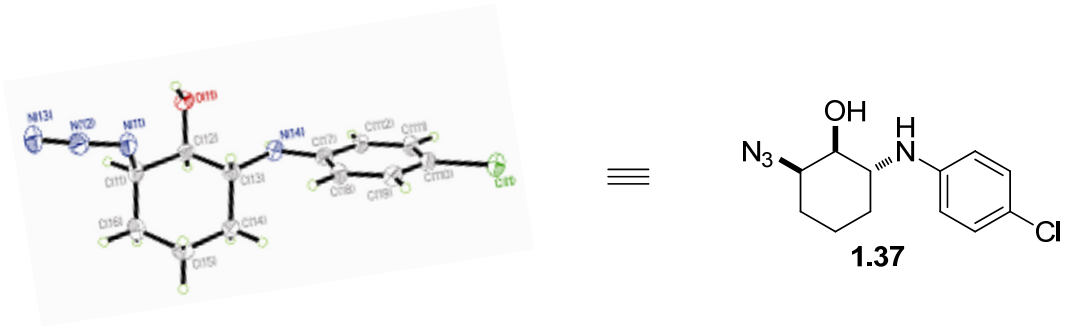


Figure 1.6 X-ray of **1.37**

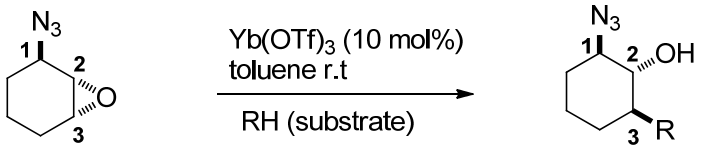
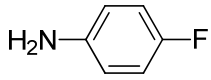
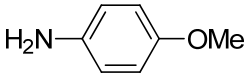
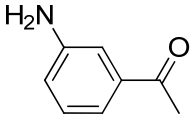
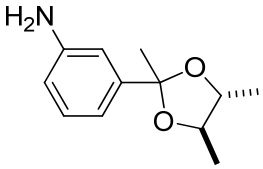


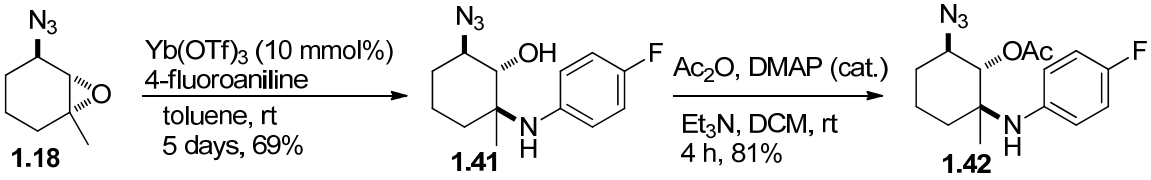
Table 1.6 Epoxy azide opening reactions with different anilines

Entry	Compound	RH (substrate)	Time (day)	Yield (%)[a]
1	**1.38a**		4	78
2	**1.38b**		3	77
3	**1.39**		4	78

4	**1.40**		2	78

a. Yields are for isolated compounds.

The regioselectivity of the ring-opening of 3-azidocyclohex-1-ene epoxide was confirmed by single-crystal X-ray analysis of **1.42** (Figure 1.7), which was prepared from **1.18** (Scheme 1.16).



Scheme 1.16 Preparation of **1.42**

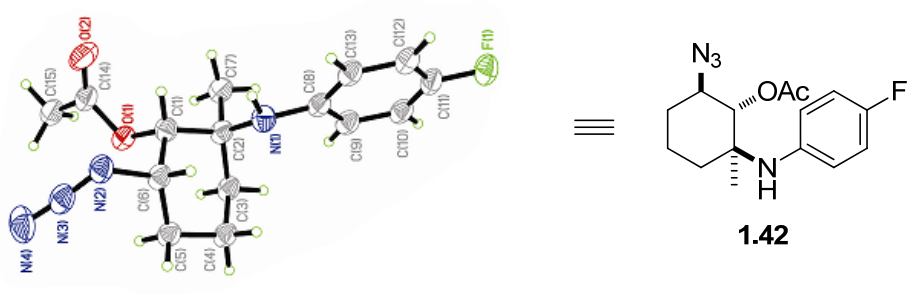
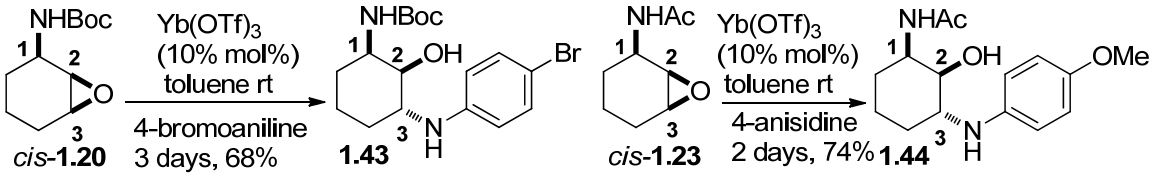


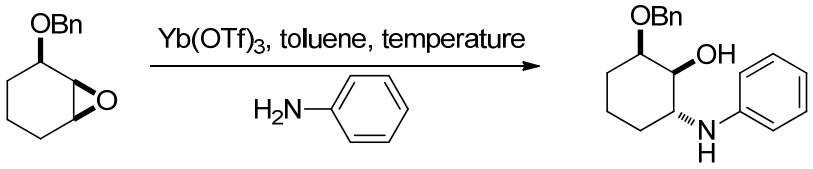
Figure 1.7 X-ray of **1.42**

The epoxide opening reactions of the corresponding NHBoc and NHAc epoxides were also studied, resulting in the C-3 adducts that are shown in Scheme 1.17.



Scheme 1.17 Epoxide ring-opening reactions of epoxy NHBoc and NHAc

1.1.4.2.5 Effects of reaction temperature and solvent



The results of varying the temperature in the cyclohexane epoxide series and the solubility of the $Yb(OTf)_3$ in the toluene are shown in Table 1.7. Heating the reaction mixture accelerated the rate of the reaction, albeit at the expense of yield.

Table 1.7 Different reaction temperatures

Entry	Catalyst	Temperature	Solubility	Time (h)	Yield (%)[a]
1	$Yb(OTf)_3$ (10%)	rt	7 mg/100mL	48	71
2	$Yb(OTf)_3$ (10%)	40 ^oC	12 mg/100mL	20	66
3	$Yb(OTf)_3$ (10%)	80 ^oC	17 mg/100mL	6	54

a. Yield are for isolated compounds

We also studied the nature of the solvent in which the Lewis acid was soluble, thus reaction times were shorted at rt in CH_3CN or aniline (neat), while yields remained good (Table 1.8).

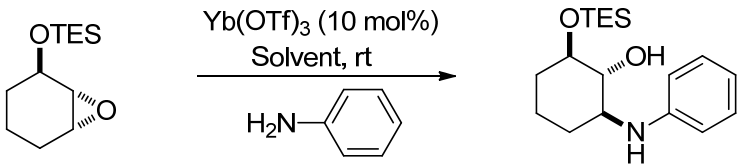


Table 1.8 Different solvents

Entry	Solvent	Time (day)	Yield (%)[a]
1	toluene	4	71
2	CH_3CN	2	73
3	aniline	2	70

a. Yields are for isolated compounds

It should be noted that the epoxide opening reactions were efficient even though the medium was heterogeneous in toluene. Thus, the small amount of dissolved $Yb(OTf)_3$ appears to be sufficient to activate the epoxide oxygen atom with or without chelation. However, the higher solubility in acetonitrile resulted in relatively shorter reaction time but did not improve the yield. In a control experiment, it was shown that $Yb(OTf)_3$ was not coordinated to the acetonitrile (^1H, ^{13}C, ^{19}F NMR with CD_3CN)

1.1.4.2.6 Different catalysts

Different catalysts were tried for the epoxide ring-opening reactions as shown in Table 1.9. There are a number of reports in the literature describing the opening of epoxides in the presence of different catalysts such as the ones listed.

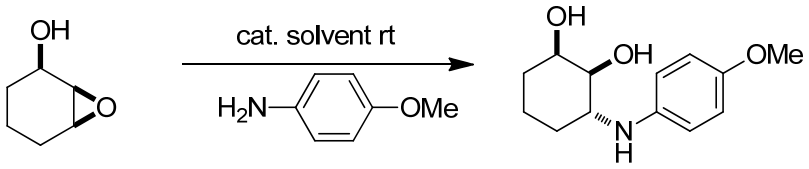


Table 1.9 Different catalysts

Entry	Catalyst	Solvent	Time	Yield (%)[a]
1	$SnCl_2$[11] (10%)	CH_3CN	5 days	61
2	$CuSO_4$[18] (10%)	Toluene	4 h	32
3	VCl_3[21] (10%)	DCM	7 h	71
4	$LiClO_4$[12](10%)	CH_3CN	24 h	33

5	$Yb(OTf)_3$[12] (10%)	Toluene	24 h	77
6	----	Toluene	4 days	11
7	$H_3PMo_{12}O_{40}$[26]	H_2O	10 days	10

a. Yields are for isolated compounds.

Among these, the most efficient catalyst was $CuSO_4$ in toluene, followed by VCl_3.

1.1.5 Conclusion

The influence of different protecting groups on the hydroxyl group in the ring-opening reactions of *cis*- and *trans*- 3-hydroxy-1,2-cycloalkane epoxides with aromatic amines was studied. It was shown that $Yb(OTf)_3$ was a mild catalyst for regioselective ring-opening affording β-anilino cycloalkanols in good yields. The aniline moiety was regioselectively added at the carbon furthest from the hydroxyl or ether group to yield a single regioisomer. The reaction time became shorter when $Yb(OTf)_3$ was dissolved in acetonitrile.

The same trend was also observed with 3-azidocyclohex-1-ene epoxides and the corresponding 3-carbamates.

1.2 Ring-opening of cycloalkane aziridines

1.2.1 Introduction

Aziridines[1], the nitrogen analogues of epoxides, are synthetically important compounds. Furthermore, some natural products that contain an aziridine ring such as mitomycin C, exhibit both anti-tumor and antibiotic activity[41].

Due to the diminished electronegativity of nitrogen compared to oxygen, ring-opening reactions of aziridines are less facile than the corresponding reactions of epoxides. The reactivity of this strained heterocyclic ring system is dependent upon the nature of the substituent on the nitrogen atom. Electron withdrawing groups enhance the reactivity of

the ring. A number of nucleophilic ring-opening reactions have been studied on such activated aziridines with various nucleophiles[42]. Fewer examples are known for the ring-opening of non-activated aziridines (*N*-alkyl or aryl) mainly due to their lack of reactivity.

1.2.2 Aziridine formation

Compared to the diversity of the procedures used for the preparation of the analogous epoxides, the scope of the synthetic methods available for the preparation of aziridines is rather narrow. Classical methods for the synthesis of N-aryl aziridines are: 1) Ring closure of N-aryl amino alcohol by Gabriel and Wenker synthesis[43]. 2) Addition of carbenoids to imines or addition of nitrenoids to electron deficient alkenes catalyzed either by Lewis acid or transition metal complexes[44]. 3) The cyclodehydration of N-alkyl amino alcohol using triphenylphosphine dihalide and diethoxytriphenylphosphorane[45].

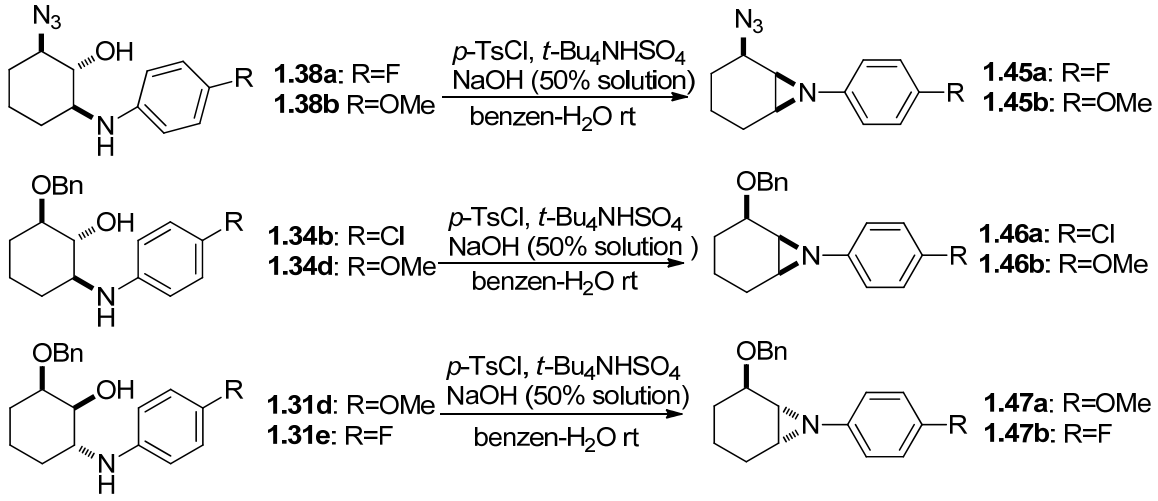
1.2.3 Aziridine opening reactions

Several nucleophilic ring-opening reactions have been studied on activated and non-activated aziridines (*N*-alkyl or aryl)[46]. The ring-opening reaction of aziridines with nitrogen nucleophiles such as the azide[47] ion and aromatic amines[48] have special significance, because the products are azido amines and vicinal diamines, which have varied applications in organic synthesis[49]. The ring-opening reactions of mainly activated aziridines by amines have been reported in the presence of lanthanide triflates as catalysts[50]. While working on epoxide cleavage reactions with aromatic amines, we discovered that aziridines were efficiently cleaved with aromatic amines in the presence of $Yb(OTf)_3$.

1.2.4 Results and discussion

1.2.4.1 Synthesis of model aziridines

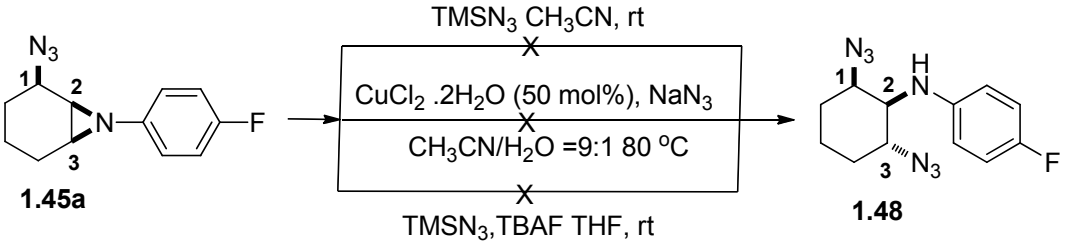
All the aziridines (**1.45a**, **1.45b**, **1.46a**, **1.46b**, **1.47a**, **1.47b**) were formed by reaction of *N*-aryl amino alcohols with *p*-toluenesulphonyl chloride (*p*-TsCl) under phase transfer catalytic conditions[51] (Scheme 1.18).



Scheme 1.18 Aziridine formation

1.2.4.2 Aziridine opening with azide

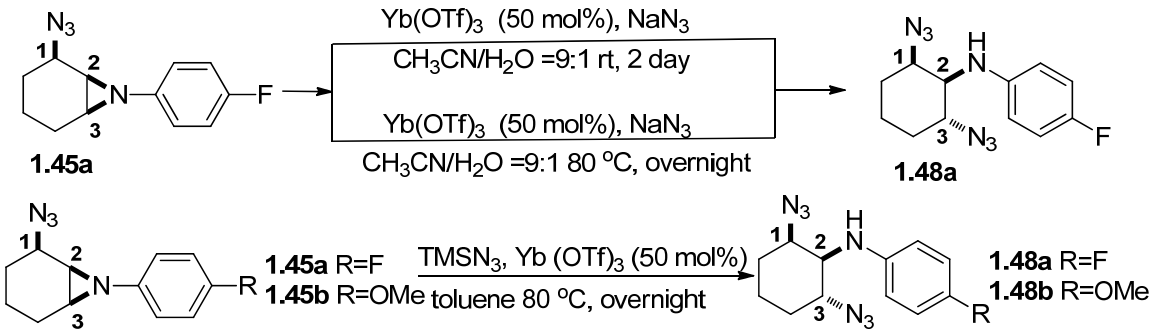
Generally, the vicinal azidoamines are prepared by ring-opening reactions of aziridines with azide. Singh and co-workers had[46] reported that non-activated aziridine could be opened with $TMSN_3$ in the absence of Lewis acid, and with NaN_3 in the presence of $CuCl_2.2H_2O$[52]. Another report describes the ring-opening of aziridines with $TMSN_3$ by using TBAF as a trigger[53]. However, all these methods failed to open the aziridine azide **1.45a** (Scheme 1.19).



Scheme 1.19 Attempted aziridine opening reactions

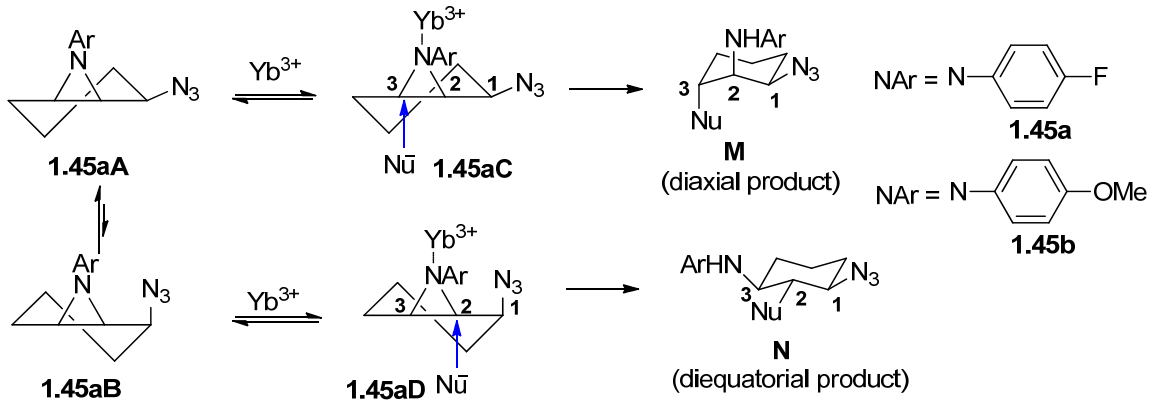
When the reaction of **1.45a** was carried out in the presence of 50 mol% $Yb(OTf)_3$ instead of $CuCl_2.2H_2O$ at rt, a 10% yield of **1.48a** was obtained after stirring 2 days. When heated to 80 ^{o}C, the reaction gave a yield of 77%. While treating **1.45a** and **1.45b**

with $TMSN_3$, a similar result was observed (Scheme 1.20). NMR analysis indicated regioselective opening at C-3.



Scheme 1.20 Aziridine opening reactions with NaN_3 and $TMSN_3$

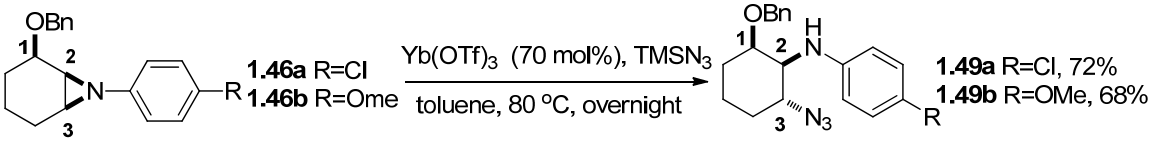
The need for a large amount of $Yb(OTf)_3$ is due to the diminish by considering coordinating ability of the aziridine nitrogen. The regioselectivity could be explained that the conformation **1.45aD** was less stable than conformation **1.45aC**, based on a diaxial opening of the aziridine at the C-3 in chair conformation corresponding to **1.45aC** (Scheme 1.21).



Scheme 1.21 The regioselectivity of the *cis*-aziridine azide opening reactions

When the azide group on the six-membered ring was replaced by a benzyl ether (**1.46a**, **1.46b**), the aziridine opening reaction with $TMSN_3$ required 70 mol% $Yb(OTf)_3$ as catalyst (Scheme 1.22). The reason was not clear, although the oxophilic $Yb(OTf)_3$ may

be coordinated by the OBn in spite of the electron donating ability of the *p*-methoxy group on the aryl ring. The regioselective attack at C-3 was confirmed by an X-ray analysis of **1.49b** (Figure 1.8).



Scheme 1.22 *cis*-Aziridine benzyl ether opening reaction with $TMSN_3$

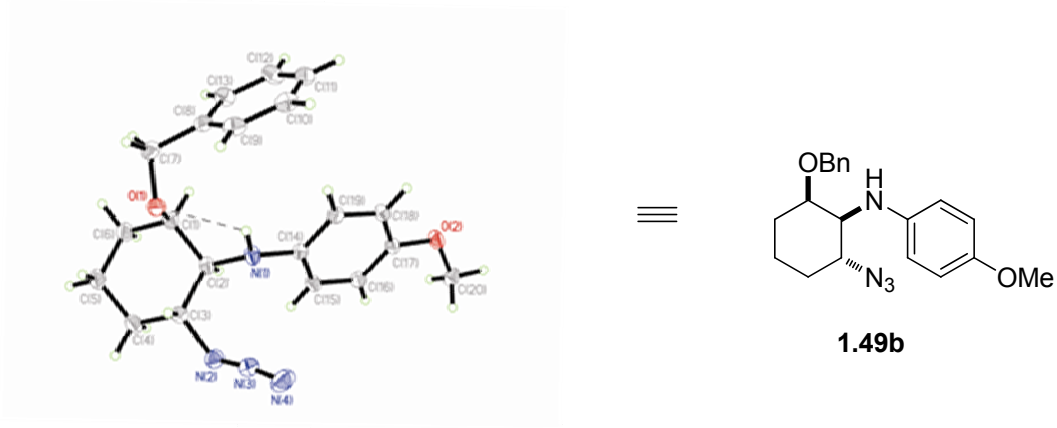
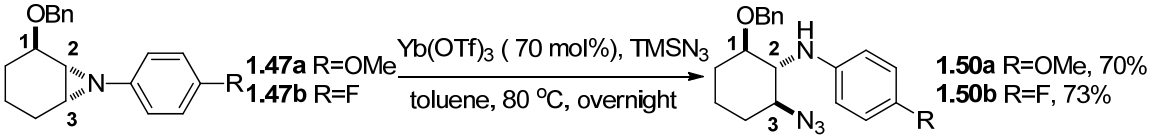


Figure 1.8 X-ray of **1.49b**

The opening of *trans*-aziridine benzyl ether (**1.47a**, **1.47b**) with $TMSN_3$, also afforded the C-3 opening product **1.50a**, **1.50b** (Scheme 1.23). This could be rationalized in the same manor as discussed for the epoxide analogues.

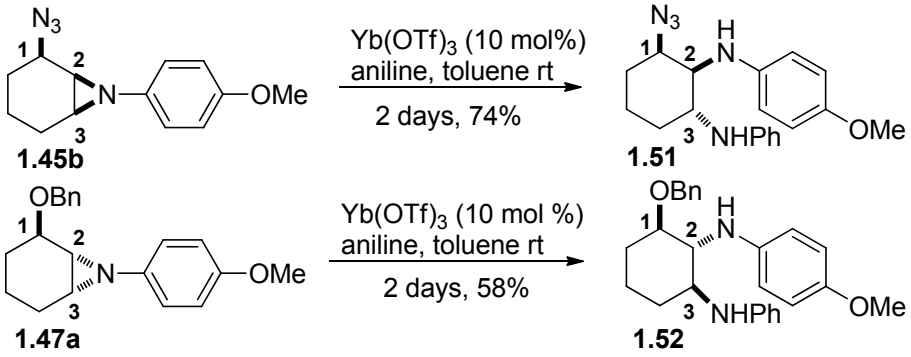


Scheme 1.23 *Trans*-aziridine benzyl ether opening reactions with $TMSN_3$

1.2.4.3 Aziridine opening with aniline

The aziridine ring-opening reactions with aniline were studied, for which there were only few examples in the literature[48]. The reaction could be performed at rt and low

catalyst loading (10 mol%) giving C-3 regioselectivity (Scheme 1.24) , which was proved by an X-ray analysis of **1.51** (Figure 1.9).



Scheme 1.24 Aziridine opening reactions by aniline

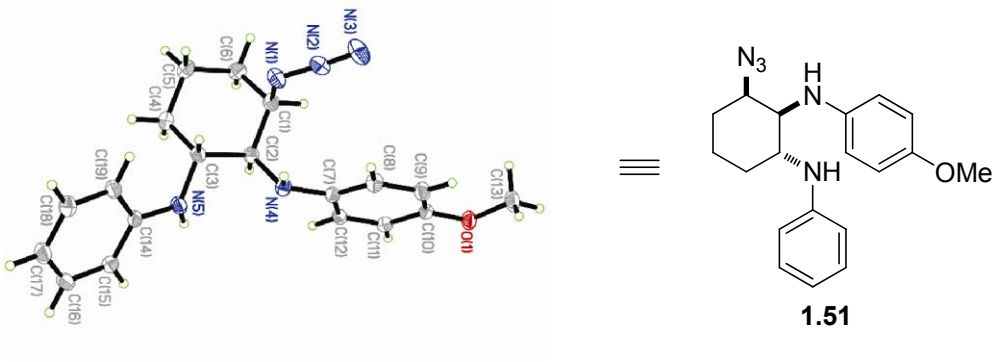


Figure 1.9 X-ray of **1.51**

1.2.5 Conclusions

$Yb(OTf)_3$ has been used as the catalyst for the regioselective ring-opening of unactivated aziridines in cyclohexanes having an azide or benzyl ether substituent. Azide ion or aniline forms the corresponding *trans*-products giving access to vicinal diamines in good yields.

1.3 Experimental procedures

General Experimental Notes

All original data are available from Professor Stephen Hanessian, Université de Montréal.

All yields reported are isolated yields except where indicated. The regio- stereoselectivity was determined by NMR and/or X-Ray.

All commercially available reagents were used without further purification. All reactions were performed under argon atmosphere and monitored by thin-layer chromatography or/and MS.

Spectra of nuclear magnetic resonance of proton (^{1}H NMR) and carbon-13 (^{13}C NMR) were recorded on a Bruker AV-300 (300 MHz)，400 (400 MHz) in a deuterated solvent as indicated with $CDCl_3$ (H, δ=7.27 ppm；C, δ=77.23 ppm) or CD_3OD (H, δ=4.87, 3.31 ppm；C, δ=49.15 ppm) as the internal reference. Chemical shifts (δ) and coupling constants (*J*) are expressed in ppm (part per million) and Hz (Herz), respectively. When necessary, assignments were aided by DEPT, COSY, NOESY, HMBC and HMQC correlation experiments. All chemical shifts are measured from the center of the resolved peaks, the unresolved multiplet and broad peaks are normally indicated as a range.

Low- and high-resolution mass spectra were recorded using fast atom bombardement (FAB) or electrospray techniques.

Infrared spectra (IR) were recorded on a Perkin-Elmer FTIR Paragon 1000 with a KBr pellet.

Optical rotations were recorded in a 1 dm cell at 20 ^{o}C (PerkinElmer 343).

The X-Ray diffraction measurements were performed by Dr. Michel Simard and Dr. Benoit Deschenes Simard with a Nonius CAD-4 diffractometer and monochromatic radiation.

Anhydrous Reaction Conditions

The glass vessels, luer lock syringes, needles and stirring bars were oven-dried at 110-140 ^{o}C or flame-dried with a propane torch, and cooled to rt under a current of dry argon. Micro-syringes were dried under vacuum using an oil pump at rt for at least 2 hours prior to use.

Chromatography

Flash chromatography was performed using (40-60 μm) silica gel at increased pressure.

Thin layer chromatography (TLC) was performed using commercial precoated glass-backed Sillca Gel 60 F254 plates with a layer thickness of 250 μm (E. Merck). Visualization was performed by ultraviolet light and/or by staining with ceric ammonium molybdate, potassium permanganate. The technique was used to follow the course of reactions, to determine the suitable solvent system for flash chromatography, a mixture of ethyl acetate-hexane on v/v basis, as indicated, was used as eluant.

TLC visualization

UV 254 lamp was used to view TLC plates with UV light active compounds. To develop plates, they were dipped into the stain solution and heated to develop the colored spots.

(a) CAM (Molybdate-ceric solution)

This solution was prepared by dissolving 2.5 g of $(NH_4)_6Mo_7O_{24}.4H_2O$ and 1.0 g of $Ce(SO_4)_2$ in a solution of 90 mL of distilled water and 10 mL of concentrated H_2SO_4.

(b) Potassium Permanganate

This stain is prepared by dissolving 3 g of $KMnO_4$ and 20 g of K_2CO_3 in 5 mL of 5% NaOH and 300 mL of water.

Solvents

Hexane, ethyl acetate and dichloromethane were distilled to remove any nonvolatile material for chromatography and general use.

Anhydrous solvents such as THF, ether, DCM and toluene were taken from the SDS (*Solvent Delivery System*).

1.3.1 Representative procedures

The procedure of the Luche reduction (method A)

Sodium boron hydride (1.2 equiv.) was added portion-wise to a stirred solution of enone and $CeCl_3.7H_2O$ (1.5 equiv.) in MeOH (4 mL/mmol enone) at 0 ^oC. The resulting suspension was allowed to warm to rt and stirred at rt for 2 h. Saturated NH_4Cl was added to the suspension, and the layers were separated. The aqueous layer was extracted with DCM and the combined organic layers were washed with water, dried over Na_2SO_4 and concentrated under reduced pressure, the residue was purified by flash column chromatography (ethyl acetate/hexanes) to give the corresponding enol.

General epoxidation procedure (method B)

To a solution of the corresponding cyclohexene or cyclopentene in DCM (4 mL/mmol olefin), was added *m*-CPBA (2.0 equiv.) at 0 ^oC in small portions. The solution was allowed to warm to rt and stirred vigorously for 3-5 h. The resulting suspension was filtered, and the solute was washed with saturated solutions of sodium bisulfate and $NaHCO_3$, and finally with brine. The solution was dried over Na_2SO_4, and concentrated under reduced pressure, the residue was purified by flash column chromatography (ethyl acetate/hexanes) to give the corresponding epoxides.

General procedure for the epoxide opening reactions (method C)

To a stirred solution of the epoxide (1 mmol) in toluene (3 mL), was added $Yb(OTf)_3$ (10 mol%) and the aniline analogue (1.5 equiv.). The suspension was stirred at rt until total conversion (TLC check). The reaction mixture was concentrated under reduced pressure,

and the residue was purified by the flash column chromatography (ethyl acetate/hexanes) to give the corresponding amino alcohols.

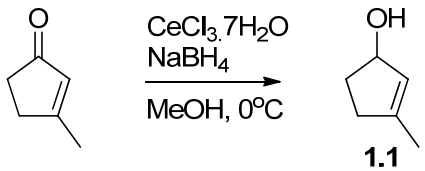
General aziridine formation procedure (method D)

To a stirred solution of the *N*-ary-*β*-amino alcohol (0.05 mol) in benzene (50 mL), was added *p*-toluenesulfonyl chloride (0.06 mol), tetrabutylammonium hydrogensulphate (0.2 equiv.) and 50% aqueous solution of NaOH (5 mL). After stirred at rt for 3 days, the reaction mixture was extracted twice with ethyl acetate (25 mL × 2). The organic layers were combined, washed several times with water and brine, dried over Na_2SO_4, and concentrated under reduced pressure to a residue, that was purified by the flash column chromatography to give the corresponding aziridines.

General aziridine opening reaction procedure (method E)

To a stirred solution of the *N*-aryl aziridine (0.2 mmol) in toluene (3.5 mL), $Yb(OTf)_3$ (70 mmol% or 10 mmol%) and $TMSN_3$ (5 equiv.) or aniline (1.2 equiv.) were added. The reaction mixture was stirred untill total conversion was observed by TLC at 80 °C or at rt, quenched with H_2O and extracted with DCM twice. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography, eluting with ethyl acetate/hexane, evaporation of the collected fractions afforded the corresponding azido amine or diamine product.

1.3.2 Epoxide formation



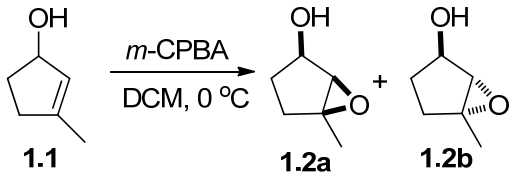
1.1

3-Methylcyclopent-2-enol

Compound **1.1** was prepared according to the general procedure (method A**)** starting

from the 3-methylcyclopentenone (13.0 g, 135.2 mmol), $CeCl_3.7H_2O$ (39.2 g, 202.8 mmol) and $NaBH_4$ (5.1 g, 135.2 mmol) in MeOH (300 mL) at 0 °C. Purification by the flash column chromatography with ethyl acetate/hexane (1:4) as eluant afforded **1.1** (10.6 g, 80%) as a colorless oil. (The NMR data are identical with the literature)[54]

^{1}H NMR (300 MHz $CDCl_3$): δ 5.51-5.47 (m, 1H), 4.60 (s, 1H), 2.47-2.35 (m, 1H), 2.32-2.22 (m, 1H), 2.18-2.09 (m, 1H), 1.78 (s, 3H), 1.76-1.74 (m, 1H).



Compounds *cis*-**1.2** and *trans*-**1.2** were prepared according to the general procedure (method B) starting from **1.1** (5 g, 51.0 mmol), *m*-CPBA (25 g, 102 mmol) in DCM (150 mL) at 0 °C. Purification by the flash column chromatography with ethyl acetate/hexane (1:9) as eluant afforded *cis*-**1.2** (1.56 g, 27%), and *trans*-**1.2** (300 mg, 5%) as a colorless oils.

(±) (1*R*,2*R*,5*S*)-5-Methyl-6-oxabicyclo[3.1.0]hexan-2-ol (*cis*-1.2)

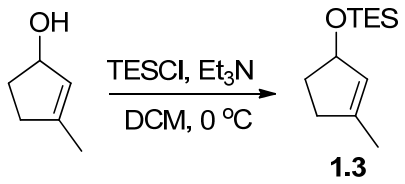
^{1}H NMR (400 MHz $CDCl_3$): δ 4.27 (t, *J*=7.8 Hz, 1H), 3.31 (d, *J*= 1.3 Hz, 1H), 2.03-1.91 (m, 2H), 1.8 (br, 1H), 1.61-1.50 (m, 1H), 1.44 (s, 3H), 1.34-1.24 (m, 1H).

^{13}C NMR (100 MHz $CDCl_3$): δ 74.0, 65.5, 64.0, 30.5, 29.2, 18.2.

(±) (1*R*,2*S*,5*S*)-5-Methyl-6-oxabicyclo[3.1.0]hexan-2-ol (*trans*-1.2)

^{1}H NMR (400 MHz $CDCl_3$): δ 4.20 (d, *J*= 5.4 Hz, 1H), 3.14 (s, 1H), 1.82 – 1.73 (m, 2H), 1.68 – 1.54 (m, 1H), 1.54 – 1.47 (m, 1H), 1.44 (s, 3H).

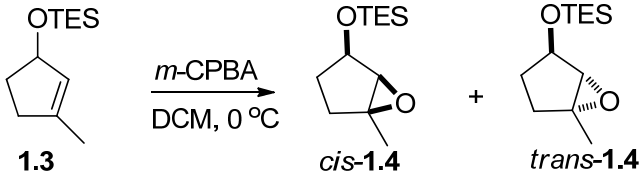
^{13}C NMR (100 MHz $CDCl_3$): δ 72.1, 65.3, 65.0, 30.7, 29.2, 17.4.



Triethyl(3-methylcyclopent-2-enyloxy)silane

To a stirred solution of the starting alcohol (2.86 g, 27 mmol) in DCM (150 mL), was added Et_3N (8.1 mL, 54 mmol) and TESCl (5.9 mL, 32.4 mmol) at 0 °C. After stirring for 3 h, the reaction mixture was quenched with saturated NH_4Cl and extracted with DCM 3 times. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography with ethyl acetate/hexane (3 :97) as eluant, to give **1.3** (5.15 g, 83%) as colorless oil. (The NMR data are identical with the literature)[55]

^{1}H NMR (300 MHz $CDCl_3$): δ 5.33 (q, *J*= 1.6 Hz, 1H), 4.85-4.83 (m, 1H), 2.37-2.31 (m, 1H), 2.25-2.19 (m, 1H), 2.15-2.06 (m, 1H), 1.74-1.69 (m, 1H), 1.71 (s, 3H), 1.03 (t, *J*= 7.9 Hz, 9H), 0.63 (q, *J* = 7.9 Hz, 6H).



Compounds *cis*-**1.4** and *trans*-**1.4** were prepared according to the general procedure (method B), starting from **1.3** (5 g, 23.5 mmol), *m*-CPBA (11.5 g, 47.1 mmol) in DCM (150 mL) at 0 °C. Purification by the flash column chromatography with ethyl acetate/hexane (1:99) as eluant afforded *cis*-**1.4** (620 mg, 12%), and *trans*-**1.4** (1.85 g, 35%) as a colorless oils.

(±) Triethyl((1*R*,2*R*,5*S*)-5-methyl-6-oxabicyclo[3.1.0]hexan-2-yloxy)silane (*cis*-1.4)

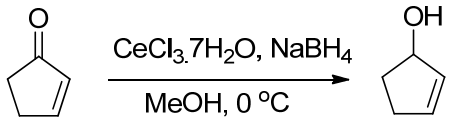
^{1}H NMR (300 MHz $CDCl_3$): δ 4.25-2.30 (t, *J*=7.1 Hz, 1H), 3.17 (s, 1H), 1.91-1.95 (m, 1H), 1.71-1.77 (m, 1H), 1.46-1.56 (m, 2H), 1.42 (s, 3H), 0.96 (t, *J*=7.9 Hz, 9H), 0.63 (q, *J*=7.5 Hz, 6H).

^{13}C NMR (75 MHz $CDCl_3$): δ 74.0, 65.3, 62.3, 30.2, 28.5, 18.2, 6.9, 4.9.

(±) Triethyl((1*S*,2*R*,5*R*)-5-methyl-6-oxabicyclo[3.1.0]hexan-2-yloxy)silane (*trans*-1.4)

^{1}H NMR (400 MHz $CDCl_3$): δ 4.28-4.27 (d, *J*=5.2 Hz, 1H), 3.12 (d, *J*=0.9 Hz, 1H), 1.86-1.80 (m, 2H), 1.68-1.65 (m, 1H), 1.51 (s, 3H), 1.54-1.48 (m, 1H), 0.93 (t, *J*=7.9 Hz, 9H), 0.62 (q, *J*=8 Hz, 6H).

^{13}C NMR (100 MHz $CDCl_3$): δ 73.0, 65.6, 65.1, 31.8, 29.7, 17.7, 6.9, 5.0.

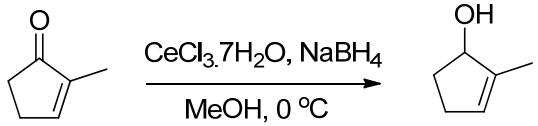


1.5

Cyclopent-2-enol

Compound **1.5** was prepared according to the general procedure (method A**)** starting from the cyclopentenone (0.8 g, 8.3 mmol), $CeCl_3.7H_2O$ (4.84 g, 12.5 mmol) and $NaBH_4$ (377 mg, 10 mmol) in MeOH (35 mL) at 0 °C. Purification by the flash column chromatography with ether/petane (1:3) as eluant afforded the enol **1.5** (603 mg, 78%) as a colorless oil.

^{1}H NMR (300 MHz $CDCl_3$): δ 5.91-5.89 (m, 1H), 5.78-5.74 (m, 1H), 4.79 (dd, *J*=8.2, 6.7 Hz, 1H), 2.91 (br, 1H), 2.47-2.44 (m, 1H), 2.22-2.16 (m, 2H), 1.65-1.63 (m, 1H).

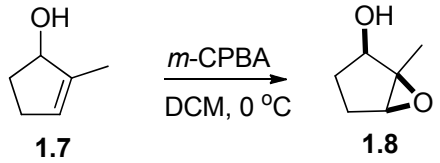


1.7

2-Methylcyclopent-2-enol

Compound **1.7** was prepared according to the gereneral procedure (method A) starting from the 2-methylcyclopentenone (400 mg, 4.16 mmol), $CeCl_3.7H_2O$ (2.33 g, 6.25 mmol) and $NaBH_4$ (189 mg, 5 mmol) in MeOH (20 mL) at 0 ^oC. Purification by the flash column chromatography with ether/petane (1:3) as eluant afforded the enol **1.7** as a colorless oil (204 mg, 50%). (The NMR data are identical with the literature)[56]

^1H NMR (300 MHz $CDCl_3$): δ 5.53 (s, 1H), 4.57-4.54 (m, 1H), 2.40-.2.26 (m, 3H), 1.86 (br, 1H), 1.76 (s, 3H), 1.70-1.66 (m, 1H).

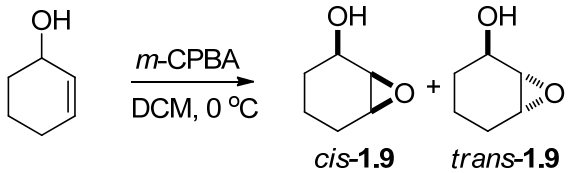


1.7 **1.8**

(±) (1*R*,2*R*,5*S*)-1-Methyl-6-oxabicyclo[3.1.0]hexan-2-ol

Compound **1.8** was prepared according to the general (method B) starting from the 2-methyl cyclopentenol (100 mg, 1.2 mmol), *m*-CPBA (414 mg, 2.4 mmol) in DCM (5 mL). Purification by the flash column chromatography with ethyl acetate/hexane (2:8) as eluant afforded **1.8** (75 mg, 55%) as a colorless oil. (The NMR data are identical with the literature)[57]

^1H NMR (400 MHz $CDCl_3$): δ 4.07-4.03 (t, *J*=7.8 Hz, 1H), 3.33 (s, 1H), 2.02-1.96 (m, 2H), 1.65-1.61 (m, 1H), 1.50 (s, 3H), 1.33-1.27 (m, 1H).



cis-**1.9** *trans*-**1.9**

Compounds *cis*-**1.9** and *trans*-**1.9** were prepared according to the general procedure (method B) starting from cyclohexenol (5 g, 51 mmol), *m*-CPBA (25 g, 102 mmol) in

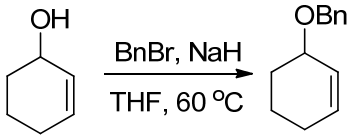
DCM (150 mL) at 0 °C. Purification by the flash column chromatography with ethyl acetate/hexane (1:9) as eluant afforded *cis*-**1.9** (3.1 g, 53%), and *trans*-**1.9** (400 mg, 7%) as colorless oils. (The NMR data are identical with the literature)[58]

(±) (1S,2*S*,6*R*)-7-Oxabicyclo[4.1.0]heptan-2-ol (*cis*-1.9)

^{1}H NMR (400 MHz $CDCl_3$): δ 4.05-4.01 (m, 1H), 3.37 (t, *J*=3.4 Hz, 1H), 3.33 (t, *J*=3.8 Hz, 1H), 1.60-1.56 (m, 3H), 1.48-1.46 (m, 2H), 1.31-1.28 (m, 1H).

(±) (1*S*,2*R*,6*R*)-7-Oxabicyclo[4.1.0]heptan-2-ol (*trans*-1.9)

^{1}H NMR (300 MHz $CDCl_3$): δ 3.97-3.94 (m, 1H), 3.21-3.20 (m, 1H), 3.05 (d, *J*=3.2, 0.5 Hz, 1H), 1.98-1.94 (m, 1H), 1.82-1.71 (m, 2H), 1.41-1.39 (m, 1H), 1.23-1.11 (m, 2H).



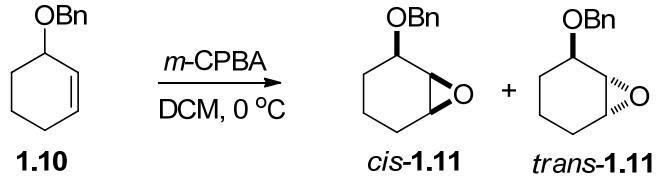
1.10

((Cyclohex-2-enyloxy)methyl)benzene

To a stirred solution of the cyclohexenol (5 g, 51 mmol) in anhydrous THF (50 mL), NaH (4.08 g of a 60% dispersion in mineral oil, 102 mmol) was added, followed by benzyl bromide (6 mL, 51 mmol). After stirring at 60 °C for 18 h, the reaction mixture was cooled to 0 °C, treated with water was to destroy excess hydride, diluted with ether and evaporated to afford a residue, which was purified by filtration through a short silica gel column, with elution using petroleum ether, evaporation of the collected fractions gave 3-benzyloxycyclohexene **1.10** (8.2 g, 85%) as a colorless liquid.

^{1}H NMR (300 MHz $CDCl_3$): δ 7.31-7.45 (m, 5H), 5.88-5.97 (m, 2H), 4.62, 4.68 (dd, *J*=13.3, 12.0 Hz, 2H), 3.92-3.97 (m, 1H), 1.58-1.67 (m, 1H), 1.80-1.97 (m, 3H), 2.00-2.05 (m, 1H), 2.11-2.17 (m, 1H).

^{13}C NMR (75 MHz $CDCl_3$): δ 139.2, 131.0, 128.5, 128.4, 128.2, 127.8, 127.7, 127.5, 72.3, 70.1, 28.5, 25.4, 19.4.



1.10 *cis*-**1.11** *trans*-**1.11**

Compounds *cis*-**1.11** and *trans*-**1.11** were prepared according to the general procedure (method B) starting from **1.10** (1 g, 5.3 mmol), *m*-CPBA (1.8 g, 106 mmol) in dry DCM (20 mL) at 0 ^{o}C. Purification by the flash column chromatography with ethyl acetate/hexane (1:4) as eluant afforded *cis*-**1.11** (410 mg, 37%), and *trans*-**1.11 (**136 mg, 13%) as colorless oils. (The NMR data are identical with the literature)[59]

(±) (1*S*,2*R*,6*S*)-2-(Benzyloxy)-7-oxabicyclo[4.1.0]heptane (*cis*-1.11)

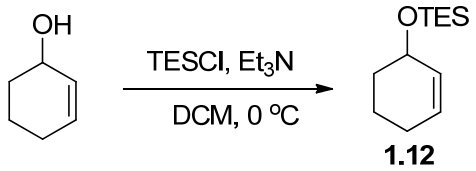
^{1}H NMR (300 MHz $CDCl_3$): δ 7.27-7.42 (m, 5H), 4.66-4.75 (s, 2H), 3.79-3.84 (m, 1H), 3.27-3.33 (m, 2H), 1.80-1.85 (m, 2H), 1.50-1.71 (m, 3H), 1.15-1.31 (m, 1H).

^{13}C NMR (75 MHz $CDCl_3$): δ 138.8, 128.5, 127.8, 127.7, 74.8, 70.3, 54.2, 53.6, 25.1, 23.2, 19.8.

(±) (1*R*,2*R*,6*R*)-2-(Benzyloxy)-7-oxabicyclo[4.1.0]heptane (*trans*-1.11)

^{1}H NMR (400 MHz $CDCl_3$): δ 7.31-7.42 (m, 5H), 4.67 (s, 2H), 3.74-3.77 (m, 1H), 3.24-3.26 (m, 1H), 3.19-3.20 (m, 1H), 2.02-2.06 (m, 1H), 1.79-1.87 (m, 2H), 1.49-1.51 (m, 1H), 1.27-1.34 (m, 2H).

^{13}C NMR (100 MHz $CDCl_3$): δ 138.5, 128.6, 127.87, 127.85, 73.2, 71.4, 54.6, 53.1, 26.8, 24.4, 14.8.



1.12

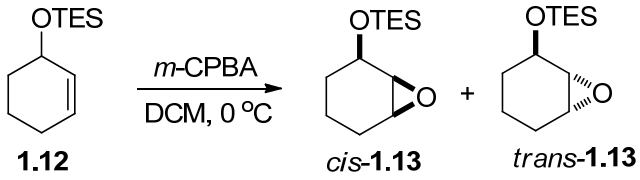
(Cyclohex-2-enyloxy)triethylsilane

To a stirred solution of cyclohexenol (700 mg, 7.1 mmol) in DCM (30 mL), Et_3N (2 mL, 14.2 mmol) and TESCl (1.4 mL, 8.5 mmol) were added at 0 ^{o}C. After stirring for 3 h,

the reaction mixture was quenched with H_2O (15 mL) and extracted with DCM (20 mL × 2). The combined organic layers were dried over Na_2SO_4, concentrated under reduced pressure and the residue was purified by flash column chromatography, eluting with ethyl acetate/hexane (1:3) as eluant to give **1.12** (1.1 g, 73%) as a colorless oil.

^{1}H NMR (400 MHz $CDCl_3$): δ 5.80-5.76 (m, 1H), 5.68-5.64 (m, 1H), 4.24 (s, 1H), 2.04-1.77 (m, 4H), 1.64-1.54 (m, 2H), 0.99 (t, *J*=7.9 Hz, 9H), 0.64 (q, 7.8 Hz, 6H).

^{13}C NMR (100 MHz $CDCl_3$): δ 131.3, 129.5, 66.6, 32.8, 25.2, 19.9, 7.1, 5.1.



1.12 *cis*-**1.13** *trans*-**1.13**

Compounds *cis*-**1.13** and *trans*-**1.13** were prepared according to the general procedure (method B) starting from **1.12** (980 mg, 4.6 mmol), *m*-CPBA (1.59 g, 9.2mmol) in DCM (30 mL) at 0 °C. Purification by the flash column chromatography with ethyl acetate/hexane (2:98) as eluant afforded *cis*-**1.13** (115 mg, 11%), and *trans*-**1.13** (620 mg, 59%) as colorless oils.

(±) ((1*S*,2*R*,6*S*)-7-Oxabicyclo[4.1.0]heptan-2-yloxy)triethylsilane (*cis*-1.13)

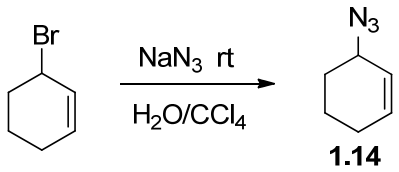
^{1}H NMR (300 MHz $CDCl_3$): δ 4.05-3.99 (m, 1H), 3.26-3.24 (m, 1H), 3.3 (t, *J*=4.1 Hz, 1H), 1.81-1.77 (m, 2H), 1.59-1.27 (m, 2H), 1.02-0.99 (m, 2H), 0.96 (t, *J*=7.9 Hz, 9H), 0.66 (q, *J*=8.0 Hz, 6H).

^{13}C NMR (75 MHz $CDCl_3$): δ 69.7, 56.5, 54.8, 28.4, 22.8, 20.7, 7.1, 5.1.

(±) ((1*R*,2*R*,6*R*)-7-Oxabicyclo[4.1.0]heptan-2-yloxy)triethylsilane (*trans*-1.13)

^{1}H NMR (400 MHz $CDCl_3$): δ 3.95-3.92 (t, *J*=6.9 Hz, 1H), 3.16 (s, 1H), 2.98-2.97 (d, *J*=3.6 Hz, 1H), 1.92-1.73 (m, 1H), 1.72-1.69 (m, 2H), 1.23-1.19 (m, 1H), 1.18-1.15 (m, 2H), 0.95 (t, *J*=8.0 Hz, 9H), 0.61 (q, *J*=8.0 Hz, 6H).

^{13}C NMR (100 MHz $CDCl_3$): δ 66.7, 56.8, 53.2, 30.4, 24.3, 14.7, 6.8, 4.9.



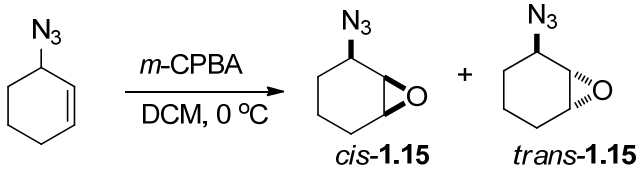
3-Azidocyclohex-1-ene

To a solution of 3-bromocyclohexene (10 g, 62.5 mmol) in CCl_4 (100 mL), a solution of NaN_3 (14.2 g, 218.5 mmol) in H_2O (100 mL) was added. After stirring this heterogeneous mixture vigorously for 48 h at rt, the CCl_4 layer was separated and the aqueous layer was extracted with CCl_4. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to give 3-azidocyclohexene **1.14** (6.9 g, 90%) as a colorless oil, which was used without further purification.

IR: 2102 cm^{-1}

^1H NMR (400 MHz $CDCl_3$): δ 5.97-6.01 (m, 1H), 5.69-5.72 (m, 1H), 3.87 (s, 1H), 1.65-2.07 (m, 6H).

^{13}C NMR (100 MHz $CDCl_3$): δ 132.7, 124.8, 56.0, 28.7, 24.8, 19.3.



Compounds *cis*-**1.15** and *trans*-**1.15** were prepared according to the general procedure (method B) starting from 3-azidocyclohex-1-ene (3 g, 24.4 mmol), *m*-CPBA (12 g, 48.8 mmol) in DCM (80 mL) at 0 °C. Purification by the flash column chromatography with ethyl acetate/hexane (2:98) as eluant afforded *cis*-**1.15** (840 mg, 25%) and *trans*-**1.15** **(**860 mg, 25%) as colorless oils.

IR: 2100.9 cm^{-1}

(±) (1*R*,2*R*,6*S*)-2-Azido-7-oxabicyclo[4.1.0]heptanes (*cis*-1.15)

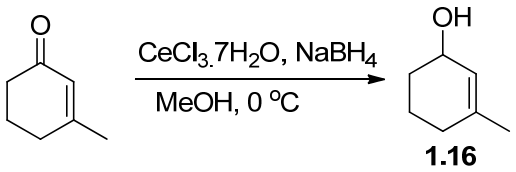
^{1}H NMR (400 MHz $CDCl_3$): δ 3.59-3.61 (m, 1H), 3.33-3.35 (m, 1H), 3.28-3.30 (m, 1H), 1.85-1.90 (m, 2H), 1.62-1.70 (m, 3H), 1.30-1.31 (m, 1H).

^{13}C NMR (100 MHz $CDCl_3$): δ 58.1, 54.0, 53.7, 24.4, 22.7, 20.0.

(±) (1*S*,2*R*,6*R*)-2-Azido-7-oxabicyclo[4.1.0]heptanes (*trans*-1.15)

^{1}H NMR (400 MHz $CDCl_3$): δ 3.79-3.82 (t, *J*=6.8 Hz, 1H), 3.20 (s, 1H), 3.056-3.065 (d, *J*=3.6 Hz, 1H), 1.96-2.02 (m, 1H), 1.74-1.88 (m, 2H), 1.44-1.46 (m, 1H), 1.28-1.33(m, 2H).

^{13}C NMR (100 MHz $CDCl_3$): δ 56.3, 53.7, 52.7, 25.8, 23.7, 15.0.



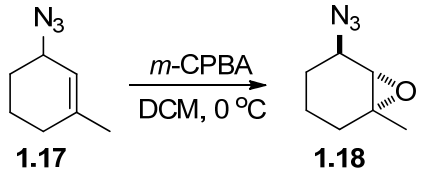
1.16

3-Methylcyclohex-2-enol

Compound **1.16** was prepared according to the general procedure (method A) starting from 3-cyclohexenone (630 mg, 5.73 mmol), $CeCl_3.7H_2O$ (3.2 g, 8.6 mmol) and $NaBH_4$ (260 mg, 6.9 mmol) in MeOH (25 mL) at 0 ^{o}C. Purification by the flash column chromatography with ethyl acetate/hexane (1:2) as eluant afforded the enol **1.16** (510 mg, 80%) as a colorless oil.

^{1}H NMR (300 MHz $CDCl_3$): δ 5.48 (s, 1H), 4.16 (s, 1H), 1.97-1.82 (m, 2H), 1.84 – 1.71 (m, 2H), 1.68 (s, 3H), 1.58-1.47 (m, 2H).

^{13}C NMR (75 MHz $CDCl_3$): δ 138.8, 124.4, 66.0, 31.8, 30.2, 23.8, 19.2.



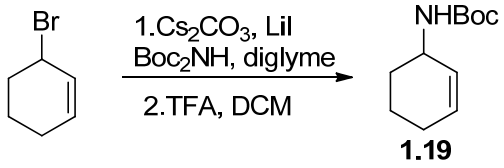
(±) (1*R*,5*R*,6*S*)-5-Azido-1-methyl-7-oxabicyclo[4.1.0]heptane

Compound **1.18** was prepared according to the general procedure (method B) starting from 3-azidocyclo-1-methylhex-1-ene (100 mg, 0.8 mmol, prepared according the literature[60] from **1.16**), *m*-CPBA (280 mg, 1.6 mmol) in DCM (10 mL) at 0 °C. Purification by the flash column chromatography with ethyl acetate/hexane (5:95) as eluant afforded *trans*-**1.18** (35 mg, 28%) as a colorless oil.

IR: 2100 cm^{-1}

^{1}H NMR (400 MHz $CDCl_3$): δ 3.61-3.57 (m, 1H), 3.18 (d, *J*=1.7 Hz, 1H), 1.92-1.84 (m, 1H), 1.77-1.58 (m, 4H), 1.37 (s, 3H), 1.32-1.28 (m, 1H).

^{13}C NMR (100 MHz $CDCl_3$): δ 60.9, 59.8, 58.0, 28.2, 24.3, 24.1, 19.8.



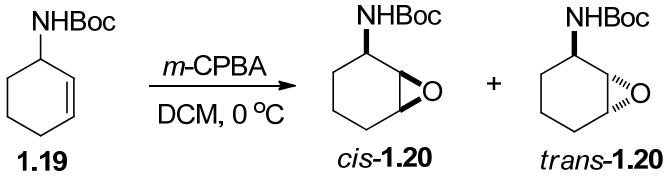
***tert*-Butyl cyclohex-2-enylcarbamate**

To a solution of 3-bromocyclohexene (970 mg, 6.0 mmol) in diglyme (15 mL), Cs_2CO_3 (2.6 g, 8.0 mmol), LiI (15 mg, 0.11 mmol) and Boc_2NH (437 mg, 2.0 mmol) were added. After stirring at rt for 3 days, the reaction mixture was treated with brine (30 mL) and extracted with DCM twice. The combined organic layers were concentrated under reduced pressure. The residue was purified by flash column chromatography, eluting with ethyl acetate/hexane (1:9) as eluant, to give the intermediate product. This intermediate was dissolved in DCM (15 mL) and TFA (0.3 mL, 4 mmol). After stirring

overnight at rt, the reaction mixture was treated drop wise with 1.0 N NaOH to adjust the pH to 8-9. The reaction mixture was extracted with DCM. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure, to a residue which was purified by flash column chromatography, eluting with ethyl acetate/hexane (1:9), to give carbomate **1.19** (245 mg, 62%) as a yellow oil. (The NMR data are identical with the literature)[61]

^{1}H NMR (400 MHz $CDCl_3$): δ 5.71-5.67 (m, 1H), 5.51-5.48 (m, 1H), 4.69-4.67 (m, 1H), 1.89-1.86 (m, 2H), 1.78-1.75 (m, 1H), 1.55-1.50 (m, 2H), 1.43-1.34 (m, 1H), 1.18 (s, 9H).

^{13}C NMR (100 MHz $CDCl_3$): δ 154.7, 129.7, 127.8, 78.4, 45.3, 29.3, 27.9, 24.3, 19.2.



1.19 *cis*-**1.20** *trans*-**1.20**

Compounds *cis*-**1.20** and *trans*-**1.20** were prepared according to the general procedure (method B) starting from **1.19** (500 mg, 2.54 mmol), *m*-CPBA (876 mg, 5.10 mmol) in DCM (9 mL). Purification by flash column chromatography eluting with ethyl acetate/hexane (1:9) afforded *cis*-**1.20** (330 mg, 61%), and *trans*-**1.20** (36 mg, 7%) as colorless oils (*trans*-**1.20** comes out first, then the *cis*-**1.20**).

(±) *tert*-Butyl (1*R*,2*R*,6*S*)-7-oxabicyclo[4.1.0]heptan-2-ylcarbamate (*cis*-1.20)

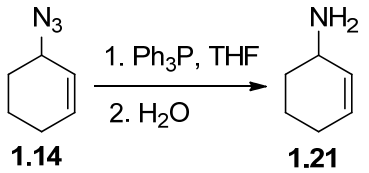
^{1}H NMR (400 MHz $CDCl_3$): δ 5.12-5.10 (d, *J*=8.8 Hz, 1H), 3.90-3.86 (m, 1H), 3.16-3.12 (m, 2H), 1.73-1.69 (m, 2H), 1.44-1.37 (m, 2H), 1.33 (s, 9H), 1.13-1.26 (m, 2H).

^{13}C NMR (100 MHz $CDCl_3$): δ 155.3, 79.1, 54.3, 46.8, 28.3, 28.1, 26.3, 23.0, 18.9.

(±) *tert*-Butyl (1*S*,2*R*,6*R*)-7-oxabicyclo[4.1.0]heptan-2-ylcarbamate (*trans*-1.20)

^{1}H NMR (400 MHz $CDCl_3$): δ 4.74-4.73 (m, 1H), 3.90-3.89 (m, 1H), 3.18-3.17(m, 1H), 3.07-3.06 (d, *J*=3.6 Hz, 1H), 2.05-1.99 (m, 1H), 1.82-1.73 (m, 2H), 1.46 (s, 9H); 1.39-1.35 (m, 2H); 1.16-1.11 (m, 1H).

^{13}C NMR (100 MHz $CDCl_3$): δ 155.4, 79.8, 55.4, 52.5, 46.1, 28.6, 27.1, 24.1, 15.7.



Cyclohex-2-enamine

To a solution of azide **1.14** (125 mg, 1.0 mmol) in dry THF (3 mL), Ph_3P (288 mg, 1.1 mmol) was added. After stirring at rt for 24 h, H_2O (2 mL, 2 mmol) was added to the reaction mixture, which was stirred for another 24 h and extracted with DCM. The combined organic layers were concentrated under reduced pressure. The residue was purified by flash column chromatography, eluting with ethyl acetate/hexane (2:8), to give **1.21** (90 mg, 93%) as a yellow oil.

^{1}H NMR (400 MHz CD_3OD): δ 6.11-6.08 (m, 1H), 5.73 (dd, *J*=8.4, 1.7 Hz, 1H), 3.83-3.82 (m, 1H), 3.36 (s, 1H), 2.14-2.09 (m, 3H), 1.88-1.86 (m, 1H), 1.72-1.65 (m, 2H).

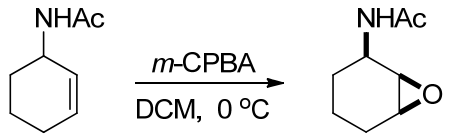
^{13}C NMR (100 MHz CD_3OD): δ 135.4, 124.5, 50.0, 28.3, 25.5, 20.3.

***N*-(Cyclohex-2-enyl)acetamide**

Cyclohex-2-enamine (90 mg, 0.93 mmol) was added to acetic anhydride (2 mL) After stirred at rt for 2 days, the reaction mixture was concentrated under reduced pressure, the residue was purified by flash column chromatography, eluting with ethyl acetate/hexane (2:8), to give **1.22** (73 mg, 56%) as a pale yellow solid.

^{1}H NMR (400 MHz $CDCl_3$): δ 5.87-5.83 (m, 1H), 5.60-5.56 (m, 1H), 5.45 (br, 1H), 4.87-447(m, 1H), 2.02-1.99 (m, 2H), 1.86(s, 3H), 1.68-1.43 (m, 4H).

^{13}C NMR (100 MHz $CDCl_3$): δ 169.5, 131.2, 127.9, 44.9, 29.7, 25.0, 23.7, 19.9.



1.22 **1.23**

(±) *N*-((1*R*,2*R*,6*S*)-7-Oxabicyclo[4.1.0]heptan-2-yl)acetamide

Compounds **1.23** was prepared according to the general procedure (method B) starting from **1.22** (210 mg, 1.62 mmol), *m*-CPBA (570 mg, 3.3 mmol) in DCM (9 mL) at 0 °C. Purification by flash column chromatography eluting with ethyl acetate/hexane (3:7) gave **1.23** (150 mg, 59%) as pale yellow oil.

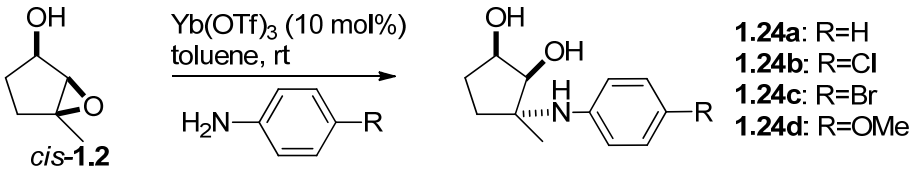
^{1}H NMR (400 MHz CD_3OD): δ 4.23-4.21 (m, 1H), 3.27-3.25 (m, 1H), 3.22-3.20 (m, 1H), 1.99 (s, 3H), 1.94-1.89 (m, 1H), 1.83-1.75 (m, 1H), 1.60-1.51 (m, 2H), 1.41-1.31 (m, 2H).

^{13}C NMR (100 MHz CD_3OD): δ 173.0, 55.3, 55.2, 47.9, 26.5, 24.1, 22.7, 20.7.

1.3.3 Epoxides opening reactions

Compounds **1.24a-d** and **1.26a-d** were prepared according to the general procedure (method C) starting from *cis*-**1.2** and *trans*-**1.2** (50 mg, 0.44 mmol), $Yb(OTf)_3$ (28 mg, 0.04 mmol) and corresponding aniline (1.5 eq). Purification by the flash column

chromatography with ethyl acetate/hexane (2:8) as eluant afforded the corresponding epoxide opening reaction product.



(±) (1*R*,2*S*,3*R*)-3-Methyl-3-(phenylamino)cyclopentane-1,2-diol (1.24a)

^{1}H NMR (400 MHz $CDCl_3$): δ 7.19-7.15 (m, 2H), 6.76-6.73 (m, 3H), 4.32-4.26 (m, 1H), 4.00 (d, *J*=5.6 Hz, 1H), 3.16 (br, NH, OH, 3H), 2.12-2.05 (m, 2H), 1.82-1.68 (m, 2H), 1.37 (s, 3H).

^{13}C NMR (100 MHz $CDCl_3$): δ 146.1, 129.3, 118.2, 116.2, 78.9, 72.4, 62.9, 37.4, 30.5, 20.2.

HRMS (ESI) calc. for $C_{12}H_{18}NO_2$: [M+H$^+$], 208.13321; found: [M+H$^+$], 208.13286.

(±) (1*R*,2*S*,3*R*)-3-(4-Chlorophenylamino)-3-methylcyclopentane-1,2-diol (1.24b)

^{1}H NMR (400 MHz $CDCl_3$): δ 7.11-7.08 (m, 2H), 6.67-6.64 (m, 2H), 4.30-4.26 (td, *J* = 3.9, 5.7 Hz, 1H), 3.96 (d, *J*=5.6 Hz, 1H), 3.35-3.09 (br, NH, OH, 3H), 2.11-2.03 (m, 2H), 1.78-1.67 (m, 2H), 1.32 (s, 3H).

^{13}C NMR (100 MHz $CDCl_3$): δ 144.8. 129.1, 122.9, 117.1, 79.0, 62.9, 37.5, 30.0, 29.5, 20.0.

HRMS (ESI) calc. for $C_{12}H_{17}ClNO_2$: [M+H$^+$], 242.09423; found: [M+H$^+$], 242.09443.

(±) (1*R*,2*S*,3*R*)-3-(4-Bromophenylamino)-3-methylcyclopentane-1,2-diol (1.24c)

^{1}H NMR (400 MHz $CDCl_3$): δ 7.23-7.21 (m, 2H), 6.61-6.59 (m, 2H), 4.29-4.25 (td, *J*= 3.7, 5.9 Hz, 1H), 3.95 (d, *J*=5.6 Hz, 1H), 3.60-3.11 (br, NH, OH, 3H), 2.12-2.03 (m, 2H), 1.78-1.67 (m, 2H), 1.33 (s, 3H).

^{13}C NMR (100 MHz $CDCl_3$): δ 145.3, 132.0, 117.0, 109.7, 78.9, 72.4, 62.8, 37.6, 30.3, 20.0.

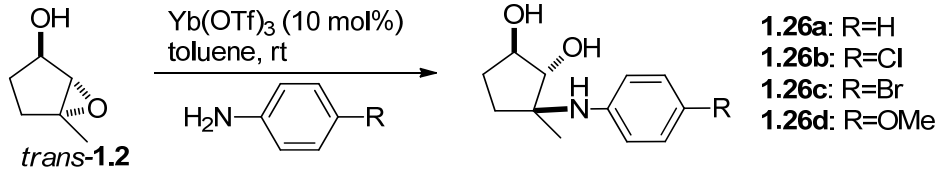
HRMS (ESI) calc. for $C_{12}H_{17}BrNO_2$: [M+H$^+$], 286.04372; found: [M+H$^+$], 286.04369.

(±) (1*R*,2*S*,3*R*)-3-(4-Methoxyphenylamino)-3-methylcyclopentane-1,2-diol (1.24d)

^{1}H NMR (400 MHz $CDCl_3$): δ 6.75 (m, 4H), 4.29-4.24 (m, 1H), 3.89 (d, *J*=5.8 Hz, 1H), 3.74 (s, 3H), 3.27 (br, NH, OH, 3H), 2.14-2.05 (m, 1H), 1.97-1.91 (m, 1H), 1.75-1.63 (m, 2H), 1.26 (s, 3H).

^{13}C NMR (100 MHz $CDCl_3$): δ 153.8, 139.2, 120.2, 115.0, 78.9, 71.9, 63.8, 55.8, 36.3, 30.3, 20.3.

HRMS (ESI) calc. for $C_{13}H_{20}NO_3$: [M+H$^+$], 238.14377; found: [M+H$^+$], 238.14379.



(±) (1*R*,2*R*,3*S*)-3-Methyl-3-(phenylamino)cyclopentane-1,2-diol (1.26a)

^{1}H NMR (400 MHz $CDCl_3$): δ 7.18-7.14 (m, 2H), 6.83-6.73 (m, 2H), 6.70-6.68 (m, 1H), 4.89 (br, NH, OH, 3H), 3.96 (q, *J*=7.4 Hz, 1H), 3.84 (d, *J*=10 Hz, 1H), 2.15-1.99 (m, 2H), 1.88-1.81 (m, 1H), 1.68-1.59 (m, 1H), 1.20 (s, 3H).

^{13}C NMR (100 MHz $CDCl_3$): δ 134.5, 129.3, 119.6, 117.6, 84.5, 76.4, 61.6, 34.5, 28.1, 20.2.

HRMS (ESI) calc. for $C_{12}H_{18}NO_2$: [M+H$^+$], 208.13321; found: [M+H$^+$], 208.13273.

(±) (1*R*,2*R*,3*S*)-3-(4-Chlorophenylamino)-3-methylcyclopentane-1,2-diol (1.26b)

^{1}H NMR (400 MHz $CDCl_3$): δ 7.10-7.08 (m, 2H), 6.60-6.64 (m, 2H), 4.45-4.23 (br, NH, OH, 3H), 3.99 (q, *J*=7.6 Hz, 1H), 3.90 (d, *J*=7.6 Hz, 1H), 2.09-1.97 (m, 2H), 1.86-1.78

(m, 1H), 1.64-1.58 (m, 1H), 1.16 (s, 3H).

^{13}C NMR (100 MHz $CDCl_3$): δ 144.4, 129.2, 124.2, 118.3, 84.5, 76.3, 61.2, 34.5, 27.9, 20.2.

HRMS (ESI) calc. for $C_{12}H_{17}ClNO_2$: [M+H$^+$], 242.09423; found: [M+H$^+$], 242.09414.

(±) (1*R*,2*R*,3*S*)-3-(4-Bromophenylamino)-3-methylcyclopentane-1,2-diol (1.26c)

^{1}H NMR (400 MHz CD_3OD): δ 7.19-7.17 (m, 2H), 6.69-6.66 (m, 2H), 4.25 (br, NH, OH, 3H), 3.94 (q, *J*=7.7 Hz, 1H), 3.83 (d, *J*=6.8 Hz, 1H), 2.07-1.96 (m, 2H), 1.87-1.82 (m, 1H), 1.67-1.61 (m, 1H), 1.22 (s, 3H).

^{13}C NMR (100 MHz CD_3OD): δ 147.1, 132.6, 118.7, 110.1, 85.2, 78.4, 62.4, 36.5, 29.6, 20.6.

HRMS (ESI) calc. for $C_{12}H_{17}BrNO_2$: [M+H$^+$], 286.04372; found: [M+H$^+$], 286.04347.

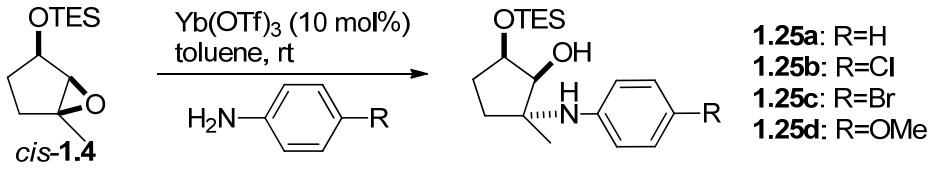
(±) (1*R*,2*R*,3*S*)-3-(4-Methoxyphenylamino)-3-methylcyclopentane-1,2-diol (1.26d)

^{1}H NMR (400 MHz CD_3OD): δ 6.84-6.87 (m, 2H), 6.79-6.77 (m, 2H), 4.3 (br, NH, OH, 3H), 3.95 (q, *J*=6.8 Hz, 1H), 3.77 (d, *J*=6.5 Hz, 1H), 3.73 (s, 3H), 2.07-1.99 (m, 2H), 1.73-1.68 (m, 1H), 1.61-1.55 (m, 1H), 1.14 (s, 3H).

^{13}C NMR (100 MHz CD_3OD): δ 156.1, 140.1, 122.9, 115.4, 84.9, 77.9, 64.0, 56.1, 35.3, 29.6, 20.9.

HRMS (ESI) calc. for $C_{13}H_{20}NO_3$: [M+H$^+$], 238.14377; found: [M+H$^+$], 238.14361.

Compounds **1.25a-d** and **1.27a-d** were prepared according to the general procedure (method C) starting from *cis*-**1.4** or *trans*-**1.4** (50 mg, 0.22 mmol), $Yb(OTf)_3$ (14 mg, 0.02 mmol) and the corresponding aniline (1.5 eq). Purification by the flash column chromatography with ethyl acetate/hexane (1:9) as eluant afforded the corresponding epoxide opening product.



(±) (1*S*,2*R*,5*R*)-2-Methyl-2-(phenylamino)-5-(triethylsilyloxy)cyclopentanol (1.25a)

^{1}H NMR (300 MHz $CDCl_3$): δ 7.13-7.27 (m, 2H), 6.45-6.77 (m, 3H), 4.29-4.34 (m, 1H), 3.91 (t, *J*=6.3 Hz, 1H), 3.00-2.98 (m, 1H), 2.00-2.14 (m, 2H), 1.62-1.79 (m, 3H), 1.34 (s, 3H), 0.98 (t, *J*=7.9 Hz, 9H), 0.64 (q, *J*=7.6 Hz, 6H).

^{13}C NMR (75 MHz $CDCl_3$): δ 146.6, 129.3, 117.8, 115.8, 79.1, 73.3, 62.7, 38.0, 31.2, 20.0, 6.9, 5.0.

HRMS (ESI) calc. for $C_{18}H_{32}NO_2Si$: [M+H$^+$], 322.21968; found: [M+H$^+$], 322.21966.

(±) (1*S*,2*R*,5*R*)-2-(4-Chlorophenylamino)-2-methyl-5-(triethylsilyloxy)cyclopentanol (1.25b)

^{1}H NMR (300 MHz $CDCl_3$): δ 7.08-7.13 (m, 2H), 6.86-6.71 (m, 2H), 4.26-4.31 (m, 1H), 3.87 (t, *J*=5.9 Hz, 1H), 2.97-2.99 (m, 1H), 2.05-2.08 (m, 2H), 1.67-1.73 (m, 2H), 1.33-1.29 (m, 1H), 1.31 (s, 3H), 0.98 (t, *J*=7.9 Hz, 9H), 0.64 (q, *J*=7.6 Hz, 6H).

^{13}C NMR (75 MHz $CDCl_3$): δ 145.2, 129.1, 122.5, 116.8, 79.0, 73.3, 62.8, 38.0, 31.1, 19.9, 6.9, 4.9.

HRMS (ESI) calc. for $C_{18}H_{31}ClNO_2Si$: [M+H$^+$], 356.17995; found: [M+H$^+$], 356.18071.

(±) (1*S*,2*R*,5*R*)-2-(4-Bromophenylamino)-2-methyl-5-(triethylsilyloxy)cyclopentanol (1.25c)

^{1}H NMR (400 MHz $CDCl_3$): δ 7.23-7.25 (m, 2H), 6.64-6.66 (m, 2H), 4.29-4.32 (m, 1H), 3.88 (t, *J*=6.7 Hz, 1H), 2.98-3.01 (m, 1H), 2.05-2.09 (m, 2H), 1.69-1.74 (m, 2H), 1.31-1.33 (m, 1H), 1.33 (s, 3H), 0.98 (t, *J*=7.9 Hz, 9H), 0.66 (q, *J*=7.9 Hz, 6H).

^{13}C NMR (100 MHz $CDCl_3$): δ 145.7, 132.0, 117.3, 109.6, 79.0, 73.4, 62.8, 38.0, 31.1, 19.9, 6.9, 5.0.

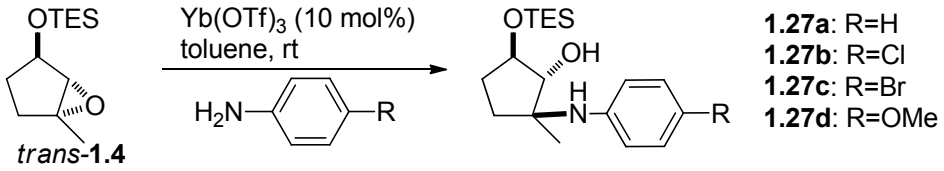
HRMS (ESI) calc. for $C_{18}H_{31}BrNO_2Si$: [M+H$^+$], 400.1302; found: [M+H$^+$], 400.13182.

(±)(1*S*,2*R*,5*R*)-2-(4-Methoxyphenylamino)-2-methyl-5-(triethylsilyloxy)cyclopentanol (1.25d)

^{1}H NMR (400 MHz $CDCl_3$): δ 6.75-6.80 (m, 4H), 4.32-4.36 (m, 1H), 3.85 (m, 1H), 3.77 (s, 3H), 2.95-2.93 (m, 1H), 1.98-2.11 (m, 2H), 1.67-1.74 (m, 2H), 1.30-1.28 (m, 1H), 1.29 (s, 3H), 1.00 (t, *J*=7.9 Hz, 9H), 0.66 (q, *J*=7.8 Hz, 6H).

^{13}C NMR (100 MHz $CDCl_3$): δ 153.2, 140.1, 119.2, 114.7, 79.0, 77.7, 63.5, 55.9, 37.1, 31.3, 14.3, 6.9, 4.9.

HRMS (ESI) calc. for $C_{19}H_{34}NO_3Si$: [M+H$^+$], 352.2307.; found: [M+H$^+$], 352.23025.



(±) (1*R*,2*S*,5*R*)-2-Methyl-2-(phenylamino)-5-(triethylsilyloxy)cyclopentanol (1.27a)

^{1}H NMR (400 MHz $CDCl_3$): δ 7.20-7.16 (m, 2H), 6.78-6.74 (m, 3H), 4.03-3.98 (q, *J*=6.9 Hz, 1H), 3.90 (d, *J*=6.5 Hz, 1H), 2.18-2.21 (m, 1H), 2.03-2.01 (m, 1H), 1.90-1.85 (m, 1H), 1.69-1.66 (m, 1H), 1.33 (s, 3H), 1.33-1.34 (m, 1H), 1.01 (t, *J*=8 Hz, 9H), 0.66 (q, *J*=8.0 Hz, 6H).

^{13}C NMR (100 MHz $CDCl_3$): δ 146.5, 129.2, 118.2, 116.4, 85.1, 77.8, 60.9, 34.8, 29.5, 20.8, 7.0, 5.1.

HRMS (ESI) calc. for $C_{18}H_{32}NO_2Si$: [M+H$^+$], 322.21968; found: [M+H$^+$], 322.22051.

(±) (1*R*,2*S*,5*R*)-2-(4-Chlorophenylamino)-2-methyl-5-(triethylsilyloxy)cyclopentanol (1.27b)

^{1}H NMR (400 MHz $CDCl_3$): δ 7.12-7.10 (m, 2H), 6.67-6.65 (m, 2H), 3.98 (q, *J*= 6.9 Hz, 1H), 3.86 (t, *J*=6.3 Hz, 1H), 2.16-2.10 (m, 1H), 2.04-1.97 (m, 1H), 1.87-1.83 (m, 1H), 1.67-1.63 (m, 1H), 1.30 (s, 3H), 1.00 (t, *J*=7.5 Hz, 9H), 0.64 (q, *J*=8.0 Hz, 6H).

^{13}C NMR (100 MHz $CDCl_3$): δ145.1, 129.1, 122.9, 117.3, 85.1, 77.8, 60.9, 34.9, 29.5, 20.6, 7.0, 5.1.

HRMS (ESI) calc. for $C_{18}H_{31}ClNO_2Si$: [M+H$^+$], 356.17991; found: [M+H$^+$], 356.18071.

(±) (1*S*,2*R*,5*S*)-2-(4-Bromophenylamino)-2-methyl-5-(triethylsilyloxy)cyclopentanol (1.27c)

^{1}H NMR (400 MHz $CDCl_3$): δ 7.28-7.23 (m, 2H), 6.60-6.63 (m, 2H), 3.98 (q, *J*=7.0 Hz, 1H), 3.86 (dt, *J*=6.4, 3.9 Hz, 1H), 2.13-2.10 (m, 1H), 2.03-2.01 (m,1H), 1.88-1.83 (m, 1H), 1.68-1.63 (m, 1H), 1.30 (s, 3H), 1.00 (t, *J*=3.2 Hz, 9H), 0.64 (q, *J*=7.8 Hz, 6H).

^{13}C NMR (100 MHz $CDCl_3$): δ 145.5, 132.0, 117.7, 109.9, 85.1, 77.8, 50.9, 34.9, 29.5, 20.6, 7.0, 5.1.

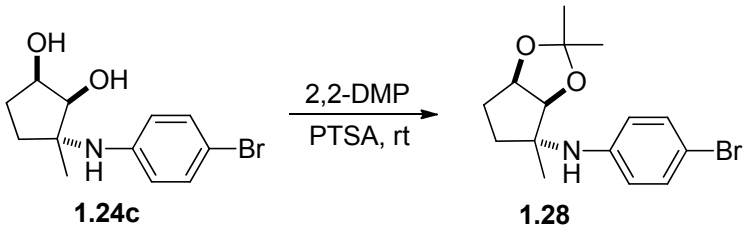
HRMS (ESI) calc. for $C_{18}H_{31}BrNO_2Si$: [M+H$^+$], 400.13020; found: [M+H$^+$], 400.13119.

(±)(1*R*,2*S*,5*R*)-2-(4-Methoxyphenylamino)-2-methyl-5-(triethylsilyloxy)cyclopentanol (1.27d)

^{1}H NMR (400 MHz $CDCl_3$): δ 6.78 (s, 4H), 3.99 (dt, *J*=6.5, 7.6 Hz, 1H), 3.84 (d, *J*=6.3 Hz, 1H), 3.77 (s, 3H), 2.13-1.97 (m, 2H), 1.77-1.70 (m, 1H), 1.64-1.56 (m, 1H), 1.24 (s, 3H), 0.99 (t, *J*=3.3 Hz, 9H), 0.64 (q, *J*=7.7 Hz, 6H).

^{13}C NMR (100 MHz $CDCl_3$): δ 153.9, 139.6, 120.7, 114.7, 84.8, 77.7, 61.9, 55.8, 34.4, 29.5, 21.0, 6.9, 5.0.

HRMS (ESI) calc. for $C_{19}H_{34}NO_3Si$: [M+H$^+$], 352.23025; found: [M+H$^+$], 352.23035.

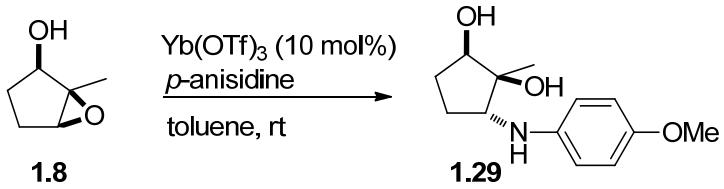


1.24c **1.28**

To a solution of **1.24c** (20 mg, 0.07 mmol) in 2,2-DMP (1 mL) was added PTSA at rt. The reaction mixture was stirred overnight, and then concentrated under reduced pressure. The residue was purified by flash column chromatography, eluting with ethyl acetate/hexane (1:9), to give **1.28** (18 mg, 79%) as a brown oil.

(3a*S*,4*R*,6a*R*)-N-(4-bromophenyl)-2,2,4-trimethyltetrahydro-3a*H*-cyclopenta[*d*][1,3] dioxol-4-amine

^{1}H NMR (400 MHz $CDCl_3$): δ 7.28-7.24 (m, 2H), 6.59-6.57 (m, 2H), 4.74 (t, *J*=4.5 Hz, 1H), 4.49 (d, *J*=5.5 Hz, 1H), 1.98-1.51 (m, 4H), 1.44 (s, 3H), 1.35 (s, 3H), 1.28 (s, 3H).
^{13}C NMR (100 MHz $CDCl_3$): δ 144.9, 131.9, 116.9, 110.4, 109.4, 83.8, 81.6, 63.5, 38.3, 29.6, 26.4, 24.3, 19.4.
MS (ESI) *m/z*: 326.0, 328.0 [$M+H^+$]



1.8 **1.29**

(±) (1*S*,2*R*,5*R*)-5-(4-Methoxyphenylamino)-1-methylcyclopentane-1,2-diol

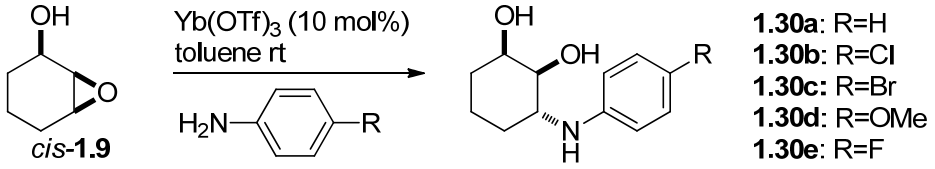
Compound **1.29** was prepared according to the general procedure (method C) starting from **1.8** (50 mg, 0.44 mmol), *p*-anisidine (83 mg, 0.66 mmol), $Yb(OTf)_3$ (27.3 mg, 0.04 mmol) in toluene (3.5 mL). Purification by flash column chromatography with ethyl acetate/hexane (1:9) as eluant afforded **1.29** (70 mg, 67%) as a brown oil.

^{1}H NMR (400 MHz $CDCl_3$): δ 6.80-6.77 (m, 2H), 6.73-6.70 (m, 2H), 3.82 (t, *J*=8.8 Hz, 1H), 3.76 (s, 3H), 3.74 (t, *J*=4 Hz, 1H), 2.99 (br, 3H), 2.43 – 2.18 (m, 1H), 2.10 – 1.90 (m, 1H), 1.81 – 1.54 (m, 1H), 1.31 – 1.22 (m, 1H), 1.20 (s, 3H).

^{13}C NMR (100 MHz $CDCl_3$): δ 152.4, 142.2, 115.2, 115.0, 79.8, 77.5, 61.7, 56.0, 28.5, 28.0, 20.4.

HRMS (ESI) calc. for $C_{13}H_{20}NO_3$: [M+H$^+$], 238.1438; found: [M+H$^+$], 238.1443.

Compounds **1.30a-e** and **1.33a-e** were prepared according to the general procedure (method C) starting from *cis*-**1.9** or *trans*-**1.9** (50 mg, 0.44 mmol), $Yb(OTf)_3$ (27 mg, 0.04 mmol) and aniline (1.5 equiv.) in toluene (3 mL) at rt. Purification by the flash column chromatography with ethyl acetate/hexane (2:8) as eluant, afforded corresponding epoxides opening products.



(±) (1*R*,2*S*,3*R*)-3-(Phenylamino)cyclohexane-1,2-diol (1.30a)

^{1}H NMR (400 MHz $CDCl_3$): δ 7.33–7.09 (m, 2H), 6.96–6.63 (m, 3H), 4.31–4.04 (m, 1H), 3.63 (dt, *J*=4.0 Hz, 1H), 3.38 (dd, *J* =2.8, 9.5 Hz, 1H), 3.15 (s, br, 3H), 2.27–2.03 (m, 1H), 2.03–1.87 (m, 1H), 1.87–1.61 (m, 1H), 1.61–1.36 (m, 3H), 1.17–0.93 (m, 1H).

^{13}C NMR (100 MHz $CDCl_3$): δ 147.7, 129.6, 118.8, 114.6, 75.9, 69.0, 54.2, 31.3, 30.2, 19.1.

HRMS (ESI) calc. for $C_{12}H_{18}NO_2$: [M+H$^+$], 208.13321; found: [M+H$^+$], 208.13314.

(±) (1*R*,2*S*,3*R*)-3-(4-Chlorophenylamino)cyclohexane-1,2-diol (1.30b)

^{1}H- NMR (400 MHz CD_3OD): δ 7.28–6.86 (m, 2H), 6.78–6.54 (m, 2H), 4.01 (dt, *J* =2.6, 5.1 Hz, 1H), 3.55 (td, *J* =4.0, 8.9 Hz, 1H), 3.48 (dd, *J* =2.7, 8.5 Hz, 1H), 2.09–1.93 (m, 1H), 1.90–1.77 (m, 1H), 1.76–1.63 (m, 1H), 1.59–1.43 (m, 2H), 1.25–1.07 (m, 1H).

^{13}C NMR (100 MHz CD_3OD): δ 148.8, 129.8, 122.1, 115.7, 75.7, 70.9, 54.7, 31.7, 30.9, 20.0.

HRMS (ESI) calc. for $C_{12}H_{17}ClNO_2$: [M+H$^+$], 242.09423; found: [M+H$^+$], 242.09468.

(±) (1*R*,2*S*,3*R*)-3-(4-Bromophenylamino)cyclohexane-1,2-diol (1.30c)

^{1}H- NMR (400 MHz CD_3OD): δ 7.20-7.12(m, 2H), 6.77–6.43 (m, 2H), 3.93 (dd, *J* =2.8, 5.8 Hz, 1H), 3.54 (dt, *J* =4.0, 8.9 Hz, 1H), 3.49 (dd, *J* =2.7, 8.5 Hz, 1H), 2.14–1.91 (m, 1H), 1.88–1.76 (m, 1H), 1.70 (m, 1H), 1.60–1.40 (m, 2H), 1.25–1.10 (m, 1H).

^{13}C NMR (100 MHz CD_3OD): δ 149.3, 132.8, 116.0, 108.8, 75.7, 70.9, 54.5, 31.7, 31.0, 20.0.

HRMS (ESI) calc. for $C_{12}H_{17}BrNO_2$: [M+H$^+$], 286.04372; found: [M+H$^+$], 286.04443.

(±) (1*R*,2*S*,3*R*)-3-(4-Methoxyphenylamino)cyclohexane-1,2-diol (1.30d)

^{1}H- NMR (400 MHz $CDCl_3$): δ 6.89–6.62 (m, 4H), 4.17 (dd, *J* =3.0, 5.8 Hz, 1H), 3.75 (s, 3H), 3.54 (dt, *J*=3.9 Hz, 1H), 3.39 (dd, *J* =2.8, 9.6 Hz, 1H), 3.17-3.19 (m, 2H), 2.17–2.01 (m, 1H), 1.95 (m, 1H), 1.82–1.62 (m, 1H), 1.57–1.36 (m, 2H), 1.13–0.96 (m, 1H).

^{13}C NMR (100 MHz $CDCl_3$): δ 153.4, 141.1, 116.8, 115.1, 75.9, 68.9, 55.9, 55.8, 31.0, 30.1, 19.3.

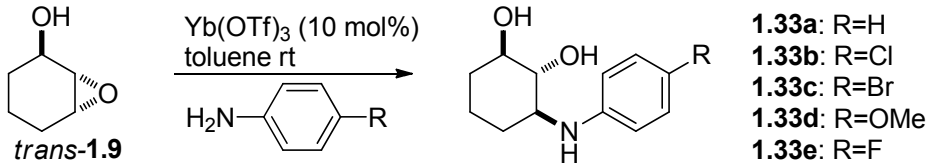
HRMS (ESI) calc. for $C_{13}H_{20}NO_3$: [M+H$^+$], 238.14377; found: [M+H$^+$], 238.14416.

(±) (1*R*,2*S*,3*R*)-3-(4-Fluorophenylamino)cyclohexane-1,2-diol (1.30e)

^{1}H- NMR (400 MHz $CDCl_3$): δ 7.13–6.76 (m, 2H), 6.78–6.48 (m, 2H), 4.16 (d, *J* =2.7 Hz, 1H), 3.52 (td, *J* =3.9, 10.9 Hz, 1H), 3.37 (dd, *J* =2.8, 9.5 Hz, 1H), 3.09 (s, 2H), 2.14–2.00 (m, 1H), 2.02–1.84 (m, 1H), 1.85–1.61 (m, 1H), 1.61–1.35 (m, 2H), 1.12–0.86 (m, 1H).

^{13}C NMR (100 MHz $CDCl_3$): δ 157.8, 143.8, 116.1, 115.8, 75.9, 69.0, 55.2, 31.0, 30.2, 19.2.

HRMS (ESI) calc. for $C_{12}H_{17}FNO_2$: [M+H$^+$], 226.12378; found: [M+H$^+$], 226.12411.



(±) (1*R*,2*R*,3*S*)-3-(Phenylamino)cyclohexane-1,2-diol (1.33a)

^{1}H NMR (400 MHz CD_3OD): δ 7.28–6.91 (m, 2H), 6.72–6.57 (m, 3H), 3.47 (dd, *J* =4.4, 9.0 Hz, 1H), 3.30–2.99 (m, 2H), 2.23–2.02 (m, 1H), 2.01–1.89 (m, 1H), 1.80–1.58 (m, 1H), 1.59–1.22 (m, 2H), 1.22–0.97 (m, 1H).

^{13}C NMR (100 MHz CD_3OD): δ 150.0, 130.2, 118.3, 115.0, 80.0, 75.2, 58.7, 34.1, 32.2, 22.3.

HRMS (ESI) calc. for $C_{12}H_{18}NO_2$: [M+H$^+$], 208.13321; found: [M+H$^+$], 208.13323.

(±) (1*R*,2*R*,3*S*)-3-(4-Chlorophenylamino)cyclohexane-1,2-diol (1.33b)

^{1}H- NMR (400 MHz CD_3OD): δ 7.25–6.87 (m, 2H), 6.79–6.42 (m, 2H), 3.47 (ddd, *J* =4.7, 8.4, 10.8 Hz, 1H), 3.19 (t, *J* =8.9 Hz, 1H), 3.16–3.09 (m, 1H), 2.09–1.99 (m, 1H), 2.00–1.90 (m, 1H), 1.76–1.64 (m, 1H), 1.45–1.26 (m, 2H), 1.18–1.03 (m, 1H).

^{13}C NMR (100 MHz CD_3OD): δ 148.9, 129.9, 122.1, 115.7, 80.1, 75.2, 58.5, 34.0, 32.1, 22.3.

HRMS (ESI) calc. for $C_{12}H_{17}ClNO_2$: [M+H$^+$], 242.09423; found: [M+H$^+$], 242.09452.

(±) (1*R*,2*R*,3*S*)-3-(4-Bromophenylamino)cyclohexane-1,2-diol (1.33c)

^{1}H NMR (400 MHz CD_3OD): δ 7.33–6.92 (m, 2H), 6.85–6.26 (m, 2H), 3.44-3.49 (m, 1H), 3.19 (t, *J* = 8.9 Hz, 1H), 3.13 (dt, *J*=4.0 Hz, 1H), 2.24–1.83 (m, 2H), 1.83–1.54 (m, 1H), 1.49–1.24 (m, 3H), 1.24–1.03 (m, 1H).

^{13}C NMR (100 MHz CD_3OD): δ 149.4, 132.8, 116.2, 108.9, 80.1, 75.1, 58.3, 34.0, 32.1, 22.2.

HRMS (ESI) calc. for $C_{12}H_{17}BrNO_2$: $[M+H^+]$, 286.04372; found: $[M+H^+]$, 286.0445.

(±) (1*R*,2*R*,3*S*)-3-(4-Methoxyphenylamino)cyclohexane-1,2-diol (1.33d)

^{1}H NMR (400 MHz $CDCl_3$): δ 7.31-6.24 (m, 4H), 3.72 (s, br, 3H), 3.74(s, 1H), 3.54 (td, *J* =4.7, 10.6 Hz, 1H), 3.20 (t, *J* =9.1 Hz, 1H), 3.02 (dt, *J*=3.9 Hz, 1H), 1.99 (m, 2H), 1.66 (m, , 1H), 1.48–1.12 (m, 2H), 1.00 (m, 1H).

^{13}C NMR (100 MHz $CDCl_3$): δ 153.2, 141.3, 116.7, 115.0, 79.4, 74.0, 59.3, 55.9, 32.2, 31.1, 21.4.

HRMS (ESI) calc. for $C_{13}H_{20}NO_3$: $[M+H^+]$, 238.14377; found: $[M+H^+]$, 238.14419.

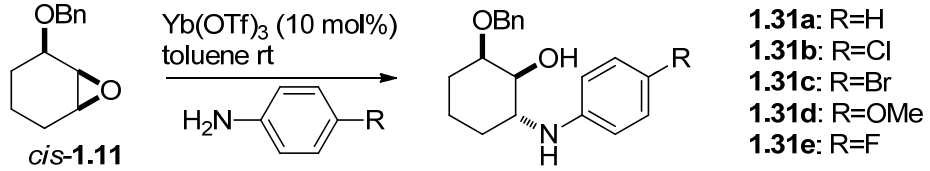
(±) (1*R*,2*R*,3*S*)-3-(4-Fluorophenylamino)cyclohexane-1,2-diol (1.33e)

^{1}H NMR (400 MHz CD_3OD): δ 6.98–6.76 (m, 2H), 6.77–6.58 (m, 2H), 3.47 (ddd, *J* =4.8, 8.7, 10.8 Hz, 1H), 3.19 (t, *J* =9.0, 1H), 3.08 (ddd, *J* =4.0, 9.6, 11.1 Hz, 1H), 2.13–2.00 (m, 1H), 2.02–1.91 (m, 1H), 1.81–1.61 (m, 1H), 1.49–1.21 (m, 2H), 1.20–1.03 (m, 1H).

^{13}C NMR (100 MHz CD_3OD): δ 158.4, 146.4, 116.5, 116.1, 80.1, 75.2, 59.5, 34.1, 32.1, 22.3.

HRMS (ESI) calc. for $C_{12}H_{17}FNO_2$: $[M+H^+]$, 226.1238; found: $[M+H^+]$, 226.1245.

Compounds **1.31a-d** and **1.34a-d** were prepared according to the general procedure (method C) starting from *cis*-**1.11** or *trans*-**1.11** (50 mg, 0.24 mmol), $Yb(OTf)_3$ (15 mg, 0.02 mmol) and aniline (1.5 equiv.) in toluene (3 mL) at rt. Purification by the flash column chromatography with ethyl acetate/hexane (1:9) as eluant afforded the corresponding epoxides opening products.



(±) (1*S*,2*R*,6*R*)-2-(Benzyloxy)-6-(phenylamino)cyclohexanol (1.31a)

^{1}H NMR (400 MHz $CDCl_3$): δ 7.43-7.33 (m, 5H), 7.22-7.18 (m, 2H), 6.78-6.71 (m, 3H), 4.71 (dd, *J*=11.6, 28.0 Hz, 2H), 3.47-3.39 (m, 2H), 3.28-3.22 (m, 2H), 2.19-2.15 (m, 2H), 1.79-1.75 (m, 1H), 1.38-1.28 (m, 2H), 1.18-1.09 (m, 1H).

^{13}C NMR (100 MHz $CDCl_3$): δ 148.0, 138.8, 129.4, 128.6, 127.9, 127.6, 118.2, 114.4, 81.6, 78.0, 71.7, 57.7, 31.0, 29.6, 21.2.

MS (ESI) *m/z*: 298.3 [M+H$^+$].

(±) (1*S*,2*R*,6*R*)-2-(Benzyloxy)-6-(4-chlorophenylamino)cyclohexanol (1.31b)

^{1}H NMR (400 MHz $CDCl_3$): δ 7.38-7.32 (m, 5H), 7.13-7.10 (m, 2H), 6.62-6.58 (m, 2H), 4.61 (dd, *J*=11.7, 57.0 Hz, 2H), 3.92-3.90 (m, 1H), 3.57-3.46 (m, 2H), 2.21-2.16 (m, 1H), 2.10-2.05 (m, 1H), 1.73-1.68 (m, 1H), 1.56-1.53 (m, 1H), 1.50-1.41 (m, 2H), 1.14-1.10 (m, 1H).

^{13}C NMR (100 MHz $CDCl_3$): δ 146.7, 138.5, 129.2, 128.6, 127.9, 127.8, 122.3, 115.0, 77.3, 74.7, 71.3, 54.9, 31.1, 27.6, 18.9.

HRMS (ESI) calc. for $C_{19}H_{23}ClNO_2$: [M+H$^+$], 332.14142; found: [M+H$^+$], 332.14118.

(±) (1*S*,2*R*,6*R*)-2-(Benzyloxy)-6-(4-bromophenylamino)cyclohexanol (1.31c)

^{1}H NMR (400 MHz $CDCl_3$): δ 7.40-7.33 (m, 5H), 7.28-7.24 (m, 2H), 6.58-6.55 (m, 2H), 4.60 (dd, *J*=11.8, 57.7 Hz, 2H), 3.92-3.91 (m, 1H), 3.55-3.48 (m, 2H), 2.21-2.17 (m, 1H), 2.11-2.07 (m, 1H), 1.73-1.67 (m, 1H), 1.56-1.39 (m, 2H), 1.18-1.08 (m, 1H).

^{13}C NMR (100 MHz $CDCl_3$): δ 147.2, 138.5, 132.0, 128.7, 127.9, 127.8, 115.4, 109.3, 77.3, 74.7, 71.3, 54.8, 30.6, 27.5, 18.9.

HRMS (ESI) calc. for $C_{19}H_{23}BrNO_2$: [M+H$^+$], 376.39067; found: [M+H$^+$],376.39074.

(±) (1*S*,2*R*,6*R*)-2-(Benzyloxy)-6-(4-methoxyphenylamino)cyclohexanol (1.31d)

^{1}H NMR (400 MHz $CDCl_3$): δ 7.40-7.28 (m, 5H), 6.82-6.80 (m, 2H), 6.71-6.69 (m, 2H), 4.64 (dd, *J*=11.8, 41.0 Hz, 2H), 3.94-3.93 (m, 1H), 3.77 (s, 3H), 3.53-3.50 (m, 2H), 2.28-2.18 (m, 1H), 2.09-2.04 (m, 1H), 1.74-1.67 (m, 1H), 1.56-1.40 (m, 2H), 1.18-1.10 (m, 1H).

^{13}C NMR (100 MHz $CDCl_3$): δ 152.7, 142.0, 138.8, 128.6, 127.8, 127.7, 116.0, 115.0, 77.2, 74.9, 71.3, 55.9, 30.8, 27.7, 19.1.

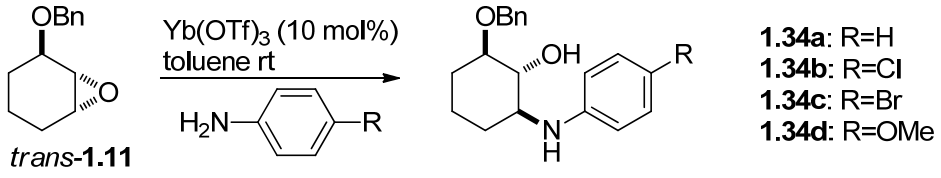
HRMS (ESI) calc. for $C_{20}H_{26}NO_3$: [M+H$^+$], 328.19106; found: [M+H$^+$], 328.19072.

(±) (1*S*,2*R*,6*R*)-2-(Benzyloxy)-6-(4-fluorophenylamino)cyclohexanol (1.31e)

^{1}H NMR (400 MHz $CDCl_3$): δ 7.40-7.32 (m, 5H), 6.93-6.88 (m, 2H), 6.66-6.62 (m, 2H), 4.64 (dd, *J*=11.7, 46.8 Hz, 2H), 3.94-3.92 (m, 1H), 3.54-3.49 (m, 2H), 2.21-2.16 (m, 1H), 2.10-2.05 (m, 1H), 1.77-1.67 (m, 1H), 1.56-1.51 (m, 1H), 1.48-1.40 (m, 1H), 1.19-1.10 (m, 1H).

^{13}C NMR (100 MHz $CDCl_3$): δ 157.4, 144.5, 138.7, 128.60, 127.8, 115.9, 115.6, 115.1, 77.3, 74.8, 71.3, 55.5, 30.8, 27.7, 19.0.

HRMS (ESI) calc. for $C_{19}H_{23}FNO_2$: [M+H$^+$], 316.17073; found: [M+H$^+$], 316.17151.



trans-**1.11**

(±) (1*R*,2*R*,6*S*)-2-(Benzyloxy)-6-(phenylamino)cyclohexanol (1.34a)

^{1}H NMR (400 MHz $CDCl_3$): δ 7.41-7.34 (m, 5H), 7.24-7.20 (m, 2H), 6.78-6.72 (m, 3H), 4.65 (dd, *J*=11.6, 56.5 Hz, 2H), 3.95-3.94 (m, 1H), 3.65 (dt, *J*=4.0, 9.3, 1H), 3.56 (dd, *J*=2.6, 8.9 Hz, 1H), 2.26-2.22 (m, 1H), 2.11-2.06 (m, 1H), 1.77-1.70 (m, 1H), 1.58-1.42 (m, 2H), 1.23-1.13 (m, 1H).

^{13}C NMR (100 MHz $CDCl_3$): δ 148.1, 138.7, 129.4, 128.6, 127.8, 127.7, 117.9, 114.0, 77.3, 74.7, 71.3, 54.7, 30.7, 27.6, 19.0.

MS (ESI) *m/z*: 298.1 [M+H$^+$].

(±) (1R,2R,6S)-2-(Benzyloxy)-6-(4-chlorophenylamino)cyclohexanol (1.34b)

^{1}H NMR (400 MHz $CDCl_3$): δ 7.45-7.33 (m, 5H), 7.16-7.13 (m, 2H), 6.62-6.59 (m, 2H), 4.69 (dd, *J*=11.7, 31.4 Hz, 2H), 3.46-3.38 (m, 2H), 3.22-3.15 (m, 1H), 2.18-2.08 (m, 2H), 1.76-1.73 (m, 1H), 1.41-1.23 (m, 2H), 1.14-1.03 (m, 1H).

^{13}C NMR (100 MHz $CDCl_3$): δ 146.4, 138.4, 128.8, 128.3, 127.62, 127.57, 121.9, 114.9, 81.2, 77.3, 71.2, 57.1, 30.3, 29.1, 20.6.

HRMS (ESI) calc. for $C_{19}H_{23}ClNO_2$: [M+H$^+$], 332.14118; found: [M+H$^+$], 332.14184.

(±) (1*R*,2*R*,6*S*)-2-(Benzyloxy)-6-(4-bromophenylamino)cyclohexanol (1.34c)

^{1}H NMR (400 MHz $CDCl_3$): δ 7.40-7.33 (m, 5H), 7.28-7.25 (m, 2H), 6.58-6.56 (m, 2H), 4.69 (dd, *J*=11.6, 53.5 Hz, 2H), 3.46-3.37 (m, 2H), 3.22-3.16 (m, 1H), 2.20-2.11 (m, 2H), 1.80-1.75 (m, 1H), 1.40-1.26 (m, 2H), 1.18-1.08 (m, 1H).

^{13}C NMR (100 MHz $CDCl_3$): δ 147.0, 138.5, 132.0, 128.6, 127.9, 115.7, 109.5, 81.5, 77.8, 71.5, 57.3, 30.8, 29.3, 21.0.

HRMS (ESI) calc. for $C_{19}H_{23}BrNO_2$: [M+H$^+$], 376.091; found: [M+H$^+$], 376.09067.

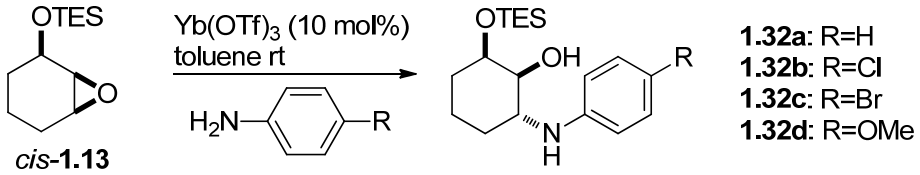
(±) (1*R*,2*R*,6*S*)-2-(Benzyloxy)-6-(4-methoxyphenylamino)cyclohexanol (1.34d)

^{1}H NMR (400 MHz $CDCl_3$): δ 7.42-7.28 (m, 5H), 6.81-6.79 (m, 2H), 6.72-6.69 (m, 2H), 4.71 (dd , *J*=11.8, 33.6 Hz, 2H), 3.77 (s, 3H), 3.46-3.39 (m, 2H), 3.14-3.08 (m, 1H), 2.17-2.12 (m, 2H), 1.78-1.71 (m, 1H), 1.40-1.26 (m, 2H), 1.18-1.08 (m, 1H).

^{13}C NMR (100 MHz $CDCl_3$): δ 153.1, 141.9, 138.9, 128.6, 128.0, 127.9, 116.7, 115.0, 81.7, 78.2, 71.8, 59.3, 31.1, 29.8, 21.3.

MS (ESI) *m/z*: 328.5 [M+H$^+$].

Compounds **1.32a-d**, and **1.35a-d** were prepared according to the general procedure (method C) starting from *cis*-**1.13** and *trans*-**1.13** (50 mg, 0.22 mmol), $Yb(OTf)_3$ (15 mg, 0.02 mmol) and aniline (1.5 equiv.) in toluene (3 mL) at rt. Purification by the flash column chromatography with ethyl acetate/hexane (1:9) as eluant afforded corresponding epoxides opening products.



(±) (1*S*,2*R*,6*R*)-2-(Phenylamino)-6-(triethylsilyloxy)cyclohexanol (1.32a)

^{1}H NMR (400 MHz $CDCl_3$): δ 7.22-7.18 (m, 2H), 6.75-6.69 (m, 3H), 4.16-4.14 (m, 1H), 3.58 (dt, *J*=4.0, 9.0 Hz, 1H), 3.43 (dd, *J*=2.7, 8.5 Hz, 1H), 2.22-2.15 (m, 1H), 1.87-1.70 (m, 2H), 1.45-1.55 (m, 2H), 1.20-1.12 (m, 1H), 1.01 (t, *J*=15.8 Hz, 9H), 0.66 (q, *J*=24.2 Hz, 6H).

^{13}C NMR (100 MHz $CDCl_3$): δ 148.4, 129.5, 117.9, 113.9, 75.4, 70.9, 54.3, 31.9, 30.6, 18.9, 7.1, 5.2.

HRMS (ESI) calc. for $C_{18}H_{32}NO_2Si$: [M+H$^+$], 322.21964; found: [M+H$^+$], 322.21968.

(±) (1*S*,2*R*,6*R*)-2-(4-Chlorophenylamino)-6-(triethylsilyloxy)cyclohexanol (1.32b)

^{1}H NMR (400 MHz $CDCl_3$): δ 7.16-7.12 (m, 2H), 6.67-6.64 (m, 2H), 4.12-4.11 (m, 1H), 3.67 (dt, *J*=3.6, 9.7 Hz, 1H), 3.43-3.37 (m, 1H), 2.14-2.09 (m, 1H), 1.96-1.89 (m, 1H),

1.80-1.74 (m, 1H), 1.55-1.45 (m, 2H), 1.22-1.15 (m, 1H), 1.00 (t, *J*=15.8 Hz, 9H), 0.66 (q, *J*=24.1 Hz, 6H).

^{13}C NMR (100 MHz $CDCl_3$): δ 145.6, 128.6, 114.9, 114.6, 74.4, 69.1, 66.7, 55.3, 32.5, 30.5, 7.9, 5.8.

HRMS (ESI) calc. for $C_{18}H_{31}ClNO_2Si$: [M+H$^+$], 356.18151; found: [M+H$^+$], 356.18071.

(±) (1*S*,2*R*,6*R*)-2-(4-Bromophenylamino)-6-(triethylsilyloxy)cyclohexanol (1.32c)

^{1}H NMR (400 MHz $CDCl_3$): δ 7.27-7.25 (m, 2H), 6.57-6.55 (m, 2H), 4.14-4.12 (m, 1H), 3.50 (dt, *J*=4.0, 8.9 Hz, 1H), 3.39 (dd, *J*=2.7, 8.5 Hz, 1H), 2.16-2.12 (m, 1H), 1.86-1.80 (m, 1H), 1.78-1.68 (m, 1H), 1.53-1.46 (m, 2H), 1.17-1.08 (m, 1H), 1.00 (t, *J*=15.8 Hz, 9H), 0.66 (q, *J*=24.0 Hz, 6H).

^{13}C NMR (100 MHz $CDCl_3$): δ 147.4, 132.1, 115.3, 109.2, 75.3, 71.0, 54.4, 31.9, 30.4, 18.8, 7.1, 5.2.

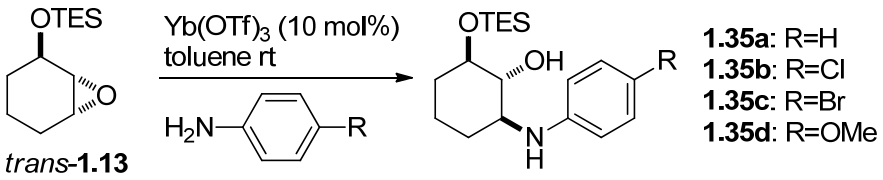
HRMS (ESI) calc. for $C_{18}H_{31}BrNO_2Si$: [M+H$^+$], 400.13095; found: [M+H$^+$], 400.1302.

(±) (1*S*,2*R*,6*R*)-2-(4-Methoxyphenylamino)-6-(triethylsilyloxy)cyclohexanol (1.32d)

^{1}H NMR (300 MHz $CDCl_3$): δ 6.81-6.78 (m, 2H), 6.70-6.67 (m, 2H), 4.14-4.12 (m, 1H), 3.76 (s, 3H), 3.48-3.37 (m, 2H), 2.15-2.10 (m, 1H), 1.82-1.64 (m, 2H), 1.53-1.43 (m, 2H), 1.14-1.10 (m, 1H), 0.99 (t, *J*=15.8 Hz, 9H), 0.64 (q, *J*=24.0 Hz, 6H).

^{13}C NMR (75MHz $CDCl_3$): δ 151.9, 141.1, 115.6, 114.6, 75.3, 70.9, 56.3, 55.9, 32.5, 31.1, 19.6, 7.9, 5.7.

HRMS (ESI) calc. for $C_{19}H_{34}NO_3Si$: [M+H$^+$], 352.23065; found: [M+H$^+$], 352.23025.



trans-**1.13**

(±) (1*R*,2*S*,6*R*)-2-(Phenylamino)-6-(triethylsilyloxy)cyclohexanol (1.35a)

^{1}H NMR (400 MHz $CDCl_3$): δ 7.20-7.17 (m, 2H), 6.75-6.69 (m, 3H), 3.62-3.57 (m, 1H), 3.32 (t, *J*=8.2, 1H), 3.23 (dt, *J*=3.9, 10.5 Hz, 1H), 2.20-2.15 (m, 1H), 1.95-1.92 (m, 1H), 1.75-1.72 (m, 1H), 1.45-1.32 (m, 2H), 1.18-1.15 (m, 1H), 1.02 (t, *J*=15.8 Hz, 9H), 0.68 (q, *J*=24.0 Hz, 6H).

^{13}C NMR (100 MHz $CDCl_3$): δ 148.2, 129.4, 118.1, 114.2, 79.2, 75.5, 57.2, 33.6, 31.2, 21.2, 7.0, 5.3.

HRMS (ESI) calc. for $C_{18}H_{32}NO_2Si$: [M+H$^+$], 322.22083; found: [M+H$^+$], 322.21968.

(±) (1*R*,2*S*,6*R*)-2-(4-Chlorophenylamino)-6-(triethylsilyloxy)cyclohexanol (1.35b)

^{1}H NMR (400 MHz $CDCl_3$): δ 7.13-7.11 (m, 2H), 6.62-6.60 (m, 2H), 3.60-3.55 (m, 1H), 3.30 (t, *J*=9.2 Hz, 1H), 3.19 (dt, *J*=4.0, 10.8 Hz, 1H), 2.15-2.12 (m, 1H), 1.95-1.92 (m, 1H), 1.75-1.72 (m, 1H), 1.44-1.34 (m, 2H), 1.18-1.15 (m, 1H), 1.01 (t, *J*=15.8 Hz, 9H), 0.67 (q, *J*=24.0 Hz, 6H).

^{13}C NMR (100 MHz $CDCl_3$): δ 146.8, 129.2, 122.4, 115.2, 79.2, 75.5, 57.1, 33.5, 31.1, 21.1, 7.0, 5.3.

HRMS (ESI) calc. for $C_{18}H_{31}ClNO_2Si$: [M+H$^+$], 356.18071; found: [M+H$^+$], 356.18072.

(±) (1*R*,2*S*,6*R*)-2-(4-Bromophenylamino)-6-(triethylsilyloxy)cyclohexanol (1.35c)

^{1}H NMR (400 MHz $CDCl_3$): δ 7.26-7.24 (m, 2H), 6.57-6.55 (m, 2H), 3.60-3.54 (m, 1H), 3.30 (t, *J*=9.0 Hz, 1H), 3.18 (dt, *J*=4.0, 10.7 Hz, 1H), 2.15-2.11 (m, 1H), 1.95-1.92 (m, 1H), 1.75-1.72 (m, 1H), 1.44-1.34 (m, 2H), 1.18-1.15 (m, 1H), 1.01 (t, *J*=15.8 Hz, 9H), 0.67 (q, *J*=24.0 Hz, 6H).

^{13}C NMR (100 MHz $CDCl_3$): δ 147.2, 132.1, 115.6, 109.5, 79.2, 75.5, 57.0, 33.5, 31.0, 21.1, 7.0, 5.3.

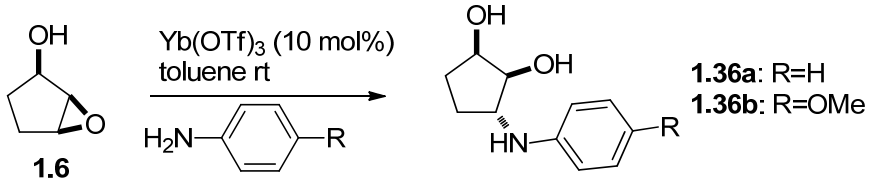
HRMS (ESI) calc. for $C_{18}H_{31}BrNO_2Si$: [M+H$^+$], 400.13051; found: [M+H$^+$], 400.1302.

(±) (1*R*,2*S*,6*R*)-2-(4-Methoxyphenylamino)-6-(triethylsilyloxy)cyclohexanol (1.35d)

^{1}H NMR (400 MHz $CDCl_3$): δ 6.80-6.77 (m, 2H), 6.71-6.67 (m, 2H), 3.76 (s, 3H), 3.60-3.55 (m, 1H), 3.28 (t, *J*=9.6 Hz, 1H), 3.09 (dt, *J*=4.0, 11.0 Hz, 1H), 2.15-2.10 (m, 1H), 1.94-1.90 (m, 1H), 1.74-1.69 (m, 1H), 1.47-1.28 (m, 2H), 1.19-1.09 (m, 1H), 1.01 (t, *J*=15.8 Hz, 9H), 0.67 (q, *J*=24.0 Hz, 6H).

^{13}C NMR (100 MHz $CDCl_3$): δ 152.9, 142.1, 116.4, 115.0, 79.2, 75.5, 58.6, 56.0, 33.7, 31.2, 21.3, 7.0, 5.3.

HRMS (ESI) calc. for $C_{19}H_{34}NO_2$: [M+H$^+$], 352.23070; found: [M+H$^+$], 352.23025.



Compounds **1.36a**, **1.36b** were prepared according to the general procedure (method C) starting from **1.6** (50 mg, 0.5 mmol), aninline (1.5 equiv.) and $Yb(OTf)_3$ (31 mg, 0.05 mmol) in toluene (3 mL) at rt. Purification by the flash column chromatography with ethyl acetate/hexane (1:9) as eluant afforded **1.36a**, **1.36b** as pale brown oils.

(±) (1*R*,2*S*,3*R*)-3-(Phenylamino)cyclopentane-1,2-diol (1.36a)

^{1}H NMR (400 MHz CD_3OD): δ 7.12-7.07 (m, 2H), 6.70-6.67 (m, 2H), 6.63-6.58 (m, 1H), 4.07 (dd, *J*=3.3, 6.4 Hz, 1H), 3.78 (t, *J*=9.6 Hz, 1H), 3.71-3.65 (m, 1H), 2.39-2.27 (m, 1H), 2.02-1.93 (m, 1H), 1.77-1.65 (m, 1H), 1.42-1.30 (m, 1H).

^{13}C NMR (100 MHz CD_3OD): δ 150.1, 130.1, 118.1, 114.6, 79.2, 73.7, 60.1, 30.2, 29.0.

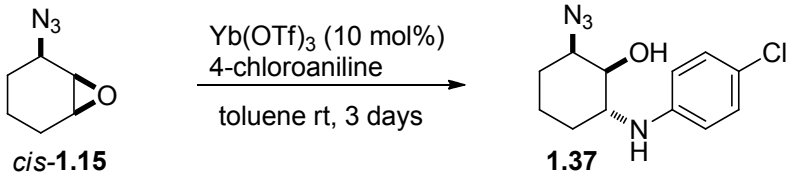
MS (ESI) *m/z*: 194.6 [M+H$^+$].

(±) (1*R*,2*S*,3*R*)-3-(4-Methoxyphenylamino)cyclopentane-1,2-diol (1.36b)

^{1}H NMR (400 MHz $CDCl_3$): δ 6.77-6.73 (m, 2H), 6.71-6.66 (m, 2H), 4.09-4.06 (q, *J*=5.5, 6.4 Hz, 1H), 3.76 (t, *J*=9.7 Hz, 1H), 3.71 (s, 3H), 2.35-2.24 (m, 1H), 2.03-1.90 (m, 1H), 1.76-1.64 (m, 1H), 1.38-1.29 (m, 1H).

^{13}C NMR (100 MHz $CDCl_3$): δ 9.0, 30.2, 56.3, 61.2, 73.7, 79.2, 115.9, 116.5, 144.1, 153.8.

MS (ESI) *m/z*: 224.4 [M+H$^+$].



cis-**1.15** **1.37**

(±) (1*S*,2*R*,6*R*)-2-Azido-6-(4-chlorophenylamino)cyclohexanol

Compound **1.37** were prepared according to the general procedure (method C) starting from *cis*-**1.15** (50 mg, 0.36 mmol), $Yb(OTf)_3$ (22 mg, 0.04 mmol) and aniline (1.5 equiv.) in toluene (3 mL) at rt. Purification by the flash column chromatography with ethyl acetate/hexane (1:9) as eluant afforded **1.37** (68 mg, 71%) as a brown solid.

IR: 2102 cm^{-1}

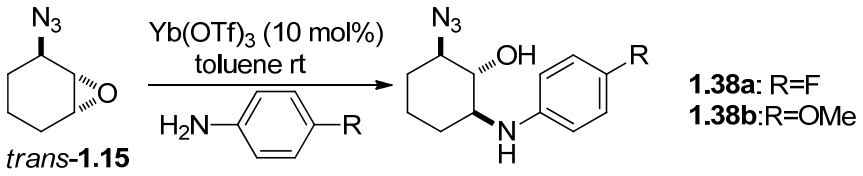
^{1}H NMR (400 MHz $CDCl_3$): δ 7.14-7.11 (m, 2H), 6.63-6.61 (m, 2H), 4.08 (s, 1H), 3.54-3.47 (m, 2H), 3.04 (s, br, 1H), 2.11-2.04 (m, 1H), 1.95-1.92 (m, 1H), 1.54-1.50 (m, 3H), 1.08-1.03 (m, 1H).

^{13}C NMR (100 MHz $CDCl_3$): δ 146.2, 145.5, 129.3, 123.2, 75.5, 62.2, 54.8, 30.8, 28.5, 19.6.

HRMS (ESI) calc. for $C_{12}H_{16}ClN_4O$: [M+H$^+$], 267.10077; found: [M+H$^+$], 267.10072.

Compounds **1.38a 1.38b**, **1.39**, **1.40** were prepared according to the general procedure (method C) starting from *trans*-**1.15** (50 mg, 0.36 mmol), $Yb(OTf)_3$ (22 mg, 0.04 mmol)

and aniline (1.5 equiv.) in toluene (3 mL) at rt. Purification by the flash column chromatography with ethyl acetate/hexane (2:8) as eluant afforded **1.38a**, **1.38b**, **1.39** and **1.40**.



(±) (1*R*,2*R*,6*S*)-2-Azido-6-(4-fluorophenylamino)cyclohexanol (1.38a)

IR: 2103 cm^{-1}

^1H NMR (400 MHz $CDCl_3$): δ 6.92-6.88 (m, 2H), 6.66-6.63 (m, 2H), 3.37 (dt, *J*=4.7, 10.2 Hz, 1H), 3.22 (t, *J*=9.3 Hz, 1H), 3.10 (dt, *J*=3.7, 8.1 Hz, 1H), 2.04 (dd, *J* =9.6, 21.5 Hz, 2H), 1.75 (s, 1H), 1.40-1.28 (m, 2H), 1.08-1.03 (m, 1H).

^{13}C NMR (100 MHz $CDCl_3$): δ 157.6, 155.3, 143.8, 115.9, 115.8, 115.7, 77.8, 64.9, 59.4, 30.7, 30.0, 21.9.

HRMS (ESI) calc. for $C_{12}H_{16}FN_4O$: $[M+H^+]$, 251.13027; found: $[M+H^+]$, 251.13066.

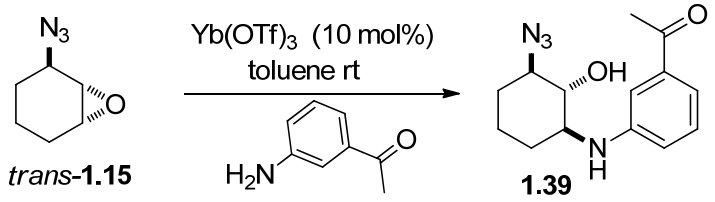
(±) (1*R*,2*R*,6*S*)-2-Azido-6-(4-methoxyphenylamino)cyclohexanol (1.38b)

IR: 2102 cm^{-1}

^1H NMR (400 MHz $CDCl_3$): δ 6.82-6.79 (m, 2H), 6.72-6.70 (m, 2H), 3.77 (s, 1H), 3.41 (ddd, *J* =4.5, 9.3, 11.2 Hz, 1H), 3.29 (t, *J*=9.37 Hz, 1H), 3.10 (ddd, *J* = 4.0, 9.6, 11.6 Hz, 1H), 2.90 (s, br, 1H), 2.12-2.04 (m, 2H), 1.80-1.78 (m, 1H), 1.40-1.37 (m, 2H), 1.10-1.06 (m, 1H).

^{13}C NMR (100 MHz $CDCl_3$): δ 153.5, 141.3, 117.0, 115.1, 78.1, 66.0, 60.4, 55.9, 30.9, 30.2, 22.2.

HRMS (ESI) calc. for $C_{13}H_{19}N_4O_2$: $[M+H^+]$, 263.15025; found: $[M+H^+]$, 263.15037.



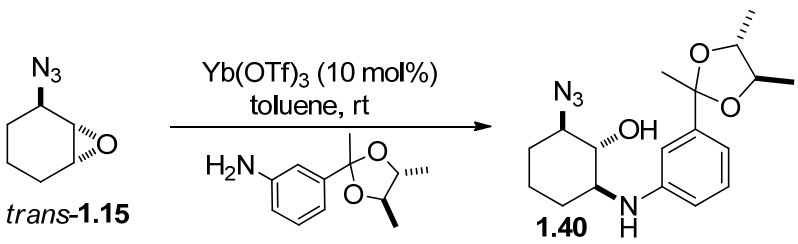
(±) 1-(3-((1*S*,2*R*,3*R*)-3-Azido-2-hydroxycyclohexylamino)phenyl)ethanone (1.39)

IR: 2103 cm^{-1}

^{1}H NMR (400 MHzCD_3OD): δ 7.25-7.21 (m, 3H), 6.93-6.90 (m, 1H), 3.37-3.28 (m, 5H), 2.55 (s, 3H), 2.09-1.97 (m, 2H), 1.78-1.71 (m, 1H), 1.52-1.41 (m, 1H), 1.36-1.26 (m, 1H), 1.21-1.10 (m, 1H).

^{13}C NMR (100 MHz CD_3OD): δ 199.7, 148.6, 137.4, 128.5, 117.6, 116.4, 111.5, 77.4, 65.2, 56.9, 30.3, 29.8, 25.0, 21.1.

HRMS (ESI) calc. for $C_{14}H_{15}N_4O_2$: [M+H^+], 275.15025; found: [M+H^+], 275.15078.



(±)(1*R*,2*R*,6*S*)-2-Azido-6-(3-((4R,5R)-2,4,5-trimethyl-1,3-dioxolan-2-yl)phenylamino) cyclohexanol (1.40)

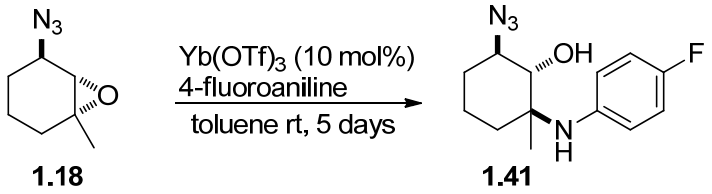
IR: 2104 cm^{-1}

^{1}H NMR (400 MHz $CDCl_3$): δ 7.25–7.06 (m, 1H), 7.02–6.80 (m, 2H), 6.64-6.59 (m, 1H), 3.81-3.75 (m, 1H), 3.67–3.35 (m, 4H), 3.35–3.18 (m, 2H), 2.26–1.94 (m, 2H), 1.79-1.77 (m, 1H), 1.63 (s, 3H), 1.37-1.41 (m, 2H), 1.29 (dd, *J* = 1.6, 6.0 Hz, 3H), 1.21 (dd, *J* = 4.2, 5.9 Hz, 3H), 1.12-1.06 (m, 1H).

^{13}C NMR (100 MHz $CDCl_3$): δ 147.3, 147.2, 146.6, 129.1, 115.8, 115.7, 113.5, 113.3,

111.6, 111.4, 107.9, 79.3, 78.3, 78.1, 77.9, 64.9, 58.5, 58.4, 30.9, 30.8, 30.1, 29.0, 22.0, 17.2, 17.1, 16.6.

HRMS (ESI) calc. for $C_{18}H_{27}N_4O_3$: [M+H$^+$], 347.20777; found: [M+H$^+$], 347.20855.



1.18 **1.41**

(±) (1*S*,2*S*,6*R*)-6-Azido-2-(4-fluorophenylamino)-2-methylcyclohexanol

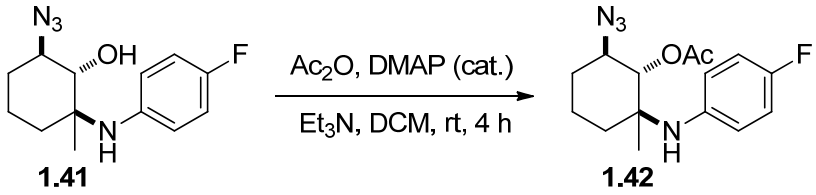
Compound **1.41** was prepared according to the general procedure (method C) starting from **1.18** (25 mg, 0.16 mmol), $Yb(OTf)_3$ (10 mg, 0.02 mmol) and aniline (1.5 equiv.) in toluene (1.5 mL) at rt. Purification by the flash column chromatography with ethyl acetate/hexane (1:9) as eluant afforded **1.41** (29 mg, 69%) as a brown oil.

IR: 2103 cm^{-1}

^{1}H NMR (400 MHz $CDCl_3$): δ 6.93-6.89 (m, 2H), 6.76-6.73 (m, 2H), 4.03 (d, *J*=3.9 Hz, 1H), 3.85 (d, *J*=1.8 Hz, 1H), 1.85-1.70 (m, 5H), 1.56-1.53 (m, 1H), 1.28 (s, 3H).

^{13}C NMR (100 MHz $CDCl_3$): δ 156.8, 141.5, 121.8, 115.8, 115.6, 74.1, 58.2, 33.3, 25.0, 23.5, 19.3.

MS (ESI) *m/z*: 265.2 [M+H$^+$].



1.41 **1.42**

To a solution of **1.41** (20 mg, 0.08 mmol) in dry DCM (2 mL), was added Ac_2O (11 μL, 0.11 mmol), Et_3N (21 μL, 0.15 mmol) and DMAP (9 mg, 0.01 mmol) at 0 ^{o}C, then the reaction mixture was allowed to warm up to rt and stirred for 4 h. The reaction mixture

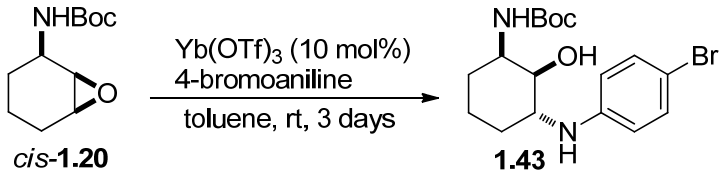
was diluted with water (2 mL), and the organic layer was separated, the aqueous layer was extracted with DCM. The combined organic layers were dried over Na_2SO_4, concentrated under reduced pressure, the residue was purified by flash column chromatography with ethyl acetate/hexane (1:9) as eluant, to afford **1.42** (19 mg, 81%) as a brown solid.

IR: 2103 cm^{-1}

^1H NMR (400 MHz $CDCl_3$): δ 6.95-6.89 (m, 2H), 6.78-6.74 (m, 2H), 5.46 (s, 1H), 3.95-3.91 (m, 1H), 2.18 (s, 3H), 1.85-1.72 (m, 5H), 1.63-1.60 (m, 1H), 1.18 (s, 3H).

^{13}C NMR (100 MHz $CDCl_3$): δ 170.6, 156.4, 144.3, 120.8, 116.0, 115.8, 74.0, 57.9, 57.2, 34.5, 25.2, 23.4, 21.2, 19.5.

HRMS (ESI) calc. for $C_{15}H_{20}FN_4O_2$: $[M+H^+]$, 307.15648; found: $[M+H^+]$, 307.15671.



cis-**1.20** **1.43**

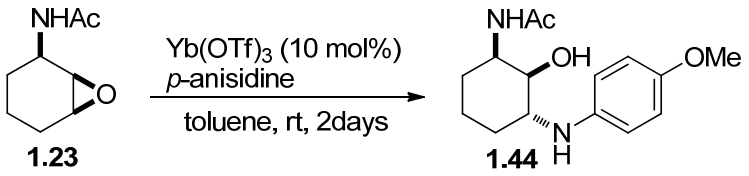
(±) t*ert*-Butyl (1*R*,2*S*,3*R*)-3-(4-bromophenylamino)-2-hydroxycyclohexylcarbamate

Compound **1.43** was prepared according to the general procedure (method D) starting from *cis*-**1.20** (50 mg, 0.23 mmol), $Yb(OTf)_3$ (15 mg, 0.02 mmol), 4-bromoaniline (59 mg, 0.35 mmol) in toluene (3 mL). Purification by the flash column chromatography with ethyl acetate/hexane (3:7) as eluant gave **1.43** (60 mg, 68%) as a brown oil.

^1H NMR (400 MHz CD_3OD): δ 7.20-7.16 (m, 2H), 6.63-6.59 (m, 2H), 3.79 (m, 1H), 3.72 (m, 1H), 3.50 (dd, *J*=4.7, 9.3 Hz, 1H), 1.99-1.89 (m, 1H), 1.68-1.62 (m, 2H), 1.58-1.53 (m, 2H), 1.43 (s, 9H), 1.42-1.39 (m, 1H).

^{13}C NMR (100 MHz CD_3OD): δ 155.0, 148.8, 132.8, 55.0, 51.0, 28.9, 28.5, 27.3, 20.6.

HRMS (ESI) calc. for $C_{17}H_{26}BrN_2O_3$: $[M+H^+]$, 385.11213; found: $[M+H^+]$, 385.11374.



(±) *N*-((1*R*,2*S*,3*R*)-2-Hydroxy-3-(4-methoxyphenylamino)cyclohexyl)acetamide

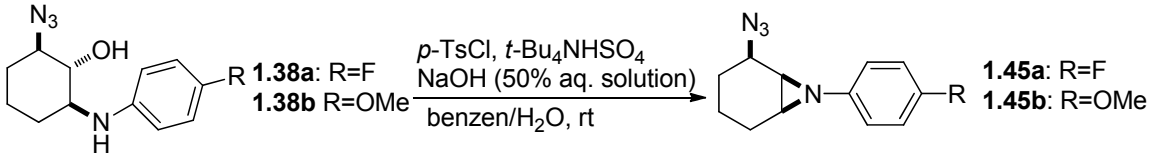
Compound **1.44 w**as prepared according to the general procedure (method C) starting from **1.23** (30 mg, 0.19 mmol), $Yb(OTf)_3$ (12 mg, 0.02 mmol), *p*-anisidine (48 mg, 0.39 mmol) in toluene (2 mL). Purification by the flash column chromatography with ethyl acetate/hexane (4:6) as eluant gave **1.44** (40 mg, 74%) as a brown oil.

^{1}H NMR (400 MHz $CDCl_3$): δ 6.77-6.74 (m, 2H), 6.63-6.61 (m, 2H), 6.20 (s, 1H), 4.21 (s, 1H), 3.73 (s, 3H), 3.70-3.68 (m, 1H), 3.58 (br, 2H), 3.36-3.34 (m, 1H), 2.05-2.00 (m, 4H), 1.82-1.74 (m, 1H), 1.63-1.46 (m, 3H), 1.36-1.23 (m, 1H).

^{13}C NMR (100 MHz $CDCl_3$): δ 171.6, 152.9, 141.2, 116.0, 115.1, 72.7, 56.0, 55.8, 49.5, 27.7, 23.7, 19.5.

HRMS (ESI) calc. for $C_{15}H_{23}N_2O_3$: [M+H$^+$], 279.1703; found: [M+H$^+$], 279.1707.

1.3.4 Aziridine formation and opening reactions



Compounds **1.45a**, **1.45b** were prepared according to the general procedure (method D) starting from **1.38a**, **1.38b** (65 mg, 0. 26 mmol), *p*-TsCl (60 mg, 0.31 mmol), *t*-Bu_4NHSO_4 (18 mg, 0.05 mmol) and 50% NaOH (0.2 mL) in benzene (2 mL). Purification by the flash column chromatography with ethyl acetate/hexane (2:8) as eluant afforded **1.45a** and **1.45b**.

(±) (1*S*,2*R*,6*S*)-2-Azido-7-(4-fluorophenyl)-7-azabicyclo[4.1.0]heptane (1.45a 43%)

IR: 2102 cm^{-1}

^{1}H NMR (400 MHz $CDCl_3$): δ 7.00-6.92 (m, 4H), 3.63-3.60 (m, 1H), 2.49-2.46 (m, 2H), 2.00-1.99 (m, 1H), 1.94-1.90 (m, 1H), 1.78-1.70 (m, 3H), 1.37-1.25 (m, 1H).

^{13}C NMR (100 MHz $CDCl_3$): δ 159.9, 157.6, 150.4, 150.3, 121.7, 121.6, 115.8, 115.6, 57.7, 42.3, 40.7, 25.1, 23.1, 21.1.

HRMS (ESI) calc. for $C_{12}H_{14}FN_4$: [M+H$^+$], 233.1197; found: [M+H$^+$], 233.11994.

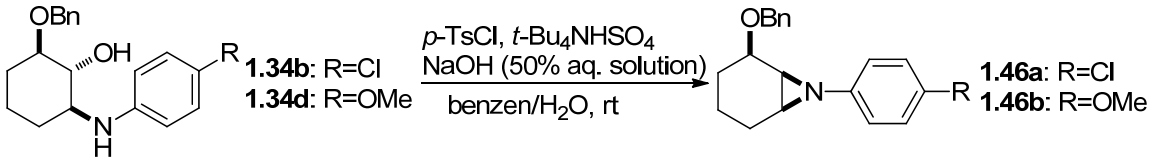
(±) (1*S*,2*R*,6*S*)-2-Azido-7-(4-methoxyphenyl)-7-azabicyclo[4.1.0]heptane (1.45b, 50%)

IR: 2101 cm^{-1}

^{1}H NMR (400 MHz $CDCl_3$): δ 7.00-6.96 (m, 2H), 6.83-6.79 (m, 2H), 3.78 (s, 3H), 3.62-3.57 (m, 1H), 2.48-2.43 (m, 2H), 2.01-1.99 (m, 1H), 1.94-1.90 (m, 1H), 1.77-1.70 (m, 3H), 1.32-1.29 (m, 1H),

^{13}C NMR (100 MHz $CDCl_3$): δ 155.4, 147.7, 121.4, 114.5, 57.8, 55.7, 42.2, 40.6, 25.1, 23.1, 21.1.

HRMS (ESI) calc. for $C_{13}H_{17}N_4O$: [M+H$^+$], 245.13969; found: [M+H$^+$], 245.13909.



Compounds **1.46a**, **1.46b** were prepared according to the general procedure (method D) starting from **1.34b**, **1.34d** (50 mg, 0.15 mmol), *p*-TsCl (35 mg, 0.18 mmol), *t*-Bu_4NHSO_4 (10 mg, 0.03 mmol) and 50% NaOH (0.1 mL) in benzene (1 mL) at rt. Purification by the flash column chromatography with ethyl acetate/hexane (1:9) as eluant afforded **1.46a** and **1.46b**.

(±) (1*S*,2*R*,6*S*)-2-(Benzyloxy)-7-(4-chlorophenyl)-7-azabicyclo[4.1.0]heptanes (1.46a)

^{1}H NMR (400 MHz $CDCl_3$): δ 7.49-7.28 (m, 5H), 7.20-7.18 (m, 2H), 6.98-6.96 (m, 2H), 4.80 (dd, *J*=12.2, 15.6 Hz, 2H), 3.85-3.80 (m, 1H), 2.53-2.47 (m, 2H), 2.00-1.55 (m, 5H), 1.30-1.18 (m, 1H).

^{13}C NMR (100 MHz $CDCl_3$): δ 153.8, 139.2, 128.9, 128.6, 127.7, 127.6, 127.1, 112.1, 74.6, 70.4, 42.7, 40.9, 25.6, 23.3, 21.3.

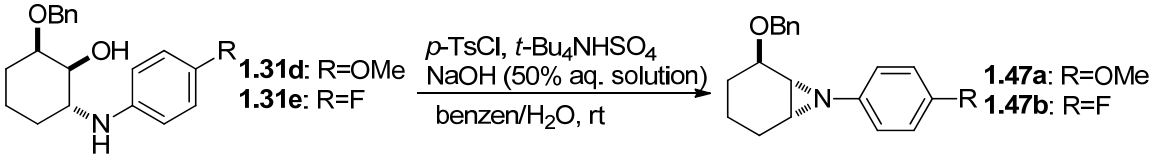
HRMS (ESI) calc. for $C_{19}H_{21}ClNO$: [M+H$^+$], 314.13062; found: [M+H$^+$], 314.1311.

(±) (1*R*,2*R*,6*S*)-2-(Benzyloxy)-7-(4-methoxyphenyl)-7-azabicyclo[4.1.0]heptane (1.46b)

^{1}H NMR (400 MHz $CDCl_3$): δ 7.49-7.28 (m, 5H), 6.98 (d, *J*=6.5 Hz, 2H), 6.79 (d, *J*=8.6 Hz, 2H), 4.80 (dd, *J*=3.2, 12.8 Hz, 2H), 7.49-7.28 (m, 5H), 3.78 (s, 3H), 3.82 (m, 1H), 2.52-2.42(m, 2H), 1.99-1.83 (m, 2H), 1.70-1.60 (m, 3H), 1.29-1.21 (m, 1H).

^{13}C NMR (100 MHz $CDCl_3$): δ 155.1, 148.6, 139.4, 128.6, 127.6, 121.5, 114.4, 74.9, 70.3, 55.8, 42.6, 40.8, 25.8, 23.6, 21.4.

HRMS (ESI) calc. for $C_{20}H_{24}NO_2$: [M+H$^+$], 310.18016; found: [M+H$^+$], 310.1806.



Compounds **1.47a**, **1.47b** were prepared according to the general procedure (method D), starting from **1.31d**, **1.31e** (50 mg, 0.15 mmol) *p*-TsCl (35 mg, 0.18 mmol), *t*-Bu_4NHSO_4 (10 mg, 0.03 mmol) and 0.1 mL 50% NaOH in benzene (1 mL). Purification by the flash column chromatography with ethyl acetate/hexane (5:95) as eluant afforded **1.47a** and **1.47b**.

(±) (1*R*,2*R*,6*R*)-2-(Benzyloxy)-7-(4-methoxyphenyl)-7-azabicyclo[4.1.0]heptane (1.47a)

^{1}H NMR (400 MHz $CDCl_3$): δ 7.47-7.28 (m, 5H), 6.90-6.87 (m, 2H), 6.81-6.77 (m, 2H), 4.75 (dd, *J*=1.9, 11.8 Hz, 2H), 3.91 (dd, *J*=5.7, 2.4 Hz, 1H), 3.78 (s, 3H), 2.42-2.38 (m, 2H), 2.12-2.07 (m, 1H), 1.92-1.85 (m, 2H), 1.57-1.56 (m, 1H), 1.38-1.33 (m, 2H).

^{13}C NMR (100 MHz $CDCl_3$): δ 155.2, 148.3, 138.8, 128.7, 128.0, 127.9, 121.2, 114.4, 74.6, 71.3, 55.7, 46.6, 42.8, 40.1, 27.6, 24.6, 16.1.

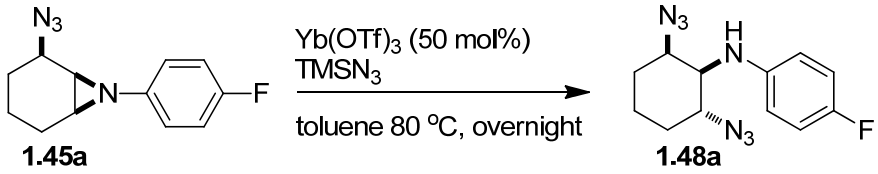
HRMS (ESI) calc. for $C_{20}H_{24}NO_2$: [M+H$^+$], 310.18016; found: [M+H$^+$], 310.18005.

(±) (1*R*,2*R*,6*R*)-2-(Benzyloxy)-7-(4-fluorophenyl)-7-azabicyclo[4.1.0]heptane (1.47b)

^{1}H NMR (400 MHz $CDCl_3$): δ 7.48-7.33 (m, 5H), 6.96-6.86 (m, 4H), 4.75 (dd, *J*=11.9, 20.6 Hz, 2H), 3.93 (dd, *J*=5.3, 7.7 Hz, 1H), 2.44-2.41 (m, 2H), 2.14-2.08 (m, 1H), 1.96-1.82 (m, 2H), 1.63-1.55 (m, 1H), 1.44-1.31 (m, 2H).

^{13}C NMR (100 MHz $CDCl_3$): δ 159.7, 157.3, 151.0, 138.7, 128.7, 127.9, 121.4, 115.8, 115.5, 74.4, 71.4, 42.9, 40.2, 27.5, 24.5, 16.0.

HRMS (ESI) calc. for $C_{19}H_{21}FNO$: [M+H$^+$], 298.16055; found: [M+H$^+$], 298.16017.



1.45a 1.48a

(±) *N*-((2*R*,6*R*)-2,6-Diazidocyclohexyl)-4-fluoroaniline

Compound **1.48a** was prepared according to the general procedure (method E) starting from **1.45a** (50 mg, 0.22 mmol), $Yb(OTf)_3$ (68 mg, 0.11 mmol) and $TMSN_3$ (14 μL, 1.08 mmol) in toluene (3.5 mL). Purification by the flash column chromatography with ethyl acetate/hexane (3:97) as eluant gave **1.48a** (47 mg, 79%) as a brown oil.

Or to a stirred solution of the *cis*-aziridine (50 mg, 0.22 mmol) in the mixture of acetonitrile (3.2 mL) and H_2O (0.1 mL), was added $Yb(OTf)_3$ (68 mg, 0.11 mmol) and NaN_3 (17 mg, 0.26 mmol). After stirred at reflux overnight, cooled to rt, then the reaction mixture was concentrated under reduced pressure, the residue was purified by the flash

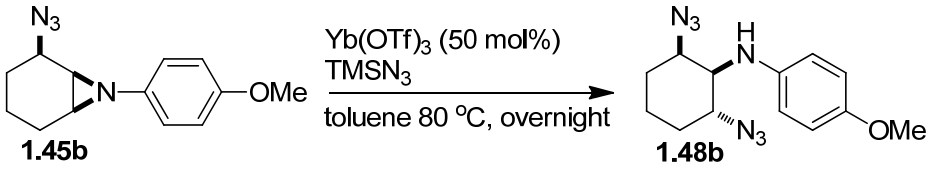
column chromatography , eluting with ethyl acetate/hexane (3:97), to give **1.48a (**45 mg, 77%).

IR: 2101 cm^{-1}

^1H NMR (400 MHz $CDCl_3$): δ 6.96-6.90 (m, 2H), 6.89-6.64 (m, 2H), 4.11 (dd, *J* = 3.3, 6.3 Hz, 1H), 3.51 (dt, *J*=4.3, 10.1 Hz, 1H), 3.29 (dd, *J*=3.3, 9.8 Hz, 1H), 2.15-2.11 (m, 1H), 2.07-2.03 (m, 1H), 1.73-1.61 (m, 3H), 1.48-1.36 (m, 1H).

^{13}C NMR (100 MHz $CDCl_3$): δ 157.8, 155.4, 142.8, 116.2, 116.0, 115.5, 115.4, 61.1, 61.0, 60.1, 30.8, 28.6, 19.0.

HRMS (ESI) calc. for $C_{12}H_{15}FN_7$: [M+H^+], 276.13675; found: [M+H^+], 276.1371.



(±) *N*-((2*R*,6*R*)-2,6-Diazidocyclohexyl)-4-methoxyaniline

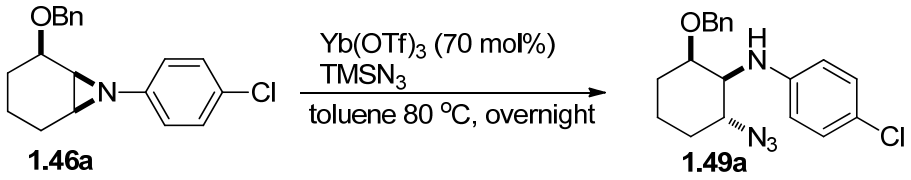
Compound **1.48b** was prepared according to the general procedure (method E) starting from **1.45b** (50 mg, 0.20 mmol) $Yb(OTf)_3$ (62 mg, 0.10 mmol) and $TMSN_3$ (13 μL, 1 mmol) in toluene (3.5 mL). Purification by the flash column chromatography with ethyl acetate/hexane (3:97) as eluant affored **1.48b** (45 mg, 77%) as a brown oil.

IR: 2101 cm^{-1}

^1H NMR (400 MHz $CDCl_3$): δ 6.84-6.80 (m, 2H), 6.73-6.69 (m, 2H), 4.11 (dd, *J* = 3.3, 6.5 Hz, 1H), 3.78(s, 3H), 3.50 (dt, *J*=4.4, 10.6 Hz, 1H), 3.27 (dd, *J*=3.3, 9.7 Hz,1H), 2.14 -2.10 (m, 1H), 2.10-2.01 (m, 1H), 1.71-1.66 (m, 3H), 1.63-1.58 (m, 1H).

^{13}C NMR (100 MHz $CDCl_3$): δ 153.3, 140.5, 116.3, 115.2, 61.0, 60.7, 55.9, 30.8, 28.6, 19.1.

HRMS (ESI) calc. for $C_{13}H_{18}N_7O$: [M+H^+], 288.15673; found: [M+H^+], 288.15657.



1.46a **1.49a**

(±) *N*-((1*S*,2*R*,6*R*)-2-Azido-6-(benzyloxy)cyclohexyl)-4-chloroaniline

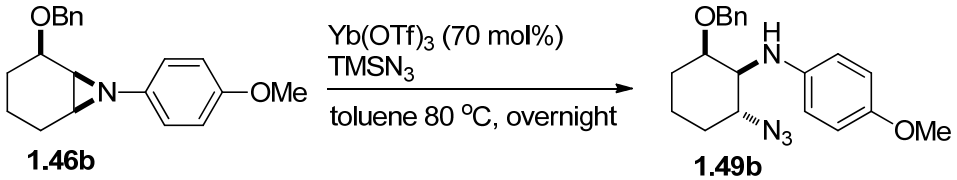
Compound **1.49a** was prepared according to the general procedure (method E) starting from **1.46a** (50 mg, 0.16 mmol) $Yb(OTf)_3$ (70 mg, 0.11 mmol) and $TMSN_3$ (110 μL, 0.8 mmol) in toluene (3.5 mL). Purification by the flash column chromatography with ethyl acetate/hexane (5:95) as eluant gave **1.49a** (41 mg, 72%) as a brown oil.

IR: 2100 cm^{-1}

^1H NMR (400 MHz $CDCl_3$): δ 1.40-1.35 (m, 2H), 1.71-1.62 (m, 2H), 2.15-2.09 (m, 2H), 3.25-3.22 (m, 1H), 3.66 (dt, *J*=21.3, 4.3 Hz, 1H), 3.85-3.83 (m, 1H), 4.44 (dd, *J*=115.9, 11.6 Hz, 2H), 6.58-6.55 (m, 2H), 7.14-7.10 (m, 2H), 7.42-7.28 (m, 5H).

^{13}C NMR (100 MHz $CDCl_3$): δ 146.2, 138.2, 129.2, 128.8, 128.1, 128.0, 122.5, 115.2, 75.9, 71.0, 62.1, 60.5, 31.0, 27.6, 18.6.

HRMS (ESI) calc. for $C_{19}H_{22}ClN_4O$: $[M+H^+]$, 357.14767; found: $[M+H^+]$, 357.14855.



1.46b **1.49b**

(±) *N*-((1*S*,2*R*,6*R*)-2-Azido-6-(benzyloxy)cyclohexyl)-4-methoxyaniline

Compound **1.49b** was prepared according to the general procedure (method E) starting from **1.46b** (50 mg, 0.16 mmol), $Yb(OTf)_3$ (70 mg, 0.11 mmol) and $TMSN_3$ (110 μL, 0.8

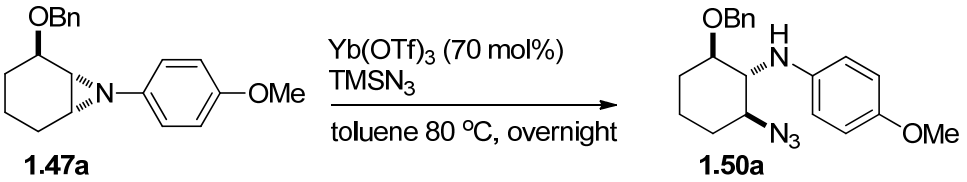
mmol) in toluene (3.5 mL). Purification by the flash column chromatography with ethyl acetate/hexane (1:19) as eluant gave **1.49b** (38 mg, 68%) as a brown oil.

IR: 2101 cm^{-1}

^1H NMR (400 MHz $CDCl_3$): δ7.42-7.34 (m, 5H), 6.81-6.77 (m, 2H), 6.64-6.60 (m, 2H), 4.48 (dd, *J*=100.1, 11.6 Hz, 2H), 3.87-3.84 (m, 1H), 3.78 (s, 3H), 3.64 (dt, *J*=10.8, 4.3 Hz, 1H), 3.19 (dd, *J*=6.9, 3.0 Hz, 1H), 2.13-2.07 (m, 2H), 1.77-1.58 (m, 2H), 1.45-1.30 (m, 2H).

^{13}C NMR (100 MHz $CDCl_3$): δ 144.8, 138.5, 128.9, 128.7, 128.1, 128.0, 116.2, 115.1, 75.7, 71.1, 62.1, 61.9, 56.0, 31.0, 27.7, 8.7.

HRMS (ESI) calc. for $C_{20}H_{25}N_4O_2$: $[M+H^+]$, 353.1972; found: $[M+H^+]$, 353.19749.



1.47a **1.50a**

(±) *N*-((1*R*,2*S*,6*R*)-2-Azido-6-(benzyloxy)cyclohexyl)-4-methoxyaniline

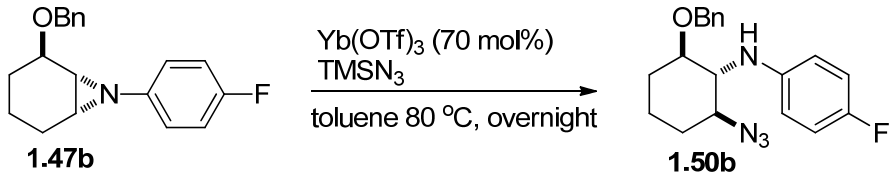
Compound **1.50a** was prepared according to the general procedure (method E) starting from **1.47a** (50 mg, 0.16 mmol), $Yb(OTf)_3$ (70 mg, 0.11 mmol) and $TMSN_3$ (110 μL, 0.8 mmol) in toluene (3.5 mL). Purification by the flash column chromatography with ethyl acetate/hexane (1:19) as eluant afforded **1.50a** (38 mg, 70%) as a brown solid.

IR: 2101 cm^{-1}

^1H NMR (400 MHz $CDCl_3$): δ 7.31-7.28 (m, 5H), 7.21-7.19 (m, 4H), 4.56 (dd, *J*=11.8, 50.3 Hz, 1H), 3.78 (s, 3H), 3.22 (ddd, *J* = 2.9, 5.6, 6.7, 2H), 3.13 (dd, *J*=9.6, 5.9 Hz,1H), 2.21-2.17 (m, 1H), 2.09-2.04 (m, 1H), 1.89-1.84 (m, 1H), 1.45-1.28 (m, 3H).

^{13}C NMR (100 MHz $CDCl_3$): δ 153.4, 143.5, 139.2, 129.4, 128.9, 128.7, 116.9, 115.9, 82.3, 72.9, 67.0, 66.6, 57.7, 33.0, 32.6, 23.2.

HRMS (ESI) calc. for $C_{20}H_{25}N_4O_2$: [M+H$^+$], 353.1972; found: [M+H$^+$], 353.19618.



(±) *N*-((1*R*,2*S*,6*R*)-2-Azido-6-(benzyloxy)cyclohexyl)-4-fluoroaniline

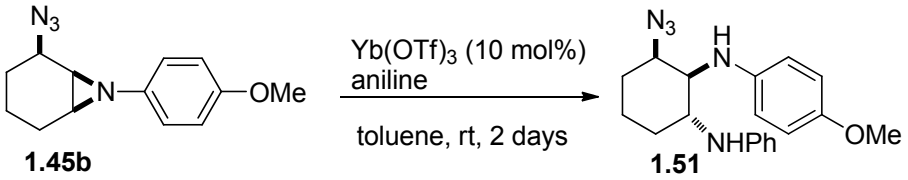
Compound **1.50b** was prepared according to the general procedure (method E) starting from **1.47b** (50 mg, 0.17 mmol), $Yb(OTf)_3$ (73 mg, 0.12 mmol) and $TMSN_3$ (110 μL, 0.84 mmol) in toluene (3.5 mL). Purification by the flash column chromatography with ethyl acetate/hexane (1:19) as eluant gave **1.50b** (42 mg, 73%) as a brown oil.

IR: 2102 cm^{-1}

^{1}H NMR (400 MHz $CDCl_3$): δ 7.38-7.16 (m, 5H), 6.93-6.87 (m, 2H), 6.77-6.72 (m, 2H), 4.54 (dd, *J*=11.9, 58.8 Hz, 2H), 3.25-3.14 (m, 3H), 2.24-2.19 (m, 1H), 2.11-2.06 (m, 1H), 1.91-186 (m, 1H), 1.48-1.31 (m, 3H).

^{13}C NMR (100 MHz $CDCl_3$): δ 145.2, 138.5, 128.7, 128.6, 128.0, 127.9, 115.8, 115.2, 81.1, 71.5, 65.6, 64.6, 31.1, 30.7, 21.1.

HRMS (ESI) calc. for $C_{19}H_{22}FN_4O$: [M+H$^+$], 341.17722; found: [M+H$^+$], 341.17776.

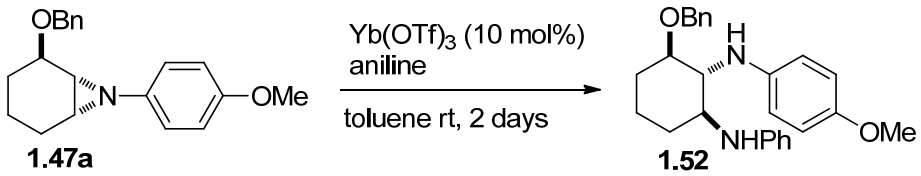


(±) (1*R*,2*S*,3*R*)-3-Azido-N^2-(4-methoxyphenyl)-N^1-phenylcyclohexane-1,2-diamine

Compound **1.51** was prepared according to the general procedure (method E) starting from **1.45b** (50 mg, 0.20 mmol), $Yb(OTf)_3$ (13 mg, 0.02 mmol) and aniline (28 μL 0.31

mmol) in toluene (3.5 mL). Purification by the flash column chromatography with ethyl acetate/hexane (1:9) as eluant afforded **1.51** (39 mg, 74%) as a brown solid.

^{1}H NMR (400 MHz $CDCl_3$): δ 7.22-7.17 (m, 2H), 6.92-6.63 (m. 3H), 6.48-6.28 (m, 4H), 4.23 (m, 1H), 3.78 (s, 3H), 3.51 (dt, *J*=3.7, 6.7 Hz, 1H), 3.34 (dd, *J*=2.8, 7.2 Hz, 1H), 2.42-2.37 (m, 1H), 2.09-2.04 (m, 1H), 1.79-1.61 (m, 3H), 1.29-1.19 (m, 1H).
^{13}C NMR (100 MHz $CDCl_3$): δ 153.2, 148.0, 140.8, 129.5, 118.1, 116.1, 115.3, 113.9, 61.2, 60.4, 56.0, 52.6, 32.8, 29.2, 19.4.
HRMS (ESI) calc. for $C_{19}H_{24}N_5O$: [M+H$^+$], 338.19725; found: [M+H$^+$], 338.19786.



(±)

(1*S*,2*R*,3*R*)-3-(Benzyloxy)-N^2-(4-methoxyphenyl)-N^1-phenylcyclohexane-1,2-diamine

Compound **1.52** was prepared according to the general procedure (method E) starting from **1.47a** (50 mg, 0.16 mmol), $Yb(OTf)_3$ (10 mg, 0.02 mmol) and aniline (22 μL, 0.24 mmol) in toluene (3.5 mL). Purification by the flash column chromatography with ethyl acetate/hexane (1:9) as eluant gave **1.52** (38 mg, 58%) as a brown solid.

^{1}H NMR (400 MHz $CDCl_3$): δ 7.34-7.16 (m, 7H), 6.80-6.57 (m, 7H), 4.62 (dd, *J*=11.6, 19.5 Hz, 2H), 3.50-3.47 (m, 1H), 3.71 (s, 3H), 3.42-3.34 (m, 2H), 2.12-2.02 (m, 2H), 1.87-1.80 (m, 1H), 1.70-1.61 (m, 1H), 1.49-1.34 (m, 2H).
^{13}C NMR (100 MHz $CDCl_3$): δ 152.7, 147.8, 142.5, 138.7, 129.5, 128.5, 128.0, 127.8, 117.5, 116.0, 115.0, 113.6, 80.7, 77.7, 71.9, 56.0, 54.8, 29.5, 19.1, 14.3.
HRMS (ESI) calc. for $C_{26}H_{31}N_2O_2$: [M+H$^+$], 403.23800; found: [M+H$^+$], 403.23801.

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Chapter Two

Synthesis ω-Alkoxy PMB Ether HDAC Inhibitor

2.1 Introduction

Histone deacetylases (HDAC) are enzymes, which can remove acetyl groups from an ε-N-acetyl lysine amino acid on a histone. The amine groups on lysine and arginine amino acids make histone tails positively charged. These positive charges help the binding between histone tails and the negatively charged phosphate groups on the DNA backbone. When the amines are changed to amides by acetylation with histone acetyl transferases (HATs), the positive charges on the histone are neutralized, thus the bonding ability of the histones to DNA is decreased. This decreased binding allows chromatin expansion, and the genetic transcription can take place. Histone deacetylases can reestablish the positive charge of histone tails by removing those acetyl groups, leading to increase the DNA binding condenses to prevent transcription. The competing acetylation and deacetylation[1] is shown in Figure 2.1.

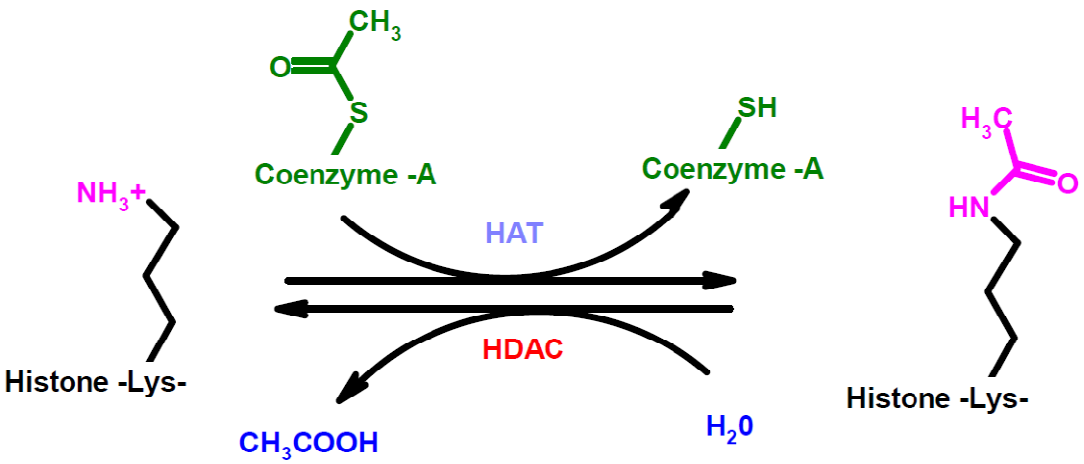


Figure 2.1 Acetylation/deacetylation reactions on lysine ε-amino groups[1]

Histone deacetylase (HDAC) inhibitors can affect the degree of acetylation of these molecules and thereby increase or repress their activity to affect gene expression[2]. It has been suggested that deregulation of acetylase and deacetylase activity can induce the generation of cancer[3]. HDAC inhibitors can inhibit deacetylation of histone and therefore

have been studied as anticancer agents[4,5]. Vorinostat (SAHA), one of the HDAC inhibitors, has recently been approved for treatment of cutaneous T cell lymphoma (CTCL)[6].

The key antitumor activities of HDAC inhibitors are activation of differentiation programs, inhibition of the cell cycle, and induction of apoptosis[7] as shown in Figure 2.2. After a G2 checkpoint, the normal cells survive during the treatment, whereas tumor cells can replicate and subsequently undergo apoptosis.

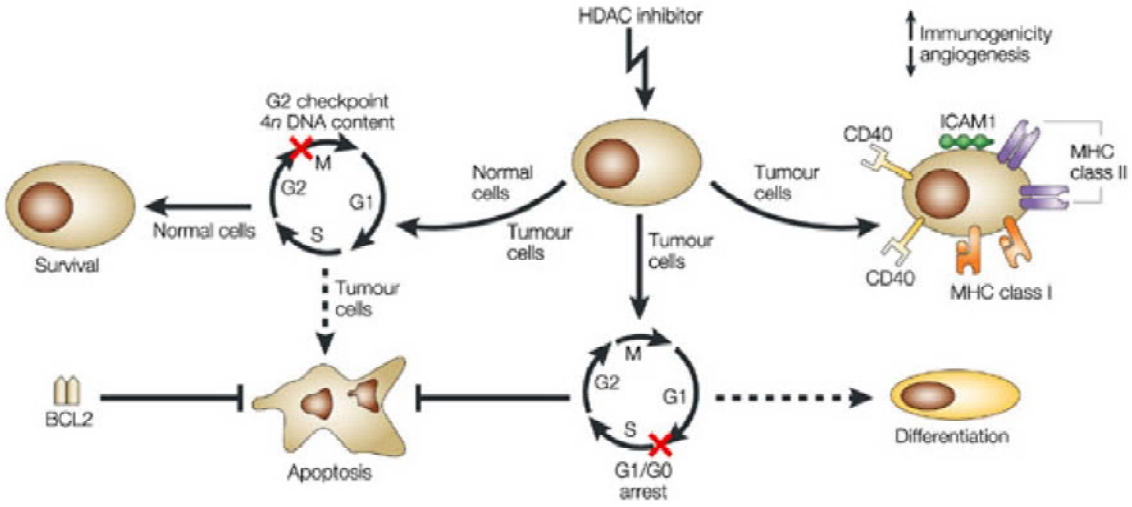


Figure 2.2 Regulation of cell growth and survival by HDAC inhibitors[7]

2.2 The mechanism of deacetylation

The X-ray crystal structure of a deacetylase protein from the hyperthermophilic bacterium *Aquifex aeolicus* with sequence homology to the class I and II HDACs (termed histone deacetylase-like protein, HDLP) has been determined alone and in complex with two inhibitors, (*R*)-TSA and SAHA trichostatin A (TSA)[8] as shown in Figure 2.3

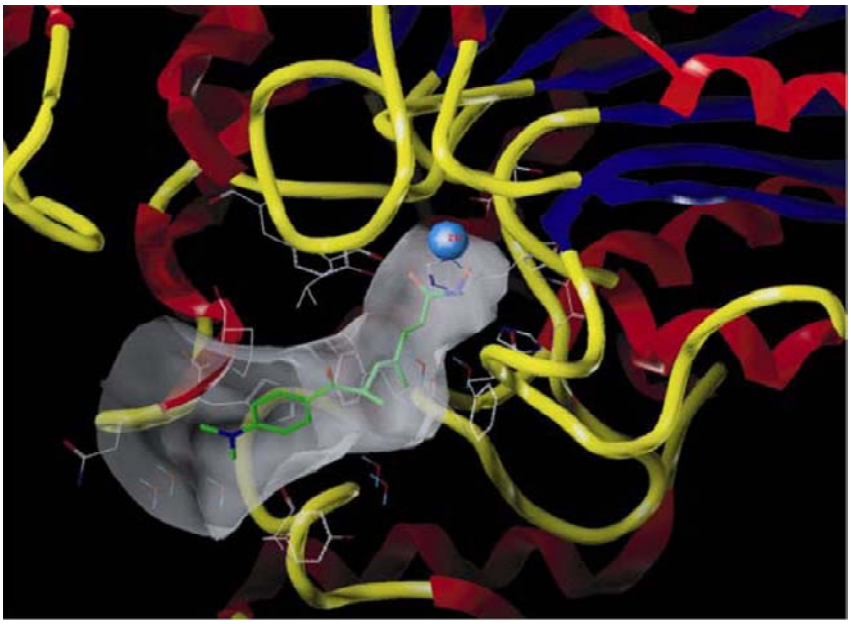


Figure 2.3 Computational representation of TSA in the active-site pocket of HDLP[8]

This crystal structure has suggested a mechanism for the deacetylation reaction[8] (Figure 2.4). The carbonyl oxygen of the *N*-acetylamide bond coordinates to the zinc cation and is activated for a nucleophilic attack by the water. The water is hydrogen bonded with the buried Asp166-His131, which could enhance the nucleophilicity of the water molecule by an interaction with the negative charge. The forming oxy-anion intermediate is stabilized by the zinc ion, and hydrogen bond to Tyr297. The collapse of this intermediate would result in cleavage of the carbon-nitrogen bond, with the nitrogen accepting a proton from the His132 residue, and would thereby produce the observed acetate and lysine products.

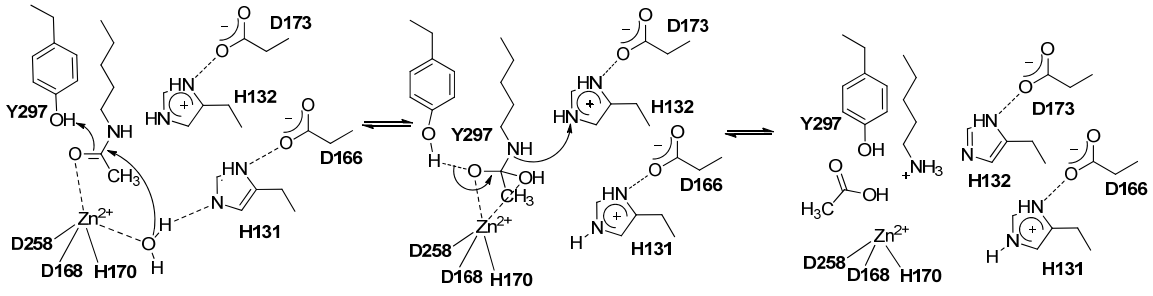


Figure 2.4 Proposed mechanism for HDAC deacetylation[8]

The mechanism of the inhibition of the deacetylation was also revealed in the same paper[8] as shown in Figure 2.5, the hydroxamic acid coordinates with the zinc through its carbonyl and hydroxyl group in a bidentate fashion. TSA also makes hydrogen bonds with both histidines and the Y297 hydroxyl group. The hydroxamate replaces the zinc-bound water molecule of the active structure with its hydroxyl group in the inhibitor complex with HDAC.

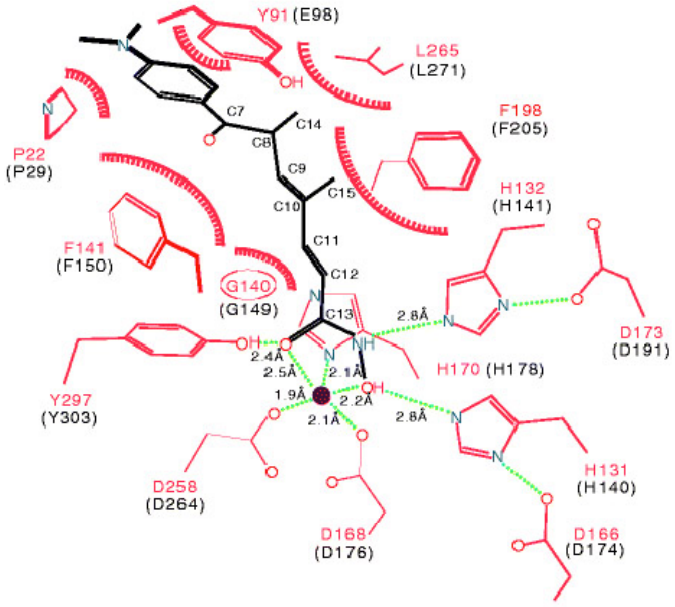


Figure 2.5 Binding of the hydroxamate inhibitor to HDAC[8]

2.3 HDAC inhibitor structures

Based on their structure, HDAC inhibitors can be divided into six groups: hydroxamic acid-derived compounds, cyclic tetrapeptides, synthetic pyridyl carbamate derivatives, synthetic benzamide derivatives and ketones[9]. Among them, hydroxamic acid analogues of acyclic and heterocyclic compounds are mostly studied[10]. Natural products such as trichostatin A (TSA)[11], and unnatural surrogates like suberoylanilide hydroxamic acid (SAHA)[12] under the name vorinostat are known hydroxamic HDAC inhibitors (Figure 2.6).

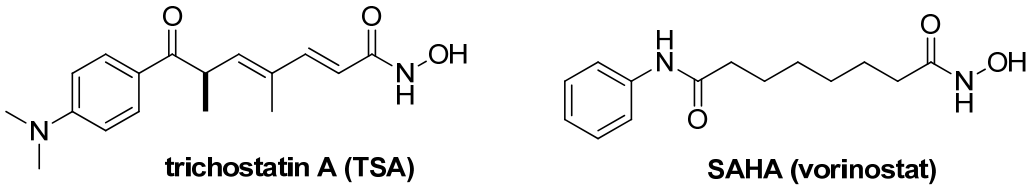


Figure 2.6 Structures of known hydroxamic acid HDAC inhibitors

Recently, our laboratory had reported the influence of the chain length of SAHA analogues possessing ω-alkoxy substituents on enzyme binding and inhibition[13]. The preferred chain length was found to be with CH_2 = 5 and there was no significant difference in inhibitory activity between the racemic analogue and the single enantiomers.

Although this special HDAC inhibitor (Figure 2.7) was synthesized successfully by a general method for series of inhibitor analogues, the steps were long and the total yields were low, especially in the PMB alkylation step[14]. Here we report a modified method to improve the yield for this HDAC inhibitor.

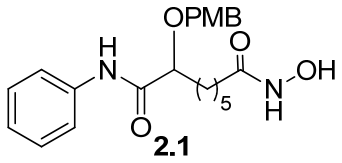
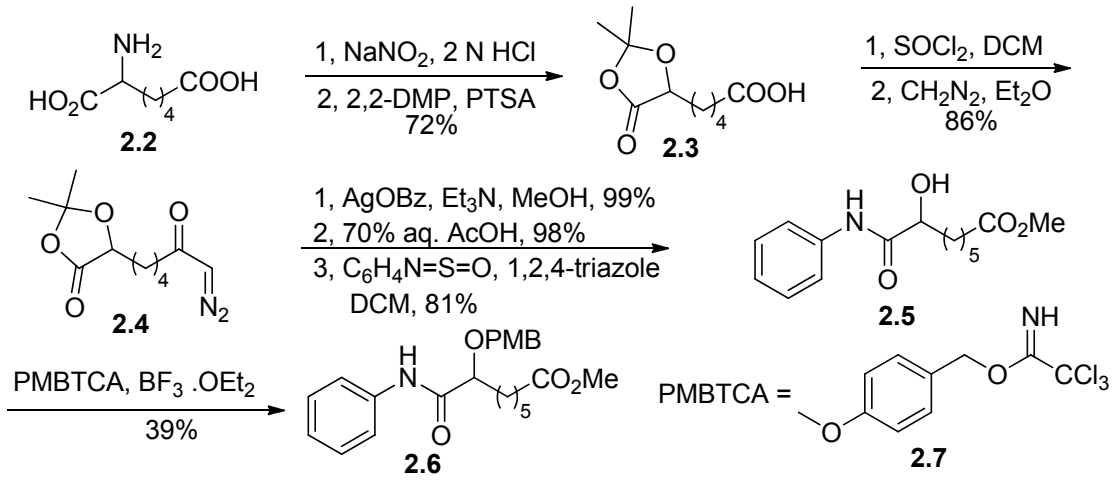


Figure 2.7 Target compound

2.4 Results and discussion

2.4.1 Published methods

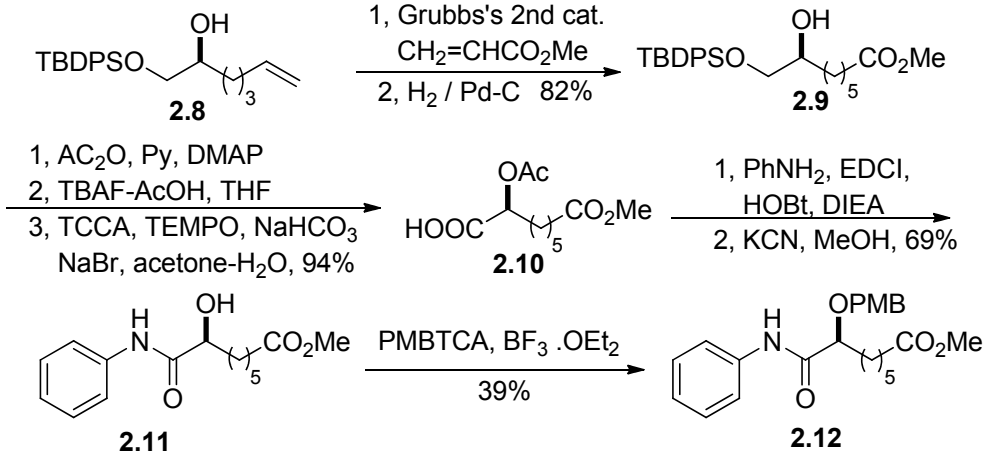
The published methods developed in our laboratory[13] to synthesize the intermediates are shown in Scheme 2.1 and 2.2 for racemic and enantiomerically pure intermediates.



Scheme 2.1 Racemic intermediates

First, racemic aminopimelic acid **2.2** was subjected to diazotization[15], and the resulting alcohol was protected as the lactone acetal **2.3**. After an Arndt–Eistert extension[16] and cleavage of the acetonide protection of **2.3**, the resulting α-hydroxy acid was converted to the anilide by reaction with N-sulfinylaniline[17], and then alkylated using PMB trichloroacetimidate to give compound **2.6**. The yield for the alkylation step was only 39%. In this strategy, 8 steps were used, and the total yield was 19% (Scheme 2.1).

Another strategy was used to prepare the enantiomerically pure intermediate (Scheme 2.2):

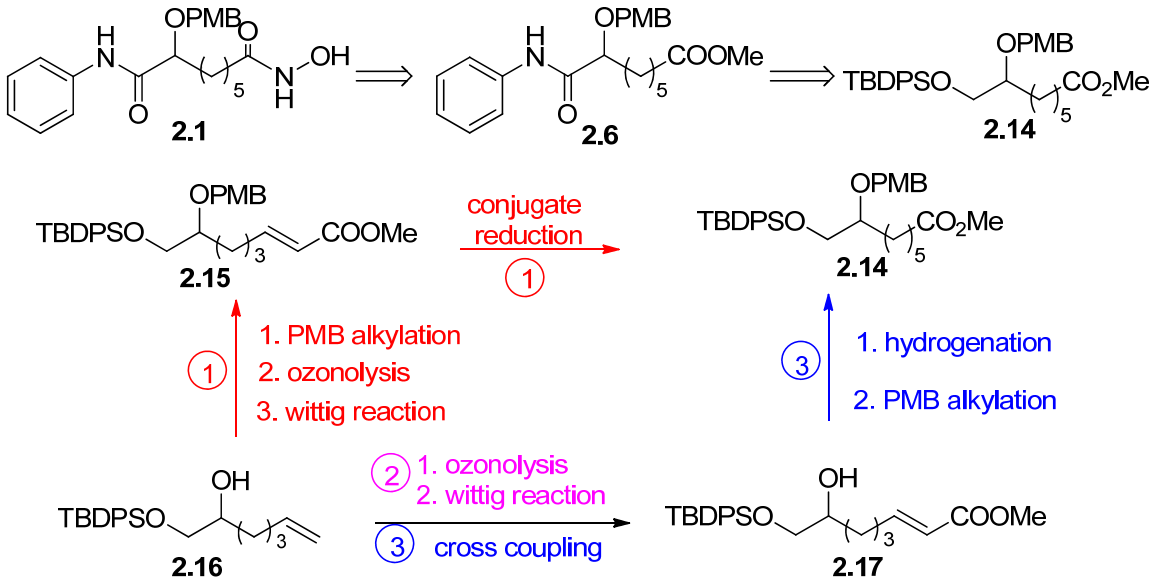


Scheme 2.2 Enantiomerically pure intermediates

Cross-metathesis of the known enantiomerically pure alkenol **2.8** with methyl acrylate in the presence of Grubbs second generation catalyst [18], followed by catalytic hydrogenation, gave the corresponding hydroxy ester **2.9** in excellent overall yield. Acetylation of the alcohol function, cleavage of the TBDPS ether, oxidation[19], anilide formation, and deacetylation with KCN in MeOH[20], gave the amide **2.11**, which was alkylated to give the PMB intermediate **2.12**. In this strategy, 8 steps were used and the total yield was 21%.

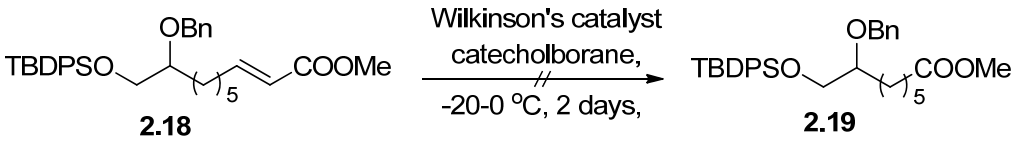
2.4.2 Synthetic plan

Because the alkylation with PMB trichloroacetimidate at the later stage led to a low yield, we decided to introduce the PMB group on earlier stage. Our retrosynthesis plan leads to the key intermediate **2.3**. Several methods to synthesize **2.3** are shown in Scheme 2.3.



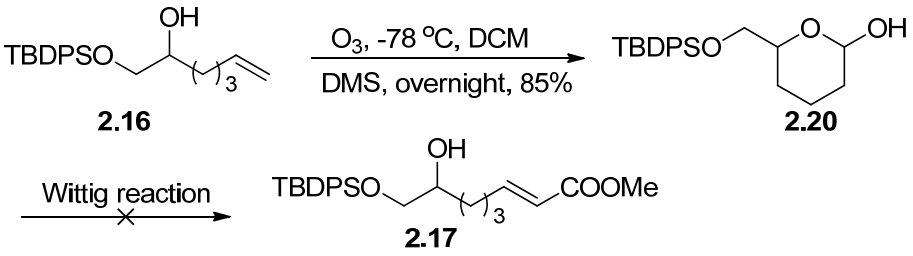
Scheme 2.3 The synthesis plan

Initially, we planned to convert **2.16** to the PMB ether, ozonolysis, followed by Wittig reaction then conjugate reduction[21] to form **2.14**. Unfortunately, a model study failed to give the reduction compound (Scheme 2.4).



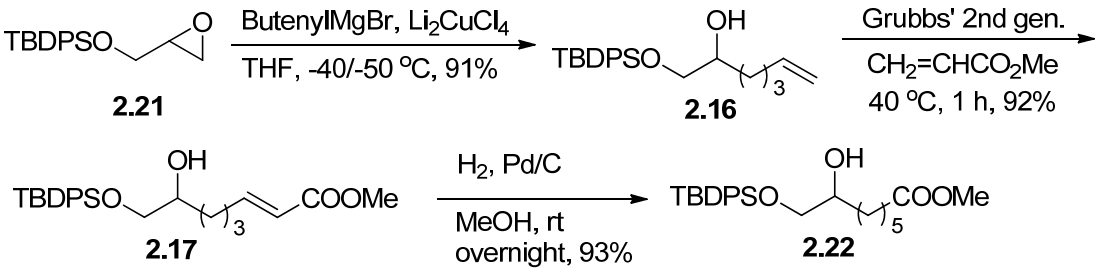
Scheme 2.4 Attempted selective reduction of the double bond **2.18**

Consequently, **2.16** was oxidized to hemiacetal **2.20**[22] then subjected to several Wittig reaction conditions[23]. None of the expected **2.17** was observed (Scheme 2.5), and this route was also abandoned.



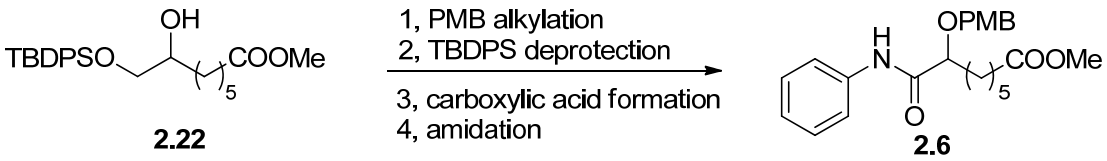
Scheme 2.5 Attempted synthesis of **2.17**

We then envisaged a third synthesis by using the cross-metathesis method. First, treatment of **2.21** with butenylMgBr formed **2.16**, which was reacted with methyl acrylate in the presence of the Grubbs' second generation catalyst, to give the unsaturated ester **2.17**. Hydrogenation of **2.17** led to **2.22** (Scheme 2.6).



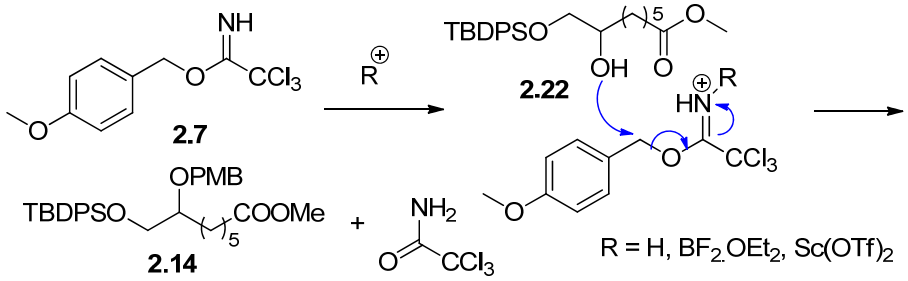
Scheme 2.6 Synthesis of **2.22** by cross-metathesis method

With intermediate **2.22** in hand, a linear synthesis plan to **2.6** was envisaged relying on PMB alkylation and TBDPS deprotection, oxidation to carboxylic acid and, finally, anilide formation (Scheme 2.7).



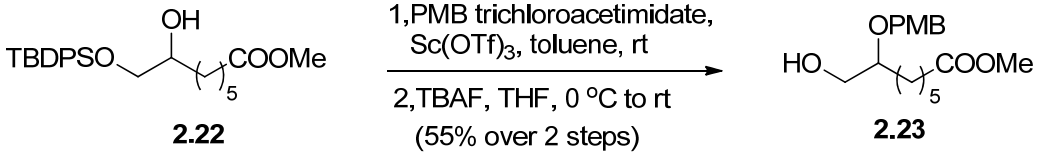
Scheme 2.7 Synthesis plan from **2.22** to **2.6**

Treatment of alcohol **2.22** with *para*-methoxybenzyl bromide in the presence of sodium hydride or Ag_2O[24] led to decomposition. The reaction of alcohol **2.22** with the trichloroacetimidate of *para*-methoxybenzyl alcohol in the presence of TfOH[25], $BF_3.OEt_2$[26] and $Sc(OTf)_3$[27] was also tried. The most effective method for PMB alkylation was found to be the $Sc(OTf)_3$. According to mechanistic studies by Cramer and Hennrich[28], the following mechanism could be proposed. In the first step, the *para*-methoxybenzyl trichloroacetimidate is protonated or coordinated with $BF_3.OEt_2$ or $Sc(OTf)_3$ to generate a very reactive electrophile which reacts rapidly with the alcohol **2.22** to give the PMB ether and trichloroacetamide (Scheme 2.8).



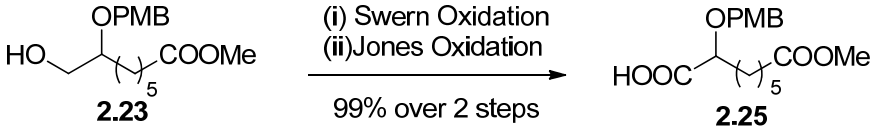
Scheme 2.8 Mechanism of PMB alkylation with PMB trichloroacetimidate

Treatment of **2.22** with PMB trichloroacetimidate in the presence of $Sc(OTf)_3$, followed by TBDPS deprotection afforded the primary alcohol **2.23** in 55% yield over two steps (Scheme 2.9).



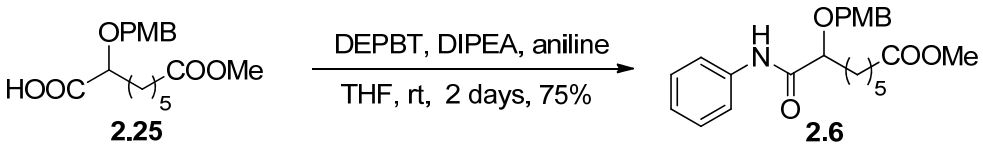
Scheme 2.9 Synthesis of **2.23**

One-pot oxidation methods using trichloro isocyanuric acid (TCCA)[19] or Jones' oxidation were tried. The former method led to decomposition, while the latter gave a very poor yield (10%), possibly due to the formation of substantial amount of esters. Therefore we decided to oxidize the alcohol to the aldehyde by Swern oxidation[29], and then to carboxylic acid by Jones' oxidation (Scheme 2.10).



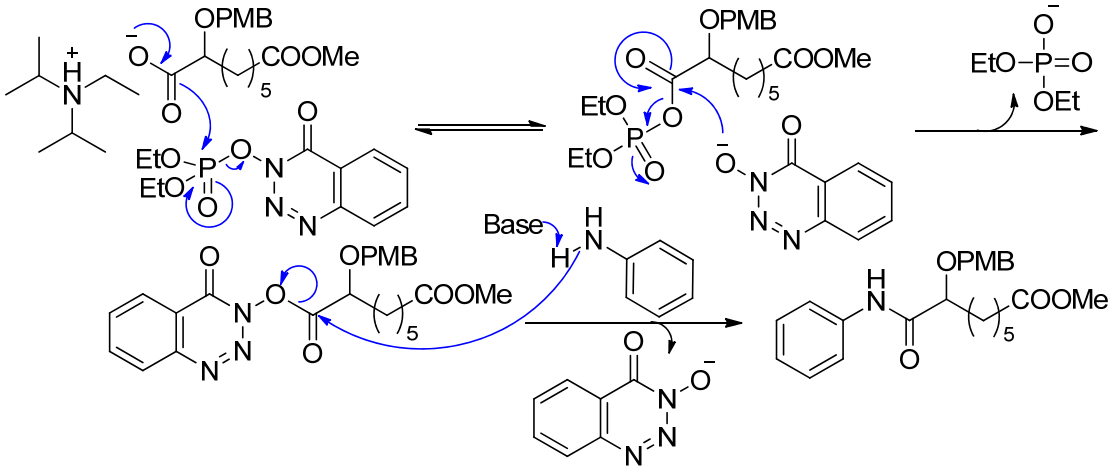
Scheme 2.10 Synthesis of **2.25**

Using 3-(diethoxyphosphoryloxy)-1,2,3-benzotriazin-4(3*H*)-one (DEPBT)[30] as the coupling agent, anilide formation of this acid with aniline gave the intermediate **2.6** (Scheme 2.11).



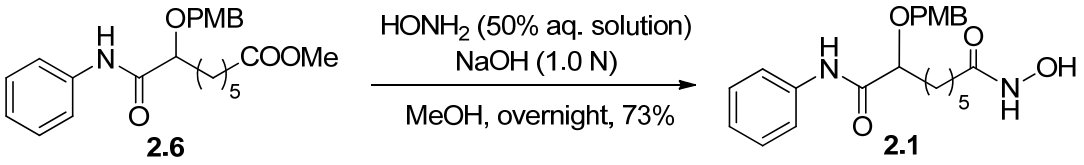
Scheme 2.11 Synthesis of **2.6**

A mechanism is proposed for this coupling (Scheme 2.12)[30].



Scheme 2.12 Mechanism of the coupling reaction using DEBPT

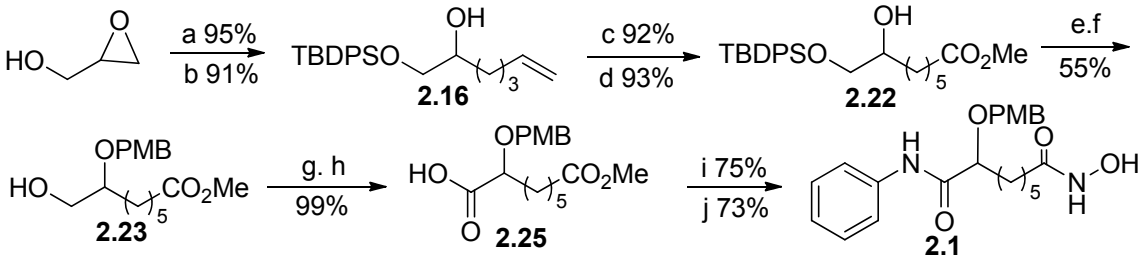
Finally, treatment of methyl ester **2.6** with hydroxylamine afforded the target compound **2.1** (Scheme 2.13).



Scheme 2.13 Synthesis of target **2.1**

2.5 Conclusion

We have synthesized racemic *p*-methoxybenzyl ether analogue **2.6** in 7 steps and 35% overall yield from **2.16** to **2.6**. The cross-metathesis method was efficient and practical in this strategy, and alkylation using PMB trichloroacetimidate in the presence of $Sc(OTf)_3$ improved the overall yield. This is an improvement over the published method (8 steps, 21% overall yield from **2.16** to **2.6**. The new synthesis is shown in Scheme 2.14:

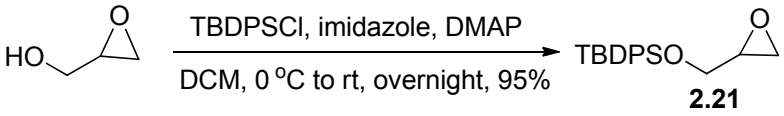


(a) TBDPSCl, imidazole, DMAP, DCM, 0 ^oC to rt, overnight; (b) ButenylMgBr, Li_2CuCl_4, THF, -40/-50 ^oC; (c) Grubbs' 2nd gen. cat., CH_2=$CHCO_2Me$, 40 ^oC, 1 h; (d) H_2, Pd/C, MeOH, rt, overnight; (e) PMB trichloroacetimidate, $Sc(OTf)_3$, toluene, rt; (f) TBAF, THF, rt; (g) Swern oxidation; (h) Jone's oxidation; (i) DEPBT, DIPEA, aniline, THF, rt, 2 days; (j) $HONH_2$ (50% aq. solution), NaOH (1.0 N), MeOH, overnight

Scheme 2.14 Overview the synthesis of **2.1**

Compound **2.1** was found to be a potent inhibitor of various isoforms of HDAC, surpassing SAHA (see Figure 2.6). Results will be published in the near future.

2.6 Experimental procedures

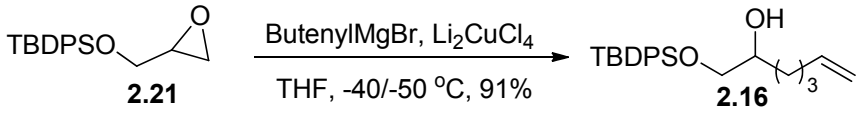


***tert*-Butyl(oxiran-2-ylmethoxy)diphenylsilane**

To a stirred solution of glycidol (1.8 g, 24.3 mmol) in anhydrous DCM (100 mL), DMAP (297 mg, 2.43 mmol), imidazole (2.48 g, 36.5 mmol) and TBDPSCl (7.5 mL, 29.2 mmol) were added at 0 °C. The reaction mixture was stirred at rt overnight, then quenched with saturated NH_4Cl (30 mL), diluted with ether, and treated with water (50 mL). After stirring for 30 min, the organic layer was separated, dried over Na_2SO_4, concentrated under reduced pressure, and the residue was purified by flash chromatography, eluting with ethyl acetate/hexane (5:95), to give glycidol **2.21** (7.16 g, 95%) as a colorless oil.

^{1}H NMR (400 MHz $CDCl_3$): δ 7.91 (m, 4H), 7.53 (m, 6H), 4.06 (dd, *J* = 3.0, 11.8 Hz, 1H), 3.87 (dd, *J* = 4.8, 11.8 Hz, 1H), 3.45–3.04 (m, 1H), 2.81 (dd, *J* = 4.1, 5.2 Hz, 1H), 2.72 (dd, *J* = 2.6, 5.3 Hz, 1H), 1.29 (s, 9H).

^{13}C NMR (100 MHz $CDCl_3$): δ 135.6, 135.5, 133.19, 133.18, 129.8, 129.7, 127.8, 127.7, 64.3, 52.1, 44.0, 26.8, 19.2.



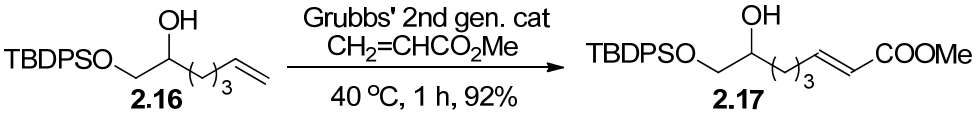
1-(*tert*-Butyldiphenylsilyloxy)hept-6-en-2-ol

To a solution of glycidol **2.21** (7.16 g, 22.95 mmol) in anhydrous THF (80 mL) at -40/-50 °C, Li_2CuCl_4 (0.1 M in THF, 23 mL) was added. To the yellow-orange solution, butenylmagnesium bromide (0.5 M in THF, 55 mL, 27.54 mmol) was quickly added under vigorous stirring (the mixture turns from blue to colorless to brown), and the mixture was allowed to stir at the same temperature for 30 min. After this time, the reaction mixture was quenched with NH_4Cl (30 mL) under vigorous stirring, and it was

allowed to reach rt. Water (50 mL) was added, to the mixture, which was stirred for 20 min and extracted with Et_2O (60 mL × 3). The combined organic layers were dried over Na_2SO_4, concentrated under reduced pressure, and the residue was purified by flash chromatography, eluting with ethyl acetate/hexane (1:9), to give pure alcohol **2.16** (7.69 g, 91%) as a colorless oil.

^{1}H NMR (400 MHz $CDCl_3$): δ 7.82 (m, 4H), 7.51 (m, 6H), 5.89 (ddt, *J* = 6.7, 10.2, 16.9 Hz, 1H), 5.10 (dd, *J* = 1.3, 17.1 Hz, 1H), 5.05 (d, *J* = 10.2 Hz, 1H), 3.85 (m, 1H), 3.79 (dd, *J* = 3.5, 10.1 Hz, 1H), 3.65 (dd, *J* = 7.3, 10.0 Hz, 1H), 2.77 (s, 1H), 2.29–2.08 (d, *J* = 6.9, 13.6 Hz, 2H), 1.79–1.60 (m, 1H), 1.60–1.42 (m, 3H), 1.20 (m, 9H).

^{13}C NMR (100 MHz $CDCl_3$): δ 138.6, 135.6, 133.3, 133.2, 129.9, 127.9, 114.7, 71.8, 68.1, 33.8, 32.3, 27.0, 24.8, 19.3.



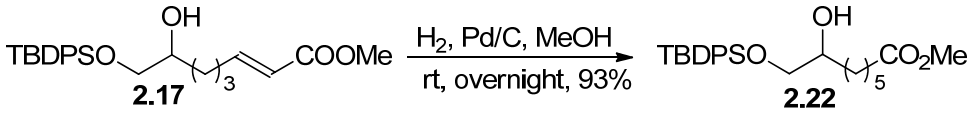
(*E*)-Methyl 8-(tert-butyldiphenylsilyloxy)-7-hydroxyoct-2-enoate

To a solution of olefin **2.16** (3.50 g, 9.51 mmol) and methyl acrylate (10.2 mL, 113.9 mmol), in anhydrous DCM (19 mL), Grubbs' catalyst second generation (241 mg, 0.28 mmol) was added in one portion under argon atmosphere. The homogeneous solution was warmed to 40 °C, and stirred until complete conversion (TLC check, Rf =0.8 for **2.16**, 0.1 for **2.17**). The volatiles were removed under reduced pressure, and the crude residue was purified by flash chromatography, eluting with ethyl acetate/hexane (15:85), to give the unsaturated methyl ester intermediate **2.17** (3.7 g, 92%) as a colorless oil.

^{1}H NMR (400 MHz $CDCl_3$): δ 7.70-7.71 (m, 4H), 7.41-7.49 (m, 6H), 6.98 (dt, *J* =7.0, 15.6 Hz, 1H), 5.85 (d, *J* =15.7 Hz, 1H), 3.75 (s, *3*H), 3.69 (dd, *J* = 3.4, 10.1 Hz, 1H), 3.53 (dd, *J* = 7.4, 10.1 Hz, 2H), 2.62 (br, 1H), 2.23 (dd, *J* = 6.5, 13.3 Hz, 2H), 1.75 – 1.35 (m, 4H), 1.11 (s, 9H).

^{13}C NMR (100 MHz $CDCl_3$): δ 167.2, 149.3, 135.7, 135.6, 133.2, 130.0, 127.9, 121.3, 71.7, 68.1, 51.5, 32.3, 32.2, 27.0, 24.1, 19.4.

MS (ESI) *m/z*: 544.2 [M+NH_4^+].



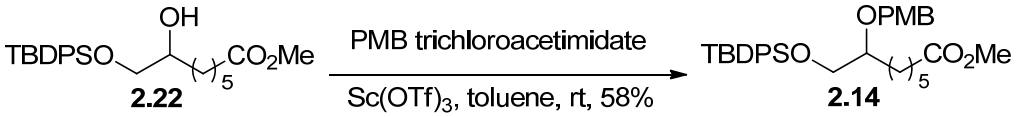
Methyl 8-(*tert*-butyldiphenylsilyloxy)-7-hydroxyoctanoate

The olefin intermediate **2.17** (3.8 g, 8.92 mmol) was hydrogenated under conventional conditions. Olefin was dissolved in MeOH (90 mL) and catalytic 10% palladium on carbon was added. The reaction flask was evacuated by aspiration and thoroughly purged with H_2 (3-6 times) and the resulting heterogeneous mixture was stirred under a balloon of H_2. After stirred 24 h, the H_2 was evacuated, the catalyst was filtered off on a pad of Celite, and the filtrate concentrated under reduced pressure and the crude residue was purified by flash chromatography, eluting with ethyl acetate/hexane (1:4), to give the saturated ester **2.22** (3.6 g, 93%) as a colorless oil.

^{1}H NMR (400 MHz $CDCl_3$): δ 7.72 (d, *J* = 6.6 Hz, 4H), 7.50–7.36 (m, 6H), 3.80–3.71 (m, 1H), 3.71–3.67 (m, 1H), 3.66 (s, 3H), 3.55 (dd, *J* = 7.3, 9.9 Hz, 1H), 2.68 (s, 1H), 2.31 (t, *J* = 7.5 Hz, 2H), 1.75–1.57 (m, 2H), 1.47 (dd, *J* = 11.7, 16.7 Hz, 3H), 1.39–1.27 (m, 3H), 1.12 (s, 9H).

^{13}C NMR (100 MHz $CDCl_3$): δ 174.1, 135.6, 135.5, 133.2, 129.8, 127.8, 71.8, 68.1, 51.4, 34.0, 32.6, 29.1, 26.9, 25.2, 24.8, 19.3.

MS (ESI) *m/z*: 546.2 [M+NH_4^+].



Methyl 8-(*tert*-butyldiphenylsilyloxy)-7-hydroxyoctanoate

A solution of *p*-methoxybenzyl alcohol (5.2 g, 37.6 mmol) in ether (35 mL) was added to a suspension of sodium hydride (90 mg, 3.8 mmol) in ether (40 mL) at room temperature. The resulting mixture was stirred at room temperature for 30 min and cooled to 0 ^{o}C. Trichloroacetonitrile (3.8 mL, 37.6 mmol) was added, and the reaction mixture

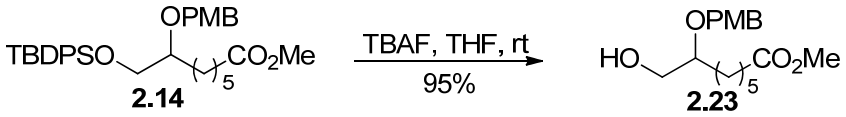
was allowed to warm slowly to room temperature for 4 h. The solution was concentrated to an orange syrup, which was dissolved in petroleum ether (50 mL) containing methanol (0.2 mL, 4.0 mmol). This suspension was filtered through Celite, and the filtrate was concentrated to a yellow syrup. The crude imidate was dissolved in toluene (120 mL), and treated with a solution of the alcohol **2.22** (3.5 g, 8.18 mmol) in toluene (30 mL), followed by $Sc(OTf)_3$ (400 mg, 0.8 mmol) at 0 °C. The reaction mixture was allowed to reach room temperature. After stirring for 12 h, the reaction mixture was concentrated under reduced pressure and the residue was purified by flash column chromatography, eluting with ethyl acetate/hexane (2:98), to give the PMB ether **2.14** (2.6 g, 58%, usually with minor impurities) as a yellow oil.

^{1}H NMR (400 MHz $CDCl_3$): δ 7.75–7.69 (m, 4H), 7.49–7.38 (m, 6H), 7.29–7.23 (m, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 4.63 (d, *J* = 11.3 Hz, 1H), 4.48 (d, *J* = 8.9 Hz, 1H), 3.83 (s, 3H), 3.76 (dd, *J* = 5.8, 10.6 Hz, 1H), 3.69 (s, 3H), 3.65 (dd, *J* = 4.8, 10.6 Hz, 1H), 3.50 (dd, *J* = 5.1, 12.4 Hz, 1H), 2.31 (t, *J* = 7.6 Hz, 2H), 1.69 – 1.36 (m, 5H), 1.29 (dd, *J* = 6.7, 10.7 Hz, 3H), 1.10 (s, 9H).

^{13}C NMR (100 MHz $CDCl_3$): δ 174.4, 159.2, 135.8, 133.8, 133.7, 131.3, 129.8, 129.6, 127.9, 113.9, 113.8, 79.4, 72.0, 66.5, 55.4, 51.6, 34.2, 31.7, 29.4, 27.0, 25.2, 25.1, 19.4.

MS (ESI) *m/z*: 571.2 [M+Na^+].

Note: when preparing the PMB trichloroacetimidate, it is better to wash the NaH (60% in mineral oil) with hexane three times.



Methyl 8-hydroxy-7-(4-methoxybenzyloxy)octanoate

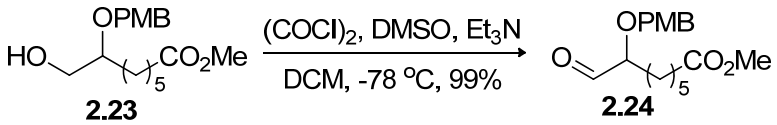
To a solution of the PMB ether **2.14** (5.7 g, 10.4 mmol) in THF (60 mL) at 0 °C, TBAF (1.0 M in THF, 20.8 mL) was added. The reaction mixture was stirred at rt for 4 h,

quenched with saturated NH_4Cl (40 mL) and extracted with ethyl acetate (30 mL× 3). The organic layers were dried over Na_2SO_4, concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with ethyl acetate/hexane (3:7), to give the primary alcohol **2.23 (**3.05 g, 95%) as a colorless oil.

^{1}H NMR (400 MHz $CDCl_3$): δ 7.33–7.23 (d, *J* = 8.5 Hz, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 4.50 (q, *J* = 11.2 Hz, 2H), 3.79 (s, 3H), 3.71–3.62 (m, 4H), 3.53-3.45 (m, 2H), 2.29 (t, *J* = 7.5 Hz, 2H), 2.25 (br, 1H), 1.71–1.55 (m, 3H), 1.55–1.23 (m, 5H).

^{13}C NMR (100 MHz $CDCl_3$): δ 174.3, 159.3, 130.6, 129.5, 113.9, 79.3, 71.3, 64.2, 55.3, 51.6, 34.0, 30.8, 29.3, 25.1, 24.9.

MS (ESI) *m/z*: 333.1 [M+Na^+].



2.23 **2.24**

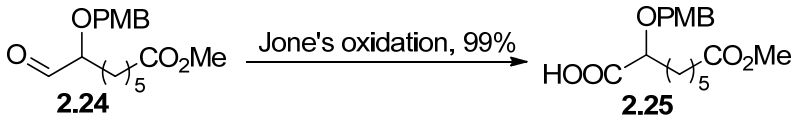
Methyl 7-(4-methoxybenzyloxy)-8-oxooctanoate

To a solution of oxalyl chroride (1.0 mL, 11.07 mmol) in DCM at -78 ^{o}C under an argon atmosphere, DMSO (1.1 mL, 14.76 mmol) was added dropwise in ca. 5 min. Stirring was continued at -78 ^{o}C for 10 min, followed by addition of a solution of alcohol **2.23** (1.15 g, 3.7 mmol) in DCM (20 mL) in ca. 15 min at the same temperature. After 1 h, Et_3N (5.1 mL, 36.9 mmol) was added at -78 ^{o}C, the reaction mixture was allowed to reach 0 ^{o}C and stirred untill complete conversion was observed by TLC. The reaction mixture was quenched with saturated NH_4Cl (20 mL) and stirred for 15 min, treated with water (60 mL) and extracted with DCM (50 mL × 3). The combined organic layers were dried over Na_2SO_4, concentrated under reduced pressure. The resulting residue was purified by flash chromatography, eluting with ethyl acetate/hexane (3:7), to give the pure aldehyde intermediate **2.24** (1.13 g, 99%) as a colorless oil.

^{1}H NMR (400 MHz $CDCl_3$): δ 9.62 (d, *J* = 2.2, 1H), 7.38–7.25 (m, 2H), 6.98–6.81 (m, 2H), 4.61 (d, *J* = 11.4 Hz, 1H), 4.48 (d, *J* = 11.4 Hz, 1H), 3.82 (s, 3H), 3.73 (td, *J* = 2.1, 6.5 Hz, 1H), 3.67 (s, 3H), 2.30 (t, *J* = 7.5 Hz, 2H), 1.77–1.54 (m, 4H), 1.54–1.20 (m, 4H).

^{13}C NMR (100 MHz $CDCl_3$): δ 204.2, 174.2, 159.7, 129.9, 129.5, 114.1, 83.1, 72.4, 55.4, 51.7, 34.0, 30.0, 29.0, 24.8, 24.6.

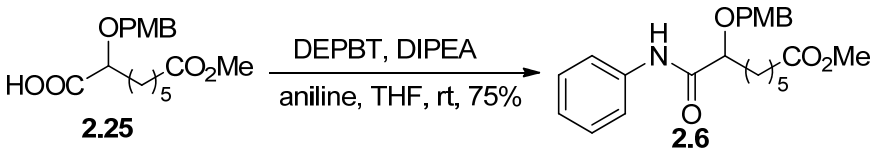
MS (ESI) *m/z*: 331.1 [M+Na^+].



8-Methoxy-2-(4-methoxybenzyloxy)-8-oxooctanoic acid

To a solution of this aldehyde intermediate **2.24** (1.13 g, 3.67 mmol) in THF (36.0 mL), Jones reagent (4.8 mL, prepared from 25.0 g of chromium (VI) oxide, 25 mL of H_2SO_4, and 75.0 mL of water) was quickly added along the walls of the flask at 0 °C under vigorous stirring. After 5-10 min, the excess reagent was destroyed by adding cold *i*-PrOH (180 mL) with stirring at 0 °C. The greenish mixture was diluted with cold ethyl acetate (300 mL), and washed with small portions of 10% aqueous $NaHSO_4$ (5 mL × 4) until complete separation of the deep green aqueous layer, then with 10% aqueous $Na_2S_2O_3$ (5 mL × 4) until the aqueous layer was completely colorless, then with water (20 mL ×3), and brine (20 mL × 2). The separated organic layer was dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure at rt (not over 25 °C), co-evaporating away traces of *i*-PrOH with cyclohexane (10 mL × 3), to give the carboxylic acid **2.25** (1.18 g, 99%) which was immediately used for the coupling reaction without further purification.

MS (ESI) *m/z*: 347.1 [M+Na^+].



Methyl 7-(4-methoxybenzyloxy)-8-oxo-8-(phenylamino)octanoate

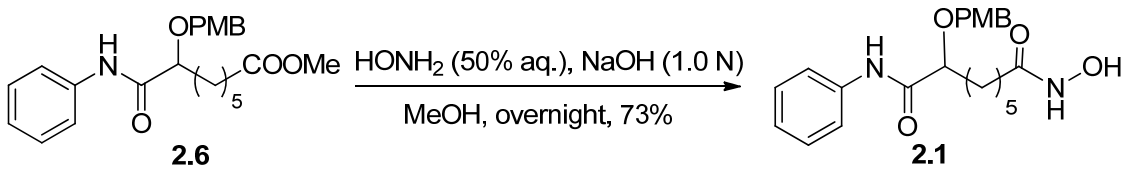
To an ice-bath cooled solution of carboxylic acid **2.25** (1.5 g, 4.63 mmol) in anhydrous THF (150 mL), DEPBT (2.77 g, 9.26 mmol) was added, followed by DIPEA (1.6 mL, 9.26 mmol), and the mixture was stirred for 15 min at rt under argon atmosphere. To the resulting bright yellow solution, the aniline (0.6 mL, 6.95 mmol) was added at 0 ^{o}C, and the mixture was stirred for 48 h at rt (monitored by MS analysis). The reaction mixture was quenched with saturated NH_4Cl (80 mL), and extracted with ethyl acetate (50 mL × 3). The organic layer was washed with $NaHCO_3$ (50 mL × 2), and brine (50 mL × 3), dried over Na_2SO_4, concentrated under reduced pressure, then the residue was purified by flash chromatography, eluting with ethyl acetate/hexane (1:3), to give the amide **2.6** (1.39g, 75%) as a yellow oil.

^{1}H NMR (400 MHz $CDCl_3$): δ 8.40 (s, 1H), 7.62–7.52 (m, 2H), 7.39–7.25 (m, 4H), 7.13 (t, *J* = 7.4 Hz, 1H), 6.98–6.89 (m, 2H), 4.57 (s, 2H), 3.97 (dd, *J* = 4.4, 7.1 Hz, 1H), 3.83 (s, 3H), 3.67 (s, 3H), 2.30 (t, *J* = 7.5 Hz, 2H), 1.84 (m, 2H), 1.72–1.56 (m, 2H), 1.46 (m , 2H), 1.39–1.24 (m, 2H).

^{13}C NMR (100 MHz $CDCl_3$): δ 174.2, 171.2, 159.8, 137.4, 130.0, 129.2, 124.5, 119.7, 114.2, 80.2, 72.9, 55.4, 51.6, 34.1, 32.8, 29.0, 24.9, 24.7.

MS (ESI) *m/z*: 400.1 [M+H^{+}].

Note: Excess of aniline can be removed by washing with 1N HCl during the workup (10 mL × 3).



2.6 **2.1**

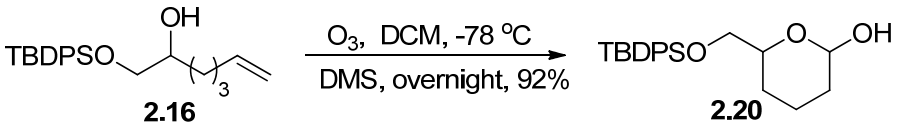
N^8-Hydroxy-2-(4-methoxybenzyloxy)-N1-phenyloctanediamide

To a solution of methyl ester **2.6** (105 mg, 0.26 mmol) in MeOH (2 mL) at 0 ^oC, $HONH_2$ (50% aqueous solution, 220 μL, 15 equiv.) was added, followed by 1.0 N NaOH (100 μL, 10 equiv.). The mixture was stirred at 0 ^oC for 3 h, warmed slowly to rt, and stirred overnight. After careful neutralization with 1.0 N HCl, the resulting mixture was extracted with ethyl acetate (5 mL ×3). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with ethyl acetate/hexane (9:1), to give the hydroxamic acid **2.1** (77 mg, 73%) as a pale yellow oil.

^1H NMR (400 MHz CD_3OD): δ 7.57 (d, J = 8.1 Hz, 2H), 7.36-7.32 (m, 4H), 7.14 (t, J = 7.4 Hz, 1H), 6.93 (d, J = 8.6 Hz, 2H), 4.63 (d, J = 11.5 Hz, 1H), 4.48 (d, J = 11.6 Hz, 1H), 3.93 (t, J = 6.1 Hz, 1H), 3.80 (s, 3H), 2.08 (t, J = 7.4 Hz, 2H), 1.77 (m, 2H), 1.61 (m, 2H), 1.46 (m, 2H), 1.33 (m, 2H).

^{13}C NMR (100 MHz CD_3OD): δ 171.0, 170.9, 159.3, 136.7, 129.6, 128.7, 128.6, 124.2, 119.3, 113.8, 79.3, 72.4, 55.0, 33.6, 32.1, 27.9, 24.6, 23.8.

MS (ESI) *m/z*: 401.2 [$M+H^+$].



2.16 **2.20**

6-(((*tert*-Butyldiphenylsilyl)oxy)methyl)tetrahydro-2H-pyran-2-ol

To a stirred solution of **2.16** (1.9 g, 5.16 mmol) in DCM (150 mL) at −78 ^oC, O_3 was bubbled through until the reaction mixture became light blue. Dimethyl sulfide (3.8 mL,

51.6 mmol) was added to the reaction mixture, which was allowed to warm to ambient temperature and stirred overnight. The volatiles were removed under reduced pressure to leave a creamy oil which was purified by flash column chromatography, eluting with ethyl acetate/hexane (1:9), to give **2.20** (1.7 g, 92%), as a colorless oil, which was a mixture of acetal (major) and aldehyde (minor).

^{1}H NMR (400 MHz $CDCl_3$): δ 9.77 (m, 1H minor), 7.71-7.61 (m, 4H), 7.47-7.38 (m, 6H), 5.31 (br, 1H minor), 4.71-4.68 (dd, *J*=1.8, 7.4 Hz, 1H minor), 4.08 (dtd, *J*=2.2, 5.7. 7.5 Hz, 2H minor), 3.81-3.48 (m, 2H major and 1H minor), 2.85 (s, 1H), 2.55(s, 1H), 2.47-2.44 (m, 1H), 1.91-1.19 (m, 6H major and 6 H minor), 1.09 (s, 9H minor), 1.08 (s, 9H).

^{13}C NMR (100 MHz $CDCl_3$): δ 135.9, 135.8, 129.8, 128.0, 127.8, 104.0, 96.5, 92.0, 77.0, 69.6, 67.7, 67.2, 32.9, 31.3, 29.9, 27.9, 27.4, 27.1, 26.9, 21.8, 19.5.

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Chapter Three

Toward the Total Synthesis of Pactamycin

3.1 Introduction

Pactamycin, a structurally unique aminocyclitol antibiotic isolated from *Streptomyces pactum*[1], consists of a 5-membered ring aminocyclitol unit, two aromatic rings (6-methyl salicylic acid and 3-aminoacetophenone) and a 1,1-dimethylurea[2]. The structure of this compound was elucidated from NMR analyses and chemical degradation[3]. However, X-ray crystallographic analysis of pactamycate, a chemical transformation product led to a revision of the structure and revealed the absolute stereochemistry of pactamycin[4] (Figure 3.1).

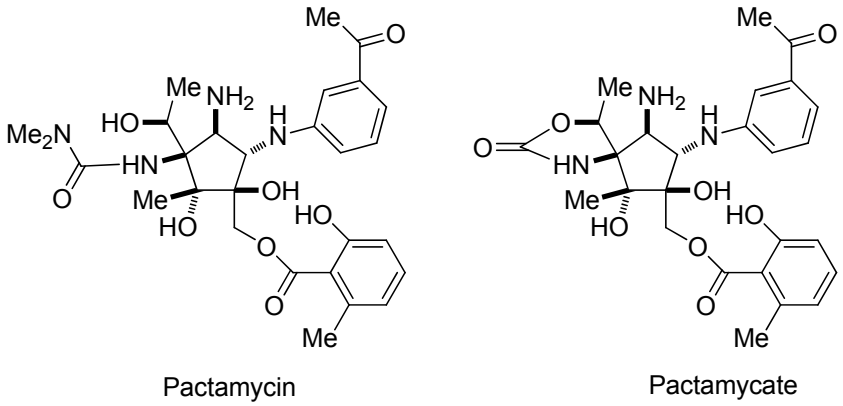


Figure 3.1 The structure of pactamycin and pactamycate

Pactamycin shows potent *in vitro* and *in vivo* antitumor activity as well as antimicrobial activity[5]. The mechanism of action is inhibition of protein synthesis[6] through binding to the ribosomal small subunit[7] (Figure 3.2).

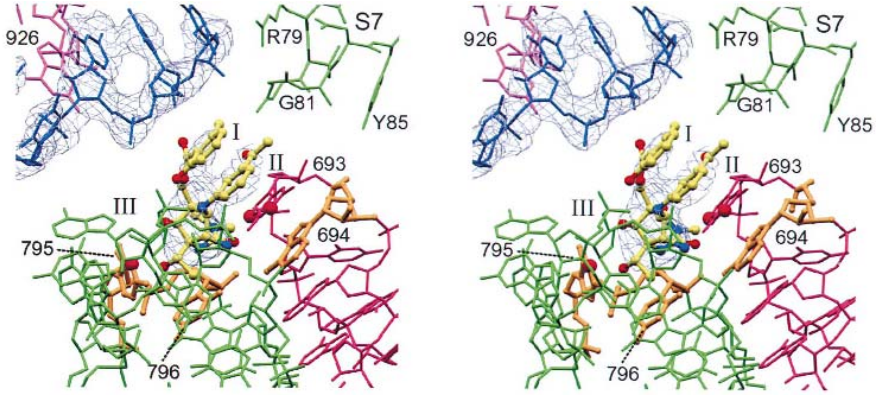
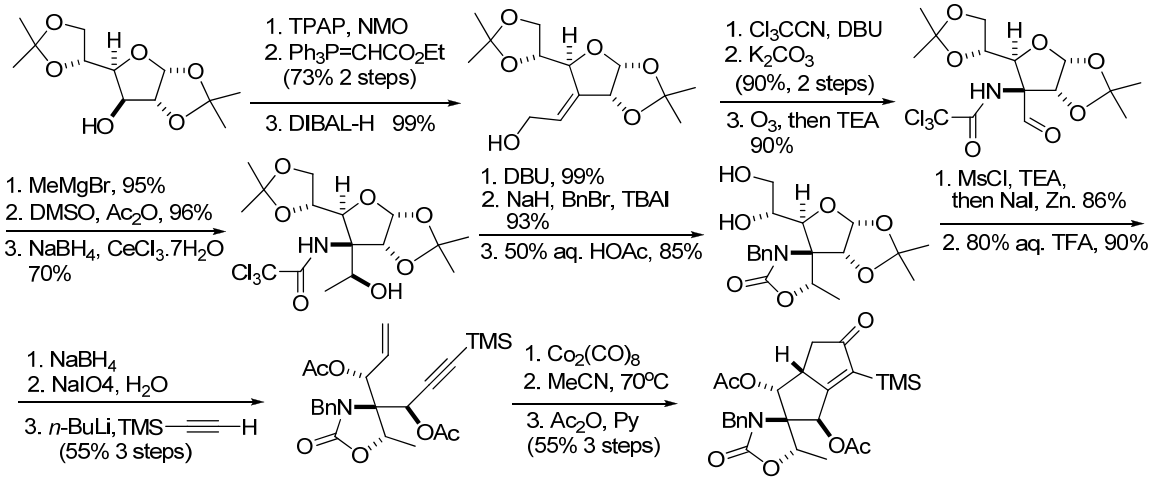


Figure 3.2 Stereofigure of pactamycin bound at the 30S E site with rings I, II, and III.

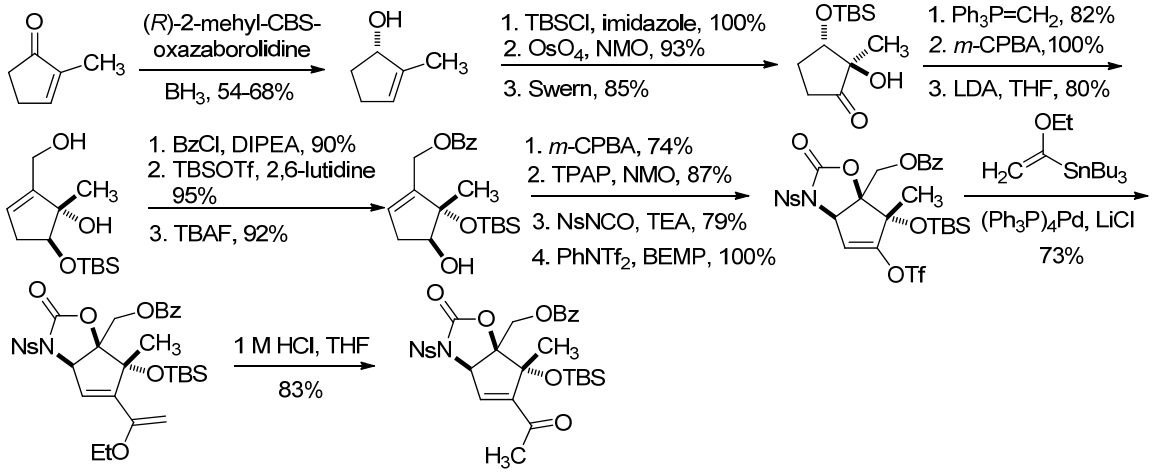
3.2 Efforts toward the synthesis of pactamycin

The total synthesis of pactamycin, a unique member of the aminocyclitol family of antibiotics, presents synthetic challenges that include a highly functionalized cyclopentane core, unusual substitution patterns and stereogenic carbons that accentuate the need for functional group compatibility.

Efforts by Isobe[8] and Knapp[9] respectively are summarized below in schematic format (Scheme 3.1 and 3.2). Further details can be found in the M. Sc. thesis of Stephane Dorich[10].



Scheme 3.1 Isobe's approach

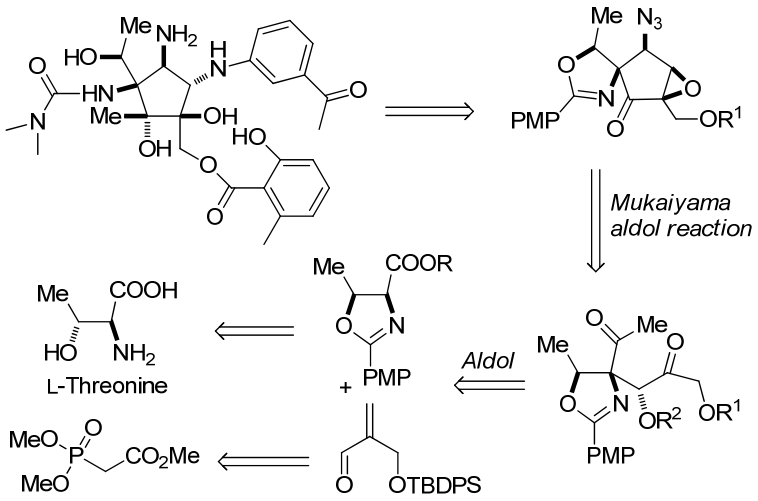


Scheme 3.2 Knapp's approach

Before I took part in this total synthesis of pactamycin, Drs. Banerjee Shayampada, Juan R. Del Valle, Fabien Lecomte, Ramkrishna Reddy Vakiti and graduate student Stephane Dorich had each made major contributions[10].

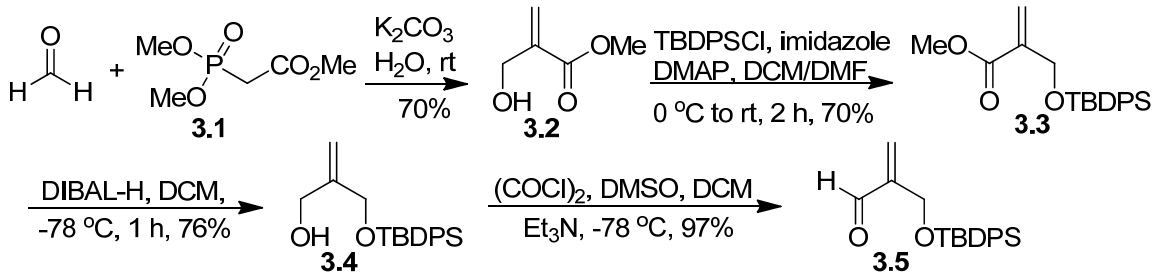
3.2.1 The synthetic plan for pactamycin

Analysis of the structure and six chiral centers in pactamycin led us to consider the disconnections shown in Scheme 3.3.



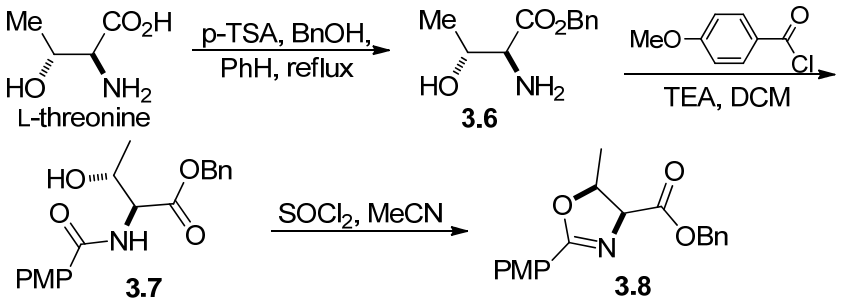
Scheme 3.3 Synthetic plan for pactamycin

First, the aldehyde **3.5** was synthesized starting from trimethyl phosphonoacetate and formaldehyde, following the procedure for the synthesis of the analogous ethyl ester[11] to afford methyl (2-hydroxymethyl)acrylate **3.2**. After protection of the hydroxyl group as the TBDPS ether and ester reduction with DIBAL-H[12], the resulting alcohol **3.4** was oxidized to aldehyde **3.5** by Swern oxidation[13](Scheme 3.2).



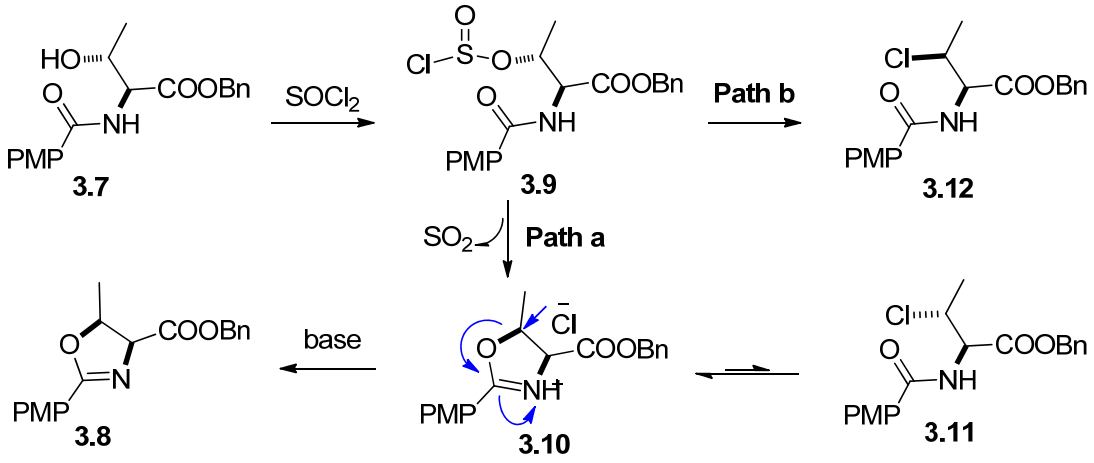
Scheme 3.4 The synthesis of the aldehyde **3.5**

The oxazoline **3.8** was prepared starting from L-threonine[10]. Condensation with benzyl alcohol gave the benzyl ester **3.6**, which was converted to the PMP amide **3.7**. Cyclization with inversion of configuration was achieved by treating with $SOCl_2$[14] to afford oxazoline **3.8** (Scheme 3.5). The products in all these three steps did not require purification by chromatography, which facilitated scale-up.



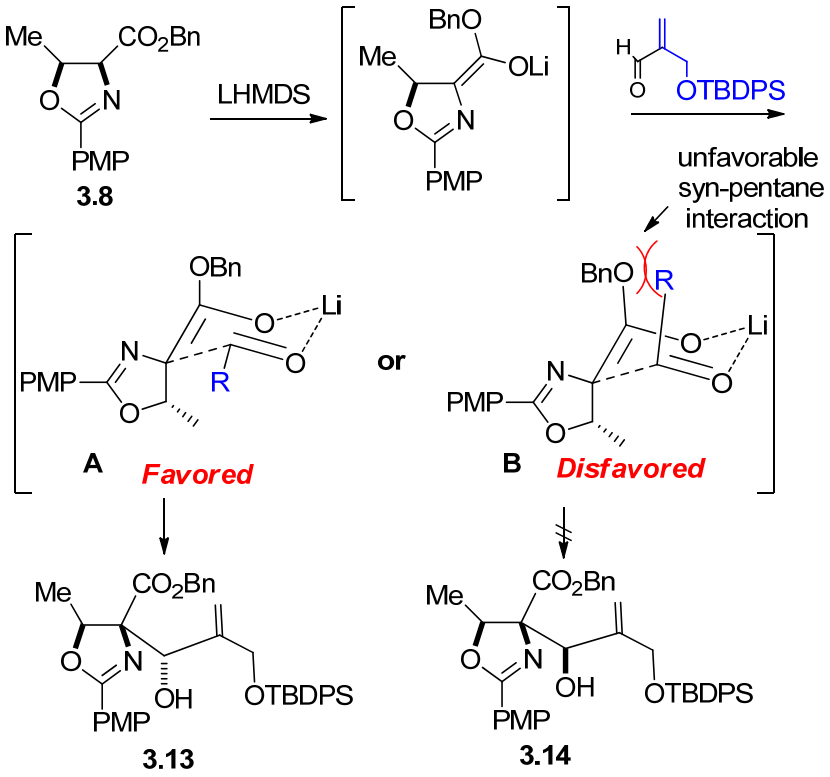
Scheme 3.5 The synthesis of the oxazoline **3.8**

A proposed mechanism for the cyclization using $SOCl_2$[15] is shown in Scheme 3.6. The *p*- methoxyphenyl group enhances the reactivity of the carbonyl group in an intramolecular attack on the chlorosulfite intermediate **3.9** to give an oxazolinium ion **3.10** (**path a**) and the oxazoline **3.8**. Displacement by chloride ion would give **3.11**, which can also give **3.8**. It is likely that **path a** predominates over the alternative **path b** (which would lead to **3.12**), because inversion takes place rather than cyclization.



Scheme 3.6 The proposed mechanism of the cyclization to form the oxazoline

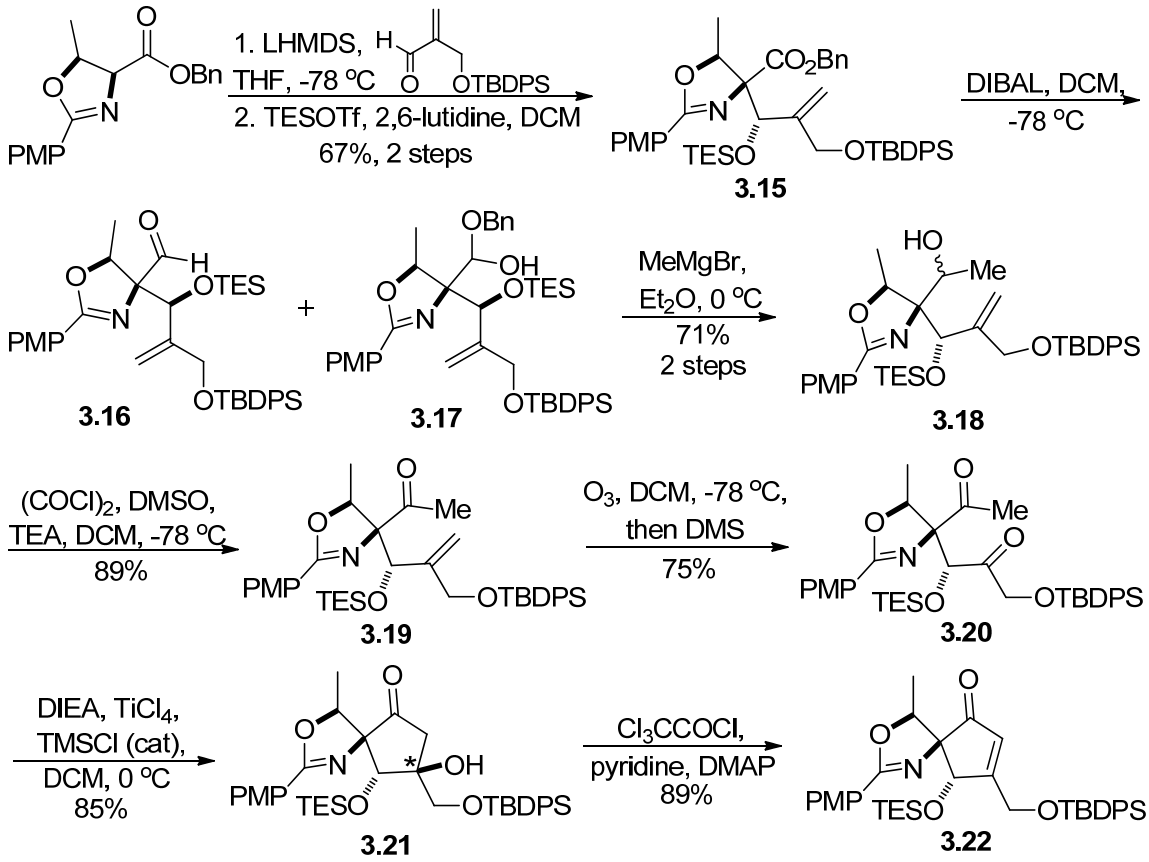
The aldol reaction[16] of oxazoline **3.8** and aldehyde **3.5** afforded alcohol **3.13** as a single isomer. The stereochemistry can be explained using the Zimmerman–Traxler model (Scheme 3.7). In this transition state, the methyl group was placed far from the electrophile to facilitate the approach and to avoid the *syn*-pentane interactions between the OBn and the R groups (highlighted in blue). Transition state **A** is favored over **B** because of the 1,3 non-bonded interaction in the latter. The diastereoisomer **3.14** was not observed.



Scheme 3.7 The proposed mechanism of the aldol reaction

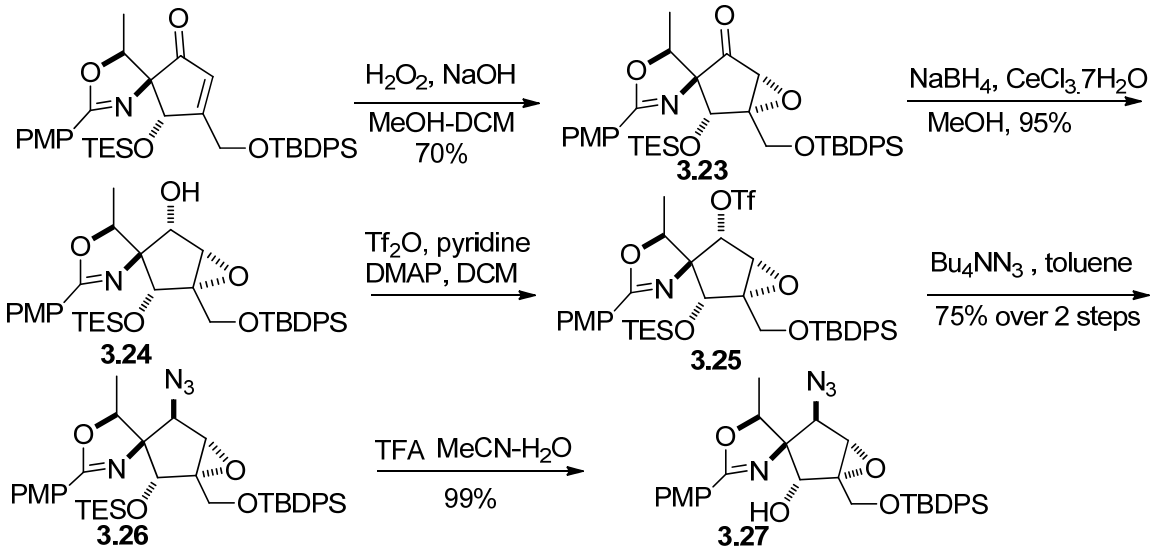
The resulted hydroxyl group of the **3.13** was protected with a TES group to prevent a retro-aldol reaction, which formed the **3.15**. Compound **3.15** was reduced with DIBAL-H to form a mixture of aldehyde **3.16** and hemiacetal **3.17**, which was treated with MeMgBr to give **3.18** as a mixture of epimers at the alcohol center. Swern oxidation to ketone **3.19**, followed by ozonolysis[17]of the double bond afforded the dione **3.20**. The cyclization product **3.21** was obtained by a Mukaiyama aldol reaction[18] as a single isomer.

Treatment of alcohol **3.21** with trichloroacetyl chloride and pyridine in DCM afforded the enone **3.22** (Scheme 3.8).



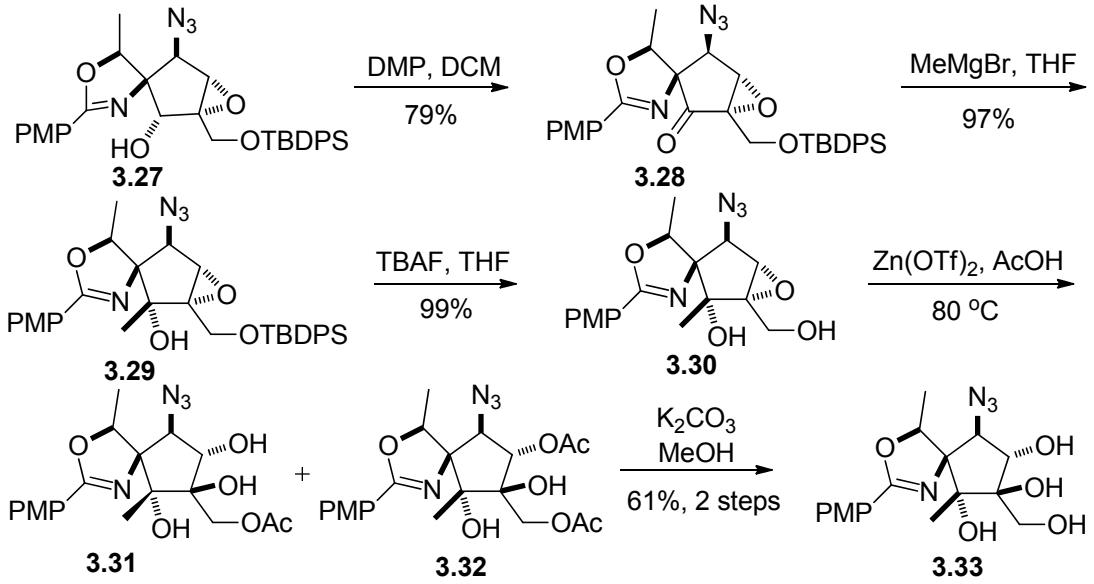
Scheme 3.8 The synthesis of the enone **3.22**

The nucleophilic epoxidation of the enone with H_2O_2 formed the epoxy ketone **3.23**, which was reduced to epoxy alcohol **3.24** under Luche reduction[19] conditions. The epoxy alcohol **3.24** was treated with premixed triflic anhydride and pyridine[20] in DCM to form the triflate **3.25**, which was replaced by azide by adding tetrabutylammonium azide[21] to give the epoxy azide **3.26**. The TES protecting group was selectively deprotected[22] with TFA in a mixture of acetonitrile and water to afford epoxy alcohol **3.27** (Scheme 3.9).



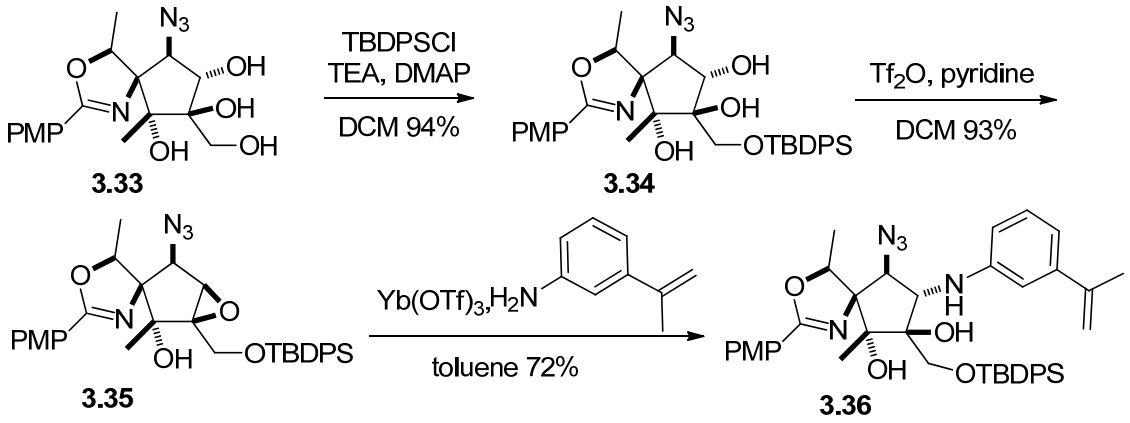
Scheme 3.9 The synthesis of the epoxy alcohol **3.27**

Compound **3.27** was oxidized to the ketone **3.28** with Dess-Martin periodinane[23]. Treatment of epoxy ketone **3.28** with MeMgBr gave the tertiary alcohol **3.29**, which, after treatment with TBAF afforded the epoxy diol **3.30**. In the presence of acetic acid and $Zn(OTf)_2$, a mixture of monoacetate **3.31** and diacetate **3.32** was formed. Cleavage of the acetate ester with K_2CO_3 in MeOH afforded the tetrol **3.33** (Scheme 3.10).



Scheme 3.10 The synthesis of the tetrol **3.33**

The primary alcohol of **3.33** was selectively protected with TBDPS to give triol **3.34** Treatment of the triol **3.34** with triflic anhydride and pyridine in DCM afforded the "up" epoxide **3.35**, which was opened with 3-(prop-1-en-2-yl)aniline in the presence of $Yb(OTf)_3$ to give the amino alcohol **3.36** as a single diastereoisomer (Scheme 3.11).



Scheme 3.11 The synthesis of the amino alcohol **3.36**

The absolute stereochemistry of **3.35** was confirmed by X-ray analyze.

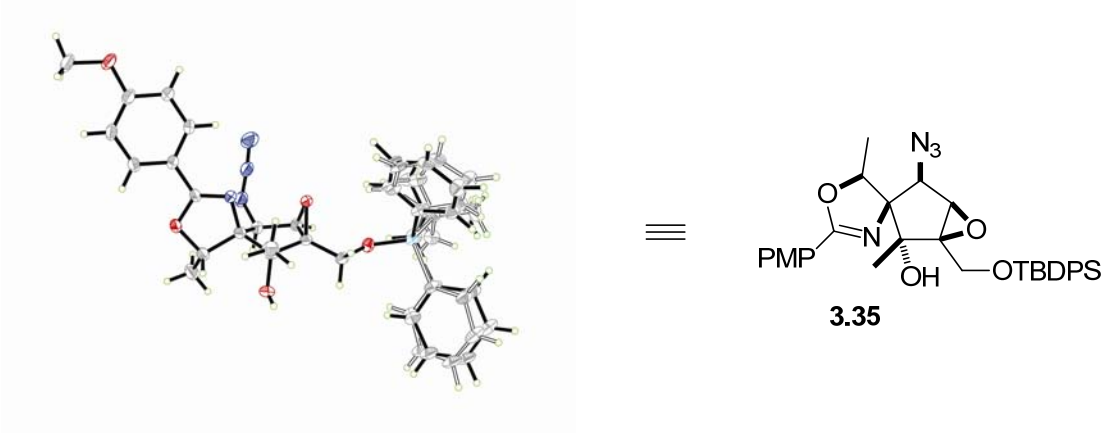
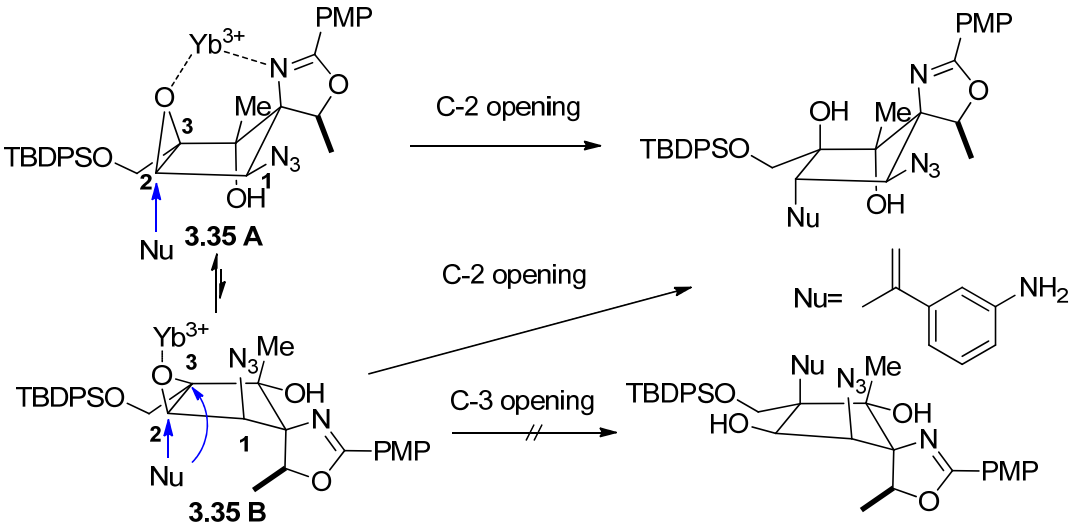


Figure 3. 3 X-ray of **3.35**

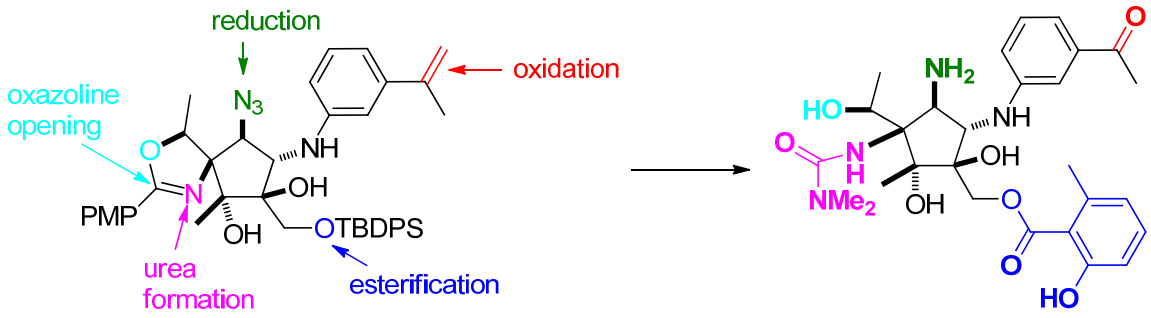
The regioselectivity of the epoxide opening reaction may be rationalized by the attack of the aniline at C-2 on the chelate structure **3.35A** (Scheme 3.12). Complete C-2 regioselectivity was observed.



Scheme 3.12 The regioselectivity of epoxide opening-reaction of **3.35**

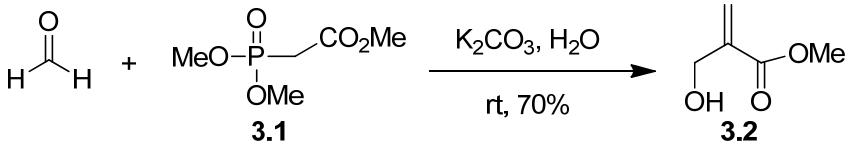
3.2.2 Conclusion

The methodology described in this thesis allows for a synthesis the key intermediate amino alcohol **3.36** (1.55 g) starting from L-threonine over 27 steps with a 2% overall yield. The advanced intermediate **3.36** contains all the required stereochemistry present in pactamycin. Subsequent steps envisaged for the completion of the synthesis are shown in Scheme 3.13.



Scheme 3.13 The last projected steps toward the total synthesis of pactamycin

3. 3 Experimental procedures



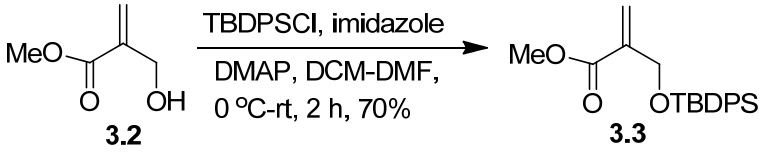
Methyl 2-(hydroxymethyl)acrylate[11]

A mixture of phosphonoacetate **3.1** (22.6 g, 124.1 mmol) and a 30% aqueous solution of formaldehyde (40 mL) was stirred at rt and treated slowly (30 min.) with a saturated solution of K_2CO_3 (24.0 g, 173.9 mmol). At the end of the addition, the temperature was reached 30-35 ^oC and stirring was continued for 1 h. Saturated NH_4Cl solution (40 mL) was added slowly to the mixture, which was extracted with ether (50 mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Flash column chromatography using ethyl acetate/hexane (1:4) as eluant afforded the unsaturated ester **3.2** (10.0 g, 70%) as a colorless liquid.

IR 1722.1, 3440.3 cm^{-1}.

^1H NMR (400 MHz $CDCl_3$): δ 6.21 (s, 1H), 5.81 (d, J = 1.3 Hz, 1H), 4.26 (s, 2H), 3.72 (s, 3H), 3.26 (s, 1H).

^{13}C NMR (100 MHz $CDCl_3$): δ 166.9, 139.5, 125.6, 61.9, 52.0.



Methyl 2-((*tert*-butyldiphenylsilyloxy)methyl)acrylate

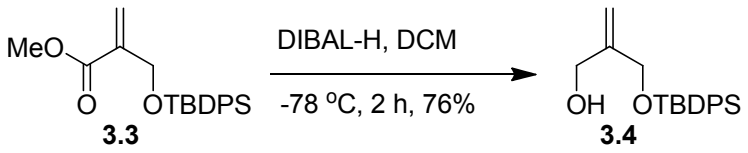
To a stirred solution of alcohol **3.2** (10.0 g, 87.0 mmol) in DCM (150 mL) and DMF (10 mL), imidazole (8.9 g, 8.5 mmol) and DMAP (10 mg) were added as solids at 0 ^oC

and the mixture was stirred for 10 min, treated dropwise with TBDPSCl (26.6 mL, 104.3 mmol) at 0 ^{o}C and stirred for 2 h at rt. The mixture was diluted with ether (400 mL) and washed with water (20 mL) and brine (20 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Flash column chromatography of the crude using ethyl acetate/hexane (9:1) as eluant afforded the TBDPS ether **3.3** (21.0 g, 70%) as a colorless viscous liquid.

IR 1638.5, 1720.9 cm^{-1}.

^{1}H NMR (400 MHz $CDCl_3$): δ 7.82 – 7.65 (m, 4H), 7.62 – 7.35 (m, 6H), 6.40 (d, *J* = 1.3 Hz, 1H), 6.19 (d, *J* = 1.9 Hz, 1H), 4.49 (s, 2H), 3.74 (d, *J* = 0.6 Hz, 3H), 1.15 (s, 9H).

^{13}C NMR (100 MHz $CDCl_3$): δ 267.0,166.4, 139.5, 135.6, 133.4, 130.0, 128.0, 124.3, 62.4, 51.8, 19.5.

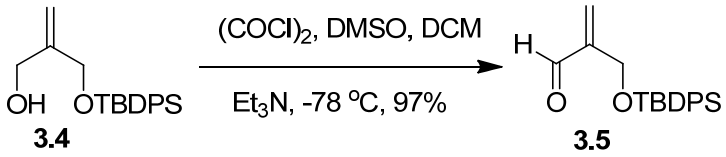


2-((*tert*-Butyldiphenylsilyloxy)methyl)prop-2-en-1-ol

To a magnetically stirred solution of unsaturated ester **3.3** (10.0 g, 28.3 mmol) in anhydrous DCM (100 mL) at -78 ^{o}C, DIBAL-H (1.0 M solution in toluene, 56.6 mL, 56.6 mmol) was added slowly over 1 h. The mixture was stirred for an additional 1 h, quenched with saturated NH_4Cl (20 mL), and treated with 20% sodium potassium tartarate solution (50 mL) with stirring for 3 h at rt. The organic layer was separated. The aqueous layer was extracted with ethyl acetate (50 mL x 2). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Flash column chromatography using a gradient of ethyl acetate/hexane (5:95 to 2:8) as eluant afforded the alcohol **3.4** (7.0 g, 76%) as a colorless viscous liquid.

^{1}H NMR (400 MHz $CDCl_3$): δ 7.73 – 7.70 (m, 4H), 7.47 – 7.42 (m, 6H),.5.20 – 5.17 (m, 1H), 5.14 (dd, *J* = 1.2, 2.4 Hz, 1H), 4.29 (s, 2H), 4.21 (s, 2H), 1.10 (s, 10H).

^{13}C NMR (100 MHz $CDCl_3$) δ 147.3, 135.7, 133.4, 130.0, 128.0, 111.4, 65.8, 64.7, 27.0, 19.4.



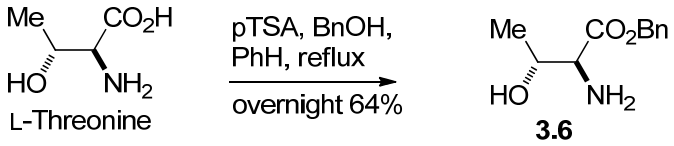
2-((*tert*-Butyldiphenylsilyloxy)methyl)acrylaldehyde

To a solution of oxalyl chloride (5.9 mL, 68.1 mmol) in DCM (300 mL) in a round bottom flask at -78 ^{o}C , DMSO (10.3 mL, 145.2 mmol) was added dropwise over ca. 10 min. Stirring was continued at -78 ^{o}C for 15 min. The alcohol **3.4** (14.8 g, 45.4 mmol) in DCM (50 mL) was added to the reaction mixture over ca. 20 min. The reaction mixture was stirred for 30 min, and treated with triethylamine (31.6 mL, 226.9 mmol) over ca. 10 min. with stirring at -78 ^{o}C. The cooling bath was removed. Saturated NH_4Cl solution (150 mL) was added to the mixture at -78 ^{o}C. After warming to rt, the mixture was treated with H_2O (50 mL). Stirring was continued for ca. 30 min. and organic layer was separated, dried over anhydrous Na_2SO_4, and the volatiles was removed under reduced pressure to afford the aldehyde **3.5** (13.3 g, 90%) as a colorless liquid after flash column chromatography using ethyl acetate/ hexane (1:19) as eluant.

IR 1695.4 cm^{-1}.

^{1}H NMR (400 MHz $CDCl_3$): δ 9.63 (s, 1H), 7.84 – 7.61 (m, 4H), 7.59 – 7.36 (m, 6H), 6.75 (dd, *J* = 2.0, 3.3 Hz, 1H), 6.19 (dd, *J* = 1.9, 3.1 Hz, 1H), 4.51 (t, *J* = 2.0 Hz, 2H), 1.14 (d, *J* = 3.0 Hz, 9H).

^{13}C NMR (100 MHz $CDCl_3$): δ 193.6, 149.3, 135.6, 133.2, 133.1, 130.1, 128.0, 60.7, 27.0, 19.5.



(2*S*,3*S*)-Benzyl 2-amino-3-hydroxybutanoate

A suspension of L-threonine (24.0 g, 201.1 mmol) in 200 mL of 4:1 benzene:BnOH was treated with *p*-toluenesulfonic acid monohydrate (42.1 g, 222.1 mmol). The flask was fitted with a Dean-Stark trap and heated at a reflux for 24 h (~115 ^{o}C) with azeotropic removal of water. The reaction was cooled to rt. The benzene was removed under reduced pressure. To the mixture, water (200 mL) was added. The aqueous layer was separated and washed with ethyl acetate (200 mL × 2). The organic washes were back-extracted with water (100 mL × 4) and the pH of the combined aqueous layers was made basic (pH > 9) with solid KOH (about 13.0 g). The aqueous solution was extracted with ethyl acetate (200 mL × 5). The organic extractions were combined, dried over Na_2SO_4 and evaporated to give the crude amino ester as a colorless oil. To the oil was added petroleum ether (100 mL) with stirring. The desired ester crystallized out of the turbid mixture over 48 h at 4 ^{o}C. After decanting the solution, the crystals were dried to give the pure benzyl ester **3.6** (27.0 g, 64%) as a white solid.

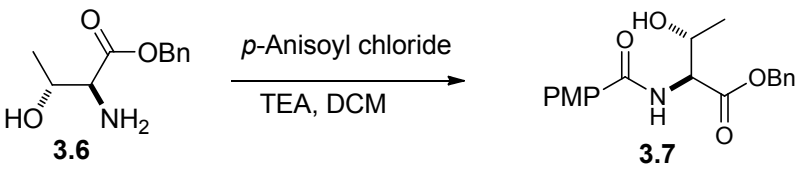
Melting point: 67-68 ^{o}C

$[\alpha]_D^{20}$ -4.2 (c 1, MeOH)

^{1}H NMR (400 MHz $CDCl_3$): δ 7.44 – 7.33 (m, 5H), 5.21 (s, 2H), 4.14 – 3.71 (m, 1H), 3.32 (d, J = 5.3 Hz, 1H), 2.19 (s, 3H), 1.23 (d, J = 6.3 Hz, 3H).

^{13}C NMR (100 MHz $CDCl_3$): δ 174.3, 135.6, 128.9, 128.7, 128.6, 68.5, 67.2, 60.2, 20.0.

HRMS (ESI) calc. for $C_{11}H_{16}NO_3$: [M+H$^+$], 210.11247; found: [M+H$^+$], 210.11244.



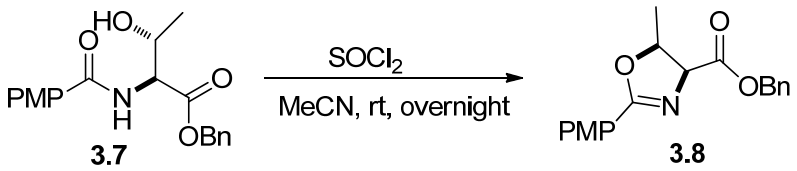
(2*S*,3*S*)-Benzyl 3-hydroxy-2-(4-methoxybenzamido)butanoate

A solution of benzyl ester **3.6** (27.0 g, 126.1 mmol) in anhydrous DCM (370 mL) was added triethylamine (175.1 mL, 151.3 mmol, 1.20 equiv.) and *p*-anisoyl chloride (32.6 g, 132.4 mmol, 1.05 equiv.) at rt. The conversion of starting material to product was followed by TLC until no more starting material and was finished after approximately two hours. A saturated solution of NH_4Cl (150 mL) was then added to the mixture. The phases were separated and the aqueous phase were extracted with DCM (100 mL × 3). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to afford colorless crystals **3.7** (58.3 g), which were used to the next step without any purification. An analytical sample was isolated by preparative TLC purification.

^{1}H NMR (400 MHz $CDCl_3$): δ 7.82 (d, *J* = 8.8 Hz, 2H), 7.38 – 7.32 (m, 5H), 7.05 (d, *J* = 8.7 Hz, 1H), 6.89 (d, *J* = 8.8 Hz, 2H), 5.26 – 5.17 (dd, *J*=12.3, 4.5 Hz, 2H), 4.86 (dd, *J* = 2.5, 8.8 Hz, 1H), 4.46 (d, *J* = 4.4 Hz, 1H), 3.84 (s, 3H), 2.93 (s, 1H), 1.26 (d, *J* = 6.4 Hz, 3H).

^{13}C NMR (100 MHz $CDCl_3$): δ 171.3, 167.8, 162.6, 135.4, 129.3, 128.8, 128.6, 128.3, 126.1, 113.9, 68.5, 67.5, 58.0, 55.6, 20.3.

HRMS (ESI) calc. for $C_{19}H_{22}NO_5$: [M+H$^+$], 344.14925; found: [M+H$^+$], 344.14958.



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

A solution of amino alcohol **3.7** (crude) in acetonitrile (300 mL) was treated with thionyl chloride (11.3 mL, 151.3 mmol) at 0 ^{o}C and left to stir overnight at rt. The reaction was quenched with saturated $NaHCO_3$ (200 mL) and extracted with ethyl acetate

(150 mL × 3). The combined organic layers were dried over Na_2SO_4, and concentrated under reduced pressure to afford a yellow solid, which was crystallized by adding ethyl acetate (50 mL) and cooling at 4 ^oC for 16 h. After filtration, oxazole **3.8** (28.7 g, 73% over two steps) was obtained as a white crystal powder.

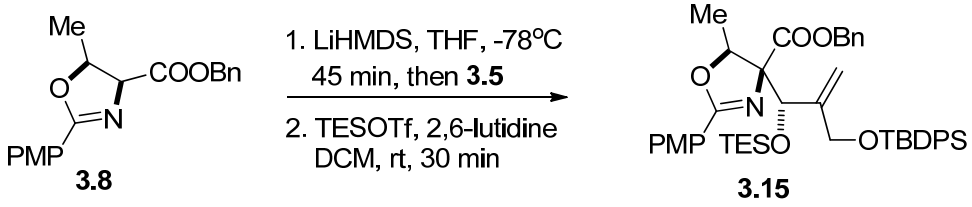
Melting point: 85.5 - 87.1 ^oC

$[\alpha]_D^{20}$ 15.2 (c 1, $CHCl_3$).

^1H NMR (400 MHz $CDCl_3$): δ7.91 (d, *J* = 8.9 Hz, 2H), 7.40 – 7.22 (m, 5H), 6.86 (s, 1H), 6.84 (s, 1H), 5.27 – 5.09 (dd, *J*=12.1, 3.1 Hz, 2H), 5.04 – 4.85 (m, 2H), 3.72 (s, 3H), 1.35 – 1.16 (m, 3H).

^{13}C NMR (100 MHz $CDCl_3$): δ 169.7, 165.7, 162.2, 135.1, 130.0, 128.4, 128.3, 128.2, 119.4, 113.4, 76.8, 71.2, 66.5, 55.0, 15.9

HRMS (ESI) calc. for $C_{19}H_{20}NO_4$: [M+H$^+$], 326.13868; found: [M+H$^+$], 326.13803.



(4*R*,5*S*)-Benzyl 4-((*S*)-3,3-diethyl-10,10-dimethyl-6-methylene-9,9-diphenyl-4,8-dioxa-3,9-disilaundecan-5-yl)-2-(4-methoxyphenyl)-5-methyl-4,5-dihydrooxazole-4-carboxylate

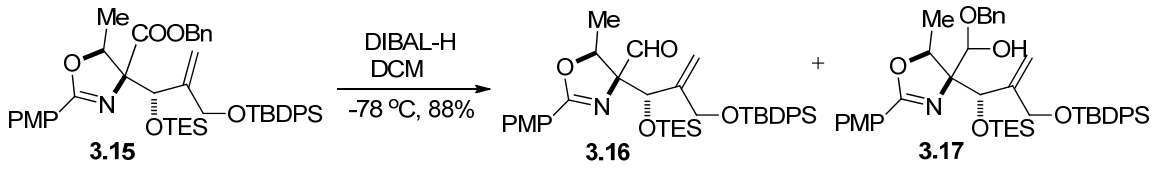
A solution of LiHMDS (1.0M in hexane, 7.4 mL, 7.4 mmol) in THF (30 mL) was cooled to -78 ^oC and treated dropwise with a solution of oxazoline **3.8** (2.0 g, 6.2 mmol) in THF (30 mL). After stirring for 45 min at -78 ^oC, a solution of α,β-unsaturated aldehyde **3.5** (3.0 g, 9.2 mmol) in THF (30 mL) was added dropwise at -78 ^oC. The mixture was stirred for 25 min and quenched rapidly with saturated aqueous NH_4Cl solution (20 mL) at -78 ^oC. The cooling bath was removed and the reaction mixture was allowed to warm to rt (40 min). The aqueous layer was extracted with ether (100 mL x 3).

The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. A crude viscous yellowish paste was obtained and dried by dissolving in toluene and evaporating the azeotrope twice. Without further purification, the crude allylic alcohol was dissolved in anhydrous DCM (20 mL), cooled to 0 ^oC, and treated with 2,6-lutidine (1.4 mL, 12.3 mmol) and TESOTf (1.4 mL, 7.4 mmol) at. After stirring for 30 min, the reaction mixture was quenched with saturated NH_4Cl (20 mL), and washed with 0.1 N HCl (50 mL x 3) and brine (50 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography, eluting with ethyl acetate/hexane (1:19), to afford the silylether **3.15** (3.1 g, 67%, 2 steps) as a colorless viscous liquid.

^1H NMR (400 MHz $CDCl_3$): δ 7.86 (d, *J* = 8.8 Hz, 2H), 7.69 (d, *J* = 6.6 Hz, 2H), 7.59 (d, *J* = 6.8 Hz, 2H), 7.52 – 7.18 (m, 11H), 6.83 (d, *J* = 8.8 Hz, 2H), 5.64 (s, 1H), 5.33 (s, 1H), 5.25 (q, *J* = 12.3 Hz, 2H), 4.83 (q, *J* = 6.4 Hz, 1H), 4.74 (s, 1H), 4.45 (dd, *J* = 15.4, 52.3 Hz, 2H), 4.16 (q, *J* = 7.2 Hz, 1H), 3.81 (s, 3H), 2.06 (s, 1H), 1.29 (t, *J* = 5.9 Hz, 3H), 1.09 (s, 9H), 0.98 (t, *J* = 7.9 Hz, 9H), 0.65 (q, *J* = 7.8 Hz, 6H).

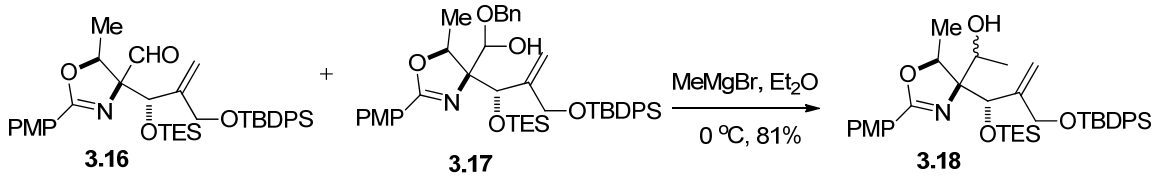
^{13}C NMR (100 MHz $CDCl_3$): δ 170.3, 164.4, 162.1, 147.5, 135.52, 135.46, 135.3, 133.6, 133.5, 130.3, 129.5, 129.4, 128.6, 128.3, 128.1, 127.54, 127.46, 119.9, 114.2, 113.4, 85.7, 79.5, 79.4, 66.7, 63.4, 55.1, 26.8, 19.2, 17.3, 6.9, 4.7.

HRMS (ESI) calc. for $C_{45}H_{58}NO_6Si_2$: [M+H$^+$], 764.37972; found: [M+H$^+$], 764.38087.



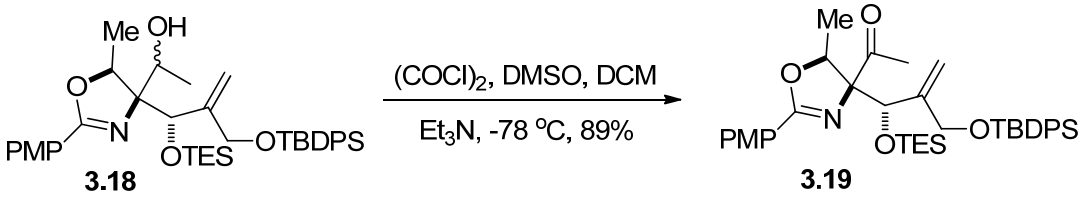
To a magnetically stirred solution of benzyl ester **3.15** (19.2 g, 25.2 mmol) in anhydrous DCM (500 mL) at -78 ^oC, DIBAL-H (1.0 M solution in toluene, 56.0 mL, 56.0 mmol) was added dropwise, additional DIBAL-H portions (0.5 equiv.) were added every

30 min. until complete consumption of starting material. The reaction mixture was quenched with 20% potassium sodium tartrate solution (200 mL) and allowed to reach rt. Et_2O (150 mL) was added to the mixture, which was stirred for 2 h at rt. The organic layer was separated. The aqueous layer was extracted with ether (200 mL x 2). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude was dried overnight under high vacuum. It is a mixture of aldehyde **3.16** and hemiacetal **3.17**. This mixture was used directly without purification in the next step.



To a stirred solution of aldehyde and hemiacetal in ether (100 mL), MeMgBr (3.0 M solution in ether, until 5 equiv.) was added dropwise at 0 ^oC. The reaction mixture was stirred for 30 min at 0 ^oC and quenched with saturated aqueous NH_4Cl (50 mL). After the layers were separated, the aqueous layer was extracted with ether (50 mL x 2), and the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography using ethyl acetate /hexane (1:19) as eluant afforded the alcohol **3.18** (19.2 g, 97%) as a colorless viscous liquid (mixture of two epimers).

HRMS (ESI) calc. for $C_{39}H_{56}NO_5Si_2$: $[M+H^+]$, 674.36915; found: $[M+H^+]$, 674.36919.



1-((4*R*,5*S*)-4-((S)-3,3-Diethyl-10,10-dimethyl-6-methylene-9,9-diphenyl-4,8-dioxa-3,9-disilaundecan-5-yl)-2-(4-methoxyphenyl)-5-methyl-4,5-dihydrooxazol-4-yl)ethanone

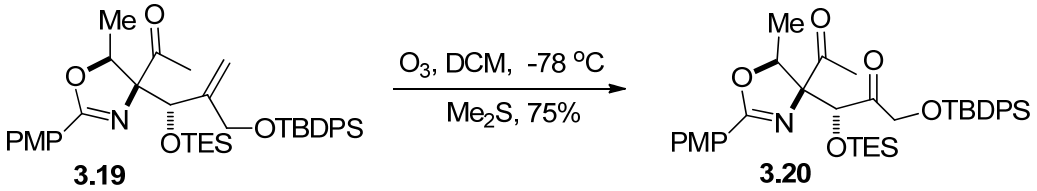
A solution of oxalyl chloride (4.8 mL, 54.6 mmol) in DCM (200 mL) was cooled to -78 ^{o}C, treated with DMSO (8.3 mL, 116.4 mmol) dropwise over 10 min, stirred for 10 min., treated with a solution of the alcohol **3.18** (24.5 g, 36.4 mmol) in DCM (50 mL) over 20 min, stirred for 30 min, treated with triethylamine (25.4 mL, 181.9 mmol) over 15 min, warmed to reach 0 ^{o}C, stirred for 2 h, warmed to rt, treated with water (50 mL) and stirred for 1 h. The organic layer was separated, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to afford **3.19** (21.7 g, 89%) as a colorless liquid after flash column chromatography using ethyl acetate/ hexane (1:19) as eluant.

$[\alpha]_D^{20}$ -18.2 (c 1, $CHCl_3$).

^{1}H NMR (400 MHz $CDCl_3$): δ 7.86 – 7.76 (m, 2H), 7.66 – 7.58 (m, 2H), 7.53 (m, 2H), 7.42 (m, 1H), 7.40 – 7.32 (m, 3H), 7.26 (m, 2H), 6.84 (d, *J* = 8.9 Hz, 2H), 5.57 (d, *J* = 1.9 Hz, 1H), 5.23 (d, *J* = 1.2 Hz, 1H), 4.72 (q, *J* = 6.6 Hz, 1H), 4.63 (s, 1H), 4.34 (dd, *J* = 15.5, 35.8 Hz, 2H), 3.87 (s, 3H), 2.27 (s, 3H), 1.24 (d, *J* = 6.6 Hz, 3H), 1.02 (s, 9H), 0.92 (t, *J* = 7.9 Hz, 9H), 0.56 (q, *J* = 7.9 Hz, 6H)

^{13}C NMR (100 MHz $CDCl_3$): δ 211.6, 164.4, 162.3, 147.7, 135.7, 135.5, 133.9, 133.7, 130.3, 130.0, 129.5, 127.7, 120.4, 114.2, 113.7, 88.7, 80.7, 80.4, 63.4, 55.5, 31.5, 27.0, 19.4, 17.9, 7.0, 4.8.

HRMS (ESI) calc. for $C_{39}H_{54}NO_5Si_2$: [M+H$^+$], 672.3535; found: [M+H$^+$], 672.35453.



(*R*)-7-((4*R*,5*S*)-4-Acetyl-2-(4-methoxyphenyl)-5-methyl-4,5-dihydrooxazol-4-yl)-9,9-diethyl-2,2-dimethyl-3,3-diphenyl-4,8-dioxa-3,9-disilaundecan-6-one

A solution of olefin **3.19** (5.0 g, 7.5 mmol) in DCM (200 mL) was treated with O_3 gas bubbles at -78 ^{o}C until a blue color was observed. The excess O_3 gas was purged with

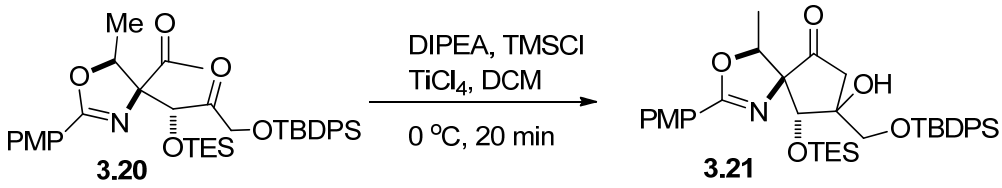
argon gas. The ozonide was decomposed with Me_2S (6 mL, 75 mmol) at -78 ^oC. The mixture was stirred overnight at rt. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography using ethyl acetate/hexane (1:19) as eluant to afford the diketone **3.20** (3.75 g, 75%) as a colorless viscous liquid.

$[\alpha]_D^{20}$ 27.0 (c 1, $CHCl_3$).

^1H NMR (400 MHz $CDCl_3$): δ 7.94 (d, *J* = 8.8 Hz, 2H), 7.65 (ddd, *J* = 1.4, 7.9, 17.8 Hz, 4H), 7.52 – 7.31 (m, 6H), 7.02 – 6.78 (m, 2H), 5.34 (q, *J* = 6.7 Hz, 1H), 4.67 (s, 1H), 4.50 (dd, *J* = 18.4, 47.7 Hz, 2H), 3.88 (s, 3H), 2.25 (s, 3H), 1.30 (d, *J* = 6.7 Hz, 3H), 1.04 (s, 9H), 0.78 (t, *J* = 7.9 Hz, 9H), 0.42 (q, *J* = 7.8 Hz, 6H).

^{13}C NMR (100 MHz $CDCl_3$): δ 210.4, 208.1, 165.9, 162.6, 135.8, 133.2, 133.1, 130.5, 130.0, 129.9, 127.9, 120.1, 113.9, 88.1, 78.9, 76.3, 69.2, 60.6, 55.6, 30.5, 26.9, 19.5, 17.6, 14.4, 6.8, 4.8.

HRMS (ESI) calc. for $C_{38}H_{52}NO_6Si_2$: $[M+H^+]$, 674.33277; found: $[M+H^+]$, 674.33561.



(4*S*,5*R*,8*S*,9*R*)-8-(((*tert*-Butyldiphenylsilyl)oxy)methyl)-8-hydroxy-2-(4-methoxyphenyl)-4-methyl-9-((triethylsilyl)oxy)-3-oxa-1-azaspiro[4.4]non-1-en-6-one

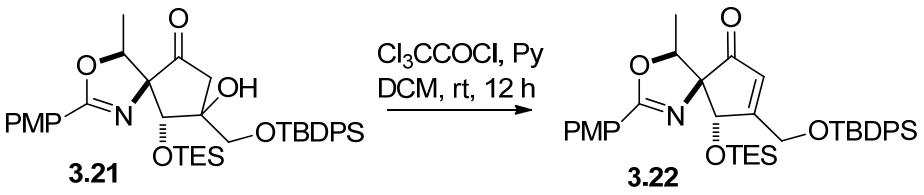
To a magnetically stirred solution of diketone **3.20** (1.0 g, 1.5 mmol) in anhydrous DCM (50 mL), diisopropyl ethylamine (1 mL, 4.6 mmol) and TMSCl (10 drop) were added at 0 ^oC and the mixture was stirred for 5 min. at 0 ^oC, treated with $TiCl_4$ (1.8 mL, 1.0 M in DCM) dropwise and stirred for 15 min. The reaction mixture was quenched with cold water (30 mL) and extracted with ether (60 mL x 2), the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash column chromatograhpy, eluting with ethyl acetate/hexane

(2:8), to give the hydroxy ketone **3.21** with minor enone product **3.22** (which was characterized in the next step.

^{1}H NMR (400 MHz $CDCl_3$): δ 7.85 (d, *J* = 8.8 Hz, 2H), 7.73 – 7.66 (m, 4H), 7.50 – 7.39 (m, 7H), 6.89 (d, *J* = 8.8 Hz, 2H), 4.85 (q, *J* = 6.6 Hz, 1H), 4.50 (s, 1H), 4.02 (d, *J* = 10.2 Hz, 1H), 3.86 (s, 3H), 3.78 (s, 1H), 3.46 (d, *J* = 10.3 Hz, 1H), 2.74 (dd, *J* = 19.7, 131.9 Hz, 2H), 1.12 (s, 9H), 1.05 (d, *J* = 6.6 Hz, 3H), 0.83 (t, *J* = 7.9 Hz, 9H), 0.52 (q, *J* = 8.0 Hz, 6H).

^{13}C NMR (100 MHz $CDCl_3$): δ 211.2, 165.5, 162.5, 135.9, 135.8, 132.8, 132.7, 130.5, 130.3, 130.2, 128.2, 128.1, 119.6, 113.8, 85.0, 82.2, 78.0, 76.9, 66.5, 55.5, 48.2, 27.1, 19.5, 17.1, 6.8, 5.0.

HRMS (ESI) calc. for $C_{38}H_{52}NO_6Si_2$: [M+H$^+$], 674.33277; found: [M+H$^+$], 674.33492.



(4*S*,5*R*,9*S*)-8-((*tert*-Butyldiphenylsilyloxy)methyl)-2-(4-methoxyphenyl)-4-methyl-9-(triethylsilyloxy)-3-oxa-1-azaspiro[4.4]nona-1,7-dien-6-one

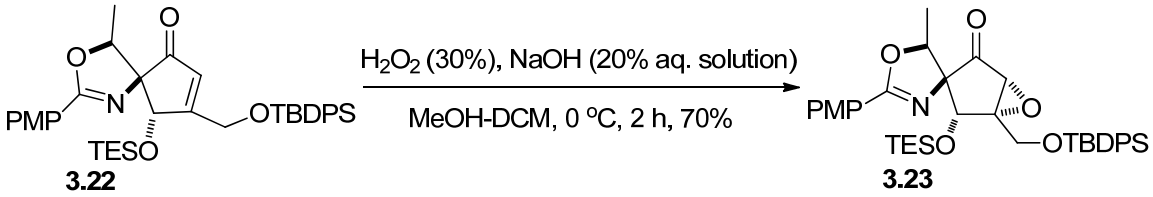
A solution of hydroxy ketone (2.0 g, 2.6 mmol) in DCM (10 mL) was treated with pyridine (2.5 mL) and trichloroacetyl chloride (0.6 mL, 5.3 mmol) dropwise at rt and stirred for overnight. The reaction mixture was diluted with ether and washed with $CuSO_4$ (10% solution) until constant color persisted. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography using ethyl acetate/hexane (1:19) as eluant to afford the cyclopentenone **3.22** (1.29 g, 75%, two steps) as a colorless viscous liquid.

$[\alpha]_D^{20}$ 108.8 (c 1, $CHCl_3$).

^{1}H NMR (400 MHz $CDCl_3$): δ 7.92 (d, *J* = 8.7 Hz, 2H), 7.68 (t, *J* = 7.8 Hz, 4H), 7.57 – 7.34 (m, 6H), 6.90 (d, *J* = 8.8 Hz, 2H), 6.54 (s, 1H), 5.12 (q, *J* = 6.5 Hz, 1H), 4.99 (s, 1H), 4.56 (dd, *J* = 18.9, 81.6 Hz, 1H), 3.81 (s, 3H), 1.35 (d, *J* = 6.6 Hz, 3H), 1.13 (s, 9H), 0.76 (t, *J* = 7.9 Hz, 10H), 0.54 – 0.33 (m, 6H).

^{13}C NMR (100 MHz $CDCl_3$): δ 200.5, 178.1, 166.5, 162.4, 135.5, 135.4, 132.8, 132.7, 130.3, 130.1, 128.0, 127.8, 119.9, 113.7, 86.0, 77.6, 62.6, 55.4, 26.8, 19.4, 17.2, 6.6, 4.7.

MS (ESI) *m/z*: 656.3 [M+H^{+}].



(1*S*,2*R*,3*R*,5*R*,5'*S*)-1-((*tert*-Butyldiphenylsilyloxy)methyl)-2'-(4-methoxyphenyl)-5'-methyl-2-(triethylsilyloxy)-5'H-6-oxaspiro[bicyclo[3.1.0]hexane-3,4'-oxazol]-4-one

To a stirred solution of enone **3.22** (6.5 g, 9.9 mmol) in MeOH-DCM (100 mL, 8 mL) at 0 ^{o}C, H_2O_2 (30% in water, 28.2 mL) and NaOH (20% aqueous solution, 7 mL) were added dropwise together and the mixture was stirred for 30 min. The reaction mixture was quenched with saturated Na_2SO_3 solution (100 mL) and extracted with ether (100 mL x 3). The organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography using ethyl acetate/hexane (1:9) as eluant to afford the epoxy ketone **3.23** (5.1 g, 70%) as a colorless liquid.

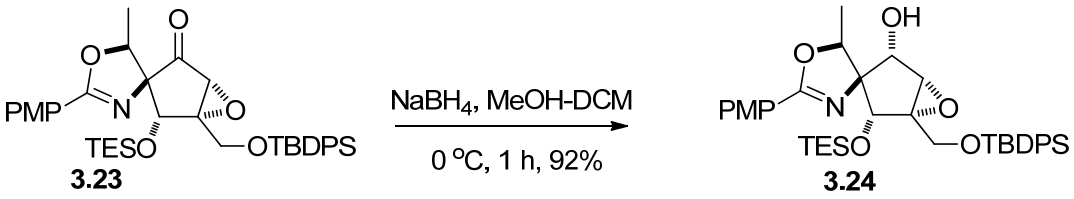
$[\alpha]_D^{20}$ 3.6 (c 1, $CHCl_3$).

^{1}H NMR (400 MHz $CDCl_3$): δ 7.90 (d, *J* = 4.4 Hz, 2H), 7.63-7-67 (m, 4H), 7.28-7.48 (m, 6H), 6.89 (d, *J* = 4.4 Hz, 2H), 5.22 (q, *J* = 4.1 Hz, 1H), 4.63 (s. 1H), 3.99 (dd, *J* = 85.2,

8.3 Hz, 2H), 3.86 (s. 3H), 3.24 (s, 1H), 1.23 (d, *J* = 3.3 Hz, 3H), 1.08 (s, 9H), 0.82 (t, *J* = 2.7 Hz, 9H), 0.51 (q, *J* = 4.0 Hz, 6H).

^{13}C NMR (100 MHz $CDCl_3$): δ 204.0, 165.9, 161.9, 135.3, 135.1, 132.2, 132.1, 130.0, 129.8, 129.7, 127.6, 127.4, 119.5, 113.2, 82.5, 74.3, 69.0, 59.1, 58.3, 55.0, 29.3, 26.4, 18.8, 16.2, 6.2, 4.4, 4.3.

HRMS (ESI) calc. for $C_{38}H_{50}NO_6Si_2$: $[M+H^+]$, 672.31712; found: $[M+H^+]$, 674.3172.



(1*S*,2*R*,3*R*,4*S*,5*S*,5'*S*)-1-((*tert*-Butyldiphenylsilyloxy)methyl)-2'-(4-methoxyphenyl)-5'-methyl-2-(triethylsilyloxy)-5'H-6-oxaspiro[bicyclo[3.1.0]hexane-3,4'-oxazol]-4-ol

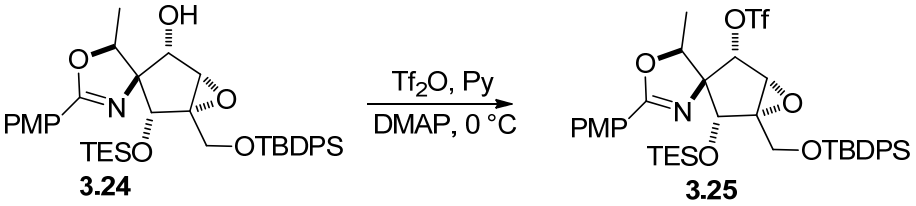
To a magnetically stirred solution of epoxy ketone **3.23** (540 mg, 0.84 mmol) in MeOH-DCM (10 mL, 1:1) at 0 ^{o}C, $NaBH_4$ (32 mg, 0.84 mmol) was added portion-wise and stirred for 1 h. The reaction mixture was quenched with saturated aqueous NH_4Cl (5 mL) and extracted with ethyl acetate (5 mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography using ethyl acetate/hexane (1:9) as eluant to afford the epoxy alcohol **3.24** (500 mg, 92%) as a viscous liquid.

$[\alpha]_D^{20}$ 36.4 (c 1, $CHCl_3$).

^{1}H NMR (400 MHz $CDCl_3$): δ 7.69 (t, *J* = 6.9 Hz, 6H), 7.53 – 7.32 (m, 6H), 6.86 (d, *J* = 8.7 Hz, 2H), 5.13 (q, *J* = 6.7 Hz, 1H), 5.06 (s, 1H), 4.54 (s, 1H), 4.21 (s, 1H), 4.15 (d, *J* = 11.7 Hz, 1H), 3.86 (s, 3H), 3.71 (d, *J* = 11.7 Hz, 1H), 3.39 (s, 1H), 1.52 (d, *J* = 6.8 Hz, 3H), 1.11 (s, 9H), 0.79 (t, *J* = 7.9 Hz, 9H), 0.45 (dd, *J* = 7.8, 15.0 Hz, 6H).

^{13}C NMR (100 MHz $CDCl_3$): δ 165.1, 162.3, 135.9, 135.7, 133.4, 133.1, 130.5, 130.2, 130.1, 128.0, 120.2, 113.7, 79.7, 77.8, 77.3, 77.0, 63.4, 60.3, 58.4, 55.5, 27.1, 19.4, 17.2, 6.8, 5.0.

HRMS (ESI) calc. for $C_{38}H_{52}NO_6Si_2$: [M+H$^+$], 674.33277; found: [M+H$^+$], 674.33519.



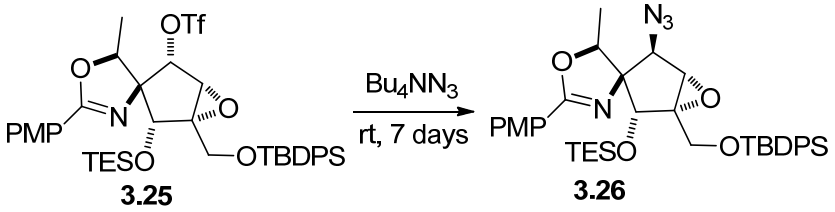
(1*S*,2*R*,3*R*,4*S*,5*S*,5'*S*)-1-(((*tert*-Butyldiphenylsilyl)oxy)methyl)-2'-(4-methoxyphenyl)-5'-methyl-2-((triethylsilyl)oxy)-5'H-6-oxaspiro[bicyclo[3.1.0]hexane-3,4'-oxazol]-4-yl trifluoromethanesulfonate

To a solution of pyridine (5 mL) in anhydrous DCM (50 mL) at -78 ^{o}C, triflic anhydride (1.5 mL, 2 equiv.) was added dropwise. The mixture was stirred for 15 min, treated with a solution of epoxy alcohol **3.24** (2.90 g, 10.6 mmol) in DCM (5 mL) and stirred at 0 ^{o}C until the triflate was totally formed (no more starting material). The mixture was then quenched with a saturated solution of $NaHCO_3$ (20 mL), diluted with ether (100 mL), and washed with $CuSO_4$ (10% solution) until a persistent color, followed by H_2O (20 mL) and brine (20 mL). The organic layer was dried over Na_2SO_4, concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using ethyl acetate/hexane (1:9) as eluant to give the triflate **3.25** as a pale yellow oil.

^{1}H NMR (400 MHz $CDCl_3$): δ 7.88 (d, *J* = 8.9 Hz, 2H), 7.67 (m, 4H), 7.59 – 7.37 (m, 6H), 6.93 (d, *J* = 8.9 Hz, 2H), 5.41 (s, 1H), 5.21 (q, *J* = 6.9 Hz, 1H), 4.39 (s, 1H), 4.21 (d, *J* = 11.8 Hz, 1H), 3.88 (s, 3H), 3.55 (d, *J* = 11.9 Hz, 1H), 3.20 (s, 1H), 1.56 (d, *J* = 6.9 Hz, 3H), 1.12 (s, 9H), 0.85 (t, *J* = 7.9 Hz, 9H), 0.53 (m, 6H).

^{13}C NMR (100 MHz $CDCl_3$): δ 165.1, 162.4, 135.8, 135.7, 132.9, 130.5, 130.3, 130.2, 128.2, 120.3, 113.9, 91.7, 78.9, 75.8, 64.8, 59.9, 56.1, 55.6, 27.1, 19.4, 17.2, 6.8, 5.0.

HRMS (ESI) calc. for $C_{39}H_{51}F_3NO_8Si_2$: [M+H$^+$], 806.28205; found: [M+H$^+$], 806.28174.



(1*S*,2*R*,3*R*,4*R*,5*S*,5'*S*)-4-Azido-1-((*tert*-butyldiphenylsilyloxy)methyl)-2'-(4-methoxyphenyl)-5'-methyl-2-(triethylsilyloxy)-5'H-6-oxaspiro[bicyclo[3.1.0]hexane-3,4'-oxazole]

A solution of epoxy triflate in toluene (120 mL), was treated with activated 4Å molecular sieves (4 g, flame dried) and tetrabutylammonium azide (5.1 g, 5.0 equiv.), stirred for 7 days, and filtered. The filtrate was treated with H_2O (50 mL) and extracted with ether (50 mL x 3). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using ethyl acetate/hexane (5:95) as eluant to afford azide **3.26** (2.4 g, 85%) as a white foam.

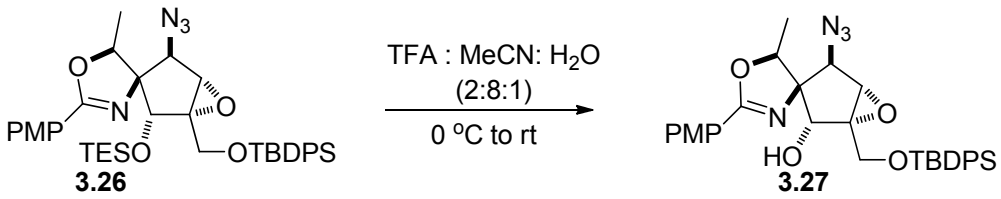
IR 1645.7, 2110.2 cm^{-1}.

$[\alpha]_D^{20}$ -44.4 (c 1, $CHCl_3$).

^{1}H NMR (400 MHz $CDCl_3$): δ 7.96 (d, *J* = 8.2 Hz, 2H), 7.72 (t, *J* = 7.5 Hz, 4H), 7.63 – 7.37 (m, 6H), 6.94 (d, *J* = 8.3 Hz, 2H), 5.16 (q, *J* = 6.1 Hz, 1H), 4.66 (s, 1H), 4.17 (d, *J* = 13.2 Hz, 2H), 3.87 (s, 3H), 3.61 (d, *J* = 11.7 Hz, 1H), 3.25 (s, 1H), 1.31 (t, *J* = 10.8 Hz, 3H), 1.13 (s, 9H), 0.83 (t, *J* = 7.8 Hz, 9H), 0.50 (q, *J* = 5.3 Hz, 6H).

^{13}C NMR (100 MHz $CDCl_3$): δ 163.9, 162.2, 136.0, 135.7, 133.3, 132.9, 130.4, 130.1, 130.0, 128.0, 120.8, 113.7, 80.9, 77.9, 77.4, 66.4, 63.1, 60.1, 56.6, 55.5, 27.0, 19.4, 17.2, 6.9, 5.1.

HRMS (ESI) calc. for $C_{38}H_{51}N_4O_5Si_2$: $[M+H^+]$, 699.33925; found: $[M+H^+]$, 699.34028.



(1*R*,2*R*,3*S*,4*R*,5*S*,5'*S*)-4-Azido-1-((*tert*-butyldiphenylsilyloxy)methyl)-2'-(4-methoxyphenyl)-5'-methyl-5'H-6-oxaspiro[bicyclo[3.1.0]hexane-3,4'-oxazol]-2-ol

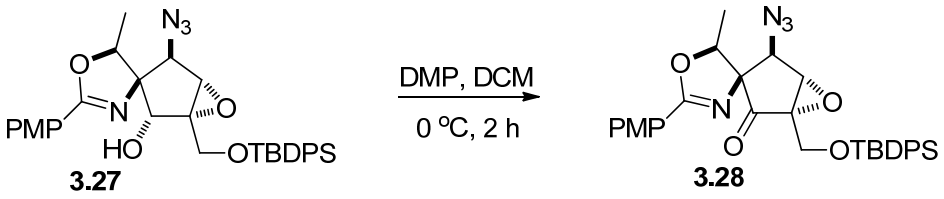
Azido-epoxide **3.26** (2.4 g, 3.5 mmol) was dissolved in a 2:8:1 mixture of TFA:MeCN:H_2O (80 mL) at 0 °C and stirred at rt untill no more starting material (5 h). The reaction mixture was slowly neutralized with a saturated solution of $NaHCO_3$ (100 mL) at 0 °C. The reaction mixture was extracted with ethyl acetate (150 mL x 3), the combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure, the residue was purified by flash chromatography on silica gel using ethyl acetate/hexane (4:6) as eluant to afford **3.27** (2.0 g, 99%) as a colorless foam.

$[\alpha]_D^{20}$ -75.3 (c 1, $CHCl_3$).

^{1}H NMR (400 MHz $CDCl_3$): δ 7.95 (d, *J* = 8.9 Hz, 2H), 7.71 (m, 4H), 7.62 – 7.36 (m, 6H), 6.92 (d, *J* = 8.9 Hz, 2H), 5.20 (q, *J* = 6.5 Hz, 1H), 4.67 (d, *J* = 3.3 Hz, 1H), 4.19 (s, 1H), 4.08 (d, *J* = 11.9 Hz, 1H), 3.96 (d, *J* = 11.9 Hz, 1H), 3.86 (s, 3H), 3.38 (d, *J* = 0.7 Hz, 1H), 2.80 (s, br, 1H), 1.36 (d, *J* = 6.6 Hz, 4H), 1.09 (s, 9H).

^{13}C NMR (100 MHz $CDCl_3$): δ 164.4, 162.5, 135.8, 132.6, 130.6, 130.2, 128.1, 120.2, 113.8, 81.3, 78.0, 65.8, 63.1, 62.7, 56.9, 55.6, 27.0, 19.4, 17.2.

HRMS (ESI) calc. for $C_{32}H_{36}N_4O_5Si$: $[M+H^+]$, 585.25493; found: $[M+H^+]$, 585.25321.



(1*S*,3*R*,4*R*,5*S*,5'*S*)-4-Azido-1-((*tert*-butyldiphenylsilyloxy)methyl)-2'-(4-methoxyphenyl)-5'-methyl-5'H-6-oxaspiro[bicyclo[3.1.0]hexane-3,4'-oxazol]-2-one

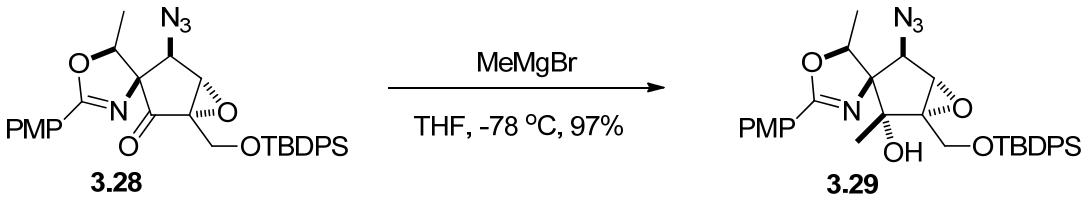
To a stirred solution of azide epoxy alcohol **3.27** (5.25 g, 9.0 mmol) in DCM (70 mL) was added Dess-Martin periodinane (5.75 g, 13.5 mmol) at 0 °C and the reaction mixture was stirred at rt for 2 h. The reaction mixture was quenched with $Na_2S_2O_3$/$NaHCO_3$ (7:1) saturated solution (30 mL). The mixture was stirred vigorously until the two layers were clear. The crude product was extracted with ether (50 mL x 3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography using ethyl acetate/hexane (1:9) as eluant, to afforded the ketone **3.28** (3.3 g, 79%) as a colorless viscous foam.

$[\alpha]_D^{20}$ -143.0 (c 1, $CHCl_3$).

^{1}H NMR (400 MHz $CDCl_3$): δ 8.24 – 7.89 (m, 2H), 7.68 (m, 4H), 7.59 – 7.37 (m, 6H), 7.06 – 6.74 (m, 2H), 4.69 (q, *J* = 6.5 Hz, 1H), 4.46 (s, 1H), 4.19 (q, *J* = 12.9 Hz, 2H), 4.11 (d, *J* = 0.8 Hz, 1H), 3.87 (s, 3H), 1.48 (d, *J* = 6.5 Hz, 3H), 1.07 (s, 9H).

^{13}C NMR (100 MHz $CDCl_3$): δ 204.1, 166.9, 162.9, 135.8, 135.7, 132.8, 132.6, 130.8, 130.1, 128.1, 128.0, 119.4, 113.9, 82.7, 81.7, 62.9, 59.9, 59.6, 56.8, 55.6, 26.9, 19.4, 17.7.

HRMS (ESI) calc. for $C_{32}H_{35}N_4O_5Si$: [M+H$^+$], 583.23712; found: [M+H$^+$], 583.23975.



3.28 **3.29**

(1*S*,2*R*,3*R*,4*R*,5*S*,5'*S*)-4-Azido-1-((*tert*-butyldiphenylsilyloxy)methyl)-2'-(4-methoxyphenyl)-2,5'-dimethyl-5'H-6-oxaspiro[bicyclo[3.1.0]hexane-3,4'-oxazol]-2-ol

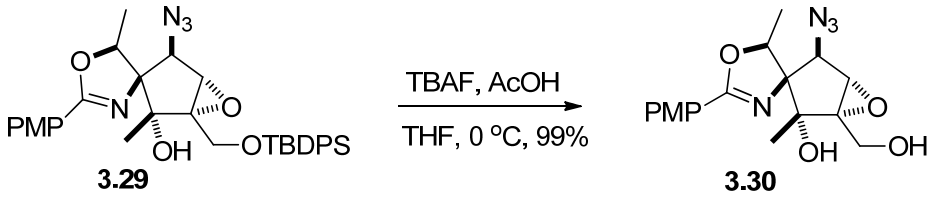
To a stirred solution of azide epoxy ketone **3.28** (4.1 g, 6.9 mmol) in anhydrous THF (70 mL), MeMgBr (3.0 M solution in ether, 5 equiv. max) was added at -78 ^{o}C and stirred for 30 min. The reaction was quenched with saturated aqueous NH_4Cl solution (50 mL) and stirred further for 30 min, then extracted with ethyl acetate (50 mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography using ethyl acetate/hexane (2:8) as eluant to afford **3.29** (2.8 g, 97%) as a foam.

$[\alpha]_D^{20}$ -54.8 (c 1, $CHCl_3$).

^{1}H NMR (400 MHz $CDCl_3$): δ 7.98 (d, *J* = 8.8 Hz, 2H), 7.73 (dd, *J* = 1.5, 7.7 Hz, 4H), 7.61 – 7.39 (m, 6H), 6.93 (d, *J* = 8.9 Hz, 2H), 5.33 (q, *J* = 6.5 Hz, 1H), 4.39 (d, *J* = 12.1 Hz, 1H), 4.10 (s, 1H), 3.87 (s, 3H), 3.76 (d, *J* = 12.1 Hz, 1H), 3.45 (d, *J* = 0.5 Hz, 1H), 3.12 (s, 1H), 1.55 (s, 3H), 1.38 (d, *J* = 6.6 Hz, 3H), 1.10 (s, 9H).

^{13}C NMR (100 MHz $CDCl_3$): δ 165.3, 163.9, 137.5, 139.1, 139.0, 133.0, 132.3, 132.2, 129.9, 122.5, 115.6, 88.1, 83.3, 81.8, 74.2, 64.0, 61.4, 57.5, 30.0, 35.2, 21.6.

HRMS (ESI) calc. for $C_{33}H_{39}N4O_5Si$: [M+H$^+$], 599.26842; found: [M+H$^+$], 599.2711.



(1*S*,2*R*,3*R*,4*R*,5*S*,5'*S*)-4-Azido-1-(hydroxymethyl)-2'-(4-methoxyphenyl)-2,5'-dimeth yl-5'H-6-oxaspiro[bicyclo[3.1.0]hexane-3,4'-oxazol]-2-ol

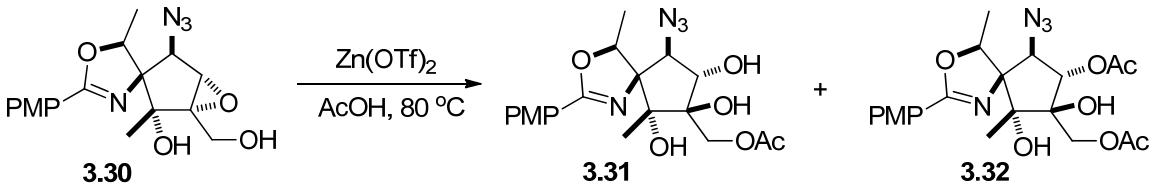
To a solution of **3.29** (3.84 g, 6.4 mmol) in THF (40 mL) was added AcOH (7.7 mL, 1 equiv.) first, then TBAF (7.7 mL, 1.0 M in THF, 1.2 equiv.) was added at 0 °C. The mixture was stirred at rt till no more starting material. Saturated NH_4Cl (20 mL) was then added and 5 min. later, H_2O (25 mL) was added, the mixture was extracted with ethyl acetate (30 mL x 3), the combined organic layers were dried over Na_2SO_4, concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using ethyl acetate/hexane (5:5) to give the desired product **3.30** (2.3 g, 99%) as a colorless oil.

$[\alpha]_D^{20}$ -71.5 (c 1, $CHCl_3$).

^{1}H NMR (400 MHz $CDCl_3$): δ 7.95 (d, *J* = 8.8 Hz, 2H), 6.93 (d, *J* = 8.8 Hz, 2H), 5.15 (q, *J* = 6.6 Hz, 1H), 4.26 (d, *J* = 12.7 Hz, 1H), 4.06 (s, 1H), 3.85 (s, 3H), 3.63 (s, 1H), 2.52 (s, 1H), 2.36 (s, br,1H), 1.49 (s, 3H), 1.38 (d, *J* = 6.6 Hz, 3H).

^{13}C NMR (100 MHz $CDCl_3$): δ 163.9, 162.5, 130.5, 120.2, 113.9, 86.9, 80.7, 79.2, 70.2, 62.6, 59.8, 59.3, 55.6, 21.1, 17.6.

HRMS (ESI) calc. for $C_{17}H_{21}N4O_5$: [M+H$^+$], 361.15065; found: [M+H$^+$], 361.15048.



((4*S*,5*R*,6*R*,7*R*,8*S*,9*R*)-8-Acetoxy-9-azido-6,7-dihydroxy-2-(4-methoxyphenyl)-4,6-di methyl-3-oxa-1-azaspiro[4.4]non-1-en-7-yl)methyl acetate

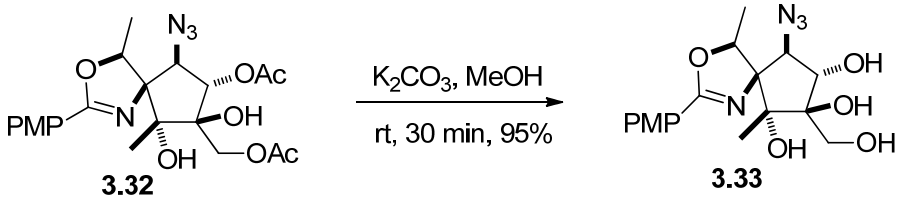
To a stirred solution of epoxy alcohol **3.30** (2.28 g, 6.5 mmol) in AcOH (50 mL), was added $Zn(OTf)_2$ (4.7 g, 12.9 mmol). After stirred at 80 ^oC for 2 days, another portion $Zn(OTf)_2$ (2.4 g, 1 equiv.) was added, the reaction mixtures was stirred till no more starting material. The reaction mixture was cooled to 0 ^oC, then quenched with saturated $NaHCO_3$ (100 mL), extracted with ethyl acetate (80 mL x 3). The combined organic layers were dried over Na_2SO_4, concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel, eluting with ethyl acetate/hexane (1:9 to 1:1), to afford a solid diacetate **3.32** (1.8 g, 60%) as the major product and minor monoacetate product **3.31** (300 mg, 11%).

Melting point: 95.1-96.9 ^oC

^1H NMR (400 MHz $CDCl_3$): δ 7.86 (d, *J* = 8.7 Hz, 2H), 6.93 (d, *J* = 8.8 Hz, 2H), 5.64 (d, *J* = 6.0 Hz, 1H), 5.59 (s, 1H), 4.88 (q, *J* = 6.6 Hz, 1H), 4.58 (d, *J* = 11.9 Hz, 1H), 4.26 (d, *J* = 11.9 Hz, 1H), 3.89 (d, *J* = 6.0 Hz, 1H), 3.85 (s, 3H), 3.26 (s, 1H), 2.14 (d, *J* = 3.8 Hz, 7H), 1.57 (d, *J* = 6.6 Hz, 3H), 1.24 (s, 4H).

^{13}C NMR (100 MHz $CDCl_3$): δ 172.5, 169.9, 164.7, 163.0, 130.7, 118.7, 114.0, 85.3, 83.0, 82.6, 81.8, 78.8, 68.2, 63.8, 55.6, 21.2, 21.0, 17.5, 17.0.

HRMS (ESI) calc. for $C_{21}H_{27}N_4O_8$: $[M+H^+]$, 463.18234; found: $[M+H^+]$, 463.18258.



3.32 **3.33**

(4*S*,5*R*,6*R*,7*R*,8*S*,9*R*)-9-Azido-7-(hydroxymethyl)-2-(4-methoxyphenyl)-4,6-dimethyl-3-oxa-1-azaspiro[4.4]non-1-ene-6,7,8-triol

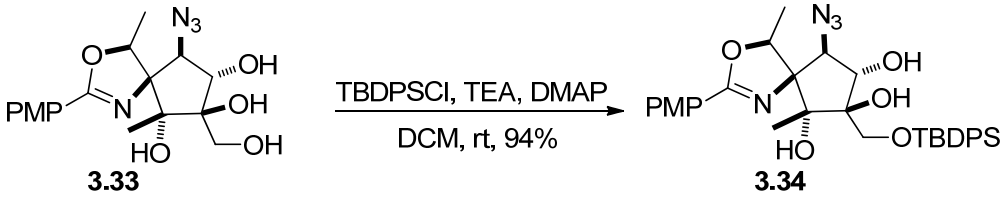
The diacetate **3.32** (1.79 g, 3.9 mmol) was dissolved in MeOH (20 mL), then K_2CO_3 (1.6 g, 11.4 mmol) was added at rt. After strirred 30 min., the reaction mixture was quenched with a saturated solution of NH_4Cl (20 mL), extracted with ethyl acetate (20 mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4, concentrated under reduced pressure, and the residue was purified by flash chromatography on silica gel using ethyl acetate/hexane (3:7) as eluant to afford tetrol **3.33** (1.39 g, 95%) as a colorless foam. (The monoacetate **3.31** was treated in the same way to afford **3.33**).

$[\alpha]_D^{20}$ 55 (c 1, $CHCl_3$).

^{1}H NMR (400 MHz $CDCl_3$): δ 7.87 (d, *J* = 8.8 Hz, 2H), 6.92 (d, *J* = 8.8 Hz, 2H), 5.71 (s,br, 1H), 4.90 (q, *J* = 6.5 Hz, 1H), 4.54 (d, *J* = 4.6 Hz, 1H), 4.34 (s,br, 1H), 4.05 (dd, *J* = 8.0 Hz, 17.9, 2H), 3.95 (d, *J* = 5.5 Hz, 2H), 3.85 (s, 3H), 3.74 (s, br, 1H), 1.58 (d, *J* = 6.5 Hz, 3H), 1.25 (s, 3H).

^{13}C NMR (100 MHz $CDCl_3$): δ 164.3, 163.0, 131.0, 119.0, 114.0, 85.1, 84.4, 83.7, 81.5, 78.9, 70.5, 63.2, 55.6, 17.3.

HRMS (ESI) calc. for $C_{17}H_{23}N_4O_6$: [M+H$^+$], 379.16121; found: [M+H$^+$], 379.16127.



3.33 **3.34**

(4*S*,5*R*,6*R*,7*R*,8*S*,9*R*)-9-Azido-7-((*tert*-butyldiphenylsilyloxy)methyl)-2-(4-methoxyphenyl)-4,6-dimethyl-3-oxa-1-azaspiro[4.4]non-1-ene-6,7,8-triol

A solution of tetrol **3.33** (1.34 g, 3.5 mmol) in DCM (60 mL) was added triethylamine (2.5 mL. 17.7 mmol, 5.0 equiv.), DMAP (43 mg, 10 mol%) and TBDPSCl (1.4 mL, 5.3 mmol, 1.50 equiv.) at 0 ^{o}C. The reaction mixture was stirred at rt until there was total conversion of the starting material. The reaction mixture was quenched with a saturated solution of NH_4Cl (20 mL) and extracted with ethyl acetate (20 mL x 3). The

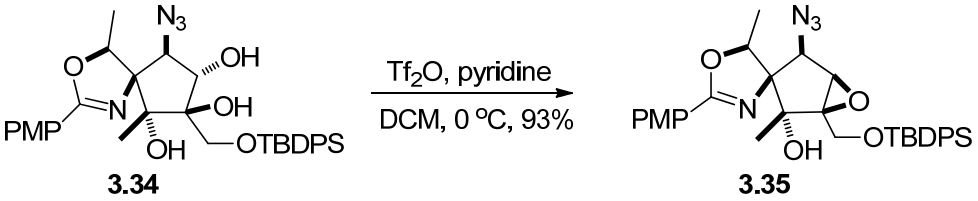
combined organic layers were dried over Na_2SO_4, concentrated under reduced pressure, and the residue was purified by flash chromatography on silica gel using ethyl acetate/hexane (4:6) as eluant to give **3.34** (2.05 g, 94%) as a white solid.

$[\alpha]_D^{20}$ 41.2 (c 1.43, $CHCl_3$).

^{1}H NMR (400 MHz $CDCl_3$)：δ 7.88 (d, *J* = 8.8 Hz, 2H), 7.84 – 7.78 (m, 2H), 7.74 (m, 2H), 7.57 – 7.38 (m, 6H), 6.94 (d, *J* = 8.8 Hz, 2H), 5.55 (s, 1H), 4.93 (q, *J* = 6.6 Hz, 1H), 4.56 (t, *J* = 5.6 Hz, 1H), 4.11 (q, *J* = 11.0 Hz, 2H), 3.98 (d, *J* = 4.9 Hz, 1H), 3.87 (s, 3H), 3.64 (s, 1H), 3.38 (d, *J* = 6.3 Hz, 1H), 1.60 (d, *J* = 6.6 Hz, 3H), 1.17 (s, 3H), 1.13 (s, 9H).

^{13}C NMR (100 MHz) δ 164.0, 162.9, 136.0, 135.8, 132.1, 131.6, 130.7, 130.4, 128.2, 119.1, 114.0, 85.4, 85.2, 84.3, 80.9, 78.9, 71.0, 66.2, 55.6, 27.1, 19.3, 17.5, 17.3.

HRMS (ESI) calc. for $C_{33}H_{41}N_4O_6Si$: $[M+H^+]$, 617,27899; found: $[M+H^+]$, 617.27653.



3.34 **3.35**

(1*R*,2*R*,3*R*,4*R*,5*R*,5'*S*)-4-Azido-1-((*tert*-butyldiphenylsilyloxy)methyl)-2'-(4-methoxyphenyl)-2,5'-dimethyl-5'H-6-oxaspiro[bicyclo[3.1.0]hexane-3,4'-oxazol]-2-ol

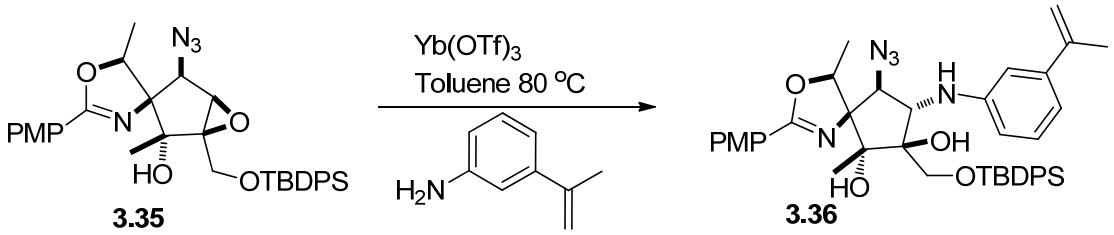
To a solution of triol **3.34** (2.0 g, 3.3 mmol) in anhydrous DCM (15 mL) was added pyridine (2 mL) and triflic anhydride (1.7 mL, 9.9 mmol, 3 equiv.) at 0 °C. The reaction was then continued at 0 °C until all the triflate was converted *in situ* to the epoxide. The reaction mixture was quenched with a saturated solution of $NaHCO_3$ (10 mL) and kept it at 0 °C for 30 min, and extracted with DCM (10 mL x 3). The combined organic layers were dried over Na_2SO_4, concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel using ethyl acetate/hexane (2:8) as eluant to give **3.35** (1.8 g, 93%) as a turbid oil.

$[\alpha]_D^{20}$ 102.7 (c 1, $CHCl_3$).

^{1}H NMR (400 MHz $CDCl_3$): δ 7.90 (d, *J* = 8.5 Hz, 2H), 7.66 (d, *J* = 6.7 Hz, 3H), 7.56 – 7.32 (m, 7H), 7.35 – 7.23 (m, 3H), 7.17 (t, *J* = 7.9 Hz, 1H), 6.92 (dd, *J* = 8.4, 14.9 Hz, 3H), 6.81 (s, 1H), 6.65 (dd, *J* = 1.9, 8.1 Hz, 1H) 5.65 (s, 1H), 5.32 (s, 1H), 5.04 (m, 1H), 4.98 (q, *J* = 7.2 Hz, 1H), 4.91 (s, 1H), 4.48 (d, *J* = 9.2 Hz, 1H), 4.43 – 4.33 (m, 1H), 4.16 (d, *J* = 11.2 Hz, 1H), 3.97 (d, *J* = 6.6 Hz, 1H), 3.87 (s, 3H), 3.84 (d, *J* = 11.1 Hz, 1H), 2.11 (s, 3H), 1.61 (d, *J* = 6.5 Hz, 4H), 1.19 (s, 3H), 1.12 (s, 9H).

^{13}C NMR (100 MHz $CDCl_3$): δ 164.3, 162.4, 135.7, 132.0, 131.6, 130.8, 130.6, 130.5, 128.2, 120.2, 113.7, 83.7, 81.0, 78.5, 62.8, 62.7, 62.5, 55.5, 27.0, 19.2, 17.7.

HRMS (ESI) calc. for $C_{33}H_{39}N_4O_5$: [M+H$^+$], 599.26842; found: [M+H$^+$], 599.26858.



(4*S*,5*R*,6*R*,7*S*,8*S*,9*S*)-9-Azido-7-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2-(4-methoxyphenyl)-4,6-dimethyl-8-((3-(prop-1-en-2-yl)phenyl)amino)-3-oxa-1-azaspiro[4.4]non-1-ene-6,7-diol

To a stirred solution of epoxyalcohol **3.35** (1.75 g, 2.9 mmol) in toluene (50 mL) at rt, the aniline derivative (3.9 g, 29.3 mmol, 10 equiv.) and $Yb(OTf)_3$ (0.91 g, 1.5 mmol, 0.50 equiv.) were added and heated at 80 ^{o}C for 5 h. The reaction mixture was cooled to rt, quenched with water (10 mL) and extracted with DCM (10 mL x 3). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography using ethyl acetate/hexane (3:17) as eluant to afford the amino alcohol **3.36** (1.55 g, 72%) as a pale yellow viscous liquid.

$[\alpha]_D^{20}$ 6.7 (c 1, $CHCl_3$).

^{1}H NMR (400 MHz $CDCl_3$): δ 7.90 (d, *J* = 8.5 Hz, 2H), 7.66 (d, *J* = 6.7 Hz, 3H), 7.56 – 7.32 (m, 7H), 7.35 – 7.23 (m, 3H), 7.17 (t, *J* = 7.9 Hz, 1H), 6.92 (dd, *J* = 8.4, 14.9 Hz, 3H), 6.81 (s, 1H), 6.65 (dd, *J* = 1.9, 8.1 Hz, 1H) 5.65 (s, 1H), 5.32 (s, 1H), 5.04 (m, 1H), 4.98 (q, *J* = 7.2 Hz, 1H), 4.91 (s, 1H), 4.48 (d, *J* = 9.2 Hz, 1H), 4.43 – 4.33 (m, 1H), 4.16 (d, *J* = 11.2 Hz, 1H), 3.97 (d, *J* = 6.6 Hz, 1H), 3.87 (s, 3H), 3.84 (d, *J* = 11.1 Hz, 1H), 2.11 (s, 3H), 1.61 (d, *J* = 6.5 Hz, 4H), 1.19 (s, 3H), 1.12 (s, 9H).

^{13}C NMR (100 MHz $CDCl_3$) δ 164.3, 162.9, 147.2, 143.8, 142.7, 136.0, 135.8, 131.3, 130.7, 130.5, 130.2, 129.5, 128.2, 128.1, 119.2, 115.6, 114.0, 112.3, 112.2, 111.0, 84.8, 80.4, 78.9, 71.2, 68.3, 66.7, 55.6, 27.1, 22.0, 19.2, 17.6, 17.3.

HRMS (ESI) calc. for $C_{42}H_{50}N_5O_5Si$: [M+H^+], 732.35757; found: [M+H^+], 732.35788.

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Annex

Crystallographic Data

Université de Montréal

CRYSTAL AND MOLECULAR STRUCTURE OF

C12 H15 N O2 COMPOUND (HAN435)

Saturday, March 06, 2010

Equipe Hanessian

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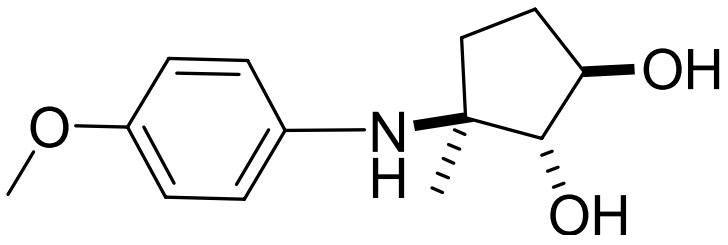


Structure solved and refined in the laboratory of X-ray diffraction
Université de Montréal by Michel Simard.

Table 1. Crystal data and structure refinement for C12 H15 N O2.

Identification code	HAN435
Empirical formula	C12 H15 N O2
Formula weight	205.25
Temperature	220(2)K
Wavelength	1.54178 Å
Crystal system	Triclinic
Space group	P-1
Unit cell dimensions	a = 6.6735(4) Å α = 101.109(3)° b = 7.6585(5) Å β = 96.392(3)° c = 13.2130(8) Å γ = 112.598(3)°
Volume	598.83(6)Å^3
Z	2
Density (calculated)	1.138 g/cm^3
Absorption coefficient	0.624 mm^{-1}
F(000)	220
Crystal size	0.32 x 0.19 x 0.10 mm
Theta range for data collection	3.48 to 71.87°
Index ranges	$-6 \leq h \leq 7$, $-9 \leq k \leq 9$, $-16 \leq \ell \leq 16$
Reflections collected	6828
Independent reflections	2243 [R_{int} = 0.047]
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9400 and 0.5700
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2243 / 0 / 162
Goodness-of-fit on F^2	1.067
Final R indices [I>2sigma(I)]	R_1 = 0.0545, wR_2 = 0.1473
R indices (all data)	R_1 = 0.0574, wR_2 = 0.1517
Largest diff. peak and hole	0.282 and -0.319 e/Å^3

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^2 x 10^3) for C12 H15 N O2.

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

	x	y	z	U_{eq}
O(1)	3050(2)	-2106(1)	152(1)	25(1)
O(2)	-2085(2)	-4126(1)	-328(1)	29(1)
O(3)	9302(2)	7806(2)	5106(1)	39(1)
N(1)	4019(2)	1967(2)	1463(1)	22(1)
C(1)	2465(2)	87(2)	1631(1)	20(1)
C(2)	1537(2)	-1402(2)	546(1)	19(1)
C(3)	-633(2)	-2962(2)	659(1)	23(1)
C(4)	-1588(2)	-1816(2)	1398(1)	27(1)
C(5)	350(2)	187(2)	1950(1)	26(1)
C(6)	3599(2)	-657(2)	2410(1)	28(1)
C(7)	5418(2)	3460(2)	2385(1)	22(1)
C(8)	7687(2)	4023(2)	2598(1)	26(1)
C(9)	9060(2)	5488(2)	3488(1)	28(1)
C(10)	8141(2)	6399(2)	4187(1)	27(1)
C(11)	5877(3)	5875(2)	3969(1)	38(1)
C(12)	4528(3)	4433(2)	3079(1)	37(1)
C(13)	11649(3)	8545(2)	5295(1)	40(1)

Table 3. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^2 x 10^3) for C12 H15 N O2.

	x	y	z	U_{eq}
H(1)	2900	-3124	330	37
H(2)	-2603	-3457	-599	43
H(1A)	4960(30)	1690(30)	1078(15)	32(4)
H(2A)	1144	-726	42	23
H(3)	-265	-3843	1027	27
H(4A)	-2177	-2521	1919	32
H(4B)	-2787	-1636	995	32
H(5A)	88	1241	1724	31
H(5B)	500	438	2717	31
H(6A)	4885	-760	2175	42
H(6B)	2568	-1933	2447	42
H(6C)	4064	251	3101	42
H(8)	8318	3401	2131	31
H(9)	10599	5857	3613	34
H(11)	5250	6509	4431	45
H(12)	2997	4106	2941	44
H(13A)	12096	7499	5360	60
H(13B)	12277	9582	5943	60
H(13C)	12178	9058	4713	60

Table 4. Anisotropic parameters ($Å^2$ x 10^3) for C12 H15 N O2.

The anisotropic displacement factor exponent takes the form:

$$-2\pi^2 [h^2 a^{*2} U_{11} + ... + 2 h k a^* b^* U_{12}]$$

	U11	U22	U33	U23	U13	U12
O(1)	28(1)	21(1)	28(1)	7(1)	13(1)	10(1)
O(2)	26(1)	20(1)	33(1)	3(1)	-5(1)	7(1)
O(3)	38(1)	37(1)	26(1)	-6(1)	-1(1)	7(1)
N(1)	23(1)	20(1)	19(1)	3(1)	5(1)	6(1)
C(1)	21(1)	20(1)	17(1)	5(1)	4(1)	7(1)
C(2)	22(1)	19(1)	17(1)	5(1)	4(1)	9(1)
C(3)	21(1)	20(1)	25(1)	6(1)	2(1)	7(1)
C(4)	22(1)	28(1)	31(1)	10(1)	9(1)	10(1)
C(5)	25(1)	30(1)	24(1)	4(1)	8(1)	12(1)
C(6)	29(1)	31(1)	22(1)	10(1)	2(1)	12(1)
C(7)	26(1)	20(1)	19(1)	4(1)	4(1)	7(1)
C(8)	28(1)	25(1)	23(1)	5(1)	6(1)	11(1)
C(9)	25(1)	28(1)	28(1)	6(1)	2(1)	8(1)
C(10)	32(1)	22(1)	20(1)	3(1)	2(1)	5(1)
C(11)	33(1)	35(1)	35(1)	-7(1)	9(1)	11(1)
C(12)	25(1)	35(1)	39(1)	-7(1)	6(1)	9(1)
C(13)	37(1)	37(1)	30(1)	2(1)	-7(1)	6(1)

Table 5. Bond lengths [Å] and angles [°] for C12 H15 N O2

O(1)-C(2)	1.4175(15)	C(6)-C(1)-C(2)	110.83(10)
O(2)-C(3)	1.4285(15)	N(1)-C(1)-C(5)	112.87(10)
O(3)-C(10)	1.3708(16)	C(6)-C(1)-C(5)	111.18(11)
O(3)-C(13)	1.419(2)	C(2)-C(1)-C(5)	102.18(10)
N(1)-C(7)	1.4324(16)	O(1)-C(2)-C(3)	115.65(10)
N(1)-C(1)	1.4915(15)	O(1)-C(2)-C(1)	114.75(10)
C(1)-C(6)	1.5299(17)	C(3)-C(2)-C(1)	105.01(10)
C(1)-C(2)	1.5391(16)	O(2)-C(3)-C(2)	113.37(10)
C(1)-C(5)	1.5422(18)	O(2)-C(3)-C(4)	115.00(11)
C(2)-C(3)	1.5275(17)	C(2)-C(3)-C(4)	104.37(10)
C(3)-C(4)	1.5392(18)	C(3)-C(4)-C(5)	106.43(10)
C(4)-C(5)	1.5467(19)	C(1)-C(5)-C(4)	106.76(10)
C(7)-C(8)	1.383(2)	C(8)-C(7)-C(12)	118.01(12)
C(7)-C(12)	1.3961(19)	C(8)-C(7)-N(1)	121.39(12)
C(8)-C(9)	1.3937(19)	C(12)-C(7)-N(1)	120.57(12)
C(9)-C(10)	1.387(2)	C(7)-C(8)-C(9)	121.66(13)
C(10)-C(11)	1.385(2)	C(10)-C(9)-C(8)	119.60(13)
C(11)-C(12)	1.382(2)	O(3)-C(10)-C(11)	115.79(13)
		O(3)-C(10)-C(9)	125.07(14)
C(10)-O(3)-C(13)	117.33(12)	C(11)-C(10)-C(9)	119.14(13)
C(7)-N(1)-C(1)	116.86(10)	C(12)-C(11)-C(10)	120.92(14)
N(1)-C(1)-C(6)	112.28(10)	C(11)-C(12)-C(7)	120.61(14)
N(1)-C(1)-C(2)	106.95(9)		

Table 6. Torsion angles [°] for C12 H15 N O2.

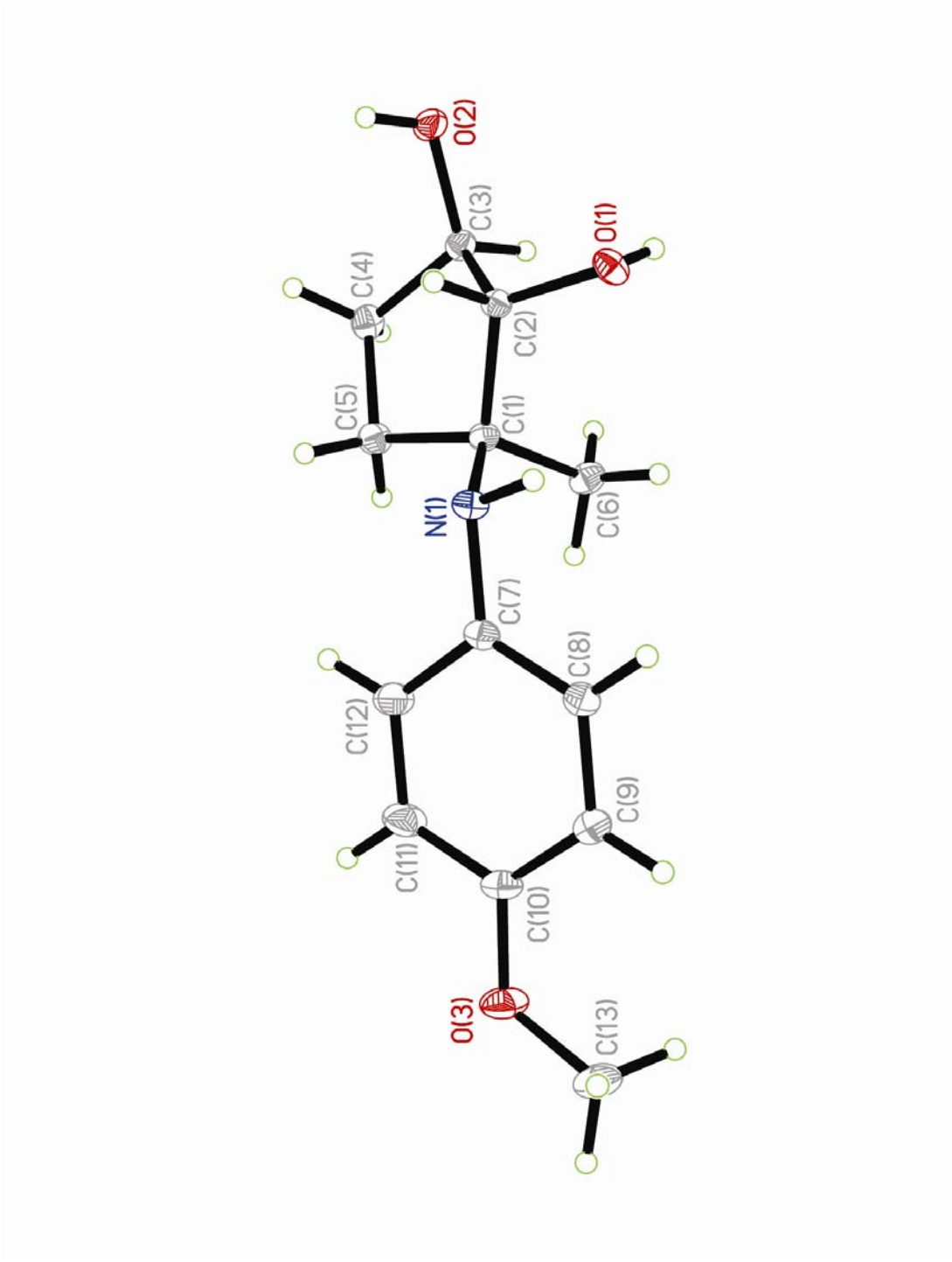
C(7)-N(1)-C(1)-C(6)	-46.15(15)	C(2)-C(1)-C(5)-C(4)	27.94(13)
C(7)-N(1)-C(1)-C(2)	-167.94(10)	C(3)-C(4)-C(5)-C(1)	-6.86(14)
C(7)-N(1)-C(1)-C(5)	80.47(13)	C(1)-N(1)-C(7)-C(8)	111.61(14)
N(1)-C(1)-C(2)-O(1)	73.96(12)	C(1)-N(1)-C(7)-C(12)	-70.40(17)
C(6)-C(1)-C(2)-O(1)	-48.73(14)	C(12)-C(7)-C(8)-C(9)	1.3(2)
C(5)-C(1)-C(2)-O(1)	-167.25(10)	N(1)-C(7)-C(8)-C(9)	179.32(12)
N(1)-C(1)-C(2)-C(3)	-157.93(10)	C(7)-C(8)-C(9)-C(10)	0.7(2)
C(6)-C(1)-C(2)-C(3)	79.37(12)	C(13)-O(3)-C(10)-C(11)	-172.79(14)
C(5)-C(1)-C(2)-C(3)	-39.15(12)	C(13)-O(3)-C(10)-C(9)	7.6(2)
O(1)-C(2)-C(3)-O(2)	-71.19(13)	C(8)-C(9)-C(10)-O(3)	177.58(12)
C(1)-C(2)-C(3)-O(2)	161.25(10)	C(8)-C(9)-C(10)-C(11)	-2.1(2)
O(1)-C(2)-C(3)-C(4)	162.93(10)	O(3)-C(10)-C(11)-C(12)	-178.21(15)
C(1)-C(2)-C(3)-C(4)	35.38(12)	C(9)-C(10)-C(11)-C(12)	1.5(2)
O(2)-C(3)-C(4)-C(5)	-142.16(11)	C(10)-C(11)-C(12)-C(7)	0.5(3)
C(2)-C(3)-C(4)-C(5)	-17.32(13)	C(8)-C(7)-C(12)-C(11)	-1.9(2)
N(1)-C(1)-C(5)-C(4)	142.45(11)	N(1)-C(7)-C(12)-C(11)	-179.95(14)
C(6)-C(1)-C(5)-C(4)	-90.34(13)		

Table 7. Bond lengths [Å] and angles [°] related to the hydrogen bonding for C12 H15 N O2.

D-H	..A	d(D-H)	d(H..A)	d(D..A)	<DHA
O(1)-H(1)	O(2)#1	0.83	1.96	2.7676(13)	163.4
O(2)-H(2)	N(1)#2	0.83	2.14	2.9686(15)	173.5
N(1)-H(1A)	O(1)#3	0.91(2)	2.20(2)	3.0405(14)	152.50(16)

Symmetry transformations used to generate equivalent atoms:

#1 -x,-y-1,-z #2 -x,-y,-z #3 -x+1,-y,-z



ORTEP view of the C12 H15 N 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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Université de Montréal

CRYSTAL AND MOLECULAR STRUCTURE OF

C19 H22 Cl N O2 COMPOUND (han446)

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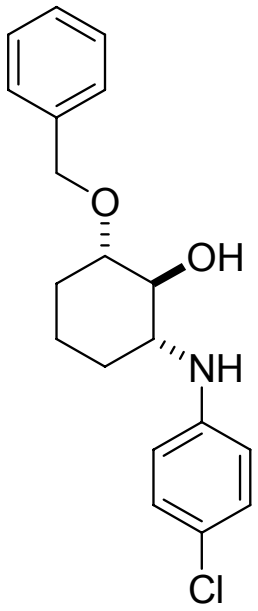


Structure solved and refined in the laboratory of X-ray diffraction Université de Montréal by Benoît Deschênes Simard.

Table 1. Crystal data and structure refinement for C19 H22 Cl N O2.

Identification code	han446
Empirical formula	C19 H22 Cl N O2
Formula weight	331.83
Temperature	100(2)K
Wavelength	1.54178 Å
Crystal system	Monoclinic
Space group	C2/c
Unit cell dimensions	a = 33.7807(4) Å α = 90° b = 5.7461(1) Å β = 133.992(1)° c = 24.1148(3) Å γ = 90°
Volume	3367.58(10)Å^3
Z	8
Density (calculated)	1.309 g/cm^3
Absorption coefficient	2.077 mm^{-1}
F(000)	1408
Crystal size	0.13 x 0.09 x 0.06 mm
Theta range for data collection	3.64 to 67.86°
Index ranges	$-40 \le h \le 40$, $-6 \le k \le 6$, $-27 \le \ell \le 26$
Reflections collected	26556
Independent reflections	2813 [R_{int} = 0.032]
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.8828 and 0.8382
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2813 / 0 / 216
Goodness-of-fit on F^2	1.063
Final R indices [I>2sigma(I)]	R_1 = 0.0304, wR_2 = 0.0845
R indices (all data)	R_1 = 0.0320, wR_2 = 0.0857
Largest diff. peak and hole	0.278 and -0.243 e/Å^3

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^2 x 10^3) for C19 H22 Cl N O2.

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

	x	y	z	U_{eq}
Cl(1)	10439(1)	12602(1)	1127(1)	32(1)
O(1)	7519(1)	3904(1)	741(1)	24(1)
O(2)	7938(1)	5125(2)	92(1)	24(1)
N(1)	9023(1)	6203(2)	1044(1)	25(1)
C(1)	7941(1)	5651(2)	1099(1)	20(1)
C(2)	8267(1)	5047(2)	895(1)	20(1)
C(3)	8734(1)	6808(2)	1273(1)	21(1)
C(4)	9107(1)	6795(2)	2142(1)	27(1)
C(5)	8781(1)	7420(2)	2347(1)	28(1)
C(6)	8304(1)	5716(2)	1959(1)	25(1)
C(7)	7066(1)	4568(2)	648(1)	25(1)
C(8)	6962(1)	2815(2)	1000(1)	22(1)
C(9)	7335(1)	1097(2)	1506(1)	26(1)
C(10)	7215(1)	-491(2)	1807(1)	31(1)
C(11)	6716(1)	-383(2)	1599(1)	33(1)
C(12)	6345(1)	1352(3)	1103(1)	37(1)
C(13)	6464(1)	2939(3)	804(1)	30(1)
C(14)	9334(1)	7813(2)	1051(1)	22(1)
C(15)	9516(1)	7198(2)	696(1)	24(1)
C(16)	9849(1)	8661(2)	715(1)	24(1)
C(17)	10004(1)	10787(2)	1087(1)	24(1)
C(18)	9819(1)	11472(2)	1424(1)	23(1)
C(19)	9484(1)	9994(2)	1404(1)	22(1)

Table 3. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^2 x 10^3) for C19 H22 Cl N O2.

	x	y	z	U_{eq}
H(2)	7753(7)	3830(30)	-120(11)	46(5)
H(1)	8830(6)	5250(30)	640(10)	27(4)
H(1A)	7764	7207	876	24
H(2A)	8426	3453	1090	24
H(3)	8571	8397	1072	26
H(4A)	9408	7932	2382	32
H(4B)	9273	5233	2348	32
H(5A)	9026	7357	2913	34
H(5B)	8636	9025	2173	34
H(6A)	8451	4139	2175	30
H(6B)	8082	6191	2069	30
H(7A)	6731	4728	92	30
H(7B)	7145	6102	894	30
H(9)	7677	1002	1649	32
H(10)	7476	-1655	2157	37
H(11)	6630	-1489	1795	40
H(12)	6006	1456	967	44
H(13)	6206	4121	463	36
H(15)	9409	5745	438	29
H(16)	9971	8215	475	29
H(18)	9921	12947	1668	28
H(19)	9355	10472	1633	27

Table 4. Anisotropic parameters ($Å^2$ x 10^3) for C19 H22 Cl N O2.

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
Cl(1)	32(1)	30(1)	41(1)	0(1)	28(1)	-6(1)
O(1)	24(1)	23(1)	29(1)	-5(1)	20(1)	-6(1)
O(2)	29(1)	24(1)	20(1)	-3(1)	17(1)	-6(1)
N(1)	28(1)	22(1)	33(1)	-5(1)	24(1)	-5(1)
C(1)	22(1)	18(1)	21(1)	-1(1)	15(1)	-3(1)
C(2)	22(1)	20(1)	19(1)	1(1)	14(1)	-1(1)
C(3)	22(1)	20(1)	24(1)	0(1)	16(1)	-1(1)
C(4)	22(1)	29(1)	24(1)	1(1)	14(1)	-3(1)
C(5)	28(1)	33(1)	19(1)	-4(1)	15(1)	-6(1)
C(6)	26(1)	28(1)	24(1)	-1(1)	18(1)	-3(1)
C(7)	23(1)	27(1)	28(1)	1(1)	19(1)	0(1)
C(8)	24(1)	25(1)	19(1)	-6(1)	15(1)	-6(1)
C(9)	32(1)	26(1)	29(1)	-1(1)	24(1)	1(1)
C(10)	46(1)	25(1)	33(1)	1(1)	32(1)	3(1)
C(11)	48(1)	33(1)	33(1)	-7(1)	34(1)	-11(1)
C(12)	31(1)	52(1)	34(1)	-3(1)	25(1)	-9(1)
C(13)	24(1)	41(1)	25(1)	2(1)	17(1)	-1(1)
C(14)	19(1)	21(1)	22(1)	3(1)	14(1)	2(1)
C(15)	25(1)	22(1)	25(1)	-1(1)	17(1)	1(1)
C(16)	24(1)	28(1)	25(1)	4(1)	18(1)	4(1)
C(17)	20(1)	24(1)	26(1)	5(1)	15(1)	0(1)
C(18)	21(1)	22(1)	22(1)	0(1)	13(1)	-1(1)
C(19)	21(1)	24(1)	22(1)	1(1)	15(1)	1(1)

Table 5. Bond lengths [Å] and angles [°] for C19 H22 Cl N O2

Cl(1)-C(17)	1.7497(12)	C(6)-C(1)-C(2)	111.74(10)
O(1)-C(7)	1.4352(14)	O(2)-C(2)-C(1)	112.18(9)
O(1)-C(1)	1.4407(14)	O(2)-C(2)-C(3)	107.42(10)
O(2)-C(2)	1.4118(17)	C(1)-C(2)-C(3)	109.52(10)
N(1)-C(14)	1.3917(16)	N(1)-C(3)-C(4)	112.86(10)
N(1)-C(3)	1.4577(16)	N(1)-C(3)-C(2)	107.52(10)
C(1)-C(6)	1.509(2)	C(4)-C(3)-C(2)	110.01(11)
C(1)-C(2)	1.5246(17)	C(3)-C(4)-C(5)	110.52(10)
C(2)-C(3)	1.5320(16)	C(6)-C(5)-C(4)	110.02(11)
C(3)-C(4)	1.520(2)	C(1)-C(6)-C(5)	111.16(11)
C(4)-C(5)	1.5298(19)	O(1)-C(7)-C(8)	112.04(10)
C(5)-C(6)	1.5295(17)	C(9)-C(8)-C(13)	118.66(12)
C(7)-C(8)	1.5077(18)	C(9)-C(8)-C(7)	123.15(11)
C(8)-C(9)	1.3838(19)	C(13)-C(8)-C(7)	118.19(12)
C(8)-C(13)	1.3971(18)	C(8)-C(9)-C(10)	120.75(12)
C(9)-C(10)	1.3901(19)	C(11)-C(10)-C(9)	120.24(13)
C(10)-C(11)	1.386(2)	C(12)-C(11)-C(10)	119.33(13)
C(11)-C(12)	1.383(2)	C(11)-C(12)-C(13)	120.50(13)
C(12)-C(13)	1.385(2)	C(12)-C(13)-C(8)	120.48(13)
C(14)-C(19)	1.3982(18)	N(1)-C(14)-C(19)	123.64(12)
C(14)-C(15)	1.4041(19)	N(1)-C(14)-C(15)	118.25(11)
C(15)-C(16)	1.3789(18)	C(19)-C(14)-C(15)	118.09(11)
C(16)-C(17)	1.3862(19)	C(16)-C(15)-C(14)	121.34(12)
C(17)-C(18)	1.3813(19)	C(15)-C(16)-C(17)	119.37(12)
C(18)-C(19)	1.3906(17)	C(18)-C(17)-C(16)	120.73(11)
		C(18)-C(17)-CL1	120.23(10)
C(7)-O(1)-C(1)	114.33(9)	C(16)-C(17)-CL1	119.04(10)
C(14)-N(1)-C(3)	122.35(10)	C(17)-C(18)-C(19)	119.79(12)
O(1)-C(1)-C(6)	111.21(10)	C(18)-C(19)-C(14)	120.62(12)
O(1)-C(1)-C(2)	106.50(9)		

Table 6. Torsion angles [°] for C19 H22 Cl N O2.

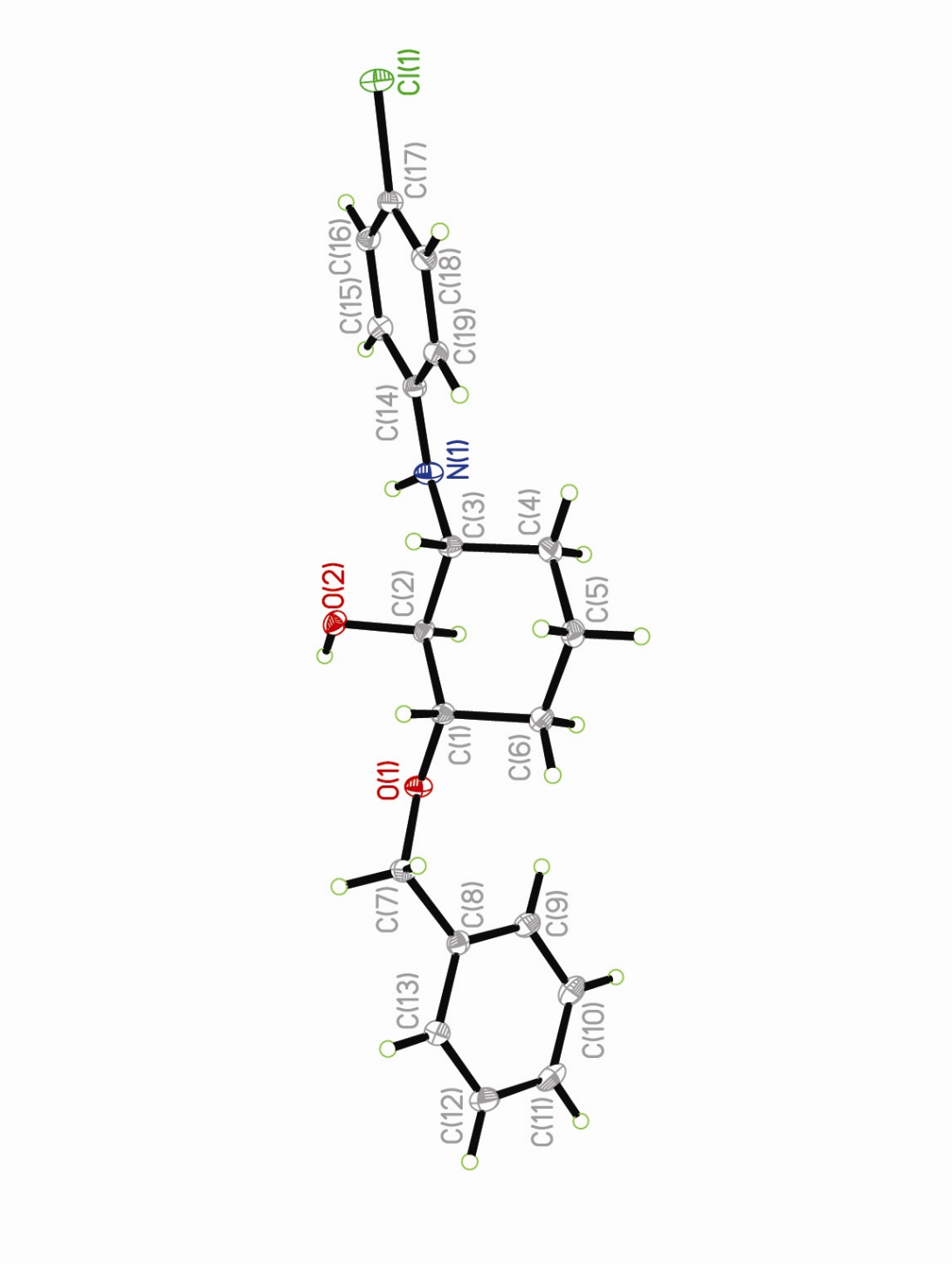
C(7)-O(1)-C(1)-C(6)	77.62(12)	C(13)-C(8)-C(9)-C(10)	0.7(2)
C(7)-O(1)-C(1)-C(2)	-160.41(10)	C(7)-C(8)-C(9)-C(10)	-179.33(13)
O(1)-C(1)-C(2)-O(2)	62.10(12)	C(8)-C(9)-C(10)-C(11)	0.4(2)
C(6)-C(1)-C(2)-O(2)	-176.27(9)	C(9)-C(10)-C(11)-C(12)	-1.5(2)
O(1)-C(1)-C(2)-C(3)	-178.72(9)	C(10)-C(11)-C(12)-C(13)	1.3(2)
C(6)-C(1)-C(2)-C(3)	-57.09(13)	C(11)-C(12)-C(13)-C(8)	-0.1(2)
C(14)-N(1)-C(3)-C(4)	-81.32(15)	C(9)-C(8)-C(13)-C(12)	-0.9(2)
C(14)-N(1)-C(3)-C(2)	157.18(12)	C(7)-C(8)-C(13)-C(12)	179.17(14)
O(2)-C(2)-C(3)-N(1)	-56.31(12)	C(3)-N(1)-C(14)-C(19)	12.3(2)
C(1)-C(2)-C(3)-N(1)	-178.39(10)	C(3)-N(1)-C(14)-C(15)	-168.98(12)
O(2)-C(2)-C(3)-C(4)	-179.58(10)	N(1)-C(14)-C(15)-C(16)	-176.70(12)
C(1)-C(2)-C(3)-C(4)	58.34(13)	C(19)-C(14)-C(15)-C(16)	2.10(19)
N(1)-C(3)-C(4)-C(5)	-179.48(10)	C(14)-C(15)-C(16)-C(17)	-0.41(19)
C(2)-C(3)-C(4)-C(5)	-59.40(13)	C(15)-C(16)-C(17)-C(18)	-1.35(19)
C(3)-C(4)-C(5)-C(6)	57.55(14)	C(15)-C(16)-C(17)-CL1	178.55(10)
O(1)-C(1)-C(6)-C(5)	175.05(10)	C(16)-C(17)-C(18)-C(19)	1.36(19)
C(2)-C(1)-C(6)-C(5)	56.18(13)	CL1-C(17)-C(18)-C(19)	-178.54(9)
C(4)-C(5)-C(6)-C(1)	-55.66(14)	C(17)-C(18)-C(19)-C(14)	0.40(19)
C(1)-O(1)-C(7)-C(8)	-125.86(11)	N(1)-C(14)-C(19)-C(18)	176.65(12)
O(1)-C(7)-C(8)-C(9)	14.56(18)	C(15)-C(14)-C(19)-C(18)	-2.08(19)
O(1)-C(7)-C(8)-C(13)	-165.51(12)		

Table 7. Bond lengths [Å] and angles [°] related to the hydrogen bonding for C19 H22 Cl N O2.

D-H	..A	d(D-H)	d(H..A)	d(D..A)	<DHA
O(2)-H(2)	O(1)#1	0.871(19)	1.91(2)	2.7329(12)	156.9(18)

Symmetry transformations used to generate equivalent atoms:

#1 -x+3/2,-y+1/2,-z



ORTEP view of the C19 H22 Cl N O2 compound with the numbering scheme adopted. Ellipsoids drawn at 50% probability level. Hydrogen atoms are represented by sphere of arbitrary size.

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Université de Montréal

CRYSTAL AND MOLECULAR STRUCTURE OF

C12 H15 Cl N4 O COMPOUND (bent42)

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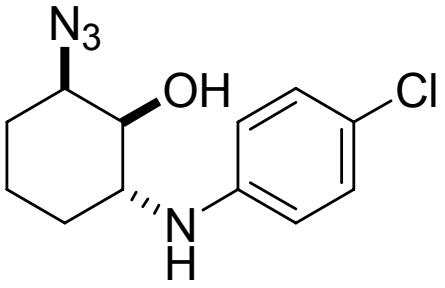


Structure solved and refined in the laboratory of X-ray diffraction Université de Montréal by Benoît Deschênes Simard.

Table 1. Crystal data and structure refinement for C12 H15 Cl N4 O.

Identification code	bent42
Empirical formula	C12 H15 Cl N4 O
Formula weight	266.73
Temperature	150K
Wavelength	1.54178 Å
Crystal system	Monoclinic
Space group	P21/c
Unit cell dimensions	a = 23.9893(4) Å α = 90° b = 5.0402(1) Å β = 117.471(1)° c = 23.3512(4) Å γ = 90°
Volume	2505.06(8)Å^3
Z	8
Density (calculated)	1.414 g/cm^3
Absorption coefficient	2.659 mm^{-1}
F(000)	1120
Crystal size	0.21 x 0.14 x 0.09 mm
Theta range for data collection	2.08 to 72.40°
Index ranges	$-29 \leq h \leq 29$, $-6 \leq k \leq 6$, $-28 \leq \ell \leq 28$
Reflections collected	27674
Independent reflections	4911 [R_{int} = 0.043]
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.7872 and 0.4873
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4911 / 1 / 335
Goodness-of-fit on F^2	0.983
Final R indices [I>2sigma(I)]	R_1 = 0.0461, wR_2 = 0.1214
R indices (all data)	R_1 = 0.0598, wR_2 = 0.1274
Largest diff. peak and hole	0.733 and -0.307 e/Å^3

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for C12 H15 Cl N4 O.

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

	x	y	z	U_{eq}
Cl(1)	3002(1)	12607(1)	11511(1)	34(1)
C(11)	4297(1)	7401(4)	8459(1)	24(1)
C(12)	4448(1)	6826(4)	9160(1)	21(1)
C(13)	3975(1)	8140(4)	9342(1)	21(1)
C(14)	3311(1)	7187(4)	8876(1)	26(1)
C(15)	3149(1)	7930(4)	8184(1)	28(1)
C(16)	3619(1)	6702(5)	7987(1)	28(1)
C(17)	3853(1)	8712(4)	10341(1)	21(1)
C(18)	3454(1)	10903(4)	10100(1)	23(1)
C(19)	3195(1)	12106(4)	10461(1)	25(1)
C(110)	3332(1)	11104(5)	11062(1)	25(1)
C(111)	3724(1)	8935(5)	11311(1)	28(1)
C(112)	3980(1)	7731(4)	10952(1)	24(1)
N(11)	4422(1)	10295(4)	8428(1)	28(1)
N(12)	4522(1)	10858(4)	7965(1)	28(1)
N(13)	4618(1)	11598(4)	7558(1)	39(1)
N(14)	4162(1)	7592(3)	10020(1)	23(1)
O(11)	5083(1)	7454(3)	9591(1)	23(1)
Cl(2)	1994(1)	2335(1)	3392(1)	34(1)
C(21)	697(1)	7648(4)	-878(1)	23(1)
C(22)	549(1)	8211(4)	-319(1)	21(1)
C(23)	1028(1)	6913(4)	312(1)	21(1)
C(24)	1689(1)	7894(4)	465(1)	25(1)
C(25)	1847(1)	7163(4)	-78(1)	27(1)
C(26)	1371(1)	8381(4)	-716(1)	28(1)
C(27)	1148(1)	6301(4)	1422(1)	21(1)
C(28)	1552(1)	4118(4)	1560(1)	24(1)
C(29)	1809(1)	2906(4)	2161(1)	24(1)
C(210)	1665(1)	3854(4)	2631(1)	25(1)
C(211)	1267(1)	6006(5)	2508(1)	27(1)
C(212)	1015(1)	7233(4)	1913(1)	24(1)
N(21)	576(1)	4746(4)	-1028(1)	27(1)
N(22)	479(1)	4185(4)	-1584(1)	28(1)
N(23)	380(1)	3444(4)	-2082(1)	40(1)
N(24)	846(1)	7451(4)	815(1)	24(1)
O(21)	-83(1)	7537(3)	-484(1)	24(1)

Table 3. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^2 x 10^3) for C12 H15 Cl N4 O.

	x	y	z	U_{eq}
H(11A)	4587	6346	8348	28
H(12)	4402	4867	9192	26
H(13)	3994	10102	9289	25
H(14A)	3287	5237	8910	31
H(14B)	3004	8004	8994	31
H(15A)	3153	9885	8145	33
H(15B)	2720	7296	7889	33
H(16A)	3570	4749	7966	34
H(16B)	3525	7340	7551	34
H(18)	3357	11581	9685	28
H(19)	2927	13602	10295	30
H(111)	3816	8272	11727	33
H(112)	4245	6226	11121	29
H(11)	5151	9060	9549	35
H(14C)	4315(12)	6070(50)	10154(12)	34(7)
H(21A)	403	8694	-1263	28
H(22)	588	10172	-245	25
H(23)	1013	4950	243	25
H(24A)	1710	9844	521	30
H(24B)	2002	7087	874	30
H(25A)	1844	5209	-121	32
H(25B)	2273	7811	29	32
H(26A)	1462	7756	-1066	34
H(26B)	1416	10336	-690	34
H(28)	1651	3457	1237	28
H(29)	2083	1431	2248	29
H(211)	1168	6639	2834	32
H(212)	748	8727	1834	28
H(21)	-134	5895	-547	36
H(24C)	684(12)	8940(50)	801(12)	31(7)

Table 4. Anisotropic parameters ($Å^2$ x 10^3) for C12 H15 Cl N4 O.

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
Cl(1)	33(1)	41(1)	36(1)	-4(1)	22(1)	5(1)
C(11)	30(1)	19(1)	26(1)	-2(1)	16(1)	1(1)
C(12)	22(1)	19(1)	24(1)	1(1)	11(1)	-1(1)
C(13)	21(1)	22(1)	21(1)	0(1)	10(1)	-1(1)
C(14)	20(1)	27(1)	28(1)	-3(1)	10(1)	-3(1)
C(15)	23(1)	29(1)	26(1)	-1(1)	7(1)	-2(1)
C(16)	36(1)	26(1)	23(1)	-4(1)	13(1)	-2(1)
C(17)	19(1)	20(1)	22(1)	0(1)	9(1)	-2(1)
C(18)	25(1)	23(1)	22(1)	2(1)	12(1)	2(1)
C(19)	21(1)	25(1)	29(1)	0(1)	12(1)	1(1)
C(110)	22(1)	31(1)	27(1)	-5(1)	14(1)	-1(1)
C(111)	32(1)	31(1)	23(1)	2(1)	15(1)	1(1)
C(112)	26(1)	22(1)	23(1)	3(1)	11(1)	1(1)
N(11)	39(1)	22(1)	29(1)	1(1)	21(1)	0(1)
N(12)	30(1)	25(1)	29(1)	3(1)	14(1)	1(1)
N(13)	48(1)	43(1)	33(1)	8(1)	23(1)	-2(1)
N(14)	25(1)	20(1)	25(1)	3(1)	14(1)	6(1)
O(11)	19(1)	19(1)	30(1)	2(1)	10(1)	0(1)
Cl(2)	33(1)	41(1)	25(1)	7(1)	11(1)	7(1)
C(21)	30(1)	17(1)	23(1)	1(1)	12(1)	0(1)
C(22)	21(1)	19(1)	22(1)	0(1)	9(1)	1(1)
C(23)	21(1)	21(1)	21(1)	0(1)	9(1)	2(1)
C(24)	22(1)	25(1)	27(1)	-1(1)	9(1)	-1(1)
C(25)	21(1)	27(1)	33(1)	1(1)	13(1)	0(1)
C(26)	35(1)	24(1)	31(1)	1(1)	20(1)	-1(1)
C(27)	19(1)	20(1)	23(1)	-1(1)	9(1)	-2(1)
C(28)	25(1)	23(1)	23(1)	-2(1)	12(1)	2(1)
C(29)	22(1)	24(1)	25(1)	-1(1)	10(1)	2(1)
C(210)	21(1)	29(1)	21(1)	1(1)	8(1)	0(1)
C(211)	28(1)	31(1)	22(1)	-4(1)	13(1)	0(1)
C(212)	24(1)	22(1)	25(1)	-2(1)	11(1)	2(1)
N(21)	38(1)	22(1)	23(1)	-1(1)	15(1)	0(1)
N(22)	30(1)	25(1)	29(1)	-3(1)	15(1)	1(1)
N(23)	49(1)	43(1)	33(1)	-12(1)	23(1)	-2(1)
N(24)	27(1)	23(1)	23(1)	1(1)	12(1)	7(1)
O(21)	19(1)	20(1)	31(1)	-1(1)	9(1)	1(1)

Table 5. Bond lengths [Å] and angles [°] for C12 H15 Cl N4 O

Cl(1)-C(110)	1.751(2)	N(14)-C(13)-C(12)	108.84(17)
C(11)-N(11)	1.498(3)	N(14)-C(13)-C(14)	114.19(17)
		C(12)-C(13)-C(14)	109.02(17)
C(11)-C(16)	1.527(3)	C(15)-C(14)-C(13)	110.52(18)
C(11)-C(12)	1.532(3)	C(14)-C(15)-C(16)	110.79(18)
C(12)-O(11)	1.421(2)	C(11)-C(16)-C(15)	112.10(17)
C(12)-C(13)	1.533(3)	N(14)-C(17)-C(18)	122.74(18)
C(13)-N(14)	1.459(3)	N(14)-C(17)-C(112)	118.92(19)
C(13)-C(14)	1.534(3)	C(18)-C(17)-C(112)	118.18(19)
C(14)-C(15)	1.524(3)	C(19)-C(18)-C(17)	120.98(19)
C(15)-C(16)	1.532(3)	C(110)-C(19)-C(18)	119.4(2)
C(17)-N(14)	1.391(3)	C(19)-C(110)-C(111)	121.0(2)
C(17)-C(18)	1.399(3)	C(19)-C(110)-CL1	119.23(17)
C(17)-C(112)	1.405(3)	C(111)-C(110)-CL1	119.78(17)
C(18)-C(19)	1.395(3)	C(110)-C(111)-C(112)	119.7(2)
C(19)-C(110)	1.381(3)	C(111)-C(112)-C(17)	120.8(2)
C(110)-C(111)	1.382(3)	N(12)-N(11)-C(11)	112.84(18)
C(111)-C(112)	1.389(3)	N(13)-N(12)-N(11)	174.0(2)
N(11)-N(12)	1.243(2)	C(17)-N(14)-C(13)	122.22(17)
N(12)-N(13)	1.139(3)	N(21)-C(21)-C(26)	111.22(18)
Cl(2)-C(210)	1.753(2)	N(21)-C(21)-C(22)	106.54(16)
C(21)-N(21)	1.501(3)	C(26)-C(21)-C(22)	112.38(18)
C(21)-C(26)	1.527(3)	O(21)-C(22)-C(21)	111.29(17)
C(21)-C(22)	1.530(3)	O(21)-C(22)-C(23)	113.08(16)
C(22)-O(21)	1.422(2)	C(21)-C(22)-C(23)	111.85(17)
C(22)-C(23)	1.535(3)	N(24)-C(23)-C(22)	108.83(17)
C(23)-N(24)	1.455(3)	N(24)-C(23)-C(24)	114.46(17)
C(23)-C(24)	1.538(3)	C(22)-C(23)-C(24)	108.81(17)
C(24)-C(25)	1.524(3)	C(25)-C(24)-C(23)	110.69(18)
C(25)-C(26)	1.526(3)	C(24)-C(25)-C(26)	110.74(18)
C(27)-N(24)	1.386(3)	C(25)-C(26)-C(21)	111.94(18)
C(27)-C(28)	1.402(3)	N(24)-C(27)-C(28)	122.91(19)
C(27)-C(212)	1.405(3)	N(24)-C(27)-C(212)	119.12(19)
C(28)-C(29)	1.386(3)	C(28)-C(27)-C(212)	117.83(19)
C(29)-C(210)	1.379(3)	C(29)-C(28)-C(27)	121.14(19)
C(210)-C(211)	1.385(3)	C(210)-C(29)-C(28)	119.6(2)
C(211)-C(212)	1.381(3)	C(29)-C(210)-C(211)	120.6(2)
N(21)-N(22)	1.240(2)	C(29)-C(210)-CL2	119.66(17)
N(22)-N(23)	1.138(3)	C(211)-C(210)-CL2	119.77(16)
		C(212)-C(211)-C(210)	119.98(19)
N(11)-C(11)-C(16)	111.10(18)	C(211)-C(212)-C(27)	120.9(2)
N(11)-C(11)-C(12)	106.41(16)	N(22)-N(21)-C(21)	112.97(17)
C(16)-C(11)-C(12)	112.13(18)	N(23)-N(22)-N(21)	173.9(2)
O(11)-C(12)-C(11)	111.21(17)	C(27)-N(24)-C(23)	122.53(18)
O(11)-C(12)-C(13)	113.38(16)		
C(11)-C(12)-C(13)	111.94(17)		

Table 6. Torsion angles [°] for C12 H15 Cl N4 O.

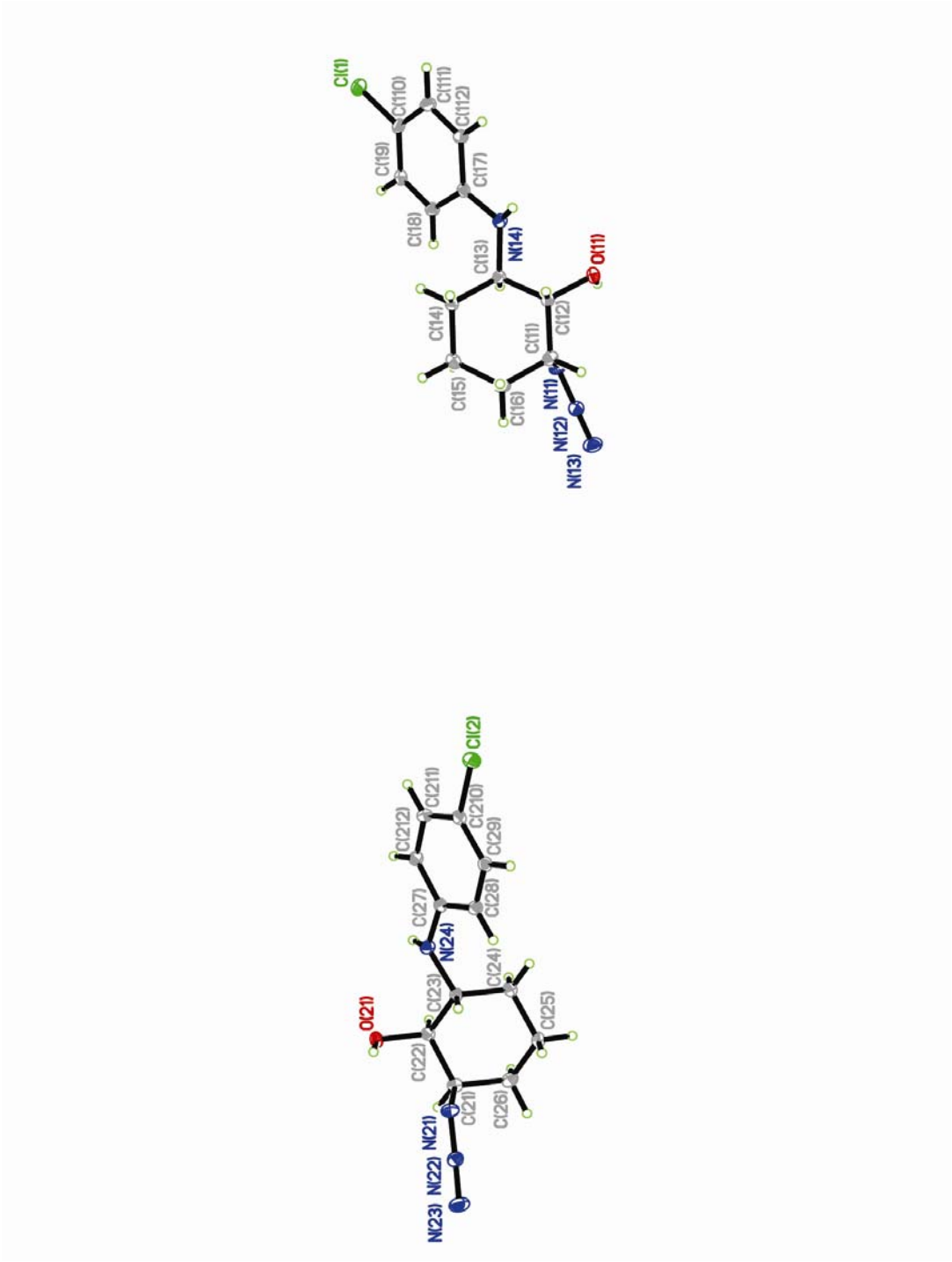
N(11)-C(11)-C(12)-O(11) -59.2(2)	C(26)-C(21)-C(22)-O(21) 179.42(16)
C(16)-C(11)-C(12)-O(11) 179.13(16)	N(21)-C(21)-C(22)-C(23) 69.0(2)
N(11)-C(11)-C(12)-C(13) 68.8(2)	C(26)-C(21)-C(22)-C(23) -53.0(2)
C(16)-C(11)-C(12)-C(13) -52.9(2)	O(21)-C(22)-C(23)-N(24) -51.4(2)
O(11)-C(12)-C(13)-N(14) -51.1(2)	C(21)-C(22)-C(23)-N(24) -178.04(16)
C(11)-C(12)-C(13)-N(14) -177.89(17)	O(21)-C(22)-C(23)-C(24) -176.78(16)
O(11)-C(12)-C(13)-C(14) -176.23(16)	C(21)-C(22)-C(23)-C(24) 56.6(2)
C(11)-C(12)-C(13)-C(14) 57.0(2)	N(24)-C(23)-C(24)-C(25) 178.12(17)
N(14)-C(13)-C(14)-C(15) 177.93(17)	C(22)-C(23)-C(24)-C(25) -59.9(2)
C(12)-C(13)-C(14)-C(15) -60.1(2)	C(23)-C(24)-C(25)-C(26) 59.2(2)
C(13)-C(14)-C(15)-C(16) 59.0(2)	C(24)-C(25)-C(26)-C(21) -54.2(2)
N(11)-C(11)-C(16)-C(15) -68.1(2)	N(21)-C(21)-C(26)-C(25) -68.1(2)
C(12)-C(11)-C(16)-C(15) 50.8(2)	C(22)-C(21)-C(26)-C(25) 51.2(2)
C(14)-C(15)-C(16)-C(11) -54.0(2)	N(24)-C(27)-C(28)-C(29) -175.3(2)
N(14)-C(17)-C(18)-C(19) -174.5(2)	C(212)-C(27)-C(28)-C(29) 0.4(3)
C(112)-C(17)-C(18)-C(19) 0.9(3)	C(27)-C(28)-C(29)-C(210) 0.2(3)
C(17)-C(18)-C(19)-C(110) -0.5(3)	C(28)-C(29)-C(210)-C(211) -0.2(3)
C(18)-C(19)-C(110)-C(111) 0.2(3)	C(28)-C(29)-C(210)-CL2 -179.60(17)
C(18)-C(19)-C(110)-CL1 -179.56(17)	C(29)-C(210)-C(211)-C(212)-0.4(3)
C(19)-C(110)-C(111)-C(112)-0.4(3)	CL2-C(210)-C(211)-C(212) 179.02(17)
CL1-C(110)-C(111)-C(112) 179.39(17)	C(210)-C(211)-C(212)-C(27) 1.0(3)
C(110)-C(111)-C(112)-C(17) 0.8(3)	N(24)-C(27)-C(212)-C(211)174.9(2)
N(14)-C(17)-C(112)-C(111)174.5(2)	C(28)-C(27)-C(212)-C(211) -1.0(3)
C(18)-C(17)-C(112)-C(111) -1.1(3)	C(26)-C(21)-N(21)-N(22) -79.3(2)
C(16)-C(11)-N(11)-N(12) -80.2(2)	C(22)-C(21)-N(21)-N(22) 157.96(19)
C(12)-C(11)-N(11)-N(12) 157.54(19)	C(28)-C(27)-N(24)-C(23) -14.5(3)
C(18)-C(17)-N(14)-C(13) -16.2(3)	C(212)-C(27)-N(24)-C(23) 169.80(19)
C(112)-C(17)-N(14)-C(13) 168.41(19)	C(22)-C(23)-N(24)-C(27) 172.81(18)
C(12)-C(13)-N(14)-C(17) 174.47(18)	C(24)-C(23)-N(24)-C(27) -65.2(3)
C(14)-C(13)-N(14)-C(17) -63.5(3)	
N(21)-C(21)-C(22)-O(21) -58.5(2)	

Table 7. Bond lengths [Å] and angles [°] related to the hydrogen bonding for C12 H15 Cl N4 O.

D-H	..A	d(D-H)	d(H..A)	d(D..A)	<DHA
O(11)-H(11)	N(14)#1	0.84	2.25	2.970(2)	144.4
N(14)-H(14C)	O(11)#2	0.85(2)	2.19(2)	3.009(2)	163(2)
O(21)-H(21)	N(24)#3	0.84	2.27	2.993(2)	144
N(24)-H(24C)	O(21)#4	0.84(2)	2.19(2)	3.004(2)	164(2)

Symmetry transformations used to generate equivalent atoms:

#1 -x+1,-y+2,-z+2 #2 -x+1,-y+1,-z+2
#3 -x,-y+1,-z #4 -x,-y+2,-z



ORTEP view of the C12 H15 Cl N4 O compound with the numbering scheme adopted. Ellipsoids drawn at 30% probability level. Hydrogen atoms are represented by sphere of arbitrary size.

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Université de Montréal

CRYSTAL AND MOLECULAR STRUCTURE OF

C15 H19 F N4 O2 COMPOUND (HAN450)

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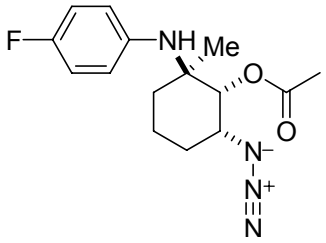


Structure solved and refined in the laboratory of X-ray diffraction Université de Montréal by Benoît Deschênes Simard

Table 1. Crystal data and structure refinement for C15 H19 F N4 O2.

Identification code	HAN450
Empirical formula	C15 H19 F N4 O2
Formula weight	306.34
Temperature	150(2)K
Wavelength	1.54178 Å
Crystal system	Monoclinic
Space group	$P2_1/n$
Unit cell dimensions	a = 10.7033(14) Å α = 90° b = 11.2000(15) Å β = 112.692(5)° c = 13.8575(19) Å γ = 90°
Volume	1532.6(4)Å^3
Z	4
Density (calculated)	1.328 g/cm^3
Absorption coefficient	0.824 mm^{-1}
F(000)	648
Crystal size	0.20 x 0.20 x 0.03 mm
Theta range for data collection	4.48 to 72.59°
Index ranges	$-12 \leq h \leq 13$, $-13 \leq k \leq 13$, $-17 \leq \ell \leq 17$
Reflections collected	20399
Independent reflections	3011 [R_{int} = 0.065]
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9756 and 0.8713
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3011 / 1 / 205
Goodness-of-fit on F^2	0.910
Final R indices [I>2sigma(I)]	R_1 = 0.0655, wR_2 = 0.1653
R indices (all data)	R_1 = 0.1257, wR_2 = 0.2058
Extinction coefficient	0.0032(7)
Largest diff. peak and hole	0.225 and -0.252 e/Å^3

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for C15 H19 F N4 O2.

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

	x	y	z	U_{eq}
F(1)	7889(2)	614(2)	4038(2)	80(1)
O(1)	-1218(2)	1020(2)	1453(2)	57(1)
O(2)	-1719(3)	1867(2)	-126(2)	88(1)
N(1)	2309(3)	140(2)	2127(2)	61(1)
N(2)	-1584(3)	-1221(2)	396(2)	63(1)
N(3)	-2664(3)	-1281(2)	501(2)	69(1)
N(4)	-3736(4)	-1367(4)	496(2)	100(1)
C(1)	-70(3)	390(3)	1381(2)	54(1)
C(2)	1215(3)	761(3)	2327(2)	55(1)
C(3)	1079(3)	322(3)	3326(2)	58(1)
C(4)	808(3)	-1017(3)	3314(2)	60(1)
C(5)	-472(3)	-1353(3)	2385(2)	58(1)
C(6)	-374(3)	-951(3)	1370(2)	56(1)
C(7)	1366(3)	2128(3)	2322(2)	67(1)
C(8)	3700(3)	345(3)	2630(2)	55(1)
C(9)	4346(3)	785(3)	3652(2)	60(1)
C(10)	5736(3)	866(3)	4121(3)	61(1)
C(11)	6505(3)	527(3)	3581(3)	64(1)
C(12)	5920(3)	110(3)	2572(3)	63(1)
C(13)	4529(3)	25(3)	2113(3)	58(1)
C(14)	-1949(3)	1759(3)	657(3)	62(1)
C(15)	-3012(3)	2376(3)	890(3)	71(1)

Table 3. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^2 x 10^3) for C15 H19 F N4 O2.

	x	y	z	U_{eq}
H(1)	2150(40)	0(30)	1442(8)	91
H(1A)	31	615	717	65
H(3A)	1922	511	3932	70
H(3B)	328	758	3419	70
H(4A)	1588	-1460	3275	72
H(4B)	711	-1247	3971	72
H(5A)	-601	-2229	2372	69
H(5B)	-1266	-972	2458	69
H(6)	412	-1382	1312	67
H(7A)	2233	2363	2866	100
H(7B)	624	2505	2458	100
H(7C)	1336	2387	1638	100
H(9)	3814	1033	4028	72
H(10)	6156	1155	4817	74
H(12)	6464	-115	2198	76
H(13)	4123	-265	1416	70
H(15A)	-3535	2889	299	106
H(15B)	-2595	2865	1520	106
H(15C)	-3615	1786	1006	106

Table 4. Anisotropic parameters ($Å^2$ x 10^3) for C15 H19 F N4 O2.

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
F(1)	59(1)	91(1)	71(1)	-2(1)	3(1)	1(1)
O(1)	61(1)	53(1)	50(1)	1(1)	13(1)	3(1)
O(2)	90(2)	107(2)	62(2)	26(1)	27(1)	31(1)
N(1)	60(2)	66(2)	52(2)	-9(1)	16(2)	-3(1)
N(2)	58(2)	69(2)	51(2)	-5(1)	9(1)	-4(1)
N(3)	70(2)	73(2)	49(2)	-9(1)	6(2)	-4(2)
N(4)	66(2)	151(3)	69(2)	-22(2)	11(2)	-19(2)
C(1)	54(2)	55(2)	50(2)	-4(1)	15(2)	-1(1)
C(2)	59(2)	51(2)	46(2)	-5(1)	11(2)	-4(1)
C(3)	61(2)	54(2)	50(2)	-4(1)	10(2)	-1(1)
C(4)	62(2)	60(2)	49(2)	1(2)	11(2)	1(2)
C(5)	61(2)	53(2)	51(2)	1(1)	12(2)	-3(1)
C(6)	57(2)	53(2)	47(2)	-5(1)	7(2)	-3(1)
C(7)	71(2)	54(2)	62(2)	-1(2)	13(2)	-7(2)
C(8)	58(2)	50(2)	48(2)	3(1)	10(2)	-1(1)
C(9)	65(2)	55(2)	51(2)	0(1)	12(2)	-2(2)
C(10)	63(2)	57(2)	50(2)	2(2)	6(2)	-2(2)
C(11)	53(2)	59(2)	63(2)	6(2)	4(2)	2(2)
C(12)	62(2)	58(2)	58(2)	5(2)	11(2)	5(2)
C(13)	61(2)	53(2)	50(2)	0(1)	9(2)	0(2)
C(14)	60(2)	63(2)	51(2)	0(2)	8(2)	2(2)
C(15)	68(2)	65(2)	65(2)	4(2)	12(2)	3(2)

Table 5. Bond lengths [Å] and angles [°] for C15 H19 F N4 O2

F(1)-C(11)	1.372(3)	O(1)-C(1)-C(2)	108.1(2)
O(1)-C(14)	1.359(4)	C(6)-C(1)-C(2)	112.8(2)
O(1)-C(1)	1.453(3)	N(1)-C(2)-C(3)	112.2(2)
O(2)-C(14)	1.208(4)	N(1)-C(2)-C(7)	112.1(3)
N(1)-C(8)	1.398(4)	C(3)-C(2)-C(7)	111.7(2)
N(1)-C(2)	1.476(4)	N(1)-C(2)-C(1)	103.0(2)
N(2)-N(3)	1.222(4)	C(3)-C(2)-C(1)	108.5(2)
N(2)-C(6)	1.497(4)	C(7)-C(2)-C(1)	108.9(2)
N(3)-N(4)	1.148(4)	C(4)-C(3)-C(2)	113.0(2)
C(1)-C(6)	1.535(4)	C(5)-C(4)-C(3)	111.0(2)
C(1)-C(2)	1.547(4)	C(6)-C(5)-C(4)	110.4(2)
C(2)-C(3)	1.528(4)	N(2)-C(6)-C(5)	115.5(2)
C(2)-C(7)	1.540(4)	N(2)-C(6)-C(1)	108.3(2)
C(3)-C(4)	1.526(4)	C(5)-C(6)-C(1)	111.8(2)
C(4)-C(5)	1.522(4)	C(13)-C(8)-N(1)	118.0(3)
C(5)-C(6)	1.520(4)	C(13)-C(8)-C(9)	116.6(3)
C(8)-C(13)	1.386(4)	N(1)-C(8)-C(9)	125.2(3)
C(8)-C(9)	1.403(4)	C(10)-C(9)-C(8)	121.4(3)
C(9)-C(10)	1.378(4)	C(11)-C(10)-C(9)	119.6(3)
C(10)-C(11)	1.362(4)	C(10)-C(11)-F(1)	120.1(3)
C(11)-C(12)	1.375(4)	C(10)-C(11)-C(12)	121.3(3)
C(12)-C(13)	1.379(4)	F(1)-C(11)-C(12)	118.7(3)
C(14)-C(15)	1.469(5)	C(11)-C(12)-C(13)	118.6(3)
		C(12)-C(13)-C(8)	122.4(3)
C(14)-O(1)-C(1)	118.5(2)	O(2)-C(14)-O(1)	122.5(3)
C(8)-N(1)-C(2)	126.7(3)	O(2)-C(14)-C(15)	126.4(3)
N(3)-N(2)-C(6)	115.6(3)	O(1)-C(14)-C(15)	111.2(3)
N(4)-N(3)-N(2)	173.1(3)		
O(1)-C(1)-C(6)	107.1(2)		

Table 6. Torsion angles [°] for C15 H19 F N4 O2.

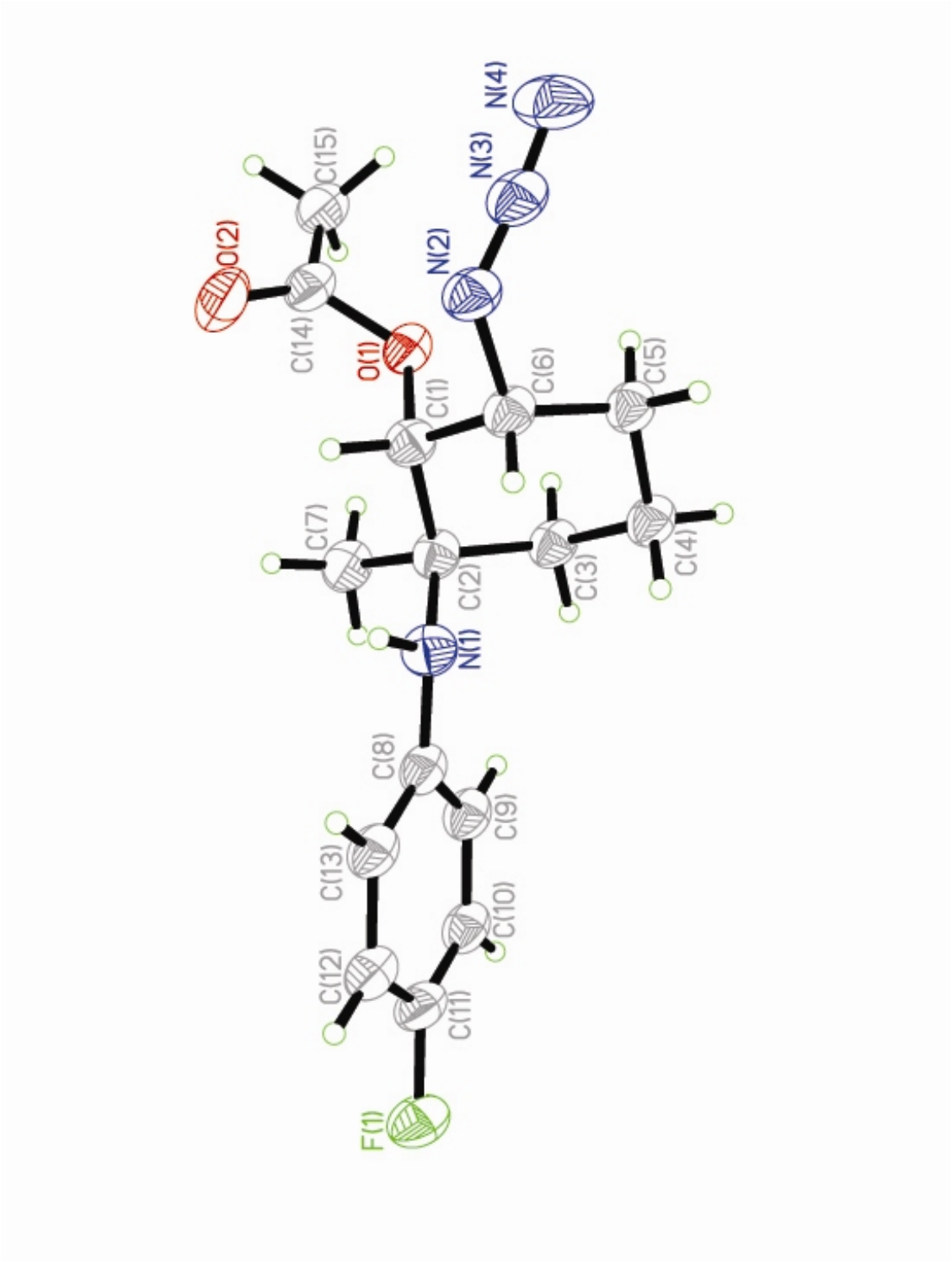
C(6)-N(2)-N(3)-N(4)	-177(3)	C(4)-C(5)-C(6)-C(1)	-55.1(3)
C(14)-O(1)-C(1)-C(6)	-118.0(3)	O(1)-C(1)-C(6)-N(2)	64.4(3)
C(14)-O(1)-C(1)-C(2)	120.3(3)	C(2)-C(1)-C(6)-N(2)	-176.8(2)
C(8)-N(1)-C(2)-C(3)	-76.8(3)	O(1)-C(1)-C(6)-C(5)	-63.9(3)
C(8)-N(1)-C(2)-C(7)	49.9(4)	C(2)-C(1)-C(6)-C(5)	54.9(3)
C(8)-N(1)-C(2)-C(1)	166.8(3)	C(2)-N(1)-C(8)-C(13)	-156.7(3)
O(1)-C(1)-C(2)-N(1)	-176.1(2)	C(2)-N(1)-C(8)-C(9)	27.5(5)
C(6)-C(1)-C(2)-N(1)	65.7(3)	C(13)-C(8)-C(9)-C(10)	-1.5(4)
O(1)-C(1)-C(2)-C(3)	64.8(3)	N(1)-C(8)-C(9)-C(10)	174.4(3)
C(6)-C(1)-C(2)-C(3)	-53.4(3)	C(8)-C(9)-C(10)-C(11)	0.9(5)
O(1)-C(1)-C(2)-C(7)	-56.9(3)	C(9)-C(10)-C(11)-F(1)	179.4(3)
C(6)-C(1)-C(2)-C(7)	-175.2(3)	C(9)-C(10)-C(11)-C(12)	0.3(5)
N(1)-C(2)-C(3)-C(4)	-58.0(3)	C(10)-C(11)-C(12)-C(13)	-0.8(5)
C(7)-C(2)-C(3)-C(4)	175.1(2)	F(1)-C(11)-C(12)-C(13)	-179.9(3)
C(1)-C(2)-C(3)-C(4)	55.1(3)	C(11)-C(12)-C(13)-C(8)	0.1(4)
C(2)-C(3)-C(4)-C(5)	-57.9(3)	N(1)-C(8)-C(13)-C(12)	-175.2(3)
C(3)-C(4)-C(5)-C(6)	56.2(3)	C(9)-C(8)-C(13)-C(12)	1.0(4)
N(3)-N(2)-C(6)-C(5)	27.9(4)	C(1)-O(1)-C(14)-O(2)	3.6(4)
N(3)-N(2)-C(6)-C(1)	-98.3(3)	C(1)-O(1)-C(14)-C(15)	-176.4(3)
C(4)-C(5)-C(6)-N(2)	-179.4(2)		

Table 7. Bond lengths [Å] and angles [°] related to the hydrogen bonding for C15 H19 F N4 O2.

D-H	..A	d(D-H)	d(H..A)	d(D..A)	<DHA
N(1)-H(1)	N(2)#1	0.911(15)	2.74(2)	3.493(4)	140(3)

Symmetry transformations used to generate equivalent atoms:

#1 -x,-y,-z



ORTEP view of the C15 H19 F N4 O2 compound with the numbering scheme adopted. Ellipsoids drawn at 50% probability level. Hydrogen atoms are represented by sphere of arbitrary size.

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Université de Montréal

CRYSTAL AND MOLECULAR STRUCTURE OF

C20 H24 N4 O2 COMPOUND (bent39)

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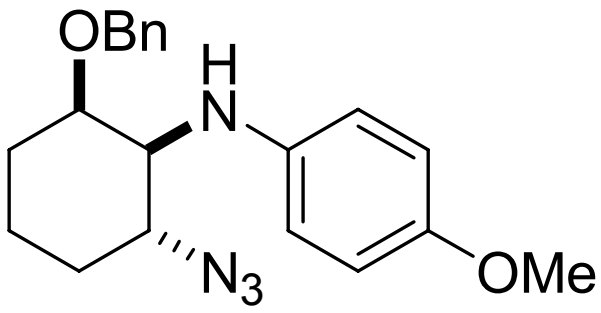


Structure solved and refined in the laboratory of X-ray diffraction Université de Montréal by Benoît Deschênes Simard.

Table 1. Crystal data and structure refinement for C20 H24 N4 O2.

Identification code	bent39
Empirical formula	C20 H24 N4 O2
Formula weight	352.43
Temperature	175K
Wavelength	1.54178 Å
Crystal system	Monoclinic
Space group	P21/c
Unit cell dimensions	a = 19.0271(5) Å α = 90° b = 5.6071(1) Å β = 104.337(1)° c = 18.0411(5) Å γ = 90°
Volume	1864.80(8)Å^3
Z	4
Density (calculated)	1.255 g/cm^3
Absorption coefficient	0.668 mm^{-1}
F(000)	752
Crystal size	0.08 x 0.07 x 0.06 mm
Theta range for data collection	2.40 to 72.23°
Index ranges	$-23 \leq h \leq 23$, $-6 \leq k \leq 6$, $-21 \leq \ell \leq 22$
Reflections collected	24026
Independent reflections	3654 [R_{int} = 0.037]
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9607 and 0.9007
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3654 / 0 / 241
Goodness-of-fit on F^2	0.840
Final R indices [I>2sigma(I)]	R_1 = 0.0349, wR_2 = 0.0861
R indices (all data)	R_1 = 0.0492, wR_2 = 0.0915
Extinction coefficient	0.0014(2)
Largest diff. peak and hole	0.180 and -0.144 e/Å^3

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^2 x 10^3) for C20 H24 N4 O2.

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

	x	y	z	U_{eq}
O(1)	8416(1)	-490(2)	5272(1)	40(1)
O(2)	5623(1)	7511(2)	6962(1)	44(1)
N(1)	7802(1)	1722(2)	6355(1)	37(1)
N(2)	9126(1)	2419(2)	7566(1)	45(1)
N(3)	8711(1)	1333(2)	7879(1)	47(1)
N(4)	8372(1)	491(3)	8245(1)	64(1)
C(1)	8504(1)	2043(2)	5379(1)	37(1)
C(2)	8471(1)	2601(2)	6201(1)	34(1)
C(3)	9133(1)	1600(2)	6779(1)	37(1)
C(4)	9836(1)	2488(3)	6619(1)	43(1)
C(5)	9866(1)	1821(3)	5807(1)	47(1)
C(6)	9217(1)	2871(3)	5222(1)	45(1)
C(7)	8003(1)	-1147(3)	4517(1)	45(1)
C(8)	7198(1)	-873(2)	4431(1)	38(1)
C(9)	6827(1)	-2477(2)	4784(1)	43(1)
C(10)	6093(1)	-2215(3)	4729(1)	45(1)
C(11)	5717(1)	-324(3)	4323(1)	43(1)
C(12)	6075(1)	1281(3)	3971(1)	46(1)
C(13)	6811(1)	1003(3)	4020(1)	43(1)
C(14)	7274(1)	3285(2)	6501(1)	31(1)
C(15)	7453(1)	5305(2)	6956(1)	36(1)
C(16)	6920(1)	6765(2)	7123(1)	36(1)
C(17)	6196(1)	6203(2)	6837(1)	33(1)
C(18)	6010(1)	4195(2)	6381(1)	36(1)
C(19)	6540(1)	2760(2)	6212(1)	34(1)
C(20)	5779(1)	9188(3)	7573(1)	43(1)

Table 3. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^2 x 10^3) for C20 H24 N4 O2.

	x	y	z	U_{eq}
H(1A)	8093	2871	5016	44
H(2)	8478	4374	6261	41
H(3)	9120	-183	6760	44
H(4A)	10254	1770	6990	52
H(4B)	9868	4242	6680	52
H(5A)	9863	63	5755	56
H(5B)	10321	2432	5705	56
H(6A)	9242	4634	5246	54
H(6B)	9236	2372	4701	54
H(7A)	8110	-2825	4415	54
H(7B)	8152	-132	4134	54
H(9)	7082	-3775	5067	51
H(10)	5847	-3334	4970	54
H(11)	5213	-133	4288	51
H(12)	5818	2583	3692	55
H(13)	7052	2110	3769	52
H(15)	7949	5699	7157	44
H(16)	7054	8141	7433	43
H(18)	5514	3803	6183	43
H(19)	6403	1400	5895	41
H(20A)	6083	10469	7453	65
H(20B)	6037	8386	8045	65
H(20C)	5325	9863	7642	65
H(1B)	7625(8)	520(30)	6052(8)	47(4)

Table 4. Anisotropic parameters ($Å^2$ x 10^3) for C20 H24 N4 O2.

The anisotropic displacement factor exponent takes the form:

$$-2\pi^2 [h^2 a^{*2} U_{11} + ... + 2 h k a^* b^* U_{12}]$$

	U11	U22	U33	U23	U13	U12
O(1)	42(1)	37(1)	38(1)	-4(1)	4(1)	9(1)
O(2)	32(1)	44(1)	56(1)	-9(1)	11(1)	6(1)
N(1)	33(1)	32(1)	50(1)	-11(1)	14(1)	-4(1)
N(2)	44(1)	50(1)	41(1)	-4(1)	11(1)	-7(1)
N(3)	49(1)	51(1)	38(1)	-2(1)	9(1)	0(1)
N(4)	71(1)	82(1)	44(1)	3(1)	22(1)	-13(1)
C(1)	34(1)	36(1)	39(1)	2(1)	8(1)	7(1)
C(2)	31(1)	31(1)	42(1)	-3(1)	11(1)	1(1)
C(3)	35(1)	38(1)	37(1)	-2(1)	8(1)	1(1)
C(4)	31(1)	49(1)	49(1)	2(1)	7(1)	1(1)
C(5)	32(1)	56(1)	54(1)	5(1)	17(1)	5(1)
C(6)	42(1)	51(1)	44(1)	5(1)	16(1)	6(1)
C(7)	50(1)	46(1)	38(1)	-8(1)	8(1)	9(1)
C(8)	44(1)	34(1)	31(1)	-5(1)	4(1)	3(1)
C(9)	55(1)	31(1)	37(1)	2(1)	1(1)	3(1)
C(10)	55(1)	38(1)	39(1)	1(1)	9(1)	-11(1)
C(11)	42(1)	41(1)	43(1)	-6(1)	6(1)	-6(1)
C(12)	43(1)	38(1)	52(1)	9(1)	1(1)	1(1)
C(13)	43(1)	40(1)	44(1)	8(1)	6(1)	-3(1)
C(14)	32(1)	29(1)	34(1)	0(1)	11(1)	-1(1)
C(15)	27(1)	37(1)	44(1)	-7(1)	6(1)	-3(1)
C(16)	35(1)	32(1)	40(1)	-7(1)	10(1)	-2(1)
C(17)	31(1)	32(1)	37(1)	3(1)	10(1)	3(1)
C(18)	27(1)	37(1)	43(1)	-1(1)	6(1)	-4(1)
C(19)	35(1)	29(1)	37(1)	-4(1)	8(1)	-5(1)
C(20)	48(1)	40(1)	46(1)	-2(1)	19(1)	8(1)

Table 5. Bond lengths [Å] and angles [°] for C20 H24 N4 O2

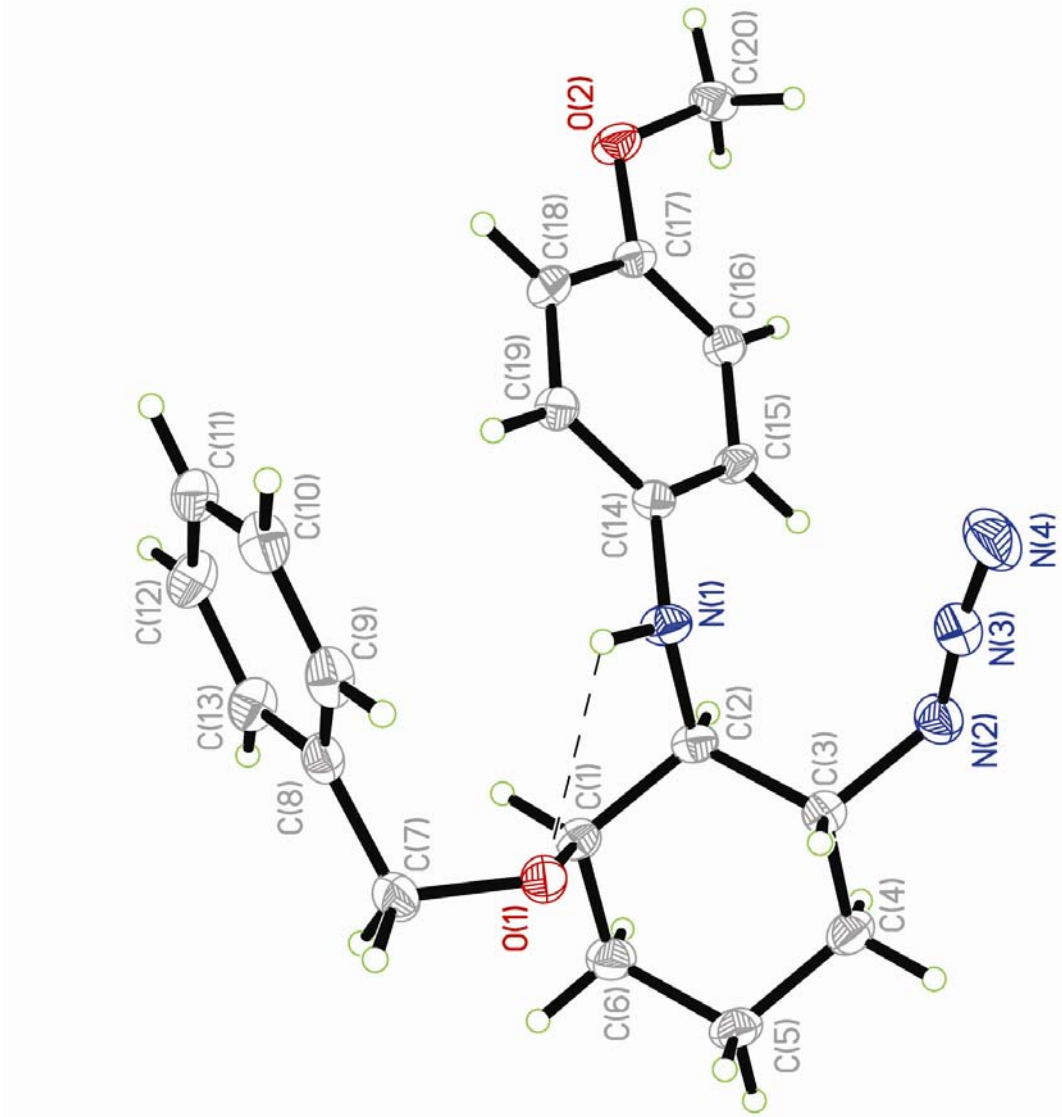
O(1)-C(1)	1.4374(16)	N(4)-N(3)-N(2)	171.50(15)
O(1)-C(7)	1.4423(16)	O(1)-C(1)-C(6)	110.82(11)
O(2)-C(17)	1.3766(14)	O(1)-C(1)-C(2)	107.42(10)
O(2)-C(20)	1.4238(16)	C(6)-C(1)-C(2)	111.61(11)
N(1)-C(14)	1.4056(16)	N(1)-C(2)-C(3)	110.89(11)
N(1)-C(2)	1.4546(16)	N(1)-C(2)-C(1)	111.35(11)
N(2)-N(3)	1.2380(17)	C(3)-C(2)-C(1)	111.19(10)
N(2)-C(3)	1.4938(17)	N(2)-C(3)-C(4)	107.18(11)
N(3)-N(4)	1.1344(17)	N(2)-C(3)-C(2)	109.62(11)
C(1)-C(6)	1.5243(18)	C(4)-C(3)-C(2)	111.36(11)
C(1)-C(2)	1.5325(18)	C(3)-C(4)-C(5)	110.25(11)
C(2)-C(3)	1.5298(18)	C(4)-C(5)-C(6)	110.59(12)
C(3)-C(4)	1.5215(18)	C(1)-C(6)-C(5)	111.05(12)
C(4)-C(5)	1.526(2)	O(1)-C(7)-C(8)	111.96(11)
C(5)-C(6)	1.5290(19)	C(13)-C(8)-C(9)	118.15(13)
C(7)-C(8)	1.5076(19)	C(13)-C(8)-C(7)	121.55(13)
C(8)-C(13)	1.3884(19)	C(9)-C(8)-C(7)	120.28(13)
C(8)-C(9)	1.392(2)	C(10)-C(9)-C(8)	121.10(13)
C(9)-C(10)	1.383(2)	C(11)-C(10)-C(9)	120.00(14)
C(10)-C(11)	1.383(2)	C(12)-C(11)-C(10)	119.69(14)
C(11)-C(12)	1.376(2)	C(11)-C(12)-C(13)	120.25(13)
C(12)-C(13)	1.3896(19)	C(8)-C(13)-C(12)	120.81(14)
C(14)-C(15)	1.3907(18)	C(15)-C(14)-C(19)	117.89(11)
C(14)-C(19)	1.3967(17)	C(15)-C(14)-N(1)	122.46(11)
C(15)-C(16)	1.3926(17)	C(19)-C(14)-N(1)	119.58(11)
C(16)-C(17)	1.3833(17)	C(14)-C(15)-C(16)	121.44(12)
C(17)-C(18)	1.3873(18)	C(17)-C(16)-C(15)	119.80(12)
C(18)-C(19)	1.3810(18)	O(2)-C(17)-C(16)	124.98(12)
		O(2)-C(17)-C(18)	115.71(11)
C(1)-O(1)-C(7)	113.35(10)	C(16)-C(17)-C(18)	119.30(12)
C(17)-O(2)-C(20)	117.19(10)	C(19)-C(18)-C(17)	120.77(12)
C(14)-N(1)-C(2)	121.61(11)	C(18)-C(19)-C(14)	120.78(12)
N(3)-N(2)-C(3)	116.01(12)		

Table 6. Torsion angles [°] for C20 H24 N4 O2.

C(3)-N(2)-N(3)-N(4)	171.1(11)	C(13)-C(8)-C(9)-C(10)	-0.1(2)
C(7)-O(1)-C(1)-C(6)	-94.32(13)	C(7)-C(8)-C(9)-C(10)	178.13(12)
C(7)-O(1)-C(1)-C(2)	143.51(11)	C(8)-C(9)-C(10)-C(11)	-0.5(2)
C(14)-N(1)-C(2)-C(3)	121.82(13)	C(9)-C(10)-C(11)-C(12)	0.5(2)
C(14)-N(1)-C(2)-C(1)	-113.80(13)	C(10)-C(11)-C(12)-C(13)	0.1(2)
O(1)-C(1)-C(2)-N(1)	-56.05(13)	C(9)-C(8)-C(13)-C(12)	0.7(2)
C(6)-C(1)-C(2)-N(1)	-177.72(11)	C(7)-C(8)-C(13)-C(12)	-177.51(13)
O(1)-C(1)-C(2)-C(3)	68.15(13)	C(11)-C(12)-C(13)-C(8)	-0.7(2)
C(6)-C(1)-C(2)-C(3)	-53.51(15)	C(2)-N(1)-C(14)-C(15)	-41.05(18)
N(3)-N(2)-C(3)-C(4)	-160.28(12)	C(2)-N(1)-C(14)-C(19)	141.91(13)
N(3)-N(2)-C(3)-C(2)	78.72(15)	C(19)-C(14)-C(15)-C(16)	0.3(2)
N(1)-C(2)-C(3)-N(2)	-62.13(14)	N(1)-C(14)-C(15)-C(16)	-176.82(12)
C(1)-C(2)-C(3)-N(2)	173.41(10)	C(14)-C(15)-C(16)-C(17)	0.3(2)
N(1)-C(2)-C(3)-C(4)	179.44(11)	C(20)-O(2)-C(17)-C(16)	-16.60(18)
C(1)-C(2)-C(3)-C(4)	54.97(15)	C(20)-O(2)-C(17)-C(18)	164.07(12)
N(2)-C(3)-C(4)-C(5)	-177.25(12)	C(15)-C(16)-C(17)-O(2)	-179.78(12)
C(2)-C(3)-C(4)-C(5)	-57.35(15)	C(15)-C(16)-C(17)-C(18)	-0.48(19)
C(3)-C(4)-C(5)-C(6)	58.20(16)	O(2)-C(17)-C(18)-C(19)	179.41(12)
O(1)-C(1)-C(6)-C(5)	-64.97(15)	C(16)-C(17)-C(18)-C(19)	0.0(2)
C(2)-C(1)-C(6)-C(5)	54.71(16)	C(17)-C(18)-C(19)-C(14)	0.6(2)
C(4)-C(5)-C(6)-C(1)	-57.05(17)	C(15)-C(14)-C(19)-C(18)	-0.70(19)
C(1)-O(1)-C(7)-C(8)	-79.58(15)	N(1)-C(14)-C(19)-C(18)	176.47(12)
O(1)-C(7)-C(8)-C(13)	105.29(15)		
O(1)-C(7)-C(8)-C(9)	-72.90(17)		

Table 7. Bond lengths [Å] and angles [°] related to the hydrogen bonding for C20 H24 N4 O2.

D-H	..A	d(D-H)	d(H..A)	d(D..A)	<DHA
N(1)-H(1B)	O(1)	0.879(16)	2.369(15)	2.8024(14)	110.6(11)



ORTEP view of the C20 H24 N4 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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Université de Montréal

CRYSTAL AND MOLECULAR STRUCTURE OF

C19 H23 N5 O COMPOUND (bent40)

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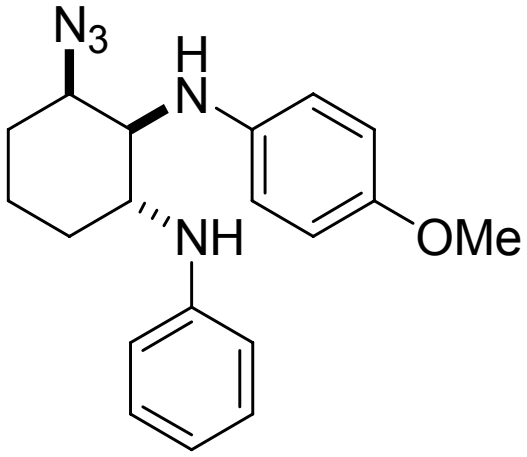


Structure solved and refined in the laboratory of X-ray diffraction Université de Montréal by Benoît Deschênes Simard.

Table 1. Crystal data and structure refinement for C19 H23 N5 O.

Identification code	bent40
Empirical formula	C19 H23 N5 O
Formula weight	337.42
Temperature	175K
Wavelength	1.54178 Å
Crystal system	Monoclinic
Space group	P21/c
Unit cell dimensions	a = 11.4990(7) Å α = 90° b = 17.9408(12) Å β = 101.441(3)° c = 8.7339(5) Å γ = 90°
Volume	1766.01(19)Å^3
Z	4
Density (calculated)	1.269 g/cm^3
Absorption coefficient	0.655 mm^{-1}
F(000)	720
Crystal size	0.18 x 0.07 x 0.05 mm
Theta range for data collection	3.92 to 72.60°
Index ranges	$-14 \le h \le 14$, $-22 \le k \le 21$, $-10 \le \ell \le 10$
Reflections collected	23332
Independent reflections	3475 [R_{int} = 0.042]
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9678 and 0.7604
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3475 / 0 / 236
Goodness-of-fit on F^2	1.041
Final R indices [I>2sigma(I)]	R_1 = 0.0368, wR_2 = 0.1041
R indices (all data)	R_1 = 0.0471, wR_2 = 0.1089
Largest diff. peak and hole	0.183 and -0.180 e/Å^3

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^2 x 10^3) for C19 H23 N5 O.

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

	x	y	z	U_{eq}
O(1)	12645(1)	9342(1)	10050(1)	41(1)
N(1)	10148(1)	5863(1)	7889(1)	44(1)
N(2)	11224(1)	5913(1)	8329(1)	47(1)
N(3)	12227(1)	5909(1)	8635(2)	72(1)
N(4)	9462(1)	7325(1)	6582(1)	34(1)
N(5)	7125(1)	6929(1)	5072(1)	37(1)
C(1)	9416(1)	6376(1)	8672(1)	36(1)
C(2)	8702(1)	6890(1)	7411(1)	31(1)
C(3)	7816(1)	6435(1)	6233(1)	32(1)
C(4)	7027(1)	5959(1)	7074(2)	39(1)
C(5)	7742(1)	5452(1)	8309(2)	43(1)
C(6)	8609(1)	5908(1)	9487(2)	42(1)
C(7)	10293(1)	7822(1)	7468(1)	31(1)
C(8)	11498(1)	7759(1)	7494(2)	38(1)
C(9)	12310(1)	8258(1)	8332(2)	39(1)
C(10)	11914(1)	8829(1)	9164(1)	33(1)
C(11)	10707(1)	8912(1)	9109(1)	33(1)
C(12)	9905(1)	8417(1)	8266(1)	32(1)
C(13)	13884(1)	9203(1)	10301(2)	55(1)
C(14)	6447(1)	6674(1)	3679(1)	32(1)
C(15)	5548(1)	7128(1)	2843(2)	36(1)
C(16)	4886(1)	6903(1)	1416(2)	42(1)
C(17)	5101(1)	6224(1)	774(2)	45(1)
C(18)	5986(1)	5771(1)	1588(2)	43(1)
C(19)	6650(1)	5983(1)	3024(2)	36(1)

Table 3. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for C19 H23 N5 O.

	x	y	z	U_{eq}
H(1)	9954	6685	9465	43
H(2)	8242	7247	7940	37
H(3)	8278	6090	5680	38
H(4A)	6527	6292	7576	46
H(4B)	6493	5651	6295	46
H(5A)	7198	5176	8854	51
H(5B)	8184	5084	7802	51
H(6A)	9098	5569	10248	50
H(6B)	8161	6240	10067	50
H(8)	11775	7368	6927	46
H(9)	13133	8206	8334	47
H(11)	10429	9312	9654	39
H(12)	9080	8482	8230	38
H(13A)	14142	9207	9297	83
H(13B)	14055	8715	10799	83
H(13C)	14309	9591	10980	83
H(15)	5390	7597	3262	43
H(16)	4278	7218	873	50
H(17)	4650	6071	-208	54
H(18)	6142	5305	1153	51
H(19)	7246	5660	3568	44
H(4C)	9844(13)	7014(9)	6003(18)	48(4)
H(5C)	6815(13)	7341(9)	5458(18)	52(5)

Table 4. Anisotropic parameters ($Å^2$ x 10^3) for C19 H23 N5 O.

The anisotropic displacement factor exponent takes the form:

$$-2\pi^2 [h^2 a^{*2} U_{11} + ... + 2 h k a^* b^* U_{12}]$$

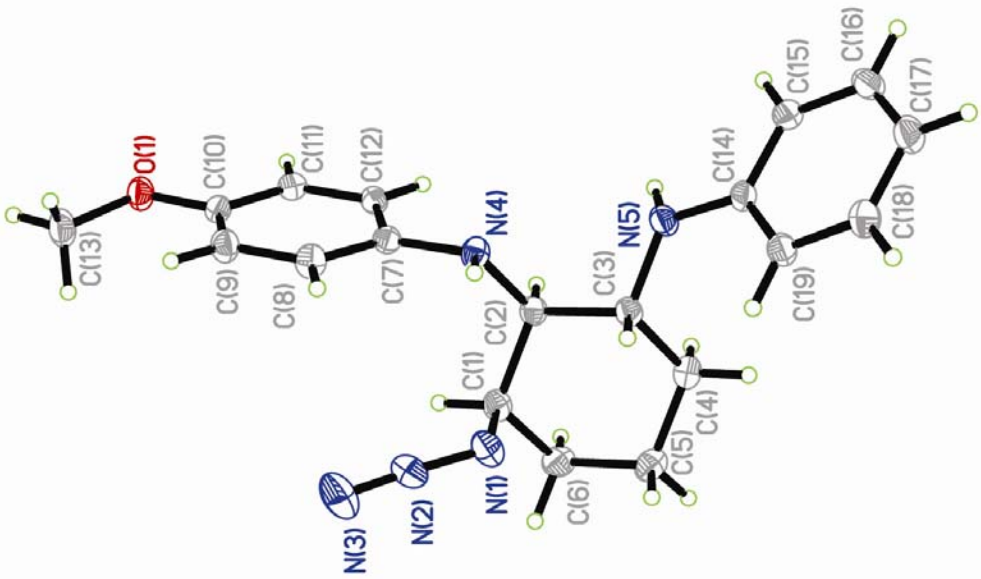
	U11	U22	U33	U23	U13	U12
O(1)	33(1)	39(1)	48(1)	-8(1)	1(1)	-5(1)
N(1)	37(1)	50(1)	42(1)	-7(1)	-1(1)	7(1)
N(2)	44(1)	51(1)	43(1)	7(1)	2(1)	8(1)
N(3)	40(1)	90(1)	83(1)	2(1)	-1(1)	13(1)
N(4)	36(1)	38(1)	29(1)	-5(1)	7(1)	-6(1)
N(5)	35(1)	36(1)	36(1)	-4(1)	-3(1)	2(1)
C(1)	37(1)	40(1)	28(1)	-5(1)	2(1)	-2(1)
C(2)	31(1)	33(1)	29(1)	-3(1)	5(1)	-2(1)
C(3)	30(1)	33(1)	30(1)	-3(1)	2(1)	1(1)
C(4)	35(1)	40(1)	41(1)	-6(1)	7(1)	-7(1)
C(5)	52(1)	38(1)	38(1)	-1(1)	11(1)	-9(1)
C(6)	54(1)	41(1)	30(1)	1(1)	6(1)	-4(1)
C(7)	33(1)	34(1)	25(1)	2(1)	4(1)	-3(1)
C(8)	37(1)	38(1)	41(1)	-7(1)	10(1)	0(1)
C(9)	29(1)	41(1)	48(1)	-4(1)	8(1)	-1(1)
C(10)	33(1)	31(1)	33(1)	2(1)	3(1)	-5(1)
C(11)	35(1)	32(1)	31(1)	0(1)	7(1)	0(1)
C(12)	28(1)	37(1)	29(1)	2(1)	5(1)	-1(1)
C(13)	34(1)	44(1)	80(1)	-10(1)	-8(1)	-5(1)
C(14)	27(1)	34(1)	33(1)	1(1)	5(1)	-6(1)
C(15)	35(1)	36(1)	38(1)	4(1)	6(1)	-2(1)
C(16)	36(1)	49(1)	38(1)	11(1)	1(1)	0(1)
C(17)	44(1)	54(1)	34(1)	-1(1)	-2(1)	-9(1)
C(18)	43(1)	44(1)	39(1)	-7(1)	4(1)	-5(1)
C(19)	31(1)	39(1)	37(1)	-2(1)	2(1)	0(1)

Table 5. Bond lengths [Å] and angles [°] for C19 H23 N5 O

O(1)-C(10)	1.3766(14)	C(14)-N(5)-C(3)	123.00(11)
O(1)-C(13)	1.4203(16)	N(1)-C(1)-C(6)	108.81(11)
N(1)-N(2)	1.2238(15)	N(1)-C(1)-C(2)	108.01(9)
N(1)-C(1)	1.4996(16)	C(6)-C(1)-C(2)	111.96(10)
N(2)-N(3)	1.1313(16)	N(4)-C(2)-C(3)	109.53(9)
N(4)-C(7)	1.4184(15)	N(4)-C(2)-C(1)	112.66(10)
N(4)-C(2)	1.4663(15)	C(3)-C(2)-C(1)	110.47(10)
N(5)-C(14)	1.3860(15)	N(5)-C(3)-C(2)	109.97(10)
N(5)-C(3)	1.4579(15)	N(5)-C(3)-C(4)	112.22(10)
C(1)-C(6)	1.5291(18)	C(2)-C(3)-C(4)	110.63(10)
C(1)-C(2)	1.5424(16)	C(5)-C(4)-C(3)	112.61(11)
C(2)-C(3)	1.5321(15)	C(6)-C(5)-C(4)	110.30(11)
C(3)-C(4)	1.5344(17)	C(5)-C(6)-C(1)	110.96(10)
C(4)-C(5)	1.5219(18)	C(8)-C(7)-C(12)	118.10(11)
C(5)-C(6)	1.5209(17)	C(8)-C(7)-N(4)	121.40(11)
C(7)-C(8)	1.3854(17)	C(12)-C(7)-N(4)	120.38(11)
C(7)-C(12)	1.3957(17)	C(7)-C(8)-C(9)	121.43(12)
C(8)-C(9)	1.3918(18)	C(10)-C(9)-C(8)	119.67(12)
C(9)-C(10)	1.3850(18)	O(1)-C(10)-C(9)	124.20(11)
C(10)-C(11)	1.3872(17)	O(1)-C(10)-C(11)	116.29(11)
C(11)-C(12)	1.3825(16)	C(9)-C(10)-C(11)	119.50(11)
C(14)-C(15)	1.4018(17)	C(12)-C(11)-C(10)	120.41(11)
C(14)-C(19)	1.4030(18)	C(11)-C(12)-C(7)	120.82(11)
C(15)-C(16)	1.3850(18)	N(5)-C(14)-C(15)	119.58(12)
C(16)-C(17)	1.384(2)	N(5)-C(14)-C(19)	122.58(12)
C(17)-C(18)	1.383(2)	C(15)-C(14)-C(19)	117.80(11)
C(18)-C(19)	1.3865(17)	C(16)-C(15)-C(14)	121.04(12)
		C(17)-C(16)-C(15)	120.74(13)
C(10)-O(1)-C(13)	116.79(10)	C(18)-C(17)-C(16)	118.71(12)
N(2)-N(1)-C(1)	115.81(11)	C(17)-C(18)-C(19)	121.43(13)
N(3)-N(2)-N(1)	173.55(17)	C(18)-C(19)-C(14)	120.28(12)
C(7)-N(4)-C(2)	117.90(9)		

Table 6. Torsion angles [°] for C19 H23 N5 O.

C(1)-N(1)-N(2)-N(3)	-179(10)	C(12)-C(7)-C(8)-C(9)	2.20(19)
N(2)-N(1)-C(1)-C(6)	-119.83(13)	N(4)-C(7)-C(8)-C(9)	178.39(12)
N(2)-N(1)-C(1)-C(2)	118.43(13)	C(7)-C(8)-C(9)-C(10)	0.1(2)
C(7)-N(4)-C(2)-C(3)	175.99(10)	C(13)-O(1)-C(10)-C(9)	-9.76(18)
C(7)-N(4)-C(2)-C(1)	-60.62(14)	C(13)-O(1)-C(10)-C(11)	171.19(12)
N(1)-C(1)-C(2)-N(4)	-58.32(13)	C(8)-C(9)-C(10)-O(1)	178.86(11)
C(6)-C(1)-C(2)-N(4)	-178.1(1)	C(8)-C(9)-C(10)-C(11)	-2.12(19)
N(1)-C(1)-C(2)-C(3)	64.54(12)	O(1)-C(10)-C(11)-C(12)	-179.12(10)
C(6)-C(1)-C(2)-C(3)	-55.24(13)	C(9)-C(10)-C(11)-C(12)	1.78(18)
C(14)-N(5)-C(3)-C(2)	165.35(11)	C(10)-C(11)-C(12)-C(7)	0.59(18)
C(14)-N(5)-C(3)-C(4)	-71.05(15)	C(8)-C(7)-C(12)-C(11)	-2.55(17)
N(4)-C(2)-C(3)-N(5)	-56.82(13)	N(4)-C(7)-C(12)-C(11)	-178.78(10)
C(1)-C(2)-C(3)-N(5)	178.51(9)	C(3)-N(5)-C(14)-C(15)	161.17(11)
N(4)-C(2)-C(3)-C(4)	178.65(10)	C(3)-N(5)-C(14)-C(19)	-21.36(19)
C(1)-C(2)-C(3)-C(4)	53.98(13)	N(5)-C(14)-C(15)-C(16)	177.34(11)
N(5)-C(3)-C(4)-C(5)	-178.98(10)	C(19)-C(14)-C(15)-C(16)	-0.24(18)
C(2)-C(3)-C(4)-C(5)	-55.75(14)	C(14)-C(15)-C(16)-C(17)	-0.3(2)
C(3)-C(4)-C(5)-C(6)	56.42(15)	C(15)-C(16)-C(17)-C(18)	0.3(2)
C(4)-C(5)-C(6)-C(1)	-55.97(15)	C(16)-C(17)-C(18)-C(19)	0.3(2)
N(1)-C(1)-C(6)-C(5)	-62.94(14)	C(17)-C(18)-C(19)-C(14)	-0.9(2)
C(2)-C(1)-C(6)-C(5)	56.36(15)	N(5)-C(14)-C(19)-C(18)	-176.67(12)
C(2)-N(4)-C(7)-C(8)	121.82(13)	C(15)-C(14)-C(19)-C(18)	0.84(19)
C(2)-N(4)-C(7)-C(12)	-62.07(15)		



ORTEP view of the C19 H23 N5 O compound with the numbering scheme adopted. Ellipsoids drawn at 30% probability level. Hydrogen atoms are represented by sphere of arbitrary size.

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Université de Montréal

CRYSTAL AND MOLECULAR STRUCTURE OF

C33 H38 N4 O5 Si COMPOUND (bent51)

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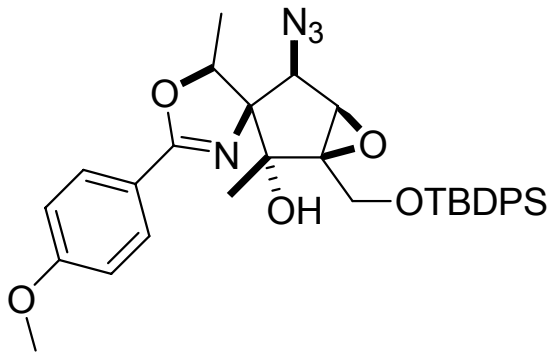


Structure solved and refined in the laboratory of X-ray diffraction Université de Montréal by Michel Simard and Benoît Deschênes Simard.

Table 1. Crystal data and structure refinement for C33 H38 N4 O5 Si.

Identification code	bent51
Empirical formula	C33 H38 N4 O5 Si
Formula weight	598.76
Temperature	150K
Wavelength	1.54178 Å
Crystal system	Monoclinic
Space group	C2
Unit cell dimensions	a = 17.8975(7) Å α = 90° b = 7.3027(3) Å β = 103.955(2)° c = 28.5293(11) Å γ = 90°
Volume	3618.7(2)Å^3
Z	4
Density (calculated)	1.099 g/cm^3
Absorption coefficient	0.903 mm^{-1}
F(000)	1272
Crystal size	0.15 x 0.12 x 0.12 mm
Theta range for data collection	1.60 to 72.43°
Index ranges	$-20 \leq h \leq 22$, $-8 \leq k \leq 9$, $-35 \leq \ell \leq 34$
Reflections collected	22572
Independent reflections	6683 [R_{int} = 0.045]
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.8973 and 0.6820
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	6683 / 193 / 441
Goodness-of-fit on F^2	1.048
Final R indices [I>2sigma(I)]	R_1 = 0.0612, wR_2 = 0.1641
R indices (all data)	R_1 = 0.0643, wR_2 = 0.1676
Absolute structure parameter	0.16(3)
Extinction coefficient	0.00095(15)

Largest diff. peak and hole	1.341 and -0.228 e/Å^3

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for C33 H38 N4 O5 Si.

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

	Occ.	x	y	z	U_{eq}
Si(1)	1	2002(1)	10545(1)	3694(1)	32(1)
O(1)	1	-234(1)	7504(4)	745(1)	52(1)
O(2)	1	1675(1)	7144(3)	1864(1)	52(1)
O(3)	1	466(1)	10208(3)	2359(1)	42(1)
O(4)	1	1835(1)	10346(3)	3102(1)	41(1)
O(5)	1	-3869(1)	8295(4)	227(1)	61(1)
N(1)	1	-353(1)	8585(4)	1468(1)	44(1)
N(2)	1	280(2)	11994(4)	1292(1)	57(1)
N(3)	1	-315(2)	12309(5)	1422(1)	60(1)
N(4)	1	-863(2)	12844(6)	1489(2)	85(1)
C(1)	1	1032(2)	8470(7)	725(1)	64(1)
C(2)	1	557(2)	7601(5)	1031(1)	50(1)
C(3)	1	478(2)	8580(5)	1508(1)	43(1)
C(4)	1	956(2)	7615(4)	1969(1)	41(1)
C(5)	1	1122(2)	9110(4)	2351(1)	37(1)
C(6)	1	1032(2)	10890(4)	2113(1)	42(1)
C(7)	1	802(2)	10584(5)	1572(1)	44(1)
C(8)	1	554(2)	5955(5)	2120(1)	54(1)
C(9)	1	1673(2)	8719(4)	2831(1)	44(1)
C(10)	1	-679(2)	8041(5)	1042(1)	43(1)
C(11)	1	-1512(2)	8007(5)	829(1)	47(1)
C(12)	1	-2008(2)	8943(6)	1053(1)	59(1)
C(13)	1	-2796(2)	8978(6)	846(1)	60(1)
C(14)	1	-3087(2)	8079(5)	411(1)	52(1)
C(15)	1	-2607(2)	7129(5)	188(1)	51(1)
C(16)	1	-1824(2)	7097(5)	399(1)	46(1)
C(17)	1	-4180(2)	7549(7)	-247(1)	69(1)
C(18)	0.63	1192(6)	9344(18)	3879(4)	37(1)
C(19)	0.63	1278(5)	8566(10)	4338(3)	45(2)
C(20)	0.63	661(5)	7698(10)	4467(3)	54(2)
C(21)	0.63	-40(5)	7466(14)	4129(3)	45(2)
C(22)	0.63	-135(5)	8347(10)	3683(3)	43(2)
C(23)	0.63	469(7)	9200(20)	3549(4)	40(2)
C(34)	0.37	1217(10)	9450(30)	3941(7)	37(1)
C(35)	0.37	1245(9)	9090(20)	4427(6)	45(2)
C(36)	0.37	660(9)	8254(18)	4593(5)	54(2)
C(37)	0.37	-3(10)	7770(30)	4250(6)	45(2)
C(38)	0.37	-33(9)	7970(20)	3763(6)	43(2)
C(39)	0.37	526(13)	8950(40)	3609(8)	40(2)
C(24)	0.53	2971(6)	9460(20)	3973(4)	40(1)
C(25)	0.53	3415(6)	8714(10)	3672(4)	42(2)
C(26)	0.53	4128(7)	7885(16)	3869(4)	57(3)
C(27)	0.53	4408(6)	7755(15)	4358(4)	59(3)
C(28)	0.53	3977(4)	8444(13)	4660(3)	68(2)
C(29)	0.53	3280(4)	9349(11)	4475(3)	52(2)
C(40)	0.47	2954(7)	9410(30)	3939(5)	40(1)
C(41)	0.47	3439(7)	9298(13)	3624(5)	42(2)
C(42)	0.47	4137(8)	8363(18)	3745(5)	57(3)
C(43)	0.47	4335(7)	7454(18)	4185(4)	59(3)

C(44)	0.47	3879(5)	7611(14)	4505(4)	68(2)
C(45)	0.47	3185(5)	8530(12)	4382(4)	52(2)
C(30)	0.86	2015(2)	13088(4)	3805(1)	34(1)
C(31)	0.86	2253(4)	13477(7)	4346(2)	69(1)
C(32)	0.86	1213(3)	13872(6)	3585(2)	59(1)
C(33)	0.86	2593(2)	13993(5)	3560(2)	51(1)
C(46)	0.14	2052(12)	12980(20)	3930(7)	34(1)
C(47)	0.14	2180(20)	12910(30)	4480(6)	69(1)
C(48)	0.14	1297(15)	13960(30)	3705(13)	59(1)
C(49)	0.14	2726(14)	14020(20)	3811(9)	51(1)

Table 3. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for C33 H38 N4 O5 Si.

	Occ.	x	y	z	U_{eq}
H(2)	1	1842	6168	2007	78
H(1A)	1	971	7778	423	96
H(1B)	1	1575	8464	900	96
H(1C)	1	862	9735	651	96
H(2A)	1	749	6327	1113	60
H(6)	1	1378	11931	2252	50
H(7)	1	1285	10597	1454	52
H(8A)	1	84	6350	2210	80
H(8B)	1	899	5358	2397	80
H(8C)	1	420	5090	1850	80
H(9A)	1	1441	7811	3012	53
H(9B)	1	2156	8196	2778	53
H(12)	1	-1807	9564	1349	70
H(13)	1	-3132	9613	1002	72
H(15)	1	-2809	6503	-107	61
H(16)	1	-1492	6436	246	55
H(17A)	1	-3923	8113	-477	104
H(17B)	1	-4733	7803	-345	104
H(17C)	1	-4095	6222	-240	104
H(19)	0.63	1763	8629	4564	54
H(20)	0.63	719	7262	4787	65
H(21)	0.63	-439	6737	4200	54
H(22)	0.63	-630	8358	3466	51
H(23)	0.63	397	9687	3232	48
H(35)	0.37	1696	9438	4660	54
H(36)	0.37	711	8022	4927	65
H(37)	0.37	-436	7310	4349	54
H(38)	0.37	-444	7432	3531	51
H(39)	0.37	445	9288	3279	48
H(25)	0.53	3229	8775	3331	51
H(26)	0.53	4421	7406	3660	69
H(27)	0.53	4893	7198	4488	70
H(28)	0.53	4159	8299	5000	81
H(29)	0.53	3012	9892	4690	62
H(41)	0.47	3289	9875	3317	51
H(42)	0.47	4471	8347	3532	69
H(43)	0.47	4787	6723	4264	70
H(44)	0.47	4042	7078	4816	81
H(45)	0.47	2863	8558	4603	62
H(31A)	0.86	2776	13015	4478	103
H(31B)	0.86	1896	12865	4506	103
H(31C)	0.86	2242	14800	4401	103
H(32A)	0.86	1218	15198	3638	88
H(32B)	0.86	838	13300	3740	88
H(32C)	0.86	1071	13618	3238	88
H(33A)	0.86	2436	13769	3211	77
H(33B)	0.86	3106	13474	3690	77
H(33C)	0.86	2605	15314	3621	77
H(47A)	0.14	2097	14131	4601	103
H(47B)	0.14	2701	12496	4626	103
H(47C)	0.14	1807	12051	4564	103
H(48A)	0.14	1399	15258	3665	88

H(48B)	0.14	944	13826	3917	88
H(48C)	0.14	1064	13414	3390	88
H(49A)	0.14	2946	13290	3590	77
H(49B)	0.14	3121	14244	4110	77
H(49C)	0.14	2542	15191	3659	77

Table 4. Anisotropic parameters ($Å^2$ x 10^3) for C33 H38 N4 O5 Si.

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
Si(1)	23(1)	34(1)	35(1)	2(1)	1(1)	0(1)
O(1)	38(1)	75(2)	42(1)	-25(1)	9(1)	-3(1)
O(2)	38(1)	61(1)	58(1)	-8(1)	13(1)	15(1)
O(3)	35(1)	49(1)	38(1)	-11(1)	1(1)	11(1)
O(4)	41(1)	39(1)	38(1)	-1(1)	2(1)	-5(1)
O(5)	33(1)	96(2)	47(1)	-4(1)	-4(1)	-8(1)
N(1)	32(1)	57(1)	38(1)	-13(1)	1(1)	6(1)
N(2)	63(2)	55(2)	45(2)	-1(1)	-4(1)	10(1)
N(3)	57(2)	59(2)	53(2)	-12(1)	-10(1)	17(2)
N(4)	69(2)	78(2)	95(3)	-16(2)	-7(2)	26(2)
C(1)	54(2)	87(3)	56(2)	-25(2)	22(2)	-11(2)
C(2)	36(2)	64(2)	49(2)	-21(2)	11(1)	-2(1)
C(3)	32(1)	52(2)	45(2)	-15(1)	8(1)	1(1)
C(4)	33(1)	42(1)	46(1)	-11(1)	6(1)	3(1)
C(5)	26(1)	42(1)	41(1)	-7(1)	7(1)	2(1)
C(6)	38(1)	40(2)	43(1)	-7(1)	2(1)	4(1)
C(7)	42(1)	46(1)	39(1)	-8(1)	3(1)	4(1)
C(8)	47(2)	48(2)	63(2)	-11(1)	8(2)	-4(1)
C(9)	33(1)	47(2)	48(2)	-8(1)	2(1)	6(1)
C(10)	38(2)	58(2)	35(1)	-17(1)	9(1)	-1(1)
C(11)	36(2)	65(2)	37(1)	-12(1)	4(1)	-2(1)
C(12)	44(2)	85(3)	42(2)	-26(2)	-1(1)	3(2)
C(13)	35(2)	100(3)	42(2)	-16(2)	4(1)	4(2)
C(14)	38(2)	73(2)	41(2)	0(1)	1(1)	-6(2)
C(15)	49(2)	68(2)	32(1)	-7(1)	2(1)	-9(2)
C(16)	45(2)	57(2)	37(1)	-11(1)	12(1)	-6(1)
C(17)	43(2)	109(3)	47(2)	-7(2)	-7(2)	-13(2)
C(18)	27(1)	35(2)	46(3)	4(2)	5(2)	2(1)
C(19)	34(2)	52(5)	49(4)	4(3)	9(2)	-1(3)
C(20)	55(2)	53(5)	54(4)	12(3)	11(3)	-6(3)
C(21)	33(2)	46(4)	62(5)	-9(3)	21(3)	-7(2)
C(22)	26(3)	37(4)	59(4)	10(3)	0(2)	20(2)
C(23)	28(2)	39(5)	49(3)	8(2)	3(2)	5(3)
C(34)	27(1)	35(2)	46(3)	4(2)	5(2)	2(1)
C(35)	34(2)	52(5)	49(4)	4(3)	9(2)	-1(3)
C(36)	55(2)	53(5)	54(4)	12(3)	11(3)	-6(3)
C(37)	33(2)	46(4)	62(5)	-9(3)	21(3)	-7(2)
C(38)	26(3)	37(4)	59(4)	10(3)	0(2)	20(2)
C(39)	28(2)	39(5)	49(3)	8(2)	3(2)	5(3)
C(24)	26(1)	41(2)	51(2)	8(2)	5(1)	1(1)
C(25)	26(2)	29(6)	66(3)	-3(4)	0(2)	-10(3)
C(26)	32(2)	49(6)	82(7)	-7(5)	-2(3)	6(3)
C(27)	26(2)	40(4)	96(8)	-8(4)	-12(4)	5(2)
C(28)	40(3)	75(6)	78(5)	27(4)	-6(3)	4(4)
C(29)	40(2)	58(5)	55(3)	19(4)	8(2)	11(3)
C(40)	26(1)	41(2)	51(2)	8(2)	5(1)	1(1)
C(41)	26(2)	29(6)	66(3)	-3(4)	0(2)	-10(3)
C(42)	32(2)	49(6)	82(7)	-7(5)	-2(3)	6(3)
C(43)	26(2)	40(4)	96(8)	-8(4)	-12(4)	5(2)

C(44)	40(3)	75(6)	78(5)	27(4)	-6(3)	4(4)
C(45)	40(2)	58(5)	55(3)	19(4)	8(2)	11(3)
C(30)	33(1)	35(1)	33(2)	6(1)	5(1)	-1(1)
C(31)	112(4)	50(2)	42(2)	-8(2)	15(2)	-7(3)
C(32)	42(2)	45(2)	89(4)	6(2)	14(2)	4(2)
C(33)	52(2)	38(2)	67(2)	3(2)	20(2)	-10(2)
C(46)	33(1)	35(1)	33(2)	6(1)	5(1)	-1(1)
C(47)	112(4)	50(2)	42(2)	-8(2)	15(2)	-7(3)
C(48)	42(2)	45(2)	89(4)	6(2)	14(2)	4(2)
C(49)	52(2)	38(2)	67(2)	3(2)	20(2)	-10(2)

Table 5. Bond lengths [Å] and angles [°] for C33 H38 N4 O5 Si

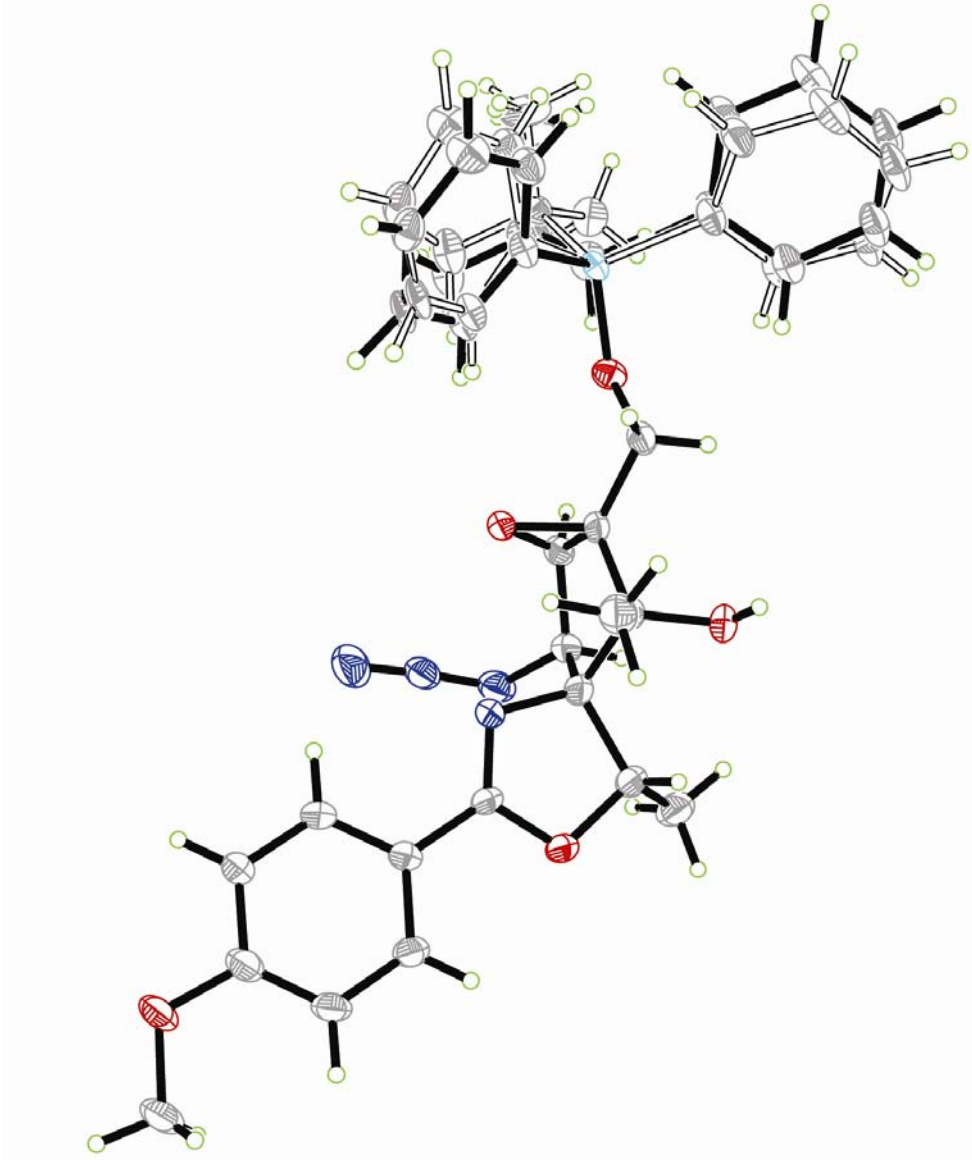
Si(1)-O(4)	1.6498(19)	C(42)-C(43)	1.387(12)
Si(1)-C(40)	1.870(9)	C(43)-C(44)	1.368(12)
Si(1)-C(18)	1.876(7)	C(44)-C(45)	1.380(10)
Si(1)-C(30)	1.883(3)	C(30)-C(31)	1.525(5)
Si(1)-C(34)	1.893(11)	C(30)-C(33)	1.530(5)
Si(1)-C(46)	1.893(14)	C(30)-C(32)	1.532(5)
Si(1)-C(24)	1.898(8)	C(46)-C(48)	1.526(13)
O(1)-C(10)	1.352(4)	C(46)-C(49)	1.531(13)
O(1)-C(2)	1.454(4)	C(46)-C(47)	1.532(13)
O(2)-C(4)	1.432(4)		
O(3)-C(5)	1.427(3)	O(4)-SI1-C(40)	105.5(5)
O(3)-C(6)	1.453(4)	O(4)-SI1-C(18)	106.6(3)
O(4)-C(9)	1.408(4)	C(40)-SI1-C(18)	112.6(7)
O(5)-C(14)	1.381(4)	O(4)-SI1-C(30)	104.55(12)
O(5)-C(17)	1.437(4)	C(40)-SI1-C(30)	113.5(6)
N(1)-C(10)	1.279(4)	C(18)-SI1-C(30)	113.2(4)
N(1)-C(3)	1.463(4)	O(4)-SI1-C(34)	112.1(6)
N(2)-N(3)	1.231(5)	C(40)-SI1-C(34)	111.4(9)
N(2)-C(7)	1.487(4)	C(30)-SI1-C(34)	109.5(8)
N(3)-N(4)	1.114(5)	O(4)-SI1-C(46)	115.3(6)
C(1)-C(2)	1.500(5)	C(40)-SI1-C(46)	108.7(9)
C(2)-C(3)	1.574(4)	C(18)-SI1-C(46)	108.2(7)
C(3)-C(4)	1.554(4)	C(34)-SI1-C(46)	103.8(10)
C(3)-C(7)	1.569(5)	O(4)-SI1-C(24)	108.3(4)
C(4)-C(5)	1.520(4)	C(18)-SI1-C(24)	112.1(6)
C(4)-C(8)	1.523(5)	C(30)-SI1-C(24)	111.6(6)
C(5)-C(6)	1.457(4)	C(34)-SI1-C(24)	110.6(8)
C(5)-C(9)	1.510(4)	C(46)-SI1-C(24)	106.4(8)
C(6)-C(7)	1.515(4)	C(10)-O(1)-C(2)	106.0(2)
C(10)-C(11)	1.468(4)	C(5)-O(3)-C(6)	60.77(17)
C(11)-C(16)	1.389(4)	C(9)-O(4)-SI1	126.75(19)
C(11)-C(12)	1.391(4)	C(14)-O(5)-C(17)	116.2(3)
C(12)-C(13)	1.392(4)	C(10)-N(1)-C(3)	107.1(2)
C(13)-C(14)	1.389(4)	N(3)-N(2)-C(7)	116.4(3)
C(14)-C(15)	1.374(5)	N(4)-N(3)-N(2)	168.1(5)
C(15)-C(16)	1.386(4)	O(1)-C(2)-C(1)	107.8(3)
C(18)-C(19)	1.401(8)	O(1)-C(2)-C(3)	103.2(2)
C(18)-C(23)	1.410(8)	C(1)-C(2)-C(3)	119.6(3)
C(19)-C(20)	1.398(8)	N(1)-C(3)-C(4)	114.1(3)
C(20)-C(21)	1.396(8)	N(1)-C(3)-C(7)	110.3(2)
C(21)-C(22)	1.401(9)	C(4)-C(3)-C(7)	102.2(2)
C(22)-C(23)	1.379(8)	N(1)-C(3)-C(2)	103.6(2)
C(34)-C(35)	1.400(12)	C(4)-C(3)-C(2)	112.3(2)
C(34)-C(39)	1.412(12)	C(7)-C(3)-C(2)	114.6(3)
C(35)-C(36)	1.390(12)	O(2)-C(4)-C(5)	107.0(2)
C(36)-C(37)	1.388(12)	O(2)-C(4)-C(8)	112.2(3)
C(37)-C(38)	1.385(13)	C(5)-C(4)-C(8)	113.2(3)
C(38)-C(39)	1.385(12)	O(2)-C(4)-C(3)	105.7(2)
C(24)-C(29)	1.408(10)	C(5)-C(4)-C(3)	104.7(2)
C(24)-C(25)	1.415(10)	C(8)-C(4)-C(3)	113.5(2)
C(25)-C(26)	1.402(9)	O(3)-C(5)-C(6)	60.51(19)
C(26)-C(27)	1.365(11)	O(3)-C(5)-C(9)	116.7(2)
C(27)-C(28)	1.384(11)	C(6)-C(5)-C(9)	124.5(2)
C(28)-C(29)	1.399(9)	O(3)-C(5)-C(4)	113.3(2)
C(40)-C(45)	1.392(11)	C(6)-C(5)-C(4)	109.1(2)
C(40)-C(41)	1.394(11)	C(9)-C(5)-C(4)	119.1(2)
C(41)-C(42)	1.392(11)	O(3)-C(6)-C(5)	58.71(18)

O(3)-C(6)-C(7)	113.1(2)	C(37)-C(38)-C(39)	121.1(14)
C(5)-C(6)-C(7)	108.4(2)	C(38)-C(39)-C(34)	120.2(14)
N(2)-C(7)-C(6)	115.2(3)	C(29)-C(24)-C(25)	117.2(7)
N(2)-C(7)-C(3)	114.6(2)	C(29)-C(24)-SI1	123.1(8)
C(6)-C(7)-C(3)	104.9(3)	C(25)-C(24)-SI1	119.8(7)
O(4)-C(9)-C(5)	110.0(2)	C(26)-C(25)-C(24)	120.8(9)
N(1)-C(10)-O(1)	118.9(3)	C(27)-C(26)-C(25)	121.0(10)
N(1)-C(10)-C(11)	125.6(3)	C(26)-C(27)-C(28)	119.3(9)
O(1)-C(10)-C(11)	115.5(2)	C(27)-C(28)-C(29)	121.2(8)
C(16)-C(11)-C(12)	118.4(3)	C(28)-C(29)-C(24)	120.4(8)
C(16)-C(11)-C(10)	121.6(3)	C(45)-C(40)-C(41)	117.5(8)
C(12)-C(11)-C(10)	120.0(3)	C(45)-C(40)-SI1	126.1(9)
C(11)-C(12)-C(13)	120.5(3)	C(41)-C(40)-SI1	116.0(8)
C(14)-C(13)-C(12)	119.6(3)	C(42)-C(41)-C(40)	122.1(10)
C(15)-C(14)-O(5)	124.8(3)	C(43)-C(42)-C(41)	118.5(11)
C(15)-C(14)-C(13)	120.7(3)	C(44)-C(43)-C(42)	120.0(11)
O(5)-C(14)-C(13)	114.5(3)	C(43)-C(44)-C(45)	121.2(9)
C(14)-C(15)-C(16)	119.1(3)	C(44)-C(45)-C(40)	120.5(9)
C(15)-C(16)-C(11)	121.6(3)	C(31)-C(30)-C(33)	109.1(3)
C(19)-C(18)-C(23)	118.0(7)	C(31)-C(30)-C(32)	110.5(3)
C(19)-C(18)-SI1	122.3(7)	C(33)-C(30)-C(32)	108.7(3)
C(23)-C(18)-SI1	119.7(7)	C(31)-C(30)-SI1	110.1(3)
C(20)-C(19)-C(18)	121.0(7)	C(33)-C(30)-SI1	109.3(2)
C(21)-C(20)-C(19)	120.6(7)	C(32)-C(30)-SI1	109.1(3)
C(20)-C(21)-C(22)	117.7(7)	C(48)-C(46)-C(49)	109.8(11)
C(23)-C(22)-C(21)	121.8(7)	C(48)-C(46)-C(47)	109.9(12)
C(22)-C(23)-C(18)	120.3(7)	C(49)-C(46)-C(47)	108.4(11)
C(35)-C(34)-C(39)	115.5(11)	C(48)-C(46)-SI1	109.2(11)
C(35)-C(34)-SI1	126.6(12)	C(49)-C(46)-SI1	111.1(10)
C(39)-C(34)-SI1	117.9(12)	C(47)-C(46)-SI1	108.4(10)
C(36)-C(35)-C(34)	124.9(12)		
C(37)-C(36)-C(35)	117.1(12)		
C(38)-C(37)-C(36)	120.0(13)		

Table 6. Torsion angles [°] for C33 H38 N4 O5 Si.

C(40)-SI1-O(4)-C(9)	68.8(7)	O(3)-C(5)-C(9)-O(4)	-46.8(3)
C(18)-SI1-O(4)-C(9)	-51.1(5)	C(6)-C(5)-C(9)-O(4)	24.4(4)
C(30)-SI1-O(4)-C(9)	-171.2(2)	C(4)-C(5)-C(9)-O(4)	171.2(2)
C(34)-SI1-O(4)-C(9)	-52.7(9)	C(3)-N(1)-C(10)-O(1)	3.7(4)
C(46)-SI1-O(4)-C(9)	-171.2(7)	C(3)-N(1)-C(10)-C(11)	-173.7(3)
C(24)-SI1-O(4)-C(9)	69.7(6)	C(2)-O(1)-C(10)-N(1)	3.7(4)
C(7)-N(2)-N(3)-N(4)	167.8(17)	C(2)-O(1)-C(10)-C(11)	-178.6(3)
C(10)-O(1)-C(2)-C(1)	-136.2(3)	N(1)-C(10)-C(11)-C(16)	-168.2(4)
C(10)-O(1)-C(2)-C(3)	-8.7(4)	O(1)-C(10)-C(11)-C(16)	14.3(5)
C(10)-N(1)-C(3)-C(4)	-131.2(3)	N(1)-C(10)-C(11)-C(12)	13.5(6)
C(10)-N(1)-C(3)-C(7)	114.3(3)	O(1)-C(10)-C(11)-C(12)	-164.0(3)
C(10)-N(1)-C(3)-C(2)	-8.8(4)	C(16)-C(11)-C(12)-C(13)	-0.7(6)
O(1)-C(2)-C(3)-N(1)	10.6(3)	C(10)-C(11)-C(12)-C(13)	177.6(4)
C(1)-C(2)-C(3)-N(1)	130.2(3)	C(11)-C(12)-C(13)-C(14)	-0.4(7)
O(1)-C(2)-C(3)-C(4)	134.2(3)	C(17)-O(5)-C(14)-C(15)	-3.8(5)
C(1)-C(2)-C(3)-C(4)	-106.1(4)	C(17)-O(5)-C(14)-C(13)	173.7(4)
O(1)-C(2)-C(3)-C(7)	-109.7(3)	C(12)-C(13)-C(14)-C(15)	1.2(6)
C(1)-C(2)-C(3)-C(7)	10.0(4)	C(12)-C(13)-C(14)-O(5)	-176.4(4)
N(1)-C(3)-C(4)-O(2)	159.1(2)	O(5)-C(14)-C(15)-C(16)	176.5(3)
C(7)-C(3)-C(4)-O(2)	-81.7(3)	C(13)-C(14)-C(15)-C(16)	-0.8(6)
C(2)-C(3)-C(4)-O(2)	41.6(3)	C(14)-C(15)-C(16)-C(11)	-0.3(5)
N(1)-C(3)-C(4)-C(5)	-88.1(3)	C(12)-C(11)-C(16)-C(15)	1.1(5)
C(7)-C(3)-C(4)-C(5)	31.1(3)	C(10)-C(11)-C(16)-C(15)	-177.2(3)
C(2)-C(3)-C(4)-C(5)	154.3(2)	O(4)-SI1-C(18)-C(19)	152.8(8)
N(1)-C(3)-C(4)-C(8)	35.8(3)	C(40)-SI1-C(18)-C(19)	37.6(12)
C(7)-C(3)-C(4)-C(8)	154.9(2)	C(30)-SI1-C(18)-C(19)	-92.8(9)
C(2)-C(3)-C(4)-C(8)	-81.8(3)	C(46)-SI1-C(18)-C(19)	-82.6(11)
C(6)-O(3)-C(5)-C(9)	116.3(3)	C(24)-SI1-C(18)-C(19)	34.5(12)
C(6)-O(3)-C(5)-C(4)	-99.5(3)	O(4)-SI1-C(18)-C(23)	-26.9(11)
O(2)-C(4)-C(5)-O(3)	156.9(2)	C(40)-SI1-C(18)-C(23)	-142.1(12)
C(8)-C(4)-C(5)-O(3)	-79.1(3)	C(30)-SI1-C(18)-C(23)	87.5(10)
C(3)-C(4)-C(5)-O(3)	45.0(3)	C(46)-SI1-C(18)-C(23)	97.7(12)
O(2)-C(4)-C(5)-C(6)	91.6(3)	C(24)-SI1-C(18)-C(23)	-145.2(11)
C(8)-C(4)-C(5)-C(6)	-144.4(3)	C(23)-C(18)-C(19)-C(20)	-1.1(13)
C(3)-C(4)-C(5)-C(6)	-20.3(3)	SI1-C(18)-C(19)-C(20)	179.2(8)
O(2)-C(4)-C(5)-C(9)	-59.9(3)	C(18)-C(19)-C(20)-C(21)	4.8(9)
C(8)-C(4)-C(5)-C(9)	64.2(3)	C(19)-C(20)-C(21)-C(22)	-8.6(11)
C(3)-C(4)-C(5)-C(9)	-171.7(3)	C(20)-C(21)-C(22)-C(23)	9.1(15)
C(5)-O(3)-C(6)-C(7)	98.2(3)	C(21)-C(22)-C(23)-C(18)	-6(2)
C(9)-C(5)-C(6)-O(3)	-103.8(3)	C(19)-C(18)-C(23)-C(22)	1.5(19)
C(4)-C(5)-C(6)-O(3)	106.6(2)	SI1-C(18)-C(23)-C(22)	-178.8(12)
O(3)-C(5)-C(6)-C(7)	-106.4(2)	O(4)-SI1-C(34)-C(35)	167.8(13)
C(9)-C(5)-C(6)-C(7)	149.8(3)	C(40)-SI1-C(34)-C(35)	49.7(19)
C(4)-C(5)-C(6)-C(7)	0.2(3)	C(30)-SI1-C(34)-C(35)	-76.7(17)
N(3)-N(2)-C(7)-C(6)	-53.5(4)	C(46)-SI1-C(34)-C(35)	-67.1(18)
N(3)-N(2)-C(7)-C(3)	68.4(4)	C(24)-SI1-C(34)-C(35)	46.7(18)
O(3)-C(6)-C(7)-N(2)	83.7(3)	O(4)-SI1-C(34)-C(39)	-13(2)
C(5)-C(6)-C(7)-N(2)	146.7(3)	C(40)-SI1-C(34)-C(39)	-130.7(19)
O(3)-C(6)-C(7)-C(3)	-43.3(3)	C(30)-SI1-C(34)-C(39)	102.8(18)
C(5)-C(6)-C(7)-C(3)	19.7(3)	C(46)-SI1-C(34)-C(39)	112.4(19)
N(1)-C(3)-C(7)-N(2)	-36.7(4)	C(24)-SI1-C(34)-C(39)	-133.7(19)
C(4)-C(3)-C(7)-N(2)	-158.5(3)	C(39)-C(34)-C(35)-C(36)	1.6(19)
C(2)-C(3)-C(7)-N(2)	79.8(3)	SI1-C(34)-C(35)-C(36)	-178.9(17)
N(1)-C(3)-C(7)-C(6)	90.7(3)	C(34)-C(35)-C(36)-C(37)	-1.0(15)
C(4)-C(3)-C(7)-C(6)	-31.1(3)	C(35)-C(36)-C(37)-C(38)	6(2)
C(2)-C(3)-C(7)-C(6)	-152.9(2)	C(36)-C(37)-C(38)-C(39)	-12(3)
SI1-O(4)-C(9)-C(5)	146.3(2)	C(37)-C(38)-C(39)-C(34)	13(4)

C(35)-C(34)-C(39)-C(38)	-7(3)
SI1-C(34)-C(39)-C(38)	173(2)
O(4)-SI1-C(24)-C(29)	-178.2(11)
C(18)-SI1-C(24)-C(29)	-60.9(14)
C(30)-SI1-C(24)-C(29)	67.2(13)
C(34)-SI1-C(24)-C(29)	-54.9(15)
C(46)-SI1-C(24)-C(29)	57.2(14)
O(4)-SI1-C(24)-C(25)	1.8(12)
C(18)-SI1-C(24)-C(25)	119.0(10)
C(30)-SI1-C(24)-C(25)	-112.8(10)
C(34)-SI1-C(24)-C(25)	125.0(12)
C(46)-SI1-C(24)-C(25)	-122.8(12)
C(29)-C(24)-C(25)-C(26)	0.7(13)
SI1-C(24)-C(25)-C(26)	-179.2(11)
C(24)-C(25)-C(26)-C(27)	0.8(12)
C(25)-C(26)-C(27)-C(28)	0.4(16)
C(26)-C(27)-C(28)-C(29)	-3.2(15)
C(27)-C(28)-C(29)-C(24)	4.8(15)
C(25)-C(24)-C(29)-C(28)	-3.4(17)
SI1-C(24)-C(29)-C(28)	176.5(9)
O(4)-SI1-C(40)-C(45)	-149.8(14)
C(18)-SI1-C(40)-C(45)	-34.0(17)
C(30)-SI1-C(40)-C(45)	96.3(15)
C(34)-SI1-C(40)-C(45)	-27.9(19)
C(46)-SI1-C(40)-C(45)	85.9(17)
O(4)-SI1-C(40)-C(41)	23.3(13)
C(18)-SI1-C(40)-C(41)	139.1(11)
C(30)-SI1-C(40)-C(41)	-90.6(11)
C(34)-SI1-C(40)-C(41)	145.2(12)
C(46)-SI1-C(40)-C(41)	-101.0(13)
C(45)-C(40)-C(41)-C(42)	-1.0(15)
SI1-C(40)-C(41)-C(42)	-174.7(13)
C(40)-C(41)-C(42)-C(43)	2.9(13)
C(41)-C(42)-C(43)-C(44)	-5.2(18)
C(42)-C(43)-C(44)-C(45)	5.8(17)
C(43)-C(44)-C(45)-C(40)	-3.8(18)
C(41)-C(40)-C(45)-C(44)	1(2)
SI1-C(40)-C(45)-C(44)	174.4(11)
O(4)-SI1-C(30)-C(31)	-173.8(3)
C(40)-SI1-C(30)-C(31)	-59.3(5)
C(18)-SI1-C(30)-C(31)	70.7(5)
C(34)-SI1-C(30)-C(31)	65.9(7)
C(24)-SI1-C(30)-C(31)	-56.9(5)
O(4)-SI1-C(30)-C(33)	-53.9(3)
C(40)-SI1-C(30)-C(33)	60.5(5)
C(18)-SI1-C(30)-C(33)	-169.5(4)
C(34)-SI1-C(30)-C(33)	-174.2(7)
C(24)-SI1-C(30)-C(33)	63.0(5)
O(4)-SI1-C(30)-C(32)	64.8(3)
C(40)-SI1-C(30)-C(32)	179.3(5)
C(18)-SI1-C(30)-C(32)	-50.7(5)
C(34)-SI1-C(30)-C(32)	-55.4(7)
C(24)-SI1-C(30)-C(32)	-178.3(5)
O(4)-SI1-C(46)-C(48)	57.9(15)
C(40)-SI1-C(46)-C(48)	176.2(15)
C(18)-SI1-C(46)-C(48)	-61.2(15)
C(34)-SI1-C(46)-C(48)	-65.1(15)
C(24)-SI1-C(46)-C(48)	178.1(14)
O(4)-SI1-C(46)-C(49)	-63.4(13)
C(40)-SI1-C(46)-C(49)	54.8(14)
C(18)-SI1-C(46)-C(49)	177.5(12)
C(34)-SI1-C(46)-C(49)	173.6(13)
C(24)-SI1-C(46)-C(49)	56.8(14)
O(4)-SI1-C(46)-C(47)	177.6(13)
C(40)-SI1-C(46)-C(47)	-64.1(15)
C(18)-SI1-C(46)-C(47)	58.5(14)
C(34)-SI1-C(46)-C(47)	54.6(15)
C(24)-SI1-C(46)-C(47)	-62.2(14)



ORTEP view of the C33 H38 N4 O5 Si 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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