

Ammonium-Directed Epoxidation in the Asymmetric Syntheses of Dihydroconduramines and Conduramines

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by

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“Like all sciences, chemistry is marked by magic moments. For someone fortunate enough to live such a moment, it is an instant of intense emotion: an immense field of investigation suddenly opens up before you.”

Yves Chauvin, Nobel prize 2005
(1930-2015)

The work described in this thesis was carried out in the Chemistry Research Laboratory, University of Oxford from October 2015 until July 2019, under the supervision of Professor Stephen G. Davies. All of the work is my own unless otherwise stated and has not been submitted previously for any other degree at this or any other university.



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Abstract

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This thesis centres on the asymmetric syntheses of a family of synthetic products: dihydroconduramines and conduramines. The work aims to use the ammonium-directed epoxidation methodology as a key step in all cases.

Chapter 1 introduces a review of literature reports relating to the biological activity and synthetic strategies to access dihydroconduramines and conduramines.

Chapter 2 investigates the olefinic oxidation protocol of racemic *N*-protected *anti*- and *syn*-2-aminocyclohex-3-en-1-ols. Concise syntheses of racemic dihydroconduramines ($\pm$)-A-2 and ($\pm$)-C-2 are also presented.

Chapter 3 describes the syntheses of enantiopure *N*-protected *anti*- and *syn*-2-aminocyclohex-3-en-1-ols in order to access enantiopure dihydroconduramines. Investigation of the surrogacy of these substrates to the racemate is also undertaken.

Chapter 4 details the asymmetric synthesis of four new enantiopure dihydroconduramines from an appropriate enantiopure *anti*-2 aminocyclohex-3-en-1-ols.

Chapter 5 details the asymmetric synthesis of four six enantiopure dihydroconduramines from an appropriate enantiopure *syn*-2 aminocyclohex-3-en-1-ols.

Chapter 6 investigates the olefinic oxidation protocol of primary, secondary and tertiary racemic allylic amino alcohols, derived from ring-opening of benzene oxide with primary, secondary and tertiary amines.

Chapter 7 describes concise asymmetric syntheses of six conduramines, including four new, from enantiopure allylic amino alcohols, derived from ring-opening of benzene oxide with (*R*)- α -methylbenzylamine.

Chapter 8 contains full experimental procedures and characterisation for all compounds synthesised in chapter 2-7.

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Abbreviations

~	Approximately
(+)	Dextrorotary
(-)	Levorotatory
°	Degrees
$[\alpha]_D$	Specific rotation
δ	NMR chemical shift
μ	Micro
Δ	Difference
$\nu_{\max}$	Infrared absorption maximum
α	Alpha
$\text{\AA}$	Angstrom
Ac	Acetyl
all	Allylic
app	Apparent
Ar	Aryl
atm	Atmospheres
ATR	Attenuated total reflectance
aq	Aqueous
Bn	Benzyl
β	<i>Bêta</i>

Abbreviations

Boc	<i>tert</i> -Butoxycarbonyl
br	Broad
Bu	Butyl
^t Bu	<i>tert</i> -Butyl
Bz	Benzoyl
c	Centi
<i>c</i>	Concentration
C	Celsius
cat	Catalytic
Cbz	Carboxybenzyl
conc	concentrated
d	Doublet
D	Dextrorotary relative to (+)-glyceraldehyde
DBU	1,8-Diazabicyclo-[5.4.0]-undec-7-ene
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	Diethyl azodicarboxylate
deg	Degrees
DIBAL-H	Diisobutylaluminium hydride
DIPEA	<i>N,N</i> -Diisopropylethylamine
DIPHOS	1,2-Bis(diphenylphosphino)ethane

Abbreviations

DMAP	4-Dimethylaminopyridine
DMP	Dess-Martin Periodinane
DMF	<i>N,N</i> -Dimethylformamide
dr	Diastereomeric ratio
<i>E</i>	Entgegen
ee	Enantiomeric excess
<i>ent</i>	Enantiomer
er	Enantiomeric ratio
ESI ⁺	Positive electrospray ionisation
<i>et al.</i>	<i>et alia</i>
Et	Ethyl
equiv	Equivalents
FT	Fourier transform
g	Grams
h	Hours
HFIP	1,1,1,3,3,3-Hexafluoro-2-propanol
HMDS	Bis(trimethylsilyl)amide
HPLC	High-performance liquid chromatography
HRMS	High resolution mass spectrometry
Hz	Hertz
<i>i</i>	iso

Abbreviations

<i>i</i>	<i>ipso</i>
IR	Infrared
<i>J</i>	Coupling constant
K	Kelvin
L	Litres
lit.	Literature
m	Multiplet
m	Milli
m	Metre
<i>m</i>	Meta
M	Molar
M	Mega
m/z	Mass to charge ratio
<i>m</i> -CBA	<i>meta</i> -Chlorobenzoic acid
<i>m</i> -CPBA	<i>meta</i> -Chloroperoxybenzoic acid
Me	Methyl
min	Minutes
mL	Millilitres
mol	Moles
mp	Melting point
MPM	<i>para</i> -methoxybenzyl

Abbreviations

Ms	Methanesulfonyl
MS	Molecular sieves
n	Nano
NDMBA	1,3-Dimethylbarbituric acid
NMO	4-Methylmorpholine <i>N</i> -oxide
NMR	Nuclear magnetic resonance
Nu	Nucleophile
<i>o</i>	Ortho
<i>p</i>	Para
Ph	Phenyl
PMP	<i>para</i> -Methoxyphenyl
ppm	Parts per million
PPTS	Pyridinium <i>para</i> -toluenesulfonate
Pr	Propyl
q	Quartet
quant	Quantitative
R	Rectus
R	Unspecified organic group
®	Registered trademark
rt	Room temperature
s	Singlet

Abbreviations

<i>S</i>	Sinister
S _N 2	Substitution, nucleophilic, bimolecular
satd	Saturated
<i>t</i>	Tertiary
t	Triplet
TBAF	Tetrabutylammonium fluoride
TBDPS	<i>tert</i> -Butyldiphenylsilyl
TBS	<i>tert</i> -Butyldimethylsilyl
<i>tert</i>	Tertiary
TMS	Trimethylsilyl
Tf	Trifluoromethanesulfonyl
THF	Tetrahydrofuran
TLC	Thin layer chromatography
Tol	<i>para</i> -Methylphenyl
Ts	<i>para</i> -Toluenesulfonyl
UV	Ultraviolet
v	Volume
Vit.	Vitamine
w	Weight
wt	Weight
Z	Zusammen

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Abstract

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Chapter 1

Introduction

1.1 Carbohydrates

Carbohydrates have prompted a great curiosity for the scientific community. Their structural diversity originating from the presence of multiple linkages and/or branches in each monomer of the carbohydrate, and their α or β anomeric configuration adopted during the glycosidic linkage make them one of the most abundant and interesting classes of biological compound in Nature.¹ These energy storage compounds fall into four distinct types: monosaccharides, disaccharides, oligosaccharides and polysaccharides. When covalently linked – by a glycosidic bond – to another non-sugar molecule such as protein, peptide, lipid or saccharide or to another functional group, carbohydrates form glycoconjugates.² Cellulose **1** is certainly one of the most well known carbohydrates: represented as the most abundant polymer on earth, this polysaccharide is constituted of a linear succession from 15 to 15,000 β -D-glucose units linked by glycosidic bonds.³ Salicin **2** is also another notable molecule showing biologically interesting activity. This glycoconjugate, isolated from willow *salix* bark and containing a D-glucose unit linked to a salicyl alcohol moiety, presents similarities with aspirin and has been used as an anti-inflammatory agent in the human body. Finally, oleander *Nerium Oleander L.* has been used, for centuries, as a remedy for indigestion, malaria, leprosy, mental or venereal diseases and as an abortifacient. Oleandrin **3**, a glycoside extracted from this plant, is commonly used as a toxic agent in a wide range of tumor cells as well as to treat heart failure (Figure 1).⁴

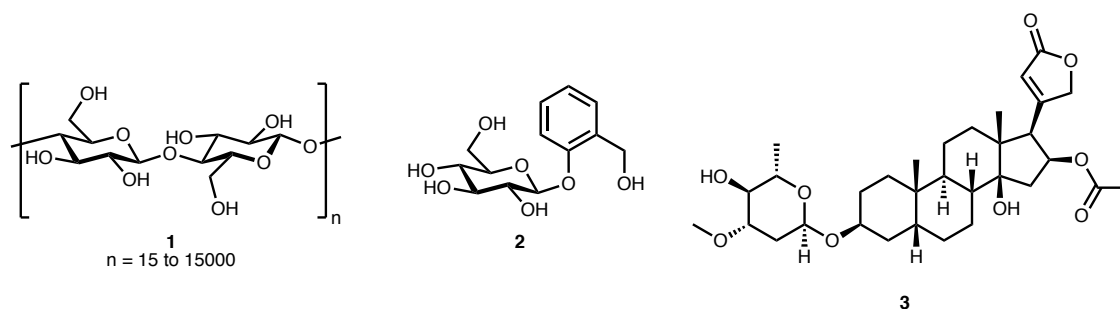


Figure 1. Structures of cellulose **1**, salicin **2** and oleandrin **3**.

Although the first natural glycoside synthesis, helicin **4** (Figure 2), by Arthur Michael dates back 140 years,^{5,6,7} the synthesis of carbohydrates or glucoconjugates remains a modern challenge. Indeed, the regio- and stereocontrol as well as the selective reaction of one of the hydroxyl functional group *via* a succession of protection/deprotection steps during the chemistry process constitute a considerable endeavour.^{8,9}

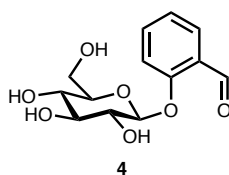


Figure 2. Structure of helicin **4**.

Carbohydrates are also considered as potent agents involved in a wide range of biological events such as, diabetes, cancer, inflammations, pathogen infections, and cell-to-cell communication. Syntheses of molecules mimicking natural carbohydrates thanks to their structural similarities were therefore envisaged to inhibit enzymes and counter biological malfunction process. Glycosidase enzymes are well known for their capacity to cleave (by hydrolysis) carbohydrates into monosaccharides. Inhibiting these enzymes can have a real impact on the sugar level control and these inhibitors are considered as potential therapeutic agents against diabetes, obesity, viral infection, cancer, and some genetic disorders such as Gaucher's diseases.^{10,11,12} In 1966, nojirimycin **5** was the first glycosidase inhibitor discovered from the cultured broth of *Streptomyces roseochromogenes* and *S.*

lavendulae.¹³ This antibiotic is an inhibitor of α - and β -glucosidases from various sources and has the capacity to mimic glucose although it contains a nitrogen atom instead of an oxygen atom. Since this very first discovery, over a hundred glycosidase inhibitors have been isolated from plants and microorganisms.^{11,14} Nowadays, commercially available drugs contain the core of nojirimycin. For instance, miglitol **6**, a deoxynojirimycin derivative, is used in the treatment of non-insulin-dependent type II diabetes mellitus (Glyset[®] and Diastabol[®]). By inhibiting the α -glucosidase enzyme, **6** postpones the hydrolysis of carbohydrates into monosaccharides in the small intestine and thus controls the glucose level in blood. Miglustat **7**, another deoxynojirimycin derivative, is used in the treatment of Gaucher's disease, the most common of lysosomal storage disorders (LSDs). Gaucher's disease is linked to an incapacity of the glucosylceramide β -glucosidases to degrade glucosylceramides, leading to their overabundance in cells. Therefore, **7** acts as an inhibitor of the glucosylceramide synthase enzymes responsible for the first step in their synthesis (Figure 3).

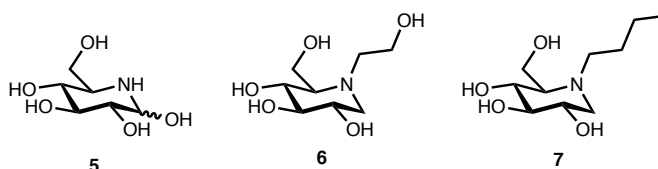


Figure 3. Structures of nojirimycin **5**, miglitol **6** and miglustat **7**.

1.2 Conduritols

Cycloalkanes containing at least three hydroxyl groups are known as cyclitols. However, in the case of cyclohex-5-ene-1,2,3,4-tetrols, where a C=C double bond is present, the isomers are called conduritols.¹⁵ Ten stereoisomers are possible but, due to the presence of two *meso*-forms (conduritols A **8** and D **11**), only six different diastereoisomers exist. A letter, A–F, is assigned to distinguish the 6 different relative configurations (Figure 4).

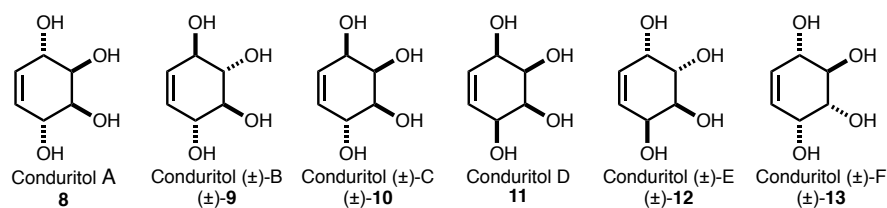


Figure 4. Structures of racemic conduritols **8**, (±)-**9**, (±)-**10**, **11**, (±)-**12**, (±)-**13**.

In 1908, the very first racemic conduritol (A **8**) was isolated from the bark of the vine *Marsdenia condurango*,¹⁶ but the relative configuration was only assigned 30 years later by Dangschat and Fischer by degradation of **8** into mucic acid.¹⁷ In 2000, (–)-conduritol F **13** was isolated by Abe and co-workers from Asclepiadaceous *Tylophora tanakae*, *Asclepias curassavica* and *A. fruticosa* plants.¹⁸ Although only conduritols A and F¹⁸ have been found in Nature, syntheses of all six conduritols were achieved in both racemic and enantiomerically pure forms.^{17,19,20} These cyclic polyols and their derivatives have antibiotic, antileukemic and tumor-inhibitory activities,^{17,21} and conduritols are also valued as intermediates in the synthesis of therapeutical agents. For instance, cyclohexan-1,2,3,4,5,6-hexaols or inositols were synthesised from conduritols. These cyclitols, abundant in brain and mammalian tissues, have prompted a great curiosity for research, such as *myo*-inositol **14** and *D-chiro*-inositol **15**, which have therapeutical effect for the treatment of polycystic ovary syndrome [(PCOS), Figure 5].²²

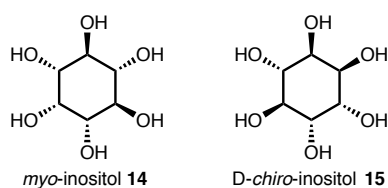


Figure 5. Structures of *myo*-inositol **14** and *D-chiro*-inositol **15**.

1.3 Conduramines and dihydroconduramines

Among all the derivatives of conduritols, a synthetic, non-natural, class of products showed interesting inhibitory activities toward glycosidases: conduramines, the deoxyamino counterparts, and dihydroconduramines, their saturated analogues. The same letters as for conduritols, A–F, are given to conduramines and dihydroconduramines on the basis of the relative configurations therein. A number from 1–4 assigns the position of the amino group within the molecule. The exchange of the hydroxyl functionality by an amino moiety within the conduritols core either at positions C(1)/C(4) or C(2)/C(3) renders two different regioisomers. The presence of internal symmetry within the conduramines A, B, D and E (σ or C2) turns the ‘O for N’ substitution at C(1)/C(4) and C(2)/C(3) identical, whereas the absence of symmetry within aminoconduritols C and F gives access to two distinct diastereoisomers. Therefore, 32 enantiopure structures (i.e., 16 diastereoisomers and their enantiomers) are possible for the conduramines ($\pm$)-**16**–($\pm$)-**31** (Figure 6). The same rational could be given to the aminocyclitol analogues: dihydroconduramines ($\pm$)-**32**–($\pm$)-**47** (Figure 7).

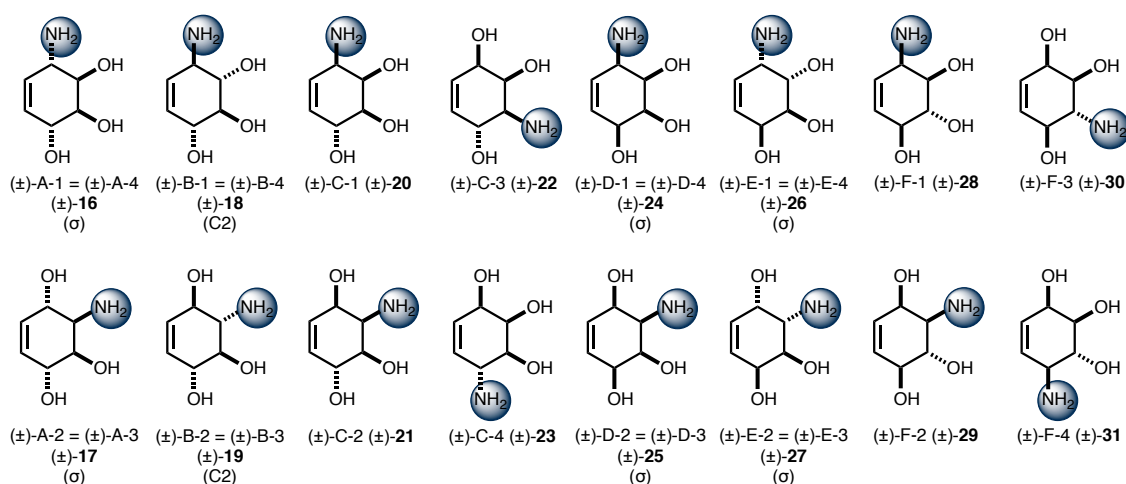


Figure 6. Structures of conduramines ($\pm$)-**16**–($\pm$)-**31**.

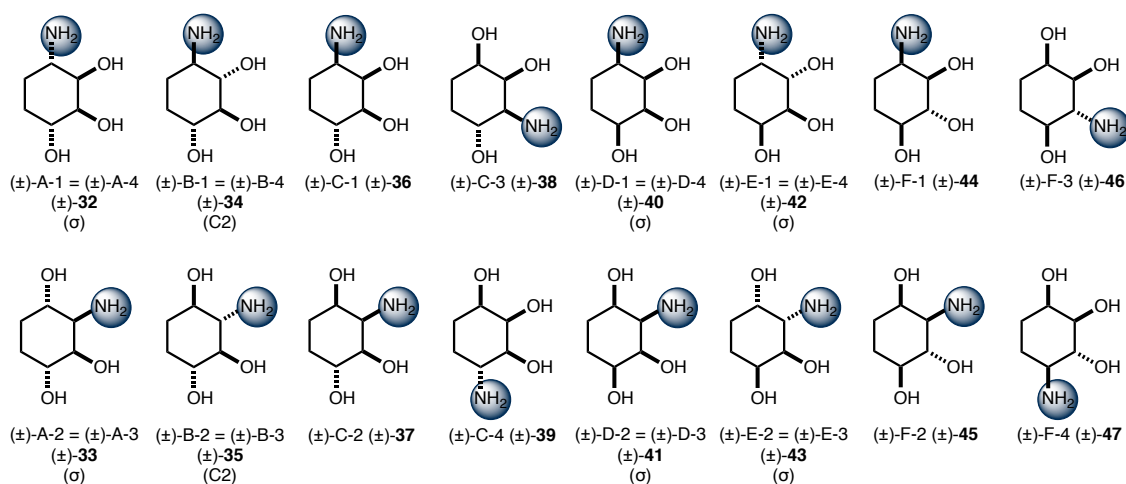


Figure 7. Structures of dihydroconduramines (±)-32–(±)-47.

The conduramine core has been found in many biologically active products. Commercialised under the name Glucobay[®] in Europe, arcabose **48**, an antidiabetic, contains the core of conduramine F-1. Also, (+)-narciclasine **49**, isolated from several varieties of *Narcissus* bulbs in 1967 by Ceriotti,^{23,24} and (+)-lycoricidine **50**, isolated from the bulbs of *Lycoris radiata* herb in 1989 by Okamoto *et al.*,²⁵ are also two natural products containing the core of conduramine A-1 and have generated a great interest due to their antibacterial and antihypersensitive properties and unique biological inhibition activity against several human cancer cells (Figure 8).²⁶

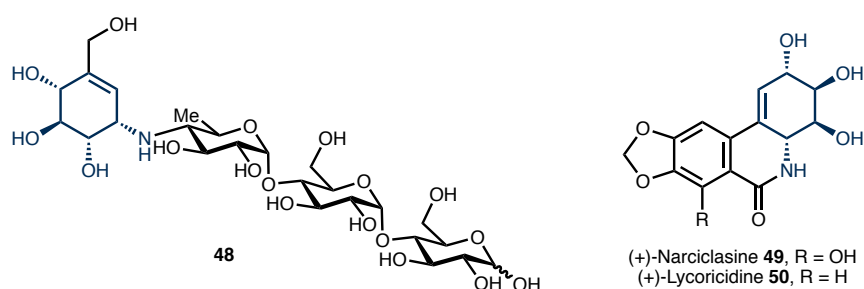
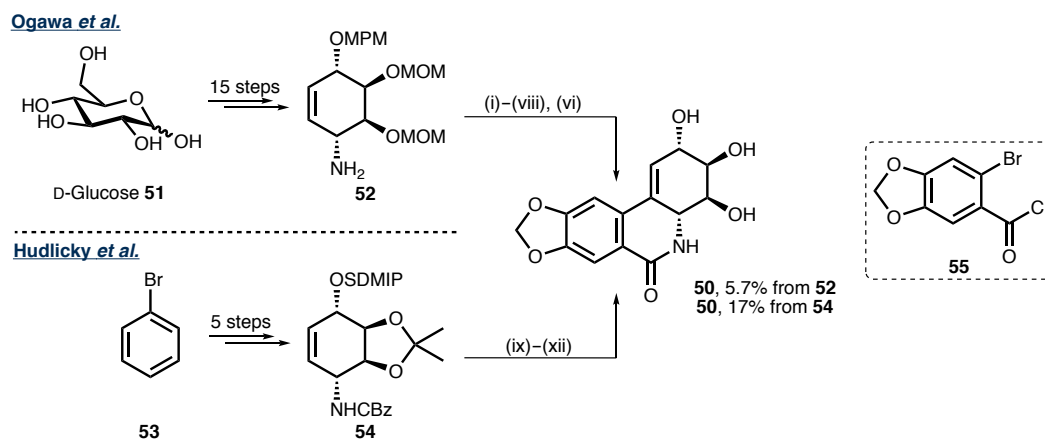


Figure 8. Structures of arcabose **48**, (+)-narciclasine **49** and (+)-lycoricidine **50**. The core of conduramines F-1 and A-1 is highlighted in blue

In 1991, Ogawa and co-workers synthesised (+)-lycoricidine **50**, in 24 steps from D-glucose **51**, using a protected conduramine A-1 **52** as an intermediate.²⁷ Two years later, Hudlicky and co-workers succeeded in synthesising **50**, in 9 steps from bromobenzene **53**, using

different *O*- and *N*-protecting groups on the intermediate conduramine A-1 **54** (Scheme 1).²⁸



Scheme 1. Reagents and condition: (i) **55**, (EtO)₂P(O)CN, Et₃N, DMF; (ii) NaH, MPMCl, DMF; (iii) Pd(OAc)₂, DIPHOS, TIOAc, DMF, 140 °C, 48 h; (iv) DDQ, CH₂Cl₂/H₂O (19:1, v/v); (v) PPh₃, diethyl azodicarboxylate, benzoic acid, THF; (vi) MeONa, MeOH, rt; (vii) HCl (1 M aq)/THF (1:1, v/v), 50 °C, then Ac₂O, pyridine; (viii) CF₃CO₂H/CHCl₃ (1:1, v/v), rt, 2 h; (ix) BuLi, THF, –78 °C, then **55** in THF (0.24 M), –78 °C, then –78 °C to 0 °C, then KHCO₃, 0 °C, 1 h; (x) Pd(OAc)₂, DIPHOS, TIOAc, anisole, 135 °C, 7 h; (xi) Pd/C, cyclohexadiene, reflux, 2 h; (xii) CF₃CO₂H, 0 °C, 20 min.

Conduramine derivatives are also useful intermediates for the syntheses of aza sugars^{29,30,31}, such as (+)-D-mannoirimycin **56** or (+)-kifunensine **57**, lactams,³² such as D-glucaro-1,5-lactam derivatives **58–60**, or even sphingosines,³³ such as D-*erythro*-C₁₈- and L-*threo*-C₁₈-sphingosines **61** and **62**. All these compounds show interesting biological activities as inhibitors of glycosidases (Figure 9).

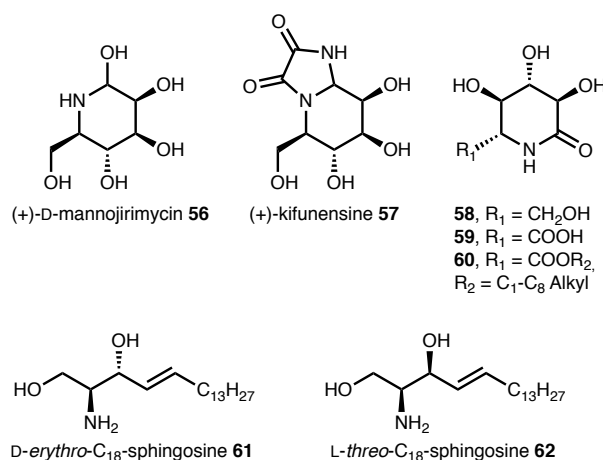


Figure 9. Structures of (+)-D-mannoirimycin **56**, (+)-kifunensine **57**, D-glucaro-1,5-lactam derivatives **58–60**, and D-*erythro*-C₁₈- and L-*threo*-C₁₈-sphingosines **61** and **62**.

1.4 Biological activities of conduramines and dihydroconduramines

Due to their potential inhibition effect on glycosidases, needless to say that conduramines and dihydroconduramines had to be assayed. Łysek *et al.* have reported the inhibitory activity of (±)-conduramine F-1 (±)-**28**, its enantiomerically pure forms (–)-F-1 **28** and (+)-F-1 *ent*-**28** and (±)-dihydroconduramine F-1 (±)-**44** towards seventeen glycosidases³⁴. These results revealed a highly selective but moderate competitive inhibition of *ent*-**28** for maltase from yeast (96%, $IC_{50} = 250 \mu M$ and $K_i = 42 \mu M$) and no inhibition towards the other enzymes at 1 mM. **28** showed weak inhibition toward α -mannosidase from jack bean (34% at 1 mM) and β -N-acetylglucosaminidase from jack bean (23% at 1 mM) to no inhibition towards the other enzymes. Unsurprisingly, (±)-**28** displayed a less selective inhibition [β -galactosidase from bovine liver (70%), maltase from yeast (45%, $IC_{50} = 550 \mu M$), amyloglucosidase from *Rhizopus* mold (45%), α -mannosidase from jack bean (40%)]. (±)-Dihydroconduramine F-1 (±)-**44** appeared to be inactive toward the seventeen glycosidases. It was suggested that the flat shape of these unsaturated molecules and their rigidity were determining for the inhibition of these glycosidases. Furthermore, due to the hydrophobic character around the active site of the glycosidase, it was also envisaged that the introduction of an *N*-protecting group on conduramines could improve their inhibitory activity toward some prevalent enzymes. Derivatives of (±)-**28**, **28** and *ent*-**28** were synthesised and assayed towards the same glycosidases: they proved to be better potent inhibitors against maltase for yeast (α -glucosidases) than their *N*-free source [Best cases: (*N*-PG: *p*-OH-C₆H₄CH₂, 97%, $IC_{50} = 3.5 \mu M$ and $K_i = 0.9 \mu M$), (*N*-PG: 4-(4-pyridinyl)phenylmethyl, 98%, $IC_{50} = 6.0 \mu M$ and $K_i = 0.54 \mu M$), (*N*-PG: 5-bromothiophene-2-yl, 97%, $IC_{50} = 7.5 \mu M$ and $K_i = 0.45 \mu M$)]. They were also weakly active toward amyloglucosidases from *Rhizopus* mold compared to their protecting-group free conduramines, which were not (Table 1).¹²

Inhibited glycosidases among the 17	(±)-F-1 (±)- 28	(-)-F-1 28	(+)-F-1 <i>ent</i> - 28	(±)-F-1 (±)- 28	N-derivatives of (±)- 28 , 28 and <i>ent</i> - 28 ^[a]
α-glucosidase maltase from yeast	45% at 1 mM		97%, K _i = 42 μM IC ₅₀ = 250 μM		97%, K _i = 42 μM, IC ₅₀ = 250 μM <i>p</i> -OHC ₆ H ₄ CH ₂
α-glucosidase maltase from rice					
α-mannosidase from jack bean	40% at 1 mM	34% at 1 mM			
β-N-acetylglucosaminidase from jack bean		23% at 1 mM			
β-galactosidase from bovine liver	70% at 1 mM				84%, <i>m</i> -(<i>p</i> -CO ₂ Me-C ₆ H ₄)-C ₆ H ₄ CH ₂
amyloglucosidase from <i>Rhizopus</i> mold	45% at 1 mM		40% at 1 mM		84%, IC ₅₀ = 156 μM <i>m</i> -(<i>p</i> -CO ₂ Me-C ₆ H ₄)-C ₆ H ₄ CH ₂
amyloglucosidase from <i>A. Niger</i>					60%, IC ₅₀ = 300 μM <i>p</i> -PhC ₆ H ₄ CH ₂

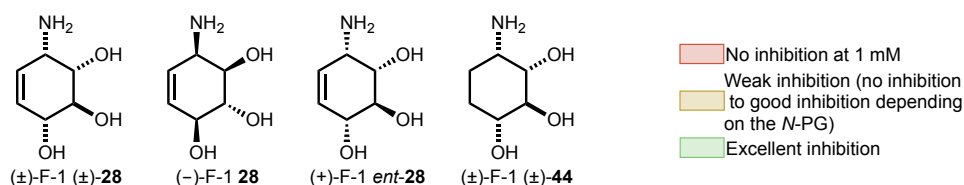


Table 1. Summary of inhibition activity towards various glycosidases of (±)-F-1 (±)-**28**, (-)-F-1 **28**, (+)-F-1 *ent*-**28**, (±)-F-1 (±)-**44** and some of their N-substituted derivatives. ^[a] best result].

Lysek *et al.* also studied the inhibition activity of (-)-conduramine B-1 **18**, its enantiomer (+)-B-1 *ent*-**18** and (±)-dihydroconduramine B-1 (±)-**34** towards 21 commercially available glycosidases.³⁵ These assays revealed that **18** was a highly selective and moderate inhibitor toward α-mannosidase from jack bean (72%) and from almonds (67%) and stayed inactive towards the other enzymes. As before, its enantiomer *ent*-**18** was inactive towards of all the 21 glycosidases, as well as its saturated analogue (±)-**34**, which showed weak activity toward a single enzyme: β-xylosidase from *A. niger* (57% at 1 mM).³⁶ As before, the inhibition activity of N-derivatives of conduramines (±)-**18**, **18** and its enantiomer *ent*-**18** towards seven glycosidases³⁷ were studied. Although (±)-**18**, **18** and *ent*-**18** were inactive towards these seven glycosidases, their derivatives were weak to excellent inhibitors toward β-glucosidases from almonds mainly. Indeed, the presence of either an N-linear alkyl chain on (±)-**18** or an N-benzyl or N-substituted benzyl on **18** appeared to enhance their inhibitory activity. The best competitive inhibitions toward β-glucosidases from almonds were observed for compounds with a Bn, *p*-Ph-C₆H₄CH₂ and *p*-(OPh)-C₆H₄CH₂ N-

protecting group, which showed an IC_{50} value of 32, 32 and 43 μM , respectively, and a K_i of 10, 8 and 13 μM . Nevertheless, N,N -disubstitutions (N,N -PG : $n-C_6H_{13}$, $n-C_8H_{17}$, CH_2CH_2Ph) on racemic ($\pm$)-**18** showed a decrease in the inhibition (Table 2).³⁸

Inhibited glycosidases among the 21	($\pm$)-B-1 ($\pm$)- 18	(-)-B-1 18	(+)-B-1 <i>ent</i> - 18	($\pm$)-B-1 ($\pm$)- 34	<i>N</i> -linear alkyl chain on ($\pm$)-B-1 ($\pm$)- 18 [a]	<i>N</i> -substituted benzyl on 18 and <i>ent</i> - 18 [a]	<i>N,N</i> -linear alkyl chain on ($\pm$)-B-1 ($\pm$)- 18 [a]
α -glucosidase maltase from yeast							
α -glucosidase maltase from rice							
α -mannosidase from jack bean		72% at 1 mM					
α -mannosidase from almonds		67% at 1 mM					
β -xylosidase from <i>A. Niger</i>				57% at 1 mM		30% at 1 mM Bn	
amylglucosidase from <i>Rhizopus</i> mold					30% at 1 mM <i>n</i> -C ₃ H ₇	85% at 1 mM <i>p</i> -OHC ₆ H ₄ CH ₂	
amylglucosidase from <i>A. Niger</i>						94% at 1 mM <i>p</i> -OHC ₆ H ₄ CH ₂	
β -glucosidase from almonds					92%, IC_{50} = 32 μM <i>n</i> -C ₆ H ₁₃	97%, K_i = 8 μM IC_{50} = 32 μM <i>p</i> -PhC ₆ H ₄ CH ₂	36% at 1 mM <i>n</i> -C ₃ H ₇
β -glucosidase from <i>C. Saccharolyticum</i>						94%, IC_{50} = 35 μM <i>p</i> -PhC ₆ H ₄ CH ₂	

($\pm$)-B-1 ($\pm$)-**18**
(-)-B-1 **18**
(+)-B-1 *ent*-**18**
($\pm$)-B-1 ($\pm$)-**34**

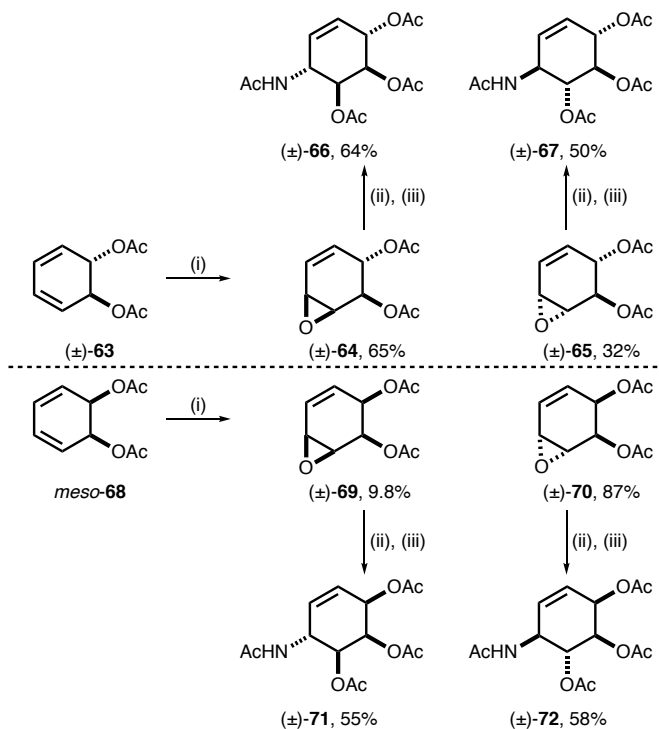
- No inhibition at 1 mM
- Weak inhibition (no inhibition to good inhibition depending on the *N*-PG)
- Excellent inhibition
- Not measured

Table 2. Summary of inhibition activity towards various glycosidases of ($\pm$)-B-1 ($\pm$)-**18**, (-)-B-1 **18** and (+)-B-1 *ent*-**18**, ($\pm$)-B-1 ($\pm$)-**34** their *N*-substituted derivatives. [a] best case].

1.5 Syntheses of conduramines and dihydroconduramines

Due to their potential interesting glycosidase inhibition properties and their presence in biologically active compounds, the development of new methods for an efficient synthesis of conduramines and dihydroconduramines has been a focus of the synthetic community. In 1962, racemic conduramine tetraacyl ($\pm$)-A-1 ($\pm$)-**66**, ($\pm$)-B-1 ($\pm$)-**67**, ($\pm$)-C-4 ($\pm$)-**71** and ($\pm$)-F-4 ($\pm$)-**72** were diastereoselectively synthesised from either *anti*- or *syn*-cyclohexa-3,5-diene-1,2-yl diacetates ($\pm$)-**63** or *meso*-**68**. Indeed, epoxidation of ($\pm$)-**63** with $PhCO_3H$ gave epoxides ($\pm$)-**64** and ($\pm$)-**65**, which were separated by crystallization, in 65% and 32% yield, respectively. Then, regioselective and stereospecific ring-opening of ($\pm$)-**64** and ($\pm$)-**65** with NH_3 in MeOH followed by *N,O*-acetylation gave ($\pm$)-conduramine A-1 tetraacyl ($\pm$)-**66** and ($\pm$)-conduramine B-1 tetraacyl ($\pm$)-**67** in 63% and 50% yield, respectively. Meanwhile,

application of this three-step synthesis to *meso*-**68** afforded ($\pm$)-conduramine C-4 tetraacyl ($\pm$)-**71** and ($\pm$)-conduramine F-4 tetraacyl ($\pm$)-**72** in 5.4% and 50% yield, respectively (Scheme 2).³⁹



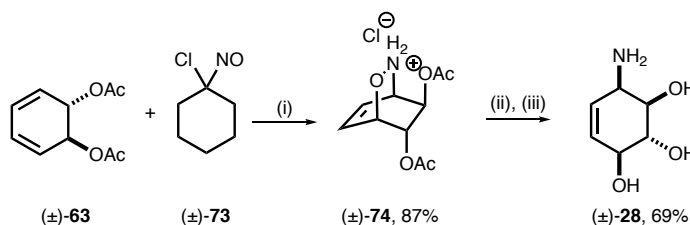
Scheme 2. Reagents and conditions: (i) PhCO_3H , CHCl_3 , rt, 3 days; (ii) NH_3 , MeOH; (iii) Ac_2O , pyridine.

Although this route easily provided four *N,O*-protected conduramines, several strategies were deployed to access these amino-conduritols and cyclitols by selectively controlling the stereochemistry of the four stereogenic centres. Some approaches to synthesise conduramines and dihydroconduramines are detailed in the following section.

1.5.1 Hetero Diels-Alder strategy

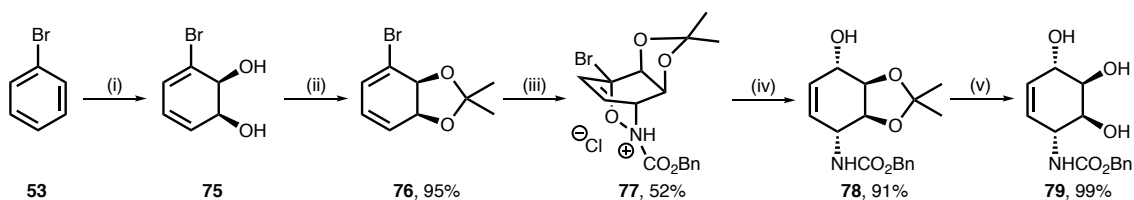
1.5.1.1 Nitroso Diels-Alder cycloaddition

In 1981, Kresze and Dittel implemented a concise route to access racemic ($\pm$)-F-1 ($\pm$)-**28** by using a nitroso Diels-Alder reaction as a key step.⁴⁰ A [4+2]-cycloaddition of ($\pm$)-**63** and 1-chloro-1-nitrosocyclohexane ($\pm$)-**73** in a 2:1 mixture of EtOH and hexane (v/v) at -20 °C gave the adduct ($\pm$)-**74** as a single diastereoisomer in 87% yield. Treatment of the dihydro oxazine ($\pm$)-**74** with NH_3 in MeOH followed by subsequent reduction in presence of Zn/HCl provided racemic ($\pm$)-F-1 ($\pm$)-**28** in 69% yield from ($\pm$)-**63** (Scheme 3).



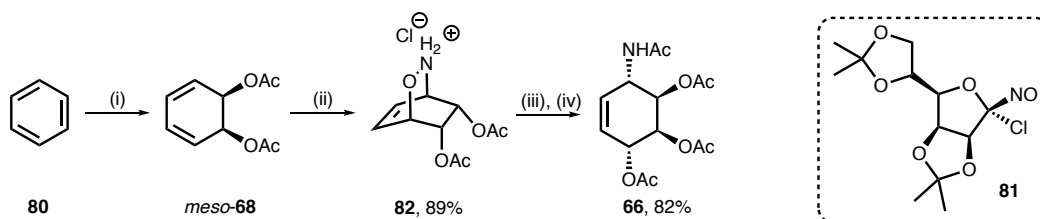
Scheme 3. Reagents and conditions: (i) EtOH, H_2O , -20 °C; (ii) NH_3 , MeOH, rt; (iii) Zn/HCl.

Investigation of a diastereo- and enantioselective nitroso Diels-Alder cycloaddition was also undertaken to access enantiopure conduramines using for instance either chiral enantiopure starting material,⁴¹ chiral enantiopure nitroso reagents⁴² or complexes containing chiral ligands.^{43,44} Hudlicky and Olivo have synthesised enantiopure *N*-protected conduramine A-1 **79** in five steps from bromobenzene **53**. First, acetalisation of **75**, synthesised *via* a microbial deoxygenase oxidation of **53** using mutants of *Pseudomonas putida* enzyme, gave **76** in 95% yield. Then, nitroso Diels-Alder of **76** with BnOCONHOH provided adduct **77** in 52% yield, as a single enantiomer. Finally, reduction of oxazine **77** with dehalogenation gave **78** in 91% yield, which was *O*-deprotected to **79** in 99% yield (Scheme 4).⁴¹



Scheme 4. Reagents and conditions: (i) *Pseudomonas putida* Pp 39D; (ii) DMP, acetone, *p*-TsOH; (iii) NaIO₄, BnOCONHOH; (iv) Al/Hg, THF, H₂O; (v) AcOH, THF, H₂O.

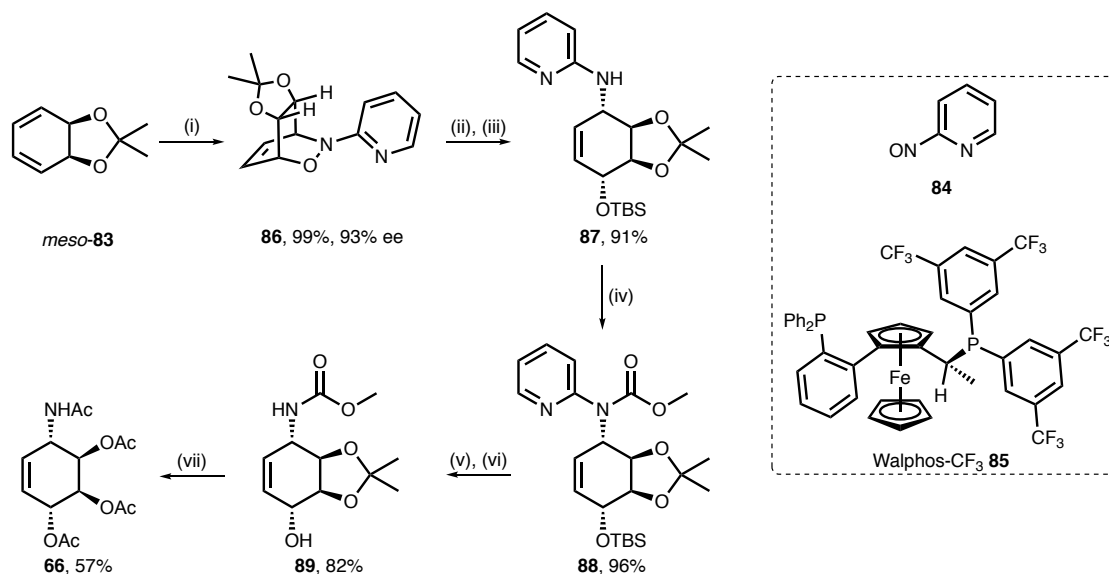
Werbitzky and co-workers have synthesised enantiopure conduramine A-1 tetraacyl **66** in four steps from benzene **80**. Nitroso Diels-Alder cycloaddition of *meso*-**68**, prepared in multikilogram scale *via* a microbial deoxygenase oxidation of benzene using mutants of *Pseudomonas putida* enzyme, with chiral enantiopure 1-chloro-1-nitrosomannose **81** gave adduct **82** in 89% yield as single enantiomer. Then, N–O bond cleavage within the dihydro oxazine **82**, followed by subsequent *N,O*-acetylation gave **66** in 82% over the 2 steps (Scheme 5).⁴²



Scheme 5. Reagents and conditions: (i) *Pseudomonas putida* Pp 39D; (ii) **81**, CHCl₃, EtOH; (iii) Zn/HCl; (iv) Ac₂O.

Studer and co-workers have synthesised enantiopure conduramine A-1 tetraacyl **66** in five steps from *meso*-**83**. First, nitroso Diels-Alder cycloaddition of *meso*-**83** with 2-nitrosopyridine **84** in presence of [CuPF₆(MeCN)₄] and Walphos-CF₃ ligand **85** gave **86** in 99% yield and 93% ee. Then, reductive cleavage of the N–O bond within **86** with [Mo(CO)₆] and NaBH₄ followed by *O*-silylation provided **87** in 91% yield. *N*-Protection of **87** with methyl chloroformate gave **88** in 96% yield. *N*-Methylation of the pyridyl group within carbamate **88** followed by subsequent hydrolysis of the pyridinium substituent allowed *N*-deprotection by C–N bond cleavage forming **89** in 82% yield. Finally, removal

of the acetal and carbamate protections and *N,O*-peracylation gave **66** in 57% yield (Scheme 6).⁴³



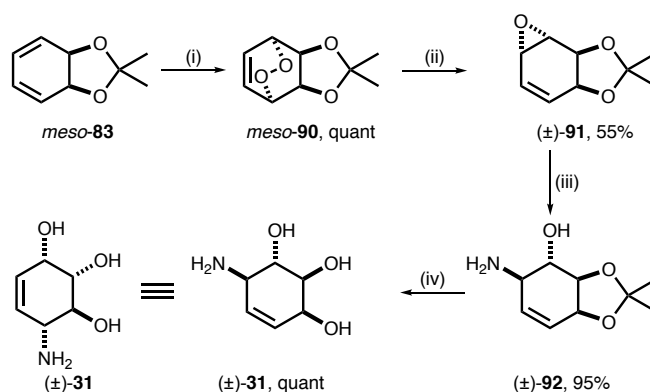
Scheme 6. Reagents and conditions: (i) **84**, [CuPF₆(MeCN)₄], Walphos-CF₃ **85** (10 mol%), CH₂Cl₂, -86 °C to -20 °C; (ii) [Mo(CO)₆], NaBH₄, MeOH, H₂O; (iii) TBSCl, imidazole, DMF; (iv) MeMgCl, MeOCOCl, THF; (v) MeOTf, CH₂Cl₂, 0 °C; (vi) NaOH, MeOH, H₂O, 50 °C; (vii) AcCl, NaI, MeCN, 60 °C.

This enantioselective strategy toward the synthesis of *N*-protected conduramines with asymmetric insertion of four stereogenic stereocentres in a short and concise route proved to be very effective.

1.5.1.2 Singlet oxygen Diels-Alder cycloaddition

Precedent in the literature showed that it was also possible to perform a Diels Alder cycloaddition using a photooxygenation with O₂, selective epoxidation and ring-opening as key steps to access conduramines. For example, Seçen and co-workers have synthesised (±)-conduramine F-4 (±)-**31** in 4 steps from *meso*-**83** in 52% yield. First, *meso*-**83** was obtained *via* microbial oxidation of benzene **80** using *Pseudomonas putida* followed by acetonide protection. Then, [4+2]-cycloaddition of singlet oxygen to *meso*-**83** gave *meso*-**90**, which was treated under reductive conditions [i.e., P(OEt)₃] to provide epoxide (±)-**91** in 55% yield. Then, regio- and stereospecific ring-opening of (±)-**91** with NH₃ in MeOH gave

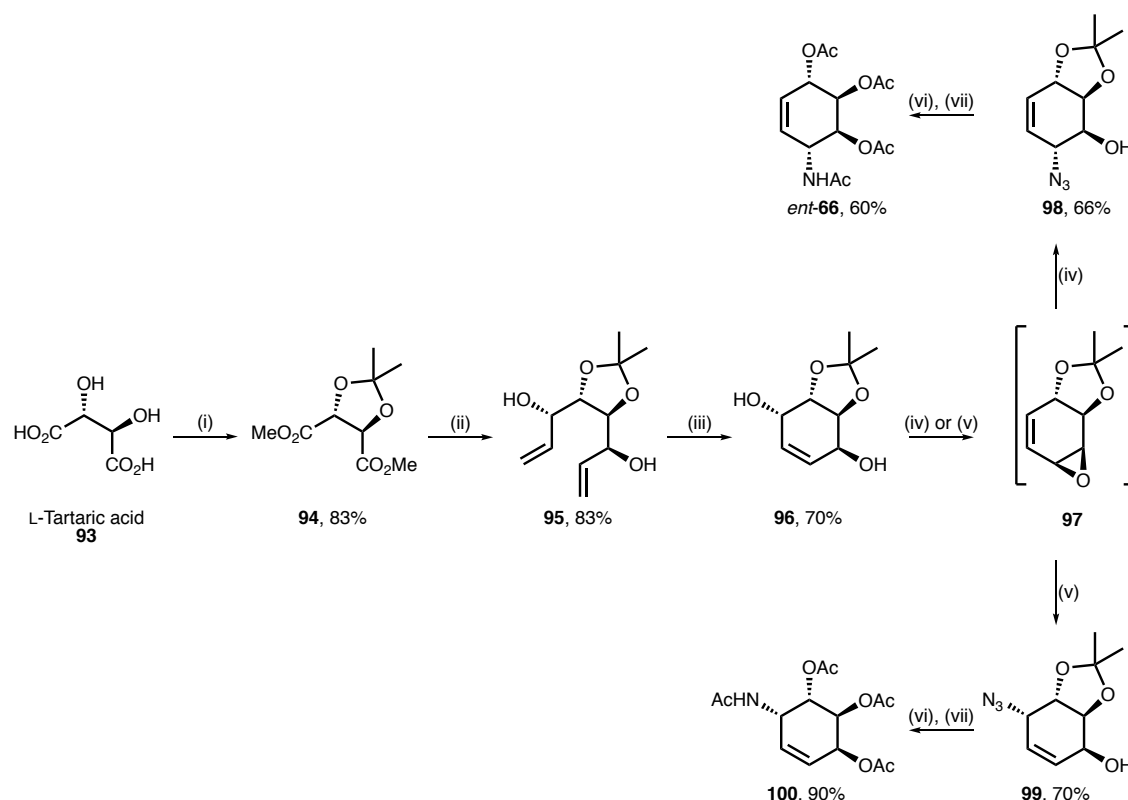
the amino alcohol ($\pm$)-**92** in 95% yield. Finally, ketal deprotection of ($\pm$)-**92** provided ($\pm$)-conduramine F-4 ($\pm$)-**31** in quantitative yield (Scheme 7).⁴⁵



Scheme 7. Reagents and conditions: (i) O_2 , tetraphenylporphyrin, CCl_4 ; (ii) $\text{P}(\text{OEt})_3$, CHCl_3 ; (iii) NH_3 , MeOH ; (iv) BaCO_3 , H_2SO_4 , H_2O .

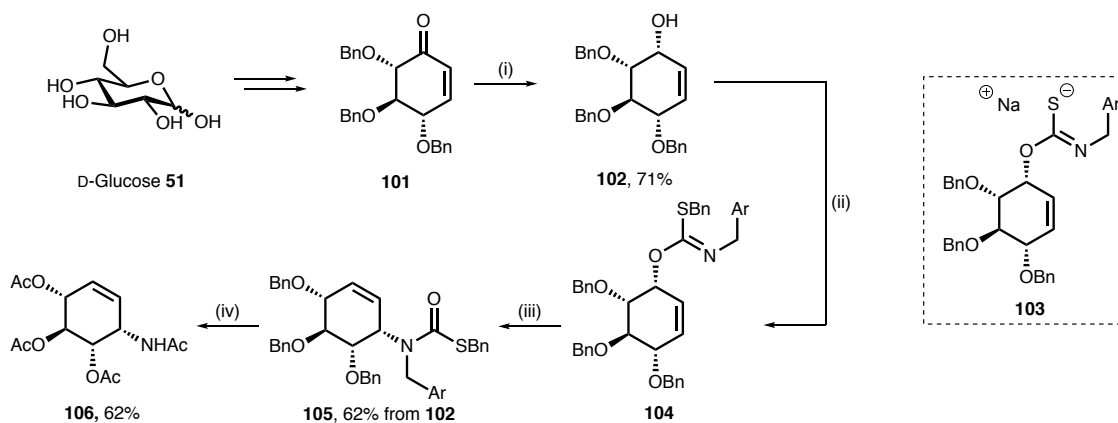
1.5.2 [3,3]-Sigmatropic rearrangement chemistry

A [3,3]-sigmatropic rearrangement strategy was also used as a key step to access conduramines. In 2009, Chang *et al.* synthesised diastereo- and enantioselectively conduramines A-1 tetraacyl *ent*-**66** and E-1 tetraacyl **100** in both 6 steps from L-tartaric acid **93** and in 25% and 30% yield, respectively. Protection *via* esterification and acetalisation of the chiral pool **93** gave **94** in 83% yield. Then, reduction of the bis ester **94** to the dialdehyde followed by a highly diastereoselective *in situ* divinylzinc addition gave **95** in 83% yield. Treatment of **95** under ring-closing metathesis conditions (i.e., Grubbs II catalyst) gave cyclised ketal **96** in 70% yield. O-Protection using triflimide followed by NaH-promoted epoxide-closure gave *in situ* **97**, which was subsequently opened with NaN_3 at 25 °C and 90 °C. At 25 °C, regio- and stereospecific ring-opening of the epoxide **97** gave compound **98** in 66% yield whereas at 90 °C, azide **98** underwent [3,3]-sigmatropic rearrangement to provide 1,4-azido alcohol **99** in 70% yield. Finally, reduction of the ketal within **98** or **99** followed by subsequent acylation gave conduramines A-1 tetraacyl *ent*-**66** and E-1 tetraacyl **100** in 79% and 90% yield, respectively (Scheme 8).⁴⁶



Scheme 8. Reagents and conditions: (i) $\text{Me}_2\text{C}(\text{OMe})_2$, TsOH, MeOH, reflux, 48 h; (ii) DIBALH, -78°C , then ZnCl_2 , $\text{H}_2\text{C}=\text{CHMgBr}$; (iii) Grubbs II, CH_2Cl_2 , reflux, 2 h; (iv) $\text{PhN}(\text{Tf})_2$, NaH, DMF, 25°C , 15 min, then NaN_3 , EtOH, H_2O , 25°C , 12 h; (v) $\text{PhN}(\text{Tf})_2$, NaH, DMF, 25°C , 15 min, then NaN_3 , EtOH, H_2O , 90°C , 12 h; (vi) LiAlH_4 , Et_2O , 0°C , 1 h, then quenching with AcOH, H_2O , 0°C , then 0°C to 50°C , 22 h; (vii) Ac_2O , pyridine, rt, overnight.

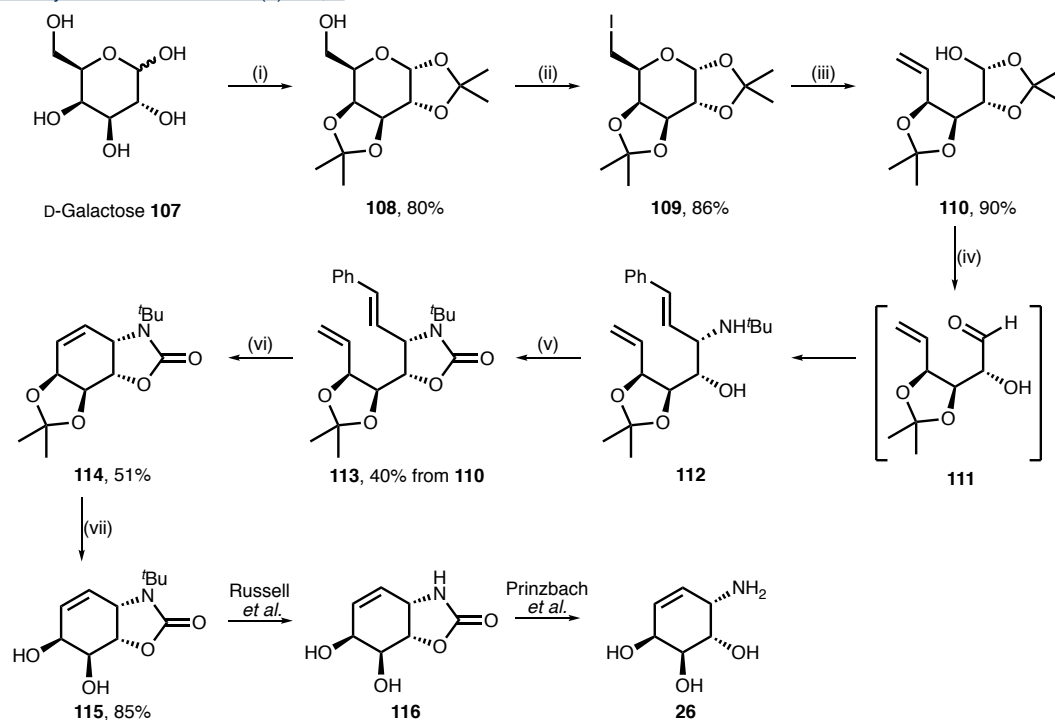
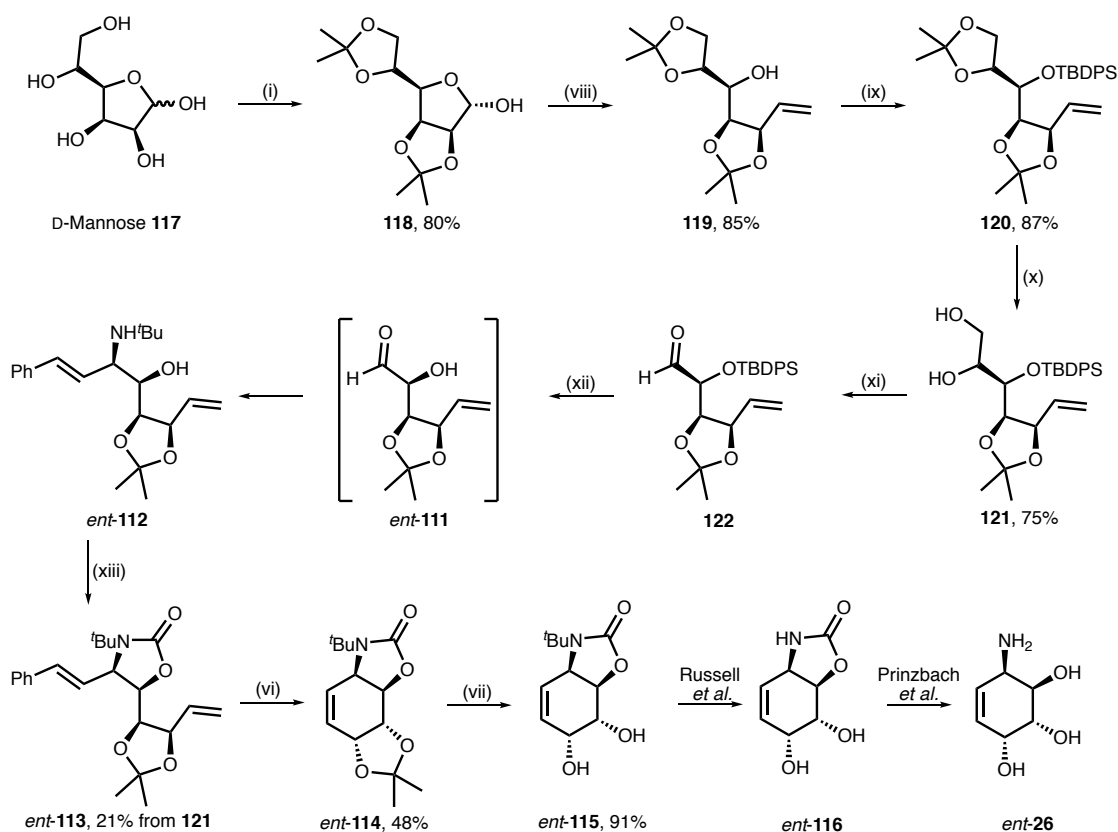
Synthesis of conduramine F-1 tetraacyl **106** was also achieved by Knapp and co-workers using a [3,3]-sigmatropic rearrangement of a carbonimidothioate. First, reduction of enone **101** (prepared from D-glucose **51**) under Luche's conditions (i.e., NaBH_4 , CeCl_3 aq, MeOH) followed by an inversion of configuration of the alcohol stereogenic centre *via* Mitsunobu protocol and then methanolysis gave allylic alcohol **102** in 71% over three steps from enone **101**. O-Deprotonation of **102** with NaH followed by condensation with *p*-methoxybenzyl isocyanate provided carboimidothionate sodium salt **103**, which was subsequently trapped with benzyl bromide to form carboimidothionate **104**. Then, **104** underwent [3,3]-sigmatropic rearrangement to afford thiocarbamate **105** in 62% yield from **102**. Finally, *N,O*-deprotection and acetylation of **104** gave conduramine F-4 tetraacyl **106** in 62% yield (Scheme 9).⁴⁷



Scheme 9. Reagents and conditions: (i) NaBH₄, CeCl₃, MeOH, then PhCO₂H, DEAD, PPh₃, then KOH (aq), MeOH, 60 °C; (ii) NaH, THF, then ArCH₂NCS, then BnBr; (iii) toluene, reflux, 48 h; (iv) CF₃CO₂H, 2 h, then Na, NH₃, THF, -55 °C, 3 min, then Ac₂O, DMAP, pyridine, 12 h. [Ar = *p*-(MeO)C₆H₄].

1.5.3 Petasis Borono Mannich strategy

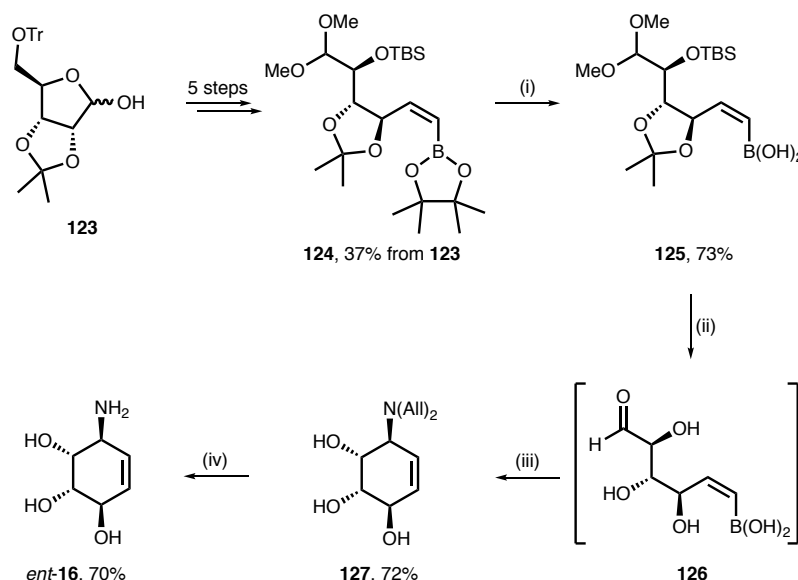
Other routes to access conduramines implemented the use of Petasis Borono Mannich chemistry, which involved the formation of an iminium ion *via* the condensation of an aldehyde and an amine followed by an *in situ* boronic acid attack to give the corresponding amine. Ghosal and co-workers have introduced a formal synthesis of (+)-conduramine E-1 **26** from D-galactose **107**. Diketal **108** was prepared by iodination of **107** in 80% yield. Then, alcohol substitution with I₂ and PPh₃ gave iodide **109** in 86% yield, which was treated with Zn dust and cyanocobalt amine catalyst (i.e., Vit. B₁₂) to give alkene **110** in 90% yield. Regioselective ketal deprotection formed *in situ* aldehyde **111**, which was subjected to Petasis-Borono Mannich reaction with *trans*-2-phenylvinyl boronic acid and *tert*-butylamine to give allylic amine **112**. Formation of oxazolidinone **113** was achieved by treatment of **112** with (Boc)₂O in 40% yield from alcohol **110**. Then, ring-closure metathesis with Grubbs II catalyst gave cyclic alkene **114** in 51% yield, which was subjected to acidic conditions to form diol **115** in 85% yield. From this intermediate, a formal synthesis of (+)-conduramine E-1 **26** was performed using Russell *et al.*⁴⁸ followed by Prinzbach *et al.*⁴⁹ routes. Using the same ideology, Ghosal *et al.* have also deployed a formal synthesis of (–)-conduramine E-1 *ent*-**26** from D-mannose **117** (Scheme 10).⁵⁰

Formal synthesis of conduramine (+)-E-1 **26**Formal synthesis of conduramine (-)-E-1 *ent*-**26**

Scheme 10. Reagents and conditions: (i) I_2 , acetone, 24 h; (ii) I_2 , PPh_3 , imidazole, toluene, 80 °C, 3 h; (iii) Zn, NH_4Cl , Vit. B₁₂, MeOH, 15 min; (iv) TBAF, EtOH, 30 min, then *trans*-2-phenylvinyl boronic acid, $tBuNH_2$, EtOH, rt, 24 h; (v) (Boc)₂O, Et₃N, DMAP, THF, rt, 12 h; (vi) Grubbs II, CH_2Cl_2 , reflux, 24 h; (vii) CF_3CO_2H , CH_2Cl_2 , 2 h, then H_2O , 1 h; (viii) Ph_3PCH_3Br , $tBuOK$, THF, -20 °C, 4 h; (ix) TBDPSCl, imidazole, DMF, rt, 24 h; (x) AcOH (80%), rt, 6 h; (xi) $NaIO_4$, THF, H_2O , 0 °C to rt, 1.5 h; (xii) TBAF,

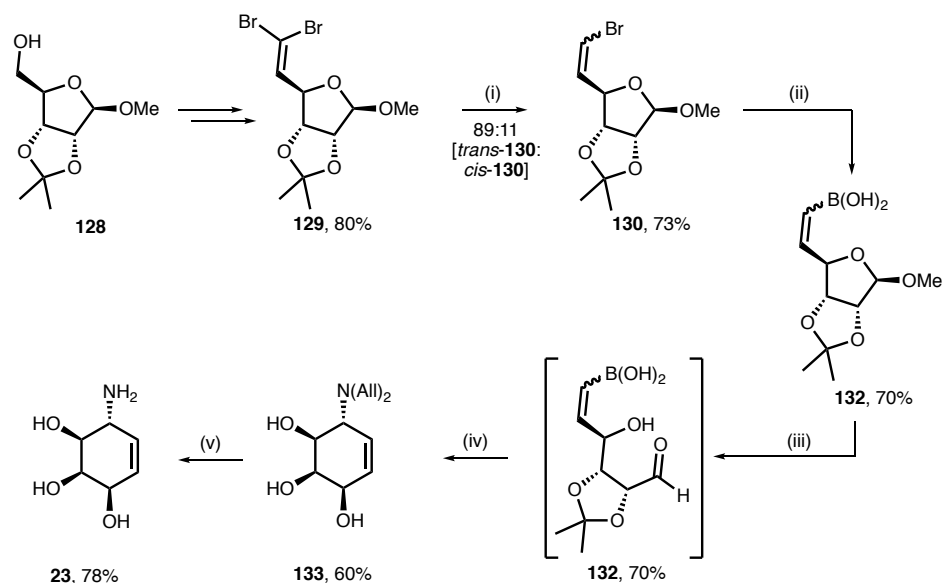
EtOH, 30 min, then *trans*-2-phenylvinyl boronic acid, $t\text{BuNH}_2$, 80 °C, 24 h; (xiii) $(\text{Boc})_2\text{O}$, Et_3N , DMAP, 0 °C to rt, 12 h.

Norsikian and co-workers have also synthesised conduramines (+)-A-1 *ent*-**16** and (–)-C-4 **23** from D- ribofuranoside derivatives using an intramolecular Petasis-Borono Mannich reaction as a key step. First, boronic ester **124**, prepared from 2,3-*O*-isopropylidene-5-*O*-trityl-D-ribofuranose **123** in 5 steps and 37% overall yield, was treated with sodium metaperiodate to give boronic acid **125** in 73% yield. Subjection to acidic conditions provided *in situ* aldehyde **126** and Petasis Borono Mannich reaction on **126** with diallylic amine afforded **127** in 72% yield as a single diastereoisomer. Finally, *N*-deprotection of **127** with $\text{Pd}(\text{PPh}_3)_4$ and NDMBA gave (+)-conduramine A-1 *ent*-**16** in 70% yield (Scheme 11).⁵¹



Scheme 11. Reagents and conditions: (i) NaIO_4 , NH_4OAc , acetone, H_2O , rt, 5 days; (ii) HCl , THF, H_2O ; (iii) $(\text{All})_2\text{NH}$, EtOH, H_2O , 80 °C, 8 days; (iv) $\text{Pd}(\text{PPh}_3)_4$, NDMBA.

To synthesise (–)-conduramine C-4 **23**, boronic acid **131**, prepared from 2,3-*O*-isopropylidene- β -D-ribofuranoside **128** in 3 steps and 41% yield, was also treated under acidic conditions to provide *in situ* aldehyde **132**, which was subjected to Petasis Borono Mannich reaction conditions with diallylic amine to give **133** in 60% yield as a single diastereoisomer. Finally, as before, *N*-deprotection with $\text{Pd}(\text{PPh}_3)_4$ and NDMBA gave (–)-conduramine C-4 **23** in 78% yield (Scheme 12).⁵¹



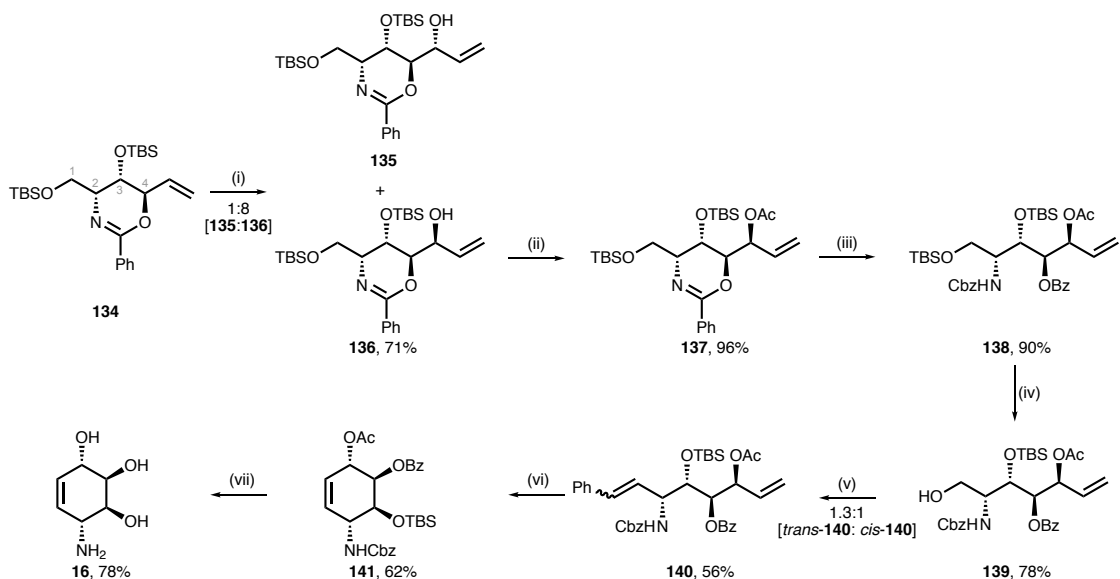
Scheme 12. Reagents and conditions: (i) Pd(0), Bu₃SnH; ^tBuLi, Et₂O, -95 °C; (ii) B(OMe)₃, then pinacol, then NaIO₄, NH₄OAc, acetone, H₂O; (iii) CF₃CO₂H, H₂O; (iv) (All)₂NH, HFIP, CH₂Cl₂, 50 °C, 64 h; (v) Pd(PPh₃)₄, NDMBA.

1.5.4 Oxazine chemistry

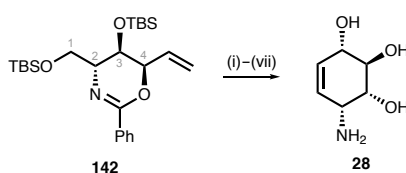
Ham and co-workers have also developed a diastereo- and enantioselective route to access (–)-conduramine A-1 **16** using a chiral 2,3-*syn*-3,4-*anti*-oxazine **134** and (–)-conduramine F-1 **28** from chiral 2,3-*anti*-3,4-*syn*-oxazine **142**. First, ozonolysis of **134** followed by stereoselective addition of vinylmagnesium bromide in presence of ZnCl₂ gave a 1:8 mixture of 2,3-*syn*-3,4-*anti*-4,5-*anti*-oxazine **135** and 2,3-*syn*-3,4-*anti*-4,5-*syn*-oxazine **136**. Purification *via* column chromatography afforded **136** in 71% yield and >95:5 dr. Then, *O*-acylation of **136** gave **137** in 96% yield and cleavage of **137** under Schotten-Baumann conditions (i.e., PhOCOCl, NaHCO₃) provided carbamate **138** in 90% yield. Selective *O*-desilylation of **138** with HF in pyridine gave alcohol **139** in 78% yield, which was subjected to Dess-Martin oxidation conditions (i.e., DMP) followed by Wittig conditions (i.e., BnPPH₃I, LiHMDS) to afford a 1.3:1 mixture of *trans*-**140** and *cis*-**140**, respectively, in 56% from alcohol **139**. This mixture was then treated with Grubbs II catalyst to give the ring-closed product **141** in 62% yield, which was *N,O*-deprotected under acidic conditions to form (–)-conduramine A-1 **16** in 78% yield.⁵² Furthermore, using a similar route,

synthesis of (–)-conduramine F-1 **28** was achieved in 7 steps from 2,3-*anti*-3,4-*syn*-oxazine **142** (Scheme 13).^{53,54}

Synthesis of conduramine (–)-A-1 **16**



Synthesis of conduramine (–)-F-1 **28**

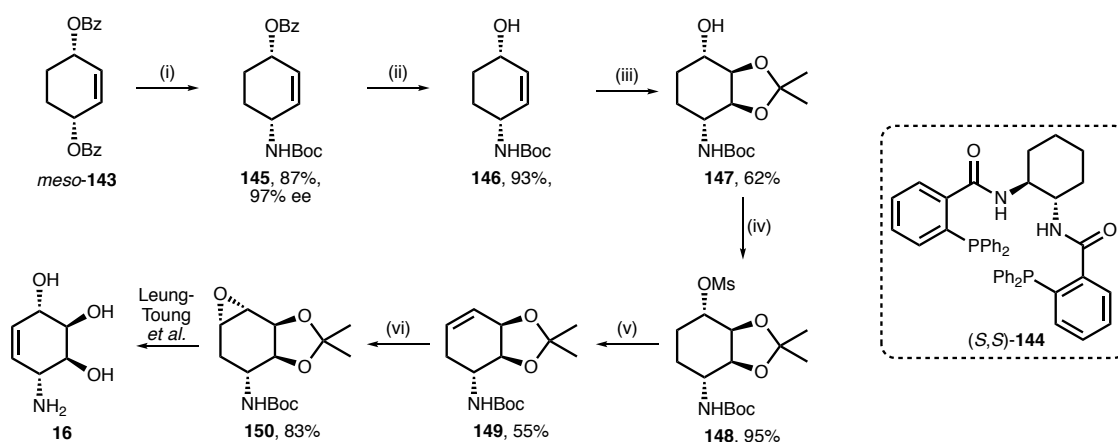


Scheme 13. Reagents and conditions: (i) O_3 , MeOH, $-78^\circ C$, then Me_2S , then $ZnCl_2$, $CH_2=CHMgBr$, THF, $-78^\circ C$; (ii) Ac_2O , DMAP, pyridine, CH_2Cl_2 ; (iii) $CbzCl$, $NaHCO_3$, H_2O , CH_2Cl_2 ; (iv) HF, pyridine; (v) DMP, CH_2Cl_2 , then $BnPPH_3I$, $LiHMDS$; (vi) Grubbs II, CH_2Cl_2 , reflux, 24 h; (vii) HCl (6 M aq), reflux, 4 h.

1.5.5 Desymmetrization strategy

Trost and co-workers have implemented a formal synthesis to access (–)-conduramine A-1 **16** from a palladium catalysed asymmetric desymmetrization of *meso*-**143**. First, one-pot desymmetrization of *meso*-**143** followed by reduction of the azide group and *N*-Boc protection gave carbamate **145**, as a single diastereoisomer in 87% yield and 97% ee. Then, methanolysis of the benzoate group within **145** afforded allylic alcohol **146** in 93% yield. Alcohol **147** was achieved by diastereoselective osmylation of **146** followed by subsequent acetalisation in 62% over the two steps. *O*-Mesylation of **147** provided **148** in 95% yield and elimination of the mesylate functionality formed alkene **149** in 55% yield, which was treated with *m*-CPBA to give epoxide **150** as a single diastereoisomer in 83% yield. This

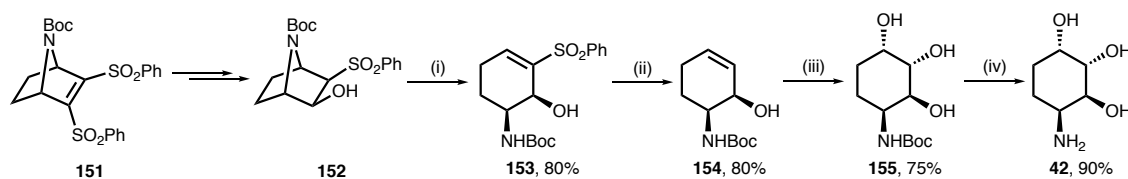
intermediate was used by Leung-Toung *et al.*⁵⁵ to synthesise (–)-conduramine A-1 **16** in 5 steps and 70% yield (Scheme 14).⁵⁶



Scheme 14. Reagents and conditions: (i) (η^3 -C₃H₅)PdCl₂, (*S,S*)-**144**, TMSN₃, THF, then Me₃P, THF, H₂O, then (Boc)₂O, Et₃N; (ii) K₂CO₃, MeOH; (iii) OsO₄, NMO, acetone, then 2,2-dimethoxypropane, PPTS; (iv) MsCl, DIPEA, CH₂Cl₂; (v) DBU, microwave, 150 °C; (vi) *m*-CPBA, CHCl₃.

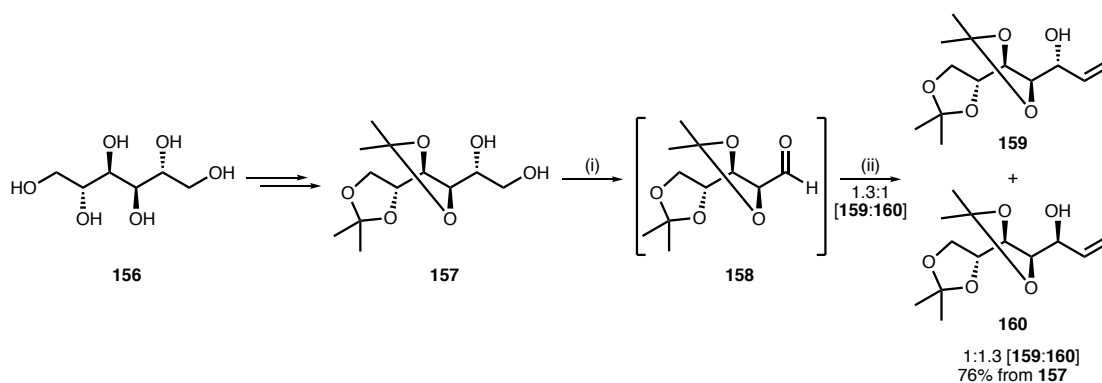
1.5.6 Syntheses of dihydroconduramines

Precedent in the literature described the synthesis of dihydroconduramines. In this section, two routes will be explained in detail. Pandey and co-workers have deployed an enantioselective route to access (+)-dihydroconduramine E-1 **42** from a non-racemic compound **152**, prepared from asymmetric desymmetrization of **151**. Anionic rearrangement of alcohol **152** with MeMgBr gave **153** in 80% yield and removal of the phenylsulfonyl group within **153** with Na/Hg in a buffered methanol afforded alkene **154** in 80% yield. Then, diastereoselective osmylation of **154** formed triol **155** in 75% yield. Finally, *N*-deprotection of **155** with concentrated acid provided (+)-dihydroconduramine E-1 **42** in 90% yield (Scheme 15).⁵⁷

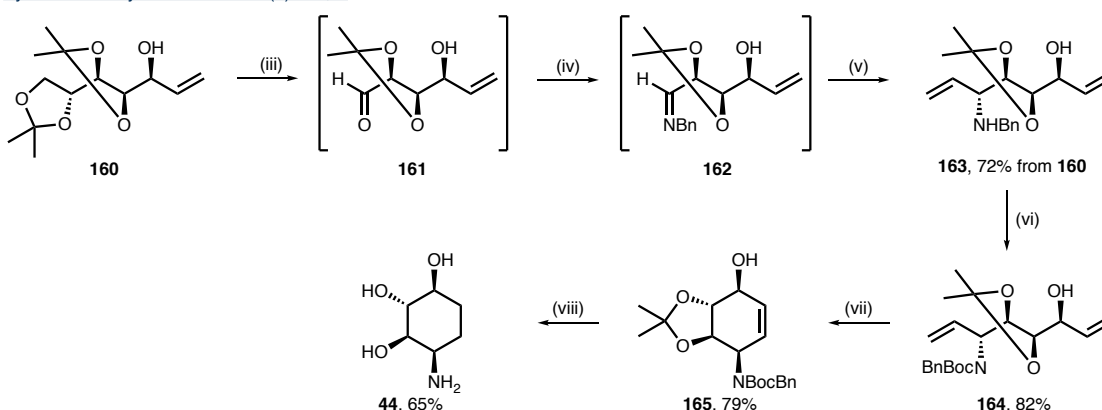


Scheme 15. Reagents and conditions: (i) MeMgBr, THF, rt, 2 h; (ii) Na, Hg (6%), Na₂HPO₄, THF, MeOH, –6 °C; (iii) OsO₄, NMO, NaHCO₃, tBuOH, H₂O, THF; (iv) HCl (12 N), 1,4-dioxane, 100 °C.

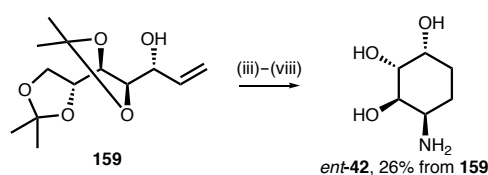
Batchu and co-workers have synthesised (+)-dihydroconduramine F-1 **44** and (–)-dihydroconduramine E-1 *ent*-**42** from diol **157**, prepared from D-mannitol **156**. First, oxidative cleavage of **157** with NaOI₄ gave aldehyde **158**, which was subjected under Grignard conditions (vinylmagnesium bromide, THF) to provide 1.3:1 mixture of allylic alcohols **159** and **160**, respectively, in 76% yield. Selective deprotection of the primary acetonide within isolated **160** with H₅IO₆ formed *in situ* aldehyde **161**, which was treated with benzylamine to afford imine **162**. Nucleophilic addition of a vinyl magnesium bromide to imine **162** gave the corresponding allylic amine **164** in 72% yield from allylic alcohol **160**. N-Boc protection provided **163** in 82% yield and ring-closure metathesis with Grubbs II afforded cyclic alkene **165** in 79% yield. Finally, hydrogenolysis followed by deprotection of the acetonide group gave (+)-dihydroconduramine F-1 **44** in 65% yield. Meanwhile, the same conditions were applied to the other diastereoisomeric allylic alcohol **159** and afforded (+)-dihydroconduramine E-1 *ent*-**42** (Scheme 16).⁵⁸



Synthesis of dihydroconduramine (+)-F-1 44



Synthesis of dihydroconduramine (+)-E-1 ent-42



Scheme 16. *Reagents and conditions:* (i) NaIO₄, THF, H₂O, rt, 15 min; (ii) CH₂=CHMgBr, THF, 0 °C, 3 h; (iii) H₅IO₆, Et₂O, 0 °C to rt, 6 h; (iv) BnNH₂, CH₂Cl₂, 4 Å, Na₂SO₄, 0 °C, 2 h; (v) CH₂=CHMgBr, THF, -10 °C, 3 h; (vi) (Boc)₂O, MeOH, NaHCO₃, rt, 8 h; (vii) Grubbs II, CH₂Cl₂, reflux, 3 h; (viii) H₂, Pd/C, MeOH, rt, 12 h, then HCl (6 N), MeOH, rt, 6 h.

1.6. Thesis aims

This thesis describes investigations into the development of routes for the diastereoselective and asymmetric syntheses of dihydroconduramines and conduramines using the ammonium-directed epoxidation methodology as a stereodefining key step. Investigation of the efficiency of this methodology will be performed on different substrates: either *anti*- and *syn*-homoallylic alcohol/allylic amines **166**, **168**, **171** and **173** or allylic amino alcohols **176**, **179** and **182** (Figure 10).^{59,60}

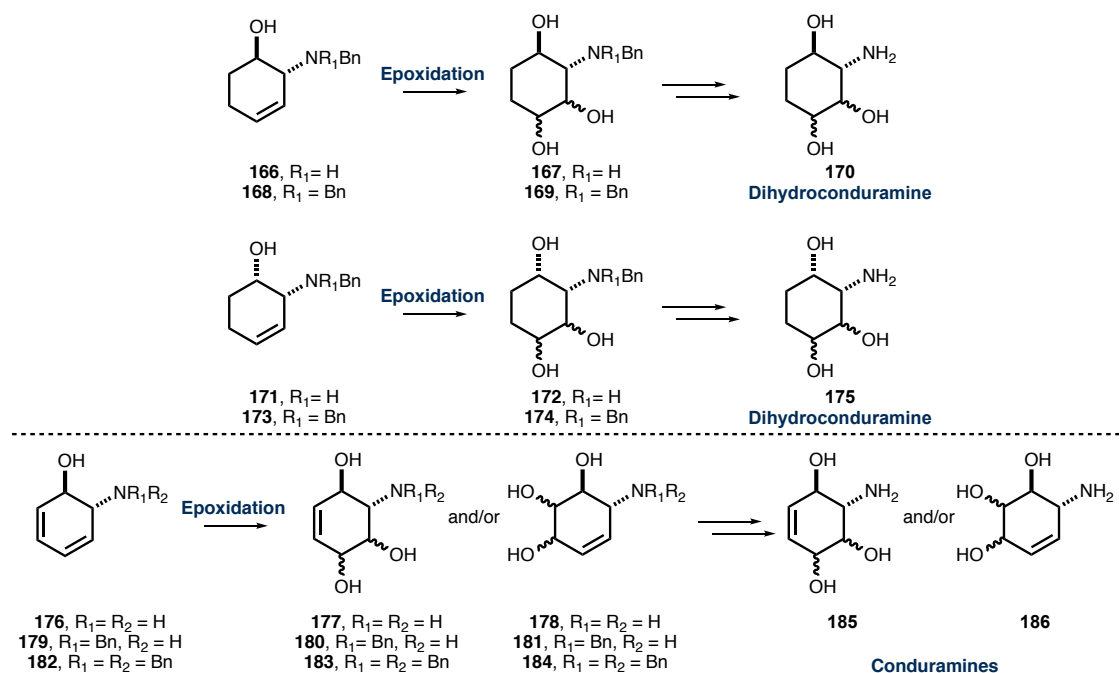


Figure 10. Thesis aims.

1.7 Notes and references

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- (35) **List of the main glycosidases:** α -L-fucosidase, α -galactosidases, β -galactosidases, α -glucosidases, amyloglucosidases, β -glucosidases, β -mannosidases, β -xylosidases, α -N-acetylglucosaminidases.
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Chapter 2

Epoxidation of Cyclic Homoallylic Alcohols/Allylic Amines

This chapter investigates the olefinic oxidation protocol (H^+ then *m*-CPBA) of racemic *N*-protected *anti*- and *syn*-2-aminocyclohex-3-en-1-ols ($\pm$ -**166**, ($\pm$ -**168**, ($\pm$ -**171** and ($\pm$ -**173**. Synthesis allows a concise route to access unknown dihydroconduramines ($\pm$)-A-2 ($\pm$)-**32** and ($\pm$)-C-2 ($\pm$)-**37** (Figure 11).^{1,2}

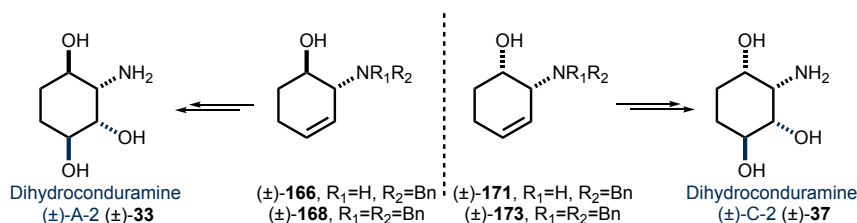
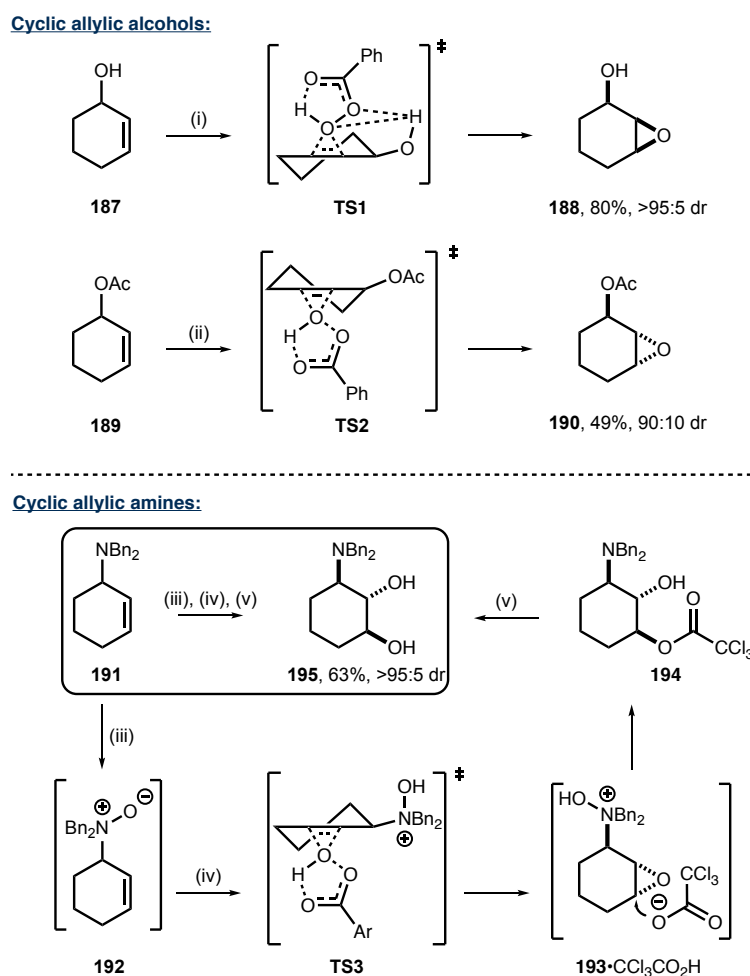


Figure 11. Proposed route for the diastereoselective synthesis of racemic dihydroconduramines ($\pm$)-A-2 ($\pm$)-**33** and ($\pm$)-C-2 ($\pm$)-**37**.

2.1 Background

Previous pioneering work by Henbest³ showed that epoxidation of 2-cyclohexene-1-ol **187** with perbenzoic acid gave diastereoselectively *syn*-epoxide **188** in 80% yield and 95:5 dr. However, epoxidation of **189**, product of *O*-acetylation of **187**, gave epoxide **190** in 49% yield and high *anti*-diastereofacial selectivity was observed (90:10 dr). In the former case, the stereochemical outcome of the reaction could be rationalized in the transition state **TS1** by an H-bond interaction between the hydroxyl group and the incoming peracid resulting in *syn*-oxidation of the olefin. In the latter case, *O*-acetylation prevented any H-bonding in the transition state **TS2** between the *O*-acetyl group and the incoming perbenzoic acid. Then, due to steric/stereoelectronic effects and minimisation of dipolar interactions, the *anti*-oxidation was preferred. Davies *et al.* showed that epoxidation of 1-(*N,N*-

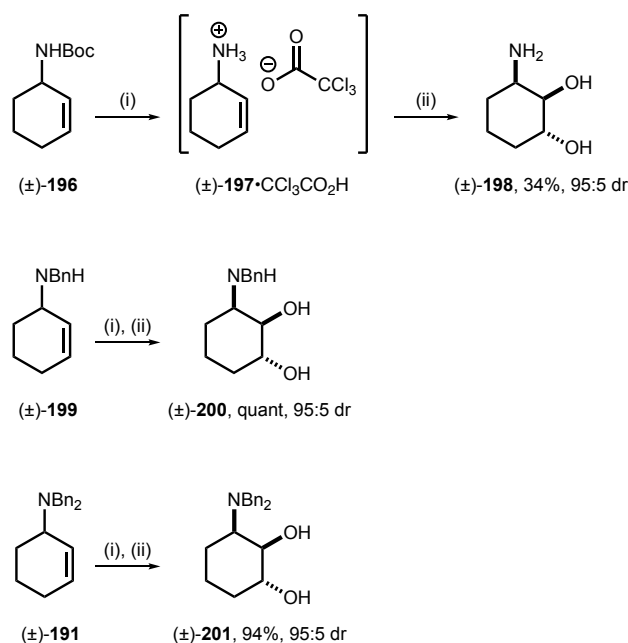
dibenzylamino)cyclohex-2-ene **191** with *m*-CPBA afforded, after methanolysis, diastereoselectively **195** in 63% yield and >95:5 dr. The opposing stereochemical outcome of cyclic allylic alcohols *versus* cyclic allylic amines could be explained by a transition state **TS3** in which repulsions due to steric effects or minimization of the dipolar interactions between the *N*-oxide (resulting from competitive *N*-oxidation) and the oxidant allowed epoxidation at the opposite face of the olefin (Scheme 17).⁴



Scheme 17. Reagents and conditions: (i) PhCO_3H , C_6H_6 , 0 °C, 31 h; (ii) PhCO_3H , C_6H_6 , 0 °C, 2.5 h; (iii) *m*-CPBA, CH_2Cl_2 , 0 °C, 30 min; (iv) $\text{CCl}_3\text{CO}_2\text{H}$, *m*-CPBA, CH_2Cl_2 , rt, 3 days; (v) K_2CO_3 , MeOH, rt, 16 h [Ar=*m*-ClC₆H₄].

In conclusion, peracid-mediated epoxidation of cyclic allylic alcohols and cyclic allylic amines revealed a diastereofacial divergence. However, Davies *et al.* developed an effective ammonium-directed epoxidation methodology to invert the stereochemical outcome of cyclic allylic amines. One-pot dihydroxylation of ($\pm$)-**196**, ($\pm$)-**199** and ($\pm$)-**191** gave

diastereoselectively ($\pm$)-**198**, ($\pm$)-**200** and ($\pm$)-**201** in 34%, quantitative and 94% yield (>95:5 dr), respectively. The mechanism of this protocol (general for primary, secondary and tertiary allylic amines) could be rationalised by protection of the *N*-atom against oxidation upon protonation with a Brønsted acid, which allows the resultant ammonium ion to act as an H-bond donor and to direct *syn*-epoxidation. Then regioselective and stereospecific ring-opening upon the attack of the Brønsted conjugate base at the carbon distal to the ammonium moiety and methanolysis (if needed) gives the desired product (Scheme 18).⁵



Scheme 18. Reagents and conditions: (i) $\text{CCl}_3\text{CO}_2\text{H}$, *m*-CPBA, CH_2Cl_2 , rt, 21 h; (ii) K_2CO_3 , MeOH, rt 16 h.

2.2 Chapter aim

It was envisaged that epoxidation of racemic *N*-protected *anti*- and *syn*-2-aminocyclohex-3-en-1-ol scaffolds ($\pm$)-**166**, ($\pm$)-**168**, ($\pm$)-**171** and ($\pm$)-**173** could be used as a key step to access dihydroconduramines ($\pm$)-**170** and ($\pm$)-**175** in a stereoselective manner. This chapter outlines the application of this protocol to ($\pm$)-**166**, ($\pm$)-**168**, ($\pm$)-**171** and ($\pm$)-**173** to investigate the stereochemical outcomes.^{1,2} Scaffolds ($\pm$)-**166**, ($\pm$)-**168**, ($\pm$)-**171** and ($\pm$)-**173** could be synthesised from commercially available 1,3-cyclohexadiene **202** *via* monoepoxidation followed by amine source ring-opening⁶ and, in the two latter cases,

subsequent S_N2 -type displacement with *O*-inversion of configuration⁷. Hydrogenolysis of *N*-protected aminotriols ($\pm$)-**167**, ($\pm$)-**169**, ($\pm$)-**172** and ($\pm$)-**174** would access dihydroconduramines ($\pm$)-**170** and ($\pm$)-**175**, respectively (Figure 12).^{1,2}

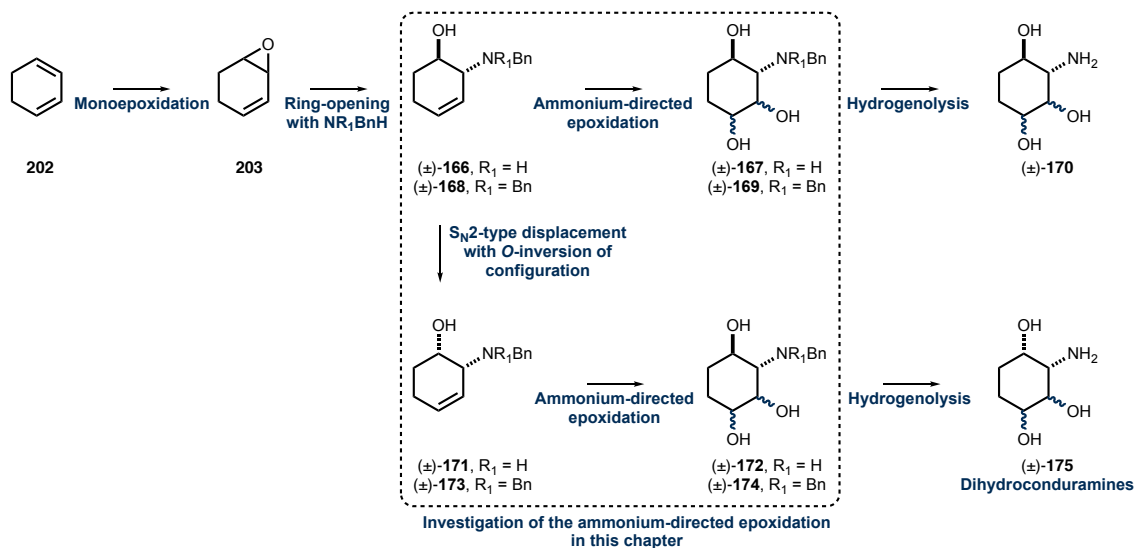


Figure 12. Chapter aim.

2.3 Preparation of racemic *N*-protected *anti*- and *syn*-2-aminocyclohex-3-en-1-ol substrates ($\pm$)-**166**, ($\pm$)-**168**, ($\pm$)-**171** and ($\pm$)-**173**

It was assumed that the identity of the *N*-protecting groups and relative configuration within the substrate could have an effect on the stereochemical outcome of the ammonium-directed epoxidation. Therefore, four substrates containing these differences ($\pm$)-**166**, ($\pm$)-**168**, ($\pm$)-**171** and ($\pm$)-**173** were prepared for this olefinic oxidation investigation (Figure 13).

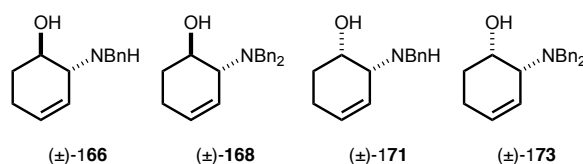
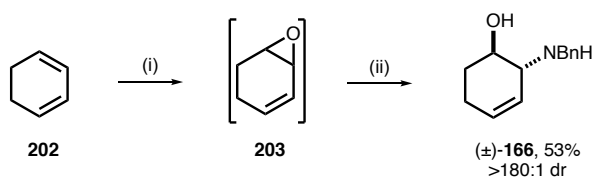


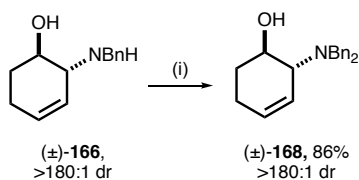
Figure 13. Structure of precursors ($\pm$)-**166**, ($\pm$)-**168**, ($\pm$)-**171** and ($\pm$)-**173**.

Starting from commercially available 1,3-cyclohexadiene **202**, mono-epoxidation was performed using peracetic acid (38–40% in AcOH) and gave epoxide **203**, which was, without purification, opened with benzylamine at 80 °C in *i*PrOH to give the first desired *anti*-substrate ($\pm$)-**166** in 53% yield (from **202**) and >180:1 dr.⁶ The diastereoisomeric ratio was determined by quantitative ¹H NMR spectroscopic analysis of the ¹³C-¹H satellite peaks (Scheme 19).⁸



Scheme 19. Reagents and conditions: (i) AcOOH (38–40% in AcOH), Na₂CO₃, CH₂Cl₂, 0 °C, 3.5 h; (ii) BnNH₂, *i*PrOH, 80 °C, 4 h.

The relative configuration within ($\pm$)-**166** was unambiguously established by single crystal X-ray diffraction analysis of the corresponding HCl salt ($\pm$)-**166**•HCl (Figure 14).⁹ The relative configuration within ($\pm$)-**166** was also assigned by ¹H NMR spectroscopic ³*J* coupling constant analysis. A large coupling constant (³*J*_{1,2} = 8.1 Hz) between C(1)*H* and C(2)*H* indicates a pseudoaxial-pseudoaxial relationship between these protons placing both C(1)*OH* and C(2)*NHBn* groups in pseudoequatorial positions in the most stable half-chair conformation in solution in *d*₁-CHCl₃ (Figure 15). With these results in hand, the conformations adopted by ($\pm$)-**166** in solution in *d*₁-CHCl₃ and in solid state are similar and both confirm the assigned (1*RS*,2*RS*)-configuration.



Scheme 21. Reagents and conditions: (i) BnBr, $i\text{-Pr}_2\text{NEt}$, DMAP, CH_2Cl_2 , rt, 24 h.

The relative (1*R*,2*R*)-configuration within (±)-**168** was unambiguously established by single crystal X-ray diffraction analysis of both the free base (±)-**168** and the corresponding HCl salt (±)-**168**·HCl (Figure 16 and 17).^{9,12}

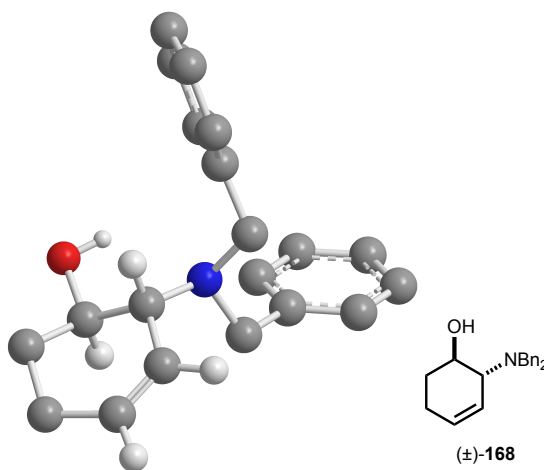


Figure 16. Chem3D representation of the X-ray crystal structure of (±)-**168** (selected H atoms are omitted for clarity).

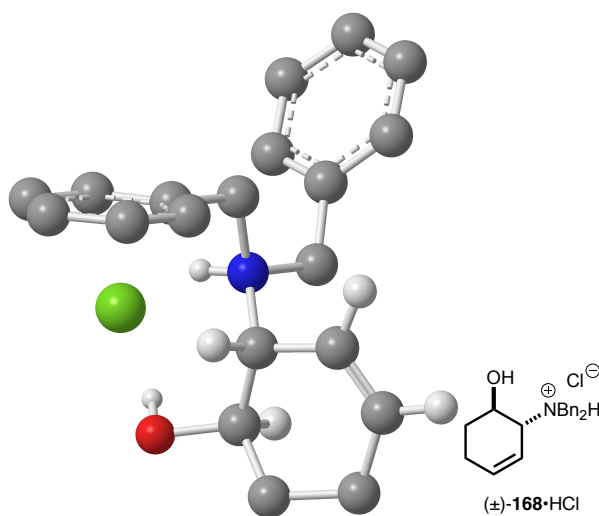
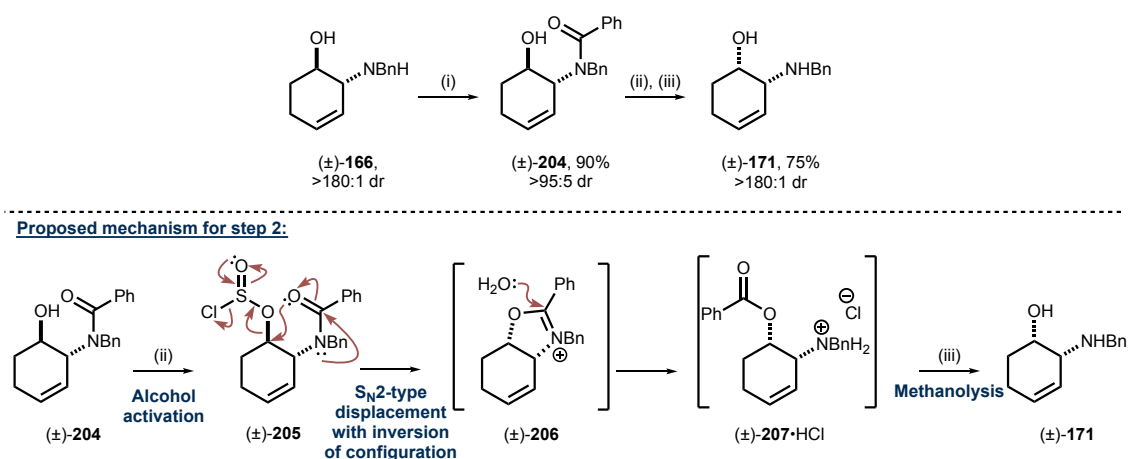


Figure 17. Chem3D representation of the X-ray crystal structure of (±)-**168**·HCl (selected H atoms are omitted for clarity).

To access *N*-protected *syn*-diastereoisomers ($\pm$)-**171** and ($\pm$)-**173**, a strategy based upon a neighbouring group participation reaction with inversion of configuration at the oxygen bearing centre was envisaged. *N*-Benzoylation of ($\pm$)-**166** under Schotten-Baumann conditions gave amide ($\pm$)-**204** in 90% yield and >95:5 dr. Then, treatment of ($\pm$)-**204** with SOCl_2 in CH_2Cl_2 at 0 °C gave intermediate ($\pm$)-**207**•HCl, which was then subjected to methanolysis to give the first *syn*-diastereoisomer ($\pm$)-**171** in 75% yield and >180:1 dr.⁸ The mechanism was consistent with an *in situ* activation of the hydroxyl group followed by an $\text{S}_{\text{N}}2$ -type displacement with inversion of configuration upon attack of the nucleophilic oxygen atom of the benzylamido carbonyl functionality (Scheme 22).⁷



Scheme 22. Reagents and conditions: (i) BzCl , Na_2CO_3 , THF, rt, 24 h; (ii) SOCl_2 , CH_2Cl_2 , rt, 4h; (iii) K_2CO_3 , MeOH, rt, 16 h.

The relative (1*R*,2*S*)-configuration within ($\pm$)-**171** was unambiguously established by single crystal X-ray diffraction analysis (Figure 18).^{9,13,14}

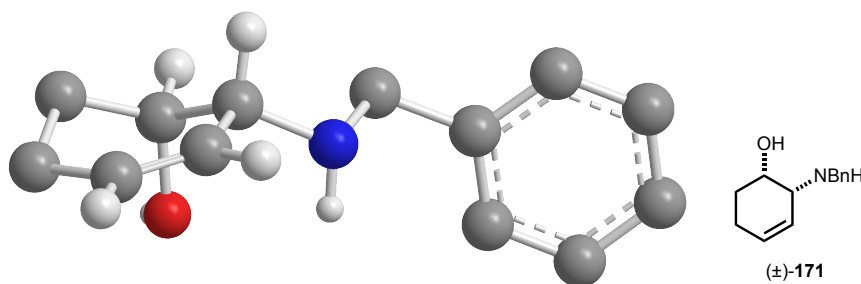
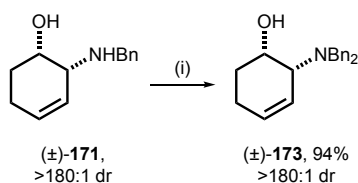


Figure 18. Chem3D representation of the X-ray crystal structure of ($\pm$)-**171** (selected H atoms are omitted for clarity).

As previously, chemoselective *N*-benzylation of ($\pm$)-**171** afforded *syn*-*N,N*-2-dibenzylaminocyclohex-3-en-1-ol ($\pm$)-**173** in 94% yield¹¹ and >180:1 dr (Scheme 23).⁸ The relative configuration within ($\pm$)-**173** was assigned by ¹H NMR spectroscopic ³*J* coupling constant analysis (³*J*_{1,2} = 6.1 Hz) and confirmed a *syn*-relative (1*R*,2*S*)-configuration within ($\pm$)-**173** in the most stable half-chair in solution in *d*₁-CHCl₃ (Figure 19).



Scheme 23. Reagents and conditions: (i) BnBr, Pr₂NEt, DMAP, CH₂Cl₂, rt, 24 h.

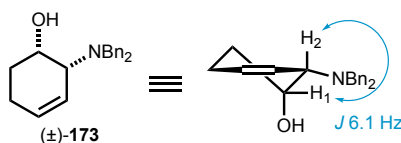


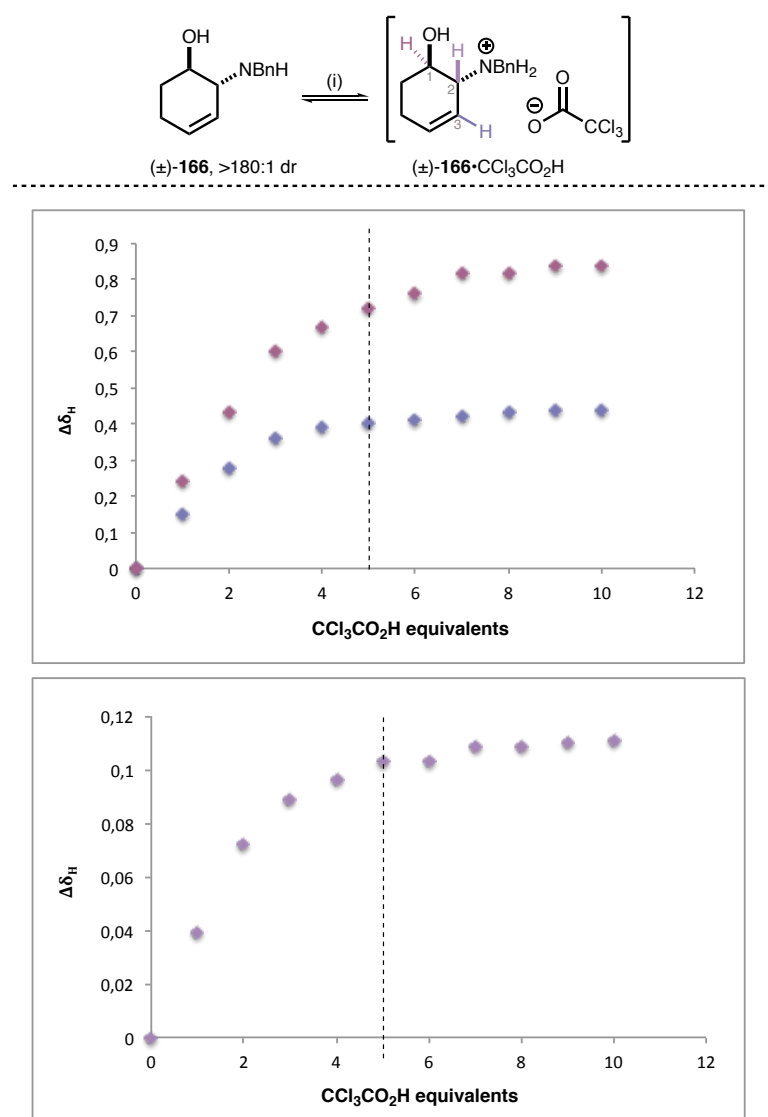
Figure 19. ¹H NMR ³*J* Coupling constant analysis of ($\pm$)-**173**.

2.4 Ammonium-directed epoxidation applied to ($\pm$)-**166**, ($\pm$)-**168**, ($\pm$)-**171** and ($\pm$)-**173**: results

2.4.1 Ammonium-directed epoxidation applied to ($\pm$)-**166**

A ¹H NMR ‘titration experiment’ published by Aciro *et al.* was performed to measure the quantity of CCl₃CO₂H needed to prevent any *N*-oxidation during the reaction.¹⁵ CCl₃CO₂H in 1.0 equivalent portions was added to a solution of ($\pm$)-**166** in *d*₂-CH₂Cl₂ (0.36 M). When the acid-base reaction was analysed by ¹H NMR spectroscopy, the chemical shift differences ($\Delta\delta_{\text{H}}$) between C(1)*H*, C(2)*H* and C(3)*H* of the ($\pm$)-**166**•CCl₃CO₂H salt and those of the free amine ($\pm$)-**166** were calculated and analysis of the graph showed the presence of a plateau around 5.0 equivalents, indicating that the equilibrium lays preferentially to the right and therefore 5.0 equivalents of acid were necessary to prevent

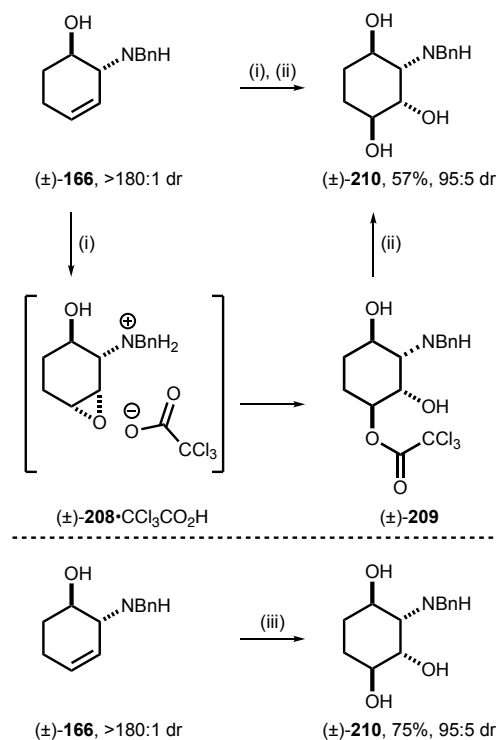
oxidation of the nitrogen atom. This result was in total agreement with previous epoxidation work made in the Davies group on cyclic allylic amines. Indeed, variation of the number of equivalence of $\text{CCl}_3\text{CO}_2\text{H}$ during the epoxidation step was monitored at that time (1, 2, 3, 4, 5 and 10 equivalents) to analyse the suppression of *N*-oxidation and it was observed that 4–5 equivalents of $\text{CCl}_3\text{CO}_2\text{H}$ were necessary to prevent *N*-oxidation (Scheme 24).



Scheme 24. Reagents and conditions: (i) $\text{CCl}_3\text{CO}_2\text{H}$, CD_2Cl_2 , rt.

N-Protonation of (±)-**166** with 5.0 equivalents of $\text{CCl}_3\text{CO}_2\text{H}$ followed by addition of *m*-CPBA gave the trichloroacetate (±)-**209**, which was identified by ^1H NMR spectroscopic

analysis of the crude reaction mixture as a single regio- and diastereoisomer (>95:5 dr). On the basis of the known relative configuration within the precursor ($\pm$)-**166**, the relative configuration within trichloroacetate ($\pm$)-**209** was assigned by ^1H NMR spectroscopic 3J coupling constant analysis. Examinations of the double doublet signal due to C(2)*H* at $\delta_{\text{C(2)H}}$ 2.82 ppm ($^3J_{1,2} = 9.5$ Hz, $^3J_{2,3} = 2.9$ Hz) and the complex multiplets due to C(3)*H* and C(4)*H* at $\delta_{\text{C(3)H}}$ 4.10–4.16 ppm and $\delta_{\text{C(4)H}}$ 5.09–5.17 ppm ($^3J_{3,4} < 4$ Hz), respectively, reveal an axial-axial relationship between C(1)*H* and C(2)*H*, an axial-equatorial relationship between C(2)*H* and C(3)*H*, an equatorial-equatorial relationship between C(3)*H* and C(4)*H*. Therefore, in the most stable chair conformation of ($\pm$)-**209** in solution in $d_1\text{-CHCl}_3$, both C(1)*OH* and C(2)*NHBn* groups occupy equatorial positions and both C(3)*OH* and C(4)*O₂CCCl₃* groups are placed in axial positions (Figure 20). Furthermore, the characteristic C(4)*H* proton and C(4)*H* carbon chemical shifts at $\delta_{\text{C(4)H}}$ ~ 5 ppm and $\delta_{\text{C(4)H}}$ ~ 75 ppm, respectively, shows that the Brønsted conjugate base opens at carbon C(4). These results are consistent with a diastereoselective epoxidation and a regioselective and stereospecific ring-opening. The ester ($\pm$)-**209** was directly subjected, without purification attempts, to $\text{K}_2\text{CO}_3/\text{MeOH}$ to provide the free triol ($\pm$)-**210** in 57% yield and >95:5 dr. Epoxidation of ($\pm$)-**166** with *m*-CPBA, in presence of HBF_4 (40% aq), gave a single compound ($\pm$)-**210** which was isolated, after purification *via* column chromatography, in 75% yield and >95:5 dr (Scheme 25). ^1H NMR Spectroscopic 3J coupling constant analysis within triol ($\pm$)-**210** ($^3J_{1,2} = 8.2$ Hz, $^3J_{2,3} = 3.5$ Hz, $^3J_{3,4} < 4.5$ Hz) was in agreement with an (1*RS*,2*SR*,3*SR*,4*SR*)-configuration (Figure 20).



Scheme 25. Reagents and conditions: (i) CCl₃CO₂H, CH₂Cl₂, rt, 5 min, then *m*-CPBA, rt, 21 h; (ii) K₂CO₃, MeOH, rt, 24 h; (iii) HBF₄ (40% aq), CH₂Cl₂, rt, 5 min, then *m*-CPBA, rt, 21 h.

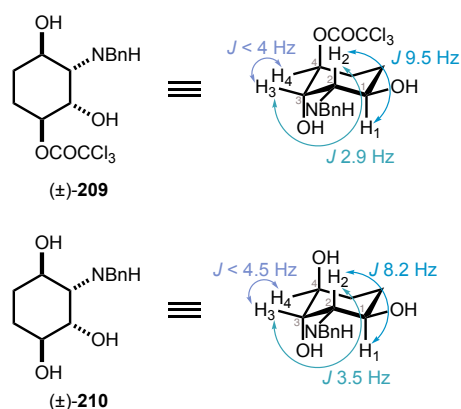
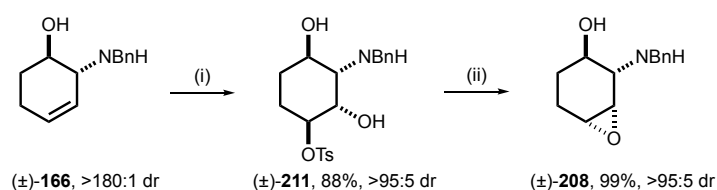


Figure 20. ¹H NMR ³J Coupling constant analyses of (±)-209 and (±)-210.

As the *in situ* epoxide (±)-208•CCl₃CO₂H could not be isolated due to straight ring-opening by the Brønsted conjugate base during the reaction, synthesis of the free aminoepoxide (±)-208 was envisaged. Epoxidation of (±)-166 in presence of TsOH under the same conditions provided tosylate (±)-211 as a single regio- and diastereoisomer (>95:5 dr) in 88% yield (Scheme 26). As previously, the regiochemistry of and relative configuration

within ($\pm$)-**211** were unambiguously established by single crystal X-ray diffraction analysis of **211**⁹ and ¹H NMR spectroscopic ³*J* coupling constant analysis (³*J*_{1,2} = 10.0 Hz, ³*J*_{2,3} = ³*J*_{3,4} = 3.2 Hz) confirmed the (1*R*,2*S*,3*S*,4*S*)-configuration (Figure 21, 22).¹⁶ All these results are consistent with a diastereoselective epoxidation and a regioselective and stereospecific ring-opening. DBU-promoted elimination of the tosylate group (TsO⁻) within ($\pm$)-**211** resulted in the formation of *syn*-epoxide ($\pm$)-**208** in 99% yield and >95:5 dr. Although attempts to assign the stereochemistry of epoxide ($\pm$)-**208** by ¹H NMR spectroscopic ³*J* coupling constant analysis were inconclusive, the presence of proton and carbon chemical shifts at $\delta_{C(3)H/C(4)H} \sim 3.2$ ppm and $\delta_{C(3)H/C(4)H} \sim 55$ ppm were characteristic of an epoxide (Scheme 26).



Scheme 26. Reagents and conditions: (i) TsOH, CH₂Cl₂, rt, 5 min, then *m*-CPBA, rt, 21 h; (ii) DBU, CH₂Cl₂, rt, 24 h.

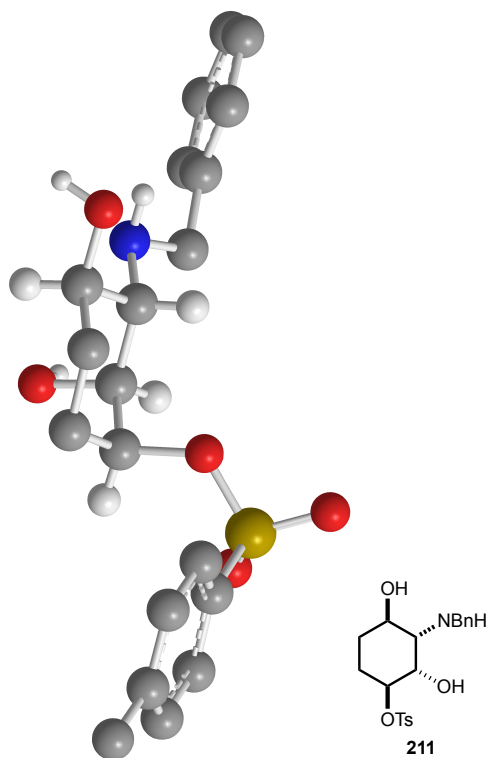


Figure 21. Chem3D representation of the X-ray crystal structure of **211** (selected H atoms are omitted for clarity).

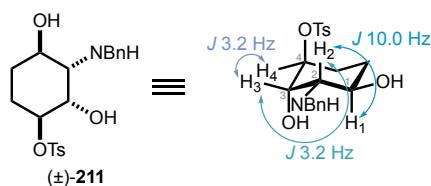
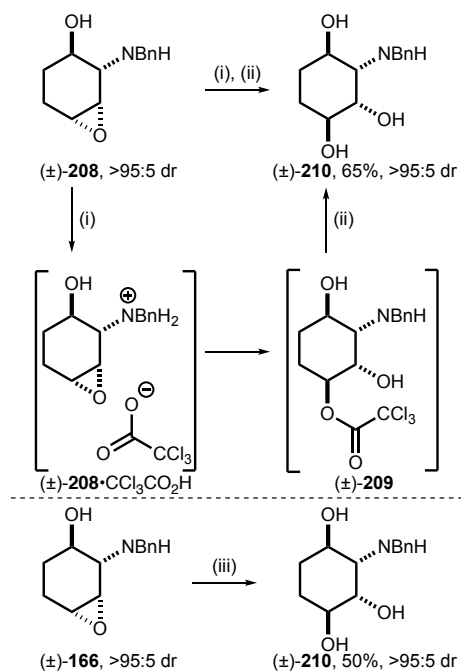


Figure 22. ^1H NMR 3J Coupling constant analysis of (±)-**211**.

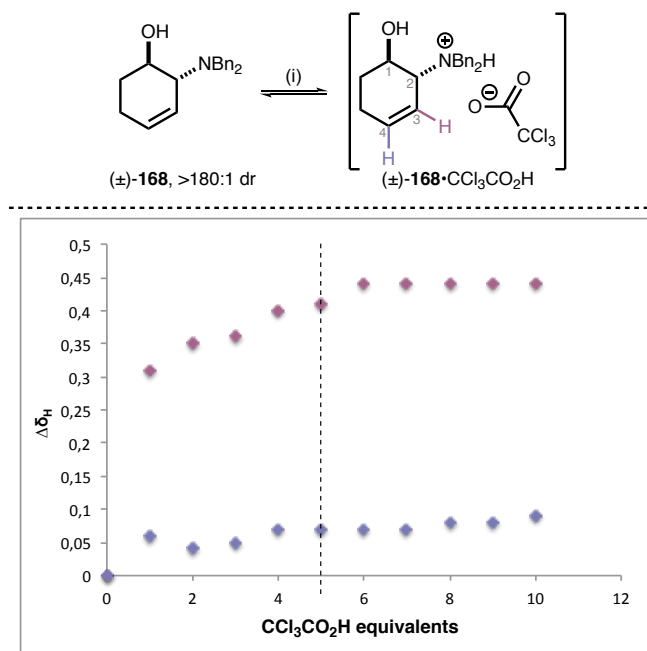
When epoxide (±)-**208** was treated with $\text{CCl}_3\text{CO}_2\text{H}$, regioselective and stereospecific ring-opening of the *in situ* formed *N*-benzylammonium epoxide (±)-**208**• $\text{CCl}_3\text{CO}_2\text{H}$ was observed and gave (±)-**209** as a single regio- and diastereoisomer (>95:5 dr), which was transesterified to provide, as previously, (±)-**210** as the sole product of the reaction in 65% yield and >95:5 dr. The ring-opening of epoxide (±)-**208** and epoxidation of alkene (±)-**166** gave the same triol (±)-**210**, which was consistent with the presence of epoxide salt (±)-**208**• $\text{CCl}_3\text{CO}_2\text{H}$ as an intermediate during the oxidation step. Meanwhile, regioselective and stereospecific ring-opening of (±)-**208** with HBF_4 (40% aq) afforded (±)-**210** in 50% isolated yield and >95:5 dr (Scheme 27). All these results are in agreement with a diastereoselective epoxidation and regioselective and stereospecific ring-opening.



Scheme 27. Reagents and conditions: (i) $\text{CCl}_3\text{CO}_2\text{H}$, CH_2Cl_2 , rt, 21 h; (ii) K_2CO_3 , MeOH, rt, 24 h; (iii) HBF_4 (40% aq), CH_2Cl_2 , rt, 21 h.

2.4.2 Ammonium-directed epoxidation applied to ($\pm$)-**168**

As previously, a ^1H NMR ‘titration experiment’ was realised using the same conditions to measure the quantity of $\text{CCl}_3\text{CO}_2\text{H}$ needed to prevent any *N*-oxidation during the reaction.¹⁵ As before, when the acid-base reaction was analysed by ^1H NMR spectroscopy, the chemical shift differences ($\Delta\delta_{\text{H}}$) between C(3)*H* and C(4)*H* of the ($\pm$)-**168**• $\text{CCl}_3\text{CO}_2\text{H}$ salt and those of the free amine ($\pm$)-**168** were calculated and analysis of the graph showed the presence of a plateau around 5.0 equivalents, indicating that 5.0 equivalents of acid were necessary to prevent oxidation of the nitrogen atom (Scheme 28).



Scheme 28. Reagents and conditions: (i) $\text{CCl}_3\text{CO}_2\text{H}$, CD_2Cl_2 , rt, (see graph).

Epoxidation of ($\pm$)-**168** with 1.6 equivalents of *m*-CPBA in presence of 5.0 equivalents of $\text{CCl}_3\text{CO}_2\text{H}$ was monitored by ^1H NMR spectroscopic analysis of the reaction mixture using 1,4-bis(trimethylsilyl)benzene **212** as an internal standard and incomplete conversion (70%) was observed. Attempts to improve the conversion rate by increasing the number of equivalents of *m*-CPBA to 5.0 equivalents promoted full consumption of starting material ($\pm$)-**168** (Entry f, Scheme 29).

(i) mixture of compounds

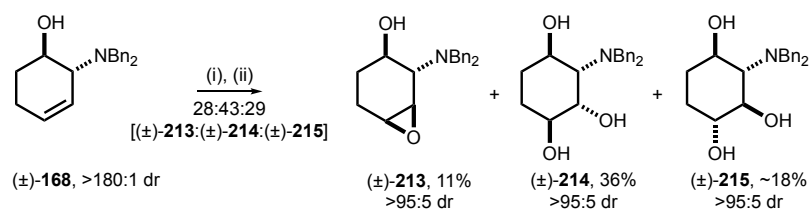
(±)-**168**, >180:1 dr

Entry	Equiv. of <i>m</i> -CPBA	Time (h)	Conversion rate (%)
a	1.6	24	70
b	1.6	48	85
c	4	24	92
d	4	48	98
e	4	60	100
f	5	24	100

212

Scheme 29. Reagents and conditions: (i) 1,4-bis(trimethylsilyl)benzene **212**, $\text{CCl}_3\text{CO}_2\text{H}$, CH_2Cl_2 , rt, 5 min, then *m*-CPBA (5 equiv.), rt, see table.

Epoxidation of (±)-**168** with both 5.0 equivalents of $\text{CCl}_3\text{CO}_2\text{H}$ and *m*-CPBA followed by transesterification under $\text{K}_2\text{CO}_3/\text{MeOH}$ conditions gave a 28:43:29 ratio of epoxide (±)-**213**, triol (±)-**214** and triol (±)-**215**, respectively. After purification *via* column chromatography, (±)-**168** was recovered in 4% yield and >95:5 dr, epoxide (±)-**213** and triol (±)-**214** were isolated in 11% and 36% yield, respectively as both single compounds (>95:5 dr), and an impure sample of triol (±)-**215** was obtained in ~18% yield (Scheme 30). Single-crystal X-ray diffraction analyses unambiguously established the regiochemistry and relative configurations within (±)-**213**–(±)-**215** (Figure 23, 24 and 25).⁹ The relative configuration within (±)-**215** was also assigned by ^1H NMR spectroscopic 3J coupling constant analysis [^1H NMR spectroscopic analyses of (±)-**213** and (±)-**214** provided broad multiplets and therefore non-exploitable 3J coupling constants]. Data showed the same (1*RS*,2*SR*,3*RS*,4*RS*)-configuration as in solid state [$^3J_{1,2} = ^3J_{2,3} = 10.2$ Hz, $^3J_{3,4} = 8.6$ Hz), (Figure 26)]. Isolation of the epoxide (±)-**213** was consistent with an epoxidation step followed by a ring-opening step. Although, the presence of a diastereomeric mixture of triols (±)-**214** and (±)-**215** suggested either a non-diastereoselective epoxidation or a non-regioselective ring-opening.



Scheme 30. Reagents and conditions: (i) CCl₃CO₂H, CH₂Cl₂, rt, 5 min, then *m*-CPBA (5 equiv.), rt, 21 h.

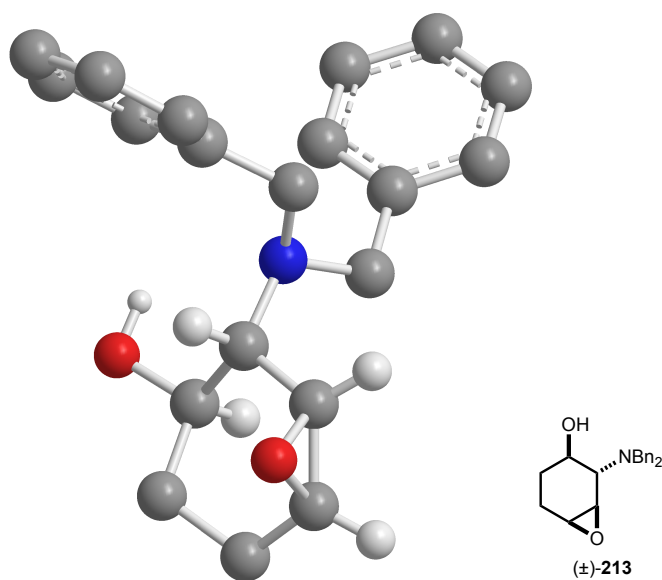


Figure 23. Chem3D representation of the X-ray crystal structure of (±)-**213** (selected H atoms are omitted for clarity).

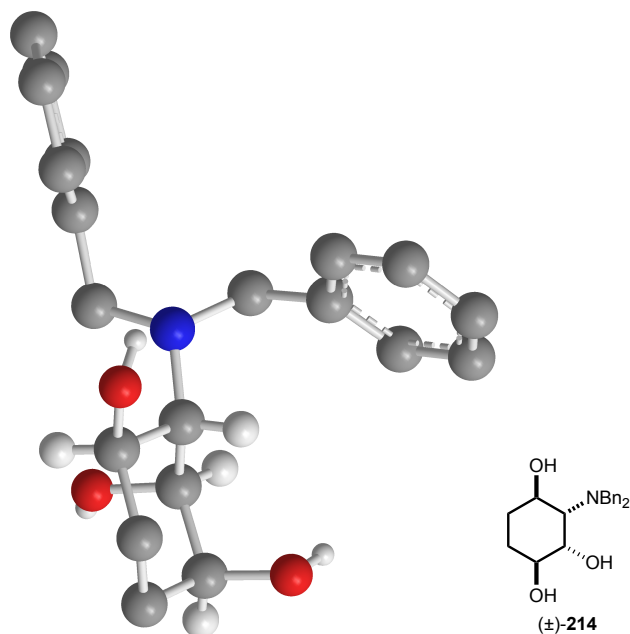


Figure 24. Chem3D representation of the X-ray crystal structure of (±)-**214** (selected H atoms are omitted for clarity).

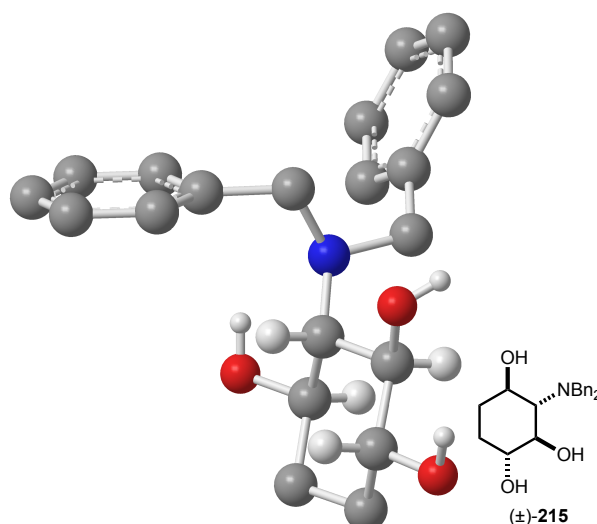


Figure 25. Chem3D representation of the X-ray crystal structure of (±)-**215** (selected H atoms are omitted for clarity).

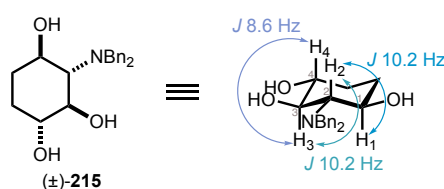
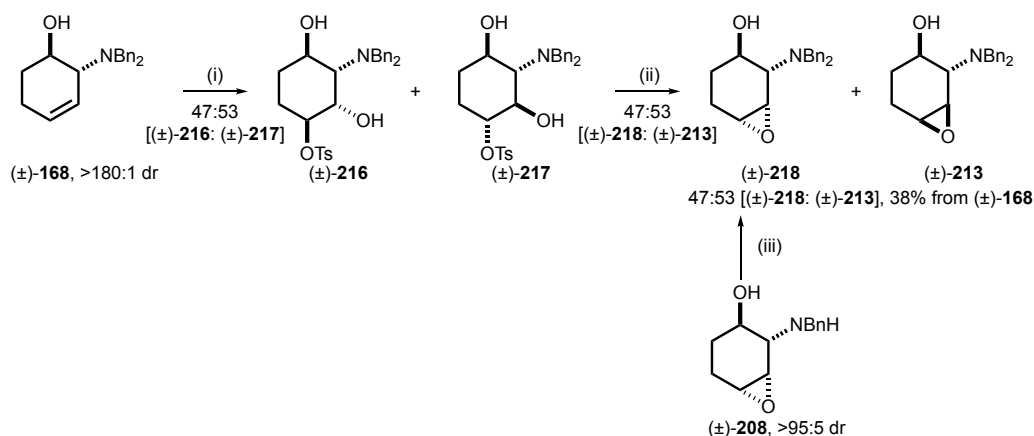


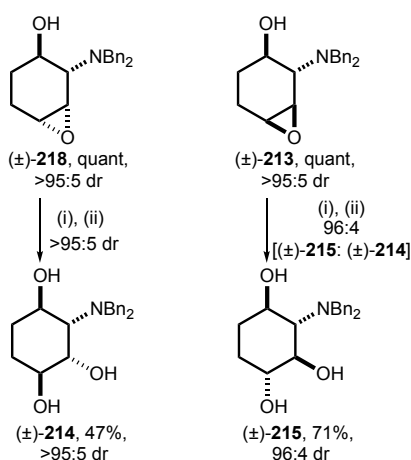
Figure 26. ^1H NMR 3J Coupling constant analysis of (±)-**215**.

A two-step process was then investigated to understand the reaction pathway. Epoxidation of (±)-**168** with *m*-CPBA was performed in presence of TsOH and gave a 47:53 mixture of (±)-**216** and (±)-**217**, respectively. Then, DBU-assisted elimination of the tosylate substituent afforded a 47:53 mixture of epoxides (±)-**218** and (±)-**213**, respectively, in 38% yield from (±)-**168**. Chemoselective *N*-benzylation of the known epoxide (±)-**208** with BnBr, $^i\text{Pr}_2\text{NEt}$ and DMAP gave an authentic sample of (±)-**218** in quantitative yield and >95:5 dr, confirming its stereochemistry.¹¹ These results proved that, due to the presence of *anti*- and *syn*-epoxides in a roughly 1:1 mixture, the epoxidation was not diastereoselective. However, by ^1H and ^{13}C NMR spectroscopic analyses, the characteristic C(4)*H* proton and C(4)*H* carbon chemical shifts at $\delta_{\text{C}(4)\text{H}} \sim 5$ ppm and $\delta_{\text{C}(4)\text{H}} \sim 80$ ppm, respectively, confirmed the position of the tosylate moieties within (±)-**216** and (±)-**217** at carbon C(4). Ring-openings of both (±)-**218**•TsOH and (±)-**213**•TsOH were therefore regioselective and stereospecific (Scheme 31).



Scheme 31. Reagents and conditions: (i) TsOH, CH₂Cl₂, rt, 5 min, then *m*-CPBA (5.0 equiv.), rt, 21 h; (ii) DBU, CH₂Cl₂, rt, 24 h; (iii) BnBr, ^tPr₂NEt, DMAP, CH₂Cl₂, rt, 24 h.

With samples of both epoxides now in hand, the regioselective and stereospecific ring-opening of epoxides (±)-218 and (±)-213 were studied in the presence of CCl₃CO₂H. Ring-opening of (±)-218, followed by subsequent methanolysis, gave triol (±)-214 in 47% isolated yield and as a single regio- and diastereoisomer (>95:5 dr), thus definitively confirming the stereochemistry of epoxide (±)-218. Meanwhile, ring-opening of (±)-213 afforded a 4:96 mixture of triols (±)-214 and (±)-215, respectively, in 71% yield. These results indicate both epoxides open regio- and stereoselectively distal to the ammonium moiety and are consistent with those obtained when TsOH was used in the epoxidation (Scheme 32).



Scheme 32. Reagents and conditions: (i) CCl₃CO₂H, CH₂Cl₂, rt, 21 h; (ii) K₂CO₃, MeOH, rt, 16 h.

Therefore, the mechanism of the epoxidation of ($\pm$)-**168** with *m*-CPBA in the presence of acid could be rationalised. A non-diastereoselective epoxidation of ($\pm$)-**168** gives a 41:59 mixture of intermediate epoxides ($\pm$)-**218**•AH and ($\pm$)-**213**•AH, respectively [AH = CCl₃CO₂H, TsOH, HBF₄ (40% aq)]. Then, regio- and stereoselective ring-opening of ($\pm$)-**218** and ($\pm$)-**213** give triols ($\pm$)-**219** and ($\pm$)-**220**, respectively (Figure 27).

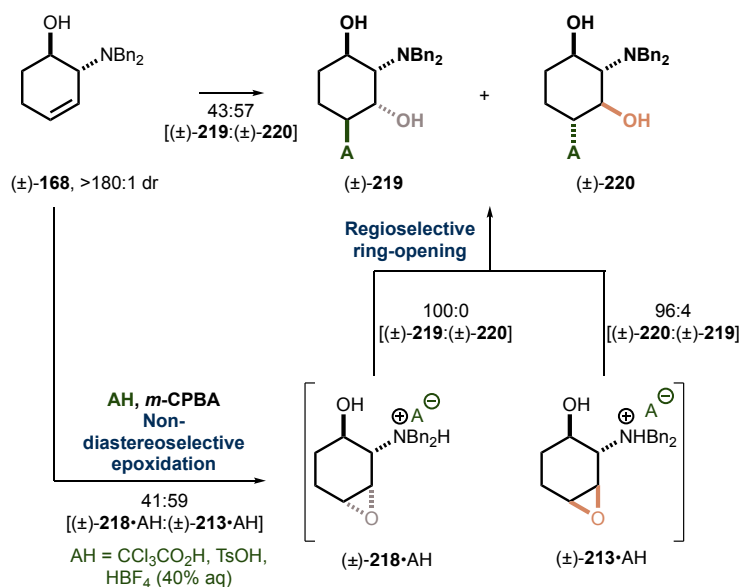
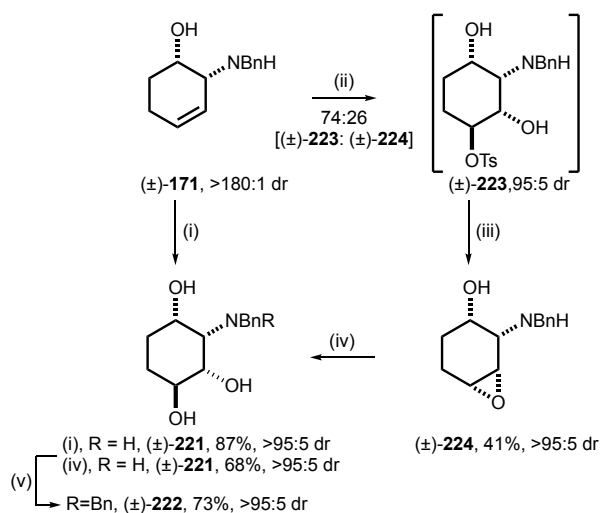


Figure 27. Summary of the non-diastereoselective epoxidation of ($\pm$)-**168** and regio- and stereoselective ring-openings of ($\pm$)-**218**•AH and ($\pm$)-**213**•AH.

2.4.3 Ammonium-directed epoxidation applied to ($\pm$)-**171**

Epoxidation of ($\pm$)-**171** with *m*-CPBA (1.6 equiv) in presence of HBF₄ (40% aq, 5 equiv) for 21 h at rt gave a single compound ($\pm$)-**221** in 87% yield and >95:5 dr, consistent with a diastereoselective epoxidation and a regioselective and stereospecific ring-opening. On the basis of the known relative configuration within the precursor ($\pm$)-**171**, the relative (1*RS*,2*RS*,3*RS*,4*RS*)-configuration within ($\pm$)-**221** was assigned by ¹H NMR spectroscopic ³*J* coupling constant analysis [³*J*_{1,2} = ³*J*_{2,3} = 3.5 Hz, ³*J*_{3,4} < 4 Hz, (Figure 28)]. *N*-Benzylation of ($\pm$)-**221** in presence of BnBr, ^{*i*}Pr₂NEt and DMAP gave chemoselectively ($\pm$)-**222** in 73%

yield and >95:5 dr.¹¹ Single-crystal X-ray diffraction analysis of ($\pm$)-**222** unambiguously established the regiochemistry and relative configuration therein (Figure 29), and thus confirmed the stereochemistry within ($\pm$)-**221**. As before, when HBF₄ (40% aq) was replaced by TsOH, epoxidation under the same set of conditions resulted in a 74:26 mixture of diol ($\pm$)-**223** and epoxide ($\pm$)-**224**, respectively, which was then subjected, without purification, to ring-closure conditions to afford epoxide ($\pm$)-**224** as a single compound in 41% isolated yield and >95:5 dr. Analysing the ¹H, ¹³C NMR and 2D NMR spectroscopic data, characteristic C(4)*H* proton and C(4)*H* carbon chemical shifts at $\delta_{C(4)H} \sim 4.6$ ppm and $\delta_{C(4)H} \sim 80$ ppm, respectively, confirmed the presence and position of the tosylate moiety within ($\pm$)-**223** at carbon C(4) confirming a regioselective and stereospecific ring-opening. Regiochemistry and relative configuration within epoxide ($\pm$)-**224** were unambiguously established by single-crystal X-ray diffraction analysis⁹ (Figure 30) and therefore relative configuration within tosylate ($\pm$)-**223** was also unambiguously determined. Finally, ring-opening of ($\pm$)-**224** in presence of HBF₄ (40% aq) provided triol ($\pm$)-**221** as a single entity in 68% yield and >95:5 dr. With all these results in hand, it is unambiguous that, in both cases, the epoxidation is diastereoselective and the ring-opening is regioselective and stereospecific (Scheme 33).



Scheme 33. Reagents and conditions: (i) HBF_4 (40% aq), CH_2Cl_2 , rt, 5 min, then *m*-CPBA (1.6 equiv.), rt, 21 h; (ii) TsOH , CH_2Cl_2 , rt, 5 min, then *m*-CPBA (1.6 equiv.), rt, 21 h; (iii) DBU, CH_2Cl_2 , rt, 24 h; (iv) HBF_4 (40% aq), CH_2Cl_2 , rt, 24 h; (v) BnBr , Pr_2NEt , DMAP, CH_2Cl_2 , rt, 24 h.

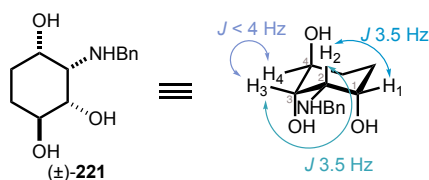


Figure 28. ^1H NMR 3J Coupling constant analysis of **(±)-221**.

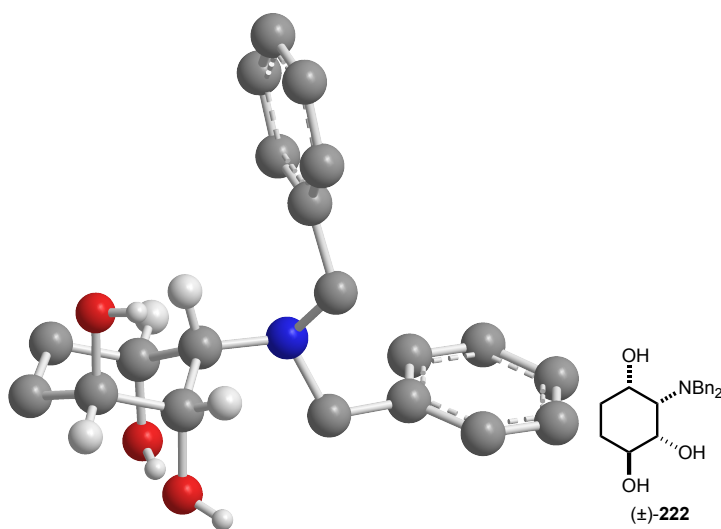


Figure 29. Chem3D representation of the X-ray crystal structure of **(±)-222** (selected H atoms are omitted for clarity).

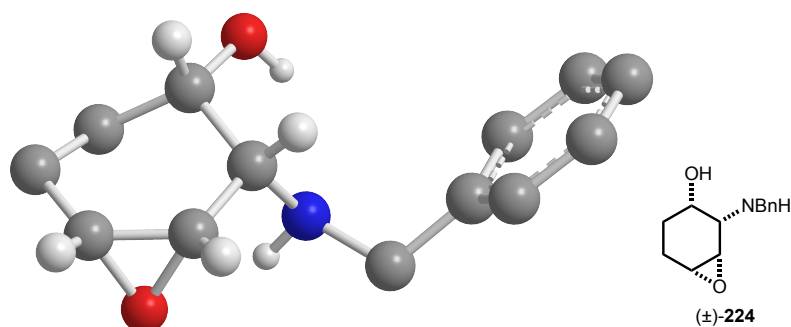
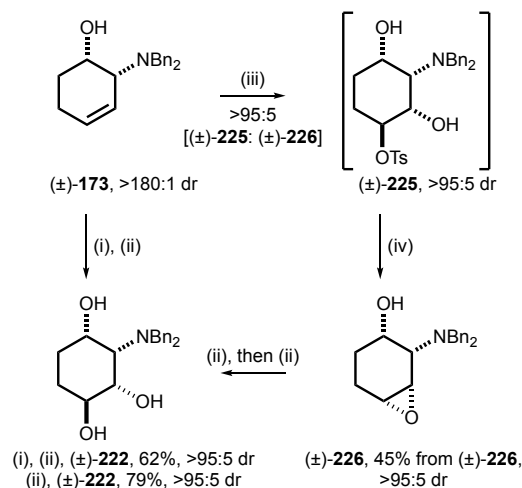


Figure 30. Chem3D representation of the X-ray crystal structure of (±)-**224** (selected H atoms are omitted for clarity).

2.4.4 Ammonium-directed epoxidation applied to (±)-**173**

Epoxidation of (±)-**173** with *m*-CPBA (1.6 equiv) in presence of HBF₄ (40% aq, 5.0 equiv) for 21 h at rt gave a 65:35 mixture of triol (±)-**222** and epoxide (±)-**226**, respectively, which was resubjected to HBF₄ (40% aq) and afforded (±)-**222** in 62% isolated yield and >95:5 dr. Meanwhile epoxidation of (±)-**173** in presence of 5.0 equivalents TsOH and 1.6 equivalents of *m*-CPBA gave a 8:92 mixture of unreacted starting material (±)-**173** and tosylate (±)-**225**, respectively.¹⁷ Full consumption of starting material (±)-**173** was observed when 2.0 equivalents of *m*-CPBA was used and the oxidation afforded a single compound (±)-**225**, which was subjected without purification to DBU-induced ring-closure resulting in (±)-**226** in 45% isolated yield from (±)-**173** and >95:5 dr. ¹H NMR ³*J* coupling constant analysis (³*J*_{1,2} = ³*J*_{2,3} = 2.6, ³*J*_{3,4} < 6.5 Hz), assigned the relative configuration within tosylate (±)-**173** in solution in *d*₁-CHCl₃ as (1*R*,2*R*,3*R*,4*R*)-configuration (Figure 31). Once more, characteristic C(4)*H* proton and C(4)*H* carbon chemical shifts at δ_{C(4)*H*} ~4.6 ppm and δ_{C(4)*H*} ~80 ppm, respectively, confirmed the presence and position of the tosylate moiety within (±)-**225** at carbon C(4). Ring-opening of (±)-**226** with HBF₄ (40% aq) afforded after 24 h an 85% conversion to triol (±)-**222** and resubjection to the same conditions gave (±)-**222** in 79% yield as a single diastereoisomer. Knowing the stereochemistry of (±)-**173**,

the relative configuration within ($\pm$)-**225** and ($\pm$)-**226** were unambiguously proved. These results show that, in both cases, the epoxidation occurs diastereoselectively to give *in situ* the *syn*-epoxide, which ring-opens regioselectively and stereospecifically (Scheme 34).



Scheme 34. Reagents and conditions: (i) HBF_4 (40% aq), CH_2Cl_2 , rt, 5 min then *m*-CPBA (1.6 equiv.), rt, 21 h; (ii) HBF_4 (40% aq), CH_2Cl_2 , rt, 24 h; (iii) TsOH , CH_2Cl_2 , rt, 5 min then *m*-CPBA (1.6 equiv.), rt, 21 h; (iv) DBU, CH_2Cl_2 , rt, 24 h.

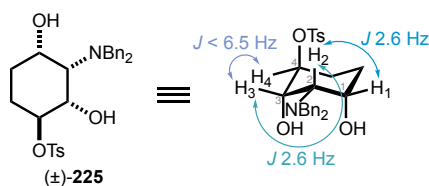


Figure 31. ^1H NMR 3J Coupling constant analysis of ($\pm$)-**225**.

2.5 Ammonium-directed epoxidation applied to ($\pm$)-**166**, ($\pm$)-**168**, ($\pm$)-**171** and ($\pm$)-**173**: discussion

Epoxidation in presence of a Brønsted acid [$\text{AH} = \text{TsOH}$, HBF_4 (40% aq) or $\text{CCl}_3\text{CO}_2\text{H}$] of *N*-benzylated substrates ($\pm$)-**166** and ($\pm$)-**171** and *N,N*-dibenzylated substrate ($\pm$)-**173** provided *in situ* a single diastereoisomer ($\pm$)-**210**, ($\pm$)-**221** and ($\pm$)-**222** (>95:5 dr), respectively. In both cases, the resulting *N*-benzylammonium or *N,N*-dibenzylammonium ion, products of an acid-base reaction between the corresponding amino alcohol [either ($\pm$)-**166**, ($\pm$)-**171** or ($\pm$)-**173**] and the acid-protecting agent, direct the *syn*-epoxidation *via* H-bonding with *m*-CPBA. The epoxidation pathway is favoured stereoelectronically and

undergoes *via* the most stable half-chair transition state **TS4**, **TS5** and **TS6** in which the *N*-benzyl or *N,N*-dibenzylammonium moieties are placed in a pseudoequatorial position in solution. Then, regioselective and stereospecific ring-opening upon attack of the conjugate base A^- distal to the ammonium substituent to minimize the inductive effect of the destabilizing electron withdrawing *N*-benzyl or *N,N*-dibenzylammonium moiety proceeds *via* the most stable chair-like transition state, which in all cases places the ammonium moieties in a pseudoequatorial position, thus respecting the Fürst-Plattner rule.^{18,19} It is noted that after epoxidation of ($\pm$)-**171** and ($\pm$)-**173**, the presence of triol ($\pm$)-**221** and ($\pm$)-**222**, respectively, as a single diastereoisomer (>95:5 dr) are the results of *m*-CPBA attacking the *syn* face to both the ammonium moiety and hydroxyl group. It is then assumed that the peracid is not only directed, *via* H-bonding, by the ammonium moiety but also by the hydroxyl substituent. In the case of the *anti-N,N*-dibenzyl substrate ($\pm$)-**168**, a non diastereoselective epoxidation and a regio- and stereoselective ring-opening of *in situ* formed epoxide were observed. The most stable half-chair transition states **TS7A** and **TS7B**, where both hydroxyl group and *N,N*-dibenzylammonium moiety behave in pseudo-equatorial positions, are assumed. It was also suggested that an hydrogen interaction between the two groups could prevent any H-bonding of the ammonium moiety with *m*-CPBA and therefore any *N*-direction. By comparing these results to the former results, diastereoselective epoxidation depends on the relative configuration within the substrate as well as the hindrance of the *N*-protecting groups (Figure 32 and 33).

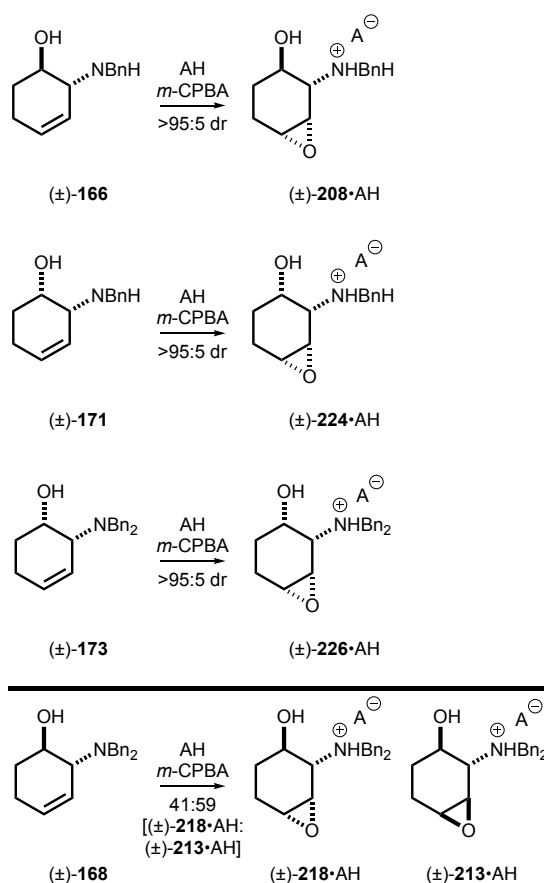


Figure 32. Summary of the diastereoselectivity of the epoxidation (H⁺, *m*-CPBA) for (±)-**166**, (±)-**168**, (±)-**171** and (±)-**171** [AH = CCl₃CO₂H, TsOH, HBF₄ (40% aq)].

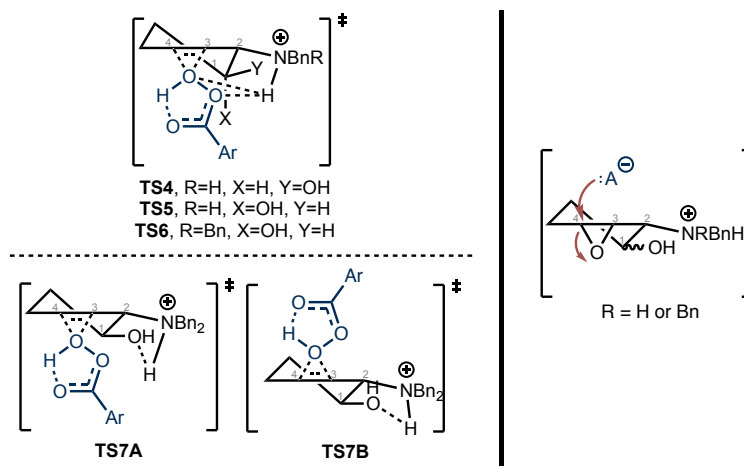
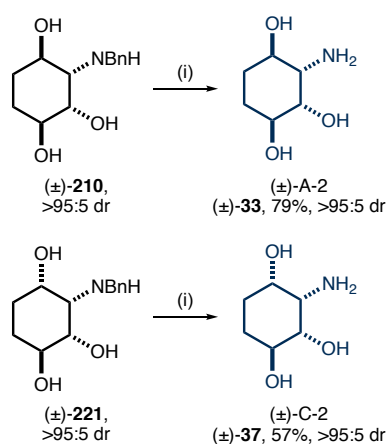


Figure 33. Ammonium directed epoxidation transition state **TS4**, **TS5**, **TS6** and **TS7A/TS7B** and regio- and stereospecific ring-opening mechanisms [Ar=*m*-ClC₆H₄, A⁻ = Cl₃CCOO⁻, TsO⁻, H₂O].

2.6 Syntheses of racemic dihydroconduramines ($\pm$)-A-2 ($\pm$)-33 and ($\pm$)-C-2 ($\pm$)-37

To establish the utility of the methodology for dihydroconduramine syntheses, hydrogenolysis of ($\pm$)-**210** and ($\pm$)-**221** were undertaken. Hydrogenolysis of ($\pm$)-**210** and ($\pm$)-**221** with $\text{Pd}(\text{OH})_2/\text{C}$ in MeOH under an atmosphere of H_2 (i.e., 1 atm) gave after 24 h ($\pm$)-dihydroconduramine A-2 ($\pm$)-**33** in 79% yield (>95:5 dr) and ($\pm$)-dihydroconduramine C-2 ($\pm$)-**37** in 57% yield (>95:5 dr), respectively, both unknown from the literature (Scheme 35).



Scheme 35. Reagents and conditions: (i) H_2 (1 atm), $\text{Pd}(\text{OH})_2/\text{C}$, MeOH, rt, 24 h.

2.7 Conclusion

Epoxidation of racemic *anti*- and *syn*-N-benzyl 2-aminocyclohex-3-en-1-ols ($\pm$)-**166** and ($\pm$)-**171** proceeded with very high diastereoselectivity (>95:5 dr). In both cases, epoxidation showed to be ammonium-directed *via* H-bonding. Epoxidation of racemic *anti*- and *syn*-N,N-dibenzyl 2-aminocyclohex-3-en-1-ols ($\pm$)-**168** and ($\pm$)-**173** proceeded with no diastereoselectivity (45:55 dr [*syn:anti*]) and very high level of diastereoselectivity (>95:5 dr), respectively. In the former case, the lack of diastereoselectivity could be due to a hindrance issue, an intramolecular H-bonding interaction between the hydroxyl group and the ammonium moiety preventing any H-bonding and *m*-CPBA and/or an intermolecular H-bonding interaction between the hydroxyl group with *m*-CPBA. In the latter case, it was

assumed that the epoxidation underwent ammonium- and hydroxyl-directed, as they are both *syn* to the same face.^{1,2} It was then decided to use a homoallylic alcohol allylic amine for the synthesis of dihydroconduramine in the next chapter.

2.8 Notes and references

- (1) Da Silva Pinto, S.; Davies, S. G.; Fletcher, A. M.; Roberts, P. M.; Thomson, J. E. *Synthesis* **2018**, 50, 64–83.
- (2) Da Silva Pinto, S.; Davies, S. G.; Fletcher, A. M.; Roberts, P. M.; Thomson, J. E. *J. Org. Chem.* **2018**, 83, 9939–9957.
- (3) Henbest, B. H. B. *J. Chem. Soc.* **1958**, 1958–1965.
- (4) Aciro, C.; Davies, S. G.; Kurosawa, W.; Roberts, P. M.; Russell, A. J.; Thomson, J. E. *Org. Lett.* **2009**, 11, 1333–1336.
- (5) Aciro, C.; Davies, S. G.; Roberts, P. M.; Russell, A. J.; Smith, A. D.; Thomson, J. E. *Org. Biomol. Chem.* **2008**, 6, 3762–3770.
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- (7) Schiffers, I.; Rantanen, T.; Schmidt, F.; Bergmans, W.; Zani, L. *J. Org. Chem.* **2006**, 7, 2320–2331.
- (8) Claridge, T. D. W.; Davies, S. G.; Polywka, M. E. C.; Roberts, P. M.; Russell, A. J.; Savory, E. D.; Smith, A. D. *Org. Lett.* **2008**, 10, 5433–5436.
- (9) X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research Laboratory, University of Oxford.
- (10) Due to the volatility of epoxide **203**, the conversion was calculated by determining the ratio of unreacted dibenzylamine to ring-opened product ($\pm$)-**168**.
- (11) Brennan, M. B.; Csatayová, K.; Davies, S. G.; Fletcher, A. M.; Green, W. D.; Lee, J. A.; Roberts, P. M.; Russell, A. J.; Thomson, J. E. *J. Org. Chem.* **2015**, 80, 6609–6618.
- (12) Attempts to assign the relative configurations within ($\pm$)-**168** and ($\pm$)-**168**•HCl by ¹H NMR spectroscopic analyses by examining ³J coupling constants were inconclusive.
- (13) Attempts to assign the relative configuration within ($\pm$)-**171** by ¹H NMR spectroscopic analyses by examining ³J coupling constants was inconclusive.
- (14) Sabate, M.; Llebaria, A.; Molins, E.; Miravittles, C.; Delgado, A. *J. Org. Chem.* **2000**, 65, 4826–4829.
- (15) Aciro, C.; Claridge, T. D. W.; Davies, S. G.; Roberts, P. M.; Russell, A. J.; Thomson, J. E. *Org. Biomol. Chem.* **2008**, 6, 3751–3761.
- (16) Recrystallization of **211**, prepared in chapter 4, yielded single crystals of suitable quality for analysis by X-ray diffraction.
- (17) Although DBU-promoted elimination of this mixture provided a 92:8 mixture of epoxide ($\pm$)-**226** and unreacted starting material ($\pm$)-**173**, respectively, these two compounds were not separable by column chromatography.
- (18) Fürst, A.; Plattner, P. A. New York, **1951**.
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Chapter 3

Syntheses of Enantiopure *anti*- and *syn*-Substrates

This chapter details the syntheses of enantiopure **166** and *ent*-**166**, the enantiomers of racemic substrate *anti*-($\pm$)-**166**, enantiopure **227** and **228** as surrogates of the enantiomers of *syn*-($\pm$)-**171** and enantiopure **229** and **230** as surrogates of the enantiomers of *syn*-($\pm$)-**173**. Establishment of the surrogacy of **227**–**230** are also described (Figure 34).^{1,2}

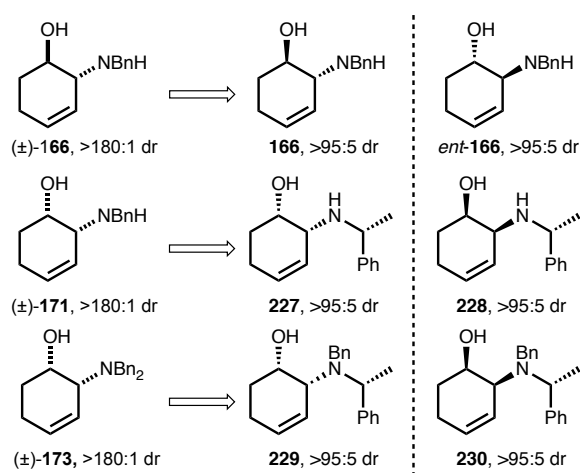


Figure 34. Structures of enantiopure substrates **166**, *ent*-**166** and **227**–**230**.

3.1 Chapter aim

The aim of this chapter is to prepare suitable enantiopure *syn*- and *anti*-substrates **227**–**232** as surrogates of the enantiomers of ($\pm$)-**171**, ($\pm$)-**173** and ($\pm$)-**166**, respectively, from commercially available 1,3-cyclohexadiene **202** for the asymmetric synthesis of dihydroconduramines. To access these substrates, use of an enantiopure amine (*R*)- α -methylbenzylamine (*R*)-**235** is required during the ring-opening process. Although the diastereoisomers **231** and **232** could hardly be separable *via* column chromatography, precedent in the literature showed that their amido derivatives **233** and **234** could be isolated individually.³ It was thus envisaged to synthesise *anti*-amides **233** and **234** as

precursor intermediates to access either *anti*-diastereoisomers **231** and **232**, after hydrolysis of the amido functionality or *syn*-configured derivatives **227** and **228**, through a neighbouring group participation with inversion of the hydroxyl bearing stereocentre, as shown in chapter 2. Chemoselective *N*-benzylation of **227** and **228** would provide **229** and **230**, respectively (Figure 35).^{1,2}

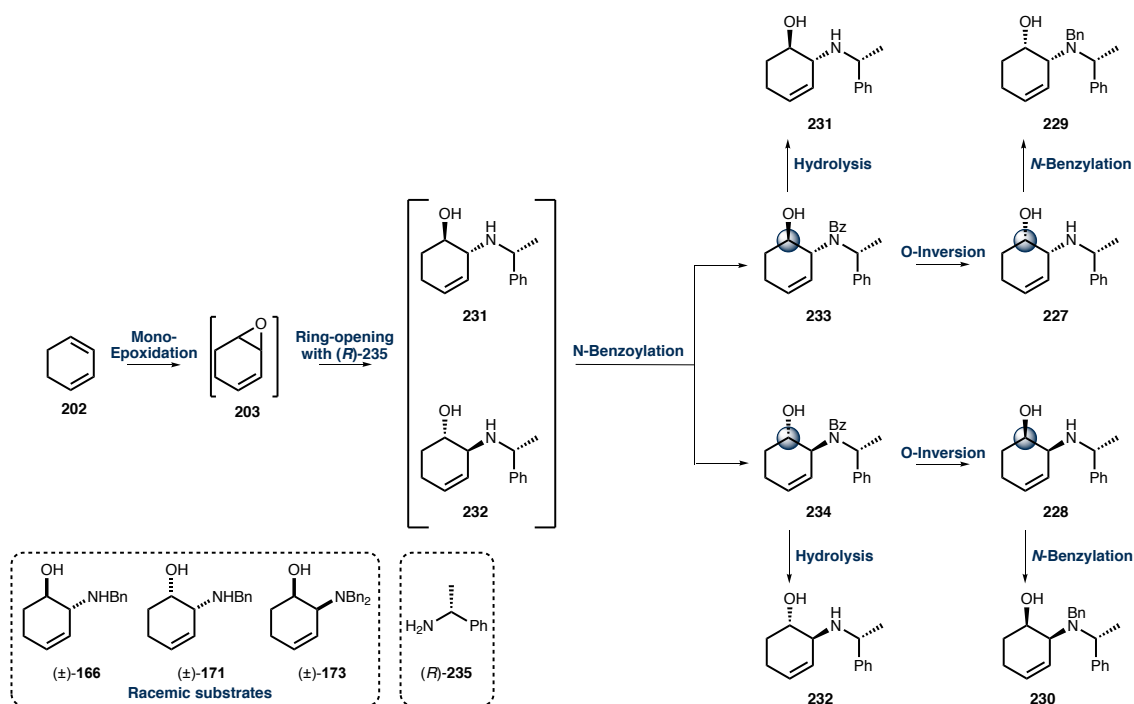
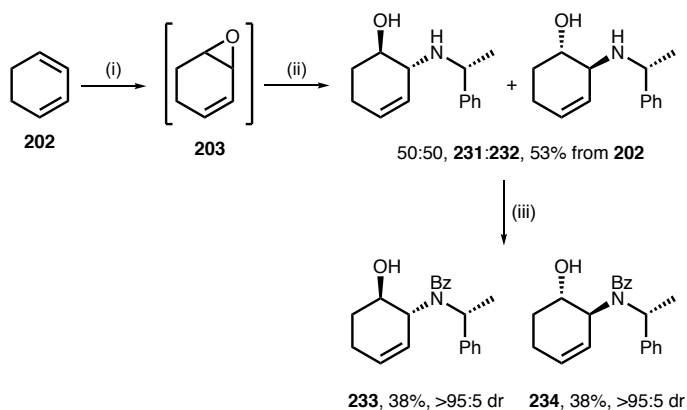


Figure 35. Chapter aim.

3.2 Synthesis of amides **233** and **234**

Following the literature procedure, starting from commercially available 1,3-cyclohexadiene **202**, mono-epoxidation with AcOOH (38–40% in AcOH) in CH_2Cl_2 followed by ring-opening with enantiopure (*R*)- α -methylbenzylamine (*R*)-**235** afforded a 50:50 mixture of diastereoisomers **231** and **232**, respectively, which were isolated by column chromatography in 53% yield from **202** as an inseparable mixture.³ Treatment of a 50:50 mixture of **231** and **232** with benzoyl chloride under Schotten-Baumann conditions gave a 50:50 mixture of amides **234** and **235** which were separated *via* column chromatography and both isolated in 38% yield and >95:5 dr (Scheme 36).³



Scheme 36. Reagents and conditions: (i) AcOOH (38–40% in AcOH), Na₂CO₃, CH₂Cl₂, 0 °C, 3.5 h; (ii) (R)-**235**, ^tPrOH, 80 °C, 4 h; (iii) BzCl, Na₂CO₃, THF, rt, 24 h.

The relative configuration within **233** was unambiguously confirmed by single crystal X-ray diffraction analysis and thus the absolute (1*R*,2*R*, α *R*)-configuration was assigned from the known (*R*)-configuration of the α -methylbenzyl stereogenic centre (Figure 36).^{4,5} This also unambiguously established the absolute configurations of its diastereoisomer **234**, and those of amines **231** and **232**.

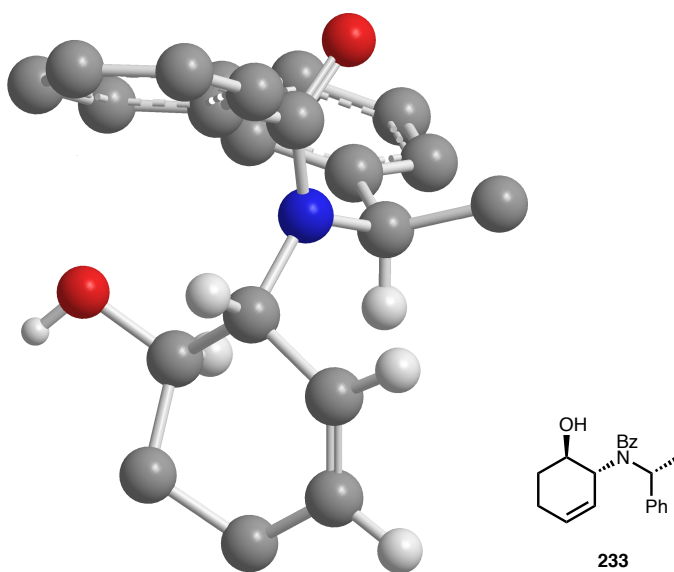
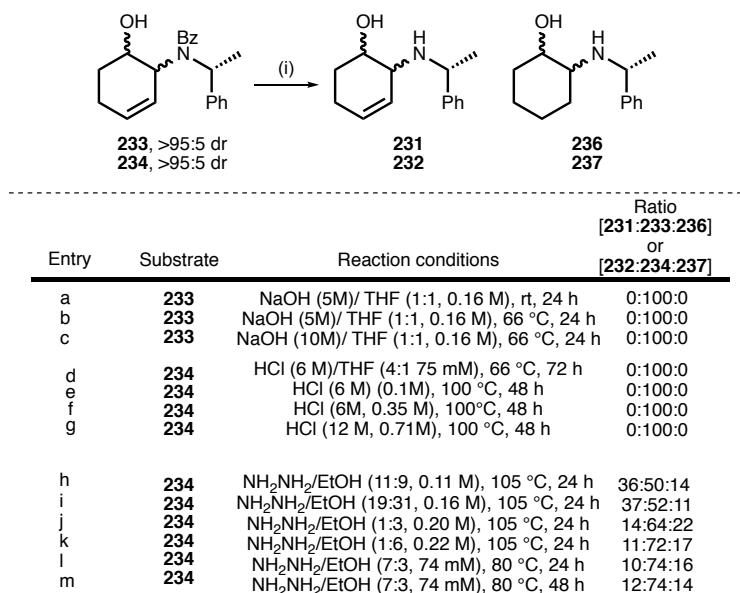


Figure 36. Chem3D representation of the X-ray crystal structure of **233** (selected H atoms are omitted for clarity).

3.3 Attempted preparation of **231** and **232**

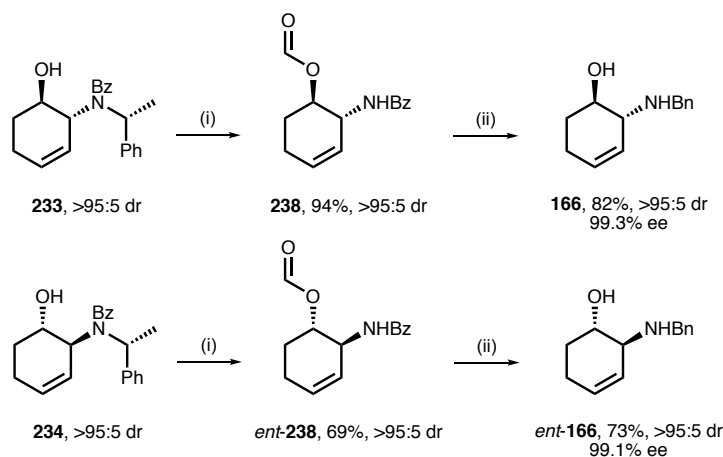
Then, removal of the benzoyl group within amides **233** and **234** was implemented *via* hydrolysis under acidic^{6,7} or basic⁸ conditions or *via* hydrazinolysis^{9,10} but these attempts proved to be unsuccessful (Scheme 37).



Scheme 37. Reagents and conditions: (i) see Table.

3.4 Strategy revision: preparation of enantiomers **166** and *ent*-**166** of racemic ($\pm$)-**166**

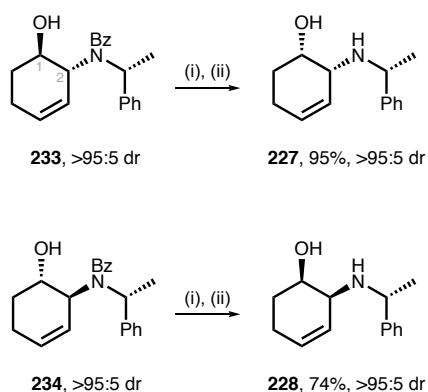
It was therefore envisaged to remove the *N*- α -methylbenzyl substituent within **233** and **234** instead and to reduce the amide functionality to obtain amines **166** and *ent*-**166**, respectively. Treatment of **233** and **234** with HCO₂H (90% aq) at 60 °C gave benzylamido esters **238** and *ent*-**238** in 94% and 69% yield, respectively (>95:5 dr).¹¹ Then, simultaneous reduction of the ester and amide functionalities within **238** and *ent*-**238** with LiAlH₄ gave enantiopure **166** in 82% yield (99.3% ee¹²) and *ent*-**166** in 73% yield (99.1% ee¹²), both >180:1 dr.¹³ The ¹H and ¹³C NMR spectroscopic data of **166** and *ent*-**166** were indistinguishable from those of the racemate ($\pm$)-**166** (Scheme 38).



Scheme 38. Reagents and conditions: (i) HCO_2H (90% aq), 60 °C, 18 h; (ii) LiAlH_4 , THF, 60 °C, 16 h.

3.5 Synthesis of enantiopure 227–230

The strategy based upon a neighbouring group participation reaction with inversion of configuration at C(1) was next used to synthesise enantiopure *syn*-configured substrates from the *anti*-configured precursors **231** and **232**. Amides **233** and **234** were treated individually with SOCl_2 in CH_2Cl_2 at rt followed with K_2CO_3 and MeOH to provide *cis*-configured diastereoisomers **227** in 95% yield and >95:5 dr and **228** in 74% yield and >95:5 dr, respectively (Scheme 39).¹⁴



Scheme 39. Reagents and conditions: (i) SOCl_2 , CH_2Cl_2 , rt, 4 h; (ii) K_2CO_3 , MeOH, rt, 16 h.

The relative configuration within **227** was unambiguously established by single crystal X-ray diffraction analysis. Its absolute (1*S*,2*R*, α *R*)-configuration was assigned from the known (*R*)-configuration of the α -methylbenzyl stereogenic centre.⁴ A Flack χ parameter

of +0.1(2) for the crystal structure of **227** was also consistent with its assigned absolute (1*S*,2*R*, α *R*)-configuration. Thus, the relative and absolute configurations of diastereoisomer **228** were established. (Figure 37).¹⁵

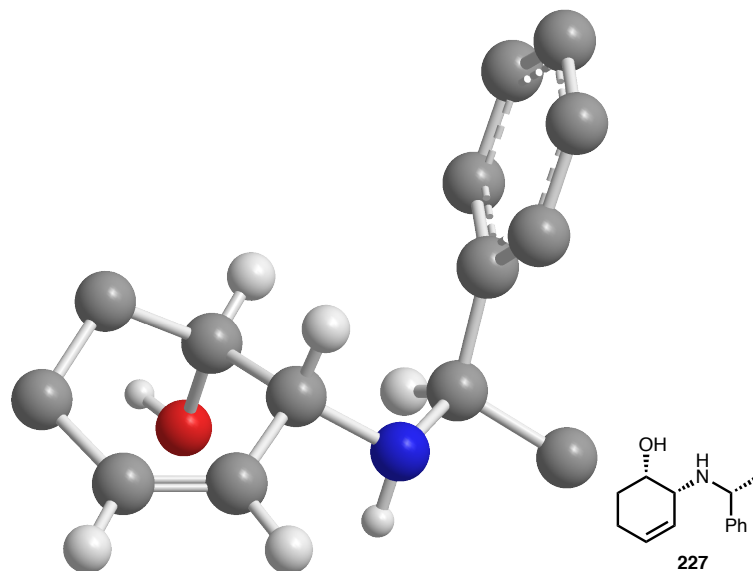
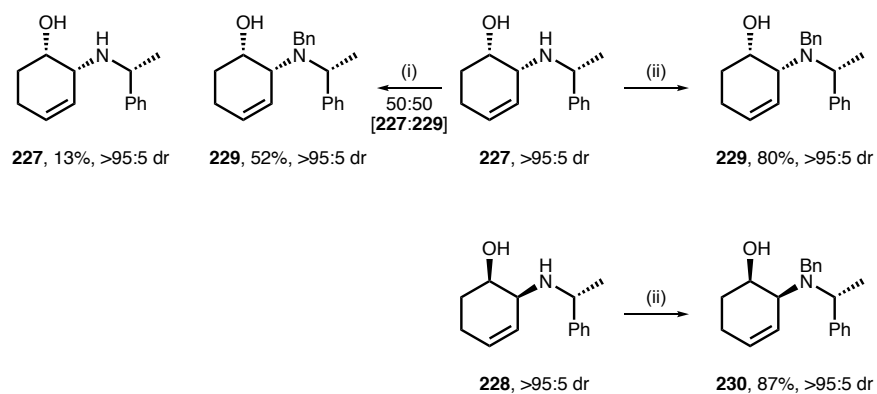


Figure 37. Chem3D representation of the X-ray crystal structure of **227** (selected H atoms are omitted for clarity).

As some of the transformations used in the proposed syntheses of dihydroconduramines required *N,N*-dibenzyl protection to be present and as epoxidation of racemic ($\pm$)-**173** provided high diastereocontrol (chapter 2), evaluations of the corresponding *N*-benzyl-*N*- α -methylbenzyl derivatives **229** and **230** as surrogates for ($\pm$)-**173** in the epoxidation reaction were also undertaken. Chemoselective *N*-benzylation of **227** with BnBr in presence of Pr_2NEt and DMAP gave, after 24 h, a 50:50 mixture of starting material **227** and *N*-benzylated substrate **229**, which were isolated in 13% and 52% yield, respectively.¹⁶ Nevertheless, subjection of **227** to BnBr and K_2CO_3 in MeCN at 80 °C afforded, after 24 h, **229** as a single compound in 80% isolated yield with full consumption of starting material **227**. When applied to **228**, chemoselective *N*-benzylation under these optimised conditions provided **230** as a single compound in 87% yield (Scheme 40).¹⁴



Scheme 40. Reagents and conditions: (i) BnBr, Pr_2NEt , DMAP, CH_2Cl_2 , rt, 24 h; (ii) BnBr, K_2CO_3 , MeCN, 80 °C, 24 h.

The relative configuration within **229** was unambiguously established by single crystal X-ray diffraction analysis. Its absolute (1*S*,2*R*, α *R*)-configuration was assigned from the known (*R*)-configuration of the α -methylbenzyl stereocentre.⁴ Thus, the relative and absolute configurations of diastereoisomer **230** were also unambiguously established. (Figure 38).¹⁵

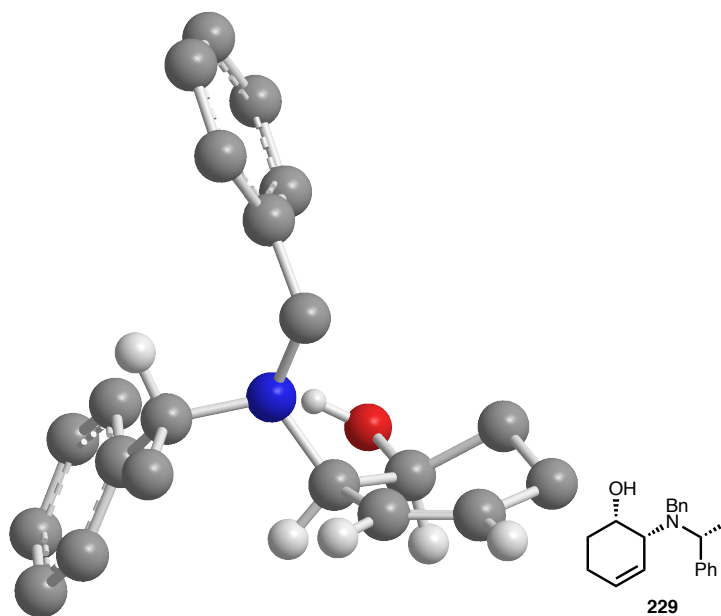


Figure 38. Chem3D representation of the X-ray crystal structure of **229** (selected H atoms are omitted for clarity).

3.6 Epoxidation of 227–230

Having successfully prepared the proposed surrogates **227–230** for enantiopure **171**, *ent*-**171**, **173** and *ent*-**173**, respectively, it was now envisaged to deploy the oxidation methodology (H^+ , *m*-CPBA) to these derivatives to establish if the presence of α -methylbenzyl stereogenic centre or its relative configuration played a role in the selectivity of the epoxidation and ring-opening steps (Figure 39).

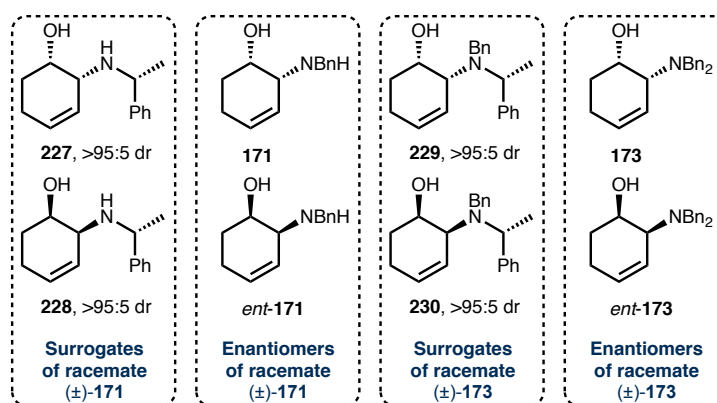
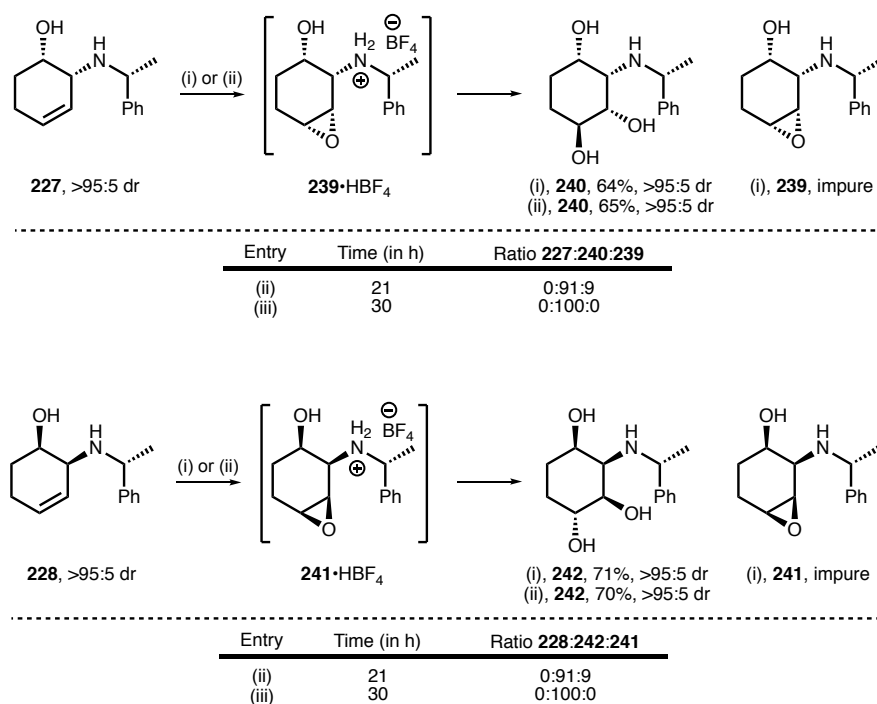


Figure 40. Structure of substrates **227** and **228**, surrogates of ($\pm$)-**171** and substrates **229** and **230**, surrogates of ($\pm$)-**173**.

3.6.1 Epoxidation of 227 and 228 with HBF_4 (40% aq)

Epoxidation of **227** with *m*-CPBA in presence of HBF_4 (40% aq) afforded, after 21 h, a 9:91 mixture of epoxide **239** and desired product **240**, respectively and purification *via* column chromatography gave **240** in 64% yield and >95:5 dr and **239**, recovered as impure (~66% pure). When the oxidation was extended to 30 h, full consumption of *in situ* epoxide **239**• HBF_4 was obtained and **240** was isolated as a single regio- and diastereoisomer in 65% yield and >95:5 dr. Meanwhile, the same results were obtained with the diastereoisomeric starting material **228**. After 21 h, epoxidation of **228** gave a 9:91 mixture of unreacted epoxide **241**, isolated impure (~66% pure), and **242** in 71% isolated yield (>95:5 dr). However, after 30 h, oxidation of **228** afforded **242** as the sole product in 70% yield and >95:5 dr (Scheme 41).



Scheme 41. Reagents and conditions: (i) HBF₄ (40% aq), CH₂Cl₂, rt, 5 min then *m*-CPBA, rt, see table; (ii) HBF₄ (40% aq), CH₂Cl₂, rt, 5 min then *m*-CPBA, rt, see table [R = (α)-methylbenzyl].

The relative configuration within **240** was unambiguously established by single crystal X-ray diffraction analysis. Its absolute (1*S*,2*S*,3*S*,4*S*,α*R*)-configuration was assigned from the known (*R*)-configuration of the α-methylbenzyl stereogenic centre.⁴ A Flack α parameter of −0.1(2) for the crystal structure of **240** was also consistent with its assigned absolute (1*S*,2*S*,3*S*,4*S*,α*R*)-configuration (Figure 40). Furthermore, the conformation adopted by **240** in solution in *d*₁-CHCl₃, assigned by ¹H NMR spectroscopic ³*J* coupling constant analysis (³*J*_{1,2} = ³*J*_{2,3} = ³*J*_{3,4} = 3.6 Hz), was consistent with the solid state one and, here also, supportive of a (1*S*,2*S*,3*S*,4*S*,α*R*)-configuration (Figure 41).

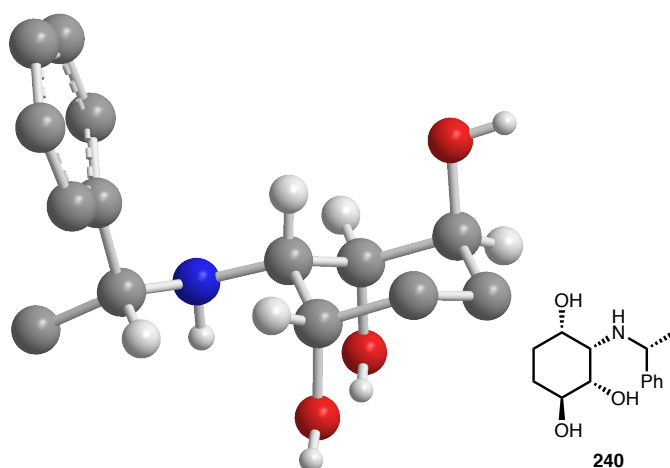


Figure 40. Chem3D representation of the X-ray crystal structure of **240** (selected H atoms are omitted for clarity).

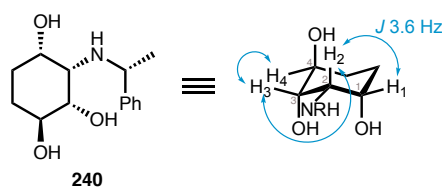


Figure 41. ^1H NMR 3J coupling constants analysis of **240**.

The relative configuration within **242** was also unambiguously established by single crystal X-ray diffraction analysis. Its absolute (1*R*,2*R*,3*R*,4*R*, α *R*)-configuration was assigned from the known (*R*)-configuration of the α -methylbenzyl stereogenic centre (Figure 42).^{4,17}

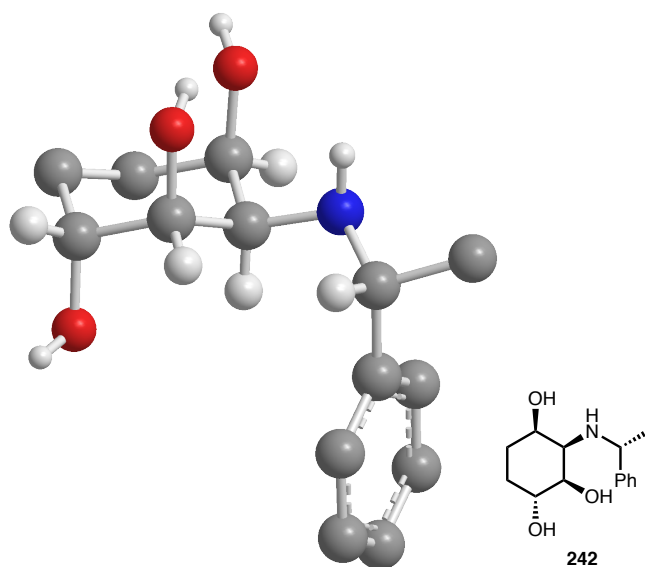
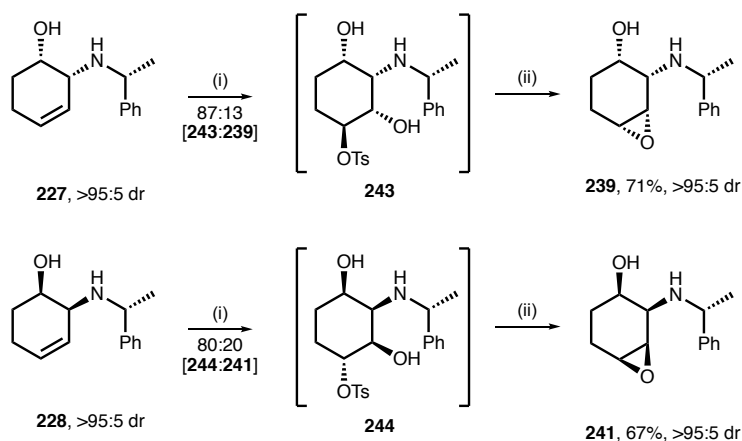


Figure 42. Chem3D representation of the X-ray crystal structure of **242** (selected H atoms are omitted for clarity).

3.6.2 Epoxidation of **227** and **228** with TsOH: epoxide synthesis

In order to prepare authentic samples of intermediate epoxides **239** and **241**, HBF₄ (40% aq) was replaced by TsOH and epoxidation of **227** provided an 13:87 mixture of unopened epoxide **239** and tosylate **243**, respectively. DBU-induced ring-closure of the 13:87 mixture of **239** and **243** provided epoxide **239** in 71% yield from **227** as a single entity (>95:5 dr). The conformation adopted by **243** in solution in *d*₁-CHCl₃ was determined by ¹H NMR spectroscopic ³*J* coupling constant analysis (³*J*_{1,2} = ³*J*_{2,3} = ³*J*_{3,4} = 3.3 Hz) establishing a (1*S*,2*S*,3*S*,4*S*,α*R*)-configuration and analysis of the location of the tosylate functionality at carbon C(4) by ¹H–¹H COSY NMR spectroscopy confirmed the regiochemistry within **243** (δ_{C(4)H} ~4.5 ppm and δ_{C(4)H} ~80 ppm). The presence of an epoxide functionality within **239** was supported by ¹H and ¹³C NMR spectroscopic analysis (δ_{C(3)H/C(4)H} ~2.92–3.59 ppm and δ_{C(3)H/C(4)H} ~54 ppm) and its stereochemistry was assigned from tosylate **243** on the basis of a stereospecific ring-closing process. In the meantime, oxidation of **228** with *m*-CPBA in presence of TsOH gave a 20:80 mixture of unreacted epoxide **241** and tosylate **244** (δ_{C(3)H/C(4)H} ~4.7 ppm and δ_{C(3)H/C(4)H} ~80 ppm, ³*J*_{1,2} = ³*J*_{2,3} = 3.0 Hz, ³*J*_{3,4} = 3.3 Hz), respectively. DBU-promoted ring-closure of 20:80 mixture of **241** and **244** gave epoxide **241** in 67% from **228** as the sole product of the reaction (>95:5 dr, δ_{C(3)H/C(4)H} ~3.3–3.4 ppm and δ_{C(3)H/C(4)H} ~54 ppm). By correlation with epoxide **239** and all the data in hand, the structure of and stereochemistry within **241** was also proven (Scheme 42, Figure 43).



Scheme 42. Reagents and conditions: (i) TsOH, CH₂Cl₂, rt, 5 min then *m*-CPBA, rt, 21 h; (ii) DBU, CH₂Cl₂, rt, 24 h [R = (α)-methylbenzyl].

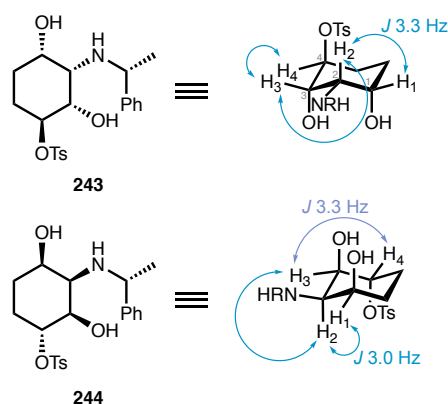
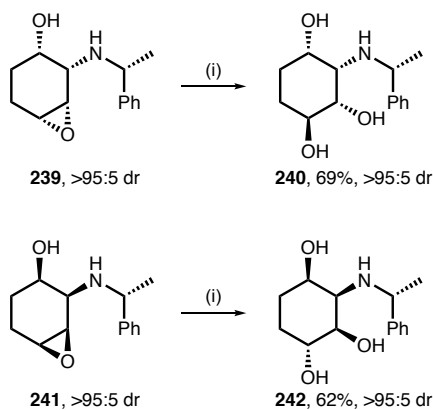


Figure 43. ¹H NMR ³J Coupling constant analyses of **243** and **244**.

3.6.3 Ring-opening of epoxides **239** and **241**

Ring-opening of **239** and **241** with HBF₄ (40% aq) at rt gave triols **240** and **242** in 69% and 62% yield, respectively, as the only product of the reaction (Scheme 43).



Scheme 43. Reagents and conditions: (i) HBF₄ (40% aq), CH₂Cl₂, rt, 24 h.

These results are consistent with a mechanism involving a diastereoselective epoxidation directed by the ammonium moiety and a regioselective and stereospecific S_N2 -type ring opening. In conclusion, the relative configuration within the α -methylbenzyl stereogenic centre within **227** and **228** showed negligible effects on the diastereoselectivity of the epoxidation or regioselectivity of the ring-opening, thus establishing **227** and **228** as suitable substrates for the syntheses of dihydroconduramines (Figure 44).

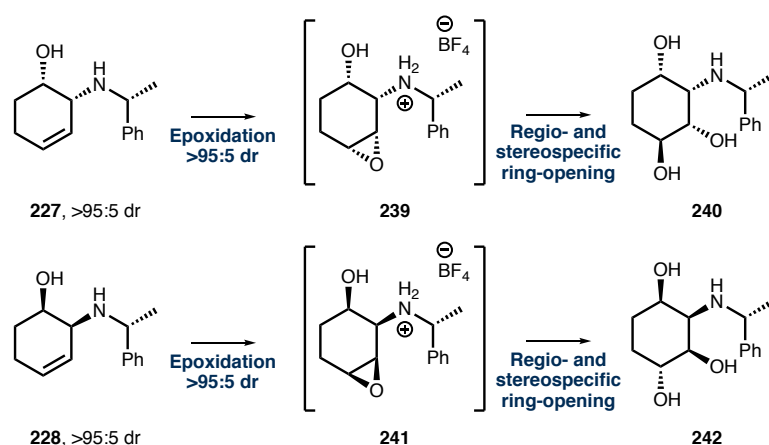
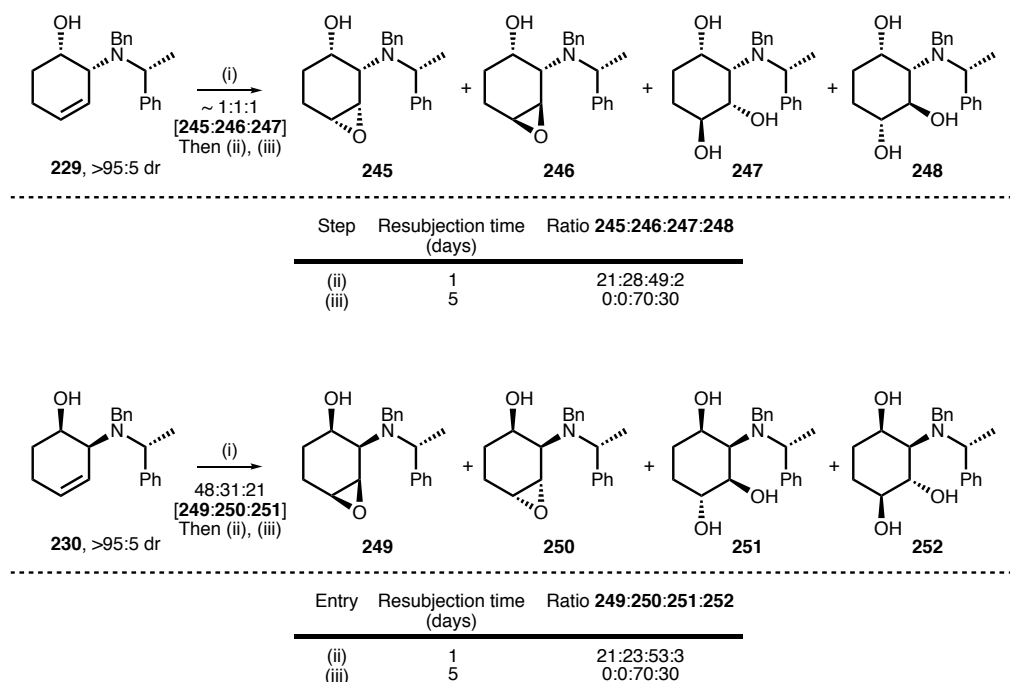


Figure 44. Ammonium-directed epoxidation summary on **227** and **228**.

3.6.4 Epoxidation of **229** and **230** with HBF_4 (40% aq)

As announced previously, the diastereoselectivity of the ammonium-directed epoxidation of **229** and **230** were also investigated to establish whether they were suitable surrogates for the enantiomers of ($\pm$)-**173** for the syntheses of dihydroconduramines. When epoxidation in the presence of HBF_4 (40% aq) was applied to the corresponding enantiopure *N*-benzyl-*N*- α -methylbenzyl compound **229**, a roughly 1:1:1 mixture of epoxide **245**, epoxide **246** and triol **247**, respectively, was obtained. This crude reaction mixture was resubjected to HBF_4 (40% aq) in CH_2Cl_2 at rt and left to react until full consumption of unreacted epoxides **245** and **246** was perceived by TLC. After 5 days, a ~70:30 mixture of triols **247** and **248**, respectively, was obtained. In a similar manner, epoxidation of **230** with HBF_4 (40% aq) gave a 48:31:21 mixture of epoxide **249**, epoxide **250** and triol **251**, respectively and

resubjection of this crude reaction mixture gave after 5 days ~70:30 mixture of triols **251** and **252**, respectively (Scheme 44).¹⁸



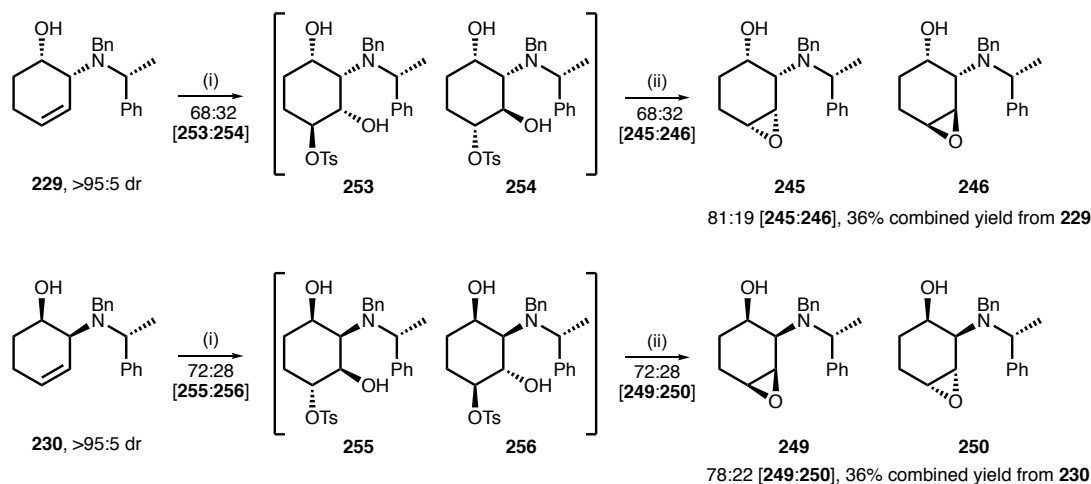
Scheme 44. Reagents and conditions: (i) HBF_4 (40% aq), CH_2Cl_2 , rt, 5 min then *m*-CPBA, rt, 30 h; (ii) HBF_4 (40% aq), CH_2Cl_2 , rt, 24 h; (iii) HBF_4 (40% aq), CH_2Cl_2 , rt, 5 days.

In both cases, the presence of epoxides **245/246** and **249/250** and triol **247** and **251** are consistent with an epoxidation step followed by ring-opening step. Despite the presence of a diastereomeric mixture of epoxides **245/246** and **249/250** suggesting a non-diastereoselective epoxidation of **229** and **230**, respectively, the results obtained do not allow any interpretation of the regioselectivity of the ring-opening. Therefore, investigation to understand this second step was also undertaken.

3.6.5 Epoxidation with TsOH: investigation

Epoxidation of **229** with *m*-CPBA was performed in presence of TsOH and gave a 68:32 mixture of **253** and **254**, respectively. By ^1H and ^{13}C NMR spectroscopic analyses, the characteristic $\text{C}(4)\text{H}$ proton and $\text{C}(4)\text{H}$ carbon chemical shifts at $\delta_{\text{C}(4)\text{H}} \sim 4.5$ ppm and $\delta_{\text{C}(4)\text{H}} \sim 80$ ppm, respectively, confirmed the position of the tosylate moiety within **253** and **254** at

carbon C(4). Then DBU-assisted elimination of the tosylate substituents afforded a 68:32 mixture of epoxides **245** and **246** isolated in 36% yield and 81:19 dr from **229**. These results confirmed a poor diastereoselectivity due to the presence of *anti*- and *syn*-epoxides in a roughly 70:30 mixture and regioselective and stereospecific S_N2-type ring-openings of epoxides **245** and **246**. The same method was implemented to **230**. Use of TsOH for the oxidation provided a 72:28 mixture of **255** and **256** ($\delta_{\text{C(4)H}} \sim 4.5$ ppm and $\delta_{\text{C(4)H}} \sim 80$ ppm), respectively, which was then ring-closed in presence of DBU resulting in a 72:28 mixture of epoxides **249** and **250**, respectively. Purification *via* column chromatography gave a 78:22 mixture of **249** and **250**, as an inseparable mixture, in a 29% yield from **230**. As before, the presence of an α -methylbenzyl stereogenic centre makes the epoxidation non-selective although the ring-opening step remains regioselective and stereospecific (Scheme 45).

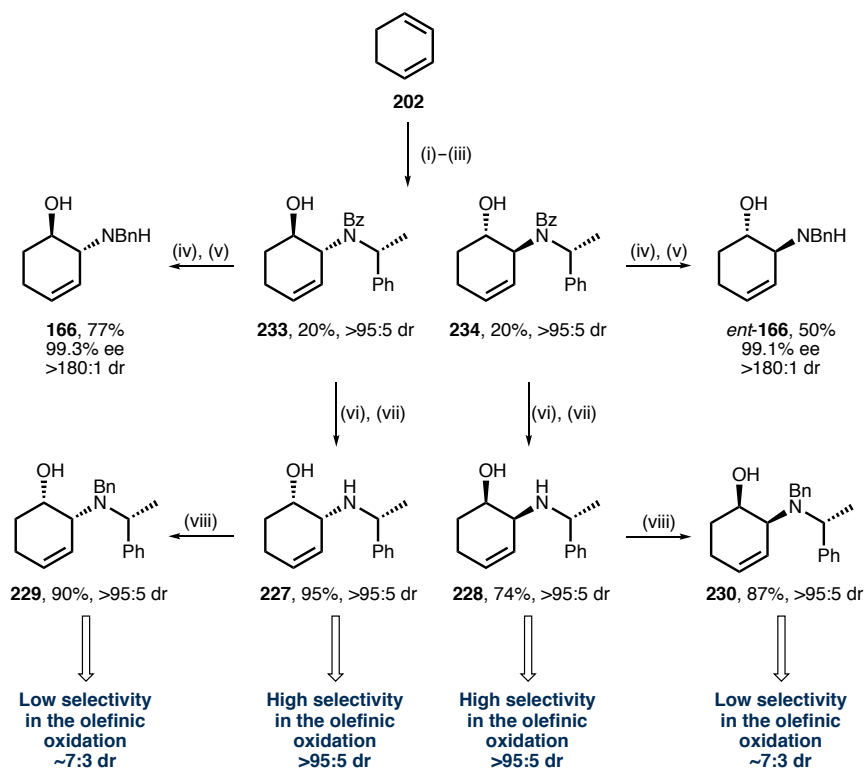


Scheme 45. Reagents and conditions: (i) TsOH, CH₂Cl₂, rt, 5 min then *m*-CPBA, rt, 30 h; (ii) DBU, CH₂Cl₂, rt, 24 h.

In conclusion, the presence of a stereogenic centre within **229** and **230** showed significant effects on the diastereoselectivity of the epoxidation and substrates **229** and **230** were not considered as suitable compounds for the syntheses of dihydroconduramines.

3.7 Conclusion

In summary, syntheses of enantiomers **166** and *ent*-**166** of racemic ($\pm$)-**166** were achieved respectively in 5 steps in 15% and 10% overall yield and >95:5 dr from **202** via a mono-epoxidation followed by subsequent ring-opening, *N*-benzoylation, removal of the *N*- α -methylbenzyl substituent and reduction of the ester and amide functionalities. Surrogates **227** and **228** of racemic ($\pm$)-**171** were synthesised from amide **233** and **234** in 95% and 74% yield, respectively (>95:5 dr) by a benzylamido group participation reaction with inversion of configuration at carbon C(1). Despite the presence of a stereogenic centre within **227** and **228**, high selectivities were observed during the olefinic oxidation making **227** and **228** suitable substrates for the syntheses of dihydroconduramines. However, *N*-benzyl-*N*-(α -methylbenzyl) derivatives **229** and **230** showed low selectivities (~70:30 dr) and were therefore not considered as acceptable substrates for the syntheses of dihydroconduramines (Scheme 46).



Scheme 46. *Reagents and conditions:* (i) AcOOH (38–40% in AcOH), Na₂CO₃, CH₂Cl₂, 0 °C, 3.5 h; (ii) (R)-**235**, *i*-PrOH, 80 °C, 4 h; (iii) BzCl, Na₂CO₃, THF, rt, 24 h; (iv) HCO₂H (90% aq), 60 °C, 18 h; (v) LiAlH₄, THF, 60 °C, 16 h; (vi) SOCl₂, CH₂Cl₂, rt, 4 h; (vii) K₂CO₃, MeOH, rt, 16 h.

3.8 Notes and references

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- (3) Knapp, S.; Sebastian, M. J.; Ramanathan, H.; Bharadwaj, P.; Potenza, J. A. *Tetrahedron* **1986**, 42, 3405–3410.
- (4) X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research Laboratory, University of Oxford.
- (5) Broad peaks in the ¹H NMR spectrum, due to the presence of rotamers of **233** and **234**, prevented any analysis of ³J coupling constants.
- (6) Ben-Ishai, D.; Altman, J.; Peled, N. *Tetrahedron* **1977**, 33, 2715–2717.
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- (12) The enantiomeric excesses of **166** and *ent*-**166** were determined by chiral HPLC analyses [with comparison to the corresponding authentic racemic standard (±)-**166**] with thanks to Professor Darren J. Dixon and Mr Sam R. Ellis.
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- (14) Schiffers, I.; Rantanen, T.; Schmidt, F.; Bergmans, W.; Zani, L. *J. Org. Chem.* **2006**, 7, 2320–2331.
- (15) Attempts to analyse the relative configurations within **227** and **228** by ¹H NMR spectroscopic analyses of ³J coupling constants were inconclusive.
- (16) Aciro, C.; Davies, S. G.; Roberts, P. M.; Russell, A. J.; Smith, A. D.; Thomson, J. E. *Org. Biomol. Chem.* **2008**, 6, 3762–3770.
- (17) Attempts to analyse the relative configuration within **242** by ¹H NMR spectroscopic analyses of ³J coupling constants were inconclusive.
- (18) Epoxidation of **229** using only 1.6 equiv of *m*-CPBA under the same conditions gave a 19:21:27:33 mixture of unreacted starting material **229**, epoxide **245**, epoxide **246** and triol **247**, respectively. Similarly, epoxidation of **230** using only 1.6 equiv of *m*-CPBA under the same conditions gave a 5:5:14:76 mixture of unreacted starting material **230**, epoxide **249**, epoxide **250** and triol **251**, respectively.

Chapter 4

Asymmetric Syntheses of Dihydroconduramines A-2, B-2, C-3 and -F-3

This chapter describes the asymmetric syntheses of four new enantiopure dihydroconduramines (–)-A-2 **33**, (–)-B-2 **35**, (–)-C-3 **38** and (+)-F-3 **46** from enantiopure **166** using the ammonium-directed epoxidation methodology as a key step (Figure 45).¹

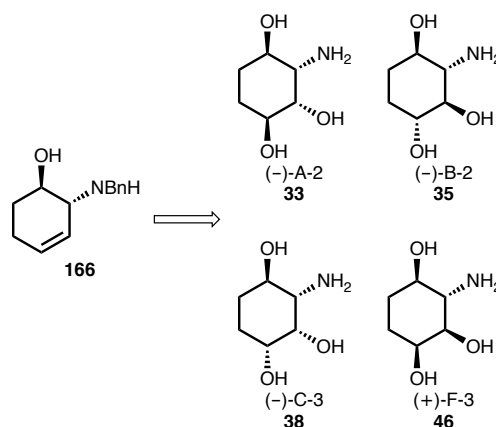


Figure 45. Structure of the four synthesised enantiopure dihydroconduramines (–)-A-2 **33**, (–)-B-2 **35**, (–)-C-3 **38** and (+)-F-3 **46**.

4.1 Introduction

Previously, Davies and co-workers employed a synthetic pathway to access (±)-**195**, (±)-**262** and (±)-**266**, the different diastereoisomers of 3-(*N,N*-dibenzylamino)cyclohexane-1,2-diol (±)-**201** using the ammonium-directed epoxidation of 3-(*N,N*-dibenzylamino)cyclohex-1-ene (±)-**191** as a key step.² Two different strategies were deployed to synthesise *syn*-configured 1,2-diols (±)-**262** and (±)-**266** and *anti*-configured 1,2-diol (±)-**195**. On one hand, (±)-**262** and (±)-**266** were accessed *via* a Winstein protocol (Prevost-Woodward type reaction) of the corresponding, differentially protected *anti*-1,2-diols, involving the

participation of a neighbouring group (OAc) in the displacement of its adjacent leaving group (OMs or OTs).^{2,3,4} On the other hand, *trans*-configured 1,2-diol ($\pm$)-**195** was afforded by an epoxide-inversion and subsequent ring-opening process (Figure 46).²

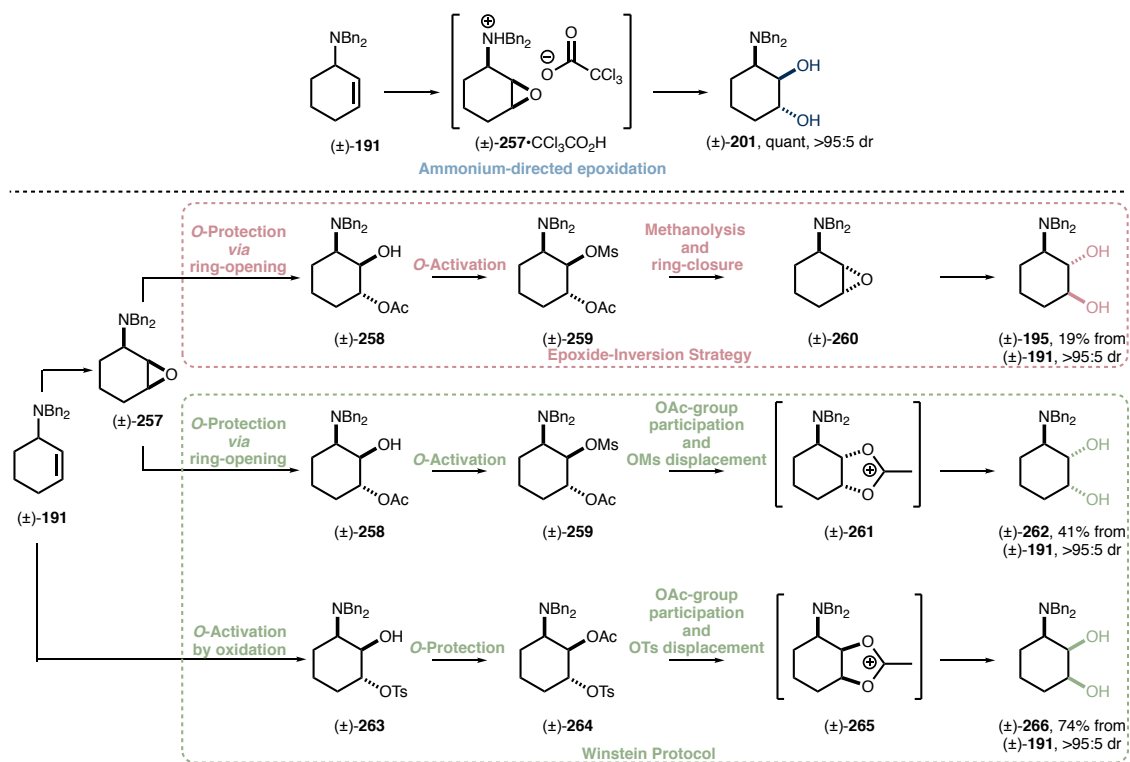


Figure 46. Stereoselective syntheses of ($\pm$)-**195**, ($\pm$)-**262** and ($\pm$)-**266**, all the diastereoisomers of ($\pm$)-**201**.

4.2 Chapter aim

The previous results obtained in Chapter 2 showed the importance of the *N*-protecting groups within the substrate in affecting the diastereoselectivity of the ammonium-directed epoxidation. Having established that ($\pm$)-**166** underwent under high diastereocontrol during the olefinic oxidation, it was envisaged to implement a synthetic route to access enantiopure dihydroconduramines A-2 **32**, B-2 **35**, C-3 **38**, and F-3 **46** from the corresponding enantiopure substrate **166** involving the ammonium-directed epoxidation methodology, the Winstein protocol and the epoxide-inversion process as stereodefining key steps. With both enantiomers **166** and *ent*-**166** in hand, it was decided to access enantiopure dihydroconduramines from **166**, arbitrarily chosen (Figure 47).¹

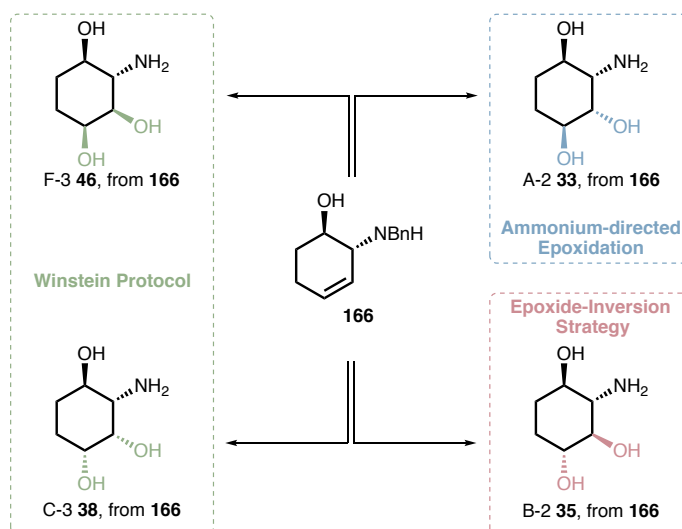
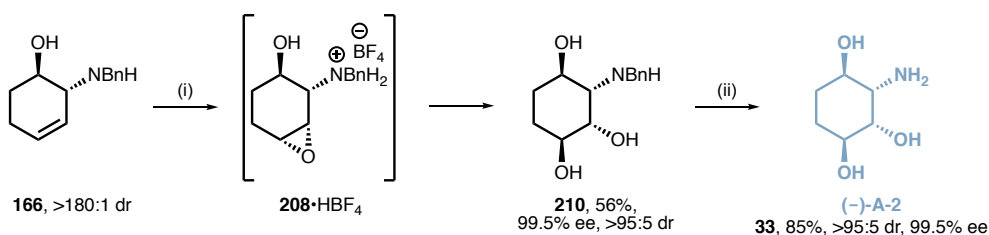


Figure 47. Chapter aim.

4.3 Syntheses of enantiopure dihydroconduramines A-2, B-2, C-3 and F-3

4.3.1 Synthesis of enantiopure (–)-dihydroconduramine A-2 **33**

Treatment of enantiopure **166** under the optimised conditions applied previously for racemic ($\pm$)-**166** [i. e., HBF_4 (40% aq, 5 equiv), *m*-CPBA (70%, 1.6 equiv)] gave **210** in 56% yield and >95:5 dr. Hydrogenolysis of **210** with Pearlman's catalyst under an atmosphere of H_2 gave enantiopure (–)-dihydroconduramine A-2 **33** in 85% yield, 99.5% ee,^{5,6} and >95:5 dr. The ^1H and ^{13}C NMR spectroscopic data of **210** and **33** were indistinguishable from those of the racemates ($\pm$)-**210** and ($\pm$)-**33**, respectively (Scheme 47).



Scheme 47. Reagents and conditions: (i) HBF_4 (40% aq), CH_2Cl_2 , rt, 5 min then *m*-CPBA, rt, 21 h; (ii) H_2 (1 atm), $\text{Pd}(\text{OH})_2/\text{C}$, MeOH, rt, 24 h.

4.3.2 Synthesis of enantiopure (–)-dihydroconduramine B-2 **35**

It was first necessary to deploy the epoxide-inversion strategy on epoxide **218** to afford **213**, which could then access, after ring-opening and hydrogenolysis, enantiopure (–)-dihydroconduramine B-2 **35** (Figure 48).²

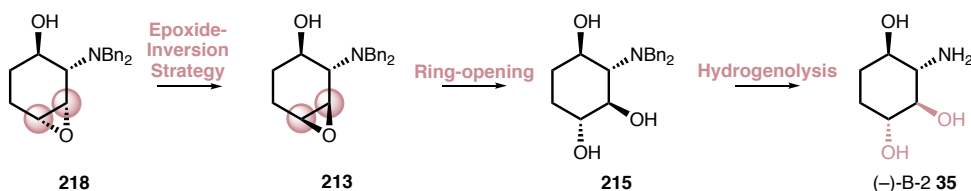
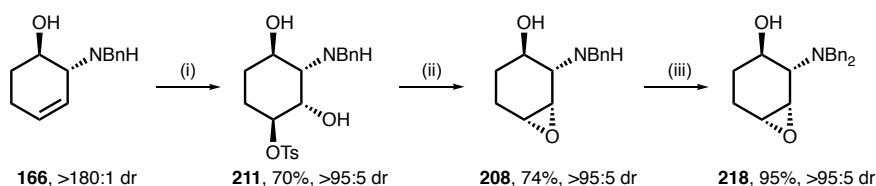


Figure 48. Epoxide-inversion strategy to access (–)-dihydroconduramine B-2 (–)-**35**.

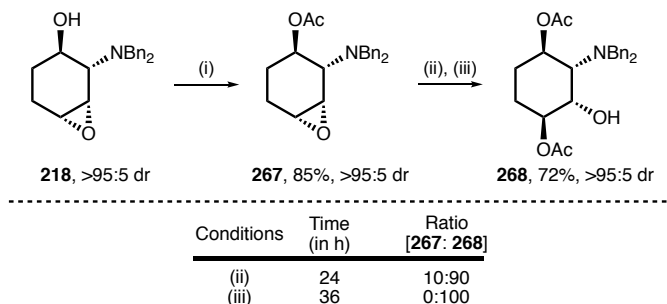
Epoxidation of **166** with *m*-CPBA in the presence of dry TsOH gave enantiopure **211** as a single regio- and diastereoisomer in 70% yield and >95:5 dr. Then, DBU-promoted ring-closure of **211** provided epoxide **208** in 74% yield and >95:5 dr, which was chemoselectively *N*-benzylated to afford **218** in 95% yield >95:5 dr (Scheme 48).⁷



Scheme 48. Reagents and conditions: (i) TsOH, CH₂Cl₂, rt, 5 min then *m*-CPBA, rt, 21 h; (ii) DBU, CH₂Cl₂, rt, 24 h; (iii) BnBr, Pr₂NEt, DMAP, CH₂Cl₂, rt, 24 h.

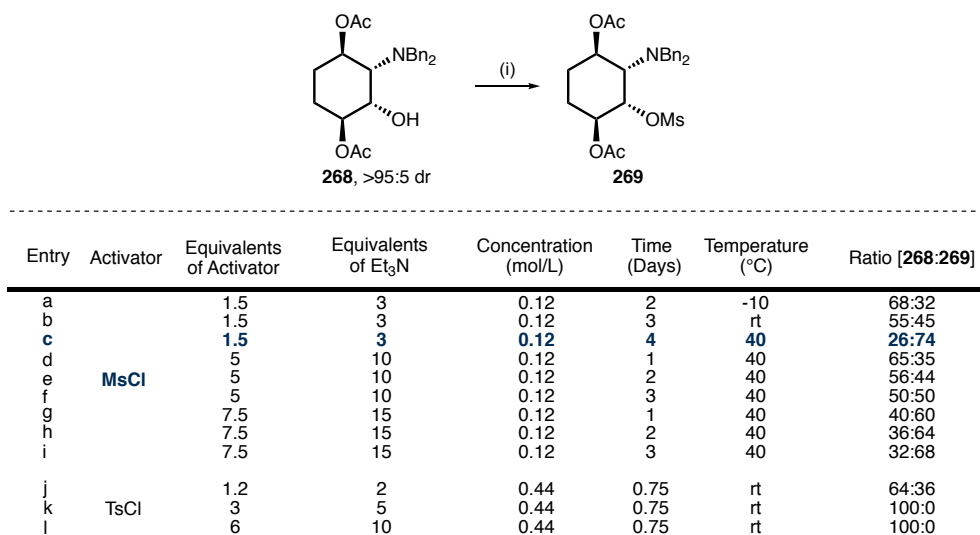
The epoxide-inversion strategy was then implemented on **218**. In order to avoid subsequent chemoselectivity issues, protection of the alcohol within **218** was compulsory and an acetyl functionality was chosen. Treatment of **218** with Ac₂O in presence of DMAP gave the corresponding acetyl protected derivative **267** in 85% yield and >95:5 dr.⁸ Then, ring-opening of **267** with AcOH at 50 °C for 24 h resulted in 90% conversion to **268**. Time extension to 36 h favoured full consumption of starting material **267** and gave **268** as the sole product of the reaction in 72% isolated yield and >95:5 dr. By ¹H and ¹³C NMR spectroscopic analyses, the characteristic C(1)HOAc and C(4)HOAc proton and C(1)HOAc and C(4)HOAc carbon chemical shifts at δ_H ~5 ppm and δ_C ~71 ppm,

respectively, confirmed the position of the acetate moieties within **268** at carbon C(1) and C(4). This is consistent, as previously, with a mechanism promoting a regioselective and stereospecific S_N2 -type ring-opening at C(4) (Scheme 49).



Scheme 49. Reagents and conditions: (i) Ac_2O , DMAP, pyridine, rt, 24 h; (ii) AcOH , 50 °C, 36 h; (iii) AcOH , 50 °C, 36 h.

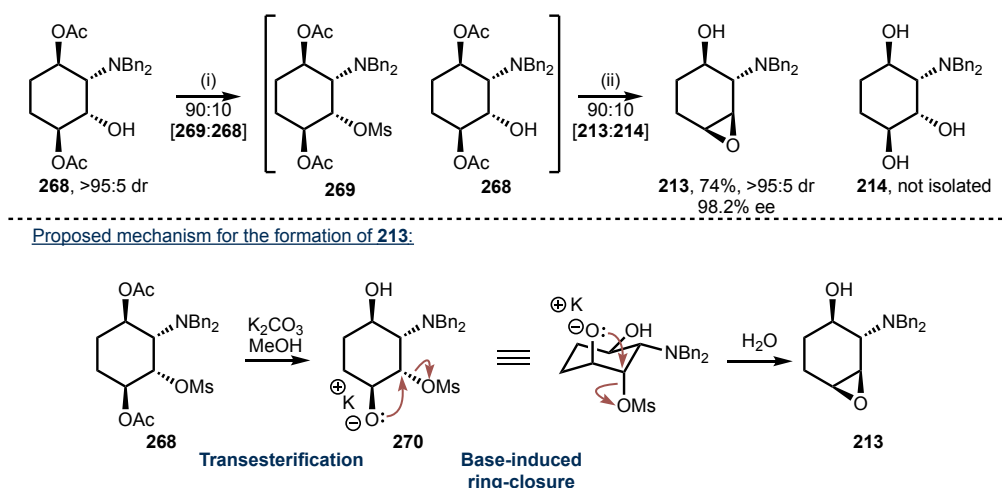
Finally, *O*-activation of **268** followed by base-induced ring-closure were deployed to access the inverted epoxide **213**. Nevertheless, efforts to activate the alcohol within **268** upon treatment with either MsCl or TsCl in CH_2Cl_2 to give **269** were vain and the condition optimisation was therefore attempted but in the best case the reaction conversion reached 74% after 4 days (Entry c, Scheme 50).



Scheme 50. Reagents and conditions: (i) CH_2Cl_2 , see table.

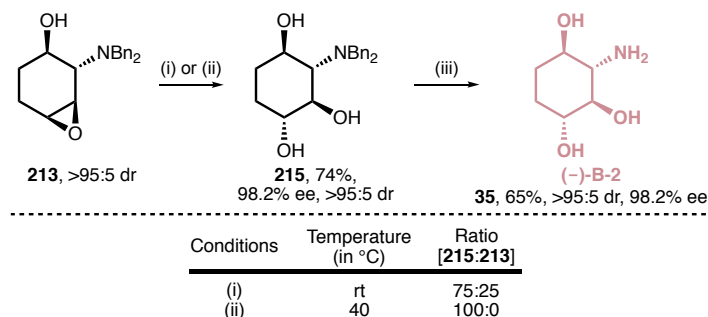
However, use of MsCl in pyridine at rt gave, after 16 h, a 10:90 mixture of **268** and *O*-mesylated product **269**, which was, without purification, subjected to K_2CO_3 and MeOH to

provide a 10:90 mixture of inverted epoxide **213** in 74% isolated yield (>95:5 dr) and triol **214**, which was not recovered.⁹ This outcome is in agreement with a transesterification of both acetates within **269** followed by an epoxide ring-closure with removal of the mesylate group to give **213**. Triol **214** comes from transesterification of the two acetates within the unreacted starting material **268** (Scheme 51).



Scheme 51. Reagents and conditions: (i) MsCl, pyridine, rt, 16 h; (ii) K_2CO_3 , MeOH, rt, 24 h.

Treatment of epoxide **213** with HBF_4 (40% aq) at rt for 24 h resulted in 75% conversion into triol **215**. When the temperature was raised to 40 °C, **213** was fully ring-opened and gave triol **215** as a single regio- and diastereoisomer (>95:5 dr, 98.2% ee¹⁰) in 74% yield.¹¹ Hydrogenolysis of **215** with Pearlman's catalyst under H_2 gave enantiopure (–)-dihydroconduramine B-2 **35** in 65% yield (98.2% ee¹²) and >95:5 dr (Scheme 52).



Scheme 52. Reagents and conditions: (i) HBF_4 (40% aq), CH_2Cl_2 , rt, 24 h, see table; (ii) HBF_4 (40% aq), CH_2Cl_2 , 40 °C, 24 h, see table; (iii) H_2 (1 atm), $Pd(OH)_2/C$, MeOH, rt, 24 h.

4.3.3 Syntheses of enantiopure dihydroconduramines (–)-C-3 **38** and (+)-F-3 **46**

To access the *syn*-configured 3,4-diol moiety within dihydroconduramines (–)-C-3 **38** and (+)-F-3 **46**, a neighbouring group participation strategy was deployed on epoxide **218** (Figure 49).^{2,3,4}

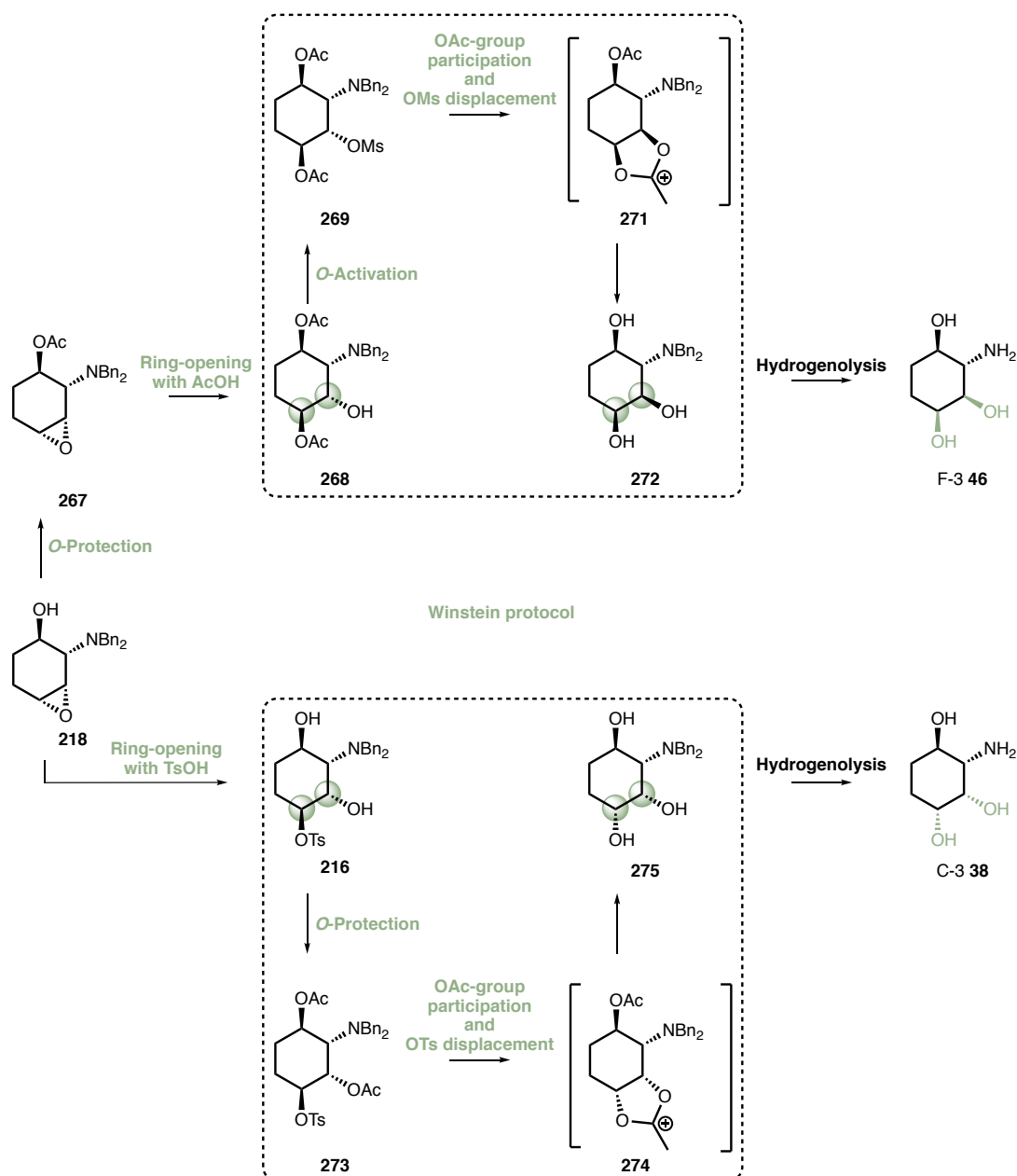
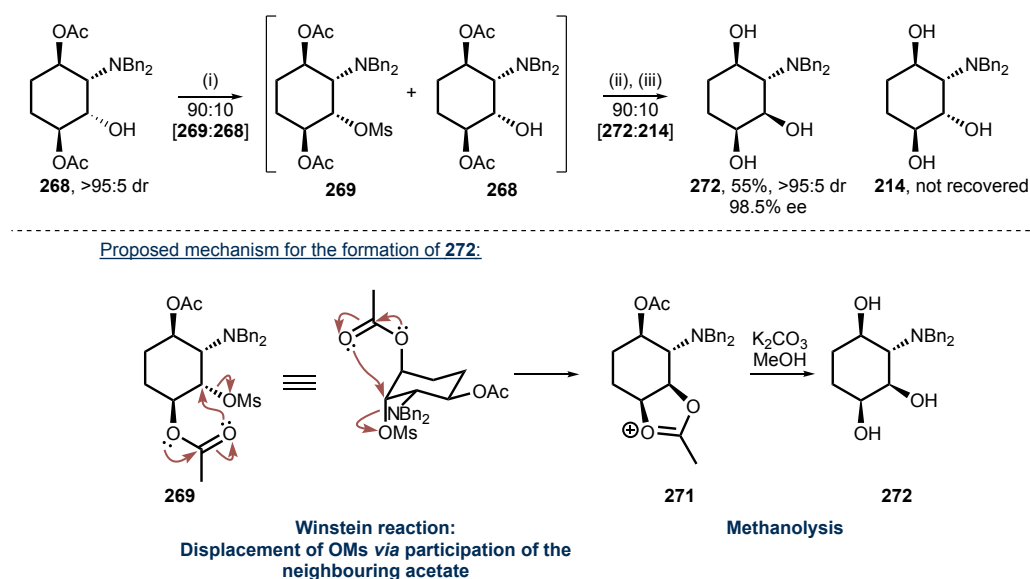


Figure 49. Winstein protocol to access (–)-C-3 **38** and (+)-F-3 **46**.

4.3.3.1 Synthesis of enantiopure (+)-dihydroconduramine F-3 46

As described previously, *O*-mesylation of **268** with MsCl in pyridine gave a 10:90 mixture of **268** and **269**, respectively, which was treated, without purification, with KOAc and EtOH/H₂O promoting a Winstein reaction. The crude reaction mixture was then directly subjected to methanolysis to provide a 10:90 mixture of triols **214** (not recovered) and **272** [isolated chromatographically in 55% yield (98.5% ee¹³) and >95:5 dr], respectively. The relative configuration within **272** was unambiguously established by single crystal X-ray diffraction analysis of an authentic racemic sample of (±)-**272**, prepared in an analogous manner to enantiopure **272** (Figure 50).¹⁴ The absolute (1*R*,2*S*,3*R*,4*S*)-configuration of enantiopure **272** was assigned from known absolute configuration of C(1) and C(2) stereogenic centres of **166**, derived from precursor **233**, of known absolute (1*R*,2*R*,α*R*)-configuration. Furthermore, ¹H NMR spectroscopic analysis revealed that **272** adopts a similar chair conformation in solution in *d*₁-CHCl₃ (³*J*_{1,2} = ³*J*_{2,3} = 10.3 Hz, ³*J*_{3,4} = 3.0 Hz, Figure 51). This is in agreement with a mechanism involving the participation of the acetate to displace its adjacent mesylate group followed by a transesterification of the acetates with K₂CO₃ and MeOH resulting in the formation of amino triol **272** (Scheme 53).



Scheme 53. Reagents and conditions: (i) MsCl, pyridine, rt, 16 h; (ii) KOAc, EtOH/H₂O, reflux, 72 h; (iii) K₂CO₃, MeOH, rt, 24 h.

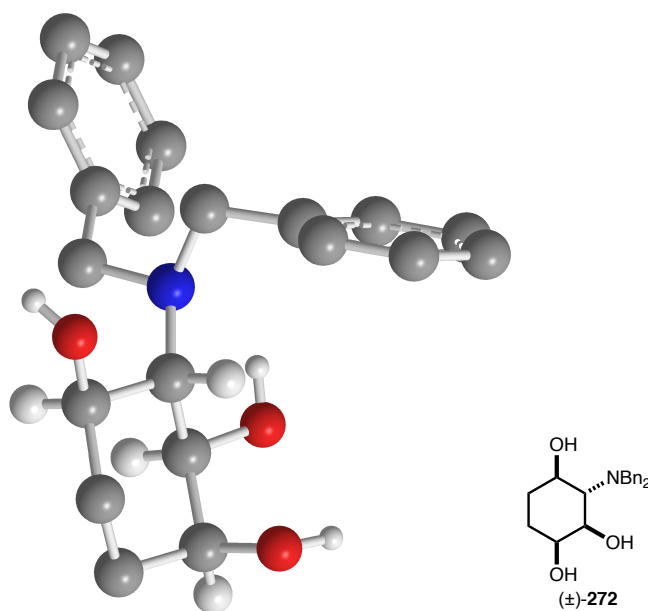


Figure 50. Chem3D representation of the X-ray crystal structure of (±)-**272** (selected H atoms are omitted for clarity).

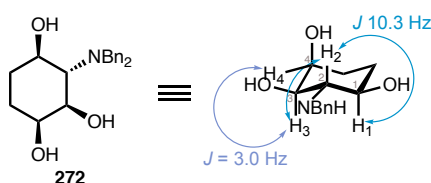
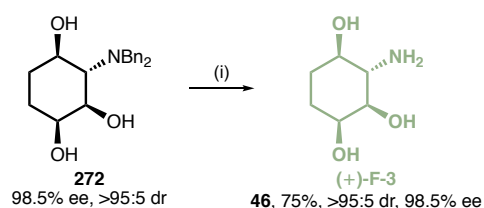


Figure 51. ^1H NMR 3J Coupling constants analysis of **272**.

Finally, enantiopure (+)-dihydroconduramine F-3 **46** was synthesised *via* hydrogenolysis of **272** with $\text{Pd}(\text{OH})_2/\text{C}$ under H_2 in 75% yield (98.5% ee¹⁵) and >95:5 dr, (Scheme 54).

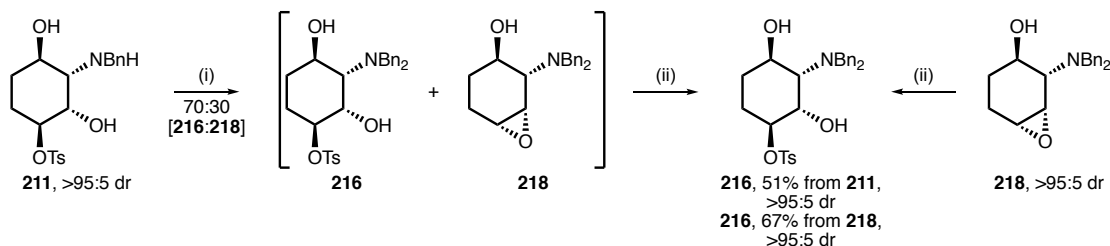


Scheme 54. Reagents and conditions: (i) H_2 (1 atm), $\text{Pd}(\text{OH})_2/\text{C}$, MeOH, rt, 24 h.

4.3.3.2 Synthesis of enantiopure (–)-dihydroconduramine C-3 **38**

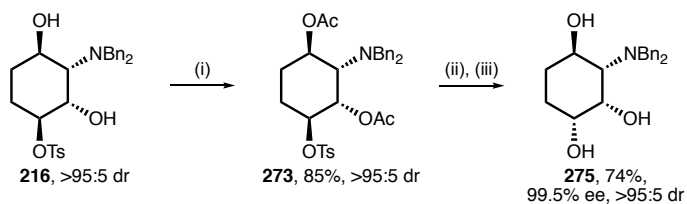
Regioselective and stereospecific $\text{S}_{\text{N}}2$ -type ring-opening of **218** with TsOH gave a single regio- and diastereoisomer **216** in 67% yield. Tosylate **216** was also accessed by chemoselective *N*-benzylation of **211** upon treatment with BnBr in presence of Pr_2NEt

and DMAP to give a 70:30 mixture of tosylate **216** and epoxide **218**, respectively.² Due to a partial ring-closure, this crude reaction mixture was subjected to ring-opening with TsOH to afford **216** as the sole product in 51% yield from **211** (Scheme 55).¹⁶



Scheme 55. Reagents and conditions: (i) BnBr, Pr_2NEt , DMAP, CH_2Cl_2 , rt, 24 h; (ii) TsOH, CH_2Cl_2 , rt, 21 h.

Then, *O*-acetylation of the diols within **216** with Ac_2O gave the corresponding diacetate **273** in 85% yield and >95:5 dr.⁸ As before, application of the Winstein protocol conditions (i. e., KOAc, EtOH/ H_2O) to **273** displaced the tosylate moiety *via* participation of the neighbouring acetate and subsequent methanolysis of the crude reaction mixture with K_2CO_3 and MeOH transesterified both of the esters and afforded triol **275** in 74% yield (99.5% ee¹⁷) and >95:5 dr (Scheme 56). The relative configuration within **275** was unambiguously established by single crystal X-ray diffraction analysis of an authentic racemic sample of ($\pm$)-**275**, prepared in an analogous manner to enantiopure **275** (Figure 52).¹⁴ The absolute (1*R*,2*S*,3*S*,4*R*)-configuration of enantiopure **275** was assigned from known absolute configuration of C(1) and C(2) stereogenic centres of **166**, derived from precursor **233**, of known absolute (1*R*,2*R*, α *R*)-configuration. Furthermore, ^1H NMR spectroscopic analysis revealed that **275** adopts a similar chair conformation in solution in $d_1\text{-CHCl}_3$ ($^3J_{1,2} = 10.5$ Hz, $^3J_{2,3} = 1.9$ Hz, $^3J_{3,4} < 5$ Hz, Figure 53).



Scheme 56. Reagents and conditions: (i) Ac_2O , DMAP, pyridine, rt, 24 h; (ii) KOAc, EtOH/ H_2O , reflux, 72 h; (iii) K_2CO_3 , MeOH, rt, 24 h.

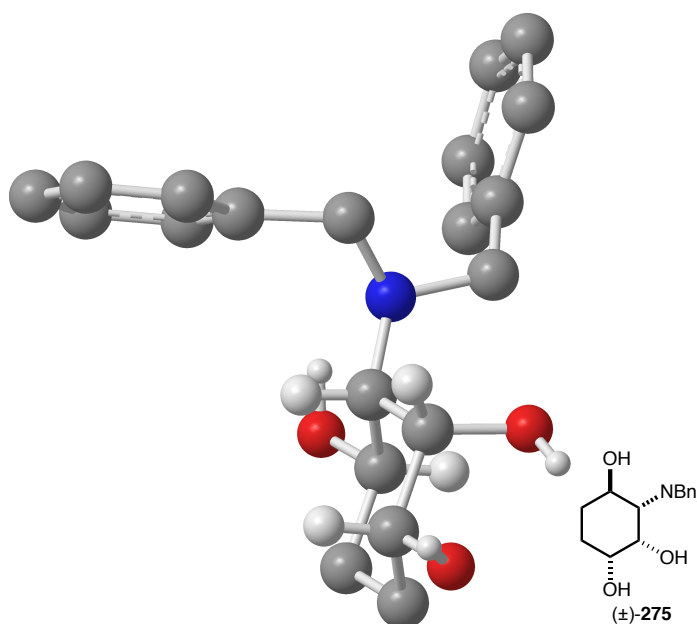


Figure 52. Chem3D representation of the X-ray crystal structure of (±)-**275** (selected H atoms are omitted for clarity).

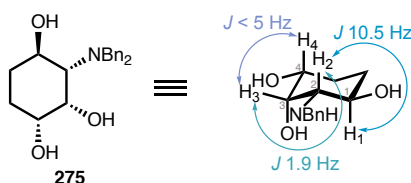
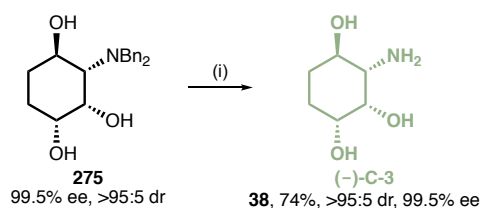


Figure 53. ^1H NMR 3J Coupling constants analysis of **275**.

Finally, hydrogenolysis of **275** with $\text{Pd}(\text{OH})_2/\text{C}$ under H_2 gave enantiopure (–)-dihydroconduramine C-3 **38** in 74% yield (99.5% ee¹⁸) and >95:5 dr (Scheme 57).

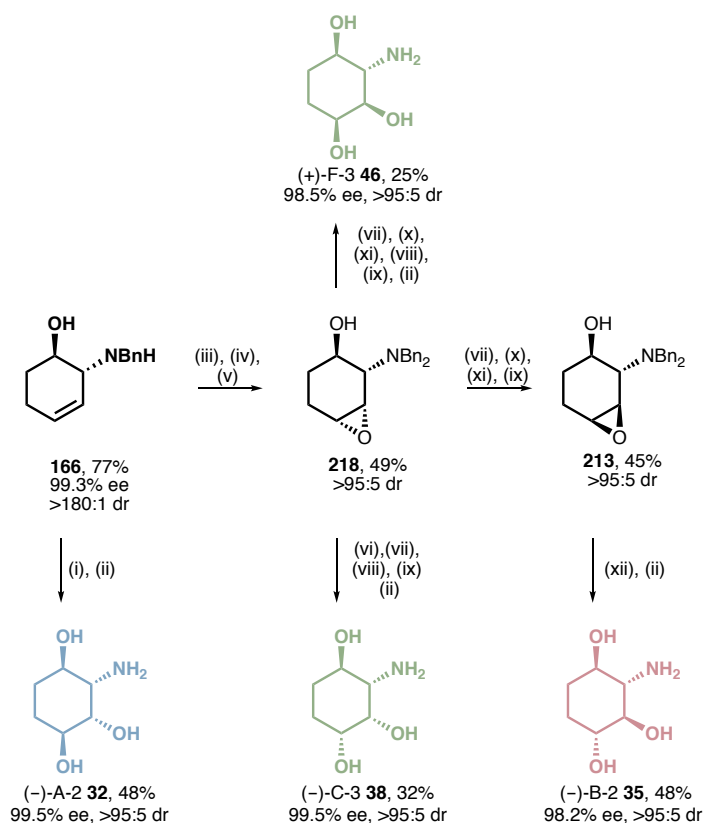


Scheme 57. Reagents and conditions: (i) H_2 (1 atm), $\text{Pd}(\text{OH})_2/\text{C}$, MeOH, rt, 24 h.

4.4 Conclusion

The syntheses of four unknown enantiopure dihydroconduramines (–)-A-2 **32**, (–)-B-2 **35**, (–)-C-3 **38** and (+)-F-3 **46** have been achieved from **166** (derived from commercially available 1,3-cyclohexadiene **202**) using the ammonium-directed epoxidation methodology

and Winstein and epoxide-inversion strategies as key stereodefining steps. Epoxidation of **166**, with *m*-CPBA in presence of HBF₄ (40 % aq) gave triol **210** as single regio- and diastereoisomers in 56% yield and its hydrogenolysis under H₂ (1 atm) with Pearlman's catalyst provided (–)-A-2 **32** in 85% (99.5% ee) and >95:5 dr. Epoxide **218** was synthesised from **166** in 49% yield over the three steps (>95:5 dr) *via* an epoxidation in presence of TsOH followed by a DBU-promoted ring-closure and subsequent *N*-benzylation. (–)-Dihydroconduramine C-3 **38** (99.5% ee) was accessed from epoxide **218** in 32% and >95:5 dr *via* a TsOH-promoted ring-opening followed sequentially by *O*-acetylation, Winstein reaction, subsequent methanolysis and hydrogenolysis. Application of the epoxide-inversion strategy on **218** (i. e., *O*-acetylation followed by AcOH-promoted ring-opening, *O*-mesylation and methanolysis) gave access to a single regio- and diastereoisomer **213** in 45% yield and >95:5 dr. Ring-opening of this inverted-epoxide **213** with HBF₄ (40% aq) and hydrogenolysis afforded (–)-dihydroconduramine B-2 **35** (98.2% ee) in 48% and >95:5 dr. Finally, *O*-acetylation of epoxide **218** followed by ring-opening with AcOH, *O*-mesylation, Winstein reaction, methanolysis and hydrogenolysis gave (+)-F-3 **46** in 25% yield, 98.5% ee and >95:5 dr (Scheme 58).¹



Scheme 58. Reagents and conditions: (i) HBF₄ (40% aq), CH₂Cl₂, rt, 5 min then *m*-CPBA, rt, 21 h; (ii) H₂ (1 atm), Pd(OH)₂/C, MeOH, rt, 24 h; (iii) TsOH, CH₂Cl₂, rt, 5 min then *m*-CPBA, rt, 21 h; (iv) DBU, CH₂Cl₂, rt, 24 h; (v) BnBr, ^tPr₂NEt, DMAP, CH₂Cl₂, rt, 24 h; (vi) TsOH, CH₂Cl₂, rt, 24 h; (vii) Ac₂O, DMAP, pyridine, rt, 24 h; (viii) KOAc, EtOH/H₂O, reflux, 72 h; (ix) K₂CO₃, MeOH, rt, 24 h; (x) AcOH, 50 °C, 36 h; (xi) MsCl, pyridine, rt, 16 h; (xii) HBF₄ (40% aq), CH₂Cl₂, 40 °C, 24 h.

4.5 Notes and references

- (1) Da Silva Pinto, S.; Davies, S. G.; Fletcher, A. M.; Roberts, P. M.; Thomson, J. E. *Synthesis* **2018**, 50, 64–83.
- (2) Aciro, C.; Davies, S. G.; Roberts, P. M.; Russell, A. J.; Smith, A. D.; Thomson, J. E. *Org. Biomol. Chem.* **2008**, 6, 3762–3770.
- (3) Winstein, S.; Hess, H. V.; Buckles, R. E. *J. Am. Chem. Soc.* **1942**, 64, 2796–2801.
- (4) Roberts, J. D.; Young, W. G.; Winstein, S. *J. Am. Chem. Soc.* **1942**, 64, 2157–2164.
- (5) The enantiomeric excess of **210** via chiral HPLC analysis was inconclusive due to the high polarity and affinity of **210** to the column. Therefore, the enantiomeric excess of **210** was determined by chiral HPLC analyses of **214** [with comparison to the corresponding authentic racemic standard (±)-**214** with thanks to Professor Darren J. Dixon and Mr Sam R. Ellis.
- (6) The enantiomeric excess of (–)-dihydroconduramine A-2 **32** was assigned from the known enantiomeric excess of the corresponding precursor **210**.
- (7) The ¹H and ¹³C NMR spectroscopic data of **211**, **208** and **218** matched those of the corresponding racemates (±)-**211**, (±)-**208** and (±)-**218**, respectively.
- (8) Brennan, M. B.; Csataiová, K.; Davies, S. G.; Fletcher, A. M.; Green, W. D.; Lee, J. A.; Roberts, P. M.; Russell, A. J.; Thomson, J. E. *J. Org. Chem.* **2015**, 80, 6609–6618.
- (9) The ¹H and ¹³C NMR spectroscopic data of **213** were identical to those of the corresponding racemate (±)-**213**.
- (10) The enantiomeric excess of **215** was determined by chiral HPLC analysis [with comparison to the corresponding authentic racemic standard (±)-**215**], with thanks to Professor Darren J. Dixon and Mr Sam R. Ellis. Sample of (±)-**215** was prepared via an analogous route to the one described for enantiopure material (see the experimental section).
- (11) The ¹H and ¹³C NMR spectroscopic data of **215** were identical to those of the corresponding

- racemate ($\pm$)-**215**.
- (12) The enantiomeric excess of (–)-dihydroconduramine B-2 **35** was assigned from the known enantiomeric excess of the corresponding precursor **215**.
- (13) The enantiomeric excess of **272** was determined by chiral HPLC analysis [with comparison to the corresponding authentic racemic standard ($\pm$)-**272**], with thanks to Professor Darren J. Dixon and Mr Sam R. Ellis. Sample of ($\pm$)-**272** was prepared *via* an analogous route to the one described for enantiopure material (see the experimental section).
- (14) X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research Laboratory, University of Oxford.
- (15) The enantiomeric excess of (+)-dihydroconduramine F-3 **46** was assigned from the known enantiomeric excess of the corresponding precursor **272**.
- (16) The ^1H and ^{13}C NMR spectroscopic data of **216** were identical to those of the corresponding racemate ($\pm$)-**216**.
- (17) The enantiomeric excess of **275** was determined by chiral HPLC analysis [with comparison to the corresponding authentic racemic standard ($\pm$)-**275**], with thanks to Professor Darren J. Dixon and Mr Sam R. Ellis. Sample of ($\pm$)-**275** was prepared *via* an analogous route to the one described for enantiopure material (see the experimental section).
- (18) The enantiomeric excess of (–)-dihydroconduramine C-3 **38** was assigned from the known enantiomeric excess of the corresponding precursor **275**.

Chapter 5

Asymmetric Syntheses of Dihydroconduramines

C-2, *ent*-C-2, D-2, E-2, F-2 and *ent*-F-2

This chapter describes the asymmetric syntheses of six new enantiopure dihydroconduramines (+)-C-2 **37**, (+)-D-2 **41**, (+)-E-2 **43** and (+)-F-2 **45** from enantiopure **227** and (–)-C-2 *ent*-**37** and (–)-F-2 *ent*-**45** from enantiopure **228** using the ammonium-directed epoxidation methodology as a key step (Figure 54).¹

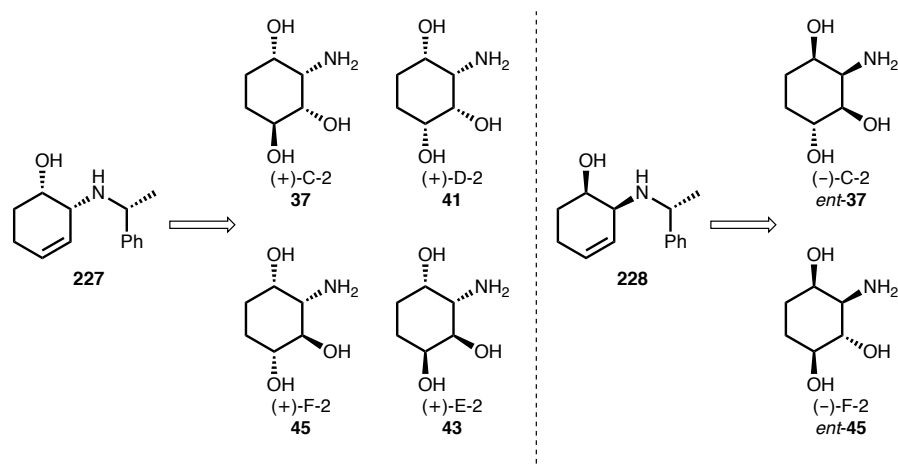


Figure 54. Structures of the six synthesised enantiopure dihydroconduramines (+)-C-2 **37**, (–)-C-2 *ent*-**37**, (+)-D-2 **41**, (+)-E-2 **43**, (+)-F-2 **45** and (–)-F-2 *ent*-**45**.

5.1 Chapter aim

As described previously in Chapter 4, it was envisaged to implement a synthetic route to access enantiopure dihydroconduramines C-2 **37**, D-2 **41**, E-2 **43** and F-2 **45** from the corresponding enantiopure *syn*-substrates **227** and **228** involving ammonium-directed epoxidation methodology, Winstein protocol and epoxide-inversion process as the stereodefining key steps.¹ It was also decided to synthesise authentic samples of the compounds obtained during the investigation of the surrogacy of diastereoisomers **229** and **230** to corroborate the NMR spectroscopic analyses (Figure 55).

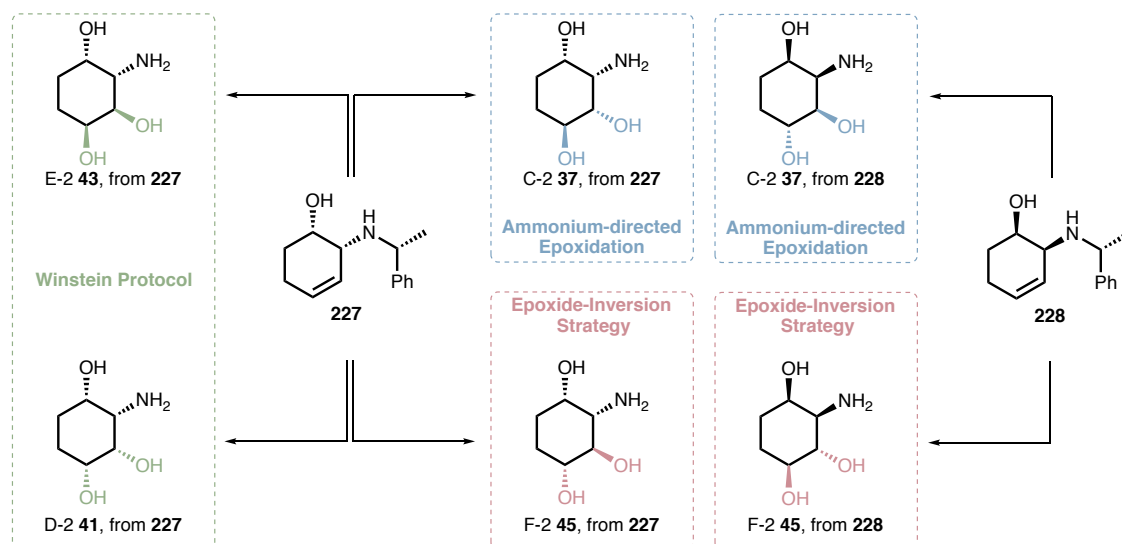
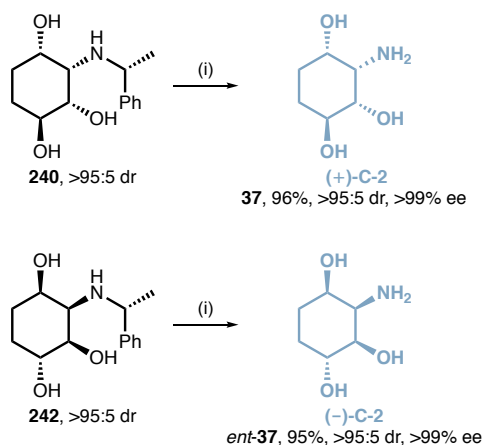


Figure 55. Chapter aim.

5.2 Syntheses of enantiopure dihydroconduramines C-2, D-2, E-2 and F-2

5.2.1 Syntheses of enantiopure dihydroconduramines (+)-C-2 37 and (–)-C-2 *ent*-37

Hydrogenolysis of triols **240** and **242**, synthesised in Chapter 3, with Pearlman's catalyst under an atmosphere of H₂ gave enantiopure (+)-dihydroconduramine C-2 **37** in 96% yield (>99% ee²) and enantiopure (–)-dihydroconduramine C-2 *ent*-**37** in 95% yield (>99% ee³), respectively, both >95:5 dr (Scheme 59).

Scheme 59. Reagents and conditions: (i) H₂ (1 atm), Pd(OH)₂/C, MeOH, rt, 24 h.

5.2.2 Syntheses of enantiopure dihydroconduramines (+)-F-2 **45** and (–)-F-2 *ent*-**45**

Dihydroconduramines (+)-F-2 **45** and (–)-F-2 *ent*-**45** were accessed *via* the epoxide-inversion strategy on epoxides **245** and **249** to provide epoxides **246** and **250**, respectively (Figure 56).⁴

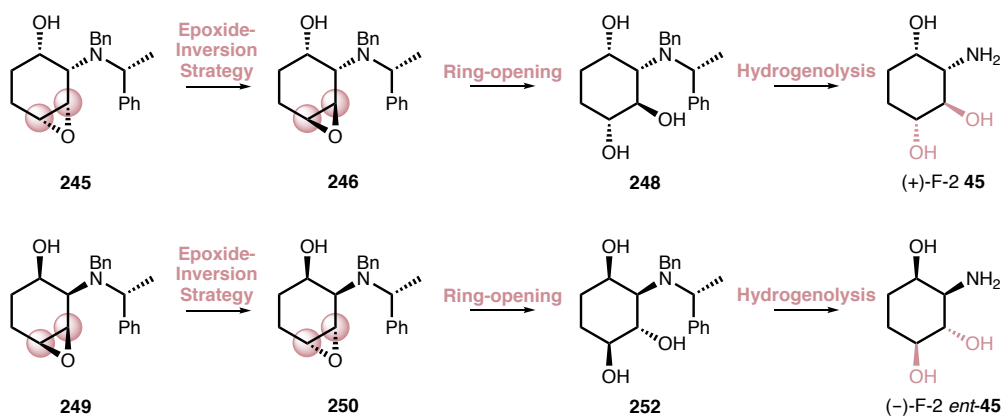


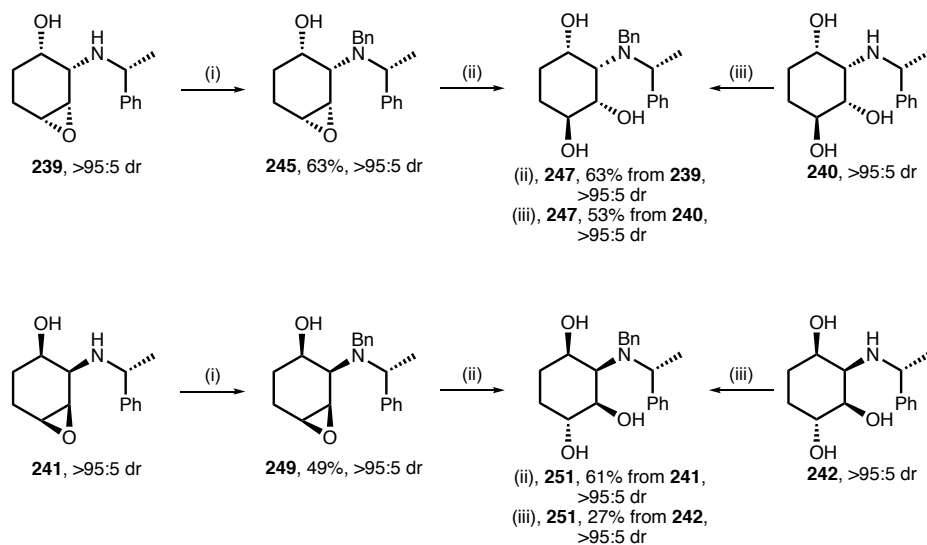
Figure 56. Epoxide-inversion strategy applied on **245** and **249** to access (+)-F-2 **45** and (–)-F-2 *ent*-**45**.

First, chemoselective *N*-benzylation of enantiopure epoxide **239**, synthesised in Chapter 3, with BnBr in presence of ^tPr₂NEt and DMAP in CH₂Cl₂⁴ was unsuccessful, and despite attempts to optimise the reaction by varying either the temperature or time or stoichiometry or concentration, conversion reached about 40% in the best case (Entry f, scheme 60).

239, >95:5 dr 245					
Entry	Time (in days)	Temperature (in °C)	Equivalents of BnBr and ^t Pr ₂ NEt	Concentration CH ₂ Cl ₂ (in mol/L)	Ratio [239 : 245]
a	1	rt	1.5	0.35	93:7
b	2	rt	1.5	0.35	93:7
c	3	rt	1.5	0.35	74:26
d	1	40	1.5	0.35	88:12
e	2	40	1.5	0.35	77:23
f	3	40	1.5	0.35	60:40
g	1	rt	3	0.35	98:2
h	1	rt	5	0.35	98:2
i	1	rt	Excess	0	99:1
j	1	rt	1.5	1	95:5
k	1	rt	1.5	1.5	94:6

Scheme 60. Reagents and conditions: (i) BnBr, ^tPr₂NEt, DMAP, CH₂Cl₂, see table.

However, use of BnBr and K₂CO₃ in MeCN at 82 °C resulted in the formation of **245** in 73% isolated yield and >95:5 dr.⁵ Regioselective and stereospecific ring-opening in the presence of HBF₄ (40% aq) provided triol **247**, as a single regio- and diastereoisomer, which was isolated in 63% yield. The absolute configuration of **247** was determined *via* preparation of an authentic sample: chemoselective *N*-benzylation of **240** (of known configuration) with BnBr in presence of ^tPr₂NEt and DMAP gave **247** in 53% yield and >95:5 dr. Meanwhile, *N*-benzylation of epoxide **241** gave **249** in 49% yield and >95:5 dr.⁵ Then, treatment of **249** with HBF₄ (40% aq) afforded **251** in 61% as a single regio- and diastereoisomer. Once again, the absolute configuration of **251** was obtained by chemoselective *N*-benzylation of the known triol **242** (27% yield and >95:5 dr).⁶ As before, these results are consistent with a regioselective and stereospecific ring-opening (Scheme 61).



Scheme 61. Reagents and conditions: (i) BnBr, K₂CO₃, MeCN, 82 °C, 24 h; (ii) HBF₄ (40% aq), CH₂Cl₂, rt, 24 h; (iii) BnBr, ^tPr₂NEt, DMAP, CH₂Cl₂, rt, 24 h.

The relative configuration within epoxide **245** was unambiguously established by single crystal X-Ray diffraction analysis.⁷ Its absolute (1*S*,2*S*,3*S*,4*R*, α *R*)-configuration was then assigned from the known (*R*)-configuration of the α -methylbenzyl stereogenic centre. A

Flack α parameter of 0.0(6) for the crystal structure of **237** was also consistent with its assigned absolute (1*S*,2*S*,3*S*,4*R*, α *R*)-configuration (Figure 57).

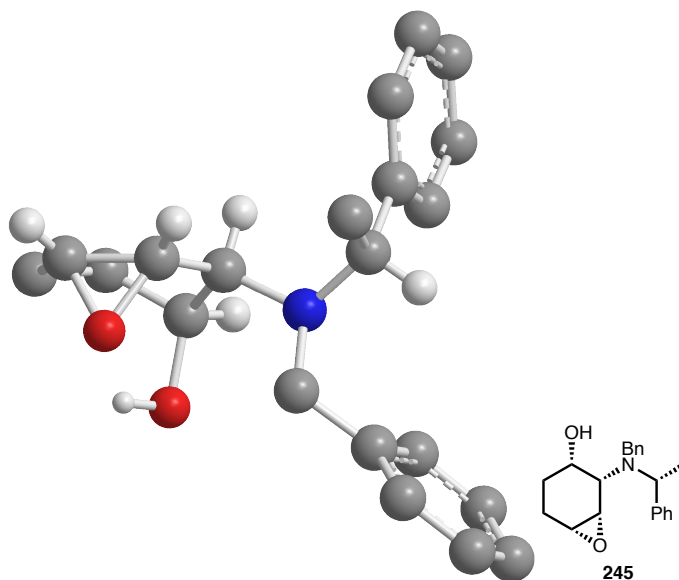


Figure 57. Chem3D representation of the X-ray crystal structure of **245** (selected H atoms are omitted for clarity).

The relative configuration within triol **247** was also unambiguously established by single crystal X-Ray diffraction analysis.⁷ The absolute (1*S*,2*S*,3*S*,4*S*, α *R*)-configuration was then assigned from the known (*R*)-configuration of the α -methylbenzyl stereogenic centre. A Flack α parameter of +0.08(3) for the crystal structure of **247** was also consistent with its assigned absolute (1*S*,2*S*,3*S*,4*S*, α *R*)-configuration (Figure 58).⁸

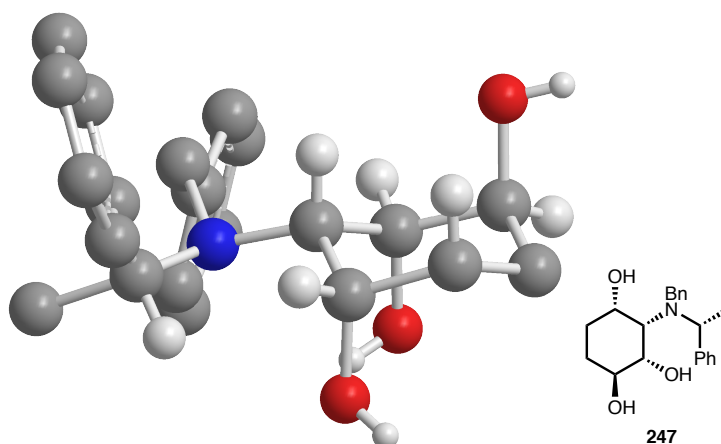
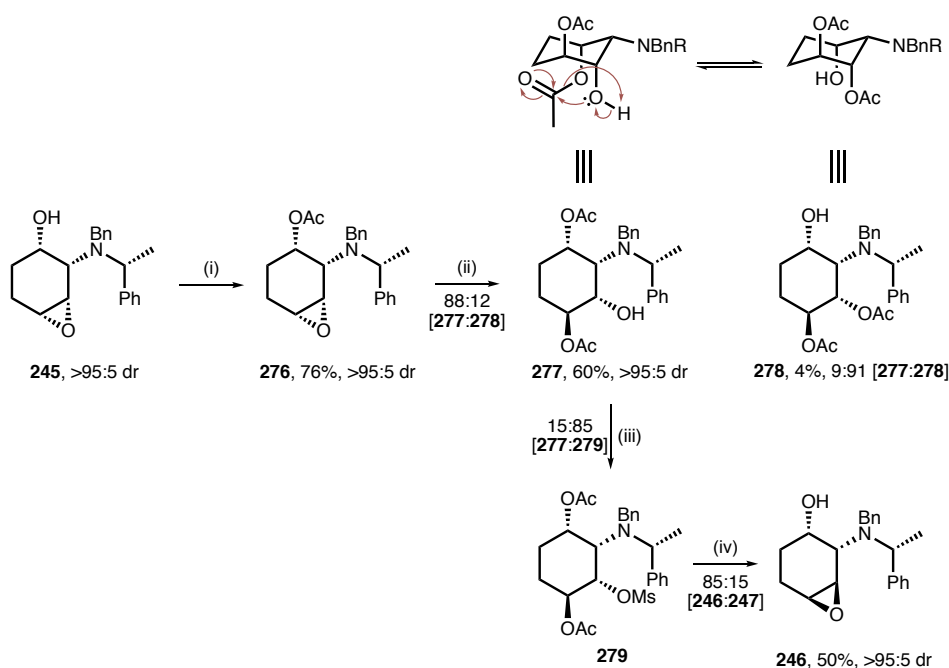


Figure 58. Chem3D representation of the X-ray crystal structure of **247** (selected H atoms are omitted for clarity).

Then, the epoxide-inversion strategy was deployed. First, *O*-acetylation of alcohol **245** gave the corresponding acetate **276** in 76% isolated yield and >95:5 dr,⁹ which was, in the presence of AcOH at 50 °C, regioselectively ring-opened providing an 88:12 mixture of diacetates **277** ($\delta_{C(1)H/C(4)H} \sim 5.0\text{--}5.1$ ppm and $\delta_{C(1)H/C(4)H} \sim 73\text{--}75$ ppm) and **278** ($\delta_{C(3)H/C(4)H} \sim 5.0\text{--}5.3$ ppm and $\delta_{C(3)H/C(4)H} \sim 70\text{--}74$ ppm). Separation of **277** and **278** *via* preparative TLC afforded **277** as single compound in 60% yield, and a 9:91 mixture of **277** and **278**, respectively, in 4% combined yield. Due to the presence of axial oxy functionalities at C(1) and C(3) within **277** and **278**, acetyl migration was easily realisable and explained the origins of **278**. Afterwards, *O*-mesylation of **277** with MsCl in pyridine gave an 85:15 mixture of mesylated **279** and unreacted starting material **277**,¹⁰ which was, without purification, treated with K₂CO₃ and MeOH to provide an 85:15 mixture of epoxide **246** and triol **247**. Purification *via* column chromatography gave **246** in 50% yield (>95:5 dr, $\delta_{C(3)H/C(4)H} \sim 3.26\text{--}3.33$ ppm and $\delta_{C(3)H/C(4)H} \sim 53$ ppm), although triol **247** was not recovered. As previously described, triol **247** comes from the transesterification of unreacted starting material **277** (Scheme 62).



Scheme 62. Reagents and conditions: (i) Ac₂O, DMAP, pyridine, rt, 24 h; (ii) AcOH, 50 °C, 36 h; (iii) MsCl, pyridine, rt, 16 h; (iv) K₂CO₃, MeOH, rt, 24 h [R = (α-methylbenzyl)].

The identity of and relative configuration within epoxide **246** was unambiguously established by single crystal X-Ray diffraction analysis.⁷ Its absolute (1*S*,2*R*,3*S*,4*R*, α *R*)-configuration was then assigned from the known (*R*)-configuration of the α -methylbenzyl stereogenic centre (Figure 59).¹¹

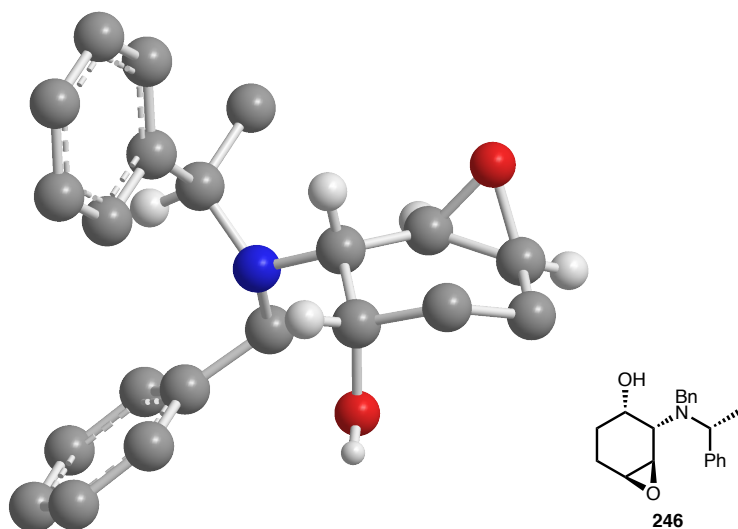
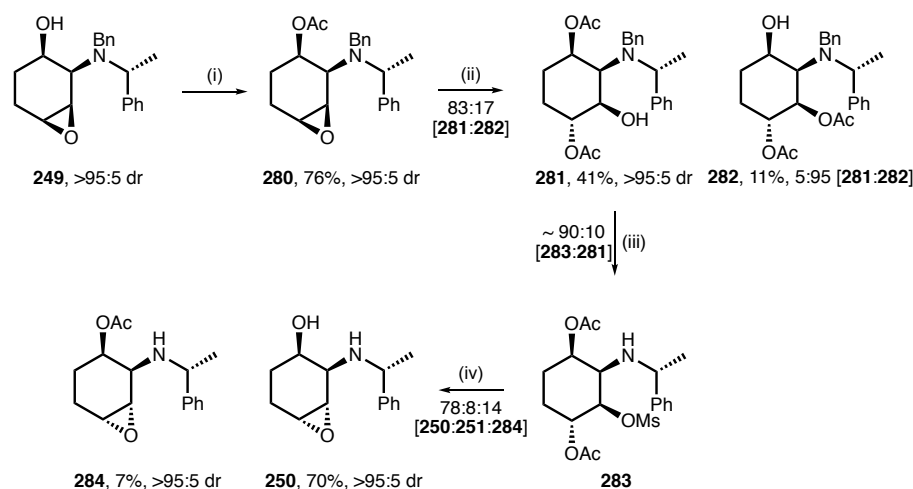


Figure 59. Chem3D representation of the X-ray crystal structure of **246** (selected H atoms are omitted for clarity).

In the meantime, the analogous sequence of reactions was first performed for diastereoisomer **249**. Treatment of **249** with Ac₂O and DMAP gave **280** in 76% yield and >95:5 dr,⁹ followed by ring-opening in AcOH to afford an 83:17 mixture of diacetates **281** ($\delta_{C(1)H/C(4)H} \sim 4.98\text{--}5.42$ ppm and $\delta_{C(1)H/C(4)H} \sim 72\text{--}75$ ppm) and **282** ($\delta_{C(3)H/C(4)H} \sim 4.83\text{--}4.98$ ppm and $\delta_{C(3)H/C(4)H} \sim 70\text{--}75$ ppm), respectively. Separation of **281** and **282** *via* preparative TLC provided **281** in 41% yield as a single compound, and a 5:95 mixture of **281** and **282**, respectively, in 11% combined yield. *O*-Mesylation of **281** with MsCl in pyridine resulted in a roughly 90% conversion to the corresponding mesylate **283**, which was, without purification, treated with K₂CO₃ and MeOH to provide a 78:8:14 mixture of epoxide **250**, triol **251** and acetate **284**, respectively. Purification *via* column chromatography gave epoxide **250** in 70% yield and >95:5 dr ($\delta_{C(3)H/C(4)H} \sim 2.53\text{--}3.06$ ppm and $\delta_{C(3)H/C(4)H} \sim 53$ ppm) and non-transesterified acetate **284**, which was isolated in 7% yield and >95:5 dr.

Methanolysis of **284** for 48 h provided **250** exclusively and confirmed its stereochemistry (Scheme 63).¹²



Scheme 63. Reagents and conditions: (i) Ac₂O, DMAP, pyridine, rt, 24 h; (ii) AcOH, 50 °C, 36 h; (iii) MsCl, pyridine, rt, 16 h; (iv) K₂CO₃, MeOH, rt, 24 h.

Ring-opening of epoxide **246** in the presence of HBF₄ (40% aq) at rt for 24 h gave a 59:41 mixture of starting material **246** and product **248**. Meanwhile, ring-opening of epoxide **250** under the same conditions resulted in 15% conversion to the corresponding triol **252**. Even if the rates of ring-opening of **246** and **250** were somewhat slower than for their diastereomeric epoxides **245** and **249**, respectively, a high regio- and stereoselectivity were observed in both cases. To encourage full consumption of **246**, ring-opening was performed at 40 °C and provided a 5:95 mixture of triols **247** and **248** in 58% yield. In the meantime, the 85:15 mixture of **250** and **252** was resubjected at 40 °C and provided a 5:95 mixture of triols **251** and **252** in 37% isolated yield. When epoxide **250** was treated under these optimised conditions, a 10:90 mixture of triols **251** and **252** were obtained in 53% yield. These results are thus consistent with a mechanism involving a regio- and stereoselective ring-opening (Scheme 64).

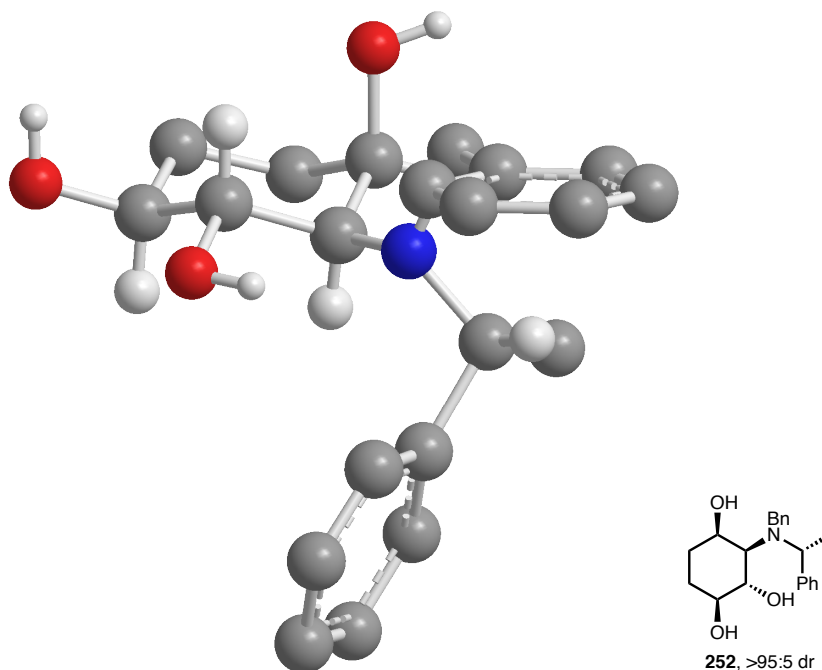


Figure 60. Chem3D representation of the X-ray crystal structure of **252** (selected H atoms are omitted for clarity).

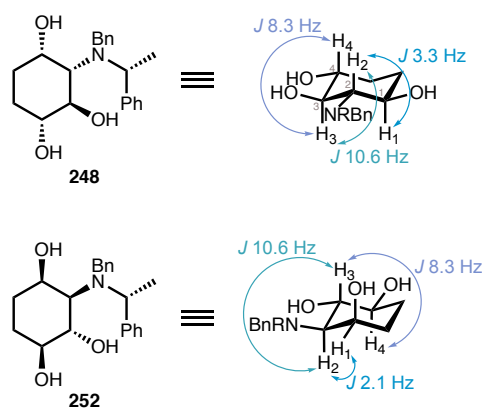
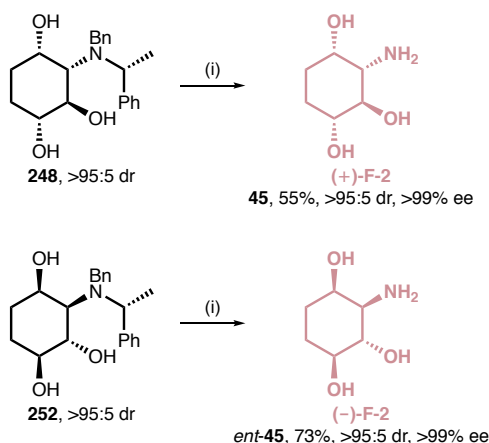


Figure 61. ^1H NMR 3J Coupling constants analyses of **248** and **252**. [R = (*R*)- α -methylbenzyl substituent].

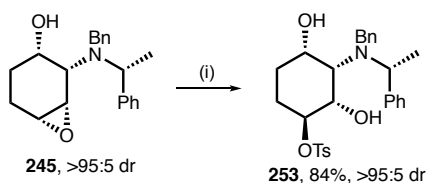
Hydrogenolysis of **248** and **252** with Pearlman's catalyst under H_2 gave enantiopure (+)-dihydroconduramine F-2 **45** in 55% yield ($>99\%$ ee¹³) and (–)-dihydroconduramine F-2 *ent*-**45** in 73% yield ($>99\%$ ee¹⁴), both $>95:5$ dr, respectively (Scheme 65).



Scheme 65. Reagents and conditions: (i) H₂ (1 atm), Pd(OH)₂/C, MeOH, rt, 24 h.

5.2.3 Syntheses of enantiopure dihydroconduramines (+)-D-2 **41** and (+)-E-2 **43**

Epoxide **245** was arbitrarily selected for the synthesis of the remaining dihydroconduramines D-2 **41** and E-2 **43**, both containing a *cis*-configured 3,4-diol moiety. As previously reported in chapter 4, a neighbouring group participation strategy was set up.^{4,15,16} To access (+)-dihydroconduramine D-2 **41**, ring-opening of epoxide **245** with TsOH afforded tosylate **253** in 84% yield as a single regio- and diastereoisomer (Scheme 66).¹⁷



Scheme 66. Reagents and conditions: (i) TsOH, CH₂Cl₂, rt, 24 h.

The relative configuration within tosylate **253** was also unambiguously established by single crystal X-Ray diffraction analysis.⁷ Its absolute (1*S*,2*S*,3*S*,4*S*, α *R*)-configuration was then assigned from the known (*R*)-configuration of the α -methylbenzyl stereogenic centre. A Flack x parameter of $-0.010(17)$ for the crystal structure of **253** was also consistent with its assigned absolute (1*S*,2*S*,3*S*,4*S*, α *R*)-configuration (Figure 62). The regio- and stereochemistry within tosylate **253** was also supported by ¹H and ¹³C NMR spectroscopic

analyses ($\delta_{C(4)HOTs} \sim 4.5$ ppm and $\delta_{C(4)HOTs} \sim 80$ ppm, $^3J_{1,2} = ^3J_{2,3} = 2.5$ Hz, $^3J_{3,4} = 3.2$ Hz) and was supportive of the similar conformation being adopted in the solid state (Figure 63).

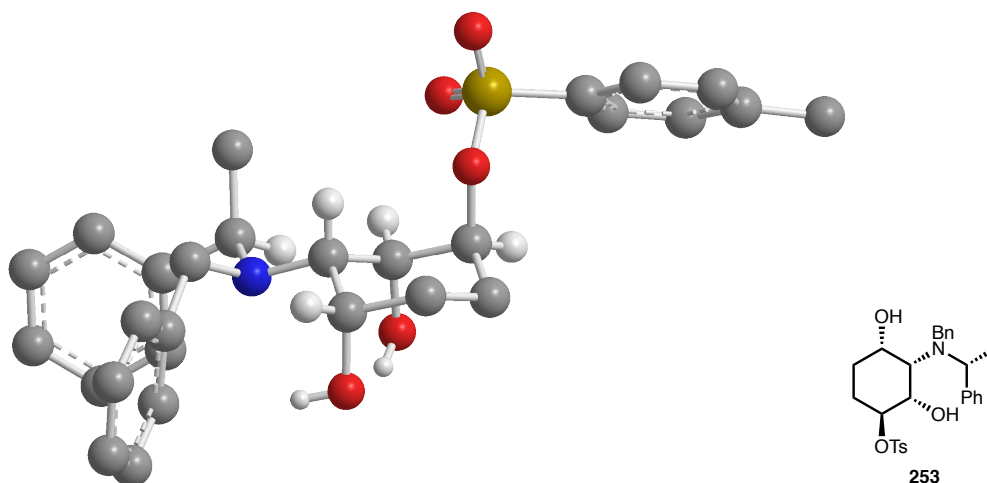


Figure 62. Chem3D representation of the X-ray crystal structure of **253** (selected H atoms are omitted for clarity).

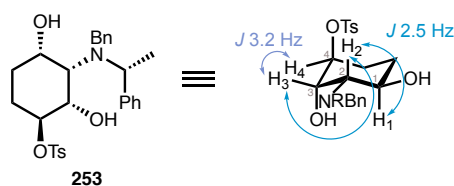
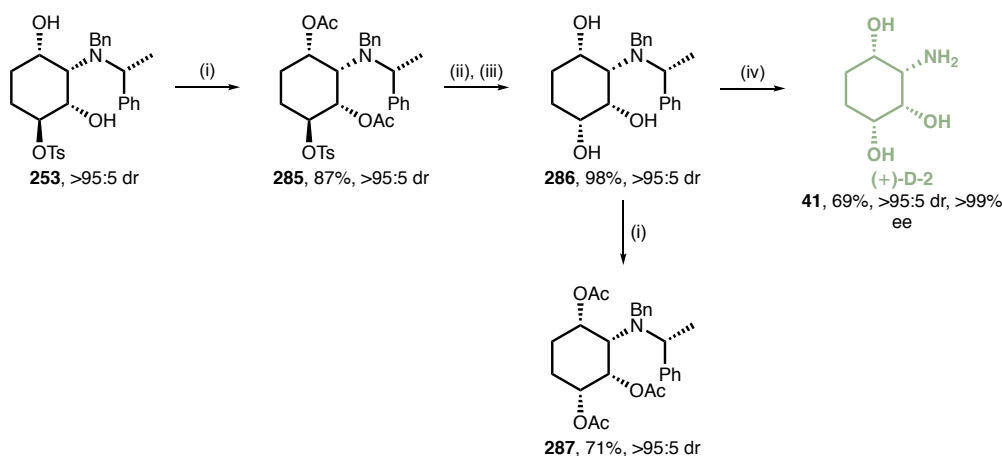


Figure 63. ^1H NMR 3J Coupling constant analysis of **253**.

Then, *O*-acetylation of **253** in presence of Ac_2O and DMAP in pyridine gave diacetate **285** in 87% yield and >95:5 dr, which was treated with KOAc in EtOH/ H_2O , followed by K_2CO_3 and MeOH to provide *cis*-3,4-configured diol **286** in 98% yield and >95:5 dr.^{4,15,16} As the ^1H NMR spectroscopic 3J coupling constant analysis was inconclusive, it was envisaged to perform an *O*-acetylation of triol **286** to analyse its stereochemistry. Treatment of **286** with Ac_2O and DMAP in pyridine gave triacetate **287** in 71% yield and >95:5 dr.⁹ The relative configuration within **287** was assigned by ^1H NMR 3J coupling constant analysis ($^3J_{1,2} = ^3J_{2,3} = ^3J_{3,4} = 2.8$ Hz, Figure 64). This is then in agreement with a displacement of tosylate group by the participation of the adjacent acetate functionality. Finally, hydrogenolysis of **286** with Pearlman's catalyst under H_2 atmosphere gave

enantiopure (+)-dihydroconduramine D-2 **41** in 69% yield, >99% ee,¹⁸ and >95:5 dr (Scheme 67).



Scheme 67. Reagents and conditions: (i) Ac₂O, DMAP, pyridine, rt, 24 h; (ii) KOAc, EtOH/H₂O, reflux, 72 h; (iii) K₂CO₃, MeOH, rt, 24 h; (iv) H₂ (1 atm), Pd(OH)₂/C, MeOH, rt, 24 h [R = (α)-methylbenzyl].

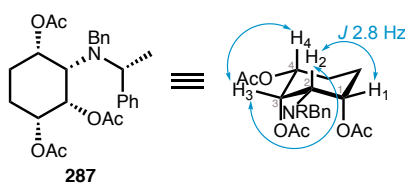
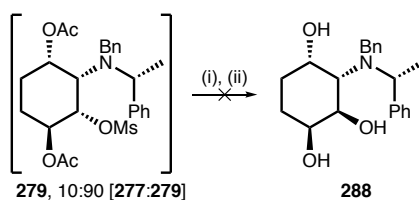


Figure 64. ¹H NMR ³J coupling constant analysis of **287**.

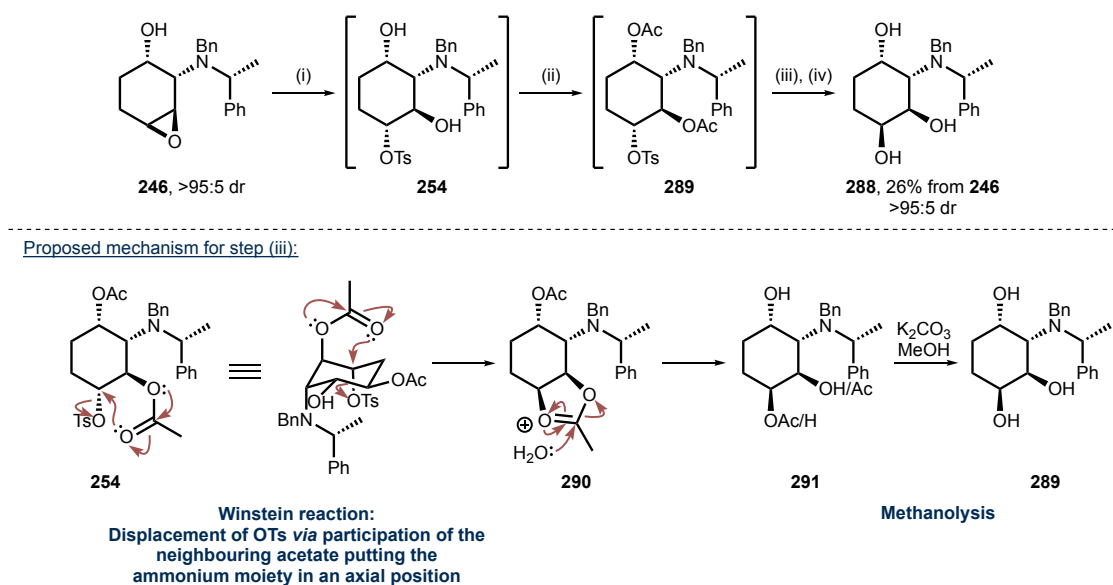
Application of the Winstein protocol and subsequent methanolysis to mesylated product **279** was envisaged to access (+)-E-2 **43**, however when this strategy was employed, a complex mixture was obtained and triol **288** was not recovered (Scheme 68).^{4,15,16}



Scheme 68. Reagents and conditions: (i) KOAc, EtOH/H₂O, reflux, 72 h; (ii) K₂CO₃, MeOH, rt, 24 h.

Modification of the route was then envisaged. Ring-opening of inverted epoxide **246** with TsOH gave tosylate **254**¹⁹ which was, without purification, O-acetylated in presence of Ac₂O and DMAP in pyridine to give diacetate **289**. Without purification, **289** was subjected

to Winstein protocol^{4,15,16} and subsequent methanolysis, which gave **288** in 26% from epoxide **246**. The stereochemistry of **288** was established by ¹H NMR spectroscopic ³*J* coupling constant analysis (³*J*_{1,2} = 1.8 Hz, ³*J*_{2,3} = 10.6 Hz, ³*J*_{3,4} = 3.0 Hz, Figure 65). As previously described in Chapter 4, the penultimate step [step (iii)] is therefore consistent with a mechanism involving the participation of the acetate functionality to displace the adjacent tosylate moiety, suggesting a pseudoaxial position of the hindered ammonium moiety. Then, the transesterification of the acetates by methanolysis results in the formation of amino triols (Scheme 69).



Scheme 69. Reagents and conditions: (i) TsOH, CH₂Cl₂, rt, 24 h; (ii) Ac₂O, DMAP, pyridine, rt, 24 h; (iii) KOAc, EtOH/H₂O, reflux, 72 h; (iv) K₂CO₃, MeOH, rt, 24 h. [R = (α)-methylbenzyl].

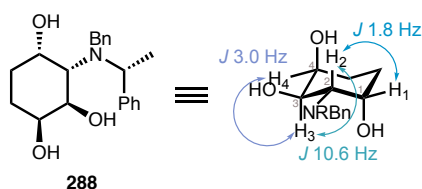
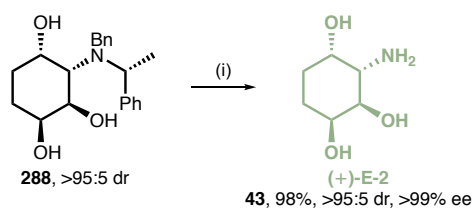


Figure 65. ¹H NMR ³*J* Coupling constant analysis of **288**.

Finally, hydrogenolysis of **288** with Pearlman's catalyst under an atmosphere of H₂ gave enantiopure (+)-dihydroconduramine E-2 **43** in 98% yield, >99% ee,²⁰ >95:5 dr (Scheme 70).

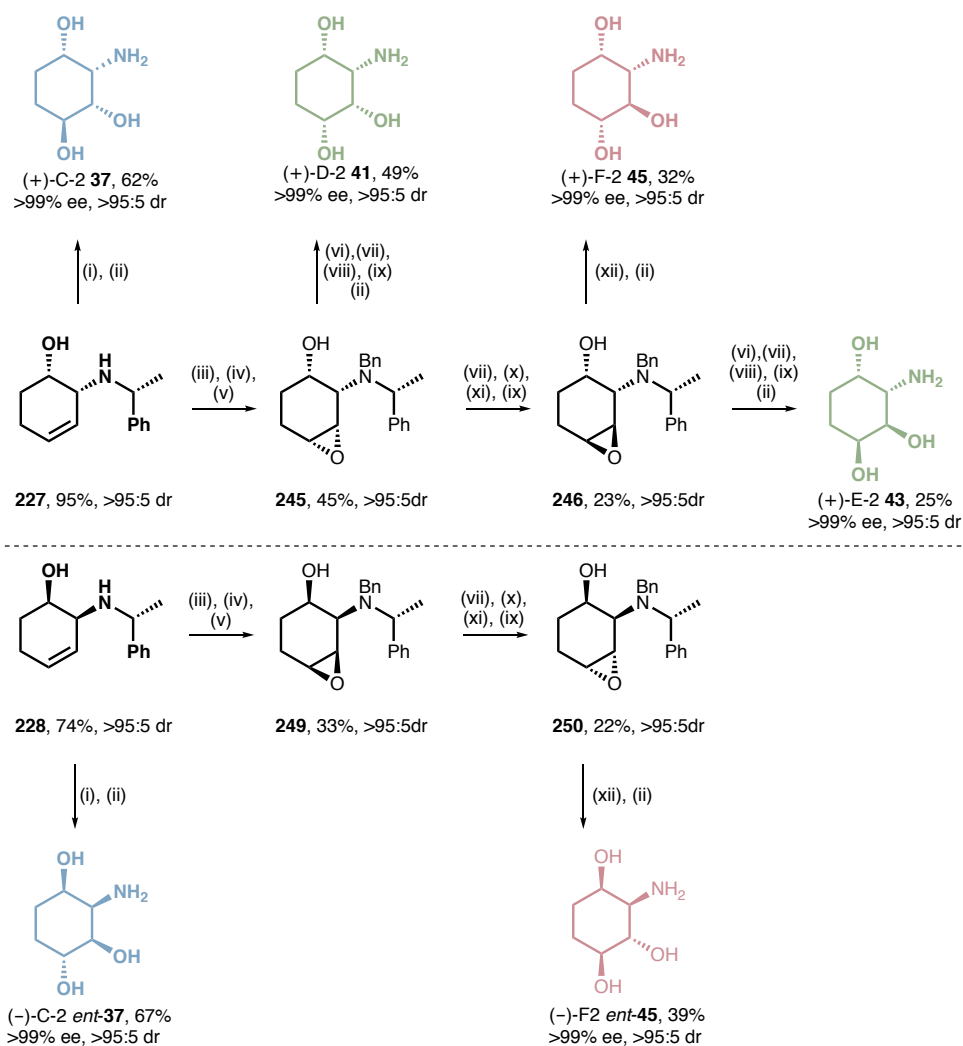


Scheme 70. Reagents and conditions: (i) H₂ (1 atm), Pd(OH)₂/C, MeOH, rt, 24 h.

5.3 Conclusion

The syntheses of six unknown enantiopure dihydroconduramines (+)-C-2 **37**, (–)-C-2 *ent*-**37**, (+)-D-2 **41**, (+)-E-2 **43**, (+)-F-2 **45** and (–)-F-2 *ent*-**45** have been achieved from either surrogates **227** or **228** using the ammonium-directed epoxidation methodology, Winstein and epoxide-inversion strategies as key stereodefining steps. Epoxidation of **227** and **228** with *m*-CPBA in presence of HBF₄ (40 % aq) gave triols **240** and **242** as single regio- and diastereoisomers in 65% and 70% yield, respectively, and their hydrogenolysis under H₂ (1 atm) with Pearlman's catalyst provided (+)-C-2 **37** (>99% ee) and (–)-C-2 *ent*-**37** (>99% ee) in 96% and 95% yield and >95:5 dr, respectively. Epoxides **245** and **249** were synthesised from **227** and **228** in 45% and 33% yield over the three steps (>95:5 dr), respectively, *via* epoxidation in presence of TsOH followed by DBU-promoted ring-closure and subsequent *N*-benzylation. (+)-Dihydroconduramine D-2 **41** (>99% ee) was accessed from epoxide **245** in 49% yield and >95:5 dr *via* TsOH-promoted ring-opening followed sequentially by *O*-acetylation, Winstein reaction, methanolysis and hydrogenolysis. Application of our epoxide-inversion strategy (i. e., *O*-acetylation of **245** and **249** followed by AcOH-promoted ring-opening, *O*-mesylation and methanolysis) gave access to the single regio- and diastereoisomers **246** and **250** in 23% and 22% yield and >95:5 dr, respectively. Ring-opening of these inverted-epoxides **246** and **250** with HBF₄ (40% aq) and hydrogenolysis afforded dihydroconduramines (+)-F-2 **45** (>99% ee) and (–)-F-2 *ent*-**45** (>99% ee) in 32% and 39% yield and >95:5 dr, respectively. Finally, ring-opening with TsOH of epoxide **246** followed by *O*-acetylation, Winstein protocol,

methanolysis and hydrogenolysis provided (+)-E-2 **43** in 25% yield (>99% ee) and >95:5 dr (Scheme 71).¹



Scheme 71. Reagents and conditions: (i) HBF₄ (40% aq), CH₂Cl₂, rt, 5 min then *m*-CPBA, rt, 30 h; (ii) H₂ (1 atm), Pd(OH)₂/C, MeOH, rt, 24 h; (iii) TsOH, CH₂Cl₂, rt, 5 min then *m*-CPBA, rt, 21 h; (iv) DBU, CH₂Cl₂, rt, 24 h; (v) BnBr, K₂CO₃, MeCN, 82 °C, 24 h; (vi) TsOH, CH₂Cl₂, rt, 24 h; (vii) Ac₂O, DMAP, pyridine, rt, 24 h; (viii) KOAc, EtOH/H₂O, reflux, 72 h; (ix) K₂CO₃, MeOH, rt, 24 h; (x) AcOH, 50 °C, 36 h; (xi) MsCl, pyridine, rt, 16 h; (xii) HBF₄ (40% aq), CH₂Cl₂, 40 °C, 24 h.

5.4 Notes and references

- (1) Da Silva Pinto, S.; Davies, S. G.; Fletcher, A. M.; Roberts, P. M.; Thomson, J. E. *J. Org. Chem.* **2018**, *83*, 9939–9957.
- (2) Given the known enantiopurity of the corresponding amide **233** (>99% ee) and that all synthetic intermediates possess multiple (at least three) stereogenic centres, the enantiopurities of the samples of (+)-C-2 **37**, as well as all intermediates prepared, could be inferred as >99% ee.
- (3) Given the known enantiopurity of the corresponding amide **234** (>99% ee) and that all synthetic intermediates possess multiple (at least three) stereogenic centres, the enantiopurities of the samples of (-)-C-2 *ent*-**37**, as well as all intermediates prepared, could be inferred as >99% ee.
- (4) Aciro, C.; Davies, S. G.; Roberts, P. M.; Russell, A. J.; Smith, A. D.; Thomson, J. E. *Org. Biomol. Chem.* **2008**, *6*, 3762–3770.

- (5) Schiffers, I.; Rantanen, T.; Schmidt, F.; Bergmans, W.; Zani, L. *J. Org. Chem.* **2006**, *71*, 2320–2331.
- (6) Attempts to assign the relative configurations within **247** and **251** by ^1H NMR spectroscopic analyses by examining 3J coupling constants were inconclusive.
- (7) X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research Laboratory, University of Oxford.
- (8) Attempts to assign the relative configuration within **245** and **249** by ^1H NMR spectroscopic analyses by examining 3J coupling constants were inconclusive.
- (9) Brennan, M. B.; Csatajová, K.; Davies, S. G.; Fletcher, A. M.; Green, W. D.; Lee, J. A.; Roberts, P. M.; Russell, A. J.; Thomson, J. E. *J. Org. Chem.* **2015**, *80*, 6609–6618.
- (10) Boerner, A.; Krause, H. *Tetrahedron* **1989**, *30*, 929–930.
- (11) Analysis of the stereochemistry within **246** by ^1H NMR spectroscopic 3J coupling constant analyses was inconclusive.
- (12) Although attempts to assign the configuration within **250** by ^1H NMR spectroscopic 3J coupling constant analyses proved to be vain, it was assumed that a *trans*-epoxide to the amino group was formed by analogy to the results obtained with **246**.
- (13) Given the known enantiopurity of the corresponding amide **233** (>99% ee) and that all synthetic intermediates possess multiple (at least three) stereogenic centres, the enantiopurities of the samples of (+)-F-2 **45**, as well as all intermediates prepared, could be inferred as >99% ee.
- (14) Given the known enantiopurity of the corresponding amide **234** (>99% ee) and that all synthetic intermediates possess multiple (at least three) stereogenic centres, the enantiopurities of the samples of (–)-F-2 *ent*-**45**, as well as all intermediates prepared, could be inferred as >99% ee.
- (15) Winstein, S.; Hess, H. V.; Buckles, R. E. *J. Am. Chem. Soc.* **1942**, *64*, 2796–2801.
- (16) Roberts, J. D.; Young, W. G.; Winstein, S. *J. Am. Chem. Soc.* **1942**, *64*, 2157–2164.
- (17) The same reaction was applied to epoxide **250** to afford an authentic sample of tosylate **255**.
- (18) Given the known enantiopurity of the corresponding amide **233** (>99% ee) and that all synthetic intermediates possess multiple (at least three) stereogenic centres, the enantiopurities of the samples of (+)-D-2 **41**, as well as all intermediates prepared, could be inferred as >99% ee.
- (19) The same reaction was applied to epoxide **250** to afford an authentic sample of tosylate **256**.
- (20) Given the known enantiopurity of the corresponding amide **233** (>99% ee) and that all synthetic intermediates possess multiple (at least three) stereogenic centres, the enantiopurities of the samples of (+)-E-2 **43**, as well as all intermediates prepared, could be inferred as >99% ee.

Chapter 6

Epoxidation of Cyclic Allylic Alcohols/Allylic Amines

This chapter describes the investigation of the chemoselectivity in the epoxidation of racemic primary, secondary and tertiary allylic amine/allylic alcohol systems ($\pm$)-**176**, ($\pm$)-**179** and ($\pm$)-**182**, derived from benzene oxide **292** (Figure 66).

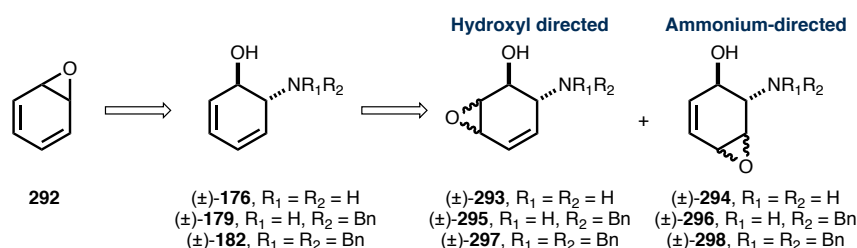
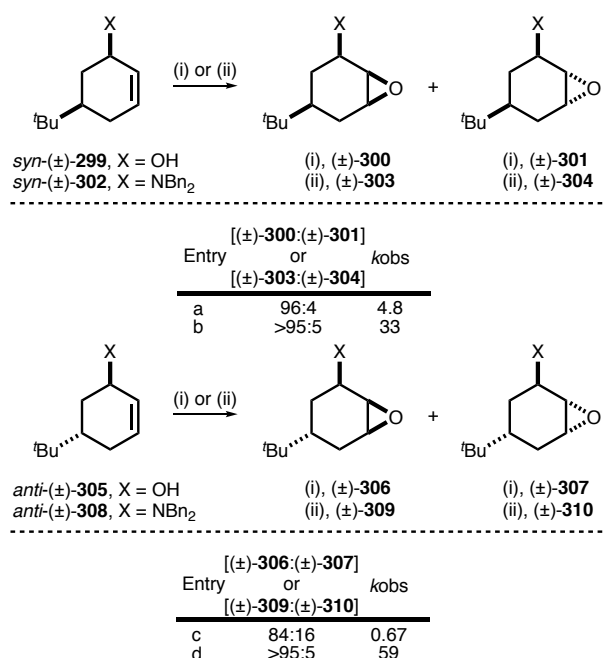


Figure 66. Investigation of the chemoselectivity of the epoxidation on allylic alcohol/allylic amine systems ($\pm$)-**176**, ($\pm$)-**179** and ($\pm$)-**182**.

6.1 Introduction

Previous work by Davies and co-workers investigated the reactivity in the epoxidation of conformationally-locked allylic alcohols 5-*tert*-butylcyclohex-2-en-1-ol *syn*-($\pm$)-**299** and *anti*-($\pm$)-**305** or conformationally-locked allylic amines *N,N*-dibenzyl-5-*tert*-butylcyclohex-2-en-1-amines *syn*-($\pm$)-**302** and *anti*-($\pm$)-**308**.¹ The relative directing group ability was measured in terms of diastereomeric ratio (dr) and rate of reaction. Higher diastereoselectivity was observed during epoxidation of allylic amines *syn*-($\pm$)-**302** and *anti*-($\pm$)-**308** than during the epoxidation of allylic alcohols [*syn*-($\pm$)-**299** and *anti*-($\pm$)-**305**]. Although *syn*-($\pm$)-**302** and *anti*-($\pm$)-**308** gave ($\pm$)-**303** and ($\pm$)-**309**, respectively, both highly diastereoselectivity (>95:5 dr), *syn*-($\pm$)-**299** proved to undergo oxidation with a high diastereocontrol [96:4 ($\pm$)-**300**:($\pm$)-**301**] compared to *anti*-($\pm$)-**305** [84:16 ($\pm$)-**306**:($\pm$)-**307**]. These results are thus in agreement with a pseudoequatorial hydroxyl group, pseudoequatorial and pseudoaxial *N,N*-

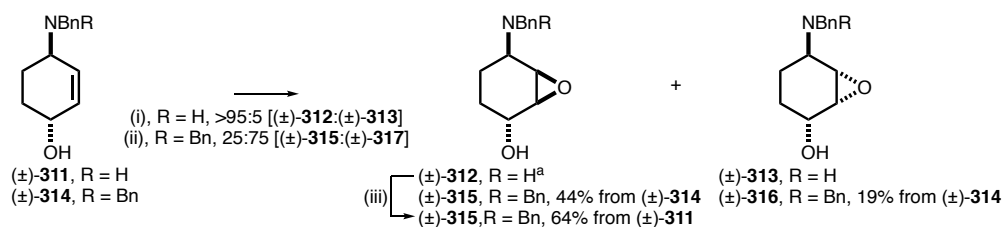
dibenzylammonium moiety conferring a higher diastereocontrol in the epoxidation reaction and acting as superior directing functionalities than the pseudoaxial hydroxyl group. In terms of the rate of reaction, in the allylic amine systems, epoxidation appeared to be faster when the *N,N*-dibenzylammonium moiety is placed in a pseudoaxial position whereas, in the allylic alcohols systems, the reaction was faster when the hydroxyl group adopts a pseudoequatorial position. These results suggest that the dihedral angle, subtended by the C-X bond (X = OH or NBN₂) with the plane defined by the olefin, is an important factor in determining the ability of the substituent X to confer high diastereoselectivity on the epoxidation reaction (Scheme 72).



Scheme 72. *Reagents and conditions:* (i) PhCO₃H, C₆H₆, 5 °C; (ii) CCl₃CO₂H, *m*-CPBA, CH₂Cl₂, rt, 21 h, then K₂CO₃, MeOH, rt, 16 h. *k* values given in units of 10³ dm³ mol⁻¹ s⁻¹.

Davies and co-workers also evaluated the relative abilities of an allylic amine and allylic alcohol to direct an epoxidation reaction in 4-*N*-benzylaminocyclohex-2-en-1-ol (±)-311 and 4-*N,N*-dibenzylaminocyclohex-2-en-1-ol (±)-314. Olefinic oxidation of (±)-311 with *m*-CPBA in presence of CCl₃CO₂H gave epoxide (±)-312 as a single diastereoisomer (>95:5 dr), which was, immediately, *N*-benzylated to afford (±)-315 in 64% yield, from (±)-311.

Meanwhile, epoxidation of ($\pm$)-**314** under the same conditions provided a 75:25 mixture of ($\pm$)-**315** and ($\pm$)-**316**, respectively. Purification *via* column chromatography afforded ($\pm$)-**315** in 44% yield and ($\pm$)-**316** in 19% yield, both in >95:5 dr (Scheme 73). In these systems, the allylic amine and allylic alcohol occupy a similar environment thanks to the presence of pseudo C₂ symmetry: in the half-chair conformations, conformers A and B are in equilibrium and both substituents are either in pseudoequatorial positions (**311A** and **314A**) or in pseudoaxial positions (**311B** or **314B**) with similar dihedral angles [$\alpha \approx \beta$], (Figure 67)]. Assuming that the rate of any background (non-directed-epoxidation reactions) is negligible, the diastereomeric excess is the result of the competition between the two potential directing groups (the hydroxyl and the ammonium moieties). The dr values indicate that the *N*-benzylammonium moiety acts as a better directing agent than the hydroxyl group, which has a better directing ability compared to the *N,N*-dibenzylammonium moiety.¹



Scheme 73. Reagents and conditions: (i) CCl₃CO₂H, *m*-CPBA, CH₂Cl₂, rt, 30 min; (ii) CCl₃CO₂H, *m*-CPBA, CH₂Cl₂, rt, 3.5 h; (iii) BnBr, ^tPr₂NEt, DMAP, CH₂Cl₂, rt, 24 h [^a epoxide ($\pm$)-**313** not purified].

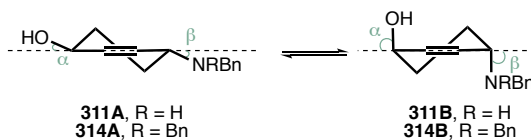


Figure 67. Half-chair conformations **311A/311B** and **314A/314B**. Dihedral angles α and β between the functional groups and the C=C double bond are highlighted in green.

6.2 Chapter aims

It was envisaged to synthesise racemic primary, secondary and tertiary allylic amine/allylic alcohol systems ($\pm$)-**176**, ($\pm$)-**179** and ($\pm$)-**182**, from benzene oxide **292**, and to investigate

the ammonium-directed and/or hydroxyl-directed epoxidation on these systems to allow the deployment of a synthetic route to quickly access conduramines (Figure 68).

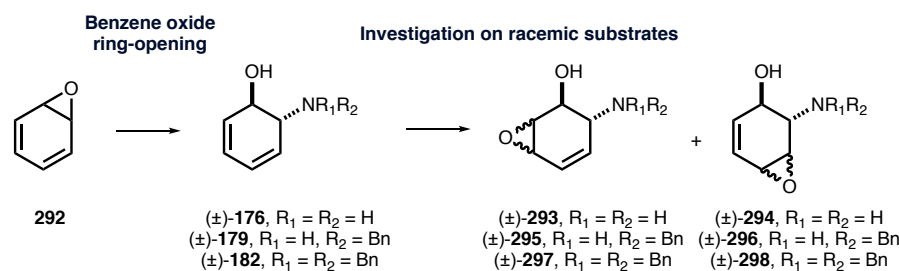


Figure 68. Chapter aims.

6.3 Synthesis of benzene oxide **292**

Although benzene oxide **292** is a commercially available product, for economic reasons, it was decided to synthesise it using the precedent in the literature. The three-step synthesis requires the mono epoxidation of commercially available 1,4-cyclohexadiene **317**, followed by bromination to give (±)-**319**. Finally, double dehydrobromination of (±)-**319** affords **292** (Figure 69).

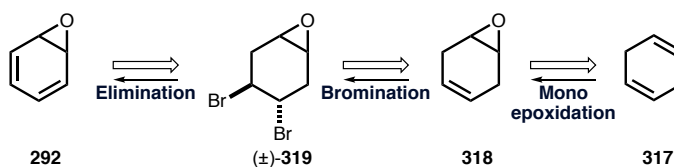


Figure 69. Retrosynthesis route of benzene oxide **292**.

First, mono-epoxidation of **317** using *m*-CPBA and NaHCO_3 in CH_2Cl_2 at 0 °C for 1 h provided epoxide **318** in 59% yield after distillation under reduced pressure.^{2,3} However, due to its viscosity, it was necessary to perform the reaction at low concentration (i.e., 0.21 M) but then the reaction scale-up was not practical enough to provide a large quantity of epoxide **318**. Previous work by Davies co-workers showed that if *m*-CPBA was replaced by AcOOH (38–40% in AcOH), the viscosity issue was suppressed allowing the reaction to be performed at higher concentration (i.e., 0.71 M) and thus the use of a larger quantity of diene **317**.⁴ Mono-epoxidation of **317** with AcOOH (38–40% in AcOH) and

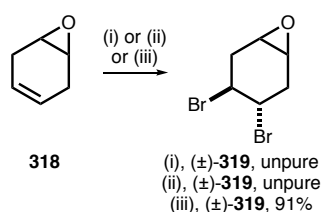
Na_2CO_3 in CH_2Cl_2 at $0\text{ }^\circ\text{C}$ gave **318** in 66% yield. The reaction scale-up to 50 g was also carried out and gave **318** in 64% isolated yield (Scheme 74).

317 **318**

Entry	Mass 317 (g)	Oxidant	Volume solvent (mL)	Mass 318 (g)	Yield (%)
a	10	<i>m</i> -CPBA	595	7.08	59
b	10	AcOOH	176	7.93	66
c	50	AcOOH	880	38.4	64

Scheme 74. *Reagents and conditions:* (i) *m*-CPBA, NaHCO_3 , CH_2Cl_2 , rt, 1 h; (ii) AcOOH, Na_2CO_3 , CH_2Cl_2 , $0\text{ }^\circ\text{C}$, then, $0\text{ }^\circ\text{C}$ to rt, 18 h.

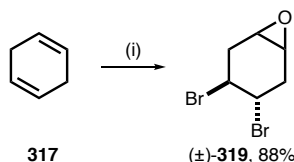
Treatment of epoxide **318** with Br_2 in CH_2Cl_2 at rt was next carried out and provided dibromide ($\pm$)-**319**.⁴ The ^1H NMR spectroscopic analysis of the crude reaction mixture showed the presence of other unknown compounds and purification by recrystallization proved unsuccessful. When the reaction was performed at $-78\text{ }^\circ\text{C}$, the same unknown compounds in the same proportions were present in the crude reaction mixture. However, bromination of **318** using a 1:1 mixture of CH_2Cl_2 and CHCl_3 (v/v), as the solvent, prevented the formation of the unknown products and ($\pm$)-**319** was isolated in 91% yield after purification *via* recrystallization (Scheme 75).⁵



Scheme 75. *Reagents and conditions:* (i) Br_2 , CH_2Cl_2 , rt, 30 min; (ii) Br_2 , CH_2Cl_2 , $-78\text{ }^\circ\text{C}$, 30 min; (iii) Br_2 , $\text{CH}_2\text{Cl}_2/\text{CHCl}_3$ (1:1, v/v), $-78\text{ }^\circ\text{C}$, 30 min.

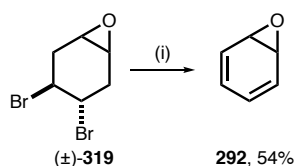
Dibromide ($\pm$)-**319** was therefore synthesised in 60% overall yield over 2 steps from 1,4-cyclohexadiene **317**. Telescoping the two-step process, however, afforded ($\pm$)-**319** in 88% yield from **317**. Indeed, mono-epoxidation of 10 g of **317** with AcOOH (38–40% in AcOH) and Na_2CO_3 in CH_2Cl_2 gave, after extraction of the crude reaction mixture with

CHCl_3 instead of CH_2Cl_2 (the volume of CHCl_3 was identical to the volume of CH_2Cl_2 required for the epoxidation), epoxide **318** in solution in CH_2Cl_2 and CHCl_3 (~1:1, v/v). Then, the addition of a solution of Br_2 in CH_2Cl_2 and CHCl_3 (1:1, v/v) gave, after recrystallization, 28 g of dibromide ($\pm$)-**319** (Scheme 76).



Scheme 76. *Reagents and conditions:* (i) AcOOH , Na_2CO_3 , CH_2Cl_2 , $0\text{ }^\circ\text{C}$, then, $0\text{ }^\circ\text{C}$ to rt, 18 h, then CHCl_3 , then Br_2 in $\text{CH}_2\text{Cl}_2/\text{CHCl}_3$ (1:1, v/v), $-78\text{ }^\circ\text{C}$, 30 min.

Finally, DBU-promoted elimination of the two bromides ($\pm$)-**319** in Et_2O provided, after distillation under reduced pressure, benzene oxide **292** in 54% yield.⁶ The ^1H and ^{13}C NMR spectroscopic data of **292** were consistent with the literature values (Scheme 77).⁷



Scheme 77. *Reagents and conditions:* (i) DBU, Et_2O , $0\text{ }^\circ\text{C}$, then $0\text{ }^\circ\text{C}$ to rt, 24 h.

6.4 Ring-opening of benzene oxide 292

To investigate the reactivity and diastereoselectivity of the olefinic oxidation, it was envisaged to prepare three different *N*-protected allylic amine/allylic alcohol systems ($\pm$)-**176**, ($\pm$)-**179** and ($\pm$)-**182**, respectively, from ring-opening of benzene oxide **292**, little explored yet (Figure 70).^{8,9,10,11,12}

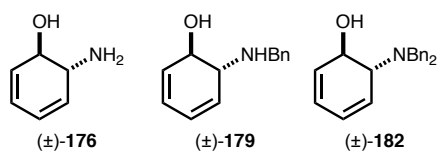
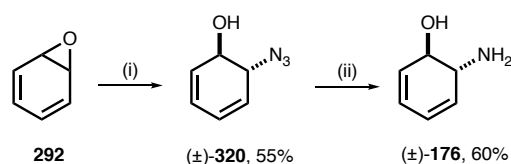


Figure 70. Structure of primary allylic amine/allylic alcohol ($\pm$)-**176**, secondary allylic amine/allylic alcohol ($\pm$)-**179** and tertiary allylic amine/allylic alcohol ($\pm$)-**182**.

6.4.1 Preparation of (±)-176

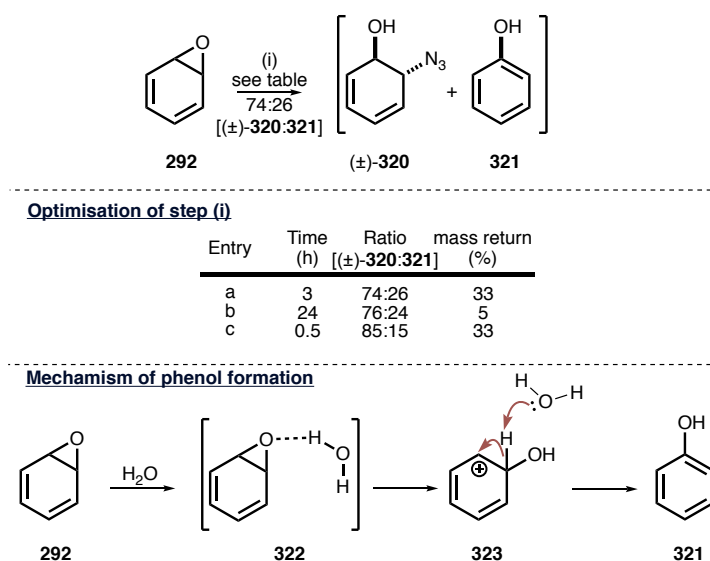
6.4.1.1 Ring-opening of (±)-176 with NaN₃

DeMarinis *et al.* showed that primary allylic amine/allylic alcohol (±)-176 could be synthesised in a two-step process in 33% yield: first, ring-opening of **292** with NaN₃ in H₂O at rt for 3 h provided (±)-320, in 55% yield, which was then reduced with LiAlH₄ to give (±)-176 in 60% yield (Scheme 78).⁸



Scheme 78. Reagents and conditions: (i) NaN₃, H₂O, rt, 3 h; (ii) LiAlH₄, Et₂O, 0 °C, 1 h.

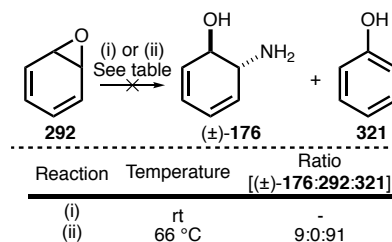
Attempts to report this procedure, however, rendered a 74:26 mixture of (±)-320 and phenol **321**, which was obtained in 33% mass return. The presence of phenol **321** in the crude reaction mixture could be explained by aromatization of the six-membered ring. Unfortunately, optimization by modifying the time of reaction did not provide a better mass return. This route was therefore abandoned (Scheme 79).



Scheme 79. Reagents and conditions: (i) NaN₃, H₂O, rt, see table; (ii) LiAlH₄, Et₂O, 0 °C, 1 h.

6.4.1.2 Ring-opening of ($\pm$)-176 with NH_3

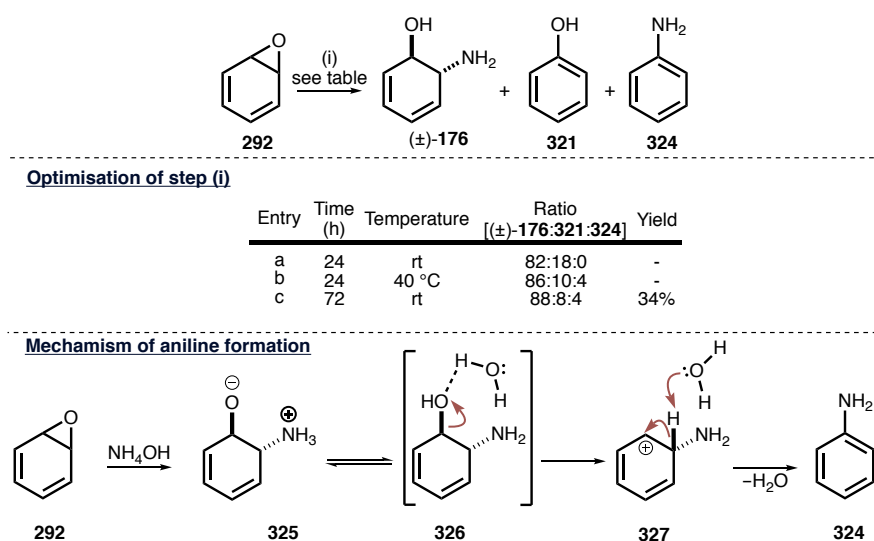
It was next envisaged to access ($\pm$)-176 in a single step using NH_3 . Treatment of **292** with NH_3 in MeOH (4.0 M) at rt for 24 h gave neither trace of the product ($\pm$)-176 nor phenol **321**, however when **292** was treated with NH_3 in MeOH (4.0 M) at 66 °C for 24 h, a 9:91 mixture of product ($\pm$)-176 and phenol **321**, respectively, was obtained (Scheme 80).



Scheme 80. Reagents and conditions: (i) NH_3 in MeOH (4.0 M), 24 h, see table.

Benzene oxide **292** was next treated with NH_4OH (35% aq) at rt for 24 h, which gave an 81:19 mixture of product ($\pm$)-176 and phenol **321**, respectively. Traces of other aromatic compounds, including aniline **324**, were noticed by ^1H NMR spectroscopic analysis of the crude reaction mixture (<5%). It was suggested that aniline **324** could come from ring-opening of **292** by NH_4OH (35% aq) followed by proton transfer to the alcoholate and aromatization with loss of H_2O . The reaction regioselectivity and configuration within ($\pm$)-176 were assigned by ^1H - ^1H COSY, ^1H - ^{13}C HSQC and ^1H NMR spectroscopic 3J coupling constant analyses [$^3J_{1,2} = 11.8$ Hz], (Figure 71)]. Monitoring the reaction by ^1H NMR spectroscopy using d_5 - NH_4OH was not feasible as **292** is only partially soluble in water and monitoring of the reaction by TLC was not possible due to the decomposition of **292** in contact with silica.¹³ Removal of the excess of NH_4OH (35% aq) by rotatory evaporation showed the presence of unreacted volatile **292**, identified by its yellow colour in solution. Optimisation, to encourage full conversion to ($\pm$)-176, was then attempted. Treatment of **292** with NH_4OH (35% aq) at 40 °C gave an 86:10:4 mixture of product ($\pm$)-176, phenol **321**, and aniline **324**, respectively. When the time was increased to 72 h, an

88:8:4 mixture of product ($\pm$)-**176**, phenol **321**, and aniline **324**, respectively, was obtained and starting material **292** was not visualised by eye (no yellow color) in the rotatory evaporator trap. Purification *via* column chromatography gave ($\pm$)-**176** in 34% yield and >95:5 dr. Obtaining of a low yield after purification could be rationalized by a possible decomposition (aromatization) of the product. These results showed that modification of neither the time nor the temperature had an impact on the crude reaction mixture ratio (Scheme 81).



Scheme 81. Reagents and conditions: (i) NH_4OH (35% aq), see table.

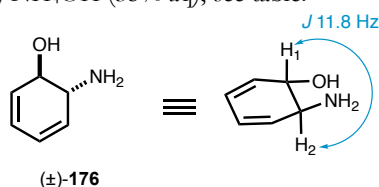


Figure 71. ^1H NMR 3J Coupling constants of ($\pm$)-**176**.

Therefore, although the ring-opening of benzene oxide **292** with NH_4OH at rt for 72 h provided ($\pm$)-**176** in low isolated yield, this protocol was kept and used to synthesise ($\pm$)-**176**.

6.4.2 Preparation of (±)-179

Ring-opening of benzene oxide **292** with benzylamine NH_2Bn could provide the second substrate needed for the investigation of the olefinic oxidation. First, treatment of benzene oxide **292** with 2 equiv of NH_2Bn was performed in different solvents (CH_2Cl_2 , THF, DMSO, MeCN) and the reaction of monitored by ^1H NMR spectroscopy. At rt, no reaction occurred after 18 h in d_2 - CH_2Cl_2 , d_8 -THF, d_6 -DMSO, and d_3 -MeCN and neither product (±)-**179** nor phenol **321** could be detected. When the reaction was heated in d_2 - CH_2Cl_2 , d_8 -THF, d_6 -DMSO, and d_3 -MeCN, once again, neither presence of product (±)-**179** nor phenol **321** could be visualized (Scheme 82).

292 (±)-**179** **321**

Entry	Solvent	Time (h)	Temperature	Ratio [(±)- 179 : 292 : 321] ^a
a	d_2 - CH_2Cl_2	18	rt	0:100:0
b	d_2 - CH_2Cl_2	18	40 °C	0:100:0
c	d_8 -THF	18	rt	0:100:0
d	d_8 -THF	18	66 °C	0:100:0
e	d_6 -DMSO	18	rt	0:100:0
f	d_6 -DMSO	18	82 °C	0:100:0
g	d_3 -MeCN	18	rt	0:100:0
h	d_3 -MeCN	18	82 °C	0:100:0

328

Scheme 82. Reagents and conditions: (i) NH_2Bn (2 equiv), 18 h, see table. [^a Mesitylene **328** was used as an internal standard].

It was also envisaged that the ring-opening of **292** could be acid-catalysed. Investigations were performed in d_2 - CH_2Cl_2 and d_8 -THF using either $\text{Al}(\text{O}^i\text{Pr})_3$ or $\text{Ti}(\text{O}^i\text{Pr})_4$, respectively, as Lewis acid. Ring-opening of **292** with NH_2Bn in presence of $\text{Ti}(\text{O}^i\text{Pr})_4$ in d_8 -THF at rt gave no conversion after 19.5 h, as before. However, when heated to 66 °C, after 19.5 h, a 21:79 mixture of product (±)-**179** and starting material **292**, respectively, was observed and full conversion was reached after 6 days to give a 40:60 mixture of product (±)-**179** and phenol **321**, respectively.¹⁴ In the meantime, when **292** was treated with NH_2Bn in presence of $\text{Al}(\text{O}^i\text{Pr})_3$ in d_2 - CH_2Cl_2 , as before, no reaction occurred at rt after 19.5 h.

However, when heated at 66 °C, after 19.5 h, a 7:28:65 mixture of product ($\pm$)-**179**, starting material **292** and phenol **321**, respectively was obtained and after 3 days, full conversion of **292** was observed and an 13:87 mixture of product ($\pm$)-**179** and phenol **321**, respectively, was afforded. These results are therefore consistent with an acid-catalysed ring-opening reaction but phenol formation is in both cases favoured (Scheme 83).

Reaction scheme: Epoxide **292** reacts with (i) NH_2Bn to yield a mixture of ($\pm$)-**179** and phenol **321**.

Entry	Lewis Acid	Solvent	Temperature	Time	Ratio [($\pm$)- 179 : 292 : 321] ^a
a	$\text{Ti}(\text{OPr})_4$	d_8 -THF	rt	19.5 h	0:100:0
b	$\text{Ti}(\text{OPr})_4$	d_8 -THF	66 °C	19.5 h	7:28:65
c	$\text{Ti}(\text{OPr})_4$	d_8 -THF	66 °C	6 days	13:0:87
d	$\text{Al}(\text{OPr})_3$	d_2 - CH_2Cl_2	rt	19.5 h	0:100:0
e	$\text{Al}(\text{OPr})_3$	d_2 - CH_2Cl_2	40 °C	19.5 h	21:79:0
f	$\text{Al}(\text{OPr})_3$	d_2 - CH_2Cl_2	40 °C	3 days	40:0:60

Scheme 83. Reagents and conditions: (i) NH_2Bn (2 equiv), see table. [^a Mesitylene **328** was used as an internal standard].

Treatment of **292** with 2 equiv of NH_2Bn in d_4 -MeOH at rt was next investigated and gave, after 18 h, an 12:88 mixture of product ($\pm$)-**179** and starting material **292**, respectively. However, when the reaction was heated at 66 °C, after 18 h, an 61:11:28 mixture of product ($\pm$)-**179**, starting material **292** and phenol **321**, respectively, was present in the crude reaction mixture and full conversion was reached after 42.5 h to afford a 66:34 mixture of product ($\pm$)-**179** and phenol **321**, respectively. Purification *via* column chromatography afforded ($\pm$)-**179** in 57% yield and >95:5 dr.¹⁵ When 5 equiv of NH_2Bn were used, ring-opening of **292** at 66 °C in d_4 -MeOH gave, after 42.5 h, a 88:12 mixture of product ($\pm$)-**179** and phenol **321**, respectively. When raised to 10 equivalents, a 97:3 mixture of product ($\pm$)-**179** and phenol **321**, respectively, was obtained under the same condition. In the latter case, purification *via* column chromatography afforded ($\pm$)-**179** as a single compound in 90% yield and >95:5 dr (Scheme 84). The relative configuration within

($\pm$)-**179** was established by ^1H NMR spectroscopic 3J coupling constant analyses ($^3J_{1,2} = 12.1$ Hz) and showed an *anti*-relationship between the hydroxyl and amino groups (Figure 72).

Entry	Equivalent	Time (h)	Temperature	Ratio [($\pm$)- 179 : 292 : 321] ^a	Yield (%)
a	2	18	rt	12:88:0	-
b	2	18	66 °C	61:11:28	-
c	2	42.5	66 °C	66:0:34	57
d	5	42.5	66 °C	88:0:12	-
e	10	42.5	66 °C	97:0:3	90

Scheme 84. Reagents and conditions: (i) NH_2Bn , d_4 -MeOH, 66 °C, 42.5 h, see table. [^a Mesitylene **328** was used as an internal standard].

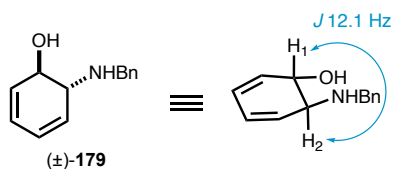
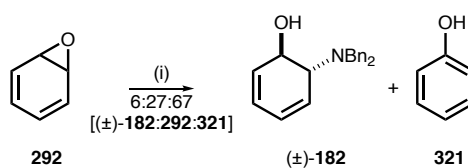


Figure 72. ^1H NMR 3J Coupling constants of ($\pm$)-**179**.

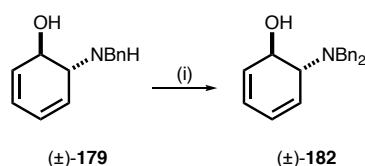
6.4.3 Preparation of ($\pm$)-**182**

Monitoring of the ring-opening of **292** with NHBn_2 under the optimised conditions (i.e., 10 equiv of requisite amine at 66 °C in d_4 -MeOH) gave, after 42.5 h, a 18:73:9 mixture of product ($\pm$)-**182**, benzene oxide **292**, phenol **321**, respectively. After 6 days, a 67:6:27 mixture of product ($\pm$)-**182**, benzene oxide **292**, phenol **321**, respectively, was visualised by ^1H NMR spectroscopic analysis. However, purification *via* column chromatography gave an inseparable mixture of ($\pm$)-**182** and NHBn_2 (Scheme 85).



Scheme 85. Reagents and conditions: (i) NHBn_2 , $\text{MeOH-}d_4$, 66 °C, 6 days.

Treatment of ($\pm$)-**179** in presence of BnBr, i Pr₂NEt and DMAP in CH₂Cl₂ at rt for 24 h was next carried out and provided ($\pm$)-**182** in 94% yield and >95:5 dr.¹⁶ This two-step synthesis from benzene oxide **292** gave ($\pm$)-**182** in 85% overall yield (Scheme 86). The relative configuration within ($\pm$)-**182** was established by ¹H NMR spectroscopic ³J coupling constant analyses (³J_{1,2} = 12.1 Hz) and showed an *anti*-relationship between the hydroxyl and amino groups (Figure 73).



Scheme 86. Reagents and conditions: (i) BnBr, i Pr₂NEt, DMAP, CH₂Cl₂, rt, 24 h.

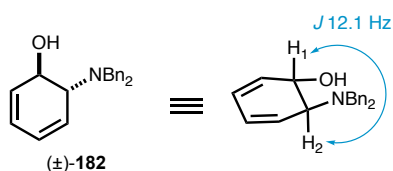


Figure 73. ¹H NMR ³J Coupling constants of ($\pm$)-**182**.

6.5 Olefinic oxidation of ($\pm$)-**176**, ($\pm$)-**179**, and ($\pm$)-**182**

Investigation of the reactivity and diastereoselectivity in the epoxidation of primary, secondary and tertiary allylic amine/allylic alcohols ($\pm$)-**176**, ($\pm$)-**179**, and ($\pm$)-**182**, respectively, was undertaken. As for epoxidation on systems ($\pm$)-**311** and ($\pm$)-**314**, described earlier, it was envisaged to observe two competitive pathways: the ammonium-directed *versus* the hydroxyl-directed epoxidations, assuming that any background (non-directed epoxidation reactions) would occur (Figure 74).

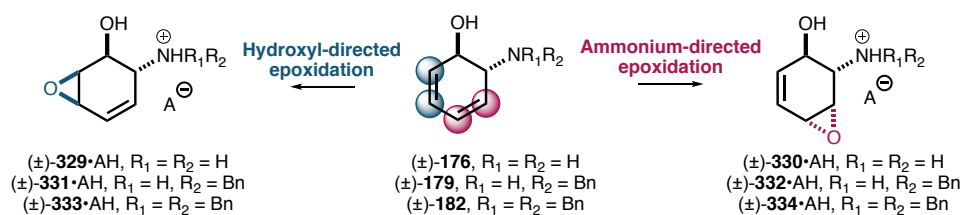
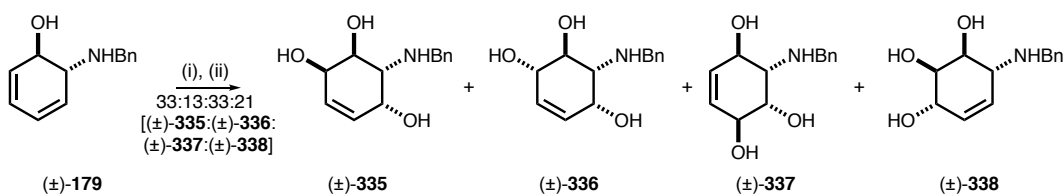


Figure 74. Ammonium-directed versus hydroxyl-directed epoxidations on racemic $(\pm)\text{-176}$, $(\pm)\text{-179}$, and $(\pm)\text{-182}$. [AH = $\text{CCl}_3\text{CO}_2\text{H}$, HBF_4 (40% aq)].

6.5.1 Epoxidation of $(\pm)\text{-179}$

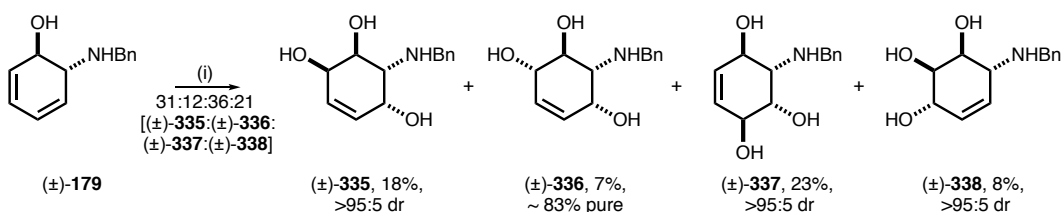
Due to the possible aromatization of $(\pm)\text{-179}$ under acid condition, the resistance of $(\pm)\text{-179}$ against aromatization under acidic condition was studied by ^1H NMR spectroscopic analysis. Addition of 5 equiv of $\text{CCl}_3\text{CO}_2\text{H}$ to a solution of $(\pm)\text{-179}$ in $d_2\text{-CH}_2\text{Cl}_2$ (0.36 M) gave $(\pm)\text{-179}\cdot\text{CCl}_3\text{CO}_2\text{H}$, which was stable after 20 min (no trace of other aromatic species than benzylic protons). Then, the addition of 1 equiv of *m*-CPBA to the crude reaction mixture gave after 1 h a complex mixture where full conversion of $(\pm)\text{-179}\cdot\text{CCl}_3\text{CO}_2\text{H}$ was visualised. Another ^1H NMR spectroscopic experiment was also performed after 18.5 h and provided the same complex mixture (Appendix 3). Quenching of the potential trace of *m*-CPBA left followed by subsequent methanolysis afforded a 33:13:33:21 mixture of $(\pm)\text{-335}$, $(\pm)\text{-336}$, $(\pm)\text{-337}$, and $(\pm)\text{-338}$, respectively (Scheme 87).



Scheme 87. Reagents and conditions: (i) $\text{CCl}_3\text{CO}_2\text{H}$, CH_2Cl_2 , rt, 15 min, then *m*-CPBA, rt; (ii) K_2CO_3 , MeOH , rt, 24 h.

When $\text{CCl}_3\text{CO}_2\text{H}$ was replaced by HBF_4 (40% aq), epoxidation of $(\pm)\text{-179}$ gave a 31:12:36:21 mixture of $(\pm)\text{-335}$, $(\pm)\text{-336}$, $(\pm)\text{-337}$, and $(\pm)\text{-338}$, respectively. This ratio was the same within error ($\pm 5\%$) to the one obtained when $\text{CCl}_3\text{CO}_2\text{H}$ was used. Purification *via* prep TLC (SiO_2 on aluminium sheets) gave $(\pm)\text{-335}$, $(\pm)\text{-337}$ and $(\pm)\text{-338}$ in 18%, 23%

and 8% yield (>95:5 dr in each case) and ($\pm$)-**336** in 7% yield and $\sim 83\%$ pure (Scheme 88). The configurations of ($\pm$)-**335** and ($\pm$)-**336** were fully assigned by ^1H NMR spectroscopic 3J coupling constant analyses [($\pm$)-**335**: $^3J_{1,2} = 4.6$ Hz, $^3J_{2,3} = 10.8$ Hz, $^3J_{3,4} = 4.8$ Hz/ ($\pm$)-**336**: $^3J_{1,2} = 4.2$ Hz, $^3J_{2,3} = 11.0$ Hz, $^3J_{3,4} = 7.8$ Hz]. The relative configurations within ($\pm$)-**337** and ($\pm$)-**338** were however partially assigned, as the 3J coupling constant between C(3)*H* and C(4)*H* did not reveal an unambiguous relationship between these two protons [($\pm$)-**337**: $^3J_{1,2} = 6.8$ Hz, $^3J_{2,3} = 2.7$ Hz, $^3J_{3,4} < 4.5$ Hz/ ($\pm$)-**338**: $^3J_{1,2} = 6.7$ Hz, $^3J_{2,3} = 2.5$ Hz, $^3J_{3,4} < 4.6$ Hz], (Figure 75)].



Scheme 88. Reagents and conditions: (i) HBF_4 (40% aq), *m*-CPBA, CH_2Cl_2 , rt, 21 h.

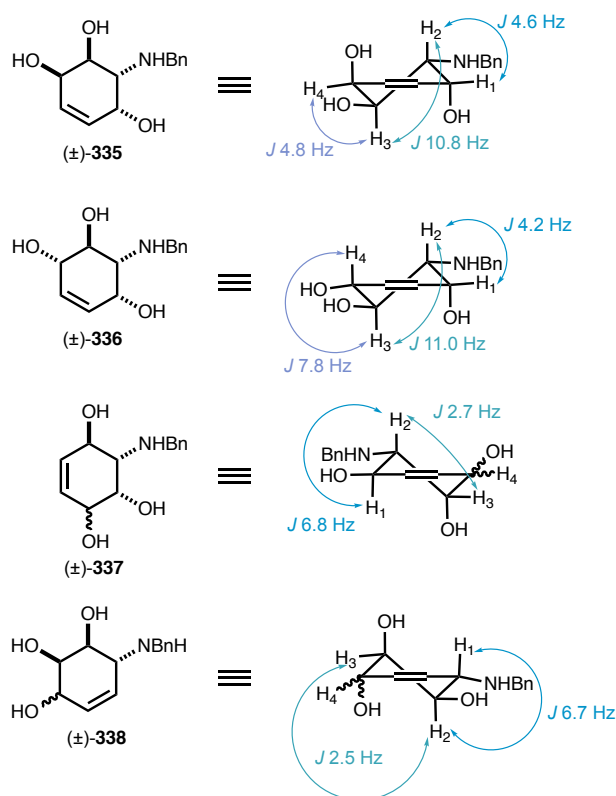
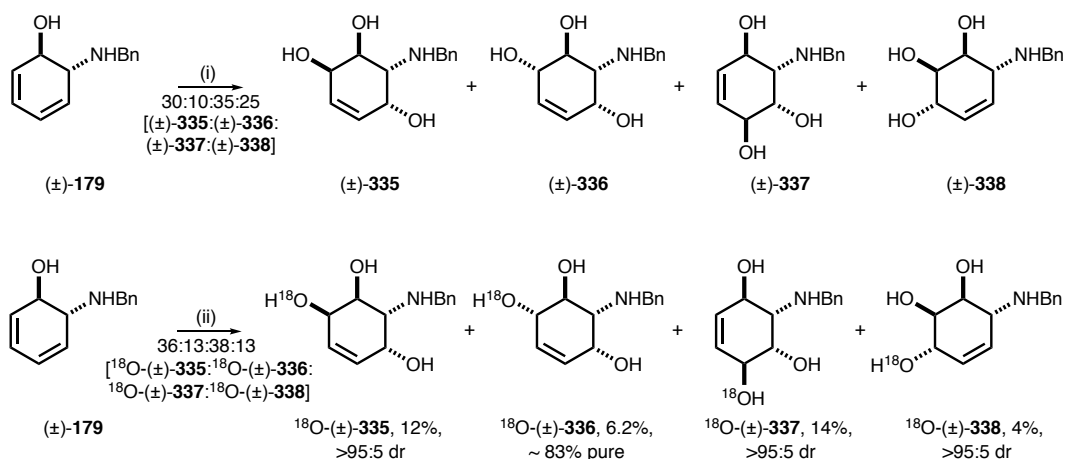


Figure 75. ^1H NMR 3J Coupling constants of ($\pm$)-**335**, ($\pm$)-**336**, ($\pm$)-**337** and ($\pm$)-**338**.

Investigations of the regioselectivity of the ring-opening of epoxide ($\pm$)-**331**•AH and ($\pm$)-**332**•AH were then undertaken [AH = CCl₃CO₂H, HBF₄ (40% aq)].¹⁷ It was suggested to replace H₂O by H₂¹⁸O and determine the position of the ¹⁸O-hydroxyl group within each compound. Use of HBF₄ (50–55% in Et₂O) instead of HBF₄ (40% aq) was then necessary to avoid competition between H₂O and H₂¹⁸O. First, epoxidation of ($\pm$)-**179** in the presence of HBF₄ (50–55% in Et₂O) and H₂O (1:1, v/v) was realised to analyse the impact of the presence of Et₂O in the reactivity and the selectivity of the reaction. A 30:10:35:25 mixture of ($\pm$)-**335**, ($\pm$)-**336**, ($\pm$)-**337** and ($\pm$)-**338**, respectively, was obtained, which was the same within error ($\pm$ 5%) to the previous ratio [i.e., 31:12:36:21 ($\pm$)-**335**:($\pm$)-**336**:($\pm$)-**337**:($\pm$)-**338**]. Therefore, epoxidation of ($\pm$)-**179** in presence of HBF₄ (50–55% in Et₂O) and H₂¹⁸O (1:1, v/v) was carried out and gave a 36:13:38:13 mixture of ¹⁸O-($\pm$)-**335**, ¹⁸O-($\pm$)-**336**, ¹⁸O-($\pm$)-**337** and ¹⁸O-($\pm$)-**338**, respectively. Purification *via* preparative TLC gave ¹⁸O-($\pm$)-**335** in 12% yield and >95:5 dr, ¹⁸O-($\pm$)-**336** in 6.2% yield and ~ 87% purity, ¹⁸O-($\pm$)-**337** in 14% yield and >95:5 dr, and ¹⁸O-($\pm$)-**338** in 4% and >95:5 dr, all with 92% ¹⁸O-incorporation, as justified by mass spectrometric analysis (Scheme 89).



Scheme 89. Reagents and conditions: (i) HBF₄ (50–55% Et₂O), H₂O, *m*-CPBA, CH₂Cl₂, rt, 21 h; (ii) HBF₄ (50–55% Et₂O), H₂¹⁸O, *m*-CPBA, CH₂Cl₂, rt, 21 h.

Identification of the position of the ^{18}O -hydroxyl group within the four compounds was first envisaged by mass spectrometry analysis but the nature of their fragmentation rendered mass spectrometry unsuitable as a tool to locate the position of the ^{18}O label. Therefore, analysis of the $^{16}\text{O}/^{18}\text{O}$ isotope induced chemical shifts in the ^{13}C NMR spectrum¹⁸ was employed to unambiguously locate the ^{18}O atom within each of these samples. Having established the position of the ^{18}O -hydroxyl group within each triol, the following hypothesis was advanced. Neglecting any background (non-directed epoxidation), two different epoxides can be formed *in situ*: ($\pm$)-**331**•AH from hydroxyl-directed epoxidation of ($\pm$)-**179** and ($\pm$)-**332**•AH from an ammonium-directed epoxidation of ($\pm$)-**179** [AH = $\text{CCl}_3\text{CO}_2\text{H}$, HBF_4 (40% aq)]. $\text{S}_{\text{N}}2$ -type ring-opening of epoxide ($\pm$)-**331**•AH and ($\pm$)-**332**•AH result in the formation of ($\pm$)-**338** and ($\pm$)-**337**, respectively whereas conjugate ring-opening of epoxide ($\pm$)-**332**•AH *via* an $\text{S}_{\text{N}}2'$ -type fashion provides epimers ($\pm$)-**335** and ($\pm$)-**336**. The absence of two carbon C(1) peaks (corresponding to the ^{16}O and ^{18}O isotopes, >95% ^{18}O -incorporation) in the ^{13}C NMR spectroscopy spectrum of ($\pm$)-**335** unambiguously confirms the origins of the formation of ($\pm$)-**335** *via* an ammonium-directing epoxidation, i.e., ring-opening at C(4), (Appendix 4). The relative directing abilities of the two functionalities could thus be measured by the ratio of the reaction, i.e., 21:79 [($\pm$)-**338**:(($\pm$)-**335**+($\pm$)-**336**+($\pm$)-**337**)] and these results are consistent with the previously described observations made by Davies and co-workers: the *N*-benzylammonium moiety acts as a superior directing group in comparison to the hydroxyl group (Figure 76).

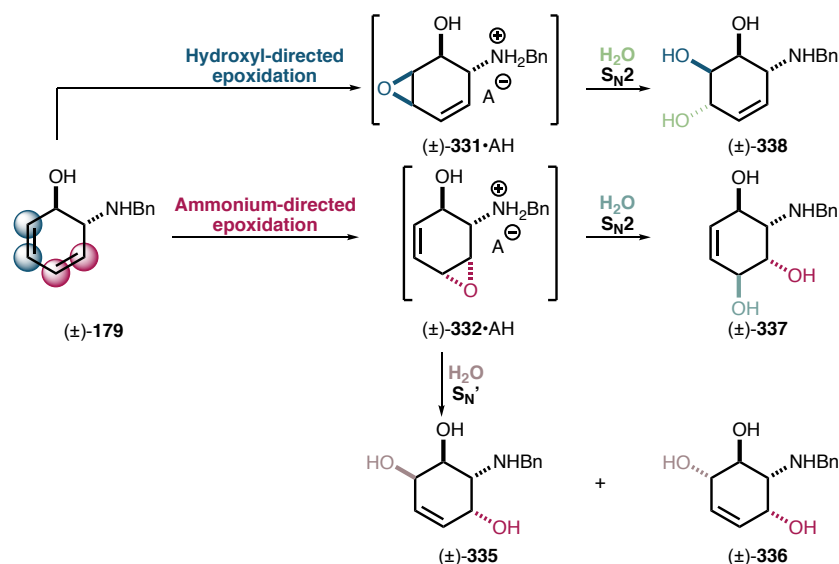
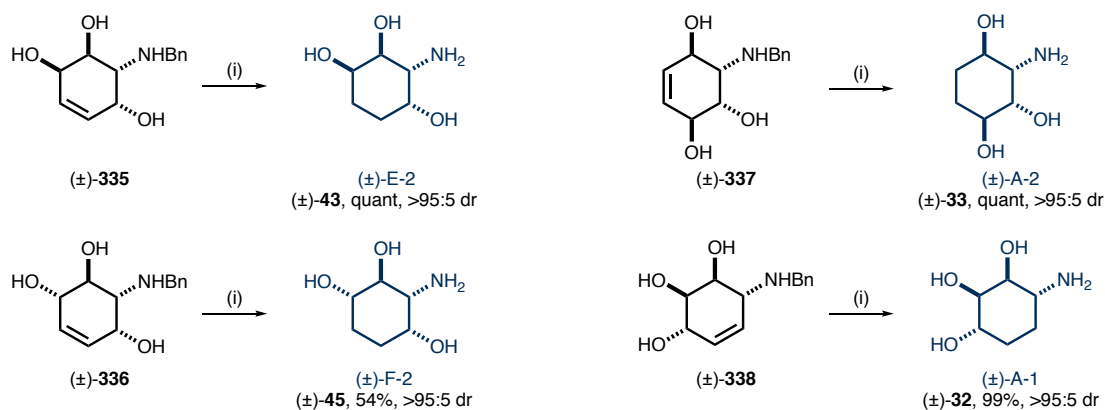


Figure 76. Epoxidation of (±)-179. [AH = CCl₃CO₂H, HBF₄ (40% aq)].

In order to confirm the stereochemistry assignments, hydrogenolysis of isolated (±)-335, (±)-337 and (±)-338 were undertaken in presence of Pearlman's catalyst and an atmosphere of H₂ and gave dihydroconduramines (±)-E-2 (±)-43 and (±)-A-2 (±)-33 in quantitative yields and (±)-dihydroconduramine A-1 (±)-32 in 99% yield, respectively, and all >95:5 dr. Hydrogenolysis of (±)-336 provided, after purification *via* column chromatography, (±)-dihydroconduramine F-2 (±)-45 in 54% yield and >95:5 dr (Scheme 90). The ¹H and ¹³C NMR spectroscopic data of dihydroconduramines (±)-E-2 (±)-43, (±)-F-2 (±)-45, and (±)-A-2 (±)-33 matched those of dihydroconduramines previously synthesised and confirmed unambiguously the relative configurations previously obtained.^{19,20} The ¹H and ¹³C NMR spectroscopic data of (±)-dihydroconduramine A-1 (±)-32 were not reported, although its synthesis was provided in the literature.²¹ The ¹H NMR spectroscopic ³J coupling constant analysis of (±)-A-1 (±)-32 unambiguously confirmed the relative configuration therein in solution in *d*₄-MeOH [³J_{1,2} = 9.2 Hz, ³J_{2,3} = 3.4 Hz, ³J_{3,4} = 3.4 Hz), (Figure 77)].



Scheme 90. Reagents and conditions: (i) H_2 (1 atm), $\text{Pd}(\text{OH})_2/\text{C}$, MeOH, rt, 24 h.

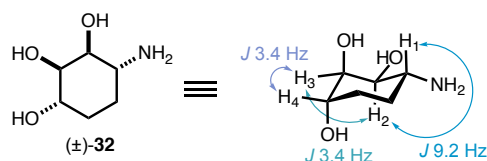
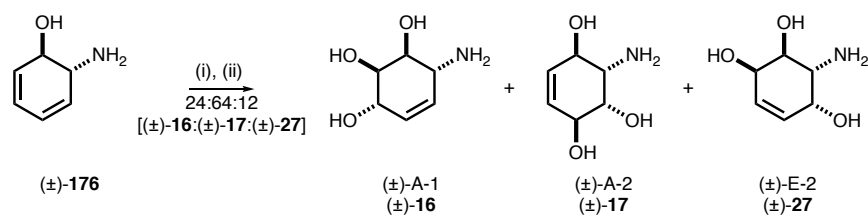


Figure 77. ^1H NMR 3J Coupling constants of ($\pm$)-32.

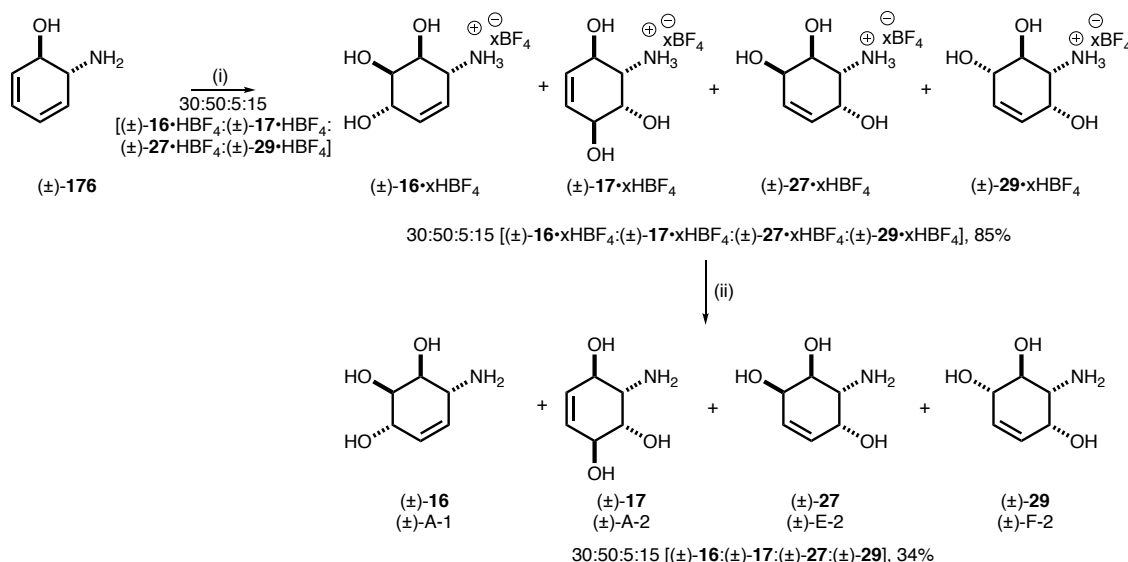
6.5.2 Epoxidation of ($\pm$)-176

As previously with ($\pm$)-179, it was decided to monitor the epoxidation of ($\pm$)-176 by ^1H NMR spectroscopy to observe the resistance of ($\pm$)-176 against aromatization. Treatment of ($\pm$)-176 with $\text{CCl}_3\text{CO}_2\text{H}$ in $d_2\text{-CH}_2\text{Cl}_2$ gave ($\pm$)-176 $\cdot\text{CCl}_3\text{CO}_2\text{H}$, resistant against aromatization (absence of protons in the aromatic region). Then, the addition of *m*-CPBA to the reaction mixture provided a mixture of unknown compounds after 1 h, with full conversion of ($\pm$)-176 $\cdot\text{CCl}_3\text{CO}_2\text{H}$. The same complex mixture was observed after 18.5 h by ^1H NMR spectroscopic experiment (Appendix 3). Quenching of the potential trace of *m*-CPBA left followed by subsequent saponification with K_2CO_3 and MeOH provided a 24:64:12 mixture of ($\pm$)-A-1 ($\pm$)-16, ($\pm$)-A-2 ($\pm$)-17 and ($\pm$)-E-2 ($\pm$)-27, respectively and ($\pm$)-F-2 ($\pm$)-29 was not observed (Scheme 91).



Scheme 91. Reagents and conditions: (i) $\text{CCl}_3\text{CO}_2\text{H}$, CH_2Cl_2 , rt, 15 min, then *m*-CPBA, rt; (ii) K_2CO_3 , MeOH, rt, 24 h.

When the epoxidation of $(\pm)\text{-176}$ was realised in presence of HBF_4 (40% aq), a 30:50:5:15 mixture of $(\pm)\text{-16}\cdot\text{HBF}_4$, $(\pm)\text{-17}\cdot\text{HBF}_4$, $(\pm)\text{-27}\cdot\text{HBF}_4$ and $(\pm)\text{-29}\cdot\text{HBF}_4$, respectively, was visualised in the crude reaction mixture. Purification *via* column chromatography gave a 30:50:5:15 mixture of $(\pm)\text{-16}\cdot\text{xHBF}_4$, $(\pm)\text{-17}\cdot\text{xHBF}_4$, $(\pm)\text{-27}\cdot\text{xHBF}_4$, and $(\pm)\text{-29}\cdot\text{xHBF}_4$, respectively, in 85% yield ($0 \leq x \leq 1$ equivalents of HBF_4). Although a basic eluent system was used during the column chromatography, the four products were still isolated as HBF_4 salts. Purification *via* ion exchange chromatography (DOWEX 50WX8-200) gave a 30:50:5:15 mixture of free racemic $(\pm)\text{-A-1 } (\pm)\text{-16}$, $(\pm)\text{-A-2 } (\pm)\text{-17}$, $(\pm)\text{-E-2 } (\pm)\text{-27}$ and $(\pm)\text{-F-2 } (\pm)\text{-29}$, respectively in 34% yield from $(\pm)\text{-176}$ (Scheme 92).



Scheme 92. Reagents and conditions: (i) HBF_4 (40% aq), *m*-CPBA, CH_2Cl_2 , rt, 21 h; (ii) DOWEX 50WX8-200.

Relative configurations within ($\pm$)-A-1 ($\pm$)-**16**, ($\pm$)-E-2 ($\pm$)-**27** and ($\pm$)-F-2 ($\pm$)-**29** were assigned by ^1H NMR spectroscopic 3J coupling constant analyses [($\pm$)-**16**: $^3J_{1,2} = 6.9$ Hz, $^3J_{2,3} = 2.4$ Hz, $^3J_{3,4} = 4.0$ Hz/($\pm$)-**27**: $^3J_{1,2} = 4.2$ Hz, $^3J_{2,3} = 10.3$ Hz, $^3J_{3,4} = 4.3$ Hz/($\pm$)-**29**: $^3J_{1,2} = 4.3$ Hz, $^3J_{2,3} = 10.7$ Hz, $^3J_{3,4} = 7.6$ Hz), (Figure 78)]. The ^1H and ^{13}C NMR spectroscopic data of ($\pm$)-conduramine A-1 ($\pm$)-**16** matched those of conduramines previously synthesised.²²

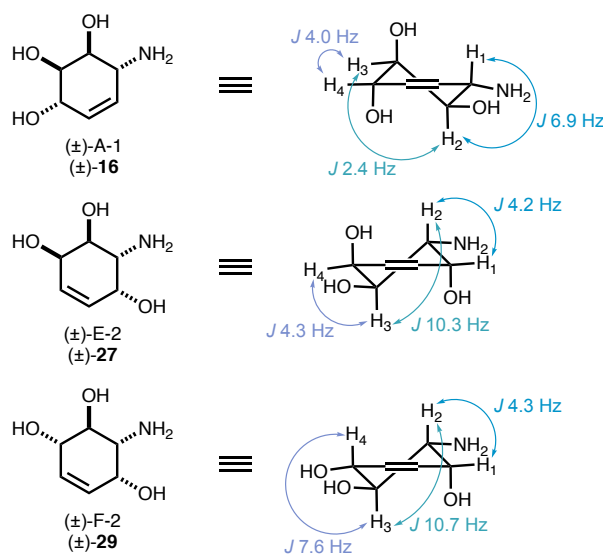
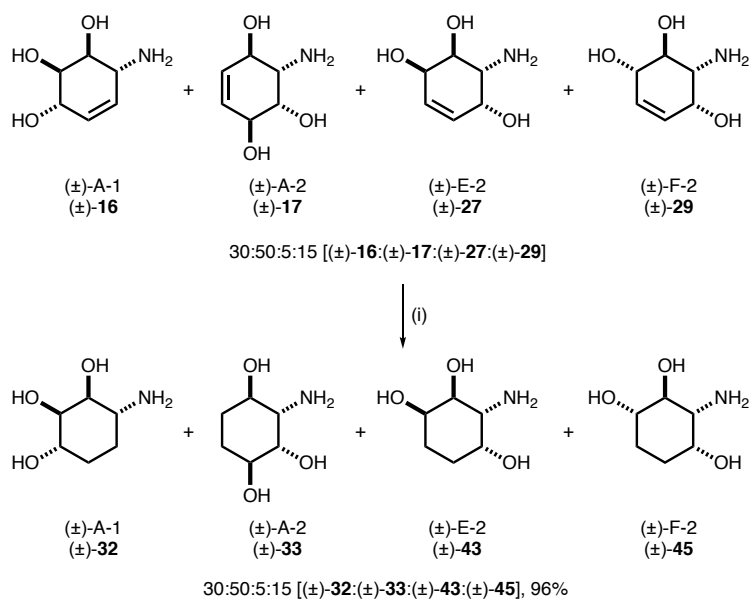


Figure 78. ^1H NMR 3J Coupling constants of ($\pm$)-**16**, ($\pm$)-**27**, and ($\pm$)-**29**.

To confirm the stereochemistry of ($\pm$)-**16**, ($\pm$)-**17**, ($\pm$)-**27** and ($\pm$)-**29**, hydrogenolysis of a 30:50:5:15 mixture of ($\pm$)-A-1 ($\pm$)-**16**, ($\pm$)-A-2 ($\pm$)-**17**, ($\pm$)-E-2 ($\pm$)-**27** and ($\pm$)-F-2 ($\pm$)-**29** under an atmosphere of H_2 (1 atm) with $\text{Pd}(\text{OH})_2/\text{C}$ gave a 30:50:5:15 mixture of dihydroconduramines ($\pm$)-A-1 ($\pm$)-**32**, ($\pm$)-A-2 ($\pm$)-**33**, ($\pm$)-E-2 ($\pm$)-**43** and ($\pm$)-F-2 ($\pm$)-**45**, respectively, in 96% yield. The ^1H and ^{13}C NMR spectroscopic data of dihydroconduramines ($\pm$)-A-1 ($\pm$)-**32**, ($\pm$)-A-2 ($\pm$)-**33**, ($\pm$)-E-2 ($\pm$)-**43** and ($\pm$)-F-2 ($\pm$)-**45** matched those of dihydroconduramines previously synthesised (Scheme 93).



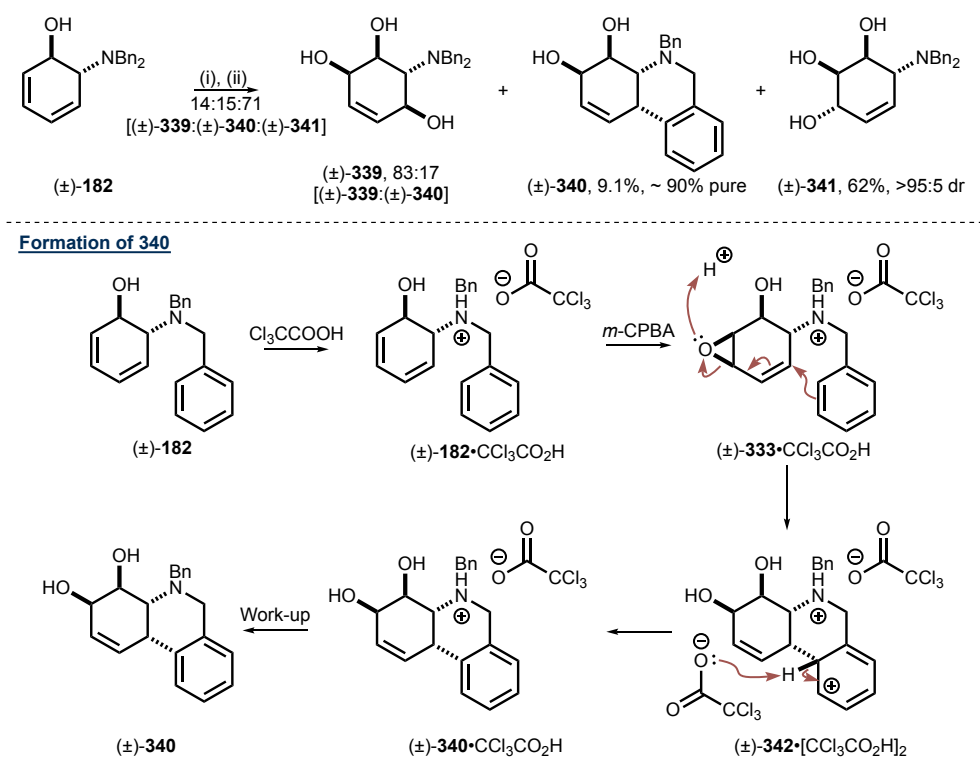
Scheme 93. Reagents and conditions: (i) H₂ (1 atm), Pd(OH)₂/C, MeOH, rt, 24 h.

As before, the same compounds were obtained during the epoxidation of (±)-179. The ratio of the reaction between hydroxyl-directed *versus* ammonium-directed epoxidations is 30:70 [(±)-16:((±)-17+(±)-27+(±)-29)] and confirms that the ammonium moiety is a superior directing group than the hydroxyl group.

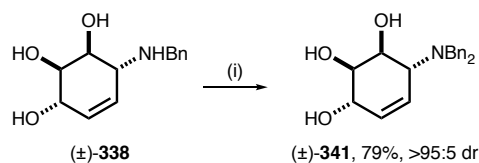
6.5.3 Epoxidation of (±)-182

As before, investigation of the resistance of (±)-182 against aromatization under CCl₃CO₂H condition was undertaken by ¹H NMR spectroscopic analyses and, once again, no trace of other aromatic species than benzylic protons were visualised after 20 min. Then, addition of *m*-CPBA to the crude reaction mixture gave after 1 h a complex mixture (no trace of (±)-182•CCl₃CO₂H) and after 19.5 h any modification of the spectrum could be noticed. Quenching of the potential trace of *m*-CPBA left followed by subsequent methanolysis afforded a 14:15:71 mixture of (±)-339, (±)-340 and (±)-341, respectively. Purification *via* column chromatography gave impure diol (±)-340 in 9.1% yield (~ 90% pure), an 83:17 mixture of triol (±)-339 and (±)-340, respectively, and (±)-341 in 62% yield and >95:5 dr

(Scheme 94). Chemoselective *N*-benzylation of ($\pm$)-**338** in presence of BnBr, i Pr₂NEt, DMAP in CH₂Cl₂ at rt for 24 h gave an authentic sample of ($\pm$)-**341** in 79% yield and >95:5 dr (Scheme 95). 1D and 2D NMR spectroscopic analyses of ($\pm$)-**340** allowed the assignment of the regiochemistry ($\delta_{C(1)H} = 32.2$ ppm, $\delta_{N(CH^2Ph)} = 46.5$ ppm, $\delta_{N(CH_2Ph)} = 58.2$ ppm). Stereochemistry of ($\pm$)-**339**, ($\pm$)-**340** and ($\pm$)-**341** were assigned by ¹H NMR spectroscopic ³*J* coupling constant analyses [($\pm$)-**339**: ³*J*_{1,2} = 9.2 Hz, ³*J*_{2,3} = 11.1 Hz, ³*J*_{3,4} = 4.4 Hz/ ($\pm$)-**340**: ³*J*_{1,2} = 6.2 Hz, ³*J*_{2,3} = 11.2 Hz, ³*J*_{3,4} = 4.0 Hz/ ($\pm$)-**341**: ³*J*_{1,2} = 7.9 Hz, ³*J*_{2,3} = 3.0 Hz, ³*J*_{3,4} = 3.0 Hz], (Figure 79)]. Formation of ($\pm$)-**340** is consistent with an hydroxyl-directed epoxidation, followed by an S_N' type ring-opening with the participation of the aromatic ring of the *N,N*-dibenzylammonium moiety.



Scheme 94. Reagents and conditions: (i) CCl_3CO_2H , CH₂Cl₂, rt, 20 min, then *m*-CPBA, rt; (ii) K₂CO₃, MeOH, rt, 24 h.



Scheme 95. Reagents and conditions: (i) BnBr, i Pr₂NEt, DMAP, CH₂Cl₂, rt, 24 h.

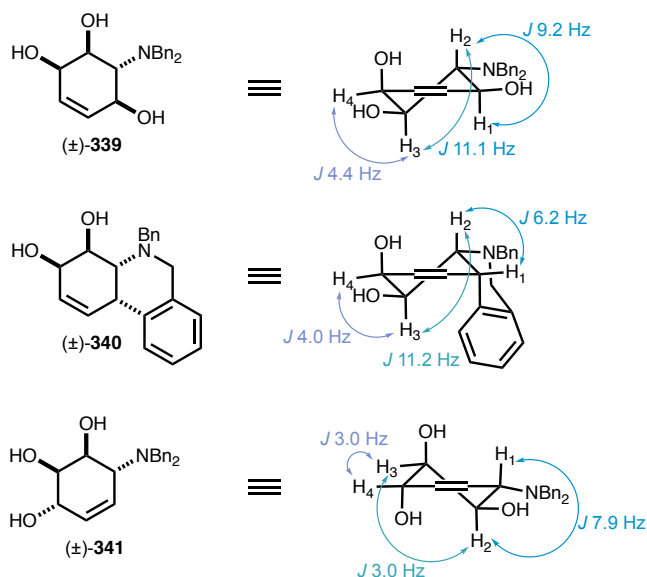
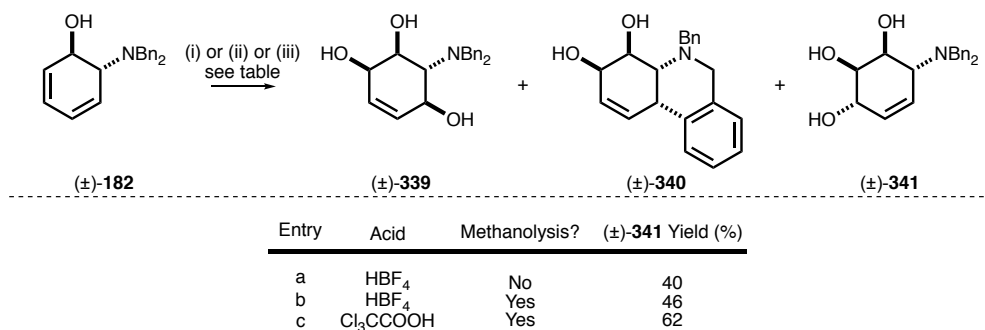


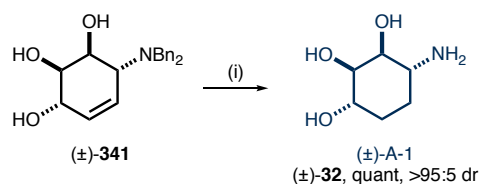
Figure 79. ^1H NMR 3J Coupling constants of (±)-339, (±)-340 and (±)-341.

When $\text{CCl}_3\text{CO}_2\text{H}$ was replaced by HBF_4 (40% aq), epoxidation of (±)-182 gave a 16:20:64 mixture of (±)-339, (±)-340, and (±)-341, respectively. Purification *via* column chromatography gave (±)-341 in 40% yield (>95:5 dr) and a 29:71 mixture of (±)-339 and triol (±)-340, respectively, identified among an impure complex mixture. Analysis of the ^1H and ^{13}C NMR spectroscopy crude reaction mixture showed a variation of the chemical shift and a broadness of the peaks suggesting presence of acid after work-up (i.e., NaOH aq).²³ Methanolysis after epoxidation of (±)-182 was next carried out to obtain the free-salt products but only showed a slightly improvement (Scheme 96).



Scheme 96. Reagents and conditions: (i) HBF_4 (40% aq), CH_2Cl_2 , rt, 5 min, then *m*-CPBA, rt, 21 h; (ii) HBF_4 (40% aq), CH_2Cl_2 , rt, 5 min, then *m*-CPBA, rt, 21 h, then K_2CO_3 , MeOH, rt, 24 h; (iii) $\text{CCl}_3\text{CO}_2\text{H}$, CH_2Cl_2 , rt, 5 min, then *m*-CPBA, rt, 21 h, then K_2CO_3 , MeOH, rt, 24 h.

Hydrogenolysis of ($\pm$)-**341** with $\text{Pd}(\text{OH})_2/\text{C}$ under an atmosphere of H_2 gave ($\pm$)-dihydroconduramine A-1 ($\pm$)-**32** in quantitative yield and >95:5 dr (Scheme 97).



Scheme 97. Reagents and conditions: (i) H_2 (1 atm), $\text{Pd}(\text{OH})_2/\text{C}$, MeOH, rt, 24 h.

In this case, neglecting any background (non-directed epoxidation reactions), it is suggested that the three products come from a diastereoselective hydroxyl-directed epoxidation followed by an $\text{S}_{\text{N}}2$ -type ring opening to provide ($\pm$)-**341** and an S_{N}' -type ring-opening by H_2O or participation of the benzyl substituent to give ($\pm$)-**339** and ($\pm$)-**340**, respectively. The ratio of the reaction between hydroxyl-directed *versus* ammonium-directed epoxidations is thus 100:0 and is consistent with the results obtained by Davies and co-workers: the hydroxyl group behaves as a superior directing group than the N,N -dibenzylammonium moiety (Figure 80).

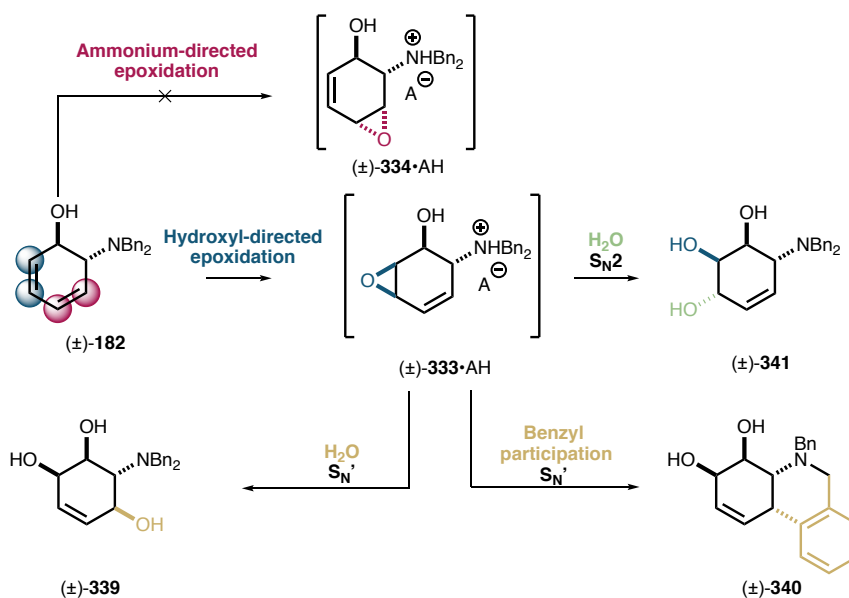


Figure 80. Epoxidation of ($\pm$)-**182**.

6.6 Olefinic oxidation on (±)-176, (±)-179 and (±)-182: discussion

Epoxidation of tertiary cyclic allylic amine/allylic alcohol (±)-182 proceeds with high diastereocontrol: the hydroxyl functionality acts as the superior directing group and directs the *syn*-epoxidation. Epoxidations of primary and secondary allylic amines/allylic alcohols (±)-176 and (±)-179, respectively, are directed by the two functionalities: the hydroxyl group and the ammonium moiety. In both cases, the ammonium and *N*-benzylammonium moieties show superior directing abilities [30:70, (±)-329•AH:(±)-330•AH and 21:79, (±)-331•AH:(±)-332•AH, respectively] compared to the hydroxyl group. In conclusion, the *N*-benzylammonium moiety acts as a better directing group than ammonium moiety, which is a better director than the hydroxyl group and the hydroxyl functionality acts as a better directing group than the *N,N*-dibenzylammonium moiety. The results obtained with (±)-179 and (±)-182 are in total agreement with those obtained by Davies and co-workers and previously described (Figure 81).

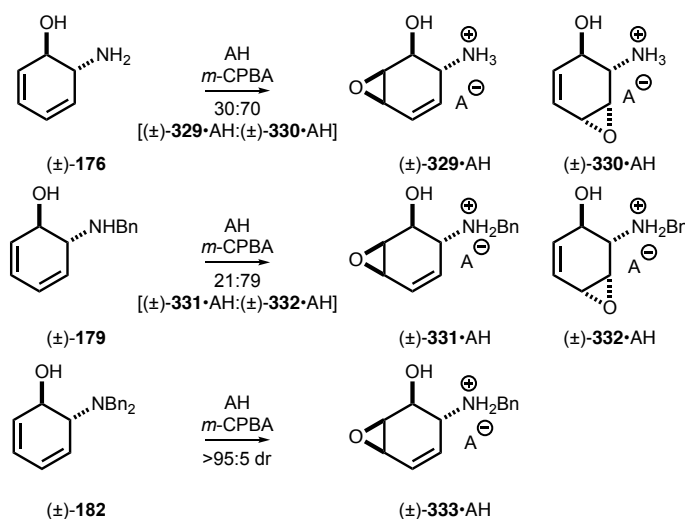


Figure 81. Summary of the epoxidation of racemic (±)-176, (±)-179 and (±)-182. [AH = CCl₃CO₂H, HBF₄ (40% aq)].

6.7 Conclusion

Epoxidations of racemic primary, secondary and tertiary cyclic allylic amines/allylic alcohols ($\pm$)-**176**, ($\pm$)-**179** and ($\pm$)-**182**, prepared from benzene oxide **292**, have been investigated. Any background (non-directed epoxidation reactions) was ignored and thus two competitive pathways were highlighted: hydroxyl-directed *versus* ammonium-directed epoxidation providing, respectively, two epoxides *in situ*. Studies to analyse the regiochemistry of their ring-opening allowed access to the ratio of the epoxidation in each case and measure the superior ability of the two functionalities.

6.8 Notes and references

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- (13) 2D TLC analysis of benzene oxide **292** was carried out and showed decomposition on silica. (14) Formation of phenol **321** over time remains unclear: it could come from decomposition of either product ($\pm$)-**179** or benzene oxide **292**.
- (15) It was decided, due to possible chelation between the lewis acid and MeOH, not to investigate the acid-catalyzed ring-opening of benzene oxide **292** in MeOH with NH₂Bn.
- (16) Brennan, M. B.; Csatayová, K.; Davies, S. G.; Fletcher, A. M.; Green, W. D.; Lee, J. A.; Roberts, P. M.; Russell, A. J.; Thomson, J. E. *J. Org. Chem.* **2015**, *80*, 6609–6618.
- (17) It was first envisaged to perform the epoxidation in presence of TsOH (non-labile functional group once inserted into the molecule) but aromatization of ($\pm$)-**179** to benzyaniline was observed under these specific conditions.
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Chapter 7

Asymmetric Syntheses of Conduramines A-1, A-2, E-2 and F-2

This chapter describes the deployment of an asymmetric synthetic route to access six enantiopure conduramines (–)-A-1 **16**, (–)-A-2 **17**, (–)-E-2 **27** and (–)-F-2 **29** from enantiopure **342** and (+)-A-1 *ent*-**16** and (+)-E-2 *ent*-**27** from enantiopure **343** using the olefinic epoxidation methodology as a key step (Figure 82).

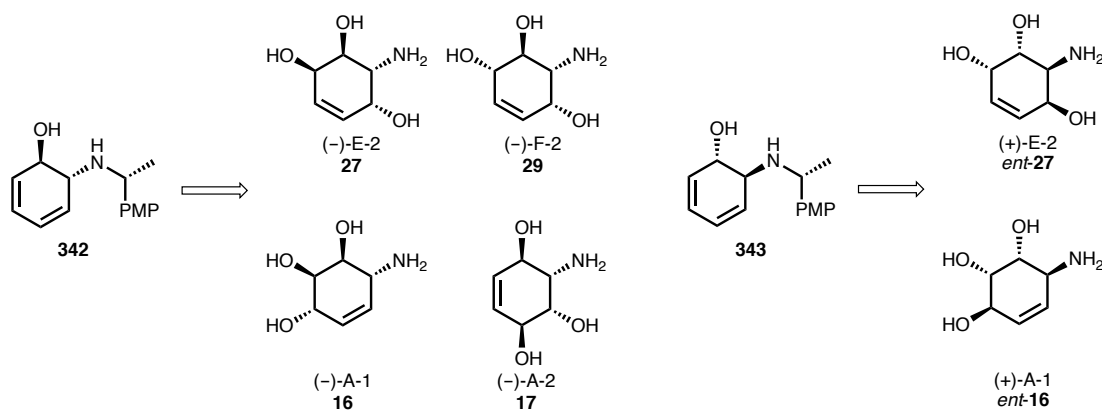


Figure 82. Structures of the six synthesised enantiopure conduramines (–)-A-1 **16**, (+)-A-1 *ent*-**16**, (–)-A-2 **17**, (–)-E-2 **27**, (+)-E-2 *ent*-**27** and (–)-F-2 **29**. [PMP = *para*-methoxyphenyl]

7.1 Chapter aims

The aims of this chapter is to access enantiopure conduramines A-1 **16**, A-2 **17**, E-2 **27** and F-2 **29** from enantiopure substrates **342** and **343**, derived from ring-opening of benzene oxide **292**, with the enantiopure amine (*R*)- α -methyl-*para*-methoxybenzylamine (*R*)-**354** and to investigate the surrogacy (i.e., behaviour under the same conditions) of enantiopure substrates **342**, **343**, **348** and **351** as counterparts to the enantiomers **179**, *ent*-**179**, **182** and *ent*-**182**, respectively (Figure 83).

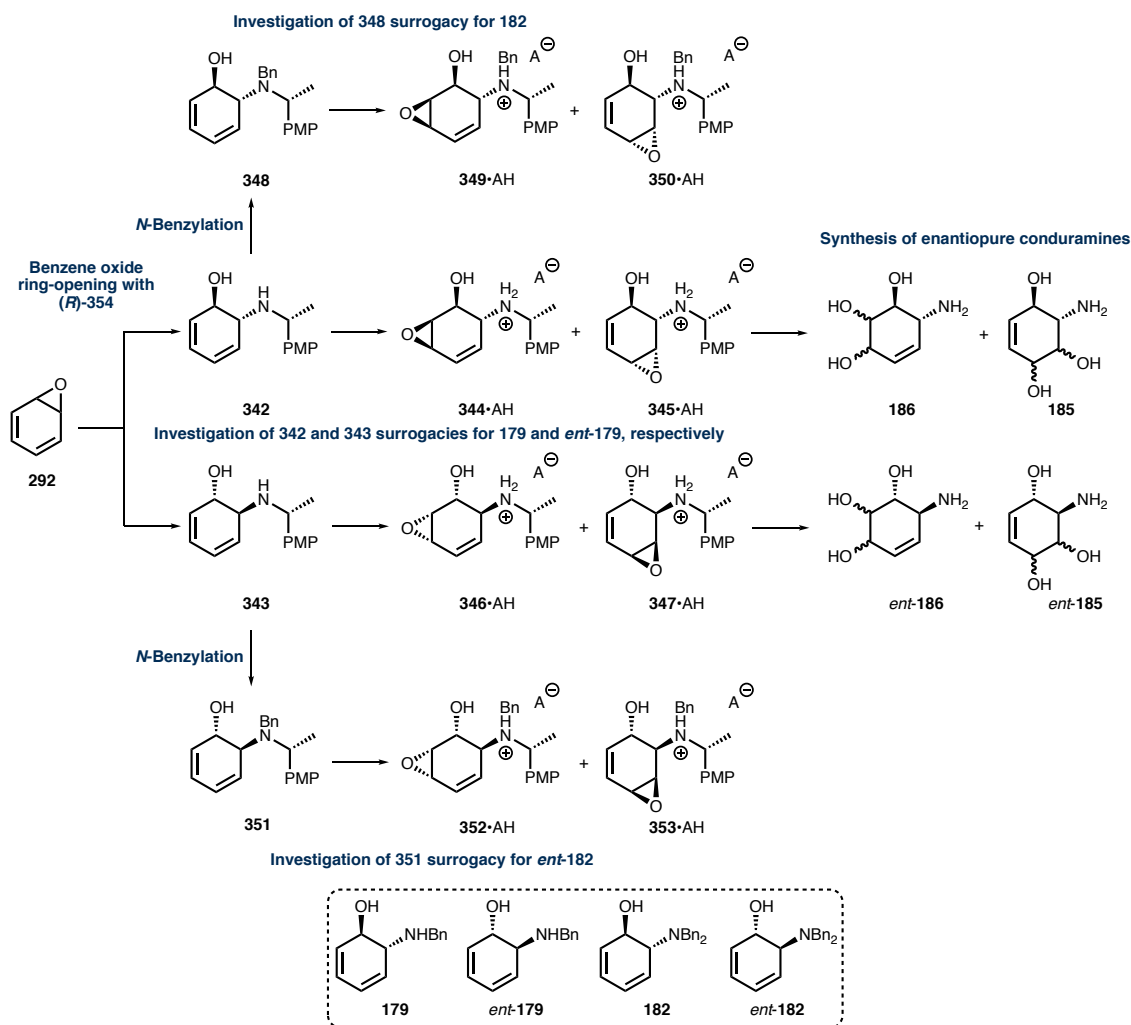


Figure 83. Chapter aims. [PMP = *para*-methoxyphenyl]

7.2 Syntheses of enantiopure surrogates

According to the previous results, it was possible to access racemic conduramines from benzene oxide **292** in 2 steps: ring-opening with NH_4OH and epoxidation of ($\pm$)-**176** under acidic conditions. Due to the relatively modest regio- and stereoselectivity of the reaction (a mixture of ammonium- and hydroxyl-directed epoxidations and mixture of pathways for the ring-opening), a non-separable mixture of free conduramines was obtained. Nevertheless, it was shown that the presence of an *N*-protecting group (i.e., *N*-benzyl versus *N,N*-dibenzyl) in the substrates ($\pm$)-**179** and ($\pm$)-**182** allowed separation of the different products. It was thus envisaged to access enantiopure conduramines from

benzene oxide **292** *via* ring-opening with an enantiopure chiral amine followed by separation of the diastereoisomers, then epoxidation and *N*-deprotection. Due to the presence of a C=C double bond, removal of the *N*-protecting group by hydrogenolysis could not be considered. The choice of the enantiopure chiral amine was thus pivotal to the success of the proposed protocol and (*R*)- α -methyl-*para*-methoxybenzylamine (*R*)-**354**, receptive to *N*-deprotection under acidic conditions, was selected (Figure 84).

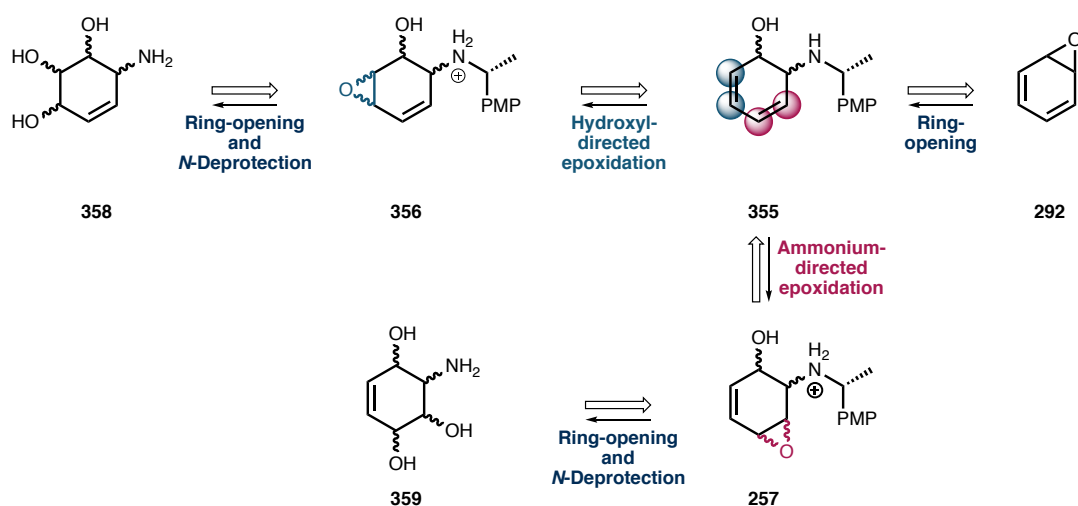
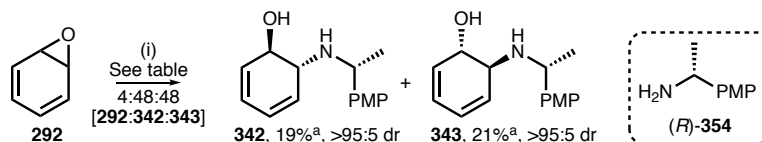


Figure 84. Retrosynthesis of conduramines **358** and **359**.

7.2.1 Preparation of enantiopure substrates **342** and **343**

The ring-opening of benzene oxide **292** with 10 equiv of (*R*)-**354** was monitored in MeOH-*d*₄ by ¹H NMR spectroscopic analyses. After 42.5 h, a 16:42:42 mixture of starting material **292**, **342** and **343**, respectively, was observed (phenol peaks could not be quantified as they were overlapping with the peaks for (*R*)- α -methyl-*para*-methoxybenzylamine). After 3 days, a 4:48:48 mixture of starting material **292**, **342** and **343**, respectively, was obtained. Separation *via* column chromatography gave **342** in 19% yield and **343** in 21% yield, both in >95:5 dr, and a 56:44 mixture of **342** and **343**, respectively, in 21% yield (Scheme 98).



Scheme 98. Reagents and conditions: (i) (R) -**354**, $\text{MeOH-}d_4$, 66°C , 72 h. [^a a 56:44 mixture of **342** and **343**, respectively, was also obtained in 21% yield].

The relative configuration within **343** was unambiguously established by single crystal X-ray diffraction analysis.¹ The absolute $(1S,2S,\alpha R)$ -configuration was then assigned from the known (R) -configuration of the α -methyl-*para*-methoxybenzyl stereogenic centre (Figure 85). The *anti*-configurations within **342** and **343** were also assigned by ^1H NMR coupling constant analyses (**342**: $^3J_{1,2} = 11.5\text{ Hz}$ / **343**: $^3J_{1,2} = 12.9\text{ Hz}$): these results were both in agreement with large ^1H NMR 3J coupling constants in solution in $d_1\text{-CHCl}_3$ and were also consistent with those obtained in the solid state, where the dihedral angle was approximately 180° (Figure 86).

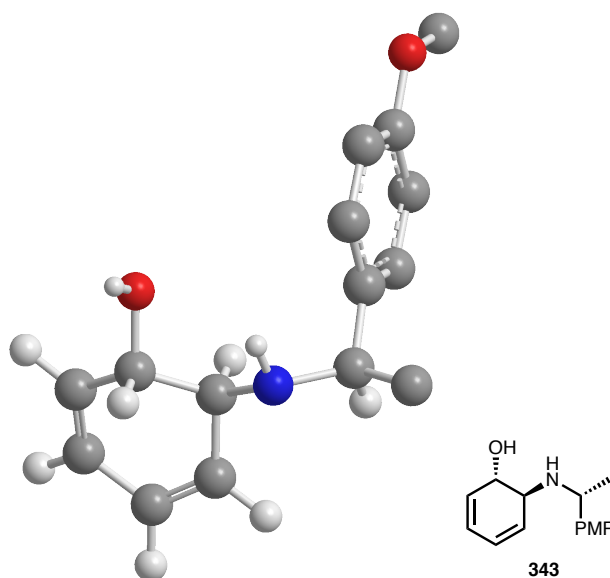


Figure 85. Chem3D representation of the X-ray crystal structure of **343** (selected H atoms are omitted for clarity).

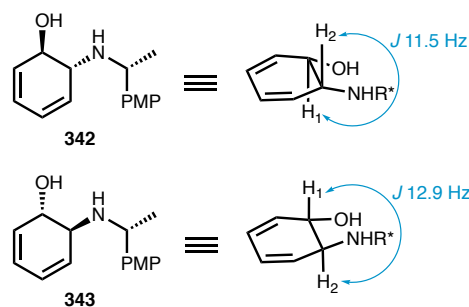


Figure 86. ^1H NMR 3J coupling constant analyses of **342** and **343**. [$\text{R}^* = \alpha$ -methyl-*para*-methoxybenzyl substituent]

7.2.2 Preparation of enantiopure substrates **348** and **351**

According to the previous results, racemic ($\pm$)-**182** was the only substrate to undergo diastereoselective hydroxyl-directed epoxidation. Although the ring-opening was not regio- and stereoselective, it was decided to synthesise enantiopure tertiary allylic amine/allylic alcohols **348** and **351** and investigate their surrogacies for the enantiomers **182** and *ent*-**182**, i.e., analysis of their behaviour under the same conditions (Figure 87).

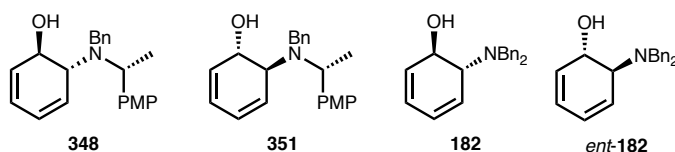
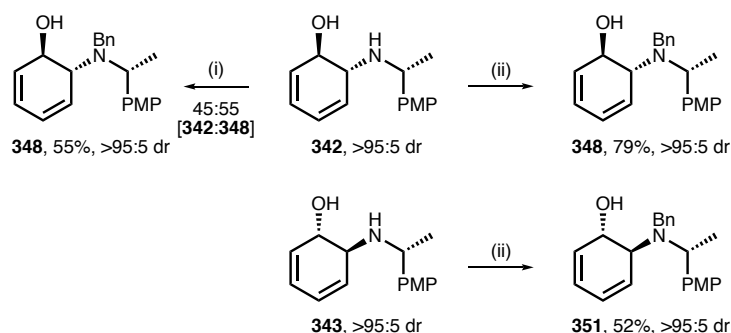


Figure 87. Structures of **348** and **351**, potential surrogates for enantiopure **182** and *ent*-**182**.

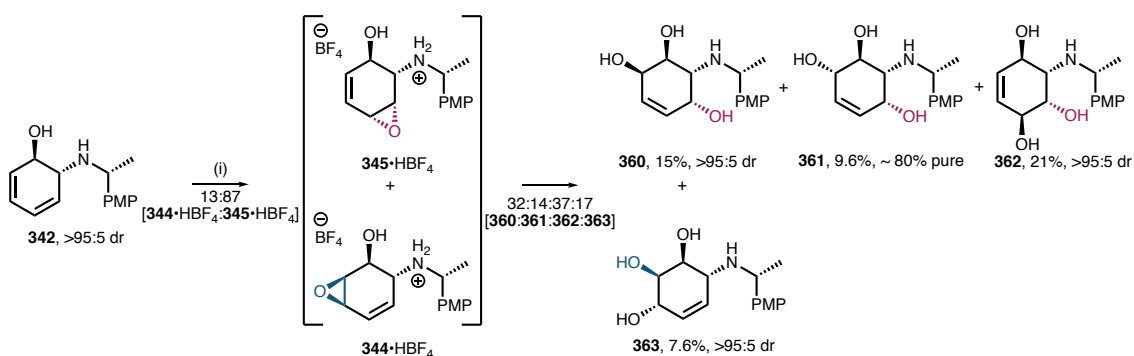
Chemoselective *N*-benzylation of **342** with BnBr in presence of Pr_2NEt and DMAP in CH_2Cl_2 at rt for 24 h gave a 55% conversion into **348**, which was isolated by column chromatography in 55% yield and >95:5 dr. When *N*-protection of **342** was performed in MeCN using BnBr and K_2CO_3 , full conversion was reached and afforded **348** in 73% yield as a single diastereoisomer. When **343** was subjected to the same optimised conditions, **351** was synthesised in 52% yield and >95:5 dr (Scheme 99).



Scheme 99. Reagents and conditions: (i) BnBr, Pr_2NEt , DMAP, CH_2Cl_2 , rt, 24 h; (ii) BnBr, K_2CO_3 , MeCN, 82 °C, 24 h

7.3 Epoxidation of **342**: results

Epoxidation of **342** in the presence of HBF_4 (40% aq) with *m*-CPBA (1 equiv) in CH_2Cl_2 at rt for 21 h gave a 32:14:37:17 mixture of triols **360**, **361**, **362** and **363**, respectively. Purification *via* preparative TLC gave **360** in 15% yield, **361** in 9.6% yield (~80% pure), **362** in 21% yield and **363** in 7.6% yield (Scheme 100). The regiochemistries within these four triols were assigned by common NMR spectroscopic techniques. The relative configurations within **360** and **361** were assigned by ^1H NMR 3J coupling constant analyses: **360**: $^3J_{1,2} = 4.3$ Hz, $^3J_{2,3} = 10.7$ Hz, $^3J_{3,4} = 4.2$ Hz and **361**: $^3J_{1,2} = 4.1$ Hz, $^3J_{2,3} = 10.8$ Hz, $^3J_{3,4} = 7.8$ Hz, (Figure 88).



Scheme 100. Reagents and conditions: (i) HBF_4 (40% aq), *m*-CPBA, CH_2Cl_2 , rt, 21 h.

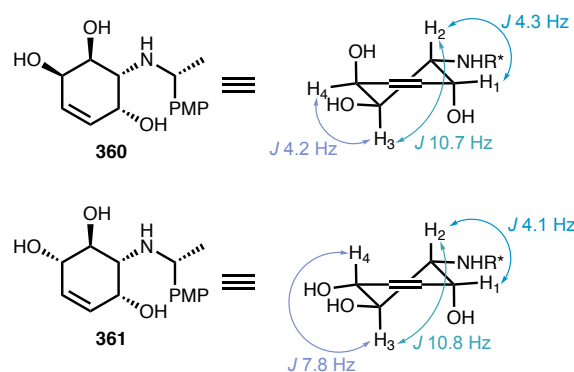


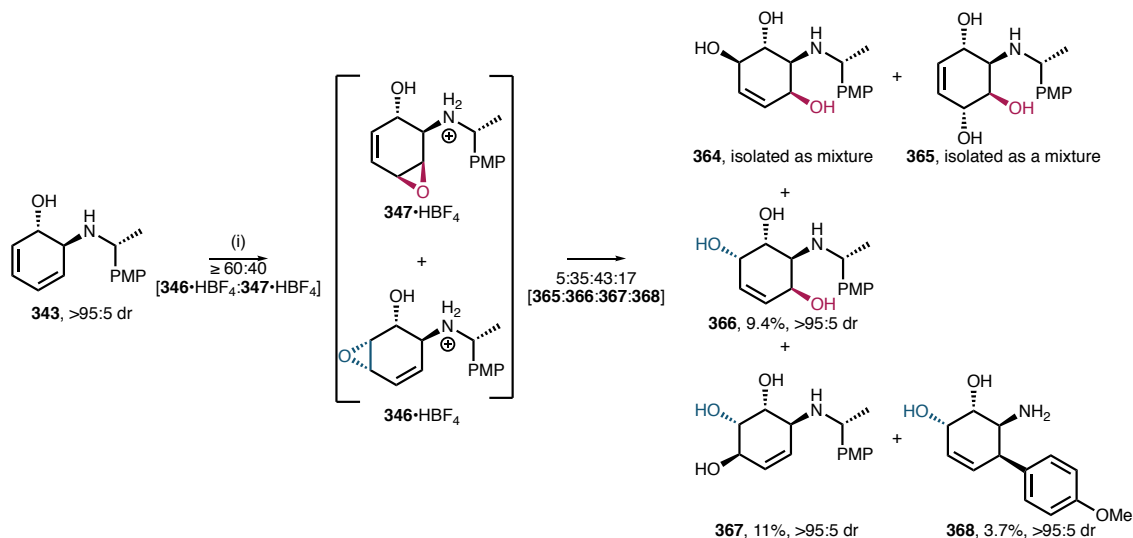
Figure 88. 3J coupling constant analyses of **360** and **361**. [$R^* = \alpha$ -methyl-*para*-methoxybenzyl substituent].

The ratio in the epoxidation (i.e., 13:87 [**344**• HBF_4 :**345**• HBF_4]) and the outcome after ring-opening are similar to those obtained during the epoxidation of racemic ($\pm$)-**179**. By extension, it is thus suggested that **360** and **361** come from an ammonium-directed epoxidation of **342** followed by S_N' -type ring-opening. Triols **362** and **363** come from an ammonium- and an hydroxyl-directed epoxidation, respectively, followed by, in both cases, an $\text{S}_\text{N}2$ -type ring-opening.

7.4 Epoxidation of **343**: results

When epoxidation was performed on **343** using the same conditions, a 5:35:43:17 mixture of **365**, **366**, **367**, and **368**, respectively, was obtained. It was presumed that a trace of **364** was also present in the ^1H NMR spectrum of the crude reaction mixture as it was subsequently isolated after purification (<5%). Purification *via* preparative TLC gave **366**, **367**, and **368** in 9.4%, 11% and 3.7% yields, all >95:5 dr, an 18:82 mixture of **364** and **365**, respectively, in 17% yield and an 7:85:8 mixture of **364**, **365**, and **368**, respectively (Scheme 101). The structures of triols **364**, **365**, **366** and **367** were determined by common NMR spectroscopic techniques. By ^1H - ^1H COSY and ^1H - ^{13}C HSQC spectroscopic analyses, the identity and regiochemistry of **368** were also established ($\delta_{\text{C}(1)\text{H}} = 46.8$ ppm, $\delta_{\text{C}(2)\text{H}} = 52.3$ ppm, $\delta_{\text{C}(3)\text{H}} = 67.5$ ppm, $\delta_{\text{C}(3)\text{H}} = 71.7$ ppm). ^1H - ^{13}C HMBC analysis confirmed the structure found, thanks to presence of correlations between the aromatic protons and carbon C(1).

The relative configurations within **364**, **366**, and **368** were assigned by ^1H NMR 3J coupling constant analyses: **364**: $^3J_{1,2} = 4.1$ Hz, $^3J_{2,3} = 10.8$ Hz, $^3J_{3,4} = 7.7$ Hz, **366**: $^3J_{1,2} = 4.1$ Hz, $^3J_{2,3} = 10.8$ Hz, $^3J_{3,4} = 4.1$ Hz, **368**: $^3J_{1,2} = 5.9$ Hz, $^3J_{2,3} = 10.5$ Hz, $^3J_{3,4} = 4.3$ Hz, (Figure 89).



Scheme 101. Reagents and conditions: (i) HBF_4 (40% aq), *m*-CPBA, CH_2Cl_2 , rt, 21 h.

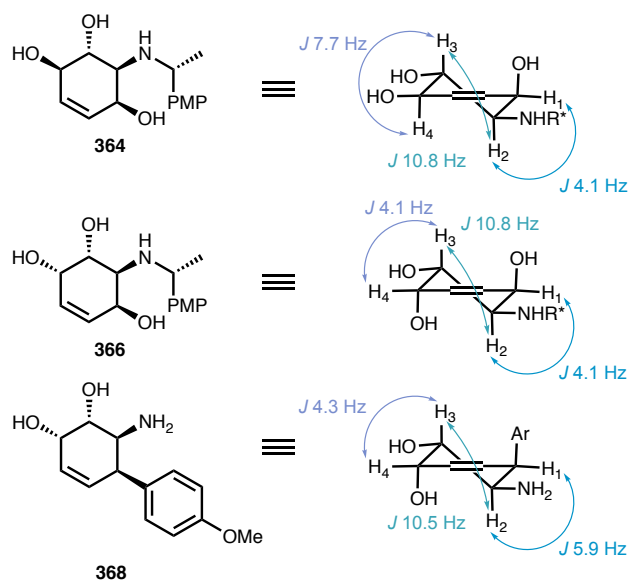


Figure 89. 3J coupling constant analyses of **364**, **366** and **368**. [R^* = α -methyl-*para*-methoxybenzyl substituent, Ar = *para*-methoxyphenyl].

The results obtained in this case are different: the diastereoselectivity of the epoxidation and the regioselectivity of the ring-opening differ. The origin of **366** remains unclear: this triol can either be the product of the $\text{S}_{\text{N}}2$ -type ring opening of **346**• HBF_4 or **347**• HBF_4 . The dr of the epoxidation is thus $\geq 60:40$ [**346**• HBF_4 : **347**• HBF_4]. The outcome of this reaction

suggested that the presence and relative configuration within the α -methyl-*para*-methoxybenzyl stereogenic centre have an effect on the diastereoselectivity of the reaction. The origins of the other products are, however, identifiable: **365** and **367** come from an ammonium- and an alcohol-directed epoxidation, respectively, followed by an S_N2 -type ring-opening in both cases. **364** is the product of an ammonium directed epoxidation followed by an S_N' -type ring-opening. Finally, it is assumed that the formation of **368** occurs from **343** via a mechanism involving hydroxyl-directed epoxidation followed by S_N' -type attack of the aromatic ring with the participation of the electron-donating methoxy group, aromatization with iminium formation and subsequently hydrolysed (Scheme 90).

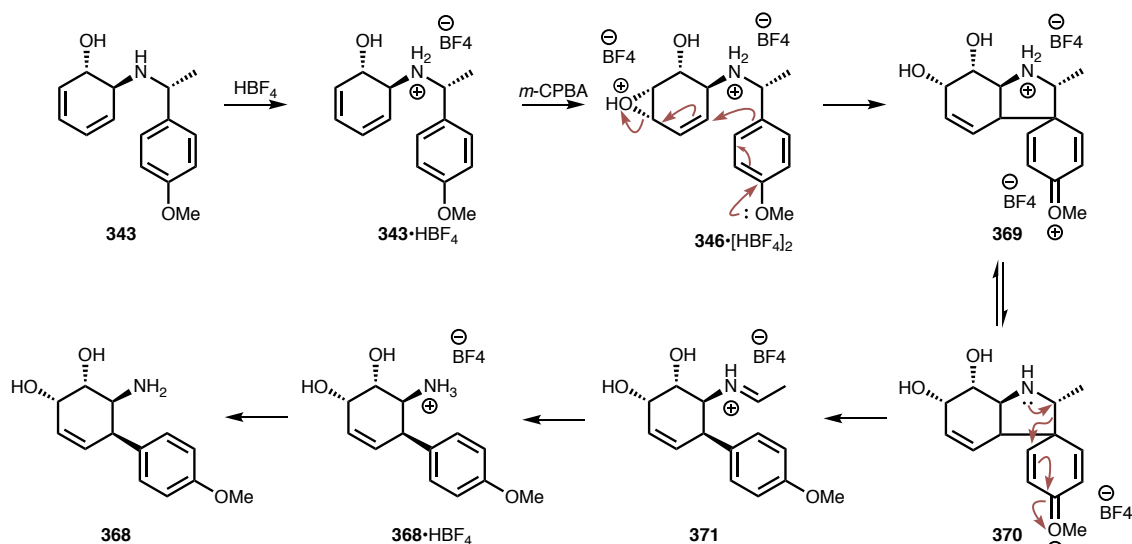
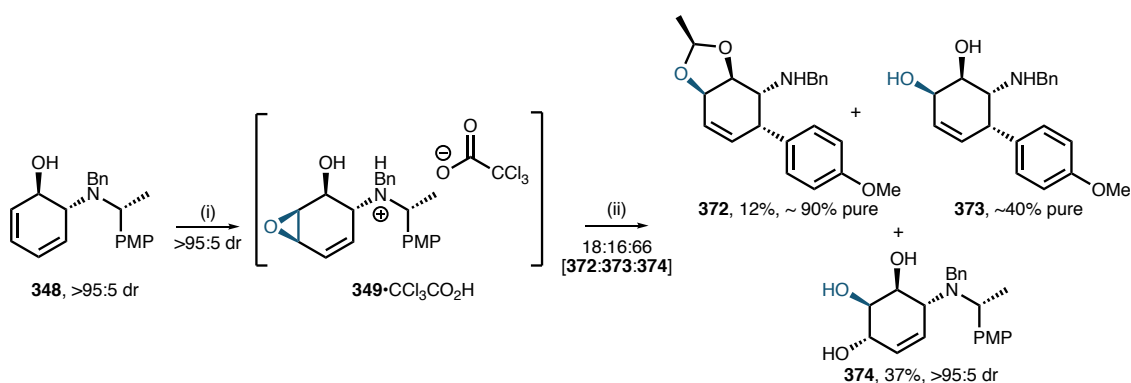


Figure 90. Formation of **368**.

7.5 Epoxidation of **348**: results

Epoxidation of **348** with *m*-CPBA (1 equiv) in presence of $\text{CCl}_3\text{CO}_2\text{H}$ followed by subsequent methanolysis gave an 18:16:66 mixture of **372**, **373**, and **374**, respectively.² Purification *via* column chromatography gave an impure sample of **372** in 12% (~90% pure), an impure sample of **373** (~40% pure) and **374** in 37% and >95:5 dr (Scheme 102). The structures of **372**, **373** and **374** were determined by NMR spectroscopic techniques. ^1H NMR 3J Coupling constant analyses allowed assignment of the configurations within **372**,

373 and **374**: **372**: $^3J_{1,2} = 5.1$ Hz, $^3J_{2,3} = 8.6$ Hz, $^3J_{3,4} = 6.5$ Hz, **373**: $^3J_{1,2} = 5.8$ Hz, $^3J_{2,3} = 11.0$ Hz, $^3J_{3,4} = 4.4$ Hz, **374**: $^3J_{1,2} = 8.5$ Hz, $^3J_{2,3} = 2.4$ Hz, $^3J_{3,4} = 3.1$ Hz. As before, by 1D and 2D spectroscopic analyses of **372** and **373**, carbon C(1) chemical shifts at 42.6 ppm and 43.7 ppm suggested the presence of a benzylic carbon (Figure 91). The presence of a ketal functionality inserted in a five-membered ring within **372** was confirmed by ^{13}C NMR spectroscopic analysis ($\delta_{\text{C(OH)}} = 101.2$ ppm). It was assumed that an acetalisation of the diol within **373** with acetaldehyde, formed *in situ*, led to the formation of **372**. According to precedent in literature, it was assumed that the stereocentre within the ketal functionality would be found under thermodynamic conditions to give the most stable product.³



Scheme 102. Reagents and conditions: (i) $\text{CCl}_3\text{CO}_2\text{H}$, CH_2Cl_2 , rt, 5 min, then *m*-CPBA, rt; (ii) K_2CO_3 , MeOH, rt, 24 h.

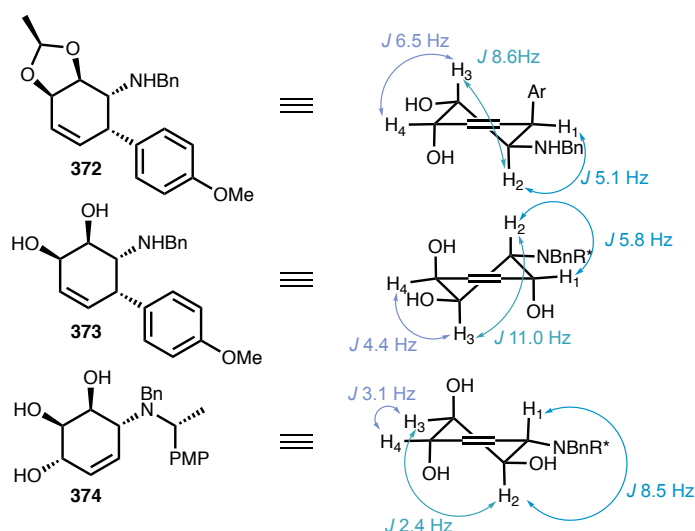
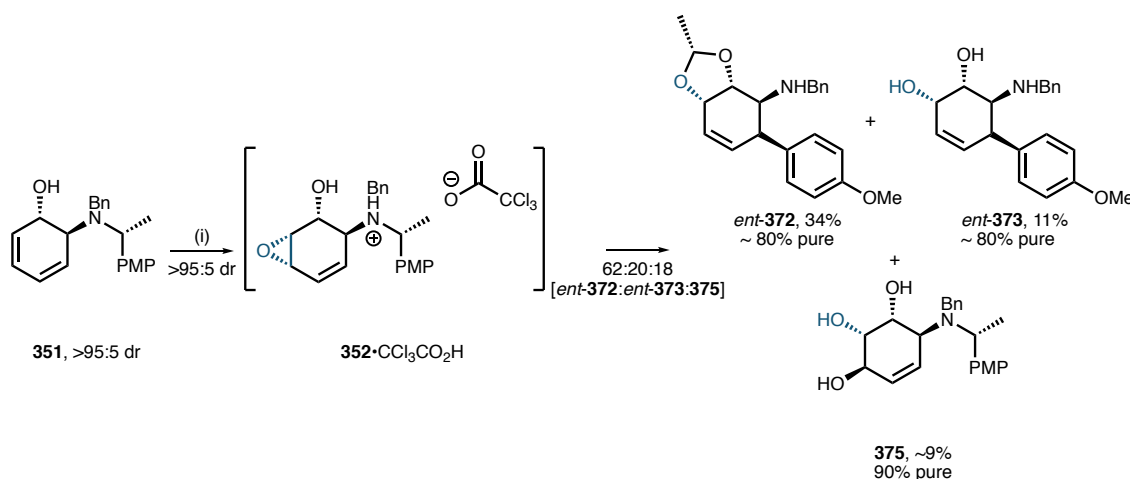


Figure 91. 3J coupling constant analyses of **372**, **373** and **374**. [$\text{R}^* = \alpha$ -methyl-*para*-methoxybenzyl substituent, Ar = *para*-methoxyphenyl]

By analogy to the racemic *N,N*-benzyl series ($\pm$)-**182**, it is suggested that **372** and **373** and **374** come from an hydroxyl-directed epoxidation of **348**. S_N2' -type ring opening of epoxide **349**• $\text{CCl}_3\text{CO}_2\text{H}$ led to **372** and **373** whilst S_N2 -type ring-opening provides **374**. Formation of epoxide **349**• $\text{CCl}_3\text{CO}_2\text{H}$ occurs with complete selectivity ($>95:5$ dr).

7.6 Epoxidation of **351**: results

When epoxidation was applied to **351**, a 62:20:18 mixture of *ent*-**372**, *ent*-**373**, and **375** was obtained and *ent*-**372** was isolated in 34% yield as well as *ent*-**373** in 11% yield, both $\sim 80\%$ pure, and **375** as an impure sample ($\sim 90\%$ pure).⁴ Analysis of the 3J coupling constants of **375** was inconclusive. The (1*S*,2*R*,3*S*,4*R*, α *R*)-configuration within **375** was assigned by analogy with the results obtained with the diastereomeric series **348**. As before, the epoxidation of **351** provides epoxide **352**• $\text{CCl}_3\text{CO}_2\text{H}$ as a single diastereoisomer ($>95:5$ dr), which leads to the formation of **375** by S_N2 -type ring-opening (Scheme 103).



Scheme 103. Reagents and conditions: (i) $\text{CCl}_3\text{CO}_2\text{H}$, CH_2Cl_2 , rt, 5 min, then *m*-CPBA, rt; (ii) K_2CO_3 , MeOH, rt, 24 h.

7.7 Epoxidation of **342**, **343**, **348** and **351**: discussion

It was assumed that any background (non-directed epoxidation reactions) was negligible during these epoxidations. The ratio of the hydroxyl- *versus* ammonium-directed epoxidation of **342** (13:87 dr) compared to the racemic case [21:79 dr, ($\pm$)-**179**] suggests that the relative configuration within the α -methyl-*para*-methoxybenzyl stereogenic centre within **342** has a negligible effect on the diastereoselectivity of the epoxidation. However, comparison of the ratio of the hydroxyl- *versus* ammonium-directed epoxidation of **343** ($\geq$ 60:40) compared to the racemic one [21:79 dr, ($\pm$)-**179**] highlights differences and it is thus assumed that in this diastereomeric series, the relative configuration within the α -methyl-*para*-methoxybenzyl stereogenic centre within **343** has a significant effect on the diastereoselectivity of the epoxidation. In the former case (i.e., epoxidation of **342**), the *N*- α -methyl-*para*-methoxybenzylammonium moiety acts as a better directing group than the hydroxyl group whereas in the latter case (i.e., epoxidation of **343**), the hydroxyl functionality has a superior ability to direct than the ammonium moiety. Furthermore, as for racemic *N,N*-dibenzylated ($\pm$)-**182**, both reactions of **348** and **351** undergo exclusively hydroxyl-directed epoxidations i.e., >95:5 dr (Figure 92).

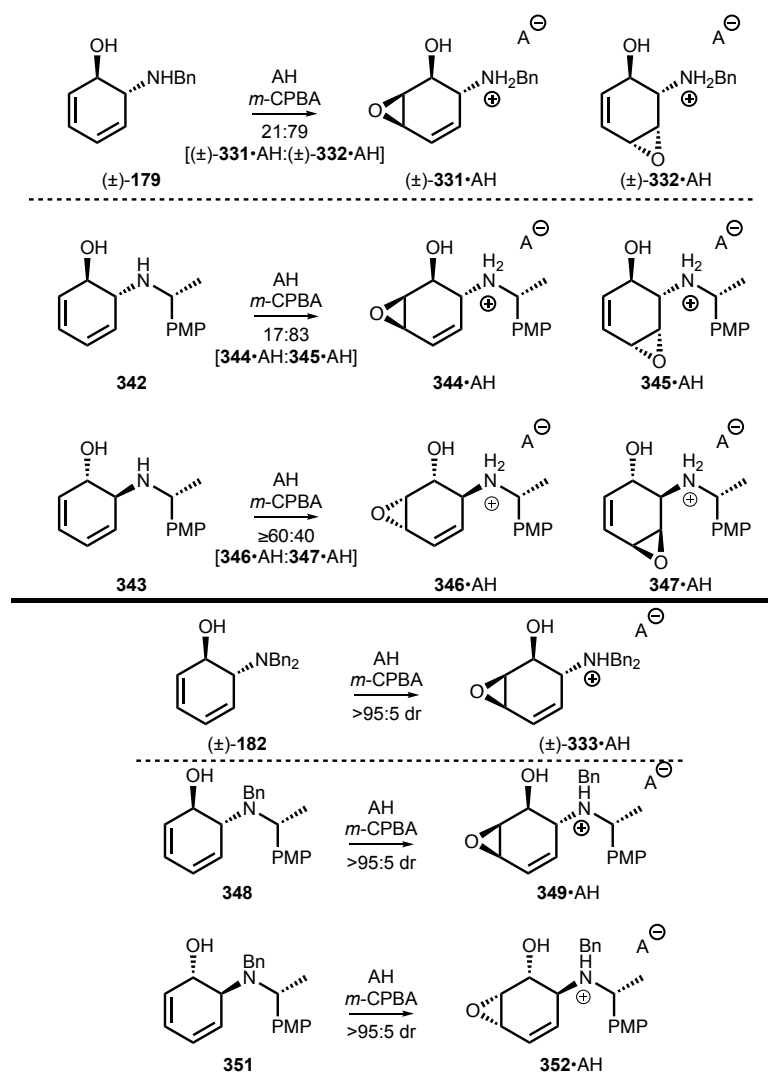


Figure 92. Summary of epoxidation of **342**, **343**, **348** and **351**.

Comparison of the ring-opening of the diastereomeric series **342** and **343** shows that intramolecular participation of the *N*-substituent ($S_E\text{Ar}$) alongside intermolecular hydrogenolysis occurs only for **343** (17:83 [*inter:intra*]). In the *N,N*-disubstituted diastereomeric series **348** and **351**, intramolecular as well as intermolecular ring-opening take place but discrepancies in the ratios are observed: 82:18 [*inter:intra*] for **348** and 34:66 [*inter:intra*] for **351**. These results also show that the two pairs (**342/348**) and (**343/351**) do not behave in a similar pattern. Indeed, although the former pair behaves in a similar process compared to the racemic one [i.e., $(\pm)\text{-179}/(\pm)\text{-182}$], the latter case shows differences in the behaviour compared to $[(\pm)\text{-179}/(\pm)\text{-182}]$. These results are in agreement

with the presence of and the relative configuration within the α -methyl-*para*-methoxybenzyl stereogenic centre having a significant effect during the reaction: in the transition state **TS8**, absence of steric effects between the methyl substituent and C(3)H allow the $\pi_{C(7)}$ -orbital of carbon C(7) to interfere with the $\pi_{C(6)}$ -orbital of carbon C(6) and thus an S_N' -type attack with participation of the aromatic ring. In the transition state **TS9**, however, the steric effects between the methyl substituent and the C(3)H prevent the aromatic to be favourably placed to promote an S_N' -type ring-opening (Figure 93).

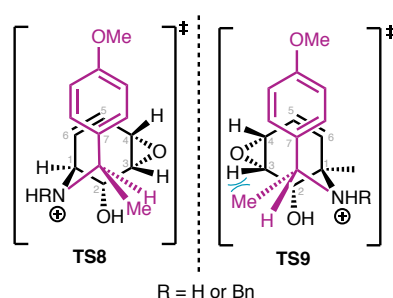
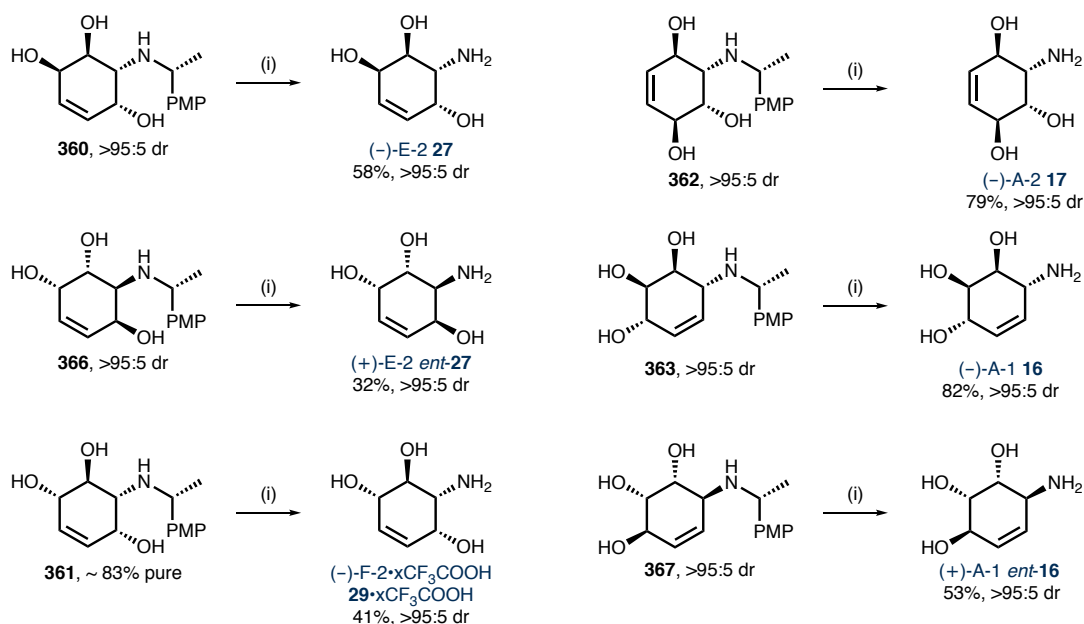


Figure 93. Possible transition states **TS8** and **TS9**.

7.8 Syntheses of conduramines

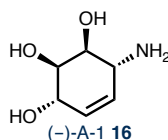
According to precedent in the literature, cleavage of an α -methyl-*para*-methoxybenzyl substituent can be performed under acid conditions.⁵ CF_3CO_2H -Mediated deprotections of **360**, **361**, **362**, **363**, **366** and **367** in presence of Et_3SiH at 50 °C for 18 h gave, after evaporation **27**• CF_3CO_2H , **29**• CF_3CO_2H , **17**• CF_3CO_2H , **16**• CF_3CO_2H , *ent*-**27**• CF_3CO_2H and *ent*-**16**• CF_3CO_2H , respectively. Purification *via* column chromatography using a highly basic eluent system⁶ gave conduramines (–)-A-1 **16**, (+)-A-1 *ent*-**16**, (–)-A-2 **17**, (–)-E-2 **27**, (+)-E-2 *ent*-**27** and (–)-F-2• xCF_3CO_2H **29**• xCF_3CO_2H , in 82%, 53%, 79%, 58%, 32% and 41%⁷ yields, respectively, all >95:5 dr ($0 \leq x \leq 1$ equivalents of CF_3CO_2H). Comparison of the 1H and ^{13}C NMR spectroscopic data of the enantiopure conduramines **16**, *ent*-**16**, **17**, **27** and *ent*-**27** with the 1H and ^{13}C spectroscopic data of the purified 30:50:5:15 mixture of free racemic **16** A-1, **17** A-2, **27** E-2 and **29** F-2 showed that conduramines (–)-A-1 **16**, (+)-A-1

ent-**16**, (–)-A-2 **17**, (–)-E-2 **27** and (+)-E-2 *ent*-**27** were isolated as free conduramines.⁸ However, discrepancies in the ¹H and ¹³C NMR spectroscopic data between (–)-conduramine F-2 and the racemic mixture of conduramines suggested that traces of CF₃CO₂H remained in the sample of (–)-conduramine F-2 (Scheme 104).



Scheme 104. Reagents and conditions: (i) Et₃SiH, CF₃CO₂H, 50 °C, 18 h.

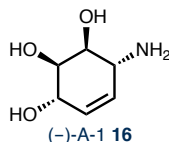
Furthermore, although conduramines (–)-A-2 **17**, (–)-E-2 **27** and (+)-E-2 *ent*-**27** are unknown from the literature, conduramines (–)-A-1 **16**, (+)-A-1 *ent*-**16** and (+)-F-2 *ent*-**29** have already been synthesised by other research groups.⁹ The spectroscopic data of these synthetic samples were compared to the reported data by the literature. The ¹H NMR spectroscopic data of (–)-A-1 **16** were in good agreement with those reported by Myeong *et al.*^{10,11} and Lu *et al.*^{12,13} ($-0.04 \leq \Delta\delta_{\text{H}} \leq +0.04$ and $-0.08 \leq \Delta\delta_{\text{H}} \leq 0.00$)¹⁴ (Table 3). The ¹³C NMR spectroscopic data of (–)-A-1 **16** were also in good agreement with those reported by Myeong *et al.*¹⁰ ($-0.4 \leq \Delta\delta_{\text{C}} \leq +0.2$)¹⁵ but were in poor agreement with those reported by Lu *et al.*¹² ($-0.7 \leq \Delta\delta_{\text{C}} \leq +1.8$)¹⁵ (Table 4). The specific rotation of the (–)-A-1 **16**, was found to be $[\alpha]_{\text{D}}^{25} -13.4$ (c 0.25 in MeOH), which is in moderate agreement with the literature values $\{[\alpha]_{\text{D}}^{25} -18.8$ (c 0.86 in MeOH)¹⁰; $[\alpha]_{\text{D}}^{25} -18.7$ (c 0.1 in MeOH)^{12}\}.}



	This work δ_H (400 MHz, d_2 -H ₂ O)	Synthetic ⁹ δ_H (700 MHz, d_2 -H ₂ O)	$\Delta\delta_H$
C(1) <i>H</i>	3.39 (br d, <i>J</i> 6.3)	3.40–3.46 (m)	–0.04
C(2) <i>H</i>	3.68 (dd, <i>J</i> 6.3, 2.5)	3.64 (dd, <i>J</i> 6.3, 2.5)	+0.04
C(3) <i>H</i>	3.80 (dd, <i>J</i> 4.8, 2.5)	3.82 (dd, <i>J</i> 4.8, 2.5)	–0.02
C(4) <i>H</i>	4.12–4.15 (m)	4.11 (dt, <i>J</i> 3.7, 1.7)	+0.02
C(5) <i>H</i> /C(6) <i>H</i>	5.67–5.73 (m)	5.66–5.76 (m)	–0.01

	This work δ_H (400 MHz, d_4 -MeOH)	Synthetic ¹¹ δ_H (600 MHz, d_4 -MeOH)	$\Delta\delta_H$
C(1) <i>H</i>	3.43 (br d, <i>J</i> 7.3)	3.51–3.52 (m)	–0.08
C(2) <i>H</i>	3.62 (dd, <i>J</i> 7.1, 2.4)	3.67 (dd, <i>J</i> 7.2, 1.8)	–0.05
C(3) <i>H</i>	3.79–3.82 (m)	3.81 (br)	0.00
C(4) <i>H</i>	4.07–4.10 (m)	4.08–4.09 (m)	0.00
C(5) <i>H</i> /C(6) <i>H</i>	5.66–5.74 (m)	5.68 (dd, <i>J</i> 10.2, 1.8) 5.75–5.77 (m)	–0.02

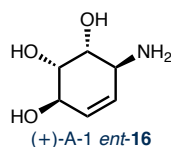
Table 3. Comparison of ¹H NMR spectroscopic data of (–)-conduramine A-1 **16**.



	This work δ_C (400 MHz, d_4 -MeOH)	Synthetic ⁹ δ_C (175 MHz, d_4 -MeOH)	$\Delta\delta_C$	Synthetic ¹¹ δ_C (150 MHz, d_4 -MeOH)	$\Delta\delta_C$
C(1)	52.2	52.2	0.00	52.0	+0.2
C(4)	70.9	71.0	–0.1	70.6	+0.4
C(2)	74.0	74.4	–0.4	72.6	+1.4
C(3)	74.5	74.5	0.00	74.4	+0.1
C(5)	129.2	129.0	+0.2	129.9	–0.7
C(6)	131.7	132.1	–0.4	129.9	–1.8

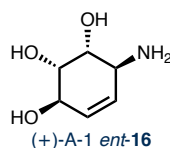
Table 4. Comparison of ¹³C NMR spectroscopic data of (–)-conduramine A-1 **16**.

The ¹H and ¹³C NMR spectroscopic data of (+)-A-1 *ent*-**16** were in excellent agreement with those reported by Norsikian *et al.* ($-0.01 \leq \Delta\delta_H \leq 0.00$ ¹⁴ and $-0.2 \leq \Delta\delta_C \leq +0.1$ ¹⁵) (Table 5 and 6).¹⁶ The specific rotation of (+)-A-1 *ent*-**16**, was found to be $[\alpha]_D^{25} +11.7$ (c 0.25 in MeOH), which is in moderate agreement with the literature value $\{[\alpha]_D^{25} +19.0$ (c 0.1 in MeOH)¹⁶ }.



	This work δ_{H} (400 MHz, d_4 -MeOH) Reference = 4.86 ppm	δ_{H} (300 MHz, d_4 -MeOH) Reference = 4.78 ppm	Synthetic ¹⁵ δ_{H} (300 MHz, d_4 -MeOH) New-reference = 4.86 ppm	$\Delta\delta_{\text{H}}$
C(1) <i>H</i>	3.41 (br d, J 7.3)	3.33 (d, J 7.0)	3.41 (d, J 7.0)	0.00
C(2) <i>H</i>	3.61 (dd, J 7.1, 2.4)	3.54 (dd, J 7.0, 2.5)	3.62 (dd, J 7.0, 2.5)	-0.01
C(3) <i>H</i>	3.78–3.82 (m)	3.73 (dd, J 4.0, 2.5)	3.81 (dd, J 4.0, 2.5)	-0.01
C(4) <i>H</i>	4.07–4.10 (m)	3.99–4.05 (m)	4.07–4.13 (m)	-0.01
C(5) <i>H</i> /C(6) <i>H</i>	5.66–5.74 (m)	5.58–5.66 (m)	5.66–5.74 (m)	0.00

Table 5. Comparison of ^1H NMR spectroscopic data of (+)-conduramine A-1 *ent*-16.



	This work δ_{C} (400 MHz, d_4 -MeOH)	Synthetic ¹⁵ δ_{C} (75 MHz, d_4 -MeOH)	$\Delta\delta_{\text{C}}$
C(1)	52.2	52.2	0.00
C(4)	71.0	71.0	0.00
C(2)	74.3	74.4	-0.1
C(3)	74.5	74.5	0.00
C(5)	129.0	128.9	+0.1
C(6)	132.0	132.2	-0.2

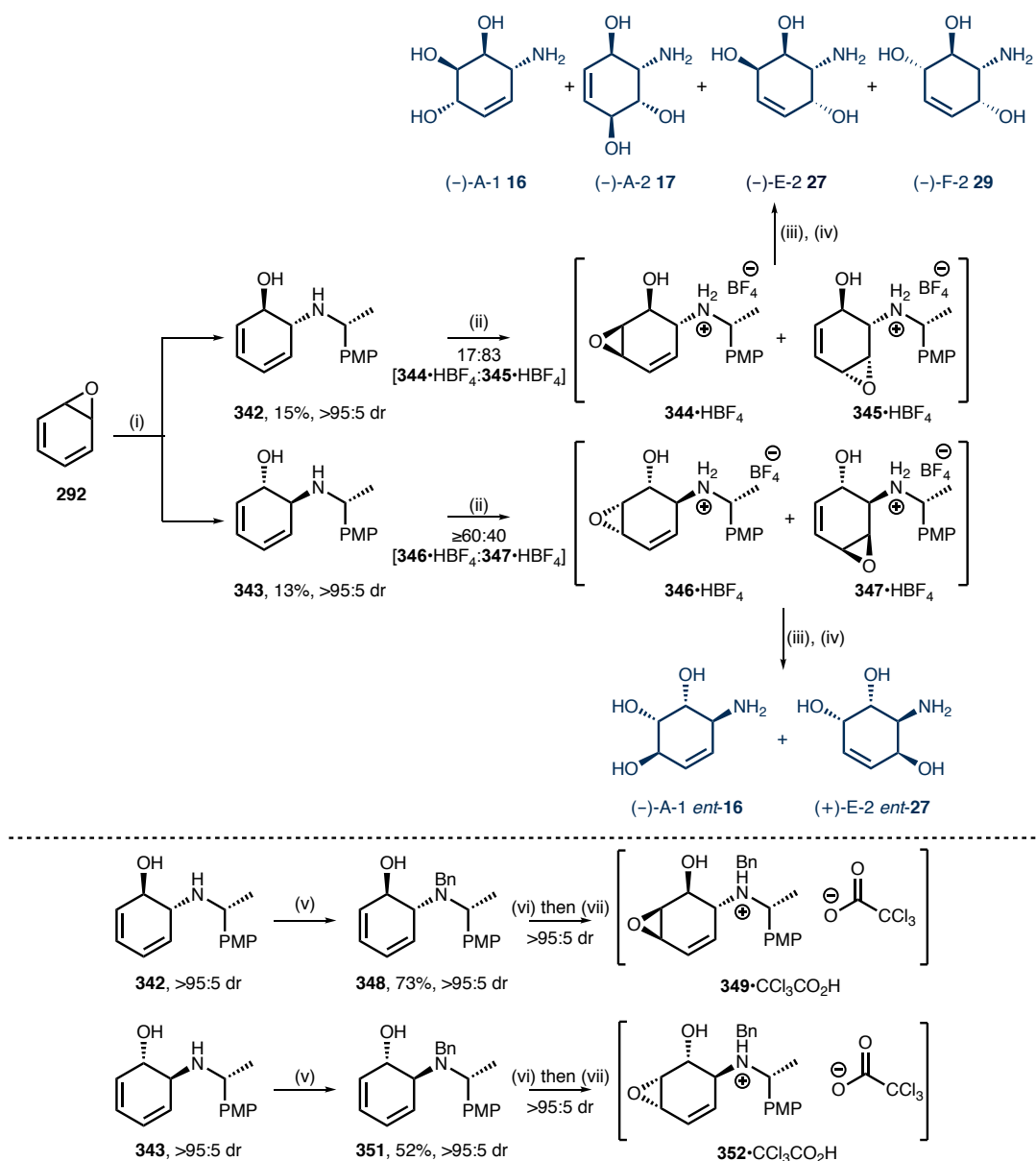
Table 6. Comparison of ^{13}C NMR spectroscopic data of (+)-conduramine A-1 *ent*-16.

Finally, comparisons of the ^1H and ^{13}C NMR spectroscopic data of (–)-F-2 with those reported for (+)-F-2 *ent*-29 by Ramesh and co-workers were not undertaken due to the presence of acid in the sample produced from this study.¹⁷ The specific rotation of the (–)-F-2 **29**, was found to be $[\alpha]_{\text{D}}^{25} -4.0$ (c 0.25 in MeOH), which is in poor agreement (in term of absolute value) with the literature value $\{[\alpha]_{\text{D}}^{25} +64.5$ (c 0.21 in MeOH)¹⁷ and consistent with the presence of acid in the sample produced from this study.

7.9 Conclusion

Concise asymmetric syntheses of six conduramines, including four unknowns from the literature, were achieved from benzene oxide **292** in three steps, derived from 1,4-cyclohexadiene **317**. First, ring-opening of benzene oxide **292** with (*R*)-**354** afforded diastereoisomers **342** and **343** in 19% and 21% yield, respectively. Then, epoxidation of **342** gave a 32:14:37:17 mixture of **360**, **361**, **362** and **363**, respectively and purification *via*

preparative TLC afforded **360** in 15% yield, **361** in 9.6% yield (~80% pure), **362** in 21% yield and **363** in 7.6% yield. As for chapter 6, two competitive pathways (i.e., hydroxyl- and ammonium directed epoxidations) were observed and the 17:83 ratio between hydroxyl- and ammonium-directed epoxidation suggested a superior directing ability of the *N*- α -methyl-*para*-methoxybenzylammonium moiety to direct the *syn*-epoxidation. When the epoxidation of **343** was carried out, a 5:35:43:17 mixture of **365**, **366**, **367**, and **368**, respectively, was obtained and purification *via* preparative TLC gave **366**, **367**, and **368** in 9.4%, 11% and 3.7% yields, all >95:5 dr, an 18:82 mixture of **364** and **365**, respectively, in 17% yield and an 7:85:8 mixtures of **364**, **365**, and **368**, respectively. In this case, the $\geq 60:40$ ratio between hydroxyl- and ammonium directed epoxidations showed an inversion in the superior directing ability of the groups: the hydroxyl group acted as a better director than the *N*- α -methyl-*para*-methoxybenzylammonium moiety. Finally, acid-mediated deprotections of **360**, **361**, **362**, **363**, **366** and **367** gave, after purification *via* column chromatography conduramines (–)-A-1 **16**, (+)-A-1 *ent*-**16**, (–)-A-2 **17**, (–)-E-2 **27**, (+)-E-2 *ent*-**27** and (–)-F-2• x CF₃CO₂H **29**• x CF₃CO₂H, in 82%, 53%, 79%, 58%, 32% and 41%⁷ yields, respectively, all in >95:5 dr ($0 \leq x \leq 1$ equivalents of CF₃CO₂H). Furthermore, investigations of the surrogacies of diastereoisomers **348** and **351** (prepared from *N*-benzylation of **342** and **343**, respectively) of racemic ($\pm$)-**182** were undertaken and in both cases, epoxidations were highly diastereoselective and directed by the hydroxyl group as for racemic ($\pm$)-**182** (Scheme 105).



Scheme 105. Reagents and conditions: (i) (R)-**354**, MeOH, 66 °C, 5 days; (ii) HBF₄ (40% aq), *m*-CPBA, CH₂Cl₂, rt; (iii) rt, 21 h; (iv) Et₃SiH, CF₃CO₂H, 50 °C, 18 h; (v) BnBr, K₂CO₃, MeCN, 82 °C, 24 h; (vi) CCl₃CO₂H, CH₂Cl₂, rt, 5 min, then *m*-CPBA, rt; (vii) K₂CO₃, MeOH, rt, 24 h.

7.10 Notes and references

- (1) X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research Laboratory, University of Oxford.
- (2) According to the previous results obtained during epoxidation of racemic (±)-**182** in presence of CCl₃CO₂H and HBF₄ (40% aq), it was decided to perform the epoxidation of **348** in presence of CCl₃CO₂H.
- (3) Kuhnert, N.; Danks, T. N. *Green Chem.* **2001**, *3*, 68–70.
- (4) According to the previous results obtained during epoxidation of racemic (±)-**182** in presence of CCl₃CO₂H and HBF₄ (40% aq), it was decided to perform the epoxidation of **351** in presence of CCl₃CO₂H.
- (5) Zimmer, D. D.Phil Thesis, University of Oxford, **2018**.
- (6) The eluent system used to purify and basify the conduramines is CHCl₃/MeOH/35% aq NH₄OH, 50:30:20 v/v/v.

- (7) The yields provided for sample (–)-F-2 **29** is not accurate due to presence of CF₃CO₂H.
- (8) It was assumed that purification *via* ion exchange chromatography of the 30:50:5:15: mixture of (±)-**16**•xHBF₄, (±)-**17**•xHBF₄, (±)-**27**•xHBF₄, and (±)-**29**•xHBF₄ provided a mixture of the corresponding free conduramines.
- (9) The synthesis of conduramine A-1 **16** has been reported many times in the literature, however, its characterization data was not included everytime.
- (10) Myeong, I.; Kim, J.; Lee, Y.; Kang, J.; Park, S.; Jung, C.; Ham, W. *Tetrahedron: Asymmetry* **2016**, *27*, 823–828.
- (11) An extra proton peak at 3.33 ppm was given in the supporting information by Myeong *et al.*, which was assumed to come from methanol left in their sample.
- (12) Lu, P.-H.; Yang, C.-S.; Devendar, B.; Liao, C.-C. *Org. Lett.* **2010**, *12*, 2642–2645.
- (13) An extra proton peak at 4.63 ppm was given in the supporting information by Lu *et al.*, which corresponded to a solvent peak.
- (14) $\Delta\delta_{\text{H}}$ is defined as the difference in the ¹H NMR spectroscopic resonances of the literature from the data from this study.
- (15) $\Delta\delta_{\text{C}}$ is defined as the difference in the ¹³C NMR spectroscopic resonances of the literature from the data from this study.
- (16) Norsikian, S.; Soulé, J.-F.; Cannillo, A.; Guillot, R.; Tran Huu Dau, M.-E.; Beau, J.-M. *Org. Lett.* **2012**, *14*, 544–547.
- (17) Harit, V. K.; Ramesh, N. G. *Org. Biomol. Chem.* **2019**, *17*, 5951–5961.

Chapter 8

Experimental

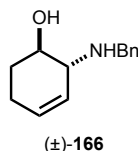
8.1 General Experimental

All reactions involving organometallic or other moisture-sensitive reagents were carried out under a nitrogen atmosphere using standard vacuum line techniques and glassware that was flame dried and cooled under nitrogen before use. Solvents were dried according to the procedure outlined by Grubbs *et al.*¹ Water was purified by an Elix[®] UV-10 system. *m*-CPBA was supplied as a 70–77% slurry in water and was titrated against sodium thiosulfate solution before use according to the procedure of Swern.² All other solvents and reagents were used as supplied (analytical or HPLC grade) without prior purification. Organic layers were dried over Na₂SO₄ unless otherwise specified. Thin layer chromatography was performed on aluminium plates coated with 60 F254 silica. Plates were visualised using UV light (254 nm) and 1% aq KMnO₄. Column chromatography was performed on Kieselgel 60 silica. For biphasic eluents, the aqueous phase was removed prior to column chromatography. Melting points were recorded on a Gallenkamp Hot Stage or Leica Gallen III apparatus and are uncorrected. Optical rotations were recorded on a Perkin-Elmer 241 or 341 polarimeter with a water-jacketed 10 cm cell. Specific rotations are reported in 10⁻¹ deg cm² g⁻¹ and concentrations in g 100⁻¹ mL⁻¹. IR spectra were recorded on Bruker Tensor 27 FT-IR spectrometer on a diamond ATR module (ATR). Selected characteristic peaks are reported in cm⁻¹. NMR spectra were recorded on Bruker Avance spectrometers in the deuterated solvent stated and at rt unless otherwise specified. The field was locked by external referencing to the relevant deuterium resonance unless otherwise specified. Chemical shifts (δ) are reported in ppm and coupling constants (*J*) in Hz. Low-resolution mass spectra were recorded on either a Micromass LCT Premier

or Agilent Quadrupole 6120 LC/MS spectrometer. Accurate mass measurements were run on a Bruker MicroToF internally calibrated with polyalanine.

8.2 Experimental for chapter 2

(*RS,RS*)-2-(*N*-Benzylamino)cyclohex-3-en-1-ol ($\pm$)-166

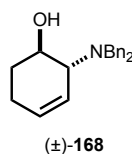


Step 1. AcOOH (39% in AcOH, 31.2 mL, 125 mmol) was added dropwise to a stirred suspension of **202** (10.0 g, 125 mmol) and Na₂CO₃ (119 g, 1.12 mol) in CH₂Cl₂ (350 mL) at 0 °C and the resultant suspension was stirred at 0 °C for 3.5 h. H₂O (200 mL) was added and the aqueous layer was extracted with CH₂Cl₂ (3 × 150 mL). The combined organics were washed with satd aq Na₂SO₃ (in 500 mL portions) until starch-iodide paper indicated that no peroxide was present, then dried and concentrated *in vacuo* at 0 °C to give **203** as a colourless oil (11.5 g); ³δ_H (400 MHz, *d*₁-CHCl₃) 1.57–1.67 (1H, m, C(6)*H*_A), 1.95–2.14 (2H, m, C(5)*H*_A, C(6)*H*_B), 2.21–2.29 (1H, m, C(5)*H*_B), 3.22–3.28 (1H, m, C(1)*H*), 3.50–3.55 (1H, m, C(2)*H*), 5.89–6.01 (2H, m, C(3)*H*, C(4)*H*). The NMR spectroscopic data of **203** are consistent with the literature values.

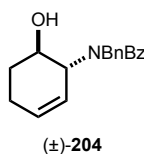
Step 2. Benzylamine (13.6 mL, 125 mmol) was added to a stirred solution of the residue from the previous step (11.5 g) in *i*PrOH (125 mL) at rt and the resultant solution was heated at 80 °C for 4 h, then allowed to cool to rt and concentrated *in vacuo*. Purification *via* column chromatography (eluent CHCl₃/MeOH/35% aq NH₄OH, 95:5:0.5) gave ($\pm$)-**166** as an orange solid (13.4 g, 53% from **202**, >180:1 dr); mp 53–56 °C; ν_{max} 3300, 3100, 2901, 2830, 1666; δ_H (500 MHz, *d*₁-CHCl₃) 1.49–1.60 (1H, m, C(6)*H*_A), 1.90–1.98 (1H, m, C(6)*H*_B), 2.06–2.11 (2H, m, C(5)*H*₂), 3.00 (1H, app dt, *J* 8.1, 2.8, C(2)*H*), 3.43 (1H, ddd, *J* 11.5, 8.1, 3.5, C(1)*H*), 3.70 (1H, d, *J* 13.0, NCH_AH_BPh), 3.89 (1H, d, *J* 13.0, NCH_AH_BPh), 5.61–5.68 (2H, m, C(3)*H*, C(4)*H*), 7.16–7.31 (5H, m, *Ph*); δ_C (125 MHz, *d*₁-

CHCl₃) 24.7 (C(5)), 28.8 (C(6)), 50.5 (NCH₂Ph), 61.0 (C(2)), 71.0 (C(1)), 126.7 (C(3)), 127.1, 128.2, 128.5 (*o,m,p*-Ph), 128.5 (C(4)), 140.4 (*i*-Ph); *m/z* (ESI⁺) 204 ([M+H]⁺, 100%); HRMS (ESI⁺) C₁₃H₁₈NO⁺ ([M+H]⁺) requires 204.1383; found 204.1382. Analysis of (±)-**166** by chiral HPLC [Chiralpak AD-H, mobile phase: hexane/*i*PrOH (v/v, 95:5), flow rate: 1 mL/min, 10 µL injection] gave complete resolution of enantiomers [**166** *t*_R = 13.6 min; *ent*-**166** *t*_R = 15.3 min].

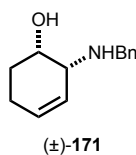
(*R,S,R,S*)-2-(*N,N*-Dibenzylamino)cyclohex-3-en-1-ol (±)-168



*i*Pr₂NEt (10.3 mL, 59.1 mmol), BnBr (7.00 mL, 59.1 mmol) and DMAP (48 mg, 0.394 mmol) were added sequentially to a stirred solution of (±)-**166** (8.00 g, 39.4 mmol, >180:1 dr) in CH₂Cl₂ (113 mL) at rt and the resultant solution was stirred at rt for 24 h, then concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 95:5) gave (±)-**168** as a white solid (10.0 g, 86%, >180:1 dr); mp 60–63 °C; *v*_{max} 3100, 2830, 1660; *δ*_H (500 MHz, *d*₁-CHCl₃) 1.40–1.53 (1H, m, C(6)*H*_A), 1.93–2.00 (1H, m, C(6)*H*_B), 2.05–2.13 (2H, m, C(5)*H*₂), 2.91 (1H, s, OH), 3.11–3.18 (1H, m, C(2)*H*), 3.46 (2H, d, *J* 13.3, N(CH_AH_BPh)₂), 3.67 (1H, ddd, *J* 11.9, 8.7, 3.7, C(1)*H*), 3.80 (2H, d, *J* 13.3, N(CH_AH_BPh)₂), 5.70–5.84 (2H, m, C(3)*H*, C(4)*H*), 7.17–7.33 (10H, m, Ph); *δ*_C (125 MHz, *d*₁-CHCl₃) 24.9 (C(5)), 28.9 (C(6)), 54.5 (N(CH₂Ph)₂), 63.1 (C(2)), 67.7 (C(1)), 123.3 (C(3)), 127.2, 128.4, 128.9 (*o,m,p*-Ph), 130.4 (C(4)), 139.6 (*i*-Ph); *m/z* (ESI⁺) 294 ([M+H]⁺, 100%); HRMS (ESI⁺) C₂₀H₂₄NO⁺ ([M+H]⁺) requires 294.1852; found 294.1848.

(1*R*,2*R*)-2-(*N*-Benzoyl-*N*-benzylamino)cyclohex-3-en-1-ol(±)-204.

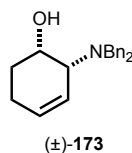
Benzoyl chloride (1.88 mL, 16.2 mmol) was added dropwise to a stirred solution of (±)-**166** (3.30 g, 16.2 mmol, >180:1 dr) and Na₂CO₃ (3.44 g, 32.5 mmol) in THF (65 mL) at 0 °C. The resultant mixture was stirred at rt for 24 h and then H₂O (30 mL) was added. The aqueous layer was extracted with Et₂O (3 × 40 mL) and the combined organics were washed with brine (100 mL), dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 3:1) gave (±)-**204** as a white solid (4.50 g, 90%, >95:5 dr); mp 126–129 °C; ν_{max} 3435, 3065, 3028, 2950, 2918, 1607, 1594; δ_{H} (500 MHz, PhMe-*d*₈, 363 K) 1.21–1.33 (1H, m, C(6)*H*_A), 1.55–1.63 (1H, m, C(6)*H*_B), 1.65–1.79 (2H, m, C(5)*H*₂), 3.54–3.62 (1H, m, C(1)*H*), 4.28 (1H, d, *J* 15.7, NCH_AH_BPh), 4.64–4.78 (2H, m, C(2)*H*, NCH_AH_BPh), 5.27–5.33 (1H, m, C(3)*H*), 5.43–5.50 (1H, m, C(4)*H*), 6.95–7.11 (6H, m, *Ph*), 7.24–7.30 (2H, m, *Ph*), 7.39–7.43 (2H, m, *Ph*); δ_{C} (125 MHz, PhMe-*d*₈, 363 K) 25.4 (C(5)), 31.5 (C(6)), 47.8 (NCH₂Ph), 63.9 (C(2)), 69.8 (C(1)), 127.6, 127.8, 128.7, 129.5 (C(3), *o,m,p-Ph*), 131.2 (C(4)), 138.4, 140.6 (*i-Ph*), 174.0 (COPh); *m/z* (ESI⁺) 308 ([M+H]⁺, 100%); HRMS (ESI⁺) C₂₀H₂₂NO₂⁺ ([M+H]⁺) requires 308.1645; found 308.1644.

(1*R*,2*S*)-2-(*N*-Benzylamino)cyclohex-3-en-1-ol (±)-171⁴

SOCl₂ (250 μ L, 3.46 mmol) was added to a stirred solution of (±)-**204** (280 mg, 0.912 mmol, >95:5 dr) in CH₂Cl₂ (0.55 mL) at 0 °C. The resultant solution was stirred at rt for 4

h and then concentrated *in vacuo*. The residue was dissolved in MeOH (12.5 mL) and K_2CO_3 (1.0 g, 7.2 mmol) was added. The resultant mixture was stirred at rt for 16 h and then concentrated *in vacuo*. The residue was partitioned between H_2O (20 mL) and CH_2Cl_2 (15 mL) and the aqueous layer was extracted with CH_2Cl_2 (3×20 mL). The combined organics were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent $CHCl_3/MeOH$, 19:1) gave ($\pm$)-**171** as a white powder (140 mg, 75%, >180:1 dr);⁵ mp 70.2–76.7 °C; δ_H (400 MHz, d_1 - $CHCl_3$) 1.53–1.68 (2H, m, C(6) H_2), 1.87–1.98 (1H, m, C(5) H_A), 2.05–2.16 (1H, m, C(5) H_B), 3.08–3.13 (1H, m, C(2) H), 3.74 (1H, ddd, J 8.4, 4.8, 3.4, C(1) H), 3.81 (1H, d, J 13.0, NCH_AH_BPh), 3.85 (1H, d, J 13.0, NCH_AH_BPh), 5.54 (1H, app ddt, J 10.0, 3.5, 1.9, C(3) H), 5.72 (1H, app dtd, J 10.0, 3.7, 1.7, C(4) H), 7.17–7.31 (5H, m, Ph). The NMR spectroscopic data of ($\pm$)-**171** are consistent with the literature values.

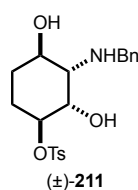
(1*R*S,2*S*R)-2-(*N,N*-Dibenzylamino)cyclohex-3-en-1-ol ($\pm$)-173.



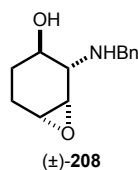
iPr_2NEt (760 μL , 4.37 mmol), $BnBr$ (520 μL , 4.37 mmol) and DMAP (3.6 mg, 29.1 μmol) were added sequentially to a stirred solution of ($\pm$)-**171** (592 mg, 2.91 mmol, >180:1 dr) in CH_2Cl_2 (8.4 mL) at rt. The resultant solution was stirred at rt for 24 h and then concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/ $EtOAc$, 9:1) gave ($\pm$)-**173** as a pale yellow oil (799 mg, 94%, >180:1 dr); ν_{max} 3427, 3084, 3061, 3025, 2921, 2838; δ_H (400 MHz, d_1 - $CHCl_3$) 1.61–1.71 (1H, m, C(6) H_A), 1.81–1.91 (1H, m, C(6) H_B), 1.97–2.10 (1H, m, C(5) H_A), 2.15–2.26 (1H, m, C(5) H_B), 3.52 (1H, app ddt, J 6.1, 4.1, 1.9, C(2) H), 3.61 (2H, d, J 14.0, $N(CH_AH_BPh)_2$), 3.74 (1H, ddd, J 10.7, 6.1, 4.1, C(1) H), 3.93 (2H, d, J 14.0, $N(CH_AH_BPh)_2$), 4.05 (1H, br s, OH),

5.75 (1H, dddd, J 10.0, 4.1, 2.4, 1.6, C(3) H), 5.98 (1H, app ddt, J 10.0, 4.7, 2.4, C(4) H), 7.23–7.38 (10H, m, Pb); δ_c (100 MHz, d_1 -CHCl₃) 23.4 (C(5)), 28.3 (C(6)), 56.1 (C(2)), 56.5 (N(CH₂Ph)₂), 66.8 (C(1)), 124.0 (C(3)), 127.2, 128.5, 128.9 (*o,m,p*- Pb), 131.7 (C(4)), 139.3 (*i*- Pb); m/z (ESI⁺) 294 ([M+H]⁺, 100%); HRMS (ESI⁺) C₂₀H₂₄NO⁺ ([M+H]⁺) requires 294.1852; found 294.1851.

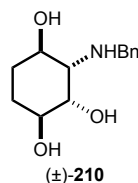
(1*R*,2*S*,3*S*,4*S*)-2-(*N*-Benzylamino)-4-tosyloxycyclohexan-1,3-diol (±)-211.



A solution of (±)-166 (6.00 g, 29.5 mmol, >180:1 dr) in CH₂Cl₂ (82 mL) was added to anhydrous TsOH (25.4 g, 148 mmol) at rt. The resultant solution was stirred at rt for 5 min and then *m*-CPBA (72% wt, 11.3 g, 47.3 mmol) was added. The resultant solution was stirred at rt for 21 h and then solid Na₂SO₃ was added until starch-iodide paper indicated that no *m*-CPBA was present. The resultant suspension was diluted with CH₂Cl₂ (50 mL), washed with 0.1 M aq NaHCO₃ (4 × 50 mL), dried and concentrated *in vacuo* to give (±)-211 as a beige solid (10.2 g, 88%, >95:5 dr); mp 136–140 °C; $\nu_{\max}$ 3323, 3033, 2942; δ_H (400 MHz, d_1 -CHCl₃) 1.53–1.93 (4H, m, C(6) H_2 , C(5) H_2), 2.46 (3H, s, ArMe), 2.74 (1H, dd, J 10.0, 3.2, C(2) H), 3.59 (1H, app td, J 10.0, 4.4, C(1) H), 3.66 (1H, d, J 13.2, NCH_AH_BPh), 3.80 (1H, d, J 13.2, NCH_AH_BPh), 3.96–4.00 (1H, m, C(3) H), 4.68–4.73 (1H, m, C(4) H), 7.25–7.40 (7H, m, Ar, Pb), 7.77–7.83 (2H, m, Ar); δ_c (100 MHz, d_1 -CHCl₃) 21.7 (Me), 24.1 (C(5)), 27.5 (C(6)), 50.8 (NCH₂Ph), 61.5 (C(2)), 66.7 (C(3)), 68.2 (C(1)), 78.8 (C(4)), 127.3, 127.7, 128.1, 128.6, 129.9, 133.7, 139.6, 144.9 (Ar, Pb); m/z (ESI⁺) 392 ([M+H]⁺, 100%); HRMS (ESI⁺) C₂₀H₂₆NO₅⁺ ([M+H]⁺) requires 392.1526; found 392.1522.

(1*R*,2*S*,3*S*,4*R*)-2-(*N*-Benzylamino)-3,4-epoxycyclohexan-1-ol (±)-208.

DBU (280 μ L, 1.93 mmol) was added to a stirred solution of (±)-**211** (700 mg, 1.79 mmol, >95:5 dr) in CH_2Cl_2 (5.2 mL) at rt and the resultant solution was stirred at rt for 24 h, then concentrated *in vacuo*. Purification *via* flash column chromatography (eluent $\text{CHCl}_3/\text{MeOH}$, 95:5) gave (±)-**208** as a colourless oil (390 mg, 99%, >95:5 dr); ν_{max} 3320, 2981, 2939, 2890; δ_{H} (400 MHz, $d_1\text{-CHCl}_3$) 1.37 (1H, dtd, J 13.0, 11.3, 7.0, $\text{C}(6)\text{H}_{\text{A}}$), 1.73–1.82 (1H, m, $\text{C}(6)\text{H}_{\text{B}}$), 1.90–2.00 (1H, m, $\text{C}(5)\text{H}_{\text{A}}$), 2.02–2.11 (1H, m, $\text{C}(5)\text{H}_{\text{B}}$), 2.72 (1H, dd, J 8.1, 2.0, $\text{C}(2)\text{H}$), 3.31 (1H, app t, J 4.4, $\text{C}(4)\text{H}$), 3.39–3.42 (1H, m, $\text{C}(3)\text{H}$), 3.51 (1H, ddd, J 11.3, 8.1, 3.2, $\text{C}(1)\text{H}$), 3.90 (1H, d, J 13.1, $\text{NCH}_{\text{A}}\text{H}_{\text{B}}\text{Ph}$), 4.11 (1H, d, 13.1, $\text{NCH}_{\text{A}}\text{H}_{\text{B}}\text{Ph}$), 7.25–7.41 (5H, m, *Ph*); δ_{C} (100 MHz, $d_1\text{-CHCl}_3$) 22.3 ($\text{C}(5)$), 28.0 ($\text{C}(6)$), 50.8 (NCH_2Ph), 54.5 ($\text{C}(4)$), 54.5 ($\text{C}(3)$), 61.0 ($\text{C}(2)$), 68.1 ($\text{C}(1)$), 127.2, 128.1, 128.5 (*o,m,p-Ph*), 140.1 (*i-Ph*); m/z (CI^+) 220 ($[\text{M}+\text{H}]^+$, 100%); HRMS (CI^+) $\text{C}_{13}\text{H}_{18}\text{NO}_2^+$ ($[\text{M}+\text{H}]^+$) requires 220.1332; found 220.1332.

(1*R*,2*S*,3*S*,4*S*)-2-(*N*-Benzylamino)cyclohexane-1,3,4-triol (±)-210.

Method A. Epoxidation of (±)-166 in the presence of $\text{Cl}_3\text{CCO}_2\text{H}$. Step 1. Anhydrous $\text{Cl}_3\text{CCO}_2\text{H}$ (1.00 g, 6.15 mmol) was added to a stirred solution of (±)-**166** (250 mg, 1.23 mmol, >180:1 dr) in CH_2Cl_2 (3.4 mL) at rt and the resultant solution was stirred at rt for 5 min. *m*-CPBA (75% wt, 452 mg, 1.97 mmol) was then added and the resultant solution was stirred at rt

for 21 h. Solid Na_2SO_3 was added until starch-iodide paper indicated that no *m*-CPBA was present. The resultant suspension was diluted with CH_2Cl_2 (30 mL), washed with 0.1 M aq NaHCO_3 (4×20 mL), dried and concentrated *in vacuo* to give ($\pm$)-**209** as a beige solid (370 mg, >95:5 dr); δ_{H} (400 MHz, d_1 - CHCl_3) 1.49–1.91 (4H, m, C(6) H_2 , C(5) H_2), 2.82 (1H, dd, J 9.5, 2.9, C(2) H), 3.74–3.84 (1H, m, C(1) H), 3.92 (1H, d, J 13.2, $\text{NCH}_A\text{H}_B\text{Ph}$), 4.01 (1H, m, J 13.2, $\text{NCH}_A\text{H}_B\text{Ph}$), 4.10–4.16 (1H, m, C(3) H), 5.09–5.17 (1H, m, C(4) H), 7.23–7.42 (5H, m, *Pb*); δ_{C} (100 MHz, d_1 - CHCl_3) 22.9 (C(5)), 27.8 (C(6)), 50.7 (NCH_2Ph), 61.3 (C(2)), 65.7 (C(3)), 67.8 (C(1)), 76.4 (C(4)), 89.7 (CCl_3), 128.1, 128.3, 128.6 (*o,m,p-Pb*), 138.4 (*i-Pb*), 160.8 (COCCl_3).

Step 2. K_2CO_3 (296 mg) was added to a stirred solution of the residue from the previous step (370 mg) in MeOH (15 mL) at rt and the resultant suspension was stirred at rt for 16 h, then concentrated *in vacuo*. 2 M aq NaOH (30 mL) was then added and the resultant mixture was extracted with CHCl_3 /*i*-PrOH (3:1, v/v, 3×50 mL). The combined organic extracts were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent CHCl_3 /MeOH/35% aq NH_4OH , 90:10:0.5) gave ($\pm$)-**210** as a pale yellow powder (166 mg, 57%, >95:5 dr); mp 136–138 °C; ν_{max} 3180, 2918, 2872; δ_{H} (500 MHz, d_1 - CHCl_3) 1.67–1.75 (2H, m, C(5) H_A , C(6) H_A), 1.77–1.84 (1H, m, C(5) H_B), 1.87–1.95 (1H, m, C(6) H_B), 2.85 (1H, dd, J 8.2, 3.5, C(2) H), 3.69–3.74 (1H, m, C(3) H), 3.76 (1H, d, J 13.1, $\text{NCH}_A\text{H}_B\text{Ph}$), 3.87 (1H, d, J 13.1, $\text{NCH}_A\text{H}_B\text{Ph}$), 3.89–3.93 (1H, m, C(1) H), 3.96–3.99 (1H, m, C(4) H), 7.27–7.36 (5H, m, *Pb*); δ_{C} (125 MHz, d_1 - CHCl_3) 26.1 (C(5)), 27.4 (C(6)), 51.3 (NCH_2Ph), 62.0 (C(2)), 68.8 (C(3)), 69.3 (C(4)), 69.7 (C(1)), 127.2, 128.1, 128.5 (*o,m,p-Pb*), 140.1 (*i-Pb*); m/z (ESI⁺) 238 ($[\text{M}+\text{H}]^+$, 100%); HRMS (ESI⁺) $\text{C}_{13}\text{H}_{20}\text{NO}_3^+$ ($[\text{M}+\text{H}]^+$) requires 238.1438; found 238.1441.

Method B. Epoxidation of ($\pm$)-166 in the presence of aq HBF_4 . HBF_4 (40% aq, 960 μL , 6.15 mmol) was added to a stirred solution of ($\pm$)-**166** (250 mg, 1.23 mmol, >180:1 dr) in

CH₂Cl₂ (3.4 mL) at rt and the resultant solution was stirred at rt for 5 min. *m*-CPBA (75% wt, 452 mg, 1.97 mmol) was then added and the resultant solution was stirred at rt for 21 h. Solid Na₂SO₃ was added until starch-iodide paper indicated that no *m*-CPBA was present. 2 M aq NaOH (20 mL) was then added and the resultant mixture was extracted with CHCl₃/ⁱPrOH (3:1, v/v, 3 × 30 mL). The combined organic extracts were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent CHCl₃/MeOH/35% aq NH₄OH, 90:10:0.5) gave (±)-**210** as a pale yellow powder (220 mg, 75%, >95:5 dr).

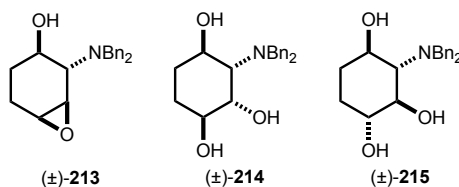
Method C. Ring-opening of epoxide (±)-208 by aq HBF₄. HBF₄ (40% aq, 460 μL, 2.97 mmol) was added to a stirred solution of (±)-**208** (130 mg, 0.593 mmol, >95:5 dr) in CH₂Cl₂ (1.6 mL) at rt and the resultant mixture was stirred at rt for 21 h. 2 M aq NaOH (5 mL) was then added and the resultant mixture was extracted with CHCl₃/ⁱPrOH (3:1, v/v, 3 × 30 mL). The combined organic extracts were dried and concentrated *in vacuo* to give a (±)-**210** as a yellow pale solid (70 mg, 50%, >95:5 dr).

Method D. Ring-opening of epoxide (±)-208 by Cl₃CCO₂H. Anhydrous Cl₃CCO₂H (490 mg, 2.97 mmol) was added to a stirred solution of (±)-**208** (130 mg, 0.593 mmol, >95:5 dr) in CH₂Cl₂ (1.6 mL) at rt and the resultant solution was stirred at rt for 21 h. MeOH (8.2 mL) and K₂CO₃ (160 mg) were then added and the resultant suspension was stirred at rt for 16 h, then concentrated *in vacuo*. 2 M aq NaOH (3 mL) was then added and the resultant mixture was extracted with CHCl₃/ⁱPrOH (3:1, v/v, 3 × 5 mL). The combined organic extracts were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent CHCl₃/MeOH/35% aq NH₄OH, 90:10:0.5) gave (±)-**210** as a pale yellow powder (91 mg, 65%, >95:5 dr).

(1*R*,2*S*,3*R*,4*S*)-2-(*N,N*-Dibenzylamino)-3,4-epoxycyclohexan-1-ol (±)-**213**,

(1*R*,2*S*,3*R*,4*S*)-2-(*N,N*-dibenzylamino)cyclohexane-1,3,4-triol (±)-**214**, and

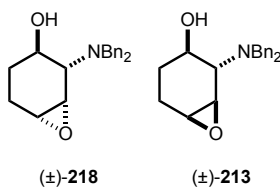
(1*R*,2*S*,3*R*,4*R*)-2-(*N,N*-dibenzylamino)cyclohexane-1,3,4-triol (±)-**215**.



Anhydrous $\text{Cl}_3\text{CCO}_2\text{H}$ (1.40 g, 8.53 mmol) was added to a stirred solution of (±)-**168** (500 mg, 1.71 mmol, >180:1 dr) in CH_2Cl_2 (4.7 mL) at rt and the resultant solution was stirred at rt for 5 min. *m*-CPBA (75% wt, 1.95 g, 8.53 mmol) was then added and the solution was stirred at rt for 21 h. Solid Na_2SO_3 was added until starch-iodide paper indicated that no *m*-CPBA was present. MeOH (23.7 mL) and K_2CO_3 (470 mg) were then added and the resultant suspension was stirred at rt for 48 h, then concentrated *in vacuo*. 2 M aq NaOH (30 mL) was then added and the resultant mixture was extracted with CHCl_3 /PrOH (3:1, v/v, 3×30 mL). The combined organic extracts were dried and concentrated *in vacuo* to give incomplete conversion to a 28:43:29 mixture of (±)-**213**, (±)-**214** and (±)-**215**, respectively. Purification *via* column chromatography (eluent CHCl_3 /MeOH/35% aq NH_4OH , 95:5:0.5) gave a mixture of (±)-**168**, (±)-**213** and (±)-**215**, respectively (346 mg). Further elution gave (±)-**214** as a white solid (200 mg, 36%, >95:5 dr); mp 193–197 °C; ν_{max} 3265, 3028, 2937, 2848; δ_{H} (400 MHz, d_1 - CHCl_3) 1.43–1.67 (2H, m, C(5) H_{A} , C(6) H_{A}), 1.88–2.00 (2H, m, C(5) H_{B} , C(6) H_{B}), 2.87 (1H, dd, J 10.3, 1.5, C(2) H), 3.67 (2H, d, J 13.8, N($\text{CH}_A\text{H}_B\text{Ph}$) $_2$), 3.86–3.92 (1H, m, C(4) H), 4.07 (1H, app dt, J 10.5, 4.4, C(1) H), 4.13 (2H, d, J 13.8, N($\text{CH}_A\text{H}_B\text{Ph}$) $_2$), 4.31–4.36 (1H, m, C(3) H), 7.21–7.37 (10H, m, *Ph*); δ_{C} (100 MHz, d_1 - CHCl_3) 25.5 (C(5)), 27.9 (C(6)), 54.7 (N(CH_2Ph) $_2$), 60.9 (C(2)), 63.8 (C(1)), 69.6 (C(3)), 71.3 (C(4)), 127.2, 128.5, 128.9 (*o,m,p-Ph*), 139.6 (*i-Ph*); m/z (ESI $^+$) 328 ([M+H] $^+$, 100%); HRMS (ESI $^+$) $\text{C}_{20}\text{H}_{26}\text{NO}_3^+$ ([M+H] $^+$) requires 328.1907; found 328.1906. Further

purification of the mixture of ($\pm$)-**168**, ($\pm$)-**213** and ($\pm$)-**215** *via* column chromatography (eluent CHCl_3 /35% aq NH_4OH 100:0.5) gave ($\pm$)-**168** as a white solid (20 mg, 4%, >95:5 dr). Further elution gave ($\pm$)-**213** as a white solid (58 mg, 11%, >95:5 dr); mp 108–112 °C; ν_{max} 3532, 2911, 2806; δ_{H} (400 MHz, d_1 - CHCl_3) 1.19 (1H, app qd, J 12.5, 4.6, C(6) H_{A}), 1.52–1.61 (1H, m, C(6) H_{B}), 1.67–1.78 (1H, m, C(5) H_{A}), 2.03–2.12 (1H, m, C(5) H_{B}), 2.69 (1H, d, J 9.5, C(2) H), 3.08–3.13 (2H, m, C(3) H , C(4) H), 3.38–3.48 (1H, m, C(1) H), 3.59 (2H, d, J 13.5, N($\text{CH}_{\text{A}}\text{H}_{\text{B}}\text{Ph}$)₂), 3.86 (2H, d, 13.5, N($\text{CH}_{\text{A}}\text{H}_{\text{B}}\text{Ph}$)₂), 7.14–7.30 (10H, m, Ph); δ_{C} (100 MHz, d_1 - CHCl_3) 23.3 (C(5)), 23.5 (C(6)), 50.6 (C(3)), 52.9 (C(4)), 54.7 (N(CH_2Ph)₂), 62.6 (C(2)), 67.2 (C(1)), 127.4, 128.5, 128.9 (*o,m,p*- Ph), 138.8 (*i*- Ph); m/z (ESI⁺) 310 ([M+H]⁺, 100%); HRMS (ESI⁺) $\text{C}_{20}\text{H}_{24}\text{NO}_2^+$ ([M+H]⁺) requires 310.1802; found 310.1800. Further elution gave an impure sample of ($\pm$)-**215** as a yellow oil (106 mg, ~18%, >95:5 dr).

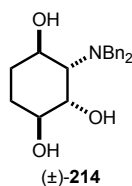
(1*R*,2*S*,3*R*,4*R*)-2-(*N,N*-Dibenzylamino)-3,4-epoxycyclohexan-1-ol ($\pm$)-218 and (1*R*,2*S*,3*R*,4*S*)-2-(*N,N*-dibenzylamino)-3,4-epoxycyclohexan-1-ol ($\pm$)-213.



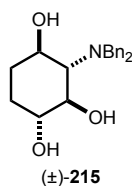
Step 1. A solution of ($\pm$)-**168** (750 mg, 2.56 mmol, >180:1 dr) in CH_2Cl_2 (7.1 mL) was added to anhydrous TsOH (2.26 g, 12.8 mmol) at rt. The resultant solution was stirred at rt for 5 min and then *m*-CPBA (75% wt, 2.93 g, 12.8 mmol) was added. The resultant solution was stirred at rt for 21 h and then Solid Na_2SO_3 was added until starch-iodide paper indicated that no *m*-CPBA was present. The resultant suspension was diluted with CH_2Cl_2 (20 mL), washed with 0.1 M aq NaHCO_3 (4 $\times$ 30 mL), dried and concentrated *in vacuo*. Filtration through a plug of silica gel (eluent 30–40 °C petroleum ether/EtOAc, 7:3) gave a 47:53

mixture of ($\pm$)-**216** and ($\pm$)-**217**, respectively, as an orange oil (500 mg); $\nu_{\max}$ 3385, 3028; m/z (ESI⁺) 482 ([M+H]⁺, 100%); HRMS (ESI⁺) C₂₇H₃₂NO₅S⁺ ([M+H]⁺) requires 482.1996; found 482.1987. Data for ($\pm$)-**216**: δ_{H} (400 MHz, *d*₁-CHCl₃) [selected peaks]⁶ 1.24–1.48 (1H, m, C(6)*H*_A), 1.52–1.59 (1H, m, C(5)*H*_A), 1.84–2.00 (2H, m, C(5)*H*_B, C(6)*H*_B), 2.79 (1H, dd, *J* 10.5, 2.0, C(2)*H*), 3.61 (2H, d, *J* 13.7, N(CH_AH_BPh)₂), 4.07 (1H, app dt, *J* 10.5, 4.2, C(1)*H*), 3.13 (2H, d, *J* 13.7, N(CH_AH_BPh)₂), 4.59–4.66 (2H, m, C(3)*H*, C(4)*H*); δ_{C} (100 MHz, *d*₁-CHCl₃) 21.6 (*Me*), 23.2 (C(5)), 27.8 (C(6)), 52.0 (N(CH₂Ph)₂), 60.4 (C(2)), 62.9 (C(1)), 67.0 (C(3)), 79.6 (C(4)). Data for ($\pm$)-**217**: δ_{H} (400 MHz, *d*₁-CHCl₃) [selected peaks]⁶ 1.04–1.17 (1H, m, C(6)*H*_A), 1.24–1.48 (1H, m, C(5)*H*_A), 1.84–2.00 (2H, m, C(5)*H*_B, C(6)*H*_B), 2.45 (1H, app t, *J* 10.4, C(2)*H*), 3.38 (1H, app dt, *J* 10.4, 4.4, C(1)*H*), 3.86–3.94 (5H, m, C(3)*H*, N(CH₂Ph)₂), 4.40 (1H, ddd, *J* 11.6, 8.6, 5.0, C(4)*H*); δ_{C} (100 MHz, *d*₁-CHCl₃) 21.6 (*Me*), 26.5 (C(5)), 28.4 (C(6)), 54.4 (N(CH₂Ph)₂), 65.5 (C(2)), 66.9 (C(1)), 72.3 (C(3)), 85.0 (C(4)).

Step 2. DBU (170 μ L, 1.12 mmol) was added to a stirred solution of the residue from the previous step (500 mg) in CH₂Cl₂ (2.1 mL) at rt and the resultant solution was stirred at rt for 24 h, then concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 7:3) gave a 47:53 mixture of ($\pm$)-**218** and ($\pm$)-**213**, respectively, as a yellow oil (300 mg, 38%); $\nu_{\max}$ 3479, 3027, 2940, 2841; m/z (ESI⁺) 310 ([M+H]⁺, 100%); HRMS (ESI⁺) C₂₀H₂₄NO₂⁺ ([M+H]⁺) requires 310.1802; found 310.1799.

(1*R,S*,2*S,R*,3*S,R*,4*S,R*)-2-(*N,N*-Dibenzylamino)cyclohexane-1,3,4-triol (±)-214.

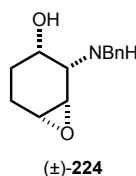
Anhydrous $\text{Cl}_3\text{CCO}_2\text{H}$ (159 mg, 0.970 mmol) was added to a stirred solution of (±)-**218** (60.0 mg, 0.194 mmol, >95:5 dr) in CH_2Cl_2 (0.54 mL) at rt and the resultant solution was stirred at rt for 21 h. MeOH (2 mL) and K_2CO_3 (40 mg) were then added and the resultant suspension was stirred at rt for 16 h, then concentrated *in vacuo*. 2 M aq NaOH (1.5 mL) was then added and the resultant mixture was extracted with CHCl_3 /*i*PrOH (3:1, v/v, 3 × 1.5 mL). The combined organic extracts were dried and concentrated *in vacuo*. Purification *via* column chromatography (eluent CHCl_3 /MeOH/35% aq NH_4OH , 90:10:0.5) gave (±)-**214** as a white solid (30 mg, 47%, >95:5 dr). Analysis of (±)-**214** by chiral HPLC [Chiralpak OD-H, mobile phase: hexane/*i*PrOH (v/v, 92:8), flow rate: 1 mL/min, 10 μL injection] gave complete resolution of enantiomers [**214** t_R = 13.9 min; *ent*-**214** t_R = 20.8 min].

(1*R,S*,2*S,R*,3*R,S*,4*R,S*)-2-(*N,N*-Dibenzylamino)cyclohexane-1,3,4-triol (±)-215.

Method A. Ring-opening of epoxide (±)-213 by aq HBF_4 . HBF_4 (40% aq, 192 μL , 1.22 mmol) was added to a stirred solution of (±)-**213** (80.0 mg, 0.244 mmol, >95:5 dr) in CH_2Cl_2 (0.72 mL) at rt and the resultant solution was stirred at 40 °C for 24 h. 2 M aq NaOH (10 mL) was then added and the resultant mixture was extracted with CHCl_3 /*i*PrOH (3:1, v/v, 3 × 15 mL). The combined organic extracts were dried and concentrated *in vacuo*. Purification *via* column chromatography (eluent CHCl_3 /MeOH, 97:3) gave (±)-**215** as a white solid (60

mg, 71%, >95:5 dr); mp 158–166 °C; $\nu_{\max}$ 3403, 3062, 3028, 2934, 2868; δ_{H} (400 MHz, d_1 -CHCl₃) 1.16–1.38 (2H, m, C(5) H_{A} , C(6) H_{A}), 1.85–2.02 (2H, m, C(5) H_{B} , C(6) H_{B}), 2.29 (1H, br s, OH), 2.43 (1H, app t, J 10.2, C(2) H), 2.85 (1H, br s, OH), 3.03 (1H, br s, OH), 3.41 (1H, app td, J 9.4, 8.6, 4.5, C(4) H), 3.52 (1H, dd, J 10.2, 8.6, C(3) H), 4.62 (1H, app td, J 10.2, 4.5, C(1) H), 4.93 (4H, app s, N(CH₂Ph)₂), 7.12–7.46 (10H, m, Pb); δ_{C} (100 MHz, d_1 -CHCl₃) 28.5 (C(5)), 30.0 (C(6)), 55* (N(CH₂Ph)₂), 65.4 (C(2)), 68.6 (C(1)), 74.4 (C(4)), 74.8 (C(3)), 127.3, 128.5, 129.3 (o,m,p - Pb), 139.5 (i - Pb);⁷ m/z (ESI⁺) 328 ([M+H]⁺, 100%); HRMS (ESI⁺) C₂₀H₂₆NO₃⁺ ([M+H]⁺) requires 328.1907; found 328.1910. Analysis of ($\pm$)-**215** by chiral HPLC [Chiralpak OD-H, mobile phase: hexane/^{*i*}PrOH (v/v, 90:10), flow rate: 1 mL/min, 10 μ L injection] gave complete resolution of enantiomers [**215** t_{R} = 11.7 min; *ent*-**215** t_{R} = 18.6 min].

Method B. Ring-opening of epoxide ($\pm$)-213 by Cl₃CCO₂H. Anhydrous Cl₃CCO₂H (251 mg, 1.54 mmol) was added to a stirred solution of ($\pm$)-**213** (95.1 mg, 0.307 mmol, >95:5 dr) in CH₂Cl₂ (0.85 mL) at rt and the resultant solution was stirred at rt for 21 h. MeOH (4.3 mL) and K₂CO₃ (85 mg) were then added and the resultant suspension was stirred at rt for 16 h, then concentrated *in vacuo*. 2 M aq NaOH (5 mL) was then added and the resultant mixture was extracted with CHCl₃/^{*i*}PrOH (3:1, v/v, 3 $\times$ 10 mL). The combined organic extracts were dried and concentrated *in vacuo* to give a 4:96 mixture of ($\pm$)-**214** and ($\pm$)-**215** as a white solid (71 mg, 71%).

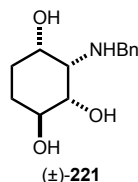
(1*R*,2*R*,3*R*,4*R*)-2-(*N*-Benzylamino)-3,4-epoxycyclohexan-1-ol (±)-224.

Step 1. A solution of (±)-**171** (250 mg, 1.23 mmol, >180:1 dr) in CH₂Cl₂ (3.4 mL) was added to anhydrous TsOH (1.06 g, 6.15 mmol) at rt. The resultant solution was stirred at rt for 5 min and then *m*-CPBA (73% wt, 463 mg, 1.97 mmol) was added. The resultant solution was stirred at rt for 21 h and then solid Na₂SO₃ was added until starch-iodide paper indicated that no *m*-CPBA was present. The resultant mixture was diluted with CH₂Cl₂ (20 mL), washed with 0.1 M aq NaHCO₃ (4 × 15 mL), dried and concentrated *in vacuo* to give a 74:26 mixture of (±)-**223** and (±)-**224**, respectively, as a yellow oil (380 mg). Data for (±)-**223**: δ_H (400 MHz, *d*₁-CHCl₃) [selected peaks] 2.40 (3H, s, ArMe), 2.73 (1H, app t, *J* 2.6, C(2)*H*), 3.90–3.94 (1H, m, C(3)*H*), 3.98–4.01 (1H, m, C(1)*H*), 4.56–4.60 (1H, m, C(4)*H*); δ_C (100 MHz, *d*₁-CHCl₃) [selected peaks] 54.3 (C(2)), 67.2 (C(1)), 68.3 (C(3)), 79.6 (C(4)).

Step 2. DBU (150 mL, 1.05 mmol) was added to a stirred solution of the 74:26 mixture of (±)-**223** and (±)-**224**, from the previous step (380 mg) in CH₂Cl₂ (2 mL) at rt. The resultant solution was stirred at rt for 24 h and then concentrated *in vacuo*. Purification *via* flash column chromatography (eluent CHCl₃/MeOH, 98:2) gave (±)-**224** as a pale yellow solid (111 mg, 41% from (±)-**171**, >95:5 dr); mp 64–69 °C; ν_{max} 3416, 3416, 3026, 2997, 2936, 2851; δ_H (400 MHz, *d*₁-CHCl₃) 1.36–1.55 (2H, m, C(6)*H*₂), 1.87 (1H, dddd, *J* 15.4, 8.9, 6.2, 2.5, C(5)*H*_A), 2.10–2.19 (1H, m, C(5)*H*_B), 3.06 (1H, dd, *J* 5.6, 4.0, C(2)*H*), 3.28 (1H, app t, *J* 4.0, C(3)*H*), 3.30–3.33 (1H, m, C(4)*H*), 3.56 (1H, ddd, *J* 9.6, 5.6, 3.9, C(1)*H*), 3.94 (1H, d, *J* 13.0, NCH_AH_BPh), 4.02 (1H, d, *J* 13.0, NCH_AH_BPh), 7.24–7.43 (5H, m, *Ph*); δ_C (100 MHz, *d*₁-CHCl₃) 22.3 (C(5)), 24.6 (C(6)), 51.9 (NCH₂Ph), 53.8 (C(2)), 54.5 (C(3)), 55.1 (C(4)), 66.4

(*C*(1)), 127.2, 128.2, 128.5 (*o,m,p-Pb*), 140.0 (*i-Pb*); m/z (ESI⁺) 220 ([M+H]⁺, 100%); HRMS (ESI⁺) C₁₃H₁₈NO₂⁺ ([M+H]⁺) requires 220.1332; found 220.1331.

(1*RS*,2*RS*,3*RS*,4*RS*)-2-(*N*-Benzylamino)cyclohexane-1,3,4-triol (±)-221.

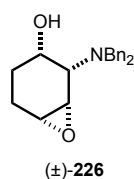


Method A. Epoxidation of (±)-171. HBF₄ (40% aq, 1.43 mL, 9.35 mmol) was added to a stirred solution of (±)-171 (380 mg, 1.87 mmol, >180:1 dr) in CH₂Cl₂ (5.2 mL) at rt. The resultant solution was stirred at rt for 5 min and then *m*-CPBA (75% wt, 686 mg, 2.99 mmol) was added. The resultant solution was stirred at rt for 21 h and then solid Na₂SO₃ was added until starch-iodide paper indicated that no *m*-CPBA was present. The resultant mixture was diluted with 2.25 M aq NaOH (20 mL) and extracted with CHCl₃/PrOH (3:1, v/v, 3 × 30 mL). The combined organics were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent CHCl₃/MeOH/35% aq NH₄OH, 180:20:1) gave (±)-221 as a colourless oil (380 mg, 87%, >95:5 dr); $\nu_{\max}$ 3300, 3090, 3042, 2929, 2876; δ_{H} (400 MHz, *d*₁-CHCl₃) 1.34–1.44 (1H, m, C(5)*H*_A), 1.61–1.72 (2H, m, C(6)*H*_A), 1.77–1.87 (1H, m, C(6)*H*_B), 1.95–2.06 (1H, m, C(5)*H*_B), 2.70 (3H, br s, OH, NH), 2.98 (1H, app t, *J* 3.5, C(2)*H*), 3.64–3.69 (1H, m, C(3)*H*), 3.80–3.86 (1H, m, C(4)*H*), 3.92 (1H, app dt, *J* 7.3, 3.5, C(1)*H*), 3.95 (2H, s, NCH₂Ph), 7.25–7.39 (5H, m, *Pb*); δ_{C} (100 MHz, *d*₁-CHCl₃) 26.3 (*C*(5)), *C*(6)), 52.6 (NCH₂Ph), 57.5 (*C*(2)), 69.5 (*C*(1)), 70.3 (*C*(4)), 73.6 (*C*(3)), 127.4, 128.4, 128.6 (*o,m,p-Pb*), 139.6 (*i-Pb*); m/z (ESI⁺) 238 ([M+H]⁺, 100%); HRMS (ESI⁺) C₁₃H₂₀NO₃⁺ ([M+H]⁺) requires 238.1438; found 238.1437.

Method B. Ring-opening of (±)-224. HBF₄ (40% aq, 250 μ L, 1.59 mmol) was added to a stirred solution of (±)-224 (69.6 mg, 0.318 mmol, >95:5 dr) in CH₂Cl₂ (0.88 mL) at rt. The

resultant solution was stirred at rt for 24 h and then 2.25 M aq NaOH (5 mL) was added. The resultant mixture was extracted with CHCl₃/iPrOH (3:1, v/v, 3 × 10 mL). The combined organics were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent CHCl₃/MeOH/35% aq NH₄OH, 180:20:1) gave (±)-**221** as a colourless oil (51 mg, 68%, >95:5 dr).

(1*R*,2*R*,3*R*,4*R*)-2-(*N,N*-Dibenzylamino)-3,4-epoxycyclohexan-1-ol (±)-226.

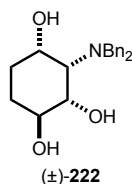


Step 1. A solution of (±)-**173** (250 mg, 0.853 mmol, >180:1 dr) in CH₂Cl₂ (2.4 mL) was added to anhydrous TsOH (734 mg, 4.26 mmol) at rt. The resultant solution was stirred at rt for 5 min and then *m*-CPBA (73% wt, 402 mg, 1.71 mmol) was added. The resultant solution was stirred at rt for 21 h and then solid Na₂SO₃ was added until starch-iodide paper indicated that no *m*-CPBA was present. The resultant mixture was diluted with CH₂Cl₂ (20 mL), washed with 0.1 M aq NaHCO₃ (4 × 15 mL), dried and concentrated *in vacuo* to give a >95:5 mixture of (±)-**225** and (±)-**226**, respectively, as a yellow oil (302 mg).

Data for (±)-**225**: δ_H (400 MHz, *d*₁-CHCl₃) 1.48–1.63 (1H, m, C(5)*H_A*), 1.79 (2H, dt, *J* 9.6, 3.3, C(6)*H₂*), 2.04–2.15 (1H, m, C(5)*H_B*), 2.45 (3H, s, *ArMe*), 2.86 (1H, t, *J* 2.6, C(2)*H*), 3.77 (2H, d, *J* 14.6, N(CH_A*H_B*Ph)₂), 4.03 (2H, d, *J* 14.6, N(CH_A*H_B*Ph)₂), 4.10–4.18 (2H, m, C(1)*H*, C(3)*H*), 4.69 (1H, app q, *J* 3.1, C(4)*H*), 7.21–7.36 (12H, m, *Ph*, *Ar*), 7.73–7.77 (2H, m, *Ar*); δ_C (100 MHz, *d*₁-CHCl₃) 19.0 (C(5)), 21.7 (*ArMe*), 25.7 (C(6)), 55.0 (N(CH₂Ph)₂), 59.6 (C(2)), 68.0 (C(1)), 68.8 (C(3)), 80.1 (C(4)), 127.2, 128.4, 128.6, 129.9, 139.9, 144.9 (*Ph*, *Ar*).

Step 2. DBU (103 μ L, 0.678 mmol) was added to a stirred solution of the >95:5 mixture of ($\pm$)-**225** and ($\pm$)-**226** from the previous step (302 mg) in CH_2Cl_2 (1.3 mL) at rt. The resultant solution was stirred at rt for 24 h and then concentrated *in vacuo*. Purification *via* flash column chromatography (eluent CHCl_3) gave ($\pm$)-**226** as a pale yellow oil (118 mg, 45% from ($\pm$)-**173**, >95:5 dr); ν_{max} 3510, 3084, 3061, 3026, 3001, 2930, 2849, 2810; δ_{H} (400 MHz, d_1 - CHCl_3) 1.34–1.45 (1H, m, $\text{C}(5)\text{H}_{\text{A}}$), 1.78–1.95 (2H, m, $\text{C}(5)\text{H}_{\text{B}}$, $\text{C}(6)\text{H}_{\text{A}}$), 2.14 (1H, ddd, J 16.7, 10.5, 6.8, $\text{C}(6)\text{H}_{\text{B}}$), 3.08 (1H, dd, J 3.9, 1.6, $\text{C}(2)\text{H}$), 3.29 (1H, app t, J 4.4, $\text{C}(4)\text{H}$), 3.41–3.47 (2H, m, $\text{C}(3)\text{H}$, OH), 4.01 (2H, d, J 14.1, $\text{N}(\text{CH}_{\text{A}}\text{H}_{\text{B}}\text{Ph})_2$), 4.11 (2H, d, J 14.1, $\text{N}(\text{CH}_{\text{A}}\text{H}_{\text{B}}\text{Ph})_2$), 4.17 (1H, app s, $\text{C}(1)\text{H}$), 7.21–7.26 (2H, m, *Pb*), 7.29–7.35 (4H, m, *Pb*), 7.38–7.44 (4H, m, *Pb*); δ_{C} (100 MHz, d_1 - CHCl_3) 19.4 ($\text{C}(6)$), 28.3 ($\text{C}(5)$), 52.9 ($\text{C}(4)$), 55.2 ($\text{N}(\text{CH}_2\text{Ph})_2$), 55.7 ($\text{C}(2)$), 56.9 ($\text{C}(3)$), 67.3 ($\text{C}(1)$), 126.9, 128.3, 128.6 (*o,m,p-Pb*), 140.2 (*i-Pb*); m/z (ESI^+) 310 ($[\text{M}+\text{H}]^+$, 100%); HRMS (ESI^+) $\text{C}_{20}\text{H}_{24}\text{NO}_2^+$ ($[\text{M}+\text{H}]^+$) requires 310.1802; found 310.1801.

(1*RS*,2*RS*,3*RS*,4*RS*)-2-(*N,N*-Dibenzylamino)cyclohexane-1,3,4-triol ($\pm$)-222**.**



Method A. Epoxidation of ($\pm$)-173. HBF_4 (40% aq, 530 μ L, 3.36 mmol) was added to a stirred solution of ($\pm$)-**173** (197 mg, 0.672 mmol, >180:1 dr) in CH_2Cl_2 (1.9 mL) at rt. The resultant solution was stirred at rt for 5 min and then *m*-CPBA (73% wt, 253 mg, 1.08 mmol) was added. The resultant solution was stirred at rt for 21 h and then solid Na_2SO_3 was added until starch-iodide paper indicated that no *m*-CPBA was present. The resultant mixture was diluted with 2.25 M aq NaOH (10 mL) and extracted with CHCl_3 /PrOH (3:1, v/v, 3×15 mL). The combined organic extracts were dried and concentrated *in vacuo* to give a 35:65

mixture of (±)-**226** and (±)-**222**, respectively (332 mg). HBF₄ (40% aq, 840 μL, 5.38 mmol) was added to a stirred solution of the 35:65 mixture of (±)-**226** and (±)-**222** (332 mg) in CH₂Cl₂ (3 mL) at rt. The resultant solution was stirred at rt for 24 h and then 2.25 M aq NaOH (10 mL) was added. The resultant mixture was extracted with CHCl₃/PrOH (3:1, v/v, 3 × 15 mL). The combined organics were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent CHCl₃/MeOH, 19:1) gave (±)-**222** as a white solid (136 mg, 62%, >95:5 dr); mp 136–139 °C; ν_{max} 3280, 3027, 2930, 2893, 2808; δ_{H} (400 MHz, *d*₁-CHCl₃) 1.43–1.58 (2H, m, C(5)*H*_A, OH), 1.75–1.93 (2H, m, C(6)*H*₂), 2.08–2.20 (1H, m, C(5)*H*_B), 2.92–3.03 (2H, m, C(2)*H*, OH), 3.58–3.76 (1H, br s, OH), 3.92 (2H, d, *J* 14.4, N(CH_AH_BPh)₂), 4.03–4.15 (4H, m, C(3)*H*, C(4)*H*, N(CH_AH_BPh)₂), 4.17–4.21 (1H, m, C(1)*H*), 7.20–7.36 (10H, m, *Ph*); δ_{C} (100 MHz, *d*₁-CHCl₃) 21.6 (*C*(5)), 25.9 (*C*(6)), 54.9 (N(CH₂Ph)₂), 59.5 (*C*(2)), 68.5 (*C*(1)), 70.4 (*C*(4)), 71.8 (*C*(3)), 127.0, 128.5, 128.6 (*o,m,p-Ph*), 140.2 (*i-Ph*); *m/z* (ESI⁺) 328 ([M+H]⁺, 100%); HRMS (ESI⁺) C₂₀H₂₆NO₃⁺ ([M+H]⁺) requires 328.1907; found 328.1903.

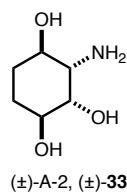
Method B. Ring-opening of (±)-226. HBF₄ (40% aq, 270 μL, 1.72 mmol) was added to a stirred solution of (±)-**226** (107 mg, 0.344 mmol, >95:5 dr) in CH₂Cl₂ (0.96 mL) at rt. The resultant solution was stirred at rt for 24 h and then 2.25 M aq NaOH (10 mL) was added. The resultant mixture was extracted with CHCl₃/PrOH (3:1, v/v, 3 × 15 mL). The combined organics were dried and concentrated *in vacuo* to give a 15:85 mixture of (±)-**226** and (±)-**222**, respectively (126 mg). HBF₄ (40% aq, 320 μL, 2.04 mmol) was added to a stirred solution of the 15:85 mixture of (±)-**226** and (±)-**222** (126 mg) in CH₂Cl₂ (1.1 mL) at rt. The resultant solution was stirred at rt for 24 h and then 2.25 M aq NaOH (10 mL) was added. The resultant mixture was extracted with CHCl₃/PrOH (3:1, v/v, 3 × 15 mL). The combined organics were dried and concentrated *in vacuo*. Purification *via* flash column

chromatography (eluent CHCl₃/MeOH, 49:1) gave (±)-**222** as a white solid (88.5 mg, 79%, >95:5 dr).

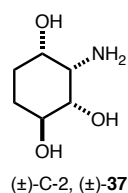
Method C. N-Benzoylation of (±)-221. Pr₂NEt (90.0 μL, 0.506 mmol), BnBr (60.0 μL, 0.506 mmol) and DMAP (1 mg, 8.2 μg) were added sequentially to a stirred solution of (±)-**221** (80.0 mg, 0.337 mmol, >95:5 dr) in CH₂Cl₂ (0.96 mL) at rt. The resultant mixture was stirred at rt for 24 h and then concentrated *in vacuo*. Purification *via* flash column chromatography (eluent CHCl₃/MeOH, 19:1) gave (±)-**222** as a white solid (80.0 mg, 73%, >95:5 dr).

(1*R*,2*S*,3*S*,4*S*)-2-Aminocyclohexane-1,3,4-triol [(±)-Dihydroconduramine A-2]

(±)-33



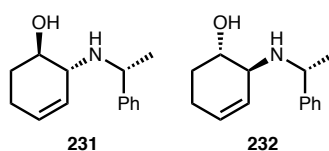
Pd(OH)₂/C (65 mg) was added to a stirred degassed solution of (±)-**210** (130 mg, 0.548 mmol, >95:5 dr) in MeOH (2 mL) and the resultant suspension was stirred at rt under H₂ (1 atm) for 24 h. The reaction mixture was then filtered through Celite® (eluent MeOH), and the filtrate was concentrated *in vacuo* to give (±)-**33** as a yellow oil (63 mg, 79%, >95:5 dr); ν_{max} 3348, 2981, 2971, 2933; δ_{H} (400 MHz, *d*₄-MeOH) 1.54–1.73 (3H, m, C(5)*H*_A, C(6)*H*₂), 1.76–1.88 (1H, m, C(5)*H*_B), 2.75 (1H, dd, *J* 8.8, 2.7, C(2)*H*), 3.50 (1H, app dt, *J* 9.6, 4.7, C(1)*H*), 3.75–3.81 (2H, m, C(3)*H*, C(4)*H*); δ_{C} (100 MHz, *d*₄-MeOH) 27.2 (C(5)), 28.7 (C(6)), 56.4 (C(2)), 70.9 (C(4)), 72.0 (C(1)), 74.2 (C(3)); *m/z* (ESI⁺) 148 ([M+H]⁺, 100%); HRMS (ESI⁺) C₆H₁₄NO₃⁺ ([M+H]⁺) requires 148.0968; found 148.0968.

(1*R*,2*R*,3*R*,4*R*)-2-Aminocyclohexane-1,3,4-triol [(±)-Dihydroconduramine C-2]**(±)-37**

Pd(OH)₂/C (43 mg) was added to a stirred degassed solution of (±)-**221** (85 mg, 0.36 mmol, >95:5 dr) in MeOH (2 mL) and the resultant suspension was stirred at rt under H₂ (1 atm) for 24 h. The reaction mixture was then filtered through Celite® (eluent MeOH), and the filtrate was concentrated *in vacuo*. Purification *via* column chromatography (eluent CHCl₃/MeOH/NH₄OH 7:3:0.5) gave (±)-**37** as a yellow oil (30 mg, 57%, >95:5 dr); $\nu_{\max}$ 3310, 2953, 2928; δ_{H} (400 MHz, MeOH-*d*₄) 1.26–1.37 (1H, m, C(6)*H*_A), 1.69–1.77 (2H, m, C(5)*H*₂), 1.88–1.97 (1H, m, C(6)*H*_B), 3.19 (1H, app t, *J* 3.4, C(2)*H*), 3.47 (1H, dd, *J* 7.3, 3.4, C(3)*H*), 3.75–3.82 (2H, m, C(1)*H*, C(4)*H*); δ_{C} (100 MHz, MeOH-*d*₄) 26.9 (C(5)), 27.4 (C(6)), 54.8 (C(2)), 70.5 (C(1)), 71.7 (C(4)), 76.0 (C(3)); *m/z* (ESI⁺) 148 ([M+H]⁺, 100%); HRMS (ESI⁺) C₆H₁₄NO₃⁺ ([M+H]⁺) requires 148.0968; found 148.0968.

8.3 Experimental for chapter 3

(1*R*,2*R*,*aR*)-2-[(*N*-(*a*-Methylbenzyl)amino]cyclohex-3-en-1-ol 231 and (1*S*,2*S*,*aR*)-2-[(*N*-(*a*-methylbenzyl)amino]cyclohex-3-en-1-ol 232.

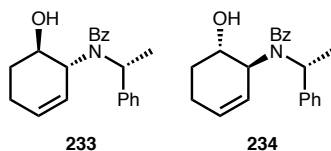


Step 1. AcOOH (39% in AcOH, 31.2 mL, 125 mmol) was added dropwise to a stirred suspension of **202** (10.0 g, 125 mmol) and Na₂CO₃ (119 g, 1.12 mol) in CH₂Cl₂ (350 mL) at 0 °C and the resultant suspension was stirred at 0 °C for 3.5 h. H₂O (200 mL) was added

and the aqueous layer was extracted with CH_2Cl_2 (3×150 mL). The combined organics were washed with satd aq Na_2SO_3 (in 500 mL portions) until starch-iodide paper indicated that no peroxide was present, then dried and concentrated *in vacuo* at 0 °C to give **203** as a colourless oil (13.0 g).³

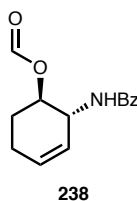
Step 2. (R)- α -Methylbenzylamine (R)-**235** (16.1 mL, 125 mmol) was added to a stirred solution of the residue from the previous step (13.0 g) in *i*-PrOH (125 mL) at rt and the resultant solution was heated at 80 °C for 4 h, then allowed to cool to rt and concentrated *in vacuo*. Purification *via* column chromatography (eluent $\text{CHCl}_3/\text{MeOH}/35\%$ aq NH_4OH 98:2:0.5) gave a 50:50 mixture of **231** and **232**, respectively, as a beige solid (14.5 g, 53% from **202**).⁸ Data for **231**: δ_{H} (400 MHz, $d_1\text{-CHCl}_3$) 1.37 (3H, d, J 6.6, C(α)Me), 1.60–1.69 (1H, m, C(6) H_{A}), 1.91–2.04 (1H, m, C(6) H_{B}), 2.08–2.15 (2H, m, C(5) H_2), 3.05–3.11 (1H, m, C(2) H), 3.35–3.44 (1H, m, C(1) H), 3.98 (1H, q, J 6.6, C(α) H), 5.41–5.46 (1H, m, C(3) H), 5.60–5.70 (1H, m, C(4) H), 7.22–7.38 (5H, m, *Ph*). Data for **232**: δ_{H} (400 MHz, $d_1\text{-CHCl}_3$) 1.37 (3H, d, J 6.6, C(α)Me), 1.41–1.52 (1H, m, C(6) H_{A}), 1.91–2.04 (1H, m, C(6) H_{B}), 2.08–2.15 (2H, m, C(5) H_2), 2.71–2.77 (1H, m, C(2) H), 3.35–3.44 (1H, m, C(1) H), 4.05 (1H, q, J 6.6, C(α) H), 5.60–5.70 (1H, m, C(4) H), 5.73–5.78 (1H, m, C(3) H), 7.22–7.38 (5H, m, *Ph*).

(1R,2R, α R)-2-[(N-Benzoyl-N- α -methylbenzyl)amino]cyclohex-3-en-1-ol **233** and (1S,2S, α R)-2-[(N-benzoyl-N- α -methylbenzyl)amino]cyclohex-3-en-1-ol **234**.

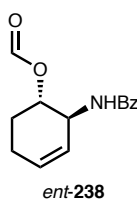


Na_2CO_3 (4.40 g, 41.4 mmol) and benzoyl chloride (2.40 mL, 20.7 mmol) were added sequentially to a stirred solution of a 50:50 mixture of **231** and **232** (4.50 g, 20.7 mmol) in THF (100 mL) at 0 °C and the resultant solution was stirred at rt for 24 h. H_2O (50 mL) was then added and the aqueous layer was extracted with Et_2O (3×60 mL). The

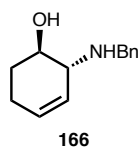
combined organic layers were washed with brine (300 mL), then dried, filtered and concentrated *in vacuo*. Purification *via* column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 7:3) gave **233** as a pale yellow solid (2.50 g, 38%, >95:5 dr); mp 148–150 °C; $[\alpha]_{\text{D}}^{25}$ –69.9 (c 1.0 in CHCl_3); ν_{max} 3393, 3059, 3026, 2939, 1616; δ_{H} (500 MHz, d_8 -PhMe, 363 K) 1.08–1.18 (1H, m, C(6) H_{A}), 1.50–1.56 (1H, m, C(6) H_{B}), 1.60–1.80 (5H, m, C(5) H_2 , C(α)Me), 3.69–3.78 (1H, m, C(1) H), 4.18–4.24 (1H, m, C(2) H), 4.52–4.60 (1H, m, C(α) H), 5.36–5.42 (1H, m, C(3) H), 5.45–5.51 (1H, m, C(4) H), 6.90–7.12 (6H, m, Pb), 7.27–7.33 (2H, m, Pb), 7.42–7.49 (2H, m, Pb); δ_{C} (125 MHz, d_8 -PhMe, 363 K) 20.5⁹ (C(α)Me), 25.1 (C(5)), 31.2 (C(6)), 56.2 (C(α)), 64.3 (C(2)), 69.0 (C(1)), 127.3 (C(3)), 127.3, 128.2,⁹ 128.4, 128.8⁹ (Pb), 130.7 (C(4)), 139.7, 144.0 (Pb), 172.6 (COPh); m/z (ESI⁺) 322 ([M+H]⁺, 100%); HRMS (ESI⁺) $\text{C}_{21}\text{H}_{24}\text{NO}_2^+$ ([M+H]⁺) requires 322.1802; found 322.1801. Further elution gave **234** as a pale yellow powder (2.50 g, 38%, >95:5 dr); mp 68–72 °C; $[\alpha]_{\text{D}}^{25}$ +163.9 (c 1.0 in CHCl_3); ν_{max} 3393, 3029, 2937, 1614; δ_{H} (500 MHz, d_8 -PhMe, 363 K) 1.21–1.35 (1H, m, C(6) H_{A}), 1.63–1.79 (5H, m, C(6) H_{B} , C(5) H_{A} , C(α)Me) 1.83–1.96 (1H, m, C(5) H_{B}), 3.99–4.14 (2H, m, C(1) H , C(2) H), 4.80–4.92 (1H, m, C(α) H), 5.19–5.30 (1H, m, C(3) H), 5.32–5.43 (1H, m, C(4) H), 6.93–7.16 (6H, m, Pb), 7.29–7.41 (4H, m, Pb); δ_{C} (125 MHz, d_8 -PhMe, 363 K) 19.0 (C(α)Me), 25.2 (C(5)), 32.2 (C(6)), 56.0 (C(α)), 62.8 (C(1)), 68.4 (C(2)), 127.3 (C(4)), 127.5, 128.2 (Pb), 128.5 (C(3)), 128.6, 128.9,⁹ 139.7, 142.6 (Pb), 171.7 (COPh); m/z (ESI⁺) 322 ([M+H]⁺, 100%); HRMS (ESI⁺) $\text{C}_{21}\text{H}_{24}\text{NO}_2^+$ ([M+H]⁺) requires 322.1802; found 322.1801.

(1R,2R)-1-Formyloxy-2-(N-benzoylamino)cyclohex-3-ene 238.

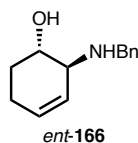
A stirred solution of **233** (6.50 g, 20.2 mmol, >95:5 dr) in HCO₂H (90% aq, 195 mL) was heated at 60 °C for 18 h, then allowed to cool to rt and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/acetone, 9:1) gave **238** as a pale yellow solid (4.70 g, 94%, >95:5 dr); mp 139–145 °C; $[\alpha]_{\text{D}}^{25}$ –126.2 (*c* 1.0 in CHCl₃); ν_{max} 3270, 2921, 1712, 1640; δ_{H} (400 MHz, *d*₁-CHCl₃) 1.97–2.05 (2H, m, C(6)*H*₂), 2.24–2.31 (2H, m, C(5)*H*₂), 4.84–4.92 (1H, m, C(2)*H*), 5.14–5.22 (1H, m, C(1)*H*), 5.59–5.65 (1H, m, C(3)*H*), 5.85–5.92 (1H, m, C(4)*H*), 6.20–6.29 (1H, m, NH), 7.42–7.47 (2H, m, *Ph*), 7.49–7.54 (1H, m, *Ph*), 7.74–7.78 (2H, m, *Ph*), 8.12 (1H, s, CHO); δ_{C} (100 MHz, *d*₁-CHCl₃) 23.7 (C(5)), 26.2 (C(6)), 50.6 (C(2)), 72.1 (C(1)), 126.1 (C(3)), 126.9, 128.5 (*Ph*), 129.4 (C(4)), 131.5, 134.0 (*Ph*), 161.1 (CHO), 167.1 (NCOPh); *m/z* (ESI⁺) 268 ([M+Na]⁺, 100%); HRMS (ESI⁺) C₁₄H₁₆NO₃⁺ ([M+H]⁺) requires 246.1125; found 246.1127.

(1S,2S)-1-Formyloxy-2-(N-benzoylamino)cyclohex-3-ene *ent*-238.

A stirred solution of **234** (1.00 g, 3.11 mmol, >95:5 dr) in HCO₂H (90% aq, 15 mL) was heated at 60 °C for 18 h, then allowed to cool to rt and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/acetone, 9:1) gave *ent*-**238** as a pale yellow solid (530 mg, 69%, >95:5 dr); mp 140–146 °C; $[\alpha]_{\text{D}}^{25}$ +130.6 (*c* 1.0 in CHCl₃).

(1R,2R)-2-(N-Benzylamino)cyclohex-3-en-1-ol **166.**

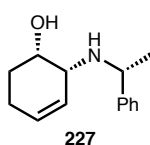
LiAlH₄ (2.4 M in THF, 3.4 mL, 8.2 mmol) was added dropwise *via* syringe to a stirred solution of **238** (500 mg, 2.04 mmol, >95:5 dr) in THF (40 mL) at 0 °C and the resultant solution was heated at 60 °C for 16 h, then allowed to cool to rt and then cooled to 0 °C. 2 M aq NaOH (5 mL) was then added dropwise and the resultant mixture was heated at 60 °C for 3 h. The resultant mixture was allowed to cool to rt, filtered through a plug of Celite® (eluent CH₂Cl₂), and the filtrate was concentrated *in vacuo*. Purification *via* flash column chromatography (eluent CHCl₃/MeOH/35% aq NH₄OH, 97:3:0.5) gave **166** as a yellow oil (340 mg, 82%, >180:1 dr, 99.3% ee); [α]_D²⁵ -123.1 (*c* 1.0 in CHCl₃). Analysis of **166** by chiral HPLC [Chiralpak AD-H, mobile phase: hexane/*i*PrOH (v/v, 95:5), flow rate: 1 mL/min, 10 μ L injection] and comparison to the racemic standard allowed **166** to be assessed as 99.3% ee [**166** *t*_R = 14.3 min].

(1S,2S)-2-(N-Benzylamino)cyclohex-3-en-1-ol *ent*-166**.**

LiAlH₄ (2.4 M in THF, 3.4 mL, 8.2 mmol) was added dropwise *via* syringe to a stirred solution of *ent*-**238** (500 mg, 2.04 mmol, >95:5 dr) in THF (40 mL) at 0 °C and the resultant solution was heated at 60 °C for 16 h, then allowed to cool to rt and then cooled to 0 °C. 2 M aq NaOH (5 mL) was then added dropwise and the resultant mixture was heated at 60 °C for 3 h. The resultant mixture was allowed to cool to rt, filtered through a plug of Celite® (eluent CH₂Cl₂), and the filtrate was concentrated *in vacuo*. Purification *via*

flash column chromatography (eluent $\text{CHCl}_3/\text{MeOH}/35\% \text{ aq } \text{NH}_4\text{OH}$, 97:3:0.5) gave *ent*-**166** as a yellow oil (300 mg, 73%, >180:1 dr, 99.1% ee); $[\alpha]_{\text{D}}^{25} +124.9$ (c 1.0 in CHCl_3). Analysis of *ent*-**166** by chiral HPLC [Chiralpak AD-H, mobile phase: hexane/ i PrOH (v/v, 95:5), flow rate: 1 mL/min, 10 μL injection] and comparison to the racemic standard allowed *ent*-**166** to be assessed as 99.1% ee [*ent*-**166** $t_{\text{R}} = 15.8$ min].

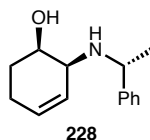
(1*S*,2*R*, α *R*)-2-[*N*-(α -Methylbenzyl)amino]cyclohex-3-en-1-ol **227**



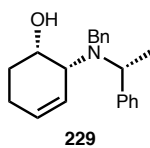
SOCl_2 (170 μL , 2.37 mmol) was added to a stirred solution of **233** (200 mg, 0.623 mmol, >95:5 dr, >99% ee) in CH_2Cl_2 (0.75 mL) at 0 °C. The resultant mixture was stirred at rt for 4 h and then concentrated *in vacuo*. MeOH (8.2 mL) and K_2CO_3 (700 mg) were then added sequentially. The resultant mixture was stirred at rt for 16 h and then concentrated *in vacuo*. H_2O (15 mL) was then added and the resultant mixture was extracted with CH_2Cl_2 (3 $\times$ 20 mL). The combined organics were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent $\text{CHCl}_3/\text{MeOH}$, 49:1) gave **227** as a white solid (130 mg, 95%, >95:5 dr); mp 50–51 °C; $[\alpha]_{\text{D}}^{25} -113.8$ (c 1.0 in CHCl_3); ν_{max} 3410, 3320, 3061, 3024, 2963, 2923, 2839; δ_{H} (400 MHz, d_1 - CHCl_3) 1.40 (3H, d, J 6.7, C(α)Me), 1.61–1.67 (2H, m, C(6) H_2), 1.88–1.99 (1H, m, C(5) H_A), 2.14 (1H, app ddtd, J 18.0, 6.0, 3.9, 1.8, C(5) H_B), 3.03–3.08 (1H, m, C(2) H), 3.76 (1H, app dt, J 7.0, 4.7, C(1) H), 3.90 (1H, q, J 6.7, C(α) H), 5.31 (1H, app ddt, J 10.0, 3.9, 2.1, C(3) H), 5.70 (1H, app dtd, J 10.0, 3.9, 1.8, C(4) H), 7.24–7.38 (5H, m, *Ph*); δ_{C} (100 MHz, d_1 - CHCl_3) 22.5 (C(5)), 24.1 (C(α)Me), 27.0 (C(6)), 53.5 (C(2)), 56.5 (C(α)), 65.3 (C(1)), 126.3 (*o,m-Ph*), 127.2, 127.4 (C(3), *p-Ph*), 128.6

(*o,m*-Ph), 129.4 (*C*(4)), 145.7 (*i*-Ph); m/z (ESI⁺) 218 ([M+H]⁺, 100%); HRMS (ESI⁺) m/z : C₁₄H₂₀NO⁺ ([M+H]⁺) requires 218.1539; found 218.1539.

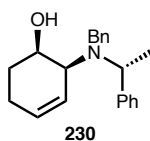
(1*R*,2*S*, α *R*)-2-[N-(α -Methylbenzyl)amino]cyclohex-3-en-1-ol **228**



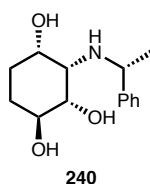
SOCl₂ (4.72 mL, 65.1 mmol) was added to a stirred solution of **234** (5.50 g, 17.1 mmol, >95:5 dr, >99% ee) in CH₂Cl₂ (20.3 mL) at 0 °C. The resultant mixture was stirred at rt for 4 h and then concentrated *in vacuo*. MeOH (139 mL) and K₂CO₃ (11.8 g) were then added sequentially. The resultant mixture was stirred at rt for 16 h and then concentrated *in vacuo*. H₂O (75 mL) was then added and the resultant mixture was extracted with CH₂Cl₂ (3 × 100 mL). The combined organics were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent CHCl₃/MeOH, 49:1) gave **228** as an orange oil (2.76 g, 74%, >95:5 dr); [α]_D²⁵ +250 (*c* 1.0 in CHCl₃); $\nu_{\max}$ 3421, 3061, 3023, 2961, 2923, 2838; δ_{H} (400 MHz, *d*₁-CHCl₃) 1.40 (3H, d, *J* 6.5, C(α)Me), 1.47–1.58 (1H, m, C(6)*H*_A), 1.66–1.75 (1H, m, C(6)*H*_B), 1.93–2.04 (1H, m, C(5)*H*_A), 2.10–2.21 (1H, m, C(5)*H*_B), 2.96–3.01 (1H, m, C(2)*H*), 3.51 (1H, ddd, *J* 9.8, 5.2, 2.8, C(1)*H*), 4.04 (1H, q, *J* 6.5, C(α)*H*), 5.76–5.83 (2H, m, C(3)*H*, C(4)*H*), 7.22–7.38 (5H, m, *Ph*); δ_{C} (100 MHz, *d*₁-CHCl₃) 23.3 (*C*(5)), 25.0 (C(α)Me), 27.2 (*C*(6)), 53.0 (*C*(2)), 56.1 (*C*(α)), 66.4 (*C*(1)), 126.8 (*o,m*-Ph), 127.1 (*C*(3)), 127.2 (*p*-Ph), 128.5 (*o,m*-Ph), 129.5 (*C*(4)), 145.0 (*i*-Ph); m/z (ESI⁺) 218 ([M+H]⁺, 100%); HRMS (ESI⁺) C₁₄H₂₀NO⁺ ([M+H]⁺) requires 218.1539; found 218.1537.

(1*S*,2*R*, α *R*)-2-[*N*-Benzyl-*N*-(α -methylbenzyl)amino]cyclohex-3-en-1-ol 229

K_2CO_3 (3.21 g, 23.3 mmol) and BnBr (1.38 mL, 11.6 mmol) were added sequentially to a stirred solution of **227** (1.01 g, 4.65 mmol, >95:5 dr) in MeCN (7.4 mL) at rt. The resultant solution was heated at reflux for 24 h and then allowed to cool to rt and concentrated *in vacuo*. H_2O (75 mL) was then added and the resultant mixture was extracted with CH_2Cl_2 (3 $\times$ 100 mL). The combined organics were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent CHCl_3) gave **229** as a yellow solid (1.14 g, 80%, >95:5 dr); mp 62–70 °C; $[\alpha]_{\text{D}}^{25}$ -220 (c 1.0 in CHCl_3); ν_{max} 3431, 3084, 3061, 3025, 2936, 2876, 2839; δ_{H} (400 MHz, d_1 - CHCl_3) 1.48 (3H, d, J 6.9, C(α)Me), 1.55–1.65 (2H, m, C(6) H_{A}), 1.72–1.82 (1H, m, C(6) H_{B}), 1.95–2.07 (1H, m, C(5) H_{A}), 2.12–2.22 (1H, m, C(5) H_{B}), 3.38 (1H, app dt, J 10.7, 5.1, C(1) H), 3.42–3.47 (1H, m, C(2) H), 3.68 (1H, s, OH), 3.74 (1H, d, J 14.4, $\text{NCH}_{\text{A}}\text{H}_{\text{B}}\text{Ph}$), 4.00–4.09 (2H, m, C(α) H , $\text{NCH}_{\text{A}}\text{H}_{\text{B}}\text{Ph}$), 5.79 (1H, dddd, J 9.9, 4.2, 2.5, 1.5, C(3) H), 5.97 (1H, app ddt, J 9.9, 4.2, 2.2, C(4) H), 7.18–7.47 (10H, m, Ph); δ_{C} (100 MHz, d_1 - CHCl_3) 12.0 (C(α)Me), 23.7 (C(5)), 27.8 (C(6)), 52.9 (C(2)), 54.2 (NCH_2Ph), 57.0 (C(α)), 67.0 (C(1)), 126.6 (C(3)), 127.2, 127.3 (p - Ph), 127.9, 128.4, 128.5, 128.8 (o,m - Ph), 131.8 (C(4)), 140.9, 143.0 (i - Ph); m/z (ESI $^{+}$) 308 ($[\text{M}+\text{H}]^{+}$, 100%); HRMS (ESI $^{+}$) $\text{C}_{21}\text{H}_{26}\text{NO}^{+}$ ($[\text{M}+\text{H}]^{+}$) requires 308.2009; found 308.2009.

(1*R*,2*S*, α *R*)-2-[*N*-Benzyl-*N*-(α -methylbenzyl)amino]cyclohex-3-en-1-ol **230**

K_2CO_3 (2.80 g, 20.1 mmol) and BnBr (1.20 mL, 10.1 mmol) were added sequentially to a stirred solution of **228** (875 mg, 4.03 mmol, >95:5 dr) in MeCN (6.4 mL) at rt. The resultant solution was heated at reflux for 24 h and then allowed to cool to rt and concentrated *in vacuo*. H_2O (50 mL) was then added and the resultant mixture was extracted with CH_2Cl_2 (3×75 mL). The combined organics were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent CHCl_3) gave **230** as a yellow solid (1.08 g, 87%, >95:5 dr); mp 75–84 °C; $[\alpha]_{\text{D}}^{25} +344$ (c 1.0 in CHCl_3); ν_{max} 3357, 3083, 3060, 3025, 2967, 2935, 2875, 2839; δ_{H} (400 MHz, d_1 - CHCl_3) 1.39–1.54 (4H, m, $\text{C}(\alpha)\text{Me}$, $\text{C}(6)\text{H}_{\text{A}}$), 1.84–1.94 (1H, m, $\text{C}(6)\text{H}_{\text{B}}$), 1.95–2.15 (2H, m, $\text{C}(5)\text{H}_2$), 3.62 (1H, d, J 15.2, $\text{NCH}_{\text{A}}\text{H}_{\text{B}}\text{Ph}$), 3.69–3.78 (1H, m, $\text{C}(1)\text{H}$), 3.79–3.84 (1H, m, $\text{C}(2)\text{H}$), 3.88–3.97 (2H, m, $\text{C}(\alpha)\text{H}$, $\text{NCH}_{\text{A}}\text{H}_{\text{B}}\text{Ph}$), 4.48 (1H, s, OH), 4.77 (1H, dddd, J 9.8, 4.3, 2.5, 1.5, $\text{C}(3)\text{H}$), 5.73 (1H, ddd, J 9.8, 4.5, 2.0, $\text{C}(4)\text{H}$), 7.25–7.48 (10H, m, *Ph*); δ_{C} (100 MHz, d_1 - CHCl_3) 19.6 ($\text{C}(\alpha)\text{Me}$), 24.0 ($\text{C}(5)$), 28.2 ($\text{C}(6)$), 52.3 ($\text{C}(2)$), 54.2 (NCH_2Ph), 57.5 ($\text{C}(\alpha)$), 67.0 ($\text{C}(1)$), 125.8 ($\text{C}(3)$), 127.0, 127.5 (*p-Ph*), 128.2, 128.3, 128.6 (*o,m-Ph*), 131.5 ($\text{C}(4)$), 140.5, 140.6 (*i-Ph*); m/z (ESI^+) 308 ($[\text{M}+\text{H}]^+$, 100%); HRMS (ESI^+) $\text{C}_{21}\text{H}_{26}\text{NO}^+$ ($[\text{M}+\text{H}]^+$) requires 308.2009; found 308.2007.

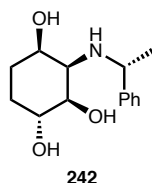
(1*S*,2*S*,3*S*,4*S*, α *R*)-2-[(*N*-(α -Methylbenzyl)amino)cyclohexane-1,3,4-triol **240**

Method A. Epoxidation of 227. HBF₄ (40% aq, 3.6 mL, 23 mmol) was added to a stirred solution of **227** (1.0 g, 4.6 mmol, >95:5 dr) in CH₂Cl₂ (13 mL) at rt. The resultant solution was stirred at rt for 5 min and then *m*-CPBA (75% wt, 1.9 g, 7.4 mmol) was added. The resultant solution was stirred at rt for 30 h and then solid Na₂SO₃ was added until starch-iodide paper indicated that no *m*-CPBA was present. The resultant mixture was diluted with 2.25 M aq NaOH (75 mL) and extracted with CHCl₃/*i*-PrOH (3:1, v/v, 3 × 100 mL). The combined organics were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent CHCl₃/MeOH/35% aq NH₄OH, 180:20:1) gave **240** as a white solid (0.75 g, 65%, >95:5 dr); mp 138–145 °C; [α]_D²⁵ +53.1 (*c* 1.0 in CHCl₃); $\nu_{\max}$ 3336, 3063, 3028, 2929; δ_{H} (400 MHz, *d*₁-CHCl₃) 1.32–1.43 (4H, m, C(5)*H*_A, C(α)*Me*), 1.64–1.86 (2H, m, C(6)*H*₂), 1.93–2.04 (1H, m, C(5)*H*_B), 2.84 (1H, app t, *J* 3.6, C(2)*H*), 3.41 (1H, app t, *J* 3.6, C(3)*H*), 3.78 (1H, app td, *J* 5.9, 3.6, C(4)*H*), 3.92 (1H, app dt, *J* 6.7, 3.6, C(1)*H*), 4.05 (1H, q, *J* 6.6, C(α)*H*), 7.23–7.37 (5H, m, *Ph*); δ_{C} (100 MHz, *d*₁-CHCl₃) 23.1 (C(5)), 24.4 (C(α)*Me*), 26.2 (C(6)), 55.1 (C(2)), 56.6 (C(α)), 69.7 (C(1)), 70.2 (C(4)), 74.3, (C(3)), 126.7, 127.3, 128.6 (*o,m,p-Ph*), 145.4 (*i-Ph*); *m/z* (ESI⁺) 252 ([M+H]⁺, 100%); HRMS (ESI⁺) C₁₄H₂₂NO₃⁺ ([M+H]⁺) requires 252.1594; found 252.1594.

Method B. Ring-opening of 239. HBF₄ (40% aq, 443 μ L, 2.83 mmol) was added to a stirred solution of **239** (132 mg, 0.566 mmol, >95:5 dr) in CH₂Cl₂ (1.6 mL) at rt. The resultant solution was stirred at rt for 24 h and then 2.25 M aq NaOH (10 mL) was added. The resultant mixture was extracted with CHCl₃/*i*-PrOH (3:1, v/v, 3 × 20 mL). The combined organics were dried and concentrated *in vacuo*. Purification *via* flash column

chromatography (eluent $\text{CHCl}_3/\text{MeOH}/35\%$ aq NH_4OH , 180:20:1) gave **240** as a white solid (98 mg, 69%, >95:5 dr).

(1R,2R,3R,4R, α R)-2-[N-(α -Methylbenzyl)amino]cyclohexane-1,3,4-triol **242**

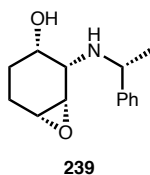


Method A. Epoxidation of 228. HBF_4 (40% aq, 502 μL , 3.22 mmol) was added to a stirred solution of **228** (140 mg, 0.645 mmol, >95:5 dr) in CH_2Cl_2 (1.8 mL) at rt. The resultant solution was stirred at rt for 5 min and then *m*-CPBA (75%, 0.243 g, 1.03 mmol) was added. The resultant solution was stirred at rt for 30 h and then solid Na_2SO_3 was added until starch-iodide paper indicated that no *m*-CPBA was present. 2.25 M aq NaOH (15 mL) was then added and the resultant mixture was extracted with $\text{CHCl}_3/i\text{PrOH}$ (3:1, v/v, 3×30 mL). The combined organics were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent $\text{CHCl}_3/\text{MeOH}/35\%$ aq NH_4OH , 180:20:1) gave **242** as a white solid (113 mg, 70%, >95:5 dr); mp 149–157 $^\circ\text{C}$; $[\alpha]_{\text{D}}^{25} +26.0$ (c 1.0 in CHCl_3); ν_{max} 3345, 3062, 3028, 2929, 2863; δ_{H} (400 MHz, $d_1\text{-CHCl}_3$) 1.32–1.43 (4H, m, $\text{C}(5)\text{H}_\text{A}$, $\text{C}(\alpha)\text{Me}$), 1.53–1.64 (1H, m, $\text{C}(6)\text{H}_\text{A}$), 1.69–1.79 (1H, m, $\text{C}(6)\text{H}_\text{B}$), 1.94–2.04 (1H, m, $\text{C}(5)\text{H}_\text{B}$), 2.85 (1H, app t, J 3.5, $\text{C}(2)\text{H}$), 3.64–3.70 (2H, m, $\text{C}(1)\text{H}$, $\text{C}(3)\text{H}$), 3.88–3.94 (1H, m, $\text{C}(4)\text{H}$), 4.04 (1H, q, J 6.6, $\text{C}(\alpha)\text{H}$), 7.22–7.39 (5H, m, *Ph*); δ_{C} (100 MHz, $d_1\text{-CHCl}_3$) 23.1 ($\text{C}(5)$), 24.5 ($\text{C}(\alpha)\text{Me}$), 26.1 ($\text{C}(6)$), 55.3 ($\text{C}(2)$), 56.9 ($\text{C}(\alpha)$), 70.3 ($\text{C}(4)$), 70.5 ($\text{C}(1)$), 73.7 ($\text{C}(3)$), 126.7, 127.2, 128.6 (*o,m,p-Ph*), 145.6 (*i-Ph*); m/z (ESI^+) 252 ($[\text{M}+\text{H}]^+$, 100%); HRMS (ESI^+) $\text{C}_{14}\text{H}_{22}\text{NO}_3^+$ ($[\text{M}+\text{H}]^+$) requires 252.1594; found 252.1594.

Method B. Ring-opening of 241. HBF_4 (40% aq, 272 μL , 1.73 mmol) was added to a stirred solution of **241** (81 mg, 0.35 mmol, >95:5 dr) in CH_2Cl_2 (0.96 mL) at rt. The resultant

solution was stirred at rt for 24 h and then 2.25 M aq NaOH (5 mL) was added. The resultant mixture was extracted with CHCl₃/iPrOH (3:1, v/v, 3 × 15 mL). The combined organics were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent CHCl₃/MeOH/35% aq NH₄OH, 180:20:1) gave **242** as a white solid (54 mg, 62%, >95:5 dr).

(1*S*,2*S*,3*S*,4*R*,*αR*)-2-[N-(*α*-Methylbenzyl)amino]-3,4-epoxycyclohexan-1-ol 239**

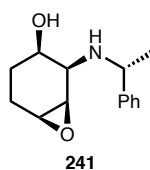


Step 1. A solution of **227** (3.10 g, 14.3 mmol, >95:5 dr) in CH₂Cl₂ (39.7 mL) was added to anhydrous TsOH (12.3 g, 71.4 mmol) at rt. The resultant solution was stirred at rt for 5 min and then *m*-CPBA (68% wt, 5.78 g, 22.8 mmol) was added. The resultant solution was stirred at rt for 21 h and then solid Na₂SO₃ was added until starch-iodide paper indicated that no *m*-CPBA was present. The resultant mixture was diluted with CH₂Cl₂ (40 mL) and washed with 0.1 M aq NaHCO₃ (4 × 50 mL), dried and concentrated *in vacuo* to give an 87:13 mixture of **243** and **239**, respectively, as a yellow oil (6.03 g). Data for **243**: δ_H (400 MHz, *d*₁-CHCl₃) [selected peaks] 1.40 (3H, d, *J* 6.8, C(*α*)Me), 2.34 (3H, s, ArMe), 2.65 (1H, app t, *J* 3.3, C(2)H), 3.63 (1H, app t, *J* 3.3, C(3)H), 3.96–4.07 (2H, m, C(1)H, C(*α*)H), 4.52 (1H, app d, *J* 3.3, C(4)H); δ_C (100 MHz, *d*₁-CHCl₃) [selected peaks] 21.6 (ArMe), 22.4 (C(*α*)Me), 53.3 (C(2)), 55.8 (C(*α*)), 67.0 (C(1)), 69.2 (C(3)), 79.5 (C(4)).

Step 2. DBU (2.29 mL, 16.1 mmol) was added to a stirred solution of the 87:13 mixture of **243** and **239** from the previous step (6.03 g) in CH₂Cl₂ (30.4 mL) at rt. The resultant solution was stirred at rt for 24 h and then concentrated *in vacuo*. Purification *via* flash column chromatography (eluent CHCl₃/MeOH, 49:1) gave **239** as a pale yellow solid (2.36

g, 71% from **227**, >95:5 dr); mp 50–52 °C; $[\alpha]_D^{25}$ –58.2 (c 1.0 in CHCl_3); ν_{max} 3387, 3053, 3061, 3020, 3000, 2953, 2920, 2873; δ_{H} (400 MHz, d_1 - CHCl_3) 1.31–1.40 (1H, m, J 13.1, 3.2, C(5) H_{A}), 1.43 (3H, d, J 6.6, C(α)Me), 1.45–1.54 (1H, m, C(5) H_{B}), 1.80 (1H, dddd, J 15.7, 8.8, 6.1, 2.8, C(6) H_{A}), 2.04–2.13 (1H, m, C(6) H_{B}), 2.84 (1H, app td, J 4.3, 0.8, C(2) H), 2.92 (1H, app t, J 4.3, C(3) H), 3.20 (1H, ddd, J 4.3, 2.8, 1.4, C(1) H), 3.50–3.59 (1H, m, C(4) H), 3.74 (1H, br s, OH), 3.95 (1H, q, J 6.6, C(α) H), 7.24–7.29 (1H, m, Pb), 7.32–7.41 (4H, m, Pb); δ_{C} (100 MHz, d_1 - CHCl_3) 21.8 (C(6)), 24.2 (C(α)Me), 24.9 (C(5)), 52.6 (C(3)), 55.3 (C(4)), 55.6 (C(2)), 57.0 (C(α)), 66.1 (C(1)), 126.6, 127.2, 128.5 (o,m,p - Pb), 145.7 (i - Pb); m/z (ESI $^+$) 234 ($[\text{M}+\text{H}]^+$, 100%); HRMS (ESI $^+$) $\text{C}_{14}\text{H}_{20}\text{NO}_2^+$ ($[\text{M}+\text{H}]^+$) requires 234.1489; found 234.1489.

(1R,2R,3R,4S, α R)-2-[N-(α -Methylbenzyl)amino]-3,4-epoxycyclohexan-1-ol **241**



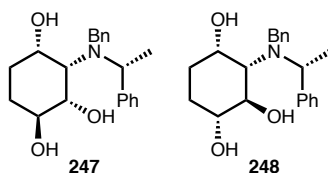
Step 1. A solution of **228** (810 mg, 3.73 mmol, >95:5 dr) in CH_2Cl_2 (10.4 mL) was added to anhydrous TsOH (3.21 g, 18.6 mmol) at rt. The resultant solution was stirred at rt for 5 min and then *m*-CPBA (70% wt, 1.47 g, 5.97 mmol) was added. The resultant solution was stirred at rt for 21 h and then solid Na_2SO_3 was added until starch-iodide paper indicated that no *m*-CPBA was present. The resultant mixture was diluted with CH_2Cl_2 (30 mL), washed with 0.1 M aq NaHCO_3 (4×30 mL), dried and concentrated *in vacuo* to give a 80:20 mixture of **244** and **241**, respectively, as a yellow oil (1.44 g). Data for **244**: δ_{H} (400 MHz, d_1 - CHCl_3) [selected peaks] 1.46 (3H, d, J 6.6, C(α)Me), 2.47 (3H, s, ArMe), 2.66 (1H, app t, J 3.0, C(2) H), 3.78–3.82 (1H, m, C(1) H), 3.91–3.95 (1H, m, C(3) H), 4.00 (1H, q, J

6.6, C(α H), 4.69 (1H, q, J 3.3, C(4)H); δ_{C} (100 MHz, d_1 -CHCl₃) [selected peaks] 21.7 (ArMe), 24.1 (C(α)Me), 53.4 (C(2)), 56.1 (C(α)), 69.5 (C(3)), 69.6 (C(1)), 79.8 (C(4)).

Step 2. DBU (582 mL, 3.84 mmol) was added to a stirred solution of the 80:20 mixture of **244** and **241** from the previous step (1.44 mg) in CH₂Cl₂ (7.2 mL) at rt. The resultant solution was stirred at rt for 24 h and then concentrated *in vacuo*. Purification *via* flash column chromatography (eluent CHCl₃) gave **241** as a pale yellow oil (586 mg, 67% from **228**, >95:5 dr); $[\alpha]_{\text{D}}^{25} +159.5$ (c 1.0 in CHCl₃); ν_{max} 3424, 3061, 3025, 2928; δ_{H} (400 MHz, d_1 -CHCl₃) 1.39–1.47 (5H, m, C(6)H₂, C(α)Me), 1.83 (1H, dddd, J 15.6, 9.1, 6.8, 2.1, C(5)H_A), 2.10–2.20 (1H, m, C(5)H_B), 2.91 (1H, dd, J 5.9, 3.8, C(2)H), 3.30–3.41 (3H, m, C(1)H, C(3)H, C(4)H), 3.78 (1H, br s, OH), 4.16 (1H, q, J 6.5, C(α)H), 7.24–7.30 (1H, m, *Pb*), 7.31–7.39 (4H, m, *Pb*); δ_{C} (100 MHz, d_1 -CHCl₃) 22.6 (C(6)), 24.4 (C(5)), 25.1 (C(α)Me), 51.1 (C(2)), 53.9 (C(4)), 55.1 (C(3)), 55.4 (C(α)), 66.7 (C(1)), 126.9, 127.3, 128.6 (*o,m,p-Pb*), 144.6 (*i-Pb*); m/z (ESI⁺) 234 ([M+H]⁺, 100%); HRMS (ESI⁺) C₁₄H₂₀NO₂⁺ ([M+H]⁺) requires 234.1489; found 234.1489.

(1*S*,2*S*,3*S*,4*S*, α R)-2-[N-Benzyl-N-(α -methylbenzyl)amino]cyclohexane-1,3,4-triol

247 and **(1*S*,2*S*,3*R*,4*R*, α R)-2-[N-benzyl-N-(α -methylbenzyl)amino]cyclohexane-1,3,4-triol** **248**.



Via Epoxidation of 229. Step 1. HBF₄ (40% aq, 510 μ L, 3.26 mmol) was added to a stirred solution of **229** (200 mg, 0.651 mmol, >95:5 dr) in CH₂Cl₂ (1.8 mL) at rt. The resultant solution was stirred at rt for 5 min and then *m*-CPBA (75% wt, 0.767 g, 3.26 mmol) was added. The resultant solution was stirred at rt for 30 h and then solid Na₂SO₃ was added

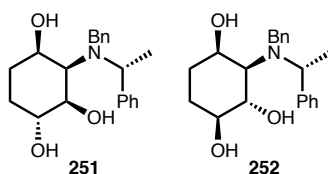
until starch-iodide paper indicated that no *m*-CPBA was present. The resultant mixture was diluted with 2.25 M aq NaOH (15 mL) and extracted with CHCl₃/*i*-PrOH (3:1, v/v, 3 × 30 mL). The combined organics were dried and concentrated *in vacuo* to give an ~1:1:1 mixture of **245**, **246** and **247** (310 mg).

Step 2. HBF₄ (40% aq, 750 μL, 4.80 mmol) was added to a stirred solution of the ~1:1:1 mixture of **245**, **246** and **247**, respectively, from the previous step (310 mg) in CH₂Cl₂ (2.7 mL) at rt. The resultant solution was stirred at rt for 24 h and then 2.25 M aq NaOH (10 mL) was added. The resultant mixture was extracted with CHCl₃/*i*-PrOH (3:1, v/v, 3 × 15 mL). The combined organic extracts were dried over Na₂SO₄ and concentrated *in vacuo* to give a 21:28:49:2 mixture of **245**, **246**, **247** and **248**, respectively (211 mg).

Step 3. HBF₄ (40% aq, 512 μL, 3.26 mmol) was added to a stirred solution of the 21:28:49:2 mixture of **245**, **246**, **247** and **248**, respectively, from the previous step (211 mg) in CH₂Cl₂ (1.8 mL) at rt. The resultant solution was stirred at rt for 5 days and then 2.25 M aq NaOH (10 mL) was added. The resultant mixture was extracted with CHCl₃/*i*-PrOH (3:1, v/v, 3 × 15 mL). The combined organics were dried and concentrated *in vacuo* to give a 70:30 mixture of **247** and **248**, respectively (144 mg).

(1R,2R,3R,4R,αR)-2-[N-Benzyl-N-(α-methylbenzyl)amino]cyclohexane-1,3,4-triol

251 and **(1R,2R,3S,4S,αR)-2-[N-benzyl-N-(α-methylbenzyl)amino]cyclohexane-1,3,4-triol 252.**



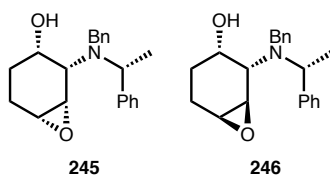
Via Epoxidation of 230. Step 1. HBF₄ (40% aq, 510 μL, 3.26 mmol) was added to a stirred solution of **230** (200 mg, 0.651 mmol, >95:5 dr) in CH₂Cl₂ (1.8 mL) at rt. The resultant solution was stirred at rt for 5 min and then *m*-CPBA (75% wt, 767 mg, 3.26 mmol) was

added. The resultant solution was stirred at rt for 30 h and then solid Na₂SO₃ was added until starch-iodide paper indicated that no *m*-CPBA was present. The resultant mixture was diluted with 2.25 M aq NaOH (2.25 M, 15 mL) and extracted with CHCl₃/*i*PrOH (3:1, v/v, 3 × 30 mL). The combined organics were dried and concentrated *in vacuo* to give a 48:31:21 mixture of **249**, **250** and **251**, respectively (315 mg).

Step 2. HBF₄ (40% aq, 760 μL, 4.87 mmol) was added to a stirred solution of the 48:31:21 mixture of **249**, **250** and **251**, respectively, from the previous step (315 mg) in CH₂Cl₂ (2.7 mL) at rt. The resultant solution was stirred at rt for 24 h and then 2.25 M aq NaOH (10 mL) was added. The resultant mixture was extracted with CHCl₃/*i*PrOH (3:1, v/v, 3 × 15 mL). The combined organics were dried and concentrated *in vacuo* to give a 21:23:53:3 mixture of **249**, **250**, **251** and **252**, respectively (200 mg).

Step 3. HBF₄ (40% aq, 485 μL, 3.09 mmol) was added to a stirred solution of the 21:23:53:3 mixture of **249**, **250**, **251** and **252**, respectively, from the previous step (200 mg) in CH₂Cl₂ (1.7 mL) at rt. The resultant solution was stirred at rt for 5 days and then 2.25 M aq NaOH (10 mL) was added. The resultant mixture was extracted with CHCl₃/*i*PrOH (3:1, v/v, 3 × 15 mL). The combined organics were dried and concentrated *in vacuo* to give an ~70:30 mixture of **251** and **252**, respectively (200 mg).

(1*S*,2*R*,3*S*,4*R*,α*R*)-2-[*N*-Benzyl-*N*-(α-methylbenzyl)amino]-3,4-epoxycyclohexan-1-ol **245** and (1*S*,2*S*,3*R*,4*S*,α*R*)-2-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3,4-epoxycyclohexan-1-ol **246**

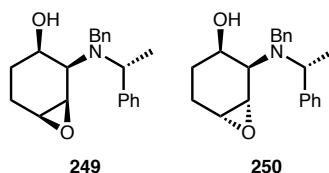


Step 1. A solution of **229** (200 mg, 0.651 mmol, >95:5 dr) in CH₂Cl₂ (1.8 mL) was added to anhydrous TsOH (561 mg, 3.26 mmol) at rt. The resultant solution was stirred at rt for 5

min and then *m*-CPBA (73% wt, 767 mg, 3.26 mmol) was added. The resultant solution was stirred at rt for 30 h and then solid Na₂SO₃ was added until starch-iodide paper indicated that no *m*-CPBA was present. The resultant mixture was diluted with CH₂Cl₂ (20 mL), washed with 0.1 M aq NaHCO₃ (4 × 20 mL), dried and concentrated *in vacuo* to give a 68:32 mixture of **253** and **254**, respectively, as a yellow oil (240 mg).

Step 2. DBU (79 μL, 0.52 mmol) was added to a stirred solution of a 68:32 mixture of **253** and **254** from the previous step (240 mg) in CH₂Cl₂ (0.99 mL) at rt. The resultant solution was stirred at rt for 24 h and then concentrated *in vacuo* to give a 68:32 mixture of **245** and **246**, respectively. Purification *via* flash column chromatography (eluent CHCl₃) gave an 81:19 mixture of **245** and **246**, respectively, as a pale yellow oil (75 mg, 36%).

(1*R*,2*S*,3*R*,4*S*,α*R*)-2-[*N*-Benzyl-*N*-(α-methylbenzyl)amino]-3,4-epoxycyclohexan-1-ol **249** and (1*R*,2*R*,3*S*,4*R*,α*R*)-2-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3,4-epoxycyclohexane **250**



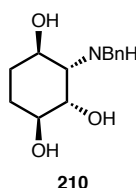
Step 1. A solution of **230** (200 mg, 0.651 mmol, >95:5 dr) in CH₂Cl₂ (1.8 mL) was added to anhydrous TsOH (561 mg, 3.26 mmol) at rt. The resultant solution was stirred at rt for 5 min and then *m*-CPBA (73% wt, 767 mg, 3.26 mmol) was added. The resultant solution was stirred at rt for 30 h and then solid Na₂SO₃ was added until starch-iodide paper indicated that no *m*-CPBA was present. The resultant mixture was diluted with CH₂Cl₂ (20 mL), washed with 0.1 M aq NaHCO₃ (4 × 20 mL), dried and concentrated *in vacuo* to give a 72:28 mixture of **255** and **256**, respectively, as a yellow oil (270 mg).

Step 2. DBU (89 μL, 0.52 mmol) was added to a stirred solution of the 72:28 mixture of **255** and **256** from the previous step (270 mg) in CH₂Cl₂ (1.1 mL) at rt. The resultant

solution was stirred at rt for 24 h and then concentrated *in vacuo* to give a 72:28 mixture of **249** and **250**, respectively. Purification *via* flash column chromatography (eluent CHCl₃) gave a 78:22 mixture of **249** and **250**, respectively, as a pale yellow oil (61 mg, 29%).

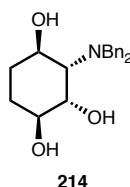
8.4 Experimental for chapter 4

(1R,2S,3S,4S)-2-(N-Benzylamino)cyclohexane-1,3,4-triol **210**



HBF₄ (40% aq, 640 μ L, 4.92 mmol) was added to a stirred solution of **166** (200 mg, 0.985 mmol, >180:1 dr) in CH₂Cl₂ (2.7 mL) at rt and the resultant solution was stirred at rt for 5 min. *m*-CPBA (75% wt, 360 mg, 1.58 mmol) was then added and the resultant solution was stirred at rt for 21 h. Solid Na₂SO₃ was added until starch-iodide paper indicated that no *m*-CPBA was present. 2 M aq NaOH (20 mL) was then added and the resultant mixture was extracted with CHCl₃/*i*-PrOH (3:1, v/v, 3 $\times$ 30 mL). The combined organic extracts were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent CHCl₃/MeOH/35% aq NH₄OH, 90:10:0.5) gave **210** as a white powder (130 mg, 56%, >95:5 dr); mp 139–143 $^{\circ}$ C; [α]_D²⁵ -14.8 (*c* 0.75 in CHCl₃).

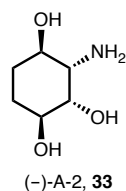
(1R,2S,3S,4S)-2-(N,N-Dibenzylamino)cyclohexane-1,3,4-triol **214**



i-Pr₂NEt (83 μ L, 0.47 mmol), BnBr (56 μ L, 0.47 mmol) and DMAP (0.4 mg, 0.003 μ mol) were added sequentially to a stirred solution of **210** (75 mg, 0.32 mmol, >95:5 dr) in CH₂Cl₂

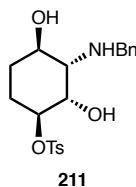
(0.90 mL) at rt and the resultant solution was stirred at rt for 24 h, then concentrated *in vacuo*. Purification *via* flash column chromatography (eluent CHCl₃/MeOH/35% aq NH₄OH, 90:10:0.5) gave **214** as a white solid (74 mg, 72%, >95:5 dr, 99.5% ee); mp 203–204 °C; $[\alpha]_{\text{D}}^{25}$ –90.7 (c 1.0 in CHCl₃). Analysis of **214** by chiral HPLC [Chiralpak OD-H, mobile phase: hexane/ⁱPrOH (v/v, 92:8), flow rate: 1 mL/min, 10 μ L injection] and comparison to the racemic standard allowed **214** to be assessed as 99.5% ee [**214** t_{R} = 14.2 min].

((1R,2S,3S,4S)-2-Aminocyclohexane-1,3,4-triol [(-)-Dihydroconduramine A-2] 33



Pd(OH)₂/C (50% wt of substrate, 45 mg) was added to a stirred degassed solution of **210** (90 mg, 0.38 mmol, >95:5 dr) in MeOH (1 mL) and the resultant suspension was stirred under H₂ (1 atm) at rt for 24 h. The resultant suspension was then filtered through Celite® (eluent MeOH), and the filtrate was concentrated *in vacuo* to give **33** as a yellow oil (47 mg, 85%, >95:5 dr, 99.5% ee);¹⁰ $[\alpha]_{\text{D}}^{25}$ –25.8 (c 1.0 in MeOH).

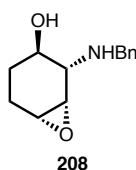
((1R,2S,3S,4S)-2-(N-Benzylamino)-4-tosyloxycyclohexan-1,3-diol 211



A solution of **166** (90 mg, 0.44 mmol, >180:1 dr) in CH₂Cl₂ (1.2 mL) was added to anhydrous TsOH (380 mg, 2.22 mmol) at rt. The resultant solution was stirred at rt for 5 min and then *m*-CPBA (75% wt, 160 mg, 0.709 mmol) was added. The resultant solution

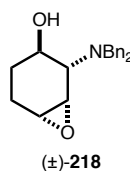
was stirred at rt for 21 h and solid Na_2SO_3 was added until starch-iodide paper indicated that no *m*-CPBA was present. The resultant suspension was diluted with CH_2Cl_2 (10 mL), washed with 0.1 M aq NaHCO_3 (4×10 mL), dried and concentrated *in vacuo* to give **211** as a white powder (120 mg, 70%, >95:5 dr); mp 138–140 °C; $[\alpha]_{\text{D}}^{25} -26.7$ (c 1.0 in CHCl_3).

(1*R*,2*S*,3*S*,4*R*)-2-(*N*-Benzylamino)-3,4-epoxycyclohexan-1-ol 208



DBU (300 μL , 1.99 mmol) was added to a stirred solution of **211** (720 mg, 1.84 mmol, >95:5 dr) in CH_2Cl_2 (3.8 mL) at rt and the resultant solution was stirred at rt for 24 h, then concentrated *in vacuo*. Purification *via* flash column chromatography (eluent $\text{CHCl}_3/\text{MeOH}$ 95:5) gave **208** as a colourless oil (300 mg, 74%, >95:5 dr); $[\alpha]_{\text{D}}^{25} -136.2$ (c 1.0 in CHCl_3).

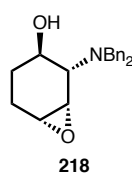
(1*R*,2*S*,3*R*,4*R*)-2-(*N,N*-Dibenzylamino)-3,4-epoxycyclohexan-1-ol ($\pm$)-218



Pr_2NEt (4.80 mL, 27.4 mmol), BnBr (3.25 mL, 27.4 mmol) and DMAP (22.3 mg, 0.183 mmol) were added sequentially to a stirred solution of ($\pm$)-**208** (4.00 g, 18.3 mmol, >95:5 dr) in CH_2Cl_2 (52 mL) at rt and the resultant solution was stirred at rt for 24 h, then concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 7:3) gave ($\pm$)-**218** as a colourless oil (6.60 g, quant, >95:5 dr); ν_{max} 3487, 2981, 2890; δ_{H} (400 MHz, d_1 - CHCl_3) 1.19–1.31 (1H, m, $\text{C}(6)\text{H}_A$), 1.79–2.06 (3H, m, $\text{C}(5)\text{H}_2$, $\text{C}(6)\text{H}_B$), 2.80 (1H, dd, J 9.3, 1.1, $\text{C}(2)\text{H}$), 3.07 (1H, s, OH), 3.18 (1H, app t, J 4.2,

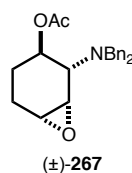
C(4)*H*), 3.43 (1H, dd, *J* 4.2, 1.1, C(3)*H*), 3.62 (2H, d, *J* 13.7, N(CH_AH_BPh)₂), 3.82 (1H, ddd, *J* 12.5, 9.3, 3.4, C(1)*H*), 4.13 (2H, d, 13.7, N(CH_AH_BPh)₂), 7.24–7.37 (10H, m, *Ph*); δ_{C} (100 MHz, *d*₁-CHCl₃) 22.5 (C(5)), 29.1 (C(6)), 51.5 (C(4)), 52.0 (C(3)), 54.8 (N(CH₂Ph)₂), 62.8 (C(2)), 63.9 (C(1)), 127.3, 128.5, 128.9 (*o,m,p-Ph*), 139.1 (*i-Ph*); *m/z* (ESI⁺) 310 ([M+H]⁺, 100%); HRMS (ESI⁺) C₂₀H₂₄NO₂⁺ ([M+H]⁺) requires 310.1802; found 310.1801.

(1*R*,2*S*,3*S*,4*R*)-2-(*N,N*-Dibenzylamino)-3,4-epoxycyclohexan-1-ol **218**



ⁱPr₂NEt (470 μ L, 2.67 mmol), BnBr (320 μ L, 2.67 mmol) and DMAP (2.2 mg, 0.018 mmol) were added sequentially to a stirred solution of **208** (350 mg, 1.78 mmol, >95:5 dr) in CH₂Cl₂ (5.1 mL) at rt and the resultant solution was stirred at rt for 24 h, then concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 7:3) gave **218** as a colourless oil (470 mg, 95%, >95:5 dr); [α]_D²⁵ –149.3 (*c* 1.0 in CHCl₃).

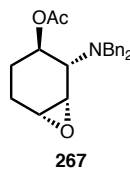
(1*R*,2*S*,3*S*,4*R*)-1-Acetoxy-2-(*N,N*-dibenzylamino)-3,4-epoxycyclohexane ($\pm$)-267****



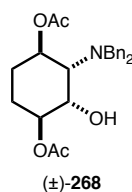
Ac₂O (6.00 mL, 64.0 mmol) and DMAP (26.0 mg, 0.213 mmol) were added sequentially to a stirred solution of ($\pm$)-**218** (6.60 g, 21.3 mmol, >95:5 dr) in pyridine (89 mL) at rt and the resultant solution was stirred at rt for 24 h. The resultant solution was diluted with CH₂Cl₂

(80 mL) and washed sequentially with H₂O (70 mL), satd aq Na₂CO₃ (70 mL) and brine (50 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 4:1) gave (±)-**267** as a yellow oil (6.8 g, 91%, >95:5 dr); $\nu_{\max}$ 3027, 2943, 2808, 1739; δ_{H} (400 MHz, *d*₁-CHCl₃) 1.30–1.42 (1H, m, C(6)*H*_A), 1.71–1.79 (1H, m, C(6)*H*_B), 1.90–1.97 (2H, m, C(5)*H*₂), 2.12 (3H, s, COMe), 3.07 (1H, dd, *J* 8.6, 1.7, C(2)*H*), 3.10–3.13 (1H, m, C(4)*H*), 3.40 (1H, dd, *J* 3.9, 1.7, C(3)*H*) 3.81 (2H, d, *J* 13.7, N(CH_AH_BPh)₂), 3.90 (2H, d, *J* 13.7, N(CH_AH_BPh)₂), 5.24 (1H, ddd, *J* 10.5, 8.6, 3.7, C(1)*H*), 7.1–7.39 (10H, m, *Ph*); δ_{C} (100 MHz, *d*₁-CHCl₃) 21.5 (COMe), 22.2 (C(5)), 27.9 (C(6)), 51.1 (C(4)), 54.9 (C(3)), 54.9 (N(CH₂Ph)₂), 58.4 (C(2)), 68.5 (C(1)), 126.8, 128.1, 128.8 (*o,m,p-Ph*), 140.0 (*i-Ph*), 170.2 (COMe); *m/z* (ESI⁺) 352 ([M+H]⁺, 100%); HRMS (ESI⁺) C₂₂H₂₆NO₃⁺ ([M+H]⁺) requires 352.1907; found 352.1909.

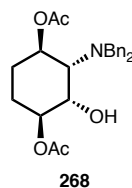
(1R,2S,3S,4R)-1-Acetoxy-2-(N,N-dibenzylamino)-3,4-epoxycyclohexane 267



Ac₂O (300 μ L, 3.12 mmol) and DMAP (1.2 mg, 0.01 μ mol) were added sequentially to a stirred solution of **218** (320 mg, 1.04 mmol, >95:5 dr) in pyridine (4.3 mL) at rt and the resultant solution was stirred at rt for 24 h. The resultant solution was diluted with CH₂Cl₂ (10 mL) and washed sequentially with H₂O (10 mL), satd aq Na₂CO₃ (10 mL) and brine (10 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 4:1) gave **267** as a colourless oil (310 mg, 85%, >95:5 dr); $[\alpha]_{\text{D}}^{25}$ –24.0 (*c* 1.0 in CHCl₃).

(1*R*,2*R*,3*S*,4*S*)-1,4-Diacetoxy-2-(*N,N*-dibenzylamino)cyclohexan-3-ol (±)-268

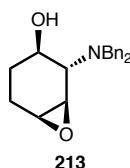
A stirred solution of (±)-**267** (6.77 g, 19.3 mmol, >95:5 dr) in AcOH (20 mL) was heated at 50 °C for 36 h, then allowed to cool to rt. 0.1 M aq NaHCO₃ (50 mL) was added and the aqueous layer was extracted with CH₂Cl₂ (3 × 40 mL). The combined organic extracts were washed with 0.1 M aq NaHCO₃ (50 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 4:1) gave (±)-**268** as a pale orange oil (6.5 g, 82%, >95:5 dr); ν_{max} 3499, 3028, 2949, 1734; δ_{H} (400 MHz, *d*₁-CHCl₃) 1.43–1.60 (1H, m, C(5)*H*_A, C(6)*H*_A) 1.67 (3H, s, COMe), 1.89–2.00 (2H, m, C(5)*H*_B, C(6)*H*_B), 2.15 (3H, s, COMe), 2.95 (1H, dd, *J* 10.8, 2.7, C(2)*H*), 3.74 (2H, d, *J* 13.7, N(CH_AH_BPh)₂), 3.98 (2H, d, *J* 13.7, N(CH_AH_BPh)₂), 4.06–4.12 (1H, m, C(3)*H*), 4.69–4.74 (1H, m, C(4)*H*), 5.38–5.47 (1H, m, C(1)*H*), 7.15–7.38 (10H, m, *Ph*); δ_{C} (100 MHz, *d*₁-CHCl₃) 20.8, 21.7 (COMe), 22.8 (C(5)), 26.7 (C(6)), 56.0 (N(CH₂Ph)₂), 57.3 (C(2)), 70.1 (C(1)), 71.9 (C(3)), 72.2 (C(4)), 126.7, 128.2, 128.5 (*o,m,p-Ph*), 140.4 (*i-Ph*), 170.2, 170.4 (COMe); *m/z* (ESI⁺) 412 ([M+H]⁺, 100%); HRMS (ESI⁺) C₂₄H₃₀NO₅⁺ ([M+H]⁺) requires 412.2118; found 412.2118.

(1*R*,2*R*,3*S*,4*S*)-1,4-Diacetoxy-2-(*N,N*-dibenzylamino)cyclohexan-3-ol **268**

A stirred solution of **267** (310 mg, 0.854 mmol, >95:5 dr) in AcOH (1 mL) was heated at 50 °C for 36 h, then allowed to cool to rt. 0.1 M aq NaHCO₃ (10 mL) was added and the

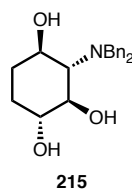
aqueous layer was extracted with CH_2Cl_2 (3×10 mL). The combined organic extracts were then washed with 0.1 M aq NaHCO_3 (10 mL), dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 4:1) gave **268** as a colourless oil (260 mg, 72%, >95:5 dr); $[\alpha]_{\text{D}}^{25} +23.0$ (c 1.0 in CHCl_3).

(1R,2S,3R,4S)-2-(N,N-Dibenzylamino)-3,4-epoxycyclohexan-1-ol 213

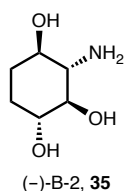


Step 1. MsCl (200 μL , 2.48 mmol) was added to a stirred solution of **268** (340 mg, 0.827 mmol, >95:5 dr) in pyridine (8.2 mL) at 0 °C and the resultant solution was stirred at rt for 16 h, then concentrated *in vacuo* to give a 10:90 mixture of **268** and **269**, respectively.

Step 2. K_2CO_3 (1.5 g) was added to a stirred solution of the residue from the previous step in MeOH (15 mL) and the resultant suspension was stirred at rt for 16 h then concentrated *in vacuo*. H_2O (15 mL) was added and the resultant mixture was extracted with CH_2Cl_2 (3×20 mL). The combined organic extracts were dried and concentrated *in vacuo* to give a 90:10 mixture of **213** and **214**, respectively. Purification *via* flash column chromatography (eluent $\text{CHCl}_3/\text{MeOH}$, 97:3) gave **213** as an orange solid (190 mg, 74%, >95:5 dr); mp 76–80 °C; $[\alpha]_{\text{D}}^{25} -98.0$ (c 1.0 in CHCl_3).

(1R,2S,3R,4R)-2-(N,N-Dibenzylamino)cyclohexane-1,3,4-triol **215**

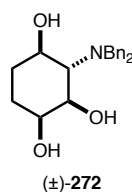
HBF₄ (40% aq, 60 μ L, 2.3 mmol) was added to a stirred solution of **213** (0.14 g, 0.45 mmol, >95:5 dr) in CH₂Cl₂ (1.25 mL) at rt and the resultant solution was stirred at 40 °C for 24 h. 2 M aq NaOH (10 mL) was then added and the resultant mixture was extracted with CHCl₃/*i*-PrOH (3:1, v/v, 3 $\times$ 15 mL). The combined organic extracts were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent CHCl₃/MeOH, 97:3) gave **215** as a colourless oil (110 mg, 74%, >95:5 dr, 98.2% ee); [α]_D²⁵ -44.7 (*c* 1.0 in CHCl₃). Analysis of **215** by chiral HPLC [Chiralpak OD-H, mobile phase: hexane/*i*-PrOH (v/v, 90:10), flow rate: 1 mL/min, 10 μ L injection] and comparison to the racemic standard allowed **215** to be assessed as 98.2% ee [**215** *t*_R = 19.0 min].

(1R,2S,3R,4R)-2-Aminocyclohexane-1,3,4-triol [(-)-Dihydroconduramine B-2] **35**

Pd(OH)₂/C (50% wt of substrate, 38 mg) was added to a stirred degassed solution of **215** (75 mg, 0.23 mmol, >95:5 dr) in MeOH (1.5 mL) and the resultant suspension was stirred under H₂ (1 atm) at rt for 24 h. The resultant suspension was then filtered through Celite® (eluent MeOH), and the filtrate was concentrated *in vacuo*. Purification *via* flash column chromatography (eluent CHCl₃/MeOH/35% aq NH₄OH, 14:5:1) gave **35** as a white solid (22 mg, 65%, >95:5 dr, 98.2% ee¹⁰); mp 168–178 °C; [α]_D²⁵ -19.9 (*c* 1.0 in MeOH); $\nu_{\max}$ 3358, 3308, 2935, 2900, 2865; δ_{H} (400 MHz, *d*₄-MeOH) 1.27–1.47 (2H, m, C(5)H_A,

$C(6)H_N$), 1.85–1.94 (2H, m, $C(5)H_B$, $C(6)H_B$), 2.48 (1H, t, J 9.5, $C(2)H$), 3.02 (1H, app t, J 9.5, $C(3)H$), 3.23–3.40 (1H, m, $C(1)H$, $C(4)H$); δ_c (100 MHz, d_4 -MeOH) 30.2 ($C(5)$), 31.5 ($C(6)$), 61.2 ($C(2)$), 73.7 ($C(1)$), 74.3 ($C(4)$), 78.9 ($C(3)$); m/z (ESI⁺) 148 ([M+H]⁺, 100%); HRMS (ESI⁺) $C_6H_{14}NO_3^+$ ([M+H]⁺) requires 148.09682; found 148.09676.

(1*R,S*,2*S,R*,3*R,S*,4*S,R*)-2-(*N,N*-Dibenzylamino)cyclohexane-1,3,4-triol ($\pm$)-272



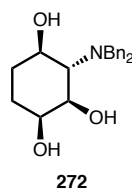
Step 1. MsCl (110 μ L, 1.39 mmol) was added to a stirred solution of ($\pm$)-268 (190 mg, 0.462 mmol, >95:5 dr) in pyridine (2.9 mL) at 0 °C and the resultant solution was stirred at rt for 16 h, then concentrated *in vacuo* to give a 10:90 mixture of ($\pm$)-268 and ($\pm$)-269, respectively, as a brown oil.

Step 2. KOAc (100 mg, 1.04 mmol) was added to a stirred solution of the residue from the previous step in EtOH/H₂O (6:1, v/v, 22.2 mL) and the resultant suspension was heated at reflux for 72 h, then allowed to cool to rt and concentrated *in vacuo*. H₂O (20 mL) was added and the resultant mixture was extracted with CH₂Cl₂ (3 $\times$ 20 mL). The combined organic extracts were dried and concentrated *in vacuo*.

Step 3. K₂CO₃ (440 mg, 3.18 mmol) was added to a stirred solution of the residue from the previous step in MeOH (44 mL) at rt and the resultant suspension was stirred at rt for 24 h, then concentrated *in vacuo*. 2 M aq NaOH (20 mL) was then added and the resultant mixture was extracted with CHCl₃/*i*PrOH (3:1, v/v, 3 $\times$ 20 mL). The combined organic extracts were dried and concentrated *in vacuo* to give a 90:10 mixture of ($\pm$)-272 and ($\pm$)-214, respectively. Purification *via* flash column chromatography (eluent CHCl₃/MeOH, 97:3) gave ($\pm$)-272 as a white solid (80 mg, 53%, >95:5 dr); mp 147–157 °C; $\nu_{\max}$ 3323, 3083,

3060, 3023, 2943, 2916, 2856; δ_{H} (400 MHz, d_1 -CHCl₃) 1.35–1.45 (1H, m, C(5) H_{A}), 1.63–1.83 (2H, m, C(6) H_2), 1.88 (1H, dd, J 14.6, 3.4, C(5) H_{B}), 2.07 (1H, br s, OH), 2.16 (1H, br d, J 3.5, OH), 2.86 (1H, app t, J 10.3, C(2) H), 3.16 (1H, br s, OH), 3.53 (1H, dd, J 10.3, 3.0, C(3) H), 3.75 (1H, td, J 10.5, 3.2, C(1) H), 3.92 (4H, app s, N(CH₂Ph)₂), 4.01–4.06 (1H, m, C(4) H), 7.17–7.41 (10H, m, Ph); δ_{C} (100 MHz, d_1 -CHCl₃) 26.5 (C(5)), 28.7 (C(6)), 56* (N(CH₂Ph)₂), 62.7 (C(2)), 68.4 (C(1)), 70.2 (C(3)), 70.9 (C(4)), 127.2, 128.5, 129.3 (*o,m,p*-Ph), 139.6 (*i*-Ph);⁷ m/z (ESI⁺) 328 ([M+H]⁺, 100%); HRMS (ESI⁺) C₂₀H₂₆NO₃⁺ ([M+H]⁺) requires 328.1907; found 328.1908. Further elution (eluent CHCl₃/MeOH, 95:5) gave an impure sample of (±)-**214** as a yellow oil (30 mg). Analysis of (±)-**272** by chiral HPLC [Chiralpak AD-H, mobile phase: hexane/*i*PrOH (v/v, 90:10), flow rate: 1 mL/min, 10 μ L injection] gave complete resolution of enantiomers [**272** t_{R} = 13.3 min; **272** t_{R} = 16.4 min].

(1R,2S,3R,4S)-2-(N,N-Dibenzylamino)cyclohexane-1,3,4-triol **272**

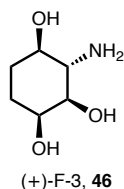


Step 1. MsCl (190 μ L, 2.41 mmol) was added to a stirred solution of **268** (330 mg, 0.803 mmol, >95:5 dr) in pyridine (8.0 mL) at 0 °C and the resultant solution was stirred at rt for 16 h, then concentrated *in vacuo* to give a 10:90 mixture of **268** and **269**, respectively, as a brown oil (500 mg).

Step 2. KOAc (200 mg, 2.08 mmol) was added to a stirred solution of the residue from the previous step (500 mg) in EtOH/H₂O (6:1, v/v, 44.4 mL) and the resultant suspension was heated at reflux for 72 h, then allowed to cool to rt and concentrated *in vacuo*. H₂O (40 mL) was added and the resultant mixture was extracted with CH₂Cl₂ (3 $\times$ 40 mL). The combined organic extracts were dried and concentrated *in vacuo*.

Step 3. K_2CO_3 (880 mg, 6.37 mmol) was added to a stirred solution of the residue from the previous step in MeOH (88 mL) at rt and the resultant suspension was stirred at rt for 24 h, then concentrated *in vacuo*. 2 M aq NaOH (40 mL) was then added and the resultant mixture was extracted with $CHCl_3$ / i PrOH (3:1, v/v, 3×40 mL). The combined organic extracts were dried and concentrated *in vacuo* to give a 90:10 mixture of **272** and **214**, respectively. Purification *via* flash column chromatography (eluent $CHCl_3$ /MeOH, 97:3) gave **272** as a white solid (145 mg, 55%, >95:5 dr, 98.5% ee); mp 159–162 °C; $[\alpha]_D^{25} +11.7$ (c 1.0 in $CHCl_3$). Further elution (eluent $CHCl_3$ /MeOH, 95:5) gave an impure sample of **214** as a yellow oil (21 mg). Analysis of **272** by chiral HPLC [Chiralpak AD-H, mobile phase: hexane/ i PrOH (v/v, 90:10), flow rate: 1 mL/min, 10 μ L injection] and comparison to the racemic standard allowed **272** to be assessed as 98.5% ee [**272** t_R = 13.3 min].

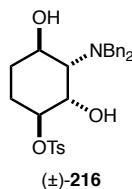
(1R,2S,3R,4S)-2-Aminocyclohexane-1,3,4-triol [(+)-Dihydroconduramine F-3] 46



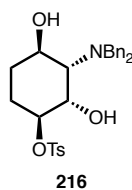
$Pd(OH)_2/C$ (50% wt of substrate, 40 mg) was added to a stirred degassed solution of **272** (80 mg, 0.24 mmol, >95:5 dr) in MeOH (1.5 mL) and the resultant suspension was stirred under H_2 (1 atm) at rt for 24 h. The resultant suspension was then filtered through Celite® (eluent MeOH), and the filtrate was concentrated *in vacuo* to give **46** as a yellow oil (27 mg, 75%, >95:5 dr, 98.5% ee¹⁰); $[\alpha]_D^{25} +26.7$ (c 1.0 in MeOH); ν_{max} 3354, 2938, 2875; δ_H (400 MHz, d_4 -MeOH) 1.48 (1H, tdd, J 13.6, 4.4, 2.7, C(5) H_A), 1.59–1.86 (3H, m, C(6) H_2 , C(5) H_B), 2.87 (1H, app t, J 9.7, C(2) H), 3.18–3.30 (2H, m, C(1) H , C(3) H), 3.88 (1H, app q, 2.7, C(4) H); δ_C (100 MHz, d_4 -MeOH) 28.4 (C(6)), 28.5 (C(5)), 57.7 (C(2)), 70.1 (C(4)), 74.3

(C(1)), 76.1 (C(3)); m/z (ESI⁺) 148 ([M+H]⁺, 100%); HRMS (ESI⁺) C₆H₁₄NO₃⁺ ([M+H]⁺) requires 148.0968; found 148.0967.

(1*R*,2*S*,3*S*,4*S*)-2-(*N,N*-Dibenzylamino)-4-tosyloxycyclohexan-1,3-diol (±)-216



A solution of (±)-**218** (160 mg, 0.517 mmol, >95:5 dr) in CH₂Cl₂ (1.4 mL) was added to anhydrous TsOH (445 mg, 2.59 mmol) at rt. The resultant solution was stirred at rt for 21 h and then washed with 0.1 M aq NaHCO₃ (5 × 15 mL), dried and concentrated *in vacuo* to give (±)-**216** as a beige solid (180 mg, 72%, >95:5 dr); mp 133–135 °C; ν_{max} 3381, 3062, 3028, 2942; δ_{H} (400 MHz, *d*₁-CHCl₃) 1.24–1.42 (1H, m, C(6)*H*_A), 1.51–1.61 (1H, m, C(5)*H*_A), 1.71–1.75 (1H, m, OH), 1.84–1.96 (2H, m, C(5)*H*_B, C(6)*H*_B) 2.47 (3H, s, *ArMe*), 2.79 (1H, dd, *J* 10.6, 1.9, C(2)*H*), 3.38 (1H, s, OH), 3.61 (2H, d, *J* 13.6, N(CH_AH_BPh)₂), 4.03 (1H, app td, *J* 10.6, 4.3, C(1)*H*), 4.12 (2H, d, *J* 13.6, N(CH_AH_BPh)₂), 4.54–4.64 (2H, m, C(3)*H*, C(4)*H*), 7.22–7.39 (12H, m, *Ar*, *Pb*), 7.69–7.75 (2H, m, *Ar*); δ_{C} (100 MHz, *d*₁-CHCl₃) 21.6 (*Me*), 23.2 (C(5)), 27.8 (C(6)), 54.5 (N(CH₂Ph)₂), 60.4 (C(2)), 63.0 (C(3)), 67.0 (C(1)), 79.6 (C(4)), 127.2, 127.5, 128.5, 129.0, 129.8, 133.7, 139.3, 144.9 (*Ar*, *Pb*); m/z (ESI⁺) 482 ([M+H]⁺, 100%); HRMS (ESI⁺) C₂₇H₃₂NO₅S⁺ ([M+H]⁺) requires 482.1996; found 485.1995.

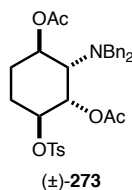
(1R,2S,3S,4S)-2-(N,N-Dibenzylamino)-4-tosyloxycyclohexan-1,3-diol **216**

*Method A. From **211**.* *Step 1.* Pr_2NEt (270 μL , 1.53 mmol), BnBr (170 μL , 1.53 mmol) and DMAP (1.2 mg, 0.01 mmol) were added sequentially to a stirred solution of **211** (400 mg, 1.02 mmol, >95:5 dr) in CH_2Cl_2 (2.9 mL) at rt and the resultant solution was stirred at rt for 24 h, then concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 $^\circ\text{C}$ petroleum ether/EtOAc, 4:1), gave a 70:30 mixture of **216** and **218**, respectively, as a white solid (270 mg).

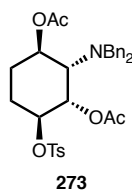
Step 2. A solution of the residue from the previous step (270 mg) in CH_2Cl_2 (1.4 mL) was added to anhydrous TsOH (167 mg, 0.970 mmol) at rt. The resultant solution was stirred at rt for 21 h and then washed with 0.1 M aq NaHCO_3 (5×20 mL), dried and concentrated *in vacuo* to give **216** as a yellow pale solid (251 mg, 51%, >95:5 dr).

*Method B. From **218**.* A solution of **218** (105 mg, 0.340 mmol, >95:5 dr) in CH_2Cl_2 (0.94 mL) was added to anhydrous TsOH (292 mg, 1.70 mmol) at rt. The resultant solution was stirred at rt for 21 h and then washed with 0.1 M aq NaHCO_3 (5×10 mL), dried and concentrated *in vacuo* to give **216** as a pale yellow solid (110 mg, 67%, >95:5 dr); mp 144–151 $^\circ\text{C}$; $[\alpha]_{\text{D}}^{25} -58.5$ (c 0.75 in CHCl_3).

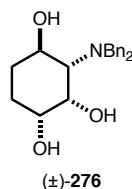
(1*R*,2*S*,3*S*,4*S*)-1,3-Diacetoxy-2-(*N,N*-dibenzylamino)-4-tosyloxycyclohexane
(±)-273



Ac₂O (100 μ L, 1.06 mmol) and DMAP (0.4 mg, 0.003 μ mol) were added sequentially to a stirred solution of (±)-**216** (170 mg, 0.353 mmol, >95:5 dr) in pyridine/CH₂Cl₂ (1:1, v/v, 7.6 mL) at rt and the resultant solution was stirred at rt for 24 h. The resultant solution was diluted with CH₂Cl₂ (15 mL) and washed sequentially with H₂O (15 mL), satd aq Na₂CO₃ (15 mL) and brine (15 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 7:3) gave (±)-**273** as a yellow oil (200 mg, quant, >95:5 dr); mp 141–146 °C; $\nu_{\max}$ 3029, 2954, 1748; δ_{H} (400 MHz, *d*₁-CHCl₃) 1.61–1.94 (6H, m, COMe, C(5)*H*₂, C(6)*H*_A), 1.95–2.04 (1H, m, C(6)*H*_B), 2.19 (3H, s, COMe), 2.50 (3H, s, ArMe), 3.23 (1H, dd, *J* 11.0, 2.8, C(2)*H*), 3.70 (2H, d, *J* 14.0, N(CH_AH_BPh)₂), 3.78 (2H, d, *J* 14.0, N(CH_AH_BPh)₂), 4.49 (1H, q, *J* 3.0, C(4)*H*), 5.00–5.10 (1H, m, C(3)*H*), 5.36 (1H, td, *J* 11.0, 4.7, C(1)*H*), 7.17–7.39 (12H, m, *Ar*, *Ph*), 7.54–7.62 (2H, m, *Ar*); δ_{C} (100 MHz, *d*₁-CHCl₃) 20.9, 21.5 (COMe), 21.7 (ArMe), 24.5 (C(5)), 25.4 (C(6)), 55.7 (C(2)), 55.7 (N(CH₂Ph)₂), 69.5 (C(1)), 73.5 (C(3)), 75.2 (C(4)), 126.9, 127.7, 128.3, 129.7, 133.2, 139.6, 144.8 (*Ar*, *Ph*), 169.4, 170.3 (COMe); *m/z* (ESI⁺) 566 ([M+H]⁺, 100%); HRMS (ESI⁺) C₃₁H₃₆NO₇S⁺ ([M+H]⁺) requires 566.2207; found 566.2209.

(1R,2S,3S,4S)-1,3-Diacetoxy-2-(N,N-dibenzylamino)-4-tosyloxycyclohexane 273

Ac₂O (60 μ L, 0.62 mmol) and DMAP (0.3 mg, 0.002 μ mol) were added sequentially to a stirred solution of **216** (100 mg, 0.208 mmol, >95:5 dr) in pyridine/CH₂Cl₂ (1:1, v/v, 4.4 mL) at rt and the resultant solution was stirred at rt for 24 h. The resultant solution was diluted with CH₂Cl₂ (15 mL) and washed sequentially with H₂O (15 mL), satd aq Na₂CO₃ (15 mL) and brine (15 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc 7:3) gave **273** as a yellow oil (100 mg, 85%, >95:5 dr); [α]_D²⁵ –2.4 (*c* 1.0 in CHCl₃).

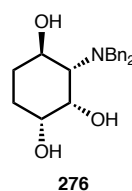
(1R,2S,3S,4R)-2-(N,N-Dibenzylamino)cyclohexane-1,3,4-triol (±)-275

Step 1. KOAc (35.4 mg, 0.361 mmol) was added to a stirred solution of (±)-**273** (200 mg, 0.354 mmol, >95:5 dr) in EtOH/H₂O (6:1, v/v, 7.45 mL) and the resultant suspension was heated at reflux for 72 h, then allowed to cool to rt and concentrated *in vacuo*. H₂O (20 mL) was added and the resultant mixture was extracted with CH₂Cl₂ (3 $\times$ 20 mL). The combined organic extracts were dried and concentrated *in vacuo*.

Step 2. K₂CO₃ (172 mg, 1.24 mmol) was added to a stirred solution of the residue from the previous step in MeOH (17 mL) at rt and the resultant suspension was stirred at rt for 24 h, then concentrated *in vacuo*. 2 M aq NaOH (20 mL) was then added and the resultant mixture was extracted with CHCl₃/PrOH (3:1, v/v, 3 $\times$ 20 mL). The combined organic

extracts were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent CHCl₃/MeOH, 97:3) gave (±)-**275** as a yellow solid (99 mg, 86%, >95:5 dr); mp 137–139 °C; ν_{max} 3398, 3028, 2940, 2862; δ_{H} (400 MHz, *d*₁-CHCl₃) 1.02–1.16 (1H, m, C(6)H_A), 1.57–1.84 (3H, m, C(5)H₂, OH), 2.08 (1H, dq, *J* 12.5, 3.9, C(6)H_B), 2.26 (1H, br s, OH), 2.32 (1H, dd, *J* 10.5, 1.9, C(2)H), 3.52 (1H, ddd, *J* 11.4, 5.0, 2.7, C(4)H), 3.65 (2H, d, *J* 13.9, N(CH_AH_BPh)₂), 4.07 (1H, app td, *J* 10.5, 4.8, C(1)H), 4.18 (2H, d, *J* 13.9, N(CH_AH_BPh)₂), 4.39–4.47 (1H, m, C(3)H), 7.21–7.39 (10H, m, *Ph*); δ_{C} (100 MHz, *d*₁-CHCl₃) 26.2 (C(5)), 29.7 (C(6)), 54.6 (N(CH₂Ph)₂), 63.0 (C(1)), 63.5 (C(2)), 68.6 (C(3)), 71.6 (C(4)), 127.2, 128.5, 128.8 (*o,m,p-Ph*), 139.5 (*i-Ph*); *m/z* (ESI⁺) 328 ([M+H]⁺, 100%); HRMS (ESI⁺) C₂₀H₂₆NO₃⁺ ([M+H]⁺) requires 328.1907; found 328.1903. Analysis of (±)-**275** by chiral HPLC [Chiralpak OD-H, mobile phase: hexane/*i*PrOH (v/v, 92:8), flow rate: 1 mL/min, 10 μ L injection] gave complete resolution of enantiomers [**275** *t*_R = 13.8 min; **275** *t*_R = 17.0 min].

(1R,2S,3S,4R)-2-(N,N-Dibenzylamino)cyclohexane-1,3,4-triol **275**

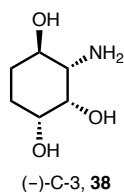


Step 1. KOAc (37.2 mg, 0.379 mmol) was added to a stirred solution of **273** (210 mg, 0.372 mmol, >95:5 dr) in EtOH/H₂O (6:1, v/v, 8.80 mL) and the resultant suspension was heated at reflux for 72 h, then allowed to cool to rt and concentrated *in vacuo*. H₂O (20 mL) was added and the resultant mixture was extracted with CH₂Cl₂ (3 × 20 mL). The combined organic extracts were dried and concentrated *in vacuo*.

Step 2. K₂CO₃ (180 mg, 1.30 mmol) was added to a stirred solution of the residue from the previous step in MeOH (18 mL) at rt and the resultant suspension was stirred at rt for 24

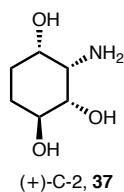
h, then concentrated *in vacuo*. 2 M aq NaOH (20 mL) was then added and the resultant mixture was extracted with CHCl₃/iPrOH (3:1, v/v, 3 × 20 mL). The combined organic extracts were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent CHCl₃/MeOH, 97:3) gave **275** as a yellow oil (90 mg, 74%, >95:5 dr, 99.5% ee); $[\alpha]_{\text{D}}^{25} -102.6$ (c 1.0 in CHCl₃). Analysis of **275** by chiral HPLC [Chiralpak OD-H, mobile phase: hexane/iPrOH (v/v, 92:8), flow rate: 1 mL/min, 10 μ L injection] and comparison to the racemic standard allowed **275** to be assessed as 99.5% ee [**275** t_{R} = 13.5 min].

(1R,2S,3S,4R)-2-Aminocyclohexane-1,3,4-triol [(–)-Dihydroconduramine C-3] 38

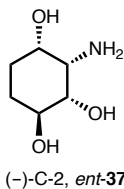


Pd(OH)₂/C (50% wt of substrate, 38 mg) was added to a stirred degassed solution of **275** (75 mg, 0.23 mmol, >95:5 dr) in MeOH (1.5 mL) and the resultant suspension was stirred under H₂ (1 atm) at rt for 24 h. The resultant suspension was then filtered through Celite® (eluent MeOH), and the filtrate was concentrated *in vacuo* to give **38** as a yellow oil (25 mg, 74%, >95:5 dr, 99.5% ee¹⁰); $[\alpha]_{\text{D}}^{25} -31.3$ (c 1.0 in MeOH); ν_{max} 3349, 2955, 2849; δ_{H} (400 MHz, *d*₄-MeOH) 1.31 (1H, app tdd, J 13.2, 11.2, 3.9, C(6)*H*_A), 1.62–1.70 (1H, m, C(5)*H*_A), 1.77 (1H, app tdd, J 13.2, 11.2, 3.9, C(5)*H*_B), 1.87–1.96 (1H, m, C(6)*H*_B), 2.70 (1H, dd, J 9.8, 2.8, C(2)*H*), 3.58–3.70 (2H, m, C(1)*H*, C(4)*H*), 3.98 (1H, J 2.8, 1.2, C(3)*H*); δ_{C} (100 MHz, *d*₄-MeOH) 27.3 (C(5)), 31.3 (C(6)), 59.0 (C(2)), 69.5 (C(1)), 71.9 (C(4)), 72.5 (C(3)); m/z (ESI⁺) 148 ([M+H]⁺, 100%); HRMS (ESI⁺) C₆H₁₄NO₃⁺ ([M+H]⁺) requires 148.0968; found 148.0966.

8.5 Experimental for chapter 5

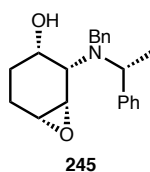
(1*S*,2*S*,3*S*,4*S*)-2-Aminocyclohexane-1,3,4-triol [(+)-Dihydroconduramine C-2] **37**

Pd(OH)₂/C (39 mg) was added to a stirred degassed solution of **240** (78 mg, 0.31 mmol, >95:5 dr) in MeOH (2 mL) at rt. The resultant mixture was stirred at rt under H₂ (1 atm) for 24 h and then filtered through Celite® (eluent MeOH). The filtrate was concentrated *in vacuo* to give **37** as a white solid (44 mg, 96%, >95:5 dr, >99% ee¹¹); mp 153–163 °C; [α]_D²⁵ +25.9 (*c* 0.25 in MeOH).

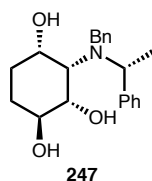
(1*R*,2*R*,3*R*,4*R*)-2-Aminocyclohexane-1,3,4-triol [(-)-Dihydroconduramine C-2] *ent*-**37**

Pd(OH)₂/C (25 mg) was added to a stirred degassed solution of **242** (49 mg, 0.20 mmol, >95:5 dr) in MeOH (1.5 mL) at rt. The resultant mixture was stirred at rt under H₂ (1 atm) for 24 h and then filtered through Celite® (eluent MeOH). The filtrate was concentrated *in vacuo* to give *ent*-**37** as a yellow solid (27 mg, 95%, >95:5 dr, >99% ee¹²); mp 151–162 °C; [α]_D²⁵ -23.4 (*c* 1.0 in MeOH).

(1*S*,2*S*,3*S*,4*R*, α *R*)-2-[*N*-Benzyl-*N*-(α -methylbenzyl)amino]-3,4-epoxycyclohexan-1-ol **245**



K_2CO_3 (6.25 g, 45.2 mmol) and BnBr (2.69 mL, 22.6 mmol) were added sequentially to a stirred solution of **239** (2.11 mg, 9.05 mmol, >95:5 dr) in MeCN (14.4 mL) at rt. The resultant solution was heated at reflux for 24 h and then allowed to cool to rt and concentrated *in vacuo*. H_2O (50 mL) was then added and the resultant mixture was extracted with CH_2Cl_2 (3×75 mL). The combined organics were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent CHCl_3) gave **245** as a yellow solid (2.14 g, 73%, >95:5 dr); mp 85–92 °C; $[\alpha]_{\text{D}}^{25} -42.8$ (c 1.0 in CHCl_3); ν_{max} 3514, 3084, 3060, 3025, 3003, 2996, 2937, 2849; δ_{H} (400 MHz, d_1 - CHCl_3) 1.30–1.40 (1H, m, C(6) H_{A}), 1.45 (3H, d, J 6.8, C(α) Me), 1.65–1.75 (1H, m, C(6) H_{B}), 1.83 (1H, app ddt, J 15.8, 7.0, 4.2, C(5) H_{A}), 2.09 (1H, ddd, J 15.8, 9.5, 6.4, C(5) H_{B}), 3.07 (1H, dd, J 4.8, 2.0, C(2) H), 3.25 (1H, app t, J 4.2, C(4) H), 3.38–3.42 (1H, m, C(3) H), 3.49 (1H, d, J 8.9, OH), 3.55–3.63 (1H, m, C(1) H), 4.19–4.27 (2H, m, C(α) H , $\text{NCH}_{\text{A}}\text{H}_{\text{B}}\text{Ph}$), 4.36 (1H, d, J 14.6, $\text{NCH}_{\text{A}}\text{H}_{\text{B}}\text{Ph}$), 7.18–7.40 (8H, m, Ph), 7.51–7.56 (2H, m, Ph); δ_{C} (100 MHz, d_1 - CHCl_3) 15.3 (C(α) Me), 19.8 (C(5)), 28.1 (C(6)), 53.0 (C(4), NCH_2Ph), 54.3 (C(2)), 56.8 (C(3)), 56.9 (C(α)), 69.4 (C(1)), 126.8, 126.9, 127.7, 128.2, 128.3, 128.5 (*o,m,p-Ph*), 141.8, 143.9 (*i-Ph*); m/z (ESI $^{+}$) 324 ($[\text{M}+\text{H}]^{+}$, 100%); HRMS (ESI $^{+}$) $\text{C}_{21}\text{H}_{26}\text{NO}_2^{+}$ ($[\text{M}+\text{H}]^{+}$) requires 324.1958; found 324.1959.

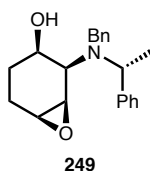
(1*S*,2*S*,3*S*,4*S*, α *R*)-2-[*N*-Benzyl-*N*-(α -methylbenzyl)amino]cyclohexane-1,3,4-triol**247**

Method A. N-Benzylation of 240. $i\text{-Pr}_2\text{NEt}$ (92 μL , 0.53 mmol), BnBr (62 μL , 0.53 mmol) and DMAP (280 μg , 23.3 μmol) were added sequentially to a stirred solution of **240** (88 mg, 0.35 mmol, >95:5 dr) in CH_2Cl_2 (1 mL) at rt. The resultant solution was stirred at rt for 24 h and then concentrated *in vacuo*. Purification *via* flash column chromatography (eluent $\text{CHCl}_3/\text{MeOH}$, 49:1) gave **247** as a white solid (63 mg, 53%, >95:5 dr); mp 146–153 °C; $[\alpha]_{\text{D}}^{25}$ -26.4 (c 1.0 in CHCl_3); ν_{max} 3368, 3084, 3061, 3027, 2933, 2839; δ_{H} (400 MHz, d_1 - CHCl_3) 1.41–1.49 (4H, m, $\text{C}(5)\text{H}_A$, $\text{C}(\alpha)\text{Me}$), 1.61–1.86 (2H, m, $\text{C}(6)\text{H}_2$), 2.10 (1H, tdd, J 14.3, 4.6, 2.1, $\text{C}(5)\text{H}_B$), 2.38 (1H, s, OH), 2.94 (1H, app t, J 2.0, $\text{C}(2)\text{H}$), 3.43 (1H, d, J 15.4, $\text{NCH}_A\text{H}_B\text{Ph}$), 3.80 (1H, s, $\text{C}(1)\text{H}$), 4.06–4.17 (4H, m, $\text{C}(3)\text{H}$, $\text{C}(4)\text{H}$, $\text{NCH}_A\text{H}_B\text{Ph}$, OH), 4.78 (1H, q, J 6.9, $\text{C}(\alpha)\text{H}$), 7.06–7.29 (6H, m, Ph), 7.34–7.40 (2H, m, Ph), 7.52–7.56 (2H, m, Ph); δ_{C} (100 MHz, d_1 - CHCl_3) 11.7 ($\text{C}(\alpha)\text{Me}$), 21.2 ($\text{C}(5)$), 24.8 ($\text{C}(6)$), 52.6 (NCH_2Ph), 54.7 ($\text{C}(\alpha)$), 60.2 ($\text{C}(2)$), 68.6 ($\text{C}(1)$), 70.8, 71.5 ($\text{C}(3)$, $\text{C}(4)$), 126.8 ($o,m\text{-Ph}$), 126.9, 126.9, 128.2, 128.6, 128.8 ($o,m,p\text{-Ph}$), 143.0, 143.9 ($i\text{-Ph}$); m/z (ESI^+) 342 ($[\text{M}+\text{H}]^+$, 100%); HRMS (ESI^+) $\text{C}_{21}\text{H}_{28}\text{NO}_3^+$ ($[\text{M}+\text{H}]^+$) requires 342.2064; found 342.2061.

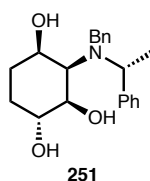
Method B. Ring-opening of 245. HBF_4 (40% aq, 400 μL , 2.55 mmol) was added to a stirred solution of **245** (165 mg, 0.511 mmol, >95:5 dr) in CH_2Cl_2 (1.4 mL) at rt. The resultant solution was stirred at rt for 24 h and then 2.25 M aq NaOH (10 mL) was added. The resultant mixture was extracted with $\text{CHCl}_3/\text{PrOH}$ (3:1, v/v, 3 $\times$ 15 mL). The combined organics were dried and concentrated *in vacuo*. Purification *via* flash column

chromatography (eluent $\text{CHCl}_3/\text{MeOH}$, 49:1) gave **247** as a white solid (110 mg, 63%, >95:5 dr).

(1R,2R,3R,4S, α R)-2-[N-Benzyl-N-(α -methylbenzyl)amino]-3,4-epoxycyclohexan-1-ol **249**



K_2CO_3 (267 mg, 1.93 mmol) and BnBr (115 μL , 965 μmol) were added sequentially to a stirred solution of **241** (90 mg, 0.39 mmol, >95:5 dr) in MeCN (0.61 mL) at rt. The resultant solution was heated at reflux for 24 h and then allowed to cool to and concentrated *in vacuo*. H_2O (10 mL) was added and the resultant mixture was extracted with CH_2Cl_2 (3×15 mL). The combined organics were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent CHCl_3) gave **249** as a yellow oil (57.9 mg, 49%, >95:5 dr); $[\alpha]_{\text{D}}^{25} +113.9$ (c 1.0 in CHCl_3); ν_{max} 3511, 3084, 3060, 3026, 3004, 2936, 2850; δ_{H} (400 MHz, $d_1\text{-CHCl}_3$) 1.47 (3H, d, J 7.0, $\text{C}(\alpha)\text{Me}$), 1.50–1.60 (1H, m, $\text{C}(6)\text{H}_{\text{A}}$), 1.68–1.89 (2H, m, $\text{C}(5)\text{H}_{\text{A}}$, $\text{C}(6)\text{H}_{\text{B}}$), 2.03–2.13 (1H, m, $\text{C}(5)\text{H}_{\text{B}}$), 2.64 (1H, dd, J 4.1, 2.1, $\text{C}(3)\text{H}$), 3.08 (1H, app t, J 4.1, $\text{C}(4)\text{H}$), 3.32 (1H, dd, J 4.8, 2.1, $\text{C}(2)\text{H}$), 3.85 (1H, br s, OH), 3.91 (1H, br s, $\text{C}(1)\text{H}$), 4.10–4.22 (2H, m, $\text{NCH}_{\text{A}}\text{H}_{\text{B}}\text{Ph}$, $\text{C}(\alpha)\text{H}$), 4.31 (1H, d, J 14.7, $\text{NCH}_{\text{A}}\text{H}_{\text{B}}\text{Ph}$), 7.24–7.31 (2H, m, Ph), 7.33–7.44 (6H, m, Ph), 7.47–7.53 (2H, m, Ph); δ_{C} (100 MHz, $d_1\text{-CHCl}_3$) 17.7 ($\text{C}(\alpha)\text{Me}$), 20.0 ($\text{C}(5)$), 28.2 ($\text{C}(6)$), 52.6 ($\text{C}(4)$), 53.0 (NCH_2Ph), 53.7 ($\text{C}(2)$), 56.1 ($\text{C}(3)$), 56.2 ($\text{C}(\alpha)$), 69.7 ($\text{C}(1)$), 126.8, 127.1, 127.7, 128.3, 128.3, 128.4 ($o,m,p\text{-Ph}$), 140.9, 142.5 ($i\text{-Ph}$); m/z (ESI^+) 324 ($[\text{M}+\text{H}]^+$, 100%); HRMS (ESI^+) $\text{C}_{21}\text{H}_{26}\text{NO}_2^+$ ($[\text{M}+\text{H}]^+$) requires 324.1958; found 324.1954.

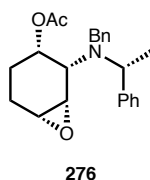
(1R,2R,3R,4R, α R)-2-[N-Benzyl-N-(α -methylbenzyl)amino]cyclohexane-1,3,4-triol**251**

Method A. N-Benzylation of 242. Pr_2NEt (104 μL , 597 μmol), BnBr (71 μL , 600 μmol) and DMAP (320 μg , 26.5 μmol) were added sequentially to a stirred solution of **242** (100 mg, 0.398 mmol, >95:5 dr) in CH_2Cl_2 (1.1 mL) at rt. The resultant mixture was stirred at rt for 24 h and then concentrated *in vacuo*. Purification *via* flash column chromatography (eluent $\text{CHCl}_3/\text{MeOH}$, 49:1) gave **251** as a white solid (35.7 mg, 27%, >95:5 dr); mp 134–138 $^\circ\text{C}$; $[\alpha]_{\text{D}}^{25}$ -7.4 (c 1.0 in CHCl_3); ν_{max} 3372, 3084, 3060, 3027, 2987, 2850; δ_{H} (400 MHz, d_1 - CHCl_3) 1.41–1.51 (4H, m, $\text{C}(\alpha)\text{Me}$, $\text{C}(5)\text{H}_{\text{A}}$), 1.75–1.95 (2H, m, $\text{C}(6)\text{H}_2$), 2.07 (1H, app tdd, J 14.1, 4.7, 2.8, $\text{C}(5)\text{H}_{\text{B}}$), 2.96 (1H, app t, J 2.6, $\text{C}(2)\text{H}$), 2.96 (1H, br s, OH), 3.34 (1H, d, J 7.2, OH), 3.67–3.80 (2H, m, $\text{NCH}_\text{A}\text{H}_\text{B}\text{Ph}$, $\text{C}(3)\text{H}$), 3.93–4.03 (2H, m, $\text{NCH}_\text{A}\text{H}_\text{B}\text{Ph}$, $\text{C}(4)\text{H}$), 4.19–4.26 (1H, m, $\text{C}(1)\text{H}$), 4.74 (1H, q, J 6.9, $\text{C}(\alpha)\text{H}$), 7.15–7.29 (6H, m, Ph), 7.34–7.40 (2H, m, Ph), 7.47–7.52 (2H, m, Ph); δ_{C} (100 MHz, d_1 - CHCl_3) 13.8 ($\text{C}(\alpha)\text{Me}$), 21.4 ($\text{C}(5)$), 26.6 ($\text{C}(6)$), 52.4 (NCH_2Ph), 55.0 ($\text{C}(\alpha)$), 60.0 ($\text{C}(2)$), 68.6 ($\text{C}(1)$), 69.6 ($\text{C}(4)$), 72.0 ($\text{C}(3)$), 126.8, 126.9, 126.9, 128.2, 128.4, 128.8 (*o,m,p*- Ph), 143.1, 143.7 (*i*- Ph); m/z (ESI^+) 342 ($[\text{M}+\text{H}]^+$, 100%); HRMS (ESI^+) $\text{C}_{21}\text{H}_{28}\text{NO}_3^+$ ($[\text{M}+\text{H}]^+$) requires 342.2064; found 342.2063.

Method B. Ring-opening of 249. HBF_4 (40% aq, 310 μL , 1.98 mmol) was added to a stirred solution of **249** (128 mg, 0.396 mmol, >95:5 dr) in CH_2Cl_2 (1.1 mL) at rt. The resultant solution was stirred at rt for 24 h and then 2.25 M aq NaOH (2.25 M, 10 mL) was added. The resultant mixture was extracted with $\text{CHCl}_3/\text{PrOH}$ (3:1, v/v, 3×15 mL). The combined organics were dried and concentrated *in vacuo*. Purification *via* flash column

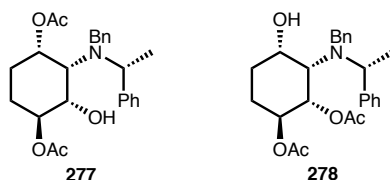
chromatography (eluent $\text{CHCl}_3/\text{MeOH}$, 49:1) gave **251** as a white solid (82 mg, 61%, >95:5 dr).

(1*S*,2*S*,3*S*,4*R*, α *R*)-1-Acetoxy-2-[*N*-benzyl-*N*-(α -methylbenzyl)amino]-3,4-epoxycyclohexane 276



Ac_2O (875 μL , 9.28 mmol) and DMAP (2.5 mg, 21 μmol) were added sequentially to a stirred solution of **245** (1.00 g, 3.09 mmol, >95:5 dr) in pyridine (12.9 mL) at rt. The resultant solution was stirred at rt for 24 h and then concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 4:1) gave **276** as a yellow oil (864 mg, 76%, >95:5 dr); $[\alpha]_{\text{D}}^{25} +17.8$ (c 1.0 in CHCl_3); ν_{max} 3061, 3024, 2970, 2848, 1730; δ_{H} (400 MHz, $d_1\text{-CHCl}_3$) 1.24 (1H, dddd, J 14.5, 12.1, 7.6, 2.3, $\text{C}(6)\text{H}_{\text{A}}$), 1.44 (3H, d, J 6.8, $\text{C}(\alpha)\text{Me}$), 1.67–1.86 (3H, m, $\text{C}(5)\text{H}_2$, $\text{C}(6)\text{H}_{\text{B}}$), 1.95 (3H, s, COMe), 3.06 (1H, dd, J 4.4, 2.0, $\text{C}(2)\text{H}$), 3.19–3.23 (1H, m, $\text{C}(4)\text{H}$), 3.28 (1H, m, $\text{C}(3)\text{H}$), 4.10 (1H, q, J 6.8, $\text{C}(\alpha)\text{H}$), 4.21 (1H, d, J 15.0, $\text{NCH}_{\text{A}}\text{H}_{\text{B}}\text{Ph}$), 4.45 (1H, d, J 15.0, $\text{NCH}_{\text{A}}\text{H}_{\text{B}}\text{Ph}$), 4.88–4.92 (1H, m, $\text{C}(1)\text{H}$), 7.19–7.26 (2H, m, *Pb*), 7.30–7.37 (4H, m, *Pb*), 7.44–7.50 (4H, m, *Pb*); δ_{C} (100 MHz, $d_1\text{-CHCl}_3$) 14.5 ($\text{C}(\alpha)\text{Me}$), 19.0 ($\text{C}(5)$), 21.5 (COMe), 25.9 ($\text{C}(6)$), 51.3 ($\text{C}(4)$), 52.6 (NCH_2Ph), 54.1 ($\text{C}(3)$), 54.2 ($\text{C}(2)$), 56.7 ($\text{C}(\alpha)$), 72.6 ($\text{C}(1)$), 126.6, 126.8, 127.6, 127.9, 128.2, 128.3 (*o,m,p-Pb*), 141.8, 144.0 (*i-Pb*), 171.3 (COMe); m/z (ESI^+) 366 ($[\text{M}+\text{H}]^+$, 100%); HRMS (ESI^+) $\text{C}_{23}\text{H}_{28}\text{NO}_3^+$ ($[\text{M}+\text{H}]^+$) requires 366.2064; found 366.2062.

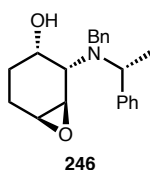
(1*S*,2*R*,3*S*,4*S*, α *R*)-1,4-Diacetoxy-2-[*N*-benzyl-*N*-(α -methylbenzyl)amino]cyclohexan-3-ol **277** and (1*S*,2*S*,3*S*,4*S*, α *R*)-3,4-diacetoxy-2-[*N*-benzyl-*N*-(α -methylbenzyl)amino]cyclohexan-1-ol **278**



A stirred solution of **276** (630 mg, 1.72 mmol, >95:5 dr) in AcOH (1.91 mL) was heated at 50 °C for 36 h and then allowed to cool to rt and diluted with 0.1 M aq NaHCO₃ (10 mL). The resultant mixture was extracted with CH₂Cl₂ (3 × 15 mL). The combined organics were washed with 0.1 M aq NaHCO₃ (20 mL), dried and concentrated *in vacuo* to give an 88:12 mixture of **277** and **278**, respectively. Purification *via* preparative thin layer chromatography (eluent 30–40 °C petroleum ether/EtOAc, 4:1) gave a >95:5 mixture of **277** and **278** as a white solid (439 mg, 60%) and a 9:91 mixture of **277** and **278** as a yellow oil (28 mg, 4%). Data for **277**: R_f = 0.57; $\nu_{\max}$ 3485, 3024, 2925, 2850, 1734; δ_{H} (400 MHz, d_1 -CHCl₃) 1.39 (3H, d, J 6.8, C(α)Me), 1.49–1.60 (2H, m, C(5) H_{A} , C(6) H_{A}), 1.73–1.82 (1H, m, C(6) H_{B}), 1.86–1.98 (4H, m, COMe, C(5) H_{B}), 2.02 (3H, s, COMe), 3.02 (1H, app t, J 2.6, C(2) H), 3.16 (1H, d, J 8.7, OH), 3.93 (1H, d, J 15.1, NCH_AH_BPh), 4.12–4.22 (2H, m, C(3) H , NCH_AH_BPh), 4.33 (1H, q, J 6.8, C(α)H), 5.00–5.07 (2H, m, C(1) H , C(4) H), 7.15–7.29 (6H, m, *Pb*), 7.30–7.36 (2H, m, *Pb*), 7.38–7.43 (2H, m, *Pb*); δ_{C} (100 MHz, d_1 -CHCl₃) 14.2 (C(α)Me), 18.9 (C(5)), 21.1, 21.3 (COMe), 24.9 (C(6)), 52.3 (NCH₂Ph), 55.8 (C(2)), 56.8 (C(α)), 71.2 (C(3)), 72.7 (C(4)), 74.8 (C(1)), 126.6, 126.9, 127.6, 127.9, 128.2, 128.2 (*o,m,p-Pb*), 141.7, 143.8 (*i-Pb*), 169.2, 169.8 (COMe); m/z (ESI⁺) 426 ([M+H]⁺, 100%); HRMS (ESI⁺) C₂₅H₃₂NO₅⁺ ([M+H]⁺) requires 426.2275; found 426.2271. Data for **278**: R_f = 0.50; $\nu_{\max}$ 3468, 3060, 3027, 2924, 2850, 1740; δ_{H} (400 MHz, d_1 -CHCl₃) 1.39 (3H, d, J 6.9, C(α)Me), 1.53–1.72 (3H, m, C(5) H_{A} , C(6) H_{A}), 1.89–1.98 (1H, m, C(5) H_{B}), 2.01 (3H, s,

C(3)(COMe), 2.03 (3H, s, C(4)(COMe)), 2.51 (1H, d, J 7.1, OH), 3.15 (1H, app t, J 2.9, C(2)H), 3.84 (1H, m, C(1)H), 4.04 (1H, d, J 15.2, NCH_AH_BPh), 4.11 (1H, d, J 15.2, NCH_AH_BPh), 4.18 (1H, q, J 6.9, C(α)H), 4.99–5.03 (1H, m, C(4)H), 5.26–5.30 (1H, m, C(3)H), 7.16–7.38 (10H, m, Ph); δ_{C} (100 MHz, d_1 -CHCl₃) 15.6 (C(α)Me), 19.4 (C(5)), 21.0, 27.8 (COMe), 29.7 (C(6)), 52.5 (NCH₂Ph), 55.5 (C(2)), 57.0 (C(α)), 69.4 (C(1)), 69.8 (C(4)), 73.6 (C(3)), 126.7, 127.0, 127.7, 127.8, 128.2, 128.3 (*o,m,p*-Ph), 141.8, 143.4 (*i*-Ph), 169.4, 169.4 (COMe); m/z (ESI⁺) 426 ([M+H]⁺, 100%); HRMS (ESI⁺) C₂₅H₃₂NO₅⁺ ([M+H]⁺) requires 426.2275; found 426.2271.

(1*S*,2*S*,3*R*,4*S*, α *R*)-2-[N-Benzyl-N-(α -methylbenzyl)amino]-3,4-epoxycyclohexan-1-ol
246

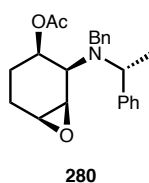


Step 1. MsCl (211 μ L, 2.73 mmol) was added to a stirred solution of **277** (387 mg, 0.910 mmol, >95:5 dr) in pyridine (9.1 mL) at 0 °C. The resultant solution was stirred at rt for 16 h and then concentrated *in vacuo* to give an ~15:85 mixture of **277** and **279**, respectively.

Step 2. K₂CO₃ (1.28 g) was added to a stirred solution of the residue from the previous step in MeOH (12.8 mL) at rt. The resultant mixture was stirred at rt for 16 h and then concentrated *in vacuo*. H₂O (15 mL) was added and the resultant mixture was extracted with CH₂Cl₂ (3 $\times$ 20 mL). The combined organics were dried and concentrated *in vacuo* to give an 85:15 mixture of **246** and **247**, respectively. Purification *via* flash column chromatography (eluent CHCl₃) gave **246** as an orange solid (148 mg, 50%, >95:5 dr); mp 123–130 °C; $[\alpha]_{\text{D}}^{25}$ –35.3 (c 1.0 in CHCl₃); ν_{max} 3459, 3084, 3061, 3026, 2968, 2932, 2850; δ_{H} (400 MHz, d_1 -CHCl₃) 1.33–1.57 (5H, m, C(6)H₂, C(α)Me), 1.84–1.93 (1H, m, C(5)H_A), 2.05

(1H, dddd, J 15.4, 9.0, 6.2, 2.6, $C(5)H_B$), 2.62 (1H, s, OH), 3.14 (1H, d, J 4.3, $C(2)H$), 3.24–3.27 (1H, m, $C(4)H$), 3.33 (1H, d, J 4.3, $C(3)H$), 3.35–3.41 (1H, m, $C(1)H$), 4.06–4.16 (2H, m, $C(\alpha)H$, NCH_AH_BPh), 4.20 (1H, d, J 14.4, NCH_AH_BPh), 7.22–7.37 (6H, m, Ph), 7.37–7.44 (2H, m, Ph), 7.48–7.53 (2H, m, Ph); δ_C (100 MHz, d_1 -CHCl₃) 12.1 ($C(\alpha)Me$), 19.1 ($C(5)$), 23.1 ($C(6)$), 52.9 ($C(4)$), 53.2 ($C(3)$), 53.6 (NCH_2Ph), 54.0 ($C(2)$), 57.0 ($C(\alpha)$), 65.5 ($C(1)$), 127.2, 127.3, 127.8, 128.0, 128.3, 128.7 ($o,m,p-Ph$), 140.6, 142.9 ($i-Ph$); m/z (ESI⁺) 324 ($[M+H]^+$, 100%); HRMS (ESI⁺) $C_{21}H_{26}NO_2^+$ ($[M+H]^+$) requires 324.1958; found 324.1958.

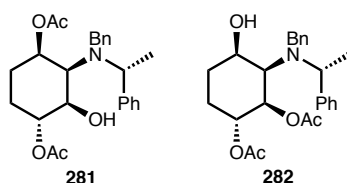
(1R,2R,3R,4S, α R)-1-Acetoxy-2-[N-benzyl-N-(α -methylbenzyl)amino]-3,4-epoxycyclohexane **280**



Ac₂O (579 μ L, 6.14 mmol) and DMAP (1.7 mg, 14 μ mmol) were added sequentially to a stirred solution of **249** (661 mg, 2.05 mmol, >95:5 dr) in pyridine (8.52 mL) at rt. The resultant solution was stirred at rt for 24 h and then concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 4:1) gave **280** as a yellow oil (570 mg, 76%, >95:5 dr); $[\alpha]_D^{25} +73.7$ (c 1.0 in CHCl₃); ν_{max} 3060, 3026, 2931, 2845, 1733; δ_H (400 MHz, d_1 -CHCl₃) 1.37 (3H, d, J 7.0, $C(\alpha)Me$), 1.42–1.55 (1H, m, $C(6)H_A$), 1.78–1.89 (6H, m, $C(5)H_2$, $C(6)H_B$, COMe), 2.50 (1H, ddd, J 4.4, 2.0, 1.1, $C(3)H$), 3.01–3.06 (1H, m, $C(4)H$), 3.36 (1H, dd, J 4.4, 2.0, $C(2)H$), 3.95–4.07 (2H, m, $C(\alpha)H$, NCH_AH_BPh), 4.57 (1H, d, J 15.6, NCH_AH_BPh), 5.14–5.19 (1H, m, $C(1)H$), 7.21–7.29 (2H, m, Ph), 7.31–7.38 (6H, m, Ph), 7.43–7.47 (2H, m, Ph); δ_C (100 MHz, d_1 -CHCl₃) 19.2 ($C(5)$), 19.4 ($C(\alpha)Me$), 21.3 (COMe), 26.0 ($C(6)$), 50.9 ($C(4)$), 52.8 ($C(3)$), 52.9 (NCH_2Ph), 53.5

(C(2)), 58.0 (C(α)), 73.7 (C(1)), 126.4, 127.2, 127.5, 127.5, 128.3, 128.4 (*o,m,p*-Ph), 142.0, 142.6 (*i*-Ph), 171.4 (COMe); m/z (ESI⁺) 366 ([M+H]⁺, 100%); HRMS (ESI⁺) C₂₃H₂₈NO₃⁺ ([M+H]⁺) requires 366.2064; found 366.2059.

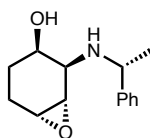
(1R,2S,3R,4R, α R)-1,4-Diacetoxy-2-[N-benzyl-N-(α -methylbenzyl)amino]cyclohexan-3-ol 281 and (1R,2R,3R,4R, α R)-3,4-diacetoxy-2-[N-benzyl-N-(α -methylbenzyl)amino]cyclohexan-1-ol 282



A stirred solution of **280** (520 mg, 1.42 mmol, >95:5 dr) in AcOH (1.58 mL) was heated at 50 °C for 36 h, then allowed to cool to rt. 0.1 M aq NaHCO₃ (10 mL) was added and the aqueous layer was extracted with CH₂Cl₂ (3 × 15 mL). The combined organics were washed with 0.1 M aq NaHCO₃ (20 mL), dried and concentrated *in vacuo* to give an 83:17 mixture of **281** and **282**, respectively. Purification *via* preparative thin layer chromatography (eluent 30–40 °C petroleum ether/EtOAc, 4:1) gave a >95:5 mixture of **281** and **282** as pale yellow oil (315 mg, 41%) and a 5:95 mixture of **281** and **282** as a yellow oil (64 mg, 11%). Data for **281**: R_f = 0.53; $\nu_{\max}$ 3483, 3028, 2934, 2841, 1734; δ_H (400 MHz, d_1 -CHCl₃) 1.43 (3H, d, J 6.9, C(α)Me), 1.49–1.56 (1H, m, C(5) H_A), 1.68–1.78 (1H, m, C(6) H_A), 1.82 (3H, s, COMe), 1.84–1.95 (2H, m, C(5) H_B , C(6) H_B), 1.98 (3H, s, COMe), 2.87 (1H, d, J 8.4, OH), 2.98 (1H, app t, J 2.7, C(2) H), 3.78–3.84 (1H, m, C(3) H), 4.07 (1H, d, J 15.0, NCH_AH_BPh), 4.12 (1H, d, J 15.0, NCH_AH_BPh), 4.23 (1H, q, J 6.9, C(α) H), 4.89–4.94 (1H, m, C(4) H), 5.37–5.42 (1H, m, C(1) H), 7.19–7.38 (10H, m, Ph); δ_C (100 MHz, d_1 -CHCl₃) 15.9 (C(α)Me), 19.1 (C(5)), 21.0, 21.4 (COMe), 25.3 (C(6)), 52.2 (NCH₂Ph), 55.0 (C(2)), 56.5 (C(α)), 72.0 (C(3)), 72.4 (C(4)), 74.4 (C(1)), 126.7, 126.9, 127.7, 127.9, 128.1, 128.3 (*o,m,p*-

Pb), 141.6, 143.3 (*i-Pb*), 169.7 (COMe); m/z (ESI⁺) 426 ([M+H]⁺, 100%); HRMS (ESI⁺) C₂₅H₃₂NO₅⁺ ([M+H]⁺) requires 426.2275; found 426.2270. Data for **282**: R_f = 0.46; $\nu_{\max}$ 3577, 3027, 2931, 2949, 1738; δ_H (400 MHz, *d*₁-CHCl₃) 1.43 (3H, d, *J* 6.8, C(α)Me), 1.54–1.62 (1H, m, C(5)*H*_A), 1.68–1.84 (5H, m, C(6)*H*₂, COMe), 1.86–1.98 (4H, m, C(5)*H*_B, COMe), 2.72 (1H, d, *J* 8.6, OH), 3.04 (1H, app t, *J* 2.7, C(2)*H*), 4.08 (1H, d, *J* 15.0, NCH_AH_BPh), 4.18–4.26 (2H, m, C(α)*H*, NCH_AH_BPh), 4.28–4.35 (1H, m, C(1)*H*), 4.83–4.88 (1H, m, C(4)*H*), 4.95–4.98 (1H, m, C(3)*H*), 7.18–7.25 (2H, m, *Pb*), 7.28–7.36 (6H, m, *Pb*), 7.38–7.43 (2H, m, *Pb*); δ_C (100 MHz, *d*₁-CHCl₃) 14.5 (C(α)Me), 19.0 (C(5)), 20.9, 21.1 (COMe), 28.5 (C(6)), 52.4 (NCH₂Ph), 54.8 (C(2)), 56.8 (C(α)), 69.4 (C(4)), 70.5 (C(1)), 74.8 (C(3)), 126.7, 126.8, 127.9, 127.9, 128.1, 128.3 (*o,m,p-Pb*), 141.6, 143.5 (*i-Pb*), 168.9, 169.2 (COMe); m/z (ESI⁺) 426 ([M+H]⁺, 100%); HRMS (ESI⁺) C₂₅H₃₂NO₅⁺ ([M+H]⁺) requires 426.2275; found 426.2270.

(1R,2R,3S,4R, α R)-2-[N-Benzyl-N-(α -methylbenzyl)amino]-3,4-epoxycyclohexan-1-ol **250**



250

Step 1. MsCl (110 μ L, 1.43 mmol) was added to a stirred solution of **281** (202 mg, 0.475 mmol, >95:5 dr) in pyridine (4.75 mL) at 0 °C. The resultant solution was stirred at rt for 16 h and then concentrated *in vacuo* to give an ~10:90 mixture of **281** and **283**, respectively.

Step 2. K₂CO₃ (640 mg) was added to a stirred solution of the residue from the previous step in MeOH (6.4 mL) at rt. The resultant mixture was stirred at rt for 16 h and then concentrated *in vacuo*. H₂O (15 mL) was added and the resultant mixture was extracted with CH₂Cl₂ (3 $\times$ 20 mL). The combined organics were dried and concentrated *in vacuo* to give a

78:8:14 mixture of **250**, **251** and **284**, respectively. Purification *via* flash column chromatography (eluent CHCl₃) gave **284** as a yellow oil (12 mg, 7%, >95:5 dr); $[\alpha]_{\text{D}}^{25} +11.6$ (*c* 0.5 in CHCl₃); ν_{max} 3059, 3027, 2933, 2848, 1736; δ_{H} (400 MHz, *d*₁-CHCl₃) 1.39 (3H, d, *J* 7.1, C(α)Me), 1.41–1.48 (1H, m, C(6)*H*_A), 1.61 (3H, s, COMe), 1.64–1.83 (2H, m, C(5)*H*_A, C(6)*H*_B), 1.87–1.95 (1H, m, C(5)*H*_B), 2.67 (1H, dd, *J* 3.9, 1.5, C(3)*H*), 3.13–3.17 (1H, m, C(4)*H*), 3.38 (1H, d, *J* 4.6, C(2)*H*), 3.87 (1H, q, *J* 7.1, C(α)*H*), 3.95 (1H, d, *J* 15.8, NCH_AH_BPh), 4.18 (1H, d, *J* 15.8, NCH_AH_BPh), 5.07 (1H, app tt, *J* 4.6, 1.5, C(1)*H*), 7.21–7.46 (10 H, m, *Pb*); δ_{C} (101 MHz, *d*₁-CHCl₃) 18.9 (C(5)), 20.1 (C(α)Me), 20.9 (COMe), 21.2 (C(6)), 52.2 (C(3)), 53.0 (C(4)), 53.6 (NCH₂Ph), 54.0 (C(2)), 59.6 (C(α)), 72.2 (C(1)), 126.6, 126.9, 127.4, 127.7, 128.4 (*o,m,p-Pb*), 141.6, 142.0 (*i-Pb*), 170.6 (COMe); *m/z* (ESI⁺) 366 ([M+H]⁺, 100%); HRMS (ESI⁺) C₂₃H₂₈NO₃⁺ ([M+H]⁺) requires 366.2064; found 366.2061.

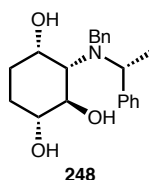
Further elution gave **250** as a yellow oil (108 mg, 70%, >95:5 dr); $[\alpha]_{\text{D}}^{25} +50.8$ (*c* 1.0 in CHCl₃); ν_{max} 3443, 3060, 3026, 2933, 2848; δ_{H} (400 MHz, *d*₁-CHCl₃) 1.45–1.63 (5H, m, C(6)*H*₂, C(α)Me), 1.85–2.04 (2H, m, C(5)*H*₂), 2.53 (1H, app dd, *J* 3.8, 1.0, C(3)*H*), 3.02–3.06 (1H, m, C(4)*H*), 3.12 (1H, d, *J* 4.6, OH), 3.59 (1H, app d, *J* 4.9, C(2)*H*), 3.79–3.86 (1H, m, C(1)*H*), 3.90–4.00 (2H, m, C(α)*H*, NCH_AH_BPh), 4.07 (1H, d, *J* 15.4, NCH_AH_BPh), 7.28–7.47 (10H, m, *Pb*); δ_{C} (100 MHz, *d*₁-CHCl₃) 19.2 (C(α)Me), 19.7 (C(5)), 23.9 (C(6)), 52.6 (C(4)), 52.8 (C(3)), 53.3 (NCH₂Ph), 53.9 (C(2)), 58.1 (C(α)), 65.6 (C(1)), 127.2, 127.4, 127.6, 128.0, 128.5, 128.8 (*o,m,p-Pb*), 140.2, 140.5 (*i-Pb*); *m/z* (ESI⁺) 324 ([M+H]⁺, 100%); HRMS (ESI⁺) C₂₁H₂₆NO₂⁺ ([M+H]⁺) requires 324.1958; found 324.1954.

Preparation of an authentic sample of 256 via ring-opening of 250. A solution of **250** (40 mg, 0.124 mmol, >95:5 dr) in CH₂Cl₂ (0.34 mL) was added to anhydrous TsOH (107 mg, 0.619 mmol) at rt and the resultant solution was stirred at rt for 24 h. The resultant mixture was diluted with CH₂Cl₂ (5 mL), washed with 0.1 M aq NaHCO₃ (4 × 10 mL), dried and concentrated *in vacuo* to give **256** as a yellow oil (34 mg); δ_{H} (400 MHz, *d*₁-CHCl₃) 1.32–1.55

(4H, m, C(6) H_A , C(α)Me), 1.68–1.76 (1H, m, C(6) H_B), 1.78–2.00 (2H, m, C(5) H_2), 2.43–2.47 (4H, m, C(2) H , ArMe), 3.87–4.02 (2H, m, C(1) H , NCH $_A$ H $_B$ Ph), 4.12–4.29 (4H, m, C(3) H , C(4) H , C(α) H , NCH $_A$ H $_B$ Ph), 7.19–7.39 (12H, m, *Pb*, *Ar*) 7.76–7.81 (2H, m, *Ar*); δ_C (101 MHz, d_1 -CHCl $_3$) 15.1 (C(α)Me), 21.6 (ArMe), 24.5 (C(5)), 29.6 (C(6)), 50.2 (NCH $_2$ Ph), 57.7 (C(α)), 63.1 (C(2)), 67.3 (C(1)), 69.0 (C(3)), 85.7 (C(4)), 127.0, 127.1, 127.7, 127.7, 128.4, 128.6, 129.5, 134.3 (*o,m,p*-*Pb*, *Ar*), 141.0, 143.4, 144.3 (*i*-*Pb*, *Ar*).

(1*S*,2*S*,3*R*,4*R*, α *R*)-2-[N-Benzyl-N-(α -methylbenzyl)amino]cyclohexane-1,3,4-triol

248

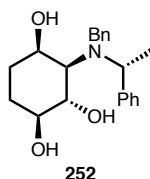


HBF $_4$ (40% aq, 199 μ L, 1.27 mmol) was added to a stirred solution of **246** (82.0 mg, 0.254 mmol, >95:5 dr) in CH $_2$ Cl $_2$ (0.71 mL) at rt. The resultant solution was stirred at 40 °C for 24 h and then 2.25 M aq NaOH (10 mL) was added. The resultant mixture was extracted with CHCl $_3$ / i PrOH (3:1, v/v, 3 $\times$ 20 mL). The combined organics were dried and concentrated *in vacuo* to give a 5:95 mixture of **247** and **248**, respectively. Purification *via* flash column chromatography (eluent CHCl $_3$ /MeOH, 99:1) gave **248** as a white solid (50 mg, 58%, 95:5 dr); mp 133–136 °C; $[\alpha]_D^{25}$ +115.6 (c 1.0 in CHCl $_3$); $\nu_{\max}$ 3403, 3084, 3061, 3027, 2935; δ_H (400 MHz, d_1 -CHCl $_3$) 1.23–1.33 (1H, m, C(6) H_A), 1.37 (3H, d, J 7.0, C(α)Me), 1.45–1.54 (1H, m, C(6) H_B), 1.67–1.77 (2H, m, C(5) H_2), 2.49 (1H, d, J 2.4, OH), 2.64 (1H, dd, J 10.6, 2.0, C(2) H), 3.24 (1H, app s, C(1) H), 3.48–3.56 (2H, m, C(4) H , OH), 3.76 (1H, dd, J 10.6, 8.3, C(3) H), 3.90 (1H, d, J 14.9, NCH $_A$ H $_B$ Ph), 4.06 (1H, q, J 7.0, C(α) H), 4.43 (1H, d, J 14.9, NCH $_A$ H $_B$ Ph), 7.28–7.45 (10H, m, *Pb*); δ_C (100 MHz, d_1 -CHCl $_3$) 19.5 (C(α)Me), 25.4 (C(5)), 30.3 (C(6)), 51.9 (NCH $_2$ Ph), 56.8 (C(α)), 61.3 (C(2)), 67.9 (C(1)),

69.9 (C(3)), 75.4 (C(4)), 127.0, 127.4, 127.7, 128.4, 128.4, 128.6 (*o,m,p*-Ph), 140.9, 142.2 (*i*-Ph); m/z (ESI⁺) 342 ([M+H]⁺, 100%); HRMS (ESI⁺) C₂₁H₂₈NO₃⁺ ([M+H]⁺) requires 342.2064; found 342.2062.

(1R,2R,3S,4S,αR)-2-[N-Benzyl-N-(α-methylbenzyl)amino]cyclohexane-1,3,4-triol

252



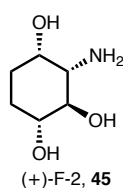
Method A. Step 1. Ring-opening of 250. HBF₄ (40% aq, 188 μL, 1.20 mmol) was added to a stirred solution of **250** (76 mg, 0.24 mmol, >95:5 dr) in CH₂Cl₂ (0.67 mL) at rt. The resultant solution was stirred at rt for 24 h and then 2.25 M aq NaOH (10 mL) was added. The resultant mixture was extracted with CHCl₃/*i*PrOH (3:1, v/v, 3 × 20 mL). The combined organics were dried over Na₂SO₄ and concentrated *in vacuo* to give an 85:15 mixture of **250** and **252**, respectively (76.5 mg).

Step 2. HBF₄ (40% aq, 185 μL, 1.18 mmol) was added to a stirred solution of the 85:15 mixture of **250** and **252** from the previous step (76.5 mg, 0.237 mmol) in CH₂Cl₂ (0.66 mL) at rt. The resultant solution was stirred at 40 °C for 24 h and then 2.25 M aq NaOH (10 mL) was added. The resultant mixture was extracted with CHCl₃/*i*PrOH (3:1, v/v, 3 × 20 mL). The combined organics were dried and concentrated *in vacuo* to give a 5:95 mixture of **251** and **252**, respectively. Purification *via* flash column chromatography (eluent CHCl₃/MeOH, 32:1) gave **252** as a white solid (30 mg, 37%, >95:5 dr); mp 185–196 °C; [α]_D²⁵ –38.5 (c 1.0 in 1:1 CHCl₃/MeOH); ν_{max} 3375, 3061, 3027, 2942, 2877, 2843; δ_H (400 MHz, *d*₁-CHCl₃) 1.42–1.56 (4H, m, C(6)*H*_A, C(α)*Me*), 1.64 (1H, s, OH) 1.70–1.79 (3H, m, C(5)*H*₂, C(6)*H*_B), 2.42 (1H, dd, *J* 10.6, 2.1, C(2)*H*), 2.49 (1H, s, OH), 2.91 (1H, s, OH),

3.19–3.28 (1H, m, C(4)H), 3.77 (1H, dd, J 10.6, 8.3, C(3)H), 3.94 (1H, d, J 14.2, NCH_AH_BPh), 4.24 (1H, q, J 6.9, C(α)H), 4.30 (1H, d, J 14.2, NCH_AH_BPh), 4.36–4.41 (1H, m, C(1)H), 7.18–7.39 (10H, m, *Pb*); δ_{C} (100 MHz, d_1 -CHCl₃) 14.6 (C(α)Me), 25.2 (C(5)), 30.6 (C(6)), 50.9 (NCH₂Ph), 56.1 (C(α)), 61.7 (C(2)), 69.8 (C(1)), 70.2 (C(3)), 75.4 (C(4)), 127.1, 127.2, 127.6, 128.5, 128.6, 128.8 (*o,m,p-Pb*), 140.7, 143.5 (*i-Pb*); m/z (ESI⁺) 342 ([M+H]⁺, 100%); HRMS (ESI⁺) C₂₁H₂₈NO₃⁺ ([M+H]⁺) requires 342.2064; found 342.2065.

Method B. Ring-opening of 250. HBF₄ (40% aq, 159 μ L, 1.01 mmol) was added to a stirred solution of **250** (65.6 mg, 0.203 mmol, >95:5 dr) in CH₂Cl₂ (0.56 mL) at rt. The resultant solution was stirred at 40 °C for 24 h and then 2.25 M aq NaOH (10 mL) was added. The resultant mixture was extracted with CHCl₃/*i*PrOH (3:1, v/v, 3 $\times$ 15 mL). The combined organics were dried over Na₂SO₄ and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent CHCl₃/MeOH, 32:1) gave **252** as a white solid (37 mg, 53%, 90:10 dr).

(1*S*,2*S*,3*R*,4*R*)-2-Aminocyclohexane-1,3,4-triol [(+)-Dihydroconduramine F-2] 45

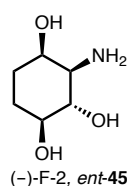


Pd(OH)₂/C (25 mg) was added to a stirred degassed solution of **248** (48 mg, 0.141 mmol, 95:5 dr) in MeOH (1.5 mL) at rt. The resultant mixture was stirred at rt under H₂ (1 atm) for 24 h and then filtered through Celite® (eluent MeOH). The filtrate was concentrated *in vacuo*. Purification *via* flash column chromatography (eluent CHCl₃/MeOH/35% aq NH₄OH, 14:5:1) gave **45** as a yellow oil (11 mg, 55%, >95:5 dr, >99% ee¹¹); $[\alpha]_{\text{D}}^{25}$ +33.2 (c 0.5 in MeOH); ν_{max} 3447, 2940, 2880, 2860; δ_{H} (400 MHz, MeOH- d_4) 1.47–1.58 (1H, m,

$C(6)H_N$), 1.67–1.85 (3H, m, $C(5)H_2, C(6)H_B$), 2.43–2.50 (1H, m, $C(2)H$), 3.32–3.38 (2H, m, $C(3)H, C(4)H$), 3.92–3.96 (1H, m, $C(1)H$); δ_C (100 MHz, MeOH- d_4) 28.1 ($C(5)$), 30.2 ($C(6)$), 58.6 ($C(2)$), 69.7 ($C(1)$), 74.8 ($C(4)$), 77.2 ($C(3)$); m/z (ESI⁺) 148 ([M+H]⁺, 100%); HRMS (ESI⁺) $C_6H_{14}NO_3^+$ ([M+H]⁺) requires 148.0968; found 148.0968.

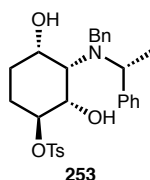
(1R,2R,3S,4S)-2-Aminocyclohexane-1,3,4-triol **[(-)-Dihydroconduramine F-2]**

ent-45



$Pd(OH)_2/C$ (10 mg) was added to a stirred degassed solution of **252** (20 mg, 0.059 mmol, 95:5 dr) in MeOH (1 mL) at rt. The resultant mixture was stirred at rt under H_2 (1 atm) for 24 h and then filtered through Celite® (eluent MeOH). The filtrate was concentrated *in vacuo*. Purification *via* flash column chromatography (eluent $CHCl_3/MeOH/35\%$ aq NH_4OH , 5:4:1) gave **45** as a yellow oil (6.3 mg, 73%, >95:5 dr, >99% ee¹²); $[\alpha]_D^{25}$ -31.0 (c 0.25 in MeOH).

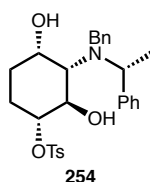
(1S,2S,3S,4S,αR)-2-[N-Benzyl-N-(α-methylbenzyl)amino]-4-tosyloxycyclohexan-1,3-diol **253**



A solution of **245** (472 mg, 1.46 mmol, >95:5 dr) in CH_2Cl_2 (4.1 mL) was added to anhydrous TsOH (1.26 g, 7.30 mmol) at rt. The resultant solution was stirred at rt for 24 h and then diluted with CH_2Cl_2 (30 mL), washed with 0.1 M aq $NaHCO_3$ (4×20 mL), dried

and concentrated *in vacuo* to give **253** as a yellow solid (611 mg, 84%, >95:5 dr); mp 133–140 °C; $[\alpha]_{\text{D}}^{25}$ -40.2 (c 1.0 in CHCl_3); ν_{max} 3453, 3061, 3028, 2936, 2836; δ_{H} (400 MHz, d_1 - CHCl_3) 1.37 (3H, d, J 6.9, $\text{C}(\alpha)\text{Me}$), 1.48–1.81 (3H, m, $\text{C}(5)\text{H}_{\text{A}}$, $\text{C}(6)\text{H}_2$), 2.00–2.13 (1H, m, $\text{C}(5)\text{H}_{\text{B}}$), 2.18–2.23 (1H, m, OH), 2.46 (3H, s, ArMe), 2.84 (1H, app t, J 2.5, $\text{C}(2)\text{H}$), 3.29 (1H, d, J 15.4, $\text{NCH}_{\text{A}}\text{H}_{\text{B}}\text{Ph}$), 3.78 (1H, app s, $\text{C}(1)\text{H}$), 4.11 (2H, m, $\text{C}(3)\text{H}$, $\text{NCH}_{\text{A}}\text{H}_{\text{B}}\text{Ph}$), 4.34 (1H, d, J 9.3, OH), 4.63 (1H, q, J 6.9, $\text{C}(\alpha)\text{H}$), 4.70 (1H, app q, J 3.2, $\text{C}(4)\text{H}$), 7.00–7.05 (2H, m, Ph), 7.11–7.26 (4H, m, Ph), 7.33–7.39 (4H, m, Ph , Ar), 7.43–7.49 (2H, m, Ph), 7.80–7.86 (2H, m, Ar); δ_{C} (100 MHz, d_1 - CHCl_3) 10.9 ($\text{C}(\alpha)\text{Me}$), 18.9 ($\text{C}(5)$), 21.7 (ArMe), 24.7 ($\text{C}(6)$), 52.4 (NCH_2Ph), 54.6 ($\text{C}(\alpha)$), 60.2 ($\text{C}(2)$), 67.8 ($\text{C}(1)$), 68.6 ($\text{C}(3)$), 80.6 ($\text{C}(4)$), 126.6, 127.1, 127.8, 128.2, 128.7, 128.9, 130.0 (o,m,p - Ph , Ar), 142.8, 143.6, 145.0 (i - Ph , Ar); m/z (ESI^+) 496 ($[\text{M}+\text{H}]^+$, 100%); HRMS (ESI^+) $\text{C}_{28}\text{H}_{34}\text{NO}_5\text{S}^+$ ($[\text{M}+\text{H}]^+$) requires 496.2152; found 496.2151.

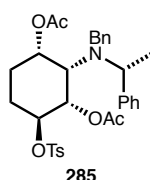
(1R,2R,3R,4R, α R)-2-[N-Benzyl-N-(α -methylbenzyl)amino]-4-tosyloxycyclohexan-1,3-diol **254**



A solution of **246** (99 mg, 0.31 mmol, >95:5 dr) in CH_2Cl_2 (0.85 mL) was added to anhydrous TsOH (263 mg, 1.53 mmol) at rt and the resultant solution was stirred at rt for 24 h. The resultant mixture was diluted with CH_2Cl_2 (10 mL), washed with 0.1 M aq NaHCO_3 (4×15 mL), dried and concentrated *in vacuo* to **254** as a yellow oil (99 mg, 66%, >95:5 dr); $[\alpha]_{\text{D}}^{25}$ $+4.6$ (c 1.0 in CHCl_3); ν_{max} 3510, 3019, 2935; δ_{H} (400 MHz, d_1 - CHCl_3) 1.48–1.59 (1H, m, $\text{C}(5)\text{H}_{\text{A}}$, $\text{C}(\alpha)\text{Me}$), 1.77–1.84 (2H, m, $\text{C}(6)\text{H}_2$), 1.97–2.08 (1H, m, $\text{C}(5)\text{H}_{\text{B}}$), 2.47 (3H, s, ArMe), 2.88 (1H, app t, J 2.5, $\text{C}(2)\text{H}$), 2.96 (1H, br s, OH), 3.31 (1H,

br s, OH), 3.82 (2H, app s, NCH₂Ph), 3.92–3.96 (1H, m, C(3)H), 4.15–4.19 (1H, m, C(1)H), 4.51–4.55 (1H, m, C(4)H), 4.66 (1H, q, *J* 7.0, C(α)H), 7.15–7.45 (12H, m, *Ph*, *Ar*), 7.69–7.73 (2H, m, *Ar*); δ_{C} (101 MHz, *d*₁-CHCl₃) 15.2 (C(α)Me), 19.0 (C(5)), 21.6 (ArMe), 26.3 (C(6)), 52.2 (NCH₂Ph), 55.1 (C(α)), 59.8 (C(2)), 68.0 (C(1)), 69.3 (C(3)), 79.7 (C(4)), 126.8, 127.0, 127.0, 127.7, 128.1, 128.3, 128.9, 129.9, 133.4 (*o,m,p-Ph*, *Ar*), 142.8, 143.1, 144.8 (*i-Ph*, *Ar*); *m/z* (ESI⁺) 496 ([M+H]⁺, 100%); HRMS (ESI⁺) C₂₈H₃₄NO₅S⁺ ([M+H]⁺) requires 496.2152; found 496.2147.

(1*S*,2*S*,3*S*,4*S*, α *R*)-1,3-Diacetoxy-2-[*N*-benzyl-*N*-(α -methylbenzyl)amino]-4-tosyloxycyclohexane **285**

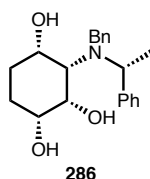


Ac₂O (579 μ L, 6.14 mmol) and DMAP (830 μ g, 6.80 μ mol) were added sequentially to a stirred solution of **253** (507 mg, 1.02 mmol, >95:5 dr) in pyridine (4.3 mL) at rt. The resultant solution was stirred at rt for 24 h and then concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 4:1) gave **285** as a yellow solid (515 mg, 87%, >95:5 dr); mp 60–62 °C; $[\alpha]_{\text{D}}^{25}$ +45.4 (*c* 1.0 in CHCl₃); ν_{max} 3028, 2937, 2807, 1736; δ_{H} (400 MHz, *d*₁-CHCl₃) 1.18 (3H, d, *J* 6.9, C(α)Me), 1.53–1.66 (3H, m, C(5)H_A, C(6)H₂), 1.77–1.88 (1H, m, C(5)H_B), 1.96 (3H, s, COMe), 1.97 (3H, s, COMe), 2.50 (3H, s, ArMe), 3.10 (1H, app t, *J* 2.8, C(2)H), 3.88 (1H, q, *J* 6.9, C(α)H), 3.97 (1H, d, *J* 14.4, NCH_AH_BPh), 4.12 (1H, d, *J* 14.4, NCH_AH_BPh), 4.67–4.71 (1H, m, C(4)H), 4.78–4.83 (1H, m, C(1)H), 5.21–5.24 (1H, m, C(3)H), 7.20–7.45 (12H, m, *Ph*, *Ar*), 7.81–7.87 (2H, m, *Ar*); δ_{C} (100 MHz, *d*₁-CHCl₃) 15.3 (C(α)Me), 20.7 (C(5)), 21.1, 21.4 (COMe), 21.7 (ArMe), 24.8 (C(6)), 50.8 (C(2)), 52.1 (NCH₂Ph), 57.2 (C(α)), 73.4 (C(1)), 73.5 (C(3)),

77.0 (C(4)), 126.8, 127.1, 127.5, 127.8, 127.8, 128.3, 128.4, 129.9, 133.7 (*o,m,p*-Ph, Ar), 141.4, 142.8, 145.0 (*i*-Ph, Ar), 169.7, 170.4 (COMe); m/z (ESI⁺) 580 ([M+H]⁺, 100%); HRMS (ESI⁺) C₃₂H₃₈NO₇S⁺ ([M+H]⁺) requires 580.2363; found 580.2357.

(1*S*,2*S*,3*S*,4*R*, α *R*)-2-[N-Benzyl-N-(α -methylbenzyl)amino]cyclohexane-1,3,4-triol

286

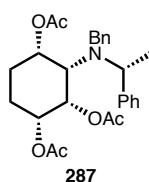


Step 1. KOAc (60 mg, 0.61 mmol) was added to a stirred solution of **285** (348 mg, 0.601 mmol, >95:5 dr) in EtOH/H₂O (6:1, v/v, 13.1 mL) at rt. The resultant mixture was heated at reflux for 72 h and then allowed to cool to rt and concentrated *in vacuo*.

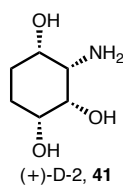
Step 2. K₂CO₃ (1.34 g, 9.70 mmol) was added to a stirred solution of the residue from the previous step in MeOH (13.4 mL) at rt. The resultant mixture was stirred at rt for 24 h and then concentrated *in vacuo*. 2.25 M aq NaOH (20 mL) was added and the resultant mixture was extracted with CHCl₃/iPrOH (3:1, v/v, 3 × 30 mL). The combined organics were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent CHCl₃/MeOH, 99:1) gave **286** as a yellow oil (201 mg, 98%, >95:5 dr); [α]_D²⁵ −1.36 (*c* 1.0 in CHCl₃); ν_{max} 3366, 3084, 3060, 3027, 2938, 2874, 2840; δ_{H} (400 MHz, *d*₁-CHCl₃) 1.25–1.37 (1H, m, C(5)*H*_A), 1.45 (3H, d, *J* 6.9, C(α)Me), 1.63–1.88 (3H, m, C(5)*H*_B, C(6)*H*₂), 2.51 (2H, m, C(2)*H*, OH), 2.60 (1H, s, OH), 3.41 (1H, d, *J* 15.4, NCH_AH_BPh), 3.45–3.54 (1H, m, C(4)*H*), 3.75 (1H, m, C(1)*H*), 3.86 (1H, d, *J* 8.9, OH), 4.15 (1H, d, *J* 15.4, NCH_AH_BPh), 4.28 (1H, dd, *J* 8.6, 2.7, C(3)*H*), 4.81 (1H, q, *J* 6.9, C(α)*H*), 7.06–7.12 (2H, m, Ph), 7.12–7.29 (4H, m, Ph), 7.35–7.41 (2H, m, Ph), 7.51–7.57 (2H, m, Ph); δ_{C} (100 MHz, *d*₁-CHCl₃) 11.7 (C(α)Me), 23.2 (C(6)), 27.8 (C(5)), 52.7 (NCH₂Ph), 54.8 (C(α)), 64.5 (C(2)), 67.6 (C(1)), 71.4

(C(4)), 72.1 (C(3)), 126.7, 127.0, 128.2, 128.5, 128.8 (*o,m,p*-Ph), 142.8, 143.7 (*i*-Ph); m/z (ESI⁺) 342 ([M+H]⁺, 100%); HRMS (ESI⁺) C₂₁H₂₈NO₃⁺ ([M+H]⁺) requires 342.2064; found 342.2059.

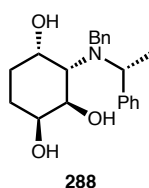
(1*S*,2*S*,3*S*,4*R*, α *R*)-1,3,4-Triacetoxy-2-[N-benzyl-N-(α -methylbenzyl)amino]cyclohexane **287**



Ac₂O (93 μ L, 0.98 mmol) and DMAP (86 μ g, 0.7 μ mol) were added sequentially to a stirred solution of **286** (37 mg, 0.11 mmol, >95:5 dr) in pyridine (0.45 mL) at rt. The resultant solution was stirred at rt for 24 h and then concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 3:1) gave **287** as a yellow oil (36 mg, 71%, >95:5 dr); [α]_D²⁵ +51.6 (c 1.0 in CHCl₃); $\nu_{\max}$ 3062, 3028, 2966, 1736; δ_{H} (400 MHz, d_1 -CHCl₃) 1.21–1.31 (1H, m, C(6)*H*_A), 1.38 (3H, d, J 6.9, C(α)*Me*), 1.45–1.52 (1H, m, C(5)*H*_A), 1.80–1.95 (2H, m, C(5)*H*_B, C(6)*H*_B), 2.01 (3H, s, COMe), 2.02 (3H, s, COMe), 2.07 (3H, s, COMe), 2.74 (1H, app t, J 2.8, C(2)*H*), 3.89–3.99 (2H, m, NCH_AH_BPh, C(α)*H*), 4.32 (1H, d, J 14.2, NCH_AH_BPh), 4.70 (1H, ddd, J 12.3, 4.4, 2.8, C(4)*H*), 4.88 (1H, app q, J 2.8, C(1)*H*), 5.76 (1H, app t, J 2.8, C(3)*H*), 7.29–7.39 (10H, m, Ph); δ_{C} (100 MHz, d_1 -CHCl₃) 14.3 (C(α)*Me*), 20.3 (C(5)), 20.9 (COMe), 21.2 (COMe), 21.5 (COMe), 27.3 (C(6)), 51.9 (NCH₂Ph), 54.6 (C(2)), 56.8 (C(α)), 71.6 (C(4)), 73.2 (C(1)), 73.3 (C(3)), 126.8, 127.0, 127.5, 128.1, 128.3, 128.4 (*o,m,p*-Ph), 141.2, 143.0 (*i*-Ph), 170.2, 170.5, 170.6 (COMe); m/z (ESI⁺) 468 ([M+H]⁺, 100%); HRMS (ESI⁺) C₂₇H₃₄NO₆⁺ ([M+H]⁺) requires 468.2381; found 468.2379.

(1*S*,2*S*,3*S*,4*R*)-2-Aminocyclohexane-1,3,4-triol**[(+)-Dihydroconduramine****D-2] 41**

Pd(OH)₂/C (37 mg) was added to a stirred degassed solution of **286** (74 mg, 0.22 mmol, >95:5 dr) in MeOH (2 mL) at rt. The resultant mixture was stirred at rt under H₂ (1 atm) for 24 h and then filtered through Celite® (eluent MeOH). The filtrate was concentrated *in vacuo* to give **41** as a yellow oil (22 mg, 69%, >95:5 dr, >99% ee¹¹); [α]_D²⁵ +10.4 (*c* 1.0 in MeOH); ν_{max} 3345, 2936, 2873; δ_H (400 MHz, MeOH-*d*₄) 1.46–1.57 (2H, m, C(5)*H*_A, C(6)*H*_A), 1.79–1.92 (2H, m, C(5)*H*_B, C(6)*H*_B), 2.84 (1H, app s, C(2)*H*), 3.62–3.68 (1H, m, C(4)*H*), 3.71 (1H, app s, C(3)*H*), 3.77 (1H, app dt, *J* 6.2, 3.0, C(1)*H*); δ_C (100 MHz, MeOH-*d*₄) 25.2 (C(5)), 28* (C(6)), 55.4 (C(2)), 71.5 (C(1)), 72.1 (C(4)), 75.0 (C(3));¹³ *m/z* (ESI⁺) 148 ([M+H]⁺, 100%); HRMS (ESI⁺) C₆H₁₄NO₃⁺ ([M+H]⁺) requires 148.0968; found 148.0968.

(1*S*,2*S*,3*R*,4*S*,α*R*)-2-[N-Benzyl-N-(α-methylbenzyl)amino]cyclohexane-1,3,4-triol**288**

Step 1. A solution of **246** (145 mg, 0.449 mmol, >95:5 dr) in CH₂Cl₂ (1.25 mL) was added to anhydrous TsOH (0.386 g, 2.24 mmol) at rt. The resultant solution was stirred at rt for 24 h and then diluted with CH₂Cl₂ (10 mL), washed with 0.1 M aq NaHCO₃ (4 × 15 mL), dried and concentrated *in vacuo* to give **254** as a yellow solid (170 mg); δ_H (400 MHz, *d*₁-CHCl₃) 1.13–1.26 (1H, m, C(6)*H*_A), 1.36 (3H, d, *J* 7.0, C(α)*Me*), 1.42–1.53 (1H, m, C(6)*H*_B),

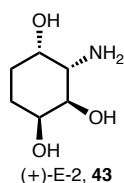
1.78–1.99 (1H, m, C(5) H_2), 2.46 (3H, s, ArMe), 2.66 (1H, dd, J 10.6, 2.1, C(2) H), 3.09–3.16 (1H, m, C(1) H), 3.39 (1H, s, OH), 3.91 (1H, d, J 14.7, NCH_AH_BPh), 3.96–4.10 (2H, m, C(3) H , C(α) H), 4.31 (1H, d, J 14.7, NCH_AH_BPh), 4.52 (1H, ddd, J 11.5, 8.6, 5.5, C(4) H), 7.24–7.44 (12H, m, Ph, Ar), 7.84–7.89 (2H, m, Ar); δ_C (100 MHz, d_1 -CHCl₃) 18.3 (C(α)Me), 21.7 (ArMe), 24.6 (C(5)), 29.6 (C(6)), 52.0 (NCH₂Ph), 56.6 (C(α)), 61.0 (C(2)), 67.0 (C(3)), 68.0 (C(1)), 85.6 (C(4)), 127.1, 127.4, 127.7, 127.8, 128.4, 128.5, 128.6, 129.6 (*o,m,p*-Ph, Ar), 140.6, 142.4, 144.4 (*i*-Ph, Ar).

Step 2. Ac₂O (194 μ L, 2.06 mmol) and DMAP (0.27 mg, 2.29 μ mol) were added sequentially to a stirred solution of the residue of **254** from the previous step (170 mg) in pyridine (1.4 mL) at rt. The resultant solution was stirred at rt for 24 h and then concentrated *in vacuo* to give **289** as a yellow oil (183 mg); δ_H (400 MHz, d_1 -CHCl₃) 0.99–1.11 (1H, m, C(6) H_A), 1.29 (3H, d, J 6.9, C(α)Me), 1.63–1.81 (3H, m, C(5) H_2 , C(6) H_B), 1.84 (3H, s, COMe), 2.11 (3H, s, COMe), 2.45 (3H, s, ArMe), 2.92 (1H, dd, J 11.2, 2.5, C(2) H), 3.88 (1H, d, J 14.7, NCH_AH_BPh), 3.96 (1H, q, J 6.9, C(α) H), 4.02 (1H, d, J 14.7, NCH_AH_BPh), 4.51 (1H, br app q, J 2.5, C(1) H), 4.58 (1H, ddd, J 11.4, 8.9, 5.6, C(4) H), 5.51 (1H, dd, J 11.2, 8.9, C(3) H), 7.21–7.37 (12H, m, Ph, Ar), 7.74–7.79 (2H, m, Ar); δ_C (100 MHz, d_1 -CHCl₃) 15.5 (C(α)Me), 21.2 (COMe), 21.4 (COMe), 21.6 (ArMe), 25.5 (C(5)), 25.7 (C(6)), 51.8 (NCH₂Ph), 56.1 (C(α)), 58.1 (C(2)), 69.5 (C(3)), 74.3 (C(1)), 82.0 (C(4)), 123.9, 127.2, 127.5, 127.8, 127.9, 128.3, 128.4, 129.8 (*o,m,p*-Ph, Ar), 140.8, 142.6 (*i*-Ph, Ar), 170.1 (COMe), 170.1 (COMe).

Step 3. KOAc (31.6 mg, 0.322 mmol) was added to a stirred solution of the residue of **289** from the previous step (183 mg) in EtOH/H₂O (6:1, v/v, 6.87 mL) at rt. The resultant mixture was heated at reflux for 72 h and then allowed to cool to rt and concentrated *in vacuo*.

Step 4. K_2CO_3 (266 mg, 1.92 mmol) was added to a stirred solution of the residue from the previous step in MeOH (5.3 mL) at rt. The resultant mixture was stirred at rt for 24 h and then concentrated in vacuo. 2.25 M aq NaOH (15 mL) was added and the resultant mixture was extracted with $CHCl_3$ /*i*PrOH (3:1, v/v, 3×20 mL). The combined organics were dried and concentrated *in vacuo*. Purification *via* preparative thin layer chromatography (eluent $CHCl_3$) gave **288** as a yellow oil (39.8 mg, 26% from **246**, >95:5 dr); $[\alpha]_D^{25} +95.0$ (c 1.0 in $CHCl_3$); ν_{max} 3422, 3061, 3027, 2929; δ_H (400 MHz, d_1 - $CHCl_3$) 1.23–1.31 (1H, m, C(6) H_A), 1.34–1.42 (3H, d, J 7.1, C(α)Me), 1.68–1.87 (3H, m, C(5) H_2 , C(6) H_B), 2.63 (1H, s, OH), 3.17–3.22 (1H, m, C(1) H), 3.28 (1H, dd, J 10.6, 1.8, C(2) H), 3.83 (1H, d, J 14.7, NCH_AH_BPh), 3.95 (1H, dd, J 10.6, 3.0, C(3) H), 4.01 (1H, q, J 7.1, C(α) H), 4.23 (1H, app q, J 3.0, C(4) H), 4.42 (1H, d, J 14.7, NCH_AH_BPh), 7.26–7.45 (10H, m, *Ph*); δ_C (100 MHz, d_1 - $CHCl_3$) 19.9 (C(α)Me), 23.4 (C(5)), 28.7 (C(6)), 51.8 (NCH_2Ph), 56.5 (C(2)), 56.6 (C(α)), 65.5 (C(3)), 68.5 (C(1)), 68.6 (C(4)), 127.0, 127.4, 127.8, 128.4, 128.5, 128.6 (*o,m,p-Ph*), 140.7, 141.8 (*i-Ph*); m/z (ESI⁺) 342 ($[M+H]^+$, 100%); HRMS (ESI⁺) $C_{21}H_{28}NO_3^+$ ($[M+H]^+$) requires 342.2064; found 342.2060.

(1*S*,2*S*,3*R*,4*S*)-2-Aminocyclohexane-1,3,4-triol [(+)-Dihydroconduramine E-2] 43

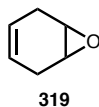


$Pd(OH)_2/C$ (36 mg) was added to a stirred degassed solution of **288** (71 mg, 0.21 mmol, >95:5 dr) in MeOH (2 mL) at rt. The resultant mixture was stirred at rt under H_2 (1 atm) for 24 h and then filtered through Celite® (eluent MeOH). The filtrate was concentrated *in vacuo* to give **43** as a yellow oil (30 mg, 98%, >95:5 dr, >99% ee¹¹); $[\alpha]_D^{25} +89.3$ (c 1.0 in MeOH); ν_{max} 3355, 2930, 2900; δ_H (400 MHz, MeOH- d_4) 1.55–1.69 (2H, m, C(5) H_A ,

$C(6)H_N$), 1.80–1.91 (2H, m, $C(5)H_B$, $C(6)H_B$), 2.85 (1H, dd, J 9.7, 3.0, $C(2)H$), 3.52 (1H, dd, J 9.7, 2.8, $C(3)H$), 3.92–4.01 (2H, m, $C(1)H$, $C(4)H$); δ_C (100 MHz, MeOH- d_4) 26.7 ($C(5)$), 27.5 ($C(6)$), 54.6 ($C(2)$), 70.2 ($C(1)$), 70.7 ($C(4)$), 73.6 ($C(3)$); m/z (ESI⁺) 148 ([M+H]⁺, 100%); HRMS (ESI⁺) $C_6H_{14}NO_3^+$ ([M+H]⁺) requires 148.0968; found 148.0968.

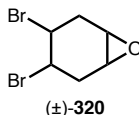
8.6 Experimental for chapter 6

1,2-Epoxycyclohex-4-ene **318**¹⁴



AcOOH (39% in AcOH, 22 mL, 125 mmol) was added dropwise to a stirred suspension of 1,4-cyclohexadiene **317** (10 g, 125 mmol) and Na_2CO_3 (17.5 g, 165 mmol) in CH_2Cl_2 (176 mL) at 0 °C and the resultant suspension was stirred at 0 °C for 18 h. H_2O (100 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3×75 mL). The combined organic extract were washed with satd aq Na_2SO_3 (200 mL) until starch-iodide paper indicated that no peroxide was present, then dried and distilled under reduced pressure (22 mbar, 45 °C) to give **318** as a colourless oil (7.93 g, 66%);¹⁴ δ_H (400 MHz, d_1 - $CHCl_3$) 1.41–1.64 (4H, m, $C(3)H_2$, $C(6)H_2$), 3.24–3.28 (2H, m, $C(1)H$, $C(2)H$), 5.42–5.50 (2H, m, $C(4)H$, $C(5)H$). The NMR spectroscopic data of **319** are consistent with the literature values.

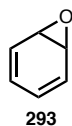
1,2-Epoxy-3,4-dibromocyclohexane ($\pm$)-**319**¹⁵



A solution of Br_2 in $CH_2Cl_2/CHCl_3$ (1:1, v/v, 36 mL) was added dropwise to a solution of **318** (20 g, 208 mmol) in $CH_2Cl_2/CHCl_3$ (1:1, v/v, 433 mL) at –78 °C. For maximum yields, the bromination mixture should never become orange. The resultant solution was stirred at –78 °C for 30 min, then allowed to warm to rt. Satd aq $Na_2S_2O_3$ (200 mL) was added and

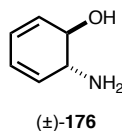
the aqueous layer was extracted with CH_2Cl_2 (3×150 mL). The combined organic extracts were dried and concentrated *in vacuo*. Purification *via* recrystallization (solvent hexane) gave ($\pm$)-**319** as a white solid (48.6 g, 91%);¹⁵ mp 46.5–59.0 °C {lit.¹⁴ mp 57.0 °C, lit.¹⁵ mp 66–67 °C }; δ_{H} (400 MHz, d_1 - CHCl_3) 2.46 (1H, ddd, J 16.1, 6.8, 3.5, $\text{C}(3)\text{H}_{\text{A}}$), 2.66 (1H, dd, J 16.5, 6.3, $\text{C}(6)\text{H}_{\text{A}}$), 2.90 (1H, ddd, J 16.5, 6.4, 3.6, $\text{C}(6)\text{H}_{\text{B}}$), 3.00 (1H, dd, J 16.0, 4.6, $\text{C}(3)\text{H}_{\text{B}}$), 3.20–3.28 (2H, m, $\text{C}(1)\text{H}$, $\text{C}(2)\text{H}$), 4.17–4.23 (1H, m, $\text{C}(5)\text{H}$), 4.28–4.34 (1H, m, $\text{C}(4)\text{H}$). The NMR spectroscopic data of ($\pm$)-**319** are consistent with the literature values.

1,2-Epoxycyclohexa-3,5-diene **292**¹⁶



DBU (82.2 mL, 576 mmol) was added dropwise in a solution of ($\pm$)-**319** (36.6 g, 144 mmol) in Et_2O (351 mL) at 0 °C and the resultant solution was stirred at rt for 24 h. H_2O (150 mL) was added and the aqueous layer was extracted with Et_2O (3×100 mL). The combined organic extracts were dried and distilled under reduced pressure (21 mbar, 30 °C) to give **292** as a orange liquid (7.27 g, 54%);¹⁶ δ_{H} (400 MHz, d_1 - CHCl_3) 5.11 (2H, d, J 4.7, $\text{C}(1)\text{H}$, $\text{C}(2)\text{H}$), 5.91–5.98 (2H, m, $\text{C}(3)\text{H}$, $\text{C}(6)\text{H}$), 6.24–6.30 (2H, m, $\text{C}(4)\text{H}$, $\text{C}(5)\text{H}$). The NMR spectroscopic data of **293** are consistent with the literature values.

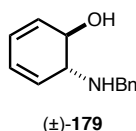
(1*R*,2*R*)-2-Aminocyclohexa-3,5-dien-1-ol ($\pm$)-**176**¹⁷



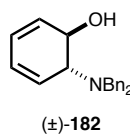
A solution of **292** (501 mg, 5.32 mmol) in ammonium hydroxide NH_4OH (35% aq, 13.3 mL) was stirred at rt for 72 h before being concentrated *in vacuo*. Purification *via* column chromatography (eluent $\text{CHCl}_3/\text{MeOH}/\text{NH}_4\text{OH}$ 35% aq 70:20:10) gave ($\pm$)-**176** as a

brown oil (202 mg, 34%, >95:5 dr);¹⁷ $\nu_{\max}$ 3279, 1588; δ_{H} (400 MHz, d_1 -CHCl₃) 3.52 (1H, br dt, J 11.9, 2.4, C(2) H), 4.20 (1H, d, J 11.9, C(1) H), 5.78–5.95 (1H, m, C(3) H , C(4) H , C(5) H , C(6) H); δ_{C} (100 MHz, d_1 -CHCl₃) 55.1 (C(2)), 74.6 (C(1)), 123.9, 124.3, 130.2, 132.4 (C(3), C(4), C(5), C(6)); m/z (ESI⁺) 112 ([M+H]⁺, 100%); HRMS (ESI⁺) C₆H₁₀NO⁺ ([M+H]⁺) requires 112.0757; found 112.0756. The NMR spectroscopic data of (±)-**176** are consistent with the literature values.

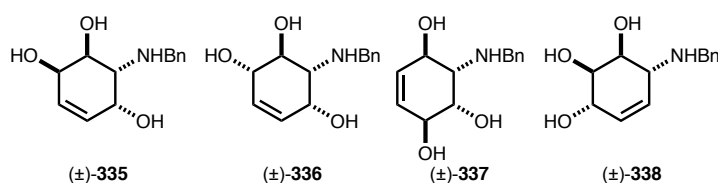
(1*R*,2*R*)-2-*N*-(Benzylamino)cyclohexa-3,5-dien-1-ol (±)-179



Benzylamine BnNH₂ (5.81 mL, 53.2 mmol) was added to a solution of **292** (501 mg, 5.32 mmol) in MeOH (5 mL) at rt and the resultant solution was stirred at 66 °C for 42.5 h, then concentrated *in vacuo*. Purification *via* column chromatography (eluent CHCl₃/ MeOH 97:3) gave (±)-**179** as a brown solid (964 mg, 90%, >95:5 dr); mp 50.5–57.2 °C; $\nu_{\max}$ 3298, 3036, 2840, 1644, 1604; δ_{H} (400 MHz, d_1 -CHCl₃) 3.44 (1H, dt, J 12.1, 1.8, C(2) H), 3.81 (1H, d, J 13.0, N(CH_AH_BPh)), 3.99 (1H, d, J 13.0, N(CH_AH_BPh)), 4.33 (1H, dt, J 12.1, 1.8, C(1) H), 5.87–6.03 (4H, m, C(3) H , C(4) H , C(5) H , C(6) H); δ_{C} (100 MHz, d_1 -CHCl₃) 50.7 (N(CH₂Ph)), 60.4 (C(2)), 71.6 (C(1)), 123.9, 124.6, 129.3, 130.2, (C(3), C(4), C(5), C(6)), 127.2, 128.2, 128.5 (*o,m,p-Ph*), 140.2 (*i-Ph*); m/z (ESI⁺) 202 ([M+H]⁺, 100%); HRMS (ESI⁺) C₁₃H₁₆NO⁺ ([M+H]⁺) requires 202.1226; found 202.1226.

(1*R*,2*R*)-2-*N,N*-(Dibenzylamino)cyclohexa-3,5-dien-1-ol (±)-182

Pr_2NEt (0.58 mL, 3.37 mmol), BnBr (0.40 mL, 3.37 mmol) and DMAP (2.7 mg, 22.5 μmol) were sequentially added to a solution of (±)-**179** (452 mg, 2.25 mmol, >95:5 dr) in CH_2Cl_2 (6.4 mL) at rt and the resultant solution was stirred at rt for 24 h, then concentrated *in vacuo*. Purification *via* column chromatography (eluent CHCl_3 100%) gave (±)-**182** as a orange oil (612 mg, 94%, >95:5 dr); ν_{max} 3408 3061, 3030, 2835, 1602, 1586; δ_{H} (400 MHz, $d_1\text{-CHCl}_3$) 2.35 (1H, d, J 2.9, OH), 3.56–3.64 (3H, m, C(2)*H*, $\text{N}(\text{CH}_\text{A}\text{H}_\text{B}\text{Ph})_2$), 3.88 (2H, d, J 13.7, $\text{N}(\text{CH}_\text{A}\text{H}_\text{B}\text{Ph})_2$), 4.66 (1H, dq, J 12.1, 2.6, C(1)*H*), 5.83–5.88 (1H, m, C(5)*H*), 5.90–5.95 (1H, m, C(6)*H*), 6.01–6.09 (2H, m, C(3)*H*, C(4)*H*); δ_{C} (100 MHz, $d_1\text{-CHCl}_3$) 54.7 ($\text{N}(\text{CH}_2\text{Ph})_2$), 62.6 (C(2)), 68.2 (C(1)), 123.5 (C(5)), 125.9, 126.4 (C(3), C(4)), 127.2, 128.4, 128.9 (*o,m,p*-Ph), 129.9 (C(6)), 139.4 (*i*-Ph); m/z (ESI⁺) 292 ($[\text{M}+\text{H}]^+$, 100%); HRMS (ESI⁺) $\text{C}_{20}\text{H}_{22}\text{NO}^+$ ($[\text{M}+\text{H}]^+$) requires 292.1696; found 292.1694.

(1*R*,2*R*,3*S*,4*R*)-2-(*N*-Benzylamino)cyclohex-5,6-ene-1,3,4-triol (±)-335,**(1*R*,2*R*,3*S*,4*R*)-2-(*N*-benzylamino)cyclohex-5,6-ene-1,3,4-triol (±)-336,****(1*R*,2*S*,3*S*,4*S*)-2-(*N*-benzylamino)cyclohex-5,6-ene-1,3,4-triol (±)-337,****(1*R*,2*S*,3*R*,4*S*)-1-(*N*-benzylamino)cyclohex-5,6-ene-1,3,4-triol (±)-338**

Method A. Epoxidation of (±)-179 with HBF_4 (40% aq). HBF_4 (40% aq, 2.48 mL, 15.8 mmol) was added to a stirred solution of (±)-**179** (636 mg, 3.16 mmol, >95:5 dr) in CH_2Cl_2 (8.8

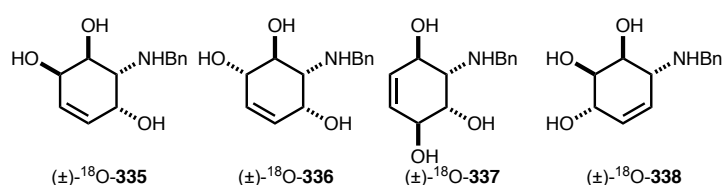
mL) at rt and the resultant solution was stirred at rt for 5 min. *m*-CPBA (70% wt, 777 mg, 3.16 mmol) was then added and the resultant solution was stirred at rt for 21 h. Solid Na₂SO₃ was added until starch-iodide paper indicated that no *m*-CPBA was present. 2 M aq NaOH (40 mL) was then added and the resultant mixture was extracted with CHCl₃/PrOH (3:1, v/v, 3 × 60 mL). The combined organic extracts were dried and concentrated *in vacuo* to give a 31:12:36:21 mixture of (±)-**335**, (±)-**336**, (±)-**337** and (±)-**338**, respectively (1.2 g). Purification *via* preparative thin layer chromatography (eluent CHCl₃/MeOH/35% aq NH₄OH, 90:10:0.5) gave (±)-**335** as a beige powder (132 mg, 18%, >95:5 dr), (±)-**336** as an orange oil (56 mg, 7%, ~ 83% pure), (±)-**337** as a pale yellow powder (169 mg, 23%, >95:5 dr) and (±)-**338** as an orange oil (61 mg, 8%, >95:5 dr); Data for (±)-**335**: R_f = 0.33; mp 96.7–102.5 °C; ν_{max} 3332, 3028, 2895, 1558; δ_H (400 MHz, d₁-CHCl₃) 2.95 (1H, dd, *J* 10.8, 4.6, C(2)*H*), 3.69–3.85 (2H, m, C(3)*H*, N(CH_AH_BPh)), 3.95 (1H, d, *J* 13.1, N(CH_AH_BPh)), 4.22 (1H, t, *J* 4.6, C(1)*H*), 4.25 (1H, t, *J* 4.8, C(4)*H*), 5.99 (1H, dd, *J* 9.8, 4.8, C(5)*H*), 6.07 (1H, dd, *J* 9.8, 4.7, C(6)*H*), 7.25–7.39 (5H, m, *Ph*); δ_C (100 MHz, d₁-CHCl₃) 51.5 (N(CH₂Ph)), 57.0 (C(2)), 63.0 (C(4)), 65.8 (C(1)), 67.4 (C(3)), 127.4, 128.1, 128.6 (*o,m,p-Ph*), 129.5 (C(5)), 131.1 (C(6)), 139.5 (*i-Ph*); *m/z* (ESI⁺) 236 ([M+H]⁺, 100%); HRMS (ESI⁺) C₁₃H₁₈NO₃⁺ ([M+H]⁺) requires 236.1281; found 236.1284; Data for (±)-**336**: R_f = 0.20; ν_{max} 3310, 3029, 2917, 1603; δ_H (400 MHz, d₁-CHCl₃) 2.48 (1H, dd, *J* 11.0, 4.2, C(2)*H*), 3.53 (1H, dd, *J* 11.0, 7.8, C(3)*H*), 3.62 (1H, d, *J* 13.1, N(CH_AH_BPh)), 3.79–3.89 (2H, m, C(4)*H*, N(CH_AH_BPh)), 4.05 (1H, t, *J* 4.6, C(1)*H*), 5.58 (1H, dd, *J* 10.0, 2.0, C(5)*H*), 5.70 (1H, dd, *J* 10.0, 4.6, 2.0, C(6)*H*), 7.27–7.38 (5H, m, *Ph*); δ_C (100 MHz, d₁-CHCl₃) 50.7 (N(CH₂Ph)), 59.8 (C(2)), 63.0 (C(1)), 71.1 (C(3)), 73.0 (C(4)), 127.2 (C(6)), 127.4, 128.4, 128.6 (*o,m,p-Ph*), 131.2 (C(5)), 138.7 (*i-Ph*); *m/z* (ESI⁺) 236 ([M+H]⁺, 100%); HRMS (ESI⁺) C₁₃H₁₈NO₃⁺ ([M+H]⁺) requires 236.1281; found 236.1281; Data for (±)-**337**: R_f = 0.13; mp 151.8–153.1 °C; ν_{max} 3300, 3029, 2899, 1660; δ_H (400 MHz, d₄-MeOH) 2.88

(1H, dd, J 6.8, 2.7, C(2) H), 3.84 (1H, d, J 13.1, N(CH_AH_BPh)), 3.90 (1H, d, J 13.1, N(CH_AH_BPh)), 3.96 (1H, ddd, J 4.5, 2.7, 0.9, C(3) H), 4.06 (1H, ddt, J 4.5, 3.4, 1.0, C(4) H), 4.14 (1H, ddt, J 6.8, 2.6, 1.3, C(1) H), 5.67–5.71 (1H, m, C(5) H), 5.75 (1H, ddd, J 10.1, 2.6, 0.9, C(6) H), 7.21–7.27 (1H, m, Pb), 7.29–7.35 (2H, m, Pb), 7.36–7.40 (2H, m, Pb); δ_C (100 MHz, d_4 -MeOH) 52.4 (N(CH₂Ph)), 61.8 (C(2)), 68.6 (C(1)), 70.0 (C(4)), 71.4 (C(3)), 128.2 (p - Pb), 129.2 (C(5)), 129.6 (o,m - Pb), 132.5 (C(6)), 141.2 (i - Pb); m/z (ESI⁺) 236 ([M+H]⁺, 100%); HRMS (ESI⁺) C₁₃H₁₈NO₃⁺ ([M+H]⁺) requires 236.1281; found 236.1279; Data for ($\pm$)-**338**: Rf = 0.05; $\nu_{\max}$ 3298, 3029, 2905, 1603; δ_H (400 MHz, d_1 -CHCl₃) 3.30 (1H, br dd, J 5.3, C(1) H), 3.73 (1H, d, J 13.1, N(CH_AH_BPh)), 3.83 (1H, d, J 13.1, N(CH_AH_BPh)), 3.88–3.94 (2H, m, C(2) H , C(3) H), 4.16 (1H, br d, J 4.9, C(4) H), 5.67 (2H, s, C(5) H , C(6) H), 7.18–7.32 (5H, m, Pb); δ_C (100 MHz, d_1 -CHCl₃) 51.3 (N(CH₂Ph)), 57.1 (C(1)), 69.1 (C(4)), 70.9 (C(2)), 72.8 (C(3)), 127.3 (p -Ph), 127.8 (C(5) or C(6)), 128.4, 128.5 (o,m - Pb), 129.2 (C(5) or C(6)), 139.1 (i - Pb); δ_H (400 MHz, d_4 -MeOH) 3.38 (1H, br d, J 6.7, C(1) H), 3.78–3.85 (2H, m, C(3) H , N(CH_AH_BPh)), 3.87 (1H, dd, J 6.7, 2.5, C(2) H), 3.92 (1H, d, J 12.9, N(CH_AH_BPh)), 4.10 (1H, ddd, J 4.6, 2.8, 1.1, C(4) H), 5.72–5.76 (1H, m, C(5) H) 5.81 (1H, ddd, J 10.1, 2.6, 0.9, C(6) H), 7.23–7.40 (5H, m, Pb); δ_C (100 MHz, d_4 -MeOH) 51.7 (N(CH₂Ph)), 58.1 (C(1)), 70.8 (C(4)), 70.9 (C(2)), 74.7 (C(3)), 128.4 (p -Ph), 129.6 (C(6)), 129.7, 129.7 (o,m - Pb), 129.9 (C(5)), 140.6 (i - Pb); m/z (ESI⁺) 236 ([M+H]⁺, 100%); HRMS (ESI⁺) C₁₃H₁₈NO₃⁺ ([M+H]⁺) requires 236.1281; found 236.1279;

Method B. Epoxidation of ($\pm$)-179 with HBF₄ (50–55% in Et₂O). HBF₄ (50–55% in Et₂O, 1.54 mL, 6.21 mmol) and H₂O (1.54 mL) were sequentially added to a stirred solution of ($\pm$)-**179** (250 mg, 1.24 mmol, >95:5 dr) in CH₂Cl₂ (3.44 mL) at rt and the resultant solution was stirred at rt for 5 min. *m*-CPBA (70% wt, 214 mg, 1.24 mmol) was then added and the resultant solution was stirred at rt for 21 h. Solid Na₂SO₃ was added until starch-iodide paper indicated that no *m*-CPBA was present. 2 M aq NaOH (20 mL) was then added and

the resultant mixture was extracted with $\text{CHCl}_3/\text{PrOH}$ (3:1, v/v, 3×20 mL). The combined organic extracts were dried and concentrated *in vacuo* to give a 30:10:35:25 mixture of ($\pm$)-**335**, ($\pm$)-**336**, ($\pm$)-**337** and ($\pm$)-**338**, respectively (0.350 g).

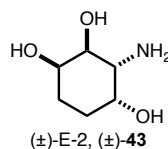
(1*R*,2*R*,3*S*,4*R*)-2-(N- Benzylamino)-4-(^{18}O -hydroxy)cyclohex-5-ene-1,3,4-triol ^{18}O -**335**, (1*R*,2*R*,3*S*,4*S*)-2-(N- benzylamino)-4-(^{18}O -hydroxy)cyclohex-5-ene-1,3,4-triol ^{18}O -**336**, (1*R*,2*R*,3*S*,4*S*)-2-(N- benzylamino)-4-(^{18}O -hydroxy)cyclohex-5-ene-1,3,4-triol ^{18}O -**337** and (1*R*,2*R*,3*S*,4*S*)-2-(N- benzylamino)-4-(^{18}O -hydroxy)cyclohex-5-ene-1,3,4-triol ^{18}O -**338**



HBF_4 (50–55% in Et_2O , 1.54 mL, 6.21 mmol) and H_2^{18}O (1.54 mL, $\geq 98\%$ ^{18}O) were sequentially added to a stirred solution of ($\pm$)-**179** (250 mg, 1.24 mmol, >95:5 dr) in CH_2Cl_2 (3.44 mL) at rt and the resultant solution was stirred at rt for 5 min. *m*-CPBA (70% wt, 214 mg, 1.24 mmol) was then added and the resultant solution was stirred at rt for 21 h. Solid Na_2SO_3 was added until starch-iodide paper indicated that no *m*-CPBA was present. 2 M aq NaOH (20 mL) was then added and the resultant mixture was extracted with $\text{CHCl}_3/\text{PrOH}$ (3:1, v/v, 3×20 mL). The combined organic extracts were dried and concentrated *in vacuo* to give a 36:13:38:13 mixture of ($\pm$)- ^{18}O -**335**, ($\pm$)- ^{18}O -**336**, ($\pm$)- ^{18}O -**337** and ($\pm$)- ^{18}O -**338**, respectively (0.350 g). Purification *via* preparative thin layer chromatography (eluent $\text{CHCl}_3/\text{MeOH}/35\%$ aq NH_4OH , 90:10:0.5) gave ($\pm$)- ^{18}O -**335** as a beige powder (35.9 mg, 12%, >95:5 dr, 92% ^{18}O), ($\pm$)- ^{18}O -**336** as an orange oil (18.3 mg, 6.2%, $\sim 87\%$ pure, 92% ^{18}O), ($\pm$)- ^{18}O -**337** as a pale yellow powder (39.9 mg, 14%, >95:5

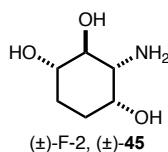
dr, 92% ^{18}O) and $(\pm)\text{-}^{18}\text{O}$ -**338** as an orange oil (11.6 mg, 4%, >95:5 dr, 92% ^{18}O). Data for $(\pm)\text{-}^{18}\text{O}$ -**335**: ν_{max} 3331, 3031, 2916, 1645; m/z (ESI $^{+}$) 238 ([M+H] $^{+}$, 100%); HRMS (ESI $^{+}$) $\text{C}_{13}\text{H}_{18}\text{NO}_2^{18}\text{O}^{+}$ ([M+H] $^{+}$) requires 238.1324; found 238.1325. Data for $(\pm)\text{-}^{18}\text{O}$ -**336**: ν_{max} 3343, 2981, 2919, 1646; m/z (ESI $^{+}$) 238 ([M+H] $^{+}$, 100%); HRMS (ESI $^{+}$) $\text{C}_{13}\text{H}_{18}\text{NO}_2^{18}\text{O}^{+}$ ([M+H] $^{+}$) requires 238.1324; found 238.1324. Data for $(\pm)\text{-}^{18}\text{O}$ -**337**: mp 144.2–150.0 °C; ν_{max} 3300, 3030, 2981, 2899, 1647; m/z (ESI $^{+}$) 238 ([M+H] $^{+}$, 100%); HRMS (ESI $^{+}$) $\text{C}_{13}\text{H}_{18}\text{NO}_2^{18}\text{O}^{+}$ ([M+H] $^{+}$) requires 238.1324; found 238.1325. Data for $(\pm)\text{-}^{18}\text{O}$ -**338**: ν_{max} 3346, 3030, 2918, 1647; m/z (ESI $^{+}$) 238 ([M+H] $^{+}$, 100%); HRMS (ESI $^{+}$) $\text{C}_{13}\text{H}_{18}\text{NO}_2^{18}\text{O}^{+}$ ([M+H] $^{+}$) requires 238.1324; found 238.1325.

(1*R*S,2*R*S,3*S*R,4*R*S)-2-Aminocyclohexane-1,3,4-triol [(±)-Dihydroconduramine E-2] (±)-43



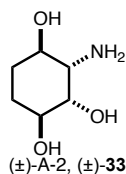
$\text{Pd}(\text{OH})_2/\text{C}$ (50% wt of substrate, 28 mg) was added to a stirred degassed solution of $(\pm)$ -**335** (56.4 mg, 0.240 mmol, >95:5 dr) in MeOH (2 mL) and the resultant suspension was stirred under H_2 (1 atm) at rt for 24 h. The resultant suspension was then filtered through Celite® (eluent MeOH), and the filtrate was concentrated *in vacuo* to give $(\pm)$ -**27** as a yellow oil (26.1 mg, quant, >95:5 dr).

(1*R*,2*R*,3*S*,4*S*)-2-Aminocyclohexane-1,3,4-triol [(±)-Dihydroconduramine F-2] (±)-45



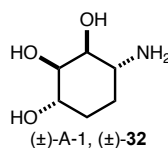
$\text{Pd}(\text{OH})_2/\text{C}$ (50% wt of substrate, 14 mg) was added to a stirred degassed solution of (±)-**336** (27 mg, 0.115 mmol, ~ 83% pure) in MeOH (1.5 mL) and the resultant suspension was stirred under H_2 (1 atm) at rt for 24 h. The resultant suspension was then filtered through Celite® (eluent MeOH), and the filtrate was concentrated *in vacuo*. Purification *via* column chromatography (eluent $\text{CHCl}_3/\text{MeOH}/\text{NH}_4\text{OH}$ 7:3:0.5) gave (±)-**45** as a yellow oil (6.6 mg, 54%, >95:5 dr).

(1*R*,2*S*,3*S*,4*S*)-2-Aminocyclohexane-1,3,4-triol [(±)-Dihydroconduramine A-2] (±)-33



$\text{Pd}(\text{OH})_2/\text{C}$ (50% wt of substrate, 10 mg) was added to a stirred degassed solution of (±)-**337** (19.5 mg, 0.083 mmol, >95:5 dr) in MeOH (2 mL) and the resultant suspension was stirred under H_2 (1 atm) at rt for 24 h. The resultant suspension was then filtered through Celite® (eluent MeOH), and the filtrate was concentrated *in vacuo* to give (±)-**33** as a yellow oil (9.1 mg, quant, >95:5 dr).

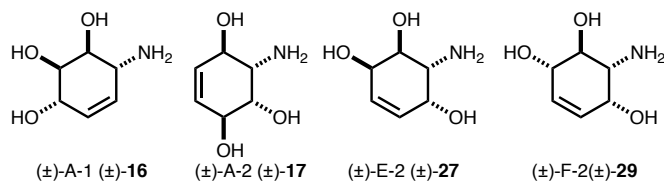
(1*R*,2*S*,3*R*,4*S*)-1-Aminocyclohexane-2,3,4-triol [(±)-Dihydroconduramine A-1] (±)-32



Method A. Pd(OH)₂/C (50% wt of substrate, 7 mg) was added to a stirred degassed solution of (±)-338 (13 mg, 0.055 mmol, >95:5 dr) in MeOH (2 mL) and the resultant suspension was stirred under H₂ (1 atm) at rt for 24 h. The resultant suspension was then filtered through Celite® (eluent MeOH), and the filtrate was concentrated *in vacuo* to give (±)-32 as a yellow oil (5.8 mg, 99%, >95:5 dr); $\nu_{\max}$ 3289, 2930; δ_{H} (400 MHz, *d*₄-MeOH) 1.45–1.70 (3H, m, C(5)*H*_A, C(6)*H*₂), 1.79–1.89 (1H, m, C(5)*H*_B), 2.87 (1H, app dt, *J* 9.2, 4.4, C(1)*H*), 3.49 (1H, dd, *J* 9.2, 3.4, C(2)*H*), 3.79 (1H, app t, *J* 3.4, C(3)*H*), 3.87 (1H, app q, *J* 3.4, C(4)*H*); δ_{C} (100 MHz, *d*₄-MeOH) 27.3 (C(6)), 27.5 (C(5)), 51.5 (C(1)), 71.6 (C(4)), 74.3 (C(3)), 75.2 (C(2)); *m/z* (ESI⁺) 148 ([M+H]⁺, 100%); HRMS (ESI⁺) C₆H₁₄NO₃⁺ ([M+H]⁺) requires 148.0968; found 148.0968.

Method B. Pd(OH)₂/C (50% wt of substrate, 22.1 mg) was added to a stirred degassed solution of (±)-341 (44.2 mg, 136 mmol, >95:5 dr) in MeOH (1.5 mL) and the resultant suspension was stirred under H₂ (1 atm) at rt for 24 h. The resultant suspension was then filtered through Celite® (eluent MeOH), and the filtrate was concentrated *in vacuo* to give (±)-32 as a yellow oil (20.2 mg, quant, >95:5 dr).

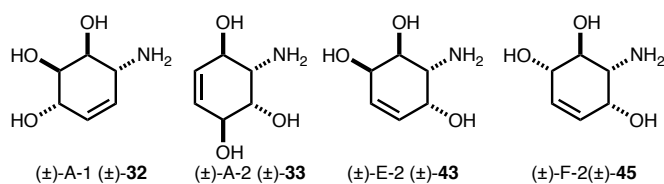
(1*R*,2*S*,3*R*,4*S*)-1-Aminocyclohex-5,6-ene-2,3,4-triol [(±)-Conduramine A-1] (±)-16, (1*R*,2*S*,3*R*,4*S*)-2-aminocyclohex-5,6-ene-1,3,4-triol [(±)-Conduramine A-2] (±)-17, (1*R*,2*S*,3*R*,4*S*)-2-aminocyclohex-5,6-ene-1,3,4-triol [(±)-Conduramine E-2] (±)-27 and (1*R*,2*S*,3*R*,4*S*)-2-aminocyclohex-5,6-ene-1,3,4-triol [(±)-Conduramine F-2] (±)-29



HBF_4 (40% aq, 706 μL , 4.50 mmol) was added to a stirred solution of (±)-176 (100 mg, 900 μmol , >95:5 dr) in CH_2Cl_2 (2.5 mL) at rt and the resultant solution was stirred at rt for 5 min. *m*-CPBA (70% wt, 221 mg, 900 μmol) was then added and the resultant solution was stirred at rt for 21 h. Solid Na_2SO_3 was added until starch-iodide paper indicated that no *m*-CPBA was present. The reaction mixture was concentrated *in vacuo*. The resultant suspension was dissolved with $\text{CHCl}_3/\text{MeOH}/35\%$ aq NH_4OH (2 mL, 55:35:10, v/v/v) and was filtered through a pad of silica (eluent $\text{CHCl}_3/\text{MeOH}/35\%$ aq NH_4OH , 55:35:10), then the filtrate was concentrated *in vacuo* to give a 30:50:5:15 mixture of (±)-16 $\cdot\text{HBF}_4$, (±)-17 $\cdot\text{HBF}_4$, (±)-27 $\cdot\text{HBF}_4$ and (±)-29 $\cdot\text{HBF}_4$, respectively as a pale yellow solid (179 mg, 85%).¹⁸ Purification *via* ion exchange chromatography (DOWEX 50WX8-200, eluent 1.0 M aq NH_4OH) gave a 30:50:5:15 mixture of (±)-16, (±)-17, (±)-27 and (±)-29 as a yellow oil (44 mg, 34%); ν_{max} 3286, 2898; m/z (ESI⁺) 146 ([M+H]⁺, 100%); HRMS (ESI⁺) $\text{C}_6\text{H}_{12}\text{NO}_3^+$ ([M+H]⁺) requires 146.08117; found 146.08093; Data for (±)-16: δ_{H} (400 MHz, d_4 -MeOH) 3.39 (1H, app d, *J* 6.9, C(1)*H*), 3.60 (1H, dd, *J* 6.9, 2.4, C(2)*H*), 3.79 (1H, dd, *J* 4.0, 2.4, C(3)*H*), 4.07–4.10 (1H, m, C(4)*H*), 5.65–5.90 (1H, m, C(5)*H*, C(6)*H*); δ_{C} (100 MHz, d_4 -MeOH) 52.2 (C(1)), 70.9 (C(4)), 74.5, 74.5 (C(2), C(3)), 128.8 (C(5)), 132.4 (C(6));

Data for ($\pm$)-**17**: δ_{H} (400 MHz, d_4 -MeOH) 2.87 (1H, dd, J 7.2, 2.5, C(2) H), 3.81–3.84 (1H, m, C(3) H), 3.98–4.05 (1H, m, C(1) H , C(4) H), 5.65–5.90 (1H, m, C(5) H , C(6) H); δ_{C} (100 MHz, d_4 -MeOH) 55.2 (C(2)), 70.4 (C(4)), 71.2 (C(1)), 74.4 (C(3)), 128.8 (C(5)), 133.0 (C(6)); Data for ($\pm$)-**27**: δ_{H} (400 MHz, d_4 -MeOH) 3.01 (1H, dd, J 10.3, 4.2, C(2) H), 3.68 (1H, dd, J 10.3, 4.3, C(3) H), 4.14 (1H, t, J 4.3, C(4) H), 4.19 (1H, t, J 4.2, C(1) H), 5.65–5.90 (1H, m, C(5) H , C(6) H); δ_{C} (100 MHz, d_4 -MeOH) 52.4 (C(2)), 67.7, 67.7 (C(1), C(4)), 70.9 (C(3)), 130.8, 132.0 (C(5), C(6)); Data for ($\pm$)-**29**: δ_{H} (400 MHz, d_4 -MeOH) 2.57 (1H, dd, J 10.7, 4.3, C(2) H), 3.36–3.45 (1H, m, C(3) H), 3.90 (1H, br d, J 7.6, C(4) H), 4.14 (1H, t, J 4.3, C(1) H), 5.65–5.90 (1H, m, C(5) H , C(6) H); δ_{C} (100 MHz, d_4 -MeOH) 55.5 (C(2)), 67.6 (C(1)), 74.2 (C(4)), 74.7 (C(3)), 129.2 (C(6)), 133.7 (C(5)).

(1*R*,2*S*,3*R*,4*S*)-1-Aminocyclohexane-2,3,4-triol [($\pm$)-Dihydroconduramine A-1] ($\pm$)-**32**, (1*R*,2*S*,3*S*,4*S*)-2-aminocyclohexane-1,3,4-triol [($\pm$)-Dihydroconduramine A-2] ($\pm$)-**33**, (1*R*,2*S*,3*S*,4*R*)-2-aminocyclohexane-1,3,4-triol [($\pm$)-Dihydroconduramine E-2] ($\pm$)-**43** and (1*R*,2*S*,3*S*,4*S*)-2-aminocyclohexane-1,3,4-triol [($\pm$)-Dihydroconduramine F-2] ($\pm$)-**45**^{19,20}



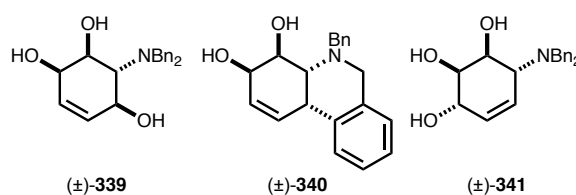
$\text{Pd}(\text{OH})_2/\text{C}$ (56% wt of substrate, 12.5 mg) was added to a stirred degassed solution of a 30:50:5:15 mixture of ($\pm$)-**16**, ($\pm$)-**17**, ($\pm$)-**27** and ($\pm$)-**29**, respectively, (22.5 mg, 155 mmol) in MeOH (1.5 mL) and the resultant suspension was stirred under H_2 (1 atm) at rt for 24 h. The resultant suspension was then filtered through Celite® (eluent MeOH), and the filtrate

was concentrated *in vacuo* to give a 5:15:45:30 mixture of ($\pm$)-**32**, ($\pm$)-**33**, ($\pm$)-**43** and ($\pm$)-**45**, respectively, as a yellow oil (21.8 mg, 96%).^{19,20}

(1*R*,2*S*,3*R*,4*R*)-1-(*N,N*-Dibenzylamino)cyclohex-5,6-ene-1,3,4-triol ($\pm$)-**339**,

(3*R*,4*S*,4*aR*,10*bS*)-3,4,4*a*,5,6,10*b*-hexahydrophenanthridine-3,4-diol ($\pm$)-**340**

(1*R*,2*S*,3*R*,4*S*)-1-(*N,N*-dibenzylamino)cyclohex-5,6-ene-1,3,4-triol ($\pm$)-**341**



Method A. Epoxidation of (±)-182. Anhydrous $\text{Cl}_3\text{CCO}_2\text{H}$ (0.167 g, 1.02 mmol) was added to a stirred solution of ($\pm$)-**182** (59.5 mg, 0.204 mmol, >95:5 dr) in CH_2Cl_2 (0.57 mL) at rt and the resultant solution was stirred at rt for 5 min. *m*-CPBA (70% wt, 50.2 mg, 0.204 mmol) was then added and the resultant solution was stirred at rt for 21 h. Solid Na_2SO_3 was added until starch-iodide paper indicated that no *m*-CPBA was present. MeOH (3.0 mL) and K_2CO_3 (600 mg) were added at rt and the resultant suspension was stirred at rt for 24 h, then concentrated *in vacuo*. The crude mixture was dissolved in CH_2Cl_2 (15 mL) and extracted with 2 M aq NaOH (3×10 mL). The combined aqueous extracts were then extracted with CH_2Cl_2 (3×10 mL) and the combined organic extracts were dried and concentrated *in vacuo* to give a 14:15:71 mixture of ($\pm$)-**339**, ($\pm$)-**340** and ($\pm$)-**341**, respectively. Purification *via* flash column chromatography (eluent $\text{CHCl}_3/\text{MeOH}$ 95:5) gave ($\pm$)-**340** as a yellow oil (5.7 mg, 9.1%, ~ 90% pure); ν_{max} 3406, 3028, 2981, 2885, 1653; δ_{H} (400 MHz, d_1 - CHCl_3) [Selected peaks] 2.73 (1H, br s, OH), 3.50 (1H, dd, J 11.2, 6.2, C(2)*H*), 3.57 (1H, d, J 17.4, $\text{N}(\text{CH}_\text{A}\text{H}_\text{B}\text{Ph})$), 3.78 (1H, dd, J 11.2, 4.0, C(3)*H*), 3.81–3.89 (3H, m, C(1)*H*, $\text{N}(\text{CH}_\text{A}\text{H}_\text{B}\text{Ph})_2$), 4.10 (1H, d, J 17.4, $\text{N}(\text{CH}_\text{A}\text{H}_\text{B}\text{Ph})$), 4.32 (1H, dd, J 5.4, 4.0, C(4)*H*), 5.97 (1H, ddd, J 9.9, 5.4, 1.9, C(5)*H*), 6.48 (1H, dd, J 9.9, 5.2, C(6)*H*); δ_{C} (100 MHz,

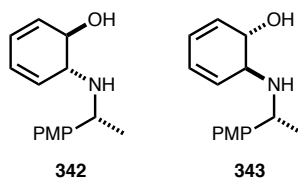
d_1 -CHCl₃) [selected peaks] 32.2 (C(1)), 46.5 (N(CH₂Ph)), 56.2 (C(2)), 58.2 (N(CH₂Ph)), 65.0 (C(4)), 67.1 (C(3)), 126.1 (C(5)), 132.8 (C(6)); m/z (ESI⁺) 308 ([M+H]⁺, 100%); HRMS (ESI⁺) C₂₀H₂₂NO₂⁺ ([M+H]⁺) requires 308.1645; found 308.1642. Further elution gave an 83:17 mixture of (±)-**339** and (±)-**340**, respectively, as a yellow oil (5.8 mg, 8.7%); $\nu_{\max}$ 3251, 3025, 2924, 2861, 1602; δ_{H} (400 MHz, d_1 -CHCl₃) 3.00 (1H, dd, J 11.1, 9.2, C(2) H), 3.66 (1H, dd, J 11.1, 4.4, C(3) H), 3.94 (2H, d, J 13.0, N(CH_AH_BPh)₂), 3.99 (2H, d, J 13.0, N(CH_AH_BPh)₂), 4.25 (1H, br t, J 4.4, C(4) H), 4.44 (1H, br d, J 9.2, C(1) H), 5.80 (1H, ddd, J 9.9, 4.8, 1.9 C(5) H), 5.86 (1H, dd, J 9.9, 1.9, C(6) H), 7.25–7.36 (10H, m, Pb); δ_{C} (100 MHz, d_1 -CHCl₃) 55.0 (N(CH₂Ph)₂), 60.8 (C(2)), 66.2 (C(4)), 67.8 (C(3)), 68.5 (C(1)), 126.1 (C(5)), 127.4, 128.6, 129.2 (*o,m,p*- Pb), 134.9 (C(6)), 139.1 (*i*- Pb); m/z (ESI⁺) 326 ([M+H]⁺, 100%); HRMS (ESI⁺) C₂₀H₂₄NO₃⁺ ([M+H]⁺) requires 326.1751; found 326.1751. Further elution gave (±)-**341** as a yellow oil (41.5 mg, 62%, >95:1 dr); $\nu_{\max}$ 3387, 3027, 2902, 1603; δ_{H} (400 MHz, d_1 -CHCl₃) 3.42–3.47 (1H, m, C(1) H), 3.59 (1H, d, J 13.6, N(CH_AH_BPh)₂), 3.80 (1H, d, J 13.1, N(CH_AH_BPh)₂), 3.92 (1H, dd, J 7.9, 3.0, C(2) H), 4.00 (1H, td, J 3.0, 1.2, C(3) H), 4.17 (1H, br t, J 3.0, C(4) H), 5.84–5.90 (1H, m, C(5) H), 5.99 (1H, dd, J 10.2, 2.1, C(6) H), 7.22–7.37 (10H, m, Pb); δ_{C} (100 MHz, d_1 -CHCl₃) 54.7 (N(CH₂Ph)), 58.1 (C(1)), 66.8 (C(2)), 68.5 (C(4)), 72.8 (C(3)), 127.3 (*p*-Ph), 128.0 (C(6)), 128.4 (Pb), 128.7 (C(5)), 128.8 (Pb), 139.2 (*i*- Pb); m/z (ESI⁺) 326 ([M+H]⁺, 100%); HRMS (ESI⁺) C₂₀H₂₄NO₃⁺ ([M+H]⁺) requires 326.1751; found 326.1751.

Method B. N-benylation of (±)-338. ^tPr₂NEt (18.4 μ L, 0.106 mmol), BnBr (12.6 μ L, 0.106 mmol) and DMAP (0.5 mg, 4.09 μ mol) were sequentially added to a solution of (±)-**338** (16.6 mg, 70.6 μ mol, >95:5 dr) in CH₂Cl₂ (0.20 mL) at rt and the resultant solution was stirred at rt for 24 h, then concentrated *in vacuo*. Purification *via* column chromatography (eluent CHCl₃/MeOH 95:5) gave (±)-**341** as a orange oil (18.2 mg, 79%, >95:5 dr).

8.7 Experimental for chapter 7

(1R,2R, α R)-2-[N-(α -Methyl-*para*-methoxybenzyl)amino]cyclohexa-3,5-dien-1-ol

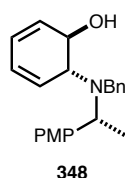
342 and (1S,2S, α R)-2-[N-(α -methyl-*para*-methoxybenzyl)amino]cyclohexa-3,5-dien-1-ol 343.



α -Methyl-*para*-methoxybenzylamine (3.92 mL, 26.6 mmol) was added to a solution of **292** (250 mg, 2.66 mmol) in MeOH (2.5 mL) at rt and the resultant solution was stirred at 66 °C for 3 days. The resultant solution was concentrated *in vacuo* to give a 4:48:48 mixture of starting material **292**, **342** and **343**, respectively. Purification *via* column chromatography (eluent Et₂O/NH₄OH 35% aq 91:9) gave **342** as a beige solid (0.127 g, 19%, >95:5 dr); mp 72.5–75.6 °C; $[\alpha]_{\text{D}}^{25}$ –228.2 (*c* 1.0 in CHCl₃); ν_{max} 3327, 3039, 2964, 2835, 1611; δ_{H} (400 MHz, *d*₁-CHCl₃) 1.34 (3H, d, *J* 6.5, C(α)Me), 2.46 (1H, br s, OH), 3.35–3.40 (1H, m, C(2)H), 3.81 (3H, s, OMe), 3.96 (1H, q, *J* 6.5, C(α)H), 4.22 (1H, br d, *J* 11.5, C(1)H), 5.72–5.77 (1H, m, C(3)H), 5.84–5.92 (2H, m, C(4)H, C(5)H), 5.93–5.98 (1H, m, C(6)H), 6.86–6.91 (2H, m, *Pb*OMe), 7.25–7.30 (2H, m, *Pb*OMe); δ_{C} (100 MHz, *d*₁-CHCl₃) 23.7 (C(α)Me), 54.7 (C(α)), 55.3 (OMe), 58.6 (C(2)), 71.5 (C(1)), 114.0 (*m*-*Pb*OMe), 124.0, 124.1 (C(4), C(5)), 127.6 (*o*-*Pb*OMe), 129.8 (C(6)), 130.2 (C(3)), 138.2 (*i*-*Pb*OMe), 158.7 (*p*-*Pb*OMe); *m/z* (ESI⁺) 246 ([M+H]⁺, 100%); HRMS (ESI⁺) C₁₅H₂₀NO₂⁺ ([M+H]⁺) requires 246.1489; found 246.1490. Further elution (eluent Et₂O/NH₄OH 35% aq 91:9) gave a 56:44 mixture of **342** and **343**, respectively, as a beige solid (0.140 g, 21%, 56:44 dr). Further elution (eluent Et₂O/NH₄OH 35% aq 91:9) gave **343** as a beige solid (0.140 g, 21%, >95:5 dr); mp 110.8–116.7 °C; $[\alpha]_{\text{D}}^{25}$ +244.0 (*c* 1.0 in CHCl₃); ν_{max} 3288, 3041, 2964, 2835, 1611; δ_{H} (400 MHz, *d*₁-CHCl₃) 1.38 (3H, d, *J* 6.6, C(α)Me), 2.38 (1H, br s, OH), 3.11 (1H, dt, *J* 12.9, 2.4,

C(2)*H*), 3.80 (3H, s, OMe), 4.01 (1H, q, *J* 6.6, C(α)*H*), 4.22 (1H, dt, *J* 12.9, 2.4, C(1)*H*), 5.79–5.93 (3H, m, C(4)*H*, C(5)*H*, C(6)*H*), 5.98–6.03 (1H, m, C(3)*H*), 6.84–6.89 (2H, m, *Pb*OMe), 7.21–7.26 (2H, m, *Pb*OMe); δ_{C} (100 MHz, *d*₁-CHCl₃) 25.3 (C(α)Me), 54.1 (C(α)), 55.2 (OMe), 57.6 (C(2)), 72.4 (C(1)), 114.0 (*m*-*Pb*OMe), 123.7 (C(5)), 124.3 (C(4)), 127.8 (*o*-*Pb*OMe), 129.6 (C(3)), 130.3 (C(6)), 136.9 (*i*-*Pb*OMe), 158.8 (*p*-*Pb*OMe); *m/z* (ESI⁺) 246 ([M+H]⁺, 100%); HRMS (ESI⁺) C₁₅H₂₀NO₂⁺ ([M+H]⁺) requires 246.1489; found 246.1488.

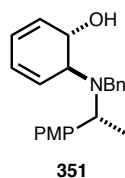
(1*R*,2*R*,α*R*)-2-[*N,N*-(α-Methyl-*para*-methoxybenzyl)benzyl]amino]cyclohexa-3,5-dien-1-ol **348**



K₂CO₃ (141 mg, 1.02 mmol) and BnBr (60.5 μL, 0.510 mmol) were added sequentially to a stirred solution of **342** (50.0 mg, 0.204 mmol, >95:5 dr) in MeCN (0.32 mL) at rt. The resultant solution was heated at reflux for 24 h, then allowed to cool to rt and concentrated *in vacuo*. H₂O (5 mL) was added and the resultant mixture was extracted with CH₂Cl₂ (3 × 10 mL). The combined organics were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent CHCl₃) gave **348** as a yellow oil (49.6 mg, 73%, >95:5 dr); $[\alpha]_{\text{D}}^{25}$ −172.6 (*c* 1.0 in CHCl₃); ν_{max} 3505, 3032, 2967, 2835, 1610; δ_{H} (400 MHz, *d*₁-CHCl₃) 1.43 (3H, d, *J* 6.9, C(α)Me), 2.24 (1H, d, *J* 1.5, OH), 3.63 (1H, br dt, *J* 13.9, 2.5, C(2)*H*), 3.78 (3H, s, OMe), 3.82 (1H, d, *J* 14.1, N(CH_AH_BPh)), 3.97–4.06 (2H, m, C(α)*H*, N(CH_AH_BPh)), 4.48–4.59 (1H, br d, *J* 13.9, C(1)*H*), 5.74–5.80 (1H, m, C(6)*H*), 5.84–5.88 (1H, m, C(5)*H*), 5.92–5.97 (1H, m, C(3)*H*), 6.01–6.06 (1H, m, C(4)*H*), 6.81–6.86 (2H, m, *Pb*OMe), 7.11–7.16 (2H, m, *Pb*OMe), 7.27–7.33 (1H, m, *Pb*), 7.36–7.39 (4H, m, *Pb*); δ_{C} (100 MHz, *d*₁-

CHCl₃) 13.3 (C(α)Me), 52.0 (NCH₂Ph), 55.1 (OMe), 56.0 (C(α)), 60.8 (C(2)), 69.6 (C(1)), 113.8 (*m*-PhOMe), 122.9 (C(5)), 125.7 (C(4)), 127.1, 128.5 (*Ph*), 128.7 (*o*-PhOMe), 128.9 (*Ph*), 129.7 (C(3)), 130.6 (C(6)), 135.8 (*i*-PhOMe), 140.8 (*i*-Ph), 158.6 (*p*-PhOMe); *m/z* (ESI⁺) 336 ([M+H]⁺, 100%); HRMS (ESI⁺) C₂₂H₂₆NO₂⁺ ([M+H]⁺) requires 336.1958; found 336.1956.

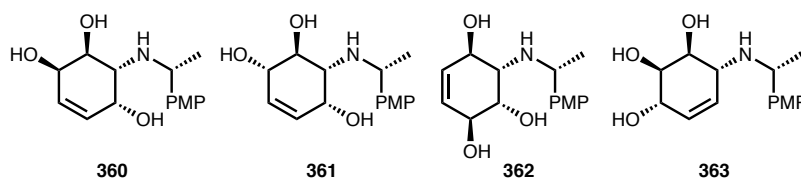
(1*S*,2*S*, α *R*)-2-[N,N-(α -Methyl-*para*-methoxybenzylbenzyl)amino]cyclohexa-3,5-dien-1-ol 351.



K₂CO₃ (141 mg, 1.02 mmol) and BnBr (60.5 μ L, 0.510 mmol) were added sequentially to a stirred solution of **343** (50.0 mg, 0.204 mmol, >95:5 dr) in MeCN (0.32 mL) at rt. The resultant solution was heated at reflux for 24 h, then allowed to cool to rt and concentrated *in vacuo*. H₂O (5 mL) was added and the resultant mixture was extracted with CH₂Cl₂ (3 $\times$ 10 mL). The combined organics were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent CHCl₃) gave **351** as a yellow oil (35.8 mg, 52%, >95:5 dr); [α]_D²⁵ +226.7 (*c* 1.0 in CHCl₃); ν_{max} 3480, 3032, 2967, 2835, 1609; δ_{H} (400 MHz, *d*₁-CHCl₃) 1.41 (3H, d, *J* 7.1, C(α)Me), 2.85 (1H, d, *J* 1.7, OH), 3.69 (1H, d, *J* 14.9, N(CH_AH_BPh)), 3.83 (3H, s, OMe), 3.88–4.00 (3H, m, C(2)H, C(α)H, N(CH_AH_BPh)), 4.52–4.58 (1H, m, C(1)H), 5.24–5.30 (1H, m, C(3)H), 5.73–5.82 (2H, m, C(4)H, C(5)H), 5.94–6.00 (1H, m, C(6)H), 6.87–6.92 (2H, m, *Ph*OMe), 7.20–7.25 (2H, m, *Ph*OMe), 7.27–7.31 (1H, m, *Ph*), 7.35–7.40 (4H, m, *Ph*); δ_{C} (100 MHz, *d*₁-CHCl₃) 20.5 (C(α)Me), 52.0 (NCH₂Ph), 55.3 (OMe), 57.0 (C(α)), 61.2 (C(2)), 69.5 (C(1)), 113.7 (*m*-PhOMe), 123.4 (C(5)), 125.2 (C(4)), 127.0, 128.3, 128.6 (*o,m,p*-Ph), 129.1 (*o*-PhOMe), 129.2 (C(3)), 130.2 (C(6)), 133.8 (*i*-PhOMe), 140.8 (*i*-Ph),

158.8 (*p-Pb*); m/z (ESI⁺) 336 ([M+H]⁺, 100%); HRMS (ESI⁺) C₂₂H₂₆NO₂⁺ ([M+H]⁺) requires 336.1958; found 336.1957.

(1*R*,2*R*,3*S*,4*R*, α *R*)-2-[N-(α -Methyl-*para*-methoxybenzyl)amino]cyclohex-5,6-en-1,3,4-triol **360**, (1*R*,2*R*,3*S*,4*S*, α *R*)-2-[N-(α -methyl-*para*-methoxybenzyl)amino]cyclohex-5,6-en-1,3,4-triol **361**, (1*R*,2*S*,3*S*,4*S*, α *R*)-2-[N-(α -methyl-*para*-methoxybenzyl)amino]cyclohex-5,6-en-1,3,4-triol **362** and (1*R*,2*S*,3*R*,4*S*, α *R*)-1-[N-(α -methyl-*para*-methoxybenzyl)amino]cyclohex-5,6-en-2,3,4-triol **363**

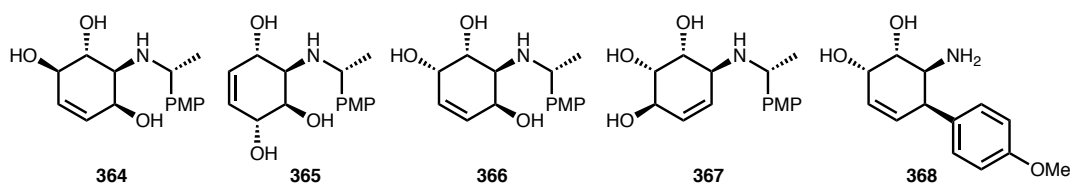


HBF₄ (40% aq, 799 μ L, 5.10 mmol) was added to a stirred solution of **342** (250 mg, 1.02 mmol, >95:5 dr) in CH₂Cl₂ (2.83 mL) at rt and the resultant solution was stirred at rt for 5 min. *m*-CPBA (70% wt, 250 mg, 1.02 mmol) was then added and the resultant solution was stirred at rt for 21 h. Solid Na₂SO₃ was added until starch-iodide paper indicated that no *m*-CPBA was present. The resultant mixture was dissolved in CHCl₃/*i*PrOH (15 mL) and extracted with 2 M aq NaOH (3 $\times$ 25 mL). The combined aqueous extracts were then extracted with CHCl₃/*i*PrOH (3:1, v/v, 3 $\times$ 25 mL) and the combined organic extracts were dried and concentrated *in vacuo* to give a 32:14:37:17 mixture of **360**, **361**, **362** and **363**, respectively (300 mg). Purification *via* preparative thin layer chromatography (eluent CHCl₃/MeOH/35% aq NH₄OH, 90:10:0.5) gave **360** as a yellow oil (46.8 mg, 15%, >95:5 dr), **361** as a yellow oil (27.3 mg, 9.6%, $\sim$ 80% pure), **362** as a beige solid (58.4 mg, 21%, >95:5 dr) and **363** as a yellow oil (21.6 mg, 7.6%, >95:5 dr); Data for **360**: R_f = 0.37; [α]_D²⁵ -67.2 (*c* 1.0 in CHCl₃); $\nu_{\max}$ 3364, 2963, 2900, 1611; δ_{H} (400 MHz, *d*₁-CHCl₃) 1.41 (3H, d, *J*

6.6, C(α)Me), 2.94 (1H, app dd, J 10.7, 4.3, C(2)H), 2.94 (3H, s, OH), 3.63 (1H, t, J 4.3, C(1)H), 3.69 (1H, dd, J 10.7, 4.2, C(3)H), 3.78–3.87 (4H, m, C(α)H, OMe), 4.23 (1H, t, J 4.2 C(4)H), 5.83–5.93 (2H, m, C(5)H, C(6)H), 6.84–6.89 (2H, m, *Pb*OMe), 7.25–7.30 (2H, m, *Pb*OMe); δ_{C} (100 MHz, d_1 -CHCl₃) 23.8 (C(α)Me), 55.2 (OMe), 56.7 (C(2)), 57.1 (C(α)), 63.8 (C(1)), 65.8 (C(4)), 67.3 (C(3)), 114.0 (*m*-*Pb*OMe), 127.5 (*o*-*Pb*OMe), 129.1 (C(5)), 131.2 (C(6)), 137.5 (*i*-*Pb*OMe), 158.9 (*p*-*Pb*OMe); m/z (ESI⁺) 302 ([M+Na]⁺, 100%); HRMS (ESI⁺) C₁₅H₂₂NO₄⁺ ([M+H]⁺) requires 280.1543; found 280.1543. Data for **361**: Rf = 0.22; ν_{max} 3331, 2963, 2917, 1611; δ_{H} (400 MHz, d_1 -CHCl₃) 1.40 (3H, d, J 6.7, C(α)Me), 2.56 (1H, app dd, J 10.8, 4.1, C(2)H), 3.49 (1H, dd, J 10.8, 7.8, C(3)H), 3.58 (1H, t, J 4.1, C(1)H), 3.80 (3H, s, OMe), 3.84 (1H, q, J 6.7, C(α)H), 4.03 (1H, d, J 7.8, C(4)H), 5.83–5.93 (2H, m, C(5)H, C(6)H), 6.84–6.91 (2H, m, *Pb*OMe), 7.24–7.30 (2H, m, *Pb*OMe); δ_{C} (100 MHz, d_1 -CHCl₃) 23.8 (C(α)Me), 55.2 (OMe), 57.0 (C(α)), 59.7 (C(2)), 64.0 (C(1)), 71.3 (C(3)), 73.3 (C(4)), 114.0 (*m*-*Pb*OMe), 127.5 (*o*-*Pb*OMe), 127.6 (C(6)), 132.3 (C(5)), 137.8 (*i*-*Pb*OMe), 158.8 (*p*-*Pb*OMe); m/z (ESI⁺) 302 ([M+Na]⁺, 100%); HRMS (ESI⁺) C₁₅H₂₂NO₄⁺ ([M+H]⁺) requires 280.1543; found 280.1544. Data for **362**: Rf = 0.17; mp 157.0–161.0 °C; $[\alpha]_{\text{D}}^{25}$ +24.8 (c 1.0 in MeOH); ν_{max} 3325, 2964, 2907, 1611; δ_{H} (400 MHz, d_4 -MeOH) 1.35 (3H, d, J 6.6, C(α)Me), 2.79 (1H, app dd, J 6.3, 2.9, C(2)H), 3.66 (1H, ddd, J 4.7, 2.9, 0.8, C(3)H), 3.77 (3H, s, OMe), 3.92–4.01 (2H, m, C(4)H, C(α)H), 4.12 (1H, ddt, J 6.3, 2.8, 1.4, C(1)H), 5.67 (1H, dddd, J 10.1, 3.4, 1.4, 0.8, C(5)H), 5.75 (1H, ddd, J 10.1, 2.8, 1.1, C(6)H), 6.85–6.90 (2H, m, *Pb*OMe), 7.28–7.32 (2H, m, *Pb*OMe); δ_{C} (100 MHz, d_4 -MeOH) 24.3 (C(α)Me), 55.8 (OMe), 56.9 (C(α)), 60.4 (C(2)), 68.9 (C(1)), 70.0 (C(4)), 72.3 (C(3)), 115.0 (*m*-*Pb*OMe), 129.0 (*o*-*Pb*OMe), 129.5 (C(5)), 132.3 (C(6)), 138.9 (*i*-*Pb*OMe), 160.3 (*p*-*Pb*OMe); m/z (ESI⁺) 302 ([M+Na]⁺, 100%); HRMS (ESI⁺) C₁₅H₂₂NO₄⁺ ([M+H]⁺) requires 280.1543; found 280.1544. Data for **363**: Rf = 0.10; $[\alpha]_{\text{D}}^{25}$ –3.0 (c 1.0 in CHCl₃); ν_{max} 3335, 2963,

2910, 1611; δ_{H} (400 MHz, d_1 -CHCl₃) 1.32 (3H, d, J 6.5, C(α)Me), 3.13–3.18 (1H, m, C(1)H), 3.78 (3H, s, OMe), 3.83–3.89 (2H, m, C(3)H, C(α)H), 3.90–3.93 (1H, m, C(2)H), 4.17–4.22 (1H, m, C(4)H), 5.42 (1H, br dd, J 10.1, 1.7, C(6)H), 5.60 (1H, br d, J 10.1, C(5)H), 6.82–6.87 (2H, m, *Pb*OMe), 7.18–7.23 (2H, m, *Pb*OMe); δ_{C} (100 MHz, d_1 -CHCl₃) 23.9 (C(α)Me), 55.2 (OMe), 56.2 (C(1)), 56.3 (C(α)), 69.1 (C(4)), 71.7 (C(2)), 72.6 (C(3)), 114.0 (*m*-*Pb*OMe), 127.6 (*o*-*Pb*OMe), 128.5 (C(6)), 129.0 (C(5)), 137.2 (*i*-*Pb*OMe), 158.7 (*p*-*Pb*OMe); m/z (ESI⁺) 302 ([M+Na]⁺, 100%); m/z (ESI⁺) 302 ([M+Na]⁺, 100%); HRMS (ESI⁺) C₁₅H₂₂NO₄⁺ ([M+H]⁺) requires 302.1363; found 302.1365.

(1*S*,2*S*,3*R*,4*R*, α *R*)-2-[*N*-(α -Methyl-*para*-methoxybenzyl)amino]cyclohex-5,6-en-1,3,4-triol 364 , (1*S*,2*R*,3*R*,4*R*, α *R*)-2-[*N*-(α -methyl-*para*-methoxybenzyl)amino]cyclohex-5,6-en-1,3,4-triol 365, (1*S*,2*S*,3*R*,4*S*, α *R*)-2-[*N*-(α -methyl-*para*-methoxybenzyl)amino]cyclohex-5,6-en-1,3,4-triol 366, (1*S*,2*R*,3*S*,4*R*, α *R*)-1-[*N*-(α -methyl-*para*-methoxybenzyl)amino]cyclohex-5,6-en-2,3,4-triol 367 and (1*S*,2*S*,3*R*,4*S*, α *R*)-1-(*para*-methoxyphenyl)-2-amino-cyclohex-5,6-en-3,4-diol 368

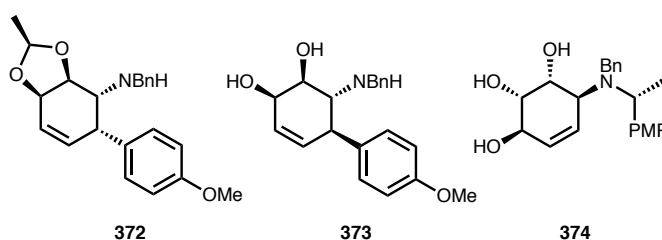


HBF₄ (40% aq, 799 μ L, 5.10 mmol) was added to a stirred solution of **343** (250 mg, 1.02 mmol, >95:5 dr) in CH₂Cl₂ (2.83 mL) at rt and the resultant solution was stirred at rt for 5 min. *m*-CPBA (70% wt, 250 mg, 1.02 mmol) was then added and the resultant solution was stirred at rt for 21 h. Solid Na₂SO₃ was added until starch-iodide paper indicated that no *m*-CPBA was present. The resultant mixture was dissolved in CHCl₃/⁴PrOH (15 mL) and extracted with 2 M aq NaOH (3 $\times$ 25 mL). The combined aqueous extracts were then

extracted with CHCl_3 / i -PrOH (3:1, v/v, 3×25 mL). The combined organic extracts were dried and concentrated *in vacuo* before being filtered through silica pad to give a 5:35:43:17 mixture of **365**, **366**, **367** and **368**, respectively (300 mg). Purification *via* preparative thin layer chromatography (eluent CHCl_3 /MeOH/35% aq NH_4OH , 90:10:0.5) gave **366** as a yellow oil (26.4 mg, 9.4%, >95:5 dr); **368** as a yellow oil (9.9 mg, 3.7%); a 7:85:8 mixture of **364**, **365**, and **368**, respectively, as a beige solid (25.4 mg), a 18:82 mixture of **364** and **365**, respectively, as a beige solid (49.1 mg, 17%) and **367** as a yellow oil (30.5 mg, 11%, >95:5 dr); Data for **366**: $R_f = 0.40$; $[\alpha]_D^{25} +145.7$ (c 1.0 in CHCl_3); $\nu_{\max}$ 3334, 2962, 2918, 1612; δ_{H} (400 MHz, d_1 - CHCl_3) 1.41 (3H, d, J 6.6, C(α)Me), 2.70 (1H, app dd, J 10.9, 4.1, C(2)H), 2.87 (3H, s, OH), 3.68 (1H, dd, J 10.8, 4.1, C(3)H), 3.79 (3H, s, OMe), 3.88 (1H, q, J 6.6, C(α)H), 4.13–4.20 (2H, m, C(1)H, C(4)H), 5.92 (1H, dd, J 9.8, 5.1, C(5)H), 6.02 (1H, dd, J 9.8, 5.1, C(6)H), 6.84–6.90 (2H, m, *Pb*OMe), 7.18–7.24 (2H, m, *Pb*OMe); δ_{C} (100 MHz, d_1 - CHCl_3) 24.9 (C(α)Me), 54.1 (C(2)), 54.4 (C(α)), 55.2 (OMe), 63.0 (C(1)), 65.6 (C(4)), 67.2 (C(3)), 114.1 (*m*-*Pb*OMe), 127.5 (*o*-*Pb*OMe), 129.3 (C(5)), 131.1 (C(6)), 136.2 (*i*-*Pb*OMe), 158.8 (*p*-*Pb*OMe); m/z (ESI $^+$) 302 ($[\text{M}+\text{Na}]^+$, 100%); HRMS (ESI $^+$) $\text{C}_{15}\text{H}_{22}\text{NO}_4^+$ ($[\text{M}+\text{H}]^+$) requires 280.1543; found 280.1544; Data for **368**: $R_f = 0.27$; $\nu_{\max}$ 3350, 3027, 2917, 2850, 1609; δ_{H} (400 MHz, d_4 -MeOH) 3.25 (1H, app dd, J 9.7, 5.7, C(2)H), 3.63 (1H, dd, J 9.7, 4.3, C(3)H), 3.58 (1H, t, J 4.1, C(1)H), 3.74–3.80 (5H, m, OH, C(1)H, OMe), 4.27 (1H, t, J 4.3, C(4)H), 5.82 (1H, ddd, J 10.0, 4.3, 0.8, C(6)H), 5.95 (1H, ddd, J 10.0, 4.3, 1.7, C(5)H), 6.87–6.92 (2H, m, *Pb*OMe), 7.11–7.16 (2H, m, *Pb*OMe); δ_{C} (100 MHz, d_4 -MeOH) 46.8 (C(1)), 52.3 (C(2)), 55.8 (OMe), 67.5 (C(4)), 71.7 (C(3)), 115.0 (*m*-*Pb*OMe), 129.3 (C(5)), 130.7 (*i*-*Pb*OMe), 132.1 (*o*-*Pb*OMe), 132.8 (C(6)), 160.6 (*p*-*Pb*OMe); m/z (ESI $^+$) 236 ($[\text{M}+\text{H}]^+$, 100%); HRMS (ESI $^+$) $\text{C}_{13}\text{H}_{18}\text{NO}_3^+$ ($[\text{M}+\text{H}]^+$) requires 236.1281; found 236.1281; Data for **364** and **365**: $R_f = 0.21$; $\nu_{\max}$ 3339, 2958, 2918, 1611; m/z (ESI $^+$) 302 ($[\text{M}+\text{Na}]^+$, 100%); HRMS (ESI $^+$) $\text{C}_{15}\text{H}_{22}\text{NO}_4^+$ ($[\text{M}+\text{H}]^+$) requires 280.1543; found 280.1543. Data for **364**: δ_{H}

(400 MHz, d_4 -MeOH) 1.37 (3H, d, J 6.6, C(α)Me), 2.29 (1H, dd, J 10.8, 4.1, C(2)H), 3.44 (1H, dd, J 10.8, 7.7, C(3)H), 3.73–3.80 (4H, m, C(4)H, OMe), 3.96–4.03 (1H, m, C(α)H), 5.59–5.65 (1H, m, C(5)H), 5.78 (1H, ddd, J 10.0, 4.9, 2.1, C(6)H), 6.83–6.89 (2H, m, *Pb*OMe), 7.23–7.30 (2H, m, *Pb*OMe); δ_{C} (100 MHz, d_4 -MeOH) [Selected peaks] 25.2 (C(α)Me), 54.9 (C(α)), 55.8 (OMe), 58.7 (C(2)), 63.8 (C(1)), 72.2 (C(3)), 74.0 (C(4)), 128.7 (C(5)), 133.6 (C(6)); Data for **365**: δ_{H} (400 MHz, d_4 -MeOH) 1.37 (3H, d, J 6.6, C(α)Me), 2.65 (1H, app dd, J 7.7, 2.4, C(2)H), 3.76 (1H, s, OMe), 3.96–4.00 (3H, m, C(1)H, C(3)H, C(α)H), 4.00–4.03 (1H, m, C(4)H), 5.59–5.65 (1H, m, C(5)H), 5.69 (1H, ddd, J 10.0, 2.3, 0.7, C(6)H), 6.83–6.89 (2H, m, *Pb*OMe), 7.23–7.30 (2H, m, *Pb*OMe); δ_{C} (100 MHz, d_4 -MeOH) 25.0 (C(α)Me), 55.6 (C(α)), 55.8 (OMe), 58.9 (C(2)), 68.9 (C(1)), 70.0 (C(4)), 70.9 (C(3)), 115.0 (*m*-*Pb*OMe), 128.2 (C(5)), 129.0 (*o*-*Pb*OMe), 133.3 (C(6)), 138.4 (*i*-*Pb*OMe), 160.3 (*p*-*Pb*OMe); Data for **367**: Rf = 0.10; $[\alpha]_{\text{D}}^{25}$ +69.2 (c 1.0 in CHCl_3); ν_{max} 3357, 2963, 2911, 1611; δ_{H} (400 MHz, d_4 -MeOH) 1.36 (3H, d, J 6.6, C(α)Me), 3.05–3.11 (1H, m, C(1)H), 3.68 (1H, d, J 6.5, 2.4, C(2)H), 3.74–3.78 (4H, m, C(3)H, OMe), 3.96–4.04 (2H, m, C(4)H, C(α)H), 5.66 (1H, dddd, J 10.1, 3.5, 1.7, 0.8, C(5)H), 5.85 (1H, ddd, J 10.1, 2.8, 1.2, C(6)H), 6.85–6.91 (2H, m, *Pb*OMe), 7.25–7.30 (2H, m, *Pb*OMe); δ_{C} (100 MHz, d_4 -MeOH) 24.6 (C(α)Me), 55.8 (OMe), 56.0 (C(1)), 56.0 (C(α)), 70.8 (C(4)), 72.6 (C(2)), 74.4 (C(3)), 115.1 (*m*-*Pb*OMe), 129.1 (*o*-*Pb*OMe), 129.2 (C(5)), 129.3 (C(6)), 137.8 (*i*-*Pb*OMe), 160.4 (*p*-*Pb*OMe); m/z (ESI $^+$) 302 ($[\text{M}+\text{Na}]^+$, 100%); m/z (ESI $^+$) 302 ($[\text{M}+\text{Na}]^+$, 100%); HRMS (ESI $^+$) $\text{C}_{15}\text{H}_{22}\text{NO}_4^+$ ($[\text{M}+\text{H}]^+$) requires 280.1543; found 280.1542.

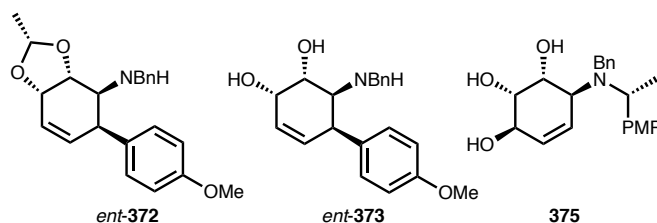
(1*R*,2*R*,3*S*,4*R*, α *R*)-1-(*para*-Methoxyphenyl)-2-(*N*-benzylamino)-3,4-[(1'-methyl)-methylenedioxy]cyclohex-5,6-ene **372**, (1*S*,2*R*,3*S*,4*R*, α *R*)-1-(*para*-methoxyphenyl)-2-(*N*-benzylamino)cyclohex-5,6-en-3,4-diol **373**, (1*R*,2*S*,3*R*,4*S*, α *R*)-1-[*N,N*-(α -methyl-*para*-methoxybenzylbenzyl)amino] cyclohex-5,6-en-2,3,4-triol **374**.



Anhydrous $\text{Cl}_3\text{CCO}_2\text{H}$ (487 mg, 2.98 mmol) was added to a stirred solution of **348** (200 mg, 0.597 mmol, >95:5 dr) in CH_2Cl_2 (1.66 mL) at rt and the resultant solution was stirred at rt for 5 min. *m*-CPBA (70% wt, 147 mg, 0.597 mmol) was then added and the resultant solution was stirred at rt for 21 h. Solid Na_2SO_3 was added until starch-iodide paper indicated that no *m*-CPBA was present. MeOH (8.0 mL) and K_2CO_3 (1.73 mg) were added at rt and the resultant suspension was stirred at rt for 24 h, then concentrated *in vacuo*. The crude mixture was dissolved in CH_2Cl_2 (15 mL) and extracted with 2 M aq NaOH (3×10 mL). The combined aqueous extracts were then extracted with CH_2Cl_2 (3×10 mL) and the combined organic extracts were dried and concentrated *in vacuo* to give a 18:16:66 mixture of **372**, triol **373** and triol **374**, respectively. Purification *via* flash column chromatography (eluent $\text{CHCl}_3/\text{MeOH}$ 95:5) gave **372** as a yellow oil (25.7 mg, 12%, $\sim 90\%$ pure); ν_{max} 3030, 2932, 2836, 1610; δ_{H} (400 MHz, $d_1\text{-CHCl}_3$) 1.39 (3H, d, J 4.8, C(α)Me), 3.00 (1H, dd, J 8.6, 5.1, C(2)H), 3.74–3.78 (1H, m, C(1)H), 3.80–3.85 (4H, m, OMe, N($\text{CH}_\text{A}\text{H}_\text{B}\text{Ph}$)), 3.94 (1H, d, J 13.8, N($\text{CH}_\text{A}\text{H}_\text{B}\text{Ph}$)), 4.01 (1H, dd, J 8.6, 6.5 C(3)H), 4.60 (1H, dd, J 6.5, 2.5, C(4)H), 5.16 (1H, q, J 4.8, C(α)H), 6.05–6.13 (2H, m, C(5)H, C(6)H), 6.87–6.92 (2H, m, *Pb*OMe), 7.09–7.11 (2H, m, *Pb*OMe), 7.21–7.33 (5H, m, *Pb*); δ_{C} (100 MHz, $d_1\text{-CHCl}_3$) 20.6

(C(α)Me), 42.6 (C(1)), 51.7 (NCH₂Ph), 55.2 (OMe), 58.5 (C(2)), 73.5 (C(4)), 76.0 (C(3)), 101.2 (C(α)), 114.8 (*m*-PbOMe), 124.5 (C(5)), 126.8, 128.0, 128.2 (*o,m,p*-Ph), 130.2 (*o*-PbOMe), 133.1 (C(6)), 134.3 (*i*-PbOMe), 140.4 (*i*-Ph), 158.6 (*p*-PbOMe); m/z (ESI⁺) 352 ([M+H]⁺, 100%); HRMS (ESI⁺) C₂₂H₂₆NO₃⁺ ([M+H]⁺) requires 352.1907; found 352.1903. Further elution gave **373** as a yellow oil (47.2 mg, ~ 40% pure); $\nu_{\max}$ 3402, 3028, 2967, 2906, 2836, 1610; δ_{H} (400 MHz, *d*₁-CHCl₃) [selected peaks] 3.26 (1H, dd, *J* 11.0, 5.8, C(2)*H*), 3.59 (1H, dd, *J* 11.0, 4.4, C(3)*H*), 3.72–3.77 (1H, m, N(CH_AH_BPh)), 3.80 (3H, s, OMe), 3.93–3.99 (1H, m, C(1)*H*), 4.10 (1H, d, *J* 12.8, N(CH_AH_BPh)), 4.46 (1H, t, *J* 4.4, C(4)*H*), 5.95–6.02 (1H, m, C(6)*H*), 6.08 (1H, ddd, *J* 9.8, 4.9, 1.4, C(5)*H*); δ_{C} (100 MHz, *d*₁-CHCl₃) [selected peaks] 43.7 (C(1)), 56.2 (C(2)), 65.5 (C(4)), 67.4 (C(3)); m/z (ESI⁺) 326 ([M+H]⁺, 100%); HRMS (ESI⁺) C₂₀H₂₄NO₃⁺ ([M+H]⁺) requires 326.1762; found 326.1752. Further elution gave **374** as a yellow oil (81.8 mg, 37%, >95:5 dr); [α]_D²⁵ –56.6 (*c* 1.0 in CHCl₃); $\nu_{\max}$ 3402, 3028, 2968, 2904, 2837, 1610; δ_{H} (400 MHz, *d*₁-CHCl₃) 1.44 (3H, d, *J* 6.9, C(α)Me), 2.58 (2H, br s, OH), 3.00 (1H, br d, *J* 8.5, C(1)*H*), 3.66 (1H, dd, *J* 8.5, 2.4, C(2)*H*), 3.75–3.79 (5H, m, OMe, NCH₂Ph), 3.91–3.93 (1H, m, C(3)*H*), 3.97 (1H, d, *J* 6.8, C(α)*H*), 4.08 (1H, br t, *J* 3.1, C(4)*H*), 5.75–5.81 (1H, m, C(5)*H*), 5.96 (1H, dd, *J* 10.5, 1.8, C(6)*H*), 6.80–6.85 (2H, m, PbOMe), 7.08–7.13 (2H, m, PbOMe), 7.26–7.40 (5H, m, Ph); δ_{C} (100 MHz, *d*₁-CHCl₃) 12.6 (C(α)Me), 51.3 (NCH₂Ph), 54.7 (C(1)), 55.1 (OMe), 55.9 (C(α)), 67.4 (C(2)), 68.3 (C(4)), 72.4 (C(3)), 113.8 (*m*-PbOMe), 127.1 (*p*-Ph), 128.2 (C(5)), 128.4, 128.7, 128.8 (*o,m*-Ph, *o*-PbOMe), 131.1 (C(6)), 135.6 (*i*-PbOMe), 140.6 (*i*-Ph), 158.5 (*p*-PbOMe); m/z (ESI⁺) 370 ([M+H]⁺, 100%); HRMS (ESI⁺) C₂₂H₂₈NO₄⁺ ([M+H]⁺) requires 370.2013; found 370.2009.

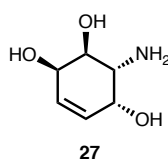
(1*S*,2*S*,3*R*,4*S*, α *R*)-1-(*para*-Methoxyphenyl)-2-(*N*-benzylamino)-3,4-[(1'-methyl)-methylenedioxy]cyclohex-5,6-ene *ent*-**372**, (1*R*,2*S*,3*R*,4*S*, α *R*)-1-(*para*-methoxyphenyl)-2-(*N*-benzylamino)cyclohex-5,6-en-3,4-diol *ent*-**373**, (1*S*,2*R*,3*S*,4*R*, α *R*)-1-[*N,N*-(α -methyl-*para*-methoxybenzylbenzyl)amino] cyclohex-5,6-en-2,3,4-triol **375**.



Anhydrous $\text{Cl}_3\text{CCO}_2\text{H}$ (487 mg, 2.98 mmol) was added to a stirred solution of **351** (200 mg, 0.597 mmol, >95:5 dr) in CH_2Cl_2 (1.66 mL) at rt and the resultant solution was stirred at rt for 5 min. *m*-CPBA (70% wt, 147 mg, 0.597 mmol) was then added and the resultant solution was stirred at rt for 21 h. Solid Na_2SO_3 was added until starch-iodide paper indicated that no *m*-CPBA was present. MeOH (8.0 mL) and K_2CO_3 (1.73 mg) were added at rt and the resultant suspension was stirred at rt for 24 h, then concentrated *in vacuo*. The crude mixture was dissolved in CH_2Cl_2 (15 mL) and extracted with 2 M aq NaOH (3×10 mL). The combined aqueous extracts were then extracted with CH_2Cl_2 (3×10 mL) and the combined organic extracts were dried and concentrated *in vacuo* to give a 62:20:18 mixture of *ent*-**372**, triol *ent*-**373** and **375**, respectively. Purification *via* flash column chromatography (eluent $\text{CHCl}_3/\text{MeOH}$ 95:5) gave *ent*-**372** as a yellow oil (70.7 mg, 34%, ~80% pure); Further elution gave *ent*-**373** as a yellow oil (24.9 mg, ~80 % pure) and **375** as a yellow oil (19.9 mg, 9%, 90% pure); ν_{max} 3431, 2981, 2925, 1609; δ_{H} (400 MHz, $d_1\text{-CHCl}_3$) 1.41 (3H, d, J 7.1, C(α)Me), 3.65 (1H, d, J 14.8, N($\text{CH}_\text{A}\text{H}_\text{B}\text{Ph}$)), 3.69–3.74 (2H, m, C(2)H, N($\text{CH}_\text{A}\text{H}_\text{B}\text{Ph}$)), 3.77–3.84 (4H, m, C(1)H, OMe), 3.91 (1H, d, J 7.1, C(α)H), 4.11–4.13 (1H, m, C(3)H), 4.14–4.17 (1H, m, C(4)H), 5.19 (1H, dd, J 10.2, 1.2, C(6)H), 5.60–5.66 (1H, m, C(5)H), 6.87–6.92 (2H, m, *Pb*OMe), 7.20–7.25 (2H, m, *Pb*OMe), 7.26–7.40 (5H, m, *Pb*); δ_{C}

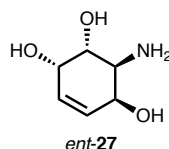
(100 MHz, d_1 -CHCl₃) 20.5 (C(α)Me), 51.3 (NCH₂Ph), 55.2 (C(1)), 55.4 (OMe), 57.4 (C(α)), 67.3 (C(2)), 68.6 (C(4)), 72.7 (C(3)), 113.8 (*m*-PbOMe), 127.0 (*p*-Pb), 127.6 (C(5)), 128.1, 128.6, 129.1 (*o,m*-Pb, *o*-PbOMe), 130.5 (C(6)), 133.4 (*i*-PbOMe), 140.6 (*i*-Pb), 158.9 (*p*-PbOMe); m/z (ESI⁺) 370 ([M+H]⁺, 100%); HRMS (ESI⁺) C₂₂H₂₈NO₄⁺ ([M+H]⁺) requires 370.2013; found 370.2012.

(1R,2R,3S,4R)-2-Aminocyclohex-5,6-en-1,3,4-triol [(-)-Conduramine E-2] 27



Et₃SiH (28.2 μ L, 0.177 mmol) was added to a stirred solution of **360** (30.8 mg, 0.110 mmol, >95:5 dr) in CF₃COOH (0.44 mL) at rt and the resultant solution was stirred at 50 °C for 18 h, then concentrated *in vacuo*. Purification *via* column chromatography (eluent CHCl₃/MeOH/35% aq NH₄OH, 50:30:20) gave **27** as yellow oil (9.3 mg, 58%, >95:5 dr); [α]_D²⁵ -219 (c 0.5 in MeOH); $\nu_{\max}$ 3351, 2963, 2916, 1636; δ_{H} (400 MHz, d_4 -MeOH) 3.03 (1H, dd, J 10.4, 4.2, C(2)H), 3.70 (1H, dd, J 10.4, 4.2, C(3)H), 4.14 (1H, t, J 4.2, C(4)H), 4.20 (1H, t, J 4.2, C(1)H), 5.84–5.92 (2H, m, C(5)H, C(6)H); δ_{C} (100 MHz, d_4 -MeOH) 52.4 (C(2)), 67.6 (C(1)), 67.7 (C(4)), 70.8 (C(3)), 130.8 (C(5)), 131.9 (C(6)); m/z (ESI⁺) 146 ([M+H]⁺, 100%); HRMS (ESI⁺) C₆H₁₂NO₃⁺ ([M+H]⁺) requires 146.0812; found 146.0811.

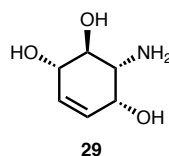
(1S,2S,3R,4S)-2-Aminocyclohex-5,6-en-1,3,4-triol [(+)-Conduramine E-2] *ent*-27



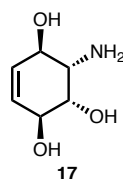
Et₃SiH (26.0 μ L, 0.163 mmol) was added to a stirred solution of **366** (28.4 mg, 0.102 mmol, >95:5 dr) in CF₃COOH (0.44 mL) at rt and the resultant solution was stirred at 50 °C for

18 h, then concentrated *in vacuo*. Purification *via* column chromatography (eluent CHCl₃/MeOH/35% aq NH₄OH, 50:30:20) gave *ent*-**27** as yellow oil (4.7 mg, 32%, >95:5 dr); [α]_D²⁵ +204 (*c* 0.25 in MeOH); $\nu_{\max}$ 3358, 2981, 2916, 1636; δ_{H} (400 MHz, *d*₄-MeOH) 3.04 (1H, dd, *J* 10.4, 4.2, C(2)*H*), 3.70 (1H, dd, *J* 10.4, 4.2, C(3)*H*), 4.14 (1H, t, *J* 4.2, C(4)*H*), 4.20 (1H, t, *J* 4.2, C(1)*H*), 5.84–5.92 (2H, m, C(5)*H*, C(6)*H*); δ_{C} (100 MHz, *d*₄-MeOH) 52.2 (C(2)), 67.5 (C(1)), 67.7 (C(4)), 70.6 (C(3)), 130.8 (C(5)), 131.9 (C(6)); *m/z* (ESI⁺) 146 ([M+H]⁺, 100%); HRMS (ESI⁺) C₆H₁₂NO₃⁺ ([M+H]⁺) requires 146.0812; found 146.0811.

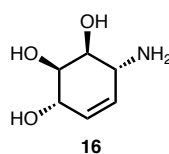
(1R,2R,3S,4S)-2-Aminocyclohex-5,6-en-1,3,4-triol [(-)-Conduramine F-2] 29²¹



Et₃SiH (12.4 μ L, 77.9 μ mol) was added to a stirred solution of **361** (13.6 mg, 48.7 μ mol, >95:5 dr) in CF₃COOH (0.21 mL) at rt and the resultant solution was stirred at 50 °C for 18 h, then concentrated *in vacuo*. Purification *via* column chromatography (eluent CHCl₃/MeOH/35% aq NH₄OH, 50:30:20) gave **29**•xCCl₃CO₂H as yellow oil (2.9 mg, 41%²², >95:5 dr)²¹; [α]_D²⁵ -4.0 (*c* 0.25 in MeOH); $\nu_{\max}$ 3353, 2973, 2918, 1587; δ_{H} (500 MHz, *d*₄-MeOH) 2.67 (1H, dd, *J* 10.6, 4.3, C(2)*H*), 3.47 (1H, br dd, *J* 10.6, 7.7, C(3)*H*), 3.92 (1H, br t, *J* 7.7, C(4)*H*), 4.17 (1H, t, *J* 4.6, C(1)*H*), 5.72 (1H, dd, *J* 10.0, 2.0, C(5)*H*), 5.81 (1H, dd, *J* 10.0, 4.6, 2.1 C(6)*H*); δ_{C} (125 MHz, *d*₄-MeOH) 55.6 (C(2)), 67.1 (C(1)), 73.9 (C(3)), 74.2 (C(4)), 128.9 (C(6)), 133.8 (C(5)); *m/z* (ESI⁺) 146 ([M+H]⁺, 100%); HRMS (ESI⁺) C₆H₁₂NO₃⁺ ([M+H]⁺) requires 146.0812; found 146.0811.

(1R,2S,3S,4S)-2-Aminocyclohex-5,6-en-1,3,4-triol [(-)-Conduramine A-2] 17

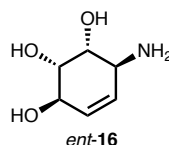
Et₃SiH (32.6 μ L, 0.204 mmol) was added to a stirred solution of **362** (35.6 mg, 0.128 mmol, >95:5 dr) in CF₃COOH (0.56 mL) at rt and the resultant solution was stirred at 50 °C for 18 h, then concentrated *in vacuo*. Purification *via* column chromatography (eluent CHCl₃/MeOH/35% aq NH₄OH, 50:30:20) gave **17** as yellow oil (14.7 mg, 79%, >95:5 dr); [α]_D²⁵ -2.46 (*c* 1.0 in CHCl₃); $\nu_{\max}$ 3342, 2981, 2911, 1652; δ_{H} (400 MHz, *d*₄-MeOH) 2.87 (1H, dd, *J* 7.2, 2.6, C(2)*H*), 3.81–3.85 (1H, m, C(3)*H*), 3.98–4.05 (2H, m, C(1)*H*, C(4)*H*), 5.69 (1H, ddt, *J* 10.1, 3.8, 1.3, C(5)*H*), 5.77 (1H, ddd, *J* 10.1, 2.4, 0.8, C(6)*H*); δ_{C} (100 MHz, *d*₄-MeOH) 55.2 (C(2)), 70.4 (C(4)), 71.2 (C(1)), 74.5 (C(3)), 128.8 (C(5)), 133.0 (C(6)); *m/z* (ESI⁺) 146 ([M+H]⁺, 100%); HRMS (ESI⁺) C₆H₁₂NO₃⁺ ([M+H]⁺) requires 146.0812; found 146.0811.

(1R,2S,3S,4S)-1-aminocyclohex-5,6-en-2,3,4-triol [(-)-Conduramine A-1] 16²³

Et₃SiH (12.5 μ L, 78.5 μ mol) was added to a stirred solution of **363** (13.7 mg, 49.1 μ mol, >95:5 dr) in CF₃COOH (0.21 mL) at rt and the resultant solution was stirred at 50 °C for 18 h, then concentrated *in vacuo*. Purification *via* column chromatography (eluent CHCl₃/MeOH/35% aq NH₄OH, 50:30:20) gave **16** as yellow oil (5.8 mg, 82%, >95:5 dr);²³ [α]_D²⁵ -13.4 (*c* 0.25 in MeOH) {lit.²³ [α]_D²⁵ -18.8 (*c* 0.86 in MeOH); lit.²⁴ [α]_D²⁵ -18.7 (*c* 0.1 in MeOH)}; $\nu_{\max}$ 3346, 2981, 2914, 1636; δ_{H} (400 MHz, *d*₄-MeOH) 3.43 (1H, br d, *J* 7.3, C(1)*H*), 3.62 (1H, dd, *J* 7.1, 2.4, C(2)*H*), 3.79–3.82 (1H, m, C(3)*H*), 4.07–4.10 (1H, m,

C(4)*H*), 5.66–5.74 (1*H*, *m*, C(5)*H*, C(6)*H*) ; δ_c (100 MHz, *d*₄-MeOH) 52.2 (*C*(1)), 70.9 (*C*(4)), 74.0 (*C*(2)), 74.5 (*C*(3)), 129.2 (*C*(5)), 131.7 (*C*(6)); *m/z* (ESI⁺) 146 ([*M*+*H*]⁺, 100%); HRMS (ESI⁺) C₆H₁₂NO₃⁺ ([*M*+*H*]⁺) requires 146.0812; found 146.0811.

(1*R*,2*S*,3*S*,4*S*)-1-Aminocyclohex-5,6-en-2,3,4-triol [(+)-Conduramine A-1] *ent*-16²⁵



Et₃SiH (15.6 μ L, 97.4 μ mol) was added to a stirred solution of **367** (17.0 mg, 60.9 μ mol, >95:5 *dr*) in CF₃COOH (0.26 mL) at rt and the resultant solution was stirred at 50 °C for 18 h, then concentrated *in vacuo*. Purification *via* column chromatography (eluent CHCl₃/MeOH/35% aq NH₄OH, 50:30:20) gave *ent*-16 as yellow oil (4.7 mg, 53%, >95:5 *dr*); [α]_D²⁵ +11.7 (*c* 0.25 in MeOH) {lit.²⁵ [α]_D²⁵ +19.0 (*c* 0.1 in MeOH)}; $\nu_{\max}$ 3348, 2981, 2919, 1636; δ_H (400 MHz, *d*₄-MeOH) 3.41 (1*H*, br d, *J* 7.3, C(1)*H*), 3.61 (1*H*, dd, *J* 7.1, 2.4, C(2)*H*), 3.78–3.82 (1*H*, *m*, C(3)*H*), 4.07–4.10 (1*H*, *m*, C(4)*H*), 5.66–5.74 (1*H*, *m*, C(5)*H*, C(6)*H*) ; δ_c (100 MHz, *d*₄-MeOH) 52.2 (*C*(1)), 71.0 (*C*(4)), 74.3 (*C*(2)), 74.5 (*C*(3)), 129.0 (*C*(5)), 132.0 (*C*(6)); *m/z* (ESI⁺) 146 ([*M*+*H*]⁺, 100%); HRMS (ESI⁺) C₆H₁₂NO₃⁺ ([*M*+*H*]⁺) requires 146.0812; found 146.0811.

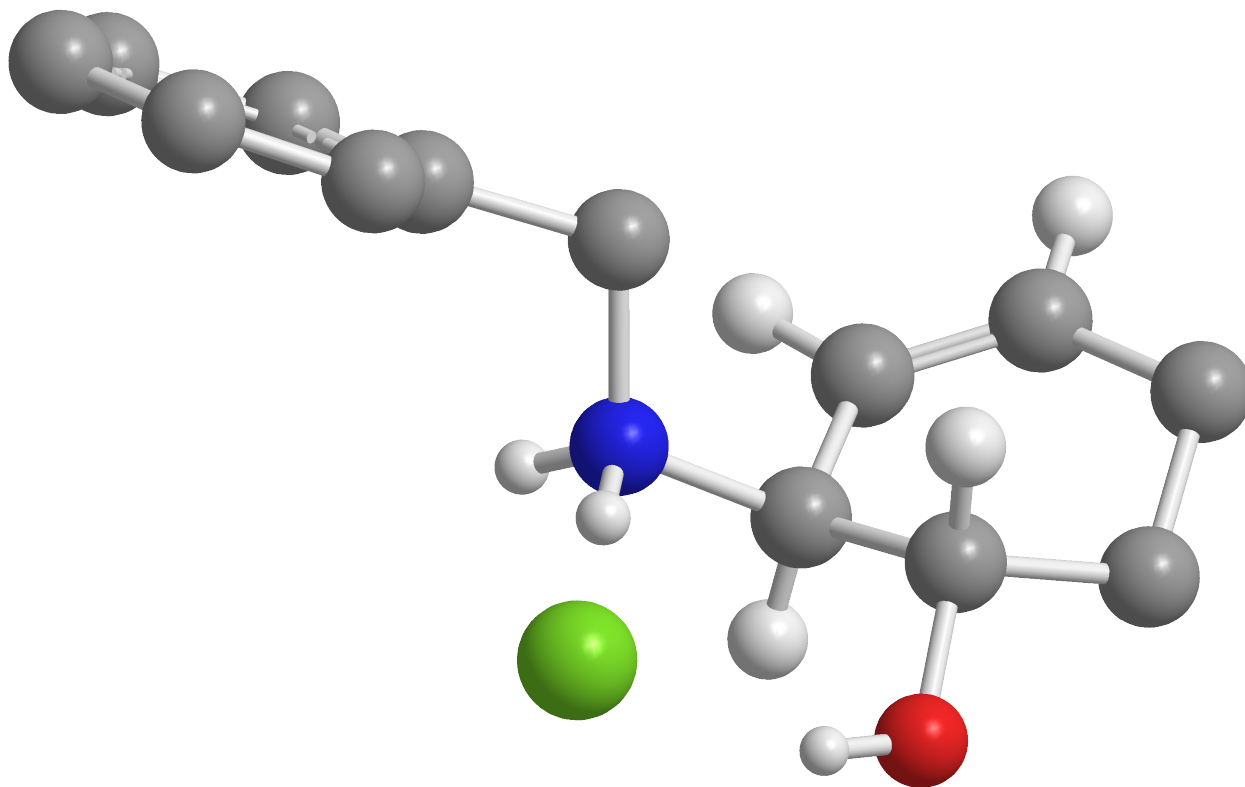
8.8 Notes and references

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- (6) Other signals associated with the aromatic rings within ($\pm$)-**216** and ($\pm$)-**217** (which could not be unambiguously assigned to their respective diastereoisomer) were observed: δ_H (400 MHz, *d*₁-CHCl₃) 2.46 (3*H*, *s*, Ar*Me*), 2.48 (3*H*, *s*, Ar*Me*), 7.22–7.88 (28*H*, *m*, Ar, *Ph*).
- (7) The signal associated with N(CH₂Ph)₂ was very broad and of low intensity; the approximate peak position (to the nearest integer) is shown in italics and marked with an asterisk.
- (8) Knapp, S.; Sebastian, M. J.; Ramanathan, H.; Bharadwaj, P.; Potenza, J. A. *Tetrahedron* **1986**, *42*, 3405–3410.

- (9) This signal was partly obscured by the signal associated with the d_8 -PhMe solvent; other signals in these regions could not be discerned.
- (10) The enantiomeric excesses of dihydroconduramines (–)-A-2 **33**, (–)-B-2 **35**, (–)-C-3 **38** and (+)-F-3 **46** were assigned from the known enantiomeric excesses of the corresponding precursors **214**, **215**, **275** and **272**, respectively.
- (11) The enantiopurities of (+)-C-2 **38**, (+)-D-2 **41**, (+)-E-2 **43** and (+)-F-2 **45** were assigned from the known enantiopurity of the starting material **233** (i.e., >99% ee).
- (12) The enantiopurities of (–)-C-2 *ent*-**38** and (–)-F-2 *ent*-**45** were assigned from the known enantiopurity of the starting material **234** (i.e., >99% ee).
- (13) A signal associated with C(6) was not evident in the ^{13}C NMR spectrum of (+)-dihydroconduramine D-2 **41**; the approximate peak position was obtained from the ^1H – ^{13}C HSQC NMR spectrum of this compound and is reported to the nearest integer (shown in italics and marked with an asterix).
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- (18) The filtrate was collected using tubes of appropriate size, then analysed by TLC. Plates were visualised using UV light (254 nm) and 1% as KMnO_4 . *m*-CBA, reduce form of *m*-CPBA, was then removed.
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- (21) Harit, V. K.; Ramesh, N. G. *Org. Biomol. Chem.* **2019**, *17*, 5951–5961.
- (22) The yields provided for sample (–)-F-2 **27** is not accurate due to presence of $\text{CF}_3\text{CO}_2\text{H}$.
- (23) Myeong, I.; Kim, J.; Lee, Y.; Kang, J.; Park, S.; Jung, C.; Ham, W. *Tetrahedron: Asymmetry* **2016**, *27*, 823–828.
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Appendix 1: X-Ray Crystal Structure Data

X-Ray crystal structure data for (1*RS*,2*RS*)-166•HCl (selected H atoms are omitted for clarity)



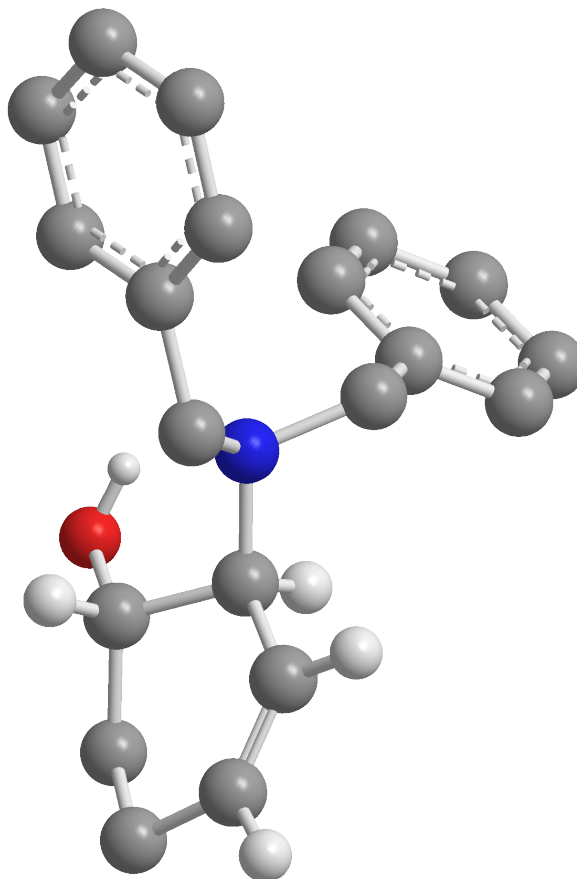
X-ray crystal structure determination for (±)-166•HCl

Data were collected using an Oxford Diffraction SuperNova diffractometer with graphite monochromated Cu-K α radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.¹

X-ray crystal structure data for (±)-166•HCl [C₁₃H₁₈ClNO]: $M = 239.74$, monoclinic, space group $P 2_1/c$, $a = 10.9697(3)$ Å, $b = 14.9855(4)$ Å, $c = 7.8711(3)$ Å, $\beta = 101.970(3)^\circ$, $V = 1265.76(7)$ Å³, $Z = 4$, $\mu = 2.496$ mm⁻¹, colourless plate, crystal dimensions = $0.09 \times 0.19 \times 0.21$ mm³. A total of 2626 unique reflections were measured for $4 < \theta < 76$ and 2143 reflections were used in the refinement. The final parameters were $wR_2 = 0.071$ and $R_1 = 0.032$ [$I > 3.0\sigma(I)$]. X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research Laboratory, University of Oxford, U.K.

¹ Betteridge, P. W.; Carruthers, J. R.; Cooper, R. I.; Prout, C. K.; Watkin, D. J. *J. Appl. Crystallogr.* **2003**, *36*, 1487.

X-Ray crystal structure data for (1*R*,2*R*)-168
(selected H atoms are omitted for clarity)



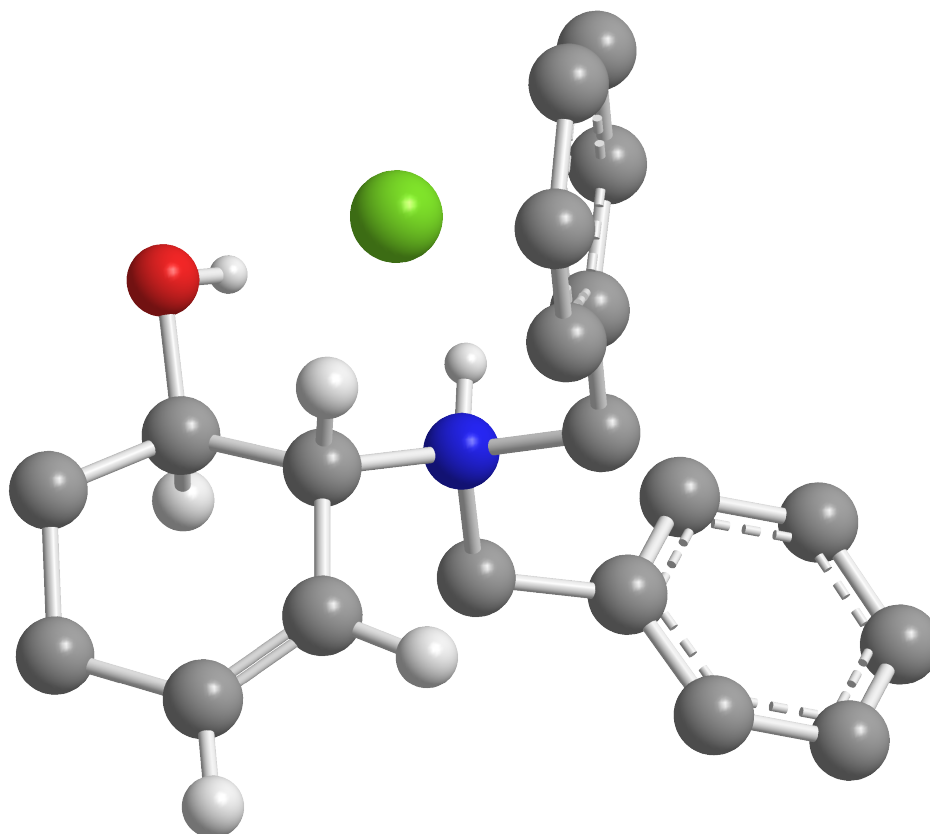
X-ray crystal structure determination for (±)-168

Data were collected using an Oxford Diffraction SuperNova diffractometer with graphite monochromated Cu-K α radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.²

X-ray crystal structure data for (±)-**168** [C₂₀H₂₃NO]: $M = 293.41$, monoclinic, space group $P 2_1/n$, $a = 11.9367(2)$ Å, $b = 15.6253(2)$ Å, $c = 18.4448(4)$ Å, $\beta = 105.971(2)^\circ$, $V = 3307.43(11)$ Å³, $Z = 8$, $\mu = 0.554$ mm⁻¹, colourless block, crystal dimensions = $0.28 \times 0.28 \times 0.30$ mm³. A total of 6857 unique reflections were measured for $4 < \theta < 76$ and 6022 reflections were used in the refinement. The final parameters were $wR_2 = 0.100$ and $R_1 = 0.043$ [$I > 3.0\sigma(I)$]. X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research Laboratory, University of Oxford, U.K.

² Betteridge, P. W.; Carruthers, J. R.; Cooper, R. I.; Prout, C. K.; Watkin, D. J. *J. Appl. Crystallogr.* **2003**, *36*, 1487.

X-Ray crystal structure data for (1*RS*,2*RS*)-168•HCl
(selected H atoms are omitted for clarity)



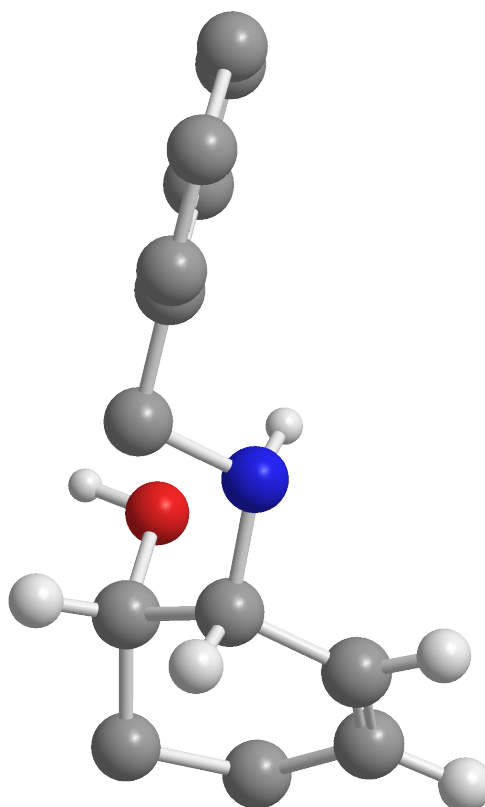
X-ray crystal structure determination for (±)-168•HCl

Data were collected using an Oxford Diffraction SuperNova diffractometer with graphite monochromated Cu-K α radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.³

X-ray crystal structure data for (±)-168•HCl [C₂₀H₂₄ClNO]: $M = 329.87$, monoclinic, space group $P 2_1/c$, $a = 10.0111(3)$ Å, $b = 13.1938(4)$ Å, $c = 13.6292(3)$ Å, $\beta = 96.250(2)^\circ$, $V = 1789.50(9)$ Å³, $Z = 4$, $\mu = 1.907$ mm⁻¹, colourless prism, crystal dimensions = $0.08 \times 0.09 \times 0.23$ mm³. A total of 3694 unique reflections were measured for $5 < \theta < 76$ and 3681 reflections were used in the refinement. The final parameters were $wR_2 = 0.119$ and $R_1 = 0.049$ [$I > 3.0\sigma(I)$]. X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research Laboratory, University of Oxford, U.K.

³ Betteridge, P. W.; Carruthers, J. R.; Cooper, R. I.; Prout, C. K.; Watkin, D. J. *J. Appl. Crystallogr.* **2003**, *36*, 1487.

X-Ray crystal structure data for (1*R*,2*S*)-171
(selected H atoms are omitted for clarity)



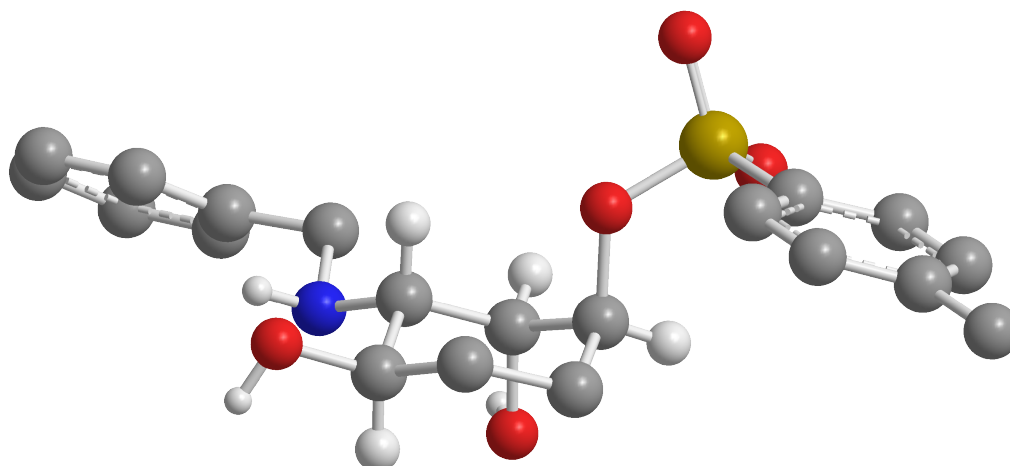
X-ray crystal structure determination for (±)-171

Data were collected using an Oxford Diffraction SuperNova diffractometer with graphite monochromated Cu-K α radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.⁴

X-ray crystal structure data for (±)-**171** [C₂₆H₃₄N₂O₂]: $M = 406.57$, orthorhombic, space group $Fdd2$, $a = 40.6426(12)$ Å, $b = 19.3429(5)$ Å, $c = 5.63427(14)$ Å, $V = 4429.4(2)$ Å³, $Z = 8$, $\mu = 0.60$ mm⁻¹, colourless prism, crystal dimensions = $0.12 \times 0.13 \times 0.24$ mm³. A total of 1854 unique reflections were measured for $4 < \theta < 76$ and 1845 reflections were used in the refinement. The final parameters were $wR_2 = 0.070$ and $R_1 = 0.028$ [$I > 3.0\sigma(I)$]. X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research Laboratory, University of Oxford, U.K.

⁴ Betteridge, P. W.; Carruthers, J. R.; Cooper, R. I.; Prout, C. K.; Watkin, D. J. *J. Appl. Crystallogr.* **2003**, *36*, 1487.

X-Ray crystal structure data for (1*R*,2*S*,3*S*,4*S*)-211
(selected H atoms are omitted for clarity)



X-ray crystal structure determination for 211

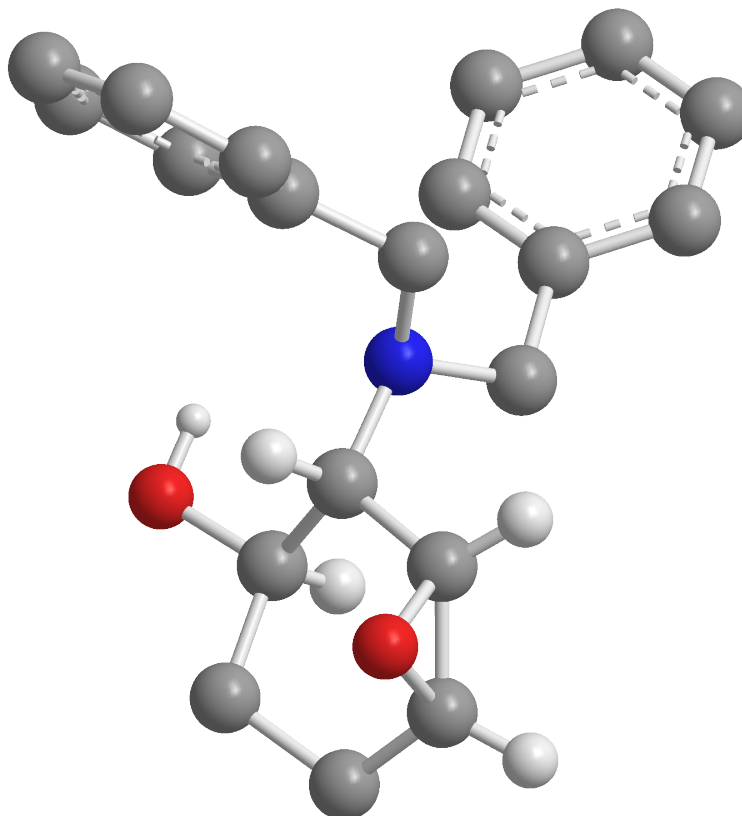
Data were collected using an Oxford Diffraction SuperNova diffractometer with graphite monochromated Cu-K α radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.⁵

X-ray crystal structure data for **211** [C₂₀H₂₅NO₅S]: $M = 391.49$, monoclinic, space group $P 2_1$, $a = 8.82793(16)$ Å, $b = 6.44177(19)$ Å, $c = 16.9810(3)$ Å, $\beta = 100.3978(19)^\circ$, $V = 949.81(4)$ Å³, $Z = 2$, $\mu = 1.785$ mm⁻¹, colourless prism, crystal dimensions = $0.18 \times 0.20 \times 0.39$ mm³. A total of 3636 unique reflections were measured for $5 < \theta < 76$ and 2918 reflections were used in the refinement. The final parameters were $wR_2 = 0.037$ and $R_1 = 0.028$ [$I > -3.0\sigma(I)$], with Flack enantiopole = $0.006(13)$.⁶ X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research Laboratory, University of Oxford, U.K.

⁵ Betteridge, P. W.; Carruthers, J. R.; Cooper, R. I.; Prout, C. K.; Watkin, D. J. *J. Appl. Crystallogr.* **2003**, *36*, 1487.

⁶ Flack, H. D.; Bernardinelli, G. *Acta. Crystallogr., Sect. A* **1999**, *55*, 908.

X-Ray crystal structure data for (1*R*S,2*S*R,3*R*S,4*S*R)-213
(selected H atoms are omitted for clarity)



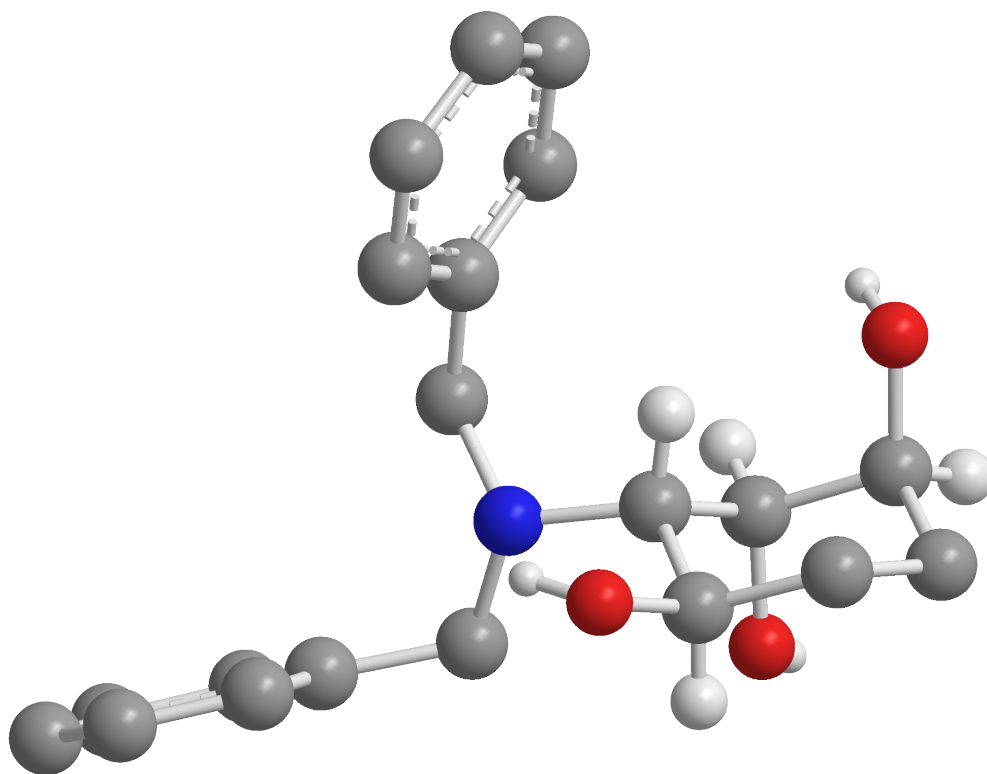
X-ray crystal structure determination for (±)-213

Data were collected using an Oxford Diffraction SuperNova diffractometer with graphite monochromated Cu-K α radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.⁷

X-ray crystal structure data for (±)-**213** [C₂₀H₂₃NO₂]: $M = 309.41$, monoclinic, space group $P 2_1/n$, $a = 12.15903(15)$ Å, $b = 15.50217(17)$ Å, $c = 18.2882(2)$ Å, $\beta = 105.4094(13)^\circ$, $V = 3323.24(7)$ Å³, $Z = 8$, $\mu = 0.624$ mm⁻¹, colourless plate, crystal dimensions = $0.20 \times 0.28 \times 0.31$ mm³. A total of 6894 unique reflections were measured for $4 < \theta < 76$ and 5880 reflections were used in the refinement. The final parameters were $wR_2 = 0.096$ and $R_1 = 0.041$ [$I > 3.0\sigma(I)$]. X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research Laboratory, University of Oxford, U.K.

⁷ Betteridge, P. W.; Carruthers, J. R.; Cooper, R. I.; Prout, C. K.; Watkin, D. J. *J. Appl. Crystallogr.* **2003**, *36*, 1487.

X-Ray crystal structure data for (1*R*,2*S*,3*S*,4*S*)-214
(selected H atoms are omitted for clarity)



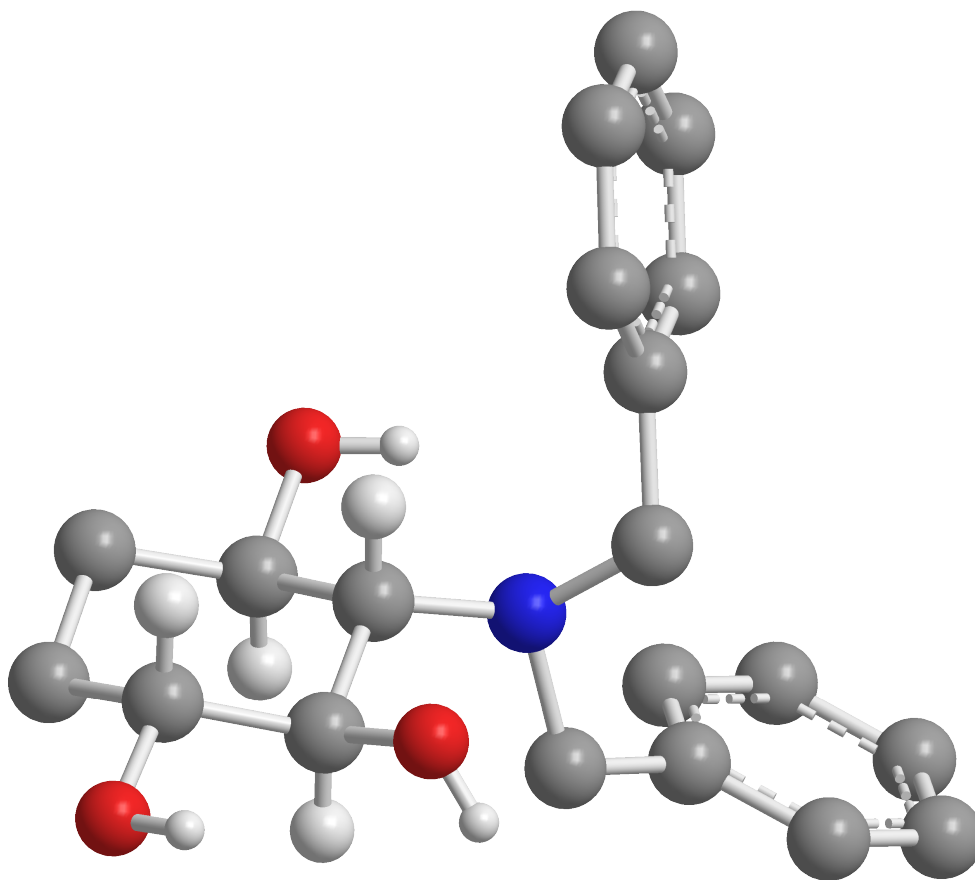
X-ray crystal structure determination for (±)-214

Data were collected using an Oxford Diffraction SuperNova diffractometer with graphite monochromated Cu-K α radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.⁸

X-ray crystal structure data for (±)-**214** [C₂₀H₂₅NO₃]: $M = 327.42$, orthorhombic, space group Pbc_a , $a = 9.96410(10)$ Å, $b = 12.9568(2)$ Å, $c = 28.1750(4)$ Å, $V = 3637.47(8)$ Å³, $Z = 8$, $\mu = 0.08$ mm⁻¹, colourless block, crystal dimensions = $0.25 \times 0.28 \times 0.33$ mm³. A total of 4089 unique reflections were measured for $5 < \theta < 27$ and 4089 reflections were used in the refinement. The final parameters were $wR_2 = 0.097$ and $R_1 = 0.086$ [$I > -3.0\sigma(I)$]. X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research Laboratory, University of Oxford, U.K.

⁸ Betteridge, P. W.; Carruthers, J. R.; Cooper, R. I.; Prout, C. K.; Watkin, D. J. *J. Appl. Crystallogr.* **2003**, *36*, 1487.

X-Ray crystal structure data for (1*R*,2*S*,3*R*,4*R*)-215
(selected H atoms are omitted for clarity)



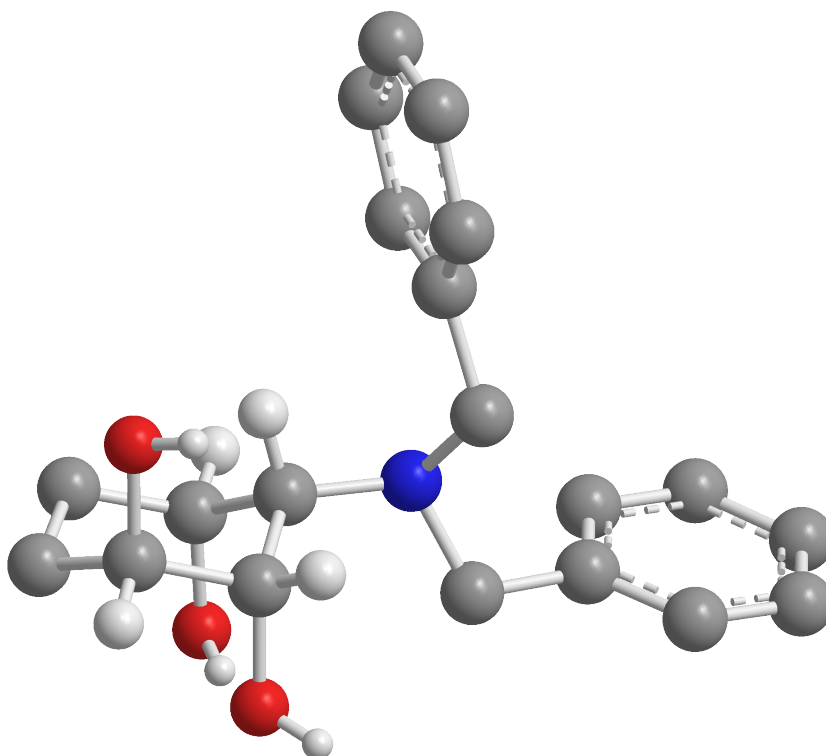
X-ray crystal structure determination for (±)-215

Data were collected using an Oxford Diffraction SuperNova diffractometer with graphite monochromated Cu-K α radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.⁹

X-ray crystal structure data for (±)-**215** [C_{20.5}H₂₇NO_{3.25}]: $M = 339.44$, triclinic, space group $P\bar{1}$, $a = 6.6205(2)$ Å, $b = 10.4767(4)$ Å, $c = 14.0976(5)$ Å, $\alpha = 101.639(3)^\circ$, $\beta = 97.784(3)^\circ$, $\gamma = 95.427(3)^\circ$, $V = 941.38(6)$ Å³, $Z = 2$, $\mu = 0.642$ mm⁻¹, colourless block, crystal dimensions = $0.04 \times 0.09 \times 0.20$ mm³. A total of 3910 unique reflections were measured for $4 < \theta < 76$ and 3523 reflections were used in the refinement. The final parameters were $wR_2 = 0.239$ and $R_1 = 0.091$ [$I > 3.0\sigma(I)$]. X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research Laboratory, University of Oxford, U.K.

⁹ Betteridge, P. W.; Carruthers, J. R.; Cooper, R. I.; Prout, C. K.; Watkin, D. J. *J. Appl. Crystallogr.* **2003**, *36*, 1487.

X-Ray crystal structure data for (1*R*,2*R*,3*R*,4*R*)-222
(selected H atoms are omitted for clarity)



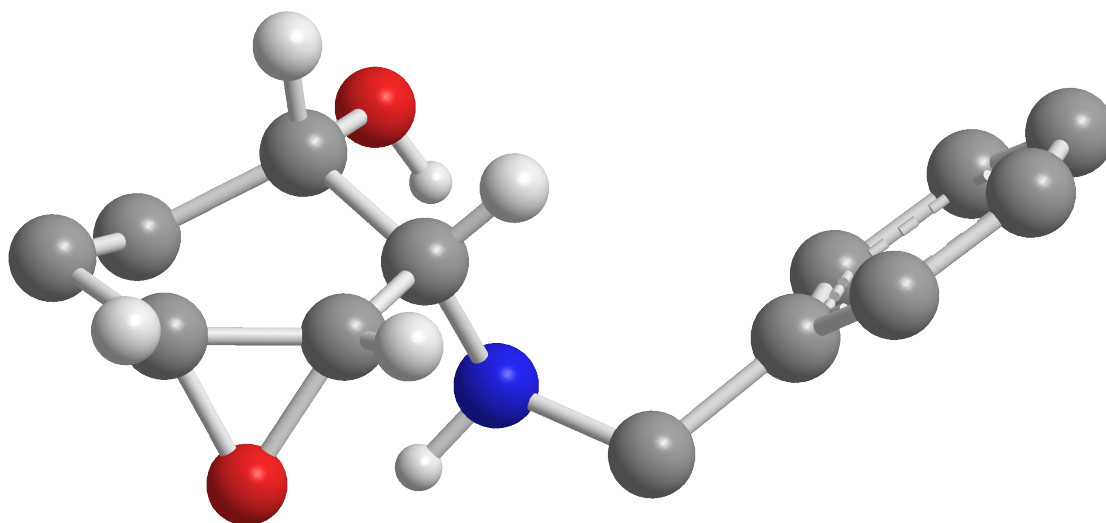
X-ray crystal structure determination for (±)-222

Data were collected using an Oxford Diffraction SuperNova diffractometer with graphite monochromated Cu-K α radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.¹⁰

X-ray crystal structure data for (±)-**22** [C₂₀H₂₅NO₃]: $M = 327.42$, monoclinic, space group $P 2_1$, $a = 0.6116(15)$ Å, $b = 0.250(2)$ Å, $c = 97.101(18)$ Å, $\beta = 92.7666(13)^\circ$, $V = 1723.28(5)$ Å³, $Z = 4$, $\mu = 0.673$ mm⁻¹, colourless block, crystal dimensions = $0.21 \times 0.22 \times 0.24$ mm³. A total of 6954 unique reflections were measured for $4 < \theta < 26$ and 6926 reflections were used in the refinement. The final parameters were $wR_2 = 0.098$ and $R_1 = 0.037$ [$I > -3.0\sigma(I)$]. X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research Laboratory, University of Oxford, U.K.

¹⁰ Betteridge, P. W.; Carruthers, J. R.; Cooper, R. I.; Prout, C. K.; Watkin, D. J. *J. Appl. Crystallogr.* **2003**, *36*, 1487.

**X-Ray crystal structure data for (1*RS*,2*RS*,3*RS*,4*SR*)-224
(selected H atoms are omitted for clarity)**



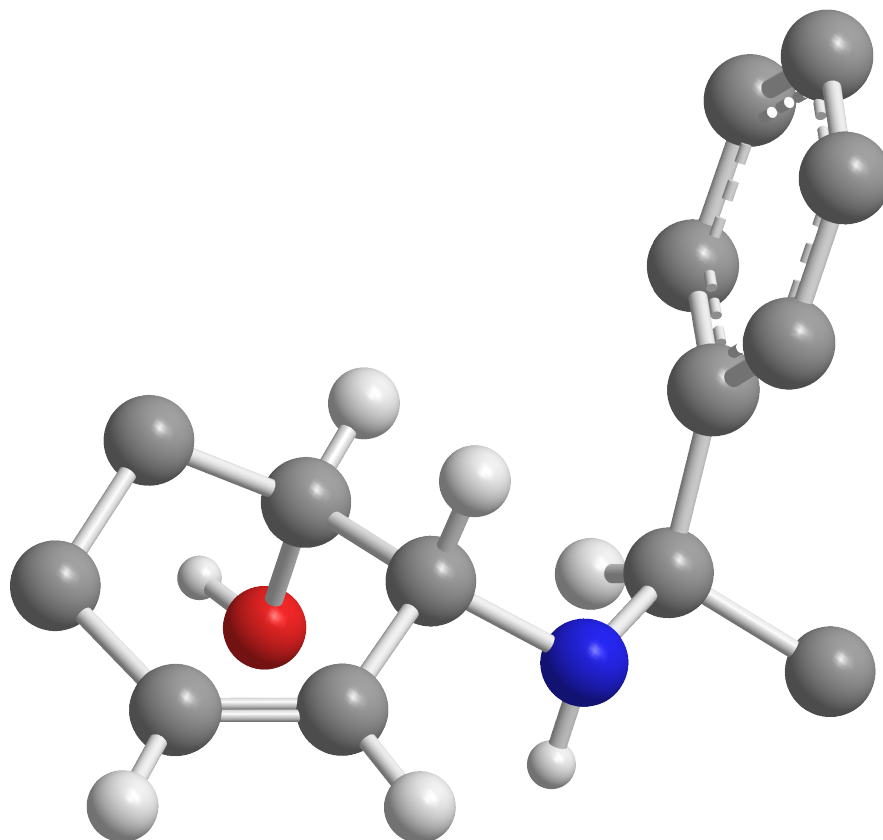
X-ray crystal structure determination for (±)-224

Data were collected using an Oxford Diffraction SuperNova diffractometer with graphite monochromated Cu-K α radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.¹¹

X-ray crystal structure data for (±)-**224** [C₁₃H₁₇NO₂]: $M = 219.28$, monoclinic, $P 2_1$, $a = 11.2423(4) \text{ \AA}$, $b = 10.2470(3) \text{ \AA}$, $c = 10.5891(3) \text{ \AA}$, $\beta = 112.855(4)^\circ$, $V = 1124.11(7) \text{ \AA}^3$, $Z = 4$, $\mu = 0.698 \text{ mm}^{-1}$, colourless plate, crystal dimensions = $0.090 \times 0.210 \times 0.230 \text{ mm}^3$. A total of 2322 unique reflections were measured for $4 < \theta < 76$ and 2162 reflections were used in the refinement. The final parameters were $wR_2 = 0.0989$ and $R_1 = 0.0398$ [$I > -3.0\sigma(I)$]. X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research Laboratory, University of Oxford, U.K.

¹¹ Betteridge, P. W.; Carruthers, J. R.; Cooper, R. I.; Prout, C. K.; Watkin, D. J. *J. Appl. Crystallogr.* **2003**, *36*, 1487.

X-Ray crystal structure data for (1*S*,2*R*, α *R*)-227
(selected H atoms are omitted for clarity)



X-ray crystal structure determination for 227

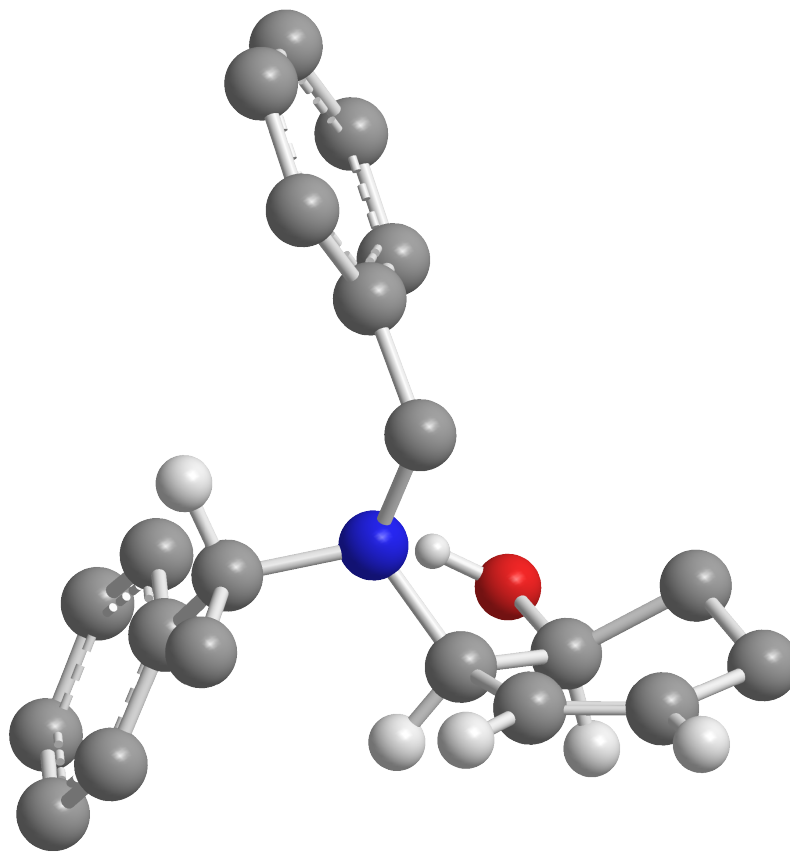
Data were collected using an Oxford Diffraction SuperNova diffractometer with graphite monochromated Cu-K α radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.¹²

X-ray crystal structure data for **227** [C₁₄H₁₉NO]: $M = 217.31$, monoclinic, space group $P 2_1$, $a = 5.71465(9)$ Å, $b = 11.1475(2)$ Å, $c = 9.5801(2)$ Å, $\beta = 106.5209(17)^\circ$, $V = 585.096(18)$ Å³, $Z = 2$, $\mu = 0.598$ mm⁻¹, colourless block, crystal dimensions = $0.12 \times 0.15 \times 0.18$ mm³. A total of 2435 unique reflections were measured for $4 < \theta < 76$ and 2052 reflections were used in the refinement. The final parameters were $wR_2 = 0.066$ and $R_1 = 0.027$ [$I > -3.0\sigma(I)$], with Flack enantiopole = $+0.1(2)$.¹³ X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research Laboratory, University of Oxford, U.K.

¹² Betteridge, P. W.; Carruthers, J. R.; Cooper, R. I.; Prout, C. K.; Watkin, D. J. *J. Appl. Crystallogr.* **2003**, *36*, 1487.

¹³ Flack, H. D.; Bernardinelli, G. *Acta. Crystallogr., Sect. A* **1999**, *55*, 908.

X-Ray crystal structure data for (1*S*,2*R*, α *R*)-229
(selected H atoms are omitted for clarity)



X-ray crystal structure determination for 229

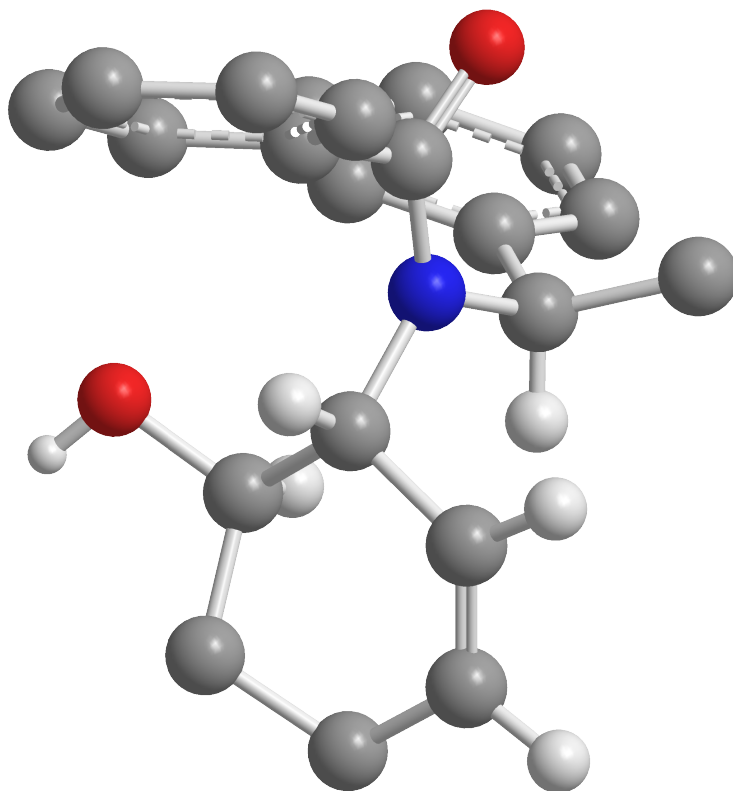
Data were collected using an Oxford Diffraction SuperNova diffractometer with graphite monochromated Cu-K α radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.¹⁴

X-ray crystal structure data for **229** [C₂₁H₂₅NO]: $M = 307.44$, orthorhombic, space group $P 2_1 2_1 2_1$, $a = 7.6974(3)$ Å, $b = 8.3857(4)$ Å, $c = 27.1665(15)$ Å, $V = 1753.57(15)$ Å³, $Z = 4$, $\mu = 0.543$ mm⁻¹, colourless plate, crystal dimensions = $0.11 \times 0.23 \times 0.25$ mm³. A total of 3577 unique reflections were measured for $5 < \theta < 76$ and 2708 reflections were used in the refinement. The final parameters were $wR_2 = 0.122$ and $R_1 = 0.049$ [$I > -3.0\sigma(I)$], with Flack enantiopole = $+0.6$ (5).¹⁵ X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research Laboratory, University of Oxford, U.K.

¹⁴ Betteridge, P. W.; Carruthers, J. R.; Cooper, R. I.; Prout, C. K.; Watkin, D. J. *J. Appl. Crystallogr.* **2003**, *36*, 1487.

¹⁵ Flack, H. D.; Bernardinelli, G. *Acta Crystallogr., Sect. A* **1999**, *55*, 908.

X-Ray crystal structure data for (1*R*,2*R*,*aR*)-233
(selected H atoms are omitted for clarity)



X-ray crystal structure determination for 233

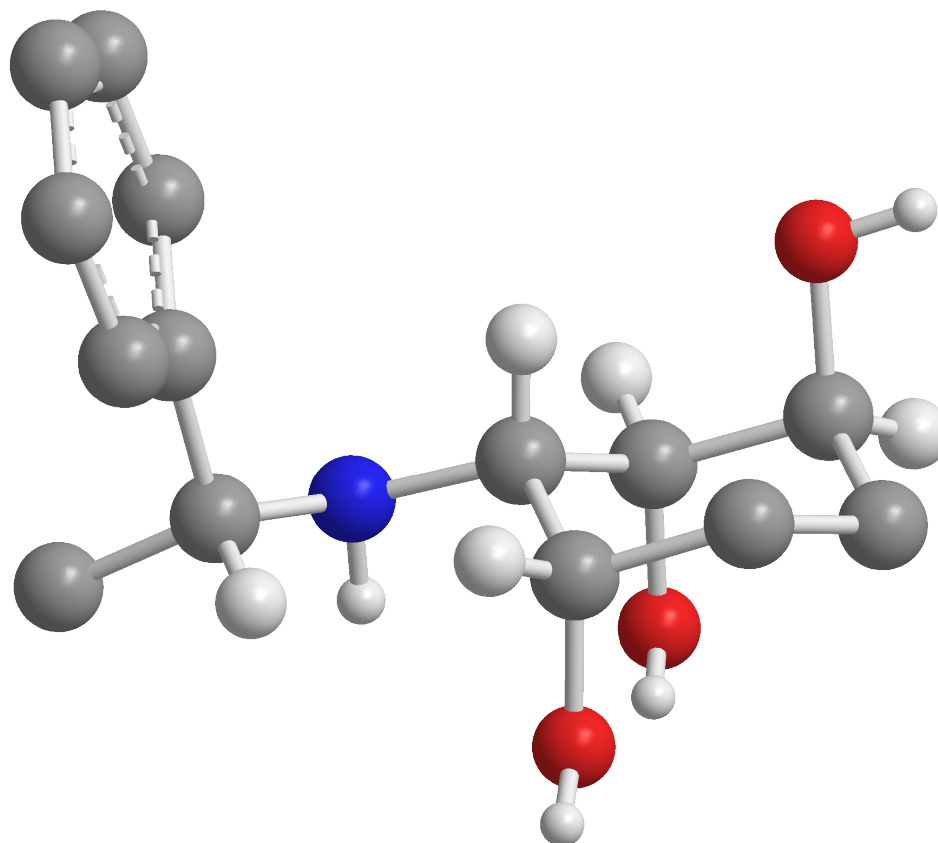
Data were collected using a Nonius κ -CCD diffractometer with graphite monochromated Mo-K α radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.¹⁶

X-ray crystal structure data for **233** [C₂₁H₂₃NO₂]: $M = 642.84$, orthorhombic, space group $P 2_1 2_1 2_1$, $a = 11.3080(3)$ Å, $b = 17.0538(5)$ Å, $c = 18.0369(5)$ Å, $V = 3478.31(17)$ Å³, $Z = 8$, $\mu = 0.078$ mm⁻¹, colourless block, crystal dimensions = $0.20 \times 0.23 \times 0.28$ mm³. A total of 4265 unique reflections were measured for $5 < \theta < 27$ and 4265 reflections were used in the refinement. The final parameters were $wR_2 = 0.106$ and $R_1 = 0.084$ [$I > 3.0\sigma(I)$], with Flack enantiopole = $-0.5(15)$.¹⁷ X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research Laboratory, University of Oxford, U.K.

¹⁶ Betteridge, P. W.; Carruthers, J. R.; Cooper, R. I.; Prout, C. K.; Watkin, D. J. *J. Appl. Crystallogr.* **2003**, *36*, 1487.

¹⁷ Flack, H. D.; Bernardinelli, G. *Acta Crystallogr., Sect. A* **1999**, *55*, 908.

X-Ray crystal structure data for (1*S*,2*S*,3*S*,4*S*, α *R*)-240
(selected H atoms are omitted for clarity)



X-ray crystal structure determination for 240

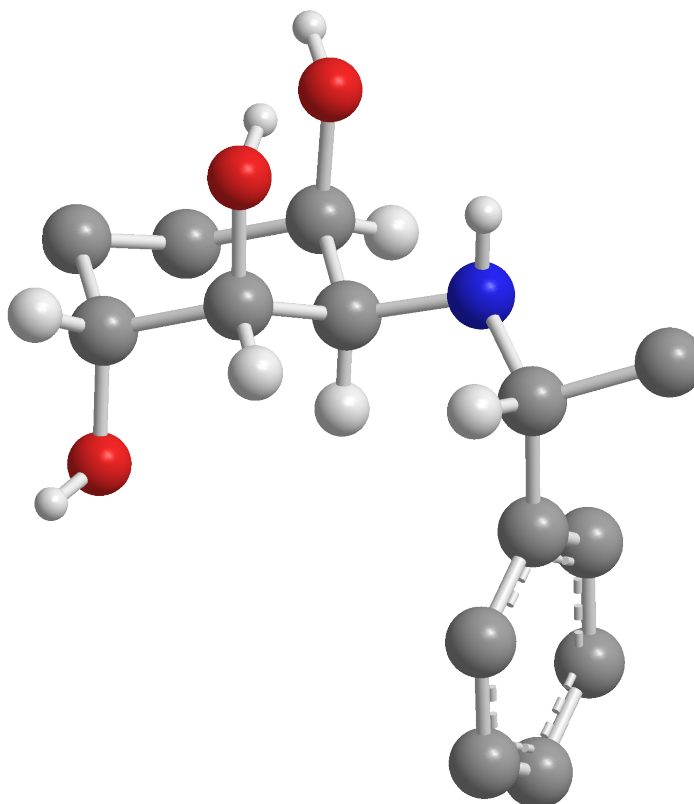
Data were collected using an Oxford Diffraction SuperNova diffractometer with graphite monochromated Cu-K α radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.¹⁸

X-ray crystal structure data for **240** [C₁₄H₂₁NO₃]: $M = 251.33$, orthorhombic, space group $P 2_1 2_1 2_1$, $a = 6.20379(19)$ Å, $b = 10.1090(4)$ Å, $c = 21.0273(7)$ Å, $V = 1318.71(8)$ Å³, $Z = 4$, $\mu = 0.715$ mm⁻¹, colourless prism, crystal dimensions = $0.030 \times 0.040 \times 0.180$ mm³. A total of 2736 unique reflections were measured for $4 < \theta < 76$ and 2064 reflections were used in the refinement. The final parameters were $wR_2 = 0.0726$ and $R_1 = 0.0310$ [$I > 3.0\sigma(I)$], with Flack enantiopole = $-0.1(2)$.¹⁹ X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research Laboratory, University of Oxford, U.K.

¹⁸ Betteridge, P. W.; Carruthers, J. R.; Cooper, R. I.; Prout, C. K.; Watkin, D. J. *J. Appl. Crystallogr.* **2003**, *36*, 1487.

¹⁹ Flack, H. D.; Bernardinelli, G. *Acta. Crystallogr., Sect. A* **1999**, *55*, 908.

X-Ray crystal structure data for (1*R*,2*R*,3*R*,4*R*, α *R*)-242
(selected H atoms are omitted for clarity)



X-ray crystal structure determination for 242

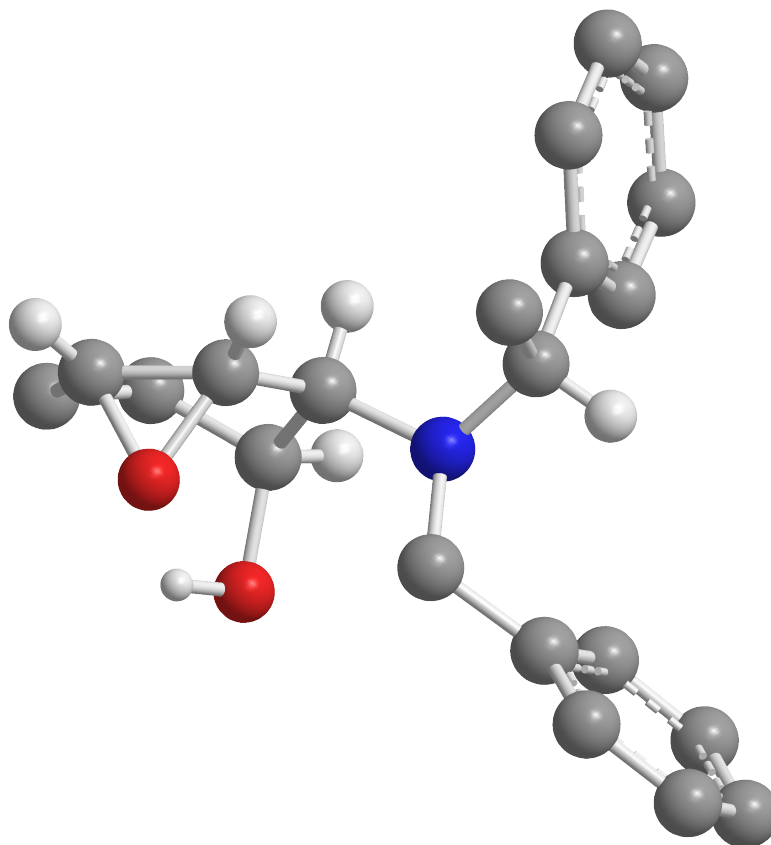
Data were collected using an Oxford Diffraction SuperNova diffractometer with graphite monochromated Cu-K α radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.²⁰

X-ray crystal structure data for **242** [C₁₄H₂₁NO₃]: $M = 251.33$, orthorhombic, space group $P 2_1 2_1 2_1$, $a = 6.4569(3)$ Å, $b = 8.3507(3)$ Å, $c = 25.6234(10)$ Å, $V = 1381.60(9)$ Å³, $Z = 4$, $\mu = 0.683$ mm⁻¹, colourless prism, crystal dimensions = $0.150 \times 0.150 \times 0.180$ mm³. A total of 2092 unique reflections were measured for $6 < \theta < 76$ and 2092 reflections were used in the refinement. The final parameters were $wR_2 = 0.070$ and $R_1 = 0.029$ [$I > -3.0\sigma(I)$], with Flack enantiopole = $-0.14(19)$.²¹ X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research Laboratory, University of Oxford, U.K.

²⁰ Betteridge, P. W.; Carruthers, J. R.; Cooper, R. I.; Prout, C. K.; Watkin, D. J. *J. Appl. Crystallogr.* **2003**, *36*, 1487.

²¹ Flack, H. D.; Bernardinelli, G. *Acta Crystallogr., Sect. A* **1999**, *55*, 908.

X-Ray crystal structure data for (1*S*,2*S*,3*S*,4*R*,*αR*)-245**
(selected H atoms are omitted for clarity)



X-ray crystal structure determination for 245

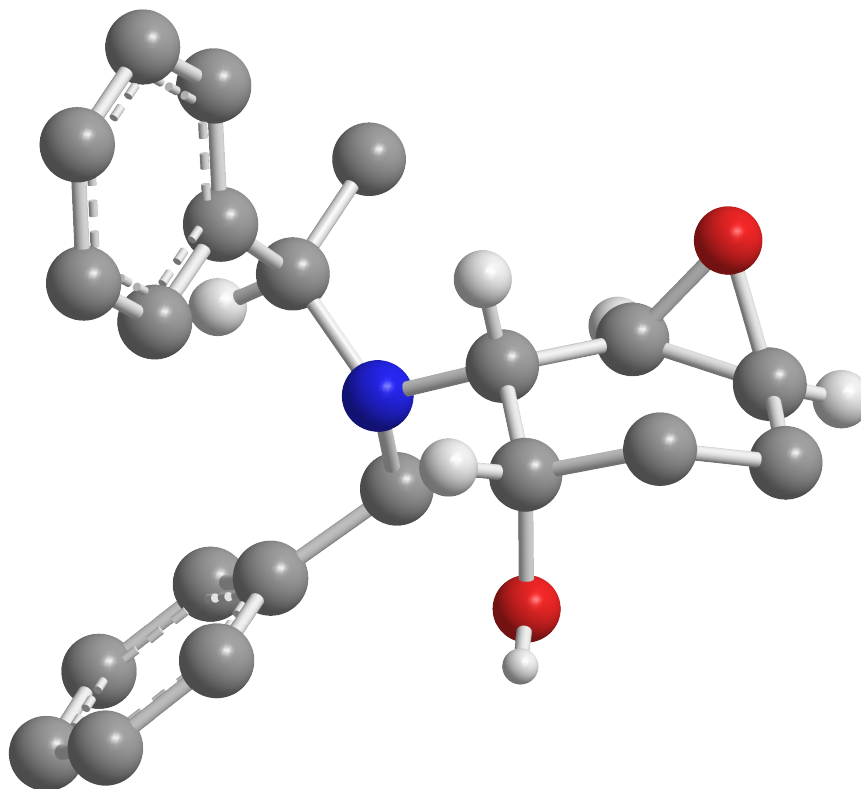
Data were collected using an Oxford Diffraction SuperNova diffractometer with graphite monochromated Cu-K α radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.²²

X-ray crystal structure data for **245** [C₂₁H₂₅NO₂]: $M = 323.43$, orthorhombic, space group $P 2_1 2_1 2_1$, $a = 7.5945(5)$ Å, $b = 14.1084(8)$ Å, $c = 16.4675(7)$ Å, $V = 1764.44(17)$ Å³, $Z = 4$, $\mu = 0.609$ mm⁻¹, colourless prism, crystal dimensions = $0.18 \times 0.20 \times 0.27$ mm³. A total of 3658 unique reflections were measured for $4 < \theta < 76$ and 3096 reflections were used in the refinement. The final parameters were $wR_2 = 0.202$ and $R_1 = 0.076$ [$I > -3.0\sigma(I)$], with Flack enantiopole = $0.0(6)$.²³ X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research Laboratory, University of Oxford, U.K.

²² Betteridge, P. W.; Carruthers, J. R.; Cooper, R. I.; Prout, C. K.; Watkin, D. J. *J. Appl. Crystallogr.* **2003**, *36*, 1487.

²³ Flack, H. D.; Bernardinelli, G. *Acta Crystallogr., Sect. A* **1999**, *55*, 908.

X-Ray crystal structure data for (1*S*,2*S*,3*R*,4*S*,*aR*)-246
(selected H atoms are omitted for clarity)



X-ray crystal structure determination for 246

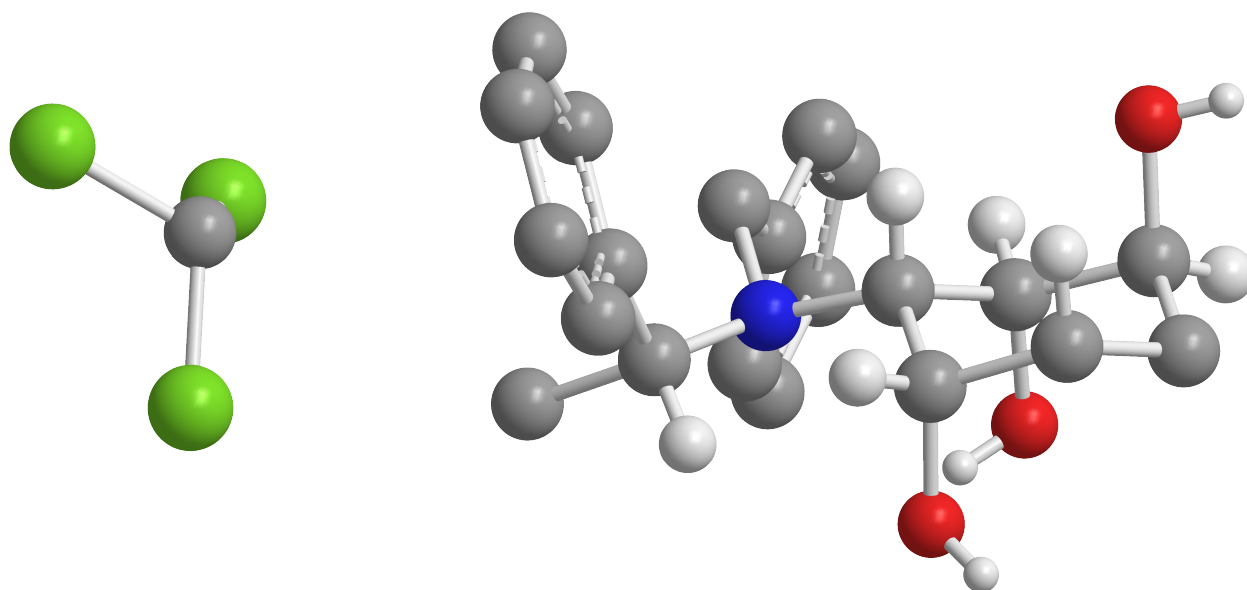
Data were collected using an Oxford Diffraction SuperNova diffractometer with graphite monochromated Cu-K α radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.²⁴

X-ray crystal structure data for **246** [C₂₁H₂₅NO₂]: $M = 323.43$, orthorhombic, space group $P 2_1 2_1 2_1$, $a = 6.6688(1)$ Å, $b = 10.2067(2)$ Å, $c = 26.0010(5)$ Å, $V = 1769.81(5)$ Å³, $Z = 4$, $\mu = 0.607$ mm⁻¹, colourless block, crystal dimensions = $0.11 \times 0.16 \times 0.16$ mm³. A total of 3543 unique reflections were measured for $3 < \theta < 76$ and 3222 reflections were used in the refinement. The final parameters were $wR_2 = 0.102$ and $R_1 = 0.041$ [$I > 3.0\sigma(I)$], with Flack enantiopole = $-0.2(3)$.²⁵ X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research Laboratory, University of Oxford, U.K.

²⁴ Betteridge, P. W.; Carruthers, J. R.; Cooper, R. I.; Prout, C. K.; Watkin, D. J. *J. Appl. Crystallogr.* **2003**, *36*, 1487.

²⁵ Flack, H. D.; Bernardinelli, G. *Acta. Crystallogr., Sect. A* **1999**, *55*, 908.

X-Ray crystal structure data for (1*S*,2*S*,3*S*,4*S*, α *R*)-247
(selected H atoms are omitted for clarity)



X-ray crystal structure determination for 247

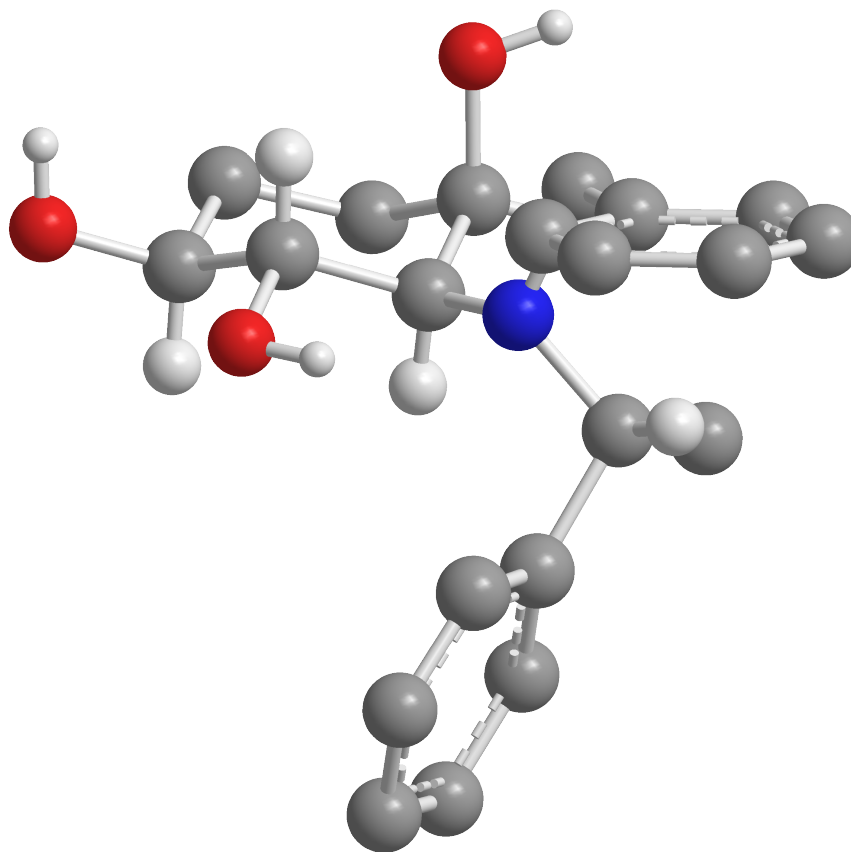
Data were collected using an Oxford Diffraction SuperNova diffractometer with graphite monochromated Cu-K α radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.²⁶

X-ray crystal structure data for **247** [C₂₂H₂₈Cl₃NO₃]: $M = 460.83$, monoclinic, space group $P 2_1$, $a = 6.1718(12)$ Å, $b = 8.9442(8)$ Å, $c = 19.711(2)$ Å, $\beta = 91.810(15)^\circ$, $V = 1087.6(3)$ Å³, $Z = 2$, $\mu = 4.009$ mm⁻¹, colourless plate, crystal dimensions = $0.05 \times 0.10 \times 0.16$ mm³. A total of 2097 unique reflections were measured for $2 < \theta < 76$ and 2020 reflections were used in the refinement. The final parameters were $wR_2 = 0.125$ and $R_1 = 0.051$ [$I > 3.0\sigma(I)$], with Flack enantiopole = $+0.08(3)$.²⁷ X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research Laboratory, University of Oxford, U.K.

²⁶ Betteridge, P. W.; Carruthers, J. R.; Cooper, R. I.; Prout, C. K.; Watkin, D. J. *J. Appl. Crystallogr.* **2003**, *36*, 1487.

²⁷ Flack, H. D.; Bernardinelli, G. *Acta. Crystallogr., Sect. A* **1999**, *55*, 908.

X-Ray crystal structure data for (1R,2R,3S,4S, α R)-252
(selected H atoms are omitted for clarity)



X-ray crystal structure determination for 252

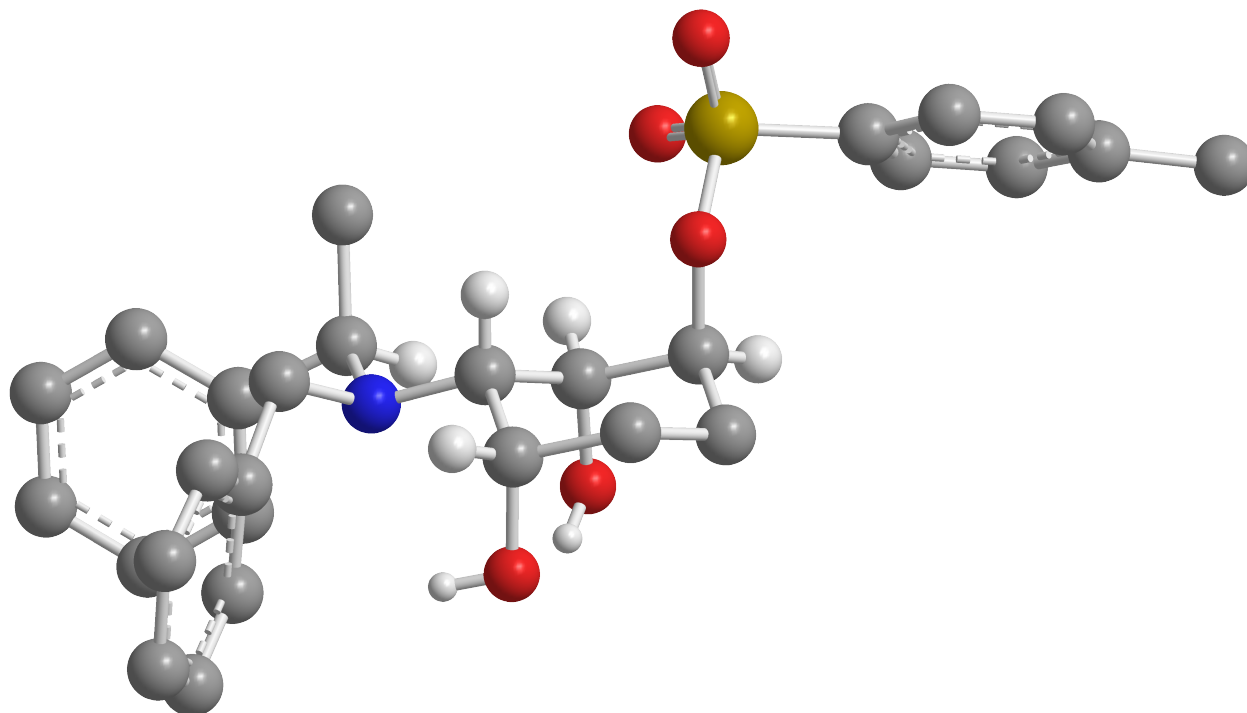
Data were collected using an Oxford Diffraction SuperNova diffractometer with graphite monochromated Cu-K α radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.²⁸

X-ray crystal structure data for **252** [C₂₁H₂₇NO₃]: $M = 341.45$, orthorhombic, space group $P 2_1 2_1 2_1$, $a = 7.15836(7)$ Å, $b = 10.6959(1)$ Å, $c = 24.2138(2)$ Å, $V = 1853.93(3)$ Å³, $Z = 4$, $\mu = 0.645$ mm⁻¹, colourless block, crystal dimensions = $0.18 \times 0.20 \times 0.21$ mm³. A total of 3873 unique reflections were measured for $4 < \theta < 76$ and 3596 reflections were used in the refinement. The final parameters were $wR_2 = 0.079$ and $R_1 = 0.031$ [$I > -3.0\sigma(I)$], with Flack enantiopole = $-0.03(15)$.²⁹ X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research Laboratory, University of Oxford, U.K.

²⁸ Betteridge, P. W.; Carruthers, J. R.; Cooper, R. I.; Prout, C. K.; Watkin, D. J. *J. Appl. Crystallogr.* **2003**, *36*, 1487.

²⁹ Flack, H. D.; Bernardinelli, G. *Acta. Crystallogr., Sect. A* **1999**, *55*, 908.

X-Ray crystal structure data for (1*S*,2*S*,3*S*,4*S*, α *R*)-253
(selected H atoms are omitted for clarity)



X-ray crystal structure determination for 253

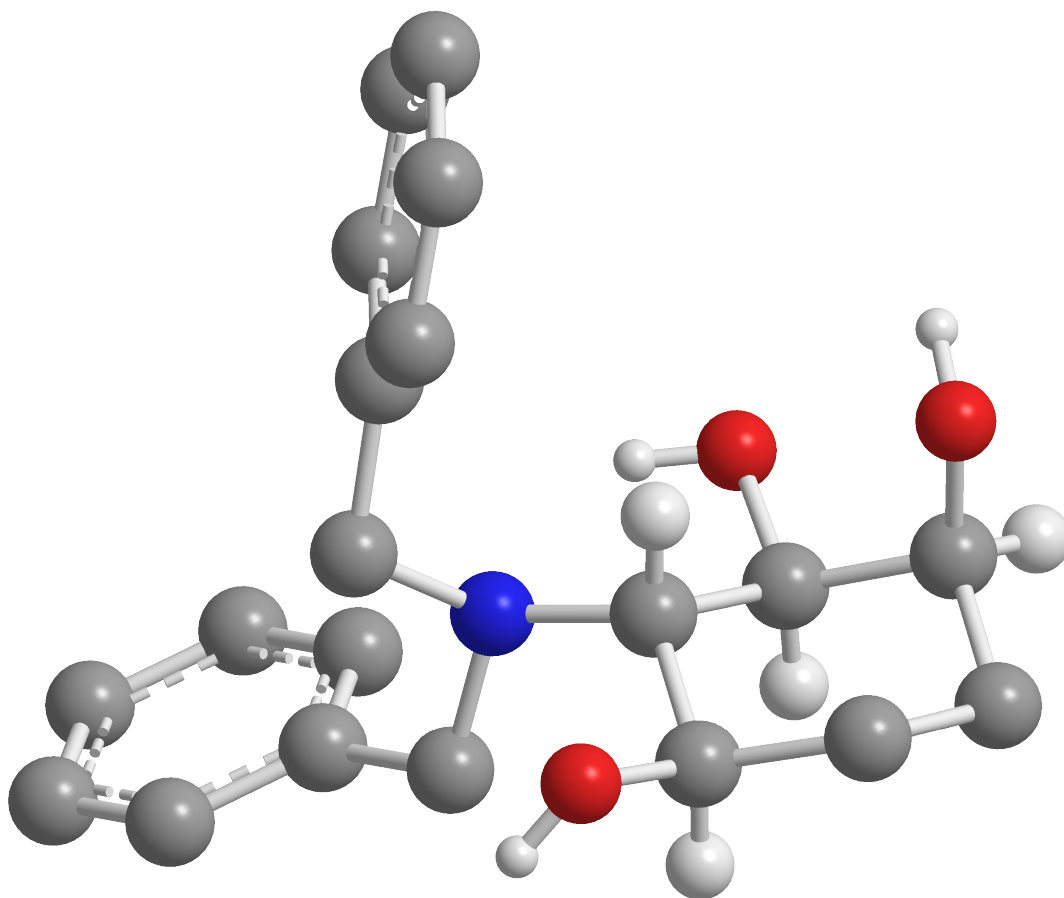
Data were collected using an Oxford Diffraction SuperNova diffractometer with graphite monochromated Cu-K α radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.³⁰

X-ray crystal structure data for **253** [C₂₈H₃₃NO₅S]: $M = 495.64$, orthorhombic, space group $P 2_1 2_1 2_1$, $a = 6.09911(9)$ Å, $b = 19.8667(3)$ Å, $c = 20.5517(3)$ Å, $V = 2490.23(6)$ Å³, $Z = 4$, $\mu = 1.478$ mm⁻¹, colourless block, crystal dimensions = $0.23 \times 0.25 \times 0.28$ mm³. A total of 5027 unique reflections were measured for $3 < \theta < 76$ and 4614 reflections were used in the refinement. The final parameters were $wR_2 = 0.109$ and $R_1 = 0.039$ [$I > 3.0\sigma(I)$], with Flack enantiopole = $-0.010(17)$.³¹ X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research Laboratory, University of Oxford, U.K.

³⁰ Betteridge, P. W.; Carruthers, J. R.; Cooper, R. I.; Prout, C. K.; Watkin, D. J. *J. Appl. Crystallogr.* **2003**, *36*, 1487.

³¹ Flack, H. D.; Bernardinelli, G. *Acta. Crystallogr., Sect. A* **1999**, *55*, 908.

X-Ray crystal structure data for (1*R*,2*S*,3*R*,4*S*)-272
(selected H atoms are omitted for clarity)



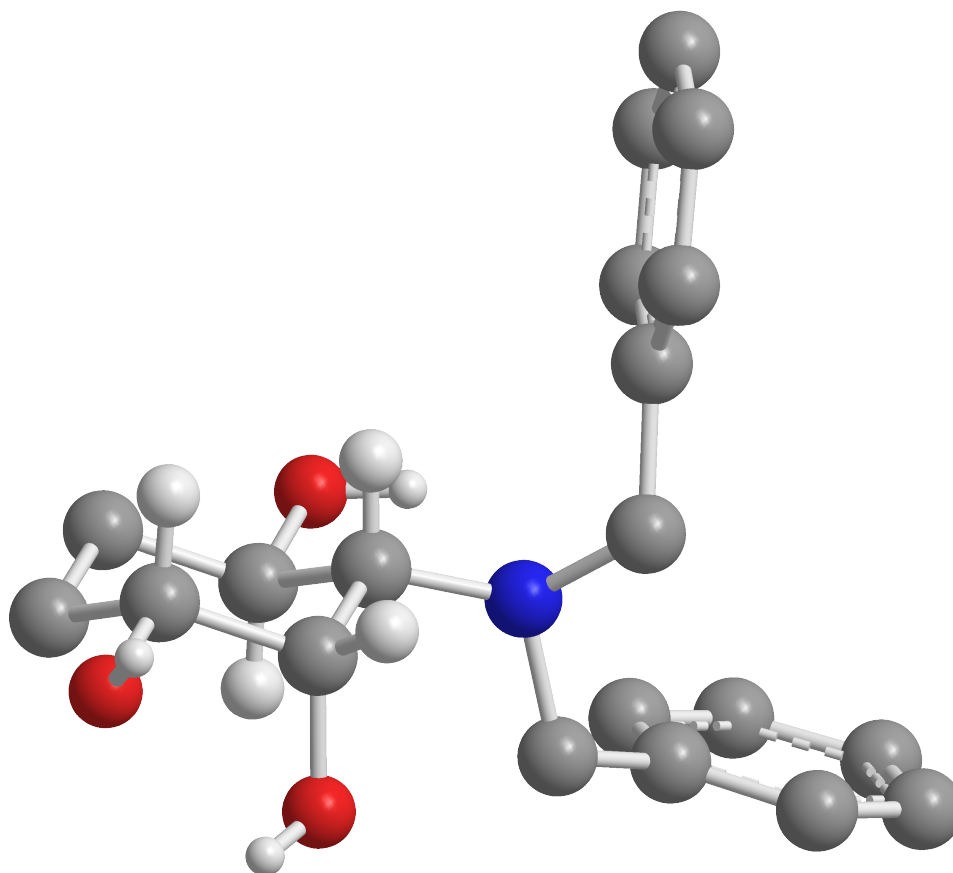
X-ray crystal structure determination for (±)-272

Data were collected using an Oxford Diffraction SuperNova diffractometer with graphite monochromated Cu-K α radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.³²

X-ray crystal structure data for (±)-272 [C₂₀H₂₅NO₃]: $M = 327.42$, monoclinic, space group $P 2_1/c$, $a = 6.5187(3)$ Å, $b = 17.2601(9)$ Å, $c = 15.8164(7)$ Å, $\beta = 90.188(5)^\circ$, $V = 1779.54(15)$ Å³, $Z = 4$, $\mu = 0.652$ mm⁻¹, colourless prism, crystal dimensions = $0.09 \times 0.11 \times 0.19$ mm³. A total of 3200 unique reflections were measured for $4 < \theta < 76$ and 2666 reflections were used in the refinement. The final parameters were $wR_2 = 0.164$ and $R_1 = 0.074$ [$I > -3.0\sigma(I)$]. X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research Laboratory, University of Oxford, U.K.

³² Betteridge, P. W.; Carruthers, J. R.; Cooper, R. I.; Prout, C. K.; Watkin, D. J. *J. Appl. Crystallogr.* **2003**, *36*, 1487.

X-Ray crystal structure data for (1*R*,2*S*,3*S*,4*R*)-275
(selected H atoms are omitted for clarity)



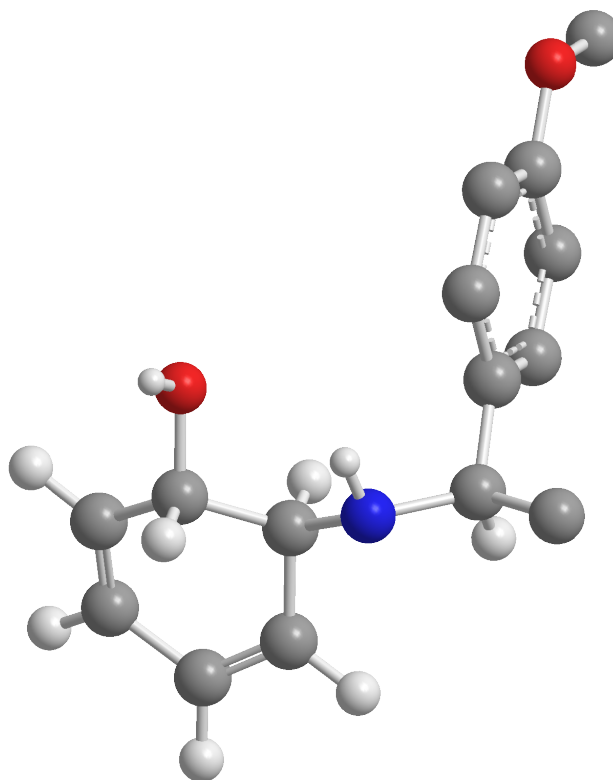
X-ray crystal structure determination for (±)-275

Data were collected using an Oxford Diffraction SuperNova diffractometer with graphite monochromated Cu-K α radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.³³

X-ray crystal structure data for (±)-275 [C₂₀H₂₅NO₃]: $M = 327.42$, triclinic, space group $P-1$, $a = 7.5839(5)$ Å, $b = 7.6020(4)$ Å, $c = 15.6554(8)$ Å, $\alpha = 83.773(4)^\circ$, $\beta = 85.989(5)^\circ$, $\gamma = 76.144(5)^\circ$, $V = 870.24(9)$ Å³, $Z = 2$, $\mu = 0.666$ mm⁻¹, colourless block, crystal dimensions = $0.20 \times 0.22 \times 0.23$ mm³. A total of 3581 unique reflections were measured for $3 < \theta < 76$ and 3355 reflections were used in the refinement. The final parameters were $wR_2 = 0.130$ and $R_1 = 0.051$ [$I > -3.0\sigma(I)$]. X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research Laboratory, University of Oxford, U.K.

³³ Betteridge, P. W.; Carruthers, J. R.; Cooper, R. I.; Prout, C. K.; Watkin, D. J. *J. Appl. Crystallogr.* **2003**, *36*, 1487.

X-Ray crystal structure data for (1*S*,2*S*,*aR*)-343
(selected H atoms are omitted for clarity)



X-ray crystal structure determination for 343

Data were collected using an Oxford Diffraction SuperNova diffractometer with graphite monochromated Cu-K α radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.³⁴

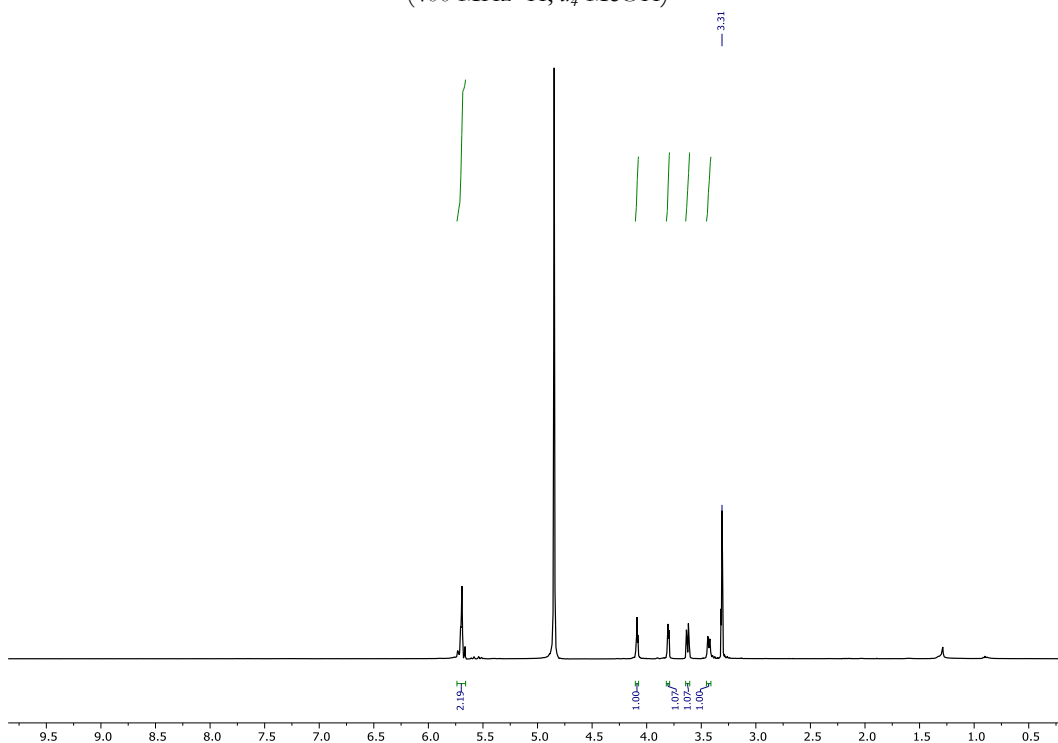
X-ray crystal structure data for **343** [C₁₅H₁₉NO₂]: $M = 245.32$, triclinic, space group $P\ 2_1\ 2_1\ 2_1$, $a = 6.9738(2)$ Å, $b = 9.2494(3)$ Å, $c = 21.0600(6)$ Å, $V = 1358(7)$ Å³, $Z = 4$, $\mu = 0.631$ mm⁻¹, colourless prism, crystal dimensions = $0.120 \times 0.150 \times 0.230$ mm³. A total of 2800 unique reflections were measured for $4 < \theta < 76$ and 2601 reflections were used in the refinement. The final parameters were $wR_2 = 0.0905$ and $R_1 = 0.094$ [$I > 3.0\sigma(I)$], with Flack enantiopole = $-0.2(2)$.³⁵ X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research Laboratory, University of Oxford, U.K.

³⁴ Betteridge, P. W.; Carruthers, J. R.; Cooper, R. I.; Prout, C. K.; Watkin, D. J. *J. Appl. Crystallogr.* **2003**, *36*, 1487.

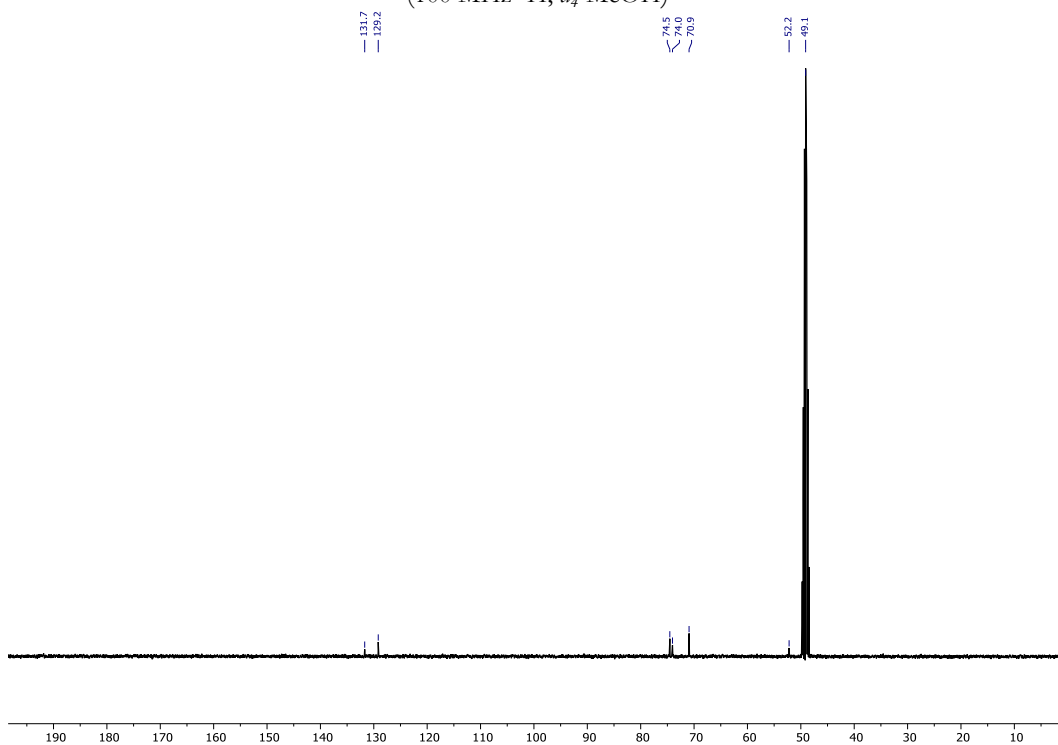
³⁵ Flack, H. D.; Bernardinelli, G. *Acta. Crystallogr., Sect. A* **1999**, *55*, 908.

Appendix 2: NMR data

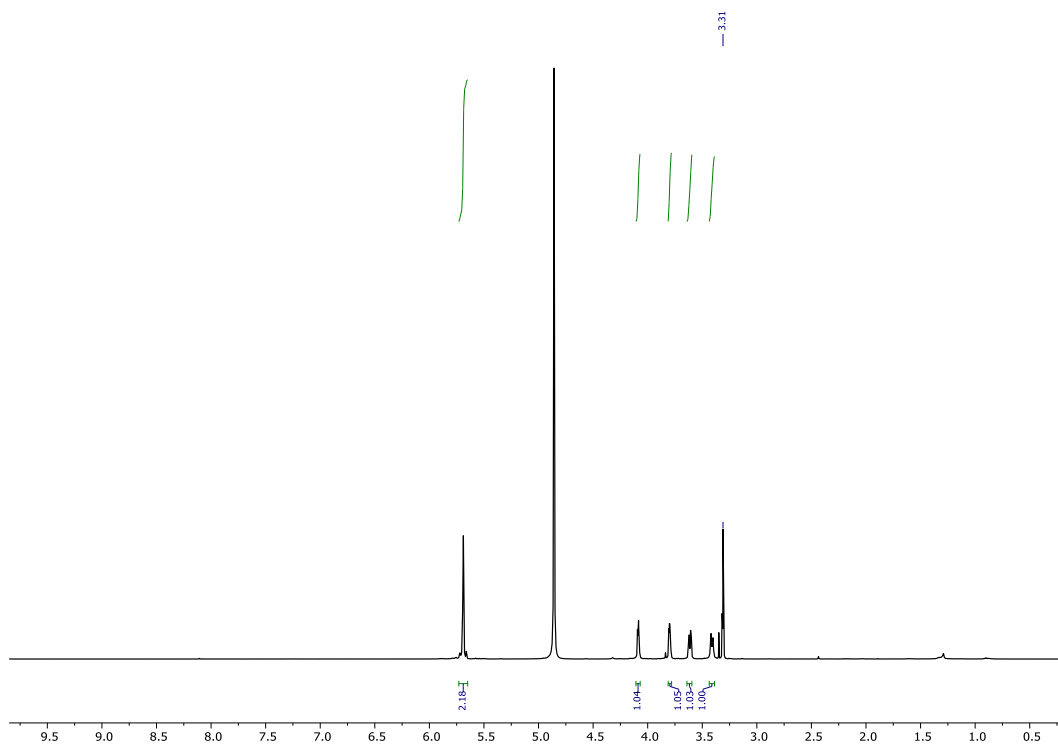
(1R,2S,3R,4S)-1-Aminocyclohex-3,5-dien-1-ol [(-)-Conduramine A-1] **16**
(400 MHz ^1H , d_4 -MeOH)



(1R,2S,3R,4S)-1-Aminocyclohex-3,5-dien-1-ol [(-)-Conduramine A-1] **16**
(100 MHz ^1H , d_4 -MeOH)



(1*S*,2*R*,3*S*,4*R*)-1-Aminocyclohex-3,5-dien-1-ol [(+)-Conduramine A-1] *ent*-16
(400 MHz ^1H , d_4 -MeOH)



(400 MHz ^1H , d_4 -MeOH)(100 MHz ^1H , d_4 -MeOH)

128.8

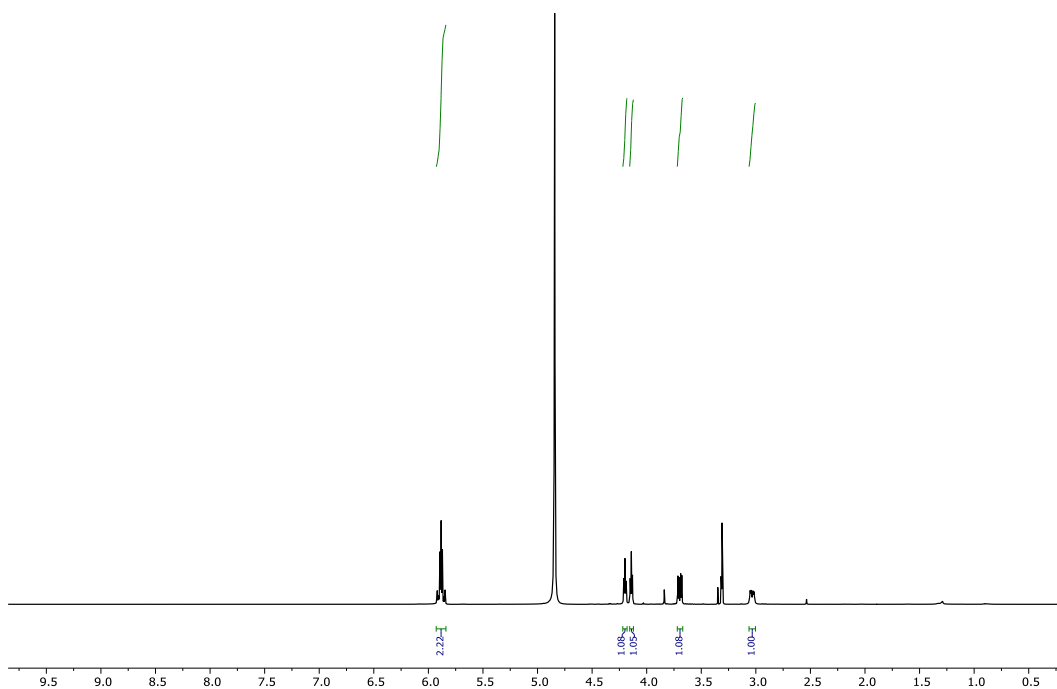
74.5

70.4

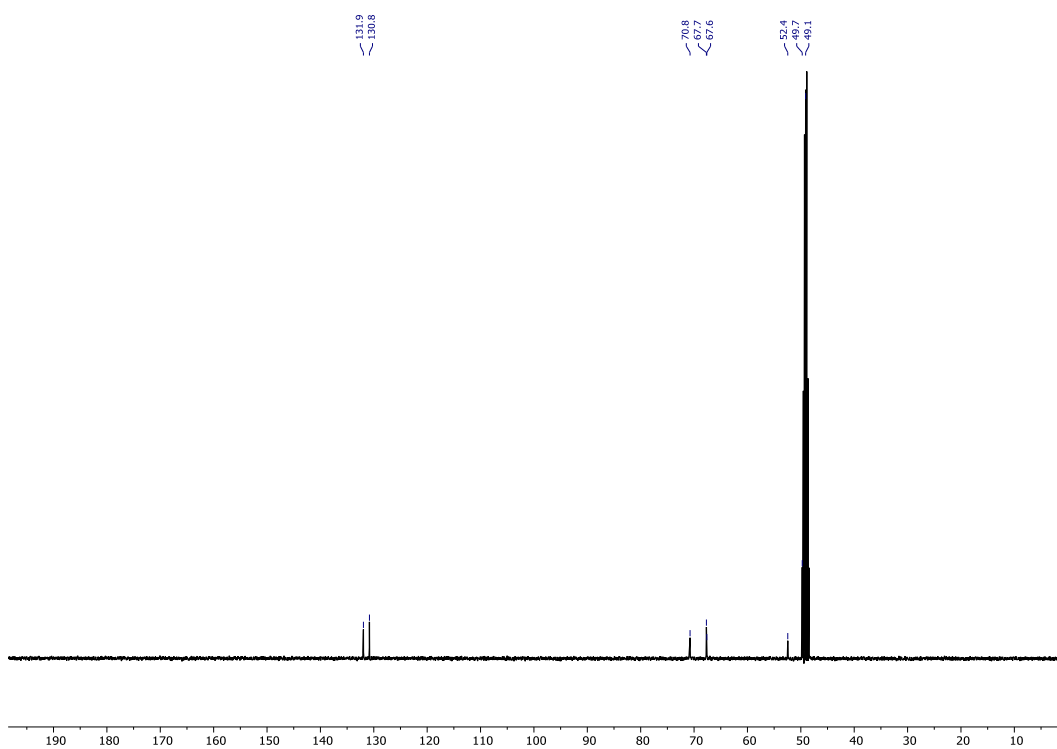
55.2

49.1

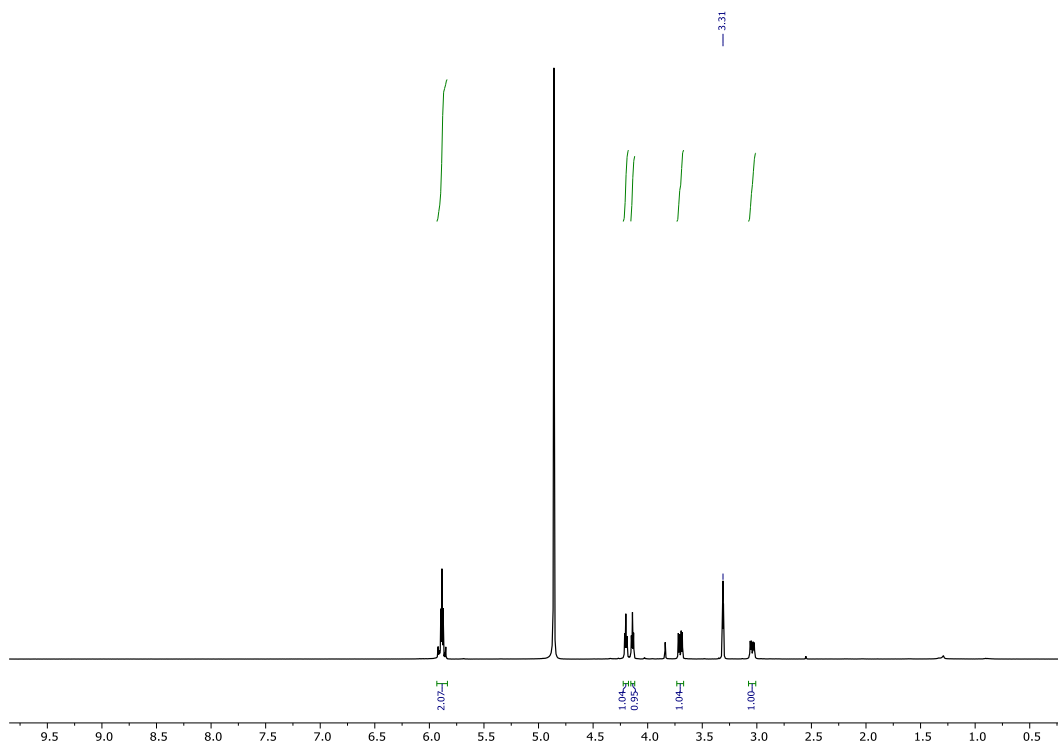
(1R,2R,3S,4R)-2-Aminocyclohex-3,5-dien-1-ol [(-)-Conduramine E-2] 27
(400 MHz ^1H , d_4 -MeOH)



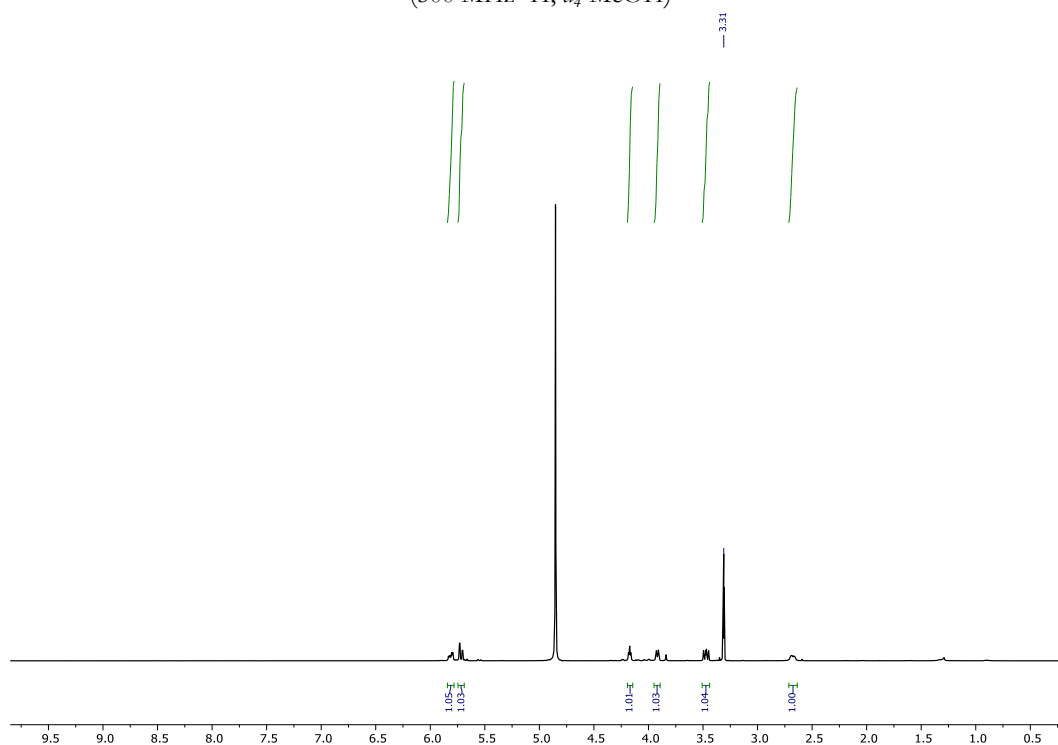
(1R,2R,3S,4R)-2-Aminocyclohex-3,5-dien-1-ol [(-)-Conduramine E-2] 27
(100 MHz ^1H , d_4 -MeOH)



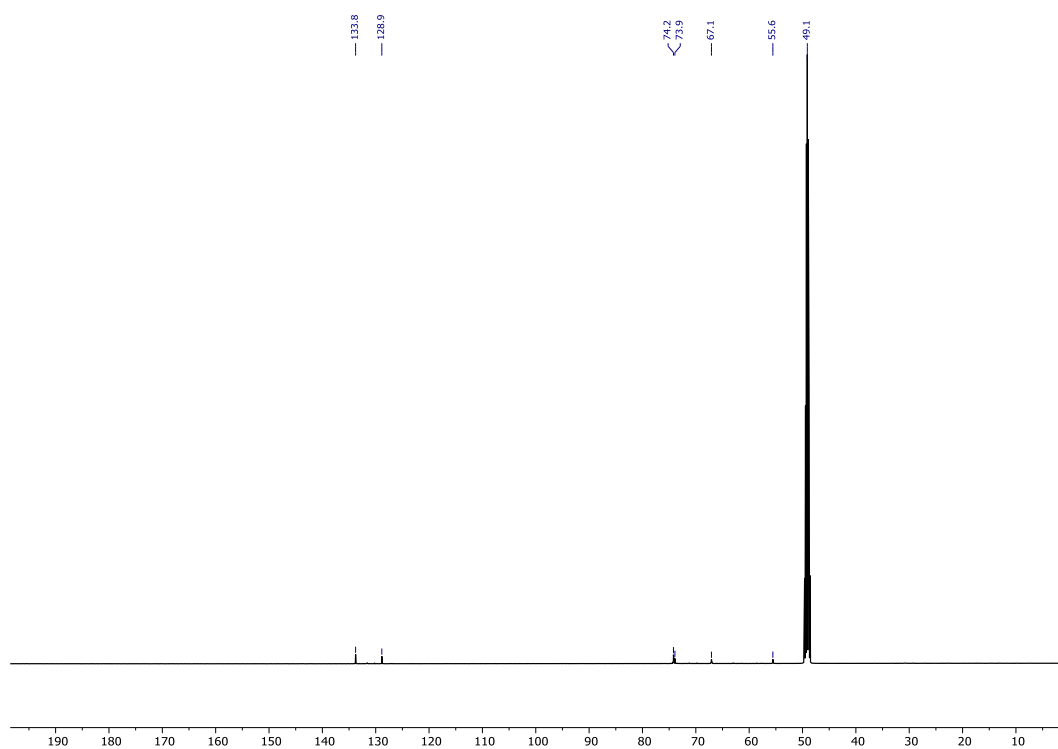
(1*S*,2*S*,3*R*,4*S*)-2-Aminocyclohex-3,5-dien-1-ol [(+)-Conduramine E-2] *ent*-27
(400 MHz ^1H , d_4 -MeOH)



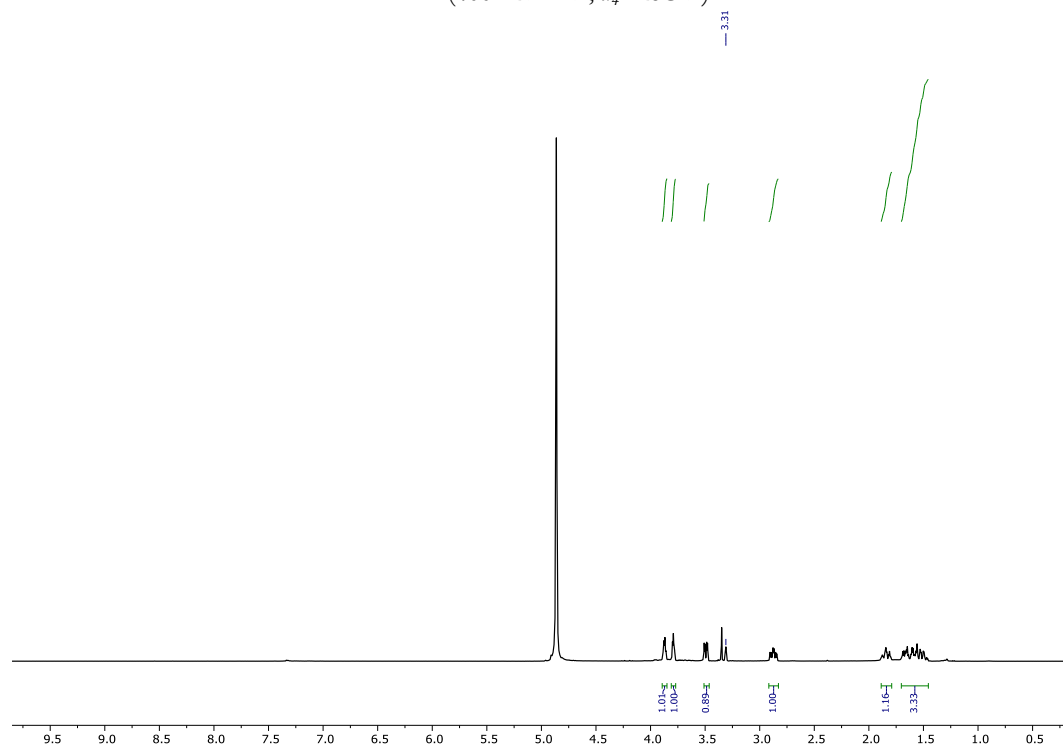
(1R,2R,3S,4S)-2-Aminocyclohex-3,5-dien-1-ol [(-)-Conduramine F-2] 29
(500 MHz ^1H , d_4 -MeOH)



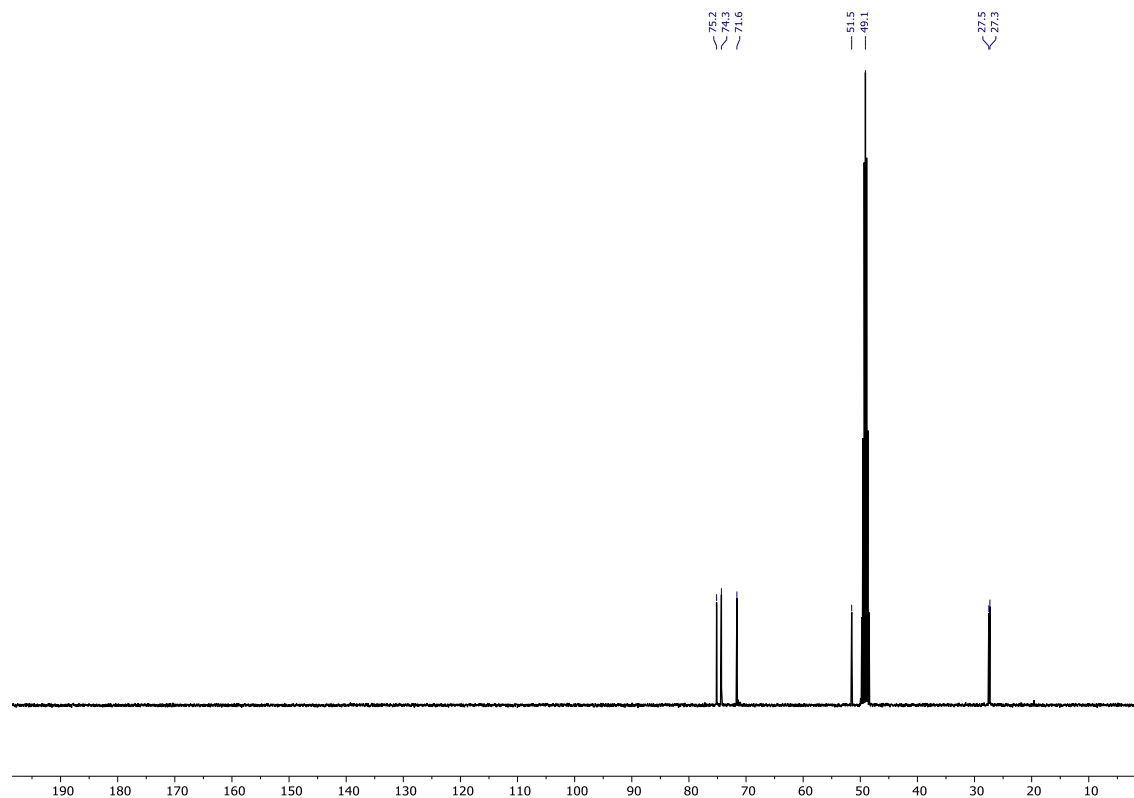
(1R,2R,3S,4S)-2-Aminocyclohex-3,5-dien-1-ol [(-)-Conduramine F-2] 29
(125 MHz ^1H , d_4 -MeOH)



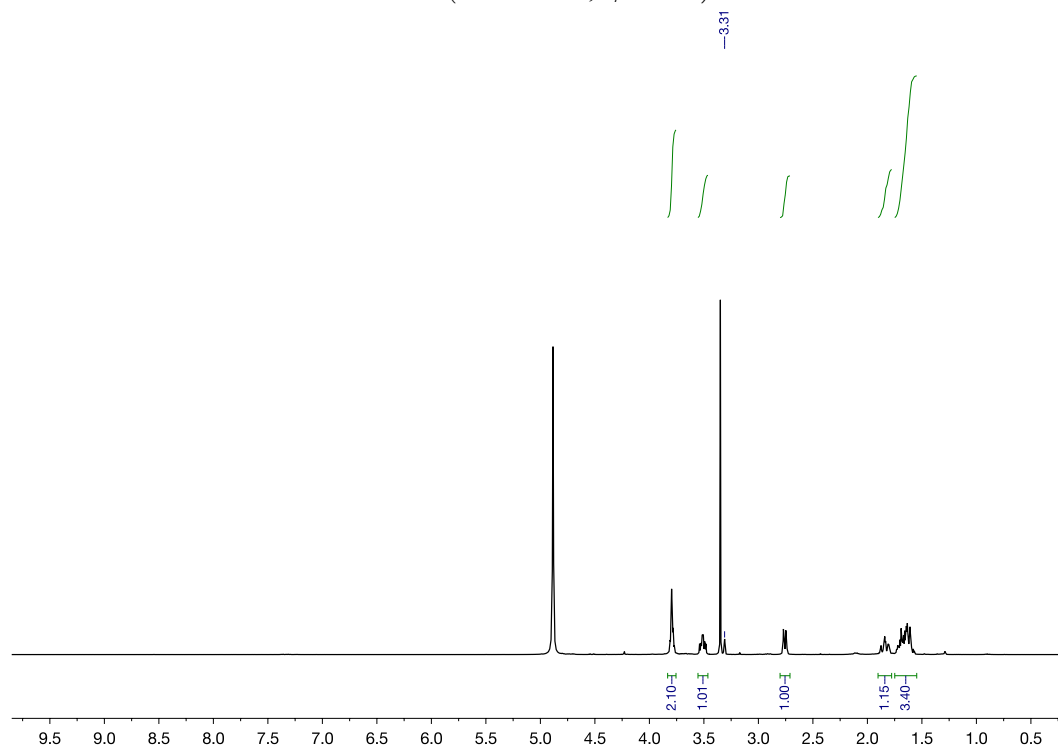
(1*R*,2*S*,3*R*,4*S*)-1-Aminocyclohexane-2,3,4-triol [(±)-Dihydroconduramine A-1] (±)-32
(400 MHz ^1H , d_4 -MeOH)



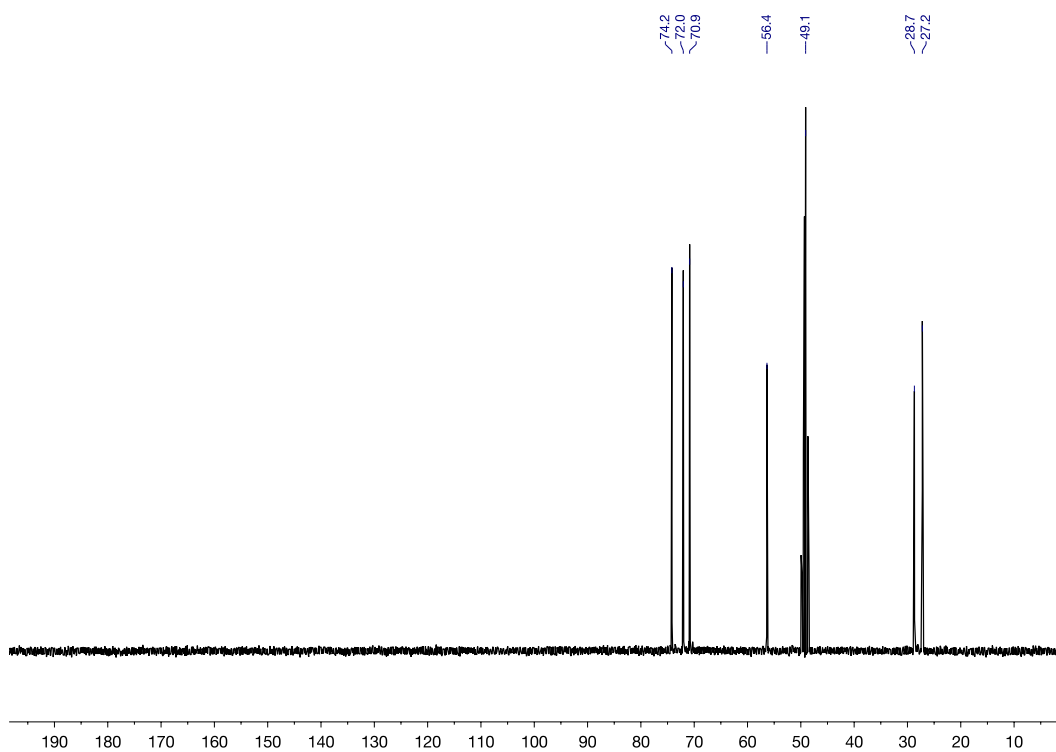
(1*R*,2*S*,3*R*,4*S*)-1-Aminocyclohexane-2,3,4-triol [(±)-Dihydroconduramine A-1] (±)-32
(100 MHz ^{13}C , d_4 -MeOH)



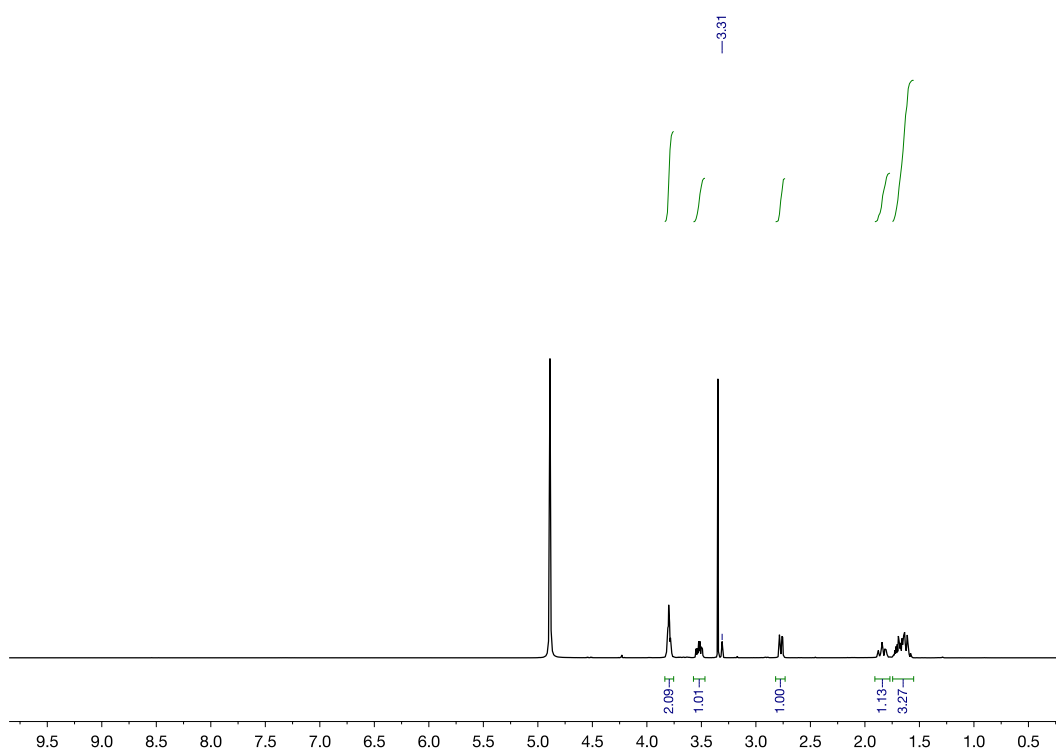
(1*R*,2*S*,3*S*,4*S*)-2-Aminocyclohexane-1,3,4-triol [(±)-Dihydroconduramine A-2] (±)-33
(400 MHz ^1H , d_4 -MeOH)



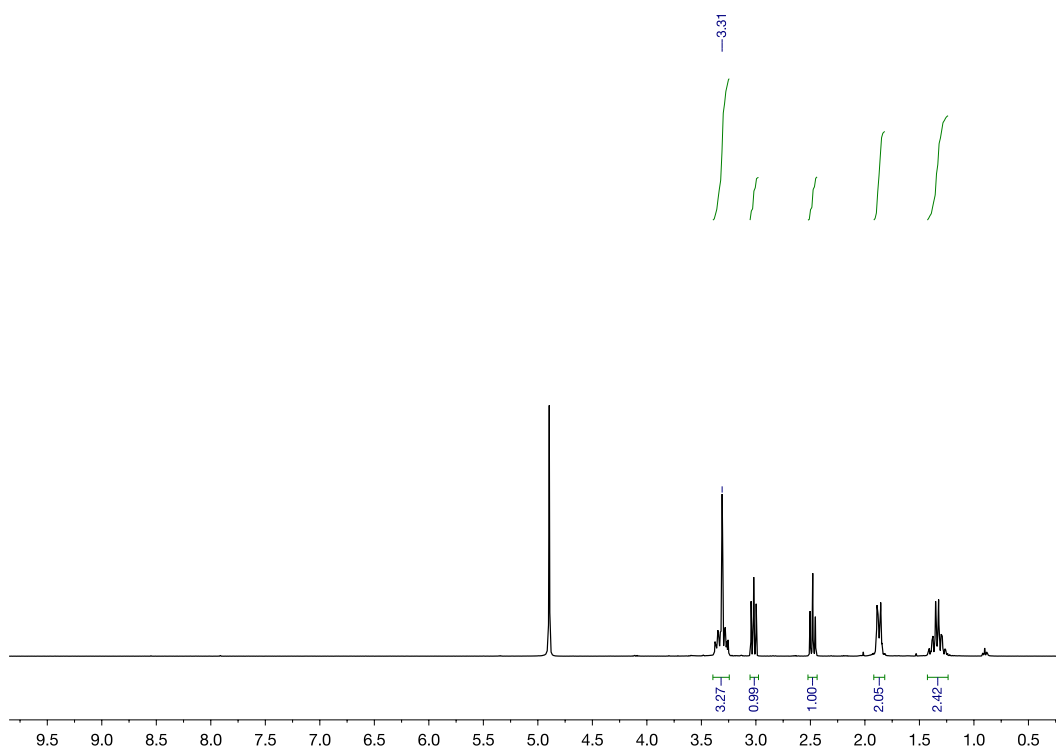
(1*R*,2*S*,3*S*,4*S*)-2-Aminocyclohexane-1,3,4-triol [(±)-Dihydroconduramine A-2] (±)-33
(100 MHz ^{13}C , d_4 -MeOH)



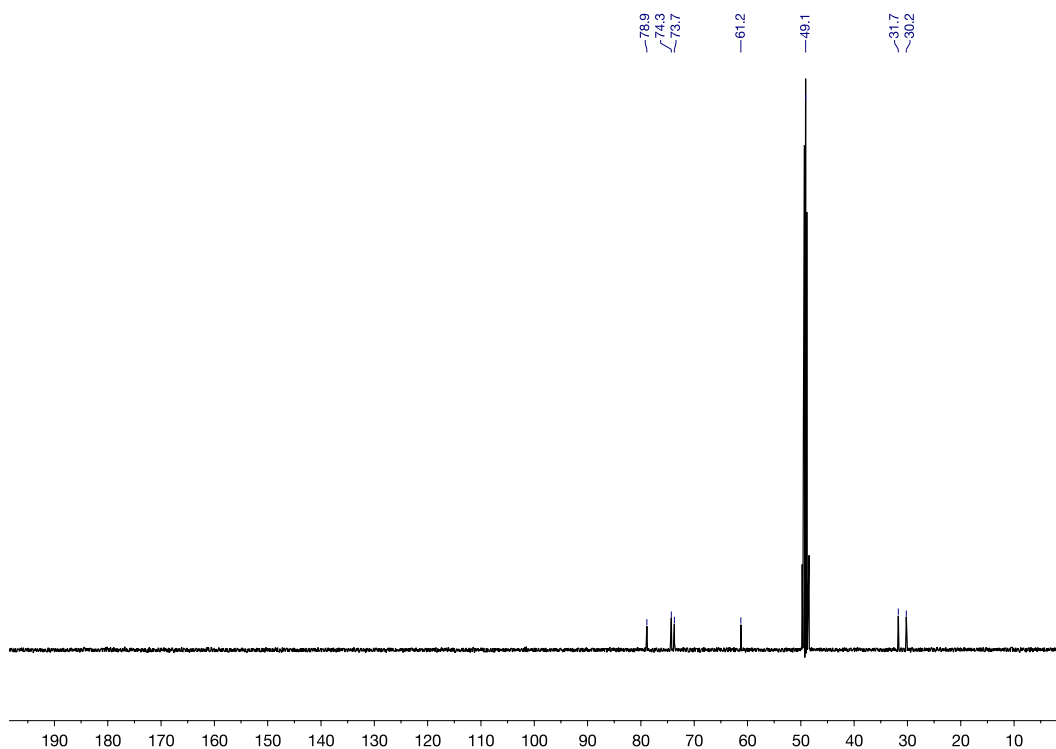
(1R,2S,3S,4S)-2-Aminocyclohexane-1,3,4-triol [(-)-Dihydroconduramine A-2] 33
(400 MHz ^1H , d_4 -MeOH)



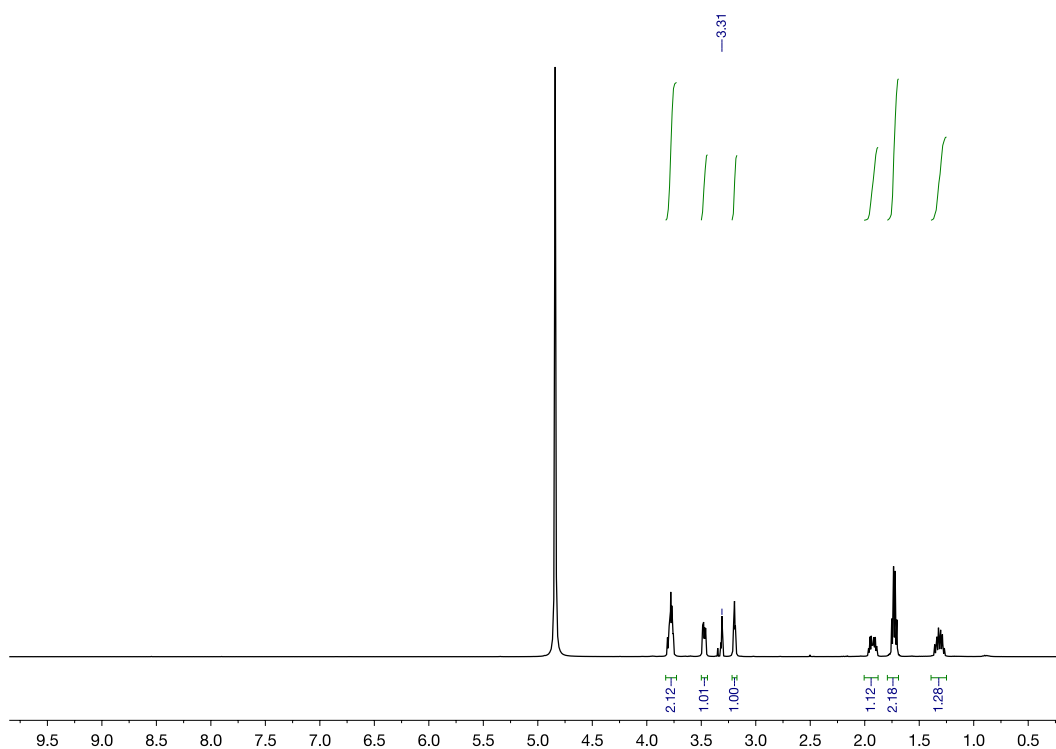
(1R,2S,3R,4R)-2-Aminocyclohexane-1,3,4-triol [(–)-Dihydroconduramine B-2] 35
(400 MHz ^1H , d_4 -MeOH)



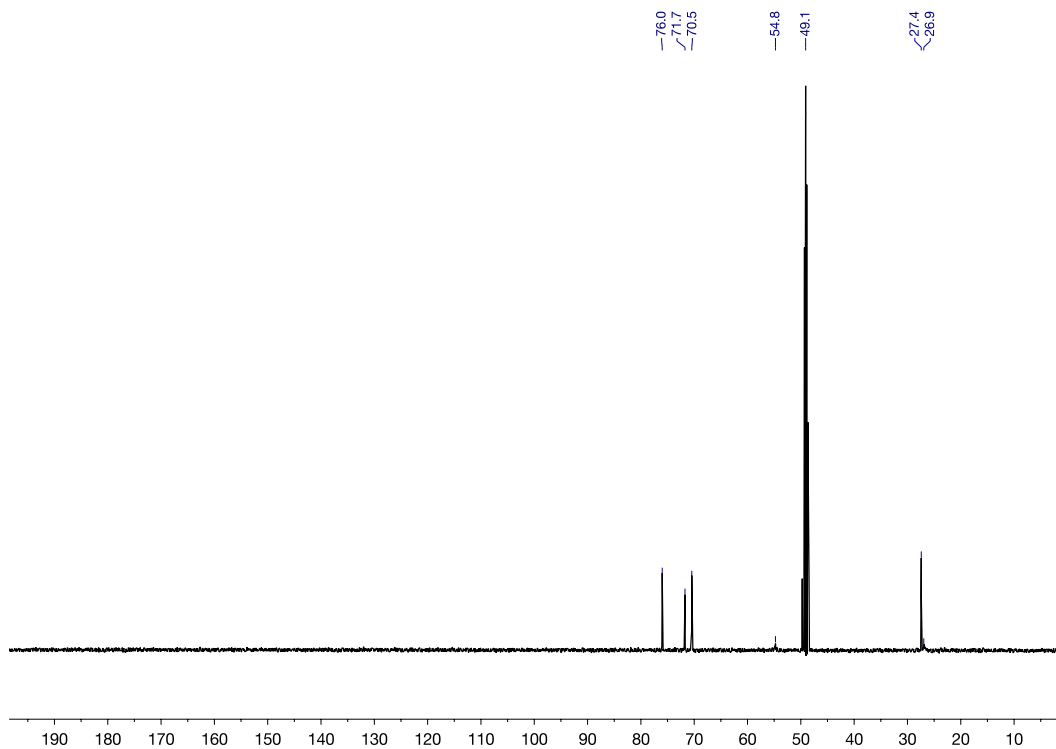
(1R,2S,3R,4R)-2-Aminocyclohexane-1,3,4-triol [(–)-Dihydroconduramine B-2] 35
(100 MHz ^{13}C , d_4 -MeOH)



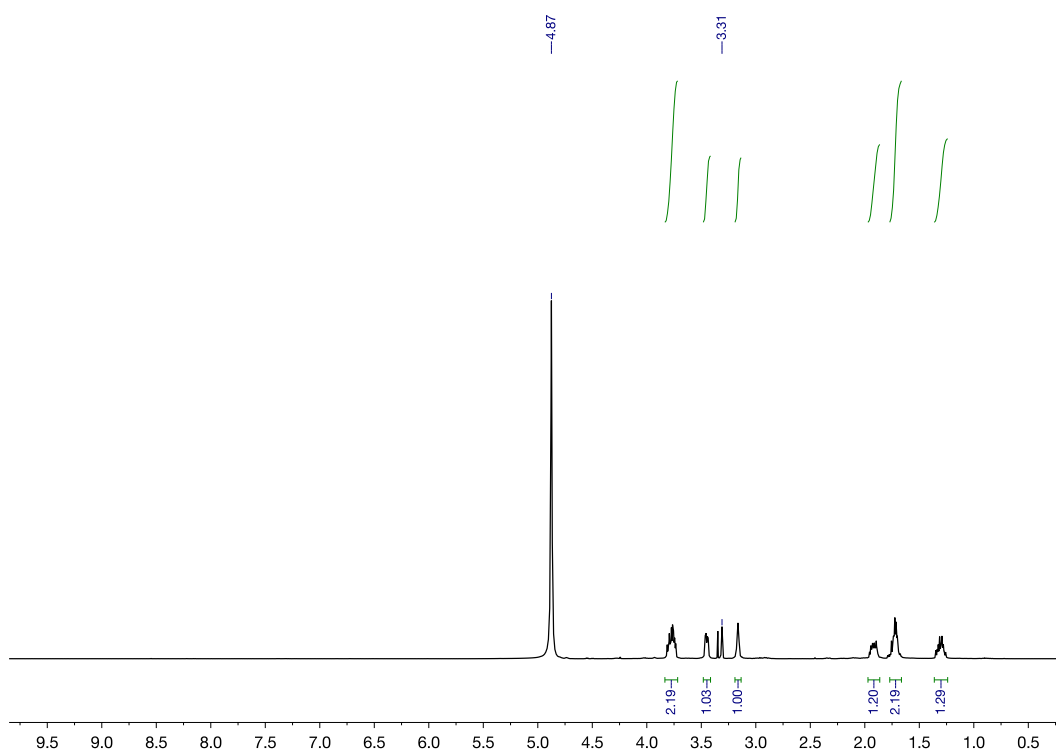
(1*R*,2*R*,3*R*,4*R*)-2-Aminocyclohexane-1,3,4-triol [(±)-Dihydroconduramine C-2] (±)-37
(400 MHz ^1H , d_4 -MeOH)



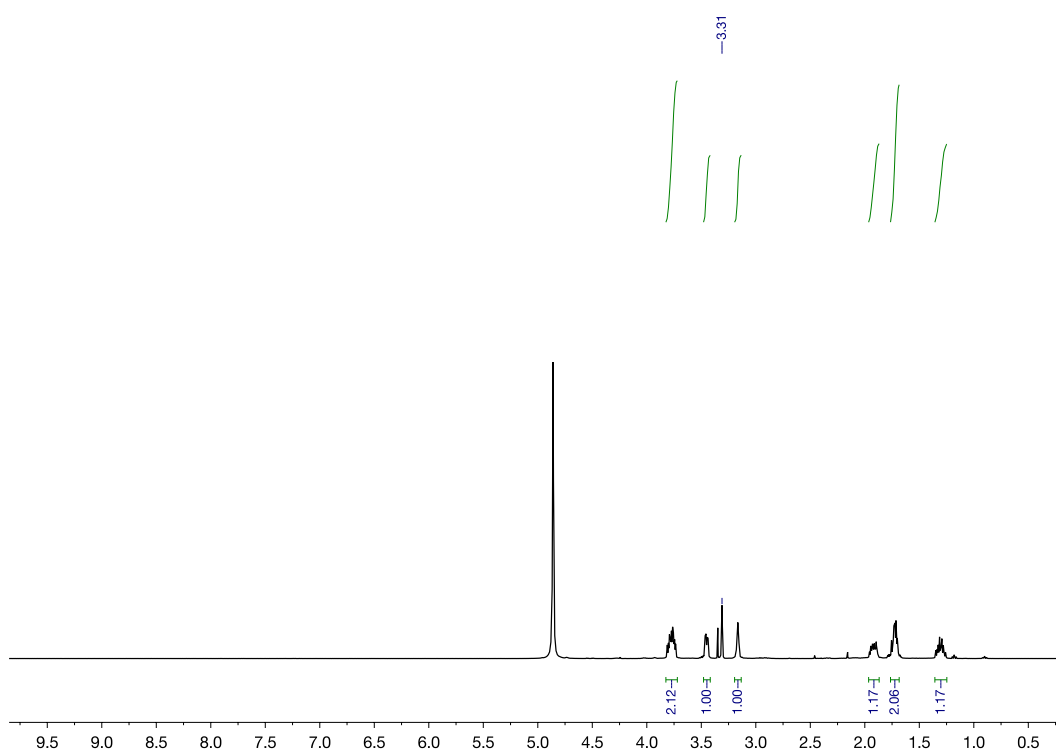
(1*R*,2*R*,3*R*,4*R*)-2-Aminocyclohexane-1,3,4-triol [(±)-Dihydroconduramine C-2] (±)-37
(100 MHz ^{13}C , d_4 -MeOH)



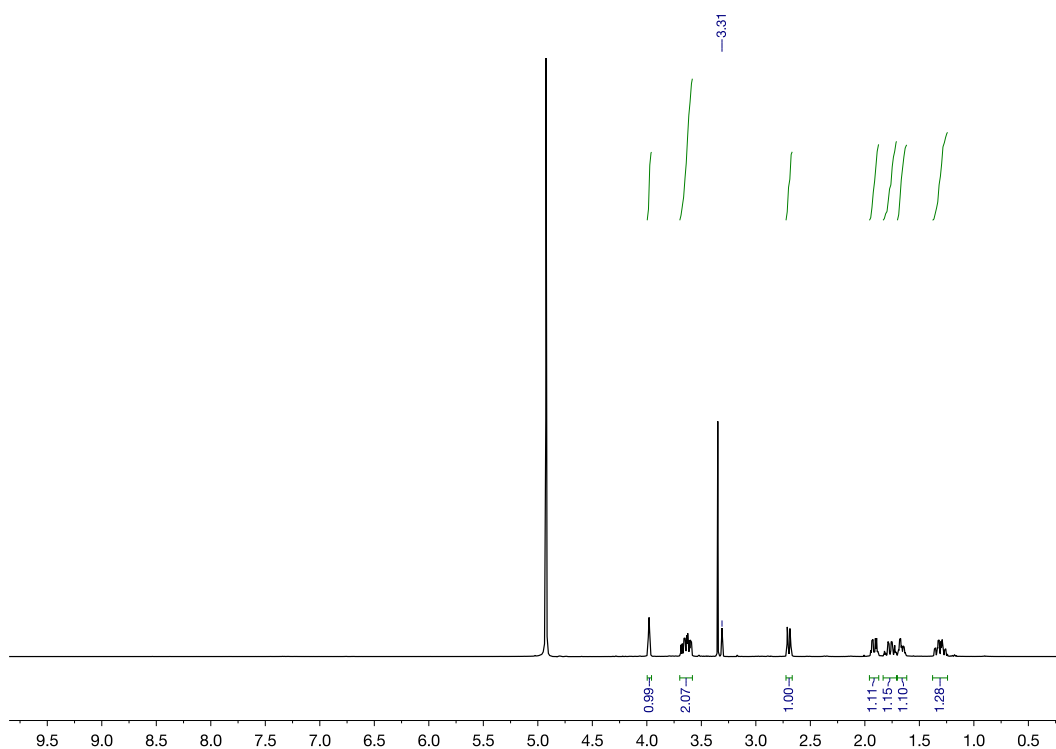
(1*S*,2*S*,3*S*,4*S*)-2-Aminocyclohexane-1,3,4-triol [(+)-Dihydroconduramine C-2] 37
(400 MHz ^1H , d_4 -MeOH)



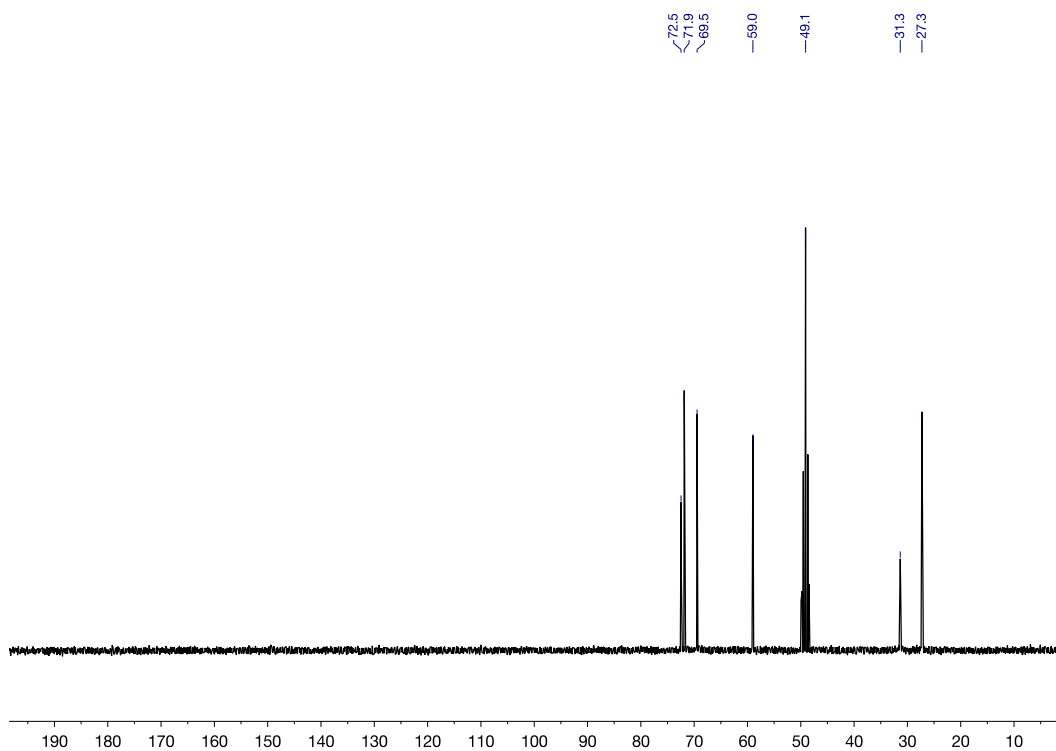
(1R,2R,3R,4R)-2-Aminocyclohexane-1,3,4-triol [(-)-Dihydroconduramine C-2] *ent*-37
(400 MHz ^1H , d_4 -MeOH)



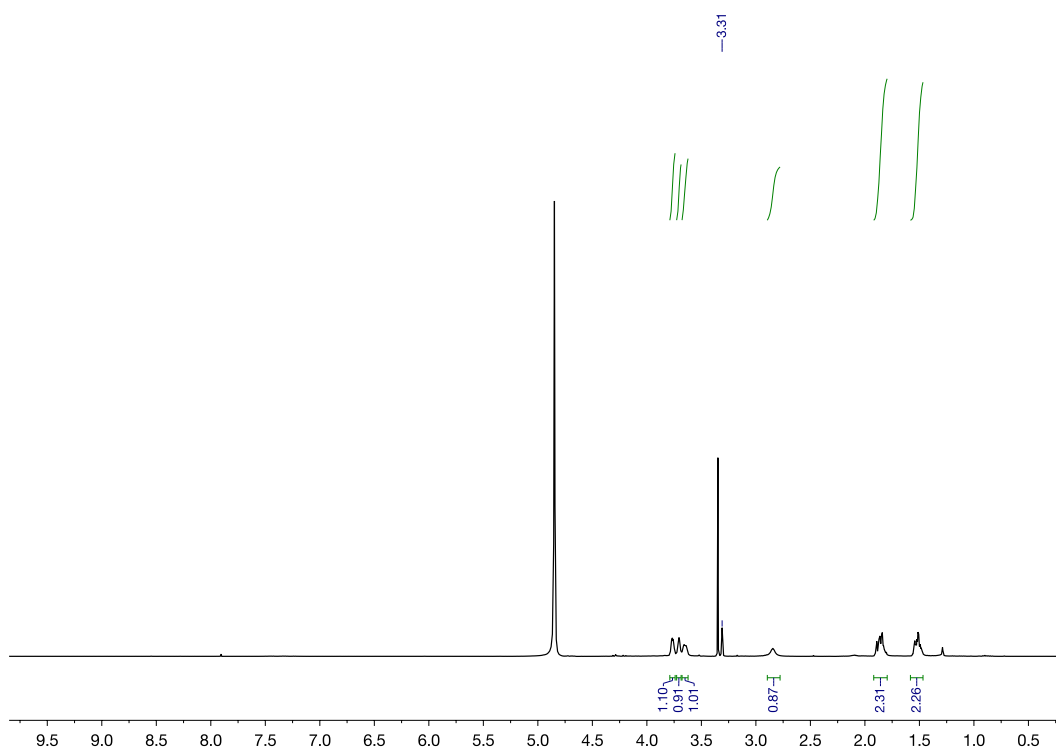
(1R,2S,3S,4R)-2-Aminocyclohexane-1,3,4-triol [(-)-Dihydroconduramine C-3] 38
(400 MHz ^1H , d_4 -MeOH)



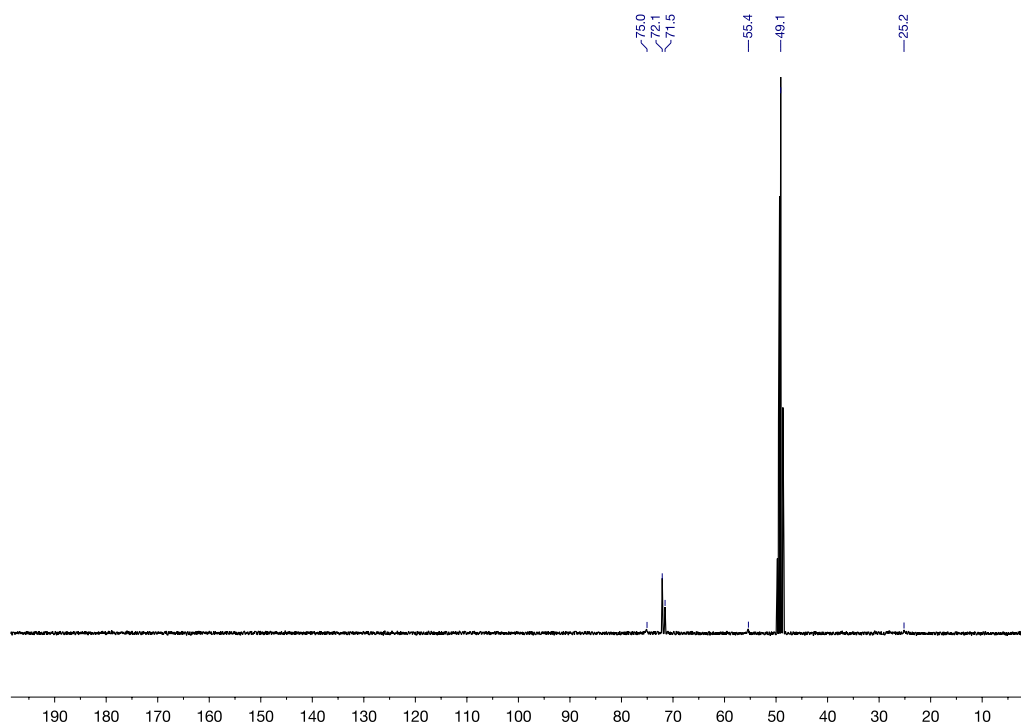
(1R,2S,3S,4R)-2-Aminocyclohexane-1,3,4-triol [(-)-Dihydroconduramine C-3] 38
(100 MHz ^{13}C , d_4 -MeOH)



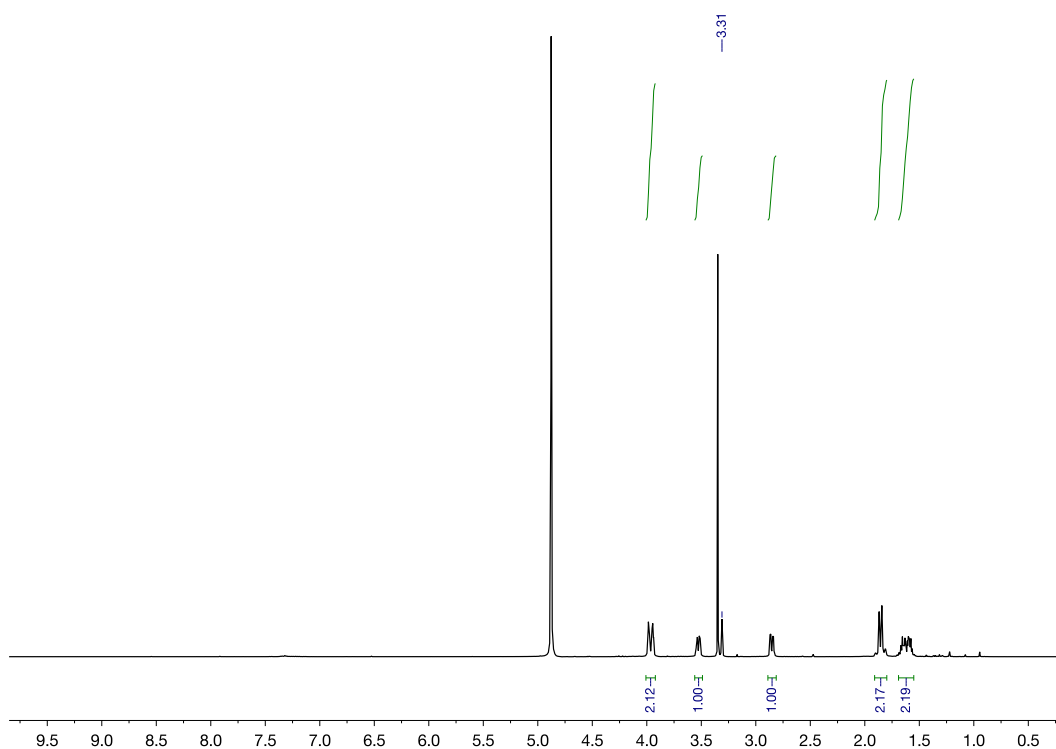
(1*S*,2*S*,3*S*,4*R*)-2-Aminocyclohexane-1,3,4-triol [(+)-Dihydroconduramine D-2] 41
(400 MHz ^1H , d_4 -MeOH)



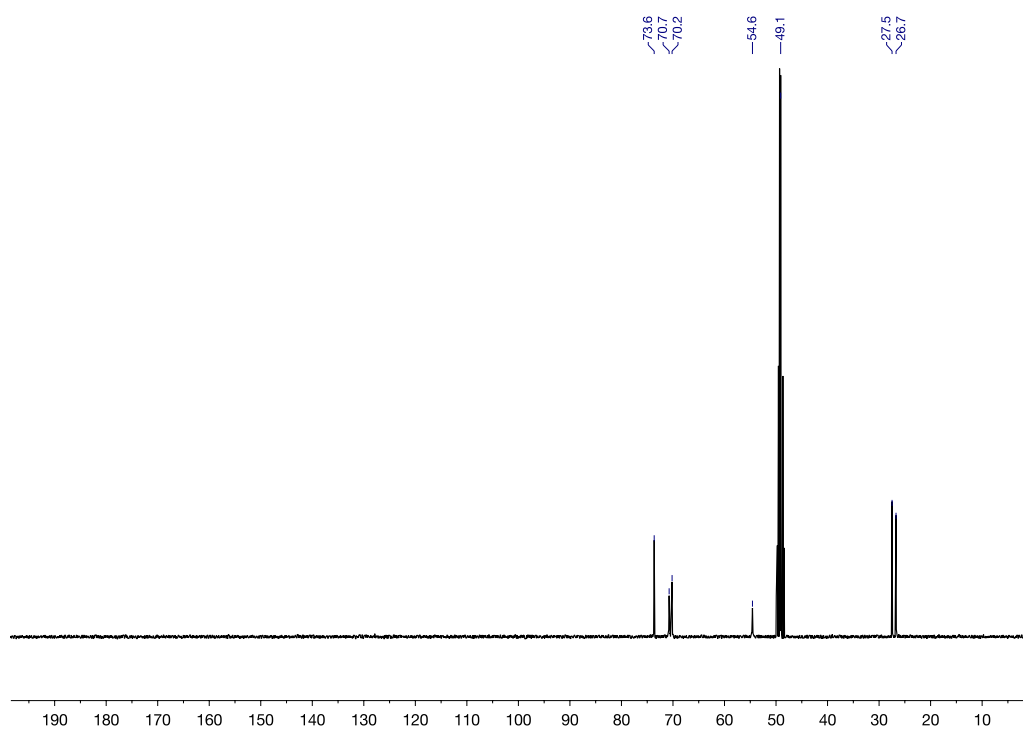
(1*S*,2*S*,3*S*,4*R*)-2-Aminocyclohexane-1,3,4-triol [(+)-Dihydroconduramine D-2] 41
(100 MHz ^{13}C , d_4 -MeOH)



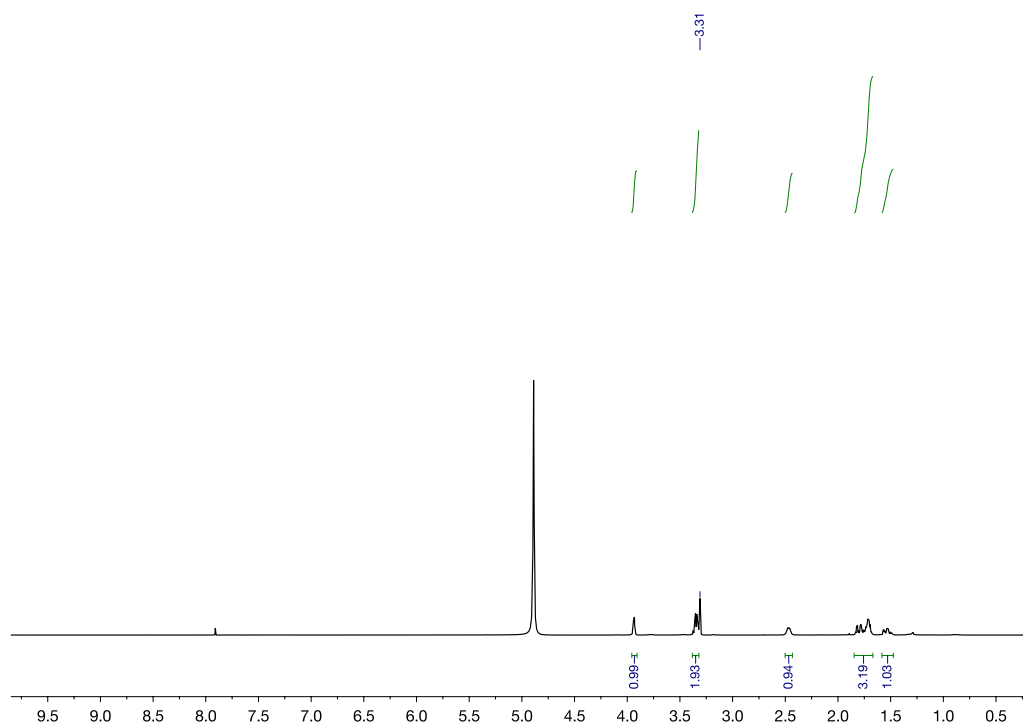
(1*S*,2*S*,3*R*,4*S*)-2-Aminocyclohexane-1,3,4-triol [(+)-Dihydroconduramine E-2] 43
(400 MHz ^1H , d_4 -MeOH)



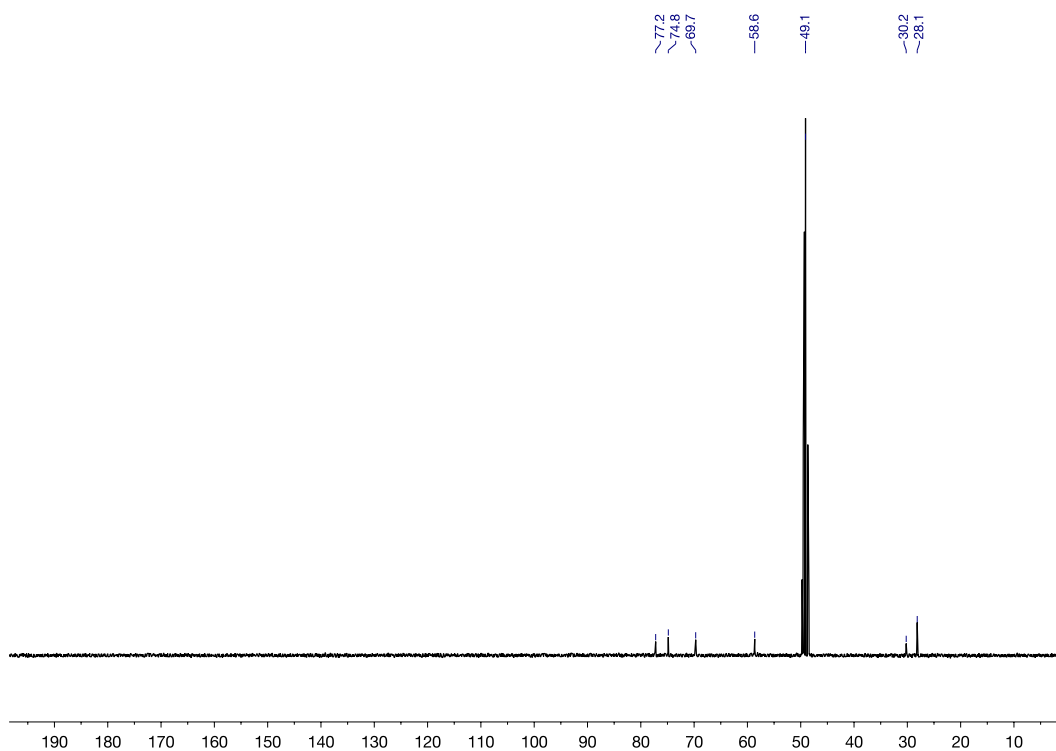
(1*S*,2*S*,3*R*,4*S*)-2-Aminocyclohexane-1,3,4-triol [(+)-Dihydroconduramine E-2] 43
(100 MHz ^{13}C , d_4 -MeOH)



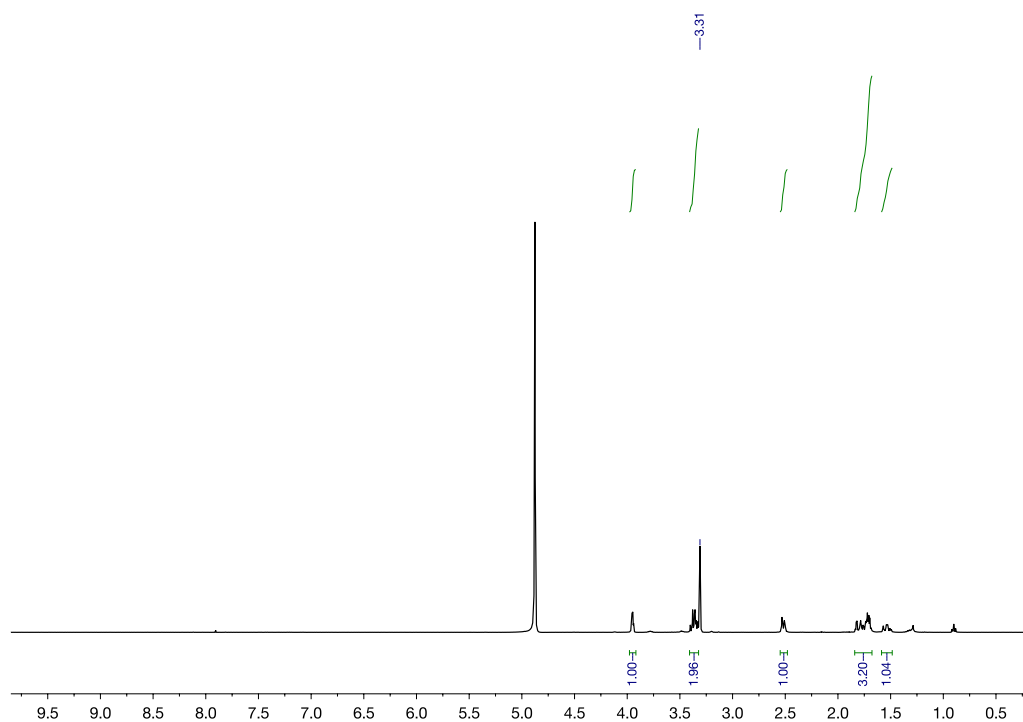
(1*S*,2*S*,3*R*,4*R*)-2-Aminocyclohexane-1,3,4-triol [(+)-Dihydroconduramine F-2] 45
(400 MHz ^1H , d_4 -MeOH)



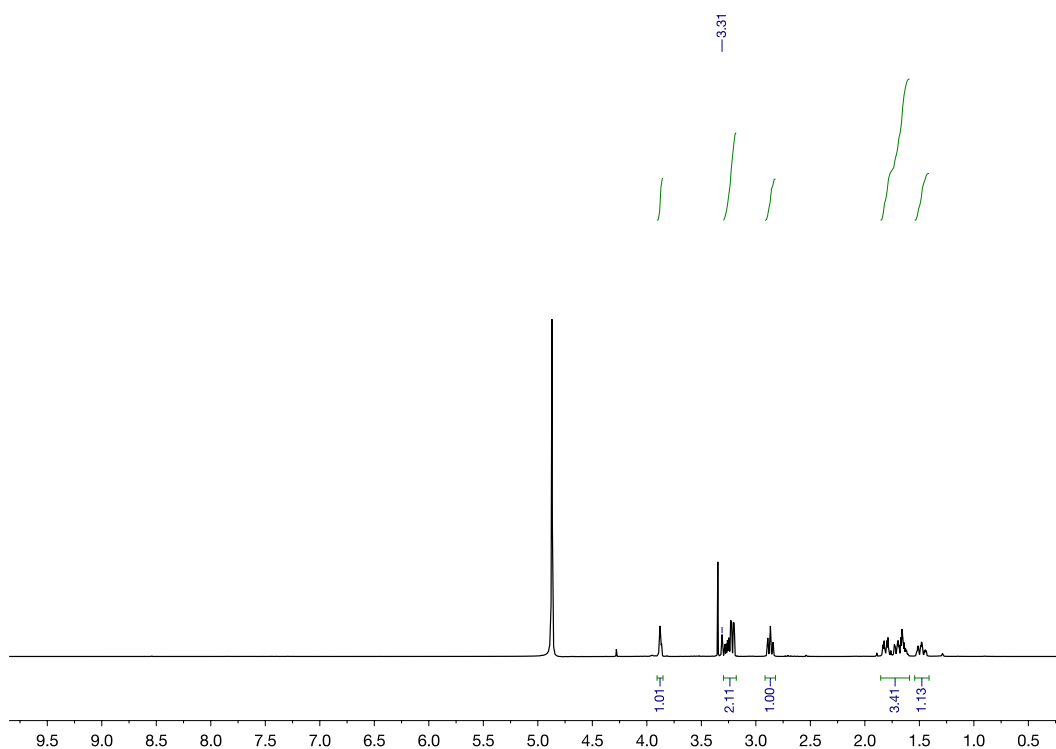
(1*S*,2*S*,3*R*,4*R*)-2-Aminocyclohexane-1,3,4-triol [(+)-Dihydroconduramine F-2] 45
(100 MHz ^{13}C , d_4 -MeOH)



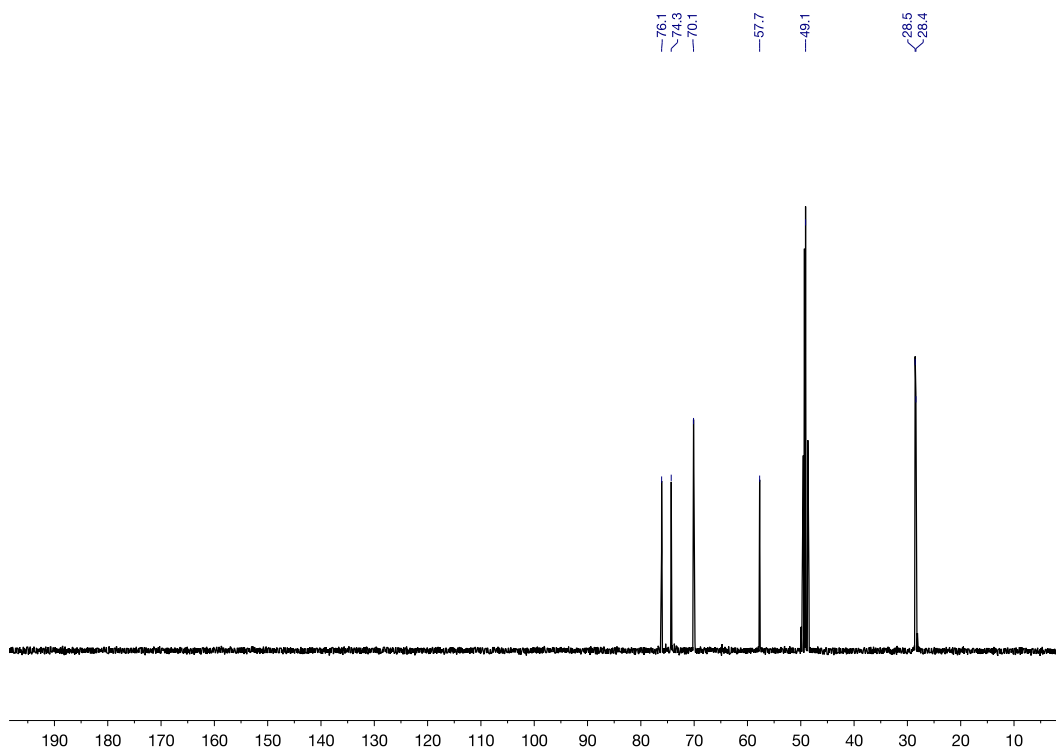
(1R,2R,3S,4S)-2-Aminocyclohexane-1,3,4-triol [(-)-Dihydroconduramine F-2] *ent*-45
(400 MHz ^1H , d_4 -MeOH)



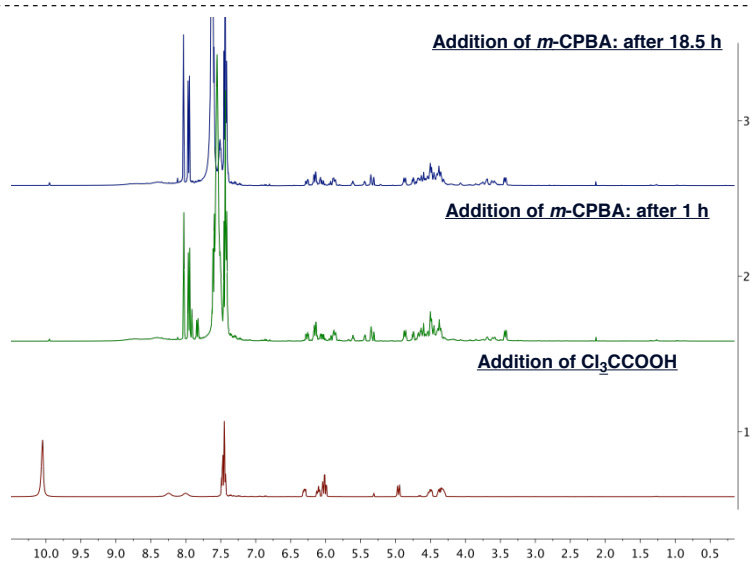
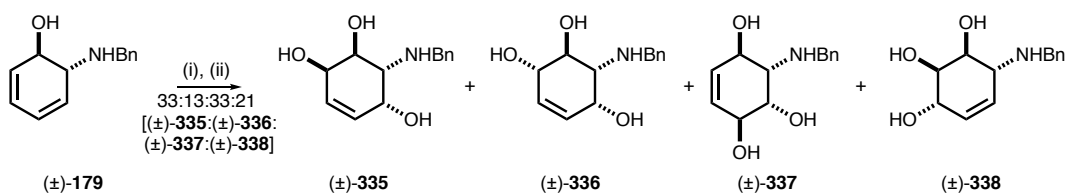
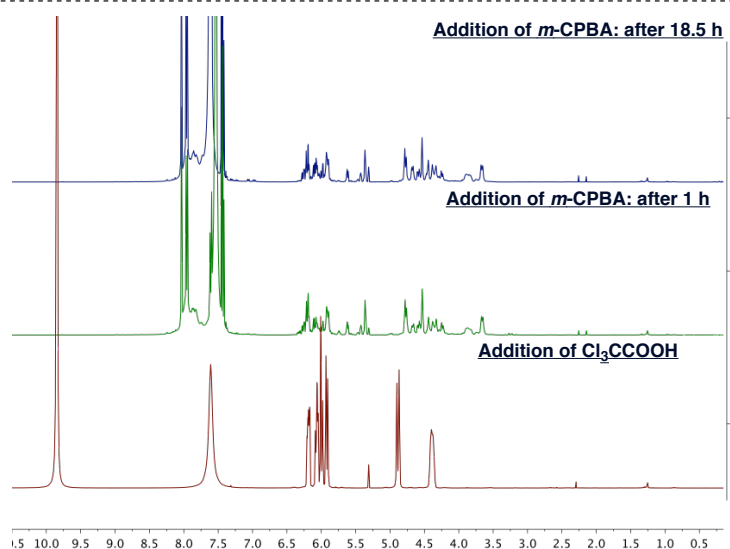
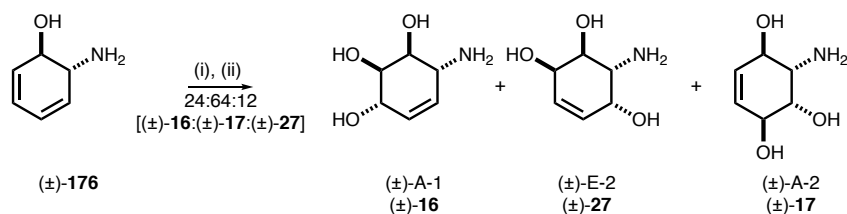
(1R,2S,3R,4S)-2-Aminocyclohexane-1,3,4-triol [(+)-Dihydroconduramine F-3] 46
(400 MHz ^1H , d_4 -MeOH)

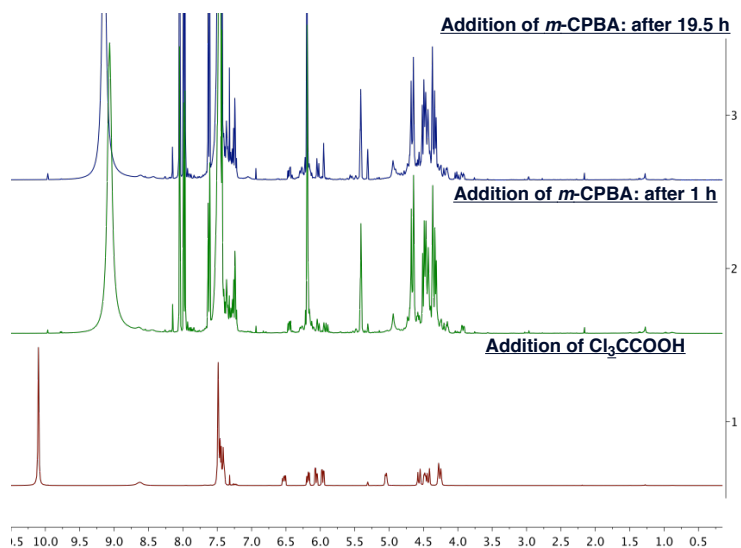
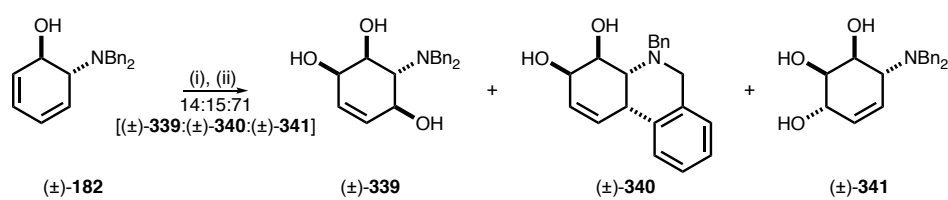


(1R,2S,3R,4S)-2-Aminocyclohexane-1,3,4-triol [(+)-Dihydroconduramine F-3] 46
(100 MHz ^{13}C , d_4 -MeOH)



Appendix 3: Epoxidation of (±)-176, (±)-179 and (±)-182

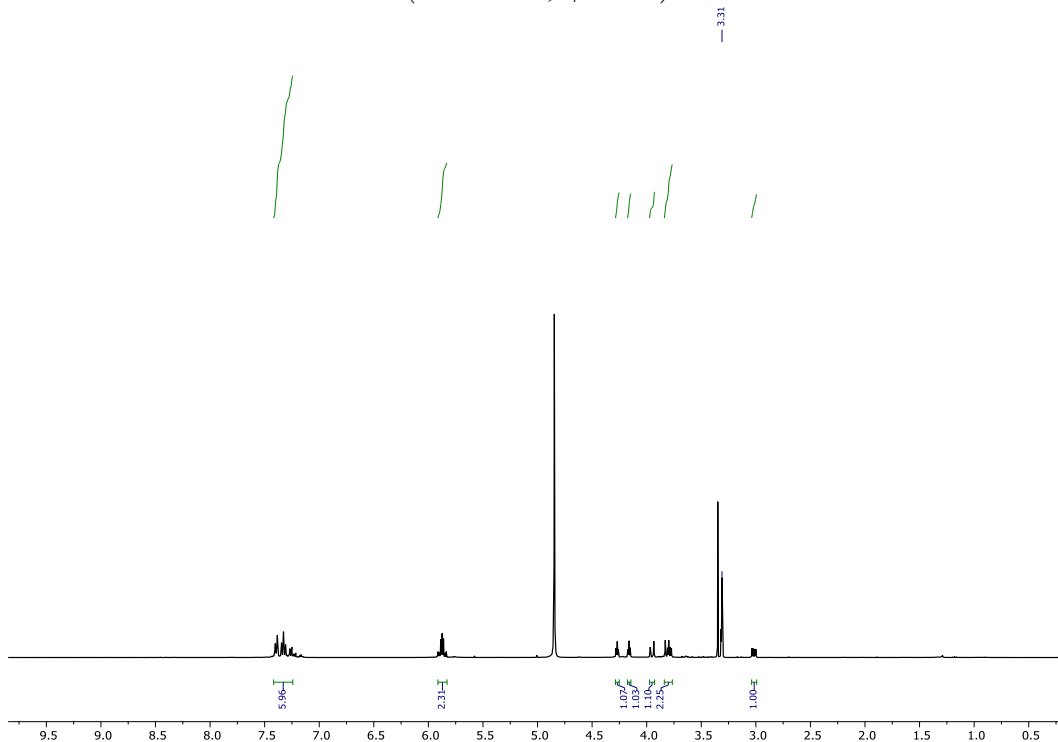




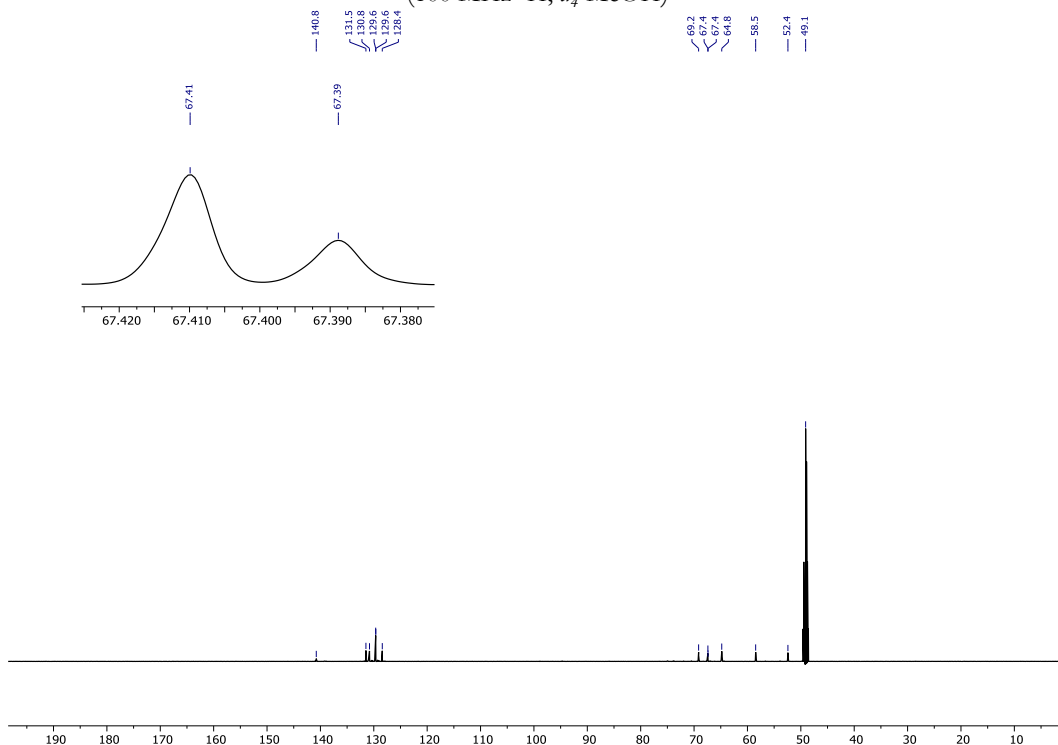
Scheme 106. Reagents and conditions: (i) CCl₃CO₂H, CH₂Cl₂, rt, 15 min, then *m*-CPBA, rt; (ii) K₂CO₃, MeOH, rt, 24 h.

Appendix 4: Analysis the $^{16}\text{O}/^{18}\text{O}$ -isotope induced chemical shifts in the ^{13}C NMR spectrum.

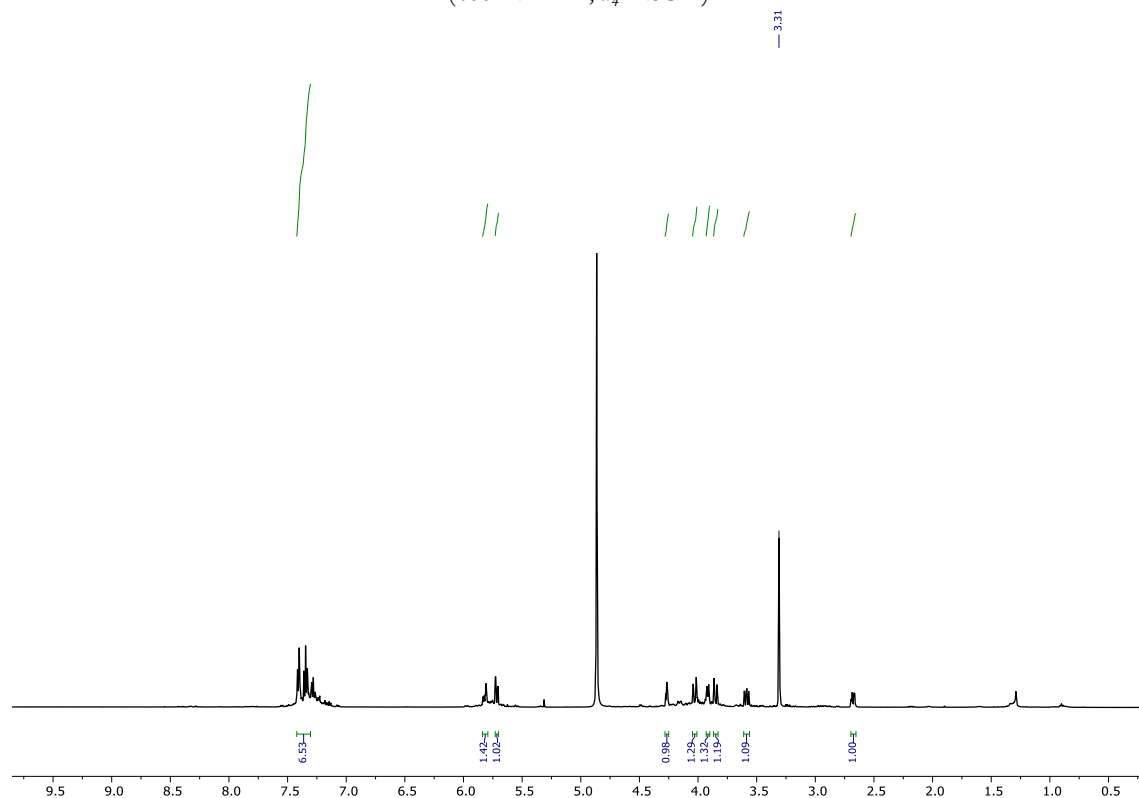
(1*R*,2*R*,3*S*,4*R*)-2-(*N*-benzylamino)cyclohex-5-ene-1,3,4-triol 335 and (1*R*,2*R*,3*S*,4*R*)-2-(*N*-benzylamino)-4-(^{18}O -hydroxy)cyclohex-5-ene-1,3,4-triol ^{18}O -335
(400 MHz ^1H , d_4 -MeOH)



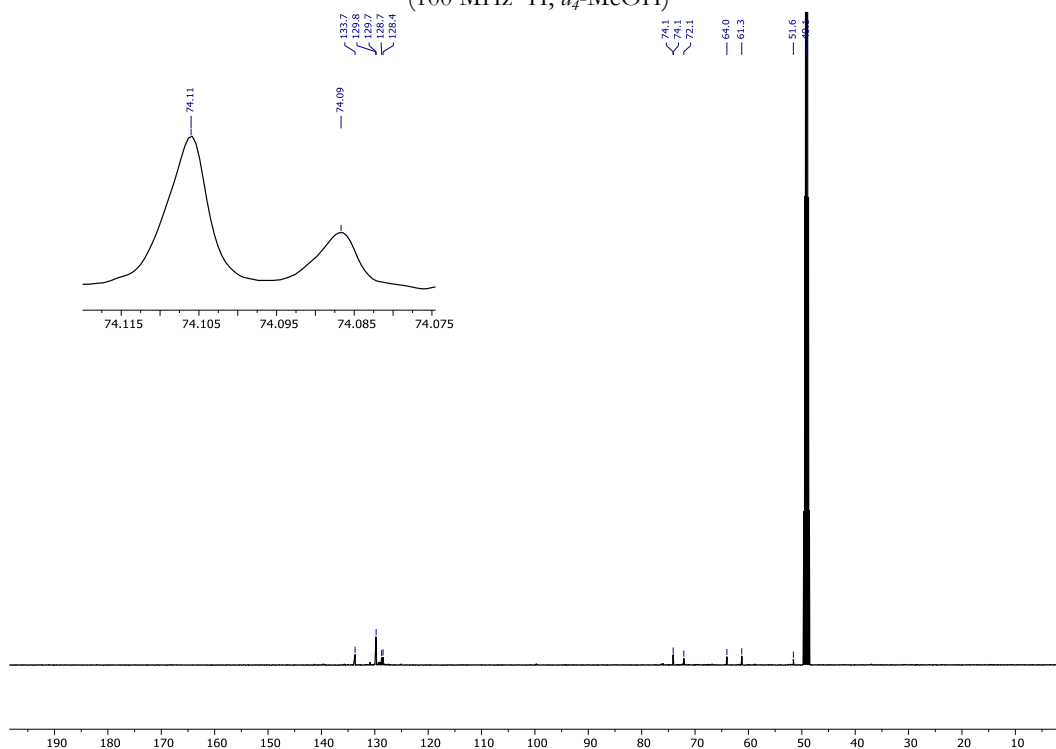
(1*R*,2*R*,3*S*,4*R*)-2-(*N*-benzylamino)cyclohex-5-ene-1,3,4-triol 335 and (1*R*,2*R*,3*S*,4*R*)-2-(*N*-benzylamino)-4-(^{18}O -hydroxy)cyclohex-5-ene-1,3,4-triol ^{18}O -335
(100 MHz ^1H , d_4 -MeOH)



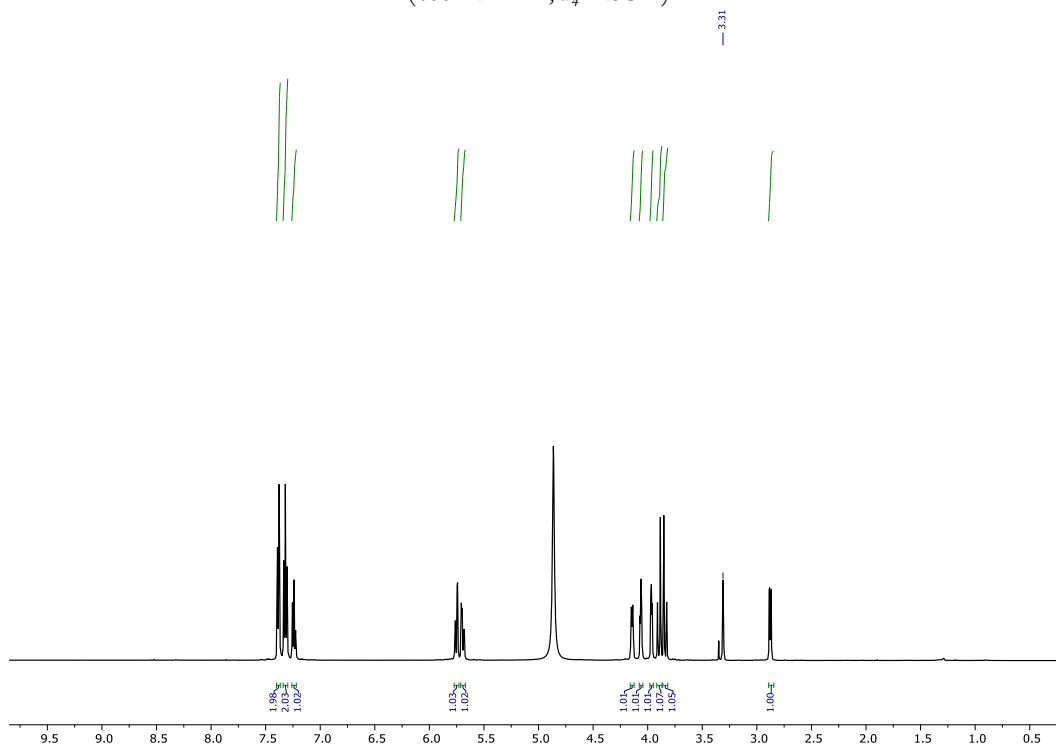
(1*R*,2*R*,3*S*,4*S*)-2-(*N*-benzylamino)cyclohex-5-ene-1,3,4-triol 336 and (1*R*,2*R*,3*S*,4*S*)-2-(*N*-benzylamino)-4-(^{18}O -hydroxy)cyclohex-5-ene-1,3,4-triol ^{18}O -336
(400 MHz ^1H , d_4 -MeOH)



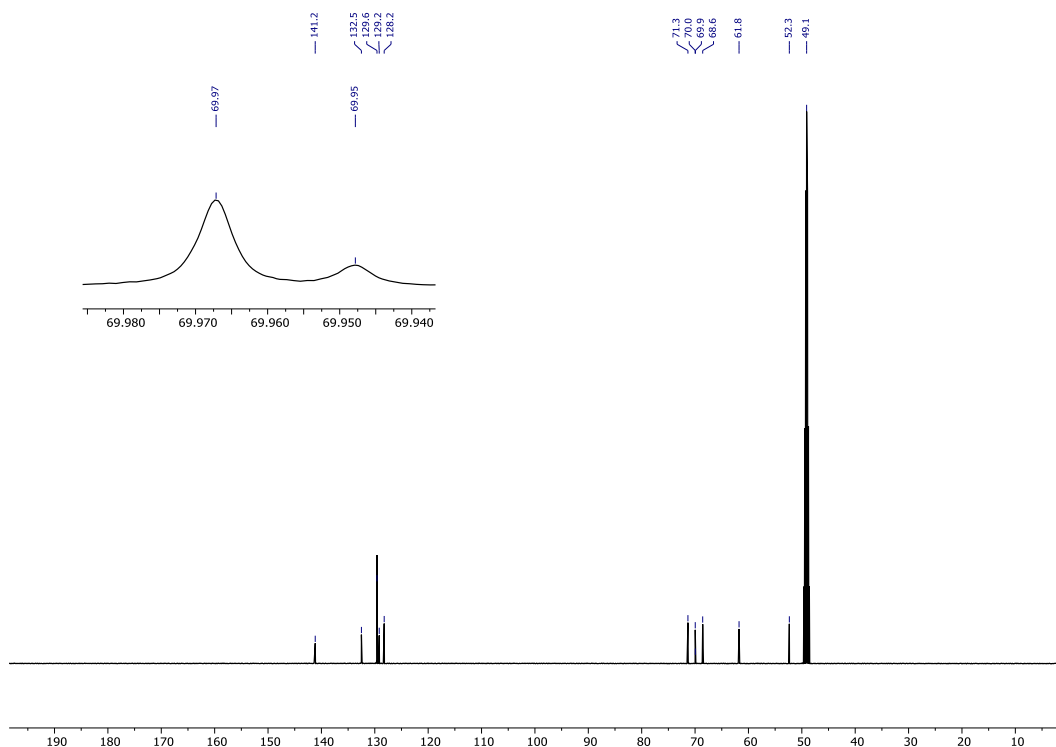
(1*R*,2*R*,3*S*,4*S*)-2-(*N*-benzylamino)cyclohex-5-ene-1,3,4-triol 336 and (1*R*,2*R*,3*S*,4*S*)-2-(*N*-benzylamino)-4-(^{18}O -hydroxy)cyclohex-5-ene-1,3,4-triol ^{18}O -336
(100 MHz ^1H , d_4 -MeOH)



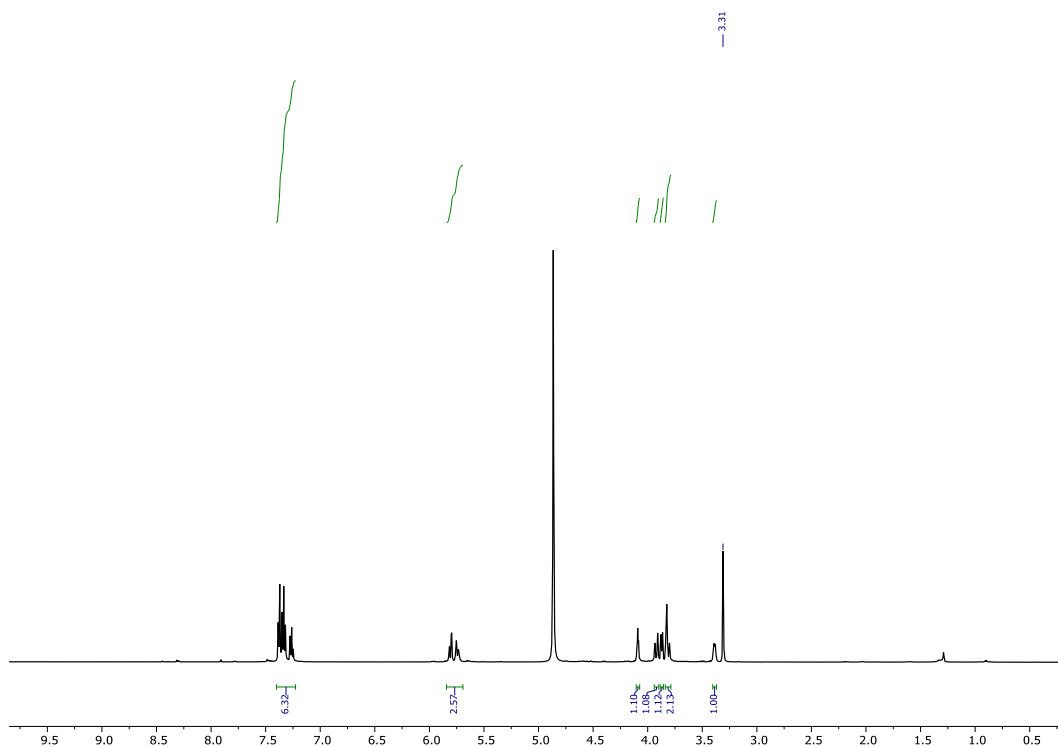
(1*R*,2*S*,3*S*,4*S*)-2-(*N*-benzylamino)cyclohex-5-ene-1,3,4-triol 337 and (1*R*,2*S*,3*S*,4*S*)-2-(*N*-benzylamino)-4-(^{18}O -hydroxy)cyclohex-5-ene-1,3,4-triol ^{18}O -337
(400 MHz ^1H , d_4 -MeOH)



(1*R*,2*S*,3*S*,4*S*)-2-(*N*-benzylamino)cyclohex-5-ene-1,3,4-triol 337 and (1*R*,2*S*,3*S*,4*S*)-2-(*N*-benzylamino)-4-(^{18}O -hydroxy)cyclohex-5-ene-1,3,4-triol ^{18}O -337
(100 MHz ^1H , d_4 -MeOH)



(1*R*,2*S*,3*R*,4*S*)-1-(*N*-benzylamino)cyclohex-5-ene-1,3,4-triol 338 and (1*R*,2*S*,3*R*,4*S*)-1-(*N*-benzylamino)-4-(^{18}O -hydroxy)cyclohex-5-ene-1,3,4-triol ^{18}O -338
(400 MHz ^1H , d_4 -MeOH)



(1*R*,2*S*,3*R*,4*S*)-1-(*N*-benzylamino)cyclohex-5-ene-1,3,4-triol 338 and (1*R*,2*S*,3*R*,4*S*)-1-(*N*-benzylamino)-4-(^{18}O -hydroxy)cyclohex-5-ene-1,3,4-triol ^{18}O -338
(100 MHz ^1H , d_4 -MeOH)

