Corrigendum

I. Page *i*, after line 8: insert "*p*–BDMA" = "*para*–methoxybenzyl dimethyl acetal".

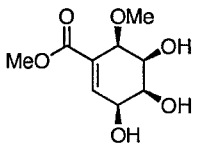
II. Page 3, line 17: replace "plasmodium" with "Plasmodium".

III. Page 4, last line: replace "Poeticus" with "poeticus".

IV. Page 14, Scheme 1.9 (**67** to **68**): replace "napthanlene" with "napthalene".

V. Page 23, line 15: delete first "of".

VI. Page 25, the correct structure of (+)–pericosine B (**115**) is:



(+)-Pericosine B (**115**)

VII. Page 54, Scheme 3.11: insert single spaces after "33%" and "Et_3N".

VIII. Page 93, line 7: replace "*R*–configuration" with (*R*)–configuration".

IX. Page 124 onwards: all the 1,3–benzodioxolyl compounds from **127** should be "5–yl" not "6–yl".

X. Page 133, lines 8 and 9: delete "benzo" and "5a,8a–yl".

XI. Page 187 and 188: compounds **279** and **277** should be named as derivatives of 5*H*–1,3–dioxolo[4,5–*f*]indol–2–one.

XII. Page 189, lines 10 and 11: compound **280** should be named as a 1,3–dioxolo 1,3–benzodioxolo[5,6–*c*][1]benzazepinone derivative.

XIII. Page 190, lines 5 and 6: the "5,6a,7,8,9,11–hexahydro" part of the name for *ent*–**18** needs to be moved earlier in the name.

Chemoenzymatic Approaches to Montanine Alkaloids: Total Synthesis of (+)-Brunsvigine

A thesis submitted for the degree of Doctor of Philosophy
of the Australian National University

by

Okanya John Kokas

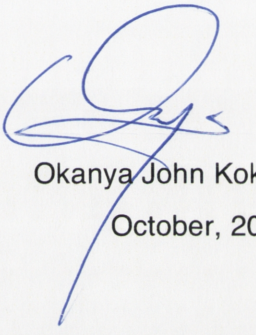
THE AUSTRALIAN NATIONAL UNIVERSITY

Research School of Chemistry
Canberra, Australia

October, 2007

Declaration

I declare that the material presented in this thesis represents the result of original work carried out by me, during the period 2003–2007 and has not been previously presented as part of an examination for any other degree. This thesis is less than 100,000 words in length. Wherever possible, established methodologies have been acknowledged by citation of the original publications from which they were derived.



Okanya John Kokas

October, 2007

Acknowledgements

With extreme gratitude, I would like to thank my PhD supervisor Professor Martin G. Banwell for his patience, encouragement and professionalism in guiding me towards a successful PhD studentship. Specifically, I am grateful that he has been able to instil confidence within me, and enable me to not only challenge my abilities as a chemist, but also to grow and develop as a person.

I would like to also give my thanks Professor Athel L. J. Beckwith for indulging me with his extraordinary knowledge of radical chemistry, particularly providing me with insightful comments on how to effect a rather difficult radical cyclization reaction that was pivotal to the success of my PhD project.

In general, I would also like to thank all past and present members of the Banwell group that I have met. In recognition of the useful advice and encouragement that I have received during my time in the group, I would like to especially thank the postdoctoral researchers: Dr Natasha Hungerford, Dr Jens Renner, Dr Jonathan Foot, Dr Daniel Offermann, Dr Delphine Dauge, Dr Mario Knoke, Dr Steffan Gross and Dr Michael Backes. Special thanks to Maria Matveenko for work on the 'Lycoricidine project', to Dr David Kvaskoff (UQ) for performing the DFT calculations, to Dr Duncan McGillivray for assistance with formatting of the appendices for this thesis, and to Dr Lorraine Axford in not only providing excellent advice, but also in assisting with the drafting of this thesis.

Being grateful for the wonderful facilities and services provided by the school, I would also like to thank Chris Blake (NMR), Dr Tony Willis (X–ray), Tony Herlt (HPLC), Gordon Lockhart (Mass Spectrometry), Vicki Withers (Microanalysis), Kurt Russell (Chemical Delivery), Joan Smith (Library) and Marilyn Holloway (Academic Secretary) for their efforts in allowing me to work efficiently and productively. Special thanks also goes to the workshop staff (Woodwork, Metalwork and Glassblowing) for their excellent skills in producing and servicing the laboratory equipment. In addition, I would like to thank the security guards that I have met during my time at the school, especially during the late nights spent in the laboratory and in the write–up room.

On a personal level, I would like to acknowledge all the people that I have had the good fortune to interact with at the Research School of Chemistry and consequently have become friends with: Jacki Kitching, Pauline Stanislawski, Andrew Phillis, Kerrie Austin, David Lupton, Matthew Smith, Mathew Jones, Mathew McDonough, Colin Jackson, Joe Hughes, Adam Perriman, Satish Chand, Amy Philbrook, Kelly Fairweather, Ollie Hutt, Giuseppe Del Signore, Nevah Tshabang, Steve McAteer, Jenn Locke, Chris Evenhuis, Gomotsang Bojase–Moleta (BJ) and David Brittain.

Finally, I would like to thank my family for always being supportive of my aspirations, especially my father (Papa, this wouldn't have been possible without you!). I appreciate the support that all of you have given me in the past.

Publications and presentations based on work carried out during the period of PhD candidature

Publications:

1. "*Chemoenzymatic Approaches to Montanine Alkaloids: Total Synthesis of (+)–Brunsvigine*". Banwell, M. G., Kokas, O. J. and Willis, A. C. *Org. Lett.*, **2007,** 9, 3503.

2. "*Chemoenzymatic Approaches to Amaryllidacae Alkaloids: Total Syntheses of ent–Lycoricidine, 3–epi–ent–Lycoridine and 4–deoxy–3–epi–ent–Lycoridine*". Matveenko M., Kokas, O. J., Banwell, M. G. and Willis, A. C. *Org. Lett.* **2007,** 9, 3683.

3. *"(2R, 3aS, 5aR, 8aR, 8bS)–4–Bromo–7,7–dimethyl–2–(4–methoxyphenyl)–3a,5a,8a,8b–tetrahydro–benzo[1,2–d:3,4–d']bis[1,3]dioxole*". Banwell, M. G., Kokas, O. J. and Willis, A. C. *Acta Cryst. Sect. E.*, **2007,** E63, o3820.

4. "*A cocrystal of (2S, 3aS, 4R, 5R, 7aS)– and (2R, 3aS, 4R, 5R, 7aS)–7–Bromo–3a,4,5,7a–tetrahydro–2–(4–methoxyphenyl)–1,3–benzodioxole–4,5–diol*".
   Banwell, M. G., Kokas, O. J. and Willis, A. C. *Acta Cryst. Sect. E.*, **2007,** E63, o4187.

Presentations:

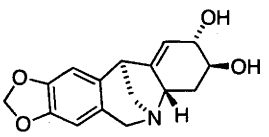
1. "*Chemoenzymatic Approach to Montanine Alkaloids: Total Synthesis of (+)–Brunsvigine*". Oral presentation at the 26th Royal Australian Chemistry Institute, NSW Branch–Organic Group Annual One Day Symposium, Canberra, Australia, November, 2006.

2. "*Chemoenzymatic Approaches to Montanine Alkaloids*". Poster presentation at the 17th Southern Highlands Conference on Heterocyclic Chemistry (SHCH), Moss Vale, Australia, August, 2006.

3. "*Towards the Total Synthesis of (+)–Brunsvigine*". Poster presentation at the 20th Royal Australian Chemistry Institute Organic Chemistry Conference (ISMC/RACIOC), Cairns, Australia, July, 2004.

Abstract

(–)–Pancracine (**13**) and (–)–brunsvigine (**18**) are representative members of the montanine–class of *Amaryllidaceae* alkaloid that possess a variety of psychopharmacological activities including anxiolytic, antidepressive and anticonvulsive effects. Although there has been extensive effort directed toward the synthesis of *Amaryllidaceae* alkaloids more generally, the construction of the novel 5,11–methanomorphanthridine ring system associated with the title compounds has received much less attention from synthetic organic chemists. Studies within the Banwell group have resulted in the establishment of an operationally simple route to the 5,11–methanomorphanthridine ring system and, thereby, a formal total synthesis of (±)–(**13**). This thesis describes a more sophisticated and general method for the asymmetric assembly of montanine alkaloids from *cis*–1,2–dihydrocatechols of the general form **92**, compounds which are available in large quantity and enantiomerically pure form *via* the whole–cell biotransformation of the corresponding halobenzenes.



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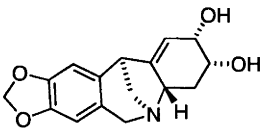

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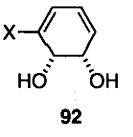
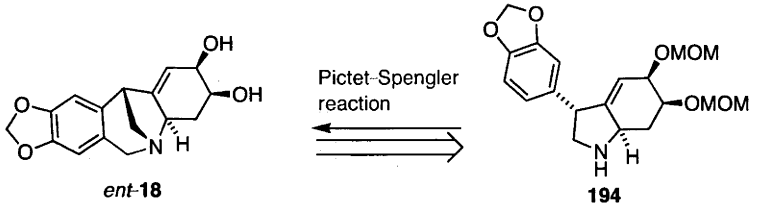


92

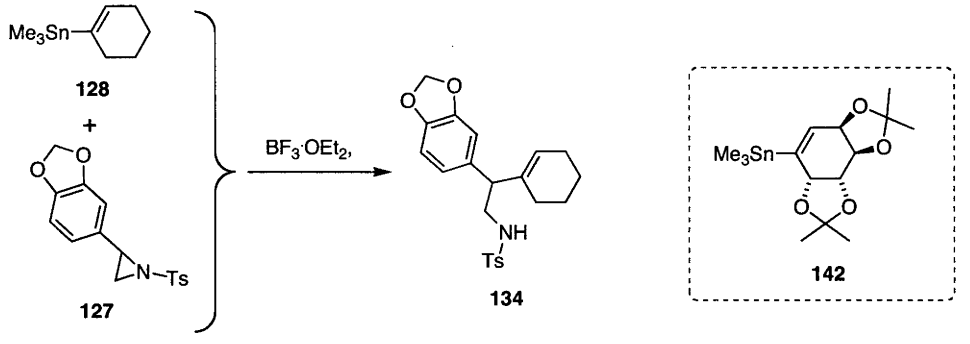
X = Cl, Br, I,

Chapter One begins with an introduction to montanine alkaloids and this is followed by an overview of the synthetic strategies previously used to obtain these natural products. The possibility of using the enantiopure *cis*–1,2–dihydrocatechols **92** and as building blocks for the enantioselective synthesis of the montanine alkaloid (+)–brunsvigine (*ent*–**18**) is then introduced and key challenges defined. These include establishing a functional route to the relevant 3–arylhexahydroindole (e.g. compound **194**) that could be used as a substrate for the key Pictet–Spengler reaction.

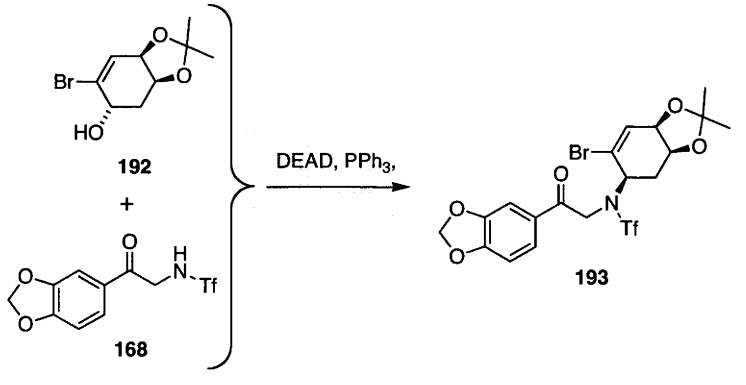


ent-**18** **194**

Approach A (Chapter Two) to 3–arylhexahydroindoles details a successful model study in which BF_3•OEt_2–mediated ring–opening of aziridine **127** was achieved using alkenyl stannane **128** as the nucleophile. However, attempts to effect such a process with oxygenated alkenyl stannanes, such as compound **142**, failed.

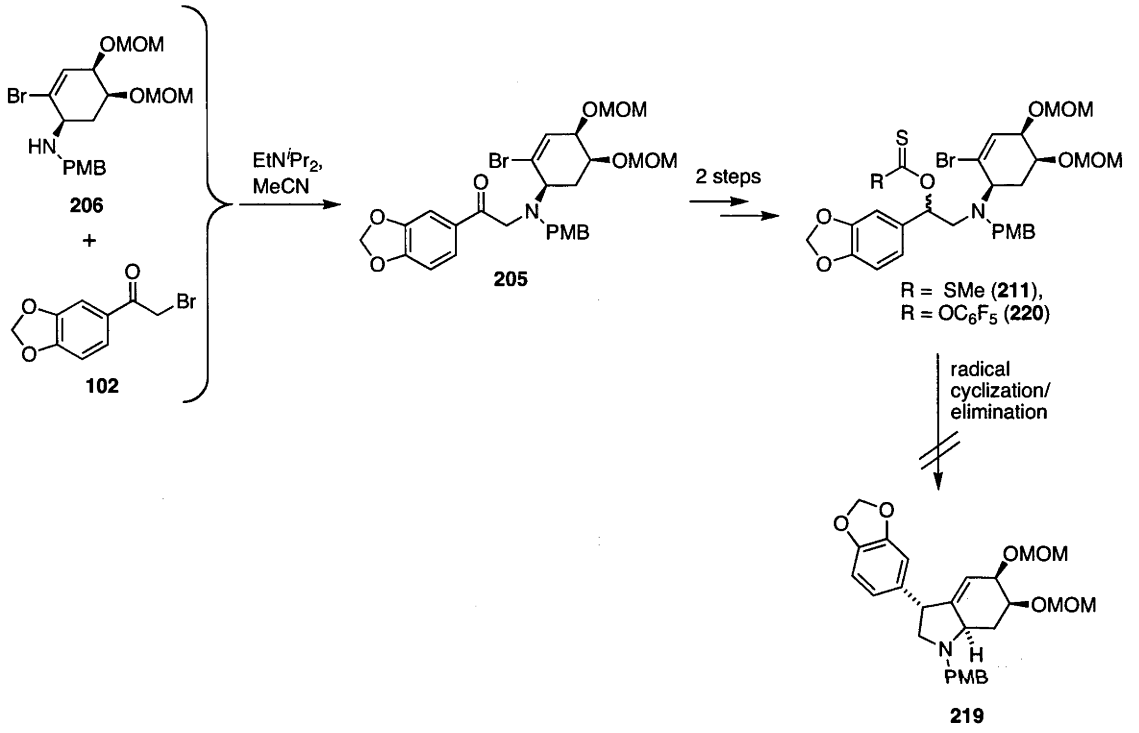


This outcome meant that a revised approach was required. Accordingly, Chapter Three details *Approach B* in which an intermolecular Mitsunobu reaction was investigated. Thus, following a successful model study, the coupling of alcohol **192** with keto–amide **168** was effected and so providing compound **193**. Frustratingly, this otherwise significant result was found to be irreproducible.

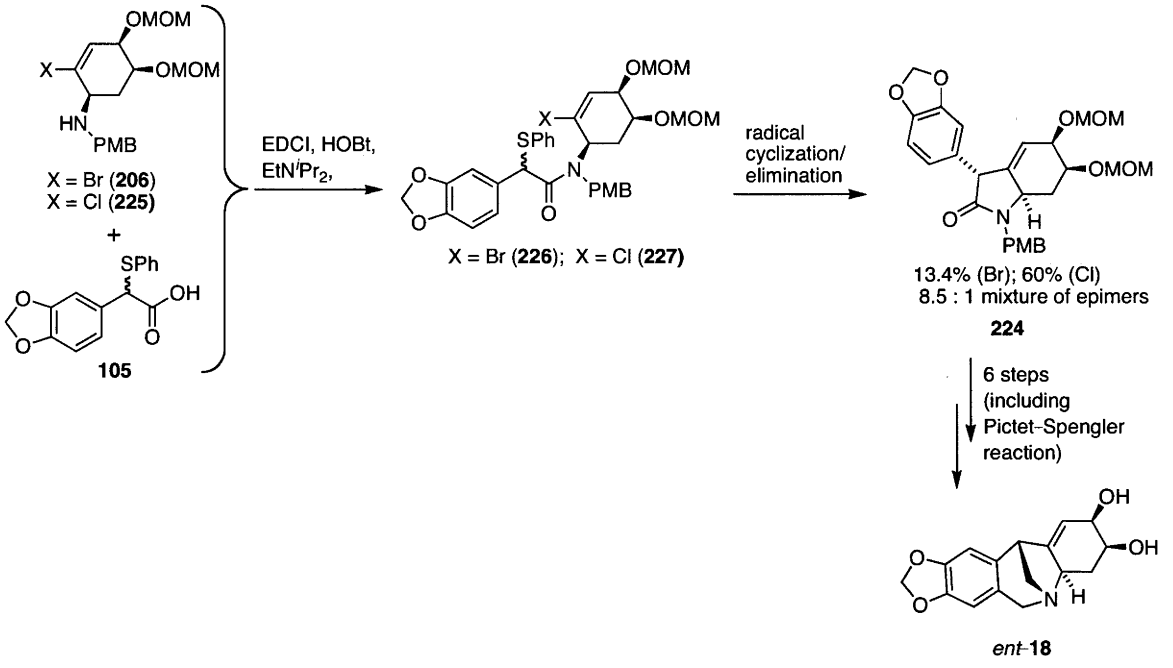


Approach C (Chapter Four), as an alternate method for the preparation of 3–arylhexahydroindoles, involved direct *N*–alkylation reaction of 2°–amine **206** with α–bromoketone **102** to give 3°–amine **205**. This pleasing outcome meant that the preparation of appropriate radical precursors (i.e. **211** and **220**) could be carried out. However, in doing so,

only low yields of the required compounds were achieved. Nevertheless, sufficient quantities of these materials could be obtained so as to test the key radical cyclization process. Sadly, this test failed to provide the expected product **219**.



The final and ultimately successful approach (*Approach D*), detailed in Chapter Five, involved the amide coupling of bromo– and chloro–derivatives of 2°–amines **206** and **225** with acid **105** to give amides **226** and **227**, respectively. Subjecting each of these compounds to a radical cyclization/halogen atom elimination reaction then provided the required 3–arylhexahydro–oxindole **224** in 15% (from **226**) and 67% (from **227**), respectively, and as a 8.5:1 mixture of epimers with the major one possessing the stereochemistry required for the preparation of (+)–brunsvigine (*ent*–**18**). Indeed, elaboration of the last compound **224** (as a mixture of epimers) over six steps, including one involving the pivotal Pictet–Spengler reaction, provided final the target, *viz.* compound *ent*–**18**, the enantiomer of the alkaloid (–)–brunsvigine.



Chapter Six provides a summary of the chemistry detailed in the preceding chapters and outlines possible future directions for the research.

The following abbreviations have been used throughout this thesis:

AIBN	1,1'–azobisisobutyronitrile
atm	atmosphere
Ac	acetyl
AcOH	acetic acid
ACE–Cl	*alpha*–chloroethyl chloroformate
Ar	aryl
Aq.	aqueous
i–Bu	*iso*-butyl
n–Bu	butyl
t–Bu	*tertiary*–butyl
Boc	*tertiary*–butoxycarbonyl
$BF_3{\cdot}OEt_2$	boron trifluoride diethyl etherate
Bn	benzyl
Bz	benzoyl
°C	degrees Celsius
Conc.	concentrated
c	concentration (g/100 mL)
ca.	*circa* (approximately)
δ	chemical shift (parts per million)
DBU	1,8–diazabicyclo[5.4.0]undecene
DMAP	4–(*N,N*-dimethylamino)pyridine
2,2–DMP	2,2–dimethoxypropane
DCC	dicyclohexylcarbodiimide
DEAD	diethyl azodicarboxylate
DIAD	diisopropyl azodicarboxylate
DIBAL–H	diisobutylaluminium hydride
DMDO	dimethyldioxirane
DME	1,2–dimethoxyethane
DDQ	2,3–dichloro–5,6–dicyano–1,4–benzoquinone
DPPA	diphenylphosphoryl azide
DCE	1,2–dichloroethane
DMF	*N,N*–dimethylformamide

equiv. or eq.	equivalent(s)
e.e.	enantiomeric excess
E	*entgegen* (opposite)
EDCI	1–ethyl–3– (3'–dimethylaminopropyl)carbodiimide
Et	ethyl
eV	electron volt
FGI	functional group interconversion(s)
g	gram(s)
h	hour(s)
hv	light
HRMS	high resolution mass spectrum
Hz	Hertz
HOBt	1–hydroxybenzotriazole
IR	infrared
^{i}Pr	*iso*-propyl
J	coupling constant (Hz)
kcal	kilocalorie(s)
KHMDS	potassium hexamethyldisilazide
$LiAlH_4$	lithium aluminium hydride
mol	mole
M	molarity (moles per litre)
L	litre
MS	mass spectrum
MeCN	acetonitrile
mp	melting point
mins	minutes(s)
MeOH	methanol
$M^{+\bullet}$	molecular ion
m/z	mass–to–charge ratio
Me	methyl
MVK	methyl vinyl ketone
Ms	mesyl (methanesulfonyl)
MOM	methoxymethyl
NOE	nuclear Overhauser enhancement
NMO	*N*–methylmorpholine–*N*–oxide

NMR	nuclear magnetic resonance
NCS	*N*-chlorosuccinimide
$Pd(PPh_3)_4$	tetrakis(triphenylphosphine)palladium(0)
pyr.	pyridine
p–TsCl	*para*–toluenesulfonyl chloride
p–TsOH	*para*–toluenesulfonic acid
pK_a	acid dissociation constant
PPh_3	triphenylphosphine
Pd/C	palladium on carbon
PCC	pyridium chlorochromate
Ph_2PCl	chlorodiphenylphosphine
Ph	phenyl
PMB	*para*–methoxybenzyl
PMP	*para*–methoxyphenyl
psi	pound–force per square inch
quant.	quantitative
R	*rectus* (clockwise)
R_f	retardation factor
S	*sinistrus* (counterclockwise)
TMEDA	tetramethylethylenediamine
THF	tetrahydrofuran
TBS	*tertiary*-butyldimethylsilyl
Tf_2O	triflic anhydride (trifluoromethanesulfonyl anhydride)
TMAD	trimethyl azodicarboxamide
TTMSS	tris(trimethylsilyl)silane
TMS	trimethylsilyl
Tf	triflyl
Ts	tosyl (*para*–toluenesulfonyl)
TLC	thin layer chromatography
UV	ultraviolet
v/v	volume–to–volume (ratio)
ν_{max}	infrared absorption maxima (cm^{-1})
w/v	weight–to–volume (ratio)
Z	*zusammen* (together)

>	greater than
<	less than

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CHAPTER ONE

Studies Directed Towards the Preparation of Montanine Alkaloids: Chemoenzymatic Approaches to (+)-Brunsvigine

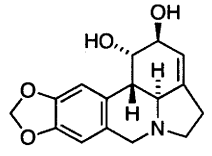
Amaryllidaceae: Candelabra flower
[Source plant for (–)–Brunsvigine]

1.1. Introduction

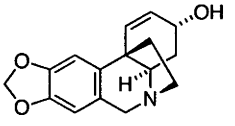
1.2. *Amaryllidaceae* Alkaloids

1.2.1. Isolation and Structural Properties

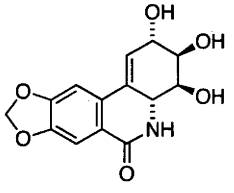
Amaryllidaceae alkaloids have been isolated from the plants of almost all the genera of the family *Amaryllidaceae*[1] that are distributed throughout the tropics and warm temperate regions of Asia, Australia, Africa and America.[2] Such compounds almost always incorporate isoquinoline–based subunits. Thus far, over 200 different compounds have been obtained and many of their structures have been determined. Lycorine (**1**), crinine (**2**), lycoricidine (**3**) and galanthamine (**4**) are representative of the most common structural types and so highlight the wide–range of molecular architectures encountered within this large class of alkaloid (**Figure 1.1**). There is also a corresponding variation in the pharmacological properties of such compounds.



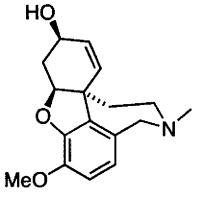
Lycorine (**1**)



Crinine (**2**)



Lycoricidine (**3**)

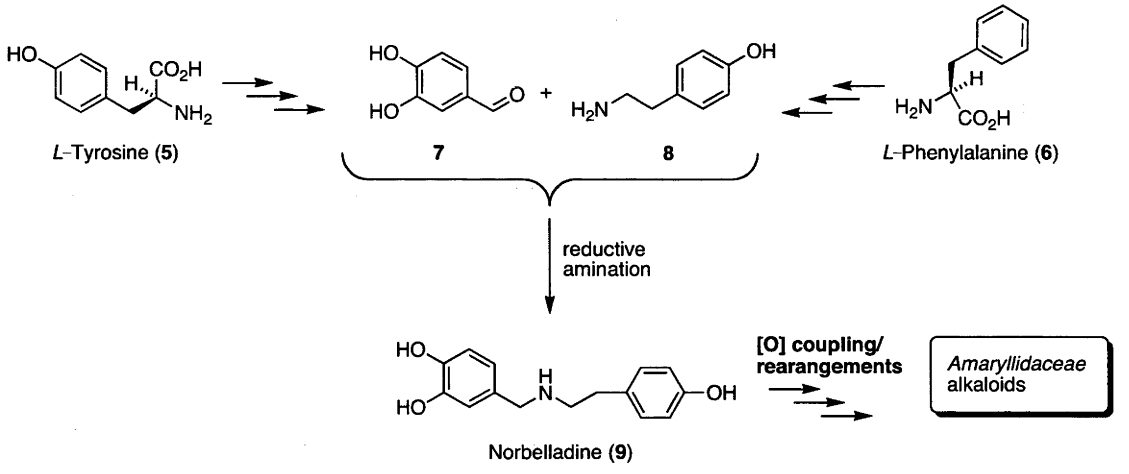


Galanthamine (**4**)

Figure 1.1: *Representative members of the major sub–classes of* Amaryllidaceae *alkaloids*

1.2.2. Biosynthesis

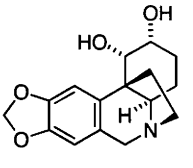
Biogenetically speaking, *Amaryllidaceae* alkaloids are derived from *L*–tyrosine (**5**) and *L*–phenylalanine (**6**). Thus, *L*–tyrosine is converted, over several steps, into protocatecualdehyde (**7**) whilst *L*–phenylalanine (**6**) is transformed into tyramine (**8**) (**Scheme 1.1**). The imine derived from condensation of protocatecualdehyde (**7**) with 1°–amine **8** is then reduced to the corresponding *N*–benzyl–*N*–*β*–phenylethylamine precursor unit, norbelladine (**9**) which, by various oxidative coupling and rearrangement processes, eventually gives rise to the observed structures associated with the title alkaloids.[3,4] Details of one such sequence are presented in the following section.



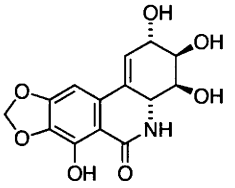
Scheme 1.1: *Early stages of the biosynthesis of* Amaryllidaceae *alkaloids*

1.2.3. Biological Activity

Extensive assessments of the pharmacological properties of *Amaryllidaceae* alkaloids have been carried out. For example, the various members of the lycorine–class of alkaloids have been reported[5] to be active against RNA–containing flaviviruses such as Japanese encephalitis, yellow fever and dengue–type 4 viruses while members of the crinine–class of alkaloids have been reported[1,5] to posses cytotoxic and antimalarial properties. Indeed, all the isolated alkaloids of this class have shown antimalarial activity against strains of *plasmodium falciparum*, while a crinine–type alkaloid, amabiline (**10**), has been reported[5] to be 10,000 times more active than the commercial antimalarial drug chloroquine.



Amabiline (**10**)



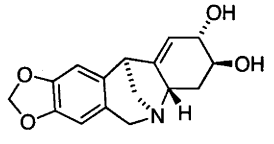
Narciclasine (**11**)

Members of the lycoricidine class of alkaloids have also attracted attention as potential antineoplastic agents. For example, narciclasine (**11**) has been shown to posses strong antitumor activity (up to 60% inhibition) against *Agrobacterium tumefacienns* found in potatoes. Members of the galanthamine class of alkaloids, in particular galanthamine itself (**4**), have also received a great deal of attention because of their ability to inhibit acetylcholinesterase activity and such that they have found use in the treatment of Alzheimer's disease.[1,4]

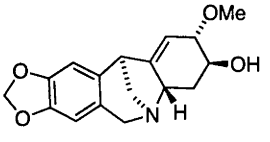
1.3. The Montanine–Subclass of *Amaryllidaceae* Alkaloids

1.3.1. Isolation and Structural Properties

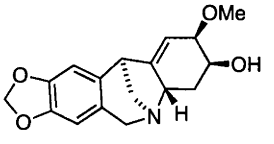
The montanine alkaloids posses the unique 5,11–methanomorphanthridine[6] framework and are a minor group in the *Amaryllidaceae* alkaloid family since only nine members have been identified thus far (**Scheme 1.2**).[4,7] The first three members (**13–15**) of this *Amaryllidaceae* subclass were isolated by Wildman and co–workers[8] from *Haemanthus* species while others (**16–20**) were obtained from a variety of species including *Pancratium maritimum*, *Narcissus Poeticus*, *Narcissus angustifolius* and *Brunsvigia cooperi* (**Figure 1.2**)[9,10]



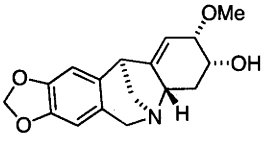
(-)-Pancracine (**13**)



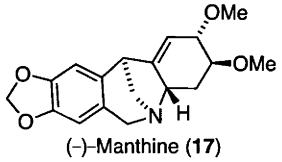
(-)-Montanine (**14**)



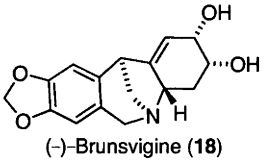
(-)-Coccinine (**15**)



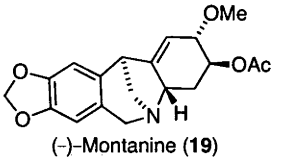
(-)-Manthidine (**16**)



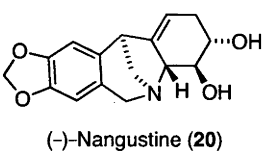
(-)-Manthine (**17**)



(-)-Brunsvigine (**18**)



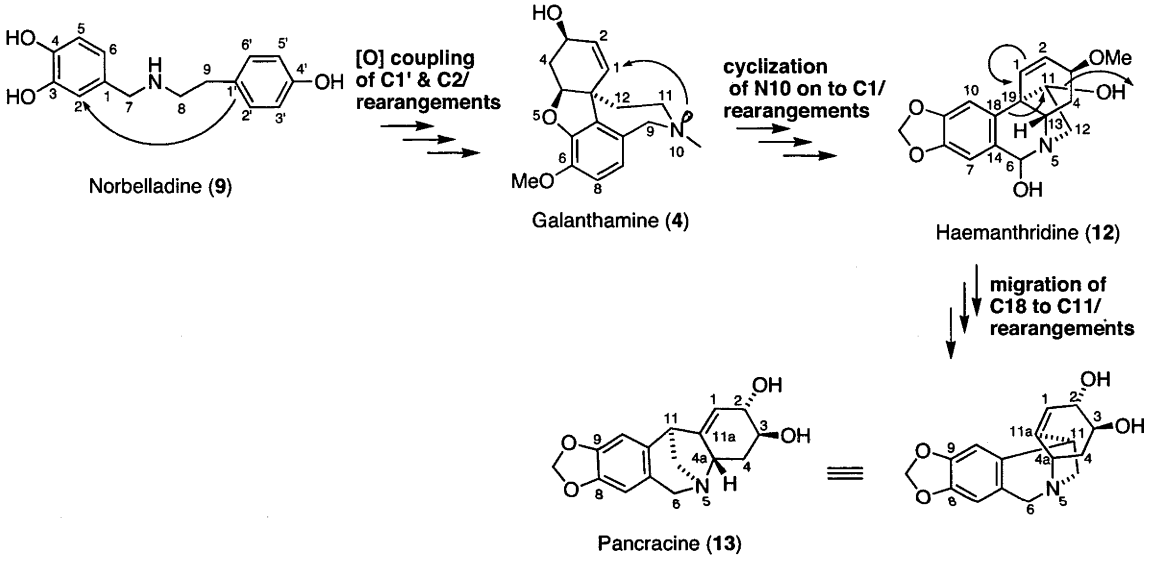
(-)-Montanine (**19**)



(-)-Nangustine (**20**)

Figure 1.2: *Members of the montanine class of alkaloid*

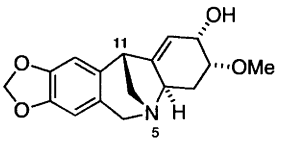
The formation of the pancracine framework is thought to occur as the result of a migration of C18 to C11 in the crinine–type precursor **12**. The 5,10–ethanomorphanthridine framework, within the crinine–type precursor **12** is, in turn, believed arise from galanthamine (**4**) *via* cyclization of N10 to C1 and this is then followed by various other rearrangements. Norbelladine (**9**), a common biosynthetic precursor, is itself thought to be transformed *via* well known intramolecular oxidative coupling between C'1 and C2 followed by various rearrangements to give the galanthamine–type precursor **4**.[3]



Scheme 1.2: *Origin of the 5,11–methanomorphanthridine framework of the montanine alkaloids*

The assignments of the illustrated structures to compounds **13–19** were originally based on chemical degradation and interconversion studies.[11,12] However, in 1974 the structure and absolute configuration of one member, (–)–brunsvigine (**18**), was secured by single–crystal X–ray analysis of the *bis*(*p*–bromobenzoate) derivative.[13] Chemical correlations then followed to secure the structures of many other members of the series.

Interestingly, the isolation of (+)–montabuphine (**21**)[14] from *Boophane flava,* found in the winter rainfall areas of South Africa, suggests that both enantiomeric forms of the montanine alkaloids can be found in nature.



(+)-Montabuphine (**21**)

1.3.2. Biological Activity

After the discovery that the alkaloid galanthamine (**4**) is a potent acetylcholinesterase (ACE) inhibitor and, thus, a very important agent for the symptomatic treatment of Alzheimer's disease,[15] the interest in the isolation and characterization of *Amaryllidaceae* alkaloids increased dramatically. Indeed, a recent pharmacological study revealed that the montanine alkaloids, in particular montanine (**14**) itself, possess a variety of psychopharmacological activities including anxiolytic, antidepressive and anticonvulsive effects.[16] In addition, compounds incorporating an ether function at C2 have been shown to exhibit weak hypotensive activity.[16,17] Therefore, and given the structural similarities between the montanine alkaloids and other biologically active *Amaryllidaceae* alkaloids, synthetic efforts in this area are warranted.

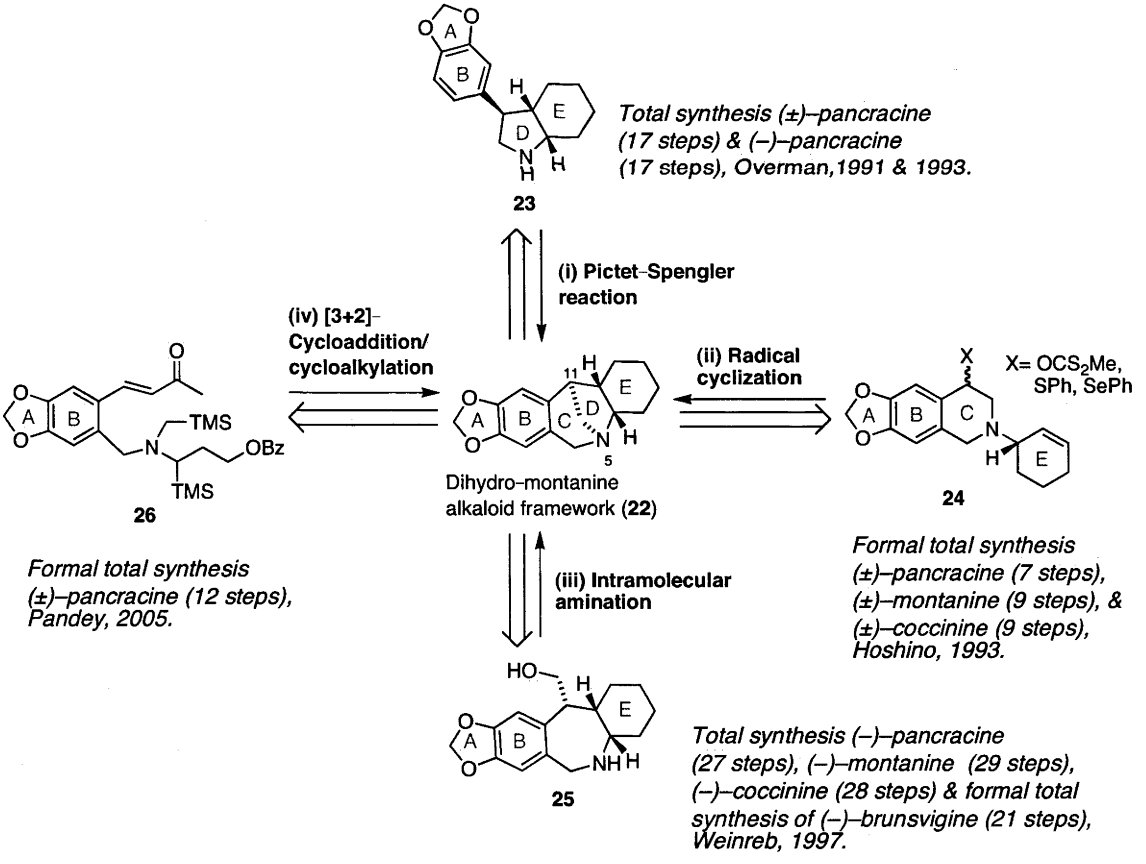
1.3.3. Synthetic Strategies for Obtaining the Montanine Alkaloids

Before discussing the strategy that has been developed through the Author's studies, a survey of existing synthetic protocols available for constructing the montanine alkaloid framework are now presented.

Although massive synthetic effort has been directed toward almost all other types of *Amaryllidaceae* alkaloids, the montanine subclass has received relatively little attention.[8,18] However, due to their unique architectures (particularly the presence of a 5,11–methanomorphanthridine framework) and recently revealed pharmacological potential,[3] they now represent attractive targets for synthetic chemists. Analysis of the literature reveals several successful strategies that have allowed six groups to achieve total syntheses of members of the montanine–type alkaloids. Overman was the first to publish (In 1991) a total synthesis of (±)–pancracine (**13**).[19] Six months later, Hoshino reported total syntheses of (±)–pancracine (**13**), (±)–montanine (**14**) and (±)–coccinine (**15**).[20] In 1993, Hoshino again reported a modified and improved approach to the same targets[21] while, in the same year, Overman published the synthesis of (–)–pancracine (**13**), and thus providing the first asymmetric synthesis of a montanine alkaloid.[22] Weinreb reported elegant, enantioselective

total syntheses of (–)–pancracine (**13**), (–)–montanine (**14**), (–)–coccinine (**15**) and a formal total synthesis of (–)–brunsvigine (**18**) in 1997[23] while, in the following year, Pearson[24] reported the enantioselective synthesis of (+)–coccinine (*ent*–**15**), the first total synthesis of a member of the less common enantiomeric series. Ikeda published a formal total synthesis of (±)–pancracine (**13**) in 1999.[25] Two years later Banwell also reported a formal total synthesis of (±)–pancracine (**13**)[26] while Sha published the first total synthesis of (–)–brunsvigine (**18**).[27] Most recently (2005), Pandey reported a formal total synthesis of (±)–pancracine (**13**).[18]

Analyses of the abovementioned syntheses reveals that the strategies used to construct the pentacyclic 5,11–methanomorphanthridine framework, **22**, of these alkaloids have largely been confined to: (i), the application of a Pictet–Spengler reaction to **23**; (ii), a radical cyclization reaction to **24**; (iii), intramolecular alkylation of amino–alcohol **25**; or finally, (iv), a [3+2]–cycloaddition/cycloalkylation reaction involving compound **26** as the substrate (**Figure 1.3**).

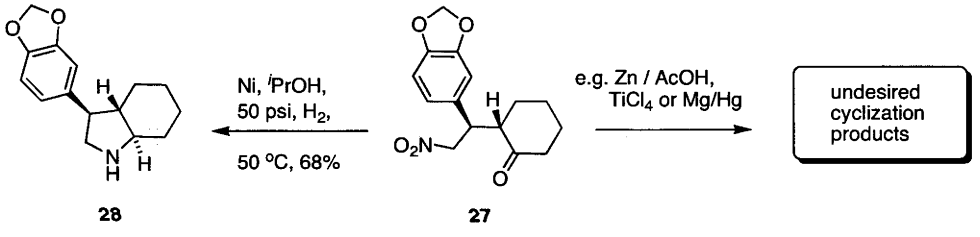


Scheme 1.3: *Synthetic strategies employed in obtaining the montanine alkaloid framework* ***22*** *lacking the E–ring double bond*

A comprehensive review of each strategy, detailing all the relevant formal and total syntheses of the montanine alkaloids, is beyond the scope of this introduction. However, an overview of each type of synthetic strategy that has been used to prepare these alkaloids is presented below.

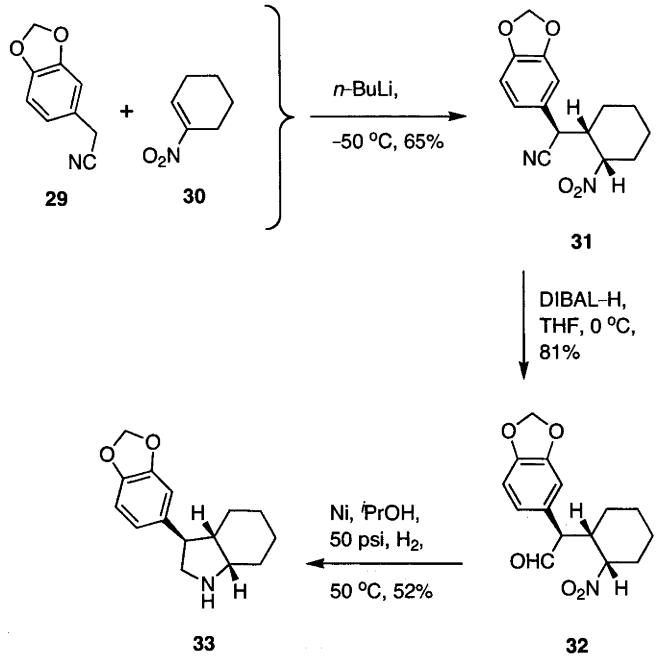
1.3.3.1. Pictet–Spengler Reaction Strategy

One of the first synthetic strategies directed towards montanine alkaloids employed the title reaction.[28] Thus, following exhaustive investigations on the reductive cyclizations of nitroketones to 3–arylhexahydroindoles, Sanchez[28] was able to convert nitroketone **27** into 3–aryloctahydroindole **28** (**Scheme 1.3**). However, this compound possesses the wrong stereochemistry for the pivotal Pictet–Spengler reaction and such that the installation the C–ring of the montanine alkaloid framework could not be generated by such means.



Scheme 1.3: *Pictet–Spengler reaction strategy – Sanchez approach to the montanine alkaloid framework*

Indeed, subjection of nitroketone **27** to various cyclization conditions produced a range of polyhydroindole derivatives, but none of these possessed the stereochemistry required for elaboration to the montanine alkaloid framework. Fortunately, a 3–aryloctahydroindole possessing the correct (*cis*–) stereochemistry, was obtained *via* a modified approach (**Scheme 1.4**), involving an initial reaction of phenylacetonitrile **29** and nitrocyclohexene **30** to afford the β–nitronitrile **31**. Subjection of this last compound to a DIBAL–H reduction followed by reductive cyclization of the product aldehyde **32** with a nickel catalyst then produced the required 3–aryloctahydroindole **33**.

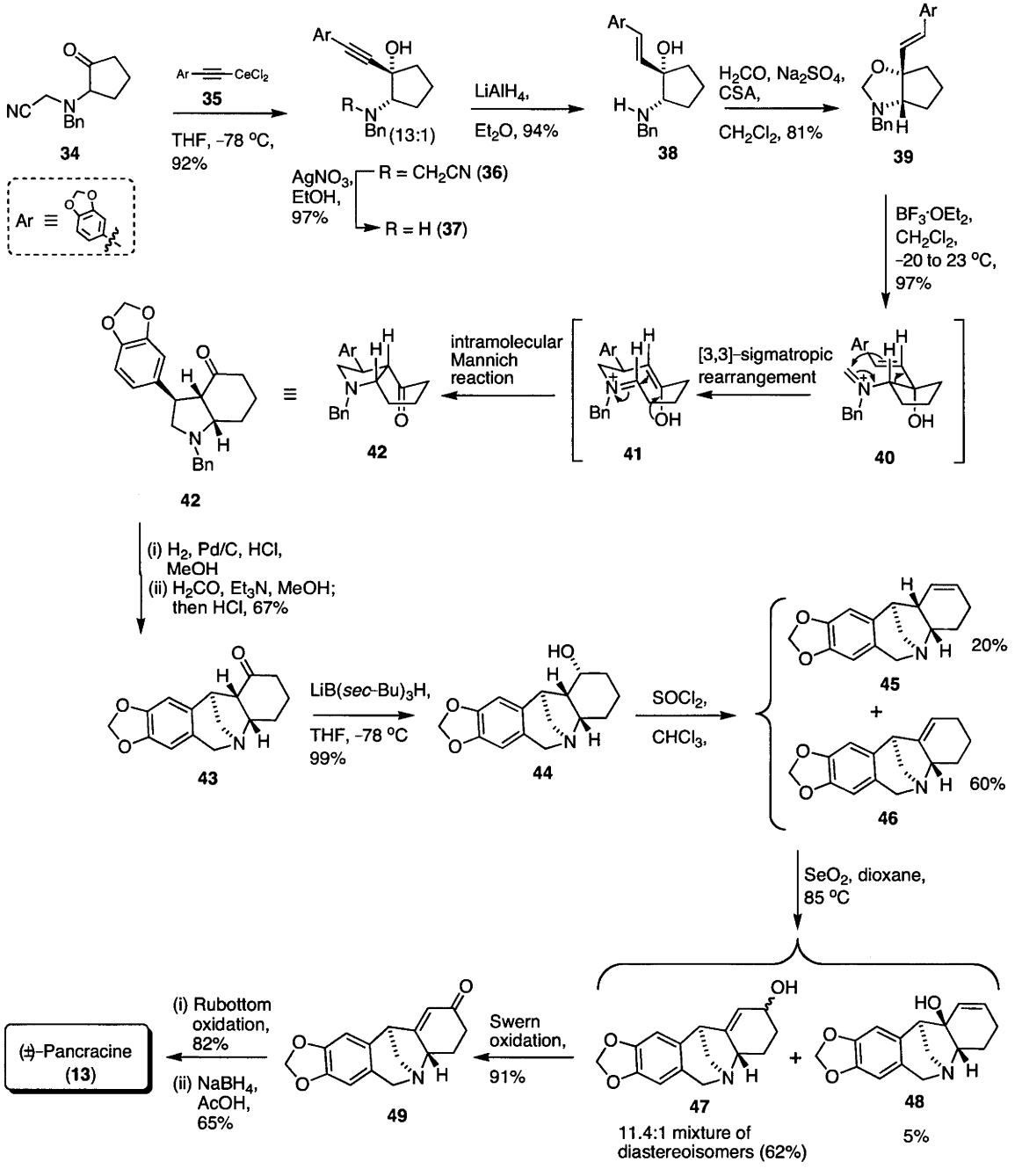


Scheme 1.4: *Modified Sanchez approach to the montanine alkaloid framework*

However, due to the low yields of the relevant products and because of a lack of good levels of stereocontrol, this reaction sequence was abandoned since it was considered unlikely to provide a useful synthetic route to montanine alkaloids.

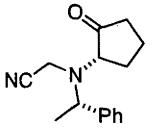
Overman[19] was able to overcome problems of the type described above by utilizing an elegant [3,3]–sigmatropic rearrangement followed by an intramolecular Mannich reaction to construct 3–aryloctahydroindoles possessing the *cis*–stereochemistry required for engagement in the key Pictet–Spengler reaction. Ultimately this sequence allowed for the establishment of the first stereocontrolled total synthesis of (±)–pancracine (**13**). This commenced with the readily available aminocyclopentanone **34** (**Scheme 1.5**), which was treated with the alkynylcerium reagent **35** to afford the propargyl alcohol **36** in a highly diastereoselective manner. The removal of the cyanomethyl protecting group within compound **36** was achieved using $AgNO_3$ and the resulting propargyl alcohol, **37**, was then reduced with $LiAlH_4$ to give allylic alcohol **38**. Treatment of this last compound with formalin then provided oxazole **39** in an overall yield of 74% from precursor **36**. Treatment of compound **39** with $BF_3{\cdot}OEt_2$ in CH_2Cl_2 initiated the key [3,3]–sigmatropic rearrangement (to give **40**) which was followed by an intramolecular Mannich reaction (*via* intermediate **41**)[29,30]

to produce 3–aryloctahydroindole **42** with high stereoselectivity and in excellent yield. In order to obtain the full target framework, all that remained was the hydrogenolysis of the *N*–benzylamine **42** and subjection of the ensuing 2°–amine to the pivotal Pictet–Spengler reaction. This sequence proved to be highly effective and afforded ketone **43** in 67% overall yield.



Scheme 1.5: *Overman's[19] synthesis of (±)–pancracine (**13**) using a Pictet–Spengler end–game*

Stereoselective reduction of compound **43** provided alcohol **44**, that underwent dehydration on exposure to $SOCl_2$ to give a mixture of products **45** and **46** with the desired one, **46**, being obtained in 60% yield. Allylic oxidation of this mixture of alkenes with SeO_2 then gave allylic alcohols **47** and **48** in 62% and 5% yields, respectively. Good yields were only obtained in this last step with the addition of Celite® to the heterogenous reaction mixture. Oxidation of alcohol **47** under Swern conditions[31] then provided the required enone **49**. With a view to installing the necessary hydroxyl groups at C2 and C3, enone **49** was subjected to Rubottom oxidation conditions[32] to give an α–hydroxyketone that was reduced with $NaBH(OAc)_3$. This finally provided (±)–pancracine (**13**) in 14% overall yield and in 17 steps from aminocyclopentanone **34**. The utility of the [3,3]–sigmatropic rearrangement/intramolecular Mannich reaction sequence and the subsequent Pictet–Spengler reaction processes have been highlighted in Overman's subsequent report[22] of the first enantioselective total synthesis of (–)–pancracine (**13**) from easily obtained and enantiopure *(S)*–aminoketone **50**.

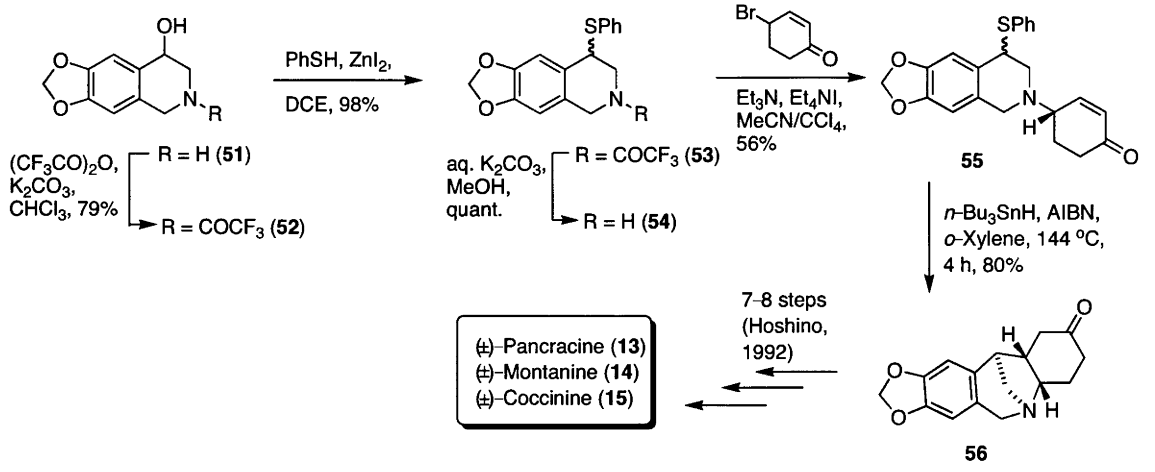


50

1.3.3.2. Radical Cyclization Strategy

An approach to the montanine alkaloids pioneered by Hoshino[21] serves to showcase the utility of radical cyclization processes in the synthesis of these types of natural products. This method allowed for the late–stage installation of the D–ring *via* a *5–exo–trig* cyclization protocol. The necessary radical cyclization precursor was obtained, after a substantial effort, from tetrahydroisoquinonol **51** (**Scheme 1.6**). Thus, *N*–selective trifluoroacetylation of this material gave tetrahydroisoquinonol **52** that was subjected to a thiolation reaction using PhSH in the presence of ZnI_2 and so generating phenylsulfide **53** in 88% yield over the two steps. Hydrolysis of compound **53** gave tetrahydroisoquinoline **54** that underwent *N*–alkylation with 4–bromocyclohex–2–enone to afford radical precursor phenylsulfide **55** as an inseparable and 1:1 mixture of diastereoisomers. Subjection of this mixture to optimised radical cyclization conditions then furnished the desired montanine alkaloid framework **56** in excellent yield. Subsequent and conventional[19,33] manipulation of product **56**

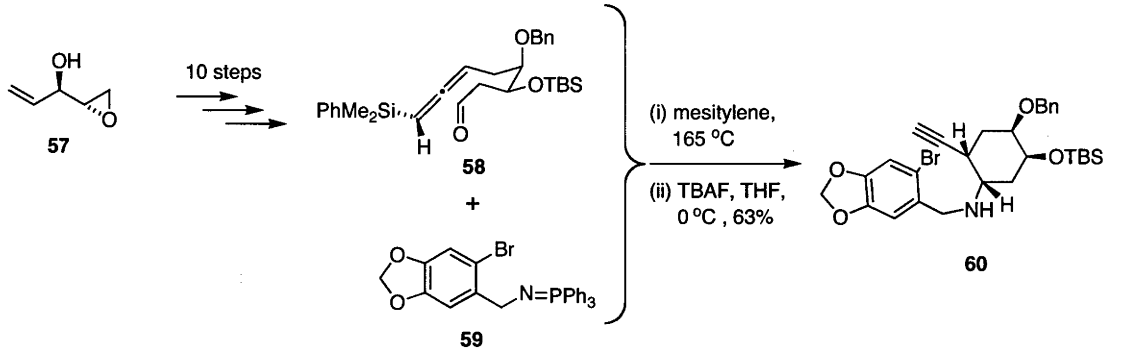
lead to previously described precursors to the montanine alkaloids (±)–pancracine (**13**), (±)–montanine (**14**) and (±)–coccinine (**15**). As such, this work represented the formal total syntheses of these alkaloids.[33]



Scheme 1.6: *Hoshino's approach to (±)–pancracine (**13**), (±)–montanine (**14**) and (±)–coccinine (**15**) using a radical cyclization strategy*

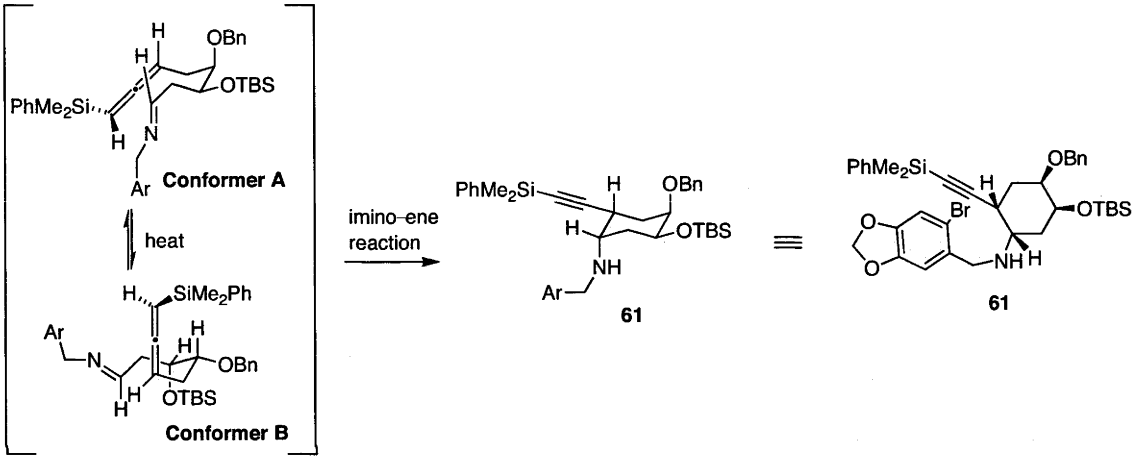
1.3.3.3. Intramolecular Amination Reaction Strategy

An intramolecular amination strategy has also been successfully applied in the construction of the montanine alkaloid framework. Weinreb,[34] for instance, reported elegant and enantioselective syntheses of (–)–pancracine (**13**), (–)–montanine (**14**) and (–)–coccinine (**15**) using novel allenyl silane chemistry followed by an intramolecular amination reaction. Thus, as shown in **Scheme 1.7**, the synthesis involved the preparation of alkyne **60** using the enantiomerically pure hydroxy epoxide **57** as starting material. The latter compound, which is readily available *via* a Sharpless asymmetric epoxidation of divinylcarbinol, could be converted, over ten steps, into aldehyde **58**.



Scheme 1.7: *Intramolecular amination strategy – Weinreb's preparation alkyne **60***

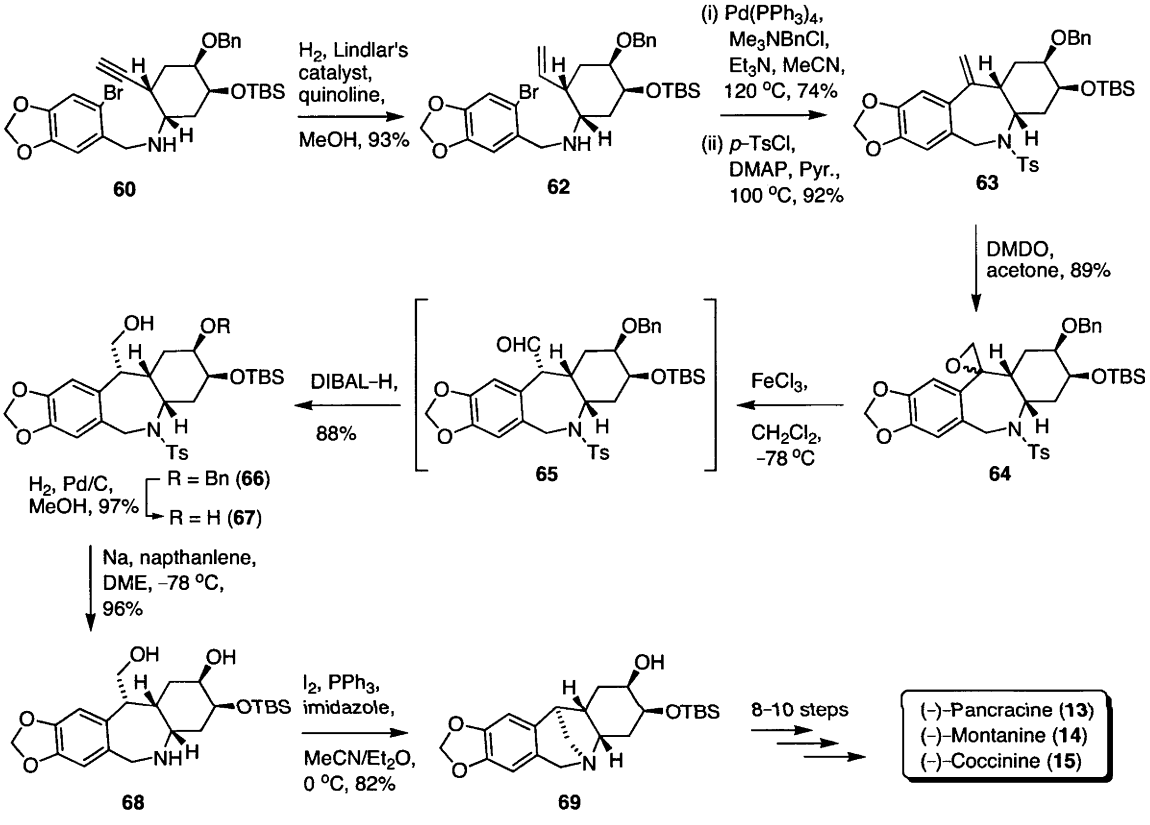
Condensation of compound **58** with iminophosphorane **59**[35] afforded an imine that, upon heating, underwent a concerted imino–ene reaction to provide, after desilylation, alkyne **60** as a single stereoisomer in 63% yield over the two steps. The formation of a single stereoisomer *via* this sequence was gratifying but not unforeseen. Thus, close inspection of this transformation (*viz* **58** + **59** → **60**) reveals two imine conformers, **A** and **B**, both of which are capable of engaging in the pivotal thermal imino–ene reaction (**Scheme 1.8**). However, this had no consequence for the synthesis since both conformers lead to the same stereoisomeric form of the cyclization product **61**.



Scheme 1.8: *Intramolecular amination strategy – Weinreb's application of the imino–ene reaction to the synthesis of a montanine alkaloid precursor*

Alkyne **60** was partially hydrogenated in the presence of Lindlar's catalyst to give the terminal olefin **62** that was subjected to a Heck cross–coupling reaction leading to the formation of an exocyclic alkene, which was *N*–protected to furnish sulfonamide **63** (**Scheme 1.9**). A number of attempts were made to produce α–hydroxymethyl compound **66** *via* hydroboration reactions, but only mixtures of stereoisomeric products were observed. Hence, an alternative route was pursued that involved epoxidation of the olefin with DMDO. Exposure of the product epoxide, **64**, to $FeCl_3$ at low temperature then lead to aldehyde **65**, which was obtained as a single stereoisomer. *In situ* reduction of compound **65** with DIBAL–H at –78 °C produced the desired α–hydroxymethyl **66** in 88% over the two steps. Catalytic hydrogenation of compound **66** with 10% Pd/C in MeOH then gave alcohol **67**, which was subjected to sodium naphthalenide–mediated cleavage of the *N*-tosyl group to produce the key amino–diol **68**. Treatment of this last compound with imidazole, PPh_3 and iodine at 0 °C

effected the pivotal intramolecular amination reaction and so affording the desired functionalised montanine alkaloid framework **69** in 94% yield. Subsequent protecting group manipulations then lead to total syntheses of (–)–pancracine (**13**), (–)–montanine (**14**) and (–)–coccinine (**15**).

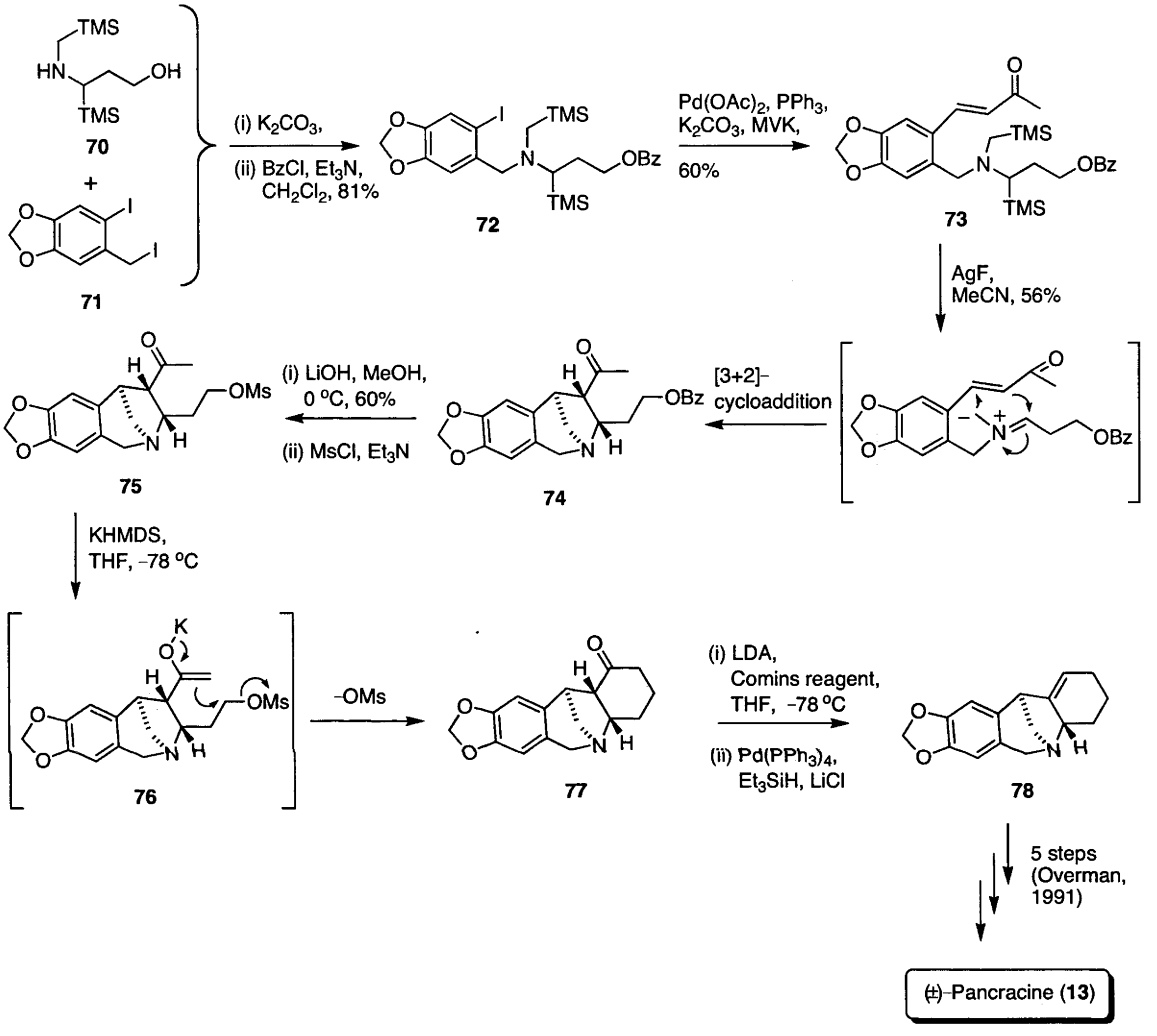


Scheme 1.9: *Weinreb's completion of total syntheses of (–)–pancracine (**13**), (–)–montanine (**14**) and (–)–coccinine (**15**)* via *an intramolecular amination strategy*

1.3.3.4. [3+2]–Cycloaddition/Cycloalkylation Strategy

Another method for the construction of montanine framework, the [3+2]–cycloaddition/cycloalkylation strategy reported by Pandey,[18] involves a two–step protocol resulting in the installation of the C–, D– and E–rings. As shown in **Scheme 1.10**, the synthesis began with the preparation of the necessary cycloaddition precursor. Thus, silylamine **70** (prepared from 3–aminopropanol) and aryl di–iodide **71** (readily obtained from piperonoyl alcohol) underwent a K_2CO_3–promoted coupling reaction followed by benzoylation using benzoyl chloride to produce silylamine **72** in 81% over the two steps.

Heck coupling of this last compound with excess methyl vinyl ketone (MVK) then provided the key cycloaddition precursor **73**.



Scheme 1.10: *Pandey's formal total synthesis of (±)–pancracine (**13**)* via *[3+2]–cycloaddition/cycloalkylation strategy*

Treatment of compound **73** with AgF in MeCN resulted in the generation of an azomethine ylide that underwent an intramolecular [3+2]–cycloaddition reaction to give ketone **74** incorporating the C– and D–rings present in the montanine alkaloid framework. However, this pivotal process proceeds in only modest (56%) yield and with low levels of stereocontrol. With a view to installing the E–ring, ester **74** was hydrolysed and the resulting alcohol was converted into mesylate **75** under standard conditions. Treatment of this last compound with KHMDS in anhydrous THF at –78 °C resulted in the formation of the kinetic enolate **76** which

underwent intramolecular C–alkylation to give ketone **77**, a compound incorporating the full framework of the montanine alkaloids. The subsequent regioselective installation of the necessary $\Delta^{1,11a}$–double bond was achieved *via* a standard protocol whereby the enol triflate, generated by a reaction of the corresponding lithium enolate with Comins reagent,[36] was reduced using Pd[O]–catalysed conditions to provide the desired montanine alkaloid framework **78**. As this compound corresponded to an advanced intermediate in Overman's total synthesis of (±)–pancracine (**13**),[19] its acquisition constituted a formal total synthesis of (±)–pancracine (**13**).

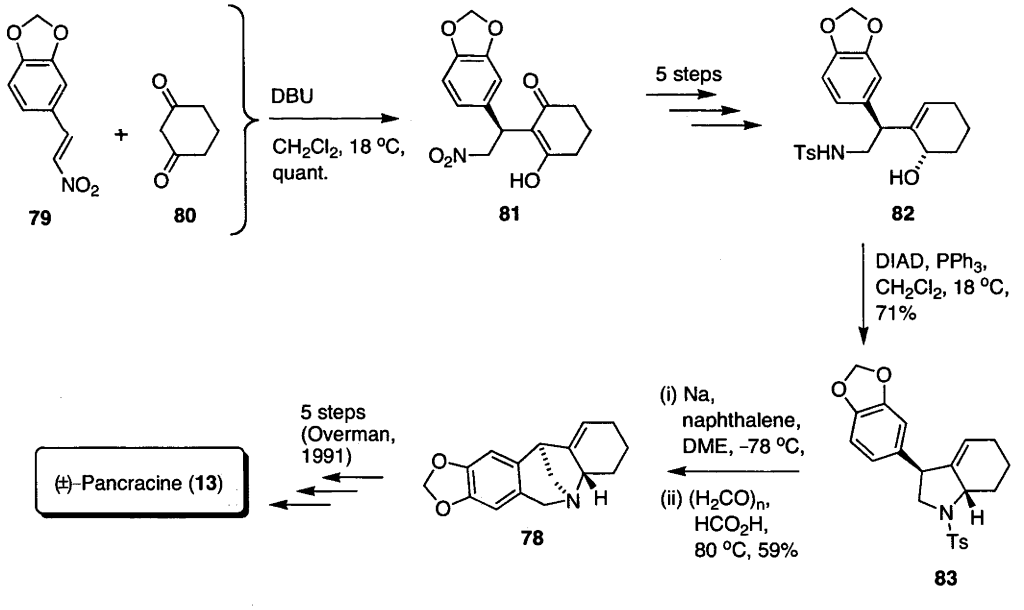
1.3.4. Evaluating Key Issues Associated with the Synthesis of the Montanine Alkaloids

In order to evaluate the strengths and the weaknesses of the four strategies just described, one has to consider whether or not these approaches can be utilized as general methods for the synthesis of montanine alkaloids by addressing problems such as low regio– and stereo–selectivity, the use of lengthy synthetic sequences, the need to employ expensive reagents and low yields. The strength of Weinreb's[23,34] enantioselective total syntheses of (–)–pancracine (**13**), (–)–montanine (**14**) and (–)–coccinine (**15**), for instance, is diminished by the fact that 28 steps (on average) are required to complete the sequences. The formal total synthesis of (±)–pancracine (**13**) reported Pandey[18] is unique in that rapid access to the montanine alkaloid framework was achieved but it lacks the appropriate stereocontrol that would permit a stereoselective synthesis of (–)–pancracine (**13**).

Another issue that is of relevance in the evaluation of these strategies involves the installation of both the $\Delta^{1,11a}$–double bond and oxygen functional groups present at C2 and C3 in the E–ring of montanine alkaloids. Analysis of all the strategies described above reveals that the installation of such a double bond and oxygen functions in a regio– and stereo–controlled manner is distinctly problematic. For example, the Overman syntheses of (±)–pancracine (**13**)[19] and (–)–pancracine (**13**)[22] suffer from these problems in that rather tedious synthetic sequences are necessary so as to regioselectively install the necessary $\Delta^{1,11a}$–double bond and to stereoselectively incorporate the hydroxyl groups.

1.3.4.1. Banwell and Sha Synthetic Approaches to Montanine Alkaloids

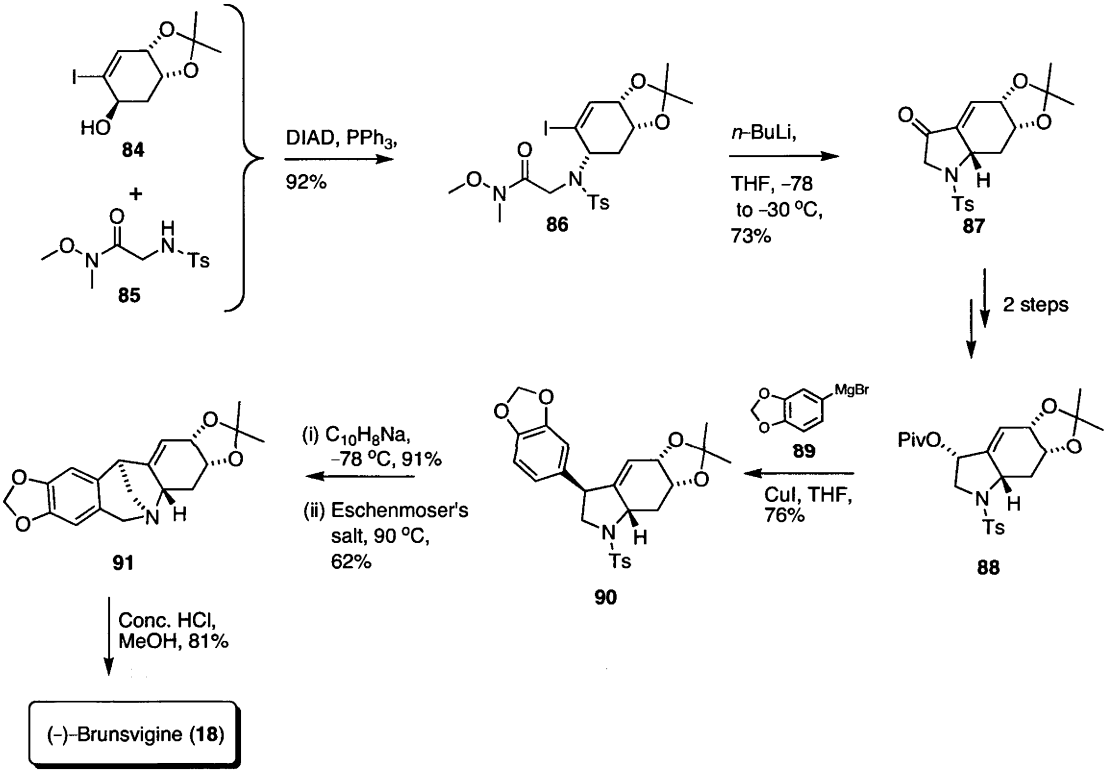
Whilst addressing some of the abovementioned issues, Banwell was able to achieve an operationally simple, relatively short (9 steps) and fully regio–controlled formal total synthesis (±)–pancracine (**13**), which involved an early stage installation of the desired and previously troublesome $\Delta^{1,11a}$–double bond. A key feature of this synthesis involved DBU–mediated Michael–addition of cyclohexan–1,3–dione (**80**) to *β*–nitrostyrene (**79**) to give product **81** in quantitative yield (**Scheme 1.11**). Elaboration of the last compound, **81**, using relatively straightforward chemistry, produced sulfonamide **82**, which was cyclized under Mitsunobu reaction conditions to give 3–arylhexahydroindole **83**. Subsequent removal of the tosylate group followed by application of the pivotal Pictet–Spengler reaction allowed for installation of the C–ring and generation of compound **78**, an advanced intermediate in Overman's total synthesis of (±)–pancracine (**13**).[19] Consequently, the acquisition of the pentacyclic compound **78** by such means constitutes a formal total synthesis of this alkaloid.



Scheme 1.11: *Banwell's formal total synthesis of (±)–pancracine (13)*

Sha's[27] approach to (–)–brunsvigine (**18**) went further in that installation of $\Delta^{1,11a}$–double bond and hydroxyl groups at C2 and C3 was achieved at an early stage. Furthermore, a regio– and stereo–controlled synthesis of (–)–brunsvigine (**18**) was undertaken whereby a

two–step annulation protocol involving a Mitsunobu reaction and anionic cyclization reaction was used to construct the D–ring of the target alkaloid. Thus, as shown in **Scheme 1.12**, the quinic acid–derived allylic alcohol **84** underwent an intermolecular Mitsunobu reaction with the glycine–derived sulfonamide **85** to give amide **86**. Treatment of this last compound with *n*–BuLi resulted in an anionic cyclization process to provide enone **87** that was then readily elaborated to the corresponding pivaloate ester **88**. Compound **88** was set up for a CuI–promoted S_N2 displacement reaction, which could be achieved by treating it with arylmagnesium bromide **89**. This resulted in the displacement of the pivaloate group to afford the arylated hexahydroindole **90** in 76% yield.



Scheme 1.12: *Sha's total synthesis of (–)–brunsvigine (**18**)*

Removal of the *N*–tosyl group followed by a Pictet–Spengler reaction using Eschenmoser's salt resulted in formation of the fully functionalised montanine alkaloid framework **91**. Cleavage of isopropylidene group in this last compound could be achieved using concentrated HCl and thus affording (–)–brunsvigine (**18**) in 81% yield. Overall, although a relatively efficient synthesis of the target montanine alkaloid (–)–brunsvigine (**18**) was achieved, this work fails to explore the applicability of these protocols for the purposes of

accessing the remaining montanine alkaloids. Accordingly, the remainder of this introduction details a new synthetic strategy for the general preparation of montanine alkaloids.

1.3.5. Towards a New Synthesis of the Montanine Alkaloids

A key feature of the synthetic approach to the montanine alkaloids that is associated with the body of work described in this thesis is the recognition that the enzymatically–derived and enantiomerically pure *cis*–1,2–dihydrocatechols of the general type **92** have considerable structural homology to the E–ring of montanine alkaloids and could, therefore, serve as precursors to the title alkaloids.

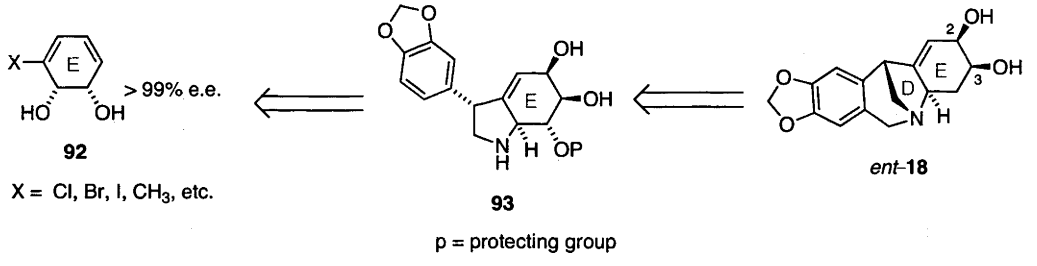


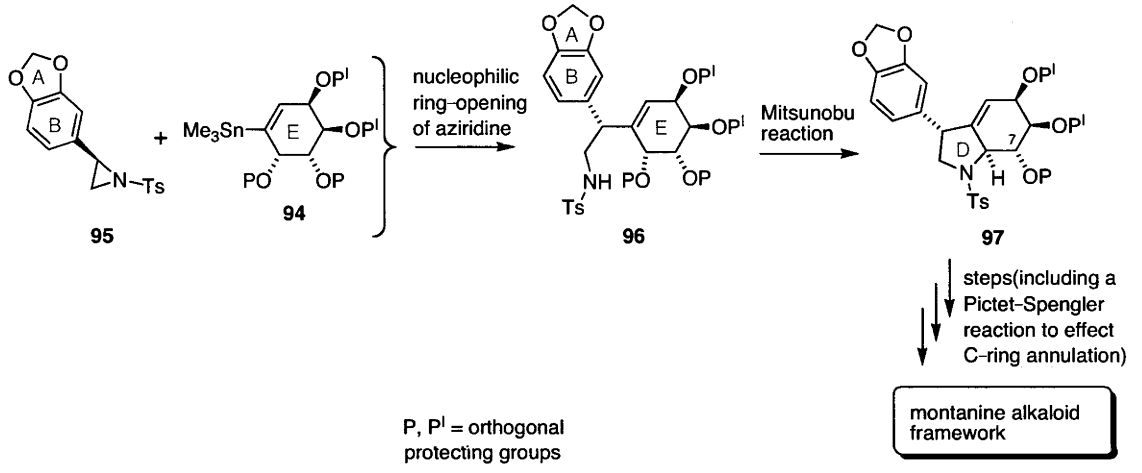
Figure 1.4: *Key intermediate and precursor in a new synthesis of the montanine alkaloids*

In particular, it is conceivable that the *cis*–1,2–dihydroxylation and annulation of the D–ring to this type of substrate would furnish the 3–arylhexahydroindole **93** that could later be transformed, *via* a Pictet–Spengler reaction, into the corresponding and fully functionalised montanine alkaloid framework (**Scheme 1.4**). This approach, although challenging, would avoid the tedious and possibly lengthy installation of the necessary $\Delta^{1,11a}$–double bond and oxygen–based functional groups present at C2 and C3 in the E–ring of montanine alkaloids. In addition, this strategy, if successful, would further highlight the value of *cis*–1,2–dihydrocatechols as building blocks in natural product synthesis.

1.3.5.1. Chemoenzymatic Approaches to Montanine Alkaloids

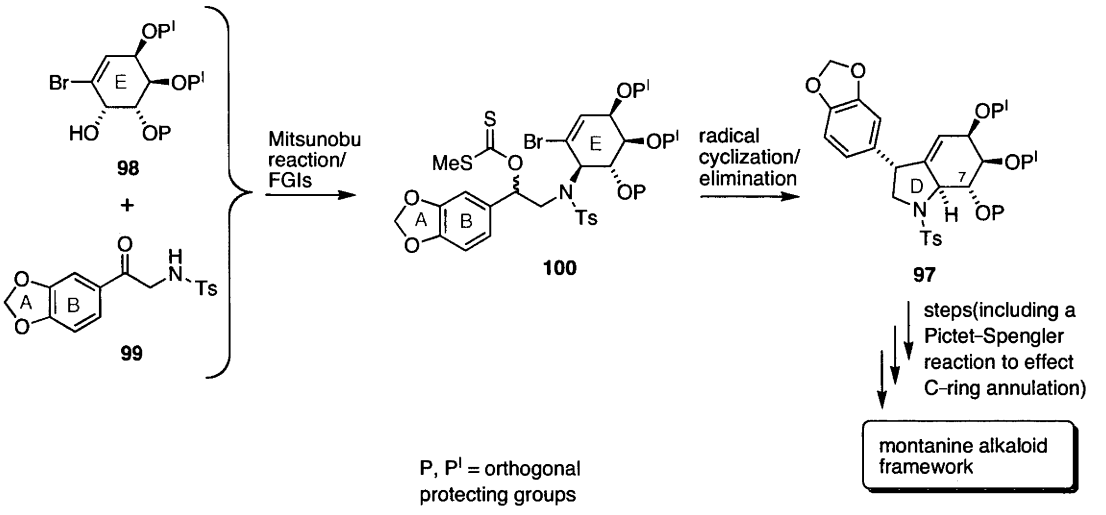
While a range of methods is likely to be applicable for the annulation of the D–ring to a *cis*–1,2–dihydrocatechol–derived precursor, four were considered in detail. The first to be

identified (*Approach A*) involved a new, two–step protocol for annulation of the D–ring. Specifically, this involved a Lewis–acid–mediated nucleophilic ring–opening of aziridine **95** with the *cis*–1,2–dihydrocatechol–derived stannane **94** (and thus leading to compound **96**) that is followed by an intramolecular Mitsunobu–type reaction to generate 3–arylhexahydroindole **97**, which incorporates the $\Delta^{1,11a}$–double bond and A–, B–, D– and E–rings of the montanine alkaloid framework (**Scheme 1.13**). Inspired by the work of Overman,[19,22] it was envisaged that the deoxygenation of 3–arylhexahydroindole **97** at C7 followed by the late–stage installation of the C–ring *via* a Pictet–Spengler reaction would provide the fully functionalised montanine alkaloid framework.



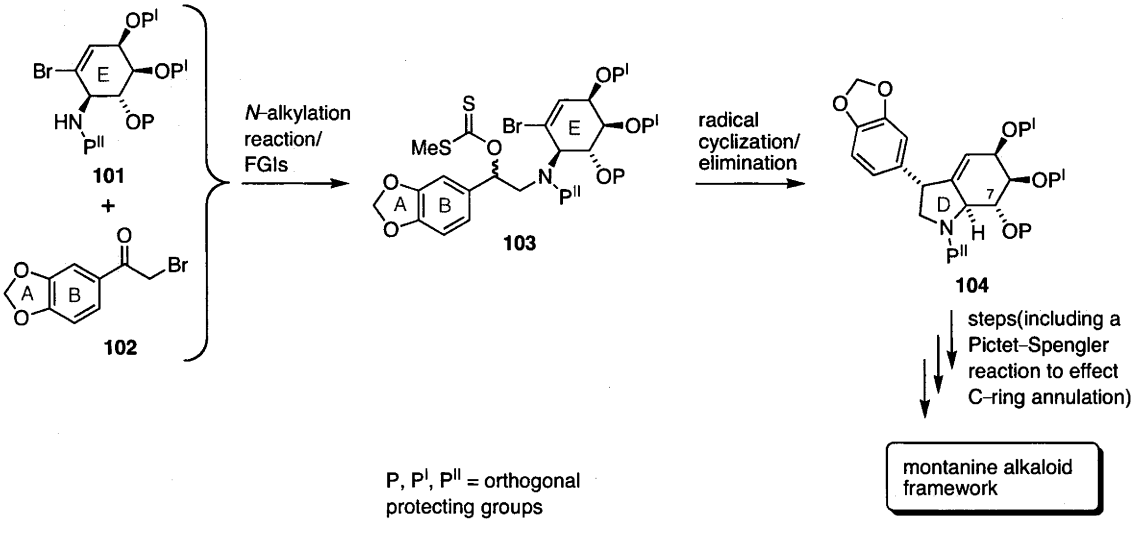
Scheme 1.13: *Possible chemoenzymatic access to the montanine alkaloids* via Approach A

The second approach (*Approach B*) also involves a two–step D–ring annulation protocol. Based on the work by Sha,[27] this would utilise an intermolecular Mitsunobu–type reaction between *cis*–1,2–dihydrocatechol–derived allylic alcohol **98** and sulfonamide **99** to produce intermediate **100** that would be subjected to a tandem radical cyclization/halogen atom elimination protocol to give 3–arylhexahydroindole **97** that also incorporates the $\Delta^{1,11a}$–double bond and A–, B–, D– and E– rings of montanine alkaloid framework (**Scheme 1.14**). As with the first approach, this one would also involve the deoxygenation of 3–arylhexahydroindole **97** at C7. Subsequent installation of the C–ring *via* Pictet–Spengler reaction would then provide the fully functionalised montanine alkaloid framework.



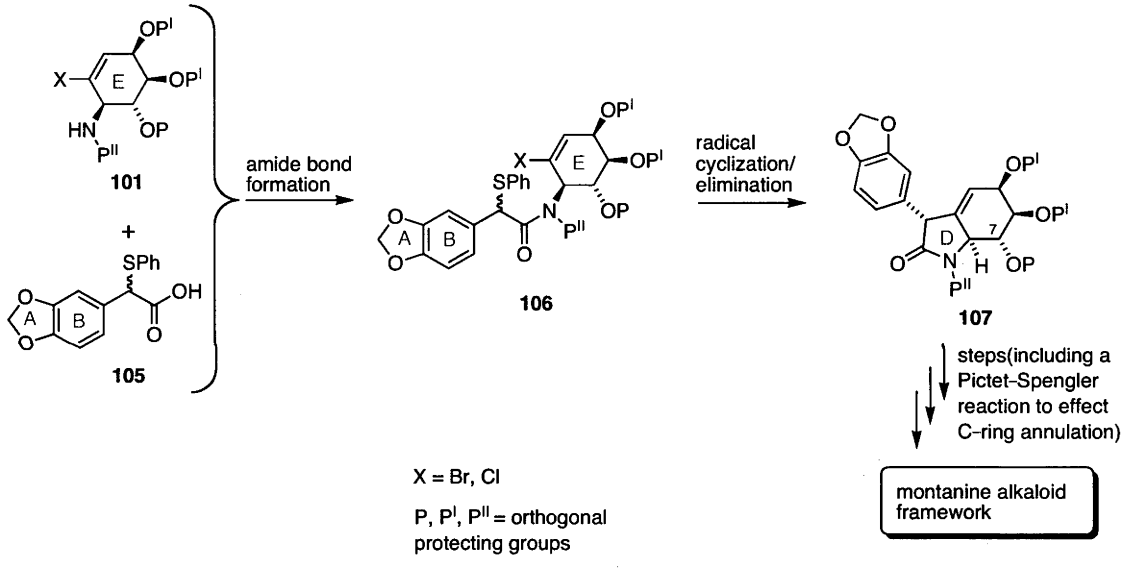
Scheme 1.14: *Possible chemoenzymatic access to the montanine alkaloids* via Approach B

A third approach (*Approach C*), once again using a two–step annulation protocol, involves the direct *N*–alkylation of *cis*–1,2–dihydrocatechol–derived 2°–amine **101** with α–bromoketone **102** to produce 3°–amine **103** (**Scheme 1.15**). After functional group interconversions (FGIs), to produce an appropriate radical precursor, a radical cyclization/halogen atom elimination reaction would then afford 3–arylhexahydroindole **104**, which also incorporates the necessary $\Delta^{1,11a}$–double bond and A–, B–, D– and E–rings present in montanine alkaloid framework. Late–stage deoxygenation at C7 of 3–arylhexahydroindole **104** followed by the installation of the C–ring *via* a Pictet–Spengler reaction would then deliver the fully functionalised montanine alkaloid framework.



Scheme 1.15: *Possible chemoenzymatic access to the montanine alkaloids* via Approach C

The fourth approach (*Approach D*), which is modification of the third, also involves a two–step D–ring annulation protocol. Based on the work of Ikeda,[25] this starts with the coupling of 2°–amine **101** (believed to be accessible from the bromo– and chloro–derivatives of *cis*–1,2–dihydrocatechol **92**) with acid **105** to produce intermediate **106** (**Scheme 1.16**). This would be followed by a tandem radical cyclization protocol to give 3–arylhexahydro–oxindole **107** that incorporates the $\Delta^{1,11a}$–double bond and A–, B–, D– and E–rings of the montanine alkaloid framework. Subsequent deoxygenation at C7 of 3–arylhexahydro–oxindole **107** followed by reduction of the amide function and installation of the C–ring *via* the pivotal Pictet–Spengler reaction should then provide the fully functionalised framework of the target alkaloids.

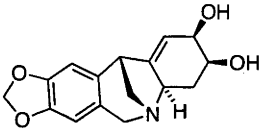


Scheme 1.16: *Possible chemoenzymatic access to the montanine alkaloids* via Approach D

1.4. Aims of the Research Described in this Thesis

By virtue of utilizing the enantiopure *cis*–1,2–dihydrocatechols as building blocks, the aim of the research presented herein was to develop a general strategy for the chemoenzymatic synthesis of the montanine alkaloids. Specifically, it was envisaged that the first chemoenzymatic total synthesis of the unnatural enantiomer of the montanine alkaloid (+)–brunsvigine (*ent*–**18**) would illustrate the viability of this procedure. Also, given the availability of either enantiomeric form of *cis*–1,2–dihydrocatechol **92** (see next section), it is

conceivable that this approach can be utilised as a general method for preparing the remaining montanine alkaloids and in either enantiomeric form. Having identified four possible synthetic approaches, the format of this thesis involves, in Chapters Two–Four, descriptions of the first three approaches (*Approach A*, *Approach B* and *Approach C*), particularly disclosing the studies undertaken to identify suitable conditions for preparing the relevant 3–arylhexahydroindoles as key intermediates for the synthesis of montanine alkaloids. Chapter Five details the implementation of the fourth (successful) approach (*Approach D*) as a means of preparing (+)–brunsvigine (*ent*–**18**). Chapter Six provides a summary of this work as well as a brief synopsis of possible future work.



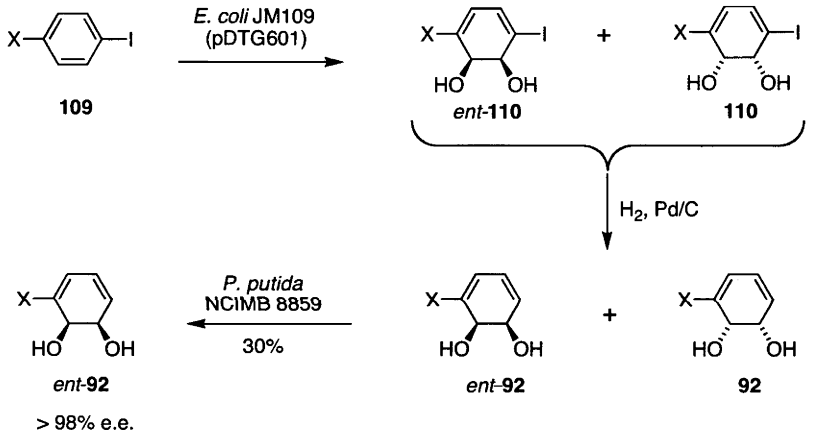
(+)–Brunsvigine (*ent*–**18**)

1.5. Production and Synthetic Applications of *cis*–1,2–Dihydrocatechols

Before the outcomes of the Author's studies are disclosed, a brief description of the production and synthetic applications of *cis*–1,2–dihydrocatechols is warranted and so presented below. Importantly, *cis*–1,2–dihydrocatechols (**92**) are readily obtained in large quantities (up to 35 grams of per litre of fermentation broth) through the application of various highly efficient whole–cell biotransformations. This is achieved, for example, *via* treatment of the genetically engineered micro–organism *Escherichia coli* JM109 (pDTG601) with abundant chemical feedstocks such as simple aromatic compounds (**108**) (e.g. chlorobenzene and toluene as shown in **Scheme 1.17**) to produce the enantiomerically pure *cis*–1,2–dihydrocatechols (**92**).[37] In fact, to date, over 250 metabolites produced through this type of process have been reported.[38]

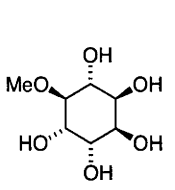
Scheme 1.17: *Preparation of* cis*–1,2–dihydrocatechols (**92**)* via *biotransformation of the corresponding arene **108***

To overcome the limitation of there being only one enantiomeric form of the *cis*–1,2–dihydrocatechols available by the means defined above, Boyd *et al.*[39] developed a useful chemoenzymatic procedure for accessing the antipode. As shown in **Scheme 1.18**, the preparation of the enantiomeric series commences with the subjection of *p*–iodinated arenes of type **109** to toluene dioxygenase–mediated dihydroxylation to produce a mixture of enantiomeric diols **110** and *ent*–**110**. Catalytic hydrogenolysis to cleave the carbon–iodine bond is then followed by the feeding of the de–iodinated material (comprised of a mixture of **92** and *ent*–**92**) to a wild strain of *Pseudomonas putida* (*P. putida*) (which contains the *cis*–1,2–dihydrocatechol dehydrogenase enzyme). This results in selective metabolism whereby only diol **92** is dehydrogenated, leaving *ent*–**92** untouched and capable of being isolated in high enantiomeric excess. Overall, these metabolites represent a group of versatile building blocks that should be considered valuable additions to the chiral pool.[37,40,41]

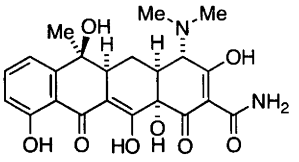


Scheme 1.18: *Preparation of the enantiomers of the more common* cis–*1,2–dihydrocatechols*

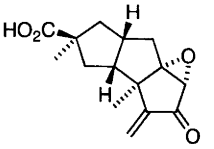
Despite their availability since the 1960's, it has only been in the last 20 years that the *cis*–1,2–dihydrocatechols have started to have an impact on the synthetic community. Since the pioneering work of Ley *et al.*,[42] in developing a total synthesis of (±)–pinitol (**111**), these metabolites have been used in a wide range of synthetic endeavours including the preparations of a variety of simple → complex natural products, particularly alkaloids, polyketides, macrolides, terpenes and cyclitols (such as compounds **111**–**118**) (**Figure 1.5**). A comprehensive description of the work carried out in this area is beyond the scope of this introduction. However, excellent reviews of this area are readily available.[37,41,43]



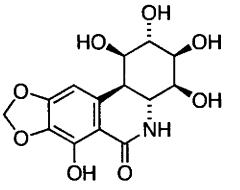
Pinitol (**111**)[42]



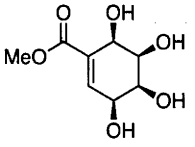
(−)−Tetracycline (**112**)[44]



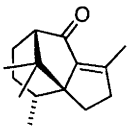
(−)−Complicatic acid (**113**)[45]



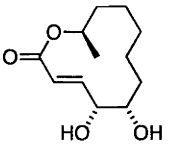
(+)−Pancratistatin (**114**)[46]



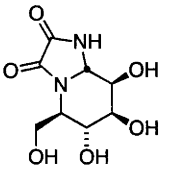
(+)−Pericosine B (**115**)[47]



(−)−Patchoulenone (**116**)[48]



(−)−Cladospolide A (**117**)[49]



(+)−Kifunensine (**118**)[50]

Figure 1.5: *Examples of natural products synthesised from* cis*−1,2−dihydrocatechols*

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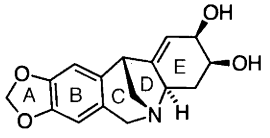
CHAPTER TWO

Towards (+)-Brunsvigine: Attempted Synthesis of 3-Arylhexahydroindoles *via Approach A*

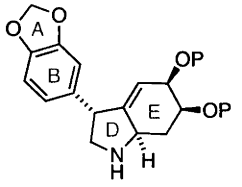
2.1. Introduction

2.1.1. Overview and Context

Having identified the Pictet–Spengler reaction as a crucial process in the proposed approach to (+)–brunsvigine (*ent*–**18**), the synthesis of a substrate, **119**, for such a reaction became a major objective of the study detailed in this chapter. Since it was thought that such a compound could be obtained from *cis*–1,2–dihydrocatechols **92**, effecting the conversion **92** → **119** became a particular focus of the work described here and details of this approach (*Approach A*) are discussed below.

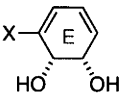


ent-**18**



119

P = protecting group

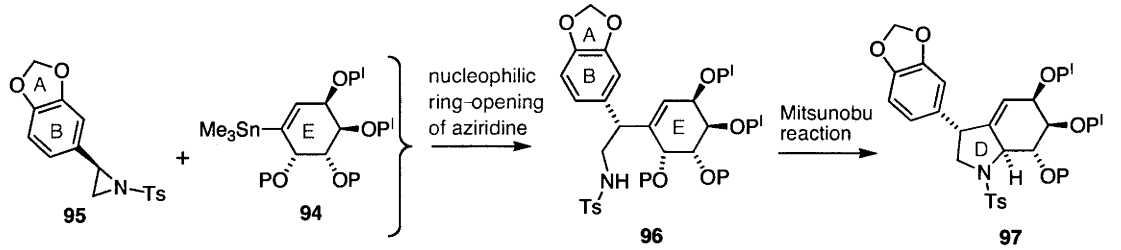


92

X = Cl, Br, I

2.1.1.1. Overview of *Approach A*

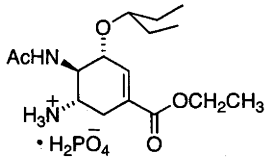
Central to *Approach A*, which involves D–ring annulation to an E–ring-containing precursor, is the nucleophilic ring–opening of aziridine **95** with chemoenzymatically–derived and stannylated conduritol **94** to produce sulfonamide **96** (**Scheme 2.1**). This was to be followed by an intramolecular Mitsunobu reaction[1] to provide the required key intermediate 3–arylhexahydroindole **97**. However, before discussing the studies undertaken by the Author in this regard, a brief overview of the use of aziridines in synthesis is presented in the following section.



Scheme 2.1: *Formation of key intermediate* ***97*** via Approach A

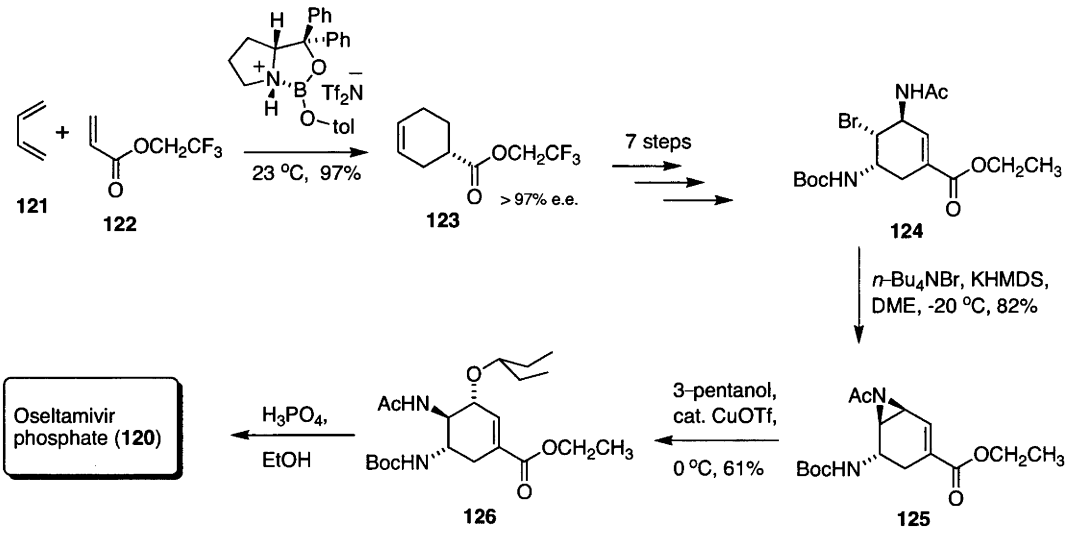
2.2. Aziridines in Synthesis: Overview and Context

Within the synthetic community aziridines have attracted considerable attention in recent years because they represent valuable three–membered ring systems that are versatile building blocks for chemical bond formation and functional group interconversions.[2-5] This has been extensively demonstrated by the publication of numerous methodologies that describe their preparation, especially asymmetric approaches, and the broad manner of their application to the synthesis of biologically active compounds.[5-9] The rapid and efficient preparation of the anti–influenza drug oseltamivir phosphate (Tamiflu®)(**120**) by Corey[10] is a brilliant example that serves to highlight the synthetic value of this heterocycle.



Oseltamivir phosphate (**120**)

Thus, as summarized in **Scheme 2.2**, the Corey synthesis of Tamiflu® began with an asymmetric Diels–Alder reaction[11] between butadiene **121** and ester **122**. Produced in excellent yield and in high enantiomeric excess, the Diels–Alder adduct **123** was elaborated, through a series of functional group interconversions, into the corresponding α,β–unsaturated ester **124**. An intramolecular S_N2 displacement of the bromine function by the *NAc* group of this last compound using *in situ* generated tetra–*n*–butylammonium hexamethyldisilazide then provided the desired aziridine **125**. Subsequent nucleophilic ring–opening of the aziridine, **125**, with 3–pentanol was effected using copper(II) triflate as a Lewis acid and so providing the oseltamivir precursor **126**, which upon exposure to phosphoric acid in EtOH afforded the target compound **120**.



Scheme 2.2: *Corey's total synthesis of oseltamivir phosphate (Tamiflu®)(**120**)*

Before disclosing the outcomes of the nucleophilic ring–opening of aziridine **127** with alkenyl stannane **128** (shown in the next section), it is appropriate to provide a rationale as to why aziridine **127** was chosen as a candidate for such a process.

127 **128**

Generally, and as a consequence of the electronegativity of the nitrogen atom and the ring–strain (Baeyer strain) present in aziridines (and related three membered rings), ring–opening reactions are a dominant feature of their chemistry. In this respect, aziridines are divided into two main types, depending upon the nature of the *N*–substituent.[5,12] The 'non–activated' aziridines (**129**) contain a basic nitrogen atom and ring–opening reactions usually occur after protonation, quaternarization at the heteroatom or formation of Lewis acid adducts. The 'activated' aziridines (**130**) (typically *N*–sulfonyl derivatives such as aziridine **127**), posses an electrophilic substituent which can conjugatively stabilize any negative charge that develops on the nitrogen atom in the transition state for the ring–opening by nucleophiles (typically alcohols, azides and thiols).[12]

129

'non-activated'

R = H, alkyl, aryl

130

'activated'

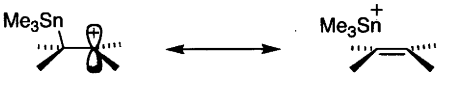
R = COR, CO_2R, SO_2R

Consequently, 'activated' aziridines are preferred over 'non–activated' ones as substrates for nucleophilic ring–opening reactions. Generally, nucleophilic ring–opening of 'activated' aziridines does not occur in the absence of a Lewis acid. This is significant because the nitrogen lone pair has increased *s*–orbital character as compared to aliphatic 2°– and 3°–amines. This results in lower basicity and, more significantly, a decreased π–donor ability which reduces the capacity for a facile ring–opening process.[12,13]

2.3. D-Ring Annulation: Attempted Synthesis of 3-arylhexahydroindole 97

2.3.1. Model Study

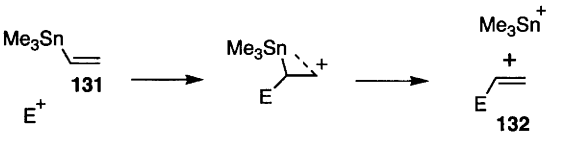
A proof–of–principle model study was undertaken that involves the testing of an alkenyl stannane's capacity to react with aziridines in the intended manner and in the presence of Lewis acid catalysts that promote nucleophilic ring–opening of aziridines. The reason alkenyl stannanes (such as compound **128**) behave as nucleophiles can be rationalized using the concept of the β–tin effect. As a special type of hyperconjugation that is general amongst the group 14 metals, the β–tin effect involves the stabilization of a carbocation by hyperconjugation through a β–carbon–tin bond (**Scheme 2.3**).[14]



Scheme 2.3: *The β–tin effect in stabilizing carbocations*

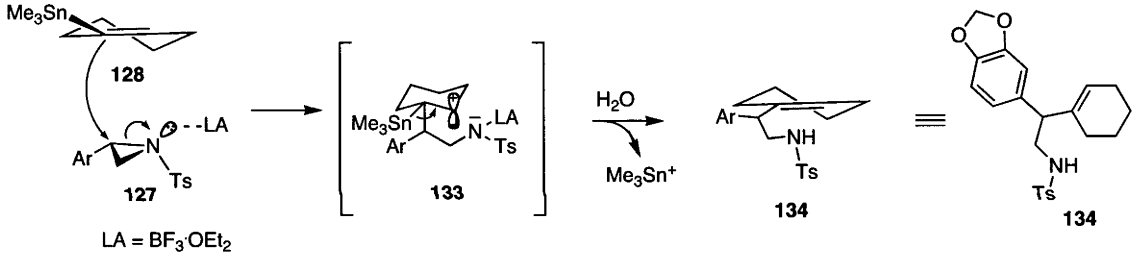
This effect enhances the nucleophilicity of alkynyl, alkenyl, allyl and aryl stannanes in their reactions with electrophiles. Alkenyl stannanes (**131**), for instance (**Scheme 2.4**), react with

electrophiles (E^+) through an *ipso*–substitution reaction that results in cleavage of the stannyl group to produce alkene **132**.[15]



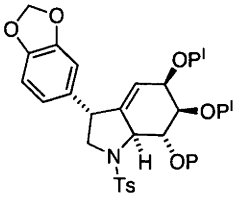
Scheme 2.4: *Reaction of alkenyl stannanes with electrophiles (E^+)*

On this basis, it is conceivable that alkenyl stannane **128** might engage in what would be an unprecedented carbon–carbon bond–forming process with aziridine **127**. Thus, as shown in **Scheme 2.5**, nucleophilic addition of alkenyl stannane **128** to the benzylic carbon of the Lewis acid–activated aziridine **127** to produce the carbocation **133**. Subsequent elimination of the trimethyltin cation from this species would then complete the *ipso*–substitution process, re–establish the double bond and so lead to alkene **134**.



Scheme 2.5: *Mechanism for the nucleophilic ring–opening of aziridine **127** with model alkenyl stannane **128***

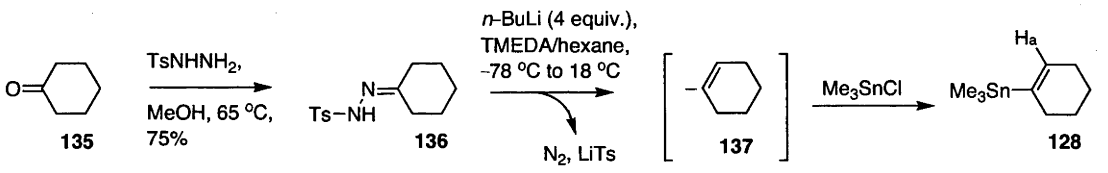
If the proposed new carbon–carbon bond forming event could be effected, this could provide a useful method for the construction of compound **97**. As a prelude to investigating such possibilities, the electrophilic aziridine **127** and the corresponding nucleophile alkenyl stannane **128** need to be synthesised.



97

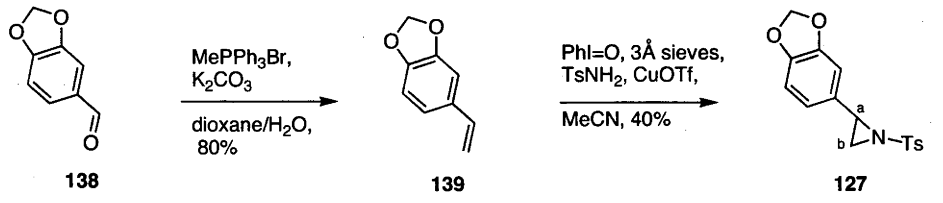
P, P^I = orthogonal protecting groups

Hence, starting with cyclohexanone (**135**), the alkenyl stannane **128** was prepared following a standard, two–step, Shapiro protocol[16] whereby the conversion of compound **135** into tosylhydrazone **136** was achieved using tosylhydrazine in refluxing MeOH (**Scheme 2.6**). Treatment of the latter compound with *n*–BuLi (4 equiv.) at low temperatures in the presence TMEDA resulted in the liberation of N_2 and *p*–toluenesulfonyl anion to provide the intermediate alkenyl carbanion **137** which was trapped with Me_3SnCl to afford alkenyl stannane **128**. The ^1H NMR spectrum of this last material showed the expected signals including one at δ 5.76, due to the olefinic proton (H_a). However, the dominant feature in this spectrum is a signal at δ 0.00 and the associated satellite doublets (J [^{117,119}Sn–H] 52 and 54 Hz) which, together, integrate to nine protons and so are assigned to the three equivalent methyl group protons associated with tin.



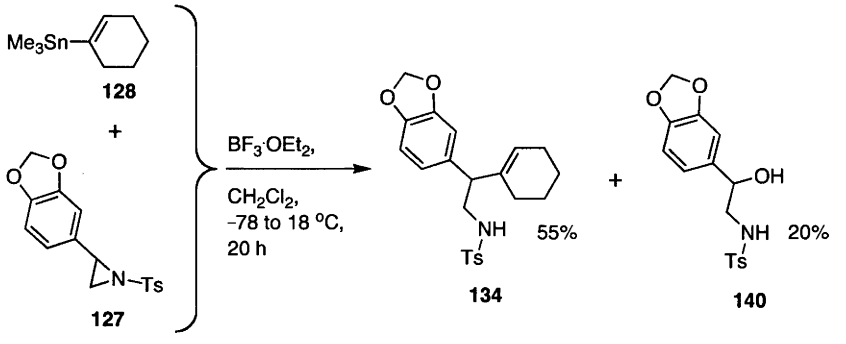
Scheme 2.6: *Synthesis of the model alkenyl stannane* ***128***

Aziridine **127** was also prepared *via* a two–step sequence, this one involving an initial Wittig olefination of piperonal (**138**) to give the known styrene **139** (**Scheme 2.7**).[17] Copper(II)–mediated nitrene addition to styrene **139** utilizing *p*–toluenesulfonamide, iodosobenzene and copper(I) triflate in the presence of 3Å molecular sieves[18] then produced aziridine **127** in 40% yield. All the data obtained on this previously unreported material were in full accord with the assigned structure. The ^{13}C NMR spectrum, for example, showed signals at δ 40.8 and 35.5, which are assigned to C_a and C_b, respectively.



Scheme 2.7: *Synthesis of aziridine* ***127***

When aziridine **127** was treated with alkenyl stannane **128** in the presence of $BF_3{\cdot}OEt_2$ as the Lewis acid[19] a nucleophilic ring–opening of the aziridine occurred and thus delivering the desired product (**134**) in 55% yield (**Scheme 2.8**). The chromatographically separable hydrolysis product **140** was also obtained in 20% yield.



Scheme 2.8: *Nucleophilic ring–opening of aziridine **127** with model alkenyl stannane **128***

All the spectral data obtained on compound **134** were in accord with the assigned structure. For example, the ^1H NMR spectrum of this product (**Figure 2.1**) showed a signal at δ 4.30 corresponding to benzylic proton (H_a), which is indicative of the new carbon–carbon bond–forming event resulting from the ring–opening of aziridine **127**.

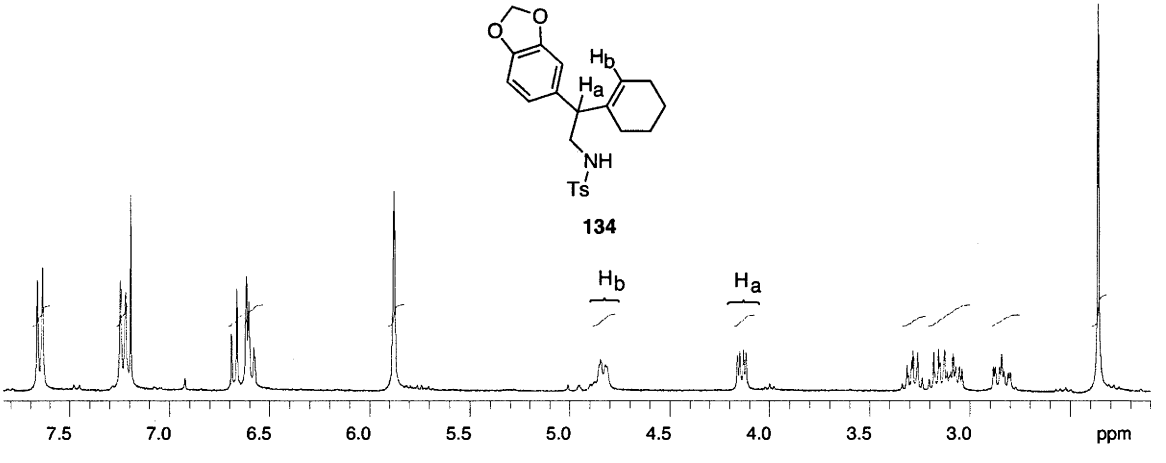
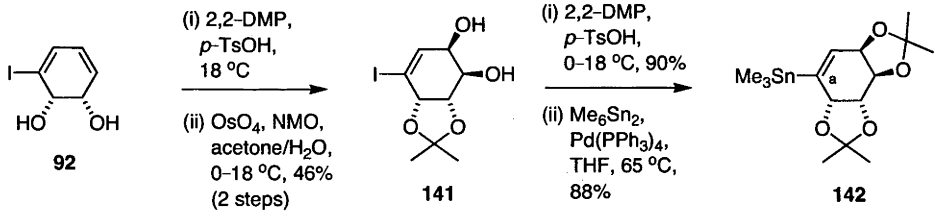


Figure 2.1: *300 MHz ^1H NMR spectrum of compound **134** recorded in $CDCl_3$*

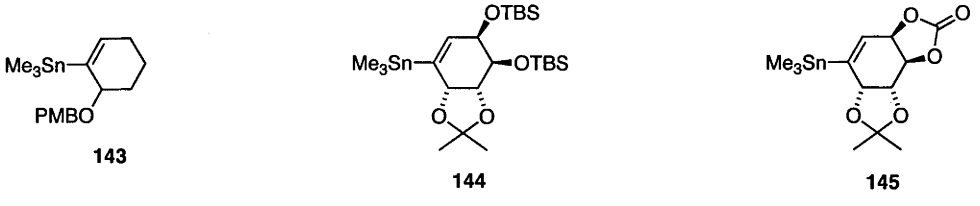
2.3.2. Attempted Nucleophilic Ring–Opening of Aziridine 127 with Alkenyl Stannanes 142–145

With the success of the model *ipso*–substitution reaction detailed in the preceding section, attention turned towards nucleophilic ring–opening of aziridine **127** with *cis*–1,2–dihydrocatechol–derived alkenyl stannane **142**. However, before this process could be investigated, the preparation of the latter compound was required. This was achieved in four steps whereby the enantiopure iodo–derivative of *cis*–1,2–dihydrocatechol **92** was first protected as the isopropylidene acetal then dihydroxylated using OsO_4 under the Upjohn conditions.[20] In this way, the illustrated diol **141** (**Scheme 2.9**) was obtained. Subsequent protection of this diol as the isopropylidene acetal followed by stannylation with hexamethylditin in the presence of catalytic amount of $Pd(PPh_3)_4$ afforded the required stannylated conduritol **142** in excellent yield. All the spectral data obtained on this previously unreported compound were consistent with the assigned structure. For instance, the ^{13}C NMR spectrum showed six signals (at δ 108.7, 108.6, 27.8, 27.5, 26.4 and 26.2) which are attributed to the two isopropylidene groups. In addition, the signal at δ 134.2 and the associated tin satellites [J ($^{117/119}Sn$–^{13}C) = 19.95 Hz] were assigned to C_a.

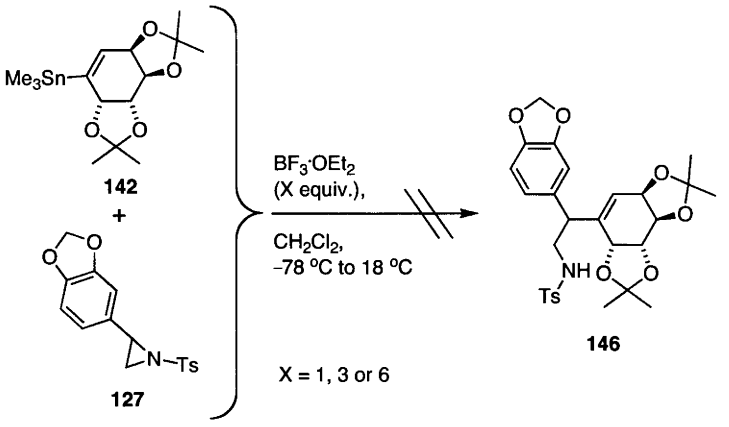


Scheme 2.9: *Synthesis of stannylated conduritol* ***142***

In order to probe the generality, or otherwise, of the new carbon–carbon bond forming reaction detailed in the preceding section, alkenyl stannanes **143**, **144** and **145** were also prepared by standard procedures detailed in the experimental section.

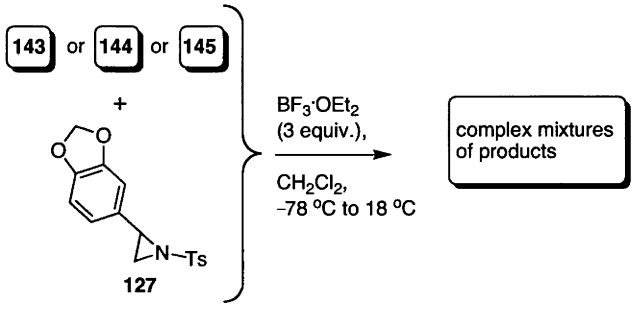


Having access to aziridine **127** and stannylated conduritol **142** meant that the pivotal nucleophilic ring–opening of aziridine **127** could be investigated. Disappointingly, initial attempts to effect the nucleophilic ring–opening reaction of aziridine **127** with stannane **142** in the presence of $BF_3{\cdot}OEt_2$ [19] failed to yield the required sulfonamide **146** (**Scheme 2.10**).



Scheme 2.10: *Attempted nucleophilic ring–opening of aziridine **127** with stannylated conduritol **142***

Varying the number of equivalents $BF_3{\cdot}OEt_2$ employed also failed to change the outcome with a chromatographically inseparable mixture of products being obtained in each instance. Indeed, the desired product **146** was never observed in any of these reaction mixtures. As shown in **Scheme 2.11**, the use of alkenyl stannanes **143**, **144** and **145** as alternative substrates for nucleophilic ring–opening of aziridine **127** also failed to yield the expected product. Once again, chromatographically inseparable mixtures of unidentified products were observed in each instance.



Scheme 2.11: *Attempted nucleophilic ring–opening of aziridine **127** with alkenyl stannanes **143**, **144** and **145***

These outcomes lead to the investigation of other Lewis acids such as $InCl_3$, $SnCl_4$, $TiCl_4$, $Ti(O^iPr)_4$ and $Sc(OTf)_3$. $InCl_3$, for instance, was found to be too mild as Lewis acid such that only recovered starting materials were observed (**Table 2.1**). Conversely, $SnCl_4$ and $TiCl_4$ appeared to be too strong and often lead to complex and chromatographically inseparable mixtures of products.

Lewis acid (equiv.)	Solvent	Temperature (°C)	Time (h)	Outcome
$InCl_3$ (3)	CH_2Cl_2	–78 → 18	18	No reaction
$Ti(O^iPr)_4$ (3)	CH_2Cl_2	–78 → 80	48	No reaction
$Sc(OTf)_3$ (3)	CH_2Cl_2	–78 → 18	2	Decomp.
$SnCl_4$ (3)	CH_2Cl_2	–78 → 18	16	Decomp.
$TiCl_4$ (3)	CH_2Cl_2	–78 → 18	20	Decomp.
$MgBr_2{\cdot}OEt_2$ (3)	CH_2Cl_2	–78 → 18	16	No reaction

Table 2.1: *Attempted nucleophilic ring–opening of aziridine **127** with conduritol **146** – the effects of different Lewis acids*

These results might suggest that the presence of the oxygen functions on the stannylated conduritol **142** inhibit nucleophilic attack of the stannyl species onto aziridine **127** by providing alternative coordination sites for the Lewis acids being used.[13,21,22] This is supported by the fact that little is known about the specific interactions of Lewis acids with oxygen functions in the presence of nitrogen and stannyl groups.[13] In fact, given that alkenyl stannanes can react with various electrophiles, it is conceivable that stannylated conduritol **142** can react directly with electrophilic species such as $SnCl_4$ and $TiCl_4$, thus contributing to the observed mixture of products. In addition, the inductive electron–withdrawing effects of the oxygen substituents may be reducing the nucleophilicity of the alkenyl stannane. Regardless of the origins of these results, they meant that an alternative approach to the synthesis of 3–arylhexahydroindoles was required.

2.4. Summary

This chapter has detailed *Approach A* as a method for preparing (+)–brunsvigine (*ent*–**18**). Key features included an interesting $BF_3{\cdot}OEt_2$–mediated nucleophilic ring–opening of aziridine **127** by alkenyl stannane **128** (**Scheme 2.8**). However, attempts to extend this protocol by using the analogous oxygenated alkenyl stannanes **142–145** failed to yield the expected ring–opened products. The failure to effect this pivotal nucleophilic ring–opening of aziridine **127** with such oxygenated alkenyl stannanes was disappointing and also meant that new approaches to (+)–brunsvigine (*ent*–**18**) had to be devised. One of these is detailed in the following chapter.

2.5. References

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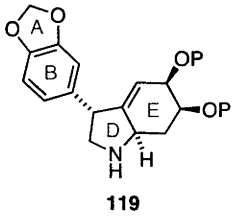
CHAPTER THREE

Towards (+)-Brunsvigine: Attempted Preparation of 3-Arylhexahydroindoles *via Approach B*

3.1. Introduction

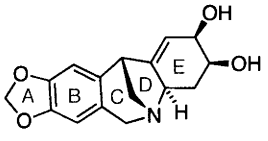
3.3.1. Overview and Context

This chapter details synthetic studies undertaken for the purposes of preparing 3–arylhexahydroindole **119**. As a key precursor to the target natural product (+)–brunsvigine (*ent*–**18**), it was hoped that such a compound (**119**) could be obtained from the chemoenzymatically–derived and enantiopure *cis*–1,2–dihydrocatechol **92**.

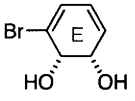


119

P = protecting groups



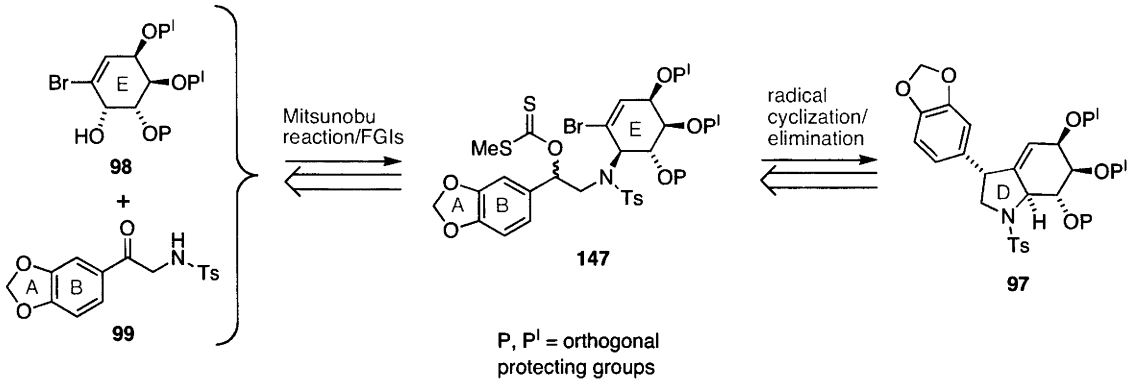
ent-**18**



92

3.1.1.1. Overview of *Approach B*

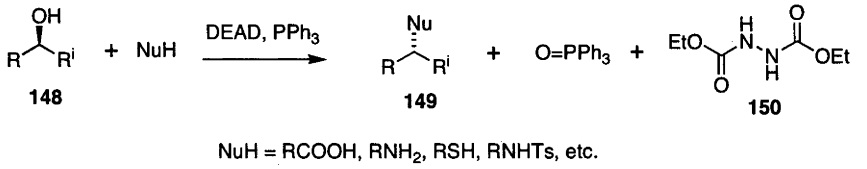
The key elements of *Approach B* (which involve the preparation of a 3–arylhexahydroindole suitable for elaboration to (+)-brunsvigine) are shown in **scheme 3.1**. Thus, the coupling (under Mitsunobu conditions) of the chemoenzymatically–derived conduritol **98** and sulfonamide **99**, followed by functional group interconversions (FGIs) should enable the preparation of the compound **147**. Subsequent radical cyclization of this last compound would then provide 3–arylhexahydroindole **97** thus completing the D–ring annulation protocol and as well as the installation of the necessary $\Delta^{1,11a}$–double bond present in the E–ring of (+)–brunsvigine (*ent*–**18**). However, before discussing the Author's efforts directed at implementing such an approach, a brief overview of the Mitsunobu reaction is presented in the next section.



Scheme 3.1: *Formation of key intermediate* ***97*** via Approach B

3.2. The Mitsunobu Reaction: Overview and Context

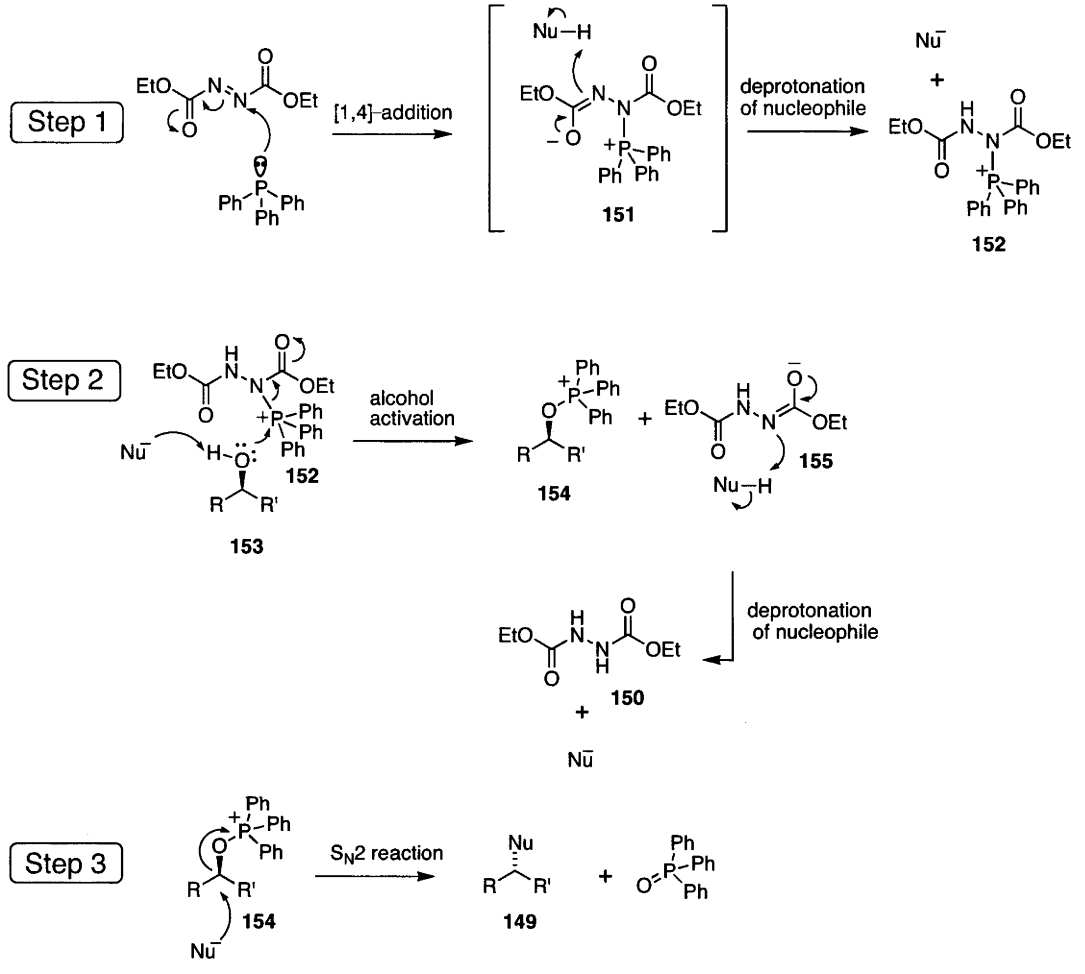
The Mitsunobu reaction, reported by its inventor in 1967 and developed extensively in the ensuing years,[1,2] is a unique S_N2–type reaction that utilizes the redox system diethylazodicarboxylate (DEAD) and PPh_3 in conjunction with a substrate alcohol **148** and appropriate nucleophile (NuH) to generate the target product **149**. Triphenylphosphine oxide ($O{=}PPh_3$) and hydrazine **150** are the inevitable by-products of this process (**Scheme 3.2**).



Scheme 3.2: *The Mitsunobu reaction*

This type of conversion is a three–step process that begins with the rapid addition of PPh_3 to DEAD to form a zwitterionic P–N adduct **151** (**Scheme 3.3**). This intermediate then undergoes protonation to form phosphonium salt **152**. The second step involves the Nu–mediated addition of alcohol **153** to salt **152** to form intermediates **154** and **155** as well as nucleophile (NuH). Subsequent protonation of compound **155** with NuH then provides the conjugate base of nucleophile (Nu^-) as well as the stable hydrazine by–product **150**. The

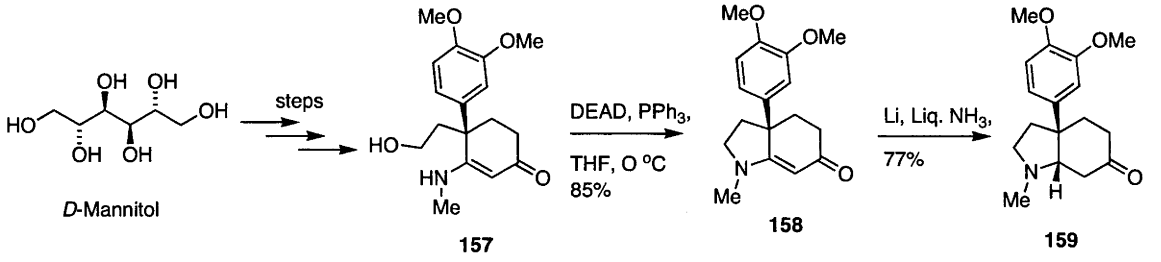
final step involves Nu^- reacting with oxyphosphonium salt **154**, in an S_N2 displacement process, to form the required product (**149**) together with $O{=}PPh_3$.[3,4]



Scheme 3.3: *Generally accepted mechanism of the Mitsunobu reaction*

Factors that can influence the outcomes of the Mitsunobu reaction include the basicity of the phosphine (such as PPh_3), the pK_a of the nucleophile and steric effects associated with the alcohol, nucleophile and phosphine. Clearly, the failure to successfully execute any one of the key steps of this process prevents the desired outcome. Nevertheless, the Mitsunobu reaction has been widely used in organic synthesis for the displacement of hydroxyl groups by carboxylic acid–based nucleophiles. In addition, nucleophiles such as amines, sulfonamides and thiols have been used.[3,4] The enantioselective total synthesis of the *Amaryllidaceae* alkaloid (–)–mesembrine (**159**) by Takano[5] provides one of many examples of the utility of this reaction.

Specifically, Takano was able to demonstrate that the mannitol–derived alcohol **157** could participate in an intramolecular Mitsunobu reaction to give the required pyrrolidine **158** in 85% yield (**Scheme 3.4**). Birch reduction of the enone moiety within the latter compound using lithium metal in liquid ammonia then afforded the target alkaloid **159** in 77% yield.[6,7]

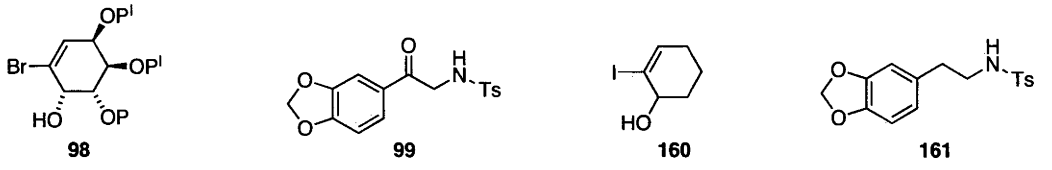


Scheme 3.4: *Takano's total synthesis of (–)–mesembrine (**159**)*

3.3. D–Ring Annulation: Attempted Synthesis of 3–Arylhexahydroindole 119

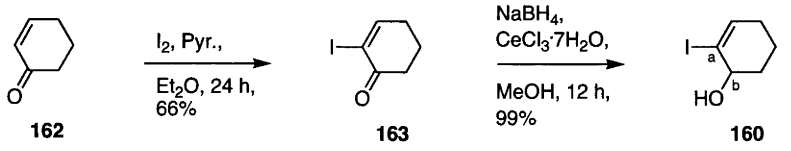
3.3.1. Model Study

As there was limited precedence for the desired intermolecular Mitsunobu reaction between alcohol **98** and sulfonamide **99**, a model study was undertaken. Following the work of Sha,[8] relevant model compounds for such studies were considered to be 2–iodocyclohexenol (**160**) and sulfonamide **161**.



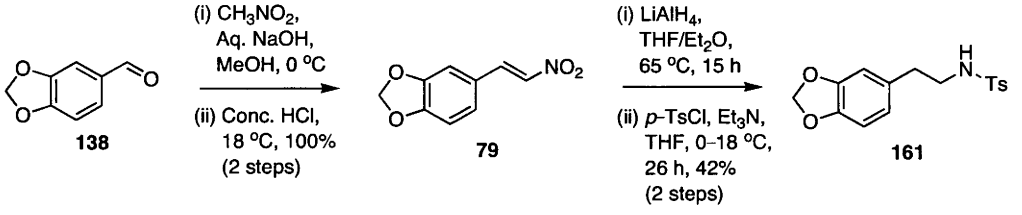
2–Iodocyclohexenol (**160**) was synthesized in two steps from cyclohexenone (**162**) *via* an initial Johnson iodination reaction,[9] to give α–iodoclohexenone (**163**), followed by a $NaBH_4$–mediated reduction of the carbonyl function under Luche conditions and so providing the target compound (**160**) (**Scheme 3.5**).[10,11] All the data obtained on this material were consistent with the assigned structure and in agreement with those reported in literature.[12]

The ^{13}C NMR spectrum, for example, showed two signals at δ 103.3 and 71.6 which are attributed to C_a and C_b, respectively.



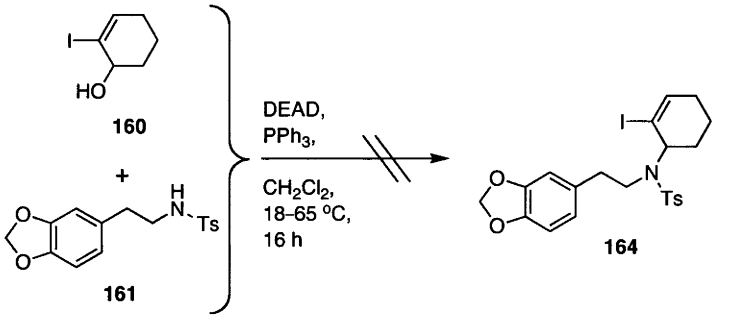
Scheme 3.5: *Synthesis of 2–iodocyclohexenol (**160**)*

The preparation of sulfonamide **161** began with a nitro–aldol condensation[13] between piperonal (**138**) and nitromethane that gave β–nitrostyrene **79** in quantitative yield (**Scheme 3.6**). $LiAlH_4$–mediated reduction of the last compound, to give the corresponding β–arylethylamine, was followed by protection of the revealed 1°–amine group using *p*–TsCl and so generating the target compound **161** in 42% over the two steps.



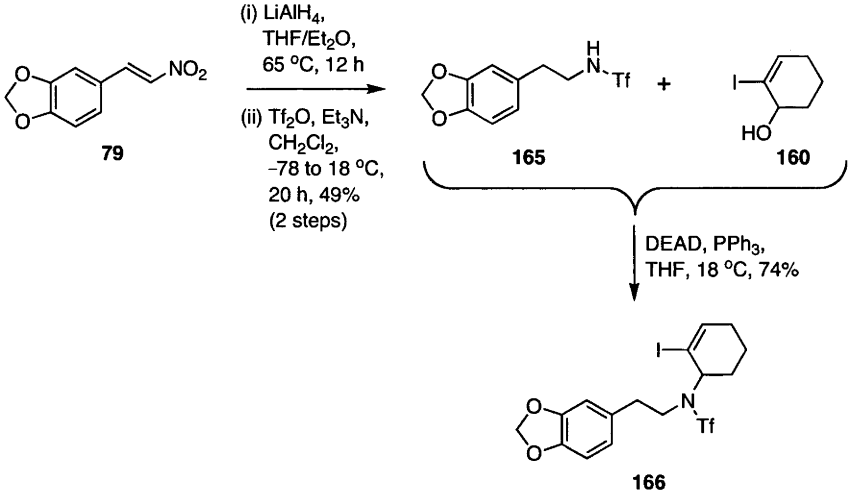
Scheme 3.6: *Synthesis of sulfonamide **161** from piperonal **138***

Despite these successes, when 2–iodocyclohexenol (**160**) and sulfonamide **161** were subjected to a Mitsunobu reaction for 22 h this failed to give the desired product **164**. Only the starting materials were recovered from the reaction mixture (**Scheme 3.7**). Attempts to effect this process by applying longer reaction times also failed.



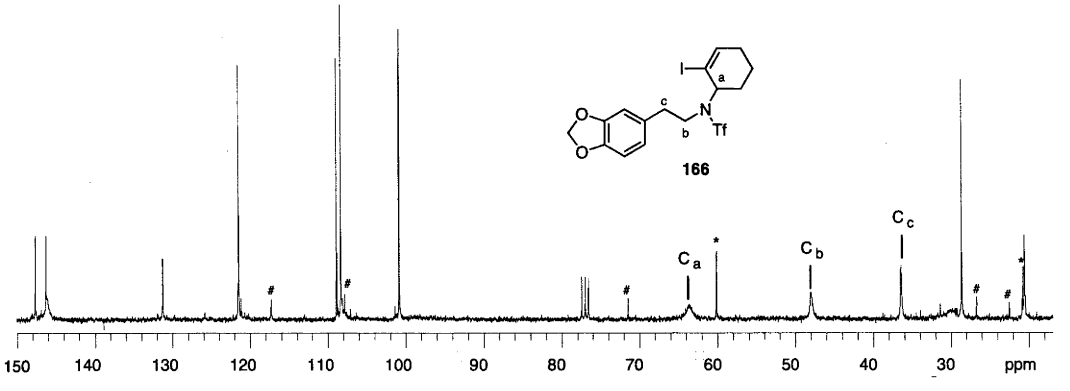
Scheme 3.7: *Attempted Mitsunobu reaction of 2–iodocyclohexenol (**160**) with sulfonamide **161***

With this disappointing outcome, the synthesis of triflamide **165** was undertaken. As shown in **Scheme 3.8**, reduction of β–nitrostyrene **79** with $LiAlH_4$ produced the corresponding β–arylethylamine that was immediately treated with Tf_2O to provide the desired triflamide **165** in 49% yield over the two steps. Gratifyingly, treatment of 2–iodocyclohexenol **160** with triflamide **165** under the Mitsunobu reaction protocol resulted in the formation of the desired product (**166**) in 74% yield.



Scheme 3.8: *Mitsunobu reaction of 2–iodocyclohexenol (**160**) with triflamide **165***

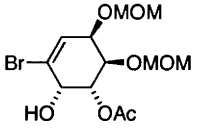
This pleasing outcome was confirmed by mass spectrometric analysis as well as ^1H NMR and ^{13}C NMR experiments. For instance, the ^{13}C NMR spectrum of triflamide **166** (**Figure 3.1**) showed a signal at δ 63.6 which is attributed to C_a and thus indicating that the desired coupling of alcohol **160** with triflamide **165** had taken place.



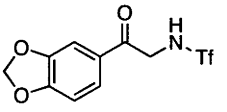
* = Ethyl acetate; # = unknown impurities

Figure 3.1: *75 MHz ^{13}C NMR spectrum of triflamide **166** recorded in $CDCl_3$*

With this encouraging result to hand, it was then envisaged that the same sort of Mitsunobu reaction could be applied to the "real" system involving the coupling of the *cis*–1,2–dihydrocatechol–derived conduritol **167** and keto–amide **168**. However, before this key process could be investigated, the preparation of these two precursors had to be carried out. Details of the relevant synthetic work are provided in the following Section.



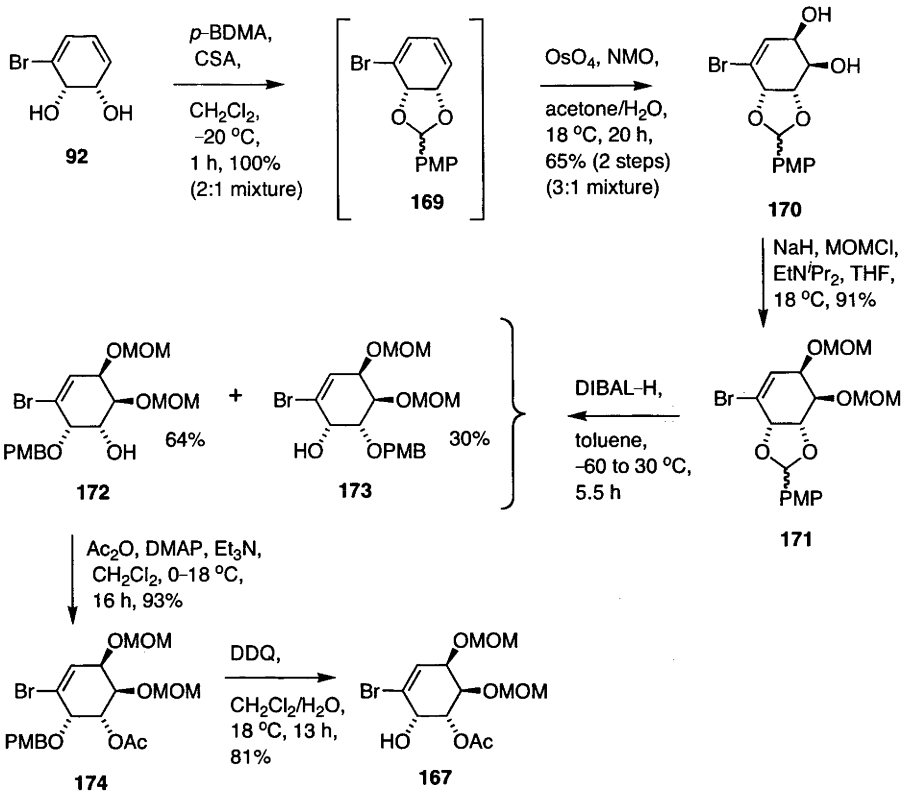
167



168

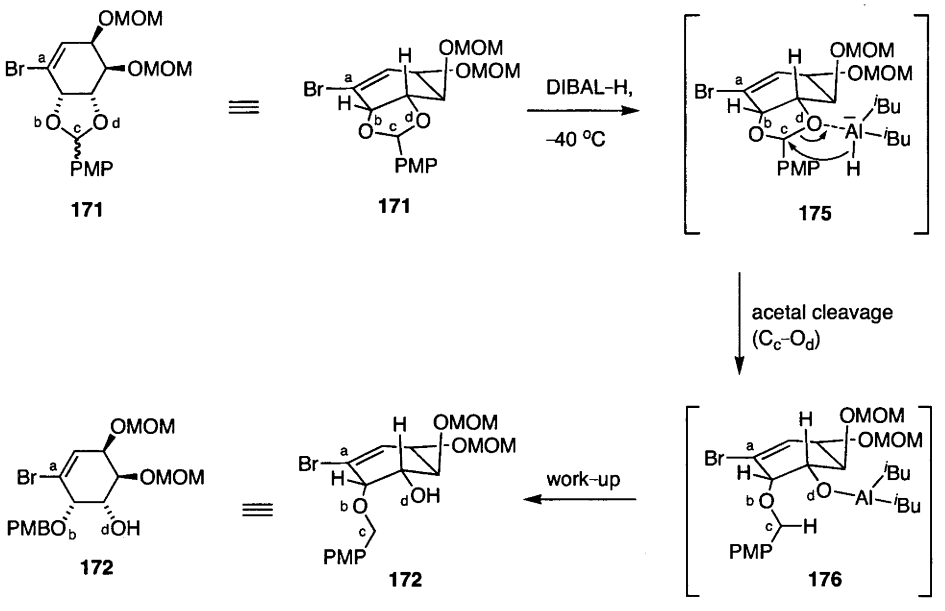
3.3.2. Preparation of Conduritol 167 and Keto–Amide 168

The synthesis of conduritol **167** commenced with the protection of the bromo–derivative of *cis*–1,2–dihydrocatechol **92** as the corresponding PMP acetal **169** (**Scheme 3.9**). As this compound proved to be somewhat unstable, it was immediately subjected to *cis*–1,2–dihydroxylation using OsO_4 under the Upjohn conditions[14] to give diol **170** as a 2:1 and inseparable mixture of diastereoisomers. Protection of this mixture of diols (**170**) with MOMCl then gave conduritol–derivative **171** (now as an inseparable 3:1 mixture of diastereoisomers due to selective enrichment of the major one), which were subjected to regioselective DIBAL–H–mediated acetal cleavage at –40 °C. This process delivered the major conduritol **172** in 64% yield together with the corresponding and chromatographically separable regioisomer **173**, which was obtained in 30% yield.



Scheme 3.9: *Synthesis of conduritol **167** from the bromo-derivative of* cis*-1,2-dihydrocatechol **92***

The regioselectivity observed in this reaction is attributed the steric bulk exerted by the bromine atom at C_a within substrate **171** (**Scheme 3.10**). From this it is thought that the coordination of DIBAL–H occurs preferentially at O_d to produce a sterically less congested intermediate **175**. This transient species can then undergo cleavage of the C_c–O_d bond (as shown in **175** → **176**) by the attack of the hydride ion of the aluminium metal from the direction *syn* to the departing oxygen and thus provide compound **172** as the major regioisomeric form of the product.[15]



***Scheme 3.10**: Regioselective reductive ring–cleavage of the benzylidene acetal function in conduritol **171** using DIBAL–H*

When conduritol **172** (major regioisomer) was treated with acetic anhydride in the presence of DMAP/triethylamine the acetylated derivative **174** was obtained (**Scheme 3.9**). The relative positions of the protecting groups (PMB and acetate) in this compound were confirmed using 2D–NMR spectroscopy. As shown in **Figure 3.2**, the observation of cross–peaks corresponding to the interaction of H_b with H_a and H_c in the ^1H–^1H COSY spectrum were taken as being indicative of the structure assigned to conduritol **174** and thus confirming the regioselectivity associated with DIBAL–H–mediated cleavage of acetal group present in conduritol **171**. Subsequent deprotection of the *p*–methoxybenzyl function within this last compound using DDQ lead to the target mono–ol, **167**, in 81% yield.

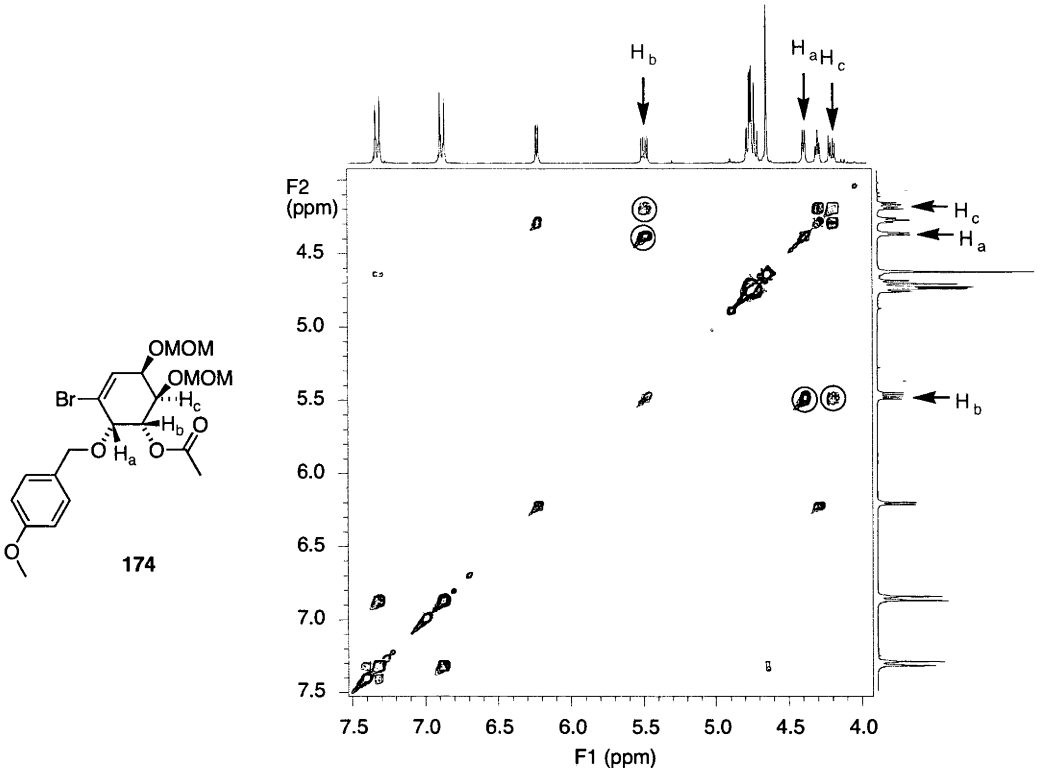
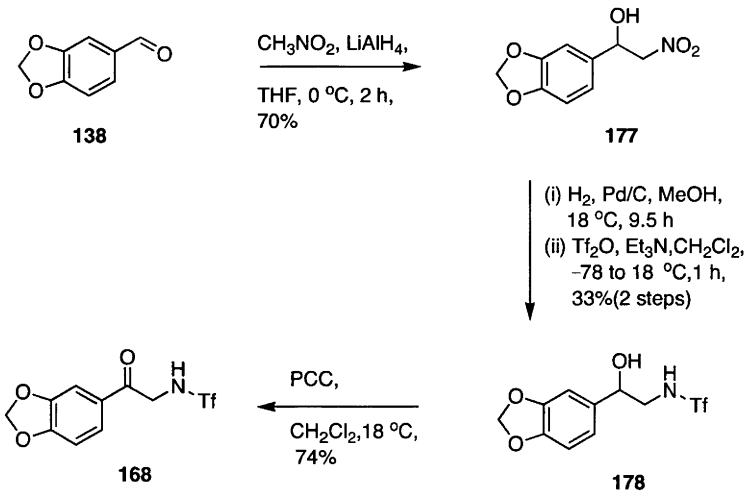


Figure 3.2: *600 MHz ^1H–^1H COSY spectrum of conduritol **174** recorded in $CDCl_3$*

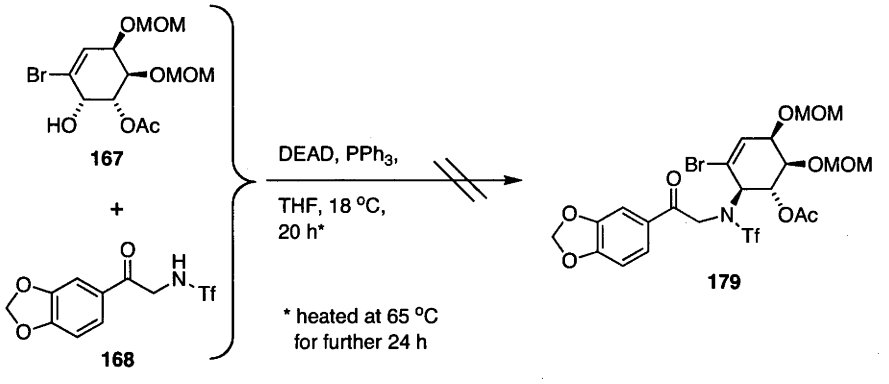
The preparation of keto–amide **168** commenced by using a protocol described by Corey *et. al.*,[13] wherein a $LiAlH_4$–mediated nitro–aldol reaction was carried out between piperonal (**138**) and nitromethane to give *β*–nitroalcohol **177** in 70% yield (**Scheme 3.11**). Since this product was prone to acid–catalysed dehydration, it was hydrogenolysed using dihydrogen in the presence of 10% Pd/C and the ensuing 1°–amine was subjected to selective *N*–protection using one equivalent of Tf_2O at low temperature and thus affording the hydroxy–amide **178** in 33% over the two steps involved. This modest yield is ascribed to the instability of the intermediate 1°–amine, the problem associated with selective *N*–triflation of the ensuing hydroxy–amine to produce hydroxy–amide **178** as well as competing hydrogenolysis of the benzylic alcohol group in *β*–nitroalcohol **177**. Oxidation of compound **178** with PCC in CH_2Cl_2 afforded the desired keto–amide **168** in 74% yield.



Scheme 3.11: *Synthesis of keto-amide **168** from piperonal (**138**)*

3.3.3. Attempted Synthesis of Amide 179

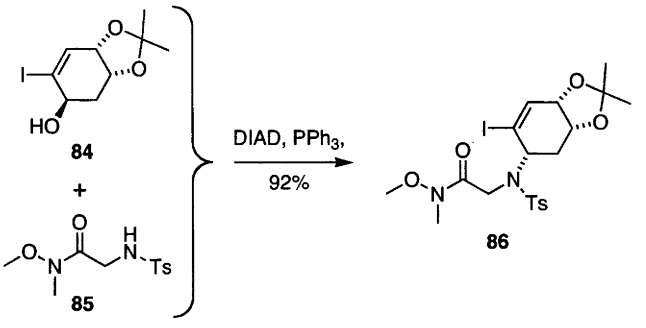
The successful preparation of conduritol **167** and keto–amide **168** meant that the pivotal Mitsunobu reaction could now be investigated. Unfortunately, subjection of conduritol **167** and keto–amide **168** to the relevant reaction conditions, *viz.* those used in the model study, resulted in a chromatographically inseparable mixture of products, none which corresponded to the target compound **179** (**Scheme 3.12**). A prolonged reaction time accompanied with an increase in temperature also failed to yield the desired material.



Scheme 3.12: *Attempted Mitsunobu reaction of conduritol **167** with keto–amide **168***

This outcome is presumably the result of adverse steric effects exerted by the adjacent acetate group in conduritol **167**. Since Sha[8] has shown that alcohol **84** lacking an adjacent

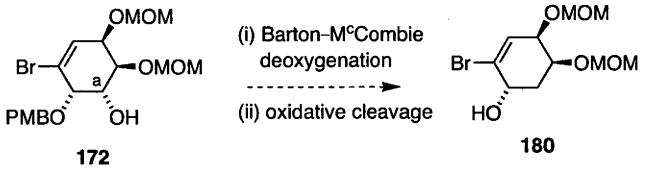
oxygen function could be reacted with amide **85** in a Mitsunobu reaction to give compound **86** in excellent yield (**Scheme 3.13**), relevant modifications to the Mitsunobu substrate were carried out as defined in the following section.



Scheme 3.13: *Successful Mitsunobu reaction of alcohol **84** and amide **85** reported by Sha[8]*

3.3.4. Attempted Synthesis of Alcohol 180 *via* Barton–M^{c}Combie Deoxygenation Reaction

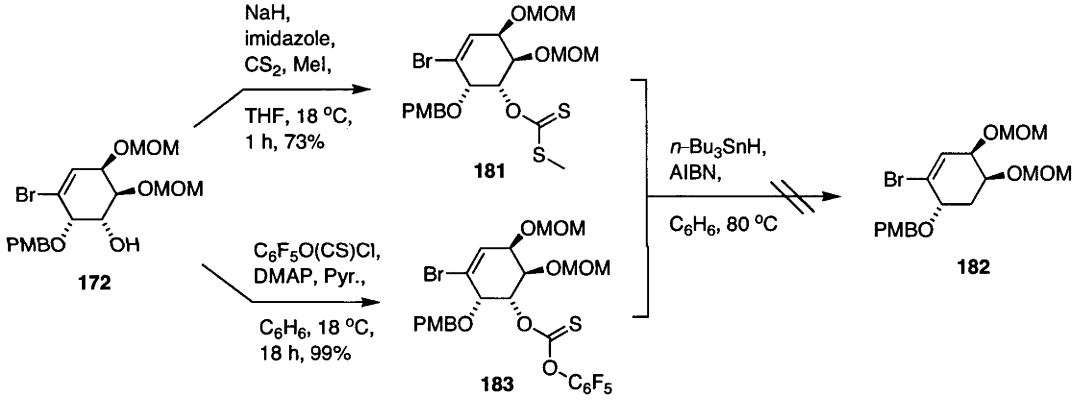
In considering an alternative approach to the one defined above, the sterically less demanding alcohol **180** was identified as a new substrate for the pivotal Mitsunobu reaction. It was considered that application of the Barton–M^{c}Combie deoxygenation protocol[16] at C_a followed by oxidative cleavage of the PMB group would be the most viable method for preparing such a compound from the readily available precursor **172** (**Scheme 3.14**).



Scheme 3.14: *Obtaining the sterically less–demanding alcohol **180** from conduritol **172***

Preparation of target **180** began with treatment of conduritol **172** with sodium hydride, followed by carbon disulfide (CS_2) in the presence of imidazole to produce an anion that was trapped with iodomethane to give xanthate ester **181** in 73% yield (**Scheme 3.15**). However, treatment of the last compound **181** with *n*–Bu_3SnH, at 80 °C, resulted in the recovery of

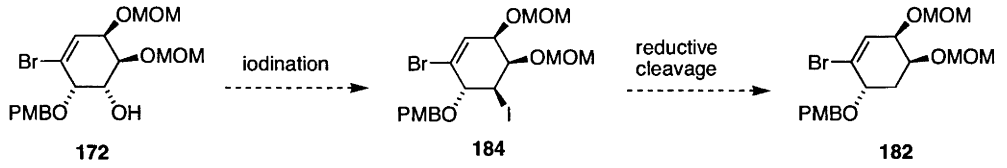
starting material. Variations on this type of protocol, including those involving the use of a longer reaction time and two additional equivalents of *n*–Bu_3SnH, also failed to yield the deoxygenated conduritol **182**. This result was rather surprising given that there are numerous examples from the literature of the deoxygenation of 2°–alcohols of complex substrates using this method.[17-20] From this the pentafluorophenylthionocarbonate analogue, **183**, of ester **181** was sought on the basis that homolysis of this group is more facile,[21] a reactivity that is attributed to the highly electron–withdrawing capacity associated the pentafluorophenyl substituent which serves to increase radicophilicity of the thione group.[21-23] Substrate **183** was prepared by the treatment of conduritol **172** with pentafluorophenyl chlorothionoformate in the presence of DMAP. Once again, however, reaction of this material (**183**) with *n*–Bu_3SnH and a catalytic amount of AIBN produced a chromatographically inseparable mixture of products, none of which corresponded to the desired deoxygenated conduritol **182**.



Scheme 3.15: *Attempted Barton–McCombie deoxygenation of conduritol **172** using the xanthate ester and thionocarbonate methods*

3.3.5. Preparation of Alcohol 180 *via* Iodination/Reductive Cleavage Method

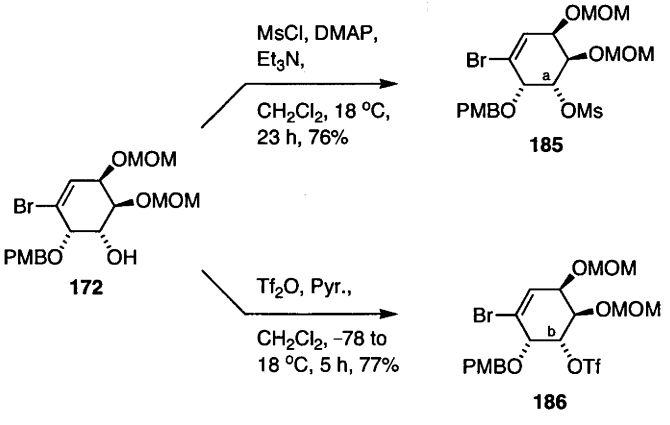
The disappointing outcomes detailed in the preceding section meant a different method for preparing the deoxygenated conduritol **180** was required. One involving a two–step iodination/reductive de–iodination protocol (**172** → **184** → **182**) (**Scheme 3.16**) was pursued.



Scheme 3.16: *Proposed two–step deoxygenation of conduritol* ***172*** via *an iodination/reductive cleavage method*

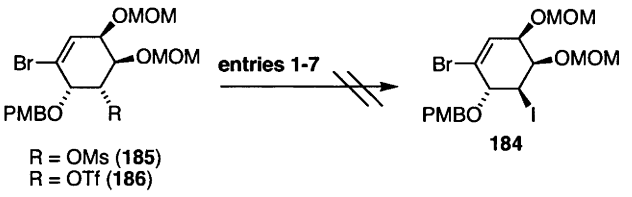
The implementation of this approach began with an investigation of a method for the conversion of conduritol **172** into the iodinated compound **184**. Sulfonates **185** and **186** were identified as substrates that could engage in S_N2–displacement reactions involving iodide ion as the nucleophile.

As shown in **Scheme 3.17**, the synthesis of the mesylate **185** was achieved through the treatment of conduritol **172** with MsCl in the presence of a catalytic amount of DMAP while triflate **186** was prepared using Tf_2O in the presence of pyridine. All the spectral data obtained on these sulfonate esters were in accord with the assigned structures. The ^{13}C NMR spectra of mesylate **185** and triflate **186** showed signals at δ 78.4 (C_a) and 83.6 (C_b), respectively, which are attributable to the ring carbons bearing the newly introduced and strongly electron–withdrawing substituents.



Scheme 3.17: *Synthesis of mesylate* ***185*** *and triflate* ***186***

However, as shown in **Table 3.1**, subjection of either compound (**185** and **186**) to reaction with various sources of iodide ion failed to give the desired product, *viz* compound **184**.



R = OMs (**185**)
R = OTf (**186**)

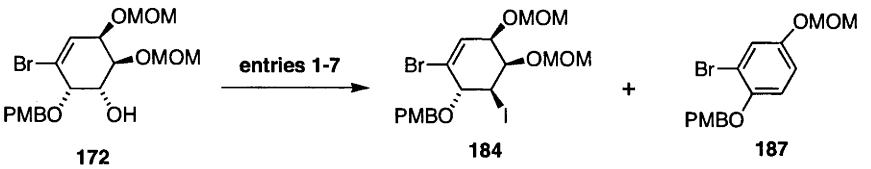
Entry	Substrate	Reagent	Solvent	Temp. (°C)	Time (h)	Outcome
1[24]	OMs	NaI	Acetone	56	16	No reaction
2[25]	OMs	NaI/$NaHCO_3$	Acetone	56	16	No reaction
3[26]	OMs	Bu_4NI	Toluene	80	16	No reaction
4[26]	OTf	Bu_4NI	Toluene	80	16	No reaction
5[27]	OTf	Bu_4NI	Toluene	120	20	Decomp.
6[28]	OTf	Bu_4NI	MeCN	90	20	No reaction
7[29]	OTf	NaI	DMF	80	20	No reaction
8[30]	OTf	Bu_4NI	DMF	80	20	No reaction

Table 3.1: *Attempted reactions of mesylate **185** and triflate **186** with various sources of iodide ion*

For example, treatment of mesylate **185** and triflate **186** (entries 3 and 4) with Bu_4NI at 80 °C only resulted in the return of starting material. In addition, subjection of the presumably more reactive triflate **186** to the higher temperature of 120 °C (entry 5) only lead to decomposition of starting material. Overall, analysis of these results suggested that compounds **185** and **186** were unsuitable substrates for the desired transformation.

In view of the results just described, a method that employed the unique PPh_3–I_2–imidazole reagent system[31] was investigated. Specifically, it was envisaged that such a system would overcome the previous difficulties and deliver the required iodide **184** in just one step. An initial attempt to effect the desired reaction at 90 °C lead to an incomplete transformation whereby the desired product **184** was obtained in only 5% yield, together with 30% of aromatic by–product **187** (entry 1 of **Table 3.2**). Although this yield (of 5%) was low, such an outcome was encouraging and indeed, subjecting conduritol **172** to a higher reaction temperature of 120 °C lead to the consumption of nearly all starting material and so

produced an increased yield (12%) of the desired product (entry 2). Interestingly, this was also accompanied by the decrease in the yield of the aromatic by–product **187**.



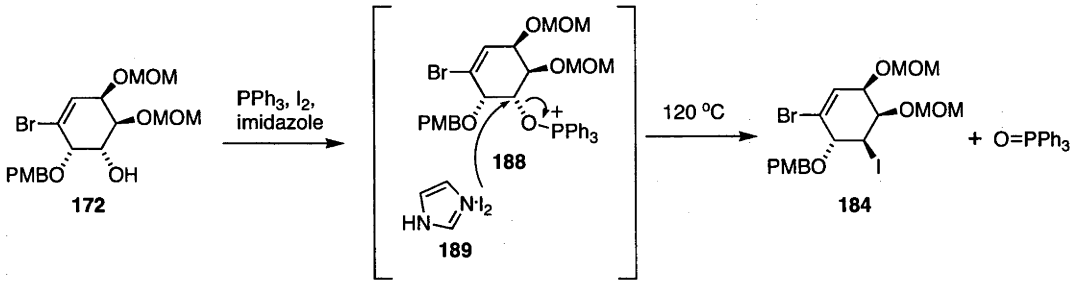
172 **184** **187**

Entry	Reagents (equiv.) (Ph_2PCl : PPh_3 : I_2 : Imid. : I_3–Imid.)	Conc. (mol/L)	Temp. (°C)	Time (h)	Product(s) (%) 172 : 184 : 187
1	0.0 : 1.5 : 0.0 : 1.2 : 1.6	0.04	90	24	60* : 5* : ~30*
2	0.0 : 1.9 : 0.0 : 2.5 : 2.0	0.17	120	16	5 : 12 : 20
3	2.0 : 0.0 : 3.0 : 7.5 : 0.0	0.01	90	2	Decomp.
4	0.0 : 3.0 : 2.0 : 3.0 : 0.0	0.04	120	5	0 : 47 : ~10*
5	0.0 : 3.0 : 2.0 : 3.0 : 0.0	0.02	120	20	0 : 57 : ~15*
6	0.0 : 4.0 : 0.0 : 1.2 : 1.0	0.02	120	18	0 : 70 : ~10*
7	0.0 : 5.0 : 0.0 : 1.2 : 1.0	0.02	120	3.5	0 : 81 : 6

* estimated by crude ^1H NMR–analysis of the crude reaction mixture; Imid = imidazole, I_3–Imid = 2,4,5–triiodoimidazole; solvent = toluene

Table 3.2: *Formation of iodide **184** by reaction of alcohol **172** using various phosphine–iodine–imidazole reagent combinations*

Although mechanistic studies were not carried out, it is conceivable that the pathway being followed in the conversion of **172** → **184** involves S_N2 displacement of the intermediate oxyphosphonium species **188** by the iodine-imidazole complex **189** (**Scheme 3.18**).[31]



172 **184**

Scheme 3.18: *Possible mechanism for the formation of iodide **184** from alcohol **172** using the PPh_3–I_2–imidazole reagent combinations*

Partial support for such a hypothesis arises from the single–crystal X–ray structure of iodide **184** which demonstrates that it possesses the expected (inverted) configuration at the iodine–bearing ring–carbon (**Figure 3.3**).

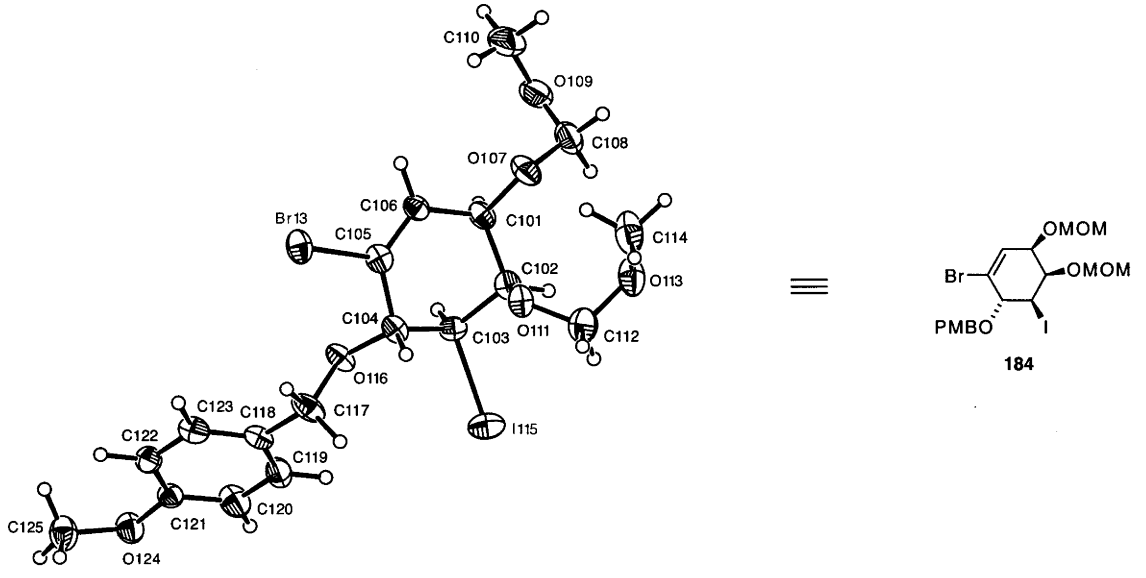
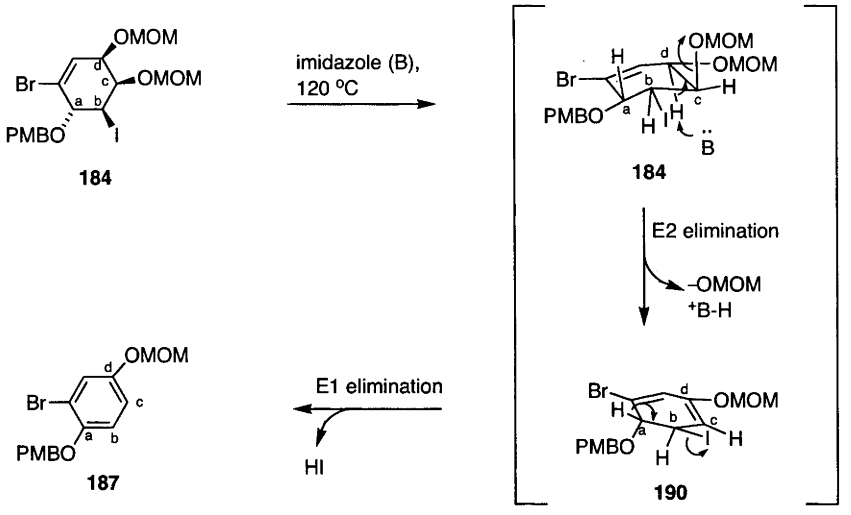


Figure 3.3: *ORTEP derived from the single–crystal X–ray analysis of iodide* ***184***

The aromatic by–product **187** was thought to result from the decomposition of iodide **184**, whereby the presence of antiperiplanar relationship between the MOM group at C_c and proton at C_d is thought to facilitate a base–promoted E2 elimination of $^-$OMOM (at C_c) leading to an intermediate diene **190** (**Scheme 3.19**). Subsequent E1 elimination of the iodine moiety (at C_b) as HI from this species then provides the observed aromatic compound **187**. The structure of this compound was confirmed using various spectrometric techniques including ^{1}H NMR, ^{13}C NMR and mass spectrometry. The ^{1}H NMR spectrum, for example, showed aromatic signals at δ 7.34 and 6.93 which are indicative of the 1,3,5–trisubstituted aromatic ring present in compound **187**. In addition, this spectrum also showed signals, at δ 5.09 and 3.47, attributable to the MOM group (at C_d) within compound **187**.

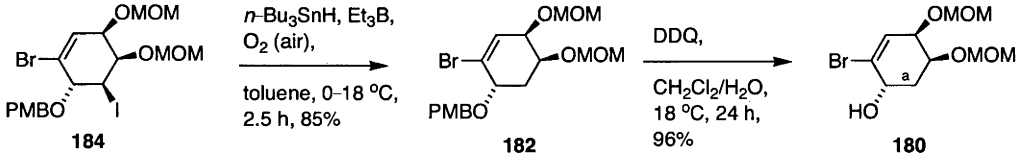


Scheme 3.19: *Proposed mechanism for the formation of the aromatic by–product* ***187*** *from iodide* ***184***

The problems created by the low yield of the product **184** were compounded by difficulties in separating the required material from the excess PPh_3 and the by–product $O{=}PPh_3$. Therefore, and as an attempt to overcome these issues, an iodination system which involved the use Ph_2PCl–I_2–imidazole reagent system was investigated. An advantage to using Ph_2PCl compared to PPh_3 is that Ph_2PCl and its by–products can be removed from the organic phase by extraction. In addition, this reagent system has been reported to be the most reactive and versatile one for converting alcohols into the corresponding alkyl iodides under relatively mild conditions.[32] However, as shown in entry 3 of **Table 3.2**, an attempt to convert conduritol **172** into the iodide **184** using this system only resulted in chromatographically inseparable mixture of products, none of which corresponded to the desired compound **184**. In re–investigating the PPh_3–I_2–Imidazole system, a further increase in the number of equivalents of PPh_3 (entries 4 and 5) followed by a decrease in concentration of the reactants, lead to a significant increase in yield (35–45%) of the iodide **184**. The use of 2,4,5–triiodoimidazole[33] as the iodide source also had a dramatic effect with the result that a now excellent yield (81%) of iodide **184** could be obtained (entry 7).

Selective removal of the iodine moiety present in iodide **184** with *n*–Bu_3SnH in the presence of a catalytic amount of Et_3B as radical initiator (and oxygen [air]) at 18 °C[34] then furnished deoxygenated conduritol **182** in excellent yield and so completing the two–step deoxygenation protocol (**Scheme 3.20**). No products arising from the loss of bromine were

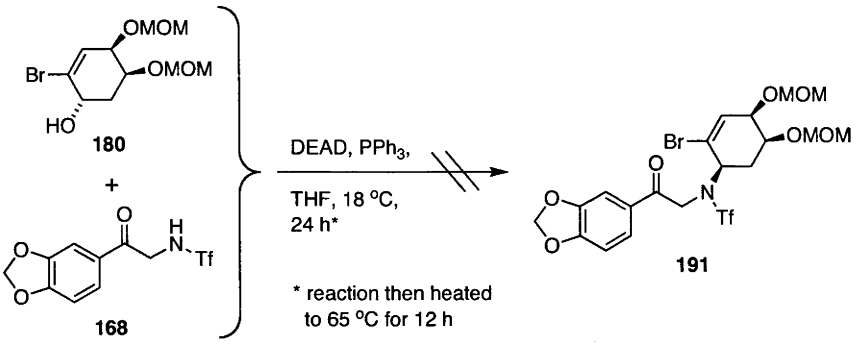
observed. This was attributed to significant differences in bond strengths (bond dissociation energies) between sp^3 iodine–carbon bonds and sp^2 bromine–carbon bonds with the latter being 26–28 kcal/mol stronger.[35,36] Oxidative cleavage of the PMB group of deoxyconduritol **182** with DDQ under biphasic conditions then afforded the, by now, long–sought after alcohol **180** in 96% yield. All the data obtained on this material were consistent with the assigned structure. For example, the ^1H NMR spectrum of this compound showed signals at δ 2.26 and 1.95, which are attributed to the diastereotopic protons at C_a, and so confirming successful de–iodination of precursor **184**. In addition, the IR spectrum showed a broad band at 3437 cm^{-1}, which was indicative of an alcohol function resulting from oxidative cleavage of the PMB group of deoxygenated conduritol **184**.



Scheme 3.20: *Synthesis of alcohol **180** from iodide **184***

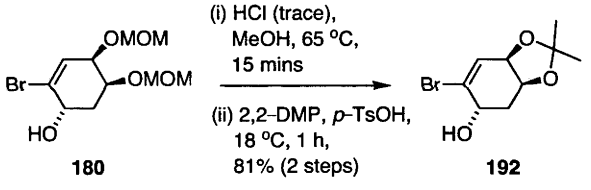
3.3.6. Mitsunobu Reaction of Alcohol 192 with Keto–Amide 168

Having prepared alcohol **180**, all that remained was the key Mitsunobu reaction. In the event, subjection of this compound and keto–amide **168** to the Mitsunobu reaction protocol failed to give the keto–amide **191**. Only a chromatographically inseparable mixture of unidentified products was obtained (**Scheme 3.21**). An increase in reaction temperature also failed to yield the expected Mitsunobu adduct. A careful re–examination of the work of Sha[8] seemed to suggest that steric effects imparted by the MOM groups might also be contributing to this unfavourable outcome.



Scheme 3.21: *Attempted Mitsunobu reaction of alcohol* ***180*** *with keto–amide* ***168***

In fact, it was envisaged that an exchange of the MOM groups of alcohol **180** for the isopropylidene group would produce a compound that was sterically less demanding and structurally analogous to the compound reported by Sha.[8] Therefore, alcohol **180** was treated with trace HCl in MeOH at 18 °C and this resulted in hydrolysis of the MOM groups to produce an intermediate triol that was immediately protected using 2,2–DMP (in the presence of catalytic *p*–TsOH) to give acetonide **192** containing a single free hydroxyl group (**Scheme 3.22**).



Scheme 3.22: *Synthesis of compound* ***192***

The structure of alcohol **192** was confirmed by single–crystal X–ray analysis and the derived ORTEP is shown in **Figure 3.4**.

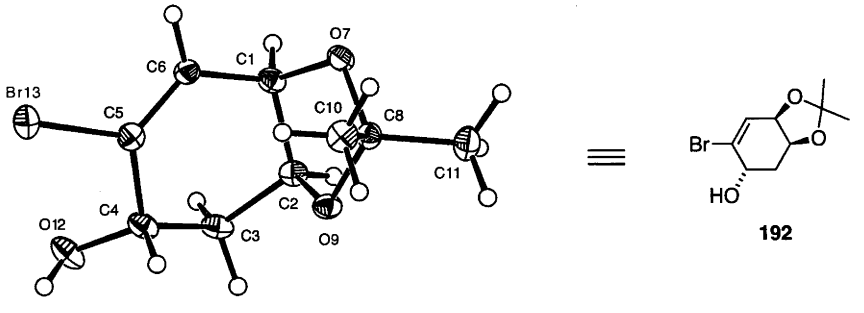
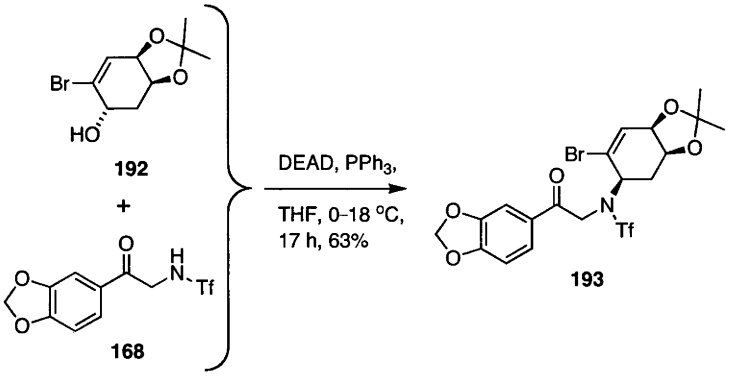


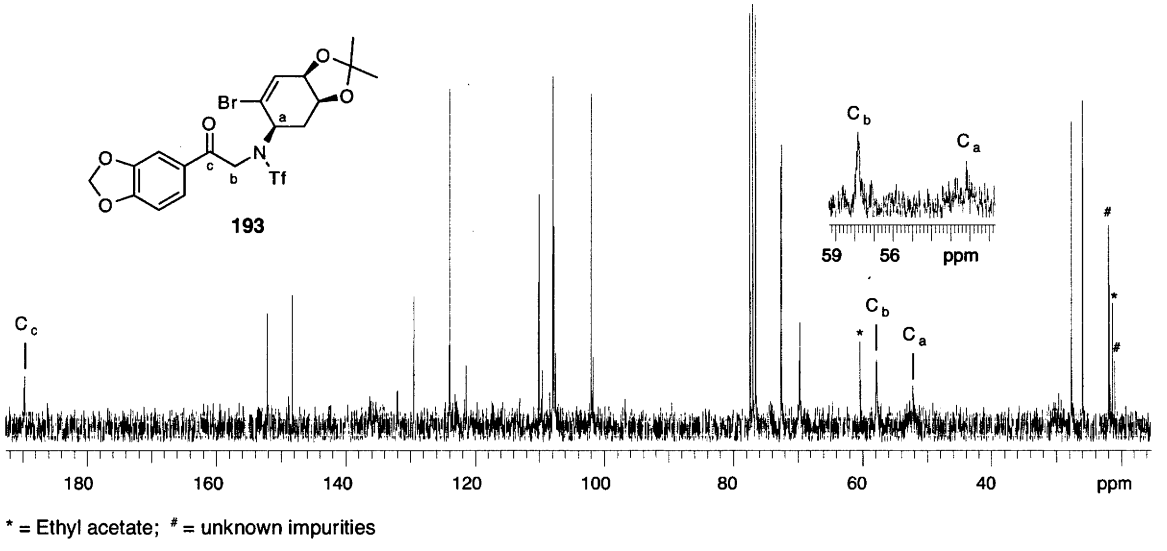
Figure 3.4: *ORTEP derived from the single–crystal X–ray analysis of alcohol* ***192***

Subjection of alcohol **192** and keto–amide **168** to Mitsunobu reaction resulted in a successful transformation whereby the desired compound **193** was produced 63% yield (**Scheme 3.23**). All the spectral data obtained on this compound were in full accord with the assigned structure.



Scheme 3.23: *Successful Mitsunobu reaction of Alcohol **192** and Keto–Amide **168***

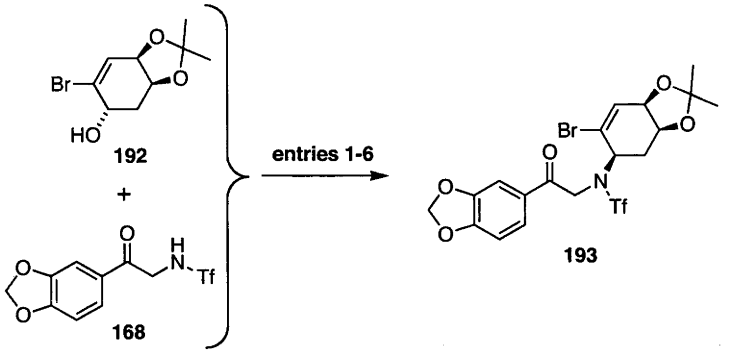
For instance, the ^{13}C NMR spectrum (**Figure 3.5**) showed a signal at δ 52.2 which is attributed to that carbon atom (C_a) involved in the newly installed carbon–nitrogen bond.



* = Ethyl acetate; # = unknown impurities

Figure 3.5: *75 MHz ^{13}C NMR spectrum of keto–amide **193** recorded in $CDCl_3$*

Unfortunately, and very frustratingly, the Mitsunobu reaction of alcohol **192** and keto–amide **168** was found to be irreproducible under the conditions just described. Additional efforts to effect this reaction by using sterically less–demanding reagent systems, such as TMAD/PMe_3[37] (entry 6 of **Table 3.3**), also failed to yield the required compound. Overall, this disappointing outcome meant that an alternative approach to the synthesis of the pivotal 3–arylhexahydroindoles was necessary.



Entry	Carboxylate	Phosphine	Solvent	Temp. (°C)	Time (h)	Outcome
1	DIAD	PPh_3	CH_2Cl_2	18	15	**193** (<1%)
2	DEAD	PPh_3	THF	18	20	**193** (<1%)
3	TMAD	PPh_3	C_6H_6	18	15	Starting material
4	TMAD	PBu_3	C_6H_6	18	15	Starting material
5	TMAD	PMe_3	THF	18	15	Starting material
6	TMAD	PMe_3	C_6H_6	18	15	Starting material

Table 3.3: *Attempted Mitsunobu reactions with different reagent systems*

3.4. Summary

In connection with the work directed towards the preparation of (+)–brunsvigine (*ent*–**18**), this chapter has detailed a synthetic approach (*Approach B*) whereby, following a successful model study, efforts were made to carry out a Mitsunobu reaction between keto–amide **168** and the *cis*–1,2–dihydrocatechol–derived alcohols **167**, **180** and **192** so as to provide intermediates necessary for preparation of the key 3–arylhexahydroindole **119**. Whilst this type of conversion proved capricious, it provided the basis for an alternative approach (*Approach C*). Details of this alternative are provided in the following chapter.

3.5. References

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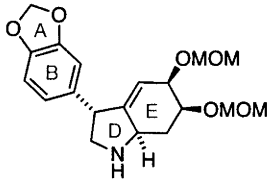
CHAPTER FOUR

Towards (+)-Brunsvigine: Attempted Preparation of 3-Arylhexahydroindoles *via Approach C*

4.1. Introduction

4.1.1. Overview and Context

As noted in Section **1.3.5.** (see Chapter One), the Pictet–Spengler reaction was identified as a crucial element in the proposed strategy for obtaining (+)–brunsvigine (*ent*–**18**). Accordingly, the focus of studies to this point remained identifying methods for the formation of 3–arylhexahydroindole **194**, the substrate required for the Pictet–Spengler reaction. Indeed, it was hoped that such a compound could be obtained *via* a new approach, *Approach C,* that still started from the enzymatically–derived and enantiopure *cis*–1,2–dihydrocatechol **92**. Details of this study are presented below.



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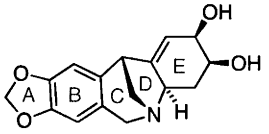
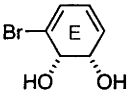


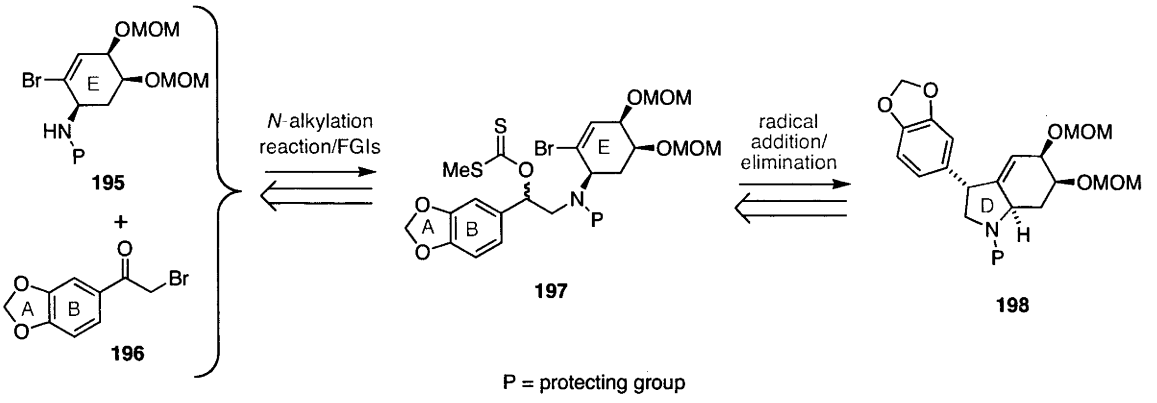
ent-**18**



92

4.1.1.1. Overview of *Approach C*

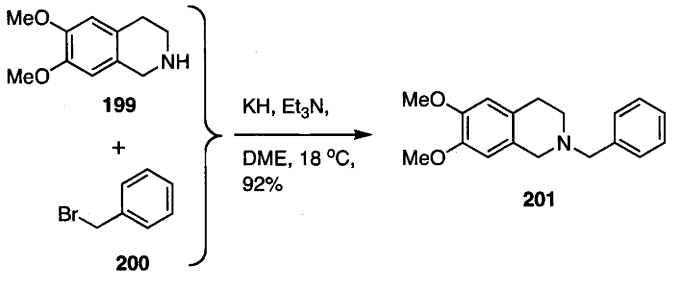
As a modification of the second approach (*Approach B*), the third one (*Approach C*), which is detailed here, would involve a two–step D–ring annulation protocol commencing with direct *N*–alkylation of *cis*–1,2–dihydrocatechol–derived 2°–amine **195** with α–bromoketone **196** (**Scheme 4.1**). Using various functional group interconversions (FGIs), it was hoped to produce compound **197** which it was anticipated would engage in a radical cyclization/halogen atom elimination reaction to give the 3–arylhexahydroindole **198** possessing the necessary $\Delta^{1,11a}$–double bond present in the E–ring of (+)–brunsvigine (*ent*–**18**). However, before discussing the outcome of these studies, a brief overview of the synthesis of 3°–amines *via* direct *N*–alkylation of 2°–amines with alkyl halides is presented in the next section.



Scheme 4.1: *Formation of key intermediate* ***198*** via *Approach C*

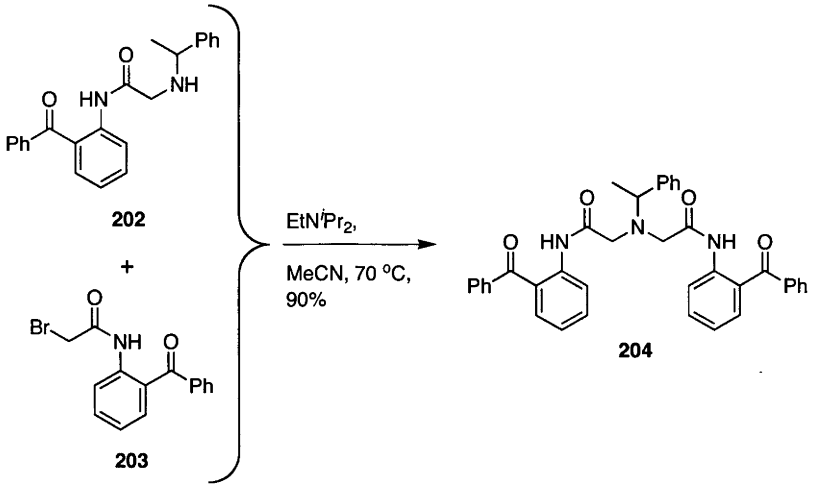
4.2. Background: Preparation of 3°–Amines *via* Direct *N*–Alkylation of 2°–Amines

Although direct *N*–alkylation of unactivated 2°–amines with alkyl halides is conceptually the most straightforward method for preparing 3°–amines, problems exist because the degree of *N*–alkylation is often difficult to control with the formation of undesired quaternary ammonium salts frequently being encountered. Accordingly, the practical applications of this approach have, until recently, been somewhat limited. In attempts to address this issue, Mohri[1], Soloshonok[2] and Varma[3] have each been able to enhance the synthetic value of this methodology by reporting operationally simple and direct *N*–alkylation protocols that normally result in moderate to high yields of 3°–amines without the accompanying formation of undesired quaternary ammonium salts. Mohri, for instance, was able to establish an efficient synthesis of 3°–amine **201** through the use of potassium hydride–mediated *N*–alkylation of 2°–amine **199** with benzyl bromide (**200**) (**Scheme 4.2**).[1]



Scheme 4.2: *Mohri's synthesis of 3°–amine* ***201***

Soloshonok was able to report the highly efficient synthesis of 3°–amine **204** *via* direct *N*–alkylation of 2°–amine **202** with alkyl bromide **203** in excellent yield (**Scheme 4.3**).[2] This conversion is particularly relevant to the one being contemplated in *Approach C*, details of which are provided in the following sections.

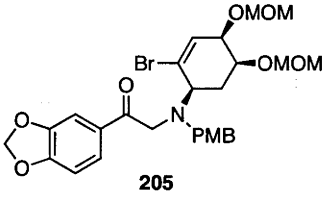


Scheme 4.3: *Soloshonok's synthesis of 3°–amine* ***204***

4.3. D–Ring Annulation: Attempted Synthesis of 3–Arylhexahydroindole 194

4.3.1. Direct *N*–Alkylation Reaction of 2°–Amine 206 and α–bromo–ketone 102

An investigation into the viability of the title approach for preparing 3°–amine **205** started with the synthesis of the relevant precursors, namely the 2°–amine **206** and the α–bromoketone **102**.



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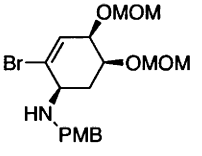

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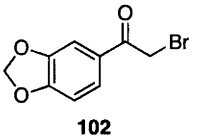
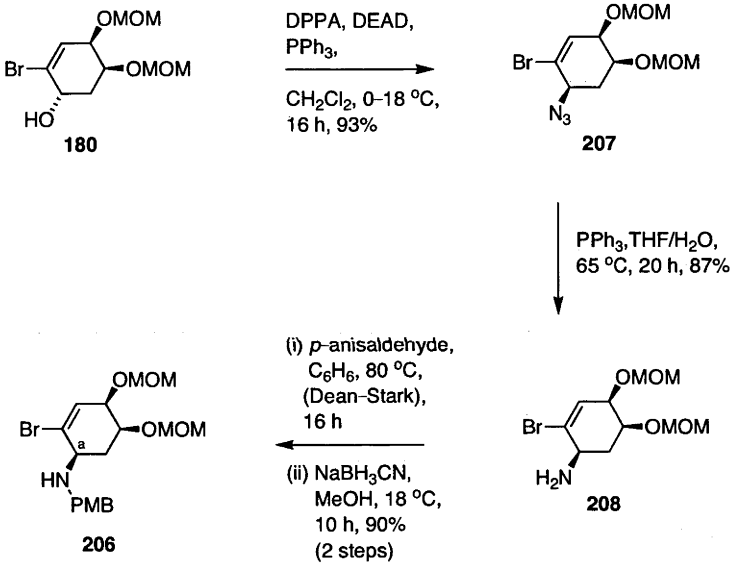


102

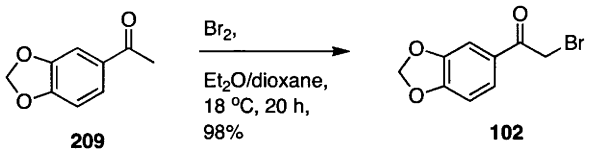
The synthesis of 2°–amine **206** began with the subjection of the previously prepared alcohol **180** (see Section **3.3.4.**) to Mitsunobu azidation reaction[4] using DPPA as the nucleophile. In this way azide **207** was produced in excellent yield (**Scheme 4.4**). Reduction of this azide under Staudinger conditions[5] then provided the corresponding 1°–amine **208** which upon subjection to a reductive amination protocol,[6] using *p*–anisaldehyde and $NaBH_3CN$, afforded 2°–amine **206** in excellent yield. All the data obtained for this compound were in accord with the assigned structure. The ^{13}C NMR spectrum, for example, showed signals at δ 57.9 and 47.6 that are attributed to C_a and the benzylic carbon of the PMB substituent, respectively. In addition, the IR spectrum showed a broad band at 3333 cm^{-1} which is indicative of the NH group present in compound **206**.



Scheme 4.4: *Synthesis of 2°–amine **206** from alcohol **180***

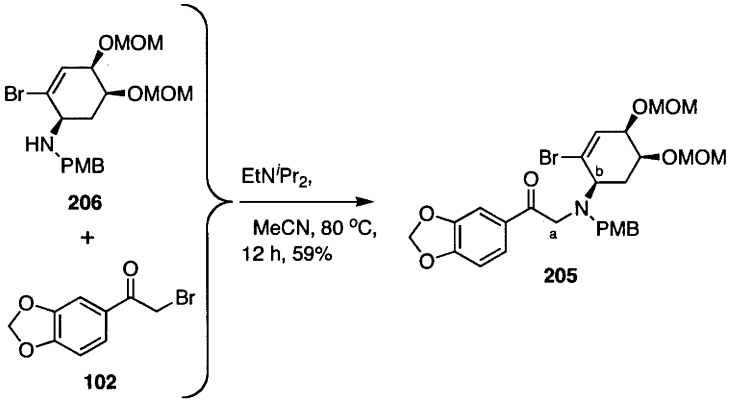
The rationale for protecting the 1°–amine **208** as a PMB derivative was based on the notion that this moiety is an electron–rich protecting substituent which would serve to activate the nitrogen atom (i.e. make it more nucleophilic) and so increase its propensity to undergo direct *N*–alkylation reactions.

The preparation of the previously unreported α–bromoketone **102** involved just one step whereby treatment of the commercially available ketone **209** with molecular bromine in a 5:4 v/v mixture of diethyl ether/dioxane, maintained 18 °C, resulted in the formation of the target substrate **102** in excellent yield (**Scheme 4.5**).



Scheme 4.5: *Synthesis of α–bromoketone* ***102***

Gratifyingly, subjection of 2°–amine **206** and α–bromoketone **102** to a direct *N*–alkylation reaction as described by Soloshonok[2], afforded 3°–amine **205** in 59% yield (**Scheme 4.6**).



Scheme 4.6: *Synthesis of 3°–amine* ***205*** *by direct* N–*alkylation reaction*

All the spectral data obtained on compound **205** were consistent with the assigned structure. In particular, the ^{13}C NMR spectrum (**Figure 4.1**) showed a signal at δ 61.0 which is attributed to C_a and so is indicative of the presence of the newly formed carbon–nitrogen bond. In addition, a signal observed at δ 53.1 was assigned to C_b.

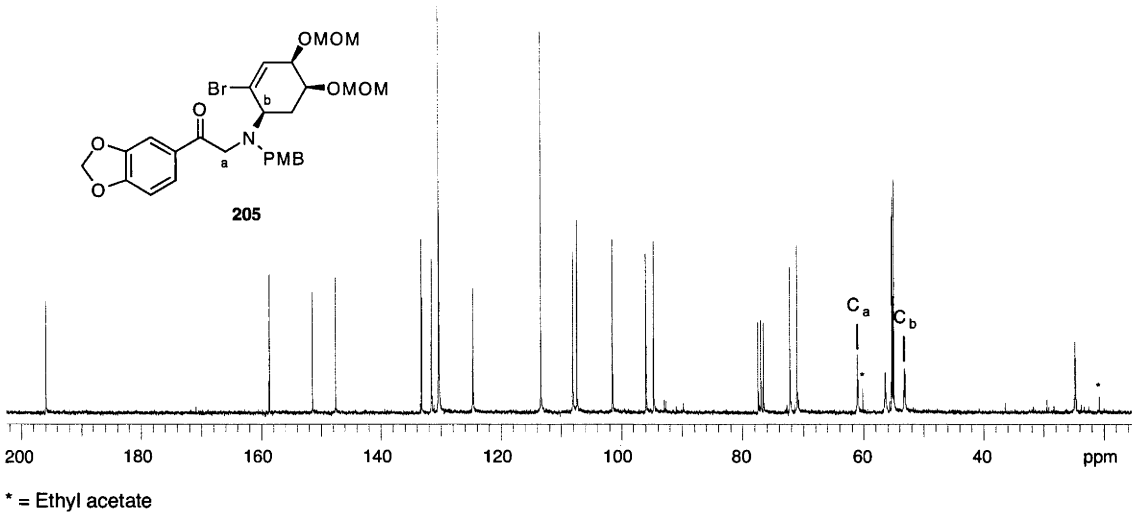
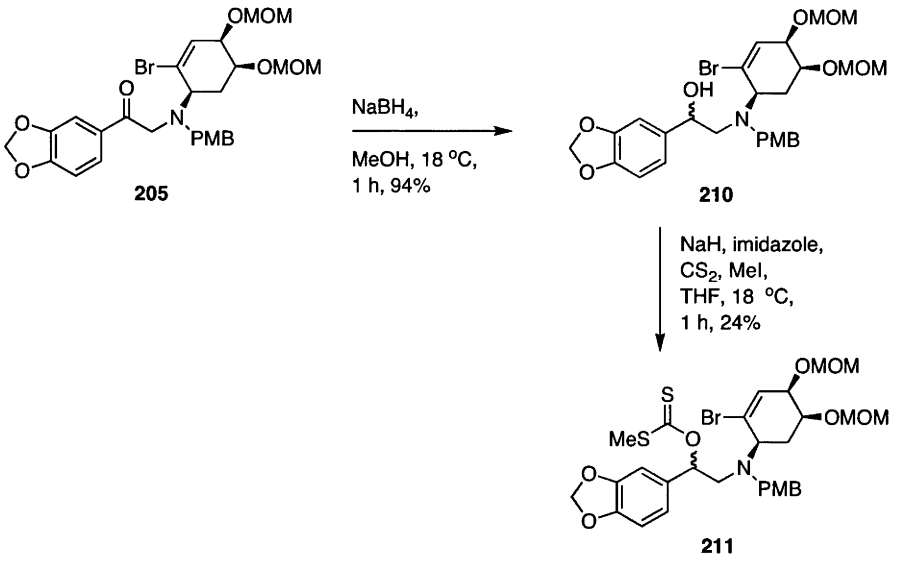


Figure 4.1: *75 MHz ^{13}C NMR spectrum of 3°–amine* ***205*** *recorded in $CDCl_3$*

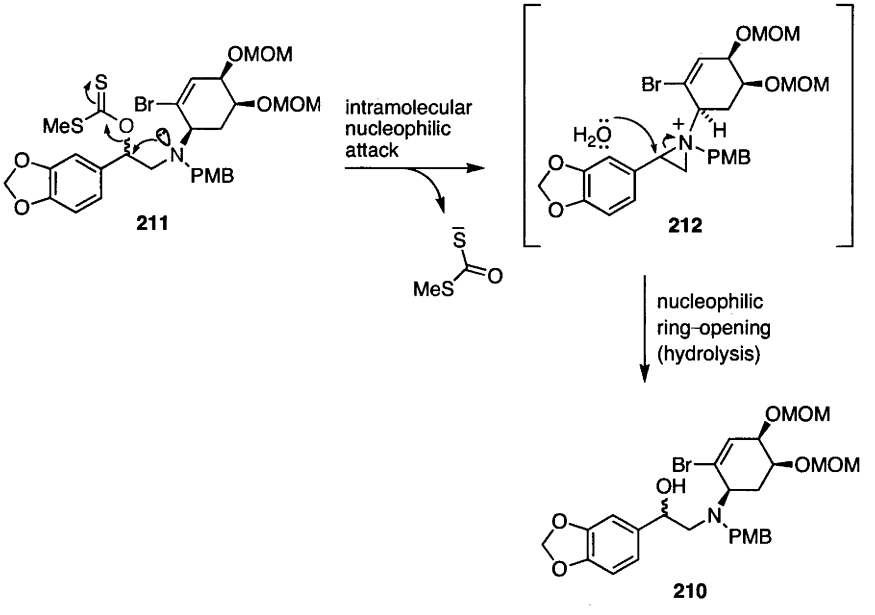
4.3.2. Synthesis of Radical Precursor 211

The successful preparation of 3°–amine **205** now meant that an appropriate radical cyclization precursor could be prepared. It was envisaged that this could be achieved *via* simple reduction of the carbonyl function within ketone **205** to the corresponding alcohol, followed by conversion of the latter into the corresponding xanthate ester **211**.[7] The preparation of this radical precursor began by subjecting 3°–amine **205** to a $NaBH_4$–mediated reduction of the carbonyl group to give alcohol **210** (as a 1:1 mixture of diastereoisomers) in 94% yield (**Scheme 4.7**). Treatment of this last compound with sodium hydride, carbon disulfide and iodomethane[8] then produced xanthate ester **211**, albeit, in low yield (*ca* 24%). This was also accompanied by 20% of recovered starting material.



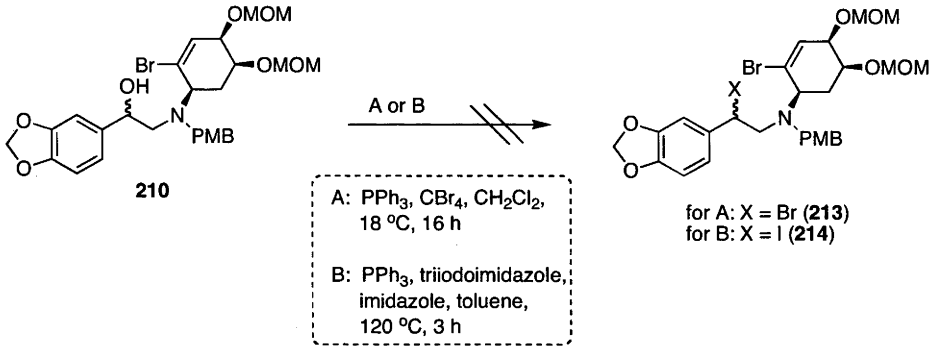
Scheme 4.7: *Synthesis of radical precursor **211***

In an attempt to find a reasonable explanation for the low yield of xanthate **211**, this compound was examined carefully. As shown in **Scheme 4.8**, the 1,2–relationship between the xanthate group and 3°–amine function in amine **211** is significant as the amine moiety can displace the xanthate ester residue to produce intermediate aziridinium ion **212** which can, in turn, react with adventitious water to give alcohol **210**.[9-11]



Scheme 4.8: *Possible pathway for the conversion of xanthate **211** into alcohol **210***

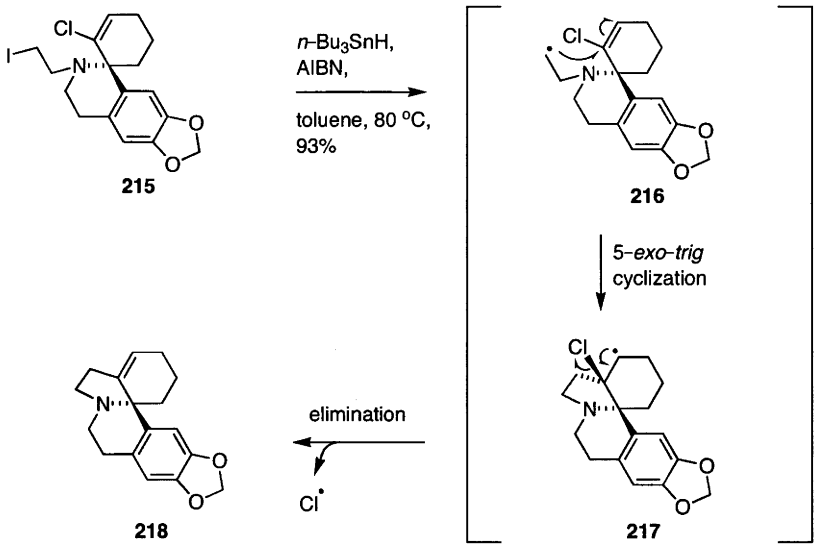
Additional evidence for involvement of this type of neighbouring group participation comes from various efforts to prepare halides **213** and **214** (**Scheme 4.9**). For instance, attempts to synthesize the radical precursor **213** under standard Appel–type reaction conditions[12] failed. Subjecting this material to the optimised iodination conditions (as described in the previous Chapter [Section **3.3.4.**]) also failed to produce the corresponding iodinated radical precursor **214**. In each instance, only starting material **210** was recovered from the reaction mixture.



Scheme 4.9: *Attempted synthesis of radical precursors **213** and **214***

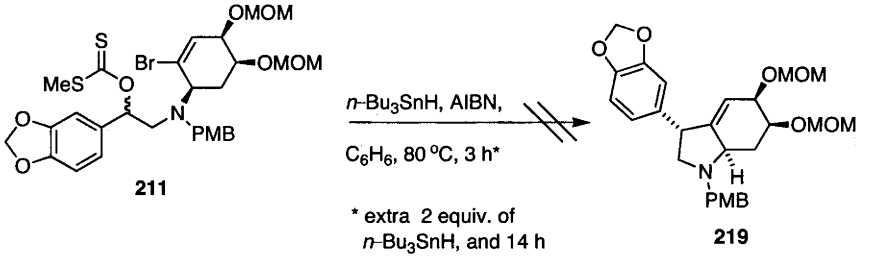
4.3.3. Radical Cyclization Reaction: Precedence from Banwell and Attempted Radical Cyclizations of Precursors 211 and 220

Although an efficient synthesis of xanthate ester **211** could not be achieved, proof that such a compound could undergo the pivotal radical cyclization reaction was required. Immediately before the work described here was undertaken, Banwell *et al.*[13] reported that treatment of alkenyl chloride **215** with *n*–Bu_3SnH, in the presence of catalytic amounts of AIBN, resulted in the formation of a 1°–radical **216** that underwent 5–*exo*–*trig* cyclization to form intermediate radical **217** (**Scheme 4.10**). Subsequent elimination of the chlorine radical then produced the desired target erythrina alkaloid framework **218** in excellent (93%) yield.



Scheme 4.10: *Banwell's method for the assembly of tetracyclic framework* ***218*** *of aromatic erythrina alkaloids* via *a carbon–radical cyclization/chlorine–radical elimination sequence*

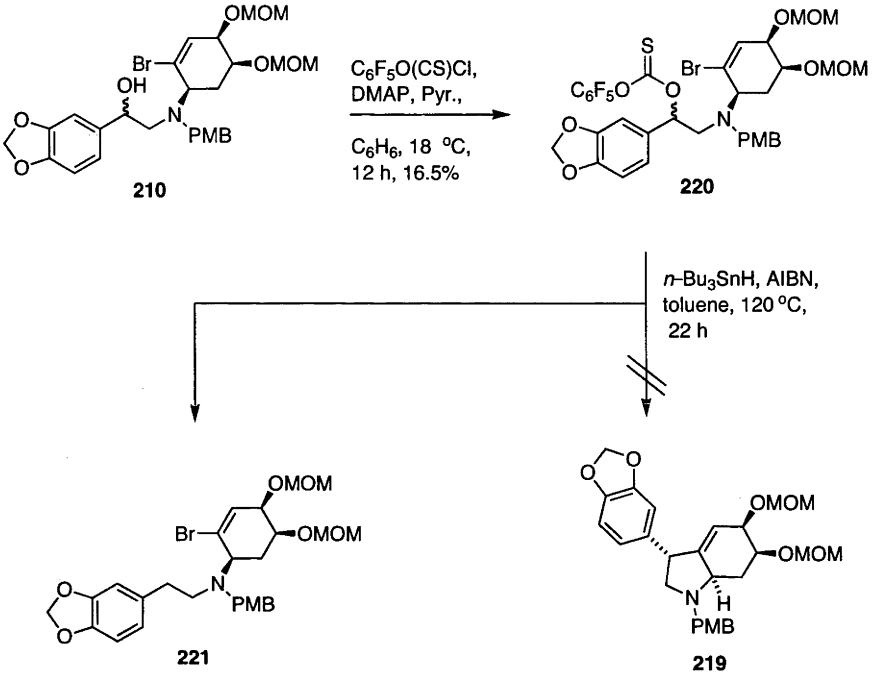
Therefore, following such work,[13] the radical precursor **211** was treated with *n*–Bu_3SnH and a catalytic amount of AIBN then the ensuing mixture was heated at 80 °C for 3 h. However, under such conditions only starting material was recovered from the reaction mixture (**Scheme 4.11**). Attempts to effect the chemical transformation by increasing the reaction time and number of equivalents of *n*–Bu_3SnH also failed to give compound **219** and now only a chromatographically inseparable mixture of products was observed.



Scheme 4.11: *Attempted radical cyclization of xanthate ester* ***211***

In pursuit of a better precursor, attention turned towards the use of the more reactive pentafluorophenyl thionocarbonate function. To such ends, alcohol **210** was treated with pentafluorophenyl thionochloroformate[14] in the presence of a catalytic amount of DMAP and in this way thionocarbonate **220** was obtained in 16.5% yield (**Scheme 4.12**).

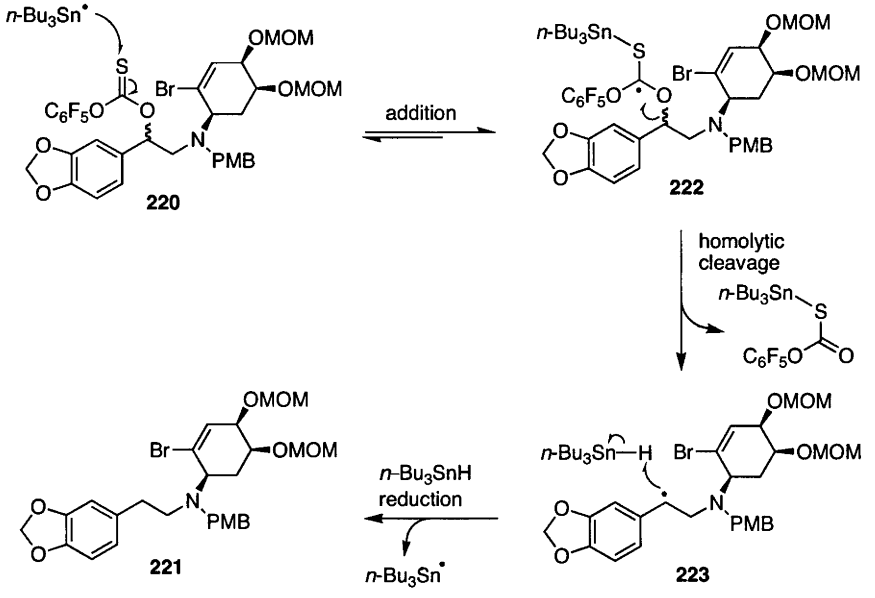
Disappointingly, subjection of this material to radical cyclization conditions failed to give the required 3–aryhexahydroindole **219**. Instead, a chromatographically inseparable mixture of products, including material tentatively identified as the reduced compound **221**, was obtained.



Scheme 4.12: *Synthesis of thionocarbonate **220** and attempted radical cyclization of it as a route to 3–aryhexahydroindole **219***

In order to explain why only reduced material was obtained, the likely reaction mechanism of the desired radical cyclization process was considered. As it is generally understood, the use of thiocarbonyl group as radical precursor in tin–mediated radical chemistry is heavily reliant upon the strong affinity of tin for sulfur. Therefore, as shown in **Scheme 4.13**, the addition of the stannyl radical (generated during the radical initiation step) to the thiocarbonyl function of compound **220** would result in the formation of intermediate radical **222**. This strong affinity of tin for sulfur leads to the formation of an equilibrium process, which lies towards intermediate radical **222**. Cleavage of this radical *via* the *β*–scission of the carbon–oxygen bond would produce benzylic radical **223**, which can then undergo hydrogen atom abstraction from tin hydride to give the reduced compound **221**. Alternatively, benzylic radical **223** can undergo radical cyclization to produce the required 3–arylhexahydroindole

219. However, this reaction is not observed, presumably, because it is slow relative to the direct reduction process.[15]



Scheme 4.13: *Mechanism associated with the reduction of thionocarbonate **220** by* n–*Bu_3SnH*

This situation can be attributed to several underlying factors such as concentration of the reactants, temperature, rate of addition of the hydride and the conformational constraints imposed on the radical by the molecular framework within which it is embedded. For instance, the failure of radical **223** to undergo cyclization might be due to insufficient conformational freedom within the radical intermediate to enable it to undergo addition onto the halogenated double bond.[16] Because a limited supply of compound **220** was available, only a few variations on the original attempts to effect the conversion **220** → **219** could be investigated. None of these proved fruitful. Accordingly, a new approach to the originally targeted 3–arylhexahydroindole **194** was required.

4.4. Summary

This Chapter has detailed work directed towards the preparation of (+)–brunsvigine (*ent*–**18**) *via Approach C*. Key features include the successful *N*–alkylation the *cis*–1,2–dihydrocatechol–derived 2°–amine **206** with α–bromoketone **102** to produce 3°–amine **205**.

However, the attempts to convert the last compound into an appropriate radical precursor proved to be somewhat problematic because only low yields of radical precursors **211** and **220** were obtained. Nevertheless, having access to these materials meant that the key radical cyclization could be attempted. Disappointingly, subjecting these compounds (**211** and **220**) to *n*–Bu_3SnH–mediated radical cyclization conditions only lead to recovered starting material (in the case of precursor **211**) or reduced material (in the case of precursor **220**) were obtained.

Although this failure to prepare the required 3–arylhexahydroindole **219** was disappointing, it provided the necessary platform for the investigation of the final and successful approach (*Approach D*; see following Chapter for a detailed discussion) to the title alkaloid.

4.5. References:

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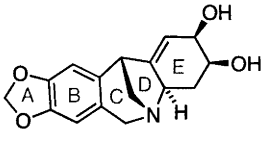
CHAPTER FIVE

Preparation of 3-Arylhexahydro-oxindoles *via Approach D*: Application to a Chemoenzymatic Total Synthesis of (+)-Brunsvigine

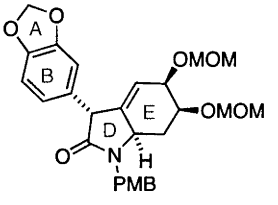
5.1. Introduction

5.1.1. Overview and Context

Having encountered difficulties associated with the pivotal radical cyclization reaction which it was hoped would enable formation of the D–ring of (+)–brunsvigine (*ent*–**18**), this Chapter details a new approach (*Approach D*) leading to a successful synthesis of 3–arylhexahydro–oxindole **224**. As will be shown, this key intermediate could then be elaborated, *via* the previously mentioned Pictet–Spengler strategy (Chapter One), to (+)–brunsvigine (*ent*–**18**).



ent-**18**

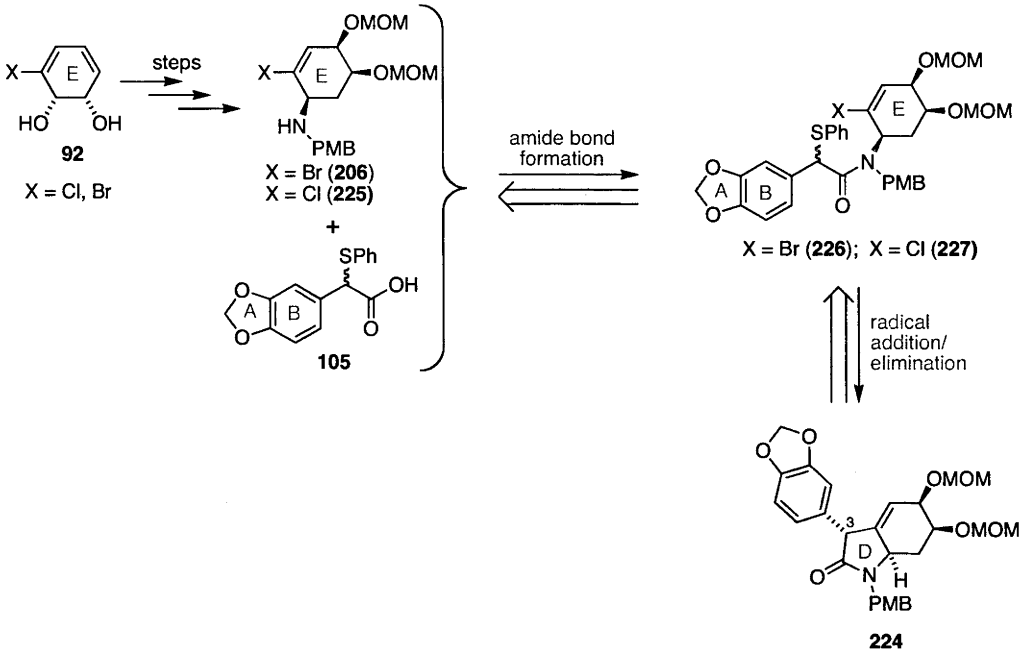


224

5.1.1.1. Overview of *Approach D*

As a modification of *Approach C*, the fourth and final one (*Approach D*) involved a two–step D–ring annulation protocol whereby it was hoped that an amide coupling of 2°–amines **206** and **225** (derived from the bromo– and chloro–derivatives of *cis*–1,2–dihydrocatechol **92**, respectively) with acid **105** would give compounds **226** and **227**. These amides were then to be subjected to a radical cyclization reaction to give the desired 3–arylhexahydro–oxindole **224** (**Scheme 5.1**). Encompassing part of the work described by Ikeda[1] and Banwell,[2] this approach involved the application of a novel radical cyclization reaction that affords compound **224** possessing the requisite stereochemistry at C3 and the necessary $\Delta^{1,11a}$–double bond present in the E–ring of the target alkaloid. The preparation of both 2°–amines **206** and **225** represented an attempt to examine differences in the ability of these halogenated compounds to undergo such a radical addition/elimination sequence and so produce 3–arylhexahydro–oxindole **224**. Subsequent elaboration of compound **224**, including the late–stage installation the C–ring *via* the Pictet–Spengler reaction (as discussed in Chapter One), would enable the total synthesis of (+)–brunsvigine (*ent*–**18**) to be achieved. However, before the details of these investigations are disclosed, a

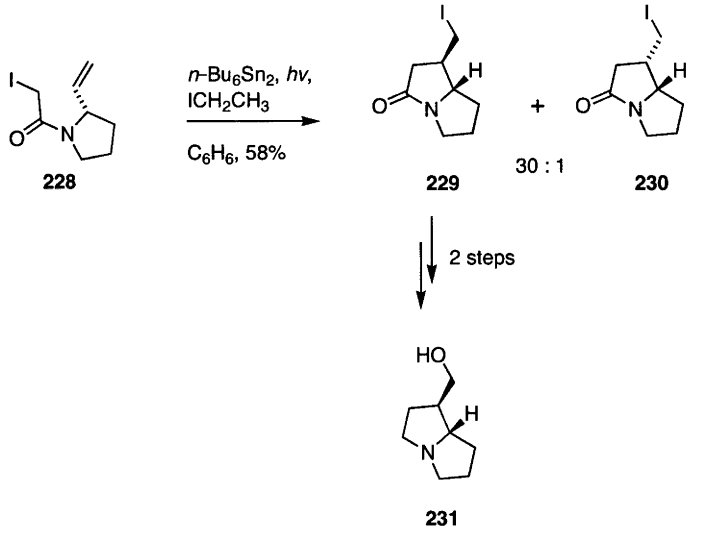
commentary on the radical cyclization reactions of amides is warranted. Such a commentary is provided in the following section.



Scheme 5.1: *Formation key intermediate* ***224*** via Approach D

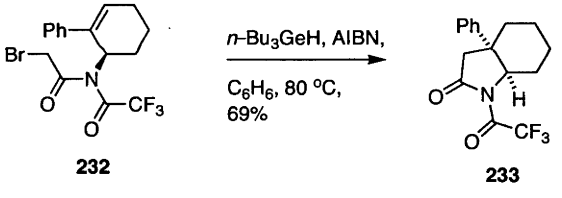
5.2. Radical Cyclizations of Amides

The failure to effect a radical cyclization reaction of the type described in Chapter Four (*viz* **220** → **219**) and so achieve D–ring annulation prompted the search for an alternative approach. A literature survey revealed a 1988 report by Livinghouse *et. al.*[3] demonstrating the ability of *N*–allyl α–haloacetamides to undergo radical cyclizations under atom transfer conditions.[4] Such a protocol was employed in the synthesis of the alkaloid (–)–trachelanthamidine (**231**) (**Scheme 5.2**). Thus, iodoacetamide **228** engaged in a 5–*exo*–*trig* radical cyclization reaction to produce a chromatographically separable mixture of pyrrolizinones **229** and **230** with the former product predominating. Elaboration of compound **229**, over two simple steps, then provided the target alkaloid **231**.



Scheme 5.2: *Livinghouse's total synthesis (–)–trachelanthamidine (**231**)*

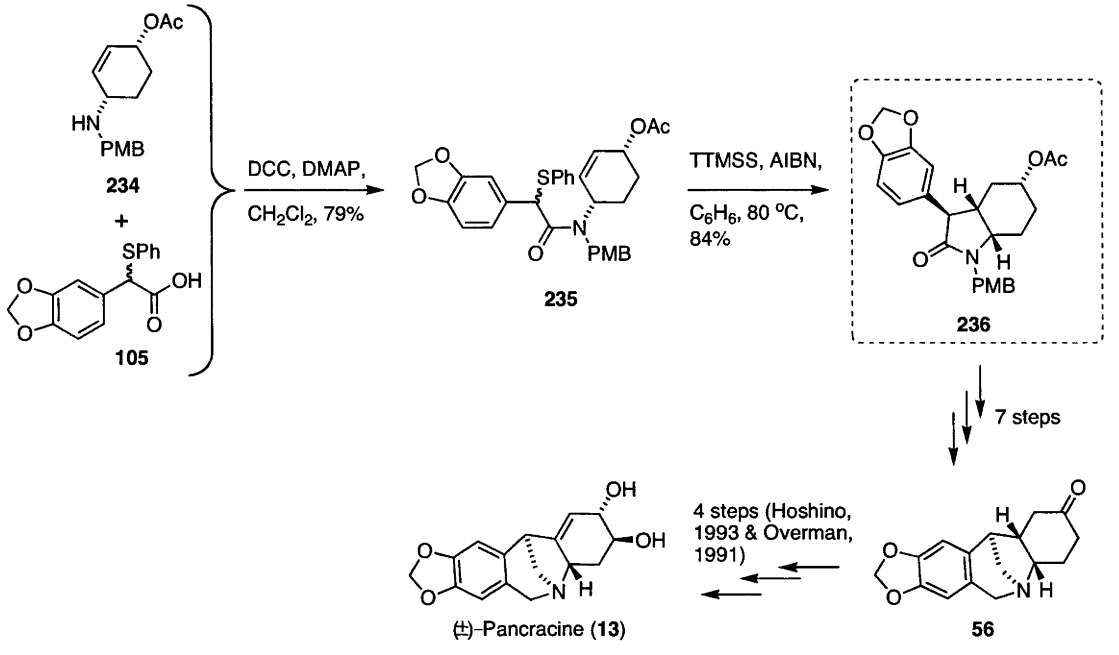
In the following year, Stork[5] was able to exploit this methodology in the preparation of *cis*–fused 3–pyrrolidones and piperidones. For example, the synthesis of pyrrolidone **233** possessing a quaternary carbon was achieved in good yield *via* germanium hydride–mediated radical cyclization of bromoacetamide **232** (**Scheme 5.3**).



Scheme 5.3: *Stork's synthesis of pyrrolidinone **233***

In extending this methodology, Ikeda[1] was able to report a stereoselective synthesis of 3–aryloctahydro–oxindole **236** (**Scheme 5.4**) and so completing a formal total synthesis of the montanine alkaloid (±)–pancracine (**13**). The preparation of the 3–aryloctahydro–oxindole **236** was achieved through a two–step annulation protocol that involved an amide bond forming reaction of 2°–amine **234** with acid **105** to produce compound **235**, the substrate for radical cyclization reaction. This reaction proceeded smoothly in the presence of TTMSS to afford the required 3–aryloctahydro–oxindole **236** in 82% yield over the two steps. Subsequent elaboration of this compound, through a series of straightforward transformations, finally lead to the construction of 5,11–methanomorphanthridine **56**, an advanced intermediate in Hoshino's formal total synthesis of (±)–pancracine (**13**).[6] The

acquisition of compound **56** by such means thus constituted a formal total synthesis of the racemic modification of this natural product.

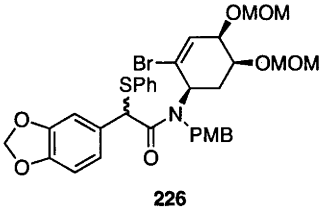


***Scheme 5.4:** Ikeda's formal total synthesis of (±)–pancracine (**13**)*

5.3. D–Ring Annulation: Synthesis of 3–Arylhexahydro–oxindole 224

5.3.1. Preparation of Radical Precursors 226 and 227

Following earlier work,[1] it was envisaged that compounds **226** and **227**, each possessing a thiophenyl group adjacent to the amide carbonyl, would be synthesized as substrates for an Ikeda–type radical cyclization reaction.



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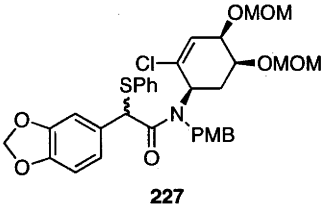
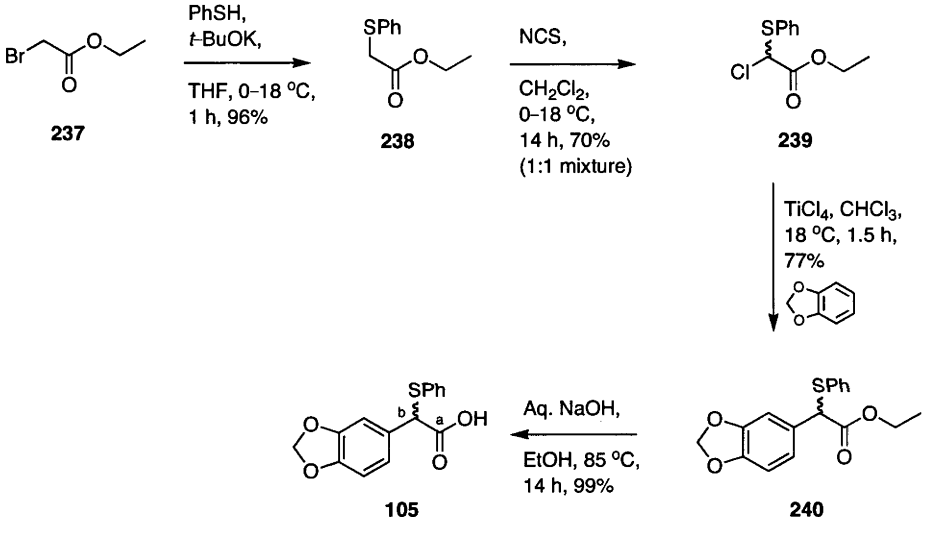


227

The α–thiophenyl–amide residue was chosen because it is less prone to solvolysis than the corresponding α–halo–amides.[7] The preparation of radical precursor **226** began with the synthesis of the known acid fragment **105** (**Scheme 5.5**) wherein commercially available ethyl α–bromoacetate (**237**) was reacted with thiophenol in the presence of *t*–BuOK to give the α–phenylthioacetate **238** in 96% yield. Subsequent α–chlorination of this compound using NCS produced chloride **239** (as a racemate) which was subjected to a $TiCl_4$–mediated Friedel–Crafts alkylation reaction using 1,2–methylenedioxybenzene as the nucleophile. This reaction thus provided the α–arylated ester **240** (also as a racemate) in 73% yield over the two steps involved.

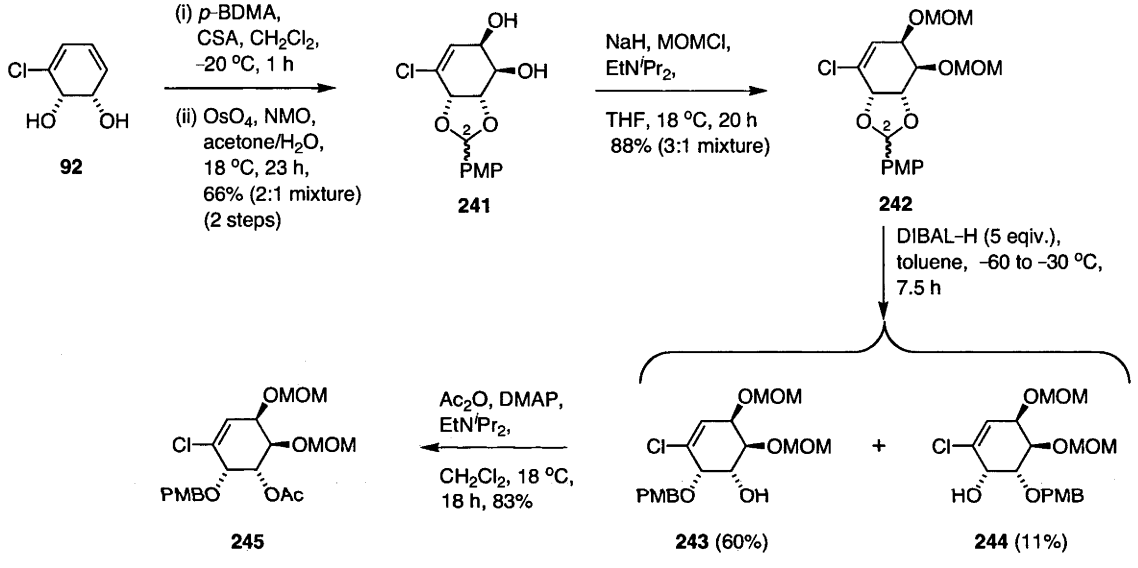


Scheme 5.5: *Synthesis of acid **105** from ethyl* α*–bromoacetate **(237)***

Saponification of ester **240** with sodium hydroxide then afforded, after acid work–up, the previously reported acid **105**.[1] All the data obtained on this compound were consistent with assigned structure. For example, the ^{13}C NMR spectrum showed signals at δ 171.6 and 55.8, which were assigned to the carbons of the acid moiety (C_a) and benzylic carbon (C_b) carrying the thiophenyl group, respectively.

Having already prepared the required bromo–alkene **206** (see Section **4.3.1.**), the synthesis of its chloro–analogue, **227**, remained. This followed established pathways that are detailed on the following pages. Thus, protection of the *cis*–1,2–dihydrocatechol **92** as the corresponding PMP acetal was followed by OsO_4–mediated *cis*–1,2–dihydroxylation under

the Upjohn reaction conditions[8] to give diol **241** in 66% yield over the two steps involved and as an inseparable 2:1 mixture of epimers (**Scheme 5.6**). Subsequent reaction of the diol function with MOMCl, NaH and triethylamine then provided fully protected conduritol **242** in 88% yield and as an inseparable 3:1 mixture of epimers. Treatment of this mixture with DIBAL–H, at –30 °C, resulted in regioselective cleavage of the acetal moiety, giving conduritols **243** and **244** as a 5.5:1 and now chromatographically separable mixture of regioisomers.



Scheme 5.6: *Synthesis conduritol **245** from* cis*–1,2–dihydrocatechol **92***

Regioisomer **243** was then reacted with acetic anhydride in the presence of a catalytic amount of DMAP to give the fully protected conduritol **245** in 83% yield. The preparation of this derivative of the target compound **243** was necessary so as to confirm the regioselectivity of the DIBAL–H–mediated cleavage reaction of the acetal moiety in precursor **242**. As shown in **Figure 5.1**, the cross–peaks appearing in the ^1H–^1H COSY spectrum of this compound are attributed to the interaction of H_b with H_a and H_c and so establishing the assigned structure for conduritol **245**.

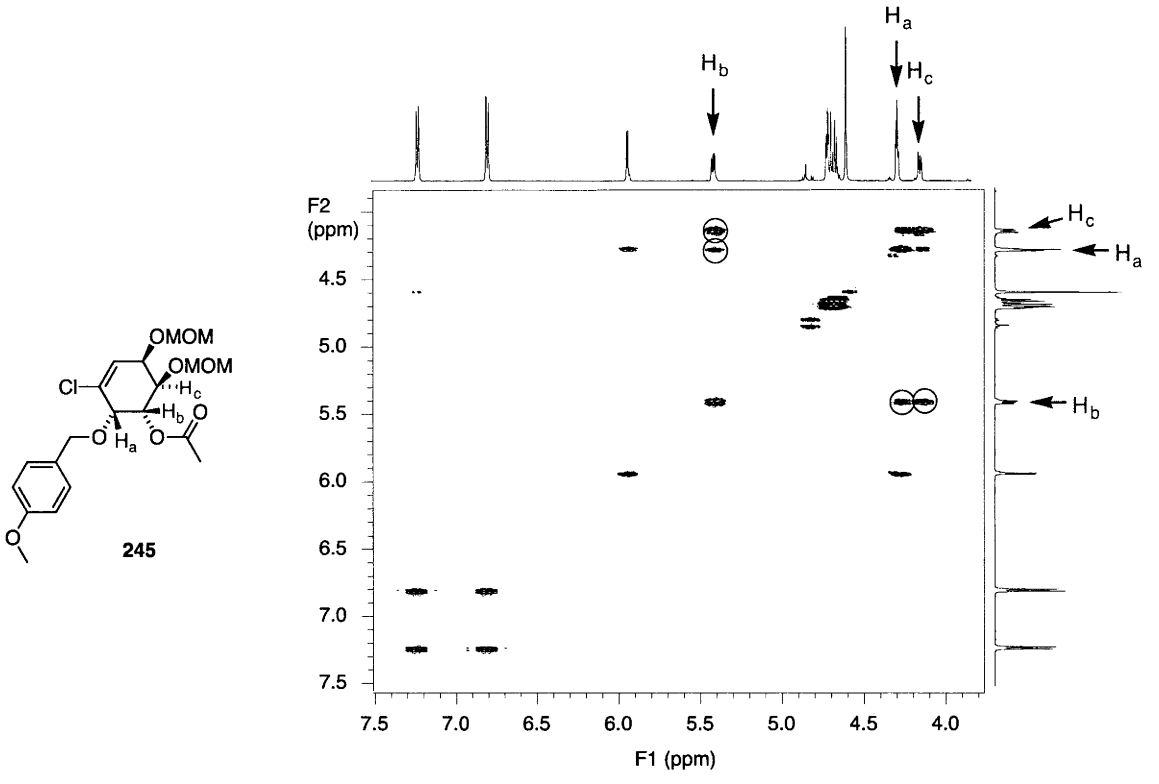
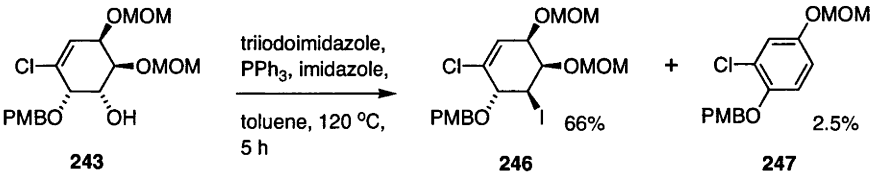


Figure 5.1: *600 MHz ^1H–^1H COSY spectrum of conduritol **245** recorded in $CDCl_3$*

Conduritol **243** was subjected to a two–step deoxygenation protocol with the first of these involving the treatment of this material with triiodoimidazole, PPh_3 and imidazole, under the previously optimised conditions (described in Chapter Three). This furnished iodide **246** and by–product **247** in 66% and 2.5% yield, respectively (**Scheme 5.7**).



Scheme 5.7: *Iodination of conduritol **243***

As discussed in Chapter Three (section **3.3.5.**), the appearance of the aromatic by–product **247** is attributed to the elimination of the elements of HOMOM and HI from precursor **246**. A single–crystal X–ray analysis of this aromatic material served to confirm the assigned structure (**Figure 5.2**).

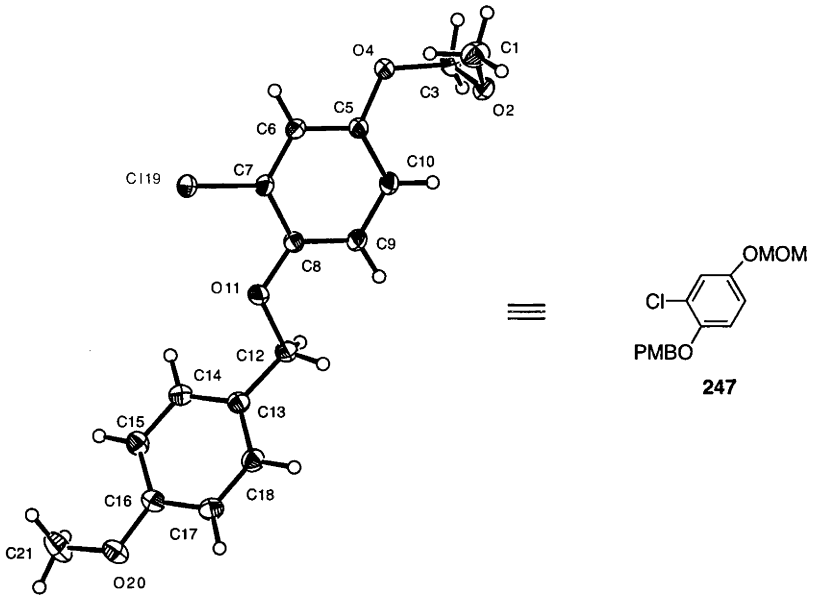
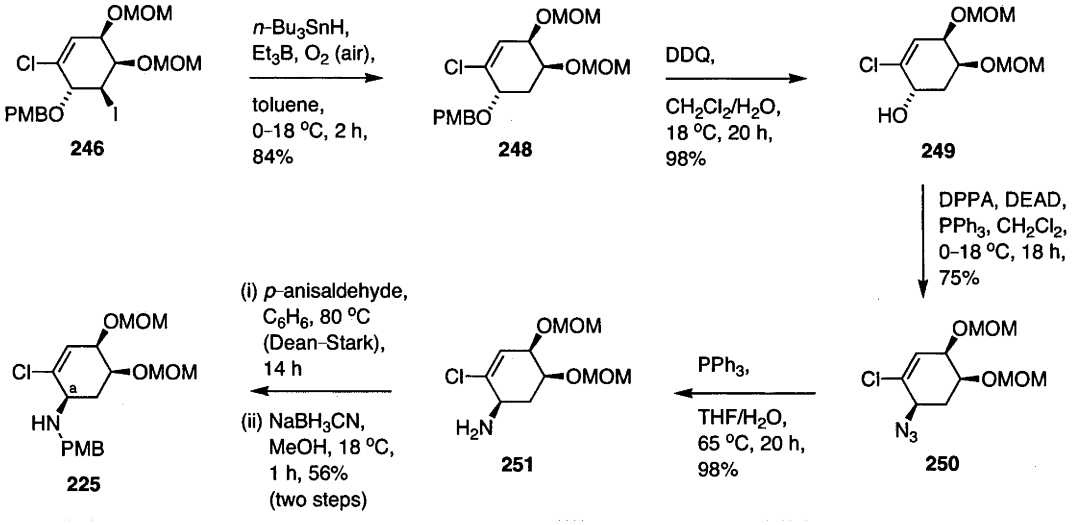


Figure 5.2: *ORTEP derived from the single-crystal X-ray analysis of aromatic by-product* ***247***

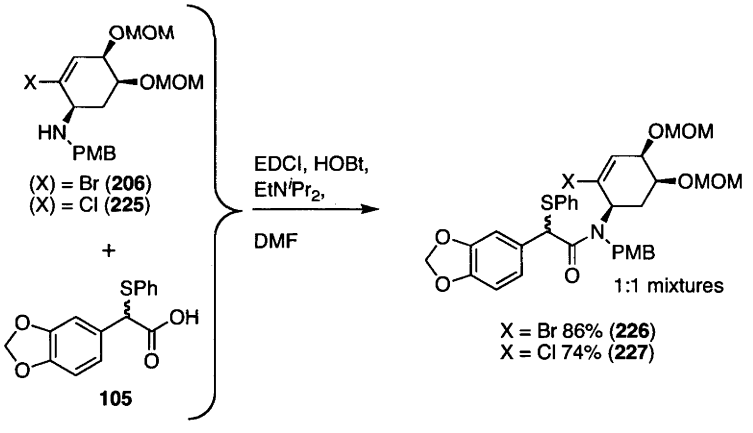
Treatment of iodide **246** with *n*-Bu_3SnH, in the presence of a catalytic amount of Et_3B in oxygen (air),[9] resulted in the reductive cleavage of the iodide to give the required deoxygenated compound **248** in excellent yield (**Scheme 5.8**).



Scheme 5.8: *Synthesis of 2°-amine* ***225***

Oxidative cleavage of the PMB group within compound **248**, using DDQ, gave alcohol **249** which was subjected to a Mitsunobu azidation reaction[10] using DPPA as the nucleophile and so providing azide **250** in 75% yield. Reduction of this azide, under standard Staudinger conditions,[11] then provided 1°–amine **251** which was subjected to a reductive amination protocol[12] (using *p*–anisaldehyde and $NaBH_3CN$) to give 2°–amine **225** in 56% yield. All the data obtained on this last compound were in accord with the assigned structure. The ^{13}C NMR spectrum, for example, showed signals at δ 56.3 and 47.7 which are attributed to C_a and the benzylic carbon of the PMB group, respectively. In addition, the IR spectrum showed an absorption band at 3337 cm^{-1} which is the result of NH stretching associated with the 2°–amine function in compound **225**.

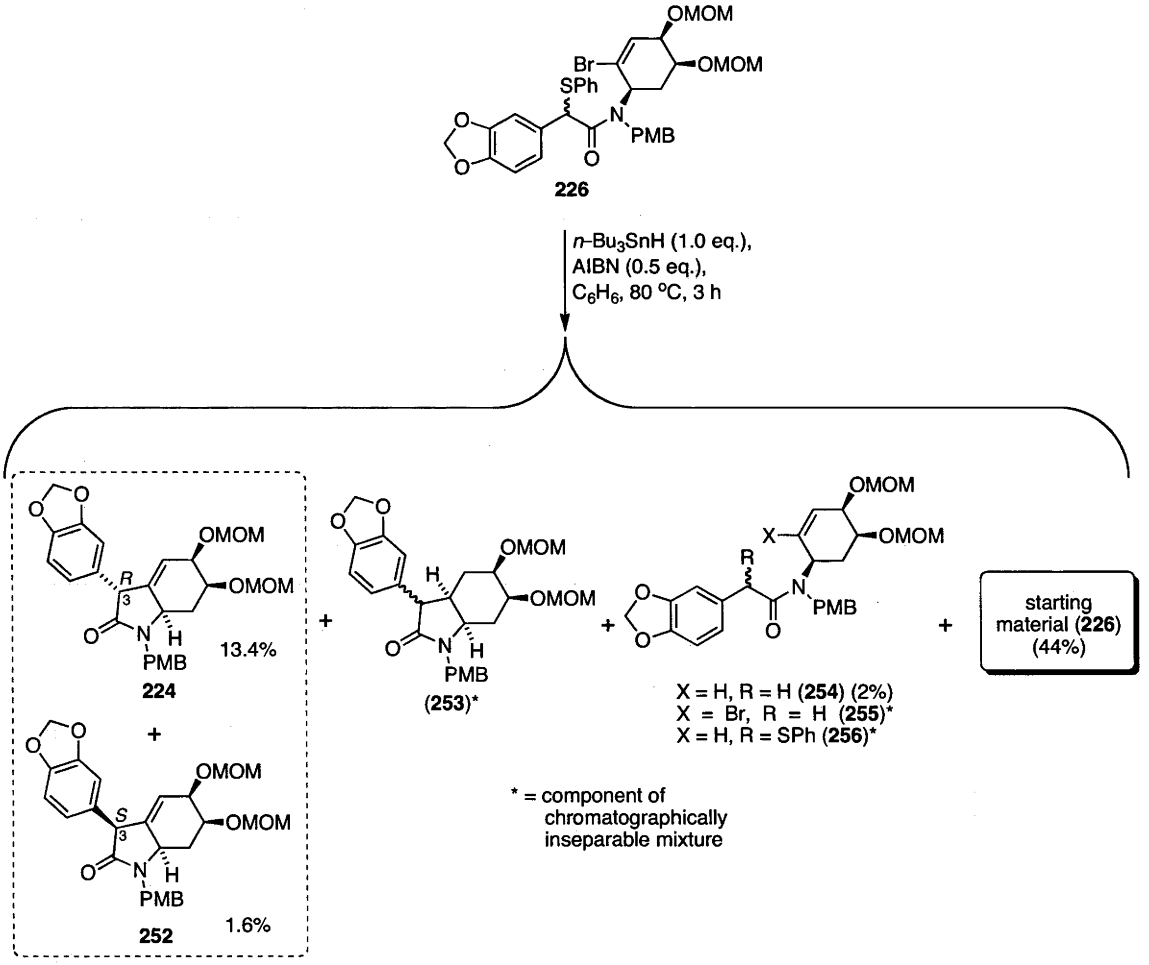
The successful preparation of the acid **105** as well as the bromo– and chloro–amines **206** and **225**, respectively, meant that the key amide bond forming reaction could be attempted. In the event, treatment of acid **105** with 2°–amine **206** at 18 °C in the presence of EDCI, HOBt and EtN^iPr_2 in DMF, resulted in formation of compound **226** in 86% yield (**Scheme 5.9**). Subjection of acid **104** and 2°–amine **225** to the same reaction conditions also lead to the desired compound **227**, this time in 74% yield.



Scheme 5.9: *Synthesis of radical cyclization precursors **226** and **227***

5.3.2. Cyclization of Radical Precursor 226

The key radical cyclization reaction was first investigated by subjecting the bromo–alkene **226** to standard radical cyclization conditions involving its treatment with *n*–Bu_3SnH (1 eq.) and a catalytic amount AIBN (0.5 eq.) in refluxing benzene. However, analysis of the ensuing reaction mixture revealed that the requisite 3–arylhexahydro–oxindoles **224/252** had only been formed in 15% yield (and as a 8.5:1 mixture of epimers) with the major one, **224**, being assigned as that possessing the desired *R*–configuration at C3. These epimers were accompanied by 44% of recovered starting material and 2% of by–product **254** (**Scheme 5.10**). In addition, a chromatographically inseparable mixture of by-products **253**, **255** and **256** was obtained. So, while the desired process appeared to have proceeded with high diastereoselectivity, this outcome was nevertheless disappointing, because of the low yield of compounds **224/252** that was obtained.



Scheme 5.10: *Outcomes of subjecting compound **226** to radical cyclization conditions*

The structures of the cyclization products **224/252** were confirmed using various techniques including ^{1}H NMR, ^{13}C NMR and IR spectroscopy as well as mass spectrometry. For example, the ^{1}H NMR spectrum of the major epimer (which was isolated using HPLC techniques) showed a signal at δ 5.87 that is assigned to H_b which is attached to one of the sp^2–carbons of the newly installed carbon–carbon double bond (**Figure 5.3**). The ^{13}C NMR spectra of the same material showed signals at δ 51.6 and 123.0 attributed to C3 and C4, respectively.

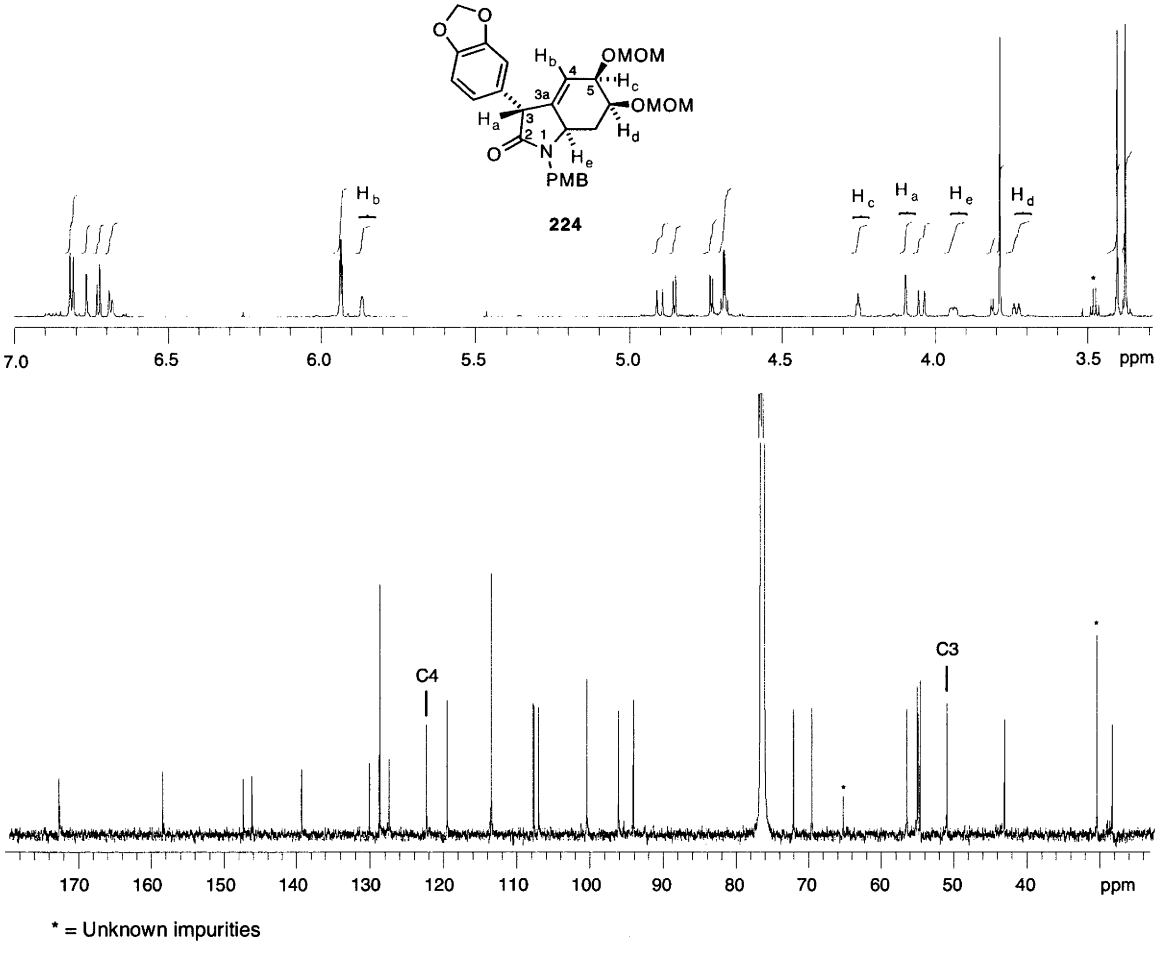
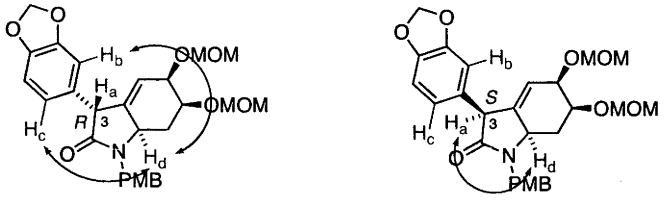


Figure 5.3: *800 MHz ^{1}H NMR (above) and 150 MHz ^{13}C NMR (below) spectra of 3–arylhexahydro–oxindole* ***224*** *(major epimer) recorded in $CDCl_3$*

In an effort to confirm the configuration of the major epimer **224**, a NOE experiment was performed but this did not allow for the unequivocal assignment of the stereochemistry

associated with the compound. This is ascribed to the lack of sufficient conformational rigidity within the framework of this compound to allow for successful observation of the relevant through–space interactions. For instance, the anticipated cross–peaks arising from a through–space interaction between the H_d and H_b/H_c in the NOESY spectrum for the major epimer **224** were not observed (**Figure 5.4**). The equivalent through–space interactions between H_a and H_d in the minor epimer **252** were also absent. Accordingly, confirmation of configurations about C3 of epimers **224** and **252** was postponed until later in the synthetic sequence and at which point the major epimer **224** was shown to possess the *R*–configuration at C3.



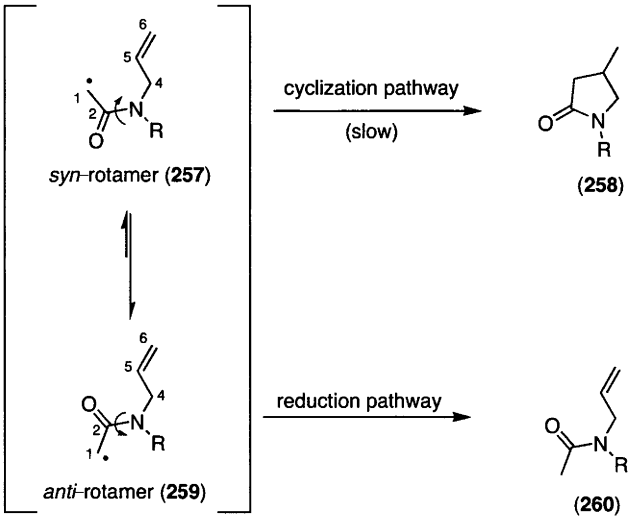
224 (major epimer) **252** (minor epimer)

Figure 5.4: *Expected ^1H–^1H through–space (NOE) interactions for compounds **224** and **252***

In order to account for the low yields of the desired radical cyclization product as well as the formation of by–products **253–256**, an analysis of the radical chemistry associated with allylic amides is required. Such an analysis is presented in the following section.

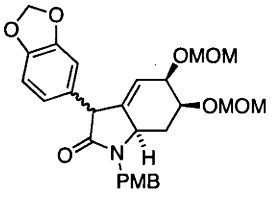
5.3.3. Radical Chemistry of *N*–Allylated Amides

In general (as shown in **Scheme 5.11**) radicals that incorporate the nitrogen atom and carbonyl functions of an allylic amide (see, for example, **257**) tend to cyclize rather slowly to produce lactams of the type **258**.[13] This results from the tendency, due to steric effects, of the initially formed radical to exist largely as a *anti*–rotamer **259** rather than the *syn*–rotamer **257**.[5] This is significant because the *anti*–rotamer (**259**) is topologically prohibited from undergoing radical cyclization, and so can only engage in direct reduction to form compounds such as **260**. The opposite is true for the *syn*–rotamer (**257**) because it is topologically capable of undergoing radical cyclization and so likely to lead to the formation of products such as lactam **258**.



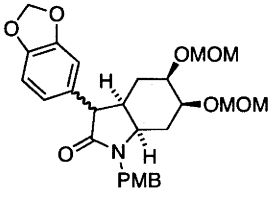
***Scheme 5.11**: Radical chemistry of* N*–allylated amides*

This sort of situation undoubtedly contributes to the formation of by–products **254–256** (reduction pathway) observed upon the treatment of compound **226** with *n*–Bu_3SnH in the presence of AIBN.

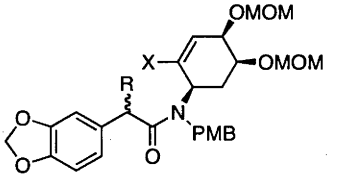


8.5:1 mixture

224/252



253

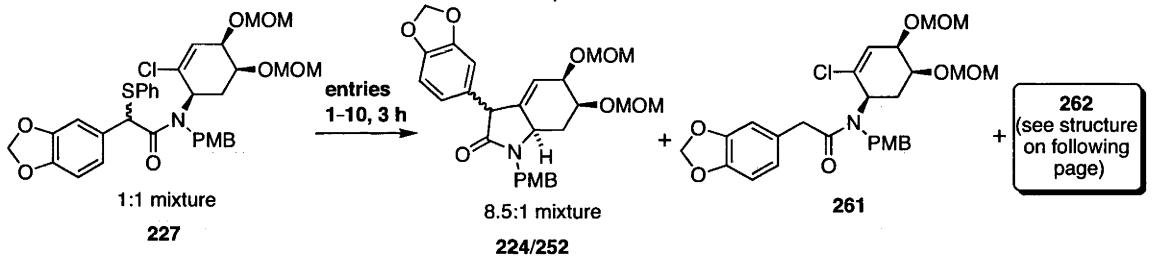


X = H, R = H (**254**)
X = Br, R = H (**255**)
X = H, R = SPh (**256**)

The by–product/product ratio will be influenced by favouring the cyclization pathway. Factors that can have such an influence include reactant and reagent concentrations, steric effects, reaction temperature, rate of addition of reactants and the use of catalytic *n*–Bu_3SnH and/or atom transfer–reagents as well as the purity of radical precursors.[7,14]

5.3.4. Improvements to the Yield of 3–Arylhexahydro–oxindole of 224

In order to obtain sufficient quantities of key compound **224** for the purposes of preparing (+)–brunsvigine, an improvement in the radical cyclization process was necessary. Therefore, having considered the factors that influence this process, optimisation studies using substrate **227** began whereby variations in reagent systems, temperature and concentrations were explored. As shown in **Table 5.1** (entry 1), subjection of compound **227** to a radical cyclization reaction at 80 °C using 1.0 eq. of *n*–Bu_3SnH and 1.5 eq. of AIBN for 3 h resulted in the formation of products **224/252** in 45% yield and as 8.5:1 mixture of epimers, respectively. This was accompanied by a 32% yield of a chromatographically inseparable mixture of by–products **261** and **262**.



1:1 mixture
227

8.5:1 mixture
224/252

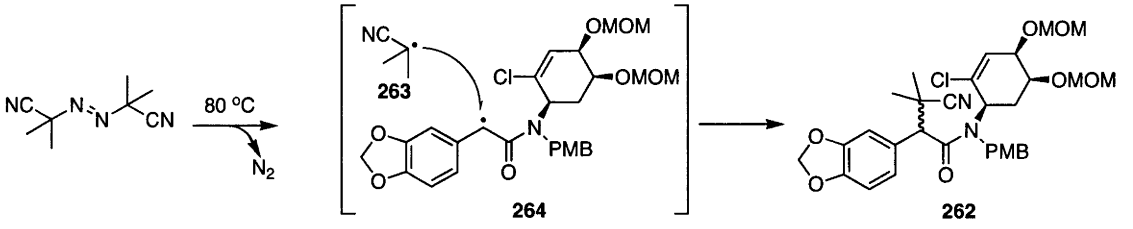
261

Entry	Reagents				Solvent	Temp.	Conc.	Products (%)		
	n–Bu_6Sn_2 :	*n*–Bu_3SnH :	TTMSS :	AIBN		(°C)	[M x 10^{-3}]	**224/252**# :	**261** :	**227**
1	0.0	1.0	0.0	1.5	C_6H_6	80	3.0	45	32*	1
2	2.5	0.0	0.0	0.0	C_6H_6	80	3.0	0	0	99
3	2.5	1.0	0.0	1.0	C_6H_6	80	3.0	39	7	0
4	2.5	1.0	0.0	1.5	C_6H_6	80	3.0	46	8	0
5	2.5	0.3	0.0	1.5	C_6H_6	80	3.0	39	0	54
6	2.5	1.0	0.0	1.5	C_6H_5Cl	130	3.0	32	6	40
7	2.5	0.0	1.0	1.5	C_6H_6	80	3.0	36	15*	39
8	2.5	1.0	0.0	1.5	C_6H_6	80	1.0	57	22*	0
9	2.5	1.0	0.0	1.0	C_6H_6	80	0.5	64	19	0
10	2.5	1.5	0.0	0.5	C_6H_6	80	0.5	67	18	0

* = accompanied with by-product **262**; # = obtained as 8.5:1 mixture of epimers

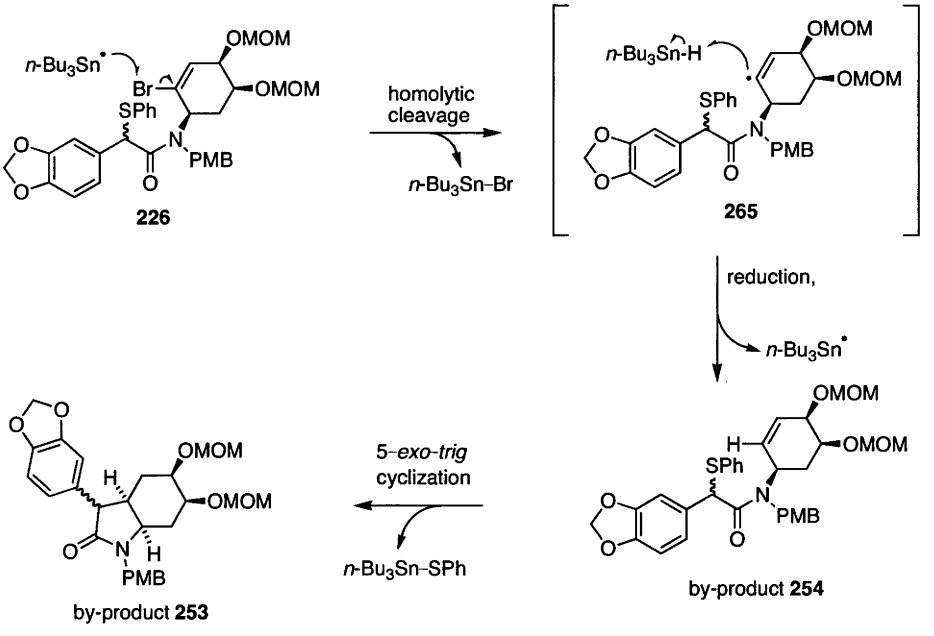
Table 5.1: *Optimization of the radical cyclization of compound **227** to give 3–arylhexahydro–oxindoles **224/252***

While compound **261** is almost certainly produced by direct reduction of the initially formed radical **264**, by–product **262** probably results from reaction of the initial radical **264** with isobutyronitrile radical **263** generated *via* thermolysis of AIBN at 80 °C (**Scheme 5.12**).



Scheme 5.12: *Possible pathway associated with the formation of by–product* ***262***

The use of the chloro–derivative of the radical precursor **227** (compared to the bromo–derivative of the radical precursor **226**) in the radical cyclization reaction resulted in a cleaner process, which also provided compounds **224/252** in higher yield (45% compared to 15%) and as 8.5:1 mixture of epimers. This phenomenon might be attributed to the stronger (by 15–16 kcal/mol[15]) sp^2–carbon–halogen bonds in alkenyl chlorides compared to alkenyl bromides. Indeed, as alkenyl bromides are more susceptible to *n*–Bu_3SnH–mediated homolytic cleavage, this theory helps to explain the occurrence of by–products **253–256.** For example, by–product **254** (**Scheme 5.13**) may arise *via* homolytic cleavage of alkenyl carbon–bromine bond in radical precursor **226** and thus producing alkenyl radical **265**.



Scheme 5.13: *Rationale for the formation of by–products* ***253*** *and* ***254***

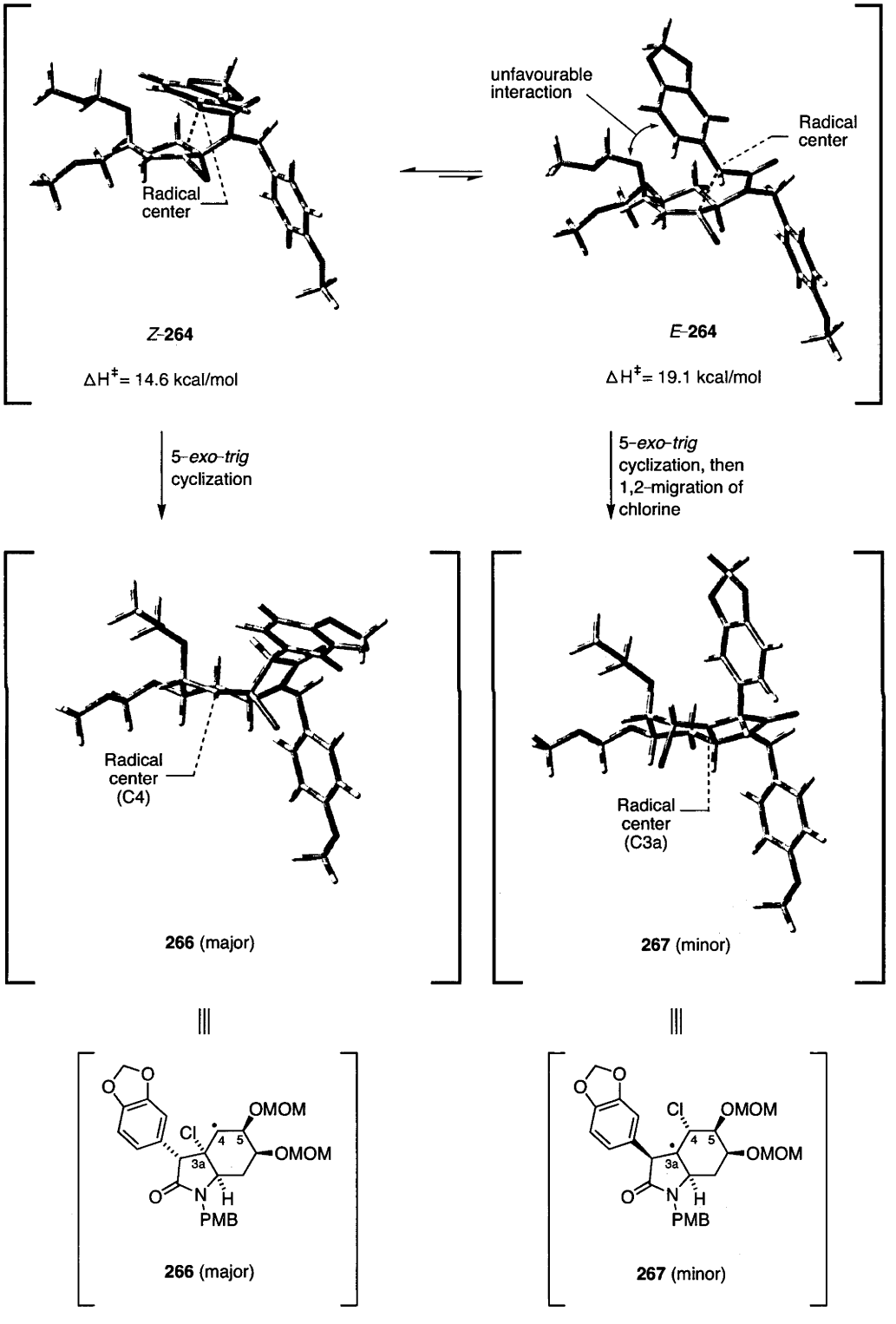
As an extremely reactive radical,[16,17] this last species can undergo rapid hydrogen–atom abstraction from *n*–Bu_3SnH to produce compound **254**. Subsequent 5–*exo*–*trig* radical cyclization of this material (**254**) would then deliver the observed by–product **253**.

In promoting the cyclization pathway, it was thought that atom transfer conditions should be investigated.[4,18] However, subjection of radical precursor **227** to *n*–Bu_6Sn_2–mediated atom transfer conditions (entry 2 of **Table 5.1**) failed to give expected products **224/252** and after 3 h only starting material (**227**) was isolated. In overcoming this outcome, the reaction was repeated with the addition of *n*–Bu_3SnH (1 eq.) (entry 3). Under such conditions compounds **224/252** were obtained in 39% yield and these were accompanied by 7% yield of reduced material **261**. Increasing the amount of AIBN (from 1.0 to 1.5 equiv.) resulted in compounds **224/252** being formed in 46% yield (entry 4). This result seemed to suggest that this radical cyclization reaction was operating *via* a poorly propagating radical chain.[13] Indeed, an attempt to use *n*–Bu_3SnH catalytically (0.3 eq.) (entry 5) resulted in formation of compounds **224/252** in a reduced yield of 39% with 54% of recovered starting material being obtained. Increasing the reaction temperature (entry 6) and using TTMSS (entry 7) as the hydrogen–atom source seemed to have a negative effect as lower yields (32 and 36%, respectively) of 3–arylhexahydro–oxindoles **224/252** were obtained. The yield obtained when TTMSS was used was especially disappointing because, as this reagent is a weaker hydrogen atom donor than *n*–Bu_3SnH, it was hoped that its use would favour the cyclization pathway since it has lower capacity to reduce the initially formed radical **264**. Indeed, as Si–H bond strength in TTMSS is 79 kcal/mol, it is 5 kcal/mol stronger than the Sn–H bond in *n*–Bu_3SnH.[19] While this outcome was interesting, it failed to deliver the required material in higher yield. So, attention quickly turned to investigating the effect of varying the concentration of the reactants. Gratifyingly, a significant increase in the yield (to 67%) of 3–arylhexahydro–oxindoles **224/252** was obtained when a lower reactant concentration (of 5×10^{-4} M) was used (entry 10).

5.3.5. Stereochemical Outcomes of the Radical Cyclization Reaction

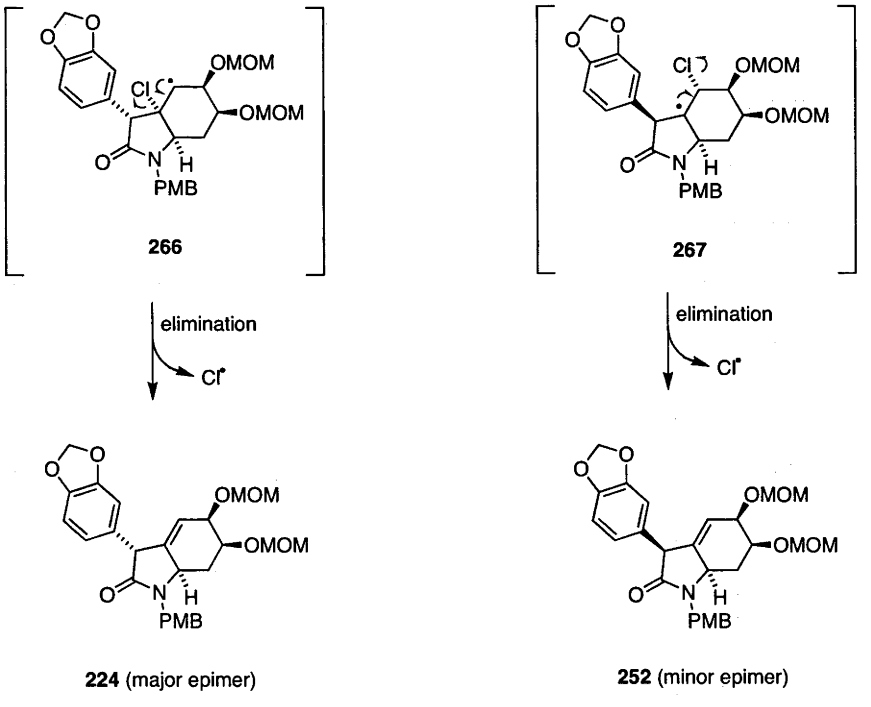
Given that the pivotal radical cyclization reaction could now be achieved with high levels of diastereoselectivity, there was a need to try and establish, reasonably promptly, the configuration of the major epimeric form of the product. Computational analysis,[20] as detailed in **Scheme 5.14**, suggests that there is a preference for the initially formed radical **264** to

pass through a transition state, *Z*–**264**, that would lead to the cyclized species **266** possessing the required stereochemistry.



Scheme 5.14: *Computational analysis of the cyclization of initial radicals* Z–***264*** *and* E–***264***

Another transition state, *E*–**264**, leading to an alternate cyclization product, **267**, is less likely to be formed because of unfavourable interactions between the 1,2–methylenedioxyaryl unit and the C5 MOM group. Interestingly, computational analysis also shows the preference of this intermediate (**267**) to exist as a 3°–radical, wherein a 1,2-migration of the chlorine atom from C3a to C4 has occurred immediately after the radical cyclization event. Each of the radical species **266** and **267**, arising from the cyclization process, might be expected to undergo (**Scheme 5.15**) rapid and irreversible loss of a chlorine radical to give the observed 3–arylhexahydro–oxindoles **224** and **252**, respectively. Accordingly, the calculations predict that the desired epimer should predominate. As subsequent studies have revealed (*vide infra.*), compound **224** is indeed the major product formed as a result of the radical cyclization process.

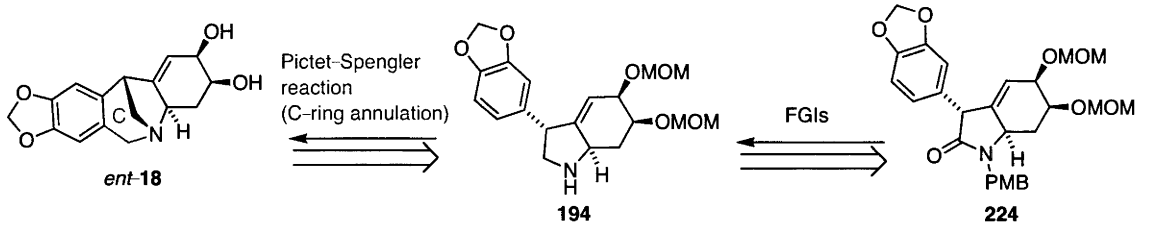


Scheme 5.15: *Elimination of chlorine radicals from intermediates **266** and **267** derived by the cyclization of radical **264***

5.4. C–Ring Annulation *via* the Pictet–Spengler Reaction

5.4.1. Attempted Synthesis of (+)–Brunsvigine from 3–Arylhexahydro–indole 194

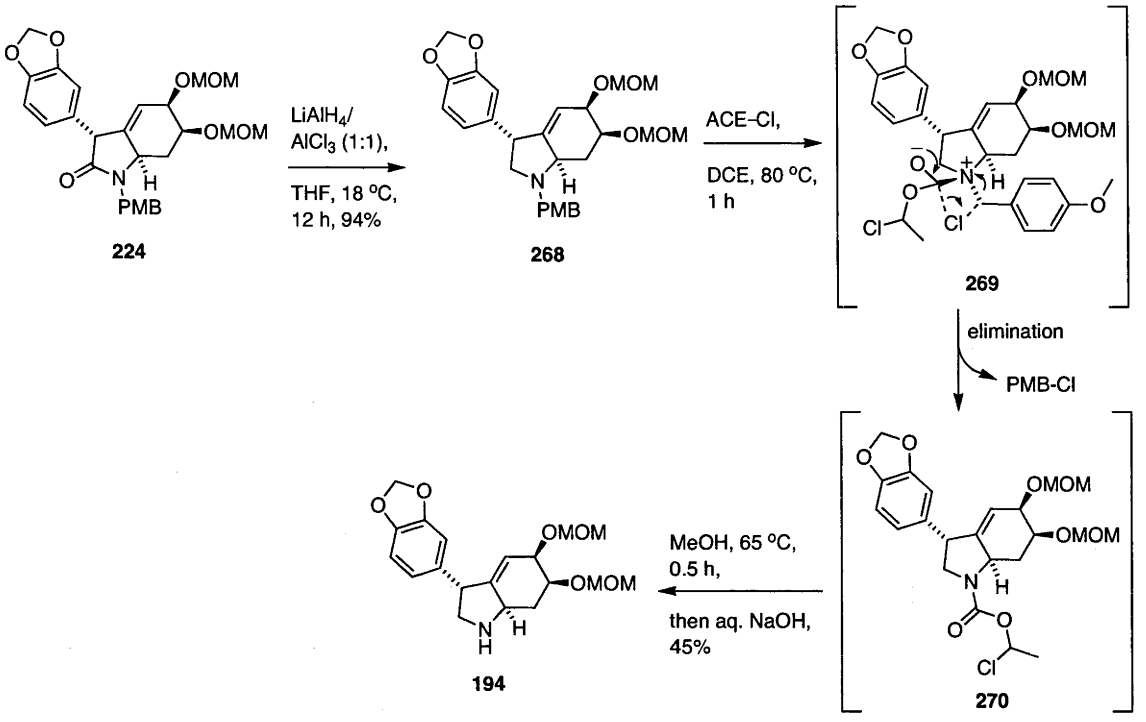
The successful synthesis of 3–arylhexahydro–oxindole **224** meant that the total synthesis of (+)–brunsvigine (*ent*–**18**) *via* the Pictet–Spengler reaction strategy (as discussed in Chapter One) could be pursued. The 3–arylhexahydroindole **194** (**Scheme 5.16**) was identified as an ideal substrate for this transformation and its preparation from compound **224** is described below.



ent-**18** **194** **224**

Scheme 5.16: *Identification of the substrate,* ***194****, for the Pictet–Spengler reaction*

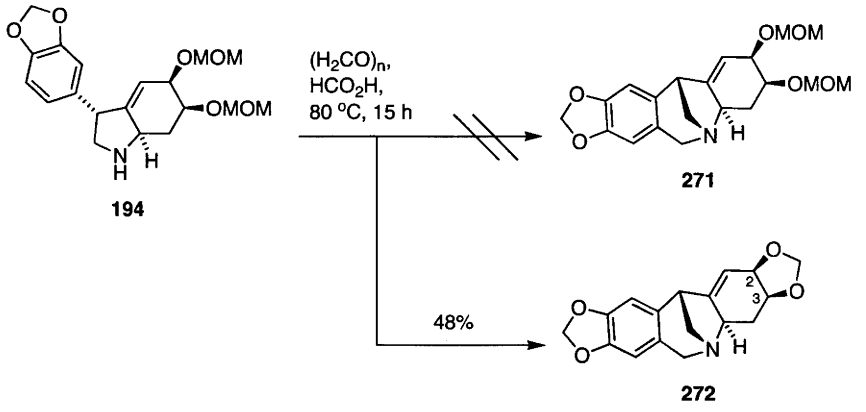
The synthesis of 3–arylhexahydroindole **194** began with the treatment of the epimeric mixture of compounds **224** and **252** with AlH_3 [prepared *in situ* by treating a THF solution of $LiAlH_4$ (1 eq.) with $AlCl_3$ (1 eq.)][1,21] at 18 °C. This resulted in selective reduction of the amide carbonyl to give 3°–amine **268** in excellent yield. A mild, two–step debenzylation protocol was then employed whereby 3°–amine **268** was treated with α–chloroethyl chloroformate (ACE–Cl) in DCE at 80 °C[22,23] to form the intermediate ammonium species **269** (**Scheme 5.17**). Subsequent displacement of the PMB group by the nucleophilic chloride ion then provided carbamate **270**.



Scheme 5.17: *Synthesis of 3–arylhexahydroindole* ***194*** *from compound* ***224***

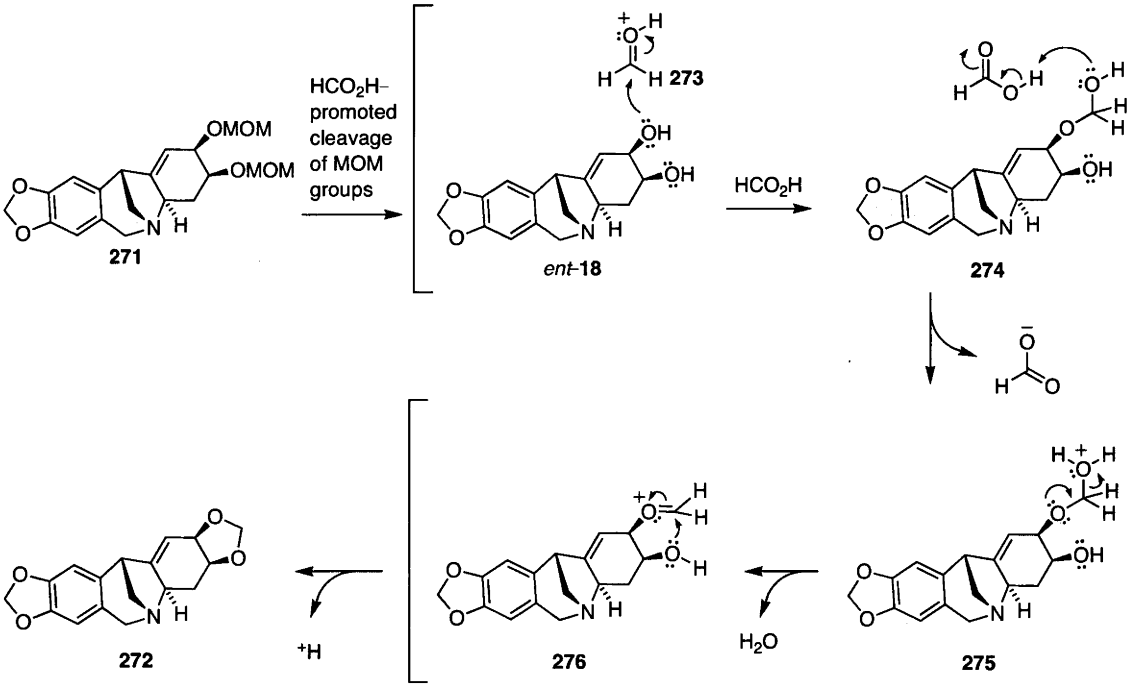
Treatment of this material with MeOH at reflux resulted in the cleavage of the carbamate function to form amine hydrochloride salt, which upon work–up with aqueous NaOH afforded the substrate for the Pictet–Spengler reaction, namely amine **194** that was obtained as a 8.5:1 mixture of diastereoisomers. All the data obtained on this material were in accord with the assigned structure. For example, the IR spectrum showed an absorption band at 3307 cm^{-1}, which is indicative of the presence of an NH group.

Disappointingly, treatment of compound **194** with paraformaldehyde in neat formic acid[2] at 80 °C failed to give the expected Pictet–Spengler product, namely compound **271** (**Scheme 5.18**). Rather, congener **272** (48%) was produced wherein the required 5,11–methanomorphanthridine framework was obtained with accompanying installation of 1,3–dioxolane function at C2 and C3.



Scheme 5.18: *Pictet–Spengler reaction of 3–arylhexahydroindole* ***194***

Product **272** presumably results from the cleavage of the MOM groups under the hot and acidic conditions employed for the Pictet–Spengler reaction.[24] As suggested in **Scheme 5.19**, formic acid–promoted removal of the MOM groups from 5,11–methanomorphanthridine **271** leads to diol *ent*–**18**. Nucleophilic attack of one of the alcohol functions within this compound on the acid–activated formaldehyde **273** would produce hemiacetal **274** that is then protonated to give the corresponding oxonium ion **275**. Elimination of water from this last intermediate would then deliver cation **276** that can engage in an intramolecular reaction whereby the free remaining hydroxyl group reacts with the oxonium moiety to afford compound **272**.[25-27]

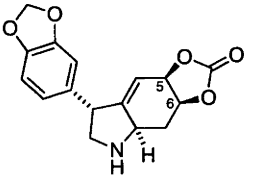


Scheme 5.19: *Possible mechanism of the formation of compound* ***272***

This unwanted MOM–cleavage/methylation sequence, although disappointing, could, in principle, be circumvented by using Eschenmoser's salt.[28,29] In the event, subjection of 3–arylhexahydroindole **194** to the reaction with this reagent in DMF at 80 °C failed to provide to 5,11–methanomorphanthridine **272**. In fact, only a chromatographically inseparable mixture of a range of uncharacterised by–products was observed.

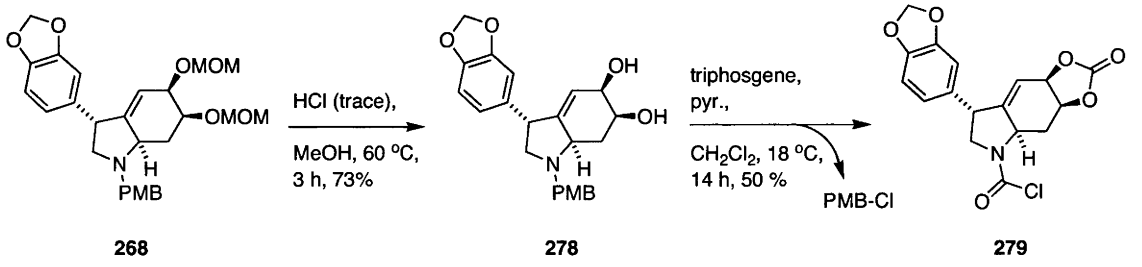
5.4.2. Completion of the Synthesis of (+)–Brunsvigine from 3–Arylhexahydroindole 277

Having encountered problems associated with the lack of stability of the MOM protecting group under the Pictet–Spengler reaction conditions, a revision of the synthetic plan was necessary. As a pivotal step in the preparation of the target alkaloid involved the Pictet–Spengler reaction (C–ring annulation), introduction of an acid–stable hydroxyl protecting group seemed necessary. Hence, 2°–amine **277**, possessing the cyclic carbonate residue at C5 and C6, was identified as an ideal substrate for such a key transformation. The rationale for this arises from the fact that this diol protecting group is extremely stable to acidic conditions as well as being more stable to base–promoted hydrolysis than an ester group.[30]



277

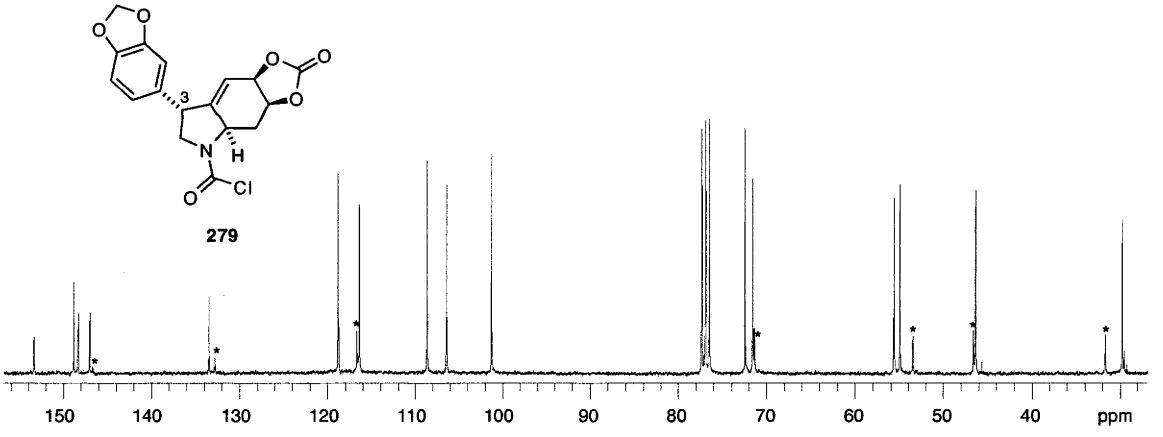
The preparation of compound **277** began with the removal of the MOM group from 3°–amine **268** using catalytic HCl in MeOH to provide diol **278** in 73% yield (**Scheme 5.20**). Treatment of the last compound with triphosgene in the presence of pyridine effected the one–pot cleavage of the PMB group and the installation of the required cyclic carbonate group[31] and so producing carbamoyl chloride **279** in 50% yield and as a 8.5:1 diastereoisomeric mixture.



268 **278** **279**

Scheme 5.20: *Synthesis of carbamoyl chloride* ***279***

This outcome was pleasing and all the data obtained on this compound (**279**) were in full accord with assigned structure. The IR spectrum, for instance, showed strong carbonyl stretching bands at 1802 and 1738 cm^{-1}, which are attributed to cyclic carbonate function (typically 1800 cm^{-1})[32] and the carbamoyl chloride group which typically absorbs in the range of 1740–1738 cm^{-1}.[33] This structure was also confirmed by the appearance of carbon signals in the ^{13}C NMR spectrum at δ 153.5 and 148.9 (**Figure 5.5**), which are due to cyclic carbonate carbonyl and carbamoyl chloride carbonyl carbons, respectively.



* = Signals due to the C3 epimer of compound **279**

Figure 5.5: *150 MHz ^{13}C NMR spectrum of carbamoyl chloride* ***279*** *recorded in $CDCl_3$*

The conformationally rigid nature of carbamoyl chloride **279** was also useful because it finally enabled the confirmation of the illustrated relative configuration of diastereoisomer **279**.

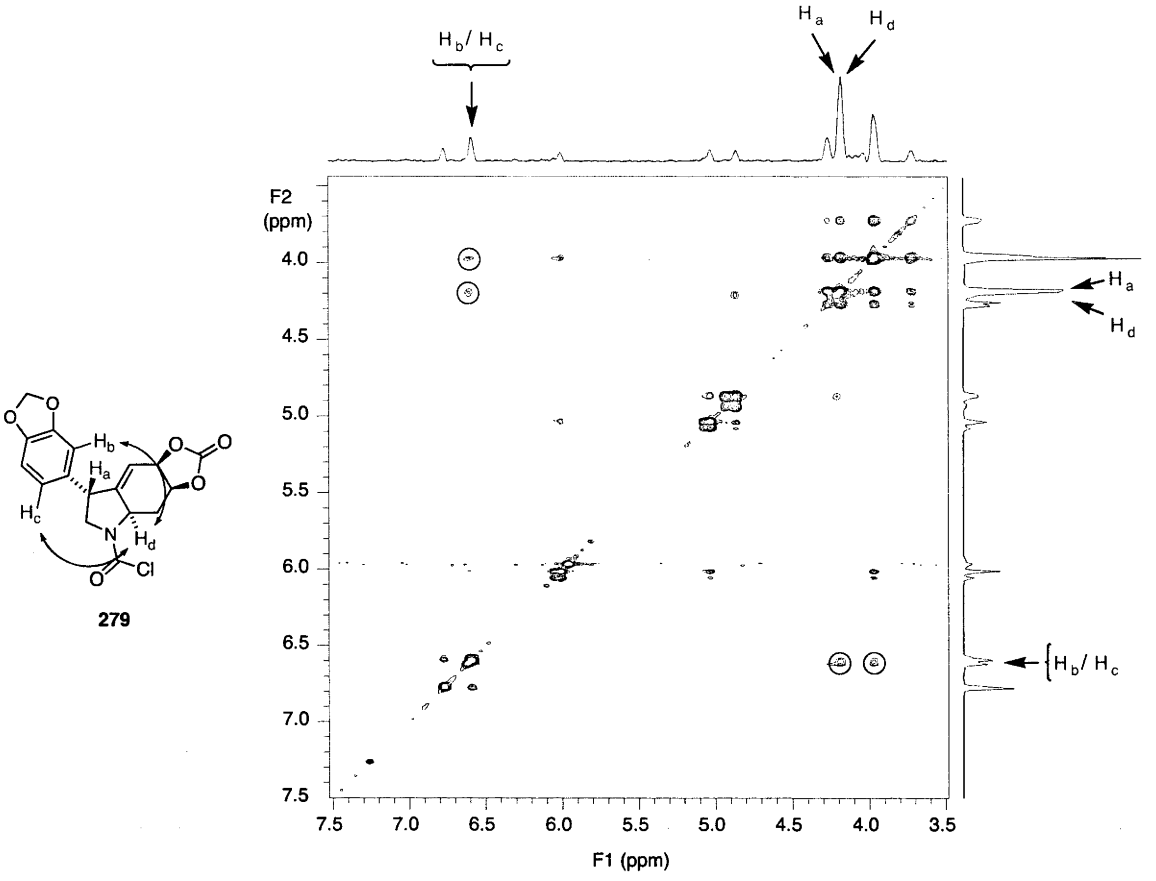
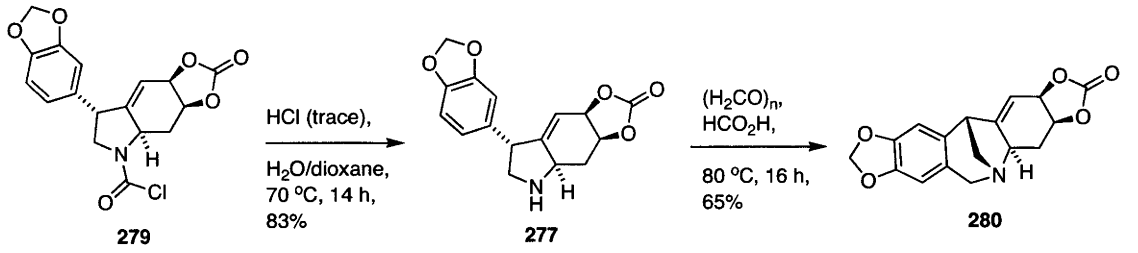


Figure 5.6: *600 MHz ^1H–^1H NOESY spectrum of carbamoyl chloride **279** (recorded in $CDCl_3$)*

Specifically, the NOESY spectrum of carbamoyl chloride **279** (**Figure 5.6**) showed the critical 1,5–through–space interaction between H_b/H_c and H_d, which is indicative of the illustrated stereochemistry at C3.

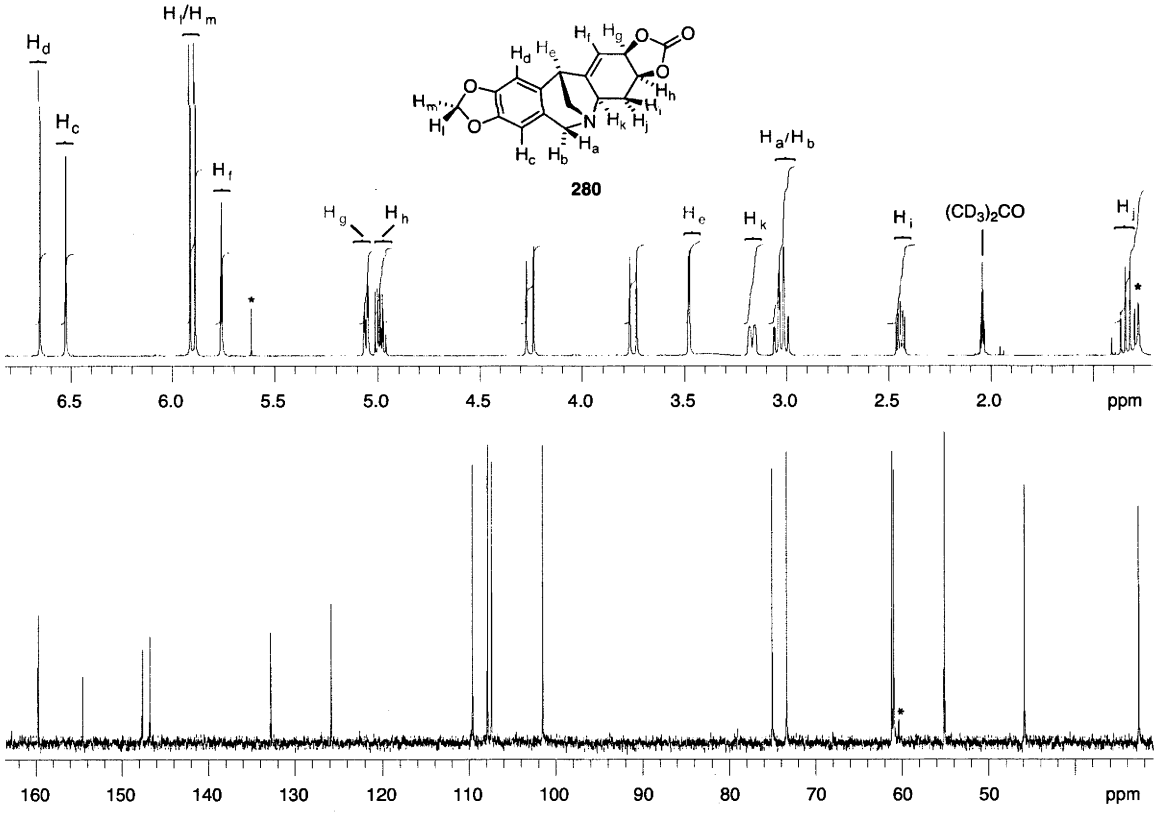
The preparation of the substrate for the Pictet–Spengler reaction, *viz* 3–arylhexahydroindole **277**, continued with the removal of the carbamoyl chloride function. Thus, hydrolysis of the carbamoyl chloride group present in compound **279** with catalytic HCl in dioxane–water[34,35] proceeded smoothly to give Pictet–Spengler reaction precursor **277** in excellent yield (**Scheme 5.21**). Gratifyingly, subjection this material to the pivotal Pictet–Spengler reaction, using paraformaldehyde in the presence of formic acid, effected the C–ring annulation to give, in 65% yield, carbonate **280** that possessed the fully functionalised 5,11–methanomorphanthridine framework of (+)–brunsvigine (*ent*–**18**). Purification of this material by flash chromatography resulted in compound **280** being isolated as a single diastereoisomer.



279 277 280

Scheme 5.21: *synthesis of 2°–amine **277** and the subsequent Pictet–Spengler reaction to achieve C–ring annulation*

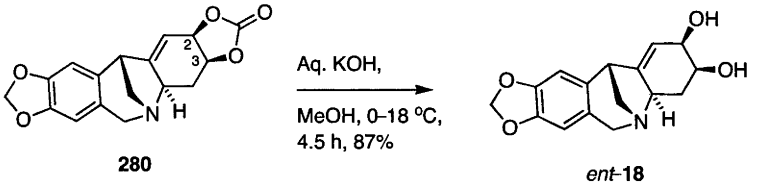
All the spectral data obtained on compound **280** were in full accord with the assigned structure. For example, analysis of the ^{1}H NMR spectrum (**Figure 5.7**) showed the two characteristic aromatic proton signals at δ 6.56 and 6.49 (H_d and H_c, respectively), which are indicative of successful C–ring annulation. In addition, the diastereotopicity associated with the methylenedioxy protons H_l and H_m (resonating at δ 5.92 and 5.89, respectively) also highlights the differences between the *Re* and *Si*–type faces of this rigid framework.



* = Unknown impurities

Figure 5.7: *600 MHz ^{1}H NMR (above) and 75 MHz ^{13}C NMR (below) spectra of carbonate **80** recorded in $(CD_3)_2CO$*

Having successfully prepared the fully functionalised framework of (+)–brunsvigine (*ent*–**18**), all that remained was the cleavage of the cyclic carbonate protecting group to reveal the free hydroxyl functions at C2 and C3. In the event, treatment of carbonate **280** with aqueous potassium hydroxide in MeOH[36] resulted in a hydrolysis reaction which produced (+)–brunsvigine (*ent*–**18**) in 87% yield (**Scheme 5.22**).



Scheme 5.22: *Completion of the synthesis of (+)–brunsvigine (*ent*–**18**)*

The spectral data obtained for this compound were in full accord with the assigned structure. In accord with the reports of Dry *et. al.*,[37] this compound was able to be crystallized from wet acetone as a sesquihydrate and the melting range of this material proved to be 130–140 °C, in reasonably good agreement with the values reported in literature (140–150 °C[37]) for the natural product. The final confirmation of the structure assigned to the synthetic material arose from single–crystal X–ray analysis (**Figure 5.8**). The specific rotation of (+)–brunsvigine (*ent*–**18**) was $[\alpha]_D^{20}$ +75.9 (*c* 0.1, EtOH) which is of similar magnitude but opposite sign to that reported[37] for the natural product, *viz.* $[\alpha]_D^{20}$ –76.6 (*c* 1, EtOH).

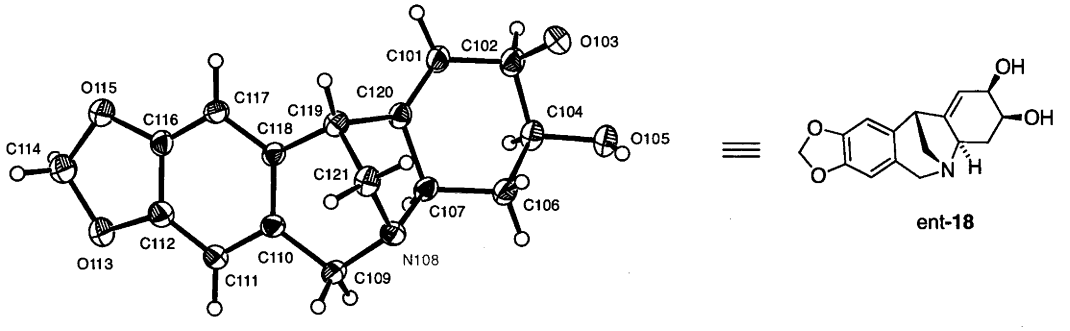


Figure 5.8: *ORTEP derived from the single–crystal X–ray analysis of (+)–brunsvigine (*ent*–**18**) sesquihydrate (water molecules omitted for clarity)*

5.5. Summary

This Chapter has detailed a 17–step total synthesis of (+)–brunsvigine (*ent*–**18**) which proceeded in 0.6% overall yield. Involving *Approach D*, the key features include the preparation of a substrate capable of undergoing a challenging 5–*exo*–*trig* radical cyclization/halogen atom elimination process to install the D–ring of the target alkaloid and thus generating the 3–arylhexahydro–oxindole **224**. Subsequent elaboration of this intermediate to a compound, **277**, suitable for participation in a Pictet–Spengler reaction was achieved in four steps including a mild one–pot, two–step protocol whereby the PMB substituent was cleaved and the acid stable cyclic carbonate group was installed. Finally, subjection of compound **277** to a Pictet–Spengler reaction followed by the hydrolysis of the cyclic carbonate group revealed the target compound (+)–brunsvigine (*ent*–**18**). Since the enantiomer (*ent*–**92**) of the starting diol (**92**) is known, this work also constitutes a formal total synthesis of (–)–brunsvigine (**18**).

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CHAPTER SIX

Summary and Future Work

6.1. Summary

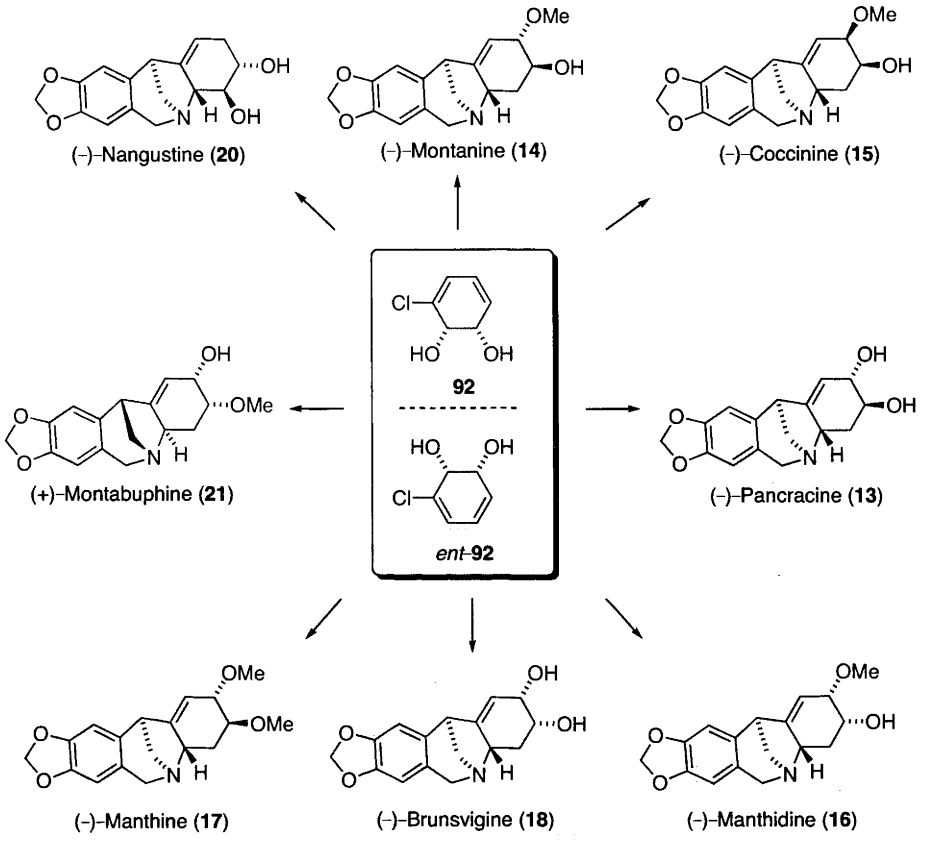
6.1.1. Chemoenzymatic Total Synthesis of (+)–Brunsvigine (*ent*–18)

The work presented in this thesis has been directed towards the development of a chemoenzymatic total synthesis of the unnatural enantiomer of the montanine alkaloid (+)–brunsvigine (*ent*–**18**). Involving four approaches, with the last being successful, three major outcomes of this study can be identified. The first is the selective manipulation of enantiopure *cis*–1,2–dihydrocatechols so as to provide an appropriately functionalised precursor for a novel radical cyclization process. The second is the successful employment of this precursor in a 5–*exo*–*trig* radical cyclization/halogen atom elimination reaction to complete the D–ring annulation, and thus constructing the framework required for the pivotal Pictet–Spengler reaction. The third involved the introduction of an acid stable alcohol protecting group that enabled the successful application of the key Pictet–Spengler reaction to achieve the C–ring annulation and so provide the fully functionalised framework of the target alkaloid. This framework was then easily converted into (+)–brunsvigine (*ent*–**18**).

6.2. Future Work

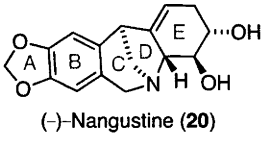
6.2.1. Chemoenzymatic Approaches to Montanine Alkaloids

Careful inspection of the reported synthetic approach to (+)–brunsvigine (*ent*–**18**) suggests a general method for the preparation of the remaining members of the montanine alkaloid family. This stems from the fact that the differences that exist between these natural products arise from variations in oxygenation at C2, C3 and C4 of the E–ring. Therefore, as both enantiomers of the chloro–derivative of the enantiopure *cis*–1,2–dihydrocatechol (**92** and *ent*–**92**) are available, it is conceivable that both the (+) and (–) series of these alkaloids can be accessed following this general method (**Scheme 6.1**).



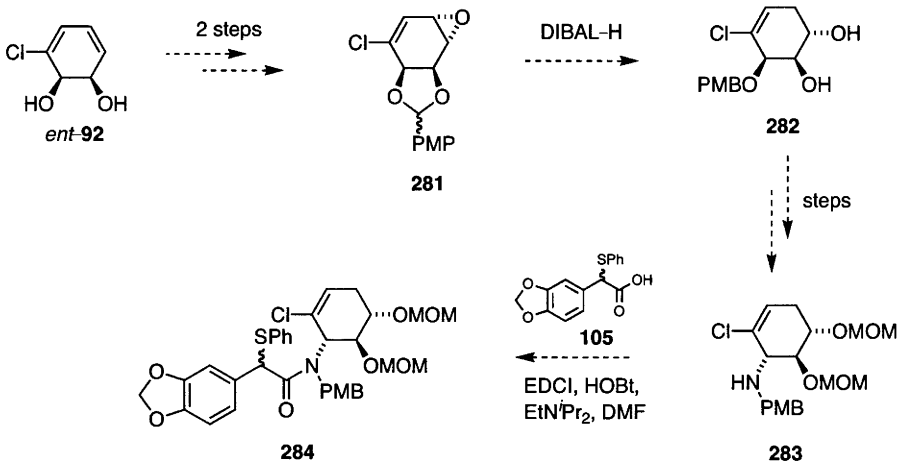
Scheme 6.1: *Chemoenzymatic approach to montanine alkaloids*

The preparation of (–)–nangustine (**20**), for instance, would entail the use of diol *ent*–**92** whereby a similar sequence, as described for the synthesis of (+)–brunsvigine, would be utilized.



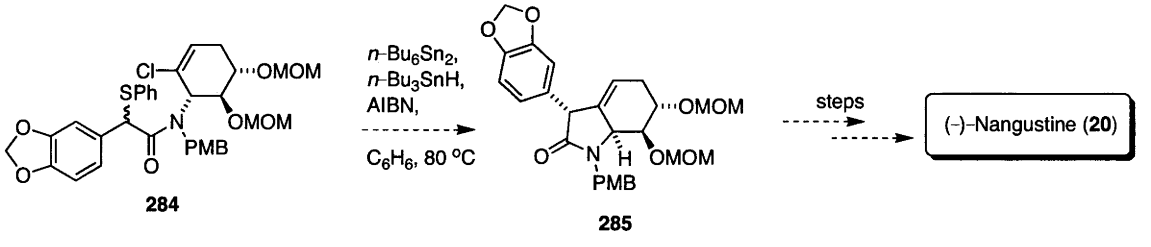
Thus, commencing with *ent*–**92**, protection of this material as the corresponding PMP acetal, followed by an epoxidation reaction with *m*–CPBA would be expected to give epoxide **281** (**Scheme 6.2**). Subsequent regioselective cleavage of the epoxide[1] and the PMP acetal moieties with DIBAL–H should then deliver *trans*–diol **282**. Elaboration of this last compound, through a sequence of known transformations, would then give 2°–amine **283**. It is important to note the presence of the 1,2–*trans* relationship between MOM groups in

compound **283** would limit the formation of an unwanted 1,3–dioxolane moiety (as observed in Section **5.4.1.**) during the execution of the pivotal Pictet–Spengler reaction. Subjection of compound **283** to a EDCI/HOBt–mediated coupling reaction acid **105** would then give radical cyclization substrate **284**.



Scheme 6.2: *Synthesis of substrate **284** for the radical cyclization reaction*

Treatment of compound **284** with *n*–Bu_6Sn_2, *n*–Bu_3SnH and AIBN in refluxing benzene should complete the D–ring annulation process by effecting the key radical cyclization reaction and producing 3–arylhexahydro–oxindole **285** as the major epimer (**Scheme 6.3**). Finally, elaboration of this compound, through several steps (which also includes the pivotal Pictet–Spengler reaction to annulate the C–ring), should then afford the target alkaloid (–)–nangustine (**20**). Work directed at implementing this plan is now underway.



Scheme 6.3: *Completion of a total synthesis of (–)–nangustine (**20**) from radical cyclization precursor **284***

6.3. References:

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CHAPTER SEVEN

Experimental Section

7.1. General Experimental

Unless otherwise specified, proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded at 20 °C in $CDCl_3$ or CD_3OD on a Varian Inova 300 spectrometer operating at 300 MHz for proton and 75 MHz for carbon nuclei. In certain cases, a Varian Inova 500 spectrometer operating at 500 MHz for proton and 125 MHz for carbon nuclei was used, a Varian Inova 600 spectrometer operating at 600 MHz for proton and 150 MHz for carbon nuclei was used and a Varian Inova 800 spectrometer operating at 800 MHz for proton and 200 MHz for carbon nuclei was used. Signals arising from the residual protio–forms of the solvent were employed as the internal standard. ^{1}H NMR data are recorded as follows: chemical shift (δ) [relative integral, multiplicity, coupling constant(s) *J* (Hz)] where multiplicity is defined as: s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet or combinations of the above. The central peak (δ 77.0) of the $CDCl_3$ triplet, the central peak (δ 49.0) of the CD_3OD septet or the central peak (δ 29.8) of the $(CD_3)_2CO$ septet was used to reference proton–decoupled ^{13}C NMR spectra. For ^{13}C NMR spectra the data are given as: chemical shift (δ). Assignment of signals observed in various NMR spectra were often assisted by conducting distortionless enhancement of polarization transfer (DEPT), attached proton test (APT), homonuclear (^{1}H–^{1}H) correlation spectroscopy (COSY), heteronuclear single quantum correlation (HSQC), heteronuclear multiple–bond correlation (HMBC) and/or nuclear Overhauser effect (NOE) experiments.

Infrared spectra (ν_{max}) were recorded on a Perkin–Elmer 1800 Series FTIR Spectrometer. Samples were analysed as KBr disks (for powdery solids) or as thin films on NaCl plates (for oils and crystalline solids).

A VG Fisons AutoSpec three sector (E/B/E) double–focussing mass spectrometer was used to obtain low– and high–resolution electron impact (EI) mass spectra. Low– and high–resolution electrospray (ESI) mass spectra were obtained on a VG Quattro II triple quadrupole MS instrument operating in either positive and/or negative ionisation modes.

Optical rotations were measured with a Perkin–Elmer 241 polarimeter at the sodium–D line (589 nm) and the concentrations (*c*) (g/100 mL) indicated, using spectroscopic grade $CHCl_3$, THF or EtOH as solvent. The measurements were carried out in a cell with a path length (l) of 1 dm. Specific rotations $[\alpha]_D$ were calculated (at 20 °C) using the equation $[\alpha]_D = 100.\alpha/(c.l)$ and are given in 10^{-1}.deg.cm^2.g^{-1}.

Melting points were measured on either a Stanford Research System "OptiMelt" apparatus or a Reichert hot–stage microscope apparatus and are uncorrected.

Elemental analyses were performed by the Australian National University's Microanalytical Services Unit based at the Research School of Chemistry, Canberra, Australia.

Analytical thin layer chromatography (TLC) was performed on glass–backed 0.25 mm thick silica gel 60 F_{254} plates as supplied by Merck. Eluted plates were visualised using a 254 nm UV lamp and/or by treatment with a suitable dip followed by heating. These dips were composed of phosphomolybdic acid, ceric sulfate, sulfuric acid (conc.) and water (37.5 g : 7.5 g : 37.5 g : 720 mL), or vanillin, MeOH and sulfuric acid (conc.) (5 g : 500 mL : 25 mL). Flash chromatography was performed using the analytical grade solvents indicated and silica gel 60 (0.040–0.0063 mm) as supplied by Merck. Room temperature is assumed to be *ca.* 18 °C.

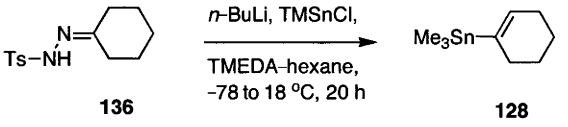
Analytical high performance liquid chromatography (HPLC) was carried out using a Waters Alliance 2695 separation module and a Waters 2996 photodiode detector set at 254 nm interfaced with Empower 2 chromatography software. Analytical HPLC separations were carried out using Alltech Altima C18, 5 μm 250 x 4.6 μm HPLC column.

Starting materials and reagents were generally available from the Sigma–Aldrich–Fluka (SAF), Merck, TCI, Strem or Lancaster Chemical Companies and were used as supplied or, in the case of some liquids, distilled. All *cis*–1,2–dihydrocatechols were generously provided by Dr G. Whited of Genencor International Inc. (Palo Alto, CA) or by Professor D. Boyd of the Queen's University, Belfast. Drying agents and other inorganic salts were purchased from the AJAX, BDH or Unilab Chemical Companies. Tetrahydrofuran (THF), dioxane, and diethyl ether were distilled from sodium benzophenone ketyl. MeOH and EtOH were distilled from calcium oxide while dichloromethane (CH_2Cl_2) and acetonitrile (MeCN) was distilled from calcium hydride. Hexane and ethyl acetate were distilled without using drying reagents. Whilst Benzene and Toluene were distilled from sodium, Triethylamine, pyridine and *N,N*–diisopropylethylamine (EtN^iPr_2) were all distllled from and stored over potassium hydroxide. *N,N*–dimethylformamide was stored over activated 4Å molecular sieves.
Concentration under reduced pressure was performed on the rotary evaporator with the water bath temperature not exceeding 45 °C unless otherwise specified. Also, all reactions were performed under an atmosphere of nitrogen unless otherwise specified.

7.2. Experimental Procedures

7.2.1. Chapter Two: Attempted Preparation of 3–Arylhexahydroindoles *via Approach A*

Cyclohexenyltrimethylstannane (128)



136 **128**

A modification of the procedure detailed by Paquette *et al.* was employed.[1]

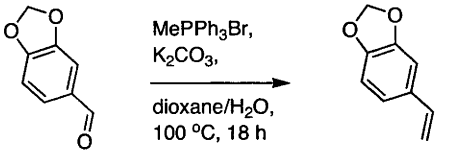
Thus, a magnetically stirred suspension of *p*–toluenesulfonylhydrazone **136**[1] (0.40 g, 1.50 mmol) in TMEDA–hexane (2 mL of a 1:1 v/v mixture) cooled to –78 °C was treated, dropwise, with *n*–BuLi (3.80 mL of a 1.6 M solution in hexane, 6.01 mmol). After 1.5 h at this temperature, the reaction mixture was warmed to 18 °C for 2 h and then cooled to 0 °C. The introduction of trimethyltin chloride (TMSnCl) (1.20 g, 6.01 mmol) to the ensuing mixture produced in an orange solution that was allowed to warm to 18 °C and for 20 h at which time TLC analysis indicated that all starting material had been consumed. Consequently, the reaction mixture was diluted with pentane (50 mL) and water (50 mL) and the separated organic fraction was washed, sequentially, with water (2 x 50 mL), $CuSO_4$ (2 x 40 mL of saturated aqueous solution) and brine (1 x 50 mL) and then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give an orange oil. Vacuum distillation using *Kugelrohr* apparatus then afforded the previously reported title compound **128**[2] (0.18 g, 49%) as a clear, colourless oil.

^{1}H NMR (300 MHz) δ_H ($CDCl_3$) 5.76 (1H, m), 2.08 (2H, m), 2.00 (2H, m), 1.55 (4H, m), 0.00 (9H, m).

^{13}C NMR (75 MHz) δ_C ($CDCl_3$) 140.7, 136.9, 30.8, 27.4, 23.6, 22.6, –9.7.

IR (NaCl) ν_{max} 2924, 2829, 1433, 1187, 764 cm^{-1}.

3,4–Methylenedioxystyrene (139)



138 **139**

A magnetically stirred suspension of piperonal (**138**) (2.96 g, 19.7 mmol), potassium carbonate (K_2CO_3) (3.50 g, 25.3 mmol) and methyltriphenylphosphonium bromide ($MePPh_3Br$) (7.00 g, 19.6 mmol) in dioxane–water (20.3 mL of a 67:1 v/v mixture) was heated at 100 °C for 18 h at which point TLC analysis indicated that all starting material had been consumed. Consequently, the reaction mixture was cooled to 18 °C, filtered through a pad of Celite® and the filtrate was concentrated under reduced pressure to produce a yellow residue that was subjected to flash chromatography (silica, neat hexane → 1:5 v/v ethyl acetate–hexane, gradient elution). Concentration of appropriate fractions (R_f = 0.8) then afforded the previously reported title compound **139**[3] (2.33 g, 80%) as an opaque, colourless oil.

^{1}H NMR (300 MHz) δ_H ($CDCl_3$) 7.09 (1H, m), 6.92 (1H, dd, J = 8.1 and 1.5 Hz), 6.85 (1H, d, J = 8.1 Hz), 6.73 (1H, dd, J = 17.7 and 10.8 Hz), 5.96 (1H, s), 5.70 (1H, d, J = 17.7 Hz), 5.24 (1H, d, J = 10.8 Hz).

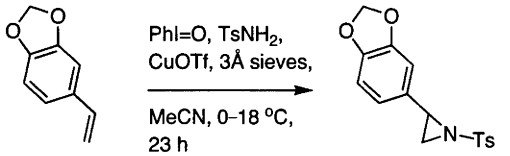
^{13}C NMR (75 MHz) δ_C ($CDCl_3$) 148.4, 147.8, 136.8, 132.4, 121.4, 112.1, 108.4, 105.7, 101.4.

IR (NaCl) ν_{max} 3087, 2894, 1630, 1604, 1489, 1444, 1248, 1191, 1042, 914 cm^{-1}.

MS (EI, 70 eV) *m/z* 148 ($M^{+\bullet}$, 100%), 111 (15), 89 (55), 69 (45), 57 (65), 43 (63).

HRMS Found: $M^{+\bullet}$, 148.0517. $C_9H_8O_2$ requires $M^{+\bullet}$, 148.0524.

2–(Benzo[*d*][1,3]dioxol–6–yl)–1–tosylaziridine (127)



139 **127**

A magnetically stirred mixture containing styrene **139** (148.0 mg, 1.00 mmol), CuOTf (24.0 mg, 0.11 mmol), *p*–toluenesulfonamide (240.0 mg, 1.40 mmol) and 3Å molecular sieves (0.5 g) in anhydrous MeCN (3 mL) was cooled to 0 °C then treated with iodosylbenzene[4] (308.0 mg, 1.40 mmol). After 1 h, the cooling bath was removed and the reaction mixture was allowed to stir at 18 °C. After 23 h, the reaction mixture was filtered through a pad of Celite® and the filtrate was concentrated under reduced pressure to provide a brown residue. Subjection of this material to flash chromatography (silica, 1:4 → 2:3 v/v ethyl acetate–hexane, gradient elution) afforded, after concentration of appropriate fractions (R_f = 0.6, 2:3 v/v ethyl acetate–hexane), the *title compound* ***127*** (127.5 mg, 40%) as a white, crystalline solid.

mp = 105–107 °C

^{1}H NMR (300 MHz) δ_H [$(CD_3)_2CO$)] 7.87 (2H, d, J = 8.4 Hz), 7.42 (2H, d, J = 8.4 Hz), 6.84 (1H, dd, J = 8.1 and 1.8 Hz) 6.76 (1H, d, J = 8.1 Hz), 6.73 (1H, d, J = 1.5 Hz), 5.96 (2H, s), 3.73 (1H, dd, J = 7.2 and 4.5 Hz), 2.90 (1H, d, J = 7.2 Hz), 2.41 (1H, d, J = 4.5 Hz), 2.41 (3H, s)

^{13}C NMR (75 MHz) δ_C [$(CD_3)_2CO$)] 148.2, 148.0, 145.0, 135.6, 130.1, 129.5, 128.1, 121.0, 108.3, 106.6, 101.6, 40.8, 35.5, 21.0.

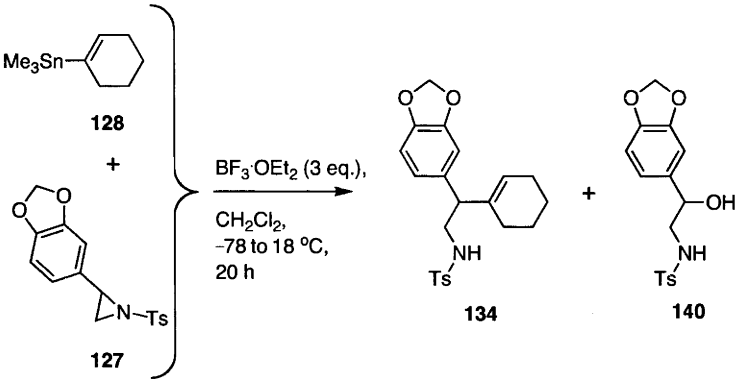
IR (KBr) ν_{max} 2923, 1718, 1490, 1445, 1330, 1250, 1160, 1038 cm^{-1}.

MS (EI, 70 eV) *m/z* 317 ($M^{+\bullet}$, 30%), 162 (100), 135 (63), 132 (43), 104 (36), 77 (32), 65 (16).

HRMS Found: $M^{+\bullet}$, 317.0710. $C_{16}H_{15}NO_4S$ requires $M^{+\bullet}$, 317.0721.

Elemental Analysis Found: C, 60.63; H, 5.06; N, 4.41. $C_{16}H_{15}NO_4S$ requires C, 60.55; H, 4.76; N, 4.41.

2-(Benzo[*d*][1,3]dioxol-6-yl)-2-(1-cyclohexenyl)-*N*-tosyl-ethanamine (134), and 1-(Benzo[*d*][1,3]dioxol-6-yl)-2-(tosylamino)ethanol (140)



A magnetically stirred solution of aziridine **127** (45.0 mg, 0.14 mmol) in anhydrous CH_2Cl_2 (3 mL) was cooled to –78 °C then treated, dropwise, with $BF_3{\cdot}OEt_2$ (60 μL, 0.47 mmol). After 5 min, the ensuing mixture was treated with stannane **128** (35.0 mg, 0.14 mmol) and allowed to warm to 18 °C. After 20 h, the mixture was diluted with CH_2Cl_2 (50 mL) and washed with ammonium hydroxide (1 x 40 mL of saturated aqueous solution), ammonium chloride (2 x 40 mL of saturated aqueous solution) and brine (1 x 40 mL). The organic fraction was then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a yellow residue. Subjection of this material to flash chromatography (silica, neat hexane → 3:7 v/v ethyl acetate–hexane, gradient elution) afforded two fractions, **A** and **B**.

Concentration of fraction **A** (R_f = 0.3, 3:7 v/v ethyl acetate–hexane) provided the *title compound **134*** (31.0 mg, 55%) as an opaque, colourless oil.

^{1}H NMR (500 MHz) δ_H ($CDCl_3$) 7.69 (2H, d, J = 8.3 Hz), 7.31 (2H, d, J = 8.3 Hz), 6.69 (1H, d, J = 8.4 Hz), 6.51 (2H, m), 5.92 (2H, s), 5.44 (1H, broad s), 4.30 (1H, broad m), 3.26 (1H, m), 3.12 (1H, complex m), 2.44 (3H, s), 2.04 (1H, broad s), 1.64–1.42 (8H, complex m).

^{13}C NMR (126 MHz) δ_C ($CDCl_3$) 147.8, 146.5, 143.5, 137.0, 137.0, 136.6, 134.1, 129.7, 127.1, 123.0, 121.0, 108.2, 107.9, 101.0, 51.5, 45.2, 27.0, 25.2, 22.6, 22.3.

IR (NaCl) ν_{max} 3292, 2925, 1722, 1503, 1488, 1328, 1246, 1161, 1039 cm^{-1}.

MS (EI, 70 eV) *m/z* 399 ($M^{+\bullet}$, 15%), 310 (6), 215 (100), 203 (15), 185 (37), 155 (23), 135 (19), 91 (43), 57 (22), 43 (17).

HRMS Found: $M^{+\bullet}$, 399.1507. $C_{22}H_{25}NO_4S$ requires $M^{+\bullet}$, 399.1504.

Concentration of fraction **B** (R_f = 0.2, 3:7 v/v ethyl acetate–hexane) provided *sulfonamide* ***140*** (10.0 mg, 20%) as an opaque, viscous oil.

^{1}H NMR (300 MHz) δ_H ($CDCl_3$) 7.72 (2H, d, J = 8.0 Hz), 7.30 (2H, d, J = 8.0 Hz), 6.75 (3H, m), 5.94 (2H, s), 4.95 (1H, broad s), 4.69 (1H, dd, J = 8.7 and 3.6 Hz), 3.18 (1H, broad m), 2.98 (1H, m), 2.42 (3H, s) (one signal due to NH obscured or overlapping).

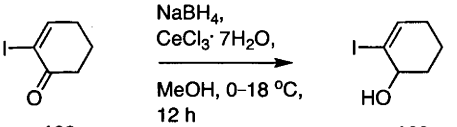
^{13}C NMR (75 MHz) δ_C ($CDCl_3$) 147.9, 147.5, 143.6, 136.6, 134.7, 129.8, 127.0, 119.3, 108.3, 106.2, 101.1, 72.5, 50.1, 21.5.

IR (NaCl) ν_{max} 3608, 3382, 3018, 1505, 1489, 1332, 1250, 1215, 1160, 1041, 749 cm^{-1}.

MS (EI, 70 eV) *m/z* 335 ($M^{+\bullet}$, 9%), 306 (25), 184 (31), 151 (100), 123 (20), 93 (77), 65 (77).

HRMS Found: $M^{+\bullet}$, 335.0818. $C_{16}H_{17}NO_5S$ requires $M^{+\bullet}$, 335.0793.

2–Iodocyclohex–2–enol (160)



163 **160**

A magnetically stirred solution known cyclohexenone **163**[5] (5.0 g, 22.5 mmol) and $CeCl_3{\cdot}7H_2O$ (8.4 g, 22.5 mmol) in anhydrous MeOH (75 mL) was cooled to 0 °C then treated with $NaBH_4$ (1.0 g, 26.3 mmol) and stirred at 18 °C for 12 h. The reaction mixture was quenched with water (100 mL) and extracted with diethyl ether (3 x 150 mL). The combined organic fractions were washed with brine (1 x 100 mL), then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a yellow residue. Subjection of this material to flash chromatography (silica, 1:4 v/v ethyl acetate–hexane elution) and concentration of appropriate fractions (R_f = 0.4) afforded the previously reported title compound **160**[6] (5.0 g, 99%) as a light–yellow, crystalline solid.

mp = 45–47 °C

^{1}H NMR (300 MHz) δ_H ($CDCl_3$) 6.40 (1H, t, J = 3.9 Hz), 4.10 (1H, m), 2.90 (1H, broad s), 2.11–1.51 (6H, complex m).

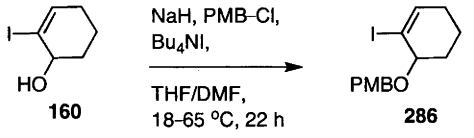
^{13}C NMR (75 MHz) δ_C ($CDCl_3$) 140.6, 103.3, 71.6, 31.9, 29.1, 17.4.

IR (NaCl) ν_{max} 3352, 2938, 2862, 1625, 1426, 1328, 1161, 1078, 1052, 989, 971 cm^{-1}.

MS (EI, 70 eV) *m/z* 224 ($M^{+\bullet}$, 83%), 206 (37), 196 (100), 183 (10), 155 (9), 127 (33), 97 (75), 79 (93), 69 (96), 55 (85), 39 (83).

HRMS Found: $M^{+\bullet}$, 223.9695. $C_6H_9{}^{127}IO$ requires $M^{+\bullet}$, 223.9698.

1–[(2–Iodocyclohex–2–enyloxy)methyl]–4–methoxybenzene (286)



A magnetically stirred solution of cyclohexenol **160** (1.25 g, 5.58 mmol) in anhydrous THF (20 mL) was treated with sodium hydride (0.80 g of a 60% mixture with paraffin oil, 20.10 mmol) then heated at 65 °C. After 1 h, the reaction mixture was cooled to 18 °C and treated with *n*–Bu_4NI (7.91 g, 21.43 mmol) and *p*–methoxybenzyl chloride (PMB–Cl) (3.35 g, 21.43 mmol) in anhydrous DMF (20 mL). The resulting mixture was then stirred for 22 h before being quenched with water (100 mL) and extracted with diethyl ether (3 x 100 mL). The combined organic fractions were washed with water (1 x 100 mL) and brine (1 x 100 mL) then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a brown residue. Subjection of this material to flash chromatography (silica, 1:19 v/v ethyl acetate–hexane elution) and concentration of appropriate fractions (R_f = 0.3) afforded the *title compound* ***286*** (1.85 g, 96%) as a clear, colourless oil.

^{1}H NMR (300 MHz) δ_H ($CDCl_3$) 7.38 (2H, d, J = 8.7 Hz), 6.87 (2H, d, J = 8.7 Hz), 6.50 (1H, m), 4.58 (1H, d, J = 11.0 Hz), 4.50 (1H, d, J = 11.0 Hz), 3.93 (1H, broad s), 3.75 (3H, s), 2.14–1.88 (3H, complex m), 1.77 (2H, m), 1.61 (1H, m).

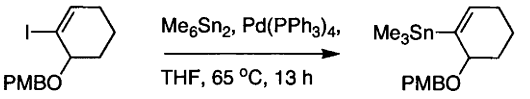
^{13}C NMR (75 MHz) δ_C ($CDCl_3$) 158.5, 140.9, 129.7, 128.9, 113.0, 99.2, 77.8, 70.7, 54.6, 28.8, 28.5, 16.7.

IR (NaCl) ν_{max} 2937, 2862, 2834, 1612, 1513, 1463, 1302, 1248, 1173, 1082, 1036, 826, 733 cm^{-1}.

MS (EI, 70 eV) *m/z* 344 ($M^{+\bullet}$, 99%), 236 (91), 208 (33), 187 (99), 137 (97), 122 (99), 109 (95), 81 (100), 65 (41), 51 (51), 39 (70).

HRMS Found: $M^{+\bullet}$, 344.0275. $C_{14}H_{17}{}^{127}IO_2$ requires $M^{+\bullet}$, 344.0273.

[6–(4–Methoxybenzyloxy)cyclohex–1–enyl]trimethylstannane (143)



286 **143**

A magnetically stirred solution of cyclohexene **286** (0.4 g, 1.16 mmol) and $Pd(PPh_3)_4$ (90 mg, 77.9 μmol) in anhydrous THF (3 mL) maintained at 18 °C was treated with hexamethylditin (0.29 mL, 1.39 mmol) then heated at 65 °C. After 13 h, TLC analysis indicated that all starting material had been consumed. Consequently, the reaction mixture was cooled to 18 °C then concentrated under reduced pressure to give a black residue that was subjected to flash chromatography (silica, 1:19 v/v ethyl acetate–hexane elution) and so providing two fractions, **A** and **B**.

Concentration of fraction **A** (R_f = 0.5, 1:19 v/v ethyl acetate–hexane) gave the *title compound **143*** (122.0 mg, 36% at 77% conversion) as a clear, colourless oil.

^{1}H NMR (300 MHz) δ_H ($CDCl_3$) 7.21 (2H, d, J = 7.5 Hz), 6.81 (2H, d, J = 7.5 Hz), 5.85 (1H, m), 7.55 (1H, d, J = 10.8 Hz), 4.30 (1H, d, J = 10.8 Hz), 3.98 (1H, m), 3.74 (3H, s), 2.14–1.92 (3H, complex m), 1.82–1.72 (1H, m), 1.56–1.42 (2H, complex m), 0.01 (9H, m).

^{13}C NMR (75 MHz) δ_C ($CDCl_3$ 158.9, 145.1, 137.8, 130.9, 129.4, 113.5, 77.4, 70.1, 55.1, 28.3, 27.2, 20.1, –9.3.

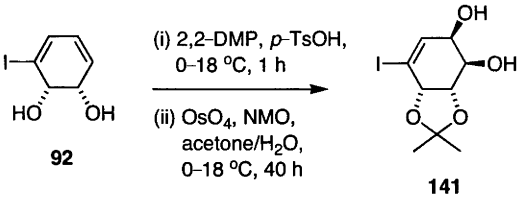
IR (NaCl) ν_{max} 2998, 2934, 2858, 2834, 1614, 1514, 1248, 1077, 1037, 909, 764, 733 cm^{-1}.

MS (EI, 70 eV) *m/z* 367 [$(M–H_3C•)^+$, 80%], 337 (72), 287 (5), 257 (12), 231 (82), 201 (17) 165 (45), 151 (39), 135 (55), 121 (100), 77 (30), 41 (41).

HRMS Found: $(M–H_3C•)^+$, 367.0721. $C_{16}H_{23}O_2{}^{120}Sn$ requires $(M–H_3C•)^+$, 367.0720.

Concentration of fraction **B** (R_f = 0.3, 1:19 v/v ethyl acetate–hexane) afforded starting *cyclohexene **286*** (93.0 mg, 23% recovery) as a colourless oil which was identical, in all respects, with the authentic material.

(3a*S*, 4*R*, 5*R*, 7a*S*)–3a,4,5,7a–Tetrahydro–7–iodo–2,2–dimethylbenzo[*d*][1,3]dioxole–4,5–diol (141)



A magnetically stirred suspension of *cis*–1,2–dihydrocatechol **92** (10.0 g, 42.0 mmol) in 2,2–DMP (100 mL) cooled to 0 °C was treated with *p*–TsOH (76.0 mg, 4.4 mmol) and warmed to 18 °C. After 1 h, the reaction mixture was treated with sodium hydroxide (100 mL of a 1 M aqueous solution) and the separated aqueous fraction of the resulting biphasic mixture was extracted with diethyl ether (2 x 150 mL). The combined organic fractions were washed with water (1 x 60 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure to give an orange residue containing the isopropylidene derivative of compound **92.** A solution of this material in acetone–water (200 mL of a 3:1 v/v mixture) cooled to 0 °C was treated with *N*–methylmorpholine–*N*–oxide (NMO) (4.0 g, 34.2 mmol) and osmium tetraoxide (11 mL of a 2.5 wt % solution in *t*–BuOH, 1.1 mmol) and stirred at 18 °C. After 40 h, the reaction mixture was treated with sodium metabisufite (100 mL of a 1:4 w/v aqueous solution) and stirred for a further 2 h. Concentration of this mixture under reduced pressure provided a brown residue that was partitioned between diethyl ether (500 mL) and water (500 mL). The separated aqueous fraction was extracted with diethyl ether (2 x 250 mL) and the combined organic fractions were washed with brine (1 x 500 mL) then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a black oil. Subjection of this material to flash chromatography (silica, 1:1 v/v ethyl acetate–hexane elution) and concentration of appropriate fractions (R_f = 0.2) afforded the previously reported title compound **141**[7] (5.4 g, 46%) as a white, crystalline solid

mp = 160–162 °C.

^{1}H NMR (300 MHz) δ_H ($CDCl_3$) 6.43 (1H, d, J = 3.0 Hz), 4.65 (1H, d, J = 4.8 Hz), 4.40 (1H, m), 4.34 (1H, m), 4.24 (1H, m), 2.38 (2H, m), 1.43 (3H, s), 1.40 (3H, s).

^{13}C NMR (75 MHz) δ_C [$(CD_3)_2CO$] 141.1, 109.3, 99.6, 78.5, 77.0, 69.0, 67.8, 27.3, 25.9.

IR (KBr) ν_{max} 3503, 3379, 2985, 2923, 2885, 1634, 1448, 1369, 1233, 1080, 1053 cm^{-1}.

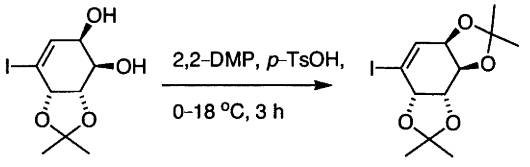
MS (EI, 70 eV) *m/z* 311 ($M^{+\bullet}$, 40%), 297 (70), 254 (61), 208 (43), 110 (81), 101 (100), 81 (54), 59 (60).

HRMS Found: $M^{+\bullet}$, 311.9862. $C_9H_{13}{}^{127}IO_4$ requires $M^{+\bullet}$, 311.9858.

Elemental Analysis Found: C, 34.63; H, 4.18. $C_9H_{13}IO_4$ requires C, 34.64; H, 4.20.

Specific Rotation $[\alpha]_D^{20}$ +21.1 (*c* 0.21, $CHCl_3$).

(3aS, 5aR, 8aR, 8bS)–4–Iodo–3a,5a,8a,8b–tetrahydro–2,2,7,7–tetramethyl–benzo[1,2–d:3,4–d']*bis*[1,3]dioxole (287)



141 **287**

A magnetically stirred suspension of diol **141** (2.75 g, 8.8 mmol) in 2,2–DMP (100 mL) cooled to 0 °C was treated with *p*–TsOH (85.0 mg, 0.49 mmol) then warmed to 18 °C. After 3 h, the reaction mixture was treated with triethylamine (5 mL) and concentrated under reduced pressure to give a yellow residue that was diluted with diethyl ether (100 mL) and treated with sodium hydroxide (100 mL of a 1 M aqueous solution). The separated aqueous fraction of the resulting biphasic mixture was extracted with diethyl ether (1 x 100 mL) and the combined organic fractions were then washed with water (1 x 60 mL) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a yellow oil. Subjection of this material to flash chromatography (silica, 1:4 v/v ethyl acetate–hexane elution) afforded, after concentration of appropriate fractions (R_f = 0.8), the previously reported title compound **287**[7] (2.80 g, 90%) as a clear, colourless oil.

^{1}H NMR (300 MHz) δ_H ($CDCl_3$) 6.31 (1H, m), 4.54 (1H, m,) 4.50 (1H, m), 4.45 (1H, m), 4.41 (1H, m), 1.34–1.30 (12H, complex m).

^{13}C NMR (75 MHz) δ_C ($CDCl_3$) 136.9, 109.5, 102.1, 76.0, 73.3, 72.3, 72.1, 27.6, 27.4, 26.3.

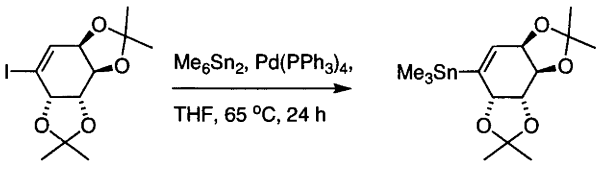
IR (NaCl) ν_{max} 2987, 2934, 2984, 1636, 1455, 1380, 1370, 1229, 1076, 1062, 947 cm^{-1}.

MS (EI, 70 eV) *m/z* 352 ($M^{+\bullet}$, 21%), 337 [$(M–H_3C\bullet)^+$, 100], 279 (22), 237 (50), 152 (35), 110 (72), 59 (45), 43 (99).

HRMS Found: $(M–H_3C\bullet)^+$, 336.9936. $C_{11}H_{14}{}^{127}IO_4$ requires $(M–H_3C\bullet)^+$, 336.9937.

Specific Rotation $[\alpha]_D^{20}$ +141.1 (*c* 0.19, $CHCl_3$).

(3aS, 5aR, 8aS, 8bS)–3a,5a,8a,8b–Tetrahydro–2,2,7,7–tetramethyl–benzo[1,2–d:3,4–d']*bis*[1,3]dioxol–4–yl)trimethylstannane (142)



287 142

Save for the use of a 24 h reaction time, *title compound* ***142*** (88% as a clear, colourless oil) was obtained using the method outlined for the preparation of compound **143**.

R_f = 0.3 (silica, 1:19 v/v ethyl acetate–hexane elution).

^{1}H NMR (300 MHz) δ_H ($CDCl_3$) 5.61 (1H, m), 4.39–4.25 (4H, complex m), 1.18–1.16 (9H, complex m), 1.11 (3H, s), 0.00 (9H, m).

^{13}C NMR (75 MHz) δ_C ($CDCl_3$) 143.5, 134.3, 108.9, 108.8, 74.5, 73.2, 72.8, 70.5, 28.0, 27.8, 26.6, 26.5, –9.5.

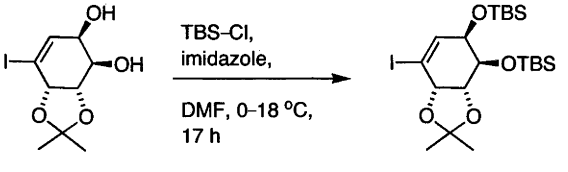
IR (NaCl) ν_{max} 2989, 2932, 2882, 1455, 1378, 1365, 1223, 1058, 854 cm^{-1}.

MS (EI, 70 eV) *m/z* 375 [$(M–H_3C•)^+$, 100%], 317 (24), 259 (44), 229 (28), 165 (38), 135 (22).

HRMS Found: $(M–H_3C•)^+$, 375.0621. $C_{14}H_{23}O_4{}^{120}Sn$ requires $(M–H_3C•)^+$, 375.0618.

Specific Rotation $[\alpha]_D^{20}$ +25.2 (*c* 0.19, $CHCl_3$).

((3aS, 4R, 5R, 7aS)–3a,4,5,7a–Tetrahydro–7–iodo–2,2–dimethylbenzo[*d*][1,3]dioxol–4,5–yl)*bis*(oxy)(*tert*–butyl)dimethylsilane (288)



141 288

A magnetically stirred solution of diol **141** (1.50 g, 4.81 mmol) and imidazole (1.31 g, 19.20 mmol) in anhydrous DMF (20 mL) cooled to 0 °C was treated with TBS–Cl (1.81 g, 12.02 mmol) and warmed to 18 °C. After 17 h, when TLC analysis indicated that all of the starting

material had been consumed, the reaction mixture was treated with diethyl ether–water (200 mL of a 1:1 v/v mixture) and the separated aqueous fraction was extracted with diethyl ether (2 x 100 mL). The combined organic fractions were dried ($MgSO_4$), filtered and concentrated under reduced pressure to give an oily residue that was subjected to flash chromatography (silica, 1:19 v/v ethyl acetate–hexane elution). Concentration of appropriate fractions (R_f = 0.6) then afforded the *title compound* ***288*** (2.36 g, 91%) as a clear, colourless oil.

^{1}H NMR (300 MHz) δ_H ($CDCl_3$) 6.17 (1H, s), 4.49 (1H, d, J = 5.4 Hz), 4.26 (1H, broad s), 4.12 (1H, m), 4.06 (1H, broad m), 1.31 (3H, s), 1.29 (3H, s), 0.83 (9H, m), 0.78 (9H, m), 0.01–0.00 (12H, complex m).

^{13}C NMR (75 MHz) δ_C ($CDCl_3$) 140.6, 109.5, 98.0, 79.2, 77.1, 71.7, 69.5, 27.4, 26.2, 25.9, 25.6, 18.2, 17.9, –4.5, –4.6, –4.9, –5.0.

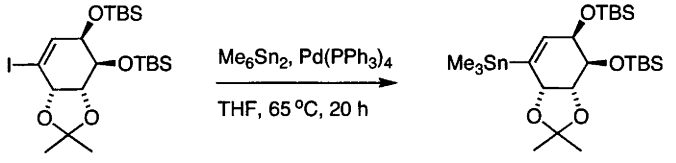
IR (NaCl) ν_{max} 2927, 2855, 1625, 1472, 1383, 1256, 1158, 1071, 1036, 956, 837 cm^{-1}.

MS (EI, 70 eV) *m/z* 540 ($M^{+\bullet}$, <1%), 525 (3), 483 (8), 425 (52), 397 (11), 355 (10), 298 (55), 241 (61), 215 (100), 166 (20), 147 (78), 73 (88)

HRMS Found: $M^{+\bullet}$, 540.1593. $C_{21}H_{41}{}^{127}IO_4Si_2$ requires $M^{+\bullet}$, 540.1588.

Specific Rotation $[\alpha]_D^{20}$–34.7 (*c* 0.22, $CHCl_3$).

((3aS, 4R, 5R, 7aS)–3a,4,5,7a–Tetrahydro–2,2–dimethyl–7–(trimethylstannyl)benzo [*d*][1,3]dioxol–4,5–yl)*bis*(oxy)(*tert*–butyl)dimethylsilane (144)



288 **144**

Save for the use of a 20 h reaction time, *title compound* ***142*** (91% as a clear, colourless oil) was obtained from conduritol **288** using the method outlined for the preparation of compound **143**.

***R*$_f$** = 0.6 (silica, 1:4 v/v ethyl acetate–hexane elution)

^{1}H NMR (300 MHz) δ_H ($CDCl_3$) 5.76 (1H, m), 4.66 (1H, m), 4.18 (1H, m), 4.12 (1H, broad m), 3.84 (1H, m), 1.27 (6H, s), 0.83 (9H, s), 0.81 (9H, s), 0.14 (3H, s), 0.10 (6H, s), 0.03–0.00 (12H, complex m).

^{13}C NMR (75 MHz) δ_C ($CDCl_3$) 143.2, 138.6, 108.4, 77.4, 77.1 73.5, 68.8, 27.7, 26.0, 25.9, 18.3, 18.2, –4.3, –4.4, –4.6, –9.6, –10.1.

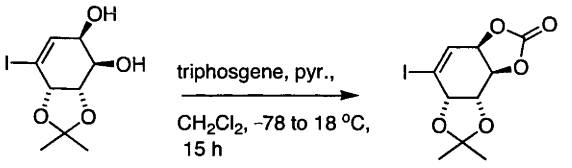
IR (NaCl) ν_{max} 2954, 2929, 2857, 1472, 1463, 1379, 1369, 1253, 1125, 1078, 835, 775 cm^{-1}.

MS (EI, 70 eV) *m/z* 563 [$(M–H_3C•)^+$, 22%], 520 (9), 503 (10), 463 (73), 348 (15), 253 (19), 215 (58), 165 (92), 147 (56), 73 (100).

HRMS Found: $(M–H_3C•)^+$, 563.2024. $C_{23}H_{47}O_4Si_2{}^{120}Sn$ requires $(M–H_3C•)^+$, 563.2035.

Specific Rotation $[\alpha]_D^{20}$ –50.9 (*c* 0.36, $CHCl_3$).

((3aS, 5aR, 8aS, 8bR)–4-Iodo–3a,5a,8a,8b–tetrahydro–2,2–dimethylbenzo[*d*][1,3]dioxol–5a,8a–yl)benzo[*d*][1,3]dioxol–7–one (289)



141 **289**

A magnetically stirred solution of diol **141** (1.20 g, 3.85 mmol) in anhydrous CH_2Cl_2 (12 mL) was cooled to –78 °C then treated with triphosgene (0.46 g, 1.54 mmol) and pyridine (1.86 mL, 23.0 mmol) and allowed to warm to 18 °C. After 15 h, point TLC analysis indicated that all of the starting material had been consumed. Consequently, the reaction mixture was treated with ammonium chloride (100mL of a saturated aqueous solution) and extracted with CH_2Cl_2 (2 x 100 mL). The combined organic fractions were washed, sequentially, with HCl (1 x 50 mL of a 1 M aqueous solution), sodium hydrogen carbonate ($NaHCO_3$) (1 x 50 mL of a saturated aqueous solution) and brine (1 x 50 mL) then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a white residue. Recrystallization of this material (diethyl ether–ethyl acetate) gave the *title compound **289*** (1.24 g, 96%) as a white, crystalline solid.

mp = 112–114 °C.

^{1}H NMR (300 MHz) δ_H ($CDCl_3$) 6.48 (1H, m), 5.17 (1H, dd, *J* = 6.9 and 2.7 Hz), 4.99 (1H, m), 4.66–4.59 (2H, complex m), 1.41 (6H, s).

^{13}C NMR (75 MHz) δ_C ($CDCl_3$) 152.8, 130.8, 110.8, 108.2, 74.8, 72.0, 71.4, 27.4, 26.4.

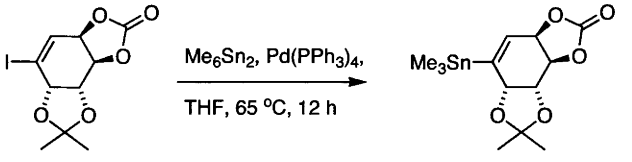
IR (NaCl) ν_{max} 2998, 2898, 1642, 1805, 1755, 1634, 1384, 1374, 1323, 1234, 1180, 1134, 1081, 1054, 1039, 1006, 840 cm^{-1}.

MS (EI, 70 eV) *m/z* 338 ($M^{+\bullet}$, 38%), 323 (95), 314 (15), 281 (11), 237 (15), 219 (18), 207 (18), 191 (14), 154 (11), 128 (10), 110 (80), 81 (47), 65 (21), 59 (24), 53 (48), 43 (100).

HRMS Found: $M^{+\bullet}$, 337.9650. $C_{10}H_{11}{}^{127}IO_5$ requires $M^{+\bullet}$, 337.9651.

Specific Rotation $[\alpha]_D^{20}$ +137.2 (*c* 0.18, $CHCl_3$).

((3aS, 5aR, 8aS, 8bR)–4-(Trimethylstannyl)–3a,5a,8a,8b–tetrahydro–2,2–dimethylbenzo[*d*][1,3]dioxol–5a,8a–yl)benzo[*d*][1,3]dioxol–7–one (145)



289 145

Save for the use of a 12 h reaction time, *title compound* ***145*** (25% as a clear, colourless oil) was obtained from conduritol **289** using the method outlined for the preparation of compound **143**.

R_f = 0.5 (silica, 1:4 v/v ethyl acetate–hexane elution)

^{1}H NMR (300 MHz) δ_H ($CDCl_3$) 5.84 (1H, m), 5.09 (1H, dd, *J* = 6.9 and 2.1 Hz), 4.99 (1H, dd, *J* = 6.3, 3.3 Hz), 4.64–4.56 (2H, complex m), 1.37 (3H, s), 1.29 (3H, s), 0.23 (9H, m).

^{13}C NMR (75 MHz) δ_C ($CDCl_3$) 153.7, 150.2, 127.3, 109.9, 73.3, 72.8, 70.5, 28.0, 26.6, 9.2.

IR (NaCl) ν_{max} 2986, 2917, 1811, 1370, 1237, 1177, 1155, 1132, 1052, 767 cm^{-1}.

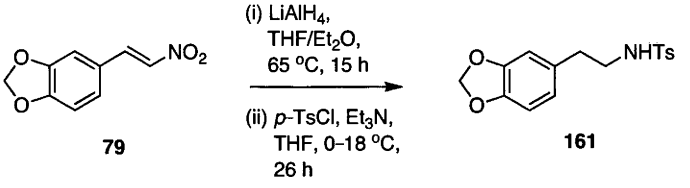
MS (EI, 70 eV) *m/z* 361 [$(M–H_3C\bullet)^+$, 100%], 302 (91), 273 (8), 244 (8), 217 (24), 165 (57), 149 (15), 135 (47), 93 (12), 81 (27), 65 (29), 53 (15), 43 (72).

HRMS Found: $(M–H_3C\bullet)^+$, 361.0105. $C_{12}H_{17}O_5{}^{120}Sn$ requires $(M–H_3C\bullet)^+$, 361.0098.

Specific Rotation $[\alpha]_D^{20}$ +75.1 (*c* 1.60, $CHCl_3$).

7.2.2. Chapter Three: Attempted Preparation of 3–arylhexahydroindoles *via Approach B*

2–(Benzo[*d*][1,3]dioxol–6–yl)–*N*–tosylethanamine (161)



79 161

A magnetically stirred suspension of $LiAlH_4$ (1.15 g, 30.2 mmol) in anhydrous diethyl ether (50 mL) was cooled to 0 °C then treated with a solution of the known *β*–nitrostyrene **79**[8] (2.00 g, 10.4 mmol) in anhydrous THF (50 mL) and heated at 65 °C. After 15 h, when TLC analysis indicated that all of the starting material had been consumed, the reaction mixture was quenched with sodium sulfate decahydrate (5 mL of a saturated aqueous solution) [CAUTION: Exotherm]. The resulting mixture was filtered through a pad of Celite® and the filtrate was concentrated under reduced pressure to give a yellow oil containing *β*–arylethylamine (a derivative of compound **79**). This material was subjected, without purification, to the next step of the reaction sequence.

A magnetically stirred solution of this yellow oil in anhydrous THF (50 mL), maintained at 18 °C, was treated with *p*–TsCl (2.40 g, 12.6 mmol) and triethylamine (1.5 mL). After 26 h, the mixture was concentrated under reduced pressure to give a brown residue that was treated with sodium hydroxide (100 mL of a 1 M aqueous solution) and extracted with CH_2Cl_2 (3 x 100 mL). The combined organic fractions were washed with HCl (100 mL of a 1 M aqueous solution) then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a viscous, brown oil. Subjection of this material to flash chromatography (silica, 1:4 v/v ethyl acetate–hexane elution) and concentration of appropriate fractions (R_f = 0.3) afforded the *title compound **161*** (1.40 g, 42%) as an off–white, crystalline solid.

mp = 83–85 °C

^{1}H NMR (300 MHz) δ_H ($CDCl_3$) 7.69 (2H, d, J = 7.2 Hz), 7.24 (2H, d, J = 8.1 Hz), 6.62 (1H, d, J = 7.8 Hz), 6.49 (2H, m), 5.83 (2H, s), 5.23 (1H, m), 3.09 (2H, q, J = 7.1 Hz), 2.63 (2H, t, J = 7.1 Hz). 2.37 (3H, s).

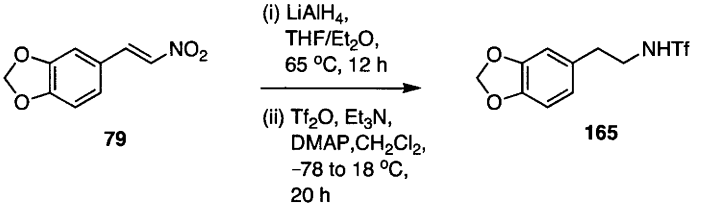
^{13}C NMR (75 MHz) δ_C ($CDCl_3$) 147.4, 145.9, 143.1, 136.6, 131.4, 129.4, 126.8, 121.4, 108.8, 108.0, 100.6, 44.3, 35.2, 21.2.

IR (KBr) ν_{max} 3283, 2923, 1490, 1443, 1324, 1247, 1159, 1094, 1039, 812 cm^{-1}.

MS (EI, 70 eV) *m/z* 319 ($M^{+\bullet}$, 50%), 184 (42), 155 (97), 135 (100), 91 (89), 77 (28), 65 (18), 51 (17).

HRMS Found: $M^{+\bullet}$, 319.0879. $C_{16}H_{17}NO_4S$ requires $M^{+\bullet}$, 319.0878.

2–(Benzo[*d*][1,3]dioxol–6–yl)–*N*–triflylethanamine (165)



79 **165**

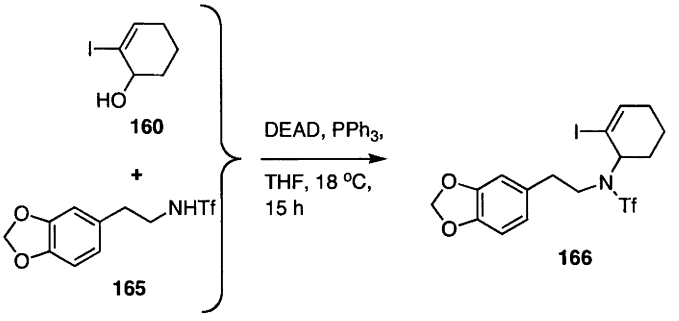
A magnetically stirred suspension of $LiAlH_4$ (30 mL of a 1 M solution in THF, 30.0 mmol) in anhydrous diethyl ether (50 mL) was cooled to 0 °C and treated with a solution of the known β–nitrostyrene **79**[8] (2.0 g, 10.4 mmol) in anhydrous THF (50 mL) and heated at 65 °C. After 12 h, when TLC analysis indicated that all of the starting material had been consumed, the reaction mixture was quenched with sodium sulfate decahydrate (20 mL of a saturated aqueous solution) [CAUTION: Exotherm]. The mixture was filtered through a pad of Celite® and the filtrate was washed with brine (1 x 100 mL) then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a yellow oil containing β–arylethylamine (a derivative of compound **79**). This material was subjected, without purification, to the next step of the reaction sequence.

A magnetically stirred solution of the yellow oil in anhydrous CH_2Cl_2 (25 mL) was treated with DMAP (120.00 mg, 0.98 mmol) and triethylamine (1.60 mL, 11.6 mmol) before being cooled to –78 °C and then treated (dropwise) with Tf_2O (1.63 mL, 9.7 mmol) and allowed to warm to 18 °C. After 20 h, the ensuing mixture was concentrated under reduced pressure to give a yellow residue. Subjection of this material to flash chromatography (silica, 1:4 v/v ethyl acetate–hexane elution) and concentration of appropriate fractions (R_f = 0.3) afforded the *title compound* ***165*** (1.35 g, 49%) as an opaque, light–yellow oil.

^{1}H NMR (300 MHz) δ_H ($CDCl_3$) 6.76 (1H, d, J = 7.8 Hz), 6.67 (2H, m), 5.93 (2H, s), 5.18 (1H, m), 3.49 (2H, m), 2.81 (2H, t, J = 6.9 Hz).

^{13}C NMR (75 MHz) δ_C ($CDCl_3$) 148.0, 146.6, 130.2, 121.7, 108.8, 108.5, 101.0, 45.4, 36.1.

N–(2–(Benzo[*d*][1,3]dioxol–6–yl)ethyl)–2–iodo–*N*–triflylcyclohex–2–enamine (166)



A magnetically stirred solution of cyclohexenol **160** (0.75 g, 3.35 mmol), triflamide **165** (1.14 g, 3.84 mmol) and PPh_3 (1.40 g, 5.34 mmol) in anhydrous THF (20 mL) maintained at 18 °C was treated with DEAD (736 μL, 4.68 mmol). After 15 h, the resulting mixture was concentrated under reduced pressure to give viscous, orange oil that was subjected to flash chromatography (silica, 1:4 v/v ethyl acetate–hexane elution). Concentration of appropriate fractions (R_f = 0.4) then afforded the *title compound* ***166*** (1.25 g, 74%) as a light–yellow, crystalline solid.

mp = 64–65 °C

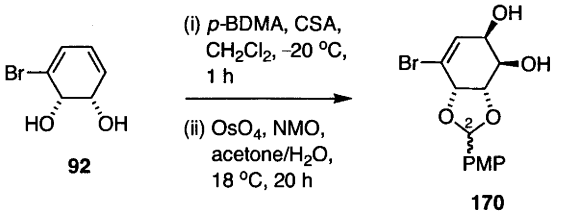
^{1}H NMR (300 MHz) δ_H ($CDCl_3$) 6.71 (1H, d, J = 7.8 Hz), 6.63 (2H, m), 5.90 (3H, m), 3.14 (2H, broad m), 2.85 (3H, broad m), 2.22–1.70 (6H, complex m).

^{13}C NMR (75 MHz) δ_C ($CDCl_3$) 147.7, 146.3, 131.3, 121.6, 121.5, 108.8, 108.3, 100.8, 63.6, 48.0, 36.4, 28.6, 20.8, 20.5. (2 signals obscured or overlapping)

MS (EI, 70 eV) *m/z* 503 ($M^{+\bullet}$, 78%), 370, 341 (11), 207 (68), 149, 135 (100), 79 (62).

HRMS Found: $M^{+\bullet}$, 502.9882. $C_{16}H_{17}F_3{}^{127}IO_4S$ requires $M^{+\bullet}$, 502.9875.

(2*S*, 3a*S*, 4*R*, 5*R*, 7a*S*)–and (2*R*, 3a*S*, 4*R*, 5*R*, 7a*S*)–7–Bromo–3a,4,5,7a–tetrahydro–2(4methoxyphenyl)benzo[*d*][1,3]–dioxole–4,5–diol (170)



A magnetically stirred suspension of *cis*–1,2–dihydrocatechol **92** (20 g, 104.7 mmol) and *p*–methoxybenzaldehyde dimethyl acetal (*p*–MBDMA) (20.9 mL, 115.2 mmol) in anhydrous CH_2Cl_2 (200 mL) was cooled to –20 °C then treated with (1*S*)–(+)–camphor–10–sulfonic acid monohydrate (CSA·H_2O) (2.42 g, 10.43 mmol). After 1 h, when TLC analysis indicated that all of the starting material had been consumed, the reaction mixture was quenched with sodium hydroxide (200 mL of a 1 M aqueous solution). The separated aqueous phase was extracted with CH_2Cl_2 (2 × 100 mL) and the combined organic fractions were then washed with brine (1 × 100 mL) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a white solid. A solution of this material in acetone–water (300 mL of 2:1 v/v mixture) was cooled to 0 °C then treated with *N*–methylmorpholine *N*–oxide (NMO) (27.1 g, 231.7 mmol) and osmium tetraoxide (7 mL of a 2.5% wt/v solution in *t*–BuOH, 0.53 mmol). The ensuing mixture was stirred at 18 °C for 20 h then treated with sodium metabisulfite (200 mL of a 20% w/v aqueous solution). After 4 h the reaction mixture was concentrated under reduced pressure to give brown residue that was treated with diethyl ether–water (1000 mL of a 1:1 v/v mixture). The separated aqueous phase was extracted with diethyl ether (4 × 150 mL) and the combined organic fractions then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a brown residue. Subjection of this material to flash chromatography (silica, 1:19 v/v MeOH–CH_2Cl_2 elution) and concentration of appropriate fractions (R_f = 0.3) afforded a 3:1 mixture of the C2–epimeric forms of the *title compound* ***170*** (23.3 g, 65%) as a white, crystalline solid.

mp = 133–134 °C

^{1}H NMR (300 MHz) δ_H [$(CD_3)_2CO$] (major) 7.42 (2H, d, J = 8.9 Hz), 6.95 (2H, d, J = 8.9 Hz), 6.29 (1H, m), 5.80 (1H, s), 4.90 (1H, d, J = 5.1 Hz), 4.55 (1H, m), 4.40 (3H, m), 4.25 (1H, m), 3.81 (3H, s); δ_H [$(CD_3)_2CO$] (minor) 7.37 (2H, d, J = 8.7 Hz), 6.93 (2H, d, 9.0 Hz), 6.17 (1H, dd, J = 2.7, 1.2 Hz), 5.88 (1H, s), 4.69 (1H, dd, J = 6.0, 1.2 Hz), 4.51 (1H, dd, J = 4.8, 4.6 Hz), 4.42 (3H, m), 4.31 (1H, m), 3.80 (3H, s).

^{13}C NMR (75 MHz) δ_C [$(CD_3)_2CO$] (major): 161.4, 136.5, 130.8, 129.0, 120.7, 114.3, 103.1, 77.9, 77.1, 69.6, 67.7, 55.5; δ_C [$(CD_3)_2CO$] (minor): 161.5, 133.7, 130.3, 129.3, 122.2, 114.3, 104.7, 79.0, 77.9, 70.0, 68.0, 55.5.

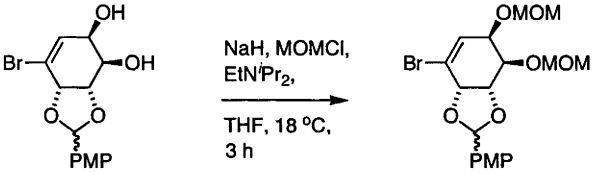
IR (NaCl) ν_{max} 3518, 3392, 2954, 2907, 2834, 1615, 1515, 1390, 1304, 1248, 1170, 1074, 1050, 1030, 924 cm^{-1}.

MS (EI, 70 eV) *m/z* 343 and 341 [$(M - H\cdot)^+$, 5 and 5%], 172 (10), 153 (13), 152 (13), 135 (100), 108 (39), 77 (22), 65 (18).

HRMS Found: $(M - H\cdot)^+$, 341.0020. $C_{14}H_{15}{}^{79}BrO_5$ requires $(M - H\cdot)^+$, 341.0025.

Elemental Analysis Found: C, 48.67; H, 4.40; Br, 23.42. $C_{14}H_{15}BrO_5$ requires C, 49.00; H, 4.41; Br, 23.28.

(2*S*, 3a*R*, 4*R*, 5*R*, 7a*R*)–and (2*R*, 3a*R*, 4*R*, 5*R*, 7a*R*)–7–Bromo–3a,4,5,7a–tetrahydro–4,5–bis(methoxymethoxy)–2–(4–methoxyphenyl)benzo[*d*][1,3]dioxole (171)



170 **171**

A magnetically stirred solution of diol **170** (35.7 g, 104.3 mmol) in anhydrous THF (500 mL) was cooled to 0 °C then treated with sodium hydride (9.20 g of a 60% mixture with paraffin oil, 229 mmol) and EtN^{i}Pr$_2$ (40.0 mL, 229 mmol). The ensuing mixture was allowed to warm to 18 °C and after 15 mins the reaction mixture was again cooled to 0 °C then methoxymethyl chloride (MOMCl) (16.6 mL, 219 mmol) was added (dropwise). After the addition was complete, the reaction mixture re–warmed to 18 °C. This protocol was repeated once more and the resulting mixture then quenched with water (200 mL) [CAUTION: Exothermic]. The separated aqueous phase was extracted with ethyl acetate (2 × 200 mL) and the combined organic fractions were then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a yellow residue. This material was subjected twice more to the reaction conditions outlined above and workup, in the usual fashion, then gave an orange residue. Subjection of this material to flash chromatography (silica, 3:7 v/v ethyl acetate–hexane elution) and concentration of appropriate fractions (R_f = 0.3) afforded the *title compound* ***171*** (40.8 g, 91%) as an opaque, light–yellow oil.

^{1}H NMR (300 MHz) δ_H [$(CD_3)_2CO$] (major): 7.43 (2H, d, J = 8.9 Hz), 6.95 (2H, d, J = 8.9 Hz), 6.39 (1H, d, J = 3.5 Hz), 5.90 (1H, s), 4.82–4.72 (4H, complex m), 4.60 (1H, m), 4.35 (1H, m), 4.20 1H, m), 3.80 (3H, s), 3.37 (3H, s), 3.36 (3H, s).

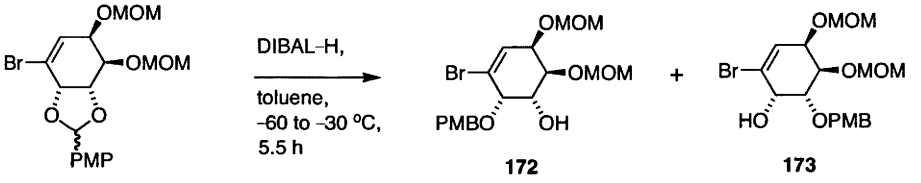
^{13}C NMR (75 MHz) δ_C [$(CD_3)_2CO$] (major): 161.5, 132.5, 129.7, 129.3, 122.7, 114.3, 104.7, 96.8, 96.5, 78.1, 77.0, 74.8, 72.4, 55.6, 55.5.

IR (KBr) ν_{max} 2936, 2893, 1614, 1518, 1398, 1305, 1250, 1151, 1080, 1034, 917, 831 cm^{-1}.

MS (EI, 70 eV) *m/z* 432 and 430 ($M^{+\bullet}$, both >1%), 389 and 387 (both ~12), 236 and 234 (both 88), 181 (63), 137 (90), 122 (95), 45 (100).

Elemental Analysis Found: C, 50.35; H, 5.35; Br, 18.64. $C_{18}H_{23}BrO_7$ requires C, 50.13; H, 5.38; Br, 18.53.

(1*S*, 2*S*, 5*R*, 6*S*)–2–(4–Methoxybenzyloxy)–3–bromo–5,6–bis(methoxymethoxy) cyclohex–3–enol (172) and (1*S*, 4*R*, 5*R*, 6*R*)–6–(4–methoxybenzyloxy)–2–bromo–4,5–bis(methoxymethoxy) cyclohex–2–enol (173)



171 172 173

A magnetically stirred solution benzylidene acetal **171** (35.3 g, 82 mmol) in anhydrous toluene (700 mL) was cooled to –60 °C then treated with DIBAL–H (410 mL of a 1 M solution in toluene, 410 mmol). The ensuing solution was allowed to warm to –30 °C and after 5.5 h, when TLC analysis indicated that all the starting material had been consumed, the reaction mixture was quenched with sodium/potassium tartrate (300 mL of a saturated aqueous solution) [CAUTION: Exothermic] and the ensuing mixture was then allowed to warm to 18 °C over period of 12 h. The separated aqueous fraction was extracted with CH_2Cl_2 (3 × 300 mL) and the combined organic fractions were then washed with brine (1 × 300 mL) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure to give an opaque, colourless oil. Subjection of this material to flash chromatography (silica, 2:3 v/v ethyl acetate–hexane elution) provided two fractions, **A** and **B**.

Concentration of fraction **A** (R_f = 0.3) afforded the *title compound* ***172*** (22.1 g, 64%) as a clear, colourless oil.

^{1}H NMR (300 MHz) δ_H ($CDCl_3$) 7.27 (2H, d, J = 8.4 Hz), 6.79 (2H, d, J = 8.4 Hz), 6.10 (1H, d, J = 3.3 Hz), 4.68–4.60 (6H, complex m), 4.28 (1H, m), 4.15–3.95 (3H, complex m), 3.69 (3H, s), 3.28 (3H, s), 3.24 (3H, s), 3.11 (1H, broad s).

^{13}C NMR (75 MHz) δ_C ($CDCl_3$) 159.1, 130.6, 129.5, 129.3, 123.8, 113.4, 96.9, 95.8, 77.6, 75.3, 73.8, 72.0, 68.5, 55.2, 55.0, 54.8.

IR (NaCl) ν_{max} 3468, 2994, 2935, 2894, 2837, 1643, 1612, 1586, 1514, 1465, 1365, 1302, 1250, 1212, 1174, 1151, 1098, 1038, 917, 831 cm^{-1}.

MS (EI, 70 eV) *m/z* 434 and 432 ($M^{+\bullet}$, both <1%), 389 and 387 [$(M - CH_3OCH_2\bullet)^+$, both 9], 280 and 278 (both 11), 236 and 234 (both 83), 181 (60), 137 (83), 122 (86), 121 (100), 109 (24), 91 (24), 78 (41), 77 (51), 45 (96).

HRMS Found: $M^{+\bullet}$, 432.0786. $C_{18}H_{25}{}^{79}BrO_7$ requires $M^{+\bullet}$, 432.0784.

Elemental Analysis Found: C, 49.93; H, 5.96; Br, 18.61. $C_{18}H_{25}BrO_7$ requires C, 49.90; H, 5.82; Br, 18.44.

Specific Rotation $[\alpha]_D^{20}$ –17.8 (*c* 0.14, $CHCl_3$).

Concentration of fraction **B** (R_f = 0.4) gave the *title compound* ***173*** (10.6 g, 30%) as a clear, colourless oil.

^{1}H NMR (300 MHz) δ_H ($CDCl_3$) 7.27 (2H, d, J = 8.6 Hz), 6.89 (2H, d, J = 8.6 Hz), 6.21 (1H, d, J = 3.9 Hz), 4.78–4.58 (6H, complex m), 4.36 (1H, m), 4.29 (1H, m), 4.05 (2H, m), 3.81 (3H, s), 3.38 (6H, s), 1.60 (1H, broad s).

^{13}C NMR (75 MHz) δ_C ($CDCl_3$) 159.6, 130.4, 129.7, 129.5, 126.3, 114.0, 97.3, 96.3, 76.8, 73.5, 73.2, 72.4, 70.3, 55.8, 55.6, 55.3.

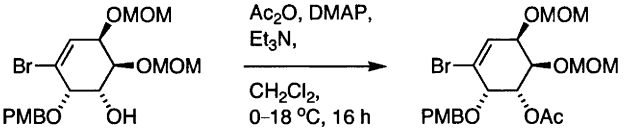
IR (NaCl) ν_{max} 3452, 2917, 1612, 1514, 1249, 1150, 1101, 1033, 917 cm^{-1}.

MS (ESI, 70 eV) *m/z* 457 and 455 [$(M + Na)^+$, both 34%], 121 (29), 102 (100), 74 (49).

HRMS Found: $(M + Na)^+$, 455.0688. $C_{18}H_{25}{}^{79}BrNaO_7$ requires $(M + Na)^+$, 455.0681.

Specific Rotation $[\alpha]_D^{20}$–53.0 (*c* 0.28, $CHCl_3$).

(1*S*,2*S*,5*R*,6*R*)–2–(4–Methoxybenzyloxy)–3–bromo–5,6–bis(methoxymethoxy)cyclohex–3–enyl acetate (174)



172 **174**

A magnetically stirred solution of conduritol **172** (198.0 mg, 0.46 mmol), DMAP (11.0 mg, 0.09 mmol) and triethylamine (95 μL, 0.68 mmol) in anhydrous CH_2Cl_2 (2 mL) was cooled to 0 °C then treated with acetic anhydride (Ac_2O) (65 μL, 0.68 mmol) and allowed to warm to 18 °C. After 16 h, point TLC analysis indicated that all starting material had been consumed. Consequently, the reaction mixture was treated with water (40 mL) and extracted with CH_2Cl_2 (3 x 40 mL). The combined organic fractions were dried ($MgSO_4$), filtered and concentrated under reduced pressure to give an opaque, colourless oil. Subjection of this material to flash chromatography (silica, 2:3 v/v ethyl acetate–hexane elution) and concentration of appropriate fractions (R_f = 0.5, 2:3 v/v ethyl acetate–hexane) afforded the *title compound* ***174*** (202.0 mg, 93%) as a clear, colourless oil.

^{1}H NMR (300 MHz) δ_H ($CDCl_3$) 7.31 (2H, d, J = 8.4 Hz), 6.87 (2H, d, J = 8.4 Hz), 6.22 (1H, d, J = 3.9 Hz), 5.48 (1H, dd, J = 8.4 and 3.9 Hz), 4.77–4.69 (4H, complex m), 4.63 (2H, s), 4.37 (1H, d, J = 3.9 Hz), 4.28 (1H, m), 4.18 (1H, dd, J = 9.0 and 3.9 Hz), 3.79 (3H, s), 3.38 (3H, s), 3.37 (3H, s), 2.06 (3H, s).

^{13}C NMR (75 MHz) δ_C ($CDCl_3$) 170.1, 159.4, 130.5, 129.8, 129.6, 124.6, 113.7, 97.0, 96.3, 77.0, 74.4, 72.1, 69.9, 55.7, 55.6, 55.2, 20.9 (one signal obscured or overlapping).

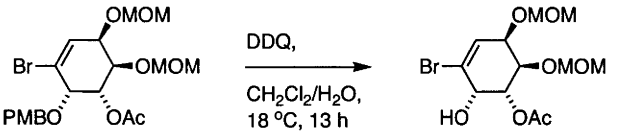
IR (NaCl) ν_{max} 2952, 2896, 1747, 1613, 1514, 1374, 1247, 1151, 1101, 1038, 910, 733 cm^{-1}.

MS (EI, 70 eV) *m/z* 476 and 474 ($M^{+\bullet}$, both > 1%), 431 and 429 (both 9), 399 and 397 (both 3), 344 (13), 265 and 263 (both 4), 214 (17), 171 (17), 146 (17), 121 (100), 107 (9), 77 (8), 69 (9), 45 (41).

HRMS Found: $M^{+\bullet}$, 474.0891. $C_{20}H_{27}{}^{79}BrO_8$ requires $M^{+\bullet}$, 474.0889.

Specific Rotation $[\alpha]_D^{20}$ –118.2 (*c* 0.22, $CHCl_3$).

(1*R*, 2*S*, 5*R*, 6*R*)-3-Bromo-2-hydroxy-5,6-bis(methoxymethoxy)cyclohex-3-enyl acetate (167)



174 **167**

A magnetically stirred solution conduritol **174** (165.0 mg, 0.34 mmol) in CH_2Cl_2–water (5.3 mL of a 17:1 v/v mixture) maintained at 18 °C was treated with DDQ (95.0 mg, 0.42 mmol). After 13 h, when TLC analysis indicated that all starting material had been consumed, the ensuing reaction mixture was treated with sodium hydrogen carbonate (50 mL of a saturated aqueous solution) and CH_2Cl_2 (40 mL). The separated aqueous fraction of the biphasic mixture was extracted with CH_2Cl_2 (2 x 40 mL) and the combined organic fractions were washed with brine (1 x 50 mL) then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a brown residue. Subjection of this material to flash chromatography (silica, 2:3 v/v ethyl acetate–hexane elution) and concentration of appropriate fractions (R_f = 0.2) afforded the *title compound **167*** (100.0 mg, 81%) as a clear, colourless oil.

^{1}H NMR (300 MHz) δ_H ($CDCl_3$) 6.24 (1H, d, J = 4.5 Hz), 5.38 (1H, dd, J = 8.7 and 4.2 Hz), 4.76–4.68 (4H, complex m), 4.56 (1H, broad s), 4.25 (1H, m), 4.15 (1H, dd, J = 9.0 and 3.9 Hz), 3.39 (3H, s), 3.37 (3H, s), 2.87 (1H, broad s), 2.11 (3H, s).

^{13}C NMR (75 MHz) δ_C ($CDCl_3$) 170.2, 130.4, 125.9, 96.8, 96.2, 71.8, 71.4, 70.6, 70.2, 55.8, 55.6, 20.9.

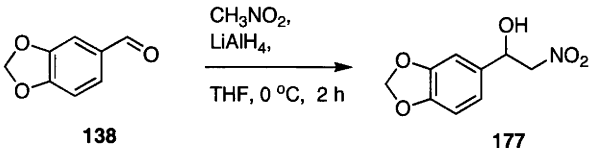
IR (NaCl) ν_{max} 3436, 2896, 1746, 1373, 1235, 1151, 1101, 1041, 917 cm^{-1}.

MS (EI, 70 eV) *m/z* 356 and 354 ($M^{+\bullet}$, both <1%), 265 and 263 (44 and 40), 207 (72), 189 and 187 (61 and 55), 159 (22), 109 (22), 81 (23), 45 (94), 43 (100)

HRMS Found: $M^{+\bullet}$, 354.0309. $C_{12}H_{19}{}^{79}BrO_7$ requires $M^{+\bullet}$, 354.0314.

Specific Rotation $[\alpha]_D^{20}$ –21.8 (*c* 0.11, $CHCl_3$).

1–(Benzo[*d*][1,3]dioxol–6–yl)–2–nitroethanol (177)



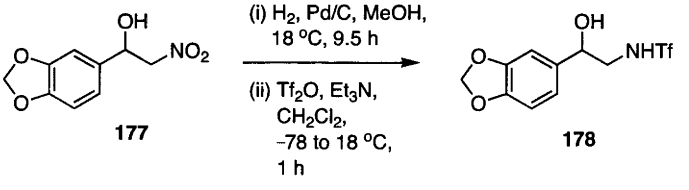
138 177

A magnetically stirred solution of piperonal **138** (3.0 g, 20.0 mmol) and nitromethane (5.4 mL, 100.0 mmol) in anhydrous THF (30 mL) was cooled to 0 °C and treated with $LiAlH_4$ (2 mL of a 1 M solution in THF, 2.0 mmol). After 2 h, the reaction mixture was quenched with phosphate buffer (pH ~ 7, 50 mL) [CAUTION: Exotherm] and extracted with CH_2Cl_2 (2 x 100 mL). The combined organic fractions were dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford *title compound* ***177*** (2.94 g, 70%) as a white, crystalline solid (R_f = 0.2, 1:4 v/v ethyl acetate–hexane). This material proved to be somewhat unstable and was therefore subjected, without purification, to the next step of the reaction sequence.

^{1}H NMR (300 MHz) δ_H ($CDCl_3$) 7.02 (1H, m), 6.97 (1H, m), 6.84 (1H, d, J = 8.1 Hz), 6.00 (2H, s), 5.39 (1H, m), 4.74–4.56 (2H, complex m) (one signal due to OH obscured or overlapping).

^{13}C NMR (75 MHz) δ_C ($CDCl_3$) 148.7, 148.3, 135.1, 120.5, 108.8, 107.3, 102.1, 82.6, 71.3.

1–(Benzo[*d*][1,3]dioxol–6–yl)–2–(triflylamino)ethanol (178)



177 178

A magnetically stirred solution of nitroalcohol **177** (2.93 g, 13.90 mmol) in MeOH (90 mL) maintained at 18 °C was treated with Pd/C (1.48 g of 10% mixture, 1.39 mmol) and hydrogen (1 atm). After 9.5 h, the ensuing mixture was filtered through a pad of Celite® and the filtrate was concentrated under reduced pressure to give a yellow oil containing the amino alcohol derivative of compound **177**. This material, dissolved in anhydrous CH_2Cl_2 (25 mL) and cooled to –78 °C, was treated (dropwise) with triethylamine (1.38 mL, 13.25 mmol) and Tf_2O (1.86 mL, 11.05 mmol). After 10 min, the reaction mixture was allowed to warm to 18 °C for 1 h, then treated with sodium hydrogen carbonate (100 mL of a saturated aqueous solution) and extracted with CH_2Cl_2 (2 x 100 mL). The combined organic fractions were dried ($MgSO_4$),

filtered and concentrated under reduced pressure to give a yellow residue that was subjected to flash chromatography (silica, 1:4 v/v ethyl acetate–hexane elution). Concentration of appropriate fractions (R_f = 0.6) afforded the *title compound* ***178*** (1.43 g, 33%) as a white, crystalline solid.

mp = 90–92 °C

^{1}H NMR (300 MHz) δ_H ($CDCl_3$) 6.81 (3H, m), 5.96 (2H, s), 4.77 (1H, dd, J = 9.0 and 3.6 Hz), 3.46 (1H, m), 3.31 (1H, m) (two signals due to OH and NH obscured or overlapping).

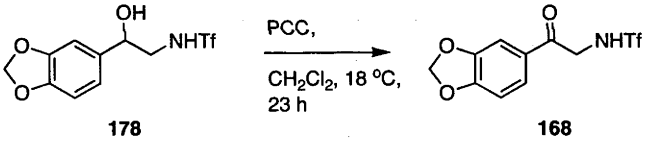
^{13}C NMR (75 MHz) δ_C ($CDCl_3$) 148.0, 147.8, 130.6, 119.4, 108.5, 106.2, 101.3, 73.3, 65.8, 50.5.

IR (NaCl) ν_{max} 3359, 3303, 2906, 1505, 1490, 1444, 1373, 1232, 1193, 1147, 1039 cm^{-1}.

MS (EI, 70 eV) *m/z* 313 ($M^{+\bullet}$, 62%), 226 (4), 185 (8), 164 (19), 151 (99), 123 (35), 93 (100), 77 (18), 69 (39), 65 (82), 51 (13), 39 (43).

HRMS Found: $M^{+\bullet}$, 313.0234. $C_{10}H_{10}F_3NO_5S$ requires $M^{+\bullet}$, 313.0232.

1–(Benzo[*d*][1,3]dioxol–6–yl)–2–(triflylamino)ethanone (168)



178 **168**

A magnetically stirred solution of keto–amide **178** (1.43 g, 4.56 mmol) in anhydrous CH_2Cl_2 (25 mL) maintained at 18 °C was treated with PCC (1.48 g, 6.80 mmol). After 23 h, the ensuing mixture was filtered through a pad of Celite® and the filtrate was concentrated under reduced pressure to give a brown solid. Subjection of this material to flash chromatography (silica, 1:4 v/v ethyl acetate–hexane elution) and concentration of appropriate fractions (R_f = 0.3) provided the *title compound* ***168*** (1.05 g, 74%) as a white, crystalline solid.

mp = 156–158 °C.

^{1}H NMR (300 MHz) δ_H [$(CD_3)_2CO$] 7.46 (1H, d, J = 8.4 Hz), 7.23 (1H, s), 6.86 (1H, d, J = 8.4 Hz), 6.02 (2H, s), 4.75 (2H, d, J = 4.8 Hz), 2.69 (1H, broad s) (one signal due to NH obscured or overlapping).

^{13}C NMR (75 MHz) δ_C [$(CD_3)_2CO$] 191.1, 153.5, 149.3, 129.7, 125.4, 120.7, 108.9, 108.1, 103.2, 50.4.

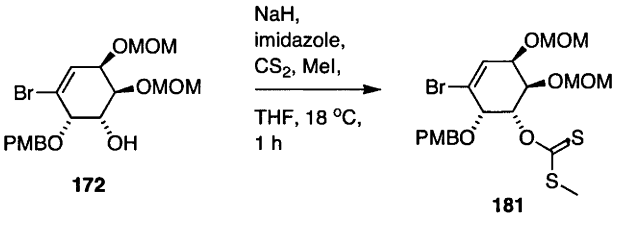
IR (NaCl) ν_{max} 3278, 2978, 2916, 1681, 1605,1506, 1444, 1397, 1370, 1328, 1264, 1231, 1181, 1008, 934, 893 cm^{-1}.

MS (EI, 70 eV) *m/z* 311 ($M^{+\bullet}$, 53%), 242 (32), 185 (11), 149 (100), 121 (90), 91 (30), 81 (23), 69 (77), 43 (52).

HRMS Found $M^{+\bullet}$, 311.0073. $C_{10}H_8F_3NO_5S$ requires $M^{+\bullet}$, 311.0075.

Elemental Analysis Found: C, 38.70; H, 2.77; N, 4.51. $C_{10}H_{10}F_3NO_5S$ requires C, 38.59; H, 2.59; N, 4.50.

O-(1*S*,2*S*,5*R*,6*R*)-2-(4-Methoxybenzyloxy)-3-bromo-5,6-bis(methoxymethoxy)cyclohex-3-enyl *S*-methyl carbonodithioate (181)



A magnetically stirred solution of conduritol **172** (2.0 g, 4.62 mmol) and imidazole (104.0 mg, 1.52 mmol) in anhydrous THF (75 mL) maintained at 18 °C was treated with sodium hydride (280.0 mg of a 60% mixture with paraffin oil, 6.92 mmol). After 20 min, the ensuing mixture was treated with carbon disulfide (CS_2) (840 μL, 13.86 mmol) and following 30 min, iodomethane (MeI) (75 μL, 8.31 mmol) was introduced (dropwise). The resulting reaction mixture was stirred for 15 mins at which it was then treated with water (300 mL) and extracted with CH_2Cl_2 (2 x 300 mL). The combined organic fractions were dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a yellow residue. Subjection of this material to flash chromatography (silica, 3:7 v/v ethyl acetate–hexane elution) and concentration of appropriate fractions (R_f = 0.5) afforded the *title compound* ***181*** (1.74 g, 73%) as a clear, light-yellow oil.

^{1}H NMR (300 MHz) δ_H ($CDCl_3$) 7.32 (2H, d, *J* = 8.6 Hz), 6.86 (2H, d, *J* = 8.6 Hz), 6.25 (1H, d, *J* = 5.1 Hz), 6.19 (1H, dd, *J* = 9.9 and 4.2 Hz), 4.77 (2H, m), 4.72 (2H, m), 4.66–4.57 (3H, m), 4.38 (1H, dd, *J* = 9.9 and 4.2 Hz), 4.26 (1H, m), 3.79 (3H, s), 3.39 (3H, s), 3.38 (3H, s), 2.58 (3H, s).

^{13}C NMR (75 MHz) δ_C ($CDCl_3$) 215.6, 159.3, 130.4, 130.0, 129.5, 124.6, 113.6, 96.8, 96.5, 78.7, 77.1, 74.9, 71.9, 71.1, 55.8, 55.5, 55.1, 19.2.

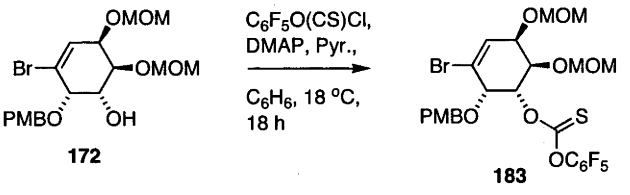
IR (NaCl) ν_{max} 2952, 2895, 1612, 1514, 1250, 1212, 1151, 1099, 1046, 911 cm^{-1}.

MS (ESI, 70 eV) *m/z* 547 and 545 [(M + Na)$^+$, 100 and 92%], 159 (43), 121 (52), 91 (90), 69 (84).

HRMS Found: (M + Na)$^+$, 545.0277. $C_{20}H_{27}{}^{79}BrNaO_7S_2$ requires (M + Na)$^+$, 455.0279.

Specific Rotation $[\alpha]_D^{20}$ –140.5 (*c* 2.74, $CHCl_3$).

O–(1*S*,2*S*,5*R*,6*R*)–2–(4–Methoxybenzyloxy)–3–bromo–5,6–bis(methoxymethoxy)cyclohex–3–enyl *O*–perfluorophenyl carbonothioate (183)



A magnetically stirred solution of conduritol **172** (150.0 mg, 0.34 mmol), pyridine (20 μL, 0.23 mmol) and DMAP (8.5 mg, 0.07 mmol) in anhydrous benzene (1 mL) maintained at 18 °C was treated with pentafluorophenyl thionochloroformate ($C_6F_5O(CS)Cl$) (280 μL, 0.41 mmol). After 18 h, when TLC analysis indicated that all starting material had been consumed, the reaction mixture was treated with water (40 mL) and extracted with CH_2Cl_2 (2 x 40 mL). The combined organic fractions were washed with sodium hydrogen carbonate (1 x 40 mL of a saturated aqueous solution) and brine (1 x 40 mL) and then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a yellow residue. Subjection of this material to flash chromatography (silica, 1:9 → 1:4 v/v ethyl acetate–hexane gradient elution) and concentration of appropriate fractions (R_f = 0.3, 1:4 ethyl acetate–hexane) afforded the *title compound* ***183*** (226.5 mg, 99%) as a clear, viscous oil.

^{1}H NMR (300 MHz) δ_H ($CDCl_3$) 7.37 (2H, d, *J* = 8.7 Hz), 6.89 (2H, d, *J* = 8.7 Hz), 6.31 (1H, d, *J* = 5.4 Hz), 5.82 (1H, dd, *J* = 10.5 and 3.9 Hz), 4.84–4.68 (7H, complex m), 4.44 (1H, dd, *J* = 10.2 and 4.2 Hz), 4.30 (1H, m), 3.80 (3H, s), 3.44 (3H, s), 3.41 (3H, s).

^{13}C NMR (75 MHz) δ_C ($CDCl_3$) 191.4, 159.6, 130.8, 130.0, 129.4, 124.2, 113.8, 96.9, 96.7, 82.3, 76.9, 75.5, 71.9, 71.1, 55.8, 55.6, 55.2 (six signals not observed).

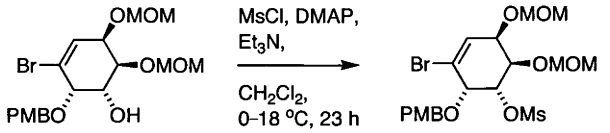
IR (NaCl) ν_{max} 2936, 2897, 2839, 1613, 1523, 1370, 1304, 1250, 1174, 1152, 1101, 1048, 997, 917 cm^{-1}.

MS (EI, 70 eV) *m/z* 660 and 658 ($M^{+\bullet}$, both < 1%), 627 and 625 (both 2), 615 and 613 (5 and 4), 519, and 517 (both 3), 477 and 475 (both 4), 445 and 443 (7 and 8), 331 (71), 280 and 278 (both 9), 181 (17), 137 (28), 121 (100), 109 (22), 77 (20).

HRMS Found: $M^{+\bullet}$, 658.0288. $C_{25}H_{24}{}^{79}BrF_5O_8S$ requires $M^{+\bullet}$, 658.0295.

Specific Rotation $[\alpha]_D^{20}$ –115.7 (*c* 0.14 $CHCl_3$).

(1*S*,2*S*,5*R*,6*R*)–2–(4–Methoxybenzyloxy)–3–bromo–5,6–bis(methoxymethoxy)cyclohex–3–enyl methanesulfonate (185)



172 **185**

A magnetically stirred solution of conduritol **172** (250.0 mg, 0.58 mmol), triethylamine (140 μL, 1.33 mmol) and DMAP (40.0 mg, 0.33 mmol) in anhydrous CH_2Cl_2 (3 mL) was cooled to 0 °C then treated, dropwise, with methanesulfonyl chloride (MsCl) (70 μL, 0.87 mmol) and allowed to warm to 18 °C. After 23 h, point TLC analysis indicated that all starting material had been consumed. Consequently, the reaction mixture was treated with sodium hydrogen carbonate (50 mL of a saturated aqueous solution) and the resulting mixture was extracted with CH_2Cl_2 (2 x 30 mL). The combined organic fractions were dried ($MgSO_4$), filtered and concentrated under reduced pressure to give yellow residue that was subjected to flash chromatography (silica, 2:3 v/v ethyl acetate–hexane elution). Concentration of appropriate fractions (R_f = 0.4) afforded the *title compound* ***185*** (225.0 mg, 76%) as a clear, light–yellow oil.

^{1}H NMR (300 MHz) δ_H ($CDCl_3$) 7.36 (2H, d, *J* = 8.7 Hz), 6.86 (2H, d, *J* = 8.7 Hz), 6.21 (1H, d, *J* = 4.8 Hz), 5.10 (1H, dd, *J* = 9.3 and 3.9 Hz), 4.86–4.67 (6H, complex m), 4.43 (1H, d, *J* = 4.2 Hz), 4.26 (1H, m), 4.20 (1H, dd, *J* = 9.3 and 3.9 Hz), 3.78 (3H, s), 3.36 (6H, m), 3.05 (3H, s).

^{13}C NMR (75 MHz) δ_C ($CDCl_3$) 159.4, 130.5, 130.2, 129.3, 123.9, 113.6, 97.0, 96.5, 78.4, 77.6, 75.5, 72.2, 71.9, 55.8, 55.5, 55.1, 38.0.

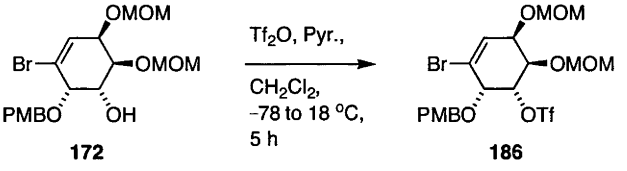
IR (NaCl) ν_{max} 2938, 2897, 1613, 1515, 1359, 1250, 1177, 1099, 1047, 966, 884 cm^{-1}.

MS (EI, 70 eV) *m/z* 512 and 510 ($M^{+\bullet}$, 13 and 12%), 467 and 465 (both 3), 278 and 280 (both 8), 181 (16), 137 (32), 121 (100), 109 (14), 91 (8), 77 (18), 45 (88).

HRMS Found: $M^{+\bullet}$, 510.0557. $C_{19}H_{27}{}^{79}BrO_9S$ requires $M^{+\bullet}$, 510.0559.

Specific Rotation $[\alpha]_D^{20}$ –103.1 (*c* 0.85, $CHCl_3$).

(1*S*,2*S*,5*R*,6*R*)–2–(4–Methoxybenzyloxy)–3–bromo–5,6–bis(methoxymethoxy)cyclohex–3–enyl trifluoromethanesulfonate (186)



A magnetically stirred solution of conduritol **172** (210.0 mg, 0.48 mmol) and pyridine (90 μL, 1.07 mmol) in anhydrous CH_2Cl_2 (4 mL) was cooled to –78 °C and treated (dropwise) with Tf_2O (100 μL, 0.58 mmol). After 1 h, the reaction was allowed to warm to 18 °C for 4 h and then treated with HCl (60 mL of a 2 M aqueous solution). The resulting mixture was extracted with CH_2Cl_2 (3 x 20 mL) and the combined organic fractions were washed with sodium hydrogen carbonate (60 mL of saturated aqueous solution) then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give an opaque, colourless oil. Subjection of this material to flash chromatography (silica, 2:3 v/v ethyl acetate–hexane elution) and concentration of appropriate fractions (R_f = 0.7) afforded the *title compound* ***186*** (211 mg, 77%) as a clear, colourless oil.

^{1}H NMR (300 MHz) δ_H ($CDCl_3$) 7.35 (2H, d, J = 8.7 Hz), 6.89 (2H, d, J = 8.7 Hz), 6.27 (1H, d, J = 5.1 Hz), 5.36 (1H, m), 4.82–4.68 (6H, complex m), 4.45 (1H, d, J = 4.2 Hz), 4.26 (2H, m), 3.80 (3H, s), 3.78 (3H, s), 3.37 (3H, s).

^{13}C NMR (75 MHz) δ_C ($CDCl_3$) 159.6, 131.0, 130.1, 128.9, 123.1, 118.4, 113.7, 97.0, 96.9, 83.6, 78.8, 75.8, 72.2, 70.8, 55.9, 55.6, 55.2.

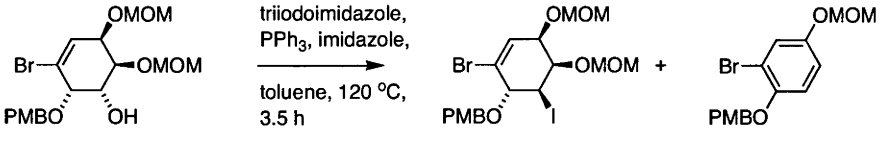
IR (NaCl) ν_{max} 2955, 1613, 1515, 1416, 1247, 1215, 1148, 1048, 909, 734 cm^{-1}.

MS (EI, 70 eV) *m/z* 566 and 564 ($M^{+\bullet}$, both 3%), 136 (3), 121 (100), 77 (3), 45 (44).

HRMS Found: $M^{+\bullet}$, 564.0311. $C_{19}H_{24}{}^{79}BrF_3O_9S$ requires $M^{+\bullet}$, 564. 0277.

Specific Rotation $[\alpha]_D^{20}$ –159.9 (*c* 0.17, $CHCl_3$).

1-(((1*R*,4*R*,5*R*,6*R*)-2-Bromo-6-iodo-4,5-bis(methoxymethoxy)cyclohex-2-enyloxy)methyl)-4-methoxybenzene (184) and 1-(4-methoxybenzyloxy)-2-bromo-4-(methoxymethoxy)benzene (187)



172 **184** **187**

A magnetically stirred solution of alcohol **172** (2.17 g, 5.01 mmol) in anhydrous toluene (250 mL) was heated to 120 °C then treated with PPh_3 (6.60 g, 25.19 mmol), triiodoimidazole (2.24 g, 5.02 mmol) and imidazole (0.41 g, 6.01 mmol). After 3.5 h, when TLC analysis indicated that all the starting material had been consumed, the reaction mixture was cooled to 18 °C and treated with sodium metabisulfite (NaS_2O_5) (200 mL of 20% w/v aqueous solution) for a further 1 h. The separated aqueous phase was extracted with toluene (2 × 200 mL) and the combined organic fractions were then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a yellow residue. Subjection of this material to flash chromatography (silica, neat hexane → 3:7 v/v ethyl acetate–hexane gradient elution) afforded two fractions, **A** and **B**. Concentration of fraction **A** (R_f = 0.4 in 3:7 v/v ethyl acetate–hexane) afforded the *title compound **184*** (2.20 g, 81%) as a white, crystalline solid.

mp = 52–54 °C

^{1}H NMR (300 MHz) δ_H ($CDCl_3$) 7.42 (2H, d, J = 8.7 Hz), 6.89 (2H, d, J = 8.7 Hz), 6.11 (1H, d, J = 1.8 Hz), 4.88 (2H, s), 4.85 (1H, m), 4.72 (2H, d, J = 9.3 Hz), 4.63 (1H, d, J = 6.9 Hz), 4.43 (1H, m), 4.32 (3H, m), 3.80 (3H, s), 3.54 (3H, s), 3.39 (3H, s).

^{13}C NMR (75 MHz) δ_C ($CDCl_3$) 159.5, 130.8, 130.0, 129.4, 122.7, 113.8, 97.6, 95.2, 81.2, 78.3, 74.3, 73.4, 56.8, 55.7, 55.2, 28.5.

IR (NaCl) ν_{max} 2950, 2895, 1613, 1514, 1465, 1250, 1152, 1084, 1048, 1032, 923, 824 cm^{-1}.

MS (EI, 70 eV) *m/z* 544 and 542 ($M^{+\bullet}$, both 1%), 311 and 309 (both 1), 135 (3), 121 (100), 77 (4), 45 (47).

HRMS Found: $M^{+\bullet}$, 543.9798. $C_{18}H_{24}{}^{81}Br^{127}IO_6$ requires $M^{+\bullet}$, 543.9781.

Elemental Analysis Found: C, 40.21; H, 4.00. $C_{18}H_{24}BrIO_6$ requires C, 39.80; H, 4.45.

Specific Rotation $[\alpha]_D^{20}$ –80.1 (*c* 0.25, $CHCl_3$).

Concentration of fraction **B** (R_f = 0.5 in 3:7 v/v ethyl acetate–hexane) provided *title compound **187*** (110 mg, 6%) as a clear, colourless oil.

^{1}H NMR (300 MHz) δ_H ($CDCl_3$) 7.40 (2H, d, J = 8.4 Hz), 7.34 (1H, d, J = 3.0 Hz), 6.93 (2H, m), 6.89 (2H, d, J = 8.4 Hz), 5.09 (2H, s), 5.01 (2H, s), 3.80 (3H, s), 3.47 (3H, s).

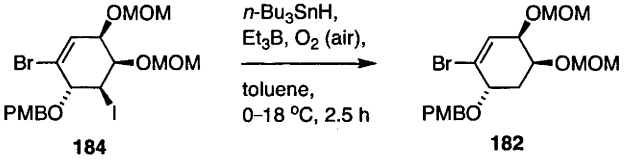
^{13}C NMR (75 MHz) δ_C ($CDCl_3$) 159.1, 151.6, 150.1, 132.1, 128.7, 128.5, 121.5, 116.0, 115.0, 113.7, 94.9, 71.2, 55.7, 55.0.

IR (NaCl) ν_{max} 2955, 2939, 2904, 2835, 1613, 1587, 1514, 1489, 1465, 1272, 1218, 1192, 1174, 1153, 1080, 1038, 1001, 922, 824 cm^{-1}.

MS (ESI) *m/z* 377 and 375 [(M + Na)$^+$, both 9%], 251 (5), 121 (100), 91 (6).

HRMS Found: (M + Na)$^+$, 377.0156. $C_{16}H_{17}{}^{81}BrO_4$ requires (M + Na)$^+$, 377.0187.

1–(((1*S*,4*R*,5*S*)–2–Bromo–4,5–bis(methoxymethoxy)cyclohex–2–enyloxy)methyl)–4–methoxybenzene (182)



A magnetically stirred solution of iodide **184** (10.69 g, 19.7 mmol), Et_3B (8.4 mL of 1 M solution in hexanes, 8.4 mmol) and *n*–Bu_3SnH (6.5 mL, 23.6 mmol) in anhydrous toluene (25 mL) was cooled to 0 °C then treated with oxygen (air) for 10 mins. The ensuing mixture was then warmed to 18 °C and after 2.5 h at this temperature, and at which point TLC analysis indicated that all the starting material had been consumed, it was concentrated under reduced pressure to give a yellow oil. Subjection of this material to flash chromatography (silica, neat hexane → 3:7 v/v ethyl acetate–hexane gradient elution) and concentration of appropriate fractions (R_f = 0.3, 3:7 v/v ethyl acetate–hexane) then afforded the *title compound* ***182*** (6.94 g, 85%) as a white, crystalline solid.

mp = 45–47 °C

^{1}H NMR (300 MHz) δ_H ($CDCl_3$) 7.29 (2H, d, J = 8.4 Hz), 6.84 (2H, d, J = 8.4 Hz), 6.21 (1H, d, J = 4.5 Hz), 4.76–4.52 (6H, complex m), 4.08 (3H, m), 3.75 (3H, s), 3.34 (3H, s), 3.33 (3H, s), 2.26 (1H, m), 1.95 (1H, m).

^{13}C NMR (75 MHz) δ_C ($CDCl_3$) 159.6, 131.4, 130.1, 129.9, 127.8, 114.0, 96.3, 95.9, 77.1, 72.4, 72.2, 71.2, 55.7(3), 55.6(7), 55.4, 31.4.

IR (NaCl) ν_{max} 2936, 2889, 2837, 1612, 1514, 1465, 1441, 1249, 1150, 1047, 917, 822 cm^{-1}.

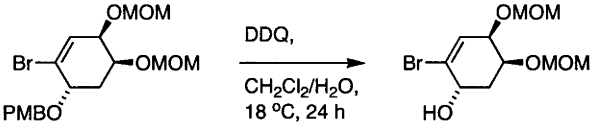
MS (EI, 70 eV) *m/z* 418 and 416 ($M^{+\bullet}$, both 4%), 330 and 328 (both 22), 249 (65), 181 (24), 173 (32), 137 and 135 (46 and 50), 122 (100), 121 (82), 109 (35), 78 (52), 77 (65), 65 (36), 45 (82).

HRMS Found: $M^{+\bullet}$, 416.0833. $C_{18}H_{25}{}^{79}BrO_6$ requires $M^{+\bullet}$, 416.0834.

Elemental Analysis Found: C, 51.84; H, 5.98. $C_{18}H_{25}{}^{79}BrO_6$ requires C, 5.81; H, 6.04.

Specific Rotation $[\alpha]_D^{20}$ –147.5 (*c* 0.08 $CHCl_3$).

(1*S*,4*R*,5*S*)–2–Bromo–4,5–bis(methoxymethoxy)cyclohex–2–enol (180)



182 **180**

A magnetically stirred solution of bromide **182** (2.93 g, 7.02 mmol) in CH_2Cl_2–water (140 mL of a 5:2 v/v mixture) maintained at 18 °C was treated with DDQ (2.40 g, 10.56 mmol). After 24 h, when TLC analysis indicated that all of the starting material had been consumed, the reaction mixture was treated with water (200 mL) and extracted with CH_2Cl_2 (3 × 200 mL). The combined organic fractions were washed with brine (1 × 200 mL) and then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a brown residue. Subjection of this material to flash chromatography (silica, 2:3 v/v ethyl acetate–hexane elution) and concentration of appropriate fractions (R_f = 0.5) afforded the *title compound* ***180*** (2.01 g, 96%) as a clear, colourless oil.

^{1}H NMR (300 MHz) δ_H ($CDCl_3$) 6.08 (1H, d, *J* = 4.2 Hz), 4.69–4.56 (4H, complex m), 4.26 (1H, m), 4.08–3.98 (2H, complex m), 3.28 (6H, s), 2.31 (1H, m), 1.77 (1H, m) (signal due to OH proton not observed).

^{13}C NMR (75 MHz) δ_C ($CDCl_3$) 129.7, 129.5, 95.5, 95.1, 72.0, 70.5, 69.3, 55.2(3), 55.1(7), 33.6.

IR (NaCl) ν_{max} 3437 (broad), 2936, 2893, 1642, 1466, 1442, 1377, 1214, 1151, 1109, 1045, 911, 733 cm^{-1}.

MS (EI, 70 eV) *m/z* 254 and 252 $(M - CH_3OCH_2\bullet)^+$, both 10%), 210 and 208 (both 80), 191 and 189 (both 40), 175 and 173 (both 21), 129 (13), 95 (29), 94 (13), 65 (19), 55 (18), 45 (100), 39 (22).

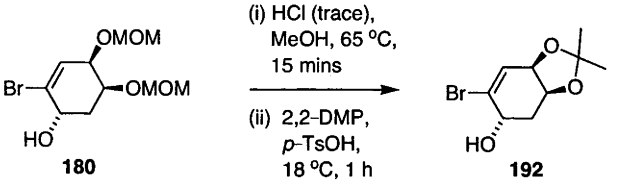
HRMS Found: $(M - CH_3OCH_2\bullet)^+$, 252.0009. $C_{10}H_{17}{}^{79}BrO_5$ requires $(M - CH_3OCH_2\bullet)^+$,

251.9997.

Elemental Analysis Found: C, 40.50; H, 5.83; Br, 27.11. $C_{10}H_{17}BrO_5$ requires C. 40.42; H, 5.77; Br, 26.89.

Specific Rotation $[\alpha]_D^{20}$ –9.0 (*c* 0.45, $CHCl_3$).

(3a*S*,5*S*,7a*R*)–6–Bromo–3a,4,5,7a–tetrahydro–2,2–dimethylbenzo[*d*][1,3]dioxol–5–ol (192)



A magnetically stirred solution of alcohol **180** (315.0 mg, 1.06 mmol) in MeOH (10 mL) was treated with concentrated HCl (trace) and heated at 65 °C. After 15 mins, ensuing mixture was cooled to 18 °C then treated with sodium hydrogen carbonate (50 mL of a saturated aqueous solution) and extracted with ethyl acetate (3 x 50 mL). The combined organic fractions were dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a white residue containing the triol derivative of compound **180**. This material was dissolved in 2,2–DMP (20 mL) and treated with *p*–TsOH (31.0 mg, 0.18 mmol) then stirred for 1 h at 18 °C. Triethylamine (1 mL) was introduced and the ensuing mixture was concentrated under reduced pressure to give yellow residue. Subjection of this material to flash chromatography (silica, 3:7 v/v ethyl acetate–hexane elution) and concentration of appropriate fractions (R_f = 0.3) afforded the *title compound **192*** (213.0 mg, 81%) as a white, crystalline solid.

mp = 133–134 °C

^{1}H NMR (300 MHz) δ_H [$(CD_3)_2CO$] 6.02 (1H, m), 4.60 (1H, broad d, J = 5.4 Hz), 4.48 (2H, complex m), 4.27 (1H, m), 2.43 (1H, m), 1.87 (1H, m). 1.30 (3H, s), 1.29 (3H, s).

^{13}C NMR (75 MHz) δ_C [$(CD_3)_2CO$] 131.7, 129.2, 108.8, 73.4, 72.5, 65.9, 35.1, 27.5, 25.9.

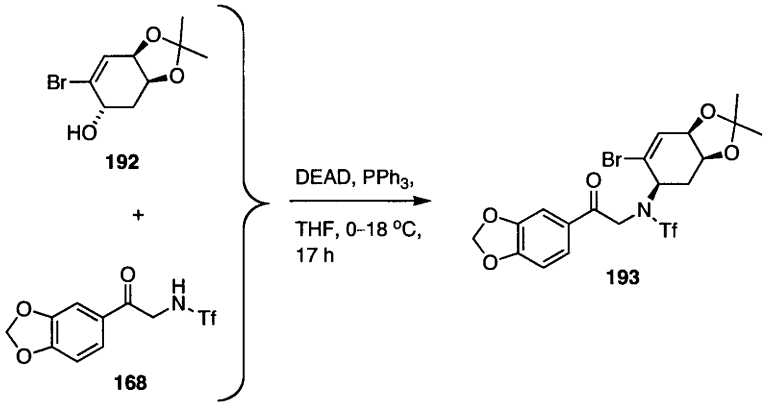
IR (NaCl) ν_{max} 3467, 2990, 2933, 1644, 1382, 1373, 1226, 1066, 907 cm^{-1}.

MS (EI, 70 eV) *m/z* 250 and 248 ($M^{+\bullet}$, both 1%), 235 and 233 (both 64), 192 and 190 (both 19), 175 and 173 (both 83), 149 and 147 (both 38), 111 (36), 94 (90), 77 (23), 65 (42), 59 (53), 55 (57), 43 (100).

HRMS Found: $M^{+\bullet}$, 248.0046. $C_9H_{13}{}^{79}BrO_3$ requires $M^{+\bullet}$, 248.0048.

Specific Rotation $[\alpha]_D^{20}$ +57.6 (*c* 0.80, $CHCl_3$).

2-(*N*-((3a*S*,5*R*,7a*R*)-6-Bromo-3a,4,5,7a-tetrahydro-2,2-dimethylbenzo[*d*][1,3]dioxol-5-yl)-*N*-triflylamino)-1-(benzo[*d*][1,3]dioxol-6-yl)ethanone (193)



A magnetically stirred solution of PPh_3 (98.0 mg, 0.37 mmol) and DEAD (51 μL, 0.32 mmol) in anhydrous THF (5 mL) was cooled to 0 °C then treated with alcohol **192** (58.0 mg, 0.23 mmol) and keto–amide **168** (87.0 mg, 0.28 mmol) and allowed to warm to 18 °C. After 17 h, the reaction mixture was concentrated under reduced pressure to give viscous, yellow oil. Subjection of this material to flash chromatography (silica, 3:7 v/v ethyl acetate–hexane elution) and concentration of appropriate fractions (R_f = 0.3) afforded the *title compound **193*** (80.0 mg, 63%) as an opaque, viscous oil.

^{1}H NMR (300 MHz) δ_H ($CDCl_3$) 7.45 (1H, d, *J* = 8.3 Hz), 7.37 (1H, m), 6.84 (1H, d, *J* = 8.3 Hz), 6.38 (1H, s), 6.05 (2H, m), 4.42 (1H, s), 4.36 (1H, m), 4.22 (1H, s), 2.38 (1H, s), 1.25 (3H, s), 1.11 (3H, s) (four signals obscured or overlapping).

^{13}C NMR (75 MHz) δ_C ($CDCl_3$) 189.7, 152.1, 148.3, 132.0, 123.9, 121.4, 110.1, 109.6, 107.9, 107.7, 101.9, 72.5, 69.7, 57.8, 52.1, 27.6, 25.9, 21.9 (one signal obscured or overlapping).

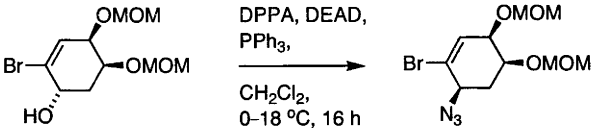
IR (NaCl) ν_{max} 2988, 1704, 1448, 1392, 1248, 1034, 961 cm^{-1}.

MS (EI, 70 eV) *m/z* 543 and 541 ($M^{+\bullet}$, both < 1%), 497 (2), 462 (18), 352 and 350 (both 2), 335 and 333 (both 1), 149 (100), 121 (10), 65 (14), 43 (17).

HRMS Found: $M^{+\bullet}$, 541.0029. $C_{19}H_{19}{}^{79}BrF_3NO_7S$ requires $M^{+\bullet}$, 541.0018.

7.2.3. Chapter Four: Attempted Preparation of 3–Arylhexahydroindoles *via Approach C*

(3*R*,4*S*,6*R*)–6–Azido–1–bromo–3,4–bis(methoxymethoxy)cyclohex–1–ene (207)



180 **207**

A magnetically stirred solution of alcohol **180** (1.64 g, 5.52 mmol) and PPh_3 (2.31 g, 8.82 mmol) in anhydrous CH_2Cl_2 (25 mL) was cooled to 0 °C then treated (dropwise) with DEAD (1.40 mL, 8.84 mmol) and DPPA (1.92 mL, 8.84 mmol). The ensuing mixture was allowed to warm to 18 °C. After 16 h at this temperature, the reaction mixture was concentrated under reduced pressure to give viscous, orange oil. Subjection of this material to flash chromatography (silica, 3:7 v/v ethyl acetate–hexane elution) and concentration of appropriate fractions (R_f = 0.5) afforded the *title compound* ***207*** (1.65 g, 93%) as a clear, colourless oil.

^{1}H NMR (300 MHz) δ_H ($CDCl_3$) 6.34 (1H, dd, J = 5.4, 1.2 Hz), 4.76–4.64 (4H, complex m), 4.06 (1H, m), 3.89 (1H, t, J = 7.2 Hz), 3.80 (1H, dt, J = 9.9, 3.6 Hz), 3.34 (3H, s), 3.33 (3H, s), 2.30–2.12 (2H, complex m).

^{13}C NMR (75 MHz) δ_C ($CDCl_3$) 132.3, 125.8, 95.9, 95.1, 71.6, 70.0, 61.1, 55.5(3), 55.4(5), 30.8.

IR (NaCl) ν_{max} 2934, 2893, 2103, 1730, 1635, 1215, 1150, 1110, 1046, 910, 730 cm^{-1}.

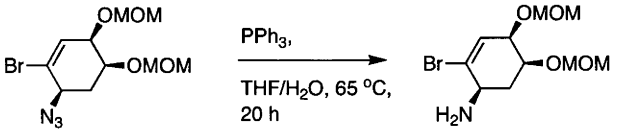
MS (EI, 70 eV) *m/z* 236 and 234 [$(M - C_4H_7O_2\bullet)^+$, both 56%], 207 and 205 (28 and 30), 176 and 174 (56 and 62), 159 (33), 123 (75), 121 (57), 108 (53), 95 (71), 77 (70), 65 (100).

HRMS Found: $(M - C_4H_7O_2\bullet)^+$, 233.9877. $C_{10}H_{16}{}^{79}BrN_3O_4$ requires $(M - C_4H_7O_2\bullet)^+$, 233.9878.

Elemental Analysis Found: C, 37.56; H, 4.83; Br, 24.54; N, 12.78. $C_{10}H_{16}BrN_3O_4$ requires C, 37.28; H, 5.01; Br, 24.80; N, 13.04.

Specific Rotation $[\alpha]_D^{20}$ +1.2 (*c* 0.82, $CHCl_3$).

(1*R*,4*R*,5*S*)-2-Bromo-4,5-bis(methoxymethoxy)cyclohex-2-enamine (208)



207 **208**

A magnetically stirred solution azide **207** (1.63 g, 5.06 mmol) in THF–water (50 mL of a 4:1 v/v mixture) maintained at 18 °C was treated with PPh_3 then heated at 65 °C. After 20 h, when TLC analysis indicated that all the starting material had been consumed, the reaction mixture was cooled to 18 °C, diluted with water (60 mL) and extracted using diethyl ether (3 × 100 mL). The combined organic fractions were then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give light-yellow oil. Subjection of this material to flash chromatography (silica, 1:11:8 v/v MeOH–ethyl acetate–$CHCl_3$ elution) and concentration of appropriate fractions (R_f = 0.4) afforded the *title compound **208*** (1.30 g, 87%) as a clear, colourless oil.

^{1}H NMR (300 MHz) δ_H ($CDCl_3$) 6.09 (1H, d, J = 4.8 Hz), 4.74–4.62 (4H, complex m), 4.09 (1H, t, J = 3.9 Hz), 3.88 (1H, dt, J = 9.3, 3.3 Hz), 3.34 (3H, s), 3.33 (3H, s), 3.32 (1H, m), 2.16–1.99 (2H, complex m), 1.89 (2H, broad s).

^{13}C NMR (75 MHz) δ_C ($CDCl_3$) 135.1, 127.4, 95.5, 94.9, 72.0, 71.0 55.4, 55.3, 52.8, 32.8.

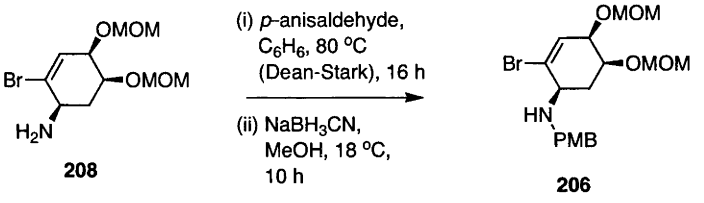
IR (NaCl) ν_{max} 3377, 3306, 3055, 2932, 2891, 1633, 1438, 1184, 1149, 1120, 1095, 1051,1034, 916, 721, 697, 542 cm^{-1}.

MS (EI, 70 eV) *m/z* 209 and 207 [$(M - C_4H_8O_2)^{+\bullet}$, both 54%], 190 and 188 (both 5), 180 and 178 (both 18), 164 and 162 (both 21), 107 (9), 93 (14), 83 (11), 45 (100).

HRMS Found: $(M - C_4H_8O_2)^{+\bullet}$, 206.9897. $C_{10}H_{18}{}^{79}BrNO_4$ requires $(M - C_4H_8O_2)^{+\bullet}$, 206.9895.

Specific Rotation $[\alpha]_D^{20}$ –38.7 (*c* 1.16, $CHCl_3$).

(1*R*,4*R*,5*S*)-*N*-(4-Methoxybenzyl)-2-bromo-4,5-bis(methoxymethoxy)cyclohex-2-enamine (206)



A magnetically stirred solution of amine **208** (1.50 g, 5.06 mmol) and *p*-anisaldehyde (0.83 g, 6.08 mmol) in anhydrous benzene (16 mL) was heated at 80 °C in an apparatus fitted with a Dean–Stark trap. After 16 h, when TLC analysis indicated that all the starting material had been consumed, the reaction mixture was cooled to 18 °C then concentrated under reduced pressure to give a yellow oil containing the imine derivative of compound **208**. A solution of this material in MeOH (10 mL) was maintained at 18 °C with stirring whilst being treated with $NaBH_3CN$ (0.49 g, 7.77 mmol). After 10 h, the reaction mixture was quenched with water (60 mL) and extracted with ethyl acetate (4 × 60 mL). The combined organic fractions were dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a yellow residue. Subjection of this material to flash chromatography (silica, 2:3 v/v ethyl acetate–hexane elution) and concentration of appropriate fractions (R_f = 0.3) afforded the *title compound* ***206*** (1.90 g, 90%) as an opaque, colourless oil.

^{1}H NMR (300 MHz) δ_H ($CDCl_3$) 7.28 (2H, d, J = 8.4 Hz), 6.84 (2H, d, J = 8.4 Hz), 6.38 (1H, d, J = 6.0 Hz), 4.80–4.68 (4H, complex m), 4.10 (1H, m), 3.81 (1H, t, J = 3.6 Hz), 3.77 (3H, s), 3.67 (2H, s), 3.47 (1H, m), 3.37 (6H, s), 2.30 (1H, m), 2.08 (1H, m), 1.99 (1H, s).

^{13}C NMR (75 MHz) δ_C ($CDCl_3$) 158.5, 134.4, 131.9, 130.2, 129.3, 113.6, 95.9, 94.8, 72.1, 71.6, 57.9, 55.3, 55.2, 55.0, 47.6, 29.4.

IR (NaCl) ν_{max} 3333, 2947, 2890, 2835, 1611, 1512, 1464, 1247, 1149, 1105, 1032, 916 cm^{-1}.

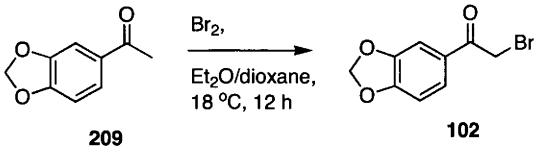
MS (EI, 70 eV) *m/z* 417 and 415 ($M^{+\bullet}$, both 9%), 416 and 414 (15 and 11), 372 and 370 (both 40), 356 and 354 (both 18), 294 (30), 284 and 282 (both 22), 269 and 267 (both 19), 212 (18), 137 (83), 136 (96), 122 (76), 121 (100), 106 (29), 91 (32), 78 (43), 77 (50), 65 (28), 45 (88).

HRMS Found: $M^{+\bullet}$, 415.0994 $C_{18}H_{26}{}^{79}BrNO_5$ requires $M^{+\bullet}$, 415.0994.

Elemental Analysis Found: C, 51.70; H, 6.25; N, 3.59; Br, 19.40. $C_{18}H_{26}BrNO_5$ requires C, 51.93; H, 6.29; N, 3.36; Br, 19.19.

Specific Rotation $[\alpha]_D^{20}$ –22.7 (*c* 2.05, $CHCl_3$).

1–(Benzo[*d*][1,3]dioxol–6–yl)–2–bromoethanone (102)



209 102

A magnetically stirred solution of ketone **209** (3.30 g, 20.1 mmol) in dioxane–diethyl ether (90 mL of a 5:4 v/v mixture) maintained at 18 °C was treated (dropwise) with bromine (1.13 mL, 22.1 mmol) and heated at 40 °C. After 20 h, the ensuing mixture was diluted with water (200 mL) and extracted with diethyl ether (3 x 100 mL). The combined organic fractions were dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a brown residue that was subjected to flash chromatography (silica, 1:4 v/v ethyl acetate–hexane elution). Concentration of appropriate fractions (R_f = 0.4) then afforded the *title compound* ***102*** (4.80 g, 98%) as a brown, crystalline solid.

mp = 90–92 °C

^{1}H NMR (300 MHz) δ_H ($CDCl_3$) 7.53 (1H, d, J = 8.1 Hz), 7.37 (1H, s), 6.82 (1H, d, J = 8.1 Hz), 6.02 (2H, s), 4.35 (2H, s).

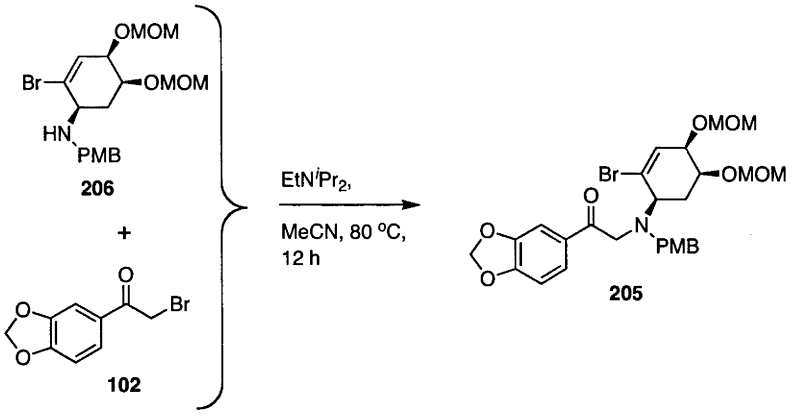
^{13}C NMR (75 MHz) δ_C ($CDCl_3$) 189.3, 152.3, 148.2, 128.3, 125.4, 108.3, 107.9, 102.0, 30.8.

IR (NaCl) ν_{max} 2953, 1681, 1601, 1502, 1487, 1441, 1393, 1362, 1272, 1241, 1200, 1106, 1036, 931, 805 cm^{-1}.

MS (EI, 70 eV) *m/z* 244 and 242 ($M^{+\bullet}$, both 14%), 200 and 198 (4 and 11), 149 (100), 135 (13), 121 (19), 91 (8), 77 (9), 65 (20), 51 (10).

HRMS Found: $M^{+\bullet}$, 241.9577. $C_9H_7{}^{79}BrO_3$ requires $M^{+\bullet}$, 241.9579.

2-(*N*-(4-Methoxybenzyl)-*N*-((1*R*,4*R*,5*S*)-2-bromo-4,5-bis(methoxymethoxy)cyclohex-2-enyl)amino)-1-(benzo[*d*][1,3]dioxol-6-yl)ethanone (205)



A magnetically stirred solution of 2°-amine **206** (168.0 mg, 0.40 mmol) and α-bromoketone **102** (147.0 mg, 0.60 mmol) in anhydrous MeCN (5 mL) was treated with EtN^{i}Pr$_2$ (140 μL, 0.81 mmol) then heated at 80 °C for 12 h, at which TLC analysis indicated that all starting material had been consumed. Consequently, the ensuing mixture was cooled to 18 °C then diluted with water (50 mL) and extracted with ethyl acetate (3 x 30 mL). The combined organic fractions were dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a brown residue. Subjection of this material to flash chromatography (silica, 3:7 v/v ethyl acetate–hexane elution) and concentration of appropriate fractions (R_f = 0.4) afforded the *title compound **205*** (138.0 mg, 59%) as a viscous, light-yellow oil.

^{1}H NMR (300 MHz) δ_H ($CDCl_3$) 7.49 (1H, dd, J = 8.1 and 1.5 Hz), 7.39 (2H, d, J = 8.6 Hz), 7.33 (1H, d, J = 1.5 Hz), 6.81 (2H, d, J = 8.6 Hz), 6.71 (1H, d, J = 8.1 Hz), 6.40 (1H, dd, J = 6.3 and 1.8 Hz), 5.94 (2H, s), 4.74–4.63 (4H, complex m), 4.03 (2H, m), 3.85 (1H, d, J = 13.2 Hz), 3.74 (3H, s), 3.65 (2H, m), 3.55 (1H, m), 3.48 (1H, d, J = 13.2 Hz), 3.34 (3H, s), 3.32 (3H, s), 2.28–2.08 (2H, complex m).

^{13}C NMR (75 MHz) δ_C ($CDCl_3$) 195.9, 158.7, 151.4, 147.6, 133.2, 131.6, 130.4, 130.3, 124.7, 113.4, 108.1, 107.4, 101.5, 95.9, 94.7, 72.2, 71.1, 61.0, 60.1, 56.4, 55.3, 55.2, 55.0, 53.2, 24.7.

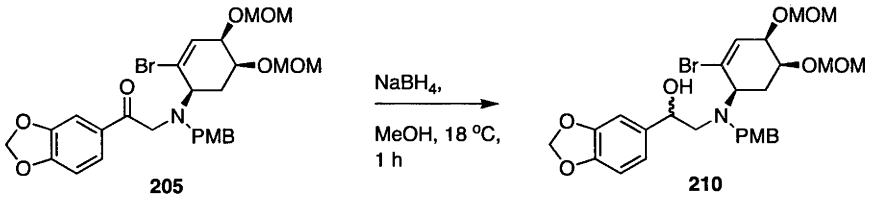
IR (NaCl) ν_{max} 2935, 2893, 1688, 1671, 1611, 1511, 1443, 1362, 1289, 1250, 1148, 1105, 1038, 917 cm^{-1}.

MS (EI, 70 eV) *m/z* 578 and 576 ($M^{+\bullet}$, both < 1%), 548 and 546 (both 2), 518 and 516 (both 4), 458 and 456 (both 15), 428 and 426 (both 72), 414 and 412 (both 10), 298 (20), 149 (48), 121 (100), 91 (15), 77 (20), 65 (19), 45 (77).

HRMS Found: $M^{+\bullet}$, 578.1386. $C_{27}H_{33}{}^{81}BrNO_8$ requires $M^{+\bullet}$, 578.1390.

Specific Rotation $[\alpha]_D^{20}$ –8.1 (*c* 1.00, $CHCl_3$).

2–(*N*–(4–Methoxybenzyl)–*N*–((1*R*,4*R*,5*S*)–2–bromo–4,5–bis(methoxymethoxy)cyclohex–2–enyl)amino)–1–(benzo[*d*][1,3]dioxol–6–yl)ethanol (210)



A magnetically stirred solution of 3°–amine **205** (560.0 mg, 0.97 mmol) in MeOH (20 mL) maintained at 18 °C was treated with $NaBH_4$ (368.0 mg, 9.68 mmol). After 1 h, when TLC analysis indicated that all starting material had been consumed, the ensuing mixture was treated with water (40 mL) and extracted with ethyl acetate (3 x 80 mL). The combined organic fractions were dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford the *title compound **210*** (530.0 mg, 94%) as a light–yellow oil. This material was used in next step of the reaction sequence without purification.

^{1}H NMR (300 MHz) δ_H [$(CD_3)_2CO$] 7.41 (2H, d, *J* = 8.6 Hz), 6.92 (2H, d, *J* = 8.6 Hz), 6.76 (3H, broad m), 6.51 (1H, m), 5.92 (2H, broad s), 4.70 (5H, broad m), 4.11 (2H, m), 3.80 (3H, s), 3.71–3.53 (3H complex m), 3.33 (3H, m), 3.28 (3H, m), 2.90–267 (1H, complex m), 2.53 (1H, m), 2.19 (2H, m) (one signal due to OH obscured or overlapping).

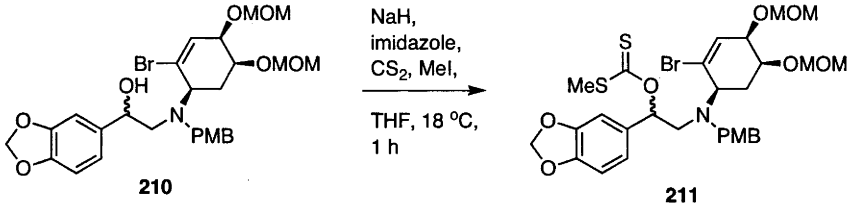
^{13}C NMR (75 MHz) δ_C [$(CD_3)_2CO$]) 159.6, 148.2, 147.3, 137.8, 134.2, 133.4, 132.7, 132.2, 130.9, 119.8, 114.4, 108.3, 107.0, 101.6, 96.9, 95.3, 73.4, 72.9, 72.2, 69.8, 58.4, 55.4, 55.3, 24.3 (one signal obscured of overlapping).

IR (NaCl) ν_{max} 3458, 3232, 2937, 2891, 1511, 1488, 1443, 1249, 1148, 1105, 1038, 917, 811 cm^{-1}.

MS (ESI, 70 eV) *m/z* 582 and 580 [$(M + H)^+$, 98 and 100%], 564 and 562 (12 and 13), 444 and 442 (both 7), 121 (41).

HRMS Found: $(M + H)^+$, 582.1510. $C_{27}H_{35}{}^{81}BrNO_8$ requires $(M + H)^+$, 582 1525.

2-(*N*-(4-Methoxybenzyl)-*O*-2-((1*R*,4*R*,5*S*)-2-bromo-4,5-bis(methoxymethoxy)cyclohex-2-enylamino)-1-(benzo[*d*][1,3]dioxol-6-yl)ethyl *S*-methyl carbonodithioate (211)



A magnetically stirred solution of alcohol **210** (114.0 mg, 0.19 mmol) and imidazole (5.0 mg, 0.06 mmol) in anhydrous THF (75 mL) maintained at 18 °C was treated with sodium hydride (12.0 mg of a 60% mixture with paraffin oil, 0.29 mmol) and stirred for 20 mins. CS_2 (35 μL, 0.59 mmol) was added and the ensuing mixture was stirred for 30 mins before iodomethane (22 μL, 0.35 mmol) was introduced (dropwise). After 15 mins, the ensuing mixture was then treated with water (40 mL) and extracted with CH_2Cl_2 (2 x 40 mL). The combined organic fractions were dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a yellow residue which was subjected to flash chromatography (silica, 1:9 → 3:7 v/v ethyl acetate–hexane gradient elution) and so providing two fractions, **A** and **B**.

Concentration fraction **A** (R_f = 0.4, 3:7 v/v ethyl acetate–hexane) afforded the *title compound **211*** (32.0 mg, 24%) as viscous, yellow oil.

^{1}H NMR (300 MHz) δ_H ($CDCl_3$) 7.26 (2H, d, J = 8.9 Hz), 6.82 (2H, d, J = 8.9 Hz), 6.67 (3H, m), 5.91 (2H, m), 4.73 (5H, broad m), 4.07 (2H, m), 3.74 (3H, s), 3.73 (3H, s), 3.43–3.35 (3H, complex m), 3.34 (3H, m), 3.19–2.86 (2H, complex m), 2.37 (3H, s).

^{13}C NMR (75 MHz) δ_C ($CDCl_3$) 189.0, 158.7, 147.6, 146.9, 133.9, 133.4, 132.6, 130.9, 130.1, 122.2, 121.6, 120.5, 113.5, 108.4, 101.0, 96.1, 94.9, 72.6, 71.3, 71.2, 55.5, 55.4, 55.2, 49.4, 29.7 (one signal obscured or overlapping).

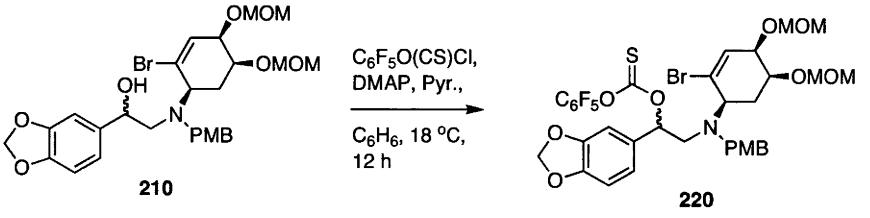
IR (NaCl) ν_{max} 2930, 2993, 1642, 1511, 1442, 1248, 1148, 1105, 1039, 869 cm^{-1}.

MS (ESI, 70 eV) *m/z* 672 and 670 [(M + H)$^+$, 100 and 92%], 656 and 654 (both 41), 625 and 623 (38 and 36), 582 and 580 (31 and 33), 552 and 550 (13 and 12), 418 and 416 (15 and 20), 291 and 289 (73 and 53), 215 and 213 (15), 102 (35).

HRMS Found: (M + H)$^+$, 672.1159. $C_{29}H_{37}{}^{81}BrNO_8S_2$ requires (M + H)$^+$, 672.1123.

Concentration fraction **B** (R_f = 0.4, 3:7 v/v ethyl acetate–hexane) provided the starting material **210** (23.0 mg, 20%) which was identical, in all respects, with authentic material.

2-(*N*-(4-Methoxybenzyl)-*O*-2-((1*R*,4*R*,5*S*)-2-bromo-4,5-bis(methoxymethoxy)cyclohex-2-enylamino)-1-(benzo[*d*][1,3]dioxol-6-yl)ethyl *O*-perfluorophenyl carbonothioate (220)



A magnetically stirred solution of alcohol **210** (150.0 mg, 0.26 mmol), pyridine (63 μL, 0.77 mmol) and DMAP (32.0 mg, 0.26 mmol) in anhydrous benzene (2 mL) maintained at 18 °C was treated with pentafluorophenyl thionochloroformate (340.0 mg, 1.29 mmol). After 12 h, when TLC analysis indicated that all starting material had been consumed, the reaction mixture was treated with water (40 mL) and extracted with CH_2Cl_2 (2 x 40 mL). The combined organic fractions were dried ($MgSO_4$), filtered and concentrated under reduced pressure to give an orange oil that was subjected to flash chromatography (silica, 1:9 → 1:4 v/v ethyl acetate–hexane gradient elution) and so providing two fractions, **A** and **B**.

Concentration fraction **A** (R_f = 0.3, 3:7 v/v ethyl acetate–hexane) afforded the *title compound* ***220*** (34.5 mg, 16.5%) as viscous, yellow oil.

^{1}H NMR (300 MHz) δ_H ($CDCl_3$) 7.29 (2H, d, J = 8.6 Hz), 6.81 (2H, d, J = 8.6 Hz), 6.66 (3H, broad m), 6.43 (1H, d, J = 6.6 Hz), 5.88 (2H, s), 4.68 (4H, m), 4.06 (1H, m), 3.76 (4H, s), 3.69–3.50 (3H, complex m), 3.35 (6H, m), 3.20–3.01 (2H, complex m), 2.28–1.80 (2H, complex m).

^{13}C NMR (75 MHz) δ_C ($CDCl_3$) 167.5, 158.7, 147.6, 147.1, 142.8, 141.1, 139.3, 137.8, 133.4, 132.6, 131.7, 129.9, 125.1, 121.5, 113.4, 107.9, 101.0, 95.9 94.8, 72.4, 71.0, 65.6, 55.2, 55.1, 54.9, 51.1, 29.5 (seven signals obscured or overlapping).

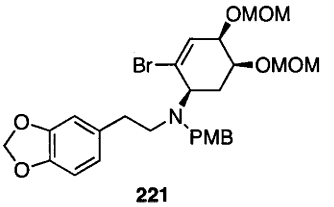
IR (NaCl) ν_{max} 2930, 1740, 1611, 1521, 1443, 1379, 1248, 1148, 1104, 1040 cm^{-1}.

MS (ESI, 70 eV) *m/z* 808 and 806 [(M + H)$^+$, both 5%], 586 and 584 (5 and 5), 425 (5), 306 (16), 227 (16), 121 (100).

HRMS Found: (M + H)$^+$, 806.1074. $C_{34}H_{34}{}^{79}BrF_5NO_9S$ requires (M + H)$^+$, 806.1057.

Concentration fraction **B** (R_f = 0.4, 3:7 v/v ethyl acetate–hexane) gave the starting material **207** (31.0 mg, 21%) which was identical, in all respects, with authentic material.

(1*R*,4*R*,5*S*)–*N*–(4–methoxybenzyl)–*N*–(2–(benzo[*d*][1,3]dioxol–6–yl)ethyl)–2–bromo–4,5–bis(methoxymethoxy)cyclohex–2–enamine (221)



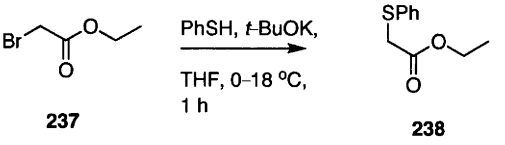
221

R_f= 0.3, 3:7 v/v ethyl acetate–hexane

HRMS Found: $(M + H)^+$, 564.1592. $C_{27}H_{35}{}^{79}BrNO_7$ requires $(M + H)^+$, 564.1597.

7.2.4. Chapter Five: Preparation of 3–Arylhexahydro–oxindoles *via Approach D:* Application to a Chemoenzymatic Total Synthesis of (+)–Brunsvigine

Ethyl 2–(phenylthio)acetate (238)



237 **238**

Following a protocol defined by Babin *et al.*,[9] a magnetically stirred solution of thiophenol (5.50 g, 49.9 mmol) in anhydrous THF (100 mL) was cooled to 0 °C and treated with *t*–BuOK (6.17 g, 55.0 mmol). After 15 mins, the ensuing mixture was treated with a solution of ethyl α–bromoacetate **237** (8.35 g, 50.0 mmol) in anhydrous THF (50 mL) then stirred for 1 h at which time TLC analysis indicated that all starting material had been consumed. Consequently, the reaction mixture was treated with brine (200 mL) and the separated aqueous fraction of the biphasic mixture was extracted with diethyl ether (2 x 100 mL). The combined organic fractions were dried ($MgSO_4$), filtered and concentrated under reduced pressure to give yellow oil [CAUTION: Stench!]. Subjection of this material to flash chromatography (silica, 1:19 v/v ethyl acetate–hexane elution) and concentration of appropriate fractions (R_f = 0.4) afforded the previously reported title compound **238**[10] (9.48 g, 96%) as a clear, light–yellow oil.

^{1}H NMR (300 MHz) δ_H ($CDCl_3$) 7.34 (2H, d, J = 7.5 Hz), 7.17 (3H, m), 4.07 (2H, q, J = 7.2 Hz), 3.55 (2H, m), 1.13 (3H, t, J = 7.2 Hz).

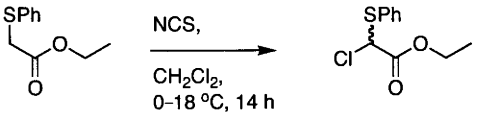
^{13}C NMR (75 MHz) δ_C ($CDCl_3$) 169.1, 134.7, 129.3, 128.5, 126.4, 61.0, 36.1, 13.6.

IR (NaCl) ν_{max} 3060, 2982, 1734, 1583, 1481, 1439, 1269, 1132, 1026, 740 cm^{-1}.

MS (EI, 70 eV) *m/z* 196 ($M^{+\bullet}$, 72%), 123 (100), 109 (31), 77 (19), 69 (21), 65 (18), 43 (42).

HRMS Found: $M^{+\bullet}$, 196.0558. $C_{10}H_{12}O_2S$ requires $M^{+\bullet}$, 196.0558.

Ethyl 2–chloro–2–(phenylthio)acetate (239)



238 **239**

Following a protocol defined by Tamura *et al.*,[10] a magnetically stirred solution of α–thiophenylacetate **238** (9.45 g, 48.1 mmol) in anhydrous CH_2Cl_2 (150 mL) was cooled to 0 °C then treated with NCS (6.44 g, 48.2 mmol) and allowed to warm to 18 °C. After 14 h, when TLC analysis indicated that all starting material had been consumed, the ensuing mixture was treated with water (200 mL) and the separated aqueous fraction of the biphasic mixture was extracted with CH_2Cl_2 (2 x 100 mL). The combined organic fractions were washed, sequentially, with HCl (3 x 200 mL of a 2 M aqueous solution), water (2 x 300 mL) and brine (1 x 300 mL) then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a yellow oil [Caution: Stench!]. Subjection of this material to flash chromatography (silica, 1:4 v/v ethyl acetate–hexane elution) and concentration of appropriate fractions (R_f = 0.7) afforded the previously reported title compound **239**[10] (7.78 g, 70%) as a clear, light–yellow oil.

^{1}H NMR (300 MHz) δ_H ($CDCl_3$) 7.55–7.51 (2H, complex m), 7.33 (3H, m), 5.54 (1H, s), 4.15 (2H, q, J = 7.2 Hz), 1.20 (3H, t, J = 7.2 Hz).

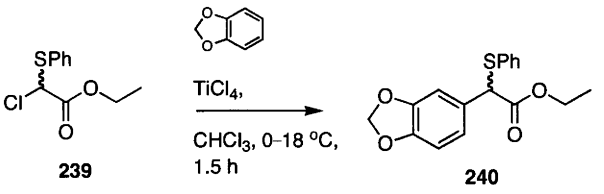
^{13}C NMR (75 MHz) δ_C ($CDCl_3$) 165.3, 133.6, 129.9, 129.1, 128.8, 64.4, 62.4, 13.5.

IR (NaCl) ν_{max} 3060, 2983, 1747, 1583, 1472, 1440, 1368, 1297, 1263, 1151, 1024, 868, 742 cm^{-1}.

MS (EI, 70 eV) *m/z* 230 ($M^{+\bullet}$, 11%), 157 (24), 142 (25), 137 (13), 121 (19), 109 (14), 97 (18), 81 (42), 69 (100), 57 (45), 43 (63).

HRMS Found: $M^{+\bullet}$, 230.0167. $C_{10}H_{11}{}^{35}ClO_2S$ requires $M^{+\bullet}$, 230.0168.

Ethyl 2–(benzo[*d*][1,3]dioxol–6–yl)–2–(phenylthio)acetate (240)



A magnetically stirred solution of 1,2–methylenedioxybenzene (3.80 g, 31.1 mmol) and α–chloro–α–thiophenylacetate **239** (5.97 g, 25.9 mmol) in anhydrous $CHCl_3$ (100 mL) was cooled to 0 °C then treated with $TiCl_4$ (2.85 mL, 25.9 mmol). The ensuing mixture was allowed to warm to 18 °C and after 1.5 h, when TLC analysis indicated that all the starting material had been consumed, the reaction mixture was quenched with water (200 mL). The separated aqueous phase was extracted with $CHCl_3$ (2 × 200 mL) and the combined organic fractions were then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a black residue. Subjection of this material to flash chromatography (silica, 1:19 v/v ethyl acetate–hexane elution) and concentration of appropriate fractions (R_f = 0.3) afforded the previously reported title compound **240**[11] (4.02 g, 77%) as viscous, light–yellow oil.

^{1}H NMR (300 MHz) δ_H ($CDCl_3$) 7.38 (2H, m), 7.23 (3H, m), 7.07 (1H, d, J = 1.8 Hz), 6.85 (1H, m), 6.68 (1H, d, J = 8.1 Hz), 5.86 (2H,s), 4.87 (1H, s), 4.08 (2H, m), 1.12 (3H, t, J = 7.2 Hz),

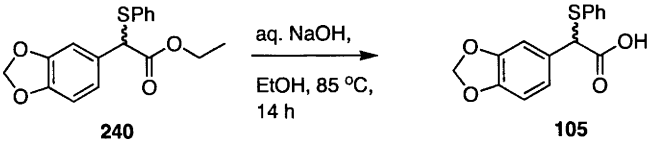
^{13}C NMR (75 MHz) δ_C ($CDCl_3$) 169.9, 147.3, 133.5, 132.1, 128.9, 128.6, 127.9, 121.9, 108.5, 107.7, 100.9, 61.3, 55.7, 13.6.

IR (NaCl) ν_{max} 3059, 2982, 2900, 1732, 1503, 1489, 1442, 1368, 1303, 1247, 1148, 1038, 930, 744 cm^{-1}.

MS (ESI, 70 eV) *m/z* 339 [$(M + Na)^+$, 100%], 261 (8), 207 (95), 135 (20).

HRMS Found: $(M + Na)^+$, 339.0666. $C_{17}H_{16}NaO_4S$ requires $(M + Na)^+$, 339.0667.

2–(Benzo[*d*][1,3]dioxol–6–yl)–2–(phenylthio)acetic acid (105)



240 **105**

A magnetically stirred solution of ester **240** (4.02 g, 12.7 mmol) in water–EtOH (50 mL of a 1:4 mixture) maintained at 18 °C was treated with sodium hydroxide (2.53 g, 6.3 mmol) and heated at 85 °C. After 14 h, the ensuing mixture was cooled to 18 °C and concentrated under reduced pressure to give a brown residue that was treated with HCl (excess of a 2 M aqueous solution, pH ~ 4-5). This mixture was then diluted with ethyl acetate–water (400 mL of a 1:1 v/v mixture) and the separated aqueous phase was extracted with ethyl acetate (2 × 100 mL). The combined organic fractions were dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford the previously reported title compound **105**[11] (3.65 g, 99%) as an off–white, crystalline solid.

mp = 116–118 °C

^{1}H NMR (300 MHz) δ_H ($CDCl_3$) 7.41 (2H, m), 7.32–7.24 (3H, complex m), 7.09 (1H, d, J = 1.8 Hz), 6.97 (1H, dd, J = 8.1, 1.8 Hz), 6.78 (1H, d, J = 8.1 Hz), 5.99 (2H, s), 5.10 (1H, s) (signal due to acid proton not observed).

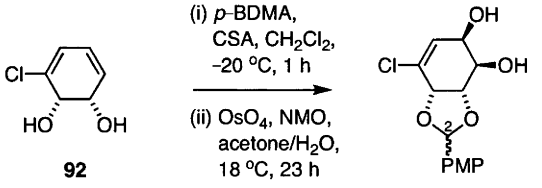
^{13}C NMR (75 MHz) δ_C ($CDCl_3$) 171.6, 148.6, 148.3, 135.0, 132.1, 130.6, 129.7, 128.1, 123.0, 109.3, 108.6, 102.1, 55.8.

IR (NaCl) ν_{max} 3058, 2981, 2898, 1709, 1502, 1488, 1443, 1412, 1249, 1039, 931, 804, 744, 690 cm^{-1}.

MS (EI, 70 eV) *m/z* 288 ($M^{+\bullet}$, 32%), 276 (22), 243 (10), 207 (19), 180 (25), 179 (100), 167 (35), 151 (22), 149 (50), 121 (53), 109 (27), 93 (37), 77 (33), 65 (44), 51 (31).

HRMS Found: $M^{+\bullet}$, 288.0455. $C_{15}H_{12}O_4S$ requires $M^{+\bullet}$, 288.0456.

(2*S*, 3a*S*, 4*R*, 5*R*, 7a*S*)–and (2*R*, 3a*S*, 4*R*, 5*R*, 7a*S*)–7–Chloro–3a,4,5,7a–tetrahydro–2(4methoxyphenyl)benzo[*d*][1,3] dioxole-4,5-diol (241)



Save for the use of a 23 h reaction time in the osmium tetraoxide–mediated *cis*–dihydroxylation step, compound **92** was converted into a *ca.* 2:1 mixture of the C2–epimeric forms of *title compound **241*** (66% as a white, crystalline solid) by the same method as outlined above for the preparation of compound **170**.

R_f = 0.3 (silica, 1:19 v/v MeOH–CH_2Cl_2).

mp = 114–116 °C

^{1}H NMR (300 MHz) δ_H ($CDCl_3$) (major): 7.34 (2H, d, J = 9.0 Hz), 6.89 (2H, d, J = 9.0 Hz), 5.98 (1H, d, J = 3.6 Hz), 5.89 (1H, s), 4.67 (1H, dd, J = 6.6, 1.2 Hz), 4.48 (1H, t, J = 6.0 Hz), 4.34 (1H, m), 4.09 (1H, m), 3.80 (3H, s), 3.14 (1H, s), 2.96 (1H, m); δ_H ($CDCl_3$) (minor): 7.38 (2H, d, J = 8.6 Hz), 6.90 (2H, d, J = 8.6 Hz), 6.03 (1H, dd, J = 3.0, 0.6 Hz), 5.85 (1H, s), 4.83 (1H, dd, J = 5.7, 1.2 Hz), 4.56 (1H, t, 5.1 Hz), 4.44 (1H, m), 4.21 (1H, m), 3.81 (3H, s), 3.02 (1H, s) (signal due to one OH obscured or overlapping).

^{13}C NMR (75 MHz) δ_C ($CDCl_3$) (major): 160.9, 132.2, 129.3, 128.6, 127.5, 114.1, 104.7, 77.6, 76.1, 70.1, 66.7, 55.5; δ_C ($CDCl_3$) (minor): 160.8, 131.1, 129.0, 128.2, 114.0, 102.9, 76.6, 75.9, 68.9, 66.4, 55.5 (one signal obscured or overlapping).

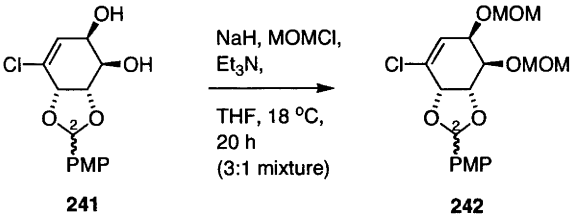
IR (NaCl) ν_{max} 3415, 3271, 3000, 2932, 2905, 2868, 2838, 1651,1612, 1518, 1460, 1437, 1394, 1303, 1172, 1031, 911, 832, 731 cm^{-1}.

MS (EI, 70 eV) *m/z* 299 and 297 ($M^{+\bullet}$, 22 and 48%), 225 and 223 (3 and 7), 179 (27), 146 and 144 (20 and 38), 137 (78), 135 (100), 108 (91), 77 (38), 65 (18), 39 (23).

HRMS Found: $(M - H\bullet)^+$, 297.0532. $C_{14}H_{15}{}^{35}ClO_5$ requires $(M - H\bullet)^+$, 297.0530.

Elemental Analysis Found: C, 56.09; H, 4.98; Cl, 11.73. $C_{14}H_{15}ClO_5$ requires C, 56.29; H, 5.06; Cl, 11.87.

(3a*R*, 4*R*, 5*R*, 7a*R*)–7–Chloro–3a,4,5,7a–tetrahydro–4,5–bis(methoxymethoxy)–2–(4–methoxyphenyl)benzo[*d*][1,3]dioxole (242)



241 **242**

Save for the use of a 20 h reaction time, compound **241** was converted into a *ca.* 3:1 mixture of the C2–epimeric forms of the *title compound **242*** (88% as a clear, viscous oil) by the same method as outlined above for the preparation of compound **171**.

R_f = 0.5 (silica, 2:3 v/v ethyl acetate–hexane).

^{1}H NMR (300 MHz) δ_H ($CDCl_3$) (major): 7.37 (2H, d, J = 8.4 Hz), 6.89 (2H, d, J = 8.7 Hz), 6.11 (1H, d, J = 3.9 Hz), 5.89 (1H, s), 4.81–4.70 (5H, complex m), 4.60, (1H, t, J = 6.6 Hz), 4.35 (1H, m), 4.17–4.10 (1H, complex m), 3.80 (3H, s), 3.39 (3H, s), 3.38 (3H, s).

^{13}C NMR (75 MHz) δ_C ($CDCl_3$) (major): 160.5, 131.9, 128.3, 127.8, 126.8, 113.5, 104.4, 96.3, 95.9, 76.2, 75.7, 74.5, 70.9, 55.4, 55.3, 55.0.

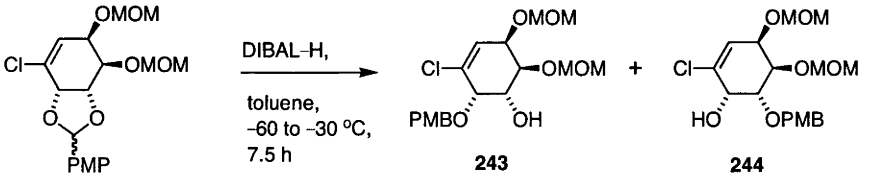
IR (NaCl) ν_{max} 2937, 2834, 1650, 1615, 1589, 1518, 1465, 1440, 1399, 1305, 1251, 1172, 1151, 1080, 1035, 918, 831 cm^{-1}.

MS (ESI) *m/z* 411 and 409 [(M + Na)$^+$, 35 and 100%], 389 and 387 [(M + H)$^+$, 3 and 10], 181 (22), 151 (19), 137 (45), 121 (78), 99 (40).

HRMS Found: (M + Na)$^+$, 409.1029. $C_{18}H_{23}{}^{35}ClNaO_7$ requires (M + Na)$^+$, 409.1030.

Elemental Analysis Found: C, 55.94; H, 5.65; Cl, 8.92. $C_{18}H_{23}ClO_7$ requires C, 55.89; H, 5.99; Cl, 9.17.

(1*S*, 2*S*, 5*R*, 6*S*)–2–(4–Methoxybenzyloxy)–3–chloro–5,6–bis(methoxymethoxy) cyclohex–3–enol (243) and (1*S*, 4*R*, 5*R*, 6*R*)–6–(4–methoxybenzyloxy)–2–chloro–4,5–bis(methoxymethoxy) cyclohex–2–enol (244)



242 **243** **244**

Save for the use of a 7.5 h reaction time, compound **242** was converted into *title compound **243*** (60% as a clear, colourless oil) and *title compound **244*** (11% as a clear, viscous oil) by the same method as outlined above for the preparation of compound **172**.

Compound 243

R_f = 0.3 (silica, 2:3 v/v ethyl acetate–hexane).

^{1}H NMR (300 MHz) δ_H ($CDCl_3$) 7.32 (2H, d, J = 8.4 Hz), 6.87 (2H, d, J = 8.4 Hz), 5.96 (1H, d, J = 4.2 Hz), 4.88–4.67 (6H, complex m), 4.37 (1H, m), 4.17 (2H, m), 4.02 (1H, m), 3.78 (3H, s), 3.36 (3H, s), 3.33 (3H, s), 2.86 (1H, d, J = 3.0 Hz).

^{13}C NMR (75 MHz) δ_C ($CDCl_3$) 159.2, 133.3, 129.6, 129.4, 126.5, 113.5, 97.0, 95.9, 76.8, 75.4, 74.1, 71.2, 68.4, 55.4, 55.2, 54.9.

IR (NaCl) ν_{max} 3468, 2936, 2895, 1648, 1612, 1514, 1465, 1302, 1250, 1151, 1098, 1044, 917, 823 cm^{-1}.

MS (ESI) *m/z* 413 and 411 [$(M + Na)^+$, 35 and 100%], 121 (96), 75 (19), 61 (86).

HRMS Found: $(M + Na)^+$, 411.1186. $C_{18}H_{25}{}^{35}ClNaO_7$ requires $(M + Na)^+$, 411.1187.

Elemental Analysis Found: C, 55.47; H, 6.60; Cl, 8.84. $C_{18}H_{25}ClO_7$ requires C, 55.60; H, 6.48; Cl, 9.12.

Specific Rotation $[\alpha]_D^{20}$ –11.7 (*c* 0.175, $CHCl_3$).

Compound 244

R_f = 0.4 (2:3 v/v ethyl acetate–hexane)

^{1}H NMR (300 MHz) δ_H ($CDCl_3$) 7.27 (2H, d, J = 8.7 Hz), 6.89 (2H, d, J = 8.7 Hz), 5.98 (1H, d, J = 3.9 Hz), 4.79–4.70 (4H, complex m), 4.70 (1H, d, J = 11.1 Hz), 4.61 (1H, d, J = 11.1 Hz), 4.35–4.30 (2H, complex m), 4.05 (2H, m), 3.81 (3H, s), 3.39 (3H, s), 3.38 (3H, s) (one signal due to OH obscured or overlapping).

^{13}C NMR (75 MHz) δ_C ($CDCl_3$) 159.5, 135.1, 129.6, 129.5, 126.1, 113.9, 97.2, 96.2, 76.5, 73.4, 73.1, 71.5, 69.1, 55.7, 55.5, 55.1.

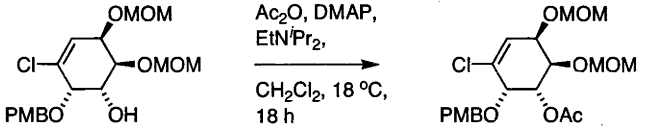
IR (NaCl) ν_{max} 3467, 2932, 1612, 1514, 1250, 1151, 1100, 1035, 917 cm^{-1}.

MS (ESI, 70 eV) *m/z* 413 and 411 [$(M + Na)^+$, 40 and 100%], 121 (40), 102 (6).

HRMS Found: $(M + Na)^+$, 411.1182. $C_{18}H_{25}{}^{35}ClNaO_7$ requires $(M + Na)^+$, 411.1187.

Specific Rotation $[\alpha]_D^{20}$ –51.2 (*c* 1.45, $CHCl_3$).

(1*S*,2*S*,5*R*,6*R*)–2–(4–Methoxybenzyloxy)–3–chloro–5,6–bis(methoxymethoxy)cyclohex–3–enyl acetate (245)



243 **245**

Save for the use of EtN^{i}Pr$_2$ instead of triethylamine and 18 h reaction time, *title compound* ***245*** (83% as a clear, colourless oil) was prepared from compound **243** using the method outlined for the preparation of compound **174.**

R_f = 0.4 (silica, 2:3 v/v ethyl acetate–hexane).

^{1}H NMR (300 MHz) δ_H ($CDCl_3$) 7.23 (2H, d, *J* = 8.6 Hz), 6.80 (2H, d, *J* = 8.6 Hz), 5.93 (1H, d, *J* = 5.1 Hz), 5.39 (1H, m), 4.71–4.62 (4H, complex m), 4.56 (2H, s), 4.26 (2H, m), 4.12 (1H, m), 3.72 (3H, m), 3.31 (6H, m), 2.00 (3H, s).

^{13}C NMR (75 MHz) δ_C ($CDCl_3$) 169.8, 159.1, 133.8, 129.5, 129.4, 126.1, 113.4, 96.7, 96.0, 75.7, 74.2, 71.8, 70.9, 69.6, 55.5, 55.3, 54.9, 20.7.

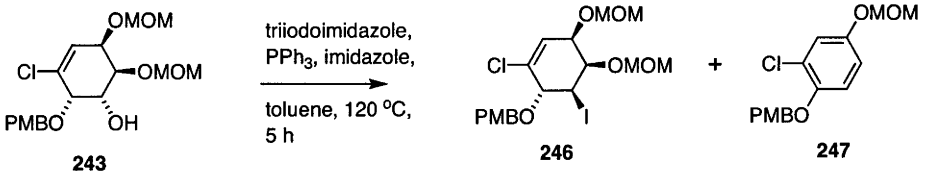
IR (NaCl) ν_{max} 2936, 2896, 1748, 1649, 1613, 1514, 1465, 1442, 1374, 1302, 1235, 1151, 1101, 1044, 918, 825 cm^{-1}.

MS (ESI, 70 eV) *m/z* 455 and 453 [$(M + Na)^+$, 10 and 28%], 241(4), 145 (6), 121 (100).

HRMS Found: $(M + Na)^+$, 453.1308. $C_{20}H_{27}{}^{35}ClNaO_8$ requires $(M + Na)^+$, 453.1292.

Specific Rotation $[\alpha]_D^{20}$ –93.2 (*c* 2.25, $CHCl_3$).

1-(((1*R*,4*R*,5*R*,6*R*)-2-Chloro-6-iodo-4,5-bis(methoxymethoxy)cyclohex-2-enyloxy)methyl)-4-methoxybenzene (246) and 1-(4-methoxybenzyloxy)-2-chloro-4-(methoxymethoxy)benzene (247)



*Title compound **246*** (66% as a clear, viscous oil) and *title compound **247*** (2.5% as a white, crystalline solid) were formed by treating compound **243** under the same conditions as defined above for preparing compound **184** but now using a reaction time of 5 h.

Compound 246

R_f = 0.7 (silica, 2:3 v/v ethyl acetate–hexane).

^{1}H NMR (300 MHz) δ_H ($CDCl_3$) 7.40 (2H, d, *J* = 8.4 Hz), 6.89 (2H, d, *J* = 8.4 Hz), 5.88 (1H, m), 4.87 (2H, s), 4.82 (2H, d, *J* = 9.6 Hz), 4.72 (1H, d, *J* = 7.2 Hz), 4.71 (1H, d, *J* = 9.6 Hz), 4.64 (1H, d, *J* = 7.2 Hz), 4.41–4.37 (2H, complex m), 4.30–4.27 (2H, complex m), 3.80 (3H, s), 3.53 (3H, s), 3.39 (3H, s).

^{13}C NMR (75 MHz) δ_C ($CDCl_3$) 159.2, 131.9, 129.8, 129.2, 126.5, 113.5, 97.4, 94.8, 80.3, 78.0, 74.5, 72.3, 56.5, 55.4, 54.9, 28.9.

IR (NaCl) ν_{max} 2951, 2894, 1648, 1613, 1586, 1515, 1465, 1303, 1250, 1152, 1090, 1018, 921, 824, 653 cm^{-1}.

MS (ESI) *m/z* 522 and 520 [(M + Na)$^+$, 19 and 43%], 241 (6), 121(100), 89 (19), 61 (31).

HRMS Found: (M + Na)$^+$, 521.0223. $C_{18}H_{24}{}^{35}Cl^{127}IO_6$ requires (M + Na)$^+$, 521.0204.

Elemental Analysis Found: C, 43.58; H, 4.85; Cl, 6.82; I, 25.12. $C_{18}H_{24}ClIO_6$ requires C, 43.35; H, 4.85; Cl, 7.11; I, 25.44.

Specific Rotation $[\alpha]_D^{20}$ –90.8 (*c* 1.63, $CHCl_3$).

Compound 247

R_f = 0.8 (2:3 v/v ethyl acetate–hexane).

mp = 62–63 °C

^{1}H NMR (300 MHz) δ_H ($CDCl_3$) 7.37 (2H, d, *J* = 8.7 Hz), 7.12 (1H, m), 6.91 (2H, d, *J* = 8.7 Hz), 6.87 (2H, m), 5.10 (2H, s), 5.02 (2H, s), 3.01 (3H, s), 3.47 (3H, s).

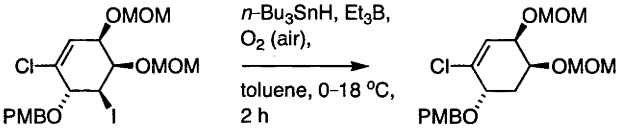
^{13}C NMR (75 MHz) δ_C ($CDCl_3$) 159.2, 151.4, 149.2, 128.8, 128.5, 123.6, 118.6, 115.3, 115.2, 113.7, 94.8, 71.2, 55.7, 55.0.

IR (NaCl) ν_{max} 2959, 2919, 1612, 1515, 1497, 1462, 1386, 1279, 1250, 1236, 1215, 1172, 1149, 1083, 999, 920, 806 cm^{-1}.

MS (ESI) *m/z* 333 and 331 [(M + Na)$^+$, 4 and 7%], 279 (9), 137 (10), 121 (57), 89 (28), 79 (100).

HRMS Found: (M + Na)$^+$, 331.0714. $C_{16}H_{17}{}^{35}ClO_4$ requires (M + Na)$^+$, 331.0713.

1-(((1*S*,4*R*,5*S*)-2-Chloro-4,5-bis(methoxymethoxy)cyclohex-2-enyloxy)methyl)-4-methoxybenzene (248)



246 **248**

Save for the use of a 2 h reaction time, *title compound* ***248*** (84% as a clear, viscous oil) was prepared from compound **246** using the same method as outlined above for the preparation of compound **182**.

R_f = 0.5 (silica, 2:3 v/v ethyl acetate–hexane).

^{1}H NMR (300 MHz) δ_H ($CDCl_3$) 7.311 (2H, d, *J* = 8.7 Hz), 6.87 (2H, d, *J* = 8.7 Hz), 6.02 (1H, d, *J* = 5.1 Hz), 4.40–4.55 (6H, complex m), 4.20 (1H, t, *J* = 4.5 Hz), 4.14–4.06 (2H, complex m), 3.80 (3H, s), 3.38 (3H, s), 3.37 (3H, s), 2.26 (1H, m), 1.99 (1H, m).

^{13}C NMR (75 MHz) δ_C ($CDCl_3$) 159.0, 136.2, 129.6, 129.2, 126.5, 113.4, 95.8, 95.2, 75.3, 71.7, 70.8, 70.9, 55.1, 55.0, 54.8, 30.4.

IR (NaCl) ν_{max} 2936, 2891, 1648, 1612, 1586, 1514, 1465, 1442, 1386, 1356, 1302, 1249, 1150, 1034, 824 cm^{-1}.

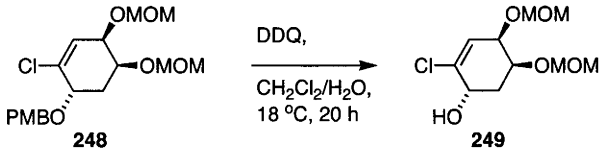
MS (ESI) *m/z* 397 and 395 [(M + Na)$^+$, 19 and 54%], 121 (100), 60 (19).

HRMS Found: (M + Na)$^+$, 395.1223. $C_{18}H_{25}{}^{35}ClO_6$ requires (M + Na)$^+$, 395.1237.

Elemental Analysis Found: C, 57.77; H, 6.71; Cl, 9.46. $C_{18}H_{25}ClO_6$ requires C, 57.99; H, 6.76; Cl, 9.51.

Specific Rotation $[\alpha]_D^{20}$ –41.2 (*c* 2.03, $CHCl_3$).

(1*S*,4*R*,5*S*)–2–Chloro–4,5–bis(methoxymethoxy)cyclohex–2–enol (249)



Save for the use of a 20 h reaction time, *title compound* ***249*** (98% as a clear, viscous oil) was prepared from compound **248** using the method as outlined above for the preparation of compound **180**.

R_f = 0.5 (silica, 2:3 v/v ethyl acetate–hexane).

^{1}H NMR (300 MHz) δ_H ($CDCl_3$) 5.98 (1H, d, J = 4.5 Hz), 4.79–4.69 (4H, complex m), 4.35 (1H, t, J = 5.1 Hz), 4.23 (1H, t, J = 4.2 Hz), 4.12 (1H, dt, J = 9.6, 3.0 Hz), 3.39 (3H, s), 3.38 (3H, s), 2.48–2.38 (1H, complex m), 2.37 (1H, broad s), 1.88 (1H, m).

^{13}C NMR (75 MHz) δ_C ($CDCl_3$) 137.6, 125.4, 95.5, 95.0, 71.1, 70.5, 68.0, 55.2, 55.1, 33.2.

IR (NaCl) ν_{max} 3437, 2939, 2893, 1647, 1442, 1381, 1290, 1214, 1150, 1110, 1046, 955, 917 cm^{-1}.

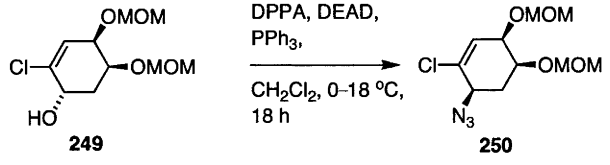
MS (ESI) *m/z* 277 and 275 [(M + Na)$^+$, 20 and 59%], 135 (11), 131 (33), 129 (100).

HRMS Found: (M + Na)$^+$, 275.0655. $C_{10}H_{17}{}^{35}ClO_5$ requires (M + Na)$^+$, 275.0662.

Elemental Analysis Found: C, 47.21; H, 6.55; Cl, 13.85. $C_{10}H_{17}ClO_5$ requires C, 47.53; H, 6.78; Cl, 14.03.

Specific Rotation $[\alpha]_D^{20}$ –95.5 (*c* 1.83, $CHCl_3$).

(3*R*,4*S*,6*R*)–6–Azido–1–chloro–3,4–bis(methoxymethoxy)cyclohex–1–ene (250)



Save for the use of an 18 h reaction time, *title compound* ***250*** (75% as a clear, viscous oil) was prepared from compound **249** using the method outlined above for the preparation of compound **207**.

R_f = 0.3 (silica, 3:7 v/v ethyl acetate–hexane).

^{1}H NMR (300 MHz) δ_H ($CDCl_3$) 6.14 (1H, dd, J = 5.4, 1.2 Hz), 4.78–4.69 (4H, complex m),

4.17 (1H, t, J = 3.6 Hz), 3.93 (1H, t, J = 6.9 Hz), 3.83 (1H, dt, J = 9.6, 3.6 Hz), 3.39 (3H, s), 3.37 (3H, s), 2.33–2.15 (2H, complex m).

^{13}C NMR (75 MHz) δ_C ($CDCl_3$) 135.0, 127.8, 95.7, 94.9, 70.6, 70.1, 59.8, 55.4, 55.3, 30.3.

IR (NaCl) ν_{max} 2948, 2892, 2103, 1642, 1467, 1449, 1252, 1215, 1150, 1110, 1047, 956, 917 cm^{-1}.

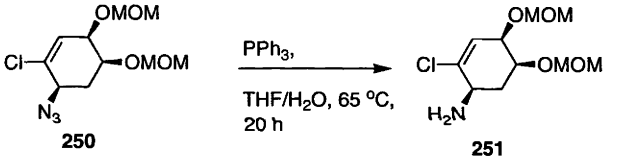
MS (ESI) *m/z* 302 and 300 [$(M + Na)^+$, 33 and 100%], 218 (20), 188 (40), 145 (30), 128 (53), 117 (51), 108 (81), 99 (57), 92 (49), 80 (73), 65 (64).

HRMS Found: $(M + Na)^+$, 300.0725. $C_{10}H_{16}{}^{35}ClN_3O_4$ requires $(M + Na)^+$, 300.0727.

Elemental Analysis Found: C, 43.32; H, 5.65; N, 15.06; Cl, 12.77. $C_{10}H_{16}ClN_3O_4$ requires C, 43.25; H, 5.81; N, 15.13; Cl, 12.77.

Specific Rotation $[\alpha]_D^{20}$ +51.1 (*c* 1.37, $CHCl_3$).

(1*R*,4*R*,5*S*)–2–Chloro–4,5–bis(methoxymethoxy)cyclohex–2–enamine (251)



Save for the use of a reaction time of 20 h, *title compound* ***251*** (98% as a viscous, light–yellow oil) was prepared from compound **250** using the method outlined above for the preparation of compound **208**.

R_f = 0.4 (silica, 1:11:8 v/v MeOH–ethyl acetate–$CHCl_3$).

^{1}H NMR (300 MHz) δ_H ($CDCl_3$) 5.84 (1H, dd, J = 4.8, 1.2 Hz), 4.72–4.61 (4H, complex m), 4.14, (1H, t, J = 4.1 Hz), 3.83 (1H, dt, J = 9.9, 3.3 Hz), 3.33 (3H, s), 3.32 (3H, s), 3.25 (1H, m), 2.10 (1H, m), 1.98 (1H, m), 1.71 (2H, s).

^{13}C NMR (75 MHz) δ_C ($CDCl_3$) 141.7, 122.8, 95.2, 94.5, 71.0, 70.9, 55.0, 54.9, 51.2, 32.4.

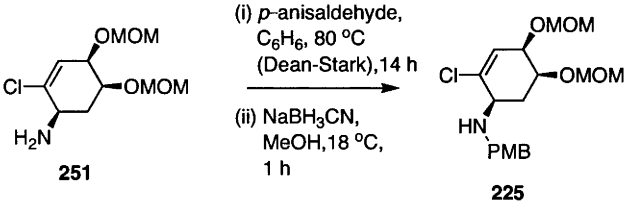
IR (NaCl) ν_{max} 3578, 3379, 3307, 2935, 2891, 2823, 1638, 1467, 1449, 1383, 1363, 1290, 1213, 1149, 1100, 1038, 916, 876 cm^{-1}.

MS (ESI) *m/z* 276 and 274 [$(M + Na)^+$, 6 and 17%], 254 and 252 [$(M + H)^+$, 9 and 27], 222 and 220 (18 and 51), 200 (55), 188 (57), 178 and 176 (20 and 60), 144 and 142 (29 and 92), 128 (100), 107 (22).

HRMS Found: $(M + H)^+$, 252.1001. $C_{10}H_{18}{}^{35}ClNO_4$ requires $(M + H)^+$, 252.1003.

Specific Rotation $[\alpha]_D^{20}$ –14.4 (*c* 1.03, $CHCl_3$).

(1*R*,4*R*,5*S*)–*N*–(4–Methoxybenzyl)–2–chloro–4,5–bis(methoxymethoxy)cyclohex–2–enamine (225)



Save for the use of a 14 h reaction period for the first step and 1 h reaction period in the second step, *title compound* ***225*** (56% as a clear, colourless oil) was prepared from compound **251** using the same method as outlined above for the preparation of compound **206**.

R_f = 0.4 (3:2 v/v ethyl acetate–hexane).

^{1}H NMR (300 MHz) δ_H ($CDCl_3$) 7.30 (2H, d, *J* = 8.7 Hz), 6.86 (2H, d, *J* = 8.7 Hz), 6.16 (1H, dd, *J* = 6.0, 1.8 Hz), 4.77 (2H, d, *J* = 6.9 Hz), 4.72 (2H, s), 4.19 (1H, t, *J* = 4.8 Hz), 3.83 (1H, t, *J* = 3.6 Hz), 3.80 (3H, s), 3.72 (2H, d, *J* = 12.3 Hz), 3.50 (1H, t, *J* = 8.1 Hz), 3.40 (3H, s), 3.39 (3H, s), 2.32 (1H, m), 2.18–2.10 (1H, complex m) (one signal, due to NH proton, not observed).

^{13}C NMR (75 MHz) δ_C ($CDCl_3$) 158.4, 141.0, 131.9, 129.3, 125.8, 113.6, 95.7, 94.7, 72.0, 70.7, 56.5, 55.3, 55.2, 55.0, 47.7, 29.2.

IR (NaCl) ν_{max} 3337, 2948, 2890, 2836, 1638, 1612, 1513, 1465, 1300, 1247, 1149, 1105, 1032, 955, 916, 824 cm^{-1}.

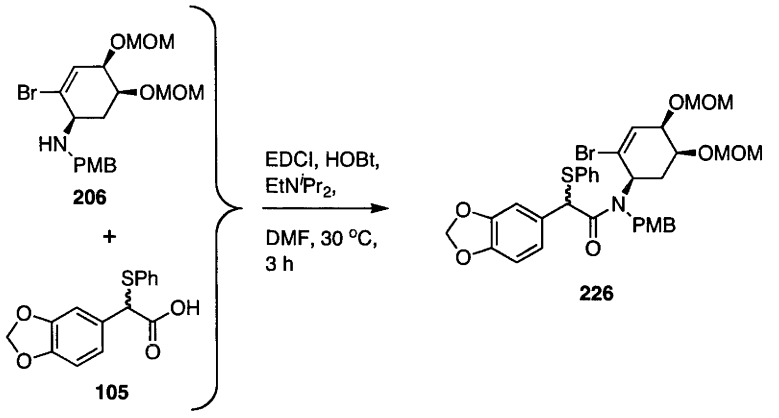
MS (ESI) *m/z* 396 and 394 [$(M + Na)^+$, 2 and 6%], 374 and 372 [$(M + H)^+$, 9 and 27), 121 (100).

HRMS Found: $(M + H)^+$, 372.1566. $C_{18}H_{26}{}^{35}ClNO_5$ requires $(M + H)^+$, 372.1578.

Elemental Analysis Found: C, 58.04; H, 7.18; N, 3.57; Cl, 9.53. $C_{18}H_{26}ClNO_5$ requires C, 58.14; H, 7.05; N, 3.77; Cl, 9.53.

Specific Rotation $[\alpha]_D^{20}$ –13.9 (*c* 0.53, $CHCl_3$).

_N_–(4–Methoxybenzyl)–2–(benzo[_d_][1,3]dioxol–6–yl)–_N_–((1_R_,4_R_,5_S_)–2–bromo–4,5–bis(methoxymethoxy)cyclohex–2–enyl)–2–(phenylthio)acetamide (226)



A magnetically stirred solution of 2°–amine **206** (1.36 g, 3.27 mmol), α–arylated acetic acid **105** (1.04 g, 3.61 mmol) and EtN^{i}Pr$_2$ (DIPEA) (1.42 mL, 8.17 mmol) in anhydrous DMF (20 mL) maintained at 18 °C was treated with EDCI (0.69 g, 3.61 mmol) and HOBt (0.53 g, 3.92 mmol) and the ensuing mixture then heated at 30 °C. After 3 h, when TLC analysis indicated that all starting material had been consumed, the reaction mixture was treated with CH_2Cl_2 (300 mL) and HCl (100 mL of a 2 M aqueous solution). The separated organic phase was washed, sequentially, with HCl (3 × 100 mL of a 2 M aqueous solution), brine (1 × 100 mL) and sodium hydrogen carbonate (1 × 100 mL of a saturated aqueous solution) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a yellow oil. Subjection of this material to flash chromatography (silica, 2:3 v/v ethyl acetate–hexane elution) and concentration of appropriate fractions (R_f = 0.3) afforded the *title compound **226*** (1.94 g, 86%) as an off–white foam.

^{13}C NMR (75 MHz) δ_C ($CDCl_3$) (mixture of diastereomers and amide rotamers) 170.9, 170.7, 169.6, 158.9, 158.8(6), 158.3, 148.2, 147.6, 147.3, 147.0, 134.1, 133.9,133.8, 133.6, 132.6, 132.5, 132.1, 130.9, 130.4, 130.3, 130.0, 129.8, 129.7, 129.2, 129.0, 128.7, 128.6, 128.5, 128.4, 127.8, 127.5, 127.0, 126.6, 122.5, 121.9, 121.6, 114.4, 114.2, 113.9, 113.6, 113.5, 109.8, 108.7, 108.2, 108.0, 107.5, 107.1, 101.0, 100.8, 96.1, 96.0, 94.7, 94.6, 71.6, 71.5, 70.5, 70.4, 70.3, 65.7, 59.0, 58.0, 55.6, 55.4, 55.3, 55.2, 55.0, 54.9, 53.9, 46.8, 46.1, 46.0, 29.5, 28.9.

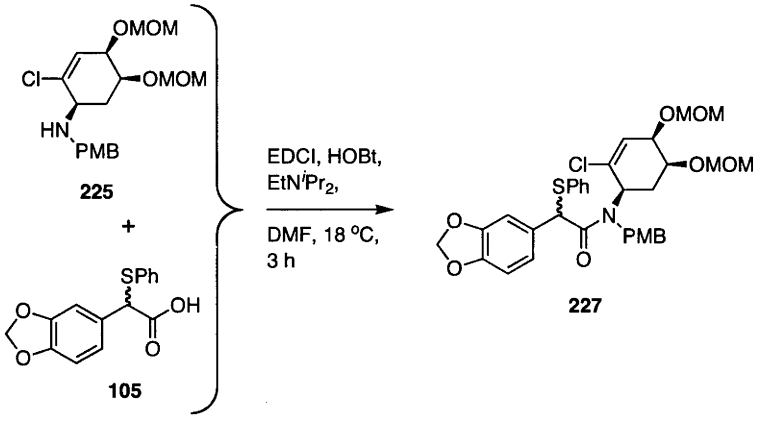
IR (NaCl) ν_{max} 3057, 2933, 2893, 1653, 1611, 1512, 1487, 1442, 1410, 1248, 1149, 1108, 1038, 918, 818, 735 cm^{-1}.

MS (ESI) *m/z* 710 and 708 [(M + Na)$^+$, both 4%], 448 and 446 (both 8), 418 and 416 (both 80), 121 (100).

HRMS Found: (M + Na)$^+$, 710.1256. $C_{33}H_{36}{}^{81}BrNO_8S$ requires (M + Na)$^+$, 710.1222.

Elemental Analysis Found: C, 57.86; H, 5.27; N, 2.16. $C_{33}H_{36}BrNO_8S$ requires C, 57.73; H, 5.28; N, 2.04.

N-(4-Methoxybenzyl)-2-(benzo[*d*][1,3]dioxol-6-yl)-*N*-((1*R*,4*R*,5*S*)-2-chloro-4,5-bis(methoxymethoxy)cyclohex-2-enyl)-2-(phenylthio)acetamide (227)



Save for the use of the reaction temperature of 18 °C, *title compound* ***227*** (74% as an off-white foam) was prepared from compound **225** and compound **105** using the method outlined above for the preparation of congener **226**.

R_f = 0.6 (silica, 3:2 v/v ethyl acetate–hexane).

^{13}C NMR (75 MHz) δ_C ($CDCl_3$) (mixture of diastereomers and amide rotamers): 170.8, 170.6, 158.6, 147.4, 147.0, 146.7, 137.6, 137.4, 133.7, 133.4, 133.3, 132.9, 131.8, 130.4, 130.0, 129.4, 129.3, 128.9, 128.4, 128.3, 128.2, 128.1, 127.9, 127.5, 127.3, 126.7, 126.3, 122.0, 121.4, 114.1, 113.8, 113.2, 113.1, 109.3, 108.1, 107.3, 106.8, 100.7, 100.6, 95.7, 94.4, 71.3, 69.4, 69.2, 57.7, 55.3, 55.0, 54.9, 54.8, 54.6, 54.1, 53.9, 46.4, 45.7, 28.2.

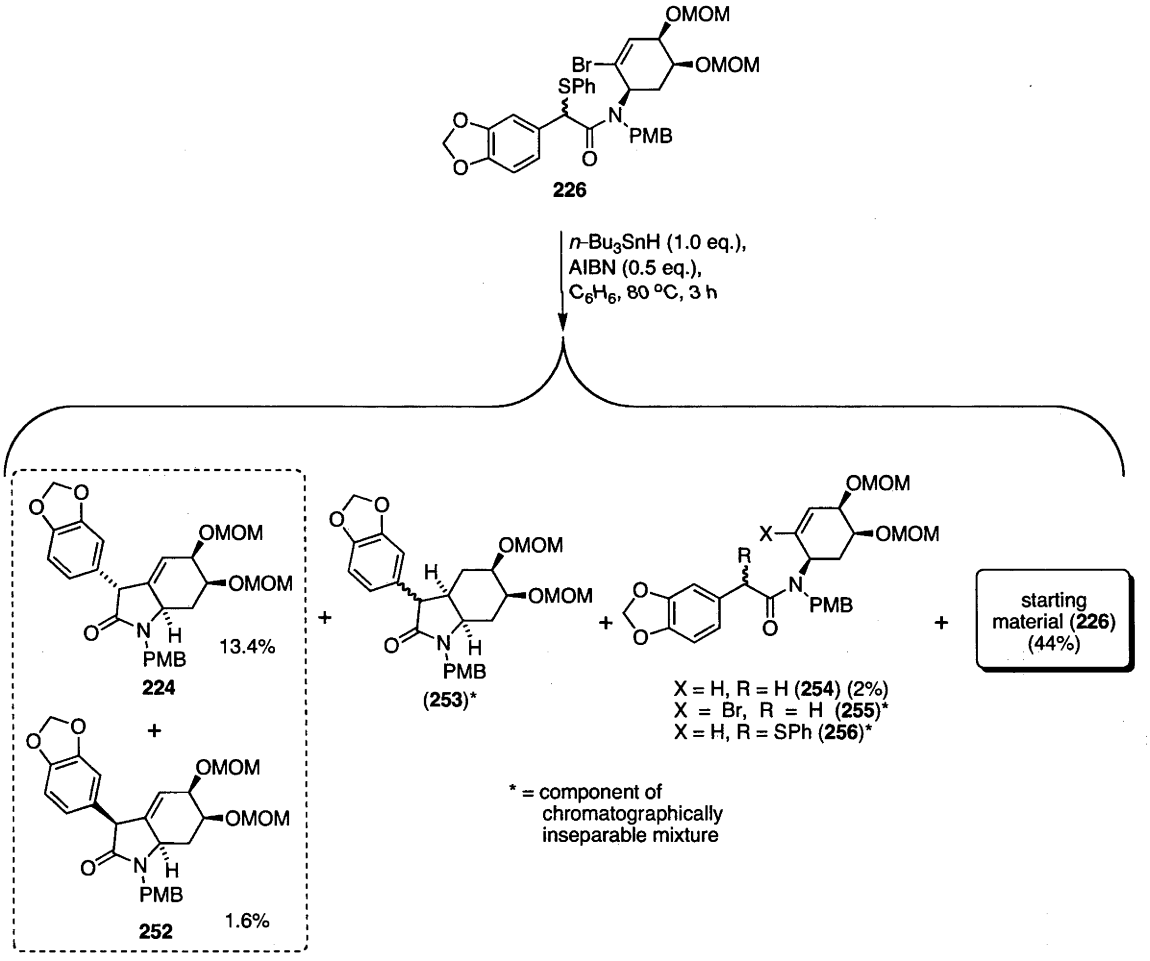
IR (NaCl) ν_{max} 3058, 2947, 2893, 1653, 1612, 1584, 1512, 1487, 1442, 1411, 1361, 1248, 1149, 1109, 1038, 918, 733 cm^{-1}.

MS (ESI) *m/z* 666 and 664 [(M + Na)$^+$, 45 and 100%], 644 and 642 [(M + H)$^+$, 27 and 61], 582 and 580 (12 and 28), 472 and 470 (3 and 9), 374 and 372 (7 and 29), 352 and 350 (4 and 11), 121 (43).

HRMS Found: (M + H)$^+$, 642.1893. $C_{33}H_{36}{}^{35}ClNO_8S$ requires (M + H)$^+$, 642.1928.

Elemental Analysis Found: C, 61.93; H, 5.90; N, 2.23; Cl, 5.57. $C_{33}H_{36}ClNO_8S$ requires C, 61.72; H, 5.65; N, 2.18; Cl, 5.52.

(3*R*,5*R*,6*S*,7a*R*)–1–(4–Methoxybenzyl)–3–(benzo[*d*][1,3]dioxol–6–yl)–5,6,7,7a–tetrahydro–5,6–bis(methoxymethoxy)–1*H*–indol–2(3*H*)–one) (224), (3*S*,5*R*,6*S*,7a*R*)–1–(4–Methoxybenzyl)–3–(benzo[*d*][1,3]dioxol–6–yl)–5,6,7,7a–tetrahydro–5,6–bis(methoxymethoxy)–1*H*–indol–2(3*H*)–one) (252), (3a*R*,5*R*,6*S*,7a*R*)–1–(4–methoxybenzyl)–3–(benzo[*d*][1,3]dioxol–6–yl)–hexahydro–5,6–bis(methoxymethoxy)–1*H*–indol–2(3*H*)–one (253), *N*–((1*R*,4*R*,5*S*)–4,5–bis(methoxymethoxy)cyclohex–2–enyl)–*N*–(4–methoxybenzyl)–2–(benzo[*d*][1,3]dioxol–6–yl)acetamide (254), *N*–(4–methoxybenzyl)–2–(benzo[*d*][1,3]dioxol–6–yl)–*N*–((1*R*,4*R*,5*S*)–2–bromo–4,5–bis(methoxymethoxy)cyclohex–2–enyl)acetamide (255) and *N*–((1*R*,4*R*,5*S*)–4,5–bis(methoxymethoxy)cyclohex–2–enyl)–*N*–(4–methoxybenzyl)–2–(benzo[*d*][1,3]dioxol–6–yl)–2–(phenylthio)acetamide (256)



A magnetically stirred mixture of amide **226** (90.0 mg, 0.13 mmol) in anhydrous benzene (2 mL) that had been degassed (3 × freeze–pump–thaw method) was heated to 80 °C under an

argon atmosphere. The reaction mixture was then treated (over 3 h and *via* syringe pump) with a degassed mixture of *n*–Bu_3SnH (38 μL, 0.14 mmol) and AIBN (11.0 mg, 0.07 mmol) in anhydrous benzene (1 mL). The cooled reaction mixture was concentrated under reduced pressure to give a yellow residue. Subjection of this material to flash chromatography (silica, neat hexane → 7:3 v/v ethyl acetate–hexane gradient elution) provided fractions **A**, **B**, **C**, and **D**.

Concentration of fraction **A** (R_f = 0.4, 3:2 v/v ethyl acetate–hexane) afforded the *title compound **224/252*** (10.0 mg, 15%) as a mixture (8.5:1) of epimers.

^{1}H NMR (800 MHz) δ_H ($CDCl_3$) (major epimer) 7.12 (2H, d, *J* = 8.8 Hz), 6.81 (2H, d, *J* = 8.8 Hz), 6.77 (1H, d, *J* = 1.6 Hz), 6.73 (1H, d, *J* = 8.0 Hz), 6.68 (1H, d, *J* = 8.0 Hz), 5.93 (2H, dd, *J* = 3.2, 1.2 Hz), 5.87 (1H, m), 4.90 (1H, d, *J* = 15.2 Hz), 4.85 (1H, d, *J* = 7.2 Hz), 4.73 (1H, d, *J* = 7.2 Hz), 4.69 (2H, m), 4.25 (1H, m), 4.09 (1H, s), 4.04 (1H, d, *J* = 15.2 Hz), 3.94 (1H, m), 3.79 (3H, s), 3.73 (1H, m), 3.40 (3H, s), 3.38 (3H, s), 2.13 (1H, m), 1.72 (1H, q, *J* = 11.2 Hz).

^{13}C NMR (75 MHz) δ_C ($CDCl_3$) (major epimer) 173.3, 159.1, 148.0, 146.8, 140.0, 130.7, 129.3, 128.1, 123.0, 120.1, 114.1, 108.4, 107.7, 101.1, 96.8, 94.8, 72.7, 70.2, 57.1, 55.6(4), 55.5(6), 55.3, 51.6, 43.7, 28.9.

IR (NaCl) ν_{max} 2929,1702, 1682, 1513, 1489, 1440, 1247, 1147, 1107, 1037, 917 cm^{-1}.

MS (ESI) *m/z* 520 [$(M + Na)^+$, 41%], 498 [$(M + H)^+$, 21], 466 (6), 436 (6), 374 (11), 266 (9), 211 (8), 121 (100), 61 (10).

HRMS Found: $(M + Na)^+$, 520.1954. $C_{27}H_{31}NO_8$ requires $(M + Na)^+$, 520.1947.

Concentration of fraction **B** (R_f = 0.5, 3:2 v/v ethyl acetate–hexane) gave the *title compound **254*** (1.3 mg, 2 %) as an opaque, viscous oil.

^{1}H NMR (600 MHz) δ_H ($CDCl_3$) 7.14 (2H, d, *J* = 8.4 Hz), 6.85 [1H, s (obscured)], 6.84 (2H, d, *J* = 8.4 Hz). 6.78 (2H, m), 5.94 (2H, s), 5.32 (1H, *J* = 15.0 Hz), 4.77 (1H, *J* = 6.6 Hz), 4.71 (1H, *J* = 6.6 Hz), 4.60 (1H, *J* = 7.2 Hz), 4.51 (1H, *J* = 7.2 Hz), 4.01 (1H, broad m), 3.97 (1H, *J* = 5.0 Hz), 3.84 (1H, *J* = 6.6 Hz), 3.79 (3H, s), 3.52 (1H, m), 3.46 (4H, s), 3.45 [1H, m (obscured)] 3.28 (3H, s), 2.52–2.43 (2H, complex m), 1.72 (1H, *J* = 12.6 Hz), 1.53 (1H, m), 1.01 (1H, m).

^{13}C NMR (75 MHz) δ_C ($CDCl_3$) 174.0, 158.8, 147.4, 146.4, 129.3, 128.5, 128.4, 123.1, 114.0, 110.3, 108.1, 100.9, 96.2, 93.8, 70.8, 70.5, 55.7, 55.4, 55.2, 53.1, 51.3, 43.2, 39.5, 28.6, 24.1.

IR (NaCl) ν_{max} 2934, 1682, 1611, 1512, 1491, 1250, 1148, 1106, 1037, 917 cm^{-1}.

MS (ESI, 70 eV) *m/z* 522 [$(M + Na)^+$, 100%], 500 [$(M + H)^+$, 81], 468 (24), 436 (17), 121 (95), 102 (27).

HRMS Found: $(M + H)^+$, 500.2273. $C_{27}H_{34}NO_8$ requires $(M + H)^+$, 500.2284.

Specific Rotation $[\alpha]_D^{20}$ +126.8 (*c* 0.35, $CHCl_3$).

Concentration of fraction **C** (R_f = 0.6, 3:2 v/v ethyl acetate–hexane) gave the *title compounds* ***253, 255 and 256*** as chromatographically inseparable mixture of products.

Compound 253

HRMS Found: $(M + H)^+$, 500.2287. $C_{27}H_{34}NO_8$ requires $(M + H)^+$, 500.2284.

Compound 255

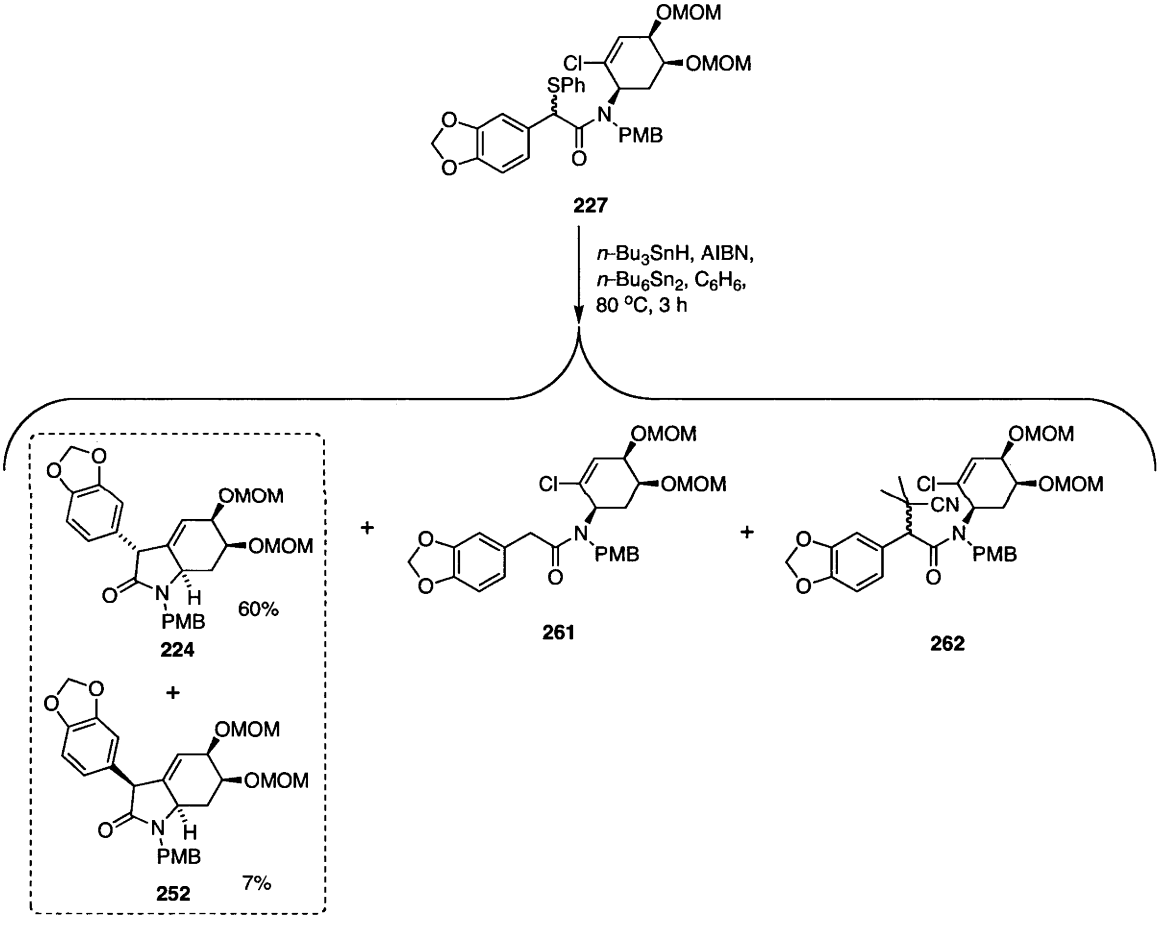
HRMS Found: $(M + H)^+$, 578.1355. $C_{27}H_{33}{}^{79}BrNO_8$ requires $(M + H)^+$, 578.1389.

Compound 256

HRMS Found: $(M + H)^+$, 608.2328. $C_{33}H_{38}NO_8S$ requires $(M + H)^+$, 608.2318.

Concentration fraction **D** (R_f = 0.3, 2:3 v/v ethyl acetate–hexane) gave the starting material **226** (40.0 mg, 44%) which was identical, in all respects, with authentic material.

**(3*R*,5*R*,6*S*,7a*R*)–1–(4–Methoxybenzyl)–3–(benzo[*d*][1,3]dioxol–6–yl)–5,6,7,7a–tetrahydro–5,6–bis(methoxymethoxy)–1*H*–indol–2(3*H*)–one) (224), (3*S*,5*R*,6*S*,7a*R*)–1–(4–Methoxybenzyl)–3–(benzo[*d*][1,3]dioxol–6–yl)–5,6,7,7a–tetrahydro–5,6–bis(methoxymethoxy)–1*H*–indol–2(3*H*)–one) (252), *N*–(4–methoxybenzyl)–2–(benzo[*d*][1,3]dioxol–6–yl)–*N*–((1*R*,4*R*,5*S*)–2–chloro–4,5–bis(methoxymethoxy)cyclohex–2–enyl)acetamide (261) and *N*–(4–methoxybenzyl)–2–(benzo[*d*][1,3]dioxol–6–yl)–*N*–((1*R*,4*R*,5*S*)–2–chloro–4,5–bis(methoxymethoxy)cyclohex–2–enyl)–3–cyano–3–methylbutanamide) (262)



A magnetically stirred mixture of amide, **227** (199.0 mg, 0.309 mmol) and *n*–Bu_6Sn_2 (300 μL, 0.774 mmol) in anhydrous benzene (650 mL) was degassed (3 x freeze–pump–thaw method) and then maintained under an argon atmosphere. After being heated at 80 °C, the ensuing mixture was treated (*via* syringe pump) with a degassed mixture containing *n*–Bu_3SnH (123 μL, 0.465 mmol) and AIBN (25.0 mg, 0.155 mmol) in anhydrous benzene (2 mL) for 3 h. The resulting mixture was then concentrated under reduced pressure to give a yellow residue.

Subjection of this material to flash chromatography (silica, neat hexane → 7:3 v/v ethyl acetate–hexane gradient elution) provided fractions **A** and **B**.

Concentration of fraction **A** provided the *title compounds **224/252*** as chromatographically inseparable mixture of epimers (8.5:1) (103.0 mg, 67%) [R_f = 0.4 (silica, 3:2 v/v ethyl acetate–hexane)].

Concentration of fraction **B** afforded the *title compound **261*** (30.6 mg, 18%) as a viscous, colourless oil.

R_f = 0.5 (3:2 v/v ethyl acetate—hexane).

^{1}H NMR (300 MHz) δ_H ($CDCl_3$) (major rotamer) 7.12 (2H, d, J = 8.7 Hz), 6.88 (2H, d, J = 8.7 Hz), 6.69 (1H, d, J = 7.8 Hz), 6.67 (2H, m), 6.54 (1H, d, J = 7.8 Hz), 6.21 (1H, dd, J = 6.6 and 2.1 Hz), 5.91 (2H, s), 5.77 (1H, m), 4.74–4.51 (5H, complex m), 4.19–4.14 (2H, complex m), 3.81 (3H, s), 3.45 (2H, s), 3.34 (3H, s), 3.33 (3H, s), 2.23–1.98 (2H, complex m).

^{13}C NMR (75 MHz) δ_C ($CDCl_3$) (major rotamer) 173.0, 158.8, 147.5, 146.4, 138.4, 129.7, 128.5, 127.9, 126.7, 114.3, 109.6, 108.0, 100.9, 96.1, 94.7, 71.8, 69.9, 55.5, 55.4, 55.3, 54.0, 46.4, 40.7, 28.6.

IR (NaCl) ν_{max} 2932, 2893, 1652, 1612, 1513, 1490, 1444, 1409, 1247, 1149, 1109, 1036, 919, 811 cm^{-1}.

MS (ESI, 70 eV) *m/z* 558 and 556 [$(M + Na)^+$, 21 and 55%], 536 and 534 [$(M + H)^+$, 12 and 30], 474 and 472 (12 and 42), 121 (100).

HRMS Found: $(M + H)^+$, 534.1883. $C_{27}H_{33}{}^{35}ClNO_8$ requires $(M + H)^+$, 534.1894.

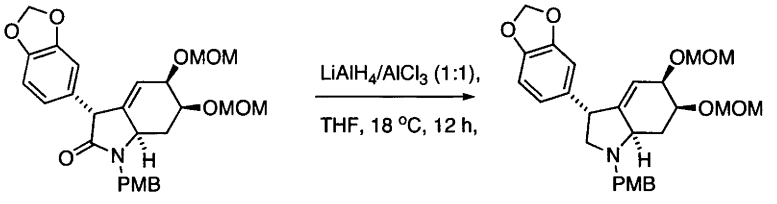
Specific Rotation $[\alpha]_D^{20}$ +23.2 (*c* 0.25 $CHCl_3$).

Compound 262

R_f = 0.5 (3:2 v/v ethyl acetate—hexane elution).

HRMS Found: $(M + H)^+$ 601.2305. $C_{31}H_{38}{}^{35}ClN_2O_8$ requires $(M + H)^+$ 601.2316.

(3*R*,5*R*,6*S*,7a*R*)–1–(4–Methoxybenzyl)–3–(benzo[*d*][1,3]dioxol–6–yl)–2,3,5,6,7,7a–hexahydro–5,6–bis(methoxymethoxy)–1*H*–indole (268)



224 **268**

A magnetically stirred suspension of aluminium trichloride ($AlCl_3$) (743.0 mg, 5.56 mmol) in anhydrous THF (15 mL) was cooled to –20 °C then treated, dropwise, with $LiAlH_4$ (5.56 mL of a 1 M solution in THF, 5.56 mmol) before being allowed to warm to 18 °C. After 1 h, a solution of the epimeric mixture (8.5:1) of compounds **224** and **252** (173.0 mg, 0.35 mmol), in anhydrous THF (10 mL), was added dropwise and the ensuing mixture was stirred for 12 h at 18 °C. TLC analysis after this time indicated that all the starting material had been consumed so the reaction mixture was treated with sodium/potassium tartrate (30 mL of a saturated aqueous solution) [CAUTION: Exothermic] and stirring continued at 18 °C for 4 h. The separated aqueous phase was extracted with diethyl ether (3 × 50 mL) and the combined organic fractions were washed with brine (2 × 50 mL) and ammonium chloride (1 × 50 mL of a saturated aqueous solution) then dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a 8.5:1 diastereoisomeric mixture of the *title compound* ***268*** (158.0 mg, 94%) as an opaque, colourless oil.

R_f = 0.4 (silica, 3:2 v/v ethyl acetate–hexane).

^{1}H NMR (600 MHz) δ_H ($CDCl_3$) 7.23 (2H, d, *J* = 8.4 Hz), 6.83 (2H, d, *J* = 8.4 Hz), 6.69 (1H, d, *J* = 7.8 Hz), 6.61 (1H, s), 6.60 (1H, partially obscured m), 5.91 (2H, s), 5.57 (1H, broad m), 4.83–4.70 (4H, complex m), 4.20 (1H, m), 4.00 (1H, d, *J* = 12.6 Hz), 3.85 (1H, m), 3.78 (3H, s), 3.41 (3H, s), 3.37 (3H, s), 3.36 (1H, partially obscured m), 3.21 (1H, broad d, *J* = 12.0 Hz), 2.91 (1H, broad s), 2.12 (2H, m), 1.80 (1H, m) (one signal obscured or overlapping).

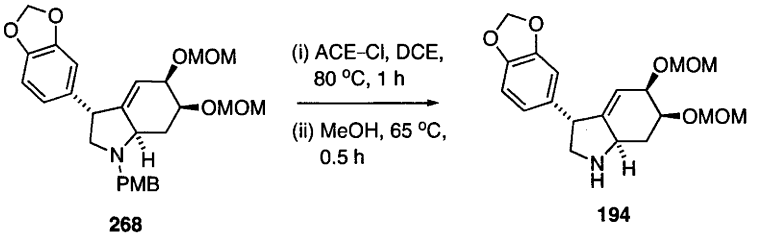
^{13}C NMR (150 MHz) δ_C ($CDCl_3$) 158.7, 149.6, 147.6, 146.0, 136.7, 130.3, 130.1, 120.8, 119.2, 113.5, 108.1, 108.0, 100.9, 96.2, 94.6, 73.4, 70.0, 66.5, 62.7, 57.8, 55.5, 55.3, 55.2, 46.1, 29.4.

IR (NaCl) ν_{max} 2934, 2890, 1611, 1512, 1488, 1441, 1357, 1248, 1147, 1103, 1039 cm^{-1}.

MS (ESI) *m/z* 484 [$(M + H)^+$, 100%], 121 (32), 54 (18).

HRMS Found: $(M + H)^+$, 484.2335. $C_{27}H_{33}NO_7$ requires $(M + H)^+$, 484.2335.

(3*R*,5*R*,6*S*,7a*R*)–3–(Benzo[*d*][1,3]dioxol–6–yl)–2,3,5,6,7,7a–hexahydro–5,6–bis(methoxymethoxy)–1*H*–indole (194)



268 **194**

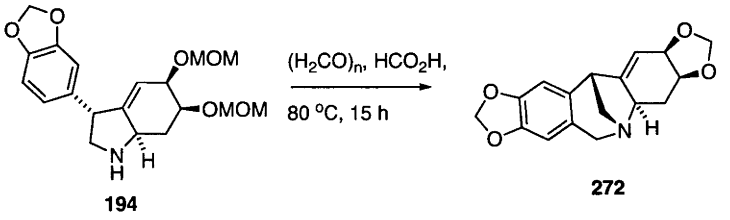
A magnetically stirred solution of 3°–amine **268** (83.5 mg, 0.173 mmol) in DCE (3 mL) maintained at 18 °C was treated with ACE–Cl (40 μL, 0.70 mmol) then heated at 80 °C. After 1 h, time TLC analysis indicated that all starting material had been consumed. Consequently, the reaction mixture was concentrated under reduced pressure to give a yellow residue. Treatment of this material with MeOH (3 mL) followed by heating at 65 °C for 30 mins produced an orange reaction mixture which, upon cooling to 18 °C then concentration under reduced pressure, provided an orange residue. This material was treated with CH_2Cl_2 (40 mL) and HCl (40 mL of a 1 M of an aqueous solution) and the separated aqueous fraction of the biphasic mixture was washed with CH_2Cl_2 (2 x 10 mL) before being treated with sodium hydroxide (40 mL of a 2 M of an aqueous solution) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic fractions were dried ($MgSO_4$), filtered and concentrated under reduced pressure to give the *title compound* ***194*** (28.7 mg, 45%) as an opaque, viscous oil. This material was used, without purification, in the next step of the reaction sequence.

IR (NaCl) ν_{max} 3307, 2961, 1503, 1488, 1259, 1093, 1037, 802 cm^{-1}.

MS (EI, 70 eV) *m/z* 388 and 386 [(M + Na)$^+$ 1 and 7%], 143 (10), 103 (24), 77 (40), 63 (100).

HRMS Found: (M + H) $^+$, 364.1753. $C_{19}H_{26}NO_6$ requires (M + H)$^+$, 364.1760.

(6aR, 7aS, 10aR, 12R)–6,12–Methano–6H–1,3–benzodioxolo[5,6–c][1]benzazepine–5,6a,7,7a,10a,12–hexahydro–7a,10a–benzo[*d*][1,3]dioxole (272)



194 272

A magnetically stirred solution 2°–amine **194** (28.7 mg, 0.08 mmol) in formic acid (3 mL) maintained at 18 °C was treated with paraformaldehyde (142.0 mg, 4.73 mmol) then heated at 80 °C. After 15 h the reaction mixture was cooled to 18 °C, quenched with sodium hydrogen carbonate (60 mL of saturated aqueous solution) and extracted with CH_2Cl_2 (3 × 60 mL). The combined organic fractions were dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a brown residue. Subjection of this material to flash chromatography (silica, 1:11:8 v/v MeOH–ethyl acetate–$CHCl_3$ elution) and concentration of appropriate fractions (R_f = 0.3) afforded the *title compound* ***272*** (11.3 mg, 48%) as a viscous, light–yellow oil.

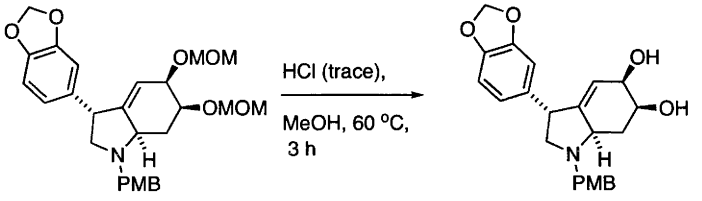
^{1}H NMR (300 MHz) δ_H [$(CD_3)_2CO$] 6.65 (1H, s), 6.57 (1H, s), 5.98 (2H, dd, J = 6.3 and 0.6 Hz), 5.94 (1H, s), 5.11 (1H, s), 4.93 (1H, s), 4.79 (1H, d, J = 8.1 Hz), 4.33–4.30 (3H, complex m), 3.76 (1H, m), 3.64 (1H, m), 3.59 (1H, m), 3.48 (1H, d, J = 5.4 Hz), 2.81 (1H, m), 1.58 [1H, m (obscured)].

^{13}C NMR (75 MHz) δ_C [$(CD_3)_2CO$] 153.4, 148.6, 147.1, 122.1, 117.3, 109.0, 108.7, 101.8, 94.8, 73.5, 73.4, 64.7, 63.4, 58.0, 47.3, 32.2.

MS (EI, 70 eV) *m/z* 300 [$(M + Na)^+$, 95%], 121 (100).

HRMS Found: $(M + H)^+$, 300.1248. $C_{17}H_{18}NO_4$ requires $(M + H)^+$, 300.1236.

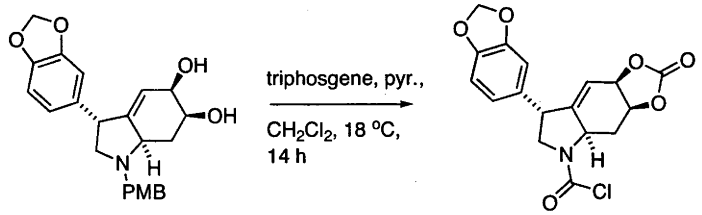
(3*R*,5*R*,6*S*,7a*R*)–1–(4–Methoxybenzyl)–3–(benzo[*d*][1,3]dioxol–6–yl)–2,3,5,6,7,7a–hexahydro–1*H*–indole–5,6–diol (278)



268 **278**

A magnetically stirred solution of 3°–amine **268** (158.0 mg, 0.327 mmol) in MeOH (20 mL) maintained at 18 °C was treated with HCl (trace of a concentrated aqueous solution) then heated at 60 °C for 3 h, after which time TLC analysis indicated that all the starting material had been consumed. Consequently, the reaction mixture was cooled to 18 °C, quenched with sodium hydrogen carbonate (1 × 40 mL of a saturated aqueous solution) then extracted with ethyl acetate (4 × 40 mL). The combined organic fractions were dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford the *title compound **278*** (95.0 mg, 73%) as a viscous oil. This material was used without purification in the next step of the reaction sequence.

(3R, 4aR, 7aS, 8aR)–3–(Benzo[*d*][1,3]dioxol–6–yl)–2,3,4a,7a,8,8a–hexahydro–4a,7a–benzo[*d*][1,3]dioxol–6–one–1*H*–indole–1–carbamoyl chloride (279)



278 **279**

A magnetically stirred solution of diol **278** (95.0 mg, 0.240 mmol) and pyridine (78 μL, 0.962 mmol) in anhydrous CH_2Cl_2 (10 mL) maintained at 18 °C was treated with triphosgene (285.0 mg, 0.962 mmol). After 14 h, the reaction mixture was concentrated under reduced pressure to give a yellow residue that was subjected to flash chromatography (silica, 2:3 v/v ethyl acetate–hexane elution). Concentration of appropriate fractions (R_f = 0.5) afforded a 8.5:1

diastereoisomeric mixture of the *title compound* ***279*** (44.0 mg, 50%) as a white, crystalline solid.

mp = 64–66 °C

^{1}H NMR (600 MHz) δ_H ($CDCl_3$) (major rotamer): 6.75 (1H, d, J = 3.9 Hz), 6.60 (1H, d, J = 1.8 Hz), 6.58 (1H, dd, J = 3.9, 1.8 Hz), 5.99 (1H, t, J = 1.2 Hz), 5.94 (2H, s), 5.01 (1H, broad d, J = 3.9 Hz), 4.85 (1H, m), 4.22–4.14 (1H, complex m), 3.97–3.92 (2H, complex m), 3.19 (1H, dd, J = 5.7, 2.4 Hz), 1.39 (1H, q, J = 5.7 Hz).

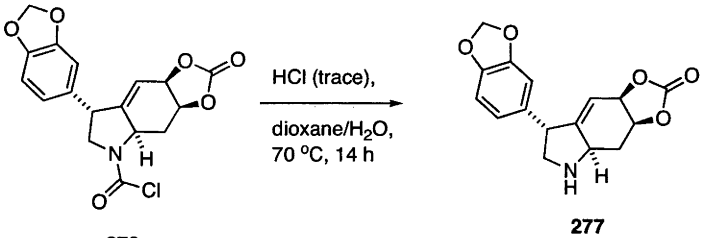
^{13}C NMR (75 MHz) δ_C ($CDCl_3$) (major rotamer): 153.5, 148.9, 148.4, 147.1(3), 147.0(8), 133.6, 118.9, 116.5, 108.8, 106.5, 101.4, 72.6, 71.7, 55.7, 55.0, 46.5, 29.9.

IR (NaCl) ν_{max} 2960, 2925, 2854, 1802, 1738, 1610, 1514, 1503, 1489, 1443, 1374, 1255, 1176, 1097, 1038, 811 cm^{-1}.

MS (EI, 70 eV) *m/z* 365 and 363 ($M^{+\bullet}$, 50 and 100%), 304 and 302 (6 and 17), 242 (25), 228 (28), 223 (31), 211 (23), 199 (28), 186 (44), 169 (28), 148 (35), 121 (55), 115 (30), 97 (21), 57 (30), 55 (28), 43 (18).

HRMS Found: $M^{+\bullet}$, 363.0496. $C_{17}H_{14}{}^{35}ClNO_6$ requires $M^{+\bullet}$, 363.0510.

(3R, 4aR, 7aS, 8aR)–3–(Benzo[*d*][1,3]dioxol–6–yl)–2,3,4a,7a,8,8a–hexahydro–1*H*–indole–4a,7a–benzo[*d*][1,3]dioxol–6–one (277)



279 **277**

A magnetically stirred solution of carbamoyl chloride **279** (20.0 mg, 0.055 mmol) in dioxane–water (3 mL of a 1:1 v/v mixture) maintained at 18 °C was treated with HCl (trace of a concentrated aqueous solution) then heated at 70 °C. After 14 h, the reaction mixture was cooled to 18 °C, treated with sodium hydrogen carbonate (40 mL of a saturated aqueous solution) then extracted with CH_2Cl_2 (4 × 40 mL). The combined organic fractions were dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a 8.5:1 diastereoisomeric mixture of the *title compound* ***277*** (14.0 mg, 83%) as a white, amorphous solid.

R_f = 0.2 (silica, 1:11:8 v/v MeOH–ethyl acetate–$CHCl_3$).

^{1}H NMR (300 MHz) δ_H [$(CD_3)_2CO$] 6.64 (3H, m), 5.84 (2H, s), 5.48 (1H, m), 5.08–5.01 (1H, complex m), 4.95 (1H, m), 3.92 (1H, q, J = 7.2 Hz), 3.76 (1H, m), 3.51 (1H, m), 3.42 (1H, m), 2.71 (1H, dd, J = 11.4, 10.8 Hz), 2.48 (1H, m), 1.28 (1H, q, J = 11.4 Hz).

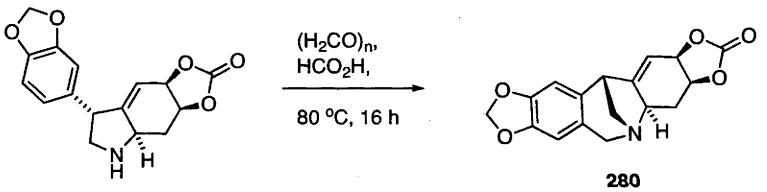
^{13}C NMR (150 MHz) δ_C [$(CD_3)_2CO$] 157.3, 154.7, 148.7, 147.1, 137.4, 121.9, 114.0, 108.8, 108.7, 101.9, 74.9, 74.1, 57.8, 55.9, 50.0, 33.1.

IR (NaCl) ν_{max} 2917, 2851, 1795, 1490, 1442, 1353, 1248, 1156, 1035, 928, 804 cm^{-1}.

MS (ESI) *m/z* 302 [(M + H)$^+$, 100%], 276 (57), 258 (20), 240 (32), 211 (5), 193 (6), 121 (20), 118 (28).

HRMS Found: (M + H)$^+$, 302.1029. $C_{16}H_{15}NO_5$ requires (M + H)$^+$, 302.1028.

(6aR, 7aS, 10aR, 12R)–6,12–Methano–6H–1,3–benzodioxolo[5,6–c][1]benzazepine–5,6a,7,7a,10a,12–hexahydro–7a,10a–benzo[*d*][1,3]dioxol–9–one (280)



277 280

A magnetically stirred solution 2°–amine **277** (118.9 mg, 0.395 mmol) in formic acid (10 mL) maintained at 18 °C was treated with paraformaldehyde (59.3 mg, 1.975 mmol) and the ensuing mixture heated at 80 °C. After 16 h, the reaction mixture was cooled to 18 °C, quenched with sodium hydrogen carbonate (60 mL of saturated aqueous solution) then extracted with CH_2Cl_2 (5 × 60 mL). The combined organic fractions were dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a brown residue. Subjection of this material to flash chromatography (silica, 1:11:8 v/v MeOH–ethyl acetate–$CHCl_3$ elution) and concentration of appropriate fractions (R_f = 0.3) afforded the *title compound* ***280*** (80.0 mg, 65%) as a white, amorphous solid.

^{1}H NMR (500 MHz) δ_H [$(CD_3)_2CO$] 6.65 (1H, s), 6.53 (1H, s), 5.91 (1H, d, J =1.2 Hz), 5.89 (1H, d, J = 1.2 Hz), 5.76 (1H, t, J = 1.8 Hz), 5.06 (1H, dt, J = 7.8, 1.5 Hz), 4.99 (1H, m), 4.26 (1H, d, J = 16.8 Hz), 3.75 (1H, d, J = 16.8 Hz), 3.48 (1H, s), 3.16 (1H, broad d, J = 12.0 Hz), 3.05 (1H, d, J = 12.0 Hz), 3.00 (1H, d, J = 12.0 Hz), 2.44 (1H, m).

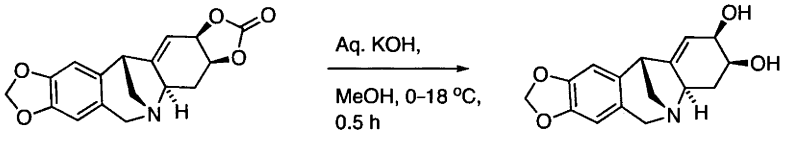
^{13}C NMR (75 MHz) δ_C [$(CD_3)_2CO$] 159.9, 154.7, 147.7, 146.8, 132.9, 126.0, 109.7, 108.0, 107.5, 101.6, 75.1, 73.4, 61.3, 61.1, 55.2, 45.9, 32.7.

IR (NaCl) ν_{max} 2925, 1799, 1482, 1235, 1196, 1159, 1043, 931, 730 cm^{-1}.

MS (ESI) *m/z* 336 [(M + Na)$^+$, 6%], 314 [(M + H)$^+$, 100%], 252 (6), 121 (4).

HRMS Found: (M + H)$^+$, 314.1019. $C_{17}H_{15}O_5$ requires (M + H)$^+$, 314.1028.

(6aR, 8S, 9R, 11R)–6,11–Methano–6H–1,3–benzodioxolo[5,6–c][1]benzazepine–5,6a,7,8,9,11–hexahydro–8,9–diol (*ent*–18)



280 *ent*-**18**

A magnetically stirred solution of carbonate **280** (72.0 mg, 0.229 mmol) in MeOH was cooled to 0 °C then treated with potassium hydroxide (6 mL of a 0.5 M aqueous solution) and allowed to warm to 18 °C. After 4.5 h, the reaction mixture was diluted with water (100 mL) and extracted with CH_2Cl_2 (5 × 60 mL). The combined organic fractions were then dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford the *title compound* ent–***18*** (58.0 mg, 87%) as a white, crystalline solid.

R_f = 0.3 (silica, 1:9 v/v MeOH–CH_2Cl_2)

mp = 130–140 °C (sesquihydrate – crystals grown from wet acetone).

^{1}H NMR (800 MHz) δ_H ($CDCl_3$) 6.56 (1H, s), 6.48 (1H, s), 5.90 (1H, d, *J* = 1.6 Hz), 5.87 (1H, d, *J* = 1.6 Hz), 5.75 (1H, m), 4.35 (1H, d, *J* = 16.8 Hz), 4.15 (1H, broad s), 3.86 (1H, d, *J* = 16.8 Hz), 3.68 (1H, m), 3.33 (1H, broad s), 3.23 (1H, broad m), 3.11 (1H, d, *J* = 11.2 Hz), 3.07 (1H, d, *J* = 11.2 Hz), 2.19 (1H, m), 1.52 (1H, m) (signals due to OH protons not observed).

^{13}C NMR (125 MHz) δ_C (CD_3OD) 149.4, 149.2, 144.9, 129.8, 122.0, 119.4, 108.7, 108.0, 103.0, 68.1, 66.2, 66.0, 58.4, 56.2, 45.0, 29.8.

IR (NaCl) ν_{max} 3369, 2957, 2926, 1482, 1334, 1235, 1070, 1031, 930.

MS (ESI) *m/z* 310 [(M + Na)$^+$, 8%], 288 [(M + H)$^+$, 100], 121 (4).

HRMS Found: (M + H)$^+$, 288.1241. $C_{16}H_{17}NO_4$ requires (M + H)$^+$, 288.1236.

Specific Rotation $[\alpha]_D^{20}$ +75.9 (*c* 0.10, EtOH).

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Appendix One

X–ray Crystal Structure Report for Compound 184

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Abstract

The crystal structure of $C_{18}H_{24}BrIO_6$ is reported.

Comment

The crystallographic asymmetric unit consists of four molecules of $C_{18}H_{24}BrIO_6$. The compound is enantiometrically pure. The absolute structure of the crystal has been determined by refinement of the Flack parameter and this establishes the absolute configuration of the molecule. The largest peaks in the final difference electron density map are located near I and Br atoms.

Experimental

The compound was prepared by OJK and recrystalized from ethyl acetate/ petroleum spirit.

Crystal data

$C_{18}H_{24}BrIO_6$
$M_r = 543.19$
Monoclinic
$P2_1$
$a = 9.3047$ (1) Å
$b = 33.0047$ (3) Å
$c = 13.9912$ (1) Å
$\beta = 91.6476$ (5)°
$V = 4294.90$ (7) Å^3
$Z = 8$
$D_x = 1.680$ Mg m^{-3}
D_m not measured
Mo Kα radiation
$\lambda = 0.71073$ Å

Cell parameters from 118346 reflections
$\theta = 3$–25°
$\mu = 3.380$ mm^{-1}
$T = 200$ K
Plate
Colourless
0.22 × 0.17 × 0.05 mm
Crystal source: local

Data collection

Nonius KappaCCD diffractometer
ϕ and ω scans with CCD
Absorption correction:
by integration *via* Gaussian method (Coppens, 1970) implemented in maXus (2000)
$T_{min} = 0.517$, $T_{max} = 0.836$
62173 measured reflections
15170 independent reflections

10297 reflections with
$I > 3.0\sigma(I)$
$R_{int} = 0.052$
$\theta_{max} = 25.108°$
$h = -11 \rightarrow 11$
$k = -38 \rightarrow 39$
$l = -16 \rightarrow 16$

Refinement

Refinement on *F*
$R = 0.0263$
$wR = 0.0288$
$S = 1.1209$
10297 reflections
938 parameters
H-atom parameters not refined
Method, part 1, Chebychev polynomial, (Carruthers & Watkin, 1979, Prince, 1982) [weight] = $1.0/[A_0 * T_0(x) + A_1 * T_1(x) \ldots + A_{n-1}] * T_{n-1}(x)]$ where A_i are the Chebychev coefficients listed below and x= Fcalc/Fmax Method = Robust Weighting (Prince, 1982) W = [weight] * $[1-(\text{deltaF}/6*\text{sigmaF})^2]^2$ A_i are: 0.754 0.0216 0.571

$(\Delta/\sigma)_{max} = 0.000543$
$\Delta\rho_{max} = 0.87$ e Å^{-3}
$\Delta\rho_{min} =$
-0.63 e Å^{-3}
Extinction correction: none
Scattering factors from International Tables Vol C 4.2.6.8 and 6.1.1.4
Absolute structure: Flack (1983), 7371 Friedel-pairs
Flack parameter = -0.016 (6)

H atoms were added at calculated positions and, during refinement, each rides on the C atom to which it is attached.

Data collection:
COLLECT (Nonius BV, 1997). Cell refinement: Denzo/Scalepack (Otwinowski & Minor, 1997). Data reduction: Denzo/Scalepack (Otwinowski & Minor, 1997). Program(s) used to solve structure: *SIR92* (Altomare *et al.* 1994). Program(s) used to refine structure: *CRYSTALS* (Watkin *et al.* 2003). Molecular graphics: *ORTEP–II* (Johnson 1976) in teXsan (MSC, 1992–1997) . Software used to prepare material for publication: *CRYSTALS* (Watkin et al. 2003).

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Table S1. *Fractional atomic coordinates and equivalent isotropic displacement parameters (Å²)*

$$U_{eq} = (1/3)\Sigma_i \Sigma_j U^{ij} a^i a^j a_i . a_j .$$

	x	*y*	*z*	U_{eq}
I15	0.31545(4)	0.181714(19)	0.52149(3)	0.0559
I115	0.17264(4)	0.31572(2)	0.23247(3)	0.0675
I215	0.88193(5)	0.212973(19)	0.24315(4)	0.0757
I315	0.59696(6)	0.28545(2)	−0.00384(4)	0.0863
Br26	0.17991(7)	0.02674(2)	0.32471(4)	0.0606
Br126	0.32795(7)	0.47589(2)	0.07087(4)	0.0638
Br226	0.67455(6)	0.06247(2)	0.42150(4)	0.0636
Br326	0.82777(6)	0.43412(2)	0.17721(4)	0.0605
O7	0.0128(4)	0.05176(11)	0.6597(3)	0.0578
O9	−0.2253(6)	0.06696(13)	0.6958(3)	0.0779
O11	0.2805(4)	0.08582(10)	0.6241(2)	0.0484
O13	0.2845(5)	0.08927(12)	0.7925(3)	0.0658
O16	0.2199(3)	0.12066(10)	0.3360(2)	0.0461
O24	0.2760(5)	0.20680(12)	−0.0643(3)	0.0706
O107	0.4766(4)	0.43941(12)	0.4092(3)	0.0655
O109	0.7221(5)	0.42835(14)	0.4422(3)	0.0795
O111	0.2063(4)	0.40877(11)	0.3527(3)	0.0560
O113	0.1994(6)	0.40447(13)	0.5198(3)	0.0768
O116	0.2747(4)	0.38224(11)	0.0650(3)	0.0527
O124	0.2453(5)	0.29228(12)	−0.3267(3)	0.0638
O207	0.8725(4)	0.05913(11)	0.0883(2)	0.0527
O209	1.0955(4)	0.02917(16)	0.0654(3)	0.0738
O211	0.7206(3)	0.12975(11)	0.1286(2)	0.0499
O213	0.7317(4)	0.13365(14)	−0.0388(3)	0.0666
O216	0.8337(3)	0.14564(11)	0.4191(3)	0.0522
O224	0.9808(5)	0.22698(17)	0.8161(3)	0.0920
O307	0.6275(4)	0.43903(12)	−0.1626(3)	0.0579
O309	0.4107(4)	0.47417(16)	−0.1861(3)	0.0793
O311	0.7678(4)	0.36574(12)	−0.1188(3)	0.0565
O313	0.7450(5)	0.35988(17)	−0.2859(3)	0.0833
O316	0.6580(4)	0.35225(10)	0.1707(3)	0.0499
O324	0.5169(4)	0.25906(11)	0.5517(3)	0.0610
C1	0.0295(6)	0.07849(14)	0.5796(4)	0.0467
C2	0.1542(5)	0.10793(15)	0.5978(3)	0.0440
C3	0.1761(5)	0.12966(14)	0.5035(3)	0.0394
C4	0.2334(5)	0.10145(16)	0.4273(3)	0.0452
C5	0.1464(5)	0.06265(14)	0.4287(3)	0.0396
C6	0.0553(5)	0.05298(15)	0.4943(3)	0.0422
C8	−0.0849(9)	0.06635(19)	0.7281(4)	0.0767
C10	−0.2783(9)	0.0275(2)	0.6749(6)	0.0928
C12	0.3534(7)	0.09934(19)	0.7087(4)	0.0588
C14	0.2932(10)	0.04652(18)	0.8147(5)	0.0842
C17	0.3518(6)	0.1226(2)	0.2866(4)	0.0609
C18	0.3222(5)	0.14443(17)	0.1926(4)	0.0492
C19	0.3212(6)	0.18627(19)	0.1873(4)	0.0577
C20	0.3005(7)	0.20621(16)	0.1016(4)	0.0572
C21	0.2857(5)	0.18438(18)	0.0184(3)	0.0457
C22	0.2823(6)	0.14256(16)	0.0208(4)	0.0487
C23	0.3009(5)	0.12283(16)	0.1086(4)	0.0505
C25	0.2908(11)	0.1856(2)	−0.1520(5)	0.0957
C101	0.4613(6)	0.41515(15)	0.3238(4)	0.0485
C102	0.3324(6)	0.38649(16)	0.3304(4)	0.0503
C103	0.3135(5)	0.36746(15)	0.2314(4)	0.0448
C104	0.2589(6)	0.39901(16)	0.1586(3)	0.0463
C105	0.3540(6)	0.43636(15)	0.1701(4)	0.0475
C106	0.4448(5)	0.44381(16)	0.2414(3)	0.0441
C108	0.5832(9)	0.4241(2)	0.4754(5)	0.0810
C110	0.7613(10)	0.4698(2)	0.4297(6)	0.1025
C112	0.1316(8)	0.3947(2)	0.4309(5)	0.0734
C114	0.1932(11)	0.4464(2)	0.5443(5)	0.0953
C117	0.1485(6)	0.3853(2)	0.0040(4)	0.0654
C118	0.1786(5)	0.36193(16)	−0.0861(4)	0.0496

C119	0.1932(7)	0.3205(2)	−0.0822(4)	0.0678
C120	0.2176(8)	0.29837(18)	−0.1635(5)	0.0732
C121	0.2255(5)	0.31729(16)	−0.2489(4)	0.0451
C122	0.2156(6)	0.35859(16)	−0.2553(4)	0.0517
C123	0.1931(6)	0.38074(17)	−0.1722(4)	0.0555
C125	0.2283(8)	0.3097(2)	−0.4189(4)	0.0710
C201	0.9086(5)	0.08286(15)	0.1712(3)	0.0443
C202	0.8687(5)	0.12741(14)	0.1565(4)	0.0429
C203	0.8931(5)	0.14774(15)	0.2539(4)	0.0430
C204	0.7869(5)	0.13322(16)	0.3268(4)	0.0474
C205	0.7784(5)	0.08784(16)	0.3206(4)	0.0470
C206	0.8328(5)	0.06478(16)	0.2542(4)	0.0474
C208	0.9868(7)	0.0532(2)	0.0261(4)	0.0641
C210	1.0489(8)	−0.0108(2)	0.0845(5)	0.0838
C212	0.6901(7)	0.15318(19)	0.0452(4)	0.0632
C214	0.6436(7)	0.1001(2)	−0.0655(5)	0.0723
C217	0.7267(6)	0.1673(2)	0.4725(4)	0.0643
C218	0.7949(5)	0.18176(18)	0.5639(4)	0.0529
C219	0.9027(6)	0.2108(2)	0.5658(4)	0.0649
C220	0.9646(7)	0.2247(2)	0.6502(4)	0.0674
C221	0.9152(6)	0.2100(2)	0.7362(4)	0.0628
C222	0.8100(6)	0.1807(2)	0.7378(4)	0.0640
C223	0.7518(6)	0.16631(17)	0.6515(4)	0.0594
C225	0.9310(9)	0.2148(3)	0.9062(5)	0.1049
C301	0.5881(6)	0.41555(16)	−0.0812(4)	0.0513
C302	0.6218(5)	0.37059(17)	−0.0943(4)	0.0505
C303	0.5981(5)	0.35074(16)	0.0043(4)	0.0499
C304	0.7063(5)	0.36416(15)	0.0798(4)	0.0454
C305	0.7206(5)	0.41000(17)	0.0751(4)	0.0476
C306	0.6677(5)	0.43276(17)	0.0050(4)	0.0484
C308	0.5102(7)	0.4483(2)	−0.2250(4)	0.0704
C310	0.4701(8)	0.5137(2)	−0.1635(6)	0.0887
C312	0.7889(8)	0.3411(2)	−0.2019(5)	0.0769
C314	0.8369(8)	0.3915(3)	−0.3153(5)	0.0876
C317	0.7633(6)	0.33074(18)	0.2283(5)	0.0628
C318	0.6949(5)	0.31417(16)	0.3157(4)	0.0529
C319	0.5804(5)	0.28746(16)	0.3073(4)	0.0490
C320	0.5224(6)	0.27005(16)	0.3870(4)	0.0536
C321	0.5783(6)	0.27851(16)	0.4765(4)	0.0487
C322	0.6907(7)	0.30612(19)	0.4873(4)	0.0641
C323	0.7463(6)	0.32347(18)	0.4054(5)	0.0655
C325	0.5715(7)	0.2670(2)	0.6460(4)	0.0686
H11	−0.0613(6)	0.09425(14)	0.5687(4)	0.0562
H21	0.1301(5)	0.12776(15)	0.6490(3)	0.0529
H31	0.0801(5)	0.13974(14)	0.4800(3)	0.0473
H41	0.3369(5)	0.09522(16)	0.4421(3)	0.0542
H61	0.0003(5)	0.02710(15)	0.4867(3)	0.0505
H81	−0.0778(9)	0.04852(19)	0.7858(4)	0.0928
H82	−0.0562(9)	0.09459(19)	0.7462(4)	0.0928
H101	−0.3807(9)	0.0293(2)	0.6516(6)	0.1119
H102	−0.2723(9)	0.0105(2)	0.7340(6)	0.1119
H103	−0.2192(9)	0.0149(2)	0.6243(6)	0.1119
H121	0.3623(7)	0.12950(19)	0.7055(4)	0.0704
H122	0.4515(7)	0.08692(19)	0.7112(4)	0.0704
H141	0.2422(10)	0.04106(18)	0.8753(5)	0.1008
H142	0.3964(10)	0.03841(18)	0.8228(5)	0.1008
H143	0.2471(10)	0.03056(18)	0.7614(5)	0.1008
H171	0.4252(6)	0.1379(2)	0.3258(4)	0.0732
H172	0.3880(6)	0.0947(2)	0.2741(4)	0.0732
H191	0.3359(6)	0.20244(19)	0.2473(4)	0.0692
H201	0.2962(7)	0.23648(16)	0.1000(4)	0.0689
H221	0.2666(6)	0.12665(16)	−0.0394(4)	0.0584
H231	0.2989(5)	0.09255(16)	0.1107(4)	0.0605
H251	0.2818(11)	0.2050(2)	−0.2066(5)	0.1151
H252	0.3872(11)	0.1722(2)	−0.1526(5)	0.1151
H253	0.2138(11)	0.1645(2)	−0.1585(5)	0.1151
H1011	0.5506(6)	0.39876(15)	0.3161(4)	0.0581
H1021	0.3521(6)	0.36510(16)	0.3797(4)	0.0604
H1031	0.4100(5)	0.35800(15)	0.2111(4)	0.0539
H1041	0.1561(6)	0.40596(16)	0.1697(3)	0.0555
H1061	0.5040(5)	0.46909(16)	0.2407(3)	0.0529

H1081	0.5762(9)	0.4392(2)	0.5371(5)	0.0966
H1082	0.5641(9)	0.3947(2)	0.4865(5)	0.0966
H1101	0.8615(10)	0.4713(2)	0.4059(6)	0.1223
H1102	0.7564(10)	0.4843(2)	0.4923(6)	0.1223
H1103	0.6935(10)	0.4827(2)	0.3822(6)	0.1223
H1121	0.0333(8)	0.4070(2)	0.4287(5)	0.0883
H1122	0.1233(8)	0.3646(2)	0.4260(5)	0.0883
H1141	0.2431(11)	0.4509(2)	0.6077(5)	0.1145
H1142	0.2417(11)	0.4628(2)	0.4944(5)	0.1145
H1143	0.0905(11)	0.4551(2)	0.5479(5)	0.1145
H1171	0.1282(6)	0.4143(2)	−0.0118(4)	0.0781
H1172	0.0640(6)	0.3733(2)	0.0364(4)	0.0781
H1191	0.1861(7)	0.3063(2)	−0.0195(4)	0.0811
H1201	0.2295(8)	0.26830(18)	−0.1594(5)	0.0875
H1221	0.2244(6)	0.37258(16)	−0.3182(4)	0.0620
H1231	0.1874(6)	0.41097(17)	−0.1757(4)	0.0663
H1251	0.2454(8)	0.2885(2)	−0.4685(4)	0.0855
H1252	0.2991(8)	0.3322(2)	−0.4258(4)	0.0855
H1253	0.1285(8)	0.3206(2)	−0.4274(4)	0.0855
H2011	1.0147(5)	0.08096(15)	0.1840(3)	0.0531
H2021	0.9301(5)	0.14016(14)	0.1072(4)	0.0515
H2031	0.9919(5)	0.14041(15)	0.2780(4)	0.0515
H2041	0.6901(5)	0.14509(16)	0.3116(4)	0.0566
H2061	0.8235(5)	0.03467(16)	0.2591(4)	0.0567
H2081	1.0282(7)	0.0803(2)	0.0100(4)	0.0771
H2082	0.9484(7)	0.0399(2)	−0.0336(4)	0.0771
H2101	1.1309(8)	−0.0269(2)	0.1126(5)	0.1003
H2102	1.0140(8)	−0.0238(2)	0.0236(5)	0.1003
H2103	0.9689(8)	−0.0100(2)	0.1307(5)	0.1003
H2121	0.7428(7)	0.17952(19)	0.0510(4)	0.0754
H2122	0.5843(7)	0.15845(19)	0.0406(4)	0.0754
H2141	0.6795(7)	0.0878(2)	−0.1256(5)	0.0863
H2142	0.6469(7)	0.0795(2)	−0.0132(5)	0.0863
H2143	0.5423(7)	0.1095(2)	−0.0765(5)	0.0863
H2171	0.6903(6)	0.1910(2)	0.4344(4)	0.0771
H2172	0.6449(6)	0.1488(2)	0.4864(4)	0.0771
H2191	0.9365(6)	0.2219(2)	0.5039(4)	0.0782
H2201	1.0439(7)	0.2451(2)	0.6495(4)	0.0810
H2221	0.7759(6)	0.1699(2)	0.8000(4)	0.0768
H2231	0.6774(6)	0.14445(17)	0.6523(4)	0.0714
H2251	0.9870(9)	0.2293(3)	0.9579(5)	0.1259
H2252	0.9442(9)	0.1849(3)	0.9139(5)	0.1259
H2253	0.8268(9)	0.2217(3)	0.9106(5)	0.1259
H3011	0.4825(6)	0.41865(16)	−0.0721(4)	0.0616
H3021	0.5564(5)	0.35834(17)	−0.1443(4)	0.0605
H3031	0.5011(5)	0.35939(16)	0.0256(4)	0.0599
H3041	0.8015(5)	0.35130(15)	0.0679(4)	0.0545
H3061	0.6810(5)	0.46278(17)	0.0092(4)	0.0581
H3081	0.5482(7)	0.4614(2)	−0.2836(4)	0.0843
H3082	0.4603(7)	0.4225(2)	−0.2430(4)	0.0843
H3101	0.3940(8)	0.5312(2)	−0.1357(6)	0.1064
H3102	0.5055(8)	0.5266(2)	−0.2231(6)	0.1064
H3103	0.5519(8)	0.5107(2)	−0.1161(6)	0.1064
H3121	0.8936(8)	0.3346(2)	−0.2055(5)	0.0925
H3122	0.7330(8)	0.3155(2)	−0.1951(5)	0.0925
H3141	0.7980(8)	0.4035(3)	−0.3764(5)	0.1052
H3142	0.8423(8)	0.4129(3)	−0.2648(5)	0.1052
H3143	0.9352(8)	0.3803(3)	−0.3255(5)	0.1052
H3171	0.8428(6)	0.34966(18)	0.2479(5)	0.0753
H3172	0.8033(6)	0.30791(18)	0.1903(5)	0.0753
H3191	0.5391(5)	0.28071(16)	0.2424(4)	0.0587
H3201	0.4390(6)	0.25110(16)	0.3796(4)	0.0642
H3221	0.7306(7)	0.31333(19)	0.5522(4)	0.0765
H3231	0.8267(6)	0.34345(18)	0.4127(5)	0.0782
H3251	0.5165(7)	0.2508(2)	0.6930(4)	0.0822
H3252	0.5609(7)	0.2965(2)	0.6606(4)	0.0822
H3253	0.6755(7)	0.2594(2)	0.6508(4)	0.0822

Table *S2. Anisotropic displacement parameters* (Å^2)

	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
I15	0.04969(19)	0.0470(2)	0.0713(2)	−0.00605(16)	0.00620(16)	0.00397(18)
I115	0.0472(2)	0.0584(2)	0.0968(3)	−0.00405(18)	0.00094(19)	−0.0097(2)
I215	0.0848(3)	0.0463(2)	0.0961(3)	0.0035(2)	0.0040(2)	−0.0025(2)
I315	0.0963(4)	0.0489(2)	0.1138(4)	−0.0100(2)	0.0046(3)	−0.0057(2)
Br26	0.0778(4)	0.0603(3)	0.0434(3)	0.0176(3)	−0.0021(3)	−0.0094(3)
Br126	0.0778(4)	0.0628(3)	0.0507(3)	0.0149(3)	−0.0016(3)	0.0072(3)
Br226	0.0630(4)	0.0759(4)	0.0522(3)	0.0002(3)	0.0066(3)	0.0139(3)
Br326	0.0648(4)	0.0613(3)	0.0549(3)	−0.0016(3)	−0.0051(3)	−0.0056(3)
O7	0.079(3)	0.049(2)	0.045(2)	−0.0049(18)	0.0130(19)	0.0069(16)
O9	0.091(3)	0.068(3)	0.077(3)	−0.018(2)	0.040(3)	−0.003(2)
O11	0.052(2)	0.049(2)	0.043(2)	0.0119(16)	−0.0077(16)	−0.0014(15)
O13	0.098(3)	0.055(2)	0.045(2)	0.011(2)	−0.006(2)	−0.0018(18)
O16	0.0418(18)	0.057(2)	0.0401(19)	0.0044(15)	0.0027(15)	0.0155(15)
O24	0.118(4)	0.048(2)	0.047(2)	0.016(2)	0.008(2)	0.0050(18)
O107	0.085(3)	0.061(2)	0.050(2)	0.002(2)	−0.016(2)	−0.0134(18)
O109	0.085(3)	0.079(3)	0.073(3)	−0.015(3)	−0.029(2)	0.002(2)
O111	0.064(2)	0.059(2)	0.044(2)	0.0125(18)	0.0043(18)	0.0049(17)
O113	0.124(4)	0.056(2)	0.051(2)	0.016(2)	0.010(2)	0.004(2)
O116	0.0438(19)	0.068(2)	0.046(2)	0.0132(17)	−0.0102(16)	−0.0172(18)
O124	0.090(3)	0.048(2)	0.053(2)	0.001(2)	−0.001(2)	−0.0027(18)
O207	0.051(2)	0.064(2)	0.0431(19)	0.0000(17)	−0.0015(16)	−0.0102(17)
O209	0.047(2)	0.101(4)	0.074(3)	−0.001(2)	0.005(2)	−0.040(3)
O211	0.0409(19)	0.062(2)	0.047(2)	0.0053(16)	−0.0041(15)	0.0043(17)
O213	0.071(3)	0.083(3)	0.046(2)	0.001(2)	0.0009(18)	0.005(2)
O216	0.0355(18)	0.068(2)	0.053(2)	0.0131(17)	0.0002(16)	−0.0130(18)
O224	0.089(3)	0.138(5)	0.049(3)	−0.027(3)	0.002(2)	−0.022(3)
O307	0.052(2)	0.070(2)	0.051(2)	0.0010(19)	−0.0023(17)	0.0102(19)
O309	0.053(2)	0.101(4)	0.082(3)	0.000(2)	−0.009(2)	0.041(3)
O311	0.0403(19)	0.074(3)	0.055(2)	0.0048(18)	−0.0019(17)	−0.0134(19)
O313	0.065(3)	0.127(4)	0.056(3)	−0.002(3)	−0.011(2)	−0.021(3)
O316	0.0398(18)	0.052(2)	0.058(2)	0.0092(16)	0.0045(16)	0.0170(17)
O324	0.070(2)	0.056(2)	0.057(2)	−0.0169(19)	−0.001(2)	0.0044(18)
C1	0.054(3)	0.036(3)	0.050(3)	−0.003(2)	0.008(2)	0.003(2)
C2	0.051(3)	0.043(3)	0.039(3)	−0.004(2)	0.004(2)	−0.001(2)
C3	0.036(2)	0.037(3)	0.046(3)	−0.0017(19)	0.002(2)	0.004(2)
C4	0.041(3)	0.059(3)	0.036(3)	0.014(2)	−0.002(2)	0.006(2)
C5	0.050(3)	0.039(2)	0.029(2)	0.005(2)	−0.008(2)	0.000(2)
C6	0.049(3)	0.038(3)	0.039(3)	−0.001(2)	−0.002(2)	0.003(2)
C8	0.127(7)	0.057(4)	0.047(3)	−0.021(4)	0.033(4)	−0.005(3)
C10	0.120(6)	0.071(4)	0.089(5)	−0.036(4)	0.028(4)	−0.002(4)
C12	0.072(4)	0.062(4)	0.042(3)	−0.002(3)	−0.006(3)	0.000(3)
C14	0.147(7)	0.055(4)	0.050(4)	0.014(4)	−0.008(4)	0.007(3)
C17	0.041(3)	0.090(4)	0.052(3)	0.007(3)	0.005(2)	0.019(3)
C18	0.045(3)	0.059(3)	0.044(3)	0.000(2)	0.001(2)	0.011(2)
C19	0.068(3)	0.060(4)	0.045(3)	−0.006(3)	0.003(3)	−0.011(3)
C20	0.083(4)	0.039(3)	0.050(3)	−0.002(3)	0.012(3)	−0.001(2)
C21	0.058(3)	0.044(3)	0.036(3)	0.009(3)	0.000(2)	0.002(2)
C22	0.053(3)	0.043(3)	0.050(3)	−0.005(2)	0.000(2)	−0.005(2)
C23	0.048(3)	0.042(3)	0.062(4)	0.002(2)	0.000(2)	0.009(3)
C25	0.162(8)	0.077(5)	0.048(4)	0.040(5)	0.015(4)	0.009(3)
C101	0.055(3)	0.047(3)	0.044(3)	0.010(2)	−0.005(2)	−0.009(2)
C102	0.049(3)	0.053(3)	0.049(3)	0.012(2)	0.001(2)	0.001(2)
C103	0.036(2)	0.043(3)	0.056(3)	0.002(2)	0.003(2)	−0.005(2)
C104	0.043(3)	0.054(3)	0.042(3)	0.014(2)	0.000(2)	−0.009(2)
C105	0.052(3)	0.041(3)	0.050(3)	0.014(2)	0.002(2)	−0.005(2)
C106	0.046(3)	0.046(3)	0.041(3)	0.004(2)	0.001(2)	−0.010(2)
C108	0.117(6)	0.074(4)	0.051(4)	−0.015(4)	−0.022(4)	0.007(3)
C110	0.136(7)	0.080(5)	0.090(5)	−0.039(5)	−0.027(5)	−0.010(4)
C112	0.078(4)	0.079(4)	0.064(4)	0.006(4)	0.014(3)	0.002(3)
C114	0.171(8)	0.059(4)	0.056(4)	0.014(5)	0.011(5)	0.001(3)
C117	0.038(3)	0.095(5)	0.063(4)	0.014(3)	−0.015(3)	−0.024(3)
C118	0.044(3)	0.051(3)	0.053(3)	0.001(2)	−0.012(2)	−0.010(3)

C119	0.090(4)	0.066(4)	0.047(3)	−0.009(3)	−0.005(3)	0.002(3)
C120	0.110(5)	0.042(3)	0.066(4)	0.005(3)	−0.014(4)	−0.005(3)
C121	0.053(3)	0.036(3)	0.046(3)	−0.001(3)	−0.003(2)	−0.002(2)
C122	0.058(3)	0.044(3)	0.053(3)	0.000(2)	−0.005(3)	0.005(3)
C123	0.053(3)	0.047(3)	0.065(4)	0.007(2)	−0.010(3)	−0.003(3)
C125	0.098(5)	0.060(4)	0.056(4)	0.009(3)	0.010(3)	−0.002(3)
C201	0.041(3)	0.051(3)	0.041(3)	0.004(2)	0.000(2)	−0.008(2)
C202	0.034(3)	0.044(3)	0.050(3)	0.002(2)	0.001(2)	0.004(2)
C203	0.033(2)	0.040(3)	0.056(3)	0.005(2)	0.002(2)	−0.007(2)
C204	0.037(3)	0.056(3)	0.048(3)	0.005(2)	−0.007(2)	−0.007(2)
C205	0.041(3)	0.055(3)	0.046(3)	0.011(2)	0.000(2)	0.010(2)
C206	0.047(3)	0.047(3)	0.048(3)	0.007(2)	−0.005(2)	0.001(2)
C208	0.072(4)	0.069(4)	0.052(3)	−0.011(3)	0.009(3)	−0.007(3)
C210	0.086(5)	0.075(5)	0.089(5)	0.022(4)	−0.013(4)	−0.028(4)
C212	0.073(4)	0.070(4)	0.045(3)	0.019(3)	−0.016(3)	0.007(3)
C214	0.057(4)	0.099(5)	0.060(4)	0.001(3)	−0.015(3)	−0.008(3)
C217	0.053(3)	0.081(4)	0.058(4)	0.018(3)	−0.004(3)	−0.018(3)
C218	0.048(3)	0.059(3)	0.052(3)	0.006(3)	0.003(2)	−0.009(3)
C219	0.058(3)	0.084(4)	0.053(4)	0.006(3)	0.012(3)	0.002(3)
C220	0.064(4)	0.077(4)	0.062(4)	−0.018(3)	0.007(3)	−0.008(3)
C221	0.050(3)	0.086(5)	0.052(4)	−0.003(3)	0.001(3)	−0.015(3)
C222	0.066(4)	0.076(4)	0.050(3)	−0.004(3)	0.002(3)	0.002(3)
C223	0.060(3)	0.051(3)	0.068(4)	0.000(3)	0.005(3)	−0.008(3)
C225	0.103(6)	0.150(8)	0.062(5)	−0.016(6)	0.004(4)	−0.027(5)
C301	0.043(3)	0.059(3)	0.053(3)	0.004(2)	0.003(2)	0.004(3)
C302	0.038(3)	0.064(3)	0.049(3)	−0.002(2)	−0.004(2)	−0.002(2)
C303	0.034(3)	0.046(3)	0.070(4)	0.002(2)	0.004(2)	−0.003(3)
C304	0.034(2)	0.047(3)	0.055(3)	0.002(2)	0.002(2)	0.007(2)
C305	0.036(3)	0.062(3)	0.044(3)	0.002(2)	0.001(2)	0.001(3)
C306	0.046(3)	0.049(3)	0.051(3)	0.005(2)	0.001(2)	−0.007(3)
C308	0.077(4)	0.087(5)	0.048(4)	−0.017(4)	−0.005(3)	0.007(3)
C310	0.084(5)	0.094(6)	0.088(5)	0.030(4)	0.001(4)	0.039(4)
C312	0.074(4)	0.090(5)	0.067(4)	0.011(4)	0.009(3)	−0.019(4)
C314	0.071(4)	0.133(7)	0.060(4)	0.003(5)	0.003(3)	0.003(4)
C317	0.043(3)	0.060(4)	0.085(4)	0.012(3)	0.002(3)	0.026(3)
C318	0.042(3)	0.046(3)	0.070(4)	0.012(3)	0.000(3)	0.015(3)
C319	0.044(3)	0.049(3)	0.054(3)	0.001(2)	−0.003(2)	0.002(3)
C320	0.049(3)	0.045(3)	0.066(4)	−0.011(2)	−0.007(3)	0.001(3)
C321	0.046(3)	0.040(3)	0.060(3)	−0.001(2)	0.008(3)	0.007(2)
C322	0.070(4)	0.061(4)	0.060(4)	−0.012(3)	−0.015(3)	0.000(3)
C323	0.059(3)	0.058(4)	0.079(4)	−0.015(3)	−0.012(3)	0.011(3)
C325	0.075(4)	0.075(4)	0.056(4)	−0.002(3)	−0.005(3)	−0.003(3)

Table *S*3. *Geometric parameters (Å,°)*

I15—C3	2.162(5)	O113—C114	1.428(8)
I115—C103	2.153(5)	O116—C104	1.433(6)
I215—C203	2.161(5)	O116—C117	1.436(6)
I315—C303	2.158(5)	O124—C121	1.382(6)
Br26—C5	1.909(4)	O124—C125	1.417(7)
Br126—C105	1.916(5)	O207—C201	1.431(6)
Br226—C205	1.925(5)	O207—C208	1.407(7)
Br326—C305	1.894(5)	O209—C208	1.387(8)
O7—C1	1.438(6)	O209—C210	1.417(9)
O7—C8	1.422(7)	O211—C202	1.424(6)
O9—C8	1.371(9)	O211—C212	1.421(6)
O9—C10	1.421(8)	O213—C212	1.405(7)
O11—C2	1.423(6)	O213—C214	1.420(8)
O11—C12	1.419(6)	O216—C204	1.412(6)
O13—C12	1.393(7)	O216—C217	1.450(6)
O13—C14	1.447(7)	O224—C221	1.378(7)
O16—C4	1.429(6)	O224—C225	1.414(9)
O16—C17	1.428(6)	O307—C301	1.434(6)
O24—C21	1.375(6)	O307—C308	1.412(7)
O24—C25	1.423(8)	O309—C308	1.382(8)
O107—C101	1.442(6)	O309—C310	1.449(9)
O107—C108	1.430(8)	O311—C302	1.419(6)
O109—C108	1.393(9)	O311—C312	1.436(7)
O109—C110	1.426(9)	O313—C312	1.380(8)
O111—C102	1.427(6)	O313—C314	1.417(9)
O111—C112	1.393(7)	O316—C304	1.418(6)
O113—C112	1.416(8)	O316—C317	1.438(6)

O324—C321	1.370(6)	C122—H1221	1.000
O324—C325	1.426(7)	C123—H1231	1.000
C1—C2	1.529(7)	C125—H1251	1.000
C1—C6	1.486(7)	C125—H1252	1.000
C1—H11	1.000	C125—H1253	1.000
C2—C3	1.521(7)	C201—C202	1.529(7)
C2—H21	1.000	C201—C206	1.500(7)
C3—C4	1.523(7)	C201—H2011	1.000
C3—H31	1.000	C202—C203	1.530(7)
C4—C5	1.515(7)	C202—H2021	1.000
C4—H41	1.000	C203—C204	1.518(7)
C5—C6	1.307(7)	C203—H2031	1.000
C6—H61	1.000	C204—C205	1.502(8)
C8—H81	1.000	C204—H2041	1.000
C8—H82	1.000	C205—C206	1.314(7)
C10—H101	1.000	C206—H2061	1.000
C10—H102	1.000	C208—H2081	1.000
C10—H103	1.000	C208—H2082	1.000
C12—H121	1.000	C210—H2101	1.000
C12—H122	1.000	C210—H2102	1.000
C14—H141	1.000	C210—H2103	1.000
C14—H142	1.000	C212—H2121	1.000
C14—H143	1.000	C212—H2122	1.000
C17—C18	1.516(7)	C214—H2141	1.000
C17—H171	1.000	C214—H2142	1.000
C17—H172	1.000	C214—H2143	1.000
C18—C19	1.383(8)	C217—C218	1.490(8)
C18—C23	1.385(8)	C217—H2171	1.000
C19—C20	1.376(8)	C217—H2172	1.000
C19—H191	1.000	C218—C219	1.385(9)
C20—C21	1.373(8)	C218—C223	1.397(8)
C20—H201	1.000	C219—C220	1.378(9)
C21—C22	1.381(8)	C219—H2191	1.000
C22—C23	1.396(7)	C220—C221	1.389(9)
C22—H221	1.000	C220—H2201	1.000
C23—H231	1.000	C221—C222	1.377(9)
C25—H251	1.000	C222—C223	1.392(8)
C25—H252	1.000	C222—H2221	1.000
C25—H253	1.000	C223—H2231	1.000
C101—C102	1.532(8)	C225—H2251	1.000
C101—C106	1.496(7)	C225—H2252	1.000
C101—H1011	1.000	C225—H2253	1.000
C102—C103	1.526(7)	C301—C302	1.529(8)
C102—H1021	1.000	C301—C306	1.509(7)
C103—C104	1.533(7)	C301—H3011	1.000
C103—H1031	1.000	C302—C303	1.548(8)
C104—C105	1.524(8)	C302—H3021	1.000
C104—H1041	1.000	C303—C304	1.505(7)
C105—C106	1.311(7)	C303—H3031	1.000
C106—H1061	1.000	C304—C305	1.520(7)
C108—H1081	1.000	C304—H3041	1.000
C108—H1082	1.000	C305—C306	1.319(7)
C110—H1101	1.000	C306—H3061	1.000
C110—H1102	1.000	C308—H3081	1.000
C110—H1103	1.000	C308—H3082	1.000
C112—H1121	1.000	C310—H3101	1.000
C112—H1122	1.000	C310—H3102	1.000
C114—H1141	1.000	C310—H3103	1.000
C114—H1142	1.000	C312—H3121	1.000
C114—H1143	1.000	C312—H3122	1.000
C117—C118	1.510(8)	C314—H3141	1.000
C117—H1171	1.000	C314—H3142	1.000
C117—H1172	1.000	C314—H3143	1.000
C118—C119	1.374(9)	C317—C318	1.498(8)
C118—C123	1.365(8)	C317—H3171	1.000
C119—C120	1.377(9)	C317—H3172	1.000
C119—H1191	1.000	C318—C319	1.386(8)
C120—C121	1.352(8)	C318—C323	1.366(8)
C120—H1201	1.000	C319—C320	1.379(8)
C121—C122	1.369(7)	C319—H3191	1.000
C122—C123	1.394(8)	C320—C321	1.371(8)

C320—H3201	1.000	H102—C10—H103	109.5
C321—C322	1.392(8)	O11—C12—O13	113.9(5)
C322—C323	1.393(9)	O11—C12—H121	108.3
C322—H3221	1.000	O13—C12—H121	108.3
C323—H3231	1.000	O11—C12—H122	108.3
C325—H3251	1.000	O13—C12—H122	108.3
C325—H3252	1.000	H121—C12—H122	109.5
C325—H3253	1.000	O13—C14—H141	109.5
C1—O7—C8	113.7(4)	O13—C14—H142	109.5
C8—O9—C10	112.1(6)	H141—C14—H142	109.5
C2—O11—C12	115.2(4)	O13—C14—H143	109.5
C12—O13—C14	112.9(5)	H141—C14—H143	109.5
C4—O16—C17	113.5(4)	H142—C14—H143	109.5
C21—O24—C25	117.1(5)	O16—C17—C18	107.7(4)
C101—O107—C108	113.0(5)	O16—C17—H171	109.9
C108—O109—C110	112.4(6)	C18—C17—H171	109.9
C102—O111—C112	115.6(4)	O16—C17—H172	109.9
C112—O113—C114	114.3(5)	C18—C17—H172	109.9
C104—O116—C117	114.4(4)	H171—C17—H172	109.5
C121—O124—C125	117.5(4)	C17—C18—C19	121.4(5)
C201—O207—C208	114.4(4)	C17—C18—C23	120.7(5)
C208—O209—C210	112.6(5)	C19—C18—C23	117.9(5)
C202—O211—C212	115.0(4)	C18—C19—C20	121.7(5)
C212—O213—C214	114.0(5)	C18—C19—H191	119.2
C204—O216—C217	114.6(4)	C20—C19—H191	119.2
C221—O224—C225	117.3(6)	C19—C20—C21	119.7(5)
C301—O307—C308	113.4(4)	C19—C20—H201	120.1
C308—O309—C310	112.7(5)	C21—C20—H201	120.1
C302—O311—C312	114.4(4)	O24—C21—C20	115.7(5)
C312—O313—C314	114.3(5)	O24—C21—C22	123.8(5)
C304—O316—C317	114.3(4)	C20—C21—C22	120.4(5)
C321—O324—C325	118.6(4)	C21—C22—C23	119.0(5)
O7—C1—C2	111.0(4)	C21—C22—H221	120.5
O7—C1—C6	107.6(4)	C23—C22—H221	120.5
C2—C1—C6	110.7(4)	C22—C23—C18	121.2(5)
O7—C1—H11	109.2	C22—C23—H231	119.4
C2—C1—H11	109.2	C18—C23—H231	119.4
C6—C1—H11	109.2	O24—C25—H251	109.5
C1—C2—O11	109.5(4)	O24—C25—H252	109.5
C1—C2—C3	106.0(4)	H251—C25—H252	109.5
O11—C2—C3	109.6(4)	O24—C25—H253	109.5
C1—C2—H21	110.5	H251—C25—H253	109.5
O11—C2—H21	110.5	H252—C25—H253	109.5
C3—C2—H21	110.5	O107—C101—C102	110.6(4)
C2—C3—I15	111.6(3)	O107—C101—C106	107.0(4)
C2—C3—C4	112.2(4)	C102—C101—C106	112.0(4)
I15—C3—C4	110.3(3)	O107—C101—H1011	109.1
C2—C3—H31	107.5	C102—C101—H1011	109.1
I15—C3—H31	107.5	C106—C101—H1011	109.1
C4—C3—H31	107.5	C101—C102—O111	110.2(4)
C3—C4—O16	109.3(4)	C101—C102—C103	105.6(4)
C3—C4—C5	108.1(4)	O111—C102—C103	109.6(4)
O16—C4—C5	110.6(4)	C101—C102—H1021	110.4
C3—C4—H41	109.6	O111—C102—H1021	110.4
O16—C4—H41	109.6	C103—C102—H1021	110.4
C5—C4—H41	109.6	C102—C103—I115	112.0(4)
C4—C5—Br26	114.6(3)	C102—C103—C104	110.5(4)
C4—C5—C6	125.0(4)	I115—C103—C104	110.7(3)
Br26—C5—C6	120.5(4)	C102—C103—H1031	107.8
C1—C6—C5	123.3(4)	I115—C103—H1031	107.8
C1—C6—H61	118.3	C104—C103—H1031	107.8
C5—C6—H61	118.3	C103—C104—O116	107.7(4)
O7—C8—O9	113.8(5)	C103—C104—C105	107.4(4)
O7—C8—H81	108.4	O116—C104—C105	109.5(4)
O9—C8—H81	108.4	C103—C104—H1041	110.7
O7—C8—H82	108.4	O116—C104—H1041	110.7
O9—C8—H82	108.4	C105—C104—H1041	110.7
H81—C8—H82	109.5	C104—C105—Br126	114.4(3)
O9—C10—H101	109.5	C104—C105—C106	126.3(5)
O9—C10—H102	109.5	Br126—C105—C106	119.3(4)
H101—C10—H102	109.5	C101—C106—C105	121.1(5)
O9—C10—H103	109.5	C101—C106—H1061	119.4
H101—C10—H103	109.5	C105—C106—H1061	119.4

O107—C108—O109	112.4(5)
O107—C108—H1081	108.7
O109—C108—H1081	108.7
O107—C108—H1082	108.7
O109—C108—H1082	108.7
H1081—C108—H1082	109.5
O109—C110—H1101	109.5
O109—C110—H1102	109.5
H1101—C110—H1102	109.5
O109—C110—H1103	109.5
H1101—C110—H1103	109.5
H1102—C110—H1103	109.5
O113—C112—O111	113.2(6)
O113—C112—H1121	108.5
O111—C112—H1121	108.5
O113—C112—H1122	108.5
O111—C112—H1122	108.5
H1121—C112—H1122	109.5
O113—C114—H1141	109.5
O113—C114—H1142	109.5
H1141—C114—H1142	109.5
O113—C114—H1143	109.5
H1141—C114—H1143	109.5
H1142—C114—H1143	109.5
O116—C117—C118	107.0(4)
O116—C117—H1171	110.1
C118—C117—H1171	110.1
O116—C117—H1172	110.1
C118—C117—H1172	110.1
H1171—C117—H1172	109.5
C117—C118—C119	119.7(6)
C117—C118—C123	122.0(5)
C119—C118—C123	118.3(5)
C118—C119—C120	121.0(6)
C118—C119—H1191	119.5
C120—C119—H1191	119.5
C119—C120—C121	119.9(6)
C119—C120—H1201	120.0
C121—C120—H1201	120.0
O124—C121—C120	115.6(5)
O124—C121—C122	123.6(5)
C120—C121—C122	120.8(5)
C121—C122—C123	118.6(5)
C121—C122—H1221	120.7
C123—C122—H1221	120.7
C122—C123—C118	121.2(5)
C122—C123—H1231	119.4
C118—C123—H1231	119.4
O124—C125—H1251	109.5
O124—C125—H1252	109.5
H1251—C125—H1252	109.5
O124—C125—H1253	109.5
H1251—C125—H1253	109.5
H1252—C125—H1253	109.5
O207—C201—C202	111.5(4)
O207—C201—C206	107.7(4)
C202—C201—C206	111.6(4)
O207—C201—H2011	108.6
C202—C201—H2011	108.6
C206—C201—H2011	108.6
C201—C202—O211	108.6(4)
C201—C202—C203	105.8(4)
O211—C202—C203	109.7(4)
C201—C202—H2021	110.9
O211—C202—H2021	110.9
C203—C202—H2021	110.9
C202—C203—I215	111.7(3)
C202—C203—C204	112.2(4)
I215—C203—C204	109.3(3)
C202—C203—H2031	107.8
I215—C203—H2031	107.8
C204—C203—H2031	107.8
C203—C204—O216	109.5(4)
C203—C204—C205	108.1(4)
O216—C204—C205	110.9(4)
C203—C204—H2041	109.5
O216—C204—H2041	109.4
C205—C204—H2041	109.4
C204—C205—Br226	114.7(4)
C204—C205—C206	126.7(5)
Br226—C205—C206	118.6(4)
C201—C206—C205	121.1(5)
C201—C206—H2061	119.4
C205—C206—H2061	119.4
O207—C208—O209	112.9(5)
O207—C208—H2081	108.6
O209—C208—H2081	108.6
O207—C208—H2082	108.6
O209—C208—H2082	108.6
H2081—C208—H2082	109.5
O209—C210—H2101	109.5
O209—C210—H2102	109.5
H2101—C210—H2102	109.5
O209—C210—H2103	109.5
H2101—C210—H2103	109.5
H2102—C210—H2103	109.5
O211—C212—O213	112.6(5)
O211—C212—H2121	108.7
O213—C212—H2121	108.7
O211—C212—H2122	108.7
O213—C212—H2122	108.7
H2121—C212—H2122	109.5
O213—C214—H2141	109.5
O213—C214—H2142	109.5
H2141—C214—H2142	109.5
O213—C214—H2143	109.5
H2141—C214—H2143	109.5
H2142—C214—H2143	109.5
O216—C217—C218	108.6(4)
O216—C217—H2171	109.7
C218—C217—H2171	109.7
O216—C217—H2172	109.7
C218—C217—H2172	109.7
H2171—C217—H2172	109.5
C217—C218—C219	121.9(5)
C217—C218—C223	120.7(5)
C219—C218—C223	117.5(5)
C218—C219—C220	122.1(6)
C218—C219—H2191	118.9
C220—C219—H2191	118.9
C219—C220—C221	119.0(6)
C219—C220—H2201	120.5
C221—C220—H2201	120.5
C220—C221—O224	114.2(6)
C220—C221—C222	120.9(5)
O224—C221—C222	124.9(6)
C221—C222—C223	118.9(5)
C221—C222—H2221	120.5
C223—C222—H2221	120.5
C218—C223—C222	121.5(5)
C218—C223—H2231	119.3
C222—C223—H2231	119.3
O224—C225—H2251	109.5
O224—C225—H2252	109.5
H2251—C225—H2252	109.5
O224—C225—H2253	109.5
H2251—C225—H2253	109.5
H2252—C225—H2253	109.5
O307—C301—C302	111.8(4)
O307—C301—C306	107.5(4)
C302—C301—C306	111.3(4)
O307—C301—H3011	108.7

C302—C301—H3011	108.7
C306—C301—H3011	108.7
C301—C302—O311	109.8(4)
C301—C302—C303	105.6(4)
O311—C302—C303	109.3(4)
C301—C302—H3021	110.7
O311—C302—H3021	110.7
C303—C302—H3021	110.7
C302—C303—I315	112.1(4)
C302—C303—C304	113.0(4)
I315—C303—C304	109.4(3)
C302—C303—H3031	107.3
I315—C303—H3031	107.3
C304—C303—H3031	107.3
C303—C304—O316	109.0(4)
C303—C304—C305	108.7(4)
O316—C304—C305	110.2(4)
C303—C304—H3041	109.7
O316—C304—H3041	109.7
C305—C304—H3041	109.7
C304—C305—Br326	115.5(4)
C304—C305—C306	124.6(5)
Br326—C305—C306	119.9(4)
C301—C306—C305	123.0(5)
C301—C306—H3061	118.5
C305—C306—H3061	118.5
O307—C308—O309	114.0(5)
O307—C308—H3081	108.3
O309—C308—H3081	108.3
O307—C308—H3082	108.3
O309—C308—H3082	108.3
H3081—C308—H3082	109.5
O309—C310—H3101	109.5
O309—C310—H3102	109.5
H3101—C310—H3102	109.5
O309—C310—H3103	109.5
H3101—C310—H3103	109.5
H3102—C310—H3103	109.5
O311—C312—O313	113.1(6)
O311—C312—H3121	108.6
O313—C312—H3121	108.6
O311—C312—H3122	108.6
O313—C312—H3122	108.6
H3121—C312—H3122	109.5
O313—C314—H3141	109.5
O313—C314—H3142	109.5
H3141—C314—H3142	109.5
O313—C314—H3143	109.5
H3141—C314—H3143	109.5
H3142—C314—H3143	109.5
O316—C317—C318	109.8(4)
O316—C317—H3171	109.4
C318—C317—H3171	109.4
O316—C317—H3172	109.4
C318—C317—H3172	109.4
H3171—C317—H3172	109.5
C317—C318—C319	120.5(5)
C317—C318—C323	121.5(5)
C319—C318—C323	118.0(5)
C318—C319—C320	121.0(5)
C318—C319—H3191	119.5
C320—C319—H3191	119.5
C319—C320—C321	120.5(5)
C319—C320—H3201	119.8
C321—C320—H3201	119.8
C320—C321—O324	116.7(5)
C320—C321—C322	119.8(5)
O324—C321—C322	123.5(5)
C321—C322—C323	118.4(5)
C321—C322—H3221	120.8
C323—C322—H3221	120.8
C322—C323—C318	122.3(5)
C322—C323—H3231	118.8
C318—C323—H3231	118.8
O324—C325—H3251	109.5
O324—C325—H3252	109.5
H3251—C325—H3252	109.5
O324—C325—H3253	109.5
H3251—C325—H3253	109.5
H3252—C325—H3253	109.5
I15—C3—C2—O11	-74.5(4)
I15—C3—C2—C1	167.4(3)
I15—C3—C4—O16	-68.4(4)
I15—C3—C4—C5	171.1(3)
I115—C103—C102—O111	-75.2(4)
I115—C103—C102—C101	166.1(3)
I115—C103—C104—O116	-68.3(4)
I115—C103—C104—C105	173.7(3)
I215—C203—C202—O211	-73.9(4)
I215—C203—C202—C201	169.1(3)
I215—C203—C204—O216	-68.7(4)
I215—C203—C204—C205	170.4(3)
I315—C303—C302—O311	-73.7(4)
I315—C303—C302—C301	168.3(3)
I315—C303—C304—O316	-67.6(4)
I315—C303—C304—C305	172.2(3)
Br26—C5—C4—O16	50.5(5)
Br26—C5—C4—C3	170.2(3)
Br26—C5—C6—C1	176.8(4)
Br126—C105—C104—O116	52.4(5)
Br126—C105—C104—C103	169.1(3)
Br126—C105—C106—C101	175.8(4)
Br226—C205—C204—O216	50.0(5)
Br226—C205—C204—C203	170.0(3)
Br226—C205—C206—C201	177.0(3)
Br326—C305—C304—O316	50.8(5)
Br326—C305—C304—C303	170.2(3)
Br326—C305—C306—C301	176.7(4)
O7—C1—C2—O11	53.0(5)
O7—C1—C2—C3	171.2(4)
O7—C1—C6—C5	-140.9(5)
O7—C8—O9—C10	63.6(7)
O9—C8—O7—C1	68.6(6)
O11—C2—C1—C6	-66.4(5)
O11—C2—C3—C4	49.8(5)
O11—C12—O13—C14	71.8(7)
O13—C12—O11—C2	73.9(6)
O16—C4—C3—C2	166.5(4)
O16—C4—C5—C6	-129.9(5)
O16—C17—C18—C19	83.5(6)
O16—C17—C18—C23	-99.1(5)
O24—C21—C20—C19	-175.4(5)
O24—C21—C22—C23	176.5(5)
O107—C101—C102—O111	53.2(6)
O107—C101—C102—C103	171.5(4)
O107—C101—C106—C105	-140.2(5)
O107—C108—O109—C110	63.0(7)
O109—C108—O107—C101	69.4(6)
O111—C102—C101—C106	-66.1(6)
O111—C102—C103—C104	48.7(5)
O111—C112—O113—C114	71.0(8)
O113—C112—O111—C102	75.4(6)
O116—C104—C103—C102	167.0(4)
O116—C104—C105—C106	-130.0(5)
O116—C117—C118—C119	67.6(6)
O116—C117—C118—C123	-111.9(6)
O124—C121—C120—C119	-177.8(6)
O124—C121—C122—C123	178.9(5)
O207—C201—C202—O211	54.5(5)
O207—C201—C202—C203	172.3(4)
O207—C201—C206—C205	-142.4(5)
O207—C208—O209—C210	63.6(6)
O209—C208—O207—C201	67.5(6)
O211—C202—C201—C206	-66.1(5)
O211—C202—C203—C204	49.2(5)
O211—C212—O213—C214	71.8(6)

O213—C212—O211—C202	72.9(6)
O216—C204—C203—C202	166.9(4)
O216—C204—C205—C206	−130.6(5)
O216—C217—C218—C219	66.2(7)
O216—C217—C218—C223	−113.7(6)
O224—C221—C220—C219	−177.7(6)
O224—C221—C222—C223	179.5(6)
O307—C301—C302—O311	53.0(6)
O307—C301—C302—C303	170.7(4)
O307—C301—C306—C305	−142.6(5)
O307—C308—O309—C310	63.2(7)
O309—C308—O307—C301	66.9(6)
O311—C302—C301—C306	−67.2(6)
O311—C302—C303—C304	50.6(6)
O311—C312—O313—C314	73.0(7)
O313—C312—O311—C302	71.3(7)
O316—C304—C303—C302	166.7(4)
O316—C304—C305—C306	−131.1(5)
O316—C317—C318—C319	59.2(7)
O316—C317—C318—C323	−123.4(5)
O324—C321—C320—C319	−178.2(5)
O324—C321—C322—C323	178.8(5)
C1—C2—O11—C12	−129.2(4)
C1—C2—C3—C4	−68.3(5)
C1—C6—C5—C4	−2.7(7)
C2—C1—O7—C8	91.7(5)
C2—C1—C6—C5	−19.4(7)
C2—C3—C4—C5	46.0(5)
C3—C2—O11—C12	115.0(4)
C3—C2—C1—C6	51.8(5)
C3—C4—O16—C17	125.5(4)
C3—C4—C5—C6	−10.2(6)
C4—O16—C17—C18	−178.7(4)
C5—C4—O16—C17	−115.6(4)
C6—C1—O7—C8	−147.0(5)
C17—C18—C19—C20	177.2(5)
C17—C18—C23—C22	−176.1(5)
C18—C19—C20—C21	−2.5(9)
C18—C23—C22—C21	0.1(8)
C19—C18—C23—C22	1.5(7)
C19—C20—C21—C22	4.1(9)
C20—C19—C18—C23	−0.3(8)
C20—C21—O24—C25	167.2(6)
C20—C21—C22—C23	−3.0(8)
C22—C21—O24—C25	−12.3(8)
C101—C102—O111—C112	−127.3(5)
C101—C102—C103—C104	−70.0(5)
C101—C106—C105—C104	−1.7(8)
C102—C101—O107—C108	99.0(5)
C102—C101—C106—C105	−18.9(7)
C102—C103—C104—C105	49.1(5)
C103—C102—O111—C112	116.8(5)
C103—C102—C101—C106	52.3(5)
C103—C104—O116—C117	130.8(5)
C103—C104—C105—C106	−13.3(7)
C104—O116—C117—C118	−173.4(4)
C105—C104—O116—C117	−112.7(5)
C106—C101—O107—C108	−138.8(5)
C117—C118—C119—C120	178.6(6)
C117—C118—C123—C122	−177.6(5)
C118—C119—C120—C121	−1(1)
C118—C123—C122—C121	−1.1(8)
C119—C118—C123—C122	2.9(8)
C119—C120—C121—C122	3(1)
C120—C119—C118—C123	−1.9(9)
C120—C121—O124—C125	168.9(6)
C120—C121—C122—C123	−1.8(8)
C122—C121—O124—C125	−11.8(8)
C201—C202—O211—C212	−129.0(4)
C201—C202—C203—C204	−67.8(5)
C201—C206—C205—C204	−2.4(8)
C202—C201—O207—C208	95.7(5)
C202—C201—C206—C205	−19.6(6)
C202—C203—C204—C205	46.0(5)
C203—C202—O211—C212	115.7(5)
C203—C202—C201—C206	51.7(5)
C203—C204—O216—C217	127.5(5)
C203—C204—C205—C206	−10.6(7)
C204—O216—C217—C218	−174.8(4)
C205—C204—O216—C217	−113.4(5)
C206—C201—O207—C208	−141.4(4)
C217—C218—C219—C220	179.0(6)
C217—C218—C223—C222	−177.2(5)
C218—C219—C220—C221	−2(1)
C218—C223—C222—C221	−1.8(9)
C219—C218—C223—C222	2.8(8)
C219—C220—C221—C222	3(1)
C220—C219—C218—C223	−1.0(9)
C220—C221—O224—C225	177.1(6)
C220—C221—C222—C223	−0.9(9)
C222—C221—O224—C225	−3(1)
C301—C302—O311—C312	−129.0(5)
C301—C302—C303—C304	−67.5(5)
C301—C306—C305—C304	−1.3(8)
C302—C301—O307—C308	99.9(5)
C302—C301—C306—C305	−19.9(7)
C302—C303—C304—C305	46.5(6)
C303—C302—O311—C312	115.6(5)
C303—C302—C301—C306	50.4(5)
C303—C304—O316—C317	129.3(4)
C303—C304—C305—C306	−11.8(7)
C304—O316—C317—C318	−171.4(4)
C305—C304—O316—C317	−111.6(5)
C306—C301—O307—C308	−137.6(5)
C317—C318—C319—C320	175.9(5)
C317—C318—C323—C322	−175.3(5)
C318—C319—C320—C321	−0.8(8)
C318—C323—C322—C321	−0.3(9)
C319—C318—C323—C322	2.1(8)
C319—C320—C321—C322	2.6(8)
C320—C319—C318—C323	−1.5(8)
C320—C321—O324—C325	−179.9(5)
C320—C321—C322—C323	−2.0(9)
C322—C321—O324—C325	−0.8(8)

Table *S4. Contact distances (Å)*

I15···O324	3.188(4)
Br26···C206^{i}	3.577(5)
O9···C223^{i}	3.343(7)
O13···C25^{ii}	3.273(8)
O16···C203^{i}	3.341(5)
O24···C225^{iii}	3.236(9)
O24···O224^{iii}	3.244(6)
O24···C120	3.363(7)
O109···C323	3.508(7)
O113···C125^{ii}	3.252(8)
O113···C122^{ii}	3.491(7)
O116···C303	3.317(6)
O124···C325^{iv}	3.181(8)
O124···O324^{iv}	3.276(6)
O124···C220^{iii}	3.443(8)
O213···C225^{iv}	3.36(1)
O213···C222^{iv}	3.584(7)
O216···C3^{v}	3.407(5)
O224···C25^{vi}	3.21(1)
O224···C120^{vi}	3.233(8)
O307···C210^{vii}	3.579(8)
O313···C325^{iv}	3.581(8)
O316···C103	3.377(6)
O316···C101	3.532(7)
O324···C125^{ii}	3.200(8)
C6···C110^{viii}	3.388(9)
C10···C106^{ix}	3.392(9)
C12···C25^{ii}	3.508(9)
C25···C225^{iii}	3.60(1)
C125···C325^{iv}	3.58(1)
C206···C310^{x}	3.491(9)
C210···C306^{xi}	3.490(9)

Appendix Two

X–ray Crystal Structure Report for Compound 192

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Abstract

The crystal structure of $C_9H_{13}BrO_3$ is reported.

Comment

The crystallographic asymmetric unit consists of one molecule of $C_9H_{13}BrO_3$. All H atoms were observed in difference electron density maps prior to their inclusion. They were included at calculated positions and then refined positionally. The compound is enantiometrically pure. The absolute structure of the crystal has been determined by refinement of the Flack parameter and this establishes the absolute configuration of the molecule. The largest peaks in the final difference electron density map are located near the Br atom or between C atoms.

Experimental

The compound was prepared by OJK and recrystalized from ethyl acetate/ petroleum spirit.

Crystal data

$C_9H_{13}BrO_3$
$Mr = 249.10$
Orthorhombic
$P2_12_12_1$
$a = 5.9587$ (1) Å
$b = 8.5961$ (2) Å
$V = 993.54$ (4) Å^3
$Z = 4$
$D_x = 1.665$ Mg m^{-3}
D_m not measured
Mo Kα radiation
$\lambda = 0.71073$ Å

Cell parameters from 10194 reflections
$\theta = 3\text{-}27.5^\circ$
$\mu = 4.110$ mm^{-1}
$T = 200$ K
Rod
Colourless
Crystal source: local

Data collection

Nonius KappaCCD diffractometer
φ and ω scans with CCD
Absorption correction:
by integration via Gaussian method
(Coppens, 1970), implemented in maXus (2000).
$T_{min} = 0.641$, $T_{max} = 0.781$
13677 measured reflections
2278 independent reflections

1957 reflections with
$I > 3.0\sigma(I)$
$R_{int} = 0.051$
$\theta_{max} = 27.468^\circ$
$h = -7 \rightarrow 6$
$k = -11 \rightarrow 11$
$l = -25 \rightarrow 25$

Refinement

Refinement on *F*
$R = 0.0220$
$wR = 0.0232$
$S = 1.1135$
1957 reflections
159 parameters
Only coordinates of H atoms refined
Method, part 1, Chebychev polynomial, Carruthers & Watkin, 1979, Prince, 1982) [weight] = $1.0/[A_0 * T_0(x) + A_1 * T_1(x) ... + A_{n-1}]*T_{n-1}(x)]$, where A_i are the Chebychev coefficients listed below and x= Fcalc/Fmax Method = Robust Weighting (Prince, 1982) W= [weight] * $[1-(deltaF/6*sigmaF)^2]^2$ A_i are: 1.55 0.140 1.41

$(\Delta/\sigma)_{max} = 0.001410$
$\Delta\rho_{max} = 0.45$ e Å^{-3}
$\Delta\rho_{min} = -0.61$ e Å^{-3}
Extinction correction: Larson (1970), Equation 22
Extinction coefficient: 131 (17)
Scattering factors from International Tables Vol C 4.2.6.8 and 6.1.1.4
Absolute structure: Flack (1983), 929 Friedel-pairs
Flack parameter = 0.002 (7)

Table 1. Selected geometric parameters (Å, °)

Br13—C5	1.911 (2)	C1—C6	1.502 (3)
O7—C1	1.437 (2)	C2—C3	1.517 (3)
O7—C8	1.427 (2)	C3—C4	1.516 (3)
O9—C2	1.446 (2)	C4—C5	1.506 (3)
O9—C8	1.438 (2)	C5—C6	1.332 (3)
O12—C4	1.427 (2)	C8—C10	1.521 (3)
C1—C2	1.520 (3)	C8—C11	1.525 (3)
C1-O7—C8)	108.15 (14	O12—C4—C5	111.54 (17)
C2—O9—C8	107.35 (13)	C4—C5—Br13	114.48 (14)
O7—C1—C2	102.50 (15)	C4—C5—C6	126.23 (19)
O7—C1—C6)	110.48 (16	Br13—C5—C6	119.22 (15)
C2—C1—C6	112.84 (16)	C1—C6—C5	122.28 (17)
C1—C2—O9	101.45 (15)	O9—C8—O7	106.58 (15)
C1—C2—C3	114.45 (16)	O9—C8—C10	108.52 (17)
O9—C2—C3	110.25 (16)	O7—C8—C10	110.84 (17)
C2—C3—C4	114.04 (16)	O9—C8—C11	109.65 (17)
C3—C4—O12	107.29 (15)	O7—C8—C11	108.46 (18)
C3—C4—C5	110.71 (15)	C10—C8—C11	112.61 (18)

Table 2. Hydrogen-bonding geometry (Å, °)

D-H···*A*	*D*-H	H···*A*	*D*-H···*A*	*D*-H···*A*
O12-H1···O9	0.83 (3)	2.01	2.822 (2)	166 (3)

Symmetry codes: (i) 1 – x, y – ½, ½ - z

H atoms were included at calculated positions or where observed in difference electron density maps and then refined positionally.

Data collection:
COLLECT (Nonius BV, 1997). Cell refinement: Denzo/Scalepack (Otwinowski & Minor, 1997). Data reduction: Denzo/Scalepack (Otwinowski & Minor, 1997). Program(s) used to solve structure: *SIR92* (Altomare *et al.* 1994). Program(s) used to refine structure: *CRYSTALS* (Watkin *et al.* 2003). Molecular graphics: *ORTEP–II* (Johnson 1976) in teXsan (MSC, 1992–1997) . Software used to prepare material for publication: *CRYSTALS* (Watkin et al. 2003).

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Table *S*1. *Fractional atomic coordinates and equivalent isotropic displacement parameters (Å²)*

$$U_{eq} = (1/3)\Sigma_i \Sigma_j U^{ij} a^i a^j a_i.a_j$$

	x	*y*	*z*	U_{eq}
Br13	0.66829 (4)	0.42134 (2)	0.380422 (11)	0.0366
O7	0.1608 (3)	0.86832 (15)	0.44763 (6)	0.0304
O9	0.2587 (2)	0.90855 (19)	0.33445 (6)	0.0300
O12	0.3605 (3)	0.4455 (2)	0.25053 (8)	0.0410
C1	0.1173 (3)	0.7276 (2)	0.40993 (10)	0.0278
C2	0.0925 (3)	0.7861 (2)	0.33638 (9)	0.0271
C3	0.1422 (4)	0.6653 (2)	0.28146 (9)	0.0326
C4	0.3679 (3)	0.5860 (3)	0.28968 (9)	0.0307
C5	0.4166 (3)	0.5545 (2)	0.36456 (10)	0.0280
C6	0.3084 (4)	0.6151 (2)	0.41830 (9)	0.0275
C8	0.2698 (3)	0.9753 (2)	0.40237 (10)	0.0272
C10	0.5153 (4)	0.9950 (3)	0.42195 (12)	0.0364
C11	0.1408 (4)	1.1284 (3)	0.40368 (13)	0.0401
H1	0.484 (6)	0.444 (4)	0.2309 (16)	0.0490
H11	-0.013 (5)	0.682 (3)	0.4265 (12)	0.0331
H21	-0.046 (5)	0.824 (3)	0.3281 (13)	0.0325
H31	0.126 (5)	0.716 (4)	0.2359 (15)	0.0388
H32	0.025 (5)	0.584 (4)	0.2852 (14)	0.0388
H41	0.491 (5)	0.658 (3)	0.2744 (13)	0.0365
H61	0.357 (5)	0.587 (3)	0.4673 (13)	0.0328
H101	0.594 (6)	1.065 (4)	0.3888 (14)	0.0435
H102	0.520 (6)	1.037 (3)	0.4686 (15)	0.0435
H103	0.585 (5)	0.898 (4)	0.4193 (15)	0.0435
H111	0.206 (6)	1.201 (4)	0.3711 (16)	0.0479
H112	0.127 (5)	1.178 (4)	0.4507 (17)	0.0479
H113	-0.010 (6)	1.109 (3)	0.3870 (14)	0.0479

Table *S*2. *Anisotropic displacement parameters* (Å²)

	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
Br13	0.03268 (11)	0.04660 (12)	0.03038 (11)	0.00326 (8)	0.00054 (9)	-0.00308 (8)
O7	0.0366 (7)	0.0273 (6)	0.0274 (5)	-0.0038 (6)	0.0080 (6)	-0.0037 (5)
O9	0.0308 (6)	0.0315 (7)	0.0276 (6)	-0.0059 (5)	0.0040 (5)	0.0029 (6)
O12	0.0375 (9)	0.0492 (10)	0.0363 (7)	-0.0064 (7)	0.0077 (6)	-0.0193 (6)
C1	0.0264 (10)	0.0302 (9)	0.0266 (8)	-0.0047 (7)	0.0032 (6)	-0.0022 (7)
C2	0.0209 (8)	0.0325 (9)	0.0280 (9)	-0.0038 (7)	0.0006 (6)	0.0015 (7)
C3	0.0346 (12)	0.0422 (10)	0.0210 (8)	-0.0068 (9)	0.0002 (7)	-0.0015 (7)
C4	0.0308 (10)	0.0343 (9)	0.0269 (8)	-0.0077 (8)	0.0050 (6)	-0.0077 (8)
C5	0.0267 (8)	0.0251 (8)	0.0321 (9)	-0.0061 (6)	-0.0001 (6)	-0.0015 (7)
C6	0.0307 (10)	0.0255 (8)	0.0262 (8)	-0.0024 (7)	0.0025 (7)	0.0021 (6)
C8	0.0269 (9)	0.0249 (8)	0.0297 (8)	-0.0001 (6)	0.0008 (7)	0.0003 (7)
C10	0.0272 (11)	0.0402 (11)	0.0418 (12)	-0.0040 (8)	-0.0033 (9)	0.0015 (9)
C11	0.0392 (13)	0.0306 (10)	0.0504 (12)	0.0064 (8)	0.0009 (10)	0.0018 (8)

Table *S*3. *Geometric parameters (Å,°)*

Br13—C5	1.911 (2)	C3—H32	0.99 (3)
O7—C1	1.437 (2)	C4—C5	1.506 (3)
O7—C8	1.427 (2)	C4—H41	1.00 (3)
O9—C2	1.446 (2)	C5—C6	1.332 (3)
O9—C8	1.438 (2)	C6—H61	1.02 (3)
O12—C4	1.427 (2)	C8—C10	1.521 (3)
O12—H1	0.83 (4)	C8—C11	1.525 (3)
C1—C2	1.520 (3)	C10—H101	1.00 (3)
C1—C6	1.502 (3)	C10—H102	0.97 (3)
C1—H11	0.93 (3)	C10—H103	0.93 (3)
C2—C3	1.517 (3)	C11—H111	0.97 (3)
C2—H21	0.90 (3)	C11—H112	1.01 (3)

C3—C4	1.516 (3)	C11—H113	0.97 (4)
C3—H31	0.99 (3)	C3—H32	0.99 (3)
C1—O7—C8	108.15 (14)	C5—C4—H41	104.7 (15)
C2—O9—C8	107.35 (13)	C4—C5—Br13	114.48 (14)
C4—O12—H1	103 (2)	C4—C5—C6	126.23 (19)
O7—C1—C2	102.50 (15)	Br13—C5—C6	119.22 (15)
O7—C1—C6	110.48 (16)	C1—C6—C5	122.28 (17)
C2—C1—C6	112.84 (16)	C1—C6—H61	117.7 (15)
O7—C1—H11	109.2 (15)	C5—C6—H61	120.0 (15)
C2—C1—H11	112.5 (15)	O9—C8—O7	106.58 (15)
C6—C1—H11	109.1 (16)	O9—C8—C10	108.52 (17)
C1—C2—O9	101.45 (15)	O7—C8—C10	110.84 (17)
C1—C2—C3	114.45 (16)	O9—C8—C11	109.65 (17)
O9—C2—C3	110.25 (16)	O7—C8—C11	108.46 (18)
C1—C2—H21	112.1 (17)	C10—C8—C11	112.61 (18)
O9—C2—H21	111.2 (17)	C8—C10—H101	111.1 (18)
C3—C2—H21	107.5 (17)	C8—C10—H102	107 (2)
C2—C3—C4	114.04 (16)	H101—C10—H102	111 (2)
C2—C3—H31	107.7 (17)	C8—C10—H103	108.4 (19)
C4—C3—H31	112.2 (17)	H101—C10—H103	107 (3)
C2—C3—H32	106.9 (16)	H102—C10—H103	112 (3)
C4—C3—H32	107.7 (17)	C8—C11—H111	110.1 (20)
H31—C3—H32	108 (2)	C8—C11—H112	114.9 (19)
C3—C4—O12	107.29 (15)	H111—C11—H112	110 (3)
C3—C4—C5	110.71 (15)	C8—C11—H113	108.2 (18)
O12—C4—C5	111.54 (17)	H111—C11—H113	105 (2)
C3—C4—H41	110.0 (17)	H112—C11—H113	107 (2)
O12—C4—H41	112.6 (15)		
Br13—C5—C4—O12	49.6 (2)	C1—O7—C8—C11	127.3 (2)
Br13—C5—C4—C3	169.0 (1)	C1—C2—O9—C8	-32.2 (2)
Br13—C5—C6—C1	176.6 (1)	C1—C2—C3—C4	-52.9 (2)
O7—C1—C2—O9	36.8 (2)	C1—C6—C5—C4	-0.3 (3)
O7—C1—C2—C3	155.5 (2)	C2—O9—C8—C10	134.9 (2)
O7—C1—C6—C5	-124.9 (2)	C2—O9—C8—C11	-101.7 (2)
O7—C8—O9—C2	15.5 (2)	C2—C1—O7—C8	-28.7 (2)
O9—C2—C1—C6	-82.1 (2)	C2—C1—C6—C5	-10.8 (3)
O9—C2—C3—C4	60.8 (2)	C2—C3—C4—C5	39.4 (2)
O9—C8—O7—C1	9.3 (2)	C3—C2—O9—C8	-153.9 (1)
O12—C4—C3—C2	161.3 (2)	C3—C2—C1—C6	36.7 (2)
O12—C4—C5—C6	-133.4 (2)	C3—C4—C5—C6	-14.0 (3)
C1—O7—C8—C10	-108.6 (2)	C6—C1—O7—C8	91.8 (2)

Table *S4. Contact distances (Å)*

O7···C6^{i}	3.345 (2)	O12···C2^{iv}	3.465 (2)
O9···O12^{ii}	2.822 (2)	O12···C4^{iii}	3.575 (3)
O12···C10^{iii}	3.453 (3)		

Symmetry codes: (i) x – ½, $^{3}/_{2}$ – y; 1 – z;
(ii) 1 – x, ½ + y, ½ – z;
(iii) 1 – x, y – ½, ½ – z;
(iv) –x, y – ½, ½ – z.

Appendix Three

X-ray Crystal Structure Report for Compound 247

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Abstract

The crystal structure of $C_{16}H_{17}ClO_4$ is reported.

Comment

The crystallographic asymmetric unit consists of one molecule of $C_{16}H_{17}ClO_4$. All H atoms were observed in difference electron density maps prior to their inclusion. They were included at calculated positions and then refined positionally. The largest peaks in the final difference electron density map are located near the Cl atom or
between C atoms.

Experimental

The compound was prepared by OJK and recrystallized from chloroform.

Crystal data

$C_{16}H_{17}ClO_4$
$M_r = 308.76$
Triclinic
$P\bar{1}$
$a = 9.1808(3)$ Å
$b = 9.4965(2)$ Å
$c = 9.8483(3)$ Å
$\beta = 70.7497\ (13)^\circ$
$\gamma = 74.6515\ (17)^\circ$
$V = 769.22\ (4)$ Å^3
$Z = 2$
$D_x = 1.333$ Mg m^{-3}
D_m not measured
Mo Kα radiation
$\lambda = 0.71073$ Å

Cell parameters from 10947 reflections
$\theta = 2.6–27.5^\circ$
$\mu = 0.261$ mm^{-1}
$T = 200$ K
Plate
Colourless
0.36 x 0.34 x 0.10 mm
Crystal source: local

Data collection

Nonius KappaCCD diffractometer
ϕ and ω scans with CCD
Absorption correction:
by integration via Gaussian method (Coppens, 1970)
implemented in maXus (2000)
$T_{min} = 0.920$, $T_{max} = 0.977$
15541 measured reflections
3515 independent reflections

2770 reflections with
$I > 3.0\sigma(I)$
$R_{int} = 0.026$
$\theta_{max} = 27.504^\circ$
$h = -11 \rightarrow 11$
$k = -12 \rightarrow 11$
$l = -12 \rightarrow 12$

Refinement

Refinement on *F*
$R = 0.0331$
$wR = 0.0359$
$S = 1.1172$
2770 reflections
241 parameters
Only coordinates of H atoms refined

Method, part 1, Chebychev polynomial,
(Carruthers & Watkin, 1979, Prince, 1982)
[weight] = $1.0/[A_0 * T_0(x) + A_1 * T_1(x) \ldots + A_{n-1}] * T_n^{-1}(x)]$
where A_i are the Chebychev coefficients
listed below and x= Fcalc/Fmax Method
= Robust Weighting (Prince, 1982) W =
[weight] * [1-(deltaF/6*sigmaF)^2]^2 A_i are:
1.83 -0.399 1.90 -0.211 0.551
(Δ/σ)max = 0.005951
$\Delta\rho_{max} = 0.31$ e Å^{-3}
$\Delta\rho_{min} = -0.37$ e Å^{-3}
Extinction correction: none
Scattering factors from International Tables
Vol C 4.2.6.8 and 6.1.1.4

H atoms were included at calculated positions or where observed in difference electron density maps and then refined positionally.

Data collection:
COLLECT (Nonius BV, 1997). Cell refinement: Denzo/Scalepack (Otwinowski & Minor, 1997). Data reduction: Denzo/Scalepack (Otwinowski & Minor, 1997). Program(s) used to solve structure: *SIR92* (Altomare *et al.* 1994). Program(s) used to refine structure: *CRYSTALS* (Watkin *et al.* 2003). Molecular graphics: *ORTEP–II* (Johnson 1976) in teXsan (MSC, 1992–1997) . Software used to prepare material for publication: *CRYSTALS* (Watkin et al. 2003).

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Table *S*1. *Fractional atomic coordinates and equivalent isotropic displacement parameters (Å²)*

$$U_{eq} = (1/3)\Sigma_i \Sigma_j U^{ij} a^i a^j a_i.a_j$$

	x	*y*	*z*	U_{eq}
Cl19	0.83557(4)	0.43108(4)	0.02459(4)	0.0541
O2	0.77201(10)	−0.26306(10)	0.36874(10)	0.0418
O4	0.81139(11)	−0.10850(9)	0.14021(9)	0.0400
O11	0.54037(10)	0.46201(9)	0.24767(10)	0.0386
O20	0.17560(13)	1.11342(10)	0.33389(12)	0.0507
C1	0.93212(19)	−0.3006(2)	0.3701(2)	0.0564
C3	0.75344(17)	−0.23602(14)	0.22986(15)	0.0404
C5	0.73491(14)	0.02794(12)	0.17945(12)	0.0323
C6	0.81091(14)	0.14464(13)	0.09967(13)	0.0345
C7	0.74095(14)	0.28658(12)	0.12586(12)	0.0334
C8	0.59679(13)	0.31759(12)	0.23029(13)	0.0317
C9	0.52458(14)	0.19907(13)	0.31084(14)	0.0361
C10	0.59331(14)	0.05491(13)	0.28569(13)	0.0358
C12	0.38392(15)	0.49595(15)	0.34199(16)	0.0429
C13	0.33620(13)	0.66071(13)	0.33485(14)	0.0356
C14	0.34664(15)	0.75817(14)	0.20261(14)	0.0391
C15	0.29517(16)	0.91060(14)	0.19671(15)	0.0403
C16	0.23061(15)	0.96635(13)	0.32631(15)	0.0381
C17	0.22073(16)	0.87016(15)	0.45934(15)	0.0420
C18	0.27316(15)	0.71923(15)	0.46326(14)	0.0399
C21	0.1754(3)	1.21488(18)	0.2010(2)	0.0666
H11	0.936(2)	−0.325(2)	0.466(2)	0.0644
H12	0.984(2)	−0.385(2)	0.327(2)	0.0644
H13	0.988(2)	−0.219(2)	0.309(2)	0.0644
H31	0.8150(19)	−0.3158(18)	0.1772(18)	0.0488
H32	0.642(2)	−0.2219(17)	0.2401(18)	0.0488
H61	0.9105(18)	0.1259(16)	0.0271(17)	0.0403
H91	0.4297(18)	0.2127(16)	0.3841(17)	0.0411
H101	0.5427(18)	−0.0262(17)	0.3422(17)	0.0418
H121	0.3808(18)	0.4458(17)	0.4459(19)	0.0474
H122	0.3158(19)	0.4589(18)	0.3058(17)	0.0474
H141	0.3912(19)	0.7189(18)	0.1149(18)	0.0467
H151	0.3050(19)	0.9722(18)	0.1040(19)	0.0486
H171	0.1779(19)	0.9129(18)	0.5438(19)	0.0510
H181	0.2635(18)	0.6530(18)	0.5591(18)	0.0473
H211	0.126(3)	1.310(3)	0.227(2)	0.0834
H212	0.286(3)	1.215(2)	0.139(3)	0.0834
H213	0.115(3)	1.189(2)	0.153(2)	0.0834

Table *S*2. *Anisotropic displacement parameters* (Å²)

Cl19	0.0524(2)	0.03532(16)	0.0591(2)	−0.02033(13)	0.01459(15)	−0.00978(13)
O2	0.0363(4)	0.0422(5)	0.0365(5)	−0.0071(4)	−0.0012(4)	−0.0016(4)
O4	0.0494(5)	0.0300(4)	0.0346(4)	−0.0105(4)	−0.0007(4)	−0.0074(3)
O11	0.0315(4)	0.0304(4)	0.0464(5)	−0.0055(3)	−0.0014(4)	−0.0076(3)
O20	0.0593(6)	0.0357(5)	0.0589(6)	−0.0029(4)	−0.0195(5)	−0.0149(4)
C1	0.0421(8)	0.0659(10)	0.0532(9)	0.0017(7)	−0.0138(7)	−0.0096(7)
C3	0.0440(7)	0.0320(6)	0.0457(7)	−0.0143(5)	−0.0089(5)	−0.0059(5)
C5	0.0367(6)	0.0303(5)	0.0298(5)	−0.0085(4)	−0.0079(4)	−0.0055(4)
C6	0.0350(6)	0.0349(6)	0.0309(6)	−0.0106(5)	−0.0016(5)	−0.0074(4)
C7	0.0349(6)	0.0322(5)	0.0315(5)	−0.0133(4)	−0.0030(4)	−0.0044(4)
C8	0.0293(5)	0.0308(5)	0.0342(6)	−0.0062(4)	−0.0086(4)	−0.0048(4)
C9	0.0269(5)	0.0371(6)	0.0386(6)	−0.0085(4)	−0.0022(5)	−0.0039(5)
C10	0.0332(6)	0.0331(6)	0.0382(6)	−0.0120(5)	−0.0055(5)	−0.0018(5)
C12	0.0315(6)	0.0370(6)	0.0505(8)	−0.0054(5)	0.0003(5)	−0.0082(5)
C13	0.0266(5)	0.0360(6)	0.0422(6)	−0.0040(4)	−0.0089(5)	−0.0072(5)
C14	0.0388(6)	0.0403(6)	0.0376(6)	−0.0048(5)	−0.0086(5)	−0.0121(5)
C15	0.0444(7)	0.0391(6)	0.0388(6)	−0.0067(5)	−0.0167(5)	−0.0044(5)
C16	0.0355(6)	0.0353(6)	0.0475(7)	−0.0048(5)	−0.0159(5)	−0.0113(5)
C17	0.0430(7)	0.0469(7)	0.0380(6)	−0.0072(5)	−0.0107(5)	−0.0141(5)
C18	0.0386(6)	0.0438(6)	0.0355(6)	−0.0068(5)	−0.0106(5)	−0.0051(5)
C21	0.0936(14)	0.0357(7)	0.0781(12)	−0.0024(8)	−0.0452(11)	−0.0064(7)

Table S3. *Geometric parameters (Å,°)*

Cl19—C7	1.7349(11)	C8—C9—H91	121.5(9)
O2—C1	1.4216(18)	C10—C9—H91	117.6(9)
O2—C3	1.3860(17)	C9—C10—C5	120.08(10)
O4—C3	1.4238(14)	C9—C10—H101	120.2(9)
O4—C5	1.3821(14)	C5—C10—H101	119.7(9)
O11—C8	1.3643(14)	O11—C12—C13	108.78(10)
O11—C12	1.4332(15)	O11—C12—H121	110.0(9)
O20—C16	1.3657(15)	C13—C12—H121	109.3(9)
O20—C21	1.419(2)	O11—C12—H122	106.5(9)
C1—H11	0.93(2)	C13—C12—H122	111.3(9)
C1—H12	0.94(2)	H121—C12—H122	110.8(13)
C1—H13	1.00(2)	C12—C13—C14	121.65(12)
C3—H31	0.968(17)	C12—C13—C18	120.00(12)
C3—H32	0.968(17)	C14—C13—C18	118.28(11)
C5—C6	1.3951(16)	C13—C14—C15	121.49(12)
C5—C10	1.3823(17)	C13—C14—H141	118.5(10)
C6—C7	1.3790(16)	C15—C14—H141	120.0(10)
C6—H61	0.962(15)	C14—C15—C16	119.23(12)
C7—C8	1.3940(16)	C14—C15—H151	118.2(10)
C8—C9	1.3923(16)	C16—C15—H151	122.5(10)
C9—C10	1.3937(17)	C15—C16—O20	124.36(12)
C9—H91	0.932(15)	C15—C16—C17	119.86(12)
C10—H101	0.962(15)	O20—C16—C17	115.78(12)
C12—C13	1.4992(17)	C16—C17—C18	120.18(12)
C12—H121	1.010(17)	C16—C17—H171	116.9(10)
C12—H122	0.984(17)	C18—C17—H171	123.0(10)
C13—C14	1.3876(18)	C13—C18—C17	120.94(12)
C13—C18	1.3931(18)	C13—C18—H181	120.4(9)
C14—C15	1.3915(18)	C17—C18—H181	118.7(9)
C14—H141	0.949(17)	O20—C21—H211	106.2(13)
C15—C16	1.3901(18)	O20—C21—H212	109.3(13)
C15—H151	0.944(17)	H211—C21—H212	110.6(18)
C16—C17	1.3884(19)	O20—C21—H213	109.6(14)
C17—C18	1.3809(19)	H211—C21—H213	109.0(18)
C17—H171	0.938(17)	H212—C21—H213	111.9(19)
C18—H181	0.986(17)	Cl19—C7—C6—C5	−179.3(1)
C21—H211	0.96(2)	Cl19—C7—C8—O11	−1.1(2)
C21—H212	1.00(2)	Cl19—C7—C8—C9	−179.3(1)
C21—H213	0.95(2)	O2—C3—O4—C5	−65.8(1)
C1—O2—C3	113.49(11)	O4—C3—O2—C1	−65.1(1)
C3—O4—C5	117.7(1)	O4—C5—C6—C7	177.2(1)
C8—O11—C12	116.46(9)	O4—C5—C10—C9	−177.2(1)
C16—O20—C21	117.66(12)	O11—C8—C7—C6	179.2(1)
O2—C1—H11	109.0(12)	O11—C8—C9—C10	−179.1(1)
O2—C1—H12	109.5(11)	O11—C12—C13—C14	52.6(2)
H11—C1—H12	107.3(16)	O11—C12—C13—C18	−130.2(1)
O2—C1—H13	110.4(10)	O20—C16—C15—C14	−179.7(1)
H11—C1—H13	114.4(16)	O20—C16—C17—C18	179.9(1)
H12—C1—H13	106.0(16)	C3—O4—C5—C6	171.3(1)
O4—C3—O2	112.33(10)	C3—O4—C5—C10	−10.0(2)
O4—C3—H31	103.8(10)	C5—C6—C7—C8	0.4(2)
O2—C3—H31	111.4(9)	C5—C10—C9—C8	−0.1(2)
O4—C3—H32	109.6(9)	C6—C5—C10—C9	1.5(2)
O2—C3—H32	107.8(10)	C6—C7—C8—C9	1.0(2)
H31—C3—H32	111.9(13)	C7—C6—C5—C10	−1.6(2)
O4—C5—C6	114.49(10)	C7—C8—O11—C12	172.7(1)
O4—C5—C10	125.54(10)	C7—C8—C9—C10	−1.1(2)
C6—C5—C10	119.95(11)	C8—O11—C12—C13	−173.9(1)
C5—C6—C7	119.13(11)	C9—C8—O11—C12	−9.3(2)
C5—C6—H61	120.2(9)	C12—C13—C14—C15	176.9(1)
C7—C6—H61	120.7(9)	C12—C13—C18—C17	−176.5(1)
Cl19—C7—C6	118.71(9)	C13—C14—C15—C16	−0.6(2)
Cl19—C7—C8	119.09(9)	C13—C18—C17—C16	−0.2(2)
C6—C7—C8	122.20(10)	C14—C13—C18—C17	0.7(2)
C7—C8—O11	116.84(10)	C14—C15—C16—C17	1.1(2)
C7—C8—C9	117.73(10)	C15—C14—C13—C18	−0.3(2)
O11—C8—C9	125.40(10)	C15—C16—O20—C21	4.1(2)
C8—C9—C10	120.89(11)	C15—C16—C17—C18	−0.8(2)

C17—C16—O20—C21	−176.6(2)

Table *S*4. *Contact distances (Å)*

I19···Cl19^{i}	3.4461(8)
Cl19···C21^{ii}	3.535(2)
O2···C12^{iii}	3.302(2)
O2···C9^{iii}	3.487(1)
O4···C6^{iv}	3.478(1)
O20···C9^{v}	3.433(2)
O20···C17^{vi}	3.519(2)
O20···C1^{vii}	3.520(2)
C1···C13^{viii}	3.537(2)
C6···C14^{ix}	3.545(2)
C6···C15^{ix}	3.557(2)
C8···C18^{vii}	3.505(2)
C9···C17^{vii}	3.599(2)
C10···C16^{x}	3.520(2)

Symmetry codes: (i) 2 − *x*, 1 − *y*, −*z* ; (ii) 1 − *x*, 2 − *y*, −*z* ; (iii) 1 − *x*, −*y*, 1 − *z* ; (iv) 2 − *x*, −*y*, −*z* ; (v) *x*, 1 + *y*, *z* ; (vi) −*x*, 2 − *y*, 1 − *z* ; (vii) 1 − *x*, 1 − *y*, 1 −*z* ; (viii) 1 + *x*, *y* − 1, *z* ; (ix) 1 − *x*, 1 − *y*, −*z* ; (x) *x*, *y* −1, *z* .

Appendix Four

X–ray Crystal Structure Report for Compound* ent–*18

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Abstract

The crystal structure of $C_{16}H_{17}NO_4 \cdot H_2O$ 2:3 is reported.

Comment

The compound is enantiometrically pure but the anomolous dispersion terms are very low for all elements in the structure and so the absolute configuration can not be determined in this experiment. Consequently Friedel-pair reflections have been averaged and the Flack parameter has not been refined. The absolute configuration of the molecule has been assigned on the basis of the synthetic precursors.

The crystallographic asymmetric unit consists of two molecules of $C_{16}H_{17}NO_4$ and three water molecules of solvation. The water molecules are disordered over six sites but close distances between some of these sites force restrictions upon their occupancies (*viz.* O2011 + O2012 ≤ 1.0, O2021 + O2022 + O204 ≤ 1.0 and O2011 + O2022 ≤ 1.0). When the occupancies were refined independently it could be seen that setting relationships 1 and 2 to equal 1.0 exactly would be appropriate, so this was performed. As a consequence of this, the water occupancies sum to 3.0. Restraints were imposed on the displacement parameters of sites which were close together so they tend to be similar.

H atoms attached to C atoms were included at calculated positions and ride on the atoms to which they are attached. Three of the alcohol H atoms were observed in difference maps and were included at these locations and refined positionally with restraints on distances and angles involving them. The remaining alcohol H and water H atoms were not directly observed and could be disordered over more than one site on account of the disordering of the water molecules to which they might hydrogen-bond. They have not been included in the final structure.

The largest peaks in the final difference electron density map are located near the disordered solvate sites.

Experimental

The compound was prepared by OJK and recrystallized from wet acetone.

Crystal data

$2(C_{16}H_{17}NO_4)\cdot 3(H_2O)$
$M_r = 628.68$
Trigonal
$R\bar{3}$
$a = 16.3003\ (4)$ Å
$b = 16.3003\ (4)$ Å
$c = 29.5212\ (10)$ Å
$\alpha = 90^\circ$
$V = 6792.9\ (3)$ Å^3
$Z = 9$
$D_x = 1.38$ Mg m^{-3}
D_m not measured
Mo Kα radiation
$\lambda = 0.71073$ Å

Cell parameters from 50810 reflections
$\theta = 2.6–27.5^\circ$
$\mu = 0.105$ mm^{-1}
$T = 200$ K
Plate
Colourless
0.27 x 0.27 x 0.09 mm
Crystal source: local

Data collection

Nonius KappaCCD diffractometer
ϕ and ω scans with CCD
Absorption correction:
by integration *via* Gaussian method (Coppens, 1970) implemented in maXus (2000)
$T_{min} = 0.979$, $T_{max} = 0.991$
29833 measured reflections
3470 independent reflections

2814 reflections with
$I > 2.0\sigma(I)$
$R_{int} = 0.045$
$\theta_{max} = 27.489^\circ$
$h = -20 \rightarrow 20$
$k = -21 \rightarrow 20$
$l = -38 \rightarrow 38$

Refinement

Refinement on F
$R = 0.0535$
$wR = 0.0457$
$S = 1.1064$
2814 reflections
446 parameters
H atoms treated by a mixture of independent and constrained refinement

Method, part 1, Chebychev polynomial, (Carruthers & Watkin, 1979, Prince, 1982)
[weight] = $1.0/[A_0 * T_0(x) + A_1 * T_1(x) \ldots + A_{n-1}] * T_{n-1}(x)]$
where Ai are the Chebychev coefficients listed below and x= Fcalc/Fmax Method = Robust Weighting (Prince, 1982) W = [weight] * [1-(deltaF/6*sigmaF)2]2 A_i are:
2.14 0.748 1.83
$(\Delta/\sigma)_{max} = 0.024924$
$\Delta\rho_{max} = 0.27$ e Å^{-3}
$\Delta\rho_{min} = -0.28$ e Å^{-3}
Extinction correction: none
Scattering factors from International Tables Vol C 4.2.6.8 and 6.1.1.4

H atoms attached to C were included at calculated positions and ride on the atoms to which they are attached. Three of the alcohol H atoms were refined positionally with restraints on distances and angles involving them. The remaining H atoms bonded to O were not located and have not been included in the final structure.

Data collection:
COLLECT (Nonius BV, 1997). Cell refinement: Denzo/Scalepack (Otwinowski & Minor, 1997). Data reduction: Denzo/Scalepack (Otwinowski & Minor, 1997). Program(s) used to solve structure: *SIR92* (Altomare *et al.* 1994). Program(s) used to refine structure: *CRYSTALS* (Watkin *et al.* 2003). Molecular graphics: *ORTEP–II* (Johnson 1976) in teXsan (MSC, 1992–1997) . Software used to prepare material for publication: *CRYSTALS* (Watkin et al. 2003).

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Table *S*1. *Fractional atomic coordinates and equivalent isotropic displacement parameters (Å²)*

$$U_{eq} = (1/3)\Sigma_i \Sigma_j U^{ij} a^i a^j a_i.a_j$$

	Occupancy	*x*	*y*	*z*	U_{eq}
O3	1.0000	0.16586(16)	0.47190(17)	0.51167(10)	0.0446
O5	1.0000	0.35283(16)	0.55813(16)	0.53976(9)	0.0447
O13	1.0000	0.28964(18)	0.00555(19)	0.38005(9)	0.0495
O15	1.0000	0.17038(17)	0.02211(19)	0.34694(9)	0.0486
O103	1.0000	0.3448(2)	0.5639(2)	0.32474(10)	0.0592
O105	1.0000	0.22425(17)	0.37932(18)	0.29965(9)	0.0470
O113	1.0000	0.5255(2)	0.28087(18)	0.56832(10)	0.0540
O115	1.0000	0.53400(19)	0.42359(18)	0.58716(9)	0.0508
O203	1.0000	0.0227(2)	0.2174(3)	0.62715(13)	0.0772
O204	0.15(1)	0.1133(13)	0.5235(15)	0.6302(6)	0.0641
O2011	0.63(3)	0.0929(10)	0.4056(11)	0.5981(6)	0.0919
O2012	0.37(3)	0.058(2)	0.366(2)	0.5796(8)	0.0945
O2021	0.57(2)	0.3021(10)	0.5572(8)	0.6289(3)	0.0552
O2022	0.28(2)	0.2529(18)	0.5242(12)	0.6204(4)	0.0429
N8	1.0000	0.23415(18)	0.21050(17)	0.54488(9)	0.0354
N108	1.0000	0.50745(19)	0.3924(2)	0.37044(10)	0.0410
C1	1.0000	0.1747(2)	0.3519(2)	0.47130(11)	0.0375
C2	1.0000	0.2313(2)	0.4534(2)	0.48706(11)	0.0351
C4	1.0000	0.3163(2)	0.46989(19)	0.51643(10)	0.0329
C6	1.0000	0.2938(2)	0.3885(2)	0.54849(10)	0.0341
C7	1.0000	0.2700(2)	0.30166(19)	0.51954(11)	0.0330
C9	1.0000	0.2756(2)	0.1553(2)	0.52540(11)	0.0373
C10	1.0000	0.2482(2)	0.1256(2)	0.47643(11)	0.0347
C11	1.0000	0.2933(2)	0.0842(2)	0.45257(11)	0.0369
C12	1.0000	0.2630(2)	0.0542(2)	0.40884(11)	0.0376
C14	1.0000	0.2470(3)	0.0046(3)	0.33709(12)	0.0507
C16	1.0000	0.1917(2)	0.0648(2)	0.38913(11)	0.0386
C17	1.0000	0.1478(2)	0.1053(2)	0.41160(11)	0.0372
C18	1.0000	0.1762(2)	0.1358(2)	0.45617(11)	0.0348
C19	1.0000	0.1286(2)	0.1795(2)	0.48355(11)	0.0354
C20	1.0000	0.1916(2)	0.2856(2)	0.48622(11)	0.0341
C21	1.0000	0.1300(2)	0.1561(2)	0.53411(12)	0.0407
C101	1.0000	0.3866(2)	0.5215(3)	0.39499(11)	0.0438
C102	1.0000	0.3096(3)	0.4931(3)	0.35962(12)	0.0488
C104	1.0000	0.2793(2)	0.3948(3)	0.33968(11)	0.0434
C106	1.0000	0.3660(2)	0.3834(2)	0.33025(11)	0.0408
C107	1.0000	0.4115(2)	0.3860(2)	0.37554(11)	0.0371
C109	1.0000	0.5155(2)	0.3286(2)	0.40270(12)	0.0433
C110	1.0000	0.5213(2)	0.3591(2)	0.45187(12)	0.0369
C111	1.0000	0.5230(2)	0.3000(2)	0.48557(12)	0.0408

C112	1.0000	0.5278(2)	0.3289(2)	0.52999(12)	0.0428
C114	1.0000	0.5299(3)	0.3396(3)	0.60513(14)	0.0523
C116	1.0000	0.5326(2)	0.4140(2)	0.54072(11)	0.0390
C117	1.0000	0.5338(2)	0.4745(2)	0.50792(12)	0.0379
C118	1.0000	0.5269(2)	0.4457(2)	0.46242(11)	0.0358
C119	1.0000	0.5280(2)	0.5085(2)	0.42411(11)	0.0383
C120	1.0000	0.4328(2)	0.4746(2)	0.40172(11)	0.0369
C121	1.0000	0.5756(2)	0.4919(2)	0.38261(12)	0.0449
H1	1.0000	0.197(3)	0.528(2)	0.5198(14)	0.0540
H2	1.0000	0.322(3)	0.552(3)	0.5623(11)	0.0540
H3	1.0000	0.260(2)	0.399(3)	0.2783(11)	0.0580
H11	1.0000	0.1228(2)	0.3345(2)	0.44877(11)	0.0451
H21	1.0000	0.2550(2)	0.4960(2)	0.46003(11)	0.0443
H41	1.0000	0.3670(2)	0.47559(19)	0.49539(10)	0.0378
H61	1.0000	0.3499(2)	0.4046(2)	0.56811(10)	0.0392
H62	1.0000	0.2384(2)	0.3755(2)	0.56796(10)	0.0392
H71	1.0000	0.3277(2)	0.31424(19)	0.50203(11)	0.0390
H91	1.0000	0.2539(2)	0.0969(2)	0.54406(11)	0.0455
H92	1.0000	0.3461(2)	0.1950(2)	0.52709(11)	0.0455
H111	1.0000	0.3449(2)	0.0768(2)	0.46671(11)	0.0456
H141	1.0000	0.2220(3)	−0.0585(3)	0.32212(12)	0.0639
H142	1.0000	0.2945(3)	0.0552(3)	0.31683(12)	0.0639
H171	1.0000	0.0969(2)	0.1130(2)	0.39673(11)	0.0449
H191	1.0000	0.0635(2)	0.1601(2)	0.47237(11)	0.0420
H211	1.0000	0.0940(2)	0.1784(2)	0.55292(12)	0.0465
H212	1.0000	0.1033(2)	0.0866(2)	0.53882(12)	0.0465
H1011	1.0000	0.4035(2)	0.5783(3)	0.41419(11)	0.0547
H1021	1.0000	0.2533(3)	0.4913(3)	0.37412(12)	0.0619
H1041	1.0000	0.2386(2)	0.3461(3)	0.36256(11)	0.0509
H1061	1.0000	0.4121(2)	0.4363(2)	0.31051(11)	0.0492
H1062	1.0000	0.3454(2)	0.3215(2)	0.31487(11)	0.0492
H1071	1.0000	0.3682(2)	0.3286(2)	0.39365(11)	0.0453
H1091	1.0000	0.5741(2)	0.3260(2)	0.39537(12)	0.0543
H1092	1.0000	0.4588(2)	0.2640(2)	0.39922(12)	0.0543
H1111	1.0000	0.5208(2)	0.2392(2)	0.47791(12)	0.0511
H1141	1.0000	0.5877(3)	0.3574(3)	0.62370(14)	0.0637
H1142	1.0000	0.4722(3)	0.3046(3)	0.62451(14)	0.0637
H1171	1.0000	0.5393(2)	0.5366(2)	0.51604(12)	0.0461
H1191	1.0000	0.5594(2)	0.5767(2)	0.43301(11)	0.0442
H1211	1.0000	0.6388(2)	0.4999(2)	0.39072(12)	0.0509
H1212	1.0000	0.5833(2)	0.5359(2)	0.35729(12)	0.0509

Table *S2. Anisotropic displacement parameters* (Å^2)

	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
O3	0.0446(12)	0.0437(12)	0.0527(13)	0.0274(10)	−0.0003(10)	−0.0081(10)
O5	0.0450(12)	0.0359(11)	0.0480(13)	0.0162(10)	0.0001(10)	−0.0037(10)
O13	0.0518(13)	0.0642(15)	0.0427(12)	0.0367(12)	0.0008(10)	−0.0142(11)
O15	0.0540(14)	0.0621(14)	0.0366(11)	0.0343(12)	−0.0026(10)	−0.0116(11)
O103	0.0778(18)	0.0620(16)	0.0544(14)	0.0474(15)	−0.0131(13)	−0.0023(13)
O105	0.0409(12)	0.0629(14)	0.0340(11)	0.0236(11)	−0.0024(9)	−0.0006(10)
O113	0.0717(16)	0.0538(14)	0.0436(13)	0.0366(13)	−0.0084(11)	0.0014(11)
O115	0.0663(15)	0.0537(14)	0.0387(12)	0.0348(12)	−0.0027(11)	−0.0015(10)
O203	0.0616(18)	0.084(2)	0.084(2)	0.0345(17)	0.0072(16)	0.0062(17)
O204	0.054(11)	0.089(14)	0.068(12)	0.049(10)	0.022(8)	0.024(10)
O2011	0.087(7)	0.108(8)	0.091(8)	0.057(6)	0.045(5)	0.045(6)
O2012	0.110(12)	0.130(13)	0.075(10)	0.083(10)	0.036(8)	0.040(8)
O2021	0.067(6)	0.054(4)	0.043(3)	0.030(4)	0.006(3)	0.009(3)
O2022	0.072(10)	0.037(6)	0.028(5)	0.034(7)	0.004(5)	0.005(4)
N8	0.0405(13)	0.0311(11)	0.0352(12)	0.0183(10)	0.0030(10)	0.0006(10)
N108	0.0396(13)	0.0472(14)	0.0429(14)	0.0268(12)	−0.0025(11)	−0.0056(11)
C1	0.0361(15)	0.0453(16)	0.0321(13)	0.0209(13)	−0.0034(11)	−0.0027(12)
C2	0.0392(15)	0.0395(14)	0.0322(14)	0.0240(12)	−0.0010(12)	−0.0006(11)
C4	0.0334(13)	0.0301(13)	0.0314(13)	0.0131(11)	−0.0001(11)	−0.0007(10)
C6	0.0344(14)	0.0324(13)	0.0318(13)	0.0140(11)	−0.0018(11)	−0.0015(11)
C7	0.0356(14)	0.0299(13)	0.0327(13)	0.0158(11)	0.0001(11)	−0.0015(11)
C9	0.0395(15)	0.0373(14)	0.0376(14)	0.0212(12)	−0.0021(12)	0.0005(12)
C10	0.0325(14)	0.0339(14)	0.0345(13)	0.0141(11)	−0.0008(11)	−0.0023(11)
C11	0.0361(14)	0.0389(15)	0.0392(15)	0.0214(12)	0.0005(12)	−0.0016(12)
C12	0.0370(15)	0.0423(16)	0.0366(15)	0.0222(13)	0.0074(12)	0.0002(12)
C14	0.0528(19)	0.066(2)	0.0405(17)	0.0354(17)	0.0050(14)	−0.0056(15)
C16	0.0403(16)	0.0373(14)	0.0342(15)	0.0164(12)	0.0017(12)	−0.0019(12)
C17	0.0372(15)	0.0416(15)	0.0340(14)	0.0206(13)	−0.0044(12)	−0.0031(12)
C18	0.0353(14)	0.0313(13)	0.0378(15)	0.0166(11)	0.0028(12)	−0.0003(11)
C19	0.0305(13)	0.0341(14)	0.0411(15)	0.0158(11)	−0.0011(11)	−0.0067(11)
C20	0.0345(14)	0.0345(14)	0.0312(13)	0.0156(12)	−0.0010(11)	−0.0053(11)
C21	0.0359(15)	0.0367(15)	0.0441(16)	0.0142(12)	0.0049(13)	−0.0027(12)
C101	0.0482(18)	0.0579(19)	0.0315(14)	0.0312(16)	−0.0032(13)	−0.0053(13)
C102	0.0470(18)	0.071(2)	0.0374(16)	0.0361(17)	−0.0038(13)	−0.0093(15)
C104	0.0374(15)	0.057(2)	0.0329(15)	0.0217(14)	−0.0012(12)	−0.0001(13)
C106	0.0402(15)	0.0491(17)	0.0340(14)	0.0230(14)	−0.0011(12)	−0.0047(13)
C107	0.0363(14)	0.0441(16)	0.0326(14)	0.0215(13)	0.0015(11)	−0.0064(12)
C109	0.0466(17)	0.0472(17)	0.0421(17)	0.0279(15)	−0.0101(14)	−0.0147(13)
C110	0.0340(14)	0.0391(15)	0.0413(15)	0.0209(12)	−0.0046(12)	−0.0081(12)
C111	0.0419(16)	0.0431(16)	0.0436(16)	0.0259(13)	−0.0061(13)	−0.0050(13)
C112	0.0421(17)	0.0432(16)	0.0446(17)	0.0225(14)	−0.0022(13)	−0.0008(13)
C114	0.062(2)	0.0512(19)	0.0461(18)	0.0302(17)	−0.0014(16)	0.0020(15)
C116	0.0363(15)	0.0485(17)	0.0359(15)	0.0239(14)	−0.0065(12)	−0.0061(12)

C117	0.0369(15)	0.0373(15)	0.0410(15)	0.0198(12)	−0.0025(13)	−0.0069(12)

Table S3. *Geometric parameters (Å,°)*

O3—C2	1.442(4)	C17—C18	1.401(4)
O3—H1	0.83(3)	C17—H171	1.000
O5—C4	1.429(4)	C18—C19	1.523(4)
O5—H2	0.81(3)	C19—C20	1.508(4)
O13—C12	1.373(4)	C19—C21	1.544(5)
O13—C14	1.443(4)	C19—H191	1.000
O15—C14	1.443(4)	C21—H211	1.000
O15—C16	1.383(4)	C21—H212	1.000
O103—C102	1.436(5)	C101—C102	1.516(5)
O105—C104	1.428(4)	C101—C120	1.329(5)
O105—H3	0.81(3)	C101—H1011	1.000
O113—C112	1.366(4)	C102—C104	1.538(5)
O113—C114	1.426(5)	C102—H1021	1.000
O115—C114	1.438(5)	C104—C106	1.540(4)
O115—C116	1.379(4)	C104—H1041	1.000
N8—C7	1.497(4)	C106—C107	1.519(4)
N8—C9	1.484(4)	C106—H1061	1.000
N8—C21	1.504(4)	C106—H1062	1.000
N108—C107	1.523(4)	C107—C120	1.517(4)
N108—C109	1.463(4)	C107—H1071	1.000
N108—C121	1.481(4)	C109—C110	1.522(4)
C1—C2	1.509(4)	C109—H1091	1.000
C1—C20	1.318(4)	C109—H1092	1.000
C1—H11	1.000	C110—C111	1.395(5)
C2—C4	1.540(4)	C110—C118	1.402(4)
C2—H21	1.000	C111—C112	1.382(5)
C4—C6	1.518(4)	C111—H1111	1.000
C4—H41	1.000	C112—C116	1.386(5)
C6—C7	1.529(4)	C114—H1141	1.000
C6—H61	1.000	C114—H1142	1.000
C6—H62	1.000	C116—C117	1.376(5)
C7—C20	1.528(4)	C117—C118	1.409(4)
C7—H71	1.000	C117—H1171	1.000
C9—C10	1.519(4)	C118—C119	1.519(4)
C9—H91	1.000	C119—C120	1.515(4)
C9—H92	1.000	C119—C121	1.545(4)
C10—C11	1.410(4)	C119—H1191	1.000
C10—C18	1.398(4)	C121—H1211	1.000
C11—C12	1.381(4)	C121—H1212	1.000
C11—H111	1.000	C2—O3—H1	106(3)
C12—C16	1.386(5)	C4—O5—H2	110(3)
C14—H141	1.000	C12—O13—C14	105.1(2)
C14—H142	1.000	C14—O15—C16	104.9(3)
C16—C17	1.363(5)	C104—O105—H3	108(3)

C112—O113—C114	105.6(3)	C11—C12—O13	128.5(3)
C114—O115—C116	105.6(3)	C11—C12—C16	121.5(3)
C7—N8—C9	109.7(2)	O13—C12—C16	109.8(3)
C7—N8—C21	104.2(2)	O15—C14—O13	106.3(2)
C9—N8—C21	106.4(2)	O15—C14—H141	110.2
C107—N108—C109	110.0(2)	O13—C14—H141	110.2
C107—N108—C121	103.5(2)	O15—C14—H142	110.3
C109—N108—C121	109.6(3)	O13—C14—H142	110.3
C2—C1—C20	122.2(3)	H141—C14—H142	109.5
C2—C1—H11	118.9	C12—C16—O15	109.3(3)
C20—C1—H11	118.9	C12—C16—C17	122.1(3)
C1—C2—O3	105.9(2)	O15—C16—C17	128.4(3)
C1—C2—C4	111.6(2)	C16—C17—C18	118.0(3)
O3—C2—C4	112.0(2)	C16—C17—H171	121.0
C1—C2—H21	109.1	C18—C17—H171	121.0
O3—C2—H21	109.0	C17—C18—C10	120.5(3)
C4—C2—H21	109.0	C17—C18—C19	120.6(3)
C2—C4—O5	109.4(2)	C10—C18—C19	118.9(3)
C2—C4—C6	113.3(2)	C18—C19—C20	110.4(2)
O5—C4—C6	112.1(2)	C18—C19—C21	108.9(2)
C2—C4—H41	107.2	C20—C19—C21	98.4(2)
O5—C4—H41	107.3	C18—C19—H191	112.7
C6—C4—H41	107.2	C20—C19—H191	112.7
C4—C6—C7	107.4(2)	C21—C19—H191	112.7
C4—C6—H61	110.0	C7—C20—C19	105.2(2)
C7—C6—H61	110.0	C7—C20—C1	125.0(3)
C4—C6—H62	110.0	C19—C20—C1	128.4(3)
C7—C6—H62	110.0	C19—C21—N8	102.2(2)
H61—C6—H62	109.5	C19—C21—H211	111.3
C6—C7—N8	115.6(2)	N8—C21—H211	111.3
C6—C7—C20	108.8(2)	C19—C21—H212	111.3
N8—C7—C20	105.9(2)	N8—C21—H212	111.2
C6—C7—H71	108.8	H211—C21—H212	109.5
N8—C7—H71	108.8	C102—C101—C120	123.2(3)
C20—C7—H71	108.8	C102—C101—H1011	118.4
N8—C9—C10	114.3(2)	C120—C101—H1011	118.4
N8—C9—H91	108.2	C101—C102—O103	108.1(3)
C10—C9—H91	108.2	C101—C102—C104	111.6(3)
N8—C9—H92	108.2	O103—C102—C104	110.8(3)
C10—C9—H92	108.3	C101—C102—H1021	108.7
H91—C9—H92	109.5	O103—C102—H1021	108.8
C9—C10—C11	119.2(3)	C104—C102—H1021	108.8
C9—C10—C18	120.0(3)	C102—C104—O105	110.4(3)
C11—C10—C18	120.8(3)	C102—C104—C106	111.0(3)
C10—C11—C12	117.1(3)	O105—C104—C106	111.2(3)
C10—C11—H111	121.4	C102—C104—H1041	108.0
C12—C11—H111	121.4	O105—C104—H1041	108.1

C106—C104—H1041	108.1	O115—C114—H1141	109.7
C104—C106—C107	107.6(2)	O113—C114—H1141	109.7
C104—C106—H1061	110.0	O115—C114—H1142	109.7
C107—C106—H1061	110.0	O113—C114—H1142	109.6
C104—C106—H1062	109.9	H1141—C114—H1142	109.5
C107—C106—H1062	109.9	C112—C116—O115	109.3(3)
H1061—C106—H1062	109.5	C112—C116—C117	122.0(3)
N108—C107—C106	112.7(2)	O115—C116—C117	128.7(3)
N108—C107—C120	104.3(2)	C116—C117—C118	117.5(3)
C106—C107—C120	110.6(3)	C116—C117—H1171	121.3
N108—C107—H1071	109.7	C118—C117—H1171	121.2
C106—C107—H1071	109.7	C117—C118—C110	120.1(3)
C120—C107—H1071	109.7	C117—C118—C119	120.8(3)
N108—C109—C110	113.6(3)	C110—C118—C119	119.0(3)
N108—C109—H1091	108.4	C118—C119—C120	114.5(2)
C110—C109—H1091	108.4	C118—C119—C121	108.1(3)
N108—C109—H1092	108.5	C120—C119—C121	95.9(2)
C110—C109—H1092	108.4	C118—C119—H1191	112.4
H1091—C109—H1092	109.5	C120—C119—H1191	112.4
C109—C110—C111	118.3(3)	C121—C119—H1191	112.4
C109—C110—C118	120.2(3)	C107—C120—C119	105.9(2)
C111—C110—C118	121.5(3)	C107—C120—C101	123.1(3)
C110—C111—C112	117.3(3)	C119—C120—C101	128.9(3)
C110—C111—H1111	121.4	C119—C121—N108	102.5(2)
C112—C111—H1111	121.3	C119—C121—H1211	111.2
C111—C112—O113	127.6(3)	N108—C121—H1211	111.1
C111—C112—C116	121.5(3)	C119—C121—H1212	111.2
O113—C112—C116	110.8(3)	N108—C121—H1212	111.2
O115—C114—O113	108.7(3)	H1211—C121—H1212	109.5
C14—O13—C12—C11	-172.1(3)	C20—C1—C2—C4	7.7(5)
C14—O13—C12—C16	12.7(4)	C2—C1—C20—C7	-1.7(5)
C12—O13—C14—O15	-20.6(4)	C2—C1—C20—C19	163.1(3)
C16—O15—C14—O13	20.8(4)	O3—C2—C4—O5	-46.8(3)
C14—O15—C16—C12	-13.3(3)	O3—C2—C4—C6	79.1(3)
C14—O15—C16—C17	171.8(3)	C1—C2—C4—O5	-165.3(3)
C9—N8—C7—C6	-140.0(3)	C1—C2—C4—C6	-39.4(4)
C9—N8—C7—C20	99.5(3)	O5—C4—C6—C7	-171.6(3)
C21—N8—C7—C6	106.4(3)	C2—C4—C6—C7	64.0(4)
C21—N8—C7—C20	-14.1(3)	C4—C6—C7—N8	-172.8(3)
C7—N8—C9—C10	-62.8(3)	C4—C6—C7—C20	-53.9(3)
C21—N8—C9—C10	49.3(3)	N8—C7—C20—C1	150.7(3)
C7—N8—C21—C19	39.3(3)	N8—C7—C20—C19	-17.0(3)
C9—N8—C21—C19	-76.6(3)	C6—C7—C20—C1	25.8(5)
C20—C1—C2—O3	-114.5(4)	C6—C7—C20—C19	-141.9(3)

N8—C9—C10—C11	171.5(3)
N8—C9—C10—C18	–11.2(4)
C9—C10—C11—C12	177.0(3)
C18—C10—C11—C12	–0.3(4)
C9—C10—C18—C17	–177.5(3)
C9—C10—C18—C19	1.8(4)
C11—C10—C18—C17	–0.3(5)
C11—C10—C18—C19	179.0(3)
C10—C11—C12—O13	–174.4(3)
C10—C11—C12—C16	0.4(4)
O13—C12—C16—O15	0.4(4)
O13—C12—C16—C17	175.7(3)
C11—C12—C16—O15	–175.2(3)
C11—C12—C16—C17	0.1(5)
O15—C16—C17—C18	173.7(3)
C12—C16—C17—C18	–0.6(4)
C16—C17—C18—C10	0.7(4)
C16—C17—C18—C19	–178.6(3)
C10—C18—C19—C20	76.9(4)
C10—C18—C19—C21	–30.2(4)
C17—C18—C19—C20	–103.8(3)
C17—C18—C19—C21	149.1(3)
C18—C19—C20—C1	118.8(4)
C18—C19—C20—C7	–74.1(3)
C21—C19—C20—C1	–127.3(4)
C21—C19—C20—C7	39.8(3)
C18—C19—C21—N8	66.5(3)
C20—C19—C21—N8	–48.7(3)
C114—O113—C112—C111	–178.4(4)
C114—O113—C112—C116	–0.5(4)
C112—O113—C114—O115	0.5(5)
C116—O115—C114—O113	–0.4(5)
C114—O115—C116—C112	0.1(4)
C114—O115—C116—C117	178.9(4)
C109—N108—C107—C106	–137.3(3)
C109—N108—C107—C120	102.8(3)
C121—N108—C107—C106	105.7(3)
C121—N108—C107—C120	–14.2(3)
C107—N108—C109—C110	–68.5(3)
C121—N108—C109—C110	44.6(4)
C107—N108—C121—C119	41.9(3)
C109—N108—C121—C119	–75.3(3)
C120—C101—C102—O103	–111.0(4)
C120—C101—C102—C104	11.0(5)
C102—C101—C120—C107	–1.7(6)
C102—C101—C120—C119	159.2(4)
O103—C102—C104—O105	–45.8(5)
O103—C102—C104—C106	78.0(4)
C101—C102—C104—O105	–166.3(3)
C101—C102—C104—C106	–42.5(4)
O105—C104—C106—C107	–171.5(3)
C102—C104—C106—C107	65.3(3)
C104—C106—C107—N108	–170.2(3)
C104—C106—C107—C120	–53.9(3)
N108—C107—C120—C101	145.5(3)
N108—C107—C120—C119	–19.2(3)
C106—C107—C120—C101	24.2(5)
C106—C107—C120—C119	–140.5(3)
N108—C109—C110—C111	175.9(3)
N108—C109—C110—C118	–5.5(5)
C109—C110—C111—C112	–179.7(3)
C118—C110—C111—C112	1.7(5)
C109—C110—C118—C117	–179.0(3)
C109—C110—C118—C119	–0.6(5)
C111—C110—C118—C117	–0.4(5)
C111—C110—C118—C119	178.0(3)
C110—C111—C112—O113	176.5(4)
C110—C111—C112—C116	–1.2(5)
O113—C112—C116—O115	0.3(4)
O113—C112—C116—C117	–178.7(3)
C111—C112—C116—O115	178.3(3)

C111—C112—C116—C117	-0.7(5)
O115—C116—C117—C118	-176.8(3)
C112—C116—C117—C118	2.0(5)
C116—C117—C118—C110	-1.4(5)
C116—C117—C118—C119	-179.8(3)
C110—C118—C119—C120	75.1(4)
C110—C118—C119—C121	-30.4(4)
C117—C118—C119—C120	-106.5(4)
C117—C118—C119—C121	148.0(3)
C118—C119—C120—C101	126.3(4)
C118—C119—C120—C107	-70.2(3)
C121—C119—C120—C101	-120.8(4)
C121—C119—C120—C107	42.7(3)
C118—C119—C121—N108	66.2(3)
C120—C119—C121—N108	-51.9(3)

Appendix Five

Single Point Energy Calculations (DFT)[1]

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Molecule (radical)	*E (Hartree)*	*Relative E*	*E (kcal/mol)*	*E (kJ/mol)*
264	-2164.77714	0.0†	0.0†	0.0†
Z-**264**	-2164.75390	0.02324	14.6	61.01
E-**264**	-2164.74672	0.03042	19.1	79.87
266	-2164.77942	-0.00227	-1.4	-5.97
267	-2164.79335	-0.01621	-10.2	-42.56

†: arbitrary reference

Table: UB3LYP/6-311+G(3df,2p)//UB3LYP/6-311G** energies

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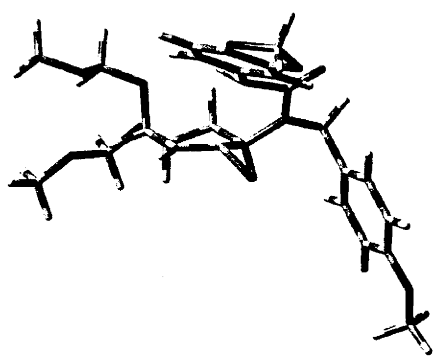
Report of the transition state for radical *Z*-264 ($C_{27}H_{31}ClNO_8^{\cdot}$)



Z-**264**

Gaussian 03, Revision B.05

Point group: C1

State = 2

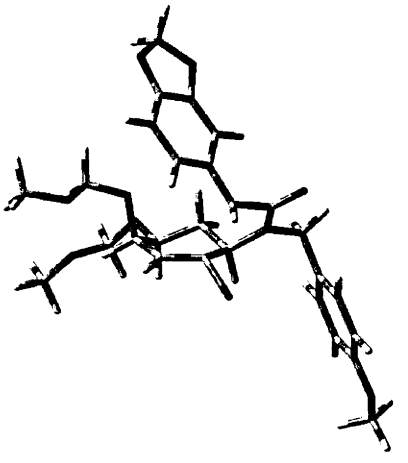
S^2 = 0.78414

UB3LYP/6-311+G(3df,2p)//UB3LYP/6-311G**; HF = -2164.753904

Atom	*x*	*y*	*z*
	Coordinates (Å)		
C	0.07829100	-2.22150000	1.13637700
C	-0.72852000	-1.08582100	0.46347400

C	0.12844500	-0.27261400	-0.50554300
C	1.26990400	-0.79683400	-1.07375300
C	2.01298600	-1.92172500	-0.41960800
C	1.01234900	-2.93091600	0.16295200
H	-1.54709400	-1.52575300	-0.11786600
H	0.68437200	-1.81865600	1.94991000
H	-0.61190000	-2.94701100	1.57364300
H	2.65882200	-2.41639500	-1.14472000
H	0.44238800	-3.36200000	-0.67234400
H	1.72207100	-0.30135500	-1.92224900
N	-1.32494100	-0.18383800	1.44243800
C	-0.68781800	1.00271600	1.70099800
O	-1.17197000	1.89297300	2.38815700
C	0.66804300	1.07092000	1.06536400
C	1.25028300	2.30524700	0.59184800
C	0.47700200	3.48172400	0.39317200
C	2.62433600	2.31283800	0.26484800
C	1.12611200	4.58400900	-0.09825000
H	-0.56957200	3.51269600	0.65525900
C	3.26075800	3.44754700	-0.24377400
H	3.19588500	1.40112200	0.39317600
C	2.48423800	4.57706900	-0.41181700
H	4.31295200	3.44585100	-0.49700900
H	1.38205700	0.36166200	1.46869400
O	2.85504400	5.80185900	-0.89848900
O	0.59981200	5.82332900	-0.38766600
C	1.71929500	6.65583500	-0.69095500
H	1.52005600	7.21759900	-1.60425200
H	1.92344600	7.32493500	0.15446200
C	-2.59806600	-0.51416900	2.08452900
H	-2.72070200	0.21921100	2.88279800
H	-2.51907200	-1.50300000	2.54908100
O	2.83528000	-1.40910700	0.66271200
O	1.66519400	-3.98717900	0.87905100
C	1.94280800	-5.13175500	0.15264900
H	2.22412600	-5.90317100	0.88074900
H	1.05920500	-5.46788000	-0.42053000
C	4.17265500	-1.78444400	0.62128200
H	4.58517700	-1.57225600	1.61643800
H	4.28208500	-2.85314400	0.38778500
C	-3.78892900	-0.48267800	1.14907600
C	-4.50591100	-1.63624800	0.84680600
C	-4.20812600	0.72621700	0.57157300
C	-5.61355600	-1.61081300	-0.00598400
H	-4.20806000	-2.58330500	1.28722600
C	-5.30104100	0.77013600	-0.27523200
H	-3.66743600	1.63818300	0.79847200
C	-6.01397800	-0.40050600	-0.57222100
H	-6.14519400	-2.52959800	-0.21399500
H	-5.63081700	1.70012700	-0.72232300
O	-7.07452700	-0.24871700	-1.41624200
O	4.83150700	-1.00685700	-0.36456600
O	3.01342000	-4.89288400	-0.74714500
C	3.33882400	-6.03467200	-1.52030200
H	4.16171200	-5.75448100	-2.17681600
H	3.65849200	-6.87345100	-0.88655000
H	2.48931300	-6.36345900	-2.13506600
C	6.19734400	-1.34976300	-0.50216800
H	6.61046500	-0.71582700	-1.28632400
H	6.75678000	-1.17275500	0.42765400
H	6.32551300	-2.40298200	-0.79014300
C	-7.83608700	-1.39659900	-1.75831300
H	-8.30018100	-1.85018000	-0.87502300
H	-8.61558200	-1.04660700	-2.43318200
H	-7.22426000	-2.14718700	-2.27172400
Cl	-0.84002200	0.80055300	-1.56711600

Report of the transition state for radical *E*-264 ($C_{27}H_{31}ClNO_8^{\cdot}$)



E-264

Gaussian 03, Revision B.05

Point group: C1

State = 2

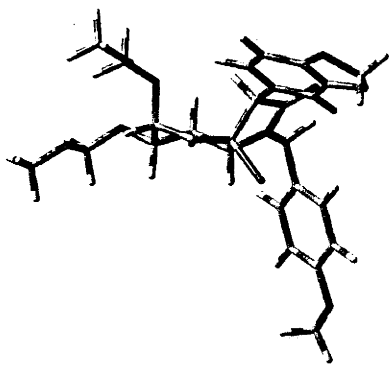
S^2 = 0.78580

UB3LYP/6-311+G(3df,2p)//UB3LYP/6-311G**; HF = -2164.7467202

		Coordinates (Å)	
Atom	*x*	*y*	*z*
C	-0.11851900	0.71991400	-1.10385900
C	-1.07025300	0.10968700	-0.05295600
C	-0.42202800	0.08896600	1.32357600
C	0.58680400	0.96167900	1.66146500
C	1.38390300	1.71296000	0.63484900
C	0.50626200	2.01137000	-0.59085100
H	-1.96909300	0.73449800	0.01640600
H	0.68360200	0.01887800	-1.33937800
H	-0.67080400	0.92110600	-2.02503400
H	1.73430700	2.65099500	1.06770400
H	-0.28177700	2.71243200	-0.27857200
H	0.86886500	1.07420800	2.70004000
N	-1.51272400	-1.23476100	-0.41426700
C	-0.92578700	-2.31736500	0.18136200
O	-1.27521600	-3.47354300	-0.00483700
C	0.22298800	-1.96775100	1.08961000
C	1.57970700	-2.17113000	0.63022700
C	1.87943900	-2.40763300	-0.73880200
C	2.63360800	-2.10484100	1.56322700
C	3.19821900	-2.54538300	-1.08423400
H	1.09916100	-2.51324600	-1.48043400
C	3.97182400	-2.24575300	1.19102000
H	2.39624600	-1.91801600	2.60335300
C	4.22719400	-2.46063500	-0.14781500
H	4.77379500	-2.18496000	1.91467300
H	0.04548800	-2.21746100	2.12879700
O	5.43368100	-2.66232800	-0.76581400
O	3.72963900	-2.81866700	-2.32282100
C	5.14594500	-2.69904400	-2.17106600
H	5.63488100	-3.56618700	-2.61679900
H	5.48792300	-1.76506700	-2.63409400
C	-2.59680100	-1.41602000	-1.38267400
H	-2.62560500	-2.48764200	-1.58654100
H	-2.33450900	-0.90546400	-2.31531400
O	2.52826600	0.93810900	0.21926900

O	1.25678900	2.60184600	-1.65859800
C	1.24449500	3.98382900	-1.71341100
H	1.67411500	4.26137500	-2.68445700
H	0.21518100	4.38084900	-1.63728800
C	3.75245700	1.57307500	0.37375100
H	4.48544500	0.95706000	-0.16238500
H	3.73420600	2.59171200	-0.04275400
C	-3.94724700	-0.92983700	-0.90003200
C	-4.62694400	0.08745100	-1.56277700
C	-4.56055500	-1.51448600	0.21891300
C	-5.88606600	0.52511500	-1.14223000
H	-4.17711400	0.55269000	-2.43490300
C	-5.80540200	-1.09232800	0.65090100
H	-4.05194400	-2.31177700	0.74941100
C	-6.48033000	-0.06733900	-0.02781600
H	-6.38185500	1.31711800	-1.68720800
H	-6.28495300	-1.54128600	1.51224600
O	-7.70099100	0.27306400	0.47581700
O	4.07295800	1.63194100	1.75533300
O	2.02464200	4.52394800	-0.65859500
C	2.02993200	5.94029900	-0.65651600
H	2.64705700	6.25844300	0.18296100
H	2.45682700	6.34433800	-1.58504500
H	1.01780400	6.34936900	-0.52903200
C	5.25834800	2.36088800	2.00384100
H	5.41379500	2.36548300	3.08271700
H	6.13193300	1.89593200	1.52406900
H	5.18090600	3.39947400	1.65041600
C	-8.43857900	1.29670700	-0.17489600
H	-8.67054600	1.02855200	-1.21196200
H	-9.36642300	1.39744100	0.38584500
H	-7.90171700	2.25207700	-0.15903400
Cl	-1.61117500	-0.24228900	2.64921200

Report for transition state for radical 266 ($C_{27}H_{31}ClNO_8^{\cdot}$)



266

Gaussian 03, Revision B.05

Point group: C1

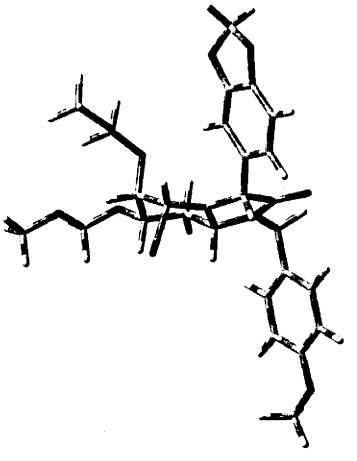
State = 2

S^2 = 0.75434

UB3LYP/6-311+G(3df,2p)//UB3LYP/6-311G**; HF = -2164.7794153

	Coordinates (Å)		
Atom	*x*	*y*	*z*
C	0.72988100	1.97304100	1.07056600
C	0.97171000	0.60249000	0.40505700
C	-0.29130600	0.03755800	-0.30173100
C	-1.17156600	1.05012600	-0.92335600
C	-1.29454500	2.41576400	-0.33395700
C	0.07561200	2.95293200	0.10259200
H	1.78078600	0.69556500	-0.32292000
H	0.08242200	1.86835000	1.94379200
H	1.68243000	2.38469700	1.41306300
H	-1.75322600	3.10234200	-1.04512400
H	0.69702300	3.06948900	-0.79763500
H	-1.93393600	0.70614300	-1.60966900
N	1.29844100	-0.44235900	1.36783700
C	0.26866700	-1.30783000	1.63006700
O	0.31279300	-2.25051400	2.39475500
C	-0.94948000	-0.82818900	0.82308100
C	-1.98794100	-1.84767700	0.42541700
C	-1.65175400	-3.20272600	0.23359500
C	-3.30510500	-1.41897300	0.23317100
C	-2.66006900	-4.05198800	-0.15908900
H	-0.65261900	-3.57068100	0.41288400
C	-4.32114900	-2.30003400	-0.16866600
H	-3.55321900	-0.37480400	0.38763800
C	-3.96467400	-3.61639700	-0.36011500
H	-5.34012100	-1.96480500	-0.31230900
O	-4.76021000	-4.68159500	-0.70923200
O	-2.59274600	-5.41065300	-0.37212400
C	-3.85120300	-5.76294400	-0.95175900
H	-3.73090400	-5.89960100	-2.03474400
H	-4.23031100	-6.66764400	-0.47587800
C	2.58249500	-0.52335700	2.05415600
H	2.48721500	-1.37101100	2.73706200
H	2.73627300	0.37323100	2.66547500
O	-2.13765400	2.33705200	0.85275300
O	-0.03190700	4.21707400	0.76481400
C	0.06249400	5.33812900	-0.04127500
H	0.19252100	6.19480400	0.63205100
H	0.92838800	5.26930600	-0.72515500
C	-3.31240500	3.07420000	0.78960900
H	-3.71528100	3.09980800	1.81040300
H	-3.12067800	4.09787200	0.43345800
C	3.76213300	-0.70913800	1.12189000
C	4.83238700	0.18009600	1.12850300
C	3.81827000	-1.80325600	0.24502100
C	5.94216600	-0.00020900	0.29775500
H	4.81518300	1.03400300	1.79917000
C	4.90695300	-1.99599100	-0.58679600
H	2.99498600	-2.50813500	0.21655600
C	5.98112400	-1.09491400	-0.56629800
H	6.75479400	0.71279500	0.33534000
H	4.95596100	-2.83929900	-1.26488900
O	7.00470300	-1.37591300	-1.42226000
O	-4.21777100	2.42356300	-0.08629900
O	-1.12111700	5.49395600	-0.80834000
C	-1.07397400	6.63012500	-1.65374500
H	-2.01938900	6.66854200	-2.19353500
H	-0.95577300	7.55758000	-1.07656100
H	-0.25204700	6.56143600	-2.37992300
C	-5.43305200	3.13327900	-0.23828300
H	-6.05037100	2.56766400	-0.93548500
H	-5.97062900	3.22680800	0.71591900
H	-5.26661600	4.14084500	-0.64509100
C	8.12846500	-0.50874400	-1.44109700
H	8.62803300	-0.47625800	-0.46619200
H	8.81162000	-0.92291100	-2.18086300
H	7.84781800	0.50808400	-1.73871500
H	-1.44553700	-0.09279800	1.46943300
Cl	0.29956400	-1.09240500	-1.66240100

Report for transition state for radical 267 ($C_{27}H_{31}ClNO_8^{\cdot}$)



267

Gaussian 03, Revision B.05

Point group: C1

State = 2

S^2 = 0.75584

UB3LYP/6-311+G(3df,2p)//UB3LYP/6-311G**; HF = -2164.7933498

	Coordinates (Å)		
Atom	*x*	*y*	*z*
C	-0.80395300	1.27049800	-1.23229700
C	-1.06803900	0.11239900	-0.25288100
C	0.14667600	-0.20904300	0.56704200
C	0.95332000	0.84772900	1.14177100
C	1.11175700	2.06565900	0.21772500
C	-0.21021800	2.45290100	-0.46494200
H	-1.89972100	0.41339500	0.40878400
H	-0.09744400	0.95782700	-2.00433500
H	-1.72698900	1.59270000	-1.71983900
H	1.50013900	2.91320000	0.77949900
H	-0.90994100	2.78260100	0.31477400
N	-1.38298400	-1.17521200	-0.86980500
C	-0.71233400	-2.23628500	-0.31731100
O	-0.89705100	-3.40767800	-0.57535700
C	0.29410800	-1.68514000	0.72639500
C	1.68231400	-2.28428500	0.59384700
C	2.60973000	-1.74029000	-0.31906200
C	2.01207300	-3.41831900	1.33593000
C	3.82480800	-2.37544500	-0.43423400
H	2.39213000	-0.84584200	-0.88820800
C	3.25714900	-4.05320500	1.20790600
H	1.28211000	-3.83078400	2.02211100
C	4.14495400	-3.50681800	0.30837400
H	3.51139700	-4.93039700	1.78851400
O	5.42930900	-3.90184000	0.01770600
O	4.89950800	-2.02193200	-1.21758900
C	5.80987600	-3.12225100	-1.12162200
H	5.73409500	-3.73919000	-2.02678000
H	6.82251000	-2.74442300	-0.97975300
C	-2.52368700	-1.37278300	-1.76286100
H	-2.39595100	-2.37206600	-2.18293100

H	-2.45794500	-0.65392900	-2.58379700
O	2.04429000	1.68274300	-0.80191300
O	-0.01635500	3.51793600	-1.40131600
C	-0.11835300	4.80365100	-0.89727600
H	-0.20927000	5.47031200	-1.76436100
H	-1.00769400	4.91183800	-0.25018300
C	3.26914700	2.34437800	-0.74866000
H	3.80607600	2.06652500	-1.66413700
H	3.12171700	3.43467800	-0.70917000
C	-3.86804400	-1.25534700	-1.07256300
C	-4.72603800	-0.18883600	-1.32386600
C	-4.28178600	-2.23567100	-0.15593100
C	-5.96685400	-0.07987200	-0.68950600
H	-4.43488300	0.57729600	-2.03613300
C	-5.50619300	-2.14274400	0.48231100
H	-3.63258900	-3.08096600	0.04551200
C	-6.36030400	-1.06157100	0.22078600
H	-6.60620700	0.76319700	-0.91396400
H	-5.83405600	-2.89805200	1.18631000
O	-7.54256900	-1.06541500	0.89913100
O	3.97218300	1.90922200	0.39845200
O	1.04193000	5.13258300	-0.14992800
C	0.97750800	6.43331300	0.40830800
H	1.90359200	6.59245300	0.95935800
H	0.89054400	7.20282500	-0.37140800
H	0.13011200	6.53589600	1.10003400
C	5.20577300	2.58047200	0.57320500
H	5.65489500	2.19160100	1.48636200
H	5.89024700	2.39401800	-0.26616800
H	5.06582300	3.66577300	0.67746100
C	-8.45319900	0.00171900	0.67915700
H	-8.77748200	0.04494100	-0.36676900
H	-9.31347300	-0.20590200	1.31332500
H	-8.01854000	0.96639400	0.96465200
H	-0.11180200	-1.99470300	1.70365700
H	1.92264000	0.52387500	1.50506100
Cl	0.10798400	1.47574000	2.77583500

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Comment:

DFT methods such as (UB3LYP) are usually good at modelling open-shell systems because they include the effects of electron correlation (*i.e.* the fact that electrons in a molecular system react to one another's motion and attempt to keep out of one another's way), whereas *ab-initio* methods including electron correlation account for the instantaneous interactions of pairs of electrons with opposite spin.
Ref.: Foresman, J. B.; Frisch, A.; *Exploring Chemistry with Electronic Structure Methods*, 2nd Ed., Gaussian Inc., Pittsburg, PA, **1996**.

The degree of spin contamination can be assessed by inspection of $\langle S^2 \rangle$, which should be 0.75 for a doublet (within 5%); Ref.: Cramer, C. J.; *Essentials of Computational Chemistry: Theories and Models;* 2nd Ed., Wiley, New York, **2004**, page 190.

The spin multiplicity for a molecule is given by the equation 2S+1, where S is the total spin for the molecule. Thus, a doublet state (one unpaired electron, i.e. a radical) has a spin multiplicity of 2. All calculated molecules here have no symmetry (*i.e.* point-group is C_1).

References

1. Gaussian 03, Revision C.01, Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, Jr., J. A.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.;

Appendix Six

Copies of Publications Arising from Work Reported in this Thesis

ORGANIC LETTERS

2007
Vol. 9, No. 18
3503−3506

Chemoenzymatic Approaches to the Montanine Alkaloids: A Total Synthesis of (+)-Brunsvigine

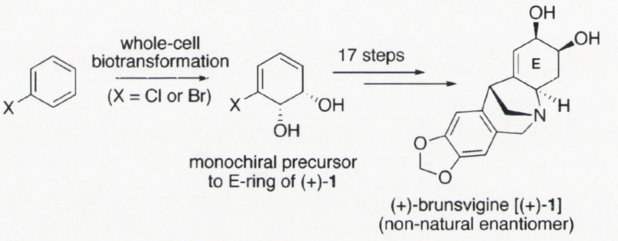
Martin G. Banwell,* Okanya J. Kokas, and Anthony C. Willis

Research School of Chemistry, Institute of Advanced Studies, The Australian National University, Canberra, ACT 0200, Australia

mgb@rsc.anu.edu.au

Received June 7, 2007

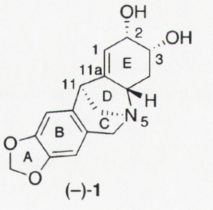
ABSTRACT

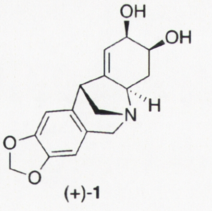


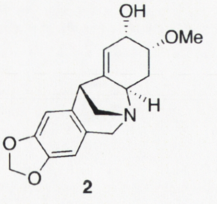
The readily available and enzymatically derived *cis*-1,2-dihydrocatechols 3a and 3b have been elaborated over 17 steps, including a novel radical addition/elimination sequence, into the enantiomer, (+)-1, of the montanine alkaloid brunsvigine [(−)-1].

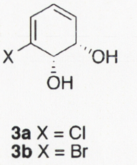
(−)-Brunsvigine [(−)-**1**][1−3] is a representative member of a relatively small group of natural products known as the montanine alkaloids which incorporate the 5,11-methanomorphanthridine framework and bear hydroxy or methoxy groups in varying configurations at C-2 and C-3.[4] The isolation of (+)-montabuphine,[5] assigned structure **2**, from the Amaryllidaceae species *Boophane flava* found in Southern Africa suggests that both enantiomeric forms of the framework can be encountered within this class of natural product. Little is known about the biological properties of such compounds,[4,6] although their structural similarity to other pharmacologically active Amaryllidaceae alkaloids suggests they deserve attention in this regard.

Two distinct end-games have been employed in the limited number of total syntheses of the montanine alkaloids reported









thus far. The first of these, as highlighted in Overman's 1992 synthesis of (±)-pancracine,[7] involves subjecting an appropriately configured 3-arylated perhydroindole to the Pictet−Spengler reaction. Pearson has exploited this same approach in the preparation of (+)-coccinine,[8] as has Sha in a synthesis of (−)-brunsvigine.[9] The second type of end-

(1) Dry, L. J.; Poynton, M.; Thompson, M. E.; Warren, F. L. *J. Chem. Soc.* **1958**, 4701.

(2) Inubushi, Y.; Fales, H. M.; Warnhoff, E. W.; Wildman, W. C. *J. Org. Chem.* **1960**, *25*, 2153.

(3) Clark, R. C.; Warren, F. L.; Pachler, K. G. R. *Tetrahedron* **1975**, *31*, 1855.

(4) For reviews dealing with this class of alkaloid, see: (a) Martin, S. F. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: San Diego, 1987; Vol. 30, p 251. (b) Hoshino, O. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: San Diego, 1998; Vol. 51, p 323. (c) Lewis, J. R. *Nat. Prod. Rep.* **2000**, *17*, 57 and previous reviews in the series.

(5) Viladomat, F.; Bastida, J.; Codina, C.; Campbell, W. E.; Mathee, S. *Phytochemistry* **1995**, *40*, 307.

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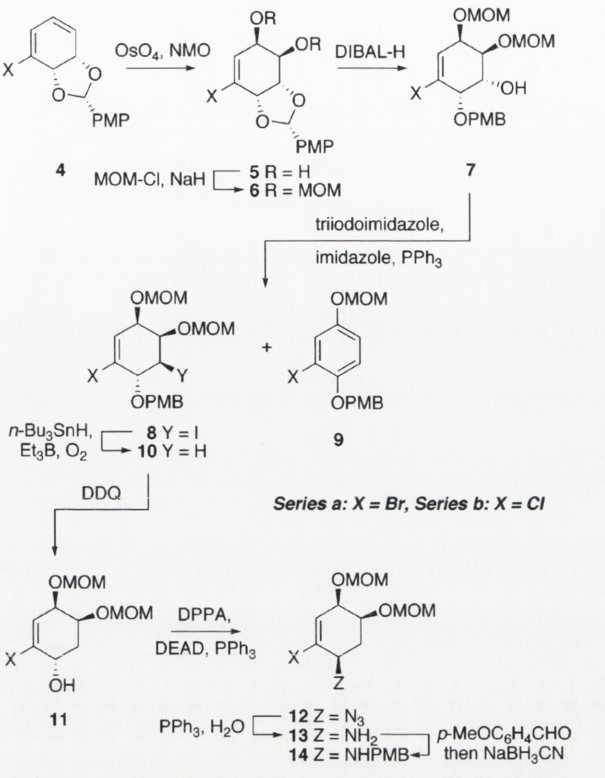
game relies on the assembly of the morphanthridine skeleton incorporating a hydroxymethyl group at C-11 and installation of the 5,11-methano bridge by activation of the hydroxyl moiety, then displacement of the activated unit by N-5. Hoshino first deployed this approach in syntheses of (±)-montanine, (±)-coccinine, (±)-*O*-acetylmontanine, (±)-pancracine, and (±)-brunsvigine.[10] Subsequently, Weinreb applied this strategy in enantioselective total syntheses of (−)-montanine, (−)-coccinine, and (−)-pancracine.[11] Several formal total syntheses of various members of the montanine alkaloid class have also been described,[12] and all but two[12a,d] rely on one or other of the two end-games just described. Herein we outline a chemoenzymatic synthesis of the enantiomer, (+)-**1**, of (−)-brunsvigine [(−)-**1**] that starts from the monochiral 3-halo-*cis*-1,2-dihydrocatechols **3a** and **3b**, each of which can be obtained in multigram quantities through the whole-cell biotransformation of the corresponding halobenzene.[13] The strategy used involves the late-stage application of the Pictet−Spengler reaction and a novel radical addition/elimination process[14] that permits the ready and completely regiocontrolled introduction of the $\Delta^{1,11a}$-alkene associated with all of the title alkaloids.

The early stages (Scheme 1) of the total synthesis of (+)-brunsvigine involved assembly of the precursor to the E-ring and began with the *p*-methoxyphenyl or PMP-based acetal derivatives **4**,[15] of compounds **3a** and **3b**. These acetals were subjected to a regio- and diastereo-selective *cis*-dihydroxylation under the UpJohn conditions,[16] and the resulting diols **5a** (65% from **3a**) and **5b** (66%) converted, under standard conditions involving MOM−Cl and sodium hydride, into the corresponding bis-MOM ethers **6a** (91%) and **6b** (88%), respectively. Reductive cleavage of the acetal moiety within these last compounds was effected regioselectively using DIBAL-H,[15] affording the *p*-methoxylbenzyl or PMB-ethers **7a** (64%) and **7b** (60%), respectively. Conversion of these alcohols into the corresponding iodides, **8a** (81%) and **8b** (66%), could be achieved using triiodoimidazole in the

Scheme 1



presence of imidazole and triphenylphosphine,[17] although in each of these reactions leading to such products they were accompanied by the hydroquinone derivative **9** (2.5−6%). The structures of compounds **8a** and **9b** follow from single-crystal X-ray analyses.[18] Reductive deiodination of dihalides **8a** and **8b** was achieved using tri-*n*-butyltin hydride and without any complications arising from competitive removal of the halogens attached to the associated alkene. The ensuing PMB-ethers **10a** (85%) and **10b** (84%) were each subjected to cleavage with DDQ, and the alcohols **11a** (96%) and **11b** (98%) so formed engaged in Mitsunobu reactions using diphenylphosphoryl azide (DPPA)[19] as the nucleophile. The ensuing azides **12a** (93%) and **12b** (75%) thus formed were then each subjected to a Staudinger reaction using triphenylphosphine in aqueous THF, and the resulting primary amines **13a** (87%) and **13b** (98%) engaged in reductive amination reactions using *p*-methoxybenzaldehyde then sodium cyanoborohydride to give the corresponding secondary amines **14a** (90%) and **14b** (56%).

The assembly of the precursor to the AB-ring substructure of (+)-brunsvigine is shown in the early parts of Scheme 2 and used protocols defined by Ikeda et al.[12b] Thus, 1,2-methylenedioxybenzene was treated with ethyl α-chloro-α-

(6) Very recently (−)-montanine has been shown to display anxiolytic, antidepressant and anticonvulsant-type effects in mice: Schürmann da Silav, A. F.; de Andrade, J. P.; Bevilaqua, L. R. M.; da Souza, M. M.; Izquierdo, I.; Henriques, A. T.; Zuanazzi, J. A. S. *Pharmacol., Biochem. Behav.* **2006**, *85*, 148.

(7) Overman, L. E.; Shim, J. *J. Org. Chem.* **1991**, *56*, 5005.

(8) Pearson, W. H.; Lian, B. W. *Angew. Chem., Int. Ed.* **1998**, *37*, 1724.

(9) Sha, C.-K.; Hong, A.-W.; Huang, C.-M. *Org. Lett.* **2001**, *3*, 2177.

(10) Ishizaki, M.; Hoshino, O.; Iitaka, Y. *J. Org. Chem.* **1992**, *57*, 7285.

(11) Jin, J.; Weinreb, S. M. *J. Am. Chem. Soc.* **1997**, *119*, 5773.

(12) (a) Ishizaki, M.; Kurihara, K.-I.; Tanazawa, E.; Hoshino, O. *J. Chem. Soc., Perkin Trans. 1* **1993**, 101. (b) Ikeda, M.; Hamada, M.; Yamashita, T.; Matsui, K.; Sato, T.; Ishibashi, H. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1949. (c) Banwell, M. G.; Edwards, A. J.; Jolliffe, K. A.; Kemmler, M. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1345. (d) Pandey, G.; Banerjee, P.; Kumar, R.; Puranik, V. G. *Org. Lett.* **2005**, *7*, 3713.

(13) For reviews on methods for generating *cis*-1,2-dihydrocatechols by microbial dihydroxylation of the corresponding aromatics, as well as the synthetic applications of these metabolites, see: (a) Hudlicky, T.; Gonzalez, D.; Gibson, D. T. *Aldrichimica Acta* **1999**, *32*, 35. (b) Banwell, M. G.; Edwards, A. J.; Harfoot, G. J.; Jolliffe, K. A.; McLeod, M. D.; McRae, K. J.; Stewart, S. G.; Vögtle, M. *Pure Appl. Chem.* **2003**, *75*, 223. (c) Johnson, R. A. *Org. React.* **2004**, *63*, 117.

(14) Stanislawski, P. C.; Willis, A. C.; Banwell, M. G. *Org. Lett.* **2006**, *8*, 2143.

(15) Compound **4b** has been described previously: Banwell, M. G.; McRae, K. J.; Willis, A. C. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2194.

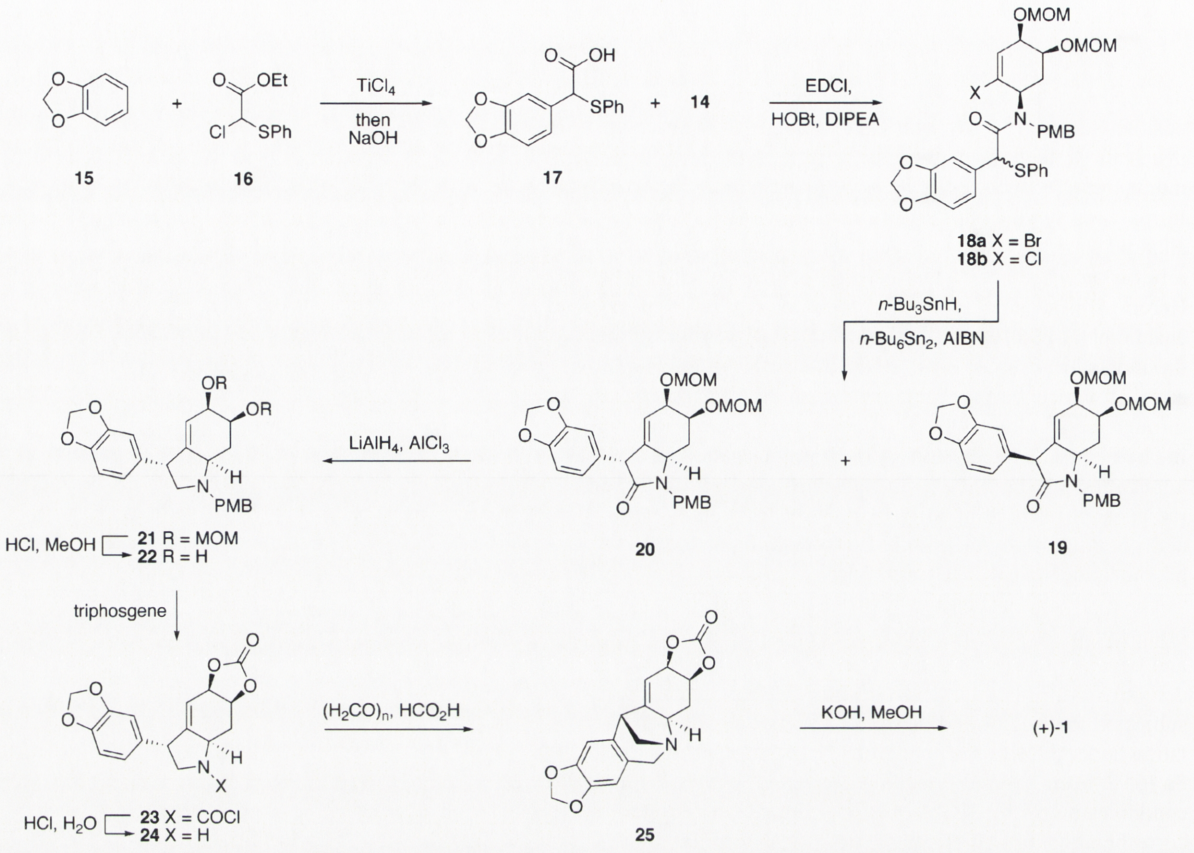
(16) VanRheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, 1973.

(17) Garegg, P. J.; Samuelsson, B. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2866.

(18) Details of X-ray analyses carried out as part of this study are provided in the Supporting Information.

(19) Lal, B.; Pramanik, B. N.; Manhas, M. S.; Bose, A. K. *Tetrahedron Lett.* **1977**, 1977.

Scheme 2



thiophenylacetate in the presence of $TiCl_4$ to give, after saponification of the product ester with NaOH, the α-arylated acetic acid **17** (99%). EDCI-promoted coupling of this compound with either amine **14a** or **14b** gave the corresponding amides **18a** (86%) and **18b** (74%), each of which was obtained as a ca. 1:1 mixture of diastereoisomers. In a pivotal step of the synthesis, compounds **18a** and **18b** were each subjected to reaction with mixtures of hexa-*n*-butylditin, tri-*n*-butyltin hydride, and AIBN so as to generate, via homolytic cleavage of the thiophenyl unit, a benzylic radical that engages in a 5-*exo*-trig cyclization/halide radical elimination reaction sequence,[14] thus forming the D-ring of target (+)-**1**. This sequence led to a mixture of the 3-arylhexahydrooxindole **19** (0% from **18a** and 7% from **18b**) and the required epimer **20** (29% from **18a** and 60% from **18b**) together with varying quantities of those compounds arising from reductive cleavage of the thiophenyl and/or halogen residue within the starting materials. The lactam carbonyl within product **20** was removed using in situ generated AlH_3 and the hexahydroindole **21** thus obtained in 94% yield. Because the looming Pictet−Spengler reaction requires the presence of acid-stable hydroxyl protecting groups, the MOM-ether residues within compound **21** were removed using aqueous HCl in methanol and the ensuing diol **22** (73%) subjected to reaction with triphosgene.[20] Use of this reagent not only resulted in the conversion of the *cis*-diol residue within substrate **22** into the acid-stable cyclic carbonate but also effected cleavage of the PMB-protected amine to form the corresponding carbamoyl chloride **23** which was immediately treated with aqueous dioxane in the presence of traces of HCl to give the cyclic secondary amine **24** (42% from **22**). Treatment of the last compound with paraformaldehyde in aqueous formic acid at 80 °C effected the pivotal Pictet−Spengler reaction to generate compound **25** (65%) embodying the full pentacyclic framework of target (+)-brunsvigine. Finally, subjection of carbonate **25** to reaction with KOH in methanol at 18 °C afforded compound (+)-**1** [mp 130−140 °C (sesquihydrate—recrystallized from wet acetone); lit.[1] mp 140−150 °C (for sesquihydrate of the enantiomer)] in 87% yield. The spectral data derived from this material were in full accord with the assigned structure, but final confirmation of this followed from a single-crystal X-ray analysis.[18] The specific rotation of (+)-brunsvigine $\{[\alpha]_D$ +75.9 (*c* 0.1, ethanol)$\}$ was of similar magnitude but opposite sign to that reported[21] for its enantiomer $\{[\alpha]_D$ −76.3 (*c* 1, ethanol)$\}$.

Given the availability of the enantiomeric forms of starting materials **3a** and **3b**,[13] the work detailed above will also

(20) Banwell, M. G.; Coster, M. J.; Harvey, M. J.; Moraes, J. *J. Org. Chem.* **2003**, *68*, 613.

(21) Pancricine. *Dictionary of Natural Products*; Buckingham, J., Ed.; Chapman & Hall: London, U.K., 1994; Vol. 4, p 4432, entry P-00106.

provide access to (−)-brunsvigine. Moreover, it seems reasonable to suggest that rather straightforward modifications to the reaction sequences defined above should permit the efficient preparation of many other members of the montanine alkaloid class. Work directed to such ends is now underway in these laboratories, and results will be reported in due course.

Acknowledgment. We thank the Institute of Advanced Studies and the Australian Research Council for generous financial support.

Supporting Information Available: Preparation and characterization of selected compounds; atomic displacement ellipsoid plots together with certain other materials derived from the single-crystal X-ray analyses of compounds **8a**, **9b**, and (+)-**1** (CCDC numbers 632321, 632322, and 641134, respectively); and ^{1}H or ^{13}C NMR spectra of compounds **11a**, **11b**, **14a**, **14b**, **20**, **25**, and (+)-**1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Chemoenzymatic Approaches to Lycorine-Type *Amaryllidaceae* Alkaloids: Total Syntheses of *ent*-Lycoricidine, 3-*epi*-*ent*-Lycoricidine, and 4-Deoxy-3-*epi*-*ent*-lycoricidine

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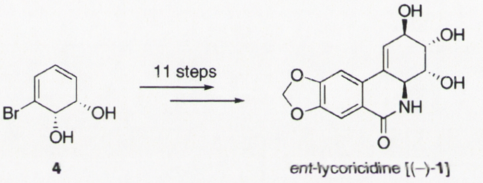
ABSTRACT



The readily available and enzymatically derived *cis*-1,2-dihydrocatechol 4 has been elaborated, over 11 steps including an Overman rearrangement, into the non-natural enantiomer, (–)-1, of the alkaloid lycoricidine [(+)-1]. Related chemistries have provided analogues 18, 19, and 26.

The lycorine-type *Amaryllidaceae* alkaloids (+)-lycoricidine [(+)-**1**], (+)-narciclasine [(+)-**2**], and (+)-pancratistatin [(+)-**3**] have been known for many years and have been isolated from, inter alia, plants of the genus *Amaryllidaceae* including the bulbs of narcissi and daffodils.[1] The potent biological properties of such compounds, particularly their carcinostatic and antiviral qualities, have resulted in their being considered for use as therapeutic agents.[2] For example, (+)-pancratistatin and some of its derivatives have been the subject of preclinical development studies as agents for the treatment of certain cancers.[2] This situation, together with the limited availability of certain of these alkaloids from natural sources, has prompted a substantial body of work directed at the development of practical synthetic routes to these compounds and various analogues. The extensive efforts devoted to this matter have been the subject of a number of recent reviews.[3] Work in the area continues unabated.[4]

As part of a continuing program to exploit readily available, microbially derived and enantiomerically pure *cis*-1,2-dihydrocatechols such as **4** as starting materials in chemical synthesis,[5] we have developed and now report efficient synthetic sequences that enable the rather rapid

(1) For reviews dealing with this class of alkaloid, see: (a) Martin, S. F. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: San Diego, 1987; Vol. 30, p 251. (b) Hoshino, O. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: San Diego, 1998; Vol. 51, p 323. (c) Jin, Z. *Nat. Prod. Rep.* **2003**, *20*, 606.

(2) For useful points on entry into the literature concerned with the biological properties of lycorine-type alkaloids and their analogues, see: (a) Pettit, G. R.; Melody, N. *J. Nat. Prod.* **2005**, *68*, 207. (b) McNulty, J.; Larichev, V.; Pandey, S. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 5315. (c) Pettit, G. R.; Eastham, S. A.; Melody, N.; Orr, B.; Herald, D. L.; McGregor, J.; Knight, J. C.; Doubek, D. L.; Pettit, G. R., III; Garner, L. C.; Bell, J. A. *J. Nat. Prod.* **2006**, *69*, 7.

(3) (a) Hudlicky, T. *J. Heterocycl. Chem.* **2000**, *37*, 535. (b) Rinner, U.; Hudlicky, T. *Synlett* **2005**, 365. (c) Chapleur, Y.; Chrétien, F.; Ibn Ahmed, S.; Khaldi, M. *Curr. Org. Synth.* **2006**, *3*, 341.

(4) For recent synthetic efforts in this area that have not been covered in the above-mentioned reviews,[3] see: (a) Zhang, H.; Padwa, A. *Synlett* **2006**, 2317. (b) Zhang, H.; Padwa, A. *Org. Lett.* **2006**, *8*, 247. (c) Shukla, K. H.; Boehmler, D. J.; Bogacyzk, S.; Duvall, B. R.; Peterson, W. A.; McElroy, W. T.; DeShong, P. *Org. Lett.* **2006**, *8*, 4183. (d) Li, M.; Wu, A.; Zhou, P. *Tetrahedron Lett.* **2006**, *47*, 3707. (e) Crich, D.; Krishnamurthy, V. *Tetrahedron* **2006**, *62*, 6830. (f) Shin, I.-J.; Choi, E.-S.; Cho, C.-G. *Angew. Chem., Int. Ed.* **2007**, *46*, 2303. (g) Padwa, A.; Zhang, H. *J. Org. Chem.* **2007**, *72*, 2570.

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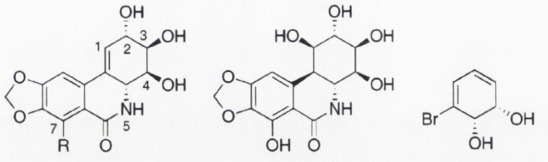
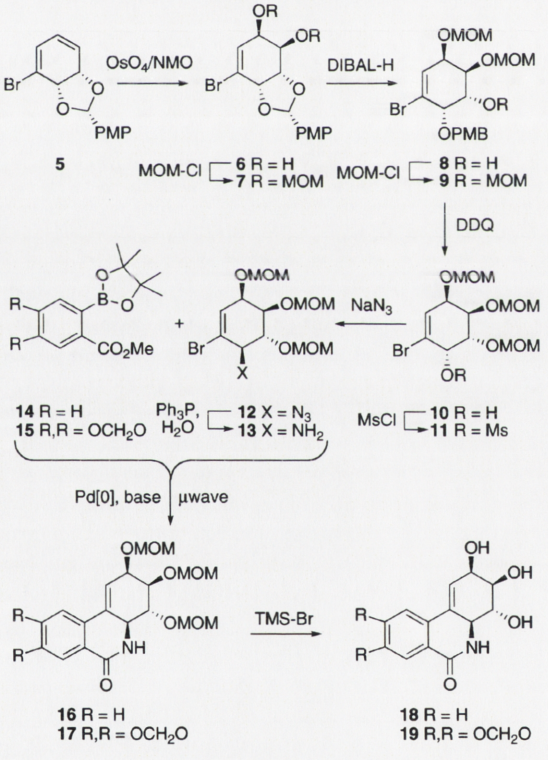
transformation of this material into *ent*-lycoricidine [(−)-**1**] and various congeners. Hudlicky and co-workers have exploited metabolite **4** and its enantiomer in cycloaddition and aziridination protocols culminating in elegant total syntheses of alkaloids **1**−**3** as well as various related (especially deoxygenated) systems.[3] The present work is distinct in that very different protocols have been applied to compound **4** in order to obtain the title compounds.



The syntheses of 3-*epi*-*ent*-lycoricidine and that analogue lacking the methylenedioxy unit are shown in Scheme 1.

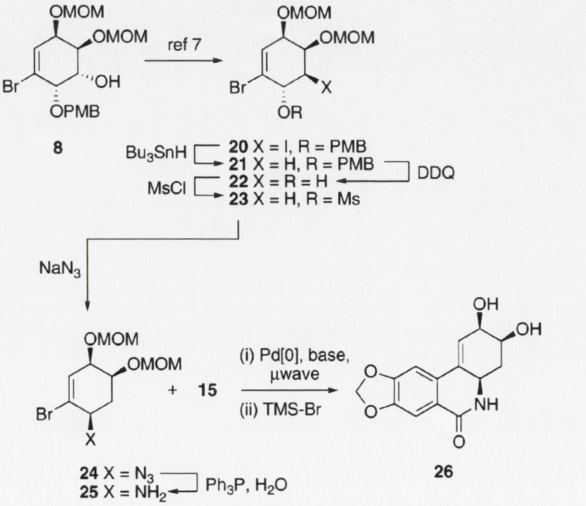
Scheme 1



Thus, *cis*-1,2-dihydroxylation of the readily accessible *p*-methoxybenzylidene acetal derivative **5**[6,7] of metabolite **4** under the UpJohn conditions[8] followed by treatment of the resulting diol (**6**) with MOM-Cl in the presence of base afforded the previously reported[7] compound **7** (59% from **5**). Treatment of this last compound with DIBAL-H resulted in essentially completely regiocontrolled cleavage of the PMP-acetal residue within the substrate and formation of the alcohol **8**[7] (84%) that was immediately protected, using standard conditions, as the corresponding MOM-ether **9** (90%). Oxidative cleavage of the PMB-ether residue within this last compound using DDQ then afforded alcohol **10** (95%), which was immediately converted into the corresponding mesylate **11** using a minor modification of the Crossland−Servis procedure.[9] Reaction of compound **11** with sodium azide afforded the expected S_N2 product **12** (95% from **10**) that was reduced to the corresponding amine **13** (99%) using the Staudinger protocol.[10] Subjection of compound **13** to reaction with the commercially available boronate ester **14** under Suzuki−Miyaura cross-coupling conditions[11] in a microwave reactor then provided the tricyclic compound **16** in 50% yield. Thus far, we have been unable to determine the precise order of events associated with the conversion **13** + **14** → **16** but presume that the cross-coupling reaction precedes the lactamization step. This last step contrasts with most other protocols[3] for establishing the lactam ring of such isocarbostyrils that often involve the application of a modified Bischler−Napieralski cyclization reaction.[3,12] Treatment of compound **16** with trimethylsilyl bromide at −30 °C[13] resulted in cleavage of the MOM-protecting groups and formation of the corresponding triol **18** (43%). Reaction of boronate **15**[14] with compound **13** under the same conditions as just described afforded the coupling product **17** (69%) that then gave 3-*epi*-*ent*-lycoricidine (**19**) (44%) upon exposure to trimethylsilyl bromide.

The synthesis of the 4-deoxy analogue of compound **19** was achieved in a similar manner (Scheme 2). Thus, treatment of alcohol **8**[7] with a mixture of triiodoimidazole, imidazole, and triphenylphosphine gave the iodide **20**[7] (81%) that was immediately reduced with tri-*n*-butyltin hydride to

Scheme 2

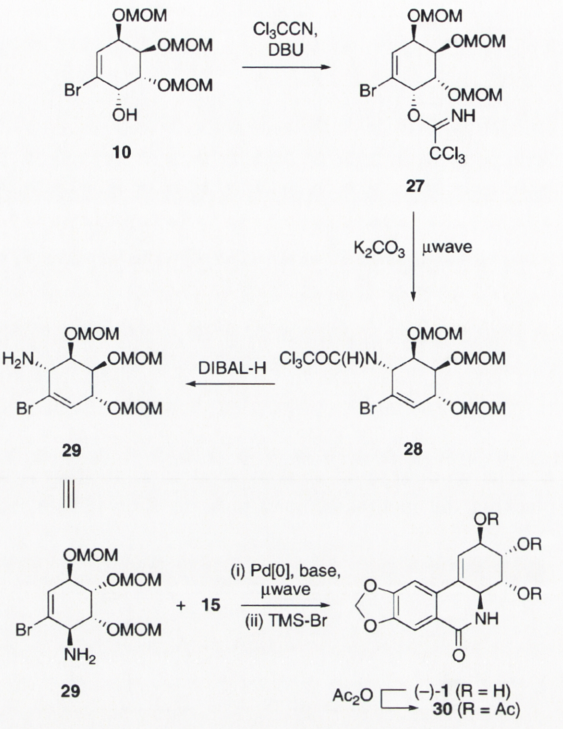


(5) For reviews on methods for generating *cis*-1,2-dihydrocatechols by microbial dihydroxylation of the corresponding aromatics, as well as the synthetic applications of these metabolites, see: (a) Hudlicky, T.; Gonzalez, D.; Gibson, D. T. *Aldrichim. Acta* **1999**, *32*, 35. (b) Banwell, M. G.; Edwards, A. J.; Harfoot, G. J.; Jolliffe, K. A.; McLeod, M. D.; McRae, K. J.; Stewart, S. G.; Vögtle, M. *Pure Appl. Chem.* **2003**, *75*, 223. (c) Johnson, R. A. *Org. React.* **2004**, *63*, 117.

give the iodinated system **21**[7] (85%). Subjection of the last compound to treatment with DDQ afforded alcohol **22** (96%) that was immediately converted into the corresponding mesylate **23** under standard conditions. Treatment of compound **23** with sodium azide afforded the expected product **24**[7] (76% from **22**) that was reduced directly to the amine **25**[7] (96%) under Staudinger conditions. Suzuki–Miyaura cross-coupling of this last compound with boronate ester **15** followed by treatment of the product lactam (62%) with trimethylsilyl bromide then gave 4-deoxy-3-*epi*-*ent*-lycoricidine (**26**) in 92% yield.

The synthesis of *ent*-lycoricidine [(−)-**1**] followed very similar lines (Scheme 3) and involved initial reaction of alcohol **10** with trichloroacetonitrile in the presence of DBU to give the acetimidate **27**. Subjection of this last compound to microwave irradiation in the presence of K_2CO_3[15] resulted in an Overman rearrangement[16] and the formation of the acetamide derivative **28** (65% from **10**). To the best of our knowledge the conversion **27** → **28** represents the first example of such a rearrangement that involves a halogenated alkene and that is effected by microwave irradiation. Hydrolysis of amide **28** was achieved using DIBAL-H[17] and provided amine **29** (89%) that could be subjected to a Suzuki–Miyaura cross-coupling reaction with boronate ester **15**. The ensuing lactam (83%) was treated with trimethylsilyl bromide to give *ent*-lycoricidine [(−)-**1**][18] in 62% yield. The NMR, MS, and IR spectral data derived from this material were completely consistent with those reported for both the natural product[18] and its enantiomer.[18] Similarly, the specific rotation of our material {$[\alpha]_D = -141$ (*c* 0.44, pyridine)} was consistent with that reported[18] previously {$[\alpha]_D = -164$ (*c* 0.45, pyridine) for (−)-**1**}. Final confirmation of structure followed a single-crystal X-ray analysis[19] of the derived triacetate **30** (70%): mp = 224–228 °C (lit.[18] mp = 205–210 °C); $[\alpha]_D = -196$ (*c* 0.40, $CHCl_3$) {lit.[18] $[\alpha]_D = -205$ (*c* 0.40, $CHCl_3$)}.

Scheme 3



Given the availability of the enantiomer of starting material **4**,[5] the work detailed above will also provide access to (+)-lycoricidine [(+)-**1**]. Moreover, it seems reasonable to suggest that rather straightforward modifications to these reaction sequences should permit the efficient preparation of other members of the lycorine alkaloid class. Work directed to such ends is now underway in these laboratories and results will be reported in due course.

Acknowledgment. We thank the Institute of Advanced Studies and the Australian Research Council for generous financial support. Mr. José Basutto (Australian National University) is warmly acknowledged for helpful discussions.

Supporting Information Available: Full experimental procedures; crystallographic data and atomic displacement ellipsoid plot for compound **30** (CCDC no. 648758); ^1H and/or ^{13}C NMR spectra of compounds **18**, **19**, **26**, **29**, (−)-**1**, and **30**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL701552R

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(7) Banwell, M. G.; Kokas, O. J.; Willis, A. C. *Org. Lett.* **2007**, *9*, 3503.
(8) VanRheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, 1973.
(9) Crossland, R. K.; Servis, K. L. *J. Org. Chem.* **1970**, *35*, 3195.
(10) Gololobov, Y. G.; Kasukhin, L. F. *Tetrahedron* **1992**, *48*, 1353.
(11) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.
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(19) Details of this analysis are provided in the Supporting Information.

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(2*R*,3a*S*,5a*R*,8a*R*,8b*S*)-4-Bromo-2-(4-methoxyphenyl)-7,7-dimethyl-3a,5a,8a,8b-tetrahydrobenzo[1,2-*d*:3,4-*d*′]bis[1,3]dioxole

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(2R,3aS,5aR,8aR,8bS)-4-Bromo-2-(4-methoxyphenyl)-7,7-dimethyl-3a,5a,-8a,8b-tetrahydrobenzo[1,2-d:3,4-d']-bis[1,3]dioxole

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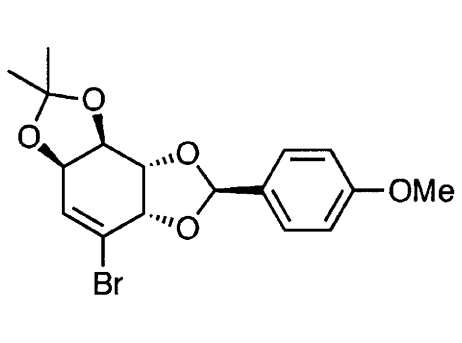
Key indicators: single-crystal X-ray study; T = 200 K; mean (C–C) = 0.005 Å; R factor = 0.034; wR factor = 0.078; data-to-parameter ratio = 13.9.

The title compound, $C_{17}H_{19}BrO_5$, bears an exo-orientated or R-configured 4-methoxyphenyl group and incorporates a C—O bond that is distinctly shorter than the three remaining acetal C—O bonds [1.415 (4) versus 1.431 (4)–1.448 (4) Å and 1.421 (4) versus 1.436 (4)–1.448 (4) Å for the two molecules in the asymmetric unit].

Related literature

For related literature, see: Banwell et al. (2003); Boyd et al. (1991); Hulme et al. (2005).



Experimental

Crystal data

$C_{17}H_{19}BrO_5$
M_r = 383.24
Monoclinic, $P2_1$
a = 5.2285 (1) Å
b = 33.4467 (9) Å
c = 9.4726 (3) Å
β = 91.7226 (12)°
V = 1655.78 (7) Å^3
Z = 4
Mo Kα radiation
μ = 2.51 mm^{-1}
T = 200 K
0.45 × 0.14 × 0.05 mm

Data collection

Nonius KappaCCD diffractometer
Absorption correction: integration via Gaussian method (Coppens, 1970) implemented in maXus (Mackay et al., 1999)
T_{min} = 0.546, T_{max} = 0.892
20604 measured reflections
5796 independent reflections
4970 reflections with I > 2σ(I)
R_{int} = 0.038

Refinement

R[F^2 > 2σ(F^2)] = 0.034
wR(F^2) = 0.078
S = 0.97
5796 reflections
416 parameters
1 restraint
H-atom parameters not refined
$\Delta\rho_{max}$ = 0.58 e Å^{-3}
$\Delta\rho_{min}$ = −0.82 e Å^{-3}
Absolute structure: Flack (1983), 2828 Friedel pairs
Flack parameter: 0.012 (6)

Data collection: COLLECT (Nonius, 1997); cell refinement: DENZO/SCALEPACK (Otwinowski & Minor, 1997); data reduction: DENZO/SCALEPACK; program(s) used to solve structure: SIR92 (Altomare et al., 1994); program(s) used to refine structure: CRYSTALS (Betteridge et al., 2003); molecular graphics: ORTEPII (Johnson, 1976) in TEXSAN (Molecular Structure Corporation, 1997); software used to prepare material for publication: CRYSTALS.

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Supplementary data and figures for this paper are available from the IUCr electronic archives (Reference: BT2471).

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supplementary materials

Acta Cryst. (2007). E**63**, o3820 [**doi:10.1107/S1600536807039232**]

(2*R*,3a*S*,5a*R*,8a*R*,8b*S*)-4-Bromo-2-(4-methoxyphenyl)-7,7-dimethyl-3a,5a,8a,8b-tetrahydrobenzo[1,2-*d*:3,4-*d*']bis[1,3]dioxole

M. G. Banwell, O. J. Kokas and A. C. Willis

Comment

As part of a program directed towards exploiting microbially derived and enantiomerically pure *cis*-1,2-dihydrocatechols in the synthesis of certain biologically active natural products (Banwell *et al.*, 2003), we generated an epimeric mixture of compounds (I) and (II) then subjected this to reaction with DIBAL-H. At 195–233 K one of these two benzylidene acetals participated more readily in the anticipated reductive cleavage reaction leading to the desired *p*-methoxybenzyl ether (III). The unreacted epimer was recovered and subjected to single-crystal X-ray analysis and thus establishing that it was compound (II) incorporating an *exo*-orientated or *R*-configured 4-methoxyphenyl group at C2. This outcome is consistent with the notion that the reactive epimer (I) can, by virtue of reduced steric effects, complex DIBAL-H at the O1-acetal oxygen more readily than (II) and thus engage, selectively, in the ring-cleavage process leading to target (III). The present structure represents only the second reported for a 4-methoxyphenylacetal derivative of a *cis*-cyclohexane-1,2-diol (Hulme *et al.*, 2005).

The crystallographic asymmetric unit within the solid-state structure of compound (II) consists of two independent molecules. The compound is enantiomerically pure and its absolute configuration has been determined by refinement of the Flack parameter. The outcome of this determination is in agreement with that predicted on the basis of the absolute configuration of the precursor, *viz.* (1*S*,2*S*)-3-bromo-3,5-cyclohexadiene-1,2-diol (Boyd *et al.*, 1991). The three non-aromatic rings within the title compound are each close to planar and with the two 1,3-dioxolane rings clearly attached to the opposite faces of the central cyclohexene residue. The allylic and homo-allylic C–O bonds associated with the two heterocyclic rings are all of similar length (1.430–1.438 Å) but the C2–O3 bond is notably shorter than the three remaining acetal carbon to oxygen bonds (1.418 *vs* 1.438–1.444 Å) within the molecule. The origins of this variation are unclear at the present time.

Experimental

A magnetically stirred solution of a 5:3 mixture of the benzylidene acetals (I) and (II) (88 mg, 0.23 mmol) in anhydrous dichloromethane/pentane (1.4 ml of a 1:1 *v*/*v* mixture) was cooled to 195 K then treated, dropwise, with DIBAL-H (1.15 ml of a 1.0 *M* solution in dichloromethane). The resulting mixture was warmed to 233 K and after 6 h at this temperature was treated with sodium potassium tartrate (5 ml of a 1 *M* aqueous solution). The ensuing mixture was allowed to stir at 291 K for 2 h then the separated aqueous fraction was extracted with dichloromethane (3 × 40 ml). The combined organic phases were washed with brine (1 × 50 ml) then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a clear, colourless oil. Subjection of this material to flash chromatography (silica, 1:4 *v*/*v* ethyl acetate/hexane elution) afforded two fractions, A and B.

Concentration of fraction A (R_f = 1/5) under reduced pressure afforded the benzyl ether (III) [41 mg, 74% based on available (I)] as a clear, colourless oil, $[\alpha]_D$ −59.9 (*c* 0.05, $CHCl_3$) (Found: $M^{+\cdot}$, 384.0570. $C_{17}H_{21}{}^{79}BrO_5$ requires $M^{+\cdot}$, 384.0572). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 (2*H*, d, *J* = 8.7 Hz), 6.90 (2*H*, d, *J* = 8.7 Hz), 6.24 (1*H*, d, *J* = 3.6 Hz), 4.84

(1*H*, d, J = 10.8 Hz), 4.68–4.61 (2*H*, complex m), 4.36 (2*H*, m), 4.15–4.10 (2*H*, complex m), 3.81 (3*H*, s), 1.43 (3*H*, s), 1.36 (3*H*, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.8, 130.1, 129.9, 128.6, 124.2, 114.1, 110.1, 77.9, 75.4, 74.0, 73.4, 70.5, 55.5, 28.1, 26.2 (one signal obscured or overlapping); ν_{max} (NaCl)/cm^{-1} 3460, 2924, 1612, 1516, 1464, 1254, 1089, 1046; MS (EI, 70 eV) 386 and 384 ($M^{+\cdot}$, both 3%), 256 (7), 137 (20), 121 (100), 101 (20), 81 (37), 69 (81), 55 (42), 43 (53).

Concentration of fraction B (R_f = 0.30) under reduced pressure afforded a solid that upon recrystallization (diethyl ether) gave the acetal (II) (30 mg, 90% recovery) as white plates, m.p. = 649–651 K, $[\alpha]_D$ = +49.4 (c 0.21, $CHCl_3$) [Found: (M – H$^{\cdot}$)$^+$, 381.0334. $C_{17}H_{19}{}^{79}BrO_5$ requires (M – H$^{\cdot}$)$^+$, 381.0338]. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 (2*H*, d, J = 8.4 Hz), 6.79 (2*H*, d, J = 8.4 Hz), 6.25 (1*H*, d, J = 3.6 Hz), 5.86 (1*H*, s), 4.91 (1*H*, d, J = 6.0 Hz), 4.64–4.60 (3*H*, complex m), 3.73 (3*H*, s), 1.40 (3*H*, s), 1.38 (3*H*, s); ν_{max} (NaCl)/cm^{-1} 2979, 2896, 1647, 1615, 1589, 1517, 1382, 1337, 1249, 1220, 1175, 1090, 1060, 1025, 948, 832; MS (EI, 70 eV) 384 and 382 ($M^{+\cdot}$, both 15%), 383 and 381 [(M – H$^{\cdot}$)$^+$, both 29], 336 and 334 (both 2), 200 (16), 161 (31), 137 (38), 136 (60), 135 (100), 108 (53), 77 (29), 43 (52).

Refinement

Hydrogen atoms were included at calculated positions and ride on the atoms to which they are bonded. The biggest features in a final difference electron density map are close to the Br atoms.

Figures

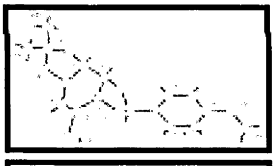


Figure 1. Anisotropic displacement ellipsoid plot of $C_{17}H_{19}BrO_5$ (molecule one) with labelling of selected atoms. Ellipsoids show 50% probability levels. Hydrogen atoms are drawn as circles with small radii.

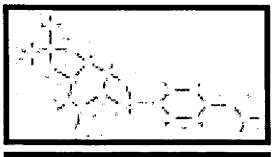
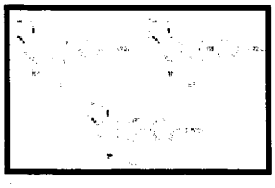


Figure 2. Anisotropic displacement ellipsoid plot of $C_{17}H_{19}BrO_5$ (molecule two) with labelling of selected atoms. Ellipsoids show 50% probability levels. Hydrogen atoms are drawn as circles with small radii.

Figure 3. Unit cell packing diagram of $C_{17}H_{19}BrO_5$ projected down the a axis. Hydrogen atoms are drawn as circles with small radii.



(2*R*,3a*S*,5a*R*,8a*R*,8 b*S*)- 4-Bromo-2-(4-methoxyphenyl)-7,7-dimethyl-3a,5a,8a,8 b-tetrahydrobenzo[1,2 – *d*:3,4 – *d*']bis[1,3]dioxole

Crystal data

$C_{17}H_{19}BrO_5$ F_{000} = 784

$M_r = 383.24$	$D_x = 1.537$ Mg m^{-3}
Monoclinic, $P2_1$	Mo $K\alpha$ radiation $\lambda = 0.71073$ Å
$a = 5.2285$ (1) Å	Cell parameters from 55931 reflections
$b = 33.4467$ (9) Å	$\theta = 2.6$–$25°$
$c = 9.4726$ (3) Å	$\mu = 2.51$ mm^{-1}
$\beta = 91.7226$ (12)°	$T = 200$ K
$V = 1655.78$ (7) Å^3	Plate, colourless
$Z = 4$	0.45 × 0.14 × 0.05 mm

Data collection

Nonius KappaCCD diffractometer	4970 reflections with $I > 2\sigma(I)$
Monochromator: graphite	$R_{int} = 0.038$
$T = 200$ K	$\theta_{max} = 25.0°$
φ and ω scans with CCD	$\theta_{min} = 2.8°$
Absorption correction: integration via Gaussian method (Coppens, 1970) implemented in maXus (Mackay *et al.*, 1999)	$h = -6 \rightarrow 6$
$T_{min} = 0.546$, $T_{max} = 0.892$	$k = -39 \rightarrow 39$
20604 measured reflections	$l = -11 \rightarrow 11$
5796 independent reflections	

Refinement

Refinement on F^2	Hydrogen site location: inferred from neighbouring sites
Least-squares matrix: full	H-atom parameters not refined
$R[F^2 > 2\sigma(F^2)] = 0.034$	Method = Modified Sheldrick $w = 1/[\sigma^2(F^2) + (0.03P)^2 + 0.44P]$, where $P = [\max(F_o^2,0) + 2F_c^2]/3$
$wR(F^2) = 0.078$	$(\Delta/\sigma)_{max} = 0.001$
$S = 0.97$	$\Delta\rho_{max} = 0.58$ e Å^{-3}
5796 reflections	$\Delta\rho_{min} = -0.82$ e Å^{-3}
416 parameters	Extinction correction: None
1 restraint	Absolute structure: Flack (1983), 2828 Friedel pairs
Primary atom site location: structure-invariant direct methods	Flack parameter: −0.012 (6)

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å^2)

	x	y	z	U_{iso}*/U_{eq}
O1	0.3464 (5)	0.40867 (9)	0.5958 (3)	0.0442
C2	0.2738 (7)	0.40850 (12)	0.7402 (4)	0.0359
O3	0.0221 (5)	0.39302 (8)	0.7424 (3)	0.0393
C4	−0.0224 (7)	0.37075 (11)	0.6148 (4)	0.0358
C5	0.0579 (8)	0.32792 (11)	0.6278 (4)	0.0382

C6	0.2260 (8)	0.30950 (12)	0.5503 (4)	0.0384
C7	0.3623 (7)	0.32944 (11)	0.4320 (4)	0.0345
O8	0.3249 (5)	0.30663 (8)	0.3051 (2)	0.0349
C9	0.1349 (7)	0.32616 (11)	0.2148 (4)	0.0348
O10	0.0409 (5)	0.35852 (8)	0.2978 (2)	0.0374
C11	0.2475 (7)	0.37002 (11)	0.3917 (4)	0.0364
C12	0.1353 (7)	0.39397 (12)	0.5098 (4)	0.0360
C13	0.2790 (7)	0.44947 (11)	0.8044 (4)	0.0333
C14	0.1061 (8)	0.47884 (12)	0.7616 (4)	0.0402
C15	0.1102 (8)	0.51620 (12)	0.8225 (4)	0.0408
C16	0.2883 (7)	0.52469 (11)	0.9305 (4)	0.0347
C17	0.4642 (8)	0.49634 (12)	0.9723 (4)	0.0422
C18	0.4595 (8)	0.45874 (12)	0.9093 (4)	0.0408
Br19	−0.11756 (10)	0.29887 (3)	0.76809 (4)	0.0609
C20	−0.0808 (7)	0.29762 (13)	0.1827 (4)	0.0448
C21	0.2636 (8)	0.34112 (13)	0.0852 (4)	0.0465
O22	0.2709 (5)	0.56229 (8)	0.9893 (3)	0.0439
C23	0.4571 (9)	0.57223 (12)	1.0977 (4)	0.0480
O101	0.8242 (5)	0.60404 (8)	0.6747 (3)	0.0444
C102	0.7448 (7)	0.60523 (11)	0.5282 (4)	0.0356
O103	0.4861 (5)	0.61825 (8)	0.5250 (3)	0.0392
C104	0.4501 (7)	0.64154 (11)	0.6503 (4)	0.0353
C105	0.5211 (7)	0.68426 (11)	0.6330 (4)	0.0337
C106	0.6957 (7)	0.70409 (11)	0.7083 (4)	0.0352
C107	0.8556 (7)	0.68488 (11)	0.8242 (4)	0.0325
O108	0.8519 (4)	0.70848 (9)	0.9508 (2)	0.0342
C109	0.6632 (7)	0.69170 (12)	1.0426 (4)	0.0358
O110	0.5563 (5)	0.65805 (8)	0.9668 (2)	0.0378
C111	0.7488 (8)	0.64532 (11)	0.8725 (4)	0.0363
C112	0.6229 (8)	0.61987 (12)	0.7581 (4)	0.0362
C113	0.7651 (7)	0.56493 (11)	0.4605 (4)	0.0323
C114	0.6019 (8)	0.53372 (12)	0.4985 (4)	0.0399
C115	0.6187 (8)	0.49680 (11)	0.4347 (4)	0.0388
C116	0.7973 (7)	0.49055 (11)	0.3318 (4)	0.0355
C117	0.9609 (8)	0.52082 (12)	0.2951 (4)	0.0414
C118	0.9423 (7)	0.55802 (12)	0.3611 (4)	0.0392
Br119	0.32031 (9)	0.71174 (3)	0.49172 (4)	0.0513
C120	0.4578 (8)	0.72146 (13)	1.0659 (5)	0.0527
C121	0.7960 (9)	0.67800 (14)	1.1778 (4)	0.0505
O122	0.7948 (6)	0.45324 (8)	0.2698 (3)	0.0429
C123	0.9839 (9)	0.44560 (13)	0.1674 (4)	0.0483
H21	0.3917	0.39055	0.7960	0.0430*
H41	−0.2078	0.37220	0.5861	0.0429*
H61	0.2651	0.28080	0.5711	0.0459*
H71	0.5489	0.33217	0.4563	0.0414*
H111	0.3748	0.38645	0.3405	0.0436*
H121	0.0332	0.41686	0.4701	0.0432*
H141	−0.0240	0.47275	0.6851	0.0480*
H151	−0.0141	0.53715	0.7893	0.0487*

H171	0.5957	0.50268	1.0478	0.0504*
H181	0.5880	0.43815	0.9403	0.0487*
H201	−0.0197	0.27581	0.1198	0.0536*
H202	−0.2251	0.31227	0.1341	0.0536*
H203	−0.1412	0.28577	0.2727	0.0536*
H211	0.1346	0.35471	0.0216	0.0560*
H212	0.4012	0.36053	0.1135	0.0560*
H213	0.3405	0.31807	0.0343	0.0560*
H231	0.4256	0.60002	1.1320	0.0576*
H232	0.6324	0.57057	1.0587	0.0576*
H233	0.4434	0.55302	1.1780	0.0576*
H1021	0.8522	0.62490	0.4770	0.0427*
H1041	0.2679	0.63956	0.6788	0.0424*
H1061	0.7226	0.73307	0.6875	0.0424*
H1071	1.0354	0.68137	0.7934	0.0391*
H1111	0.8841	0.62966	0.9249	0.0436*
H1121	0.5266	0.59745	0.8019	0.0436*
H1141	0.4723	0.53827	0.5723	0.0480*
H1151	0.5024	0.47460	0.4625	0.0465*
H1171	1.0916	0.51623	0.2219	0.0499*
H1181	1.0616	0.57999	0.3348	0.0472*
H1201	0.5305	0.74480	1.1196	0.0633*
H1202	0.3854	0.73078	0.9727	0.0633*
H1203	0.3194	0.70884	1.1213	0.0633*
H1211	0.6672	0.66636	1.2420	0.0606*
H1212	0.8821	0.70132	1.2252	0.0606*
H1213	0.9267	0.65726	1.1558	0.0606*
H1231	0.9627	0.41776	0.1303	0.0580*
H1232	0.9630	0.46507	0.0878	0.0580*
H1233	1.1584	0.44861	0.2123	0.0580*

Atomic displacement parameters (Å^2)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
O1	0.0511 (17)	0.0465 (17)	0.0355 (14)	−0.0169 (13)	0.0087 (13)	−0.0127 (13)
C2	0.035 (2)	0.039 (2)	0.034 (2)	−0.0014 (17)	−0.0008 (16)	−0.0041 (17)
O3	0.0432 (16)	0.0415 (15)	0.0333 (14)	−0.0120 (13)	0.0064 (11)	−0.0104 (12)
C4	0.037 (2)	0.039 (2)	0.0318 (19)	−0.0038 (17)	−0.0044 (16)	−0.0093 (16)
C5	0.050 (3)	0.032 (2)	0.031 (2)	−0.0090 (18)	−0.0070 (18)	−0.0013 (17)
C6	0.051 (2)	0.032 (2)	0.032 (2)	0.0052 (17)	−0.0079 (17)	0.0006 (16)
C7	0.037 (2)	0.033 (2)	0.033 (2)	0.0052 (17)	−0.0006 (17)	−0.0070 (17)
O8	0.0360 (14)	0.0368 (16)	0.0312 (13)	0.0076 (11)	−0.0078 (11)	−0.0084 (11)
C9	0.037 (2)	0.036 (2)	0.032 (2)	0.0106 (16)	−0.0030 (16)	−0.0073 (16)
O10	0.0478 (15)	0.0364 (14)	0.0277 (13)	0.0114 (12)	−0.0035 (11)	−0.0080 (11)
C11	0.045 (2)	0.034 (2)	0.0309 (19)	−0.0037 (17)	0.0001 (16)	−0.0034 (16)
C12	0.050 (2)	0.030 (2)	0.0274 (19)	0.0009 (17)	−0.0008 (17)	−0.0041 (15)
C13	0.039 (2)	0.034 (2)	0.0274 (19)	−0.0039 (17)	0.0035 (16)	−0.0057 (16)
C14	0.044 (2)	0.042 (2)	0.034 (2)	0.0015 (19)	−0.0099 (18)	−0.0020 (18)

C15	0.050 (2)	0.034 (2)	0.038 (2)	0.0044 (18)	−0.0057 (18)	0.0018 (17)
C16	0.045 (2)	0.028 (2)	0.0310 (19)	−0.0050 (17)	0.0054 (16)	−0.0016 (15)
C17	0.044 (2)	0.040 (2)	0.042 (2)	0.0012 (19)	−0.0105 (18)	−0.0111 (18)
C18	0.044 (2)	0.037 (2)	0.041 (2)	0.0050 (18)	−0.0100 (18)	−0.0079 (17)
Br19	0.0886 (4)	0.0553 (3)	0.0393 (2)	−0.0281 (3)	0.0087 (2)	0.0010 (2)
C20	0.034 (2)	0.045 (2)	0.055 (2)	0.003 (2)	−0.0052 (17)	−0.015 (2)
C21	0.053 (3)	0.052 (3)	0.035 (2)	0.006 (2)	0.0036 (19)	−0.0011 (19)
O22	0.0618 (18)	0.0291 (15)	0.0407 (16)	−0.0040 (14)	−0.0010 (13)	−0.0046 (12)
C23	0.070 (3)	0.035 (2)	0.039 (2)	−0.018 (2)	−0.001 (2)	−0.0034 (18)
O101	0.0498 (17)	0.0489 (18)	0.0337 (14)	0.0165 (14)	−0.0081 (12)	−0.0132 (12)
C102	0.034 (2)	0.038 (2)	0.034 (2)	0.0044 (17)	−0.0005 (16)	−0.0067 (17)
O103	0.0385 (15)	0.0420 (15)	0.0367 (14)	0.0062 (12)	−0.0059 (11)	−0.0133 (12)
C104	0.038 (2)	0.035 (2)	0.033 (2)	0.0003 (17)	0.0032 (16)	−0.0087 (16)
C105	0.039 (2)	0.034 (2)	0.0290 (19)	0.0018 (17)	0.0033 (16)	−0.0022 (16)
C106	0.043 (2)	0.031 (2)	0.0314 (18)	−0.0011 (17)	0.0072 (16)	0.0014 (15)
C107	0.033 (2)	0.034 (2)	0.0303 (19)	0.0008 (16)	0.0020 (15)	−0.0057 (16)
O108	0.0395 (13)	0.0340 (14)	0.0293 (13)	−0.0040 (12)	0.0048 (10)	−0.0065 (13)
C109	0.037 (2)	0.039 (2)	0.0310 (19)	−0.0071 (17)	0.0038 (16)	−0.0057 (16)
O110	0.0482 (16)	0.0351 (15)	0.0305 (13)	−0.0101 (12)	0.0081 (12)	−0.0061 (11)
C111	0.047 (2)	0.031 (2)	0.031 (2)	0.0025 (17)	0.0043 (17)	−0.0026 (16)
C112	0.051 (2)	0.031 (2)	0.0268 (19)	−0.0019 (18)	0.0058 (17)	−0.0039 (15)
C113	0.036 (2)	0.032 (2)	0.0291 (18)	−0.0013 (17)	−0.0023 (16)	−0.0030 (16)
C114	0.047 (2)	0.040 (2)	0.033 (2)	−0.0009 (19)	0.0068 (18)	−0.0068 (17)
C115	0.046 (2)	0.036 (2)	0.035 (2)	−0.0040 (18)	0.0020 (18)	−0.0010 (17)
C116	0.044 (2)	0.029 (2)	0.033 (2)	0.0036 (17)	−0.0062 (17)	−0.0038 (16)
C117	0.044 (2)	0.043 (2)	0.038 (2)	−0.0008 (19)	0.0136 (18)	−0.0103 (18)
C118	0.040 (2)	0.035 (2)	0.043 (2)	−0.0019 (18)	0.0066 (18)	−0.0076 (18)
Br119	0.0586 (3)	0.0541 (3)	0.0406 (2)	0.0124 (2)	−0.00977 (18)	0.0001 (2)
C120	0.038 (2)	0.052 (3)	0.068 (3)	0.001 (2)	0.006 (2)	−0.016 (2)
C121	0.061 (3)	0.060 (3)	0.031 (2)	−0.009 (2)	−0.003 (2)	0.002 (2)
O122	0.0602 (19)	0.0300 (15)	0.0386 (16)	0.0026 (13)	0.0018 (13)	−0.0065 (12)
C123	0.067 (3)	0.041 (2)	0.037 (2)	0.018 (2)	0.001 (2)	−0.0042 (19)

Geometric parameters (Å, °)

O1—C2	1.431 (4)	O101—C102	1.436 (4)
O1—C12	1.439 (4)	O101—C112	1.436 (4)
C2—O3	1.415 (4)	C102—O103	1.421 (4)
C2—C13	1.499 (5)	C102—C113	1.498 (5)
C2—H21	1.000	C102—H1021	1.000
O3—C4	1.433 (4)	O103—C104	1.437 (4)
C4—C5	1.497 (5)	C104—C105	1.486 (5)
C4—C12	1.524 (5)	C104—C112	1.527 (5)
C4—H41	1.000	C104—H1041	1.000
C5—C6	1.315 (5)	C105—C106	1.320 (5)
C5—Br19	1.904 (4)	C105—Br119	1.911 (4)
C6—C7	1.502 (6)	C106—C107	1.503 (5)
C6—H61	1.000	C106—H1061	1.000
C7—O8	1.432 (4)	C107—O108	1.436 (4)

C7—C11	1.528 (5)	C107—C111	1.513 (5)
C7—H71	1.000	C107—H1071	1.000
O8—C9	1.448 (4)	O108—C109	1.448 (4)
C9—O10	1.433 (4)	C109—O110	1.439 (4)
C9—C20	1.502 (5)	C109—C120	1.486 (6)
C9—C21	1.503 (5)	C109—C121	1.510 (5)
O10—C11	1.431 (4)	O110—C111	1.430 (4)
C11—C12	1.509 (5)	C111—C112	1.513 (5)
C11—H111	1.000	C111—H1111	1.000
C12—H121	1.000	C112—H1121	1.000
C13—C14	1.387 (5)	C113—C114	1.402 (5)
C13—C18	1.385 (5)	C113—C118	1.360 (5)
C14—C15	1.376 (6)	C114—C115	1.379 (5)
C14—H141	1.000	C114—H1141	1.000
C15—C16	1.391 (5)	C115—C116	1.386 (5)
C15—H151	1.000	C115—H1151	1.000
C16—C17	1.371 (5)	C116—C117	1.377 (5)
C16—O22	1.379 (4)	C116—O122	1.379 (4)
C17—C18	1.392 (5)	C117—C118	1.397 (5)
C17—H171	1.000	C117—H1171	1.000
C18—H181	1.000	C118—H1181	1.000
C20—H201	1.000	C120—H1201	1.000
C20—H202	1.000	C120—H1202	1.000
C20—H203	1.000	C120—H1203	1.000
C21—H211	1.000	C121—H1211	1.000
C21—H212	1.000	C121—H1212	1.000
C21—H213	1.000	C121—H1213	1.000
O22—C23	1.433 (4)	O122—C123	1.429 (5)
C23—H231	1.000	C123—H1231	1.000
C23—H232	1.000	C123—H1232	1.000
C23—H233	1.000	C123—H1233	1.000
C2—O1—C12	108.6 (3)	C102—O101—C112	109.0 (3)
O1—C2—O3	106.8 (3)	O101—C102—O103	106.1 (3)
O1—C2—C13	112.5 (3)	O101—C102—C113	111.5 (3)
O3—C2—C13	109.5 (3)	O103—C102—C113	110.3 (3)
O1—C2—H21	109.3	O101—C102—H1021	109.6
O3—C2—H21	109.3	O103—C102—H1021	109.6
C13—C2—H21	109.3	C113—C102—H1021	109.6
C2—O3—C4	107.8 (3)	C102—O103—C104	107.3 (3)
O3—C4—C5	113.0 (3)	O103—C104—C105	113.0 (3)
O3—C4—C12	102.1 (3)	O103—C104—C112	101.9 (3)
C5—C4—C12	112.7 (3)	C105—C104—C112	112.7 (3)
O3—C4—H41	109.6	O103—C104—H1041	109.7
C5—C4—H41	109.6	C105—C104—H1041	109.7
C12—C4—H41	109.6	C112—C104—H1041	109.7
C4—C5—C6	126.4 (4)	C104—C105—C106	126.5 (3)
C4—C5—Br19	113.9 (3)	C104—C105—Br119	113.9 (3)
C6—C5—Br19	119.7 (3)	C106—C105—Br119	119.5 (3)
C5—C6—C7	123.3 (3)	C105—C106—C107	122.7 (3)

C5—C6—H61	118.4	C105—C106—H1061	118.7
C7—C6—H61	118.4	C107—C106—H1061	118.7
C6—C7—O8	109.5 (3)	C106—C107—O108	110.7 (3)
C6—C7—C11	112.9 (3)	C106—C107—C111	113.1 (3)
O8—C7—C11	102.8 (3)	O108—C107—C111	102.3 (3)
C6—C7—H71	110.5	C106—C107—H1071	110.1
O8—C7—H71	110.5	O108—C107—H1071	110.1
C11—C7—H71	110.5	C111—C107—H1071	110.2
C7—O8—C9	109.2 (3)	C107—O108—C109	108.4 (3)
O8—C9—O10	104.9 (2)	O108—C109—O110	105.4 (3)
O8—C9—C20	109.3 (3)	O108—C109—C120	109.8 (3)
O10—C9—C20	108.9 (3)	O110—C109—C120	109.1 (3)
O8—C9—C21	108.5 (3)	O108—C109—C121	108.8 (3)
O10—C9—C21	111.4 (3)	O110—C109—C121	110.4 (3)
C20—C9—C21	113.4 (3)	C120—C109—C121	113.1 (4)
C9—O10—C11	106.2 (3)	C109—O110—C111	105.9 (3)
C7—C11—O10	101.5 (3)	C107—C111—O110	101.6 (3)
C7—C11—C12	116.5 (3)	C107—C111—C112	115.6 (3)
O10—C11—C12	107.5 (3)	O110—C111—C112	108.4 (3)
C7—C11—H111	110.3	C107—C111—H1111	110.3
O10—C11—H111	110.3	O110—C111—H1111	110.3
C12—C11—H111	110.3	C112—C111—H1111	110.3
C4—C12—C11	116.3 (3)	C104—C112—C111	116.6 (3)
C4—C12—O1	103.0 (3)	C104—C112—O101	103.6 (3)
C11—C12—O1	107.0 (3)	C111—C112—O101	106.9 (3)
C4—C12—H121	110.1	C104—C112—H1121	109.8
C11—C12—H121	110.1	C111—C112—H1121	109.8
O1—C12—H121	110.1	O101—C112—H1121	109.8
C2—C13—C14	121.7 (3)	C102—C113—C114	120.6 (3)
C2—C13—C18	119.9 (3)	C102—C113—C118	120.5 (3)
C14—C13—C18	118.4 (4)	C114—C113—C118	118.9 (3)
C13—C14—C15	121.3 (4)	C113—C114—C115	120.5 (4)
C13—C14—H141	119.4	C113—C114—H1141	119.8
C15—C14—H141	119.4	C115—C114—H1141	119.8
C14—C15—C16	119.7 (4)	C114—C115—C116	119.8 (4)
C14—C15—H151	120.2	C114—C115—H1151	120.1
C16—C15—H151	120.2	C116—C115—H1151	120.1
C15—C16—C17	119.9 (4)	C115—C116—C117	120.2 (4)
C15—C16—O22	115.6 (3)	C115—C116—O122	116.0 (3)
C17—C16—O22	124.5 (3)	C117—C116—O122	123.8 (3)
C16—C17—C18	119.9 (4)	C116—C117—C118	119.3 (4)
C16—C17—H171	120.1	C116—C117—H1171	120.3
C18—C17—H171	120.0	C118—C117—H1171	120.3
C17—C18—C13	120.8 (4)	C117—C118—C113	121.3 (4)
C17—C18—H181	119.6	C117—C118—H1181	119.4
C13—C18—H181	119.6	C113—C118—H1181	119.4
C9—C20—H201	109.5	C109—C120—H1201	109.5
C9—C20—H202	109.5	C109—C120—H1202	109.5
H201—C20—H202	109.5	H1201—C120—H1202	109.5

C9—C20—H203	109.5	C109—C120—H1203	109.5
H201—C20—H203	109.5	H1201—C120—H1203	109.5
H202—C20—H203	109.5	H1202—C120—H1203	109.5
C9—C21—H211	109.5	C109—C121—H1211	109.5
C9—C21—H212	109.5	C109—C121—H1212	109.5
H211—C21—H212	109.5	H1211—C121—H1212	109.5
C9—C21—H213	109.5	C109—C121—H1213	109.5
H211—C21—H213	109.5	H1211—C121—H1213	109.5
H212—C21—H213	109.5	H1212—C121—H1213	109.5
C16—O22—C23	116.7 (3)	C116—O122—C123	116.9 (3)
O22—C23—H231	109.5	O122—C123—H1231	109.5
O22—C23—H232	109.5	O122—C123—H1232	109.5
H231—C23—H232	109.5	H1231—C123—H1232	109.5
O22—C23—H233	109.5	O122—C123—H1233	109.5
H231—C23—H233	109.5	H1231—C123—H1233	109.5
H232—C23—H233	109.5	H1232—C123—H1233	109.5

Fig. 1

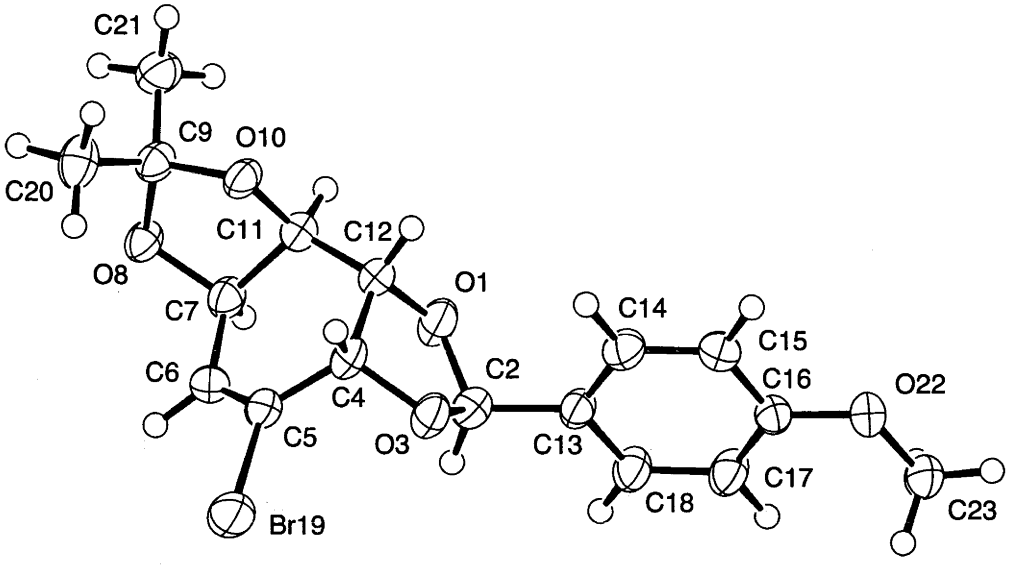
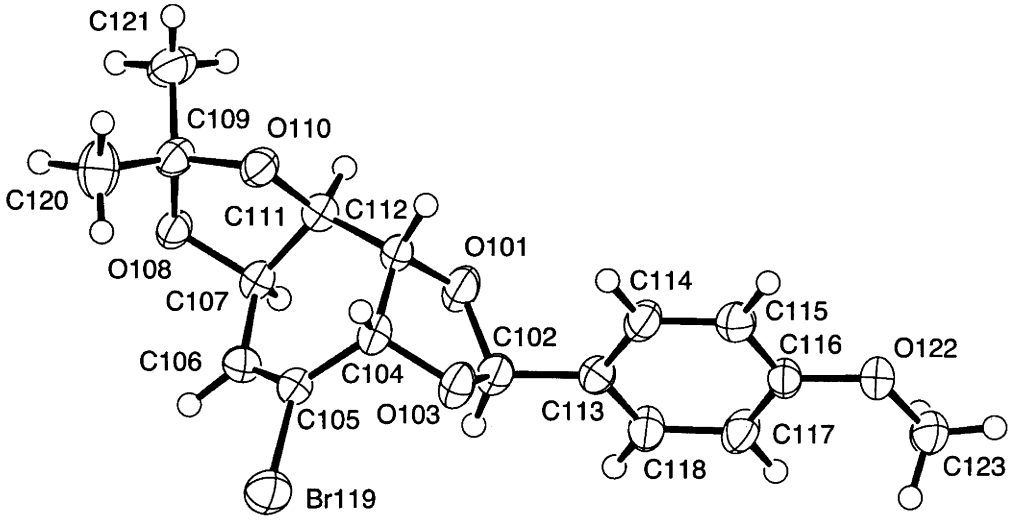

C21
C9
O10
C20
C11
C12
O8
O1
C7
C14
C15
C6
C2
C16
O22
C4
C5
O3
C13
C17
C18
C23
Br19

Fig. 2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C109
O110
C120
C111
C112
O101
O108
C107
C114
C115
C102
C116
O122
C106
C104
C105
O103
C113
C117
C118
C123
Br119

Fig. 3

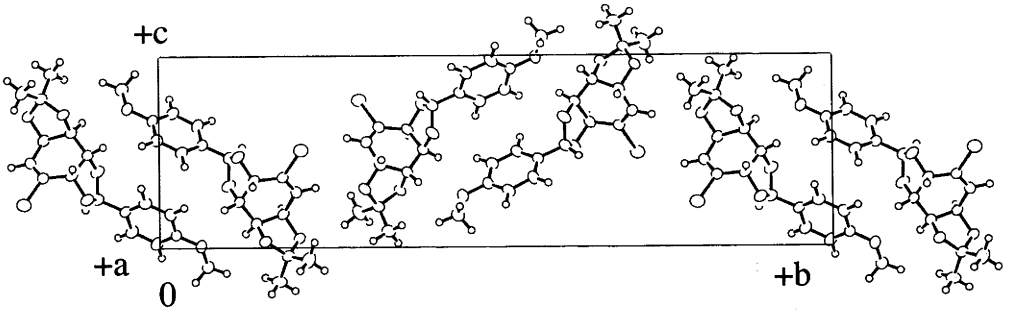
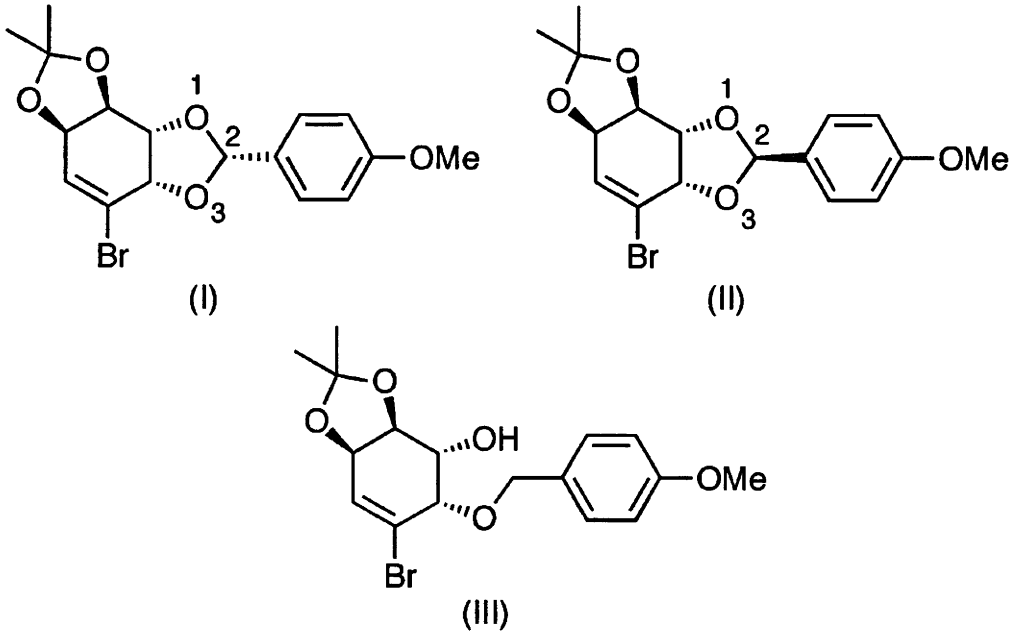


Fig. 4



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Structure Reports
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A cocrystal of (2*S*,3a*S*,4*R*,5*R*,7a*S*)- and (2*R*,3a*S*,4*R*,5*R*,7a*S*)-7-bromo-2-(4-methoxyphenyl)-3a,4,5,7a-tetrahydro-1,3-benzodioxole-4,5-diol (17:3)

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A cocrystal of (2*S*,3a*S*,4*R*,5*R*,7a*S*)- and (2*R*,3a*S*,4*R*,5*R*,7a*S*)-7-bromo-2-(4-methoxyphenyl)-3a,4,5,7a-tetrahydro-1,3-benzodioxole-4,5-diol (17:3)

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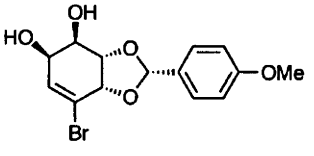
Key indicators: single-crystal X-ray study; T = 200 K; mean σ(C–C) = 0.005 Å; disorder in main residue; R factor = 0.030; *w*R factor = 0.076; data-to-parameter ratio = 14.4.

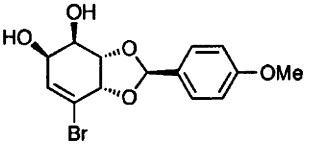
The title compounds, both $C_{14}H_{15}BrO_5$, cocrystallize and their structures, including absolute stereochemistries, have been solved simultaneously. The structures differ in the configuration (*R* versus *S*) at the acetal C atom bearing the 4-methoxyphenyl group.

Related literature

For related literature, see: Banwell et al. (2007a,b); Boyd et al. (1991); Hulme et al. (2005).



(major)



(minor)

Experimental

Crystal data

$C_{14}H_{15}BrO_5$
M_r = 343.17
Monoclinic, $P2_1$
a = 7.2245 (4) Å
b = 9.7093 (5) Å
c = 9.9373 (5) Å
β = 95.689 (3)°
V = 693.62 (6) Å^3
Z = 2
Mo $K\alpha$ radiation
μ = 2.98 mm^{-1}
T = 200 K
0.40 × 0.29 × 0.26 mm

Data collection

Nonius *KappaCCD area-detector diffractometer*
Absorption correction: integration via Gaussian method (Coppens, 1970) implemented in maXus (Mackay et al., 1999)
T_{min} = 0.372, T_{max} = 0.586
12613 measured reflections
3108 independent reflections
2802 reflections with $I > 2\sigma(I)$
R_{int} = 0.048

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.030
$wR(F^2)$ = 0.076
S = 0.99
3108 reflections
216 parameters
35 restraints
H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max}$ = 0.45 e Å^{-3}
$\Delta\rho_{min}$ = −0.90 e Å^{-3}
Absolute structure: Flack (1983), with 1430 Friedel pairs
Flack parameter: −0.019 (10)

Data collection: *COLLECT* (Nonius, 1997); *cell refinement*: *DENZO/SCALEPACK* (Otwinowski & Minor, 1997); *data reduction*: *DENZO/SCALEPACK*; *program(s) used to solve structure*: *SIR92* (Altomare *et al.*, 1994); *program(s) used to refine structure*: *CRYSTALS* (Betteridge *et al.*, 2003); *molecular graphics*: *ORTEPII* (Johnson, 1976) *in TEXSAN* (Molecular Structure Corporation, 1997); *software used to prepare material for publication*: *CRYSTALS*.

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Supplementary data and figures for this paper are available from the IUCr electronic archives (Reference: HG2294).

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supplementary materials

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A cocrystal of (2*S*,3a*S*,4*R*,5*R*,7a*S*)- and (2*R*,3a*S*,4*R*,5*R*,7a*S*)-7-bromo-2-(4-methoxyphenyl)-3a,4,5,7a-tetrahydro-1,3-benzodioxole-4,5-diol (17:3)

M. G. Banwell, O. J. Kokas and A. C. Willis

Comment

During the course of establishing a total synthesis of the non-natural enantiomeric form of the montanine alkaloid brunsvigine (Banwell *et al.*, 2007*a*) we had occasion to convert (1*S*,2*S*)-3-bromo-3,5-cyclohexadiene-1,2-diol (I) (Boyd *et al.*, 1991) into the corresponding 4-methoxybenzylidene acetal (II). This was achieved under standard conditions and provided compound (II) as a *ca* 5:3 mixture of epimers arising from a variation in stereochemistry at the newly installed acetal carbon. Subjection of this mixture to *cis*-dihydroxylation under the so-called UpJohn conditions resulted in each epimer reacting exclusively at the non-halogenated double bond and in a diastereofacially selective manner to give the corresponding mixture of *cis*-diols (III) and (IV) as a solid after recrystallization from ethyl acetate. In order to establish the relative stereochemistries within these two compounds a single-crystal X-ray analysis was undertaken. The present structures represent only the third and fourth reported for a 4-methoxyphenylacetal derivative of a *cis*-cyclohexane-1,2-diol (Banwell *et al.*, 2007*b*; Hulme *et al.*, 2005).

The crystallographic asymmetric unit consists of one molecule of $C_{14}H_{15}BrO_5$, but with some atoms disordered. The disordered atoms appear to indicate that two isomers have co-crystallized, with the atoms that are not disordered being common to both. The major epimer includes sites O18 and C10 to C19 (crystallographic labelling), and the minor epimer includes O118 and C110 to C119. The structures vary in configuration (*R versus S*) at the acetal carbon bearing the 4-methoxyphenyl group. The minor isomer atom sites have been refined with isotropic displacement parameters set equal to U_{eq} of the closest site of the major epimer. Restraints were applied to distances and angles of the minor sites so they would tend to match the corresponding values in the major epimer and so O118 and C110 to C117 would tend to be coplanar. The relative occupancies of the two isomers were refined.

The compounds are enantiomerically pure and their absolute configurations have been determined by refinement of the Flack parameter. The outcomes of these determinations are in agreement with those predicted on the basis of the absolute configuration of the precursor (I) (Boyd *et al.*, 1991).

The largest peaks in the final difference electron-density map are located near the Br atom and at the juncture between disordered and ordered parts of the structure(*s*).

Experimental

A magnetically stirred suspension of (1*S*,2*S*)-3-bromo-3,5-cyclohexadiene-1,2-diol (I) (20.0 g, 104.7 mmol) and 4-methoxybenzaldehyde dimethyl acetal (20.9 ml, 115.2 mmol) in anhydrous dichloromethane (200 ml) was cooled to 253 K then (1*S*)-(+)-camphor-10-sulfonic acid monohydrate (2.4 g, 10.4 mmol) was added. After 1 h the reaction mixture was quenched with sodium hydroxide (200 ml of a 1 *M* aqueous solution) and the separated aqueous phase extracted with dichloromethane (2 × 100 ml). The combined organic phases were washed with brine (1 × 100 ml) then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a white solid assumed to contain an epimeric mixture of the benzylidene acetals (II). A

magnetically stirred solution of this material in acetone/water (300 ml of a 2:1 *v/v* mixture) was cooled to 273 K then treated with *N*-methylmorpholine *N*-oxide (27.1 g, 232 mmol) and osmium tetraoxide (7.0 ml of a 2.5% *w/v* solution in *tert*-butanol, 0.53 mmol). The ensuing mixture was stirred at 291 K for 20 h then treated with sodium metabisulfite (200 ml of a 20% *w/v* aqueous solution). After 4 h the reaction mixture was concentrated under reduced pressure to give a brown residue that was treated with diethyl ether (500 ml) then water (500 ml). The separated aqueous phase was extracted with diethyl ether (4 × 150 ml) and the combined organic fractions were then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a brown solid. Subjection of this material to flash chromatography (silica, 1:19 *v/v* methanol/dichloromethane elution) and concentration of the appropriate fractions ($R_f = 0.3$) afforded a *ca.* 4:1 mixture of the title compounds (III) and (IV) (23.3 g, 65%) as a white, crystalline solid, m.p. = 406–407 K [Found: $(M - H?)^+$, 384.0570. C, 48.67; H, 4.40; Br 23.42. $C_{14}H_{15}{}^{79}BrO_5$ requires $(M - H?)^+$, 384.0572. C, 49.00; H, 4.41; Br 23.28%]. ^{1}H NMR [300 MHz, $(CD_3)_2CO$] δ (major epimer) 7.42 (2*H*, d, $J = 8.9$ Hz), 6.95 (2*H*, d, $J = 8.9$ Hz), 6.29 (1*H*, m), 5.80 (1*H*, s), 4.90 (1*H*, d, $J = 5.1$ Hz), 4.55 (1*H*, m), 4.40 (3*H*, m), 4.25 (1*H*, m), 3.81 (3*H*, s); δ (minor epimer) 7.37 (2*H*, d, $J = 8.7$ Hz), 6.93 (2*H*, d, $J = 8.7$ Hz), 6.17 (1*H*, dd, $J = 2.7$ and 1.2 Hz), 5.87 (1*H*, s), 4.69 (1*H*, dd, $J = 6.0$ and 1.2 Hz), 4.51 (1*H*, t, $J = 4.8$ Hz), 4.42 (3*H*, m), 4.31 (1*H*, m), 3.80 (3*H*, s); ^{13}C NMR [75 MHz, $(CD_3)_2CO$] δ (major epimer) 161.4, 135.6, 130.8, 129.0, 120.7, 114.3, 103.1, 77.9, 77.1, 69.6, 67.6, 55.5; δ (minor epimer) 161.5, 133.7, 130.3, 129.3, 122.2, 114.3, 104.7, 79.0, 77.9, 70.0, 68.0, 55.5; ν_{max} (NaCl)/cm^{-1} 3518, 3392, 2954, 2907, 2834, 1615, 1515, 1390, 1304, 1248, 1170, 1074, 1050, 1030, 924; MS (EI, 70 eV) 343 and 341 $[(M - H?)^+$, both 5%], 172 (10), 153 (13), 135 (100), 108 (39), 77 (22), 65 (18), 39 (18).

Refinement

The alcohol hydrogen atoms were included at locations revealed in a difference electron density map and were then refined positionally. Other hydrogen atoms were added at calculated positions (C—H distance 1.0 Å, $U_{iso}(H) = 1.2 \times U_{eq}(C)$) and, during refinement, each was set to ride on the carbon atom to which it is attached.

Figures

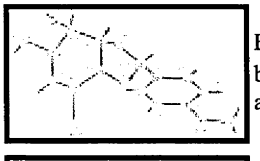


Fig. 1. Anisotropic displacement ellipsoid plot of the major isomer of $C_{14}H_{15}BrO_5$ with labelling of selected atoms. Ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

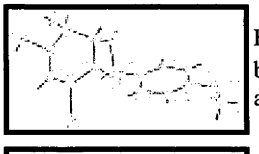


Fig. 2. Anisotropic displacement ellipsoid plot of the minor isomer of $C_{14}H_{15}BrO_5$ with labelling of selected atoms. Ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.

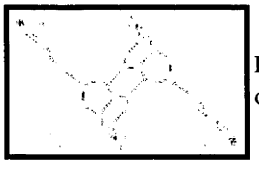


Fig. 3. Unit cell packing diagram of $C_{14}H_{15}BrO_5$ projected down the *b* axis. Hydrogen atoms of the alcohol groups are drawn as circles with small radii and the others have been deleted.

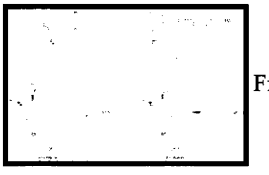


Fig. 4. The structure of (I)–(IV).

Cocrystal of (2*S*,3a*S*,4*R*,5*R*,7a*S*)- and (2*R*,3a*S*,4*R*,5*R*,7a*S*)-7-bromo- 2-(4-methoxyphenyl)-3a,4,5,7a-tetrahydro-1,3-benzodioxole-4,5-diol (17:3)

Crystal data

$C_{14}H_{15}BrO_5$	$F_{000} = 348$
$M_r = 343.17$	$D_x = 1.643$ Mg m^{-3}
Monoclinic, $P2_1$	Mo $K\alpha$ radiation $\lambda = 0.71073$ Å
Hall symbol: P 2yb	Cell parameters from 30770 reflections
$a = 7.2245$ (4) Å	$\theta = 2.6$–$27.5°$
$b = 9.7093$ (5) Å	$\mu = 2.98$ mm^{-1}
$c = 9.9373$ (5) Å	$T = 200$ K
$\beta = 95.689$ (3)°	Block, colourless
$V = 693.62$ (6) Å^3	0.40 × 0.29 × 0.26 mm
$Z = 2$	

Data collection

Nonius KappaCCD area-detector diffractometer	2802 reflections with $I > 2\sigma(I)$
Monochromator: graphite	$R_{int} = 0.048$
$T = 200$ K	$\theta_{max} = 27.5°$
φ and ω scans with CCD	$\theta_{min} = 3.5°$
Absorption correction: integration via Gaussian method (Coppens, 1970) implemented in maXus (Mackay *et al.*, 1999)	$h = -9 \rightarrow 9$
$T_{min} = 0.372$, $T_{max} = 0.586$	$k = -12 \rightarrow 11$
12613 measured reflections	$l = -12 \rightarrow 12$
3108 independent reflections	

Refinement

Refinement on F^2	Hydrogen site location: inferred from neighbouring sites
Least-squares matrix: full	H atoms treated by a mixture of independent and constrained refinement
$R[F^2 > 2\sigma(F^2)] = 0.030$	Method = Modified Sheldrick $w = 1/[\sigma^2(F^2) + (0.038P)^2 + 0.097P]$, where $P = [\max(F_o^2,0) + 2F_c^2]/3$
$wR(F^2) = 0.076$	$(\Delta/\sigma)_{max} = 0.043$
$S = 0.99$	$\Delta\rho_{max} = 0.45$ e Å^{-3}

3108 reflections	$\Delta\rho_{min} = -0.90$ e Å^{-3}
216 parameters	Extinction correction: none
35 restraints	Absolute structure: Flack (1983), with 1430 Friedel pairs
Primary atom site location: structure-invariant direct methods	Flack parameter: −0.019 (10)

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å^2)

	x	*y*	*z*	U_{iso}*/U_{eq}	Occ. (<1)
Br20	0.43964 (4)	0.3005 (3)	0.34759 (3)	0.0547	
O7	1.0479 (3)	0.0958 (4)	0.5926 (3)	0.0594	
O8	1.0545 (3)	0.3760 (4)	0.5778 (2)	0.0476	
O9	0.7101 (3)	0.3574 (4)	0.8155 (2)	0.0468	
O11	0.4712 (3)	0.4076 (4)	0.65992 (19)	0.0444	
O18	0.0214 (4)	0.1796 (4)	1.1172 (3)	0.0562	0.853 (4)
O118	0.0317 (17)	0.3946 (16)	1.1645 (12)	0.0555*	0.147 (4)
C1	0.8881 (4)	0.1684 (4)	0.6274 (3)	0.0414	
C2	0.9556 (3)	0.3090 (5)	0.6760 (2)	0.0382	
C3	0.7968 (4)	0.4054 (4)	0.7008 (3)	0.0406	
C4	0.6353 (4)	0.4100 (4)	0.5872 (3)	0.0367	
C5	0.6293 (3)	0.2884 (5)	0.4953 (2)	0.0374	
C6	0.7390 (4)	0.1786 (4)	0.5112 (3)	0.0397	
C10	0.5344 (5)	0.4276 (5)	0.7997 (3)	0.0398	0.853 (4)
C12	0.4022 (5)	0.3619 (5)	0.8875 (4)	0.0373	0.853 (4)
C13	0.3774 (6)	0.2201 (5)	0.8878 (4)	0.0411	0.853 (4)
C14	0.2495 (6)	0.1620 (5)	0.9669 (5)	0.0473	0.853 (4)
C15	0.1463 (6)	0.2471 (6)	1.0447 (4)	0.0408	0.853 (4)
C16	0.1678 (6)	0.3889 (6)	1.0432 (4)	0.0428	0.853 (4)
C17	0.2976 (6)	0.4437 (6)	0.9649 (4)	0.0411	0.853 (4)
C19	−0.1055 (9)	0.2620 (8)	1.1849 (5)	0.0683	0.853 (4)
C110	0.5244 (13)	0.3003 (17)	0.7692 (10)	0.0396*	0.147 (4)
C112	0.3909 (16)	0.3102 (19)	0.8776 (12)	0.0380*	0.147 (4)
C113	0.294 (2)	0.1981 (19)	0.9244 (16)	0.0469*	0.147 (4)
C114	0.170 (2)	0.219 (2)	1.0228 (16)	0.0414*	0.147 (4)
C115	0.1473 (18)	0.3534 (17)	1.0695 (13)	0.0433*	0.147 (4)
C116	0.246 (2)	0.4612 (17)	1.0201 (15)	0.0403*	0.147 (4)
C117	0.3638 (19)	0.4373 (19)	0.9260 (15)	0.0403*	0.147 (4)
C119	−0.089 (6)	0.292 (4)	1.213 (4)	0.0688*	0.147 (4)
H1	1.006 (7)	0.035 (5)	0.542 (4)	0.0710*	
H2	1.135 (6)	0.342 (4)	0.579 (4)	0.0570*	
H11	0.8363	0.1192	0.7038	0.0491*	
H21	1.0394	0.2984	0.7617	0.0455*	
H31	0.8463	0.5005	0.7188	0.0484*	
H41	0.6399	0.4972	0.5341	0.0439*	
H61	0.7221	0.1014	0.4445	0.0471*	
H101	0.5503	0.5278	0.8211	0.0473*	0.853
H131	0.4513	0.1600	0.8314	0.0489*	0.853
H141	0.2315	0.0599	0.9680	0.0562*	0.853

H161	0.0915	0.4498	1.0971	0.0512*	0.853
H171	0.3164	0.5458	0.9643	0.0492*	0.853
H191	−0.1880	0.2006	1.2334	0.0835*	0.853
H192	−0.0340	0.3240	1.2515	0.0835*	0.853
H193	−0.1832	0.3188	1.1169	0.0835*	0.853
H1101	0.5314	0.2051	0.7316	0.0475*	0.147
H1131	0.312	0.1036	0.8881	0.0563*	0.147
H1141	0.099	0.141	1.0585	0.0497*	0.147
H1161	0.229	0.5569	1.0541	0.0484*	0.147
H1171	0.4335	0.5165	0.8911	0.0484*	0.147
H1191	−0.165	0.335	1.281	0.0826*	0.147
H1192	−0.012	0.215	1.256	0.0826*	0.147
H1193	−0.173	0.255	1.135	0.0826*	0.147

Atomic displacement parameters (Å^2)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
Br20	0.04465 (15)	0.06961 (18)	0.04579 (15)	0.00756 (18)	−0.01518 (10)	−0.00620 (18)
O7	0.0408 (12)	0.0565 (13)	0.0777 (17)	0.0121 (10)	−0.0104 (11)	−0.0169 (12)
O8	0.0301 (10)	0.0530 (13)	0.0602 (14)	0.0004 (9)	0.0068 (10)	0.0097 (10)
O9	0.0317 (9)	0.0736 (13)	0.0343 (9)	0.0055 (8)	−0.0015 (8)	−0.0005 (8)
O11	0.0299 (9)	0.0683 (13)	0.0347 (10)	0.0063 (9)	0.0009 (7)	0.0002 (9)
O18	0.0533 (15)	0.0628 (17)	0.0538 (16)	−0.0029 (13)	0.0123 (13)	0.0109 (13)
C1	0.0332 (13)	0.0424 (14)	0.0471 (16)	0.0012 (11)	−0.0029 (12)	0.0044 (11)
C2	0.0278 (10)	0.0473 (13)	0.0386 (11)	−0.0018 (15)	−0.0018 (8)	0.0010 (16)
C3	0.0319 (13)	0.0486 (14)	0.0404 (14)	0.0008 (11)	−0.0013 (11)	−0.0020 (12)
C4	0.0302 (12)	0.0443 (13)	0.0354 (13)	0.0025 (10)	0.0014 (10)	0.0007 (11)
C5	0.0306 (10)	0.0466 (15)	0.0341 (10)	−0.0029 (13)	−0.0010 (8)	−0.0003 (14)
C6	0.0348 (13)	0.0428 (14)	0.0401 (14)	−0.0020 (11)	−0.0021 (11)	−0.0018 (11)
C10	0.0344 (16)	0.0482 (18)	0.0357 (16)	0.0023 (13)	−0.0025 (13)	−0.0012 (13)
C12	0.0325 (17)	0.045 (2)	0.0333 (17)	0.0037 (15)	−0.0030 (14)	0.0001 (16)
C13	0.036 (2)	0.044 (2)	0.042 (2)	0.0050 (16)	−0.0012 (17)	−0.0032 (16)
C14	0.043 (2)	0.049 (2)	0.048 (2)	0.0008 (17)	−0.0018 (17)	0.0051 (17)
C15	0.0352 (17)	0.053 (3)	0.0336 (18)	−0.0010 (15)	−0.0010 (14)	0.0048 (15)
C16	0.042 (2)	0.049 (2)	0.0373 (19)	−0.0002 (17)	0.0013 (15)	−0.0054 (15)
C17	0.039 (2)	0.045 (2)	0.038 (2)	0.0009 (14)	0.0008 (16)	−0.0036 (15)
C19	0.066 (3)	0.086 (4)	0.057 (3)	−0.011 (2)	0.027 (3)	−0.005 (2)

Geometric parameters (Å, °)

Br20—C5	1.910 (2)	C12—C13	1.388 (5)
O7—C1	1.424 (3)	C12—C17	1.382 (6)
O7—H1	0.82 (5)	C13—C14	1.391 (6)
O8—C2	1.422 (4)	C13—H131	1.000
O8—H2	0.67 (4)	C14—C15	1.397 (6)
O9—C3	1.432 (4)	C14—H141	1.000
O9—C10	1.436 (4)	C15—C16	1.385 (6)
O9—C110	1.482 (11)	C16—C17	1.384 (7)
O11—C4	1.449 (3)	C16—H161	1.000

O11—C10	1.432 (4)	C17—H171	1.000
O11—C110	1.527 (12)	C19—H191	1.000
O18—C15	1.376 (5)	C19—H192	1.000
O18—C19	1.433 (7)	C19—H193	1.000
O118—C115	1.380 (16)	C110—C112	1.518 (15)
O118—C119	1.434 (19)	C110—H1101	1.000
C1—C2	1.512 (5)	C112—C113	1.399 (17)
C1—C6	1.503 (4)	C112—C117	1.346 (17)
C1—H11	1.000	C113—C114	1.406 (17)
C2—C3	1.520 (4)	C113—H1131	1.000
C2—H21	1.000	C114—C115	1.397 (17)
C3—C4	1.542 (4)	C114—H1141	1.000
C3—H31	1.000	C115—C116	1.382 (16)
C4—C5	1.490 (4)	C116—C117	1.347 (16)
C4—H41	1.000	C116—H1161	1.000
C5—C6	1.328 (4)	C117—H1171	1.000
C6—H61	1.000	C119—H1191	1.000
C10—C12	1.498 (6)	C119—H1192	1.000
C10—H101	1.000	C119—H1193	1.000
C1—O7—H1	104 (4)	C14—C13—H131	120.1
C2—O8—H2	105 (3)	C13—C14—C15	119.6 (4)
C3—O9—C10	102.1 (2)	C13—C14—H141	120.2
C3—O9—C110	109.2 (4)	C15—C14—H141	120.2
C4—O11—C10	106.5 (2)	C14—C15—O18	115.0 (4)
C4—O11—C110	101.9 (5)	C14—C15—C16	121.0 (5)
C15—O18—C19	117.6 (3)	O18—C15—C16	124.0 (4)
C115—O118—C119	117.1 (16)	C15—C16—C17	118.1 (5)
O7—C1—C2	106.3 (2)	C15—C16—H161	120.9
O7—C1—C6	112.5 (2)	C17—C16—H161	120.9
C2—C1—C6	111.7 (2)	C16—C17—C12	122.0 (4)
O7—C1—H11	108.8	C16—C17—H171	119.0
C2—C1—H11	108.8	C12—C17—H171	119.0
C6—C1—H11	108.8	O18—C19—H191	109.5
C1—C2—O8	111.3 (2)	O18—C19—H192	109.5
C1—C2—C3	112.5 (2)	H191—C19—H192	109.5
O8—C2—C3	105.5 (3)	O18—C19—H193	109.5
C1—C2—H21	109.1	H191—C19—H193	109.5
O8—C2—H21	109.1	H192—C19—H193	109.5
C3—C2—H21	109.1	O11—C110—O9	97.0 (8)
C2—C3—O9	109.0 (2)	O11—C110—C112	109.2 (8)
C2—C3—C4	115.3 (2)	O9—C110—C112	112.0 (8)
O9—C3—C4	103.5 (2)	O11—C110—H1101	112.5
C2—C3—H31	109.6	O9—C110—H1101	112.6
O9—C3—H31	109.6	C112—C110—H1101	112.5
C4—C3—H31	109.6	C110—C112—C113	124.2 (12)
C3—C4—O11	103.4 (2)	C110—C112—C117	115.9 (12)
C3—C4—C5	113.5 (2)	C113—C112—C117	119.9 (11)
O11—C4—C5	108.5 (2)	C112—C113—C114	119.5 (12)
C3—C4—H41	110.4	C112—C113—H1131	120.2

O11—C4—H41	110.4	C114—C113—H1131	120.3
C5—C4—H41	110.4	C113—C114—C115	118.1 (13)
Br20—C5—C4	113.4 (2)	C113—C114—H1141	121.0
Br20—C5—C6	121.0 (2)	C115—C114—H1141	121.0
C4—C5—C6	125.6 (2)	C114—C115—O118	126.5 (12)
C1—C6—C5	121.2 (2)	C114—C115—C116	120.5 (11)
C1—C6—H61	119.4	O118—C115—C116	113.0 (11)
C5—C6—H61	119.4	C115—C116—C117	120.0 (12)
O9—C10—O11	103.6 (2)	C115—C116—H1161	120.0
O9—C10—C12	109.9 (3)	C117—C116—H1161	120.0
O11—C10—C12	110.3 (3)	C116—C117—C112	122.0 (12)
O9—C10—H101	110.9	C116—C117—H1171	119.0
O11—C10—H101	110.9	C112—C117—H1171	119.0
C12—C10—H101	110.9	O118—C119—H1191	109.4
C10—C12—C13	120.9 (4)	O118—C119—H1192	109.5
C10—C12—C17	119.6 (4)	O118—C119—H1193	109.5
C13—C12—C17	119.4 (5)	H1191—C119—H1192	109.5
C12—C13—C14	119.8 (5)	H1191—C119—H1193	109.5
C12—C13—H131	120.1	H1192—C119—H1193	109.5
C10—O9—C3—C2	−162.1 (3)	C2—C3—C4—C5	19.4 (4)
C10—O9—C3—C4	−38.9 (4)	O9—C3—C4—O11	17.8 (4)
C3—O9—C10—O11	46.4 (4)	O11—C4—C5—Br20	69.7 (3)
C3—O9—C10—C12	164.3 (3)	O11—C4—C5—C6	−109.0 (3)
C10—O11—C4—C3	10.3 (4)	C3—C4—C5—C6	5.3 (4)
C10—O11—C4—C5	131.2 (3)	C3—C4—C5—Br20	−175.9 (2)
C4—O11—C10—O9	−35.0 (4)	Br20—C5—C6—C1	−179.8 (2)
C4—O11—C10—C12	−152.7 (4)	C4—C5—C6—C1	−1.2 (5)
C19—O18—C15—C14	−172.0 (4)	O9—C10—C12—C13	−48.6 (5)
C19—O18—C15—C16	6.0 (6)	O9—C10—C12—C17	134.2 (4)
O7—C1—C2—C3	173.0 (2)	O11—C10—C12—C13	65.1 (5)
C6—C1—C2—O8	−68.3 (3)	O11—C10—C12—C17	−112.1 (4)
O7—C1—C2—O8	54.8 (3)	C10—C12—C13—C14	−177.9 (4)
C2—C1—C6—C5	−27.0 (4)	C17—C12—C13—C14	−0.7 (6)
C6—C1—C2—C3	49.9 (3)	C13—C12—C17—C16	−0.1 (6)
O7—C1—C6—C5	−146.4 (3)	C10—C12—C17—C16	177.2 (4)
C1—C2—C3—C4	−47.1 (4)	C12—C13—C14—C15	0.4 (6)
O8—C2—C3—O9	−169.8 (2)	C13—C14—C15—O18	178.9 (4)
O8—C2—C3—C4	74.3 (3)	C13—C14—C15—C16	0.7 (7)
C1—C2—C3—O9	68.7 (3)	C14—C15—C16—C17	−1.5 (6)
O9—C3—C4—C5	−99.6 (3)	O18—C15—C16—C17	−179.4 (4)
C2—C3—C4—O11	136.7 (3)	C15—C16—C17—C12	1.2 (6)

Hydrogen-bond geometry (Å, °)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
O7—H1···O8^{i}	0.81 (4)	1.97 (5)	2.779 (5)	171 (5)
O8—H2···O7	0.67 (4)	2.48 (4)	2.725 (5)	105 (4)
O8—H2···O11^{ii}	0.67 (4)	2.56 (4)	3.055 (3)	133 (4)

Symmetry codes: (i) $-x+2, y-1/2, -z+1$; (ii) $x+1, y, z$.

Fig. 1

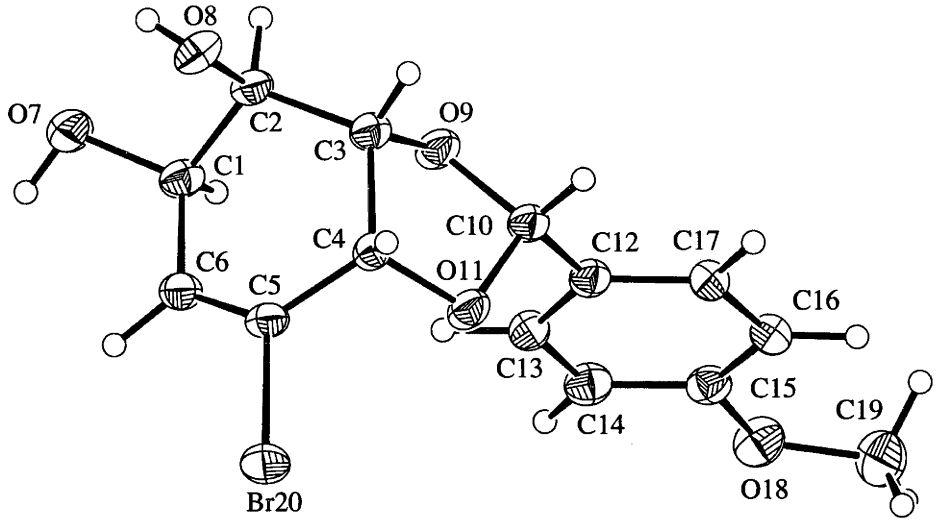


Fig. 2

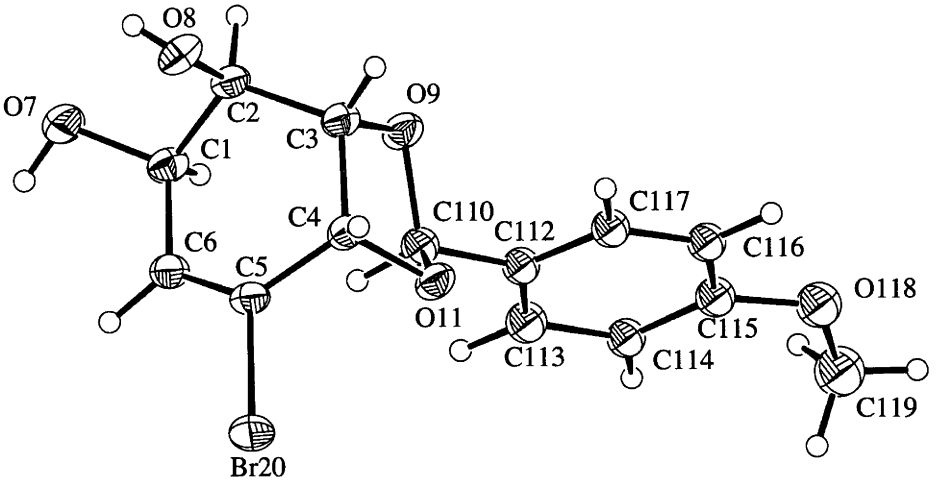

O8
O7
C2
C3
O9
C1
C4
C110
C112
C117
C116
C6
C5
O11
C115
O118
C113
C114
C119
Br20

Fig. 3

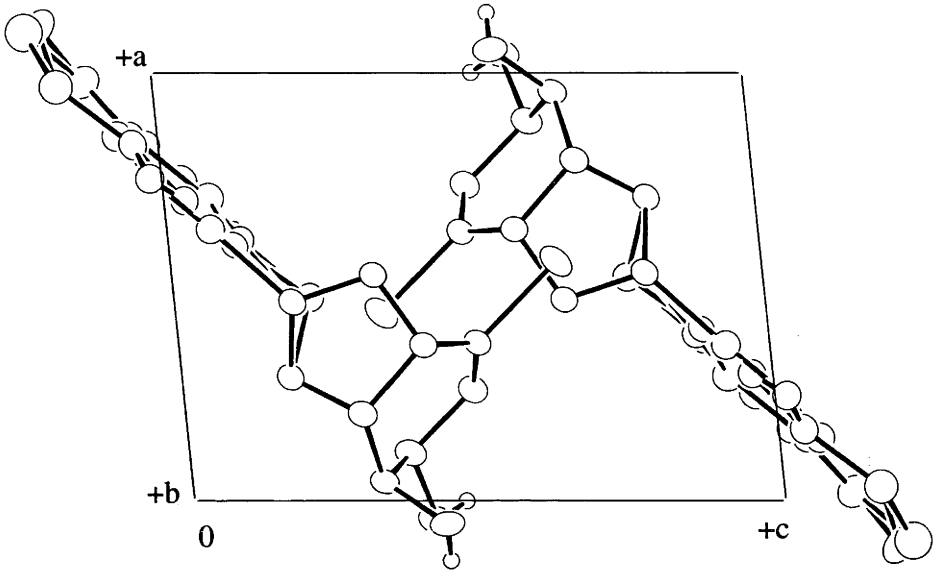
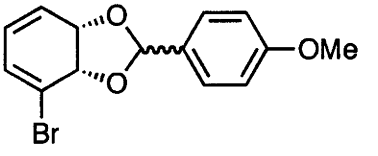
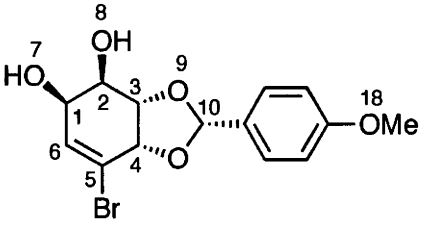


Fig. 4

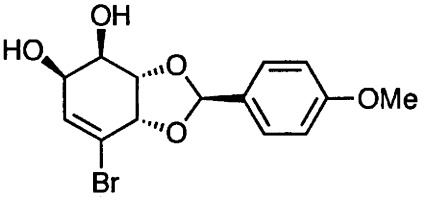
(I)



(II)



(III)
(major)



(IV)
(minor)