Chemoenzymatic Syntheses of Allocedrane and Prezizaane-type Sesquiterpenes

A Thesis submitted for the degree of
Doctor of Philosophy at the Australian National University

By

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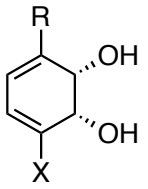
Abstract

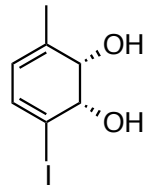
Various genetically modified microorganisms that over-express dioxygenase-type enzymes can be used for the whole-cell biotransformation of a wide range of arenes into the corresponding *cis*-1,2-dihydrocatechols (*c*-DHC, **1**). These metabolites, which are obtained in essentially enantiopure form, can serve as valuable starting materials in chemical synthesis. This thesis describes the application of certain *c*-DHCs in the synthesis of biologically active and/or synthetically challenging natural products. In particular, it details the use of type 1 intramolecular Diels-Alder (IMDA) adducts derived from *c*-DHCs in the synthesis of the tashironins and related compounds belonging to the allocedrane class of natural product. The tashironin group of compounds possess complex structures (they contain, for example, vicinal quaternary C-C centres) and display interesting biological properties including neurotropic activity. As such they are considered to be useful leads in developing new therapies for treating neurodegenerative afflictions such as Alzheimer's and Parkinson's diseases.



1

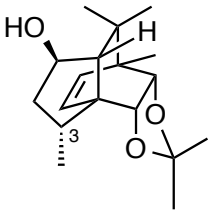
a (X = Cl, R = H)
b (X = Br, R = H)
c (X = I, R = H)
d (X = I, R = Me)
e (X = I, R = Br)
f (X = H, R = H)
g (X = Me, R = H)
h (X = CN, R = H)

As described in Chapter 2, and as a prelude to the synthesis of certain tashironins, the assembly of the tricyclic core, **43**, of the structurally related compound (–)-khusiol [(–)-**19**] using type 1 IMDA reactions of *c*-DHCs was accomplished in just 4 steps. A method for the installation of the key C3 methyl group with either the *R* or *S* configuration together with one for the selective deoxygenation of the *vic*-diol moiety were established. The total synthesis of target **19** was thereby completed in 16 steps from *c*-DHC (**1d**) and its structure was unambiguously determined through the single-crystal X-ray analysis of its 3,5-dinitrobenzoyl-derivative **71**. This chemistry was then deployed, as outlined in Chapter 3, in the synthesis of compounds closely related to (–)-11-*O*-debezoyltashironin [(–)-**17**]. So, by using a type 1 IMDA reaction and Barton-type radical cyclisation chemistry, the tetracyclic core structure, **125**, of tashironin **17** was assembled in just 13 steps from *c*-DHC (**1d**). In the process of the campaign towards tashironins, several highly oxygenated tri- and tetra-cyclic compounds were prepared. These are expected to possess similar biological properties to the natural product.



1d

(*ca.* 85% ee)



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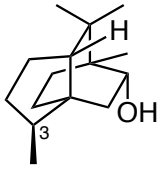
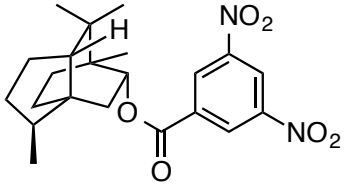
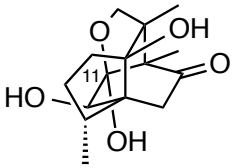


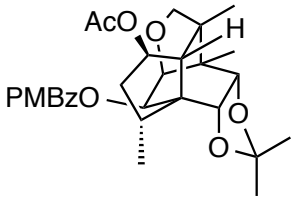
(–)-**19**



71

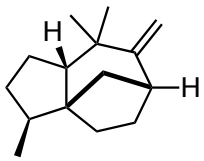


(–)-**17**

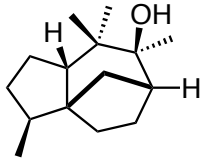


125

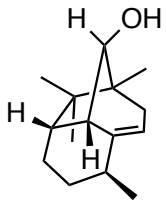
In the course of the synthesis of khusiol an opportunity arose for the examination of Wagner-Meerwein type rearrangements within the allocedrane framework. As a result, the synthesis of natural products (+)-prezizaene [(+)-**151**] and (+)-allokhusiol [(+)-**153**], which are highly prized compounds in the flavour and fragrance industry, were achieved. The high yielding route involved the formation of a 1,2-cyclopentaanulated bicyclo[3.2.1]octane ring-system from its 1,2-cyclopentaanulated bicyclo[2.2.2]octane isomer. Furthermore, a novel Wagner-Meerwein rearrangement of (–)-khusiol system was discovered that afforded the pleasantly smelling compound **185**. This embodies the enantiomeric form of the tricyclic framework associated with the natural product *β*-isopipitzol (**186**).



(+)-**151**



(+)-**153**



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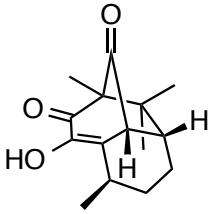

186

Table of Contents

Acknowledgements

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For the financial support, I was privileged to be the recipient of the Endeavour Postgraduate Award provided by the Australian Government and so I would like to thank them. I would also like to thank The Australian National University and The Research School of Chemistry for their financial support.

Most importantly, my heartfelt gratitude goes to my parents, (Sant Kumar - whom I sadly lost during my PhD candidature and Nira Devi), my wife (Priti Maharaj) and daughter (Mahi Sharma) for all the love, support, and encouragements.

Last, but not least, I would like to thank all my friends and extended families for their patience, understanding and overwhelming support.

Declaration

I declare that, to the best of my knowledge, the material presented in this thesis represents the result of original work carried out by the author during the period 2009-2012 and that it has not been presented for examination for any other degree. This thesis is less than 100,000 words in length. Established methodologies have been acknowledged, wherever possible, through citation of the original publications from which they derive.

Mukesh K. Sharma
January 2015

Publications and Presentations

The following list details the publications and presentations that have resulted from research performed during the author's candidature for the degree of Doctor of Philosophy.

Publications

1. Sharma, M. K., Banwell, M. G. and Willis, A. C. – Chemoenzymatic Routes to Enantiomerically Enriched and Polyoxygenated Perhydro-3,5a-methanoindeno[4,5-*c*]furans Related to the Tashironin Class of Sesquiterpenes. *J. Org. Chem*. **2015**, *80*, 2930–2936.

2. Sharma, M. K., Banwell, M. G. and Willis, A. C. – Generation of (+)-Prezizanol, (+)-Prezizaene and the *ent*-*β*-Isopipitzol Framework *via* Cationic Rearrangement of Khusiol and Related Compounds. *Asian J. Org. Chem*. **2014**, *3*, 632–663.

2. Sharma, M. K., Banwell, M. G., Willis, A. C. and Rae, A. D. – Approaches to the Neurotrophically Active Natural Product 11-*O*-Debenzoyltashironin: A Chemoenzymatic Total Synthesis of the Structurally Related Sesquiterpene Khusiol. *Chem. Asian J*. **2012**, *7*, 676–679.

3. Sharma, M. K. and Banwell, M. G. – 5-Formyl-2-furanylboronic Acid. Encyclopedia of Reagents for Organic Synthesis [Online (*eEROS*)], eds. D. Crich, A. B. Charette, P. L. Fuchs and T. Rovis, John Wiley & Sons Ltd. **2011**, http://dx.doi.org/10.1002/047084289X.rn01372.

Presentations

1. Sharma, M. K., Banwell, M. G. A Chemoenzymatic Total Synthesis of (−)-*allo*-Cedrol. Poster Presentation at the New South Wales Royal Australian Chemical Institute Organic One Day Symposium, University of Wollongong, December 2010.

2. Sharma, M. K., Banwell, M. G. Progress Towards the Synthesis of 11-*O*-Debenzoyltashironin. Poster presentation at the 19th International Conference in Organic Synthesis held in conjunction with the 24th Royal Australian Chemical Institute Organic conference, Melbourne Australia, July 2012.

3. Sharma, M. K., Banwell, M. G. Progress Towards the Synthesis of 11-*O*-Debenzoyltashironin. The Southern Highlands Conference on Heterocyclic Chemistry, Bowral Australia, August 2012.

Glossary

δ	chemical shift (ppm)
°C	degrees Celcius
μg	microgram(s)
μL	microliter(s)
Ac	acetyl
AcOH	acetic acid
AIBN	2,2'-azobis(iso-butyronitrile)
aq.	aqueous
atm	atmosphere(s)
BDMA	benzyldehyde dimethylacetyl
BHT	2,6-di-*t*-butyl-4-methylphenol
Bn	benzyl
br	broad
n-Bu	*normal*-butyl
t-Bu	*tertiary*-butyl
ca.	circa (approximately)
cat.	catalytic/catalyst
cf.	confer (compare)
cm	centimeter(s)
conc.	concentrated
d	doublet
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone

c-DHC	*cis*-dihydrocatechol
DMAP	4-(*N,N*-dimethylamino)pyridine
DMDO	dimethyldioxirane
DMF	*N,N*-dimethylformamide
2,2-DMP	2,2-dimethoxypropane
DMS	dimethyl sulfide
DVK	divinylketone
ee	enantiomeric excess
e.g.	*exempli gratia* (for example)
EIMS	electron impact mass spectrometry
ESIMS	electrospray ionization mass spectrometry
Et	ethyl
et al.	*et alia* (and others)
Et_3N	triethylamine
Et_2O	diethyl ether
EtOAc	ethyl acetate
EtOH	ethanol
eV	electron volt
g	gram(s)
GC	gas chromatography
gem	geminal
h	hour(s)
H_2O	water
HMPA	hexamethylphosphoramide
HRMS	high resolution mass spectrometry
hν	light

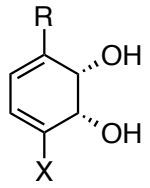
Hz	Hertz
IMDA	intramolecular Diels-Alder
IBX	2-iodoxybenzoic acid
IR	infrared
J	^{1}H-^{1}H coupling constant
L	liter(s)
lit.	literature
LRMS	low resolution mass spectrometry
m	multiplet
M	molar
$M^{+\bullet}$	molecular ion
Me	methyl
MeOH	methanol
MHz	mega-Hertz
min	minute(s)
mL	milliliter(s)
mm	millimeter(s)
mmol	millimole(s)
mp	melting point
MS	mass spectrometry
m/z	mass-to-charge ratio
NMO	*N*-methylmorpholine-*N*-oxide
NMR	nuclear magnetic resonance
ORTEP	Oak Ridge thermal ellipsoid plot
P	protecting group
p	para

Ph	phenyl
PMB	*p*-methoxybenzyl
PMP	*p*-methoxyphenyl
ppm	parts per million
i-PrMgCl	*iso*-propylmagnesium chloride
Py	pyridine
q	quartet
Ref.	reference
R_f	retardation factor
rt	room temperature
s	singlet
t	triplet
t	tertiary
TBAF	tetra-*n*-butylammonium fluoride
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy free radical
THF	tetrahydrofuran
TLC	thin layer chromatography
p-TsOH	*para*-toluenesulfonic acid
UV	ultraviolet
viz.	videlicit (that is, namely)

Chapter 1: The Enzymatic Dihydroxylation of Aromatic Compounds and the Use of the Resulting Products in Chemical Synthesis

1.1 Introduction

There is an ongoing and even an increasing need for new chirons in the flavours and fragrance, agrochemical and pharmaceutical industries.[1] Sources such as sugars, amino acids and terpenes have played extraordinarily important roles in this regard.[1] Nevertheless, recent advances in biocatalysis are now providing the synthetic chemist with a broader range of new, structurally fascinating and enantiomerically pure starting materials. One such group of compounds is the *cis*-1,2-dihydrocatechols. These are obtained through the biocatalytic dihydroxylation of aromatics and hereafter, referred to as *c*-DHCs. Some readily available and essentially enantiomerically pure members of this group are shown in Figure 1.01.



1

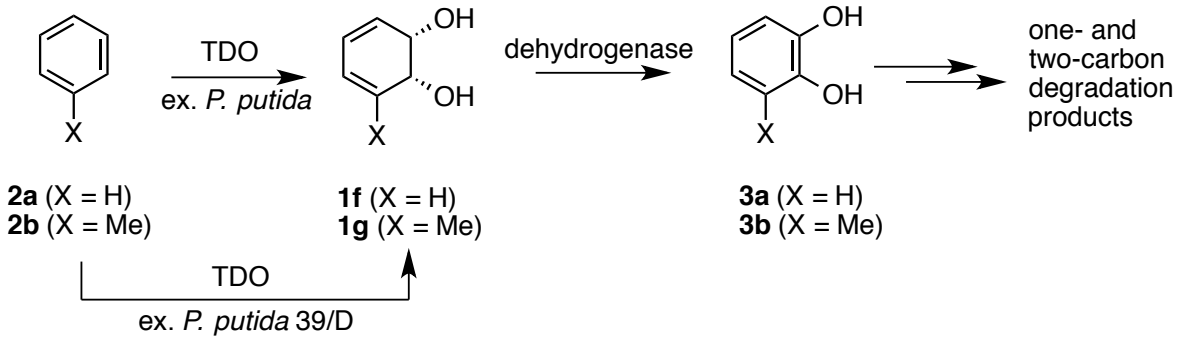
a (X = Cl, R = H)
b (X = Br, R = H)
c (X = I, R = H)
d (X = I, R = Me)
e (X = I, R = Br)
f (X = H, R = H)
g (X = Me, R = H)
h (X = CN, R = H)

Figure 1.01. Commonly available and biocatalytically-derived *cis*-1,2-dihydrocatechols

The generation, common reactions and selected applications of such chirons in the synthesis of complex natural products are presented in the next three sections. This is followed by an overview of the contents of the remaining chapters of the thesis.

1.2 Generation of *cis*-1,2-Dihydrocatechols

In the 1960's Gibson and his co-workers elucidated the pathway (Scheme 1.01) by which certain mono-nuclear aromatic compounds are degraded by the soil bacterium *Pseudomonas putid*.[2] So, for example, the degradation of benzene (**2a**) and toluene (**2b**) was shown to involve a toluene dioxygenase (TDO)-mediated dihydroxylation to give the corresponding *c*-DHCs of the types **1f** and **1g**, respectively. Compounds **1f** and **1g** are then rearomatised by a dehydrogenase enzyme to form catechols **3a** and **3b**, respectively. This last pair of compounds is then degraded to give one- and two-carbon degradation products.



Scheme 1.01. Metabolic degradation of benzene (**2a**) and toluene (**2b**) by certain soil bacteria

Gibson later generated mutant strains (e.g. *P. putida* 39D) of these organisms in which, not only is the rearomatisation process blocked, the enzyme TDO is over-expressed. As a result, the *c*-DHC metabolites accumulate and are obtained in high enantiopurity (>98%).[3] Since this discovery various other mutants have been identified and/or genetically engineered to provide access to *c*-DHCs in good yield and essentially enantiopure form. For example, TDO can be overexpressed in *E. coli* JM109 (pDTG601) and with the result that substrates such as bromobenzene (**4**) can be metabolized at large scales (20 g/L fermentation broth) and the product diol **1b** obtained in > 99.8% ee (Scheme 1.02).[4]

4 (X = Br)

> 98% ee

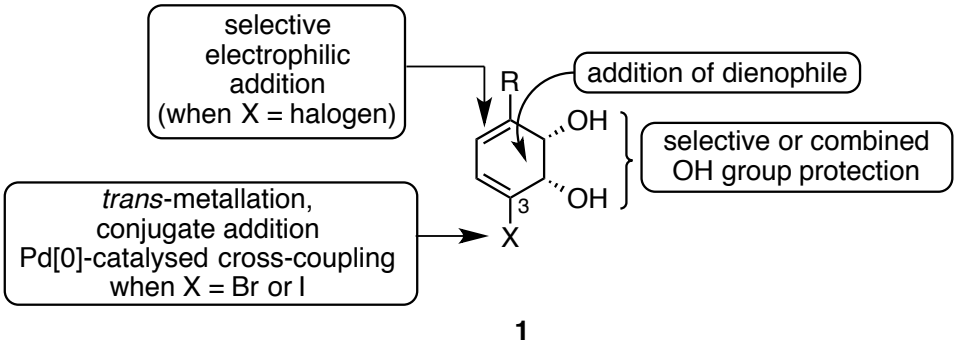
1b (X = Br)

Scheme 1.02. Metabolism of bromobenzene using a genetically engineered strain of *E. coli* that over-expresses TDO

The biocatalytic oxidation of aromatic compounds, including *di*-, and *tri*-nuclear species, using engineered and/or mutant strains of various bacterial strains has delivered literally hundreds of *c*-DHC-type metabolites and a number of these are now commercially available.[5]

1.3 Reactions of *cis*-1,2-Dihydrocatechols

Various methodologies, often involving rather conventional chemistry, have been established for the selective manipulations of *c*-DHCs. Some of the basic processes are summarized in Figure 1.02.



1

Figure 1.02. Possibilities for the selective manipulation of certain *cis*-1,2-dihydrocatechols (**1**)

Specifically, then, the following reactions have been applied to the *c*-DHCs: (a) stereoselective, intermolecular Diels-Alder (DA) and type 1[Δ] intramolecular Diels-Alder (IMDA)[φ] reactions; (b) selective or combined protection of the hydroxyl group(s) that exploit the differing steric environments of these resides; (c) metallation at C3 (when X = halogen) and subsequent C-C bond forming reactions through conjugate addition of the resulting anion (or metalloid species) to Michael acceptors such as vinyl ketones; (d) Pd[0]-mediated-cross couplings at C3 (when X = halogen); (e) regio- and stereo-selective electrophilic additions (due to the differing electronic characteristics of the two double-bonds) to the diene moiety such as epoxidation, ozonolysis, osmylation and cyclopropanation; (f) DA dimerization reactions in which one molecule acts as the diene and the other as dieneophile; (g) [4+2] singlet oxygen addition reactions; and (h) [2+2] cycloaddition reactions.

The aforementioned reactions, that proved pivotal in the synthesis of various natural products, have been reviewed by Hudlicky,[6] Banwell[7] and Carless.[8] Accordingly, no detailed discussion of their utility is required here. However, since type I IMDA reactions have been central to the work described in this thesis the following section highlights certain applications of this type process wherein the 4π-addend has been derived from a *c*-DHC.

1.4 Type 1 IMDA Reactions of *c*-DHCs

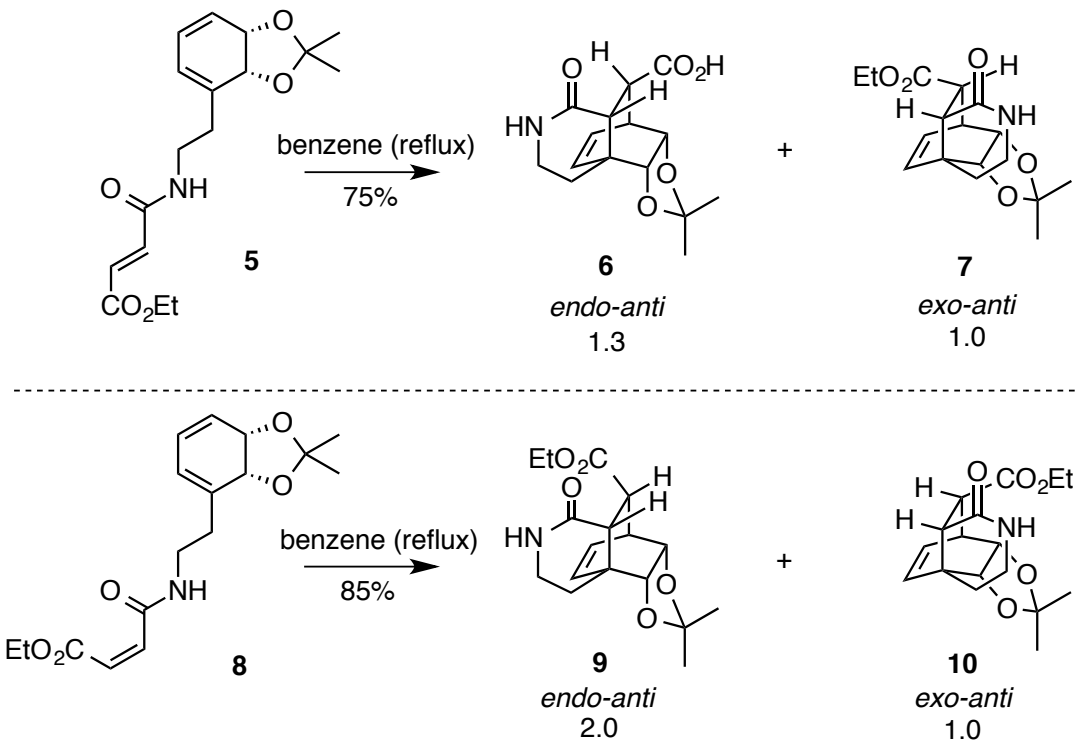
There are many examples of the application of the intermolecular DA reaction to *c*-DHC as parts of synthetic sequences leading to natural products. However, there are fewer involving its intramolecular counterpart. One reason for this is that the former reactions can be performed directly on *c*-DHCs, while the IMDA counterparts require tethering of a dieneophile to the *c*-DHC. This tethering can be particularly challenging because of the fragile nature of the *c*-DHCs, particularly arising from their propensity to aromatise.

[Δ]In a type 1 IMDA reaction the substrate has a dienophile attached to the C3 position of, for example, **1** (Figure 1.02).

[φ]IMDA reactions of *c*-DHCs in which the dienophile is attached to either one or both of the hydroxyl groups have been reported.

It should also be noted that the intermolecular DA reaction of *c*-DHCs proceeds with excellent diastereoselectivity yielding the *endo*-adducts in an almost exclusive fashion.[a] Another feature of such reaction that needs to be considered is the diastereofacial selectivity (*syn/anti*) because of the two stereogenic centres (at C1 and C3) present in *c*-DHCs. This selectivity can be effectively controlled by employing either the *c*-DHCs themselves or certain protected forms, notably the corresponding acetonides.[9] It is worth mentioning that the nature of both the solvent and the dienophile can influence the diastereofacial selectivity of the cycloaddition reaction.[10] Furthermore, a third type of selectivity (regio-selectivity *ortho/meta*) comes into play when an unsymmetrical diene or dienophile is used. In the intermolecular DA reaction of *c*-DHCs, the "*ortho"*-product, (as opposed to its "*meta"*-isomer) is favored in most cases. In contrast, the various selectivity profiles of the type 1 IMDA reactions of *c*-DHCs remains largely unexplored with just a few but nevertheless interesting examples being reported so far. Hudlicky and co-workers were the first to report[11] type 1 IMDA reaction of *c*-DHCs. Specifically, when *c*-DHC derivatives **5** and **8** (Scheme 1.03) were heated in refluxing benzene they engaged in type 1 IMDA cycloaddition reactions to yield mixture of the corresponding pairs of *exo*- and *endo*-cycloadducts **6** and **7**, and **9** and **10**, respectively.

[a]In this case the term *endo* refers to the transition state through which the DA reaction proceeds.

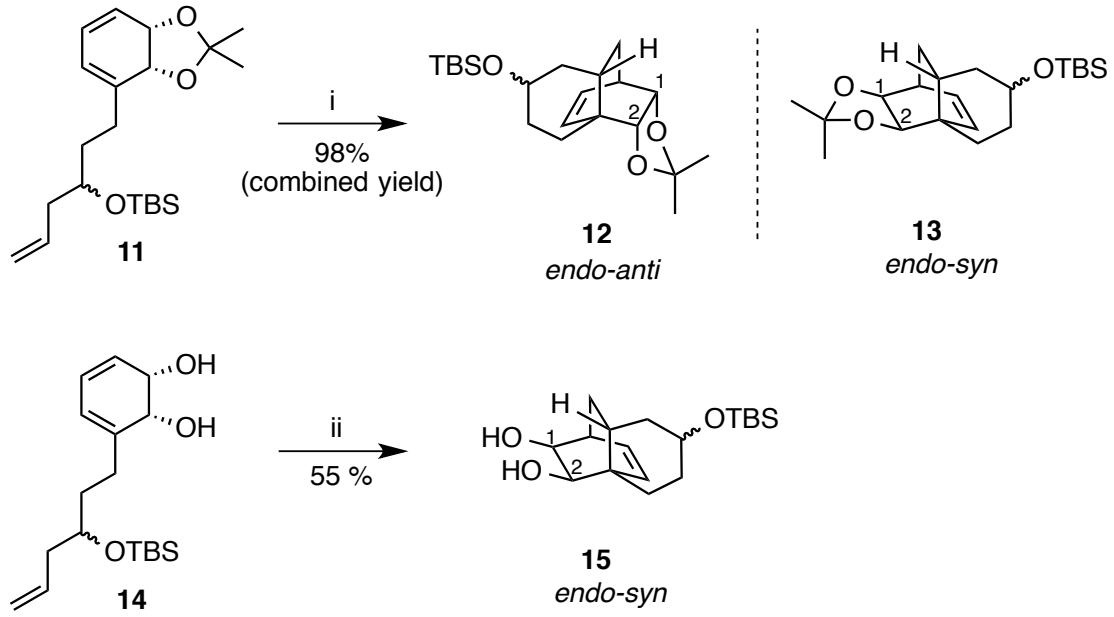


Scheme 1.03. Original examples of IMDA reactions of *c*-DHC derivatives

Following extensive NMR analysis, it was found that, in both instances, these IMDA reactions had proceeded with excellent facial selectivity and wherein there had been exclusive addition of the dieneophile to that face of the diene opposite to the acetonide moiety. However, as is common for the *intra*-molecular variant of the Diels-Alder reaction, only moderate diastereo-selectivity was observed with mixtures of both the illustrated *endo*- and *exo*-adducts being formed.[ξ]

Recently, Austin and Banwell reported[12] a type 1 IMDA reaction of a *c*-DHC derivative that proceeded with excellent levels of diastereocontrol. Specifically, upon heating triene **11** in toluene this engaged in an IMDA reaction to give *ca*. 10:1 mixture of *anti*- and *syn*-addition products, **12** and **13** respectively, in 98% combined yield. None of the corresponding *exo*-adduct was observed.

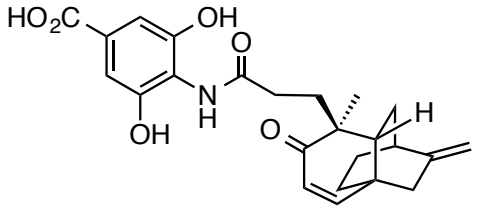
[ξ]*Endo* and *exo* assignments of these cycloadducts are based on the configuration of the amide carbonyl group in the transition state leading to the products.



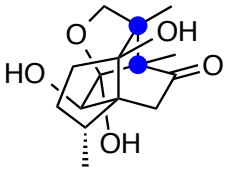
Scheme 1.04. *Reagents and Conditions*: i. tolune (reflux), BHT, 16 h; ii. xylene (reflux), BHT, 16 h

In contrast, heating the free (unprotected) diol **14** in refluxing xylene yielded the *endo-syn* adduct **15** (55%) as the only isolable product of reaction. None of the corresponding *endo-anti* product was observed in this case.[9] Interestingly, if each of compounds **12** and **13** (or **15**) was subjected to deoxygenation at C1 and C2, then enantiomerically related 1,2-cyclohexannulated bicyclo[2.2.2]octane frameworks would be obtained. Or, to put matters another way, controlling the facial selectivity of the Diels-Alder reaction (whether this involves an inter- or intra-molecular variant) dictates which enantiomeric form of the adduct is obtained.

Compounds such as **12** embody the tricyclic framework of a number of synthetically challenging and biologically interesting natural products.[13] For example, platencin (**16**), a potent antibiotic isolated[14] from certain strains of the bacterium *Streptomyces platensis*, possesses a 1,2-cyclo-hexaannulated bicyclo[2.2.2]octane core while 11-*O*-debenzoyltashironin (**17**), a potent neurotropic factor isolated[15] from the *Illicium* species of plant, possess a 1,2-cyclopentannulated bicyclo[2.2.2]octane framework.



platencin (**16**)



11-*O*-debenzoyltashironin (**17**)

Figure 1.04. Complex natural products containing 1,2-cyclopent- or cyclohex-annulated bicyclo[2.2.2]octanes substructures

Using the chemistry described above, a formal total synthesis of the natural product **16** has been achieved[16] by Austin and Banwell. Given the capacity to control the facial selectivities of the IMDA reactions by the means described immediately above, this type of chemistry could probably also be used to synthesise the non-natural enantiomeric form of platencin (**16**).

The aim of the work detailed in the remaining parts of this thesis was to deploy this same type of IMDA chemistry in the synthesis to 11-*O*-debenzoyltashironin (**17**). As mentioned above, compound **17** possess potent neurotropic activity and may thus be useful in treating neurodegenerative ailments such as Alzheimer's and Parkinson's diseases. Compound **17** is clearly a synthetically challenging target as it embodies seven stereogenic centres, two of which involve contiguous quaternary carbon ones (highlighted). Since detailed biological studies of 11-*O*-debenzoyltashironin have been hampered by lack of access to material, total synthesis studies focused on this compound and its analogues are warranted.

1.5 Overview of the Contents of the Remaining Parts of the Thesis

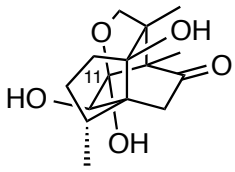
As noted on the preceding page, the work described in this Thesis was carried out with the aim of exploring and expanding upon the utility of *c*-DHCs in natural product synthesis. Specifically, type I IMDA reactions of *c*-DHCs were to be examined as a means for assembling the complex framework associated with the tashironin class of natural products. Accordingly, Chapter Two describes the total synthesis of (−)-khusiol [(−)-**19**], a compound that is structurally related to tashironines, while the following one (Chapter Three) describes analogous work directed towards the synthesis of the tashironins themselves. Chapter Four is divided into two parts. The first describes the synthesis of a group of compounds biogenetically related to khusiol, namely the prezizaanes and specifically the synthesis of (+)-prezizaene and (+)-allokhusiol. The second part describes the synthesis of a novel C_{15} alcohol that embodies *ent*-β-isopipitzol framework. This aspect of the author's research exploited a novel Wagner-Meerwein rearrangement reaction. The final chapter (Five) provides all of the experimental details associated with the work described in the preceeding three.

Chapter 2: The Total Synthesis of (−)-Khusiol [Allocedrol]

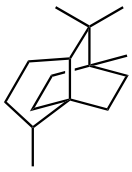
2.1 Introduction

2.1.1 Isolation and Elucidation of the Structure of (−)-Khusiol [(−)-19]

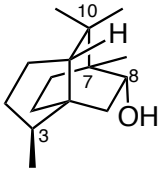
The allocedrane group of compounds constitute unusual sesquiterpenoids because they embody the tricyclo[5.2.2.0^{1,5}]undecane ring system (see structure **18**). A representative member of the group is (−)-khusiol [(−)-**19**]. In 1978, Ganguly reported[17] the isolation of this compound from the essential oil of the plant *Vertiveria zizanoides* Linn. collected from the Moosanagar area of North India. The structure of this tricyclic alcohol was determined by mass spectrometric and various NMR spectral studies that were undertaken in conjunction with certain chemical correlation studies. In another study Weyerstahl and co-workers reported[18] the isolation of compound (−)-**19** from a Haitian vetiver. Its antipodal form, (+)-**19**, was first reported[19] in 1973 as an isolate from the wood of *Juniperus rigida* Sieb. et Zucc and later from the Cedar *Biota orientalis*,[19] liverwort *Porella navicularis*[20] and *Juniperus lucayana*.[21] To date, only the (−)-form of compound **19** has been isolated from the genus *Vertiveria*.



11-*O*-debenzoyltashironin
(**17**)



the allocedrane
framework
(**18**)



(−)-khusiol
[(−)-**19**]

Figure 2.01. The allocedrane framework and two sesquiterpenoids embodying it

2.1.2 Biological Activity

There have been no reports on the biological activities of either enantiomeric form of khusiol. Nonetheless, it is considered an important molecule on both biogenetic and structural grounds. Thus, not only is it partially responsible for the pleasant woody-fruity odor[18] of the essential oil of vetiver,* it is also considered to be a key intermediate associated with the biogenesis[ϕ] of other olfactorily important constituents of vetiver oil.[17, 22] Furthermore, the core structure of khusiol is found embedded in the more complex (and highly biologically active) members of the allocedrane class of natural products known as tashironins.[o] A key member of this sub-class is 11-*O*-debenzoyltasirinin (**17**),[15] a compound that possesses remarkable neurotropic activity.[15]

2.1.3 Synthetic Challenges Associated with Target 19

There are four significant synthetic challenges presented by the structure of khusiol. These are: (i), the need to construct the tricyclo[5.2.2.$0^{1,5}$]undecane ring system and the associated *gem*-dimethyl unit at C10 (constituting a quaternary carbon centre) which is attached directly to the C7-based quaternary carbon centre; (ii), the need to control of the stereochemistry of the C3 methyl group; (iii) the establishment of what could be viewed as a *trans*-fused hydroindane ring junction and; (iv), the setting of the appropriate configuration of the C8 hydroxyl group.

2.2 Previous Studies on the Synthesis of Khusiol (19)

2.2.1 Overview

In 1994 Rao and co-workers reported[23] the first stereoselective total synthesis of (±)-khusiol [(±)-**19**]. This work was later published[24] as a comprehensive account detailing the endgame approach to the target as well as highlighting some of the difficulties encountered during the course of the original (1994) studies. The key features of the synthesis were, (i), a stereoselective conjugate

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* the essential oil of vetiver is highly prized in the perfume industry for its pleasant and long-lasting woody aroma.

[ϕ] the biogenesis of khusiol and related tricyclics isolated from the essential oil of vetiver is discussed in Chapter 4.

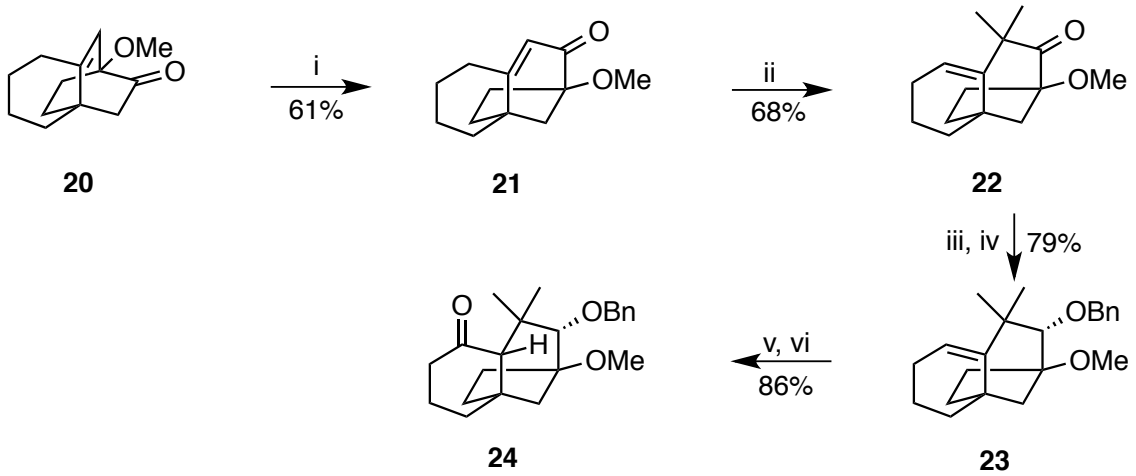
[o] the tashironin group of compounds is discussed in Chapter 3.

addition reaction to install the C3 methyl group and, (ii), the construction of the required tricyclo[5.2.2.$0^{1,5}$]undecane skeleton through the Lewis acid-catalysed rearrangement of a bicyclo[3.2.1]octane to the isomeric bicyclo[2.2.2]octane.

2.2.2 Total Syntheses

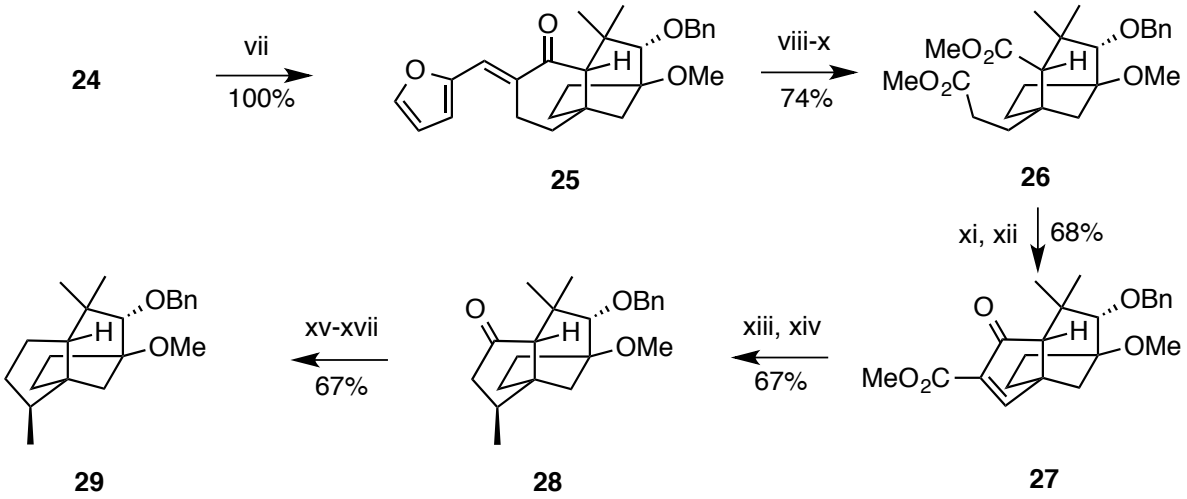
2.2.2.1 Subba Rao's Formal Total Synthesis of (±)-Khusiol (1994)

The first phase of Rao's 1994 synthesis involved construction of ketone **24** by the pathway shown in Scheme 2.01. Thus, compound **20**, which was obtained through hydrolysis of a readily available Diels-Alder adduct of 2-chloroacrylonitrile and 6-methoxy-1,2,3,4,5,8-hexahydronaphthalene,[25] was heated in refluxing benzene in the presence of anhydrous *p*-toluenesulfonic acid to give rearranged product **21** that was itself *gem*-dimethylated to give compound **22**. Ketone **22** was, in turn, reacted with sodium borohydride ($NaBH_4$) and the resulting alcohol was itself converted into the corresponding benzyl ether **23**. Hydroboration/oxidation of alkene residue within this last compound followed by oxidation of the alcohol so-formed then gave the target ketone **24** as a single diastereoisomer.



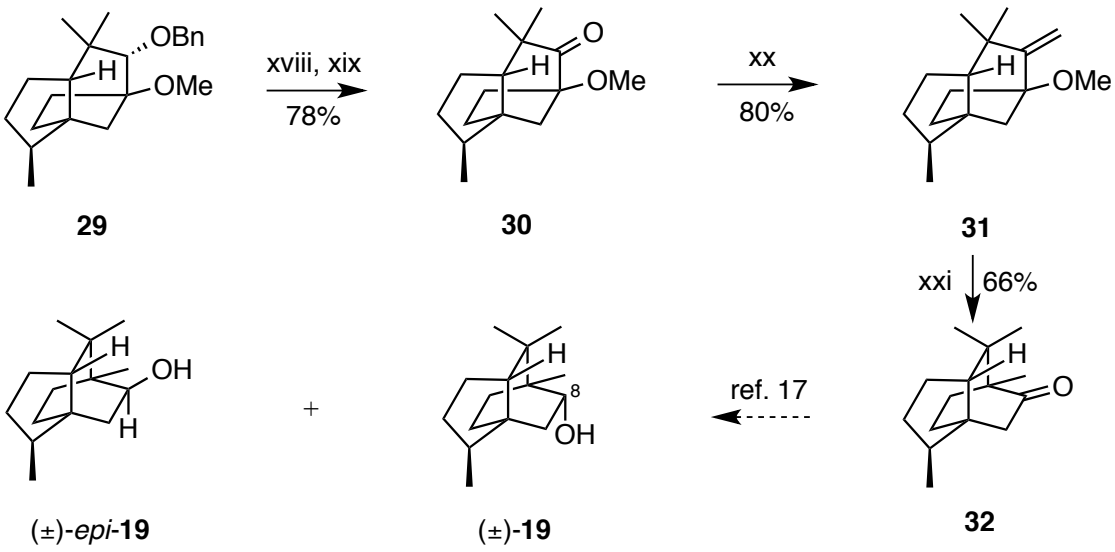
Scheme 2.01. *Reagents and conditions*: i. *p*-TsOH, PhH, reflux; ii. *t*-BuOK, *t*-BuOH, MeI, PhH; iii. $NaBH_4$, MeOH; iv. NaH, BnBr, THF, TBAI, 70 °C; v. BH_3, THF, H_2O_2, NaOH; vi. PCC, CH_2Cl_2

The next phase of the synthesis involved a ring-contraction sequence (Scheme 2.02) and stereoselective installation of the key C3 methyl group. Thus, condensation of the ketone **24** with furfural gave the furfurylidene derivative **25** that upon ozonolysis (and oxidative work-up) then esterification gave the compound **26**. Dieckman cyclisation of diester **26** followed by phenylselenylation and oxidation finally gave enone **27**. The key C3 methyl group was installed by treatment of the enone **27** with lithium dimethyl cuprate and decarboxylation of the resulting addition product and thereby providing ketone **28**. Reduction of this last compound then gave the corresponding alcohol that was converted into the corresponding xanthate, reduction of which, under Barton-McCombie conditions, furnished compound **29**.



Scheme 2.02. *Reagents and conditions*: vii. NaOH, 2-furfuraldehyde, EtOH; viii. O_3, EtOAc, –78 °C; ix.H_2O_2, AcOH; x. CH_2N_2, Et_2O; xi. NaH, THF; xii. NaH, PhSeCl, H_2O_2; xii. Me_2CuLi, Et_2O, –100 °C; xiv. DABCO, toluene, 95 °C; xv. $LiBH_4$, THF; xvi. *n*-BuLi, CS_2, MeI, THF; xvii. H_3PO_2, Et_3N, dioxane, 120 °C

The pivotal endgame required the construction of the tricyclo[5.2.2.$0^{1,5}$]undecane skeleton of khusiol and this was achieved through rearrangement of a bicyclo[3.2.1]octane system to its bicyclo[2.2.2]octane isomer. The required substrate was prepared, as shown in Scheme 2.03, by debenzylation of compound **29** and oxidation of the ensuing alcohol to ketone **30**. Wittig methylation of the last compound then gave the target substrate **31**. Upon treatment with boron trifluoride compound **31** engaged in a biogenetically inspired Wagner-Meerwein rearrangement to its thermodynamically more stable isomer **32** (= khusione).[17, 26]

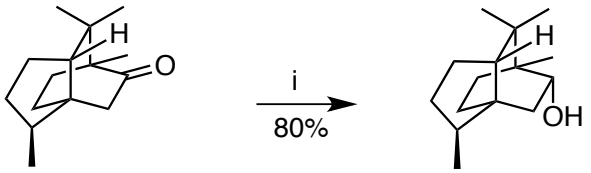


Scheme 2.03. *Reagents and conditions*: xviii. Li/liq. NH_3; xix. PCC,CH_2Cl_2; xx. Ph_3PMeI, $(CH_3)_3CCH_2OK$, toluene,120 °C; xxi. BF_3•OEt, CH_2Cl_2

By virtue of the acquisition of ketone **32,** a formal total synthesis of was realised since Ganguly *et al*. have reported[17] reduction of levorotary form of ketone **32** to (–)-khusiol [(–)-**19**] although this was obtained as the minor product of reaction (its epimer predominated). Clearly, a better reduction protocol was needed. This was eventually identified as detailed in the following section.

2.2.2.2 Subba Rao's Total Synthesis of (±)-Khusiol (1998)

In 1998 Rao and co-workers reported[24] a refined total synthesis of (±)-khusiol [(±)-**19**] that, *inter alia*, incorporated a much more stereoselective reduction of ketone **32**. Specifically, this was achieved by using lithium in liquid ammonia and with ammonium chloride as a proton source. By such means a mixture of target (±)-**19** (68%) and its C8-epimer (8-*epi*-**19**) (9%) was obtained. As such, the first stereoselective total synthesis of (±)-khusiol [(±)-**19**] has been achieved in 26 steps from ketone **20** (Scheme 2.04).

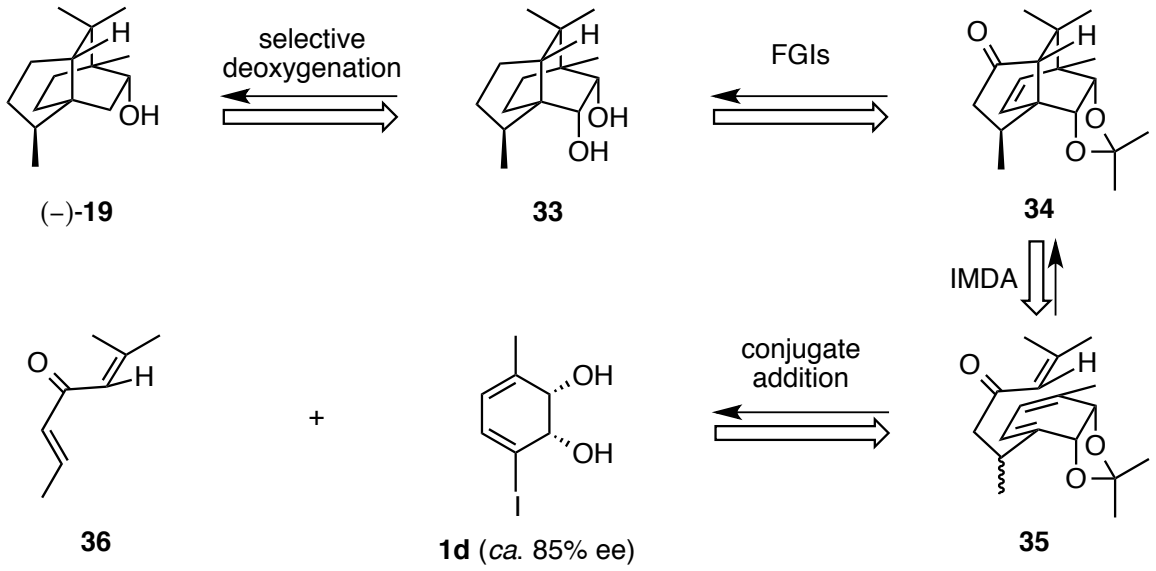


32 (±)-khusiol [(±)-**19**]

Scheme 2.04. *Reagents and conditions*: i. Li/liq. NH_3, NH_4Cl, THF, –30 °C, 1 h

2.3 Retrosynthetic Analysis and Strategy

As discussed in Chapter 1, the Banwell group has devised[12] an efficient and enantioselective route to tricyclic structures closely related to the target **19**. The key step was a type I intramolecular Diels-Alder (IMDA) reaction. Accordingly, the synthetic approach to khusiol carried out by the author and described here incorporated this key reaction. Specifically, and as shown in retrosynthetic form (Scheme 2.05), it was envisaged that (–)-khusiol [(–)-**19**] could be obtained through selective deoxygenation of diol **33**. This, in turn, could be synthesized from intermediate **34** through various conventional functional group manipulations. Ketone **34** is itself the anticipated product of a stereoselective IMDA reaction of triene **35** that it was thought could be accessed through a conjugate addition reaction between the acetonide derivative of diol **1d** (*ca.* 85% ee)[27] and the known and readily accessible dienone **36**.[28]



Scheme 2.05. Retrosynthetic analysis of (–)-khusiol [(–)-**19**]

2.4 Total Synthesis of (–)-Khusiol [(–)-19]

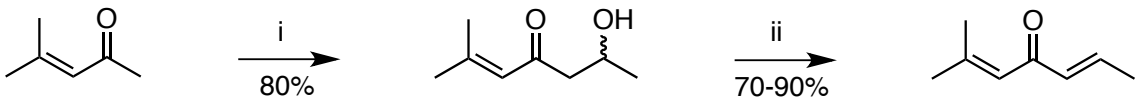
The work described immediately below, and which details the implementation of the strategy just described, has provided the first enantioselective synthesis[a] of the natural product (–)-khusiol [(–)-**19**]. The key steps involved, as foreshadowed, (i), a stereoselective type I IMDA cycloaddition reaction of a triene derived from *c*-DHC and, (ii), a substrate-controlled stereoselective conjugate addition reaction to install the key C3 methyl group.

2.4.1 Synthesis of IMDA Precursor 35

It was anticipated that a conjugate addition reaction[12, 29] could be used to generate the substrate **35** for the IMDA reaction. In order to pursue such an approach compound **36** and the acetonide derivative of diol **1d** were required. The synthesis of the former substrate (**36**) involved treating mesityl oxide (**46**) with lithium diisopropylamine (LDA) followed by acetaldehyde to give, after

[a]this work has been published (see ref. 57).

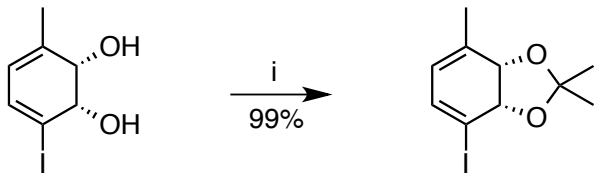
work up, *β*-hydroxyketone (**38**) (Scheme 2.06). Treatment of alcohol **38** with methanesulfonyl chloride and triethylamine ($MsCl/Et_3N$) then gave the divinyl ketone **36**[*] (DVK-**36**) in good yield (70-90%). Presumably an E1cb-type reaction is involved in the last step of this sequence which delivers the thermodynamically favoured *E*-form of the product. The crude sample of compound **36** thus obtained was found to be of > 95% geometric purity as judged by ^1H NMR spectroscopic analysis. Furthermore, the spectral data were in complete accord with those reported in the literature.[28a]



37 **38** **36**

Scheme 2.06. *Reagents and Conditions*: i. LDA, THF, –65 °C, 1 h then CH_3CHO,–65 °C, 1 h (80%); ii. MsCl, Et_3N, DCM, 0 to 18 °C, 12 h, (70-90%)

The diene moiety required for the anticipated Diel-Alder reaction was obtained by converting *c*-DHC (**1d**) into its corresponding and previously reported acetonide **39**[12, 30] through treatment of the former compound with 2,2-dimethoxypropane (2,2-DMP) in the presence of catalytic amounts of *p*-toluenesulfonic acid (*p*-TsOH) (Scheme 2.07).

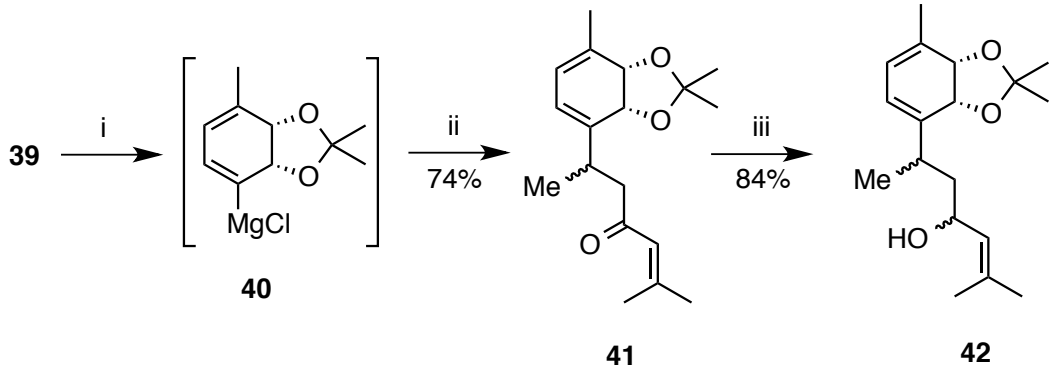


1d **39**

Scheme 2.07. *Reagents and Conditions*: i. 2,2-DMP, *p*-TsOH, 18 °C, 1 h, (99%)

[*] DVK-**36** is volatile and has an unpleasant smell. Accordingly, appropriate caution must be exercised when handling it.

With the required coupling partners in hand, the pivotal conjugate addition reaction could now be examined. To this end, the acetonide **39** was converted nto the corresponding cuprate by treatment with *iso*-propylmagnesium chloride[#] (to generate the intermediate Grignard reagent **40**) then the copper(I)bromide/dimethyl sulfide complex.[29] The ensuing cuprate was treated with dienone **36** and thereby producing, through a regioselective conjugate addition process, the α,β-unsaturated ketone **41** (74%) as a 3:1 mixture of diastereoisomers as judged by ^{13}C and ^{1}H NMR spectroscopic analysis (Scheme 2.08).



Scheme 2.08. *Reagents and Conditions:* i. *i*-PrMgCl, THF, –30 to 0 °C, 2 h then Cu(I)Br•SMe_2, HMPA, –78 °C, 10 min then ii. dienone **36**, TMSCl, –78 to18 °C, 16 h, dr = 3:2 (74%); iii. $NaBH_4$, MeOH, 0 to 18 °C, 2 h, dr = 3:3:2:1 (84%)

The EI mass spectrum of compound **41** exhibited the expected molecular ion at *m/z* 290 while the corresponding IR spectrum displayed C=O and C=C absorption bands at 1686 and 1618 cm^{-1}, respectively. The notable features in the ^{1}H NMR spectrum of this triene were the closely-spaced three proton doublets at δ 1.09 and 1.10 that arise from the methyl groups of the two diastereoisomeric products. The doubling up of resonances in ^{13}C NMR spectrum of the product mixture served to confirm the presence of diastereoisomers.

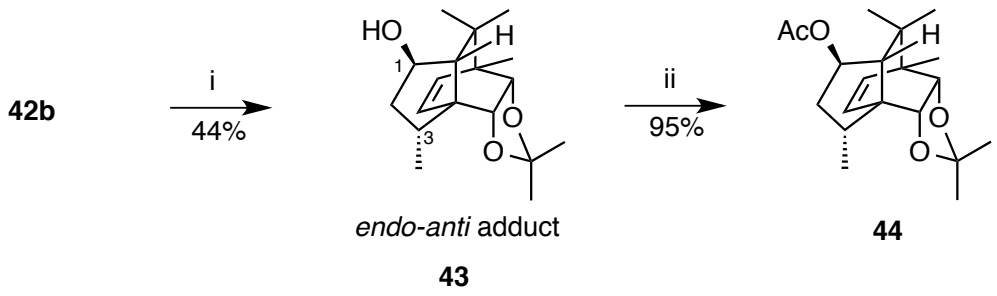
[#]the *in situ* formation of compound **40** can take from 2-4 h depending on the quality of *iso*-propylmagnesium chloride. The rate of formation of Grignard reagent **40** can be monitored using ^{1}H NMR spectroscopic techniques.

2.4.2 The IMDA Reaction and Characterisation of the Resulting Products

With the potential IMDA substrate **41** in hand, its participation in the desired process could be investigated. In the event, compound **41** failed to engage in the much hoped-for IMDA cycloaddition reaction under a range of different thermolytic conditions. Only slow dimerisation and aromatization of the starting material was observed. Such observations are not unexpected. So for example, both Austin *et al.* (2010) and Milhovilovic *et al.* (2004) independently reported the inability of similar types of systems to participate in IMDA processes.[12, 31]

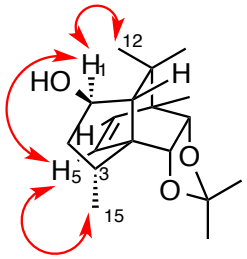
The lack of reactivity of triene **41** could be the result of conformational restrictions imposed upon it by the side-chain carbonyl group and the consequent inability of the molecule to assume the correct transition state geometry required for the IMDA reaction. Accordingly, and so as to increase the flexibility of the side chain, compound **41** was subjected to sodium borohydride ($NaBH_4$) reduction and so resulting in a 3:3:2:1 mixture of diastereomeric alcohols **42** in a combined yield of 84% (Scheme 2.08). The EI mass spectrum of this material exhibited an ion at *m/z* 274, 18 mass units lower than the anticipated molecular ion (292) and this is attributed to the facile loss of H_2O under the conditions used to acquire the spectrum. The IR spectrum of this product mixture displayed a very strong O-H absorption band at 3436 cm^{-1}.

The diastereomeric components of the alcohol **42** were partially separated through column chromatography into two major fractions, **42a** and **42b**. These fractions were then independently subjected to the IMDA reaction. Whilst the less polar fraction **42a** (comprising a 3:1 mixture of diastereoisomers) did not participate in the hoped for IMDA cycloaddition reaction, the more polar one, **42b**, (comprising a 3:2 mixture of diastereoisomers) did so upon being heated in refluxing mesitylene for 96 h. By such means the diastereomerically pure alcohol **43** was obtained in 44% yield (Scheme 2.09). The assigned structure, **43**, is based on previous work[12] on similar systems and through extensive mass spectrometric and spectroscopic studies (including X-ray analyses of related or derived compounds – see below).



Scheme 2.09. *Reagents and Conditions:* i. Mesitylene, BHT, 165 °C, 98 h (44%), ii. Ac_2O, Py, DCM, 18 °C, 12 h (95%)

The ^{1}H NMR spectrum of adduct **43** exhibited mutually coupled doublets (J = 8.2 Hz) at δ 5.87 and δ 5.76 and thus indicating the presence of *cis*-configured double bond. Also observed were two further mutually coupled doublets at δ 4.23 and δ 4.04 (J = 7.1 Hz) that are attributed to the oxymethine protons. An oxymethine mutiplet appearing at δ 3.93, five tertiary methyl singlets's at δ 1.27, 1.25, 1.19, 1.01 and 0.92 and a secondary methyl doublet at δ 1.10 (J = 6.8 Hz) were also observed and completely consistent with the assigned structure. The ^{13}C NMR spectrum exhibited all of the expected 17 carbons resonances including two due to alkenic carbons (at δ 138.2 and 126.3), three due to oxymethine carbons (δ 85.6, 81.5 and 73.9) and three due to quaternary carbons (at δ 52.6, 46.2 and 37.8). The EI mass spectrum displayed a strong fragment ion at *m/z* 277 arising from the facile loss of a methyl radical (most likely from the acetonide group) from the anticipated molecular ion. The relative stereochemical relationship at C1 and C3 were assigned using NOESY techniques. In particular, strong correlations were observed (Figure 2.02) between the signal due to H5 and those due to the three H15 protons. Similar correlations were observed between the signals due to H1 and H5 and those corresponding to H1 and the three H12 protons.

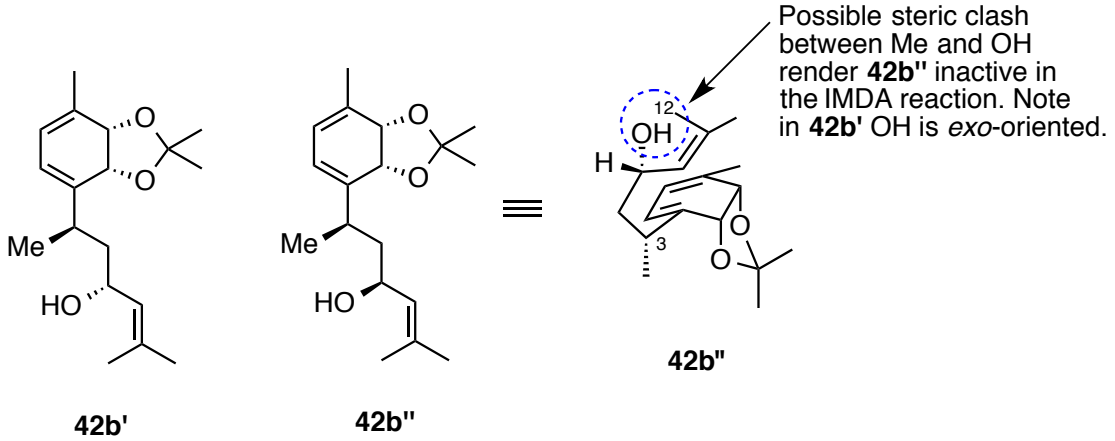


43

Figure 2.02. Key nOes observed in the ^{1}H NMR spectrum of compound **43**

Final confirmation of the assigned structure followed from a single-crystal X-ray analysis of the readily derived acetate **44** (see Appendix A.01 for details).

It was satisfying to see the highly substituted triene substrate **42b'**, the neccessay precursor to adduct **43**, possessing a notionally inactive dienophile participating in an IMDA cycloaddition reaction. In contrast, its epimer (**42b''**) did not participate in an analogous process for the reason given below and was recovered from the reaction mixture.



42b' **42b"** **42b"**

Scheme 2.10. The structures of the IMDA active (**42b'**) and inactive (**42b"**) components of the mixture **42b**

As expected, the reaction leading to compound **43** proceeded through an *endo*-transition state and displayed *anti*-facial selectivity.

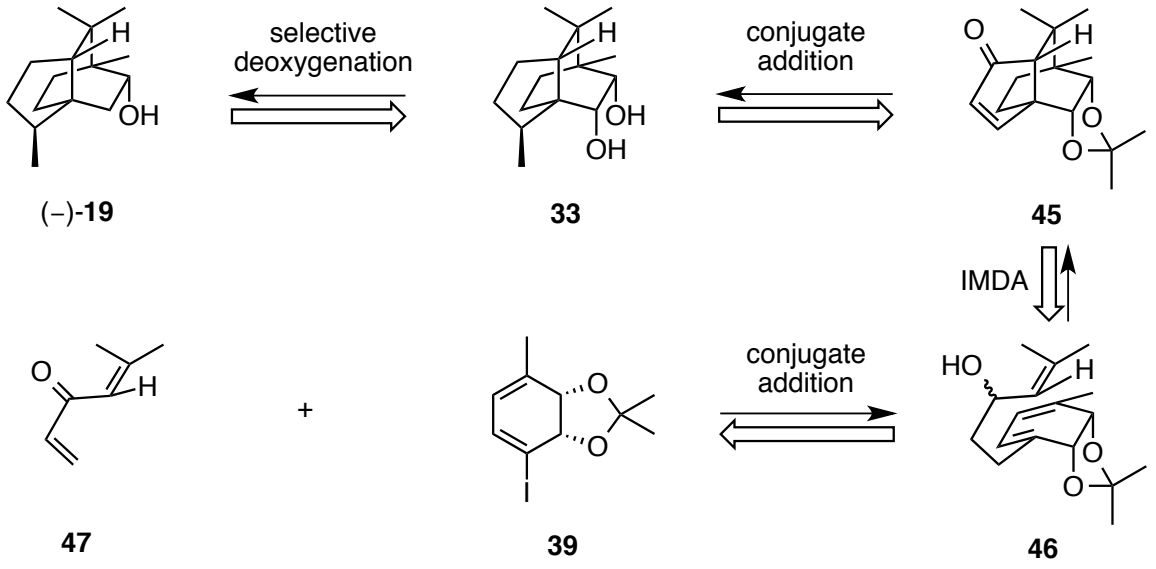
Presumably, the transition state leading from compound **42b'** to the observed adduct (**43**) is lower in energy than that associated with the analogous process involving diastereoisomer **42b''**. One of the factors influencing the reactivity of the relevant diastereomeric form of the substrate is the presence of hydroxyl group at C1. The steric effects are minimized (at transition state) when the hydroxyl group is *exo*-oriented and is projecting away from the *endo*-oriented methyl group at C12 as would be involved in the reaction of compound **42b'** (see Figure 2.02). The methyl group at C3 is probably also playing a role in the outcome of the IMDA reaction but precisely how is not clear at this point. It should also be noted that the flexibility of the tether linking the reaction partners, rather than the presence of a notionally activated dieneophile, is one of the important drivers for this successful IMDA reaction.

It was pleasing to see that in just four steps (from *c*-DHC), the tricyclic core, as embodied in compound **43**, of target **19** had been obtained. Significantly, compound **43** incorporates the two contiguous quaternary carbon centres including the one involving the bridgehead methyl group. Four of the five stereogenic centres of the target **19** were established in a single step through a stereoselective IMDA reaction. Unfortunately, the key secondary methyl group (at C3) possesses the wrong stereochemistry. Providentially, the previously mentioned tashironins (e.g. compound **17**) all have the same stereochemistries, including at C3, as embodied in intermediate **43**. While compound **43** clearly doesn't represent an effective precursor to khusiol it could serve as such in any synthetic campaign directed towards the tashironins. Indeed, relevant work in this area is presented in Chapter Three. For now, however, the problem associated with stereochemistry at C3 needed rectification and so a different approach to the required C3-epimer was required. The successful approach ultimately developed is presented in Section 2.4.3.

2.4.3 Addressing the Stereochemical Issues at C3

The necessary new strategy is closely related to one described earlier. Thus, the endgame would remain the same with a late-stage and selective deoxygenation of diol **33** being involved (Scheme 2.11). It was thought compound **33** itself could be prepared from cyclopentenone **45** *via* a

stereoselective conjugate addition (that should install the key methyl group in the correct orientation) and a subsequent series of conventional functional group manipulations. In particular, it was anticipated that the methyl group would be delivered from the less hindered *β*-face of the hydroindene-type substructure **45**. Compound **45** itself was thought accessible *via* a stereoselective type I IMDA cycloaddition reaction of precursor **46** followed by functional group manipulations. It was hoped that this substrate for the IMDA reaction would be accessible through a conjugate addition reaction[12] between acetonide derivative **39** and dienone **47**.[12, 32] Details of the implementation of this second generation plan are presented in the following section.

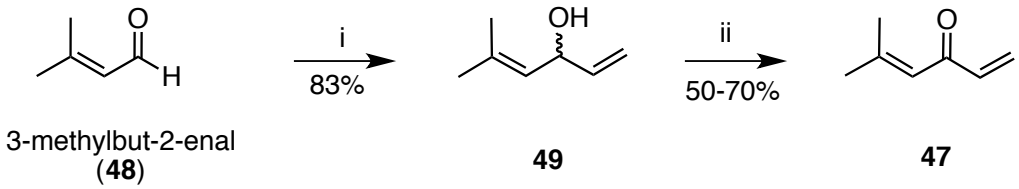


Scheme 2.11. Alternative route to (–)-khusiol [(–)-**19**]

2.4.4 Synthesis of Triene 46, a Potential Substrate for an IMDA Reaction

In order to access compound **46**, the previously reported divinylketone **47** was required as a starting material. Following a literature protocol,[12,33] commercially available aldehyde **48** (Scheme 2.12) was treated with vinylmagnesium bromide to give, after conventional work-up, divinyl alcohol **49**.[34] Treatment of this alcohol with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) then gave

dienone **47**[*][35] in about 40-60% yield. Other methods[36] for making compound **47** were explored, but none worked as well as the one just described. This proved to be entirely reproducible and always delivered clean material in moderate to high yield.

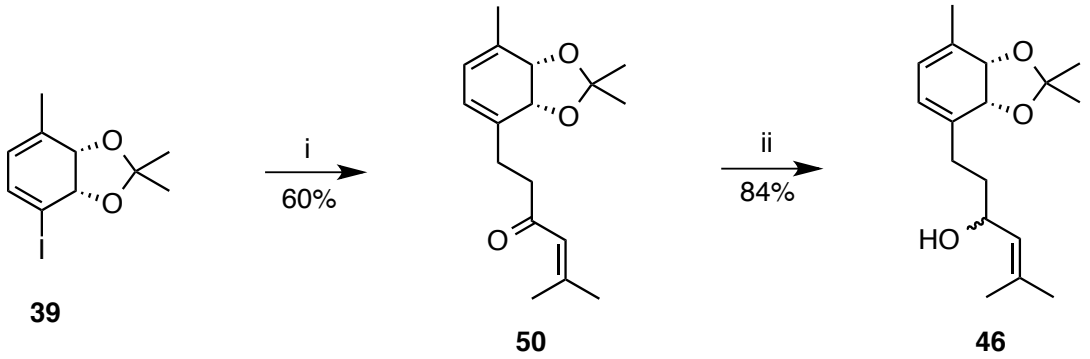


3-methylbut-2-enal (**48**) **49** **47**

Scheme 2.12. *Reagents and Conditions*: i.  MgBr, THF, 18 °C, 1 h (83%); ii. DDQ, Et_2O, 18 °C, 12 h (50-70 %)

The synthesis of subtarget **46** followed the same protocol as used earlier for the generation of congener **41**. Thus, a conjugate addition reaction between the Gilman reagent derived from acetonide **39** and the dienone **47** gave α,β-unsaturated ketone **50**[12] in 60% yield (Scheme 2.13). Interestingly, this last compound did not participate in the IMDA reaction, presumably for the same sorts of reasons as already stated. Accordingly, compound **50** was reduced with sodium borohydride to yield the alcohol **46**[12] that was obtained as *ca*. 1:1 and inseparable mixture of diastereoisomers in 83% combined yield (Scheme 2.13).

[*] Compound **47** is quite volatile and malodorous so care must be taken while concentrating it under reduced pressure.

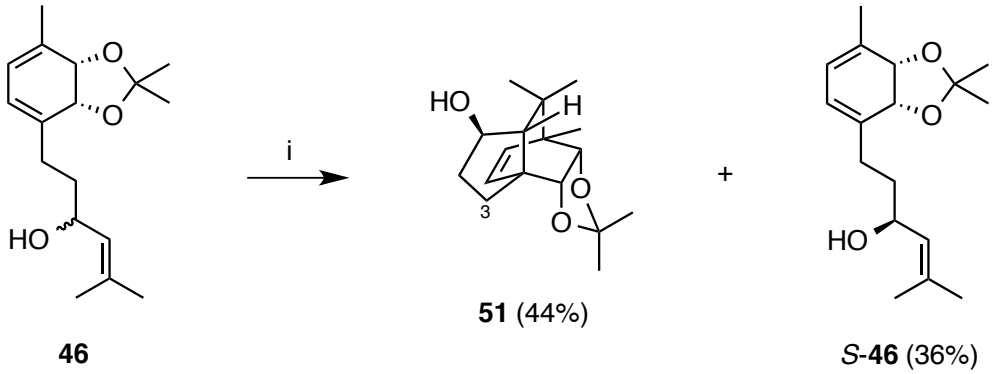


39 **50** **46**

Scheme 2.13. *Reagents and Conditions*: i. *i*-PrMgCl, THF, –30 to 0 °C, 2 h then Cu(I)Br•SMe_2, HMPA, –78 °C, 10 min, dienone **47**, TMSCl, –78 to18 °C, 16 h (60%); ii. $NaBH_4$, MeOH, 0 to 18 °C, 2 h, dr = 1:1 (84%)

2.4.5 The IMDA Reaction of Compound 46 and Characterisation of the Resulting Cycloadduct(s)

While, as noted above, compound **50** failed to engage in an IMDA reaction upon heating, one of the derived epimeric alcohols, specifically compound **46**, participated in such a process upon heating in mesitylene and thereby producing the epimerically pure tricyclic alcohol **51**[12] in 44% yield. The unreacted and now diastereomerically enriched alcohol *S*-**46** was also isolated after column chromatography (36% recovery) (Scheme 2.14). While the ^{1}H NMR spectra of compounds **46** and *S*-**46** looked very similar, the ^{13}C NMR spectrum of the latter clearly showed enrichment of one of the epimeric forms of the mixture of the alcohols **46** used in the IMDA reaction. Interestingly, prolonged heating of compound *S*-**46**, failed to deliver any IMDA cycloaddition product. With compound **51** in hand, the next phase of the synthesis was framed on establishing a protocol for introducing the pivotal C3 methyl group with appropriate stereocontrol.

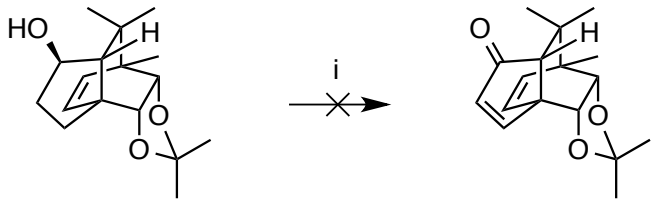


46 **51** (44%) *S*-**46** (36%)

Scheme 2.14. *Reagents and Conditions*: i. mesitylene, BHT, 165 °C, 98 h

2.4.6 Installation of the Key C3 Methyl Group

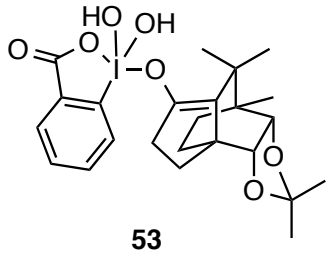
It was envisaged that the C3 methyl group could be installed in a stereoselective manner *via* a conjugate addition reaction between enone **52** and a cuprate reagent of some sort. Specifically, it was anticipated that the methyl group should be delivered from the less hindered β-face of the hydroindene substructure and thereby establishing the correct stereochemistry at C3. Accordingly, compound **51** was subjected to one-pot and two-fold oxidation process using the protocol developed by Nicolaou *et al*.[37] and which utilizes the hypervalent iodine reagent 2-iodoxybenzoic acid (IBX) to directly oxidize alcohols to the corresponding α,β-unsaturated ketone. Unfortunately, substrate **51** failed to deliver the desired compound **52** when treated under the prescribed conditions.



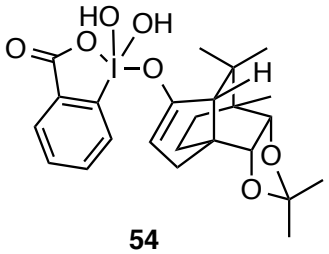
51 **52**

Scheme 2.15. *Reagents and Conditions*: i. IBX, DMSO, 80 °C, 36 h

Presumably, and based on the proposed mechanism for the conversion of cyclic alcohol to α,β-unsaturated ketone using IBX as oxidant,[37] the inability of substrate **51** to participate in the desired oxidation reaction can be attributed to the preferential formation of intermediate **53** (though no such intermediate was isolated) instead of its isomeric but thermodynamically less stable counterpart **54** that would have ultimately provided the desired cyclopentenone **52**.

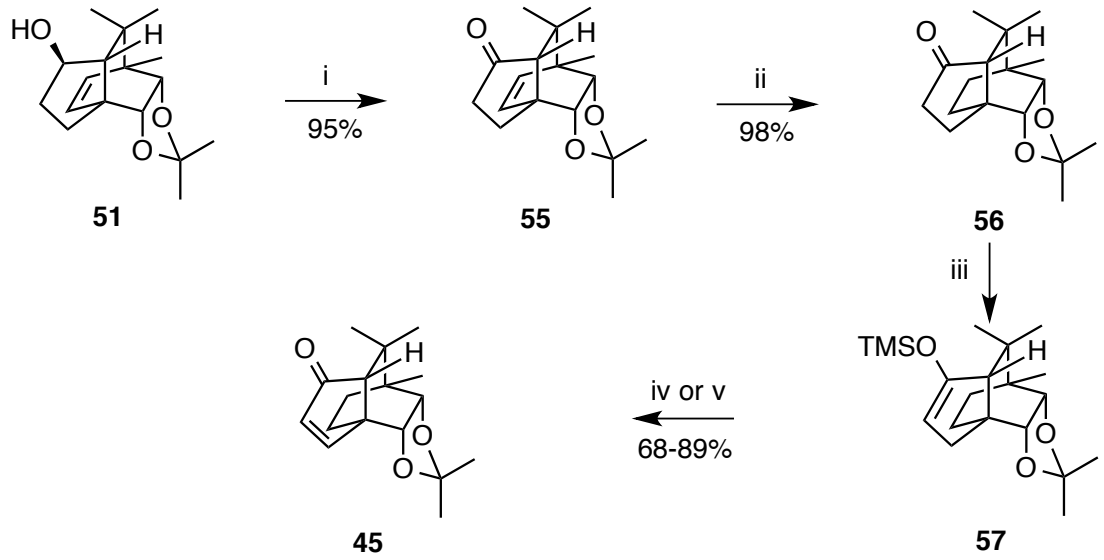


53



54

Given the inability to effect the one-pot conversion of alcohol **51** into the desired enone **52**, a rather more conventional approach (and in this case one involving a Saegusa-Ito oxidation)[38] was pursued. To this end, alcohol **51** was oxidized to the corresponding ketone **55** (95%) (Scheme 2.16) using a mixture of pyridinium dichromate (PDC) and acetic acid (AcOH). The IR spectrum of product **55** showed a =C-H absorption band at 3039 $cm^{-1}$and a strong C=O absorption band at 1735 cm^{-1} while the EI mass spectrum exhibited a molecular ion at *m/z* 276. Characteristic signals observed in the derived ^{1}H NMR spectrum included two mutually coupled (J = 8.0 Hz) one-proton doublets at δ 5.88 and 5.75 due to the double bond and five methyl group singlets at δ 1.30, 1.26, 1.17, 1.06 and 0.92. The ^{13}C NMR spectrum exhibited 17 distinct carbon resonances including one due to a carbonyl unit at δ 215.0. Hydrogenation of ketone **55** using palladium on carbon in EtOH afforded the desired dihydro-derivative **56** in 98% yield (Scheme 2.15) and the EI mass spectrum of this compound exhibited a strong fragment ion at *m/z* 263, arising from the ready loss of methyl radical from the unobserved molecular ion. The IR spectrum showed a strong C=O stretching band at 1735 cm^{-1}.

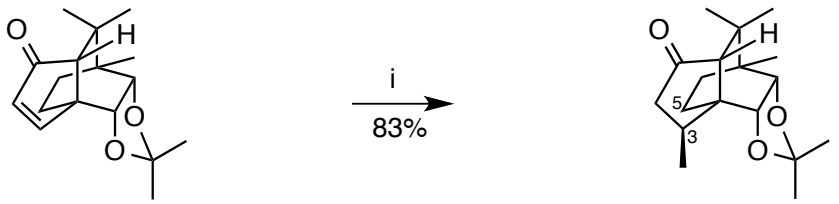


Scheme 2.16. *Reagents and Conditions*: i. PDC, AcOH, DCM, 18 °C, 12 h (95%); ii. H_2, Pd/C, EtOH, 18 °C, 16 h (98%); iii. TMSOTf, Et_3N, DCM, 0 °C, 2 h; iv. *p*-benzoquinone, $Pd(OAc)_2$, MeCN, 18 °C, 3 h (68%, 2 steps); v. IBX, MPO, DMSO,18 °C, 30 h (89%, 2 steps)

Treatment of ketone **56** with trimethylsilyl trifluoromethanesulfonate (TMSOTf) in the presence of triethylamine at 0 °C resulted in the formation of the presumably kinetically favored silyl-enol ether **57** that was subjected, without purification, to a Saegusa-Ito oxidation.[38] By such means a 5:1 and chromatographically inseparable mixture of enone **45** and ketone **56** was obtained in 68% yield over the two steps involved. Interestingly, oxidation of silyl enol ether **57** using a complex derived from 2-iodobenzoic and 4-methoxypyridine-*N*-oxide (IBX•MPO)[39] gave the desired enone **45** in 89% yield over 2 steps although there was also a 14% recovery of the starting ketone. The various spectral data obtained on this mixture clearly indicated the presence of the α,β-unsaturated compound **45**. So, for example, in the ^{1}H NMR spectrum two mutually coupled one-proton doublets (J = 6.0 Hz) appeared at δ 7.56 and 6.03 and these are attributed to the newly installed double bond associated with the enone moiety. The ^{13}C NMR spectrum displayed, *inter alia*, a carbonyl resonance at δ 205.0 and C-C double bond resonances at δ 163.8 and 134.6. The EI mass spectrum of this enone exhibited a molecular ion at *m/z* 276 while the IR spectrum displayed a strong C=O absorption band at 1712 cm^{-1}.

With the desired enone **45** in hand it was now time to pursue one of the pivotal steps of the synthesis, namely the stereoselective installation of the methyl group at C3. As noted earlier, it was

anticipated that treatment of this substrate with, for example, dimethyl cuprate would result in preferential addition of a methyl group from the *β*-face of compound **45** because the *α*-face is hindered by the presence of the ethano-bridge. Also, in *cis*-fused hydroindenes, of which enone **45** is an example, there would be a general preference for *exo*-face addition of nucleophiles. In the event, reaction of the mixture of enone **45** and ketone **56** with dimethyl cuprate[24] (generated *in situ* from methyl magnesium bromide and copper(I)bromide/dimethylsulfide complex) gave the chromatographically separable and diastereomerically pure *β*-substituted methyl derivative **58** in 83% yield. Ketone **56** was also recovered (10%) (Scheme 2.16). The structure of compound **58** was determined through extensive 2D NMR studies and comparison with an authentic sample of 3-*epi*-**58** prepared as described below. The EI mass spectrum of the former compound (**58**) exhibited a molecular ion at *m/z* 292 while the IR spectrum displayed a C=O absorption band at 1728 cm^{-1}. The ^{1}H NMR spectrum showed a characteristic three-proton doublet (J = 6.4 Hz) at δ 1.01 that is attributed to the presence of a secondary methyl group and so indicating that a successful 1,4-addition reaction had taken place. The relative stereochemistry at C3 was determined through NOESY experiments. In particular, strong correlations were observed between the H5 and the three H3 protons. The ^{13}C NMR spectrum showed 18 carbon resonances and ruled out the presence of any major diastereomeric impurities.

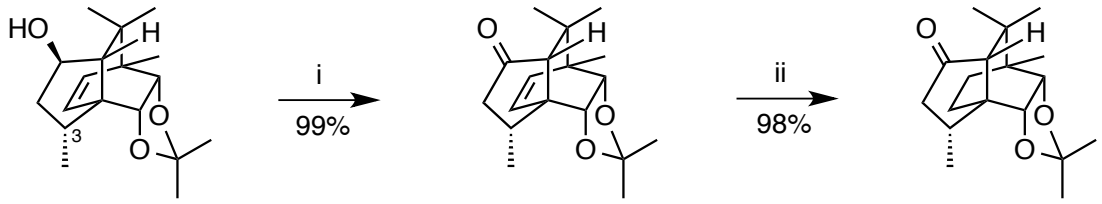


45 **58**

Scheme 2.17. *Reagents and Conditions*: i. MeMgBr, Cu(I)Br•SMe_2, Et_2O, –10 °C, 1.5 h (83%)

An authentic sample of compound 3-*epi*-**58** (Scheme 2.17) was prepared from the previously obtained alcohol **43** by oxidation of the latter using a mixture of PDC/AcOH to give ketone **59**. Hydrogenation of compound **59** using 10% palladium on carbon then gave the targeted reference compound. Most significantly this was spectroscopically distinct from compound **58** (Table 1). Some notable differences observed in the ^{1}H NMR spectra involved the resonances due to C3

methyl group (appearing at δ 1.01 for **58** and at δ 1.06 for 3-*epi*-**58**) and those arising from the mutually coupled oxymethine protons (appearing at δ 4.24 and 4.05 for **58** and at δ 4.00 and 3.95 for 3-*epi*-**58**).



43 **59** 3-*epi*-**58**

Scheme 2.18. *Reagents and Conditions*: i. PDC, AcOH, DCM, 18 °C, 12 h (99%); ii. H_2, Pd/C, EtOH, 18 °C, 16 h (98%)

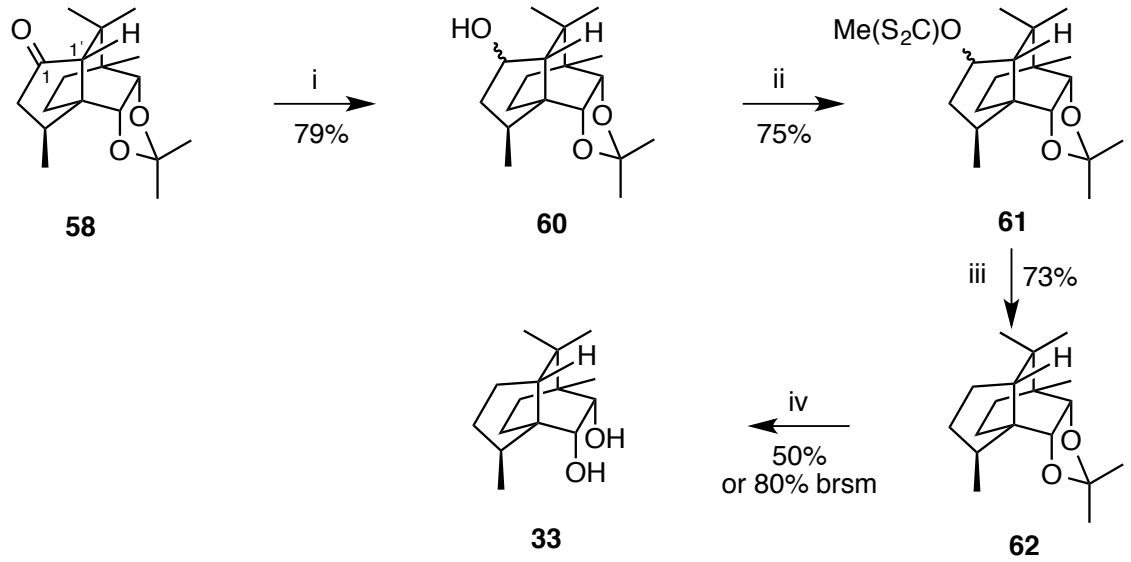
Table 1. Comparison of the ^{13}C and ^{1}H NMR data recorded for compound **58** and its C3-epimer (3-*epi*-**58**)

^{13}C NMR data (δ_C)		^{1}H NMR data (δ_H)	
58[a]	*3-epi*-**58**[b]	**58**[c]	3-*epi*-**58**[d]
217.0	216.2	4.24 (dd, *J* = 8.0 and 1.6 Hz, 1 H)	4.00 (dd, *J* = 8.4 and 1.8 Hz, 1 H)
108.9	109.1	4.05 (dd, *J* = 8.0 and 2.0 Hz, 1 H)	3.95 (d, *J* = 8.4, 1 H)
78.3	82.7	2.58 (dd, *J* = 19.2 and 8.4 Hz, 1 H)	2.3 (m, 1 H)
76.0	78.8	2.05 (quintet, *J* = 7.6 Hz, 1 H)	1.92-1.81 (m, 2 H)
56.8	62.5	1.95 (dt, *J* = 19.2 and 1.2 Hz, 1 H)	1.75 (brd, *J* = 12.9 Hz, 1 H)
47.2	46.4	1.66 (m, 2H)	1.60 (m, 1 H)
43.6	44.1	1.59 (broad t, *J* = 2.0 Hz, 1H)	1.52 (s, 3 H)
39.6	39.6	1.54 (s, 3 H)	1.49 (brs, 1 H)
33.8	44.1	1.39 (s, 3 H)	1.36 (s, 3 H)
31.8	39.6	1.38 (m, 1 H)	1.21 (m, 1.5 H)
33.1	37.5	1.20 (m, 1 H)	1.06 (d, *J* = 6.9 Hz, 3H)
26.7	34.0	1.06 (s, 3 H)	1.05 (s, 3 H)
25.9	26.5	1.02 (s, 3 H)	1.01 (s, 3 H)
24.3	26.0	1.01 (d, *J* = 6.4 Hz, 3 H)	0.83 (m, 0.5 H)
22.5	24.3	0.79 (s, 3 H)	0.78 (s, 3 H)
22.4	21.8		
20.4	20.3		
16.7	15.9		
16.1	14.8		

With the successful installation of the pivotal C3 methyl group, the assembly of allocedrane core associated with (–)-khusiol [(–)-**19**] had now been achieved in a stereoselective manner. The next phase of the synthesis involved a deoxygenation at C1 followed by hydrolysis of the corresponding acetonide to access the hoped-for advanced intermediate **33**. Accordingly, ketone **52** (Scheme 2.19) was reduced using sodium borohydride ($NaBH_4$) and a 4:1 mixture of epimeric alcohols of the general form **60** was obtained in 79% yield. The EI mass spectrum of this mixture exhibited a diagnostic fragment ion at *m/z* 279 $(M–CH_3\bullet)^+$ while the IR spectrum displayed a strong O-H absorption band at 3436 cm^{-1}. Compound **60** was subjected to the next step of the reaction sequence

[a]Data recorded in $CDCl_3$ at 75 MHz.
[b]Data recorded in $CDCl_3$ at 100 MHz.
[c]Data recorded in $CDCl_3$ at 300 MHz.
[d]Data recorded in $CDCl_3$ at 400 MHz.

in crude form. Thus, it was converted, under conventional conditions, into the corresponding mixture of xanthate esters **61** in 75% yield and immediate treatment of this with *n*-tributyltin hydride (*n*-Bu_3SnH) in the presence of catalytic quantities of AIBN (a radical initiator) furnished, *via* a Barton-McCombie deoxygenation reaction, compound **62** in 73% yield. The EI mass spectrum of acetonide **62** exhibited a diagnostic fragment ion at *m/z* 263 $(M-CH_3\bullet)^+$ while the ^1H NMR spectrum displayed a two-proton singlet at δ 4.06 that is attributed to the two oxymethine protons. Five three-proton singlets at δ 1.51, 1.36, 0.89, 0.86 and 0.77, and a three-proton doublet (J = 6.8 Hz) at 0.97 were, as would be expected, also observed in this spectrum. The ^{13}C NMR spectrum revealed the expected 18 carbon resonances although one of these, due to the oxymethine carbon (at δ 77.0) was partially masked by the signals due to the solvent ($CDCl_3$).



Scheme 2.19. *Reagents and Conditions*: i. $NaBH_4$, MeOH, 0 to 18 °C, 16 h, dr = 4:1 (79%); ii. NaH, CS_2, MeI, THF, 18 °C, 16 h (75%); iii. Bu_3SnH, AIBN, toluene,112 °C, 2 h (73%); iv. AcOH/H_2O (4:1), 65 °C, 16 h, 50% (83% brsm)

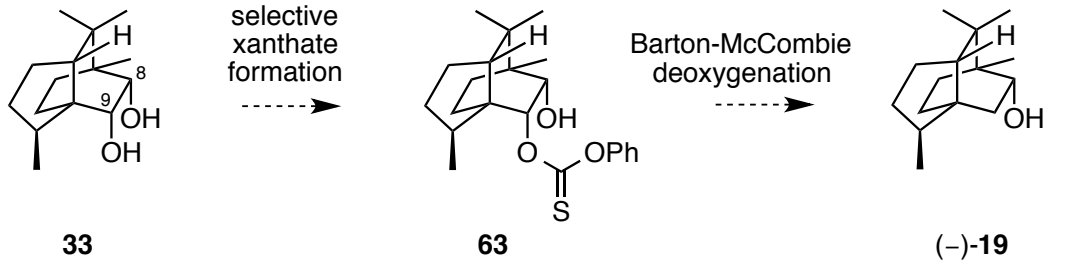
With the successful deoxygenation at C1 now accomplished the next step of the synthesis required cleavage of the acetonide residue so as to reveal the corresponding diol. This was achieved by heating compound **62** in a 4:1 v/v mixture of AcOH and H_2O at 65 °C and in this manner diol **33** was obtained in 50% yield. Complete conversion (50% or 80% brsm) was never achieved for this reaction. Prolonged heating or heating at higher temperatures only lead to degradation and lower

yields. The EI mass spectrum of diol **33** exhibited a molecular ion at *m/z* 238 while the IR spectrum displayed a strong O-H stretching band at 3370 cm^{-1}. The ^{1}H NMR spectrum exhibited oxymethine proton resonances at δ 3.86 (dd, J = 8.1 and 3.9 Hz, 1H) and 3.79 (m, 1H), a methyl doublet (J = 7.5 Hz) at δ 1.00 and three methyl group singlets at δ 0.90, 0.84 and 0.76. Consistent with expectation, 15 distinct resonances were observed in ^{13}C NMR spectrum of this material.

2.4.7 Conversion of Diol 33 into (–)-Khusiol [(–)-19]

2.4.7.1 Selective Deoxygenation of Vicinal Diols

With the advanced precursor, **33**, in hand it was time to investigate the endgame that required, *inter alia*, its selective deoxygenation to (–)-Khusiol [(–)-**19**] (Scheme 2.20). It was envisioned that site-selective formation of xanthate ester **63** using a protocol developed by Miller and coworkers[40] followed by its reduction using the venerable Barton-McCombie reaction[41] would deliver target **19**. Unfortunately, diol **33** failed to engage in such a process.[40] Thus, the application of standard conditions for xanthate formation (using carbon disulfide and methyl iodide) to diol **33** led mostly to the recovery of starting material although there was some evidence, from mass spectrometry, for *bis*-xanthate[o] formation but this was being produced in less than 10% yield.



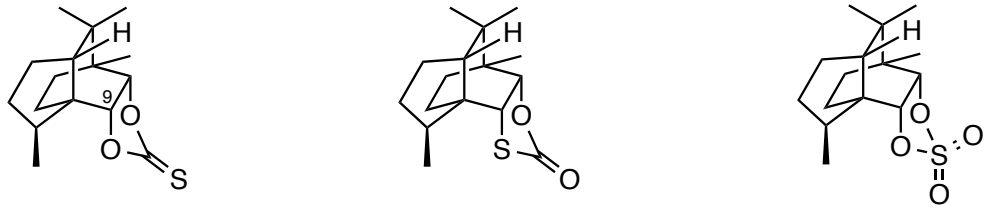
33 **63** (–)-**19**

Scheme 2.20. Proposed selective deoxygenation of diol **33**

Since differentiation between the two hydroxyl groups could not be achieved by the means defined above, other approaches to the selective deoxygenation of vicinal diols such as reductive opening of

[o]Presumably, deoxygenation of *bis*-xanthate would have furnished the known compound khusiane (ref. 17 and 26).

cyclic thiocarbonates,[42] cyclic thiolcarbonates[42b] and cyclic sulfates[42b,43] were investigated (Figure 2.03). Unfortunately, none of these proved effective because, for example, the synthesis of the cyclic thiocarbonate **64** and the thiolcarbonate **65** proved difficult. On the other hand, while the cyclic sulfate **66** was readily synthesized in two steps using a literature protocol[42b,43] its opening (using $NaBH_4$, or $LiAlH_4$) did not deliver the desired alcohol **19**. Rather, a novel tricyclic alcohol was obtained. Details of this process are presented in Chapter 4.



64 **65** **66**

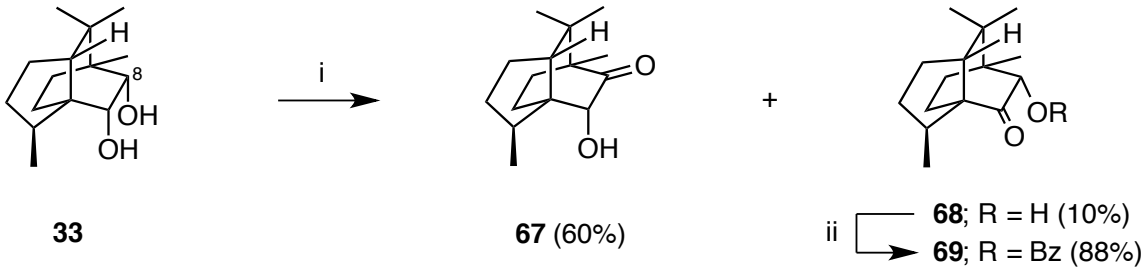
Figure 2.03. Potential derivatives for selective deoxygenation of vicinal diol **33** at C9

Given the inability to selectively deoxygenate diol **33** by the various means just described, a different approach was required. A successful one is detailed immediately below.

2.4.3.2 Selective Deoxygenation of Vicinal Diol 33 -An Alternate Approach

A common and quite successful method employed in the Banwell group for the selective deoxygenation of vicinal diols involves selective formation of one of the corresponding acyloins (α-hydroxyketones) through Bobbitt type oxidation[44] followed by the conversion of such a product into the corresponding benzoate ester followed by reductive cleavage of the -OBz group using samarium diiodide.[45] In the case of compound **33**, it was anticipated that selective mono-oxidation of this would take place at the less hindered C8 carbon. On the downside, the anticipated oxidation would destroy the already established stereocentre at C8. However, since no reasonable alternatives were apparent, this approach was pursued. Accordingly, compound **33** was subjected to Bobbitt oxidation[44] using, as oxidant, the sterically-demanding oxoammonium salt as oxidant derived from the *in-situ* disproportionation of TEMPO by *p*-TsOH. While the oxidation reaction was sluggish

(taking 48-72 h to complete), a chromatographically separable mixture of the desired acyloin **67** (60%) and its regioisomer **68**[*] (10%) was obtained (Scheme 2.20). The presence of the prominent absorption bands at both 1717 and 3436 cm^{-1} in the IR spectrum of compound **67** confirmed the presence of both carbonyl and hydroxyl moieties in the product. The ESI mass spectrum featured a molecular ion associated species at *m/z* 259 $(M+Na)^+$, consistent with a decrease of two mass units (relative to the substrate diol) and the oxidative nature of the reaction. Finally, through the use of various connectivity and proximity experiments (2D NMR) it was established that the oxidation had occurred as anticipated, namely at the less hindered C8 hydroxyl group.

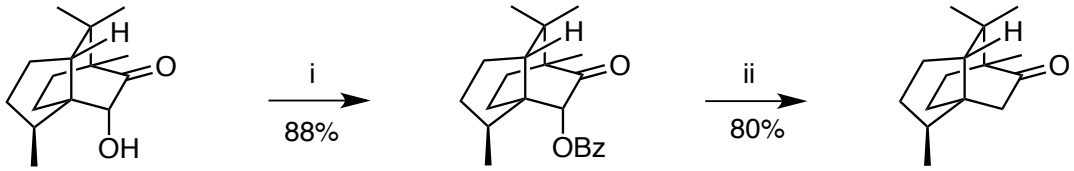


Scheme 2.21. *Reagents and Conditions*: i. 4-AcNH-TEMPO, *p*-TsOH, DCM, 18 °C, 72 h (60%); ii. BzCl, DMAP, Et_3N, DCM, 18 °C, 16 h (88%)

To facilitate the deoxygenation process compound **67** was converted into its corresponding benzoate ester **70** using standard conditions and the ester so-formed treated with samarium diiodide in THF/MeOH (Scheme 2.21).[45] By such means ketone (–)-**32** was obtained in 80% yield and the acquisition of which constitutes a formal total synthesis of target (–)-**19**.[Φ]

[*] Compound **68** was found to be quite unstable compared to its regioisomer **67** and so, for characterization purposes, it was converted to its corresponding benzoate ester **69**.

[Φ] Racemic forms of the natural product **32** has been synthesized by Shanker and Shuba Rao (ref. 23 and 24) The (+) and (–) forms of ketone **32** has also been reported by Tomita (ref. 19) and Ganguly (ref. 17) through oxidation of the natural (+) and (–)-khusiol respectively. In 2000, Weyerstahl (ref. 26) and coworkers reported the isolation of the natural (–)-**32** from the Haitian vetiver oil.



67 **70** (–)-**32**

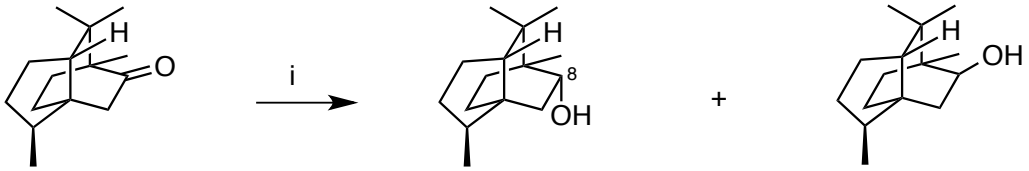
Scheme 2.22. *Reagents and Conditions*: i. BzCl, DMAP, Et_3N, DCM, 18 °C, 16 h (88%); ii. SmI_2, THF/MeOH, –78 °C, 0.5 h (80%)

The spectroscopic data acquired on the synthetic sample of compound (–)-**32** were in good agreement with those reported in the literature for the natural product khusione[26] (Table 2). Notably, the specific rotation recorded for the synthetic ketone (–)-**32** was −32.2 (*c* = 0.63, $CHCl_3$) which compares with a literature value of −42.0 (*c* = 1.8, $CHCl_3$).[17] This suggests that the synthetic sample had been obtained in *ca*. 77% ee.

With the penultimate compound **32** to hand, the final step required its stereoselective reduction to the corresponding alcohol. This was achieved using the protocol defined by Shankar and Shuba Rao.[24] Specifically, compound **32** was subjected to a dissolving metal reduction using lithium in liquid ammonia and with ammonium chloride serving as the proton source (Scheme 2.22). In this way a chromatographically separable mixture of khusiol **19** (67%, *ca*. 85% ee) and its C8-epimer (8-*epi*-**19**) (5%) was obtained. The mass spectral and other spectroscopic data obtained on the former product were in complete accord with the assigned structure and matched those recorded in the literature for the synthetic,[24] as well as the natural (+)-**19**[20] (Table 3) and (–)-**19** forms of khusiol.[18] Likewise, the data acquired on compound 8-*epi*-**19** (*epi*-khusiol) matched those reported in the literature.[18, 24]

Table 2. Comparison of the ^{13}C and ^{1}H NMR data recorded for synthetically-derived (–)-khusione [(–)-**32**] with those reported for the natural product

^{13}C NMR data (δ_C)		^{1}H NMR data (δ_H)	
synthetic (–)-**32**[a]	khusione [(–)-**32**][b]	synthetic (–)-**32**[c]	khusione [(–)-**32**][d]
218.9	218.8	2.16 (d, J = 18.0 Hz, 1H)	2.16 (d, J = 18.0 Hz, 1H)
54.3	54.2	2.08 (dd, J = 18.0 and 2.0 Hz, 1H)	2.08 (dd, J = 18.0 and 2.0 Hz, 1H)
50.2	50.2	2.05 (m, 1H)	2.05 (dddd, J = 13, 8, 8 and 1.5 Hz, 1 H)
46.9	46.9	1.76–1.57 (complex m, 4H)	1.70 (m, 2H), 1.63 (m, 2H)
44.1	44.1	1.56–1.46 (complex m, 1H)	1.52 (m, 2H)
39.2	39.1	1.38–1.24 (complex m, 3H)	1.32 (m, 2H)
34.5	34.5	1.14–1.04 (complex m, 1H)	1.08 (m, 1H)
34.0	34.0	0.93 (s, 3H)	0.93 (s, 3H)
29.4	29.4	0.88 (s, 3H)	0.88 (s, 3H)
28.7	28.7	0.83 (d, J = 7.2 Hz, 3H)	0.84 (d, J = 7 Hz, 3 H)
27.9	27.9	0.79 (s, 3H)	0.80 (s, 3H)
24.3	24.3		
19.9	19.8		
18.2	18.2		
14.0	14.0		



(–)-**32** (–)-**19** (67%) (–)-8-*epi*-**19** (5%)

Scheme 2.23. *Reagents and Conditions*: i. Li-NH_3, NH_4Cl, THF, –30 °C, 1 h

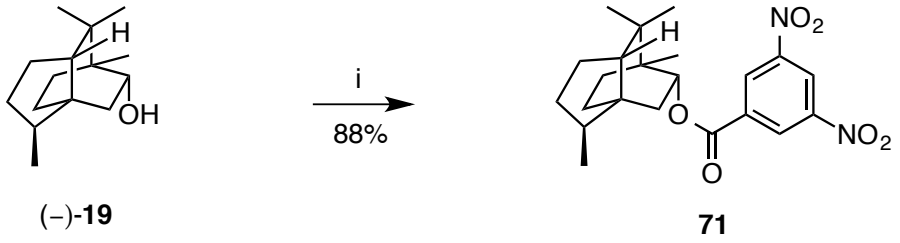
[a]Data recorded in $CDCl_3$ at 100 MHz.
[b]Data obtained from ref. 26 and recorded in $CDCl_3$ at 67 MHz.
[c]Data recorded in $CDCl_3$ at 400 MHz.
[d]Data obtained from ref. 26 and recorded in $CDCl_3$ at 270 MHz.

Table 3. Comparison of the ^{13}C and ^{1}H NMR data recorded for synthetically-derived (–)-khusiol [(–)-**19**] with those reported for its enantiomer (Allocedrol)

^{13}C NMR data (δ_C)		^{1}H NMR data (δ_H)	
synthetic (–)-**19**[a]	allocedrol [(+)-**19**][b]	synthetic (–)-**19**[c]	allocedrol [(+)-**19**][d]
71.0	71.0	3.97 (m, 1 H)	3.95 (m, 1 H)
53.1	53.1	2.08 (m, 1 H)	2.06 (m, 1 H)
41.3	41.4	1.95 (m, 1 H)	1.92 (m, 1 H)
40.7	40.7	1.60 (m, 1 H)	1.57 (m, 1 H)
40.0	40.0	1.47 (m, 1 H)	1.45 (m, 1 H)
39.8	39.8	1.39 (m, 1 H)	1.43 (m, 1 H)
			1.42 (m, 1 H)
			1.39 (m, 1 H)
35.0	35.0	1.28-1.20 (complex m, 3 H)	1.24 (m, 1 H)
			1.21 (m, 1 H)
34.5	34.5	1.14 (complex m, 3 H)	1.10 (m, 1 H)
31.0	31.0	1.07 (dd, J = 12.6 and 5.4 Hz, 1 H)	1.04 (m, 1 H)
26.3	26.3	0.98 (m, 1 H)	0.96 (m, 1 H)
24.3	24.2	0.90 (s, 3 H)	0.86 (s, 3 H)
24.2	24.2	0.86 (s, 3 H)	0.82 (s, 3 H)
21.0	21.0	0.81 (d, J = 7.2 Hz, 3 H)	0.78 (d, J = 7.2 Hz, 3 H)
17.7	17.6	0.76 (s, 3 H)	0.73 (s, 3 H)
16.2	16.1		

Final confirmation of the structure of the sample of (–)-khusiol [(–)-**19**] obtained as described above followed from a single-crystal X-ray analysis of the corresponding 3,5-dinitrobenzoate **71** (Appendix A.02) prepared by the treatment of alcohol (–)-**19** with 3,5-dinitrobenzoyl chloride under standard conditions (Scheme 2.24). Details of this analysis are presented in Appendix A.02.

[a]Data recorded in $CDCl_3$ at 100 MHz.
[b]Data obtained from ref. 24 and recorded in $CDCl_3$ at 100 MHz.
[c]Data recorded in $CDCl_3$ at 400 MHz.
[d]Data obtained from ref. 24 and recorded in $CDCl_3$ at 400 MHz.



(–)-**19** **71**

Scheme 2.24. *Reagents and Conditions*: i. BzCl, DMAP, Et_3N, DCM, 18 °C, 16 h (88%)

2.5 Summary

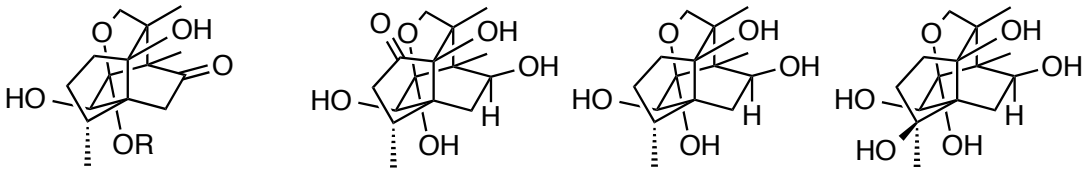
A chemoenymatic and 16 steps total synthesis of (–)-khusiol [(–)-**19**] from *p*-iodotoluene has been achieved. The only previous synthesis required 26 steps. The key steps associated with the work presented here were a type I intramolecular Diels-Alder cycloadditon reaction [which delivered the tricyclic framework associated with the khusiol and a stereoselective conjugate addition reaction that completed the installation of the key C3 methyl group. In addition, method for gaining access to intermediate **43** and its C3-epimer were established. The latter compound is a part of the core structure of tashironins class of natural products. Efforts to exploit such an intermediate in the synthesis of this fascinating class of biologically active compounds are described in Chapter 3.

Chapter 3: Towards the Total Synthesis of (–)-11-*O*-Debenzoyltashironin [(–)-17]

3.1 Introduction

3.1.1 Origins and Structures of Some Selected Tashironins

In 1995 Fukuyama *et al*. reported[46] the isolation of a natural product embodying the allocedrane carbon skeleton from the wood of *Illicium tashiroi* and named it tashironin (**72**). The structure of this compound was deduced through extensive analysis of the derived mass spectrometric and various spectroscopic data. Subsequently, Huang and his co-workers reported[15] the isolation of the debenzoylated derivative of tashironin, namely 11-*O*-debenzoyltashitonin (**17**), together with congener **72** from the pericarps of *Illicium merrillianum*. In the same year (*viz.* 2001) Schmidt *et al*.[47] described three new tashironin derivatives, debenzoyl-7-deoxo-7α-hydroxytashironin (**73**), debenzoyl-7-deoxo-1α,7α-dihydroxytashironin (**74**) and debenzoyl-7-deoxo-7α-hydroxy-3-oxotashironin (**75**), all of which were obtained from the fruits of *Illicium floridanum*. The molecular structure of compound **75**, including its absolute stereochemistry, was determined through a combination of NMR studies and single-crystal X-ray analysis of its monohydrated form. Compounds **73** and **74** were obtained as an inseparable mixture and their structures elucidated through careful analysis of the mass spectrometric and NMR spectroscopic data. Recently several other analogues of tashironin have been reported.[48] Significantly, all of the tashironin-type compounds identified so far are derived from *Illicium* species.



tashironin (**72**, R = Bz)
(–)-11-*O*-debenzoyltashironin
([(–)-**17**], R = H)

(**73**)

(**74**)

(**75**)

Figure 3.01. Some selected examples of tashironin-type compounds

3.1.2 Biological Activities of the Tashironins

Some members of the tashironin group of compounds display significant biological activities. In particular, compound **17** has been shown to induce neurite outgrowth in foetal rat cortical neurons at concentrations as low 0.1 mM[15] while compound **72** exhibits *anti*-hepatitis B virus (HVB) activity at submicromolar concentrations by inhibiting this viruses' surface antigen secretion.[48b] The biological properties of congeners **73**-**75** have not been reported.

The capacity of 11-*O*-debenzoyltashironin (**17**) to act as a neurotropic factor is of particular interest. Neurotropic factors are agents that can prevent neuronal death (neurotrophism) or promote axonal growth (neurotropism). As such, compound **17** offers potential as a lead compound for the development of new therapies for the treatment of neurodegenerative conditions such as Alzheimer's and Parkinson's diseases. Despite the very interesting biological properties of compound **17** only very limited structure activity relationship (SAR) profile studies have been conducted on it. This is undoubtedly because of the difficulty associated with accessing this compound in adequate quantities for such studies.

3.2 Previous Work on the Synthesis of Tashironins

3.2.1 Overview

To date, only one total synthesis and one formal total synthesis of the racemic modification, *viz.* (±)-**17**, of 11-*O*-debenzoyltashironin have been reported.[49] The first total synthesis was reported[49a] by Danishefsky and co-workers and the key step involved a Tamura-Pelter oxidation-transannular Diel-Alder cycloaddition cascade. Subsequently, the same group reported[50] an elegant approach to the (+) and (–) forms of a key tetracyclic intermediate associated with natural product. However, the elaboration of this intermediate into the natural product has not been reported to date.

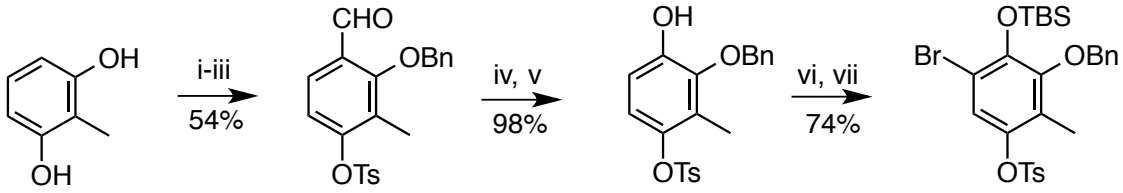
In 2011 Mehta *et al*. described[49b] a formal total synthesis of compound (±)-**17** with the key steps involving a tandem oxidative dearomatisation/intramolecular Diel-Alder/ring closing metathesis sequence. In addition, Mehta and coworkers have also reported[51] their ongoing work on the

synthesis of related natural products **73**, **74** and **75**. Details of both Danishefsky's and Mehta's work are presented in the following sections.

3.2.2 Total and Formal Total Syntheses of (±)-11-*O*-Debenzoyltashironin [(±)-17]

3.2.2.1 Danishefsky's Total Synthesis of (±)-11-O-Debenzoyltashironin [(±)-17]

As noted above, in 2006 Danishefsky and coworkers reported[49a] the first total synthesis of the racemic form, (±)-**17**, of 11-*O*-debenzoyltashironin. The opening stages of their synthesis commenced (Scheme 3.01) with the preparation of the aromatic bromide **79** from 2-methylresorcinol (**76**). Thus, formylation of of this starting material followed by phenol group tosylation and benzylation provided compound **77** that was subjected to Dakin oxidation. Hydrolysis of the resulting formate ester provided compound **78** in quantitative yield and NBS-mediated bromination and TBS protection of this gave the requisite aromatic bromide **79**.

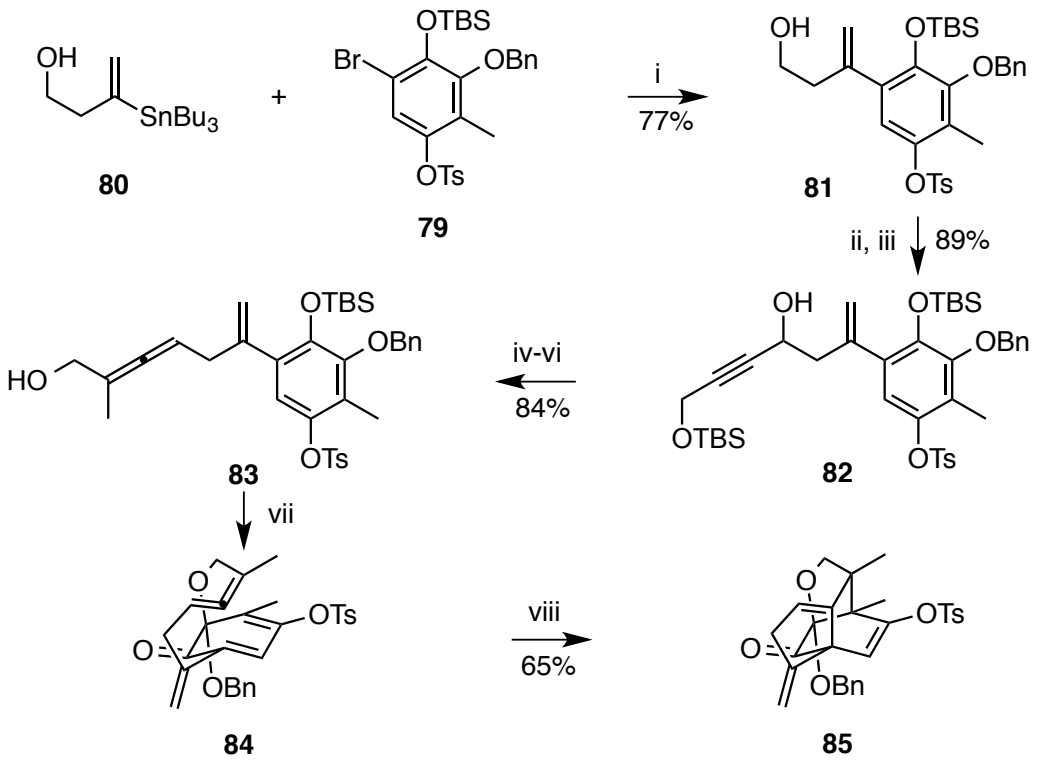


76 **77** **78** **79**

Scheme 3.01. *Reagents and Conditions*: i. $Zn(CN)_2$, HCl, Et_2O, rt, (> 99%); ii. TsCl, DCM, –10 °C, (57%); iii. BnBr, K_2CO_3, TBAI, acetone, reflux, (97%); iv. *m*-CPBA, DCM, rt, then; v. Et_3N, MeOH/DCM (1:1), rt, (98% over two steps); vi. NBS, DCM, 0 °C, (85%); vii. TBSCl, DCM, Et_3N (87%)

An allenic moiety that would be tethered to this bromide was then synthesized (Scheme 3.02). Thus, coupling of compound **79** with known vinyl stannane **80** gave compound **81** that was converted into the corresponding aldehyde using the Dess-Martin periodinane (DMP). Alkyne addition to this aldehyde then provided propargylic alcohol **82** that was mesylated then subjected to nucleophilic methylation using the higher-order Lipshutz dimethylcyanocuprate and so providing, *via* an S_N' reaction, an allene that upon deprotection gave compound **83** in 57% yield over the 6 steps involved. Treatment of allene **83** with phenyliodine diacetate (PIDA) resulted in the mixture of

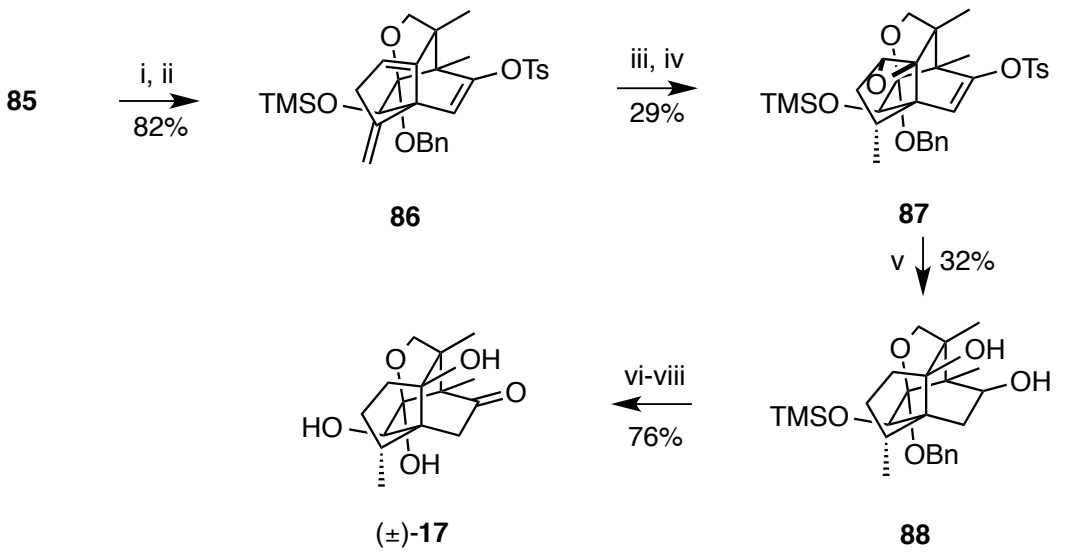
compounds **84** and **85** and subjection of this to microwave irradiation then provided the IMDA adduct **85** in 65% yield.



Scheme 3.02. *Reagents and Conditions*: i. $Pd_2(dba)_3$, *t*-BuP, DMF, 80 °C, (77%); ii. DMP, DCM, 0 °C, (98%); iii. 2-propargyloxyTBS, Et_2Zn, $Ti(O\textit{i}\text{-}Pr)_4$, rt, (91%); iv. MsCl, Et_3N, rt, then; v. $Me_2Cu(CN)Li_2$, THF, –78 °C (88% over 2 steps); vi. TBAF, AcOH, rt, (95%); vii. PIDA then viii. microwave (65%)

Adduct **85** could be converted into the racemic modification, *viz.* (±)-**17**, of the target natural product over a further eight steps (Scheme 3.03). So, $NaBH_4$-mediated reduction of compound **85** gave corresponding alcohol that was protected by treatment with neat trimethylsilylimidazole to furnish ether **86**. Careful epoxidation of compound **86** using *m*-CPBA in cold DCM and reduction of the exocyclic double bond within this mono-unsaturated epoxide using Wilkinson's catalyst provided dihydro-analogue **87**. Treatment of epoxide **87** with $LiEt_3BH$ (Superhydride™) resulted in, (a), reductive ring-opening of the epoxide and, (b), cleavage of enol tosylate thus revealing the corresponding 2°-alcohol and, by such means, compound **88** was obtained in 32% yield. Cleavage

of the ether residues within compound **88** under standard conditions then afforded (±)-**17** in 0.8% overall yield and 22 steps from 2-methylresorcinol (**76**).

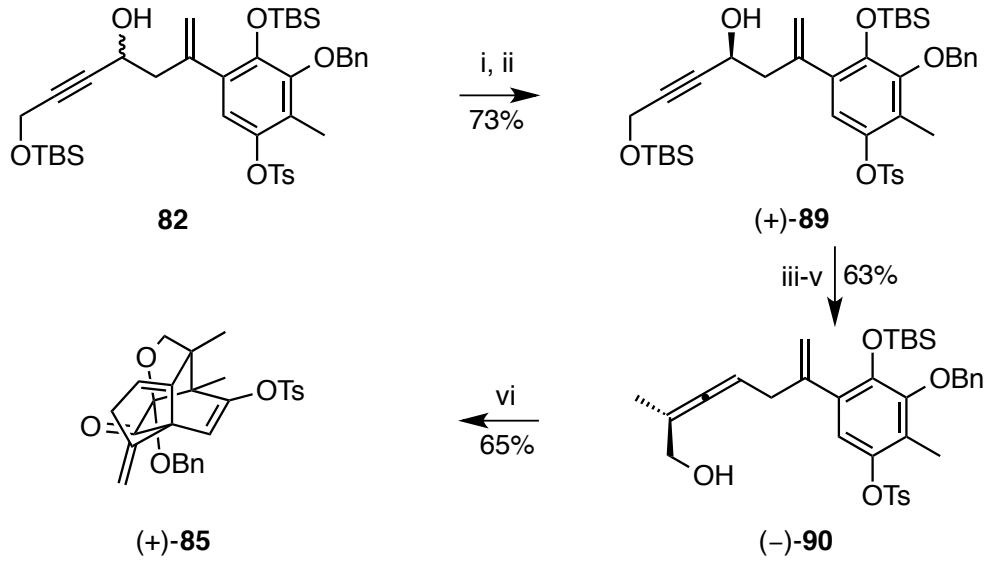


Scheme 3.03. *Reagents and Conditions*: i. $NaBH_4$, DCM/MeOH (3:1), –78 °C, (83%); ii. TMS-Imidazole, neat, rt, (>99%); iii. *m*-CPBA, DCM, 0 °C, (39% or 71% brsm); iv. $(PPh_3)_3RhCl$, H_2, PhH, 100 psi, (74%); v. $LiEt_3BH$, THF, 100 °C, (32%); vi. DMP, DCM, rt, (96%); vii. HF-Py, TBAF, THF, rt, (87%); then viii. H_2, Pd/C 10%, EtOAc, (91%)

3.2.2.2 Danishefsky's Formal Synthesis of (+)- and (–)- Forms of 11-O-Debenzoyltashironin (17)

After their successful synthesis of compound (±)-**17**, Danishefsky and his group reported[50] enantioselective syntheses of the (+) and (–) forms of the tetracyclic core **85** associated with natural product **17**. So, for example, the synthesis of enantiomer (+)-**85** commenced with the treatment of the propargylic alcohol **82** (Scheme 3.04) with Dess-Martin periodinane. The resulting propagylic ketone was then reduced in a stereoselective manner by using (*S*)-Alpine borane to give alcohol (+)-**89** in 73% chemical yield and 93% ee. Mesylation of compound (+)-**89** followed by a S_N' methylation reaction using the higher-order dimethylcyanocuprate and subsequent deprotection provided allene (–)-**90** in 63% over 3 steps (93% ee). Treatment of compound (–)-**90** with PIDA and subsequent heating provided Diels-Alder adduct (+)-**85** in 65% yield and 93% ee. Using the

same sequence but employing (*R*)-alpine borane provided access to alcohol (–)-**89** and, the tetracyclic core (–)-**85** of the natural product was thereby secured.

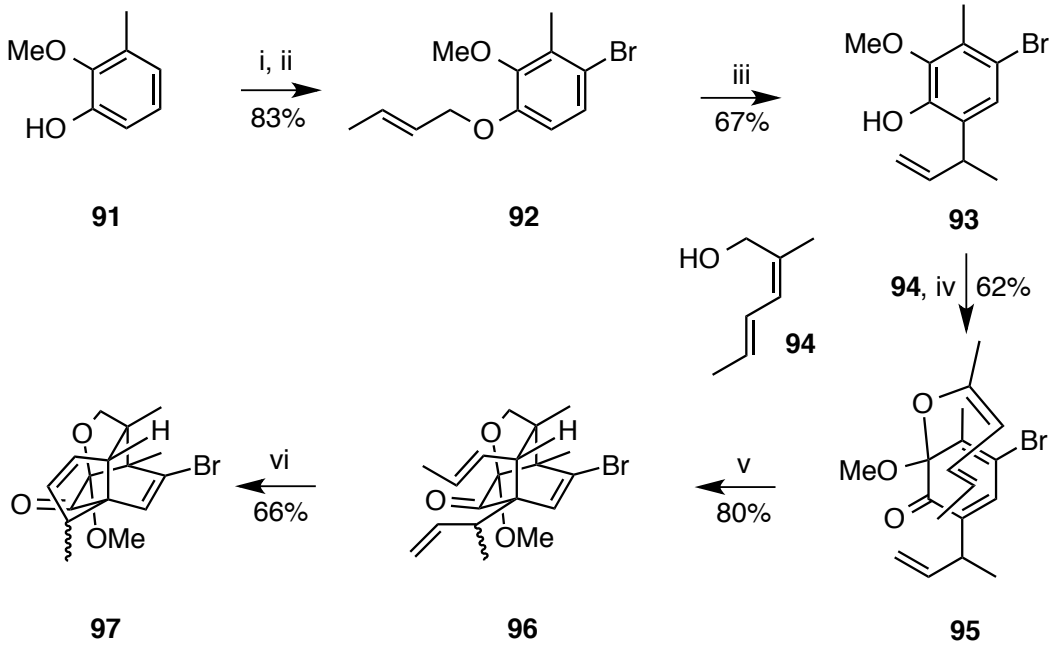


Scheme 3.04. *Reagents and Conditions*: i. DMP, DCM; ii. (*S*)-Alpine borane, –78 °C, 6 h, rt, 120 h, (73% over 2 steps, 93% ee); iii. MsCl, Et_3N, DCM then; iv. $Me_2Cu(CN)Li_2$, –78 °C, THF, (78% over 2 steps); v. TBAF, AcOH, rt, (81%, 93% ee); vi. PIDA then microwave (65%)

3.2.2.3 Mehta's Formal Synthesis of (±)-11-O-Debenzoyltashironin

In 2011 Mehta reported[49b] a short, formal total synthesis of (±)-11-*O*-debenzoyltashironin [(±)-**17**)]. The key "event" in Mehta's sequence (Scheme 3.05) was a tandem oxidative dearomatisation-intramolecular Diels-Alder (IMDA) reaction-ring closing metathesis (RCM) cascade and by which means the tetracyclic core, **97**, associated with the natural product **17** was assembled. Specifically, then, the synthesis of compound **97** started with the preparation of the pentasubstituted aromatic precursor **95**. So, the known phenol **91** was treated with pyridinium tribromide ($PyHBr_3$) to furnish the *p*-bromo-derivative that was itself converted into compound **92** on treatment with crotyl bromide in the presence of potassium carbonate (K_2CO_3). Claisen rearrangement of ether **92** then delivered the pentasubstituted aromatic **93**. Oxidative dearomatisation of this phenol using PIDA in the presence of (2*Z*,4*E*)-2-methyl-2,4-hexadien-1-ol (**94**) resulted in formation of *o*-benzoquinone-based pentaene **96** that when heated in refluxing toluene gave tricyclic [4+2]-cycloadduct **96**. The

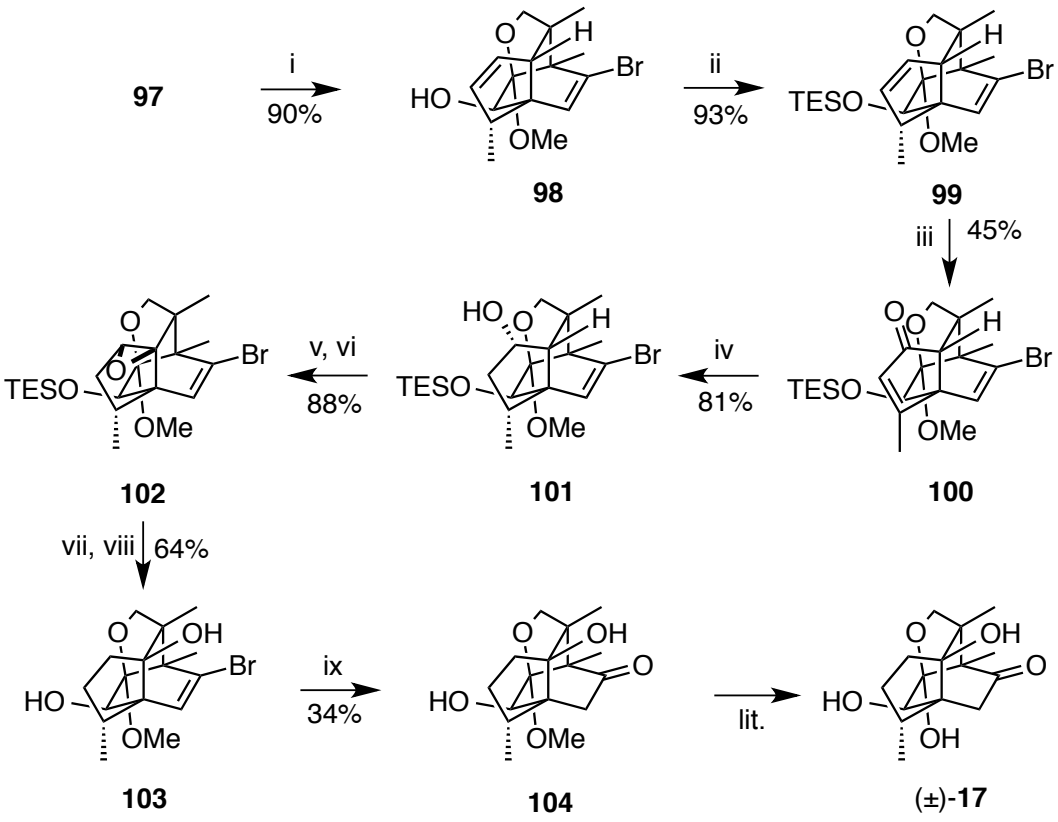
final ring was constructed by subjecting compound **96** to the Hoveyda-Grubbs' second-generation catalyst and the tetracyclic core compound **97** was thus obtained as a 1:1 mixture of diastereoisomers in 66% combined yield.



Scheme 3.05. *Reagents and Conditions*: i. $PyHBr_3$, DCM, 0 °C, 2 h, (90%); ii. K_2CO_3, crotyl bromide, acetone, reflux, 6 h, (92%); iii. $PhNEt_2$, 180 °C, 1 h, (67%); iv. PIDA, THF, rt, 5 h, (62%); v. toluene, BHT, reflux, 20 h, (80%); vi. Hoveyda-Grubbs' catalyst-II (15 mol %), toluene, reflux, 48 h, 66% or 87% brsm

The tetracyclic system **97** could be elaborated to the methyl derivative **104** of the natural product **17** over a further 9 steps as shown in Scheme 3.06. Thus, treatment of compound **97** (as a mixture of diastereoisomers) with sodium borohydride ($NaBH_4$) gave a 1: 1 and chromatographically separable mixture of alcohol **98** and its C3-epimer. Treatment of compound **98** with TESOTf provided ether **99**, allylic oxidation of which gave α,β-unsaturated enone **100** in 45% yield. Reduction of compound **100** with Superhydride™ ($LiEt_3BH$) then provided, diastereoselectively, alcohol **101** that upon treatment with thionyl chloride-pyridine and then *m*-CPBA gave epoxide **102**. Exposure of this last compound to aqueous HF gave the corresponding alcohol that, when treated with DIBAL-H, resulted in an opening of the epoxide ring to deliver compound **103**. The latent carbonyl moiety embodied within alkenyl bromide **103** was revealed through halogen-metal exchange [by treating

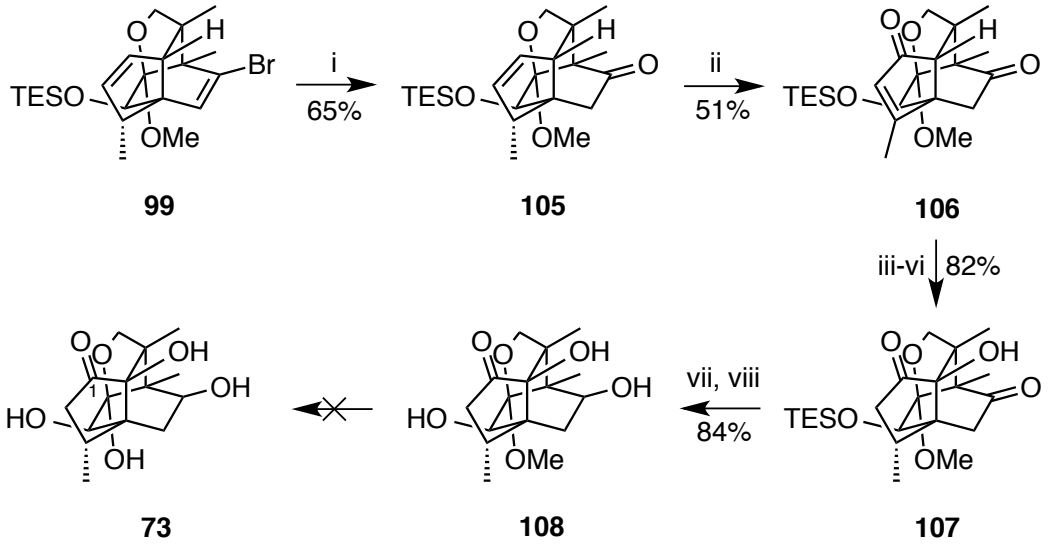
the substrate with excess *t*-butyllithium in tetramethylethylenediamine (TMEDA] followed by a quenching of the ensuing alkenyl lithium with $B(O\textit{i}\text{-}Pr)_3$ then alkaline hydrogen peroxide. Compound **104** thus obtained is the methyl ether of the natural product **17** and had been secured over a 15 step reaction sequence. Conversion of compound **104** into racemic form of the natural product **17** had been reported earlier by Danishefsky and co-workers.[52]



Scheme 3.06. *Reagents and Conditions*: i. $NaBH_4$, DCM/MeOH (2:1), 0 °C, 2 h, (90%); ii. TESOTf, Et_3N, DCM, 0 °C, 2 h, (93%); iii. PDC, 70% aq. TBHP, celite, PhH, rt, 5 h, (45%); iv. $LiEt_3BH$, THF, 0 °C, 2 h, (81%); v. $SOCl_2$, Py, 0 °C, 0.5 h, (91%); vi. *m*-CPBA, DCM, 0 °C, 1.5 h, (97%); vii. 40% aq. HF, THF, rt, 6 h, (73%); viii. DIBAL-H, DCM, 0 °C, 1.5 h, (87%); ix. *t*-BuLi, TMEDA, $B(O\textit{i}\text{-}Pr)_3$, THF, –78 °C, 2 h, then NaOH, H_2O_2, (34%)

3.2.2.4 Mehta's Work on the Synthesis of Natural Products 73 and 74

In 2011 Mehta and co-workers[51a] reported work directed towards the synthesis of natural products **73** and **74** using similar chemistry to that detailed above. The synthesis of compound **73** commenced with the advanced tetracyclic intermediate **99** obtained earlier. Thus, treatment of this material with *t*-BuLi in TMEDA then B(O*i*-Pr)$_3$ and H_2O_2 gave ketone **105** in 43% yield (Scheme 3.07). Allylic oxidation of compound **105** using PDC/TBHP in benzene then provided enone **106** reduction of which, using H_2 in the presence of 10% Pd/C, followed by a Rubottom oxidation (to install the tertiary hydroxyl group) gave compound **107** as a single diastereoisomer in 96% yield over the 2 steps involved. Regio- and stereo-selective reduction of diketone **107** using $NaBH_4$ at low temperature followed by the removal of TES protecting group (using aqueous HF in acetonitrile) gave compound **108** in 80% yield (over 2 steps). Sadly, the final step, requiring the removal of the *O*-methyl group of ketal **108**, failed despite the many and varied attempts to effect this conversion.



Scheme 3.07. *Reagents and Conditions*: i. *t*-BuLi, TMEDA, B(O*i*-Pr)$_3$, THF, −78 °C, 2 h, then NaOH, H_2O_2, (65%); ii. PDC, 70% aq. TBHP, celite, PhH, rt, 5 h, (51%); iii. 10% Pd/C, H_2, EtOAc, rt, 3 h, (85%); iv. TESOTf, Et_3N, Et_2O, rt, 2 h: v. *m*-CPBA, DCM, −100 °C, 1.5 h ; vi. TBAF, DCM, rt, 2 h (96% over 2 steps); vii. $NaBH_4$, MeOH, −100 °C, 6 h, (92%); viii. 40% aq. HF, MeCN, rt, 6 h, (91%)

In a related study directed towards the synthesis of natural products **74** and **75**, Mehta and co-workers faced the same challenge and were, once again, unable to meet this.[51b] Nonetheless, Mehta's work provided very useful chemical "intelligence" that will undoubtedly of great value in other studies.

It is against this background, together with the thus far limited information on the SAR profile of the tashironins, that the studies described below and directed towards the total synthesis of these natural products were undertaken. It is also worth noting that the total syntheses of enantiomeric forms of the natural products **17** and **73** have never been reported. The studies reported below should serve to redress such deficiencies.

4.3 Retrosynthetic Analysis and Strategy

Informed by both the earlier endeavours directed towards the synthesis of tashironins and the in-house chemistry described in Chapter 2, a synthetic approach to the tashironin class of natural products was devised. Specifically, it was envisaged that the natural product **17** could be obtained from congener **73** through straightforward functional group manipulations while the latter could be derived from intermediate **109** through functional group interconversions and by using DMDO mediated[53] C-H oxidation chemistry[*] to introduce the key hemiacetal functionality. Intermediate **109**, could, in turn, be accessible from its deoxy-analogue **110** through a series of interconversions including a Rubottom oxidation.[55] Compound **110** itself was expected to be accessible from congener **111**. Thus, it was envisaged that the formation of tetrahydrofuran ring of **110** could be accomplished through Barton-type remote oxidation chemistry.[56] Substrate **111** was thought to be accessible from the IMDA adduct **43** through functional group interconversions including a *syn*-dihydroxylation reaction involving the double bond formed during the cycloaddition process. It was anticipated that the dihydroxylation process would occur from the β-face of the double bond due to the steric hindrance imposed by the acetonide group at the α-face of the same double bond. The synthesis of compound **43** has been described in Chapter 2.

[*]The field of C-H oxidation in organic synthesis has a history dating back to the very origin of organic synthesis but for the past decade the field has seen an immense resurgence. Interested readers are directed to reviews of this topic provided in ref. 53.

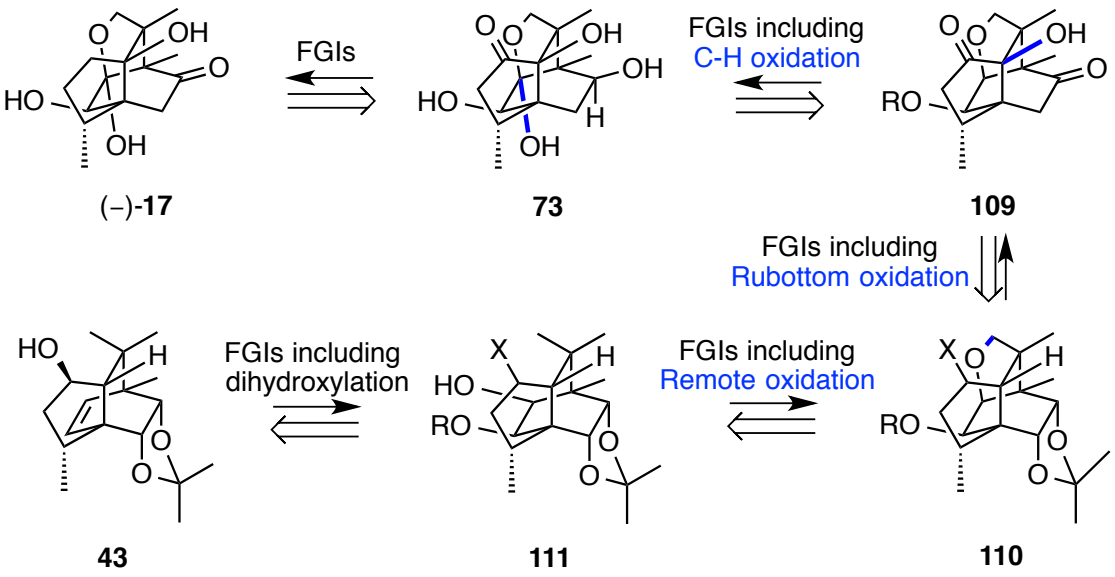
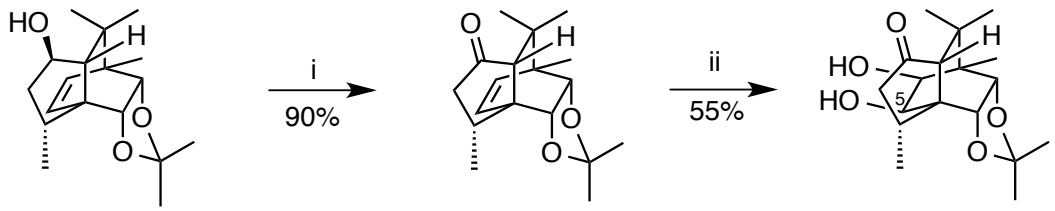


Figure 3.02 Retrosynthetic analysis of (–)-11-*O*-Debenzoyltashironin [(–)-**17**]

3.4 Studies Directed Towards the Synthesis of (–)-11-*O*-Debenzoyltashironin [(–)-17]

3.4.1 Synthesis of a General Precursor of the Type 111 *via* Remote Oxidation

The first phase of the projected synthesis of target **17** involved construction of a tetracyclic core of the general form **110**. To such ends intermediate **111** was required and so the oxidation of compound **43**[57] to ketone **59**[57] was pursued and obtained in 90% yield using PDC/AcOH (Scheme 3.08).



43 **59** **112**

Scheme 3.08. *Reagents and Conditions*: i. DMP, DCM, 18 °C, 1 h, (90%); ii. OsO_4, NMO, citric acid, CH_3CN/H_2O (3:1), 18 °C, 72 h (55% or 78% brsm)

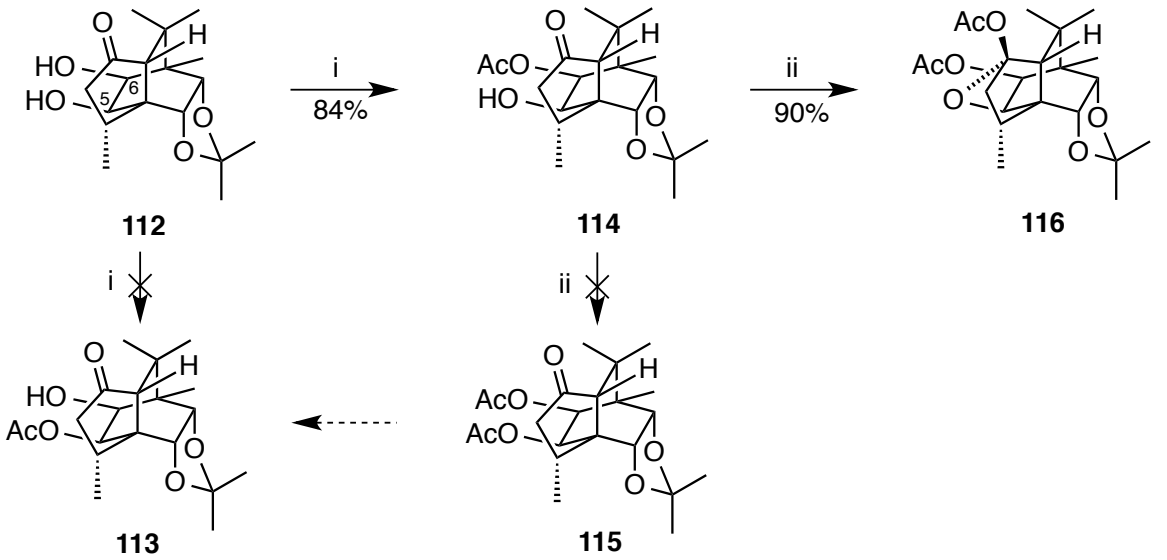
With ketone **59** in hand, the next step in the synthesis required dihydroxylation of the associated but hindered alkene. This became one of the most challenging steps of the synthesis. Osmium tetraoxide (OsO_4)-mediated *syn*-dihydroxylation such as those involved in the Sharpless asymmetric[58] and Upjohn[59] protocols failed to deliver the desired diol **112**. Accordingly, other osmium-free methods such as those involving copper (II),[60] diphenyldiselenide,[61] potassium permanganate,[62] palladium(II)[63] and ruthenium tetraoxide (RuO_4)[64]-catalysed dihydroxylations were investigated. However, in each case (except that involving RuO_4) the starting material **59** was always recovered in over 90% yield. In that instance where alkene **59** was treated with RuO_4, a complex mixture of chromatographically inseparable compounds was formed. This reaction was rapid (< 10 min) and difficult to control even when catalytic amounts of RuO_4 were used. Analysis of the crude reaction mixture by NMR spectroscopic techniques indicated over-oxidation/oxidative cleavage of the initially formed diol since a characteristic aldehyde resonance was observed (*ca.* δ 9.5) in the ^{1}H NMR spectrum. During their studies of alkene dihydroxylation using RuO_4, Piccialli *et al.*[64b] also observed over-oxidised side products in the form of hydroxyketones. Other methods, such as Woodward[65] and modified Prevost-Woodward[66] protocols that have previously been used for alkene dihydroxylation were also examined but to no avail. Since the direct dihydroxylaton of alkene **59** proved impossible, epoxidation and subsequent ring opening steps were investigated. However, when alkene **59** was treated with *m*-CPBA no reaction took place. Eventually, and after carefully scouring of the literature on alkene dihydroxylations, a paper by Sharpless[58b] was found that defined effective conditions for achieving the desired transformation. Thus, using the "citric acid modified" Upjohn protocol compound **59** was converted to diol **112** in 55% yield or 70% brsm (Scheme 3.08). The structure of diol **112** was established through mass spectrometric and various spectroscopic studies. Notably, the IR spectrum of compound **113** exhibited strong O-H and C=O

stretching bands at 3437 and 1734 cm^{-1}, respectively. Furthermore, the EI mass spectrum displayed a molecular ion at *m/z* 324 while the ^{1}H NMR spectrum exhibited four distinct oxymethine proton resonances at δ 4.33 (dd, *J* = 8 and 2 Hz), 4.12 (d, *J* = 8 Hz), 4.01 (d, *J* = 8 Hz) and 3.97 (d, *J* = 8 Hz). The ^{13}C NMR spectrum displayed eighteen carbon resonances including one at δ 214.2 (due to the cyclopentanone carbonyl) and four at δ 82.8, 78.8, 68.5, and 65.4 corresponding to the oxymethine carbons. The two hydroxyl groups were tentatively assigned as being *β*-oriented on the basis that the acetonide group of the precursor alkene **59** would inhibit OsO_4 from attacking at the α-face of the π-system.

With diol **112** in hand, the next step required the formation of a mono-protected alcohol of the general form **111**, through selective protection of the C5 hydroxyl group within the former compound. In order to achieve this, the relative reactivities of the two hydroxyl groups were investigated. In anticipation of forming a mono-protected derivative **113**, diol **112** was subjected to acetylation using acetic anhydride in pyridine (Ac_2O/Py) and, indeed, a single mono-acetylated product was obtained in 84% yield. However, careful analysis of the mass spectrometric and various spectroscopic data arising from this product revealed it to be the undesired regioisomer **114** (Scheme 3.09). The IR spectrum of compound **114** exhibited strong O-H and C=O stretching bands at 3468 and 1734 cm^{-1}, respectively while the EI mass spectrum displayed a molecular ion at *m/z* 366. The ^{1}H NMR spectrum exhibited a three-proton singlet at δ 2.09 ppm and thus indicating the presence of an acetate group. The ^{13}C NMR displayed the expected 20 distinct carbon resonances including one at δ 171.1 that is assigned to the acetate carbonyl residue.

Eager to obtain precursor of the general-type **111**, it was envisaged that exhaustive acetylation of compound **114** should provide compound **115** that upon kinetically controlled deacetylation could give access to mono-acetylated compound **113** (*c.f.* **111**; Scheme 3.09). Accordingly, diol **114** was treated with excess acetyl chloride in DCM. Unfortunately, no *bis*-acetylated product was formed under these conditions. However, treatment of compound **114** with neat acetyl chloride and in the presence of catalytic Zn dust[67] did provided a *bis*-acetylated product in 90% yield. However, upon careful analysis of the mass spectrometric and various spectroscopic data, the product was identified as the undesired diester **116**. The IR spectrum of this material exhibited a C=O stretching band 1742 cm^{-1} while the EI mass spectrum displayed a weak (4%) molecular ion *m/z* 408. The ^{1}H NMR spectrum exhibited two, three-proton singlets at δ 2.10 and 2.07 corresponding to two acetate

groups. Significantly, the ^{13}C NMR spectrum lacked a cyclopentanone carbonyl resonance at *ca.* δ 210 while 22 resonances were evident at higher fields. These included two ester carbonyl signals at δ 170.6 and 168.7 and two acetal carbon resonances at δ 110.8 and 108.6. Such data suggest an internal (cyclic) acetal had been formed during the course of the acetylation reaction. Final confirmation of the structure of compound **116** followed from a single-crystal X-ray analysis of it (Appendix A.03).



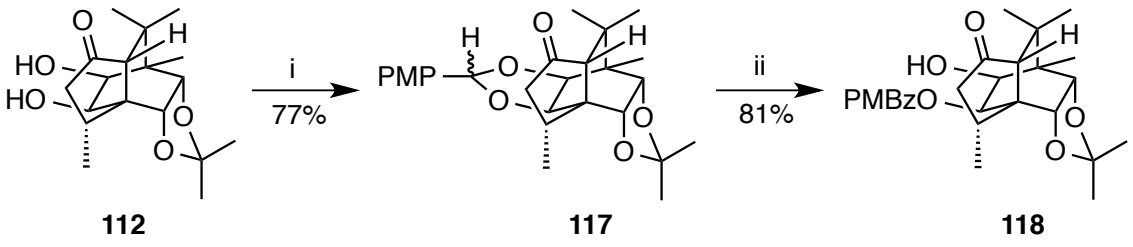
Scheme 3.09. *Reagents and Conditions*: i. Ac_2O, Py, 18 °C, 2 h (84%); ii. AcCl, DCM, Zn dust,18 °C, 4 h (90%)

While the work described immediately above did not deliver the desired compound **113**, it had nevertheless provided valuable insights into the reactivity of the two-hydroxyl groups. It was found that the hydroxyl group on C6 was the more reactive presumably because it is in a less hindered environment than its C5 counterpart. The close proximity of the C5 hydroxyl group and cyclopentanone carbonyl unit is also notable.

With the reactivity of the both hydroxyl groups within compound **112** now a little clearer, it was envisaged that synthesis of a cyclic acetal derivative followed by oxidative opening of it, should deliver the desired compound of the generic type **111**. In particular, it was anticipated that the

opening of a cyclic acetal derivative would proceed from the less hindered C6 position. Oxidative openings of cyclic acetals to selectively form mono-ester derivatives of *cis*-*vic*-diols have been reported[68] by Banwell and coworkers in similar systems. Accordingly, diol **112** was subjected to an acetalisation reaction using *p*-methoxybenzaldehyde dimethyl acetal (*p*-MBDMA) in the presence of catalytic amounts of *p*-toluenesulfonic acid monohydrate (*p*-TsOH).[68] By such means the *p*-methoxybenzylidene acetal **117** was obtained, as a single diastereoisomer of undefined configuration in 77% yield (Scheme 3.10). The structure of compound **117** was, once again, determined through mass spectrometric and various spectral studies. The IR spectrum of acetal **117** exhibited a strong C=O stretching band 1738 cm^{-1} while the EI mass spectrum displayed molecular ion at *m/z* 442. The ^{1}H NMR spectrum exhibited a characteristic acetal proton singlet at δ 5.60 and the ^{13}C NMR spectrum displayed the expected twentyfour signals. Resonances due to dioxygenated sp^3-hybridised carbons were observed at δ 102.2 and 109.0.

Treatment of compound **117** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in wet dichloromethane resulted in regioselective oxidative cleavage of the cyclic acetal moiety and so affording the desired diol mono-ester **118** in 81% yield (Scheme 3.10). Once again, the structure of this product was initially determined through mass spectrometric and various spectroscopic analyses. Thus, the IR spectrum of compound **118** exhibited O-H and C=O stretching bands at 3484 and 1738 cm^{-1}, respectively while the EI mass spectrum displayed a weak (3%) molecular ion at *m/z* 458. The ^{1}H NMR spectrum displayed a diagnostic doublet at δ 5.68 (J = 8.4 Hz) that is assigned to the oxymethine proton bearing the -PMBz group. However, final confirmation of the structure of compound **118** followed from a single-crystal X-ray analysis (Appendix A.04).

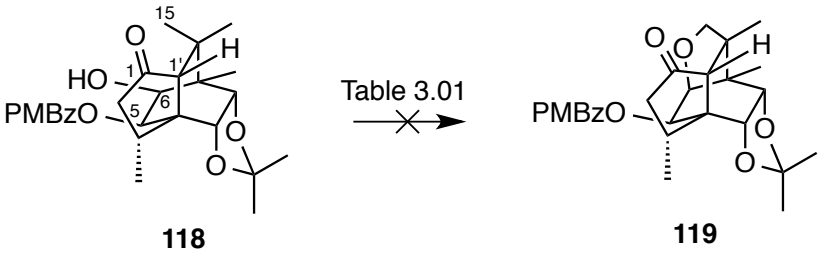


112 **117** **118**

Scheme 3.10. *Reagents and Conditions*: i. *p*-MBDMA, *p*-TsOH, THF, 18 °C, 12 h (77%); ii. DDQ, DCM, 18 °C, 4 h (81%)

3.4.2 Synthesis of the Tetrahydrofuran Ring

With the successful acquisition of compound **118**, the key and remote oxidation step required for the formation of tetrahydrofuran ring of the target natural product could now be investigated (Scheme 3.11). It was envisaged that this critical heterocyclic ring could be formed through a radical coupling initiated by intramolecular hydrogen abstraction from the C15 methyl group by an alkoxy radical[φ] intermediate[56e] that could itself be formed either by thermolysis or photolysis of the alkyl lead triacetate[69] generated by reaction of compound **118** with lead tetra-acetate or from the derived alkyl hypoiodites.[70] To such ends, substrate **118** was subjected to various conditions that it was thought might result in the desired transformation (Table 4.01).



118 **119**

Scheme 3.11. *Reagents and Conditions*: see Table 3.01

Table 4.01 Conditions used in the attempted remote oxidation of compound **118**

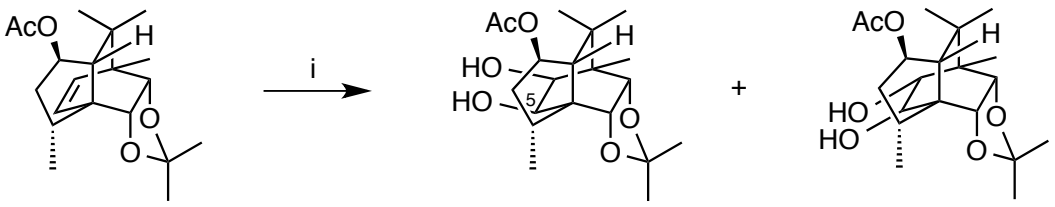
Entry	Conditions	Product **119**
1	LTA, benzene, 80 °C, 12 h	Not observed
2	PIDA, I_2, DCM, hν, 12 h	Not observed
3	LTA, I_2, cyclohexane, hν, 12 h	Not observed
4	PIDA, I_2, DCM,))))), 20-40 °C, 2 h	Not observed
5	LTA, I_2, $CaCO_3$, DCM,))))), 20-40 °C, 4 h	Not observed

[φ]Alkoxy radicals have found wide application in organic synthesis, especially in the fuctionalisation of unreactive/remote C-H bonds. Several ways to generate these radicals as well as their reactivities and applications in synthesis are the subject of various reviews and interested readers should consult ref. 56.

Unfortunately, none of these furnished the target tetrahydrofuran **119**. Rather, either migration of the PMBz group or slow decomposition of starting material was observed under most conditions. The reason for the lack of participation of substrate **118** in the remote oxidation process is not entirely clear although, based on the studies detailed below, it was suspected that the C1 ketone moiety could be hindering the remote oxidation process. Presumably, the PMBz group migrates from C5 to C6 with the free hydroxyl group on C5 then attacking the C1 ketone to form a lactol. On this basis it was decided that this functionality should be introduced further along the synthetic pathway. Such an approach would also remove any potential for epimerization at C1′ (see structure **118**).

3.4.3 Alternative Approach to the Tetracyclic Core of the General Form 110

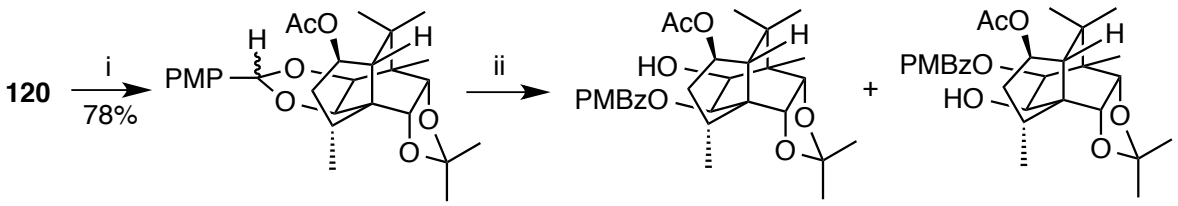
On the basis of the analysis just provided, it was envisaged that compound **120** would be an appropriate substrate for the remote oxidation step. As such, its synthesis was pursued using a reaction pathway similar to that described in Section 4.4.1. So, starting with compound **44**[57] (Scheme 3.12) and subjecting it to the dihydroxylation conditions mentioned earlier provided the desired diol **120** and its diastereoisomer **121** in 55% (79% brsm) and 5% yields, respectively. The structure of compounds **120** and **121** were determined through mass spectrometric and various spectroscopic studies. The IR spectrum of the major product **120** exhibited an O-H stretching band at 3456 cm^{-1}, as well as C=O stretching bands at 1729 and 1713 cm^{-1}. The presence of two-carbonyl bands is interesting as only one carbonyl group is present in compound **120**, and its origin could be attributed to intermolecular hydrogen bonding between the C5 hydroxyl and ketone group in the acetate moiety. The EI mass spectrum displayed a fragment ion at *m/z* 353, 15 mass units lower than the molecular mass (368). This is most likely due to the facile loss of a methyl radical from the acetonide moiety.



44 **120** (55%) **121** (4%)

Scheme 4.12. *Reagents and Conditions*: i. OsO_4, NMO, citric acid, CH_3CN/H_2O (3:1), 18 °C, 72 h

With diol **120** in hand, the next step involved selective protection of C5 hydroxyl group. To such ends and using the already optimized conditions mentioned earlier, substrate **120** was treated with *p*-MBDMA/*p*-TsOH and in this manner *p*-methoxybenzylidene **122** was obtained in 83% yield (Scheme 3.13). Oxidative cleavage of the acetyl moiety associated with compound **122** using DDQ then furnished alcohol **123** and its regioisomer **124** in 85% and 5% yields, respectively. The structures of these products were established through mass spectrometric and various spectroscopic studies. The IR spectrum of the major product, **123**, exhibited O-H and C=O stretching bands at 3514 and 1712 cm^{-1}, respectively while the EI mass spectrum displayed a fragment ion at *m/z* 487, 15 mass units lower than the molecular mass (502).

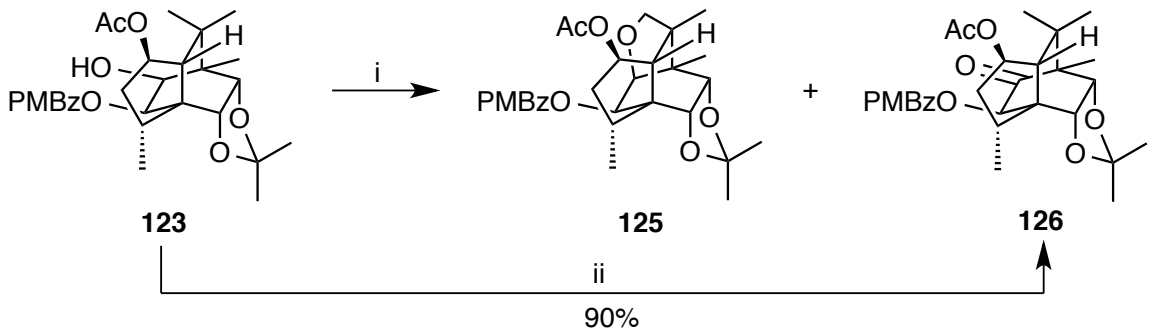


122 **123** (85%) **124** (5%)

Scheme 3.13. *Reagents and Conditions*: i. *p*-MBDMA, *p*-TsOH, THF, 18 °C, 12 h (78%); ii. DDQ, DCM, 18 °C, 4 h

With compound **123** to hand, the remote oxidation step was re-investigated and the results of relevant studies are summarised in Table 3.02. Thus, under photolytic conditions a mixture of compound **123**, PIDA or LTA and I_2 in DCM failed to give the desired compound **125** (entry 1 and 2). Thermolysis of a mixture of **123** and LTA in benzene (entry 3) also failed to generate the desired

compound **126**. However, and very gratifyingly, when a mixture of substrate **123**, PIDA or LTA and I_2 in DCM was subjected to ultrasonic irradiation then a 1:1 but inseparable mixture of the desired product **125** and by-product **126** was obtained in 80% yield (entry 4 and 5). Notably, the reaction did not proceed in the absence of iodine thus suggesting the involvement of hypoiodite type intermediate. The structure of compound **125** was determined through careful analysis of the relevant spectral data. Efforts to purify compound **125** through $NaBH_4$-mediated reduction of co-produced **126** to the corresponding alcohol failed. However, Dess-Martin periodinane (DMP)-mediated oxidation of compound **123** provided an authentic sample of ketone **126** (Scheme 3.14) and so allowing the unequivocal identification of the resonances due to this compound within the inseparable mixture.



Scheme 3.14. *Reagents and Conditions*: i. See Table 4.02; ii. DMP, DCM, 18 °C, 2 h (90%)

Table 3.02 Conditions used in efforts to effect the remote oxidation of compound **123**

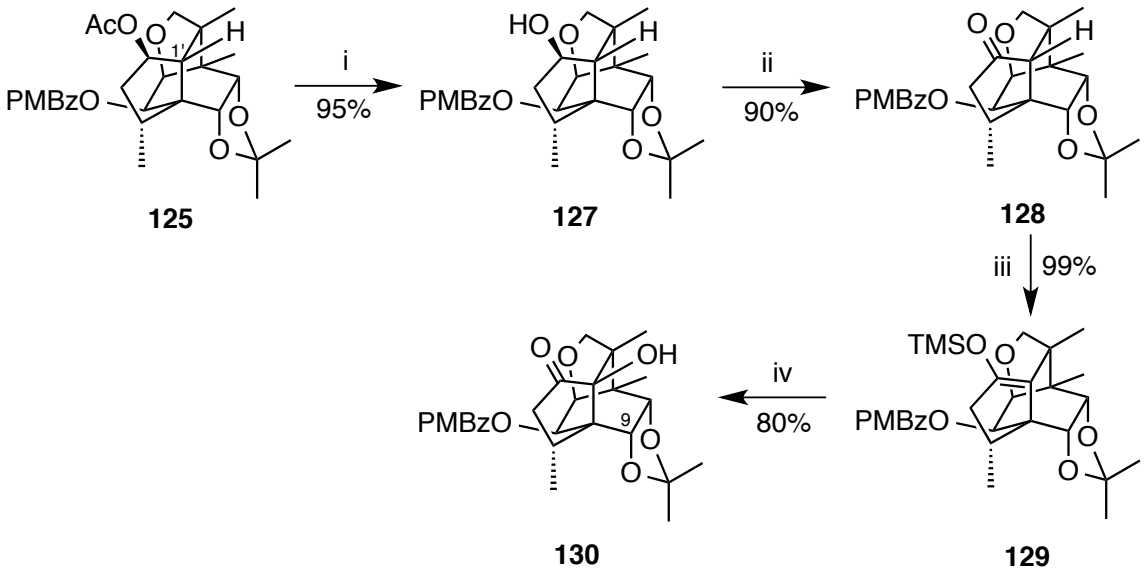
Entry	Conditions	Product Ratio **125** : **126**	% Yield
1	PIDA, I_2, DCM, hν, 12 h	0:0	-
2	LTA, I_2, DCM, hν, 12 h	0:0	-
3	LTA, benzene, 80 °C, 12 h	0:0	-
4	PIDA, I_2, DCM,))))), 20-40 °C, 1 h	1:1	> 80
5	LTA, I_2, $CaCO_3$, DCM,))))), 20-40 °C, 2 h	1:1	> 80
6	PIDA, I_2, DCM,))))), 0-5 °C, 2 h	2:1	> 80
7	LTA, I_2, $CaCO_3$, DCM,))))), 0-5 °C, 4 h	1:0	90

Final confirmation of the structure of compound **125** followed from a single-crystal X-ray analysis (Appendix A.05) after it have been obtained in the pure form by optimization of the reaction conditions (entry 7). The IR spectrum of compound **125** showed a C=O stretching band 1714 cm^{-1} while the EI mass spectrum displayed a weak (4% of the base peak) molecular ion at *m/z* 500. The ^1H NMR spectrum exhibited characteristic, diastereotopic oxymethylene proton doublets at δ 3.55 (*J* = 9.3 Hz) and 3.89. The latter doublet is partly obscured by the signal due to OCH_3 group protons. The appearance of the oxymethylene carbon signal at δ 77.2 and the disappearance of one of the methyl singlets associated with the spectrum of precursor **123** confirmed that a successful remote oxidation of a methyl group had taken place.

3.4.3 Synthesis of An Advanced Precursor of the General Form 109

3.4.3.1 Rubottom Oxidation

With the acquisition of the tetracyclic core of the tashironins (as embodied within compound **125**) now realised, the next phase of present study was focused on installation of a tertiary hydroxyl group at C1′. It was envisaged that that this could be accomplished by applying the Rubottom oxidation[55a] protocol. To obtain the relevant substrate, acetate **125** was treated (Scheme 3.15) with potassium carbonate (K_2CO_3) in wet MeOH and alcohol **127** was thereby obtained in 95% yield. The IR spectrum of product **127** exhibited O-H and C=O stretching bands at 3444 and 1710 cm^{-1}, respectively, while the EI mass spectrum displayed a prominent fragment ion at *m/z* 443 and arising from the loss of a methyl radical from the molecular ion. Oxidation of compound **127** using DMP then furnished the required ketone **128** in 90% yield.



Scheme 3.15. *Reagents and Conditions*: i. K_2CO_3, MeOH, 18 °C, 12 h (95%); ii. DMP, DCM, 18 °C, 4 h (90%); iii. TMSOTf, Et_3N, Et_2O, 18 °C, 32 h, iv. *m*-CPBA, DCM, –30 to 18 °C, 2 h (80% over 2 steps)

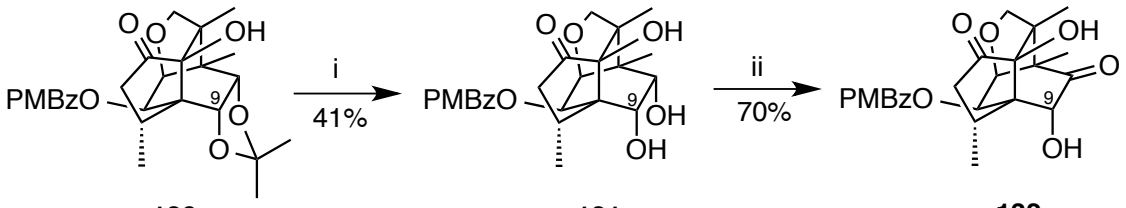
With compound **128** in hand, the installation of tertiary hydroxyl group could now be explored and when this substrate was treated with TMSOTf/Et_3N[51a,71] in dry diethyl ether (Et_2O) then the thermodynamically favoured silyl enol ether[φ] **129** was obtained. Without further purification, this was subjected to reaction with *m*-CPBA and so affording the desired Rubottom oxidation product, namely acyloin **130**, in 88% yield. The structure of compound **130** follows from various spectroscopic studies with the stereochemistry of the newly installed hydroxyl group assigned as shown based on the outcome of closely related work reported by Mehta.[51a]

3.4.3.2 Selective Deoxygenation at C9

With the successful installation of the tertiary hydroxyl group at C1′ the next phase in the synthesis focused on deoxygenation at C9. It was envisaged that acid hydrolysis of the acetonide group followed by Bobbitt-type oxidation[44b, 57] and subsequent SmI_2 mediated reduction[45] of the benzoyl

[φ]The structure of the silyl enol ether was determined by ^{1}H NMR, spectroscopic analysis and it proved to be uncontaminated by its regioisomer.

protected α-hydroxyketone should deliver a ketone of the general form **109**. Furthermore, it was anticipated that benzoyl-protection of hydroxyl groups should take place selectively at the less hindered secondary alcohol and not at its C1′-based and tertiary counterpart. In the event, when a solution of acetonide **130** in 4:1 v/v AcOH/H_2O was heated at 100 °C for 32 h triol **131** was obtained in just 43% or 80% brsm (Scheme 3.16). Efforts to improve this yield by extending the reaction time were not effective as this led to degradation and thus an even lower yield of the product **131**. Once again, the structure of product **131** followed from the usual range of spectroscopic analyses.



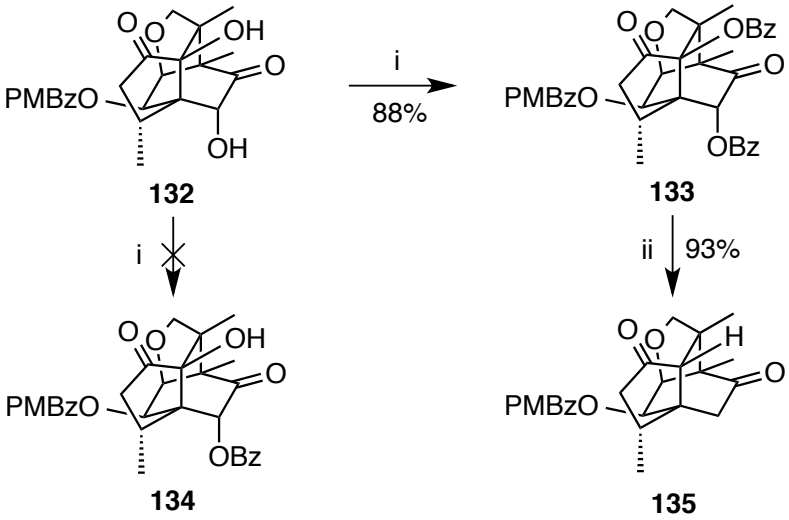
130 **131** **132**

Scheme 3.16. *Reagents and Conditions*: i. 80% aq. AcOH, 100 °C, 48 h, (41% or 80% brsm); ii. 4-AcNH-TEMPO, *p*-TsOH•H_2O, DCM, 18 °C, 72 h (70%)

With triol **131** to hand this was subjected to Bobbitt oxidation[44b] using the sterically demanding oxoammonium salt obtained by the *in-situ* and *p*-TsOH-promoted disproportionation of 4-acetamide-TEMPO. By such means the *bis*-acyloin **132** was obtained in 70% yield (Scheme 4.17) and its structure finally confirmed by single-crystal X-ray analysis (Appendix A.06).

In order to complete the C9 deoxygenation process, a solution of compound **132** and (Et_3N) in dichloromethane (DCM) was treated with benzoyl chloride but contrary to expectation (see above) the undesired *bis*-benzyl ester **133** was isolated in 88% yield (Scheme 3.17). Even using just one mole equivalent of benzoyl chloride and/or lower temperatures in an effort to effect selective formation of the desired mono-benzoate was futile. This was disappointing because the next step requiring reductive cleavage of the –OBz group would most likely also remove the tertiary hydroxyl group that had been painstakingly installed using Rubottom chemistry earlier in the synthesis. Nevertheless, it was decided to continue with the synthesis because of the time constraints and commitment of material to this part of the synthesis program. Furthermore, the tertiary hydroxyl

group could be re-installed later in the synthesis and thus the inability to selectively mono-protect the di-hydroxyl group was not considered a serious issue at this point. Of course, and in retrospect, the tertiary hydroxyl group should probably not have been installed prior to the deoxygenation at C9.



Scheme 3.17. *Reagents and Conditions*: i. BzCl, Et_3N, DCM, 18 °C, 2 h (88%); ii. SmI_2, THF:MeOH (2:1), –78 °C, 0.25 h (93%)

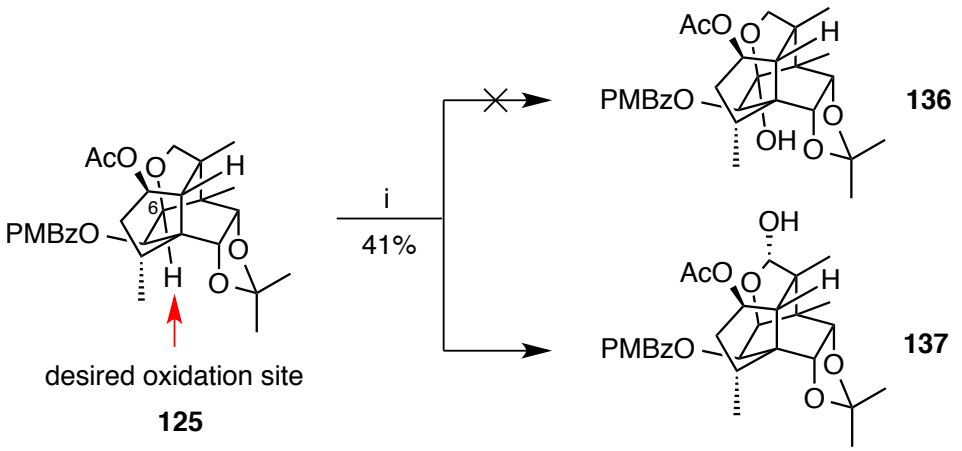
When compound **133** was treated with samarium iodide (SmI_2) in THF/MeOH[45] then, as anticipated, the doubly deoxygenated diketone **135** was obtained in 93% yield. The structure of product **135** followed from usual range of spectroscopic analyses.

3.4.4 Endgame – α-C-H Oxidation of the Tetrahydrofuran Ring

With compound **135** to hand, the final key reaction, i.e. the oxidation of C6-H bond [53] could be investigated. It was thought DMDO might be a suitable reagent for this purpose based on its small size and so most appropriate when seeking to oxidise tertiary and thus rather hindered C-H bonds. Furthermore, DMDO is known to selectively oxidise tertiary C-H bonds over its primary and

secondary counterparts.[φ] Notably, DMDO has been shown to selectivity oxidize α-C-H bonds in tetrahydrofurans[72] and tetrahydropyrans[73] even in the presence of multiple tertiary C-H centres and ketone functionalities.

On the basis of the foregoing, a test reaction was carried out on compound **125** in the hope of obtaining the desired compound **136** (Scheme 3.18). In the event, when a solution of compound **125** in acetone was exposed to freshly prepared DMDO[Φ] for 24 h, formation of a more polar compound was observed by TLC. However, careful analysis of the spectral data derived from the purified product revealed it to be the undesired regioisomer **137** (41% yield or 71% brsm).



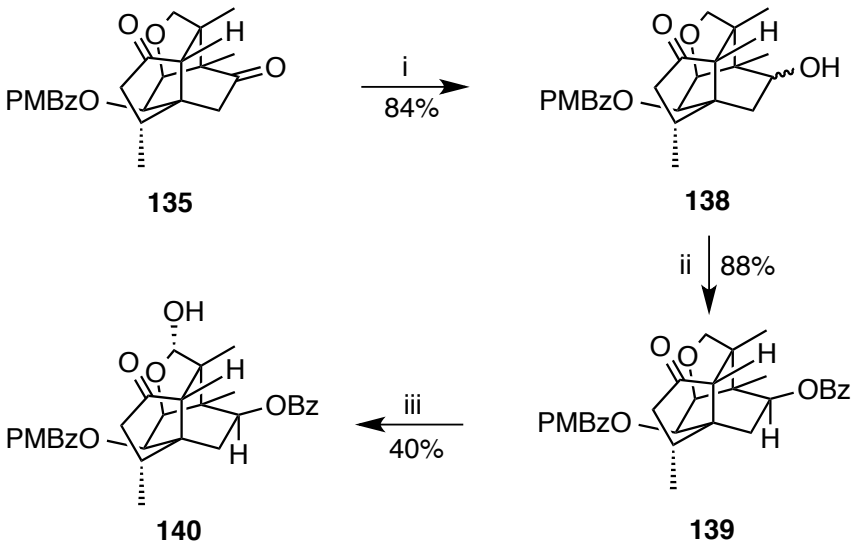
Scheme 3.18. *Reagents and Conditions*: i. DMDO, 18 °C, 72 h (41% or 70% brsm)

While all of the spectral data obtained on compound **137** were in accord with the assigned structure final confirmation of this came from a single-crystal X-ray analysis. Details are presented in Appendix A.07.

[φ]The electrophilic nature of DMDO allows it to selectively oxidize 3° C-H bonds (the most electron rich ones) over 2° and 1° ones.

[Φ]The DMDO reagent was prepared using protocol detailed in ref. 54.

In order to test if the sterically demanding acetonide group associated with compound **125** might have been preventing oxidation at the desired (C6) position, a sample of congener **139** was prepared from ketone **135** by the pathway shown in Scheme 3.19. Thus, using Mehta's procedure[51a] compound **135** was reduced in a regio- and stereo-selective manner using $NaBH_4$ in 1:1 v/v MeOH/DCM at −10 °C and so giving alcohol **138** as a single diastereoisomer in 84% yield. The structure of compound **138** followed from various spectroscopic studies although the stereochemical disposition of the hydroxyl group was tentatively assigned as shown based on the outcome of the closely related work reported by Mehta.[51a]



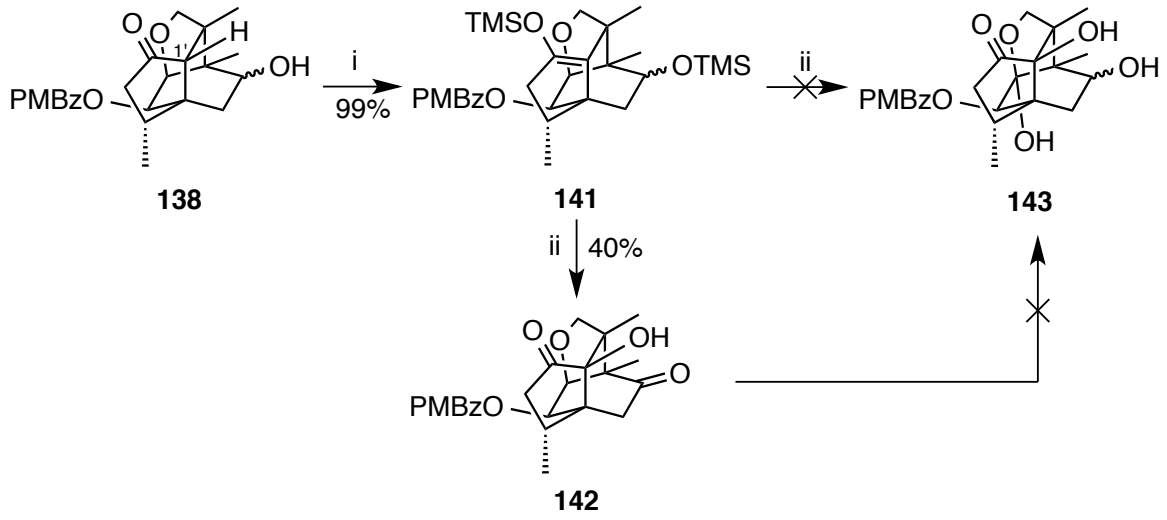
Scheme 3.19. *Reagents and Conditions*: i. $NaBH_4$, DCM:MeOH (1:1), −10 °C, 0.75 h (84%); ii. BzCl, Et_3N, DCM, 18 °C, 4 h, (88%); iii. DMDO, DCM, 18 °C, 4 h, (40% or 70% brsm)

Reaction of compound **138** with benzoyl chloride in the presence of Et_3N then gave benzoate ester **139** in 88% yield. This "acetonide-free" substrate was treated with DMDO but, once again, oxidation appeared to take place at the methylene rather than the methine carbon adjacent to the ring oxygen.

After eliminating the steric-effect of the acetonide group as the origin of the unwanted regioselectivity associated with the conversion **125** → **137**, the inability to oxidized the C-H bond of interest might now be due to the electron-withdrawing nature of the benzoate group. Through-

bond effects are one of the major factors that determines the electronic character of C-H bonds, the feature that largely determines their propensity to be oxidised.[53b] This almost certainly means that the –PMBz group could also be contributing to the undesired selectivity of the C-H oxidation reactions described above.

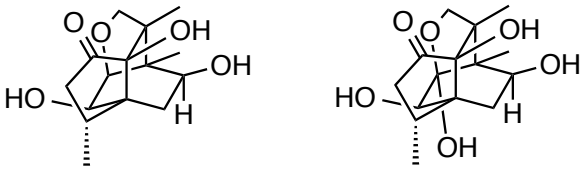
In another interesting outcome of a DMDO-mediated oxidation reaction, when the enol ether **141** (Scheme 3.20) derived from ketone **138** was subjected to treatment with this reagent, the mono-oxidation product **142** rather than its hoped for two-fold counterpart **143** was obtained. The structure of compound **142** was secured through a single-crystal X-ray analysis (Appendix A.08).



Scheme 3.20. *Reagents and Conditions*: i. TMSOTf, Et_3N, Et_2O, 18 °C, 24 h; ii. DMDO, DCM, 18 °C, 4 h, (40% or 70% brsm)

3.4.5 Approaches to the Deoxy-Analogue, 144, of Natural Product 73

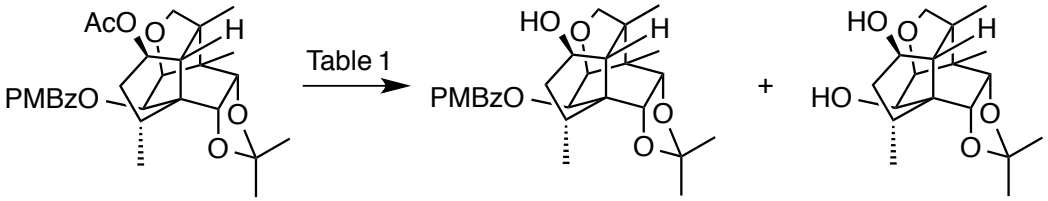
As a result of the time constraints it was decided that compound **144** (the deoxy-form of natural product **74**) would be an appropriate target for the purpose of concluding the author's work in this area.



144 **73**

Figure 3.03. Revised target: Compound **144**, the deoxy-analogue of natural product **73**

In order to effect the conversion **142** → **144**, removal of -PMBz group as well as regio- and stereo-selective reduction of one of the ketone moieties within the first of these compounds was required. The methodology for achieving the latter conversion had been established earlier so the only challenge remaining was the removal of -PMBz group. Because of the small amount of material to hand, a model study was conducted using compound **125**. However, despite examining various conditions[φ] (Table 4.03), the desired product **145** could not be obtained. Even under strongly basic (entry 2) and forcing conditions (entry 4) removal of PMBz group was difficult and the only product observed was that arising from acetate hydrolysis, *viz*. compound **127**.



125 **127** **145**

Scheme 3.21. *Reagents and Conditions*: i. see Table 4.03

[φ]The basic hydrolytic conditions were preferred over reductive ones (involving LAH or DIBAL-H) due to the fragile nature of substrate **142**.

Table 4.03. Conditions employed in attempts to remove the PMBz group within substrate **125**

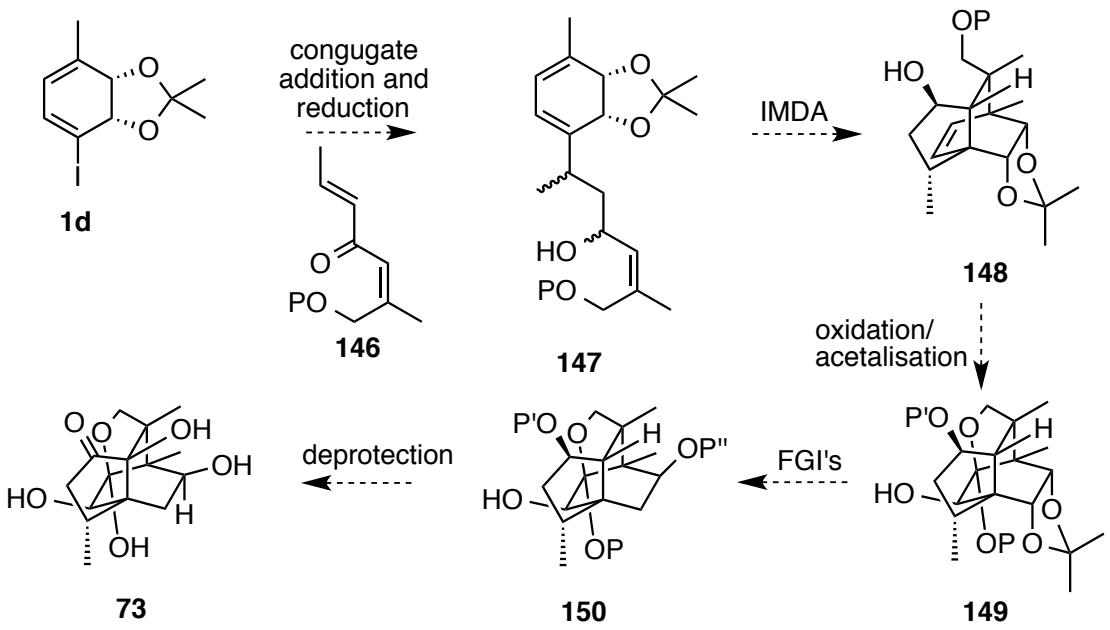
Entry	Conditions	Product Ratio **127** : **145**	Combined % Yield
1	K_2CO_3, MeOH, 18 °C, 48 h	1:0	95
2	NaOH, MeOH, 18 °C, 48 h	1:0	90
3	LiOH, THF/H_2O (1:1), 18 °C, 48 h	1:0	>80
4	LiOH, THF/H_2O (1:1), 70 °C, 96 h	1:0	>80

3.5 Future Research

In light of the outcomes defined immediately above, future efforts will be focused on identifying conditions for effecting removal of the -PMBz group within compound **142**. Also, screening for oxidants other than DMDO that could effect the desired oxidation of the C6-H bond (and thus introducing an OH group at this centre) will continue.

3.6 An Alternate Approach to the Tashironins

An alternate plan for accessing the tashironins that might more readily address the formation of the associated cyclic lactol moiety is shown in Scheme 3.22. The synthesis of the required dienone **146** would no doubt be a challenge because of the need for incorporation of a '*Z*' configured double-bond and the likely propensity for its isomerization to the more stable *E*-isomer. However, if successful, then generation of triene **147** could be envisaged through conjugate addition of iodoalkene **1d** and to Michael acceptor **146**. Subsequent reduction followed by an IMDA reaction should then give adduct **148**. The tetracyclic compound **149** should then be accessible from adduct **148** through conventional functional group interconversions including that involving a "traditional" lactol forming process. Compound **149** should be capable of elaboration to the natural product **73** *via* intermediate **150**.



Scheme 3.22. Alternate synthetic plan for obtaining tashironin **73**

3.7 Conclusion

The synthesis of the tetracyclic core, compound **142** associated with the target natural products **17** and **73** has been achieved in 15 steps from the readily accessible tricyclic precursor **43**.[57] The key reactions involved were the OsO_4-catalysed and substrate controlled, dihydroxylation of a hindered alkene and the remote fuctionalisation of an unreactive δ C-H bond using alkoxy radical chemistry. To date, however, all efforts to effect the conversion of the thus obtained compound **142** into the natural products **17** and **73** have been unsuccessful because of an inability to carry out oxidation of the C6-H bond (within, for example, **142**).

Despite the final target not being realised, the work described in this chapter has resulted in the synthesis of several highly oxygenated tricyclic and tetracyclic systems that are now available for biological evaluation and associated SAR studies. Such activities should greatly assist research in this area.

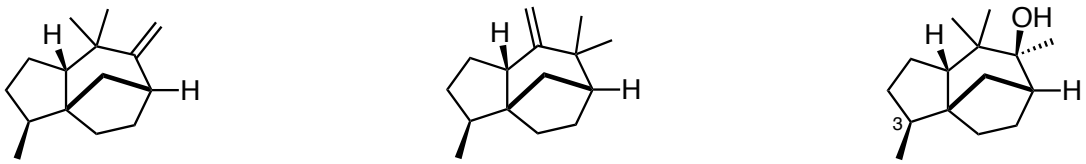
Chapter 4: Wagner-Meerwein-Type Rearrangements within the Allocedrane Framework

This two-part chapter describes extensions of the work presented in Chapter 2. The first part (Section 3.1) describes the rearrangement of the khusiol framework to the known natural products prezizaene and allokhusiol. It also outlines studies directed towards the synthesis of the important, and isomeric sesquiterpene zizaene. The second part, describes a new rearrangement reaction that allows for the conversion of the khusiol framework into an isomeric and novel system.

4.1 Part 1: Syntheses of (+)-Prezizaene, (+)-Zizaene and (+)-Allo-khusiol

4.1.1 Origins and Structures of the Sesquiterpenes (+)-Prezizaene, (+)-Zizaene and (+)-Allokhusiol

In addition to the allocedrane type of sesquiterpenoid discussed in Chapter 2, vetiver oil, which is highly prized in perfumery because of its distinct range of odiferous elements, contains another interesting class of tricyclic sesquiterpenes known as the prezizaanes. Compounds in this class incorporate a tricyclo[6.2.1.$0^{1,5}$]undecane framework and notable members include prezizaene (**151**),[74] zizaene (a.k.a. tricyclovertivene, **152**),[75] and allokhusiol (a.k.a. prezizaan-7-ol, **153**)[22, 26] (Figure 4.01).



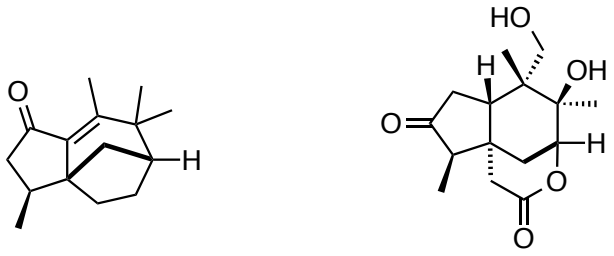
(+)-**151** (+)-**152** (+)-**153**

Figure 4.01. Examples of prezizaane-type natural products

In 1971 Anderson reported[74] the isolation of (+)-prezizaene [(+)-**151**] from both Reunion and Haitian-sourced vetiver oil. Its structure was deduced using mass spectrometric and spectroscopic techniques as well as through certain derivatisation studies. The conrotatory form of (+)-zizaene [(+)-**152**] was first reported in 1968 by Sakuma and Yoshikoshi who isolated it from vetiver oil.[75] Its structure was, once again, determined through a combination of spectroscopic and degradation studies. Compound **152** has also been obtained from vetiver oil of Moonsanagar[76] and Javanese origins.[77] The isolation of (+)-allokhusiol [(+)-**153**] was first reported[22] by Ganguly from the neutral fraction of the Moonsanagar form of vetiver oil. Later, Weyerstahl and coworkers reported[26] its isolation from Haitian vetiver oil. It is worth mentioning here that Nakanishi isolated[78] a tricyclic alcohol (jinkahol) from agarwood and claimed it had the structure (–)-**153** without citing of relevant earlier work. [22] The Nakanishi compound was later found to be the C3-epimer of sesquiterpene (+)-**153** obtained by Weyerstahl and coworkers.[26] Interestingly, the enantiomers (–)-**152** and (–)-**153** have also been isolated from *Eremophilia georgei* (a type of sandalwood) by Carrol and co-workers.[79]

The prezizaane compounds are, as mentioned earlier, olfactorily important elements of the highly valued vetiver oil. There has been some interest in the production of certain of these compounds through synthesis or by manipulation of the biosynthetic pathway. The most recent relevant patent was filed in 2010 and concerns the production and utility of these compounds as a perfumery and flavouring agents.[80]

The prezizaane framework is embedded in a number of biologically interesting compounds including albaflavenone (**154**)[81] and *seco*-prezizaane **155** (Figure 4.02). Compound **154** is an antibacterial agent isolated from certain *Streptomyces* sp.[81a] The *seco*-prezizaane family, which includes anisatin-type,[82] pseudoanisatin-type,[83] majucin-type,[83a,84] minwanensin-type (**155**),[83c,83d] cycloparvifloralone-type,[82a,85] and jiadifenin-type[84c,86] compounds, have been isolated from *Illicium* species. Several members of this family exhibit a wide range of biological activities including a capacity to promote neurite outgrowth.[84b, 84c]



154 **155**

Figure 4.02. Examples of prezizaane (**154**) and its oxa-homologue (**155**) derivatives displaying interesting biological activities

4.1.2 Biogenesis of Allocedrane and Prezizaane Type Compounds

A plausible biosynthetic pathway leading to the allocedrane, cedrane (including funebrene) and prezizaane classes of sesquiterpenes is presented in Figure 4.03. The carbon skeleta of virtually all sesquiterpenes are derived from the cyclisation of either *cis*- or *trans*-farnesyl pyrophosphate (FPP).[87] In the present case, the above-mentioned sesquiterpenes are derived from a *cis*-FPP precursor. Cyclisation followed by deprotonation of *cis*-FPP can give γ-bisabolene (**156**)[87] and protonation of the latter can yield the *β*-bisabolyl cation **157**. The critical step in this biogenesis is the cyclisation of compound **157**, the precise outcome of which determines the stereochemistry of the products. Thus, cyclisation of this cation can result in two distinct spirocyclic congeners, namely the *α*-acorenyl cation **158** and/or the *β*-acorenyl cation **159**.[88] Upon deprotonation these yield *α*- and *β*-acoradiene, respectively. Significantly, these dienes have been isolated[89] from vetiver oil. Carbocation **159** can further rearrange to the cedryl cation **160** that yields cedrene **161** upon proton loss. Carbocation **158**, on the other hand, can give rise to the allocedryl cation **162** that upon hydration yields khusiol **19**. Cation **162** can also undergo a Wagner-Meerwein (W-M) rearrangement (*viz*. a 1,2-alkyl shift) to give the prezizanyl cation **163** and the zizanyl cation **164** that upon deprotonation would afford prezizaene (**151**) and zizaene (**152**), respectively. Alternatively, cation **162** can rearrange to isomer **165** that itself delivers funebrene (**166**) upon deprotonation. Support for this proposal follows from the observation that the cedryl cation **160** can be obtained from isomer **159**.[90] Similarly, the allocedryl cation **162**, the prezizanyl cation **163** and the funebrenyl cation **165** have been produced by relevant synthetic methods.[19, 91] Anderson has also reported[74] the acid-catalysed rearrangement of compound **152** to isomer **153**.

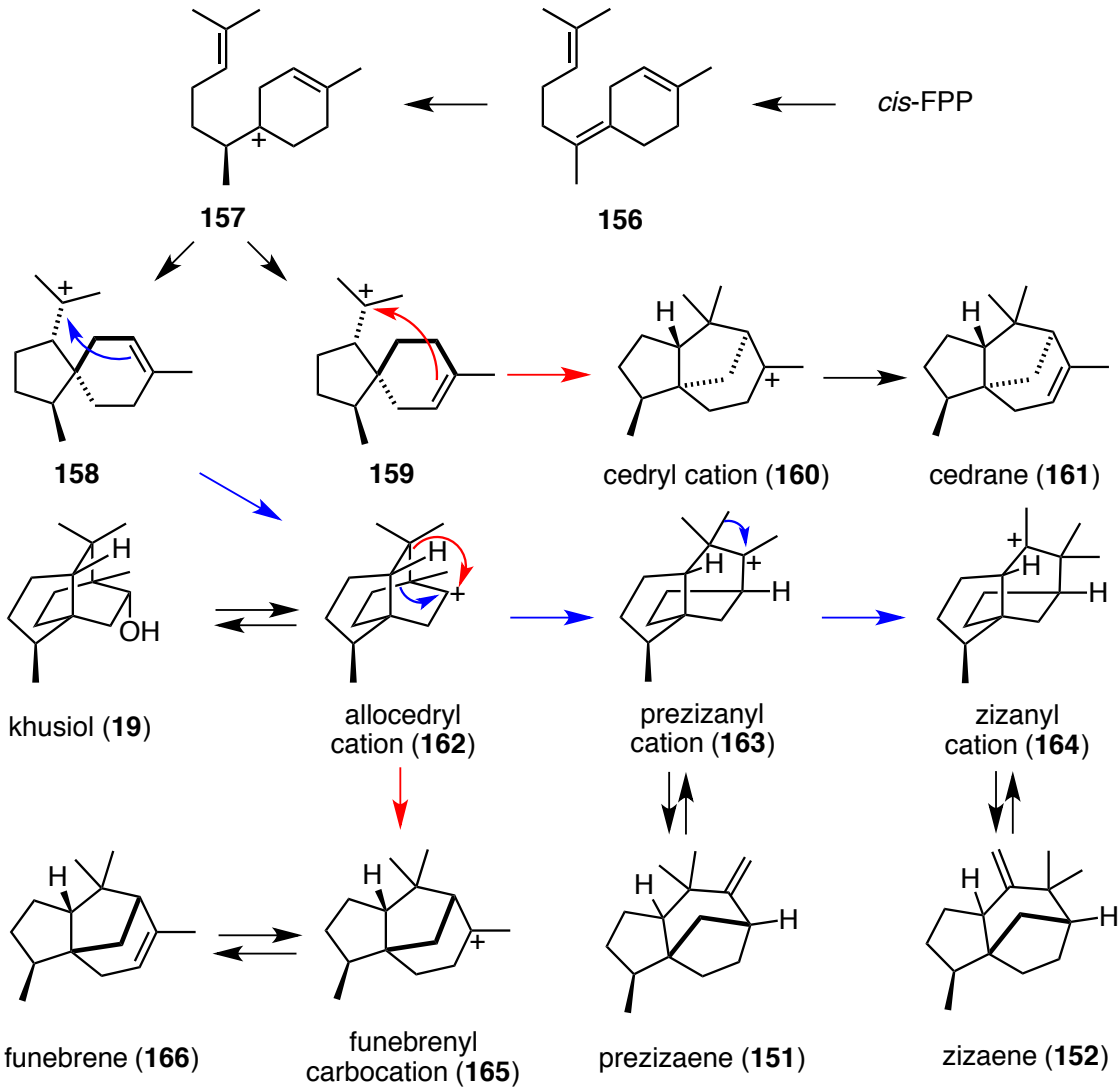
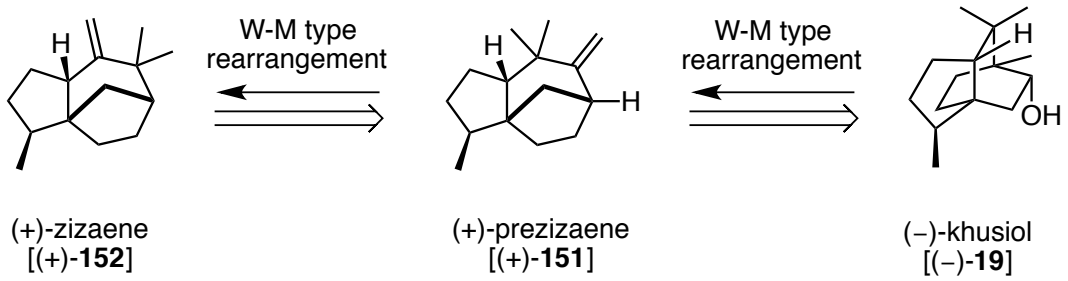


Figure 4.03. Likely biogenetic pathways leading to khusiol and related *vetiver* tricyclics

4.1.3 Retrosynthetic Analysis of (+)-Prezizaene [(+)-151] and (+)-Zizaene [(+)-152]

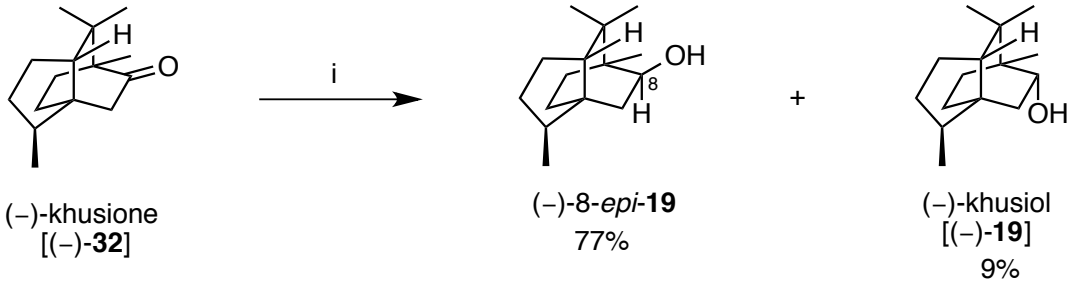
A synthetic approach to both prezizaene and zizaene was devised based on their proposed biogenesis and is shown in retrosynthetic form in Scheme 4.01. Thus, it was anticipated that (+)-zizaene [(+)-**152**] could be obtained through the W-M type rearrangement of (+)-prezizaene [(+)-**151**] that could, in turn, be prepared through the equivalent rearrangement of (−)-khusiol [(−)-**19**] (Figure 4.02). Indeed, the acid-catalysed rearrangement of prezizaene (**151**) to zizaene (**152**)[74] and of khusiol derivatives to prezizaene (**151**)[17, 19] have been reported. However, these were found to be non-selective and low yielding processes. As a result, a complex mixture of products was obtained. On this basis a re-investigation of the rearrangements of allocedrane skeleton was instigated in the hope of identifying more effective means of generating both prezizaene and zizaene type compounds.



Scheme 4.01. Proposed biomimetic syntheses of (+)-prezizaene and (+)-zizaene from (−)-khusiol

4.1.4 Synthesis of (+)-Prezizaene [(+)-151]

It was envisioned that under basic conditions dehydration of an ester derivative of (−)-khusiol [(−)-**19**] should deliver (+)-prezizaene [(+)-**151**]. As such, and because of the small quantities of (−)-khusiol to hand, a test reaction was conducted using the more abundant (−)-8-*epi*-khusiol readily obtained through reduction of (−)-khusione using sodium borohydride in MeOH and giving (−)-8-*epi*-khusiol and (−)-khusiol [(−)-**19**] in 77% and 9% yields, respectively (Scheme 4.02).



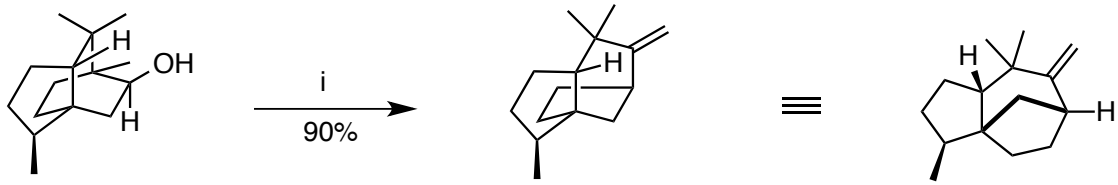
(–)-khusione
[(–)-**32**]

(–)-8-*epi*-**19**
77%

(–)-khusiol
[(–)-**19**]
9%

Scheme 4.02. *Reagents and Conditions*: $NaBH_4$, MeOH, 0-18 °C, 2 h

The mass spectrometric and various spectral data obtained on compounds (–)-8-*epi*-**19** and (–)-**19** were identical, in all respects, with authentic samples prepared earlier using the dissolving metal reduction protocol discussed in Chapter 2. With compound (–)-8-*epi*-**19** in hand, a rearrangement study could now be conducted. To this end, it was subjected to dehydrating conditions using phosphorous oxychloride ($POCl_3$) in pyridine. TLC analysis of the reaction mixture showed complete consumption of starting material within 2 h and, gratifyingly, (+)-prezizaene [(+)-**151**] was thereby obtained as the only identifiable reaction product in 90% yield (Scheme 4.03). The efficiency of this previously unreported conversion is undoubtedly a reflection of a highly favourable orbital overlap between the migrating carbon-carbon σ-bond and the rupturing carbon-oxygen σ-bond that are involved in the associated W-M rearrangement reaction.



(–)-8-*epi*-**19**

(+)-prezizaene
[(+)-**151**]

(+)-prezizaene
[(+)-**151**]

Scheme 4.03. *Reagents and Conditions*: $POCl_3$, Py, 18 °C, 2 h

The ^{1}H NMR spectrum of compound (+)-**151** exhibited a one-proton doublet (J = 2.0 Hz) at δ 4.70 and one-proton doublet (J = 2.0 Hz) at δ 4.66 (and this is attributed to the protons of the exocyclic

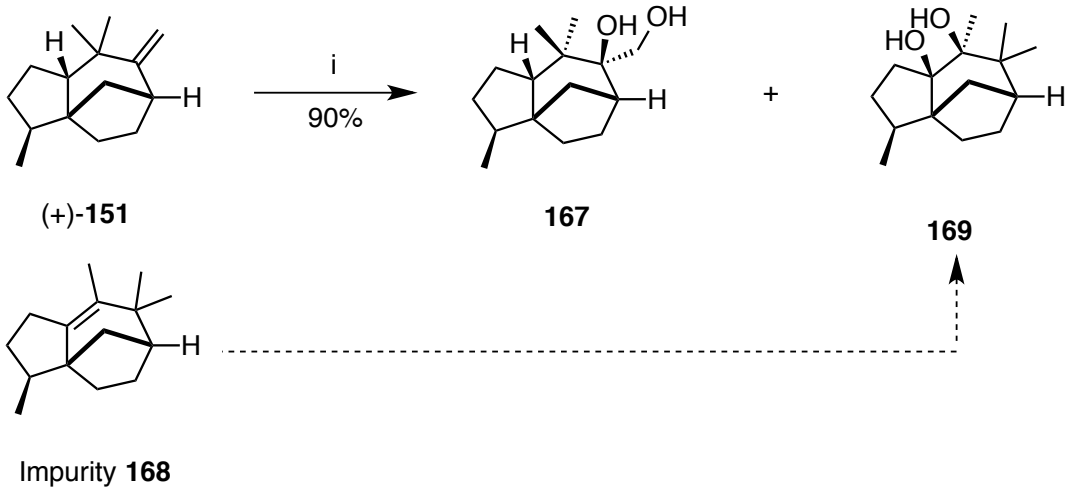
double bond), a one-proton triplet (J = 4.8 Hz) at δ 2.80 (due to the bridgehead proton), two methyl singlets at δ 1.11 and 1.07 and a secondary methyl doublet (J = 7.6 Hz) at δ 0.87. The IR spectrum exhibited =C-H and C=C stretching bands at 3078 and 1630 cm^{-1}, respectively while the ^{13}C NMR spectrum displayed the expected fifteen distinct carbon resonances, including ones due to the alkenic carbons at δ 163.1 and 105.5 (Table 4.01). The remaining spectral data were also in complete accord with the assigned structure and matched those reported in the literature for the synthetically-derived material (−)-**151** as obtained by Sakurai *et al*.[92] It should be noted that the protons of terminal alkene of compound (+)-**151** are not identical and therefore two doublets (J = 2 Hz) were observed in the ^{1}H NMR spectrum at δ 4.70 and δ 4.66. These closely spaced doublets can easily be mistaken as doublets of doublets just as Sakurai *et al*. has reported (See Table 4.01).

Table 4.01. Comparison of the ^{13}C and ^{1}H NMR spectral data recorded for synthetically-derived prezizaene (**152**) with those reported for its enantiomer [(−)-**151**]

^{13}C NMR data (δ_C)		^{1}H NMR data (δ_H)	
synthetic (+)-**151**[a]	(−)-prezizaene [(−)-**151**][b]	synthetic (+)-**151**[c]	(−)-prezizaene [(−)-**151**][d]
163.1	163.1	4.70 (d, J = 2.0 Hz, 1H)	4.71 (dd, J = 18.2 and 1.8 Hz, 1H)
105.5	105.5	4.66 (d, J = 2.0 Hz, 1H)	4.60 (dd, J = 18.2 and 1.8 Hz, 1H)
54.3	54.3	2.80 (dd, J = 6.4 and 4.8 Hz, 1H)	2.81 (dd, J = 6.3 and 4.8 Hz, 1H)
53.6	53.6	1.96 (m, 2H)	1.95 (m, 2H)
48.0	48.0	1.81 (m, 2H)	1.79 (m, 2H)
41.2	41.1	1.55 (complex m, 5H)	1.5-1.6 (m, 5H)
40.4	40.4	1.23 (brd, J = 10.4 Hz, 2H)	1.25 (dt, J = 8.3, 1.1 Hz, 2H)
37.6	37.6	1.14 (m, 1H)	1.15 (m, 1H)
32.6	32.6	1.11 (s, 3H)	1.11 (s, 3H)
32.2	32.2	1.07 (s, 3H)	1.07 (s, 3H)
31.4	31.4	0.87 (d, J = 7.6 Hz, 3H)	0.87 (d, J = 7.2 Hz, 3H)
29.9	30.0		
27.1	27.1		
22.8	22.9		
20.0	20.0		

[a]Data recorded in $CDCl_3$ at 100 MHz.
[b]Data obtained from ref. 92 and recorded in $CDCl_3$ at 67 MHz.
[c]Data recorded in $CDCl_3$ at 400 MHz.
[d]Data obtained from ref. 92 and recorded in $CDCl_3$ at 270 MHz.

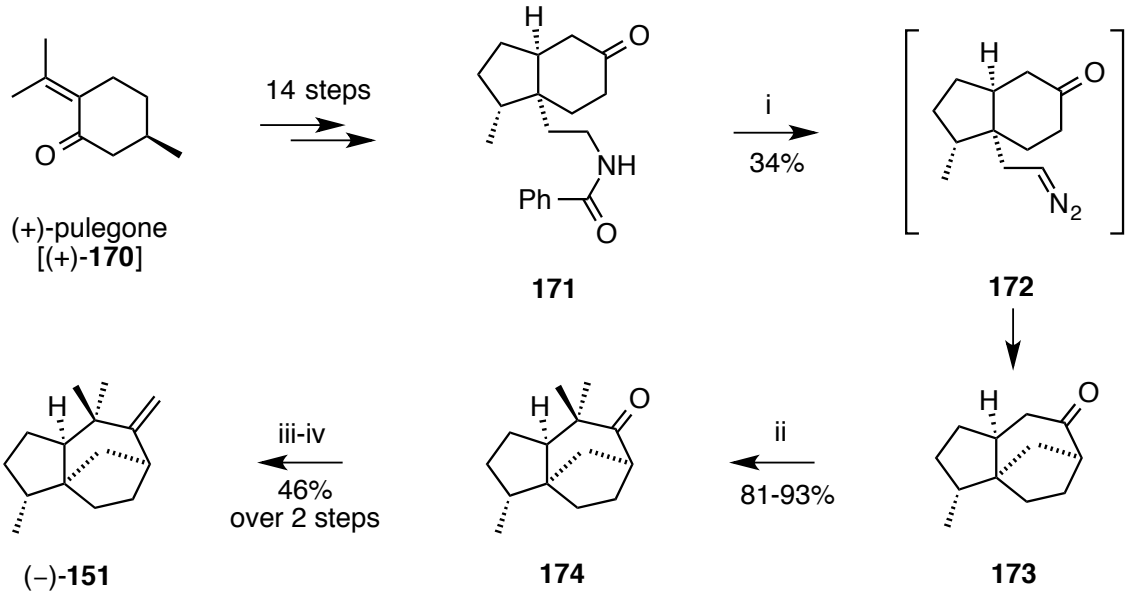
The specific rotation of compound (+)-**151** was +24.6 (c = 0.1, $CHCl_3$) and this compares with a value of –49.0 (c = 1.0, $CHCl_3$) reported[92] for its synthetically-derived enantiomer. Assuming that the enantiomer, *viz* (–)-**151**, had been obtained in optically pure form, then the *ee* of the (+)-form of the prezizaene obtained as described above is approximately 50%. The source of 'erosion' in *ee* from approximately 85% associated with the starting diene **1d** remains unclear at the present time, although partial racemization through chemical events is not possible given the nature of the reaction sequence involved. This erosion could be attributed to the presence of impurities with high and negative optical rotations contaminating the sample. Certainly, GC analysis of the material revealed the presence of some impurities. Dihydroxylation of olefin (+)-**151** with OsO_4/Py gave two products as judged by TLC analysis. The major one was identified as compound **167** (Scheme 4.04), the spectroscopic data for which matched those reported in the literature.[79] The minor product could not be isolated in sufficient quantities for complete characterization. However, and with reference to the work by Carrol,[79] who found that their natural prezizaene sample was contaminated with impurity **168**, the minor product is most likely to be diol **169**. Compound **168** is probably formed through the rearrangement of prezizanyl carbocation **163** to zizanyl carbocation **165** then deprotonation.



Scheme 4.04. *Reagents and Conditions*: OsO_4, Py, 18 °C, 2 h (90%)

Final confirmation of the structure of compound (+)-**151** came from a single-crystal X-ray analysis of derivative **167** (Appendix A.09).

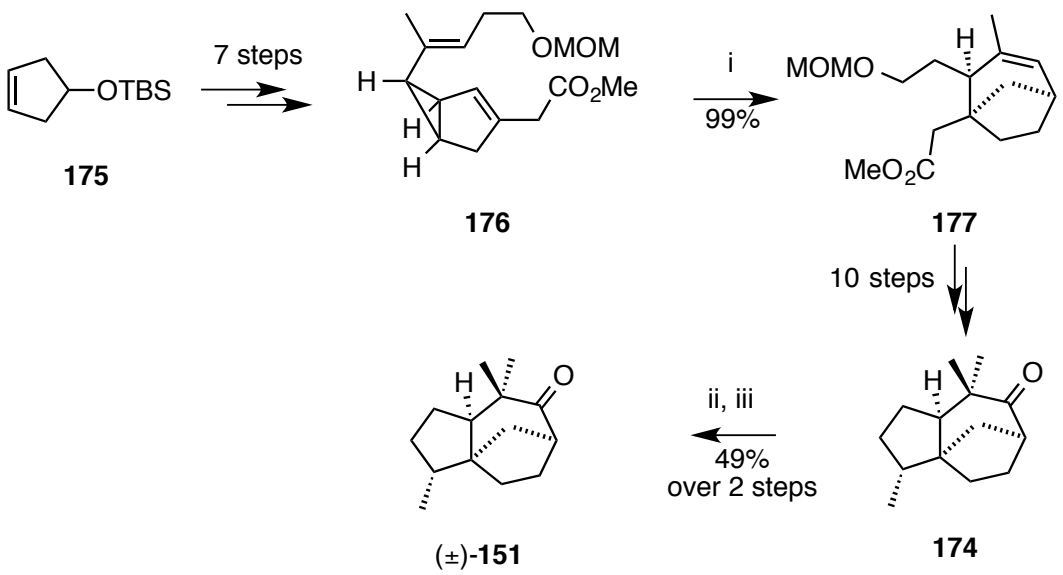
Four total syntheses of prezizaene and allokhusiol have been described previously and these are worth detailing now in order to put the author's work in a appropriate context.[92-93] Vettel and Coates reported[93a] the first total synthesis of target (–)-**151** in 18 steps from (+)-pulegone [(+)-**170**]. The key intermediate, **171**, was synthesized in 14 steps (Scheme 4.05) and on treatment with ^{t}BuOK this gave the tricylic prezizaene core **173** *via* diazoethyl hydroindanone **172**. Two-fold *C*-methylation of compound **173** then gave ketone **174** that on treatment with MeLi followed by dehydration of the product 3°-alcohol gave (–)-prezizaene [(–)-**151**].



Scheme 4.05. *Reagents and Conditions*: i. *t*-BuOH, *t*-AmOH, 25 °C, (34%); ii. KH, MeI, THF, 25 °C, 5 h, (81-93%); iii. MeLi, Et_2O, (74-85%); iv. MsCl, Et_3N, DCM, 0 °C (62%).

Later, Piers and coworkers reported[93b] a synthesis of compound (±)-**151** that involved more than 25 steps. So, starting with silyl ether **175**, the key intermediate **176** was synthesized over 7 steps (Scheme 4.06). Cope rearrangement[94] of this last compound then gave bicyclo[3.2.1]octane **177** that was itself converted over a further 10 steps into the prezizaene core compound **174**. Using a

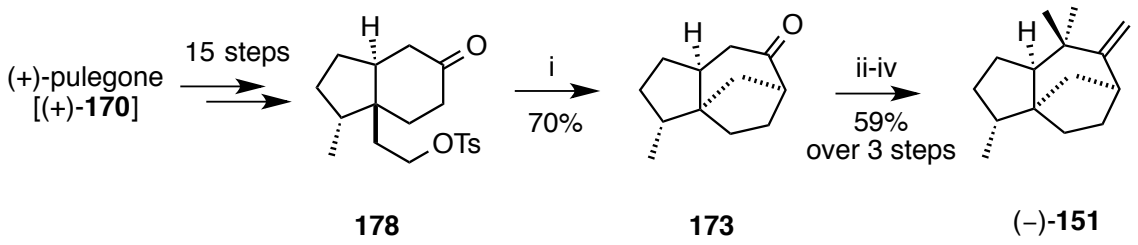
protocol similar to that employed by Vettel and Coates, compound **174** was then converted into (±)-prezizaene [(±)-**151**] over a further 2 steps.



175 **176** **177** **174** (±)-**151**

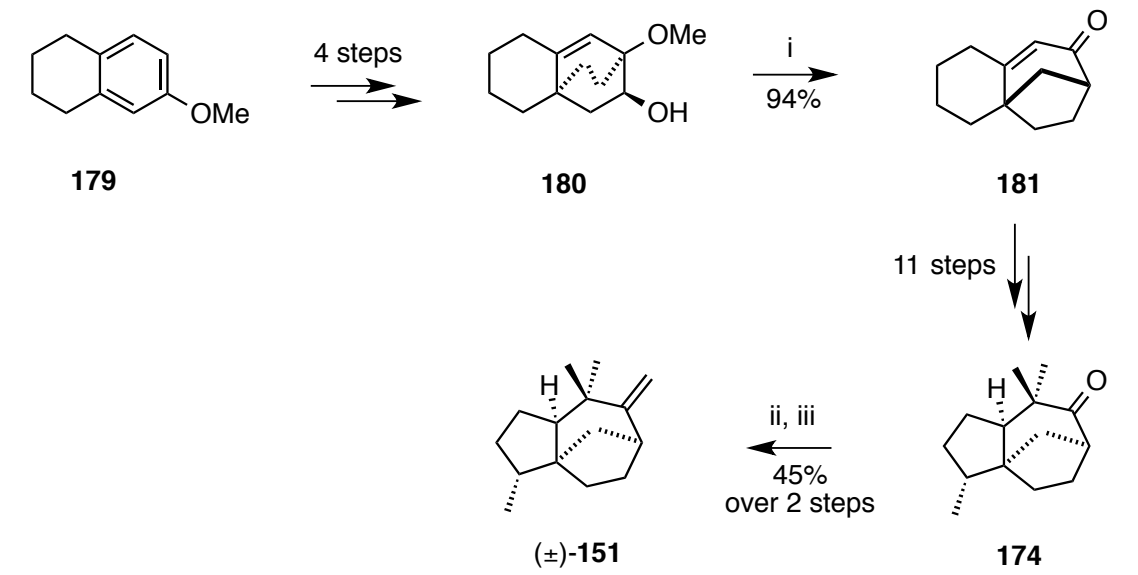
Scheme 4.06. *Reagents and Conditions*: i. 110 °C, 0.1 torr (99%); ii. MeLi, THF, –78 °C (98%); iii. MsCl, *i*-PrNEt, DCM, 0 °C (50%)

Sakurai reported[92] the enantioselective synthesis of compound (–)-**151** in 20 steps (Scheme 4.07). They used a strategy similar to that employed by Vettel and coworkers for the formation of the bicyclo[3.2.1]octane ring system associated with prezizaene. Thus, starting with (+)-pulegone (**170**), intermediate **178** was synthesized in 15 steps and treatment of this compound with ^{t}BuOK then gave the tricyclic core compound **173** associated with target (–)-**151**. Once again, using a protocol similar to that reported by Vettel and Coates, compound **173** was converted into (–)-prezizaene [(–)-**151**] over a further 3 steps.



Scheme 4.07. *Reagents and Conditions*: i. *t*-BuOH, THF, 25 °C, (70%); ii. KH, MeI, THF, 25 °C, 5 h, (90%); iii. MeLi, Et_2O, (90%); iv. MsCl, Et_3N, DCM, 0 °C (73%)

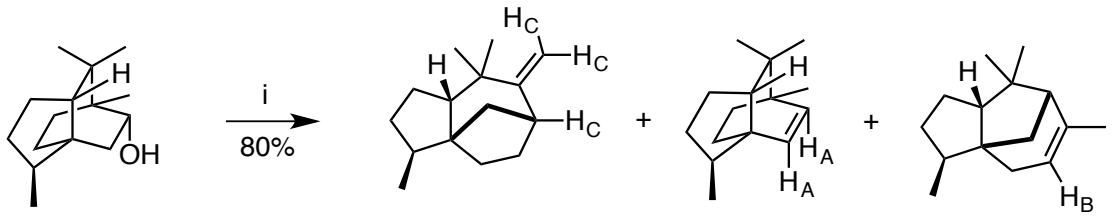
In 1994 Selvakumar reported a 20 step synthesis of compound (±)-**151** (Scheme 4.08). Formation of the requisite bicyclo[3.2.1]octane system was effected through acid-catalysed rearrangement of a precursor embodying the isomeric bicyclo[2.2.2]octane framework. Thus, starting with the aromatic **179**, bicyclo[2.2.2]octane **180** was synthesized in 4 steps. Treatment of compound **180** with boron trifluoride etherate then gave the bicyclo[3.2.1]octane **181** that was itself converted into prezizaene core compound **174** in 11 steps. Using the protocol described earlier, compound **174** was then converted into target (±)-**151** over an additional 2 steps and 45% yield.



Scheme 4.08. *Reagents and Conditions*: i. BF_3•OEt_2, PhH, reflux, 20 h (94%); ii.MeLi, Et_2O, (90%); iv. MsCl, Et_3N, DCM, 0 °C (73%)

The key reaction involved in the author's synthesis of (+)-**151** is similar to that reported by Selvakumar, in that the rearrangement of a bicyclo[2.2.2]octane into the corresponding bicyclo[3.2.1]octane is involved. However, the work about to be described represents the first synthesis of enantiomer (+)-**151** and is the shortest route reported to-date. It proceeds in just 17 steps (from *c*-DHC).

To establish if khusiol would rearrange under the same condition as its C8-epimer, a small sample of the former compound was treated with $POCl_3$/pyridine (Scheme 4.08). Interestingly, not only was the reaction sluggish (taking 48 h at room temperature) but analysis of the crude reaction mixture by GC-MS showed the presence of at least three products. Because of the small scale of this reaction, purification of the individual components was not attempted. Nevertheless, from the ^{1}H NMR spectrum (Figure 4.04) of the crude reaction mixture the major compound (characteristic resonance C) was readily identified as (+)-prezizaene. Two other (minor) components were tentatively identified as khusiene (**182**) and α-funebrene (**166**) based on the characteristic resonances A and B, respectively, and by comparison of the GC-MS fragmentation pattern of the relevant components with those reported in the literature.[95]



Scheme 4.08. *Reagents and Conditions*: i. $POCl_3$, Py, 18 °C, 48 h (80%, NMR: 4:1:1)

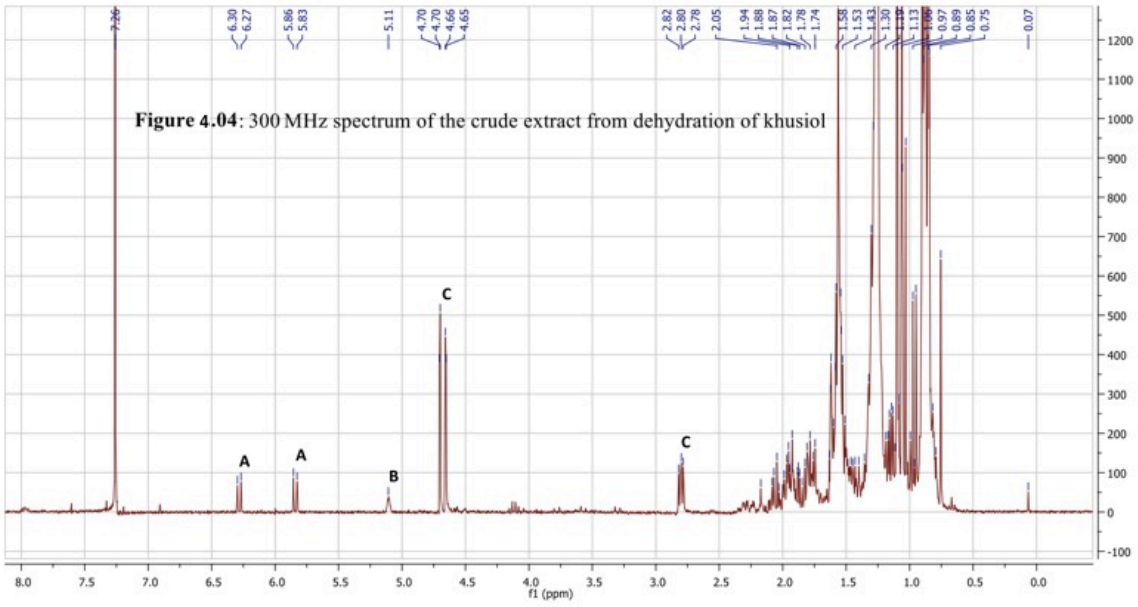
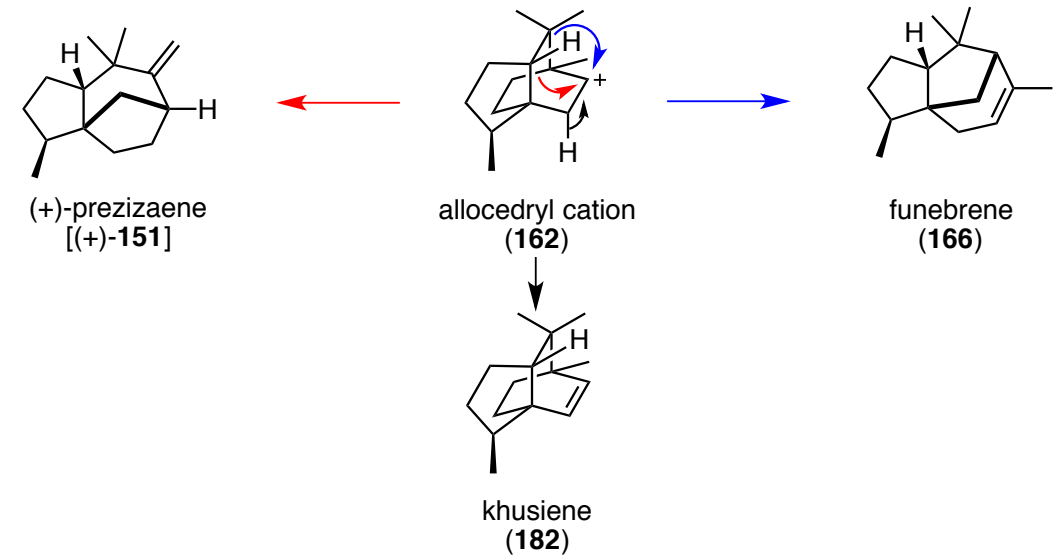


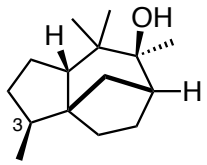
Figure 4.04: 300 MHz spectrum of the crude extract from dehydration of khusiol

Compound **182** presumably arises through the α-deprotonation of the allocedryl cation **162** while congeners (+)-**151** and **166** are almost certainly formed through 1,2-alkyl shifts as shown by red and blue arrows, respectively, followed by the relevant deprotonation event (Scheme 4.09).



Scheme 4.09. Wagner-Meerwein type rearrangements of the allocedrol cation **162**

A biogenetic approach to these three compounds have been reported by Tomita and coworkers,[19] who subjected (+)-khusiol brosylate to solvolysis and thereby obtained (−)-prezizaene [(−)-**151**], khusiene (**182**) and (−)-allokhusiol [(−)-**153**] alongside several other and at that time unidentified products. One of these was subsequently identified as α-funebrene (**166**) by Kirtany and Panikar.[96]



(+)-**153**

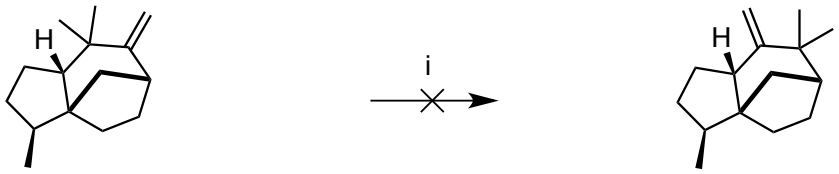
The associated rearrangement of the allocedrane skeleton most probably occurs through a concerted E2-elimination process. The antiperiplanar relationship between the ethano-bridge and the leaving group in *epi*-khusiol (**19**) might explain its ready reaction and smooth conversion into prezizaene (**151**) when compared to the behaviors of khusiol (**19**).

4.1.5 Synthetic Approach to (+)-Zizaene [(+)-152]

4.1.5.1 Acid-Catalysed Rearrangement of (+)-Prezizaene [(+)-151]

It was anticipated that treatment of the (+)-prezizaene [(+)-**151**] with catalytic amounts of a strong acid should promote its desired rearrangement to (+)-zizaene [(+)-**152**]. Accordingly, a small sample of (+)-**151** was dissolved in deuterated chloroform ($CDCl_3$) and the resulting solution was treated with triflic anhydride[o] (Scheme 4.10).

[o]The residual H_2O in chloroform was expected to effect hydrolysis of Tf_2O and so result in the formation of the necessary triflic acid.



(+)-prezizaene
[(+)-**151**]

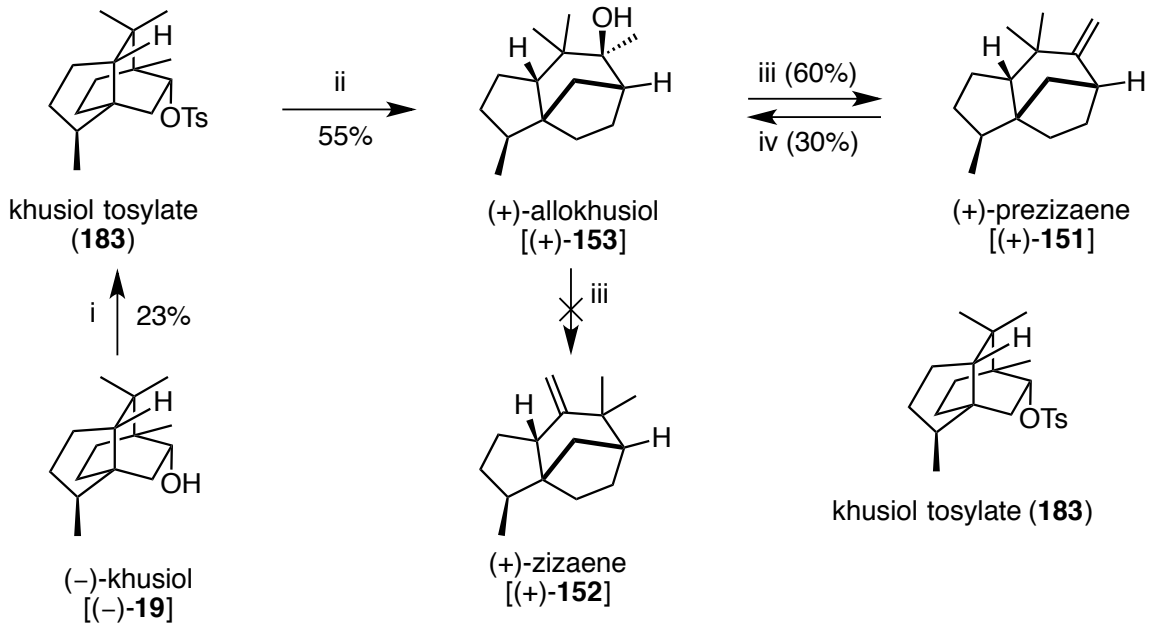
(+)-zizaene
[(+)-**152**]

Scheme 4.10. *Reagents and Conditions*: i. Tf_2O, $CDCl_3$, 18 °C, 2 h

After 2 h the starting material was completely consumed as judged by ^{1}H NMR spectroscopic analysis. GC-MS analysis of the crude reaction mixture showed the presence of at least 10 compounds but surprisingly the desired one, namely **152**, was not evident. Similarly, in the ^{1}H NMR spectrum of the crude reaction mixture the characteristic resonances for (+)-**152** (appearing at δ 4.62 and 2.48) were not evident. So this conversion was unsuccessful even though Anderson did isolate traces of zizaene (**152**) through acid-catalysed rearrangement of prezizaene (**151**) by treatment of the latter with formic acid.[74]

4.1.5.5 Dehydration of (+)-Allokhusiol [(+)-153]

In a final effort to obtain zizaene, the protocol described by Ganguly *et al*.[22] was investigated. In their study, and through dehydration of the (+)-allokhusiol using $POCl_3$/Py, these workers described the isolation of (+)-prezizaene and (+)-zizaene in 30% and 22% yields, respectively. To emulate this, a sample of compound **153** was required. Accordingly, and using the literature procedure, (−)-khusiol [(−)-**19**] was treated with tosyl chloride (TsCl) and by such means khusiol tosylate **183** was obtained albeit in just 23% yield (Scheme 4.11). The formation of compound **183** was found to be sluggish and complete conversion of the starting alcohol was never achieved even when extended reaction times (48 h) were employed. Nevertheless the spectral data obtained on ester **183** were in complete accord with the assigned structure and matched those reported in the literature.[17]



Scheme 4.11. *Reagents and Conditions*: i. TsCl, Py, 18 °C, 48 h 23% (46 brsm%); ii. Li_2CO_3, dioxane/H_2O (7:3), 100 °C, 2 h, 55%; iii. $POCl_3$, Py, 18 °C, 48 h, 60%; iv. $Hg(OAc)_2$, THF/H_2O (7:3), 18 °C, 24 h, then $NaBH_4$/NaOH, 1h 30% (90% brsm)

Solvolysis of compound **183** in a 7:3 v/v mixture of dioxane/ H_2O containing Li_2CO_3 furnished (+)-allokhusiol in 55% yield. Alternatively, oxymercuration/demecuration of (+)-prezizaene [(+)-**153**] also gave (+)-**153** although now in just 23% yield (or 90% brsm). The IR spectrum of compound (+)-**153** exhibited an O-H stretching band at 3480 cm^{-1} while the EI mass spectrum exhibited a molecular ion at *m/z* 222. The ^{13}C NMR spectrum displayed only 14 of the expected 15 carbon resonances because that due to the oxymethine carbon was obscured by the *d*-chloroform "triplet" centred at δ 77.0. Nevertheless, such data were in complete accord with the assigned structure and matched those reported by Sakurai *et al*.[92] (Table 3.02). As mentioned earlier, 4 syntheses of allokhusiol (**153**) have been reported.[92-93] However, none of these provided the (+)-form of compound **153**.

Table 4.02. Comparison of the ^{13}C and ^{1}H NMR spectral data recorded for synthetically-derived allokhusiol (**153**) with those reported for its enantiomer (−)-**153**

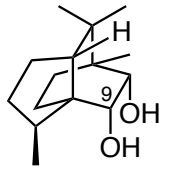
^{13}C NMR data (δ_C)		^{1}H NMR data (δ_H)	
synthetic (+)-**153**[a]	(−)-allokhusiol [(−)-**153**][b]	synthetic (+)-**153**[c]	(−)-allokhusiol [(−)-**153**)][d]
76.7	76.8	2.05 (dd, *J* = 6.8 and 4.6 4Hz, 2H),	2.05 (dd, *J* = 6.7 and 4.6 Hz, 2H)
52.6	52.6	1.94 (m, 1H)	1.95 (m, 1H)
51.7	51.7	1.84-1.64 (m, 4H),	1.75 (m, 4H)
50.6	50.6		1.58 (m, 2H)
40.2	40.2	1.60-1.40 (m, 5H)	1.52 (m, 2H)
39.7	39.7		1.44 (dq, *J* = 9.1 and 3.0 Hz, 1H)
35.9	35.9	1.27 (m, 1.5H)	1.27 (dd, *J* = 11.1 and 4.6 Hz, 2H)
33.0	33.0	1.16 (s, 3H)	
31.9	31.9	1.09 (m, 1.5H)	1.08 (m, 2H)
27.2	27.2	0.93 (s, 3H)	0.93 (s, 3H)
26.2	26.1	0.91 (s, 3H)	0.91 (s, 3H)
23.8	23.7	0.91(d, *J* = 7.2 Hz, 3H)	0.91 (d, *J* = 7.2 Hz, 3H)
23.5	23.4		
21.3	21.3		
19.8	19.7		

With compound **153** in hand the relevant rearrangement studies could now be pursued. However, when it was treated with $POCl_3$ in pyridine only sluggish consumption of compound **153** was observed and it took 72 h for it to completely disappear. Furthermore, ^{1}H NMR spectroscopic analysis of the crude reaction mixture after this time only showed the presence of prezizaene (**151**). No discernable resonances attributable to zizaene (**152**) were observed. Accordingly, it has not been possible to verify if prezizaene can indeed be converted into zizaene itself.

[a]Data recorded in $CDCl_3$ at 100 MHz.
[b]Data obtained from ref. 92 and recorded in $CDCl_3$ at 67 MHz.
[c]Data recorded in $CDCl_3$ at 400 MHz.
[d]Data obtained from ref. 92 and recorded in $CDCl_3$ at 270 MHz.

4.2 Part II: Synthesis of an ent-β-Isopipitzol Core Through a Novel Rearrangement of the Allocedrane Skeleton

During the course of the synthesis of (–)-khusiol (Chapter 2) one of the challenges encountered was the need to effect C9 deoxygenation of vicinal diol **33**. Initially, it was envisioned this could be achieved through reductive opening of the derived cyclic sulfate **66**. However, subjection of compound **66** to seemingly appropriate conditions did not furnish the desired compound. Instead, an interesting and previously unreported rearrangement of the allocedrane skeleton took place and thus giving access to a novel tricyclic alcohol. Details of this work are now presented.



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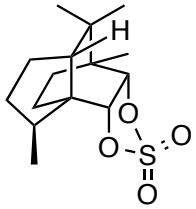
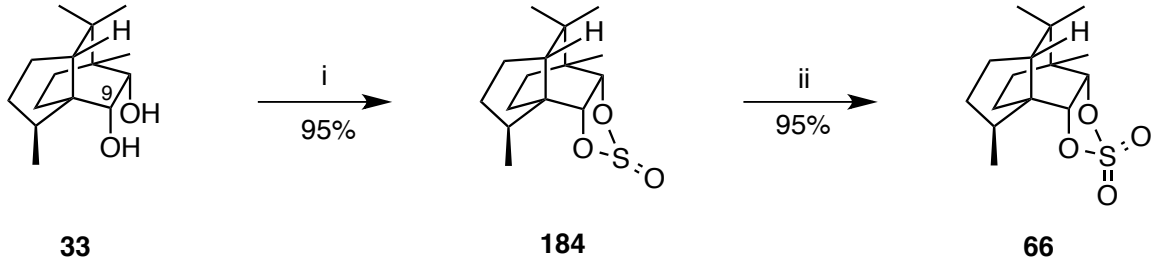


66

4.2.1 Synthesis of Cyclic Sulfate 66

Initially, it was envisaged that cyclic sulfate **66** could be obtained though the treatment of diol **33** with sulfuryl chloride (SO_2Cl_2) but this proved not to be the case. So, when the relevant treatment was undertaken only a complex mixture of products was formed. Amongst these were chlorinated compounds as evident from mass spectrum of the crude reaction mixture. Due to the small scale of this reaction no efforts were made to purify any of the individual components. Careful scrutiny of the literature on the synthesis of cyclic sulfates revealed that Sharpless *et al*.[43] had described an efficient and high yielding route to such system from the corresponding 1,2-vicinal diols. Accordingly, and following the stated procedure, diol **33** was treated with thionyl chloride ($SOCl_2$) and by such means a 1:1 and chromatographically inseparable mixture of epimeric forms of cyclic sulfite **184** was obtained in 95% combined yield (Scheme 4.12).



33 **184** **66**

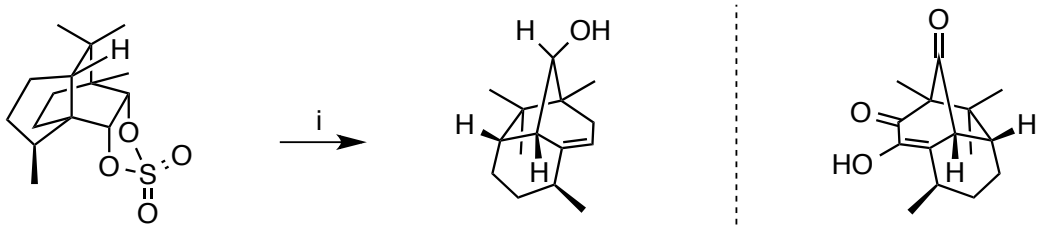
Scheme 4.12. *Reagents and Conditions*: i. $SOCl_2$, DCM, 0 to 18 °C, 0.5 h (95%, dr = 1:1); ii. $NaIO_4$, $RuCl_3 \bullet 3H_2O$, MeOH/H_2O (2:1), 18 °C, 1 h, 95 %

Oxidation of this mixture using ruthenium tetraoxide[θ] (RuO_4) then gave cyclic sulfate **66** in 95% yield. The EI mass spectrum of compound **66** displayed a molecular ion at *m/z* 300, 16 mass units higher than the starting material and so indicating that oxidation has occurred while the IR spectrum showed a strong and characteristic sulfate stretching band at 1383 cm^{-1}. The ^{1}H NMR spectrum exhibited a two-proton singlet at δ 4.83 that is attributed to the two oxymethine protons. The ^{13}C NMR spectrum displayed, as expected, 15 distinct carbon resonances.

4.2.2 Novel Rearrangement of Allocedrane Skeleton *via* Cyclic Sulfate 66

It was originally hoped that treatment of cyclic sulfate **66** under reducing conditions would deliver, through reductive cleavage of relevant C-O bond, the sulfated derivative of khusiol (**19**). However, when this substrate was treated with $NaBH_4$ in DMF at 70 °C and the cooled and crude reaction mixture subjected to acidic work-up then the rearranged alcohol **185** was obtained in 70% yield.

[θ] RuO_4 was derived *in-situ* by treatment of $RuCl_3$ with $NaIO_4$.

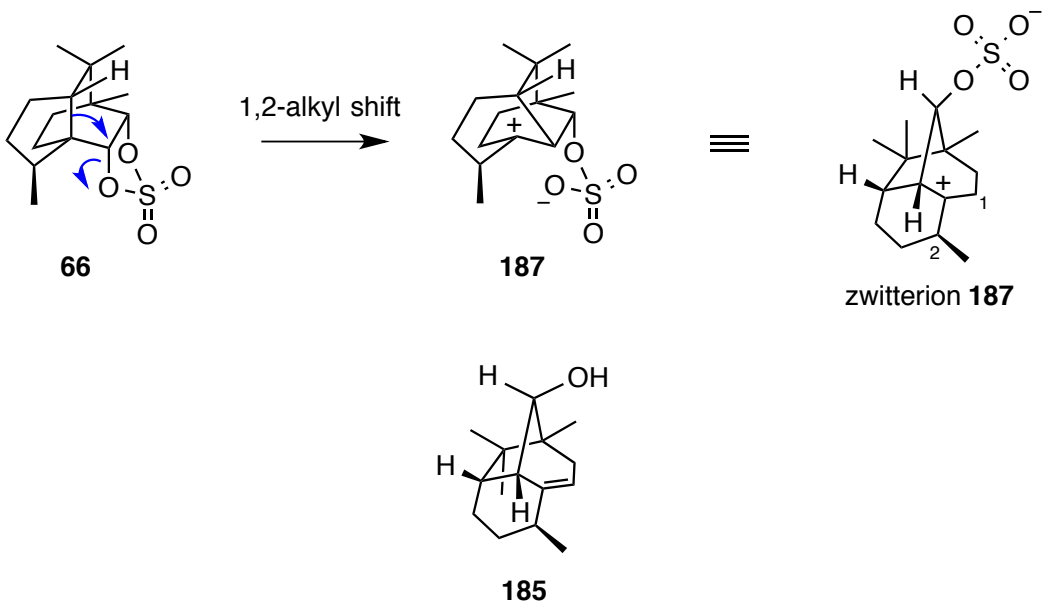


66 **185** (70%) isopipitzol (**186**)

Scheme 4.13. *Reagents and Conditions*: i. $NaBH_4$, DMF, 70 °C, 6 h then H_2SO_4, THF, 18 °C, 0.5 h

The structure of alcohol **185** was initially proposed on the basis of mass spectrometric and various spectroscopic studies. So, for example, the EI mass spectrum displayed a molecular ion at *m/z* 220 while the IR spectrum revealed a strong O-H stretching band at 3370 cm^{-1}. The ^1H NMR spectrum exhibited an alkenic resonance at δ 5.27 (d, J = 4 Hz, 1H) and an oxymethine proton resonance at δ 3.83 (d, J = 4.8 Hz, 1H). The ^{13}C NMR spectrum displayed 15 distinct carbon resonances including ones due to the carbon of a trisubstituted double bond at δ 143.9 and 117.7 as well as an oxymethine carbon resonance at δ 75.4. However, final confirmation of structure followed from a single-crystal X-ray analysis (Appendix A.10). This white crystalline alcohol had a patchouli type odor and is, therefore, a promising lead as a new flavour and fragrance ingredient. It is also interesting to note that while compound **185** is a novel alcohol, a natural product, isopipitzol (**186)** that embodies the *ent*-form of its core, has been reported.[97]

The origins of compound **185** are easily rationalized. Thus, thermolysis of cyclic sulfate **66** would produce zwitterion **187** through W-M type rearrangement (Figure 3.04) and subsequent deprotonation at C1 followed by hydrolysis of sulfate ester would then give the observed alcohol **185**.



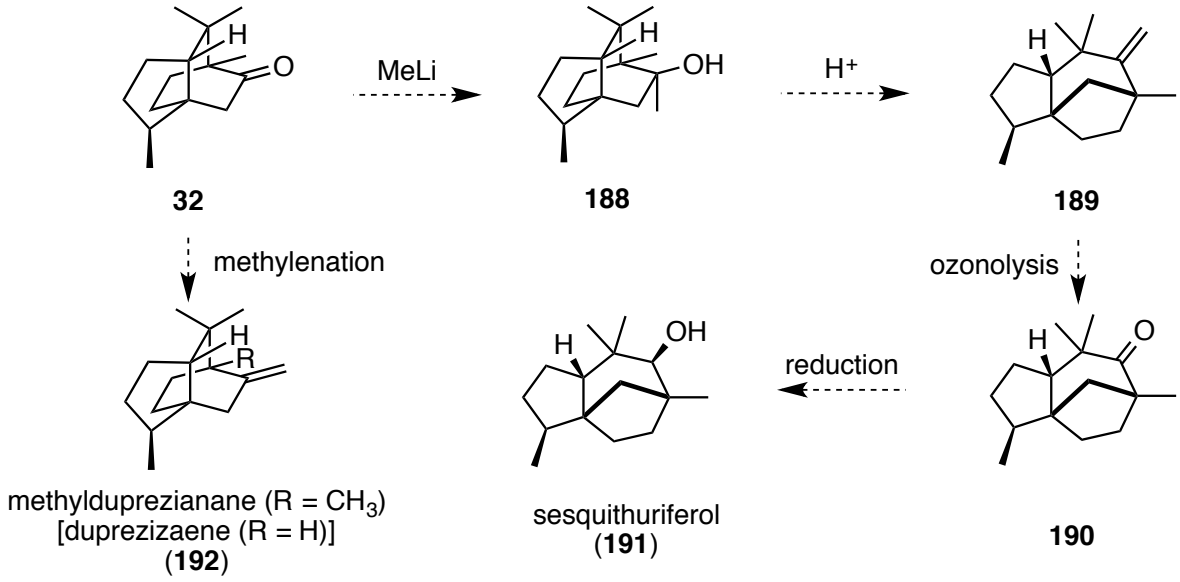
Scheme 4.14. Formation of compound **185** from precursor **66** *via* zwitterion **187**

4.3 Conclusion and Future Work

An efficient and high yielding route to (+)-prezizaene [(+)-**151**] was achieved in a single step from precursor (–)-8-*epi*-**19** through biogenetic type rearrangements of the associated tricyclo[5.2.2.$0^{1,5}$]undecane framework to the isomeric tricyclo[6.2.1.$0^{1,5}$]undecane. As a result, a 17 step synthesis of enantio-enriched (+)-prezizaene [(+)-**151**] was established from diol **1d**. Furthermore, both compound (+)-**151** and tosylate **183** were successfully converted into (+)-allokhusiol [(+)-**153**] through oxymecuration/demecuration and solvolysis reactions, respectively. In contrast, the attempted conversion of prezizaene (**151**) into zizaene (**152**) through acid-catalysed rearrangement of the former was unsuccessful.

The work described above should be capable of extension to the synthesis other normally challenging prezizaane type compounds. For example, compound **32** could be converted into tertiary alcohol **188** that should, in turn, rearrange to alkene **189**. Oxidative cleavage of the exocyclic olefin within this last compound would then give ketone **190** that upon reduction should

yield natural product sesquithuiferol (**191**). Alternately, compound **32** could be converted into analogues of the natural product duprezizaene, including compound **192** using Wittig chemistry (Scheme 4.15).



Scheme 4.15. Proposed synthesis of unnatural sesquithuriferol and methylduprezianane

Such work could also be extended to the synthesis of *seco*-prezizaane type compounds such as minwanensin (**155)**, a synthetically challenging and biologically interesting compound.

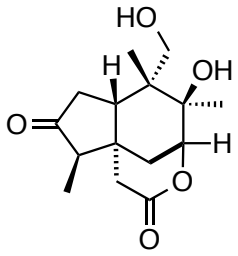


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Figure 4.05. Example of a bioactive prezizaane-type compound

The synthesis of (+)-form of the *β*-isopipitzol core (**185**) was achieved through an unprecedented rearrangement of a cyclic sulfate containing the tricyclo[5.2.2.$0^{1,5}$]undecane framework. It was found that this alcohol possessed a pleasant odor thus suggesting it is a potential ingredient in flavours and fragrances.

Chapter 5: Experimental Procedures

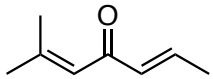
5.1 General Procedures

Unless otherwise specified, proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded at 18 °C in base-filtered $CDCl_3$ on a Varian spectrometer operating at 300 and 400 MHz for proton and 75 and 100 MHz for carbon nuclei, respectively. In some cases, experiments were performed on Bruker spectrometer operating at 600 and 800 MHz for proton and 150 and 200 MHz for carbon nuclei, respectiviely. For ^{1}H NMR spectra, signals arising from the residual protio-forms of the solvent were used as the internal standards. ^{1}H NMR data are recorded as follows: chemical shift (δ) [multiplicity, coupling constant(s) *J* (Hz), relative integral] where multiplicity is defined as: s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet or combinations of the above. The signal due to residual $CHCl_3$ appearing at δ_H 7.26 and the central resonance of the $CDCl_3$ "triplet" appearing at δ_C 77.0 were used to reference ^{1}H and ^{13}C NMR spectra, respectively. Infrared spectra (ν_{max}) were recorded on a Perkin–Elmer 1800 Series FTIR Spectrometer. Samples were analyzed as thin films on KBr plates. A VG Fisons AutoSpec mass spectrometer was used to obtain low- and high-resolution electron impact (EI) mass spectra. Low- and high-resolution electrospray ionisation (ESI) mass spectra were obtained on a VG Quattro II triple-quadrupole MS instrument operating in positive ionization mode. Optical rotation were measured on Perkin-Elmer 241 polarimeter using. Melting points were measured on an Optimelt automated melting point system and are uncorrected. Analytical thin layer chromatography (TLC) was performed on aluminum-backed 0.2 mm thick silica gel 60 F_{254} plates as supplied by Merck. Eluted plates were visualized using a 254 nm UV lamp and/or by treatment with a suitable dip followed by heating. These dips included phosphomolybdic acid : ceric sulfate : sulfuric acid (conc.) : water (H_2O) (37.5 g : 7.5 g : 37.5 g : 720 mL) or potassium permanganate : potassium carbonate : 5% sodium hydroxide aqueous solution : H_2O (3 g : 20 g: 5 mL : 300 mL). Flash chromatographic separations were carried out following protocols defined by Still *et al*.[98] with silica gel 60 (40-63 μm) as the stationary phase and using the AR- or HPLC-grade solvents indicated. Starting materials and reagents were generally available from the Sigma–Aldrich, Merck, TCI, Strem or Lancaster Chemical Companies and were used as supplied. Drying agents and other inorganic salts were purchased from the AJAX, BDH or Unilab Chemical Companies. Tetrahydrofuran (THF), methanol (MeOH) and dichloromethane (DCM) were dried using a Glass Contour solvent purification system that is based

upon a technology originally described by Grubbs *et al*.[99] Where necessary, reactions were performed under an argon atmosphere.

5.2 Experimental Procedures Associated with Work Described in Chapter Two

(*E*)-2-Methylhepta-2,5-dien-4-one (36)



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Step i: A magnetically stirred solution of diisopropylamine (2.8 mL, 20.7 mmol) in THF (120 mL) maintained at 0 °C under a nitrogen atmosphere was treated, dropwise, with *n*-butyllithium (16 mL of 1.4 M solution in hexane, 22.4 mmol). The ensuing mixture was stirred at 0 °C for 0.25 h then cooled to –65 °C and mesityl oxide **37** (2.3 mL, 20.4 mmol) added dropwise. The resulting mixture was stirred for 1 h at –65 °C then a solution of acetaldehyde (1 mL, 18 mmol) in THF (15 mL) was added dropwise and the mixture thus formed was stirred at the same temperature for a further 1 h before being quenched with NH_4Cl (50 mL of a saturated aqueous solution) and extracted with EtOAc (3 × 50 mL). The combined organic phases were washed with brine (1 × 100 mL) then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give 6-hydroxy-2-methylhept-2-en-4-one (**38**) as pale-yellow oil and of sufficient purity to be used in *Step ii* as detailed immediately below.

Step ii: Methanesulfonyl chloride (0.85 mL, 10.9 mmol) was added to a magnetically stirred solution of 6-hydroxy-2-methylhept-2-en-4-one (1.30 g, 9.15 mmol, prepared as described immediately above) and triethylamine (3.16 mL, 22.8 mmol) in DCM (50 mL) maintained at 0 °C under a nitrogen atmosphere. The ensuing mixture was warmed to 18 °C, stirred at this temperature for 12 h then diluted with $NaHCO_3$ (30 mL of a saturated aqueous solution) and extracted with DCM (3 × 50 mL). The combined organic phases were washed with brine (1 × 100 mL) then dried (Na_2SO_4), filtered and concentrated under reduced pressure (*ca.* 700 mbar) at temperatures below 20 °C. The resulting yellow liquid was subjected to column chromatography (silica, DCM elution)

and concentration of the appropriate fractions (R_f = 0.45 in 1:4 v/v EtOAc/hexane) gave dienone **36**[28a] (1.20 g, 80% over 2 steps) as pale-yellow oil with a pungent odor.

^{1}H NMR (300 MHz) δ 6.78 (m, 1H), 6.16 (m, 1H), 6.07 (dq, *J* = 15.0 and 1.8 Hz, 1H), 2.09 (s, 3H), 1.86 (m, 3H), 1.83 (dd, *J* = 5.1 and 3.3 Hz, 3H).

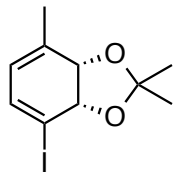
^{13}C NMR (75 MHz) δ 190.2, 155.2, 141.5, 133.4, 122.7, 27.6, 20.7, 18.0.

IR ν_{max} (KBr) 2975, 2936, 2914, 1679, 1659, 1635, 1611, 1444, 1355, 1284, 1240, 1175, 1135, 1051, 971, 909 cm^{-1}.

LREIMS (70 eV) *m/z* 124 ($M^{+\bullet}$, 18%), 109 (94), 86 (100).

HREIMS Found: $M^{+\bullet}$ = 124.0889. $C_8H_{12}O$ requires 124.0888.

(3a*S*,7a*S*)-4-Iodo-2,2,7-trimethyl-3a,7a-dihydrobenzo[*d*][1,3]dioxole (39)



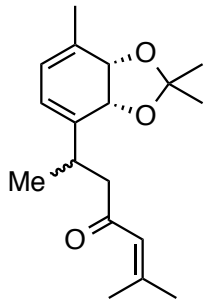
39

A solution of (1*S*,2*S*)-3-iodocyclohexa-3,5-diene-1,2-diol (**1d**) (1.00 g, 4.20 mmol) in 2,2-dimethoxypropane (20 mL) was treated with *p*-TsOH•H_2O (*ca.* 30 mg, 0.16 mmol) then stirred at 18 ºC for 1 h before being quenched with triethylamine (0.5 mL) and concentrated under reduced pressure. The resulting brown residue was partitioned between H_2O (20 mL) and Et_2O (50 mL) and the separated aqueous phase was extracted with Et_2O (2 × 100 mL). The combined organic phases were washed with NaOH (50 mL of a 2.0 M aqueous solution) and brine (50 mL) then dried (Na_2SO_4), filtered and concentrated under reduced pressure (temp. = 30 ºC) to give title acetonide **39**[12, 30] (1.06 g, 91%) as a pale-yellow oil (R_f = 0.6 in 3:7 v/v EtOAc/hexane). This material was sufficiently pure to be used directly in the next step of the reaction sequence.

^{1}H NMR (300 MHz) δ 6.63 (d, *J* = 6.0 Hz, 1H), 6.03 (dd, *J* = 9.6 and 4.1 Hz, 1H), 5.76 (dd, *J* = 9.6 and 6.0 Hz, 1H), 4.74 (d, *J* = 8.5 Hz, 1H), 4.63 (dd, *J* = 8.5 and 4.1 Hz, 1H), 1.45 (s, 3H), 1.43 (s, 3H).

The data presented above as well as all the other data acquired on this compound matched those reported in the literature.[30]

2-Methyl-6-{(3a*R*,7a*S*)-2,2,7-trimethyl-3a,7a-dihydrobenzo[*d*][1,3]dioxol-4-yl}hept-2-en-4-one (41)



41

A magnetically stirred solution of acetonide **39**,[12, 30] (680 mg, 2.33 mmol) in THF (10 mL) was cooled to −30 °C then treated dropwise with *i*-PrMgCl (2.34 mL of a 2.0 M solution in THF, 4.68 mmol). The ensuing mixture was warmed to 0 °C and stirred at this temperature until no starting material could be detected by ^{1}H NMR spectroscopic analysis (1- 2 h). The reaction mixture was then cooled to −78 °C and treated with copper(I)bromide-dimethyl sulfide complex (48 mg, 0.23 mmol) and HMPA (1.2 mL, 7 mmol). A solution of enone **36** (578 mg, 4.66 mmol) and TMSCl (0.88 mL, 7 mmol) in THF (2 mL) was then added, *via* syringe pump over 1.5 h, to the reaction mixture which was then allowed to warm to 18 ºC over 16 h before being treated with NH_4Cl (20 mL of a saturated aqueous solution) and stirred at 18 ºC for 0.17 h. The biphasic system thus formed was separated and the aqueous layer was extracted with EtOAc (3 × 30 ml). The combined organic fractions were washed with H_2O (2 × 10 mL) and brine (1 × 20 mL) then dried (Na_2SO_4), filtered, concentrated under reduced pressure. The crude material thus obtained was dissolved in THF (7 mL) and the resulting solution treated with TBAF (7 mL of a 1.0 M solution in THF, 7 mmol) then stirred at 18 ºC for 1 h. The ensuing mixture was then concentrated, under reduced pressure, onto silica (*ca.* 2 g of 230-400 mesh material) and the resulting free-flowing solid subjected to flash column chromatography (silica, 1:9 v/v EtOAc/hexane elution). Concentration of the appropriate fractions (R_f = 0.3) gave a *ca.* 3:2 mixtures of the epimeric forms of *enone **41*** (917 mg, 74%) as a clear, colourless oil.

^{1}H NMR (300 MHz) δ (major isomer) 6.06 (broad s, 1H), 5.69 (broad t, *J* = 4.8 Hz, 1H), 5.65 (broad d, *J* = 6.0 Hz, 1H), 4.57 (d, *J* = 8.7 Hz, 1H), 4.48 (m, 1H), 2.93 (m, 1H), 2.69 (m, 1H), 2.38 (dd, *J* = 15.6 and 8.1 Hz, 1H), 2.11 (s, 3H), 1.86 (s, 3H), 1.84 (s, 3H), 1.40 (s, 3H), 1.34 (s, 3H), 1.10 (d, *J* = 6.6 Hz, 3H).

^{13}C NMR (75 MHz) δ 200.0, 154.7, 138.7, 138.5, 132.9, 132.6, 124.2, 124.0, 119.4, 119.2, 105.8, 105.6, 76.1, 75.9, 73.3, 73.1, 50.5, 49.8, 33.7, 33.6, 27.6, 27.0(2), 26.9, 25.5, 25.4, 20.7, 19.6, 19.5, 19.4, 19.3.

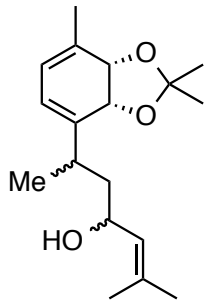
IR ν_{max} (KBr) 2980, 2934, 1686, 1619, 1448, 1378, 1209, 1157, 1118, 1035, 873 cm^{-1}.

LREIMS (70 eV) *m/z* 290 ($M^{+\bullet}$, <1%), 275 [$(M-CH_3\bullet)^+$, 1%], 232 (33), 217 (14), 199 (23), 177 (32), 149 (41), 135 (100), 132 (50), 91 (34).

HREIMS Found: $(M - CH_3\bullet)^+$, 275.1652. $C_{18}H_{26}O_3$ requires 275.1647.

Optical Rotation $[\alpha]_D = -2.3$ (*c* = 0.72, $CHCl_3$).

2-Methyl-6-{(3a*R*,7a*S*)-2,2,7-trimethyl-3a,7a-dihydrobenzo[*d*][1,3]dioxol-4-yl}hept-2-en-4-ol (42a and 42b)



42

A magnetically stirred solution of enone **41** (560 mg, 1.93 mmol) in MeOH (10 mL) was cooled to 0 ºC and treated with $NaBH_4$ (153 mg, 4.1 mmol). The ensuing mixture was stirred at 0 ºC for 1 h then warmed to 18 ºC and stirred at this temperature for a further 1 h. Water (2 mL) was then added and the reaction mixture so-formed concentrated under reduced pressure. The ensuing residue was partitioned between half-brine (10 mL) and DCM (20 mL) then the separated aqueous phase extracted with DCM (2 × 20 mL). The combined organic fractions were washed with brine (1 × 10 mL) before being dried (Na_2SO_4), filtered and concentrated under reduced pressure. The light-

yellow oil thus obtained was subjected to flash column chromatography (silica, 1:9 → 1:4 v/v EtOAc/hexane gradient elution) and thereby affording two fractions, A and B.

Concentration of fraction A (R_f = 0.2 in 1:4 v/v EtOAc/hexane) afforded a 3:1 mixture of a pair of the diastereoisomeric forms of *alcohol* ***42a*** (190 mg, 34%) as a clear, colourless oil.

^{1}H NMR (400 MHz) δ (major isomer) 5.77 (d, *J* = 6.0 Hz, 1H), 5.66 (dd, *J* = 6.0 and 1.2 Hz, 1H), 5.17 (d, *J* = 8.8 Hz, 1H), 4.52 (s, 2H), 4.43 (m, 1H), 2.56 (m, 1H), 1.85 (s, 3H), 1.71 (s, 3H), 1.66 (s, 3H), 1.61 (s, 1H), 1.61-1.50 (complex m, 1H), 1.49 (broad s, 1H), 1.40 (s, 3H), 1.33 (s, 3H), 1.12 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz) δ (major isomer) 138.8, 134.4, 133.0, 128.4, 120.4, 119.2, 105.7, 76.5, 72.2, 66.9, 43.5, 34.6, 27.1, 25.7, 25.6, 20.2, 19.2, 18.2.

IR ν_{max} (KBr) 3435, 2966, 2931, 1669, 1618, 1450, 1377, 1234, 1156, 1055, 997, 871 cm^{-1}.

LREIMS (70 eV) *m/z* 274 [$(M - H_2O)^{+\bullet}$, 2%], 234 (29), 216 (27), 201 (23), 177 (24), 135 (100), 109 (35), 107 (36), 91 (41).

HREIMS Found: $(M - H_2O)^{+\bullet}$, 274.1929. $C_{18}H_{28}O_3$ requires 274.1933.

Concentration of fraction B (R_f = 0.15 in 1:4 v/v EtOAc/hexane) afforded an 3:2 mixture of the other pair of the diastereoisomeric forms of *alcohol* ***42b*** (285 mg, 50%) as a clear, colorless oil.

^{1}H NMR (400 MHz) δ (major isomer) 5.74 (d, *J* = 5.6 Hz, 1H), 5.65 (m, 1H), 5.17 (dt, *J* = 8.8 and 1.6 Hz, 1H), 4.53 (s, 2H), 4.40 (m, 1H), 2.48 (octet, *J* = 7.2 Hz, 1H), 1.90–1.80 (complex m, 2H), 1.85 (s, 3H), 1.71 (s, 3H), 1.66 (s, 3H), 1.50–1.40 (complex m, 1H), 1.42 (s, 3H), 1.36 (s, 3H), 1.14 (d, *J* = 6.8 Hz, 3H).

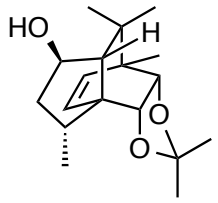
^{13}C NMR (100 MHz) δ (major isomer) 138.8, 134.5, 132.9, 128.6, 120.2, 119.3, 105.9, 76.4, 72.3, 67.3, 44.0, 35.6, 27.0, 25.8, 25.6, 20.1, 19.3, 18.2.

IR ν_{max} (KBr) 3436, 2967, 2931, 2913, 2876, 1669, 1450, 1376, 1234, 1215, 1055, 999, 871 cm^{-1}.

LREIMS (70 eV) *m/z* 274 [$(M - H_2O)^{+\bullet}$, 3%], 234 (35), 216 (20), 201 (28), 177 (26), 135 (100), 121 (21), 119 (23), 109 (35), 107 (40), 91 (43).

HREIMS Found: $(M - H_2O)^{+\bullet}$, 274.1930. $C_{18}H_{28}O_3$ requires 274.1933.

(3a*S*,4*S*,6*R*,8*R*,8a*R*,8b*R*)-2,2,4,5,5,8-Hexamethyl-3a,4,5,5a,6,7,8,8b-octahydro-4,8a-ethenoindeno[4,5-*d*][1,3]dioxol-6-ol (43)



43

A magnetically stirred solution of a mixture of the two diastereomeric forms of alcohol **42b** (35 mg, 0.12 mmol) obtained as fraction B above and BHT (*ca*. 2 mg) in mesitylene (20 mL) was heated at reflux for 96 h then cooled and concentrated under reduced pressure to give a yellow oil. Subjection of this material to flash column chromatography (silica, 3:7 v/v EtOAc/hexane elution) gave, after concentration of the appropriate fractions (R_f = 0.3), the *tricyclic alcohol **43*** (15 mg, 43% or 71% based on the isomer that reacts in the IMDA) as a white, semi-solid.

^{1}H NMR (600 MHz) δ 5.87 (d, *J* = 8.4 Hz, 1H), 5.76 (d, *J* = 8.4 Hz, 1H), 4.23 (d, *J* = 7.1 Hz, 1H), 4.04 (d, *J* = 7.1 Hz, 1H), 3.93 (m, 1H), 2.21 (m, 1H), 1.76 (m, 2H), 1.29 (m, 1H), 1.27 (s, 3H), 1.25 (s, 3H), 1.19 (s, 3H), 1.10 (d, *J* = 6.8 Hz, 3H), 1.01 (s, 3H), 0.92 (s, 3H).

^{13}C NMR (150 MHz) δ 138.2, 126.3, 108.3, 85.6, 81.4, 73.9, 62.8, 52.6, 46.2, 43.8, 37.8, 37.3, 27.1, 25.7, 25.1, 22.1, 16.1, 15.2.

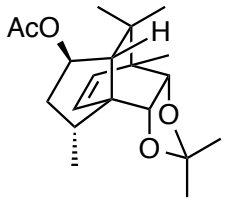
IR ν_{max} (KBr) 3392, 3039, 2970, 2936, 2876, 1455, 1378, 1370, 1256, 1207, 1168, 1083, 1056, 985, 878, 731 cm^{-1}.

LREIMS (70 eV) *m/z* 277 [$(M - CH_3\bullet)^+$, 9%], 234 (34), 216 (17), 201 (15), 192 (100), 177 (28), 133 (85).

HREIMS Found: $(M - CH_3\bullet)^+$, 277.1812. $C_{18}H_{28}O_3$ requires 277.1804.

Optical Rotation $[\alpha]_D = -22.4$ (*c* = 0.2 , $CHCl_3$).

(3a*S*,4*S*,6*R*,8*R*,8a*R*,8b*R*)-2,2,4,5,5,8-Hexamethyl-3a,4,5,5a,6,7,8,8b-octahydro-4,8a-ethenoindeno[4,5-*d*][1,3]dioxol-6-yl acetate (44)



44

A magnetically stirred solution of alcohol **43** (51 mg, 0.17 mmol), acetic anhydride (24.5 μL, 0.26 mmol) and 4-(*N,N*-dimethylamino)pyridine (DMAP, 32 mg, 0.26 mmol), and pyridine 2 mL was stirred at room temperature for 12 h then quenched with $NaHCO_3$ (5 mL of saturated aqueous solution). The aqueous layer was extracted with extracted with Et_2O (3 × 5 mL) and the combined organic fractions were washed with H_2O (1 × 5 mL), brine (5 mL) before being dried (Na_2SO_4), filtered and concentrated under reduced pressure to give a clear, colourless oil. Subjection of this material to flash column chromatography (silica, 15:85 v/v EtOAc/hexane elution) and concentration of appropriate fractions (R_f = 0.50) afforded *title acetate **44*** (54 mg, 95%) as a white, crystalline solid, mp = 81-100 °C.

^{1}H NMR (400 MHz) δ 5.88 (d, *J* = 8.0 Hz, 1H), 5.78 (d, *J* = 8.0 Hz, 1H), 4.73 (m, 1H), 4.24 (d, *J* = 6.8 Hz, 1H), 4.05 (d, *J* = 6.8 Hz, 1H), 2.14 (m, 1H), 2.00 (s, 3H), 1.91 (m, 1H), 1.73 (m, 1H), 1.61 (brs, 1H), 1.54 (d, *J* = 8.8 Hz, 1H), 1.27 (s, 3H), 1.26 (s, 3H), 1.13 (d, *J* = 6.8 Hz, 3H), 0.98 (s, 3H), 0.79 (s, 3H).

^{13}C NMR (100 MHz) δ 170.8, 138.7, 125.9, 108.4, 85.4, 81.4, 59.0, 51.9, 46.2, 40.9, 37.9, 37.6, 26.6, 25.6, 25.1, 22.2, 21.2, 15.6, 15.2.

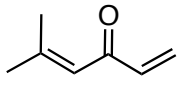
IR ν_{max} (KBr) 3041, 2972, 2935, 2878, 1738, 1455, 1370, 1257, 1243, 1208, 1169, 1134, 1087, 1050, 1014, 886, 731 cm^{-1}.

LREIMS (70 eV) m/z 334 ($M^{+\bullet}$, <1), 319[$(M - CH_3\bullet)^+$, 15], 274 (9), 216 (80), 210 (46), 187 (34), 174 (74), 159 (100), 147 (29), 135 (34), 119 (22), 105 (19), 91 (23), 85 (17), 77 (10), 67 (7), 55 (12).

HREIMS Found: $M^{+\bullet}$, 334.2144, $C_{20}H_{30}O_4$ requires 334.2144.

Optical Rotation $[\alpha]_D = -13.7$ ($c = 0.24$, $CHCl_3$).

5-Methylhexa-1,4-dien-3-one (47)



47

Step i: Following a procedure established by Szymoniak et al.,[33] a solution of 3-methyl-but-2-enal (**48**) (770 μL, 7.98 mmol) in THF (2 mL) was added dropwise to a magnetically stirred solution of vinyl magnesium bromide (10 mL of a 1.0 M solution in THF, 10.0 mmol) in THF (5 mL) maintained at 18 ºC under nitrogen atmosphere. The ensuing mixture was stirred at this temperature for 40 min then H_2O (5 mL) was added and the separated aqueous phase was extracted with Et_2O (3 × 10 mL). The combined organic phases were then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give allylic alcohol **49**[34] (800 mg, *ca.* 89%) as an orange oil. This material was sufficiently pure to be used in the next step of the reaction sequence.

^{1}H NMR (300 MHz) δ 5.88 (ddd, J = 17.1, 10.3 and 5.8 Hz, 1H), 5.22 (dt, J = 17.1 and 1.5 Hz, 1H), 5.18 (dt, J = 10.3 and 1.5 Hz, 1H), 5.07 (dt, J = 7.1 and 1.2 Hz, 1H), 4.84 (uneven t, J = 7.1 and 5.8 Hz, 1H), 1.73 (d, J = 1.0 Hz, 3H), 1.70 (d, J = 1.0 Hz, 3H) 1.67 (br s, 1H).

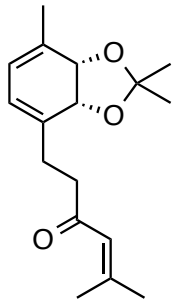
The data presented above as well as all the other data acquired on this compound matched those reported in the literature.[34]

Step ii. DDQ (555 mg, 2.44 mmol) was added to a solution of alcohol **49** (252 mg, 2.25 mmol) in Et_2O (1 mL) and the resulting slurry was stirred at 18 ºC for 24 h. The ensuing mixture was poured into pentane (10 mL) (to precipitate the $DDQH_2$), the flask washed with additional pentane (2 × 5 mL) and the resulting solid filtered off and washed with pentane (2 × 5 mL). The combined filtrates were carefully concentrated under reduced pressure (temp. = <15 ºC, pressure <750) to give (volatile) divinyl ketone **47**[12, 35] (101 mg, 41%) as a yellow liquid. This material was sufficiently pure to be used in the next step of the reaction sequence without further purification.

^{1}H NMR (300 MHz) δ 6.39 (dd, *J* = 17.5 and 10.4 Hz, 1H), 6.27 (qu, *J* = 1.3 Hz, 1H), 6.19 (dd, *J* = 17.5 and 1.5 Hz, 1H), 5.73 (dd, *J* = 10.4 and 1.5 Hz, 1H), 2.17 (d, *J* = 1.3 Hz, 3H), 1.93 (d, *J* = 1.3 Hz, 3H).

The data presented above as well as all the other data acquired on this compound matched those reported in the literature.[12, 35]

5-Methyl-1-((3a*R*,7a*S*)-2,2,7-trimethyl-3a,7a-dihydrobenzo[*d*][1,3]dioxol-4-yl)hex-4-en-3-one (50)



50

The Michael addition of the anion derived from iodo-diol **39** (1.00 g, 3.42 mmol) to enone **47** (900 μL, *ca.* 7.20 mmol) was carried out as described for compound **41** using *i*-PrMgCl (3.4 mL of a 2.0 M solution in THF, 6.8 mmol). The initially formed product was a silyl enol ether so this was dissolved in THF (7 mL) then treated with TBAF (7 mL of a 1.0 M solution in THF, 7.00 mmol) and stirred at 18 ºC for 1 h. The ensuing mixture was concentrated under reduced pressure onto silica (*ca.* 2 g, 230 – 400 mesh) and the resulting free-flowing solid subjected to flash column chromatography (silica, 1:9 v/v EtOAc/hexane elution). Concentration of the appropriate fractions (R_f = 0.4 in 3:7 v/v EtOAc/hexane) gave previously reported title enone **50**[12] (568 mg, 60%) as a clear, colourless oil.

^{1}H NMR (300 MHz) δ 6.09 (m, 1H), 5.65 (s, 2H), 4.50 (AB quartet, *J* = 8.4 Hz, 2H), 2.63 (m, 2H), 2.51 (m, 2H), 2.13 (s, 3H), 1.88 (s, 3H), 1.86 (s, 3H), 1.40 (s, 3H), 1.35 (s, 3H).

^{13}C NMR (75 MHz) δ 200.0, 155.1, 134.1, 132.3, 123.6, 119.7, 119.6, 105.8, 75.6, 74.3, 42.1, 28.3, 27.6, 27.0, 25.3, 20.7, 19.8.

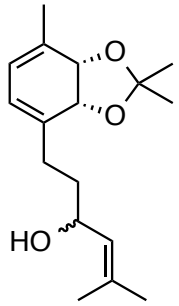
IR ν_{max} (KBr) 2982, 2933, 2912, 1688, 1620, 1447, 1278, 1269, 1235, 1208, 1180, 1158, 1110, 1062, 1039, 1013, 872 cm^{-1}.

LREIMS (70 eV) *m/z* 261 [$(M - CH_3\bullet)^+$, <1%], 218 (49), 199 (19), 191 (22), 185 (18), 163 (39), 149 (58), 135 (55), 121 (90), 108 (26), 91 (39), 83 (100), 77 (35), 55 (81), 43 (82).

HREIMS Found: $M^{+\bullet}$, 276.1722. $C_{17}H_{24}O_3$ requires 276.1725. Found: $(M - CH_3\bullet)^+$, 261.1491. $C_{17}H_{24}O_3$ requires 261.1491.

Optical Rotation $[\alpha]_D = +19$ (*c* = 0.9, $CHCl_3$).

5-Methyl-1-((3a*R*,7a*S*)-2,2,7-trimethyl-3a,7a-dihydrobenzo[*d*][1,3]dioxol-4-yl)hex-4-en-3-ol (46)



46

A magnetically stirred solution of enone **50** (100 mg, 0.40 mmol) in MeOH (4 mL) was cooled to 0 ºC and treated with $NaBH_4$ (29 mg, 0.77 mmol). The resulting mixture was stirred at 0 ºC for 1 h then warmed to 18 ºC and stirred at this temperature for a further 1 h before quenching with H_2O (1 mL). The solvents were removed under reduced pressure and the residue was partitioned between half-brine (10 mL) and DCM (20 mL). The separated aqueous phase was further extracted with DCM (2 × 20 mL). The combined organic fractions were washed with brine (10 mL) before being dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by flash column chromatography (silica, 1:9 to 3:7 v/v EtOAc/hexane gradient elution) and concentration of the appropriate fractions (R_f = 0.4 in 1:1 v/v EtOAc/hexane) afforded previously reported, *ca.* 1:1 mixture of the epimeric forms of alcohol **46**[12] (88 mg, 84%) as a clear, colourless oil.

^{1}H NMR (300 MHz) δ 5.69 (m, 2H), 5.19 (m, 1H), 4.51 (s, 2H), 4.37 (m, 1H), 2.25 (m, 2H), 1.87 (s, 3H), 1.84-1.57 (m, 2H), 1.72 (s, 3H), 1.68 (s, 1.5H), 1.66 (s, 1.5H), 1.42 (s, 3H), 1.37 (s, 1.5H), 1.35 (s, 1.5H) (OH proton resonance not observed).

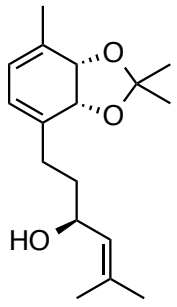
^{13}C NMR (75 MHz) δ 135.5, 135.2, 134.8, 134.6, 132.2, 132.1, 128.0, 127.9, 119.7, 119.6 (three signals overlapping), 105.7, 105.7, 75.8, 75.7, 74.4, 74.3, 68.4, 68.1, 35.4, 35.3, 29.8, 29.7, 27.0, 26.9, 25.8 (two signals overlapping), 25.4, 25.3, 19.8 (two signals overlapping), 18.3, 18.2.

IR ν_{max} (KBr) 3434, 2983, 2932, 2914, 2879, 1448, 1377, 1235, 1209, 1159, 1064, 1045, 1021, 872, 849 cm^{-1}.

LREIMS (70 eV) *m/z* 260 [$(M - H_2O)^{+\bullet}$, 6%), 245 [$(M - H_2O - CH_3\bullet)^+$, 10], 220 (92), 202 (52), 187 (67), 178 (25), 159 (40), 147 (48), 133 (27), 121 (100), 108 (59), 95 (69), 91 (53), 85 (68), 77(51), 67 (30), 55 (40), 43 (65).

HREIMS Found: $(M - H_2O)^{+\bullet}$, 260.1777. $C_{17}H_{26}O_3$ requires 260.1776.

(*S*)-5-Methyl-1-{(3a*R*,7a*S*)-2,2,7-trimethyl-3a,7a-dihydrobenzo[*d*][1,3]dioxol-4-yl}hex-4-en-3-ol [*S*-46] and (3a*S*,4*S*,6*R*,8a*R*,8b*R*)-2,2,4,5,5-Pentamethyl-3a,4,5,5a,6,7,8,8b-octahydro-4,8a-ethenoindeno[4,5-*d*][1,3]dioxol-6-ol (51)



***S*-46**

A magnetically stirred solution of a *ca.* 1:1 epimeric mixture of alcohol **46** (273 mg, 0.98 mmol) and BHT (3.5 mg, 0.02 mmol) in mesitylene (160 mL) was heated at reflux for 96 h then cooled and concentrated under reduced pressure to give a yellow oil. Subjection of this material to flash column chromatography (silica, 3:7 v/v EtOAc/hexane elution) afforded two fractions, A and B.

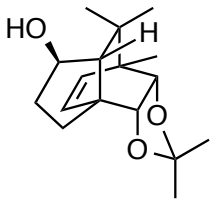
Concentration of fraction A (R_f = 0.3) afforded starting material enriched in compound *S*-**46** (100 mg, 36%) as a clear, colourless oil.

^{1}H NMR (400 MHz) δ 5.66 (m, 2H), 5.17 (m, 1H), 4.49 (m, 2H), 4.36 (m, 1H), 2.23 (m, 2H), 1.85 (s, 3H), 1.82-1.56 (complex m, 12H), 1.34 (s, 3H).

^{13}C NMR (100 MHz) δ 135.3, 134.7, 132.1, 127.9, 119.6, 119.5, 105.7, 75.7, 74.2, 68.4, 35.2, 29.8, 27.0, 25.7, 25.4, 19.7, 18.3.

Optical Rotation $[\alpha]_D$ = +15 (*c* = 2.8, $CHCl_3$).

(3a*S*,4*S*,6*R*,8a*R*,8b*R*)-2,2,4,5,5-pentamethyl-3a,4,5,5a,6,7,8,8b-octahydro-4,8a-ethenoindeno[4,5-*d*][1,3]dioxol-6-ol (51)



51

Concentration of fraction B (R_f = 0.2) afforded the previously reported compound **51**[12] (120 mg, 44% or 71% based on recovered *S*-**46**) as a clear, colourless oil. The spectral data derived from this material were identical with those reported earlier.[12]

^{1}H NMR (300 MHz) δ 5.68 (AB quartet, *J* = 8.3 Hz, 2H), 4.24 (d, *J* = 7.2 Hz, 1H), 4.08 (d, *J* = 7.2 Hz, 1H), 3.90 (m, 1H), 2.20 (m, 1H), 1.87 (m, 2H), 1.60 (m, 1H), 1.30 (s, 3H), 1.27 (s, 3H), 1.22 (d, *J* = 8.1 Hz, 1H), 1.19 (s, 3H), 1.02 (s, 3H), 0.94 (s, 3H) (OH proton resonance not observed).

^{13}C NMR (75 MHz) δ 137.9, 132.2, 108.3, 84.9, 81.4, 74.8, 61.0, 49.4, 46.3, 37.4, 34.0, 30.0, 27.0, 25.6, 25.0, 21.6, 15.0.

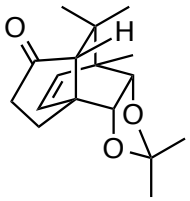
IR ν_{max} (KBr) 3429, 3036, 2967, 2872, 1455, 1370, 1282, 1255, 1207, 1167, 1085, 1056, 1017, 898, 870, 733 cm^{-1}.

LREIMS (70 eV) *m/z* 263 [$(M - CH_3\bullet)^+$, 19%], 220 (73), 202 (28), 187 (31), 178 (99), 173 (39), 163 (48), 147 (41), 134 (41), 119 (100), 105 (42), 95 (38), 91 (41), 77 (27), 69 (18), 55 (35), 43 (64).

HREIMS Found: $(M - CH_3\bullet)^+$, 263.1647. $C_{17}H_{26}O_3$ requires 263.1647.

Optical rotation $[\alpha]_D = -5$ (c = 0.4, $CHCl_3$).

(3aS,4S,8aR,8bR)-2,2,4,5,5-Pentamethyl-3a,4,5,5a,7,8-hexahydro-4,8a-ethenoindeno[4,5-d][1,3]dioxol-6(8bH)-one (55)



55

A magnetically stirred solution of alcohol **51** (250 mg, 0.91 mmol) in DCM (10 mL) maintained at 18 °C, was treated, successively, with molecular sieves (400 mg of 3 Å material), PDC (376 mg, 1 mmol) and AcOH (0.5 mL). After 12 h the reaction mixture was treated with Celite™ (400 mg), stirred for a further 0.5 h then filtered. The filtrate was concentrated under reduced pressure to give dark-brown oil that was subjected flash column chromatography (silica, 3:7 v/v EtOAc/hexane elution). Concentration of the appropriate fractions (R_f = 0.3 in 1:4 v/v EtOAc/hexane) afforded the *title compound **55*** (246 mg, 99%) as a white, waxy solid, mp = 104 –107 ºC.

^{1}H NMR (400 MHz) δ 5.88 (d, J = 8.0 Hz, 1H), 5.75 (d, J = 8.0 Hz, 1H), 4.24 (dd, J = 7.2 and 1.2 Hz, 1H), 4.15 (dd, J = 7.2 and 0.8 Hz, 1H), 2.26 (m, 3H), 1.71 (m, 1H), 1.48 (s, 1H), 1.30 (s, 3H), 1.26 (s, 3H), 1.17 (s, 3H), 1.06 (s, 3H), 0.92 (s, 3H).

^{13}C NMR (100 MHz) δ 215.0, 141.2, 129.3, 109.0, 84.5, 81.3, 60.8, 48.8, 46.8, 39.9, 39.0, 28.5, 25.9, 25.6, 25.0, 20.6, 14.7.

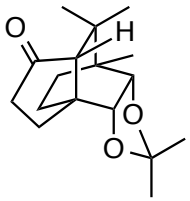
IR ν_{max} (KBr) 3039, 2974, 2957, 2937, 2902, 2876, 1735, 1377, 1366, 1206, 1085, 1064, 730 cm^{-1}.

LREIMS (70 eV) *m/z* 276 (M^+, <1%), 261 [$(M - CH_3\bullet)^+$, 14%], 218 (100), 203 (23), 189 (26), 176 (62), 161 (30), 147 (35), 133 (54), 121 (52), 105 (28), 100 (15), 91 (28), 83 (84), 77 (18), 65 (11), 55 (23).

HREIMS Found: $M^{+\bullet}$, 276.1725. $C_{17}H_{24}O_3$ requires 276.1725.

Optical Rotation $[\alpha]_D = -81.5$ ($c = 0.2$, $CHCl_3$).

(3a*S*,4*S*,8a*S*,8b*R*)-2,2,4,5,5-Pentamethylhexahydro-4,8a-ethanoindeno[4,5-*d*][1,3]dioxol-6(8b*H*)-one (56)



56

A magnetically stirred solution of the ketone derived from compound **55** (114 mg, 0.41 mmol) in ethanol (20 mL) was treated with 10% palladium on carbon (40 mg) and the resulting suspension was stirred at 18 ºC under a hydrogen atmosphere (1 atm) for 16 h. The reaction mixture was then filtered through a pad of Celite™ and the solids thus retained were washed with ethanol (2 × 5 mL) and DCM (2 × 5 mL). The combined filtrates were concentrated under reduced pressure to give *compound **56*** **(**114 mg, 99%) as a white, waxy solid.

^{1}H NMR (400 MHz) δ 4.08 (dd, J = 8.4 and 2.4 Hz, 1H), 4.00 (dd, J = 8.4 and 1.2 Hz, 1H), 2.32–2.19 (complex m, 2H), 1.87 (ddd, J = 12.4, 8.0 and 2.0 Hz, 1H), 1.70-1.58 (complex m, 3H), 1.53 (s, 3H), 1.47 (s, 1H), 1.37 (s, 3H), 1.34 (dt, J = 5.6 and 1.6 Hz, 1H), 1.19 (dt, J = 9.6 and 2.4 Hz, 1H), 1.08 (s, 3H), 1.01 (s, 3H), 0.78 (s, 3H).

^{13}C NMR (100 MHz) δ 216.5, 109.1, 82.2, 78.7, 60.5, 42.1, 39.6, 38.0, 33.9, 30.3, 26.5, 25.8, 24.3, 22.1, 20.3, 20.2, 15.9.

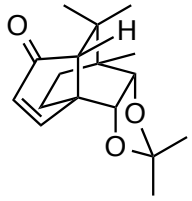
IR ν_{max} (KBr) 2964, 2873, 2810, 1735, 1466, 1409, 1393, 1379, 1369, 1285, 1262, 1207, 1167, 1116, 1084, 1061, 1042, 1015, 996, 879 cm^{-1}.

LREIMS (70 eV) *m/z* 263 [$(M - CH_3\bullet)^+$, 100%], 221 (23), 203 (52), 149 (52), 105 (36).

HREIMS Found: $(M - CH_3\bullet)^+$, 263.1646. $C_{17}H_{26}O_3$ requires 263.1647

Optical Rotation $[\alpha]_D = -103.9$ (c = 3.5, $CHCl_3$).

(3a*S*,4*S*,8a*S*,8b*R*)-2,2,4,5,5-Pentamethyl-3a,4,5,5a-tetrahydro-4,8a-ethanoindeno[4,5-*d*][1,3]dioxol-6(8b*H*)-one (45)



45

Step i: Following a protocol defined by Lalic and Corey,[39b] a magnetically stirred solution of ketone **56** (259 mg, 0.93 mmol) in DCM (10 mL) was cooled to 0 °C then treated with triethylamine (1.56 mL, 11.16 mmol) and TMSOTf (1.05 mL, 5.58 mmol). The resulting mixture was stirred at 0 °C for 1.5 h, warmed to 18 °C, stirred at this temperature for a further 0.5 h then diluted with pentane (30 mL). The resulting mixture was washed with $NaHCO_3$ (1 × 20 mL of a saturated aqueous solution) and brine (1 × 20 mL) before being dried (Na_2SO_4), filtered and concentrated under reduced pressure to give the anticipated silyl enol ether as a light-yellow oil of sufficient purity to be used in *Step ii* as detailed immediately below.

Step ii: A magnetically stirred solution of this enol ether in DMSO (3 mL) was treated with a 1:1 mixture of IBX and MPO (3.5 mL of a 0.4 M solution in DMSO, 1.4 mmol). The resulting mixture was protected from light and allowed to stir at 18 °C for 16 h then poured into $NaHCO_3$ (15 mL of a saturated aqueous solution) and extracted with EtOAc (5 × 10 mL). The combined organic fractions were washed with brine (1 × 40 mL) before being dried (Na_2SO_4), filtered and concentrated under reduced pressure to give light-yellow oil. Subjection of this material to flash column chromatography (silica, 1:4 v/v EtOAc/hexane elution) and concentration of the relevant fractions (**R_f** = 0.2) afforded a 1:5 mixture of compounds **45** and **56** (223 mg, 89%) as a white solid, mp = 90-116 °C.

^{1}H NMR (400 MHz) δ (for compound **45**) 7.56 (d, J = 6.0 Hz, 1H), 6.03 (d, J = 6.0 Hz, 1H), 4.14 (dd, J = 8.0 and 0.4 Hz, 1H), 4.09 (dd, J = 8.0 and 2.0 Hz, 1H), 2.09 (broad t, J = 12.0 Hz, 1H), 1.71

(broad d, J = 2.0 Hz, 1H), 1.65 (m, 1H), 1.56 (s, 3H), 1.38 (s, 3H), 1.22 (m, 1H), 1.17 (s, 3H), 1.08 (s, 3H), 1.02 (m, 1H), 0.82 (s, 3H).

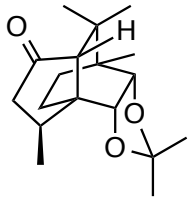
^{13}C NMR (100 MHz) δ (for compound **45**) 205.0, 163.8, 134.6, 109.8, 78.4, 76.4, 58.6, 47.7, 41.1, 34.0, 26.3, 26.2, 25.9, 24.3, 22.6, 19.8, 15.6.

IR ν_{max} (KBr) 2965, 1712, 1573, 1467, 1370, 1260, 1208, 1175, 1078, 1046, 995, 970, 879, 861, 845, 776 cm^{-1}.

LREIMS (70 eV) *m/z* 276 ($M^{+\bullet}$, 5%), 261 [$(M - CH_3\bullet)^+$, 100], 218 (23), 201 (62), 189 (14), 176 (41), 161 (34), 159 (27), 147 (23), 135 (31), 121 (17), 107 (35), 101 (43), 91 (28).

HREIMS Found: $M^{+\bullet}$, 276.1736. $C_{17}H_{24}O_3$ requires 276.1725.

(3a*S*,4*S*,8*S*,8a*S*,8b*R*)-2,2,4,5,5,8-Hexamethylhexahydro-4,8a-ethanoindeno[4,5-*d*][1,3]dioxol-6(8b*H*)-one (58)



58

Following a protocol described by Spessard and Stoltz,[100] a magnetically stirred solution of MeMgBr (0.96 mL of 3 M solution Et_2O) in dry Et_2O (10 mL) maintained at −10 °C was treated with copper bromide/dimethyl sulfide complex (29 mg, 0.14 mmol). The resulting pale-yellow solution was stirred at −10 °C for 0.25 h before a solution of a 1:5 mixture of ketone **56** and enone **45** (396 mg, 1.43 mmol) in Et_2O (5 mL) was added, *via* syringe pump, over 1 h. The ensuing mixture was stirred for an additional 0.25 h at this temperature then quenched with NH_4Cl (20 mL of a saturated aqueous solution). The separated aqueous layer was extracted with Et_2O (3 × 20 mL) then the combined organic layers were washed with brine (1 × 30 mL) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a white solid. Subjection of this material to flash column chromatography (silica, 3:7 v/v EtOAc/hexane elution) and concentration of the relevant fractions (R_f = 0.5) afforded *compound **58*** (223 mg, 85%) as a white, crystalline solid, mp = 133-136 ºC.

^{1}H NMR (400 MHz) δ 4.24 (dd, *J* = 8.0 and 1.6 Hz, 1H), 4.05 (dd, *J* = 8.0 and 2.0 Hz, 1H), 2.58 (dd, *J* = 19.2 and 8.4 Hz, 1H), 2.05 (quintet, *J* = 7.6 Hz, 1H), 1.95 (dt, *J* = 19.2 and 1.2 Hz, 1H), 1.66 (m, 2H), 1.59 (broad t, *J* = 2.0 Hz, 1H), 1.54 (s, 3H), 1.39 (s, 3H), 1.38 (m, 1H), 1.20 (m, 1H), 1.06 (s, 3H), 1.02 (s, 3H), 1.01 (d, *J* = 6.4 Hz, 3H), 0.79 (s, 3H).

^{13}C NMR (100 MHz) δ 217.0, 108.9, 78.3, 76.0, 56.8, 47.2, 43.6, 39.6, 33.8, 33.1, 26.7, 25.9, 24.3, 22.5, 22.4, 20.4, 16.7, 16.1.

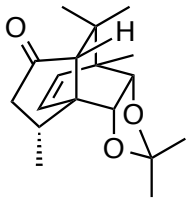
IR ν_{max} (KBr) 2964, 2909, 1728, 1466, 1368 1265, 1207, 1167, 1084, 1041, 879 cm^{-1}.

LREIMS (70 eV) *m/z* 292 ($M^{+\bullet}$, <1%), 277 [$(M - CH_3\bullet)^+$, 100], 263 (3), 235 (23), 217 (48), 175 (18), 147 (23), 119 (82), 105 (17), 91 (12).

HREIMS Found: $M^{+\bullet}$, 292.2038. $C_{18}H_{28}O_3$ requires $M^{+\bullet}$, 292.2038**.**

Optical Rotation $[\alpha]_D$ = −97.8 (*c* = 0.23, $CHCl_3$).

(3a*S*,4*S*,8*R*,8a*R*,8b*R*)-2,2,4,5,5,8-Hexamethyl-3a,4,5,5a,7,8-hexahydro-4,8a-ethenoindeno[4,5-*d*][1,3]dioxol-6(8b*H*)-one (59)



59

A magnetically stirred solution of alcohol **43** (25 mg, 0.09 mmol) in DCM (3 mL) maintained at 18 °C was treated with molecular sieves (40 mg of 3 Å material), PDC (37.6 mg, 0.1 mmol) and AcOH (0.1 mL). After 12 h the reaction mixture was treated with Celite™ (40 mg), stirred at 18 °C for 0.5 min then filtered. The filtrate was concentrated under reduced pressure to give dark- brown oil that was subjected to flash column chromatography (silica, 3:7 v/v EtOAc/hexane elution). Concentration of the appropriate fractions (R_f = 0.4) afforded *ketone* **59** (24.6 mg, 99%) as a white, crystalline solid, mp = 108 -120 ºC.

^{1}H NMR (400 MHz) δ 5.95 (m, 2H), 4.24 (d, *J* = 8.0 Hz, 1H), 4.16 (d, *J* = 8.0 Hz, 1H), 2.38 (dd, *J* = 18.0 and 6.8 Hz, 1H), 2.11 (septet, *J* = 6.8 Hz, 1H), 1.94 (dd, *J* = 18.0 and 12.8 Hz, 1H), 1.53 (s, 1H), 1.30 (s, 3H), 1.28 (d, *J* = 6.4 Hz, 3H), 1.27 (s, 3H), 1.20 (s, 3H), 1.07 (s, 3H), 0.93 (s, 3H).

^{13}C NMR (100 MHz) δ 214.6, 141.3, 124.4, 108.9, 85.5, 81.3, 63.0, 51.1, 47.7, 47.0, 40.1, 35.8, 26.0, 25.7, 25.1, 20.7, 15.1, 14.8.

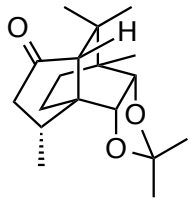
IR ν_{max} (KBr) 3038, 2973, 2937, 2901, 2878, 1736, 1459, 1379, 1370, 1263, 1207, 1168, 1087, 1070, 1044, 986, 879 cm^{-1}.

LREIMS (70 eV) *m/z* 275 [$(M - CH_3\bullet)^+$, 15%], 232 (97), 217 (23), 203 (22), 190 (80), 175 (33), 161 (38), 148 (55), 147 (43), 135 (89), 133 (92), 119 (35), 105 (27), 91 (35), 84 (53), 83 (100), 55 (45).

HREIMS Found: $(M - CH_3\bullet)^+$, 275.1648. $C_{18}H_{26}O_3$ requires 275.1647.

Optical Rotation $[\alpha]_D = -60.4$ (*c* = 0.73, $CHCl_3$).

(3a*S*,4*S*,8*R*,8a*S*,8b*R*)-2,2,4,5,5,8-Hexamethylhexahydro-4,8a-ethanoindeno[4,5-*d*][1,3]dioxol-6(8b*H*)-one (3-*epi*-58)



3-*epi*-**58**

A magnetically stirred solution of the ketone **59** (5 mg, 0.017 mmol) in ethanol (1 mL) was treated with 10% palladium on carbon (2 mg) and the resulting suspension was stirred at 18 ºC under a hydrogen atmosphere (1 atm) for 16 h. The reaction mixture was then filtered through a pad of Celite™ (in Pasteur pipette) and the solids thus retained were washed with ethanol (2 × 1 mL) and DCM (2 × 1 mL). The combined filtrates were concentrated under reduced pressure to give *title compound 3-epi-**58*** (5 mg, 98%) as a white, waxy solid.

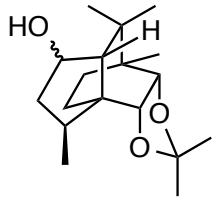
^{1}H NMR (400 MHz) δ 4.00 (dd, *J* = 8.4, 1.8 Hz, 1H), 3.95 (d, *J* = 8.4 Hz, 1H), 2.30 (m, 1H), 1.92-1.81 (m, 2H), 1.75 (brd, *J* = 12.9 Hz, 1H), 1.60 (m, 1H), 1.52 (s, 3H), 1.49 (brs, 1H), 1.36 (s, 3H), 1.21 (m, 1.5H), 1.06 (d, *J* = 6.9 Hz, 3H), 1.05 (s, 3H), 1.01 (s, 3H), 0.83 (m, 0.5H), 0.78 (s, 3H).

^{13}C NMR (100 MHz) δ 216.2, 109.1, 82.7, 78.8, 62.5, 46.4, 44.1, 39.6, 44.1, 39.6, 37.5, 34.0, 26.5, 26.0, 24.3, 21.8, 20.3, 15.9, 14.8.

IR ν_{max} (KBr) 2965, 2875, 1736, 1465, 1407, 1380, 1369, 1310, 1282, 1262, 1207, 1165, 1091, 1080, 1064, 1042, 1011, 993, 876.

GC-MS *m/z* 277 [$(M - CH_3\bullet)^+$, 100%], 235 (14), 217 (35), 175 (14), 147 (24), 133 (14), 119 (90), 105 (18), 91 (18), 83 (18), 69 (9), 55 (18), 43 (28).

(3a*S*,4*S*,8*S*,8a*S*,8b*R*)-2,2,4,5,5,8-Hexamethyloctahydro-4,8a ethanoindeno[4,5-*d*][1,3]dioxol-6-ol (60)



60

A magnetically solution of ketone **58** (55.9 mg, 0.19 mmol) in MeOH (5 mL) was cooled to 0 ºC then treated with $NaBH_4$ (36 mg, 0.95 mmol). The ensuing mixture was stirred at 0 ºC for 1 h then warmed to 18 ºC and stirred at this temperature for 15 h. After this time H_2O (1 mL) was added to the reaction mixture that was then concentrated under reduced pressure. The residue thus obtained was partitioned between half-brine (10 mL) and DCM (10 mL) then the separated aqueous phase was extracted with DCM (2 × 10 mL). The combined organic fractions were washed with brine (1 × 20 mL) before being dried (Na_2SO_4), filtered and concentrated under reduced pressure to give light-yellow oil. Subjection of this material to flash column chromatography (silica, 1:4 v/v EtOAc/hexane elution) and concentration of the appropriate fractions (R_f = 0.4 in 3:7 v/v EtOAc/hexane) gave a *ca*. 4:1 mixture of the epimeric forms of *alcohol **60*** (51 mg, 88%) as a clear, colourless oil.

^{1}H NMR (400 MHz) δ (major isomer) 4.30 (m, 1H), 4.12 (d, *J* = 8.0 Hz, 1H), 4.06 (dd, *J* = 8.0 and 1.6 Hz, 1H), 2.33 (m, 1H), 1.60-1.44 (complex m, 3H), 1.48 (s, 3H), 1.35 (s, 3H), 1.18-1.05 (complex m, 4H), 1.09 (s, 3H), 1.04 (d, *J* = 7.6 Hz, 3H), 0.94 (s, 3H), 0.76 (s, 3H) (signal due to OH proton not observed).

^{13}C NMR (100 MHz) δ (major isomer) 108.2, 78.4, 77.1, 73.4, 56.7, 44.3, 43.6, 39.3, 36.2, 33.4, 27.3, 26.0, 24.8, 24.3, 23.5, 20.3, 18.1, 16.3.

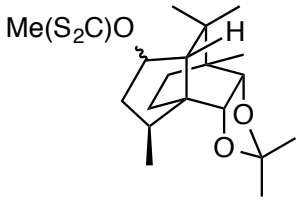
IR ν_{max} (KBr) 3436, 2962, 2874, 1465, 1372, 1262, 1207, 1167, 1145, 1088, 1051, 1020, 884 cm^{-1}.

LREIMS (70 eV) *m/z* 279 [$(M - CH_3\bullet)^+$, 100], 219 (65), 201 (29), 119 (88), 105 (52).

HREIMS Found: Found: $(M - CH_3\bullet)^+$, 279.1964. $C_{18}H_{30}O_3$ requires 279.1960.

Optical Rotation $[\alpha]_D = -42.2$ (*c* = 0.22, $CHCl_3$).

***O*-((3a*S*,4*S*,8*S*,8a*S*,8b*R*)-2,2,4,5,5,8-Hexamethyloctahydro-4,8a-ethanoindeno[4,5-*d*][1,3]dioxol-6-yl) *S*-methyl carbonodithioate (61)**



61

A magnetically stirred solution of alcohol **60 (**230 mg, 0.78 mmol) in THF (20 mL) maintained at 0 °C was treated with carbon disulfide (3.30 mL, 54.6 mmol) then iodomethane (3.4 mL, 54.6 mmol). The resulting mixture was stirred at 0 °C for 0.25 h then sodium hydride (112 mg of a 60% suspension in mineral oil, 4.68 mmol) was added. Stirring was continued at 0 ºC for 1 h then the reaction mixture was warmed to 18 ºC, stirred at this temperature for 20 h before being quenched *via* the slow addition of H_2O (5 mL) (**CAUTION**: hydrogen gas evolution). The separated aqueous phase was extracted with DCM (4 × 15 mL) and the combined organic extracts were then dried (Na_2SO_4), filtered concentrated under reduced pressure and the resulting light-yellow oil was subjected to flash chromatography (silica, hexane → 5:95 v/v EtOAc/hexane gradient elution). Concentration of the relevant fractions (R_f = 0.6 in 3:7 v/v EtOAc/hexane) gave a slightly impure sample of *xanthate ester **61*** (231 mg, 90%) as a pale-yellow oil.

^{1}H NMR (300 MHz) δ 5.88 (m, 1H), 4.17 (d, *J* = 8.1 Hz, 1H), 4.10 (dd, *J* = 8.1 and 1.6 Hz, 1H), 2.72 (m, 1H), 2.55 (s, 3H), 1.78 (d, *J* = 9.3 Hz, 1H), 1.71 (m, 1H), 1.57 (m, 2H), 1.50 (s, 3H), 1.36 (s, 3H), 1.22-1.10 (complex m, 3H), 1.05 (d, *J* = 7.5 Hz, 3H), 0.95 (s, 3H), 0.93 (s, 3H), 0.79 (s, 3H).

^{13}C NMR (75 MHz) δ 215.1, 108.4, 86.0, 78.3, 76.7, 53.6, 43.3, 39.3, 39.1, 36.6, 33.4, 27.0, 25.9, 24.2, 23.8, 23.2, 21.1, 19.0, 18.2, 16.4.

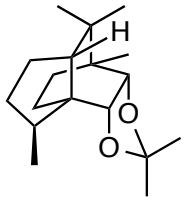
IR ν_{max} (KBr) 2963, 2931, 1705, 1465, 1370, 1238, 1207, 1061, 1025, 883 cm^{-1}.

LREIMS (70 eV) *m/z* 369 [$(M - CH_3\bullet)^+$, 14%], 353 (8), 277 (50), 276 (84), 261 (27), 219 (100), 201 (100), 191 (26), 175 (34), 174 (35), 159 (40), 145 (29), 135 (47), 133 (48), 121 (63), 119 (60), 107 (41), 95 (40), 81 (33), 69 (30), 55 (41).

HREIMS Found: $(M - CH_3\bullet)^+$, 369.1554 $C_{20}H_{32}O_3S_2$ requires 369.1558.

Optical Rotation $[\alpha]_D = -37.2$ (*c* = 0.15, $CHCl_3$).

(3a*S*,4*S*,8*S*,8a*S*,8b*R*)-2,2,4,5,5,8-Hexamethyloctahydro-4,8a-ethanoindeno[4,5-*d*][1,3]dioxole (62)



62

A magnetically stirred solution of xanthate ester **61 (**43 mg, 0.11 mmol) in toluene (4 mL) was treated with tri-*n*-butyltin hydride (0.15 mL, 0.55 mmol) and 2,2-azobisisobutyronitrile (AIBN, 2 mg, 0.1 mmol). The ensuing mixture was heated at reflux for 2 h then cooled and concentrated under reduced pressure to give a clear, colorless oil. Subjection of this material was subjected to flash chromatography (silica, hexane → 5:95 v/v EtOAc/hexane gradient elution) and concentration of the relevant fractions (R_f = 0.5 in 1:9 v/v EtOAc/hexane) gave *acetonide **62*** (22 mg, 72%) as a clear, colorless oil.

^{1}H NMR (400 MHz) δ 4.06 (s, 2H), 1.99 (m, 1H), 1.64-1.44 (complex m, 4H), 1.51 (s,3H), 1.36 (s, 3H), 1.30-0.92 (complex m, 5H), 0.97 (d, *J* = 6.8 Hz, 3H), 0.89 (s, 3H), 0.86 (s, 3H), 0.77 (s, 3H).

^{13}C NMR (100 MHz) δ 108.0, 78.6, 77.3, 51.3, 44.7, 39.3, 39.1, 34.8, 33.6, 26.8, 26.1, 24.5, 24.3, 23.9, 23.7, 21.5, 17.9, 16.7.

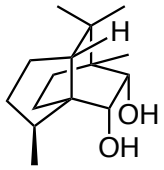
IR ν_{max} (KBr) 2953, 1459, 1371, 1261, 1206, 1166, 1087, 1042, 882 cm^{-1}.

LREIMS (70 eV) *m/z* 263 [$(M - CH_3\bullet)^+$, 70%], 221 (11), 203 (100), 175 (17), 161 (9), 147 (10), 133 (45), 119 (38), 105 (24), 91 (18).

HREIMS Found: $(M - CH_3\bullet)^+$, 263.2012. $C_{18}H_{30}O_2$ requires 263.2011.

Optical Rotation $[\alpha]_D = -32.4$ ($c = 0.7$, $CHCl_3$).

(3*S*,3a*S*,4*R*,5*S*,6*S*)-3,6,7,7-Tetramethyloctahydro-3a,6-ethanoindene-4,5-diol (33)



33

A magnetically stirred solution of acetonide **62** (8 mg, 0.02 mmol) in AcOH/H_2O (2 mL of a 4:1 v/v mixture) was heated to 60 ºC for 16 h then cooled and quenched with $NaHCO_3$ (10 mL) before being extracted with EtOAc (3 × 5 mL). The combined organic fractions were washed with brine (1 × 10 mL) then dried (Na_2SO_4), filtered and concentrated under reduced pressure to give light-yellow oil. Subjection of this material to flash column chromatography (silica, 3:7 v/v EtOAc/hexane elution) afforded two fractions, A and B.

Concentration of fraction A ($R_f = 0.3$) gave the *diol **33*** (3.5 mg, 50% or 80% based on recovered starting material) as a clear, colorless oil.

^{1}H NMR (300 MHz) δ 3.86 (dd, $J = 8.1$ and 3.9 Hz, 1H), 3.79 (m, 1H), 2.60 (d, $J = 6.6$ Hz, 1H), 2.38 (d, $J = 3.6$ Hz, 1H), 1.96 (m, 1H), 1.62-1.00 (complex m, 9H), 1.00 (d, $J = 7.5$ Hz, 3H), 0.90 (s, 3H), 0.84 (s, 3H), 0.76 (s, 3H).

^{13}C NMR (100 MHz) δ 70.4, 69.4, 50.0, 45.6, 39.8, 39.4, 34.9, 34.4, 26.3, 24.2(4), 24.1(7), 24.1(2), 21.2, 17.4, 16.5.

IR ν_{max} (KBr) 3370, 2944, 2871, 1467, 1387, 1369, 1100, 1051 cm^{-1}.

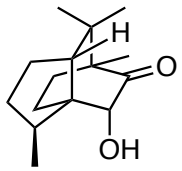
LREIMS (70 eV) *m/z* 238 ($M^{+\bullet}$, 18%), 220 (28), 205 (28), 189 (35), 187 (41), 177 (76), 163 (27), 149 (34), 136 (77), 121 (75), 107 (44), 95 (44).

HREIMS Found: $M^{+\bullet}$, 238.1935. $C_{15}H_{26}O_2$ requires $M^{+\bullet}$, 238.1933.

Optical Rotation $[\alpha]_D = -20.8$ ($c = 1.7$, $CHCl_3$).

Concentration of fraction B (R_f = 0.8 in 1:1 v/v EtOAc/hexane) gave the starting acetonide **62** (3.2 mg, 40% recovery) as a clear, colorless oil that was identical, in all respects, with an authentic sample.

(3*S*,3a*S*,4*R*,6*S*)-4-Hydroxy-3,6,7,7-tetramethylhexahydro-3a,6-ethanoinden-5(4*H*)-one (67)



67

A magnetically stirred solution of the diol **33** (4 mg, 0.02 mmol) in DCM (2.5 mL) was cooled to 0 °C while a solution of *p*-TsOH•H_2O (5.8 mg, 0.03 mmol) and 4-acetamido-TEMPO (8 mg, 0.04 mmol) in DCM (75 mL) was prepared and allowed to stir at 18 °C for 0.5 h. The latter solution was then added to the first over 1.5 h and the ensuing mixture was stirred at 18 °C for 48 h before being quenched with $NaHCO_3$ (5 mL of a saturated aqueous solution). The separated aqueous phase was extracted with DCM (3 × 5 mL) and the combined organic fractions were washed with H_2O (1 × 5 mL) and brine (1 × 10 mL) before being dried (Na_2SO_4), filtered and concentrated under reduced pressure. The resulting light-yellow oil was subjected to flash column chromatography (silica, 1:4 v/v EtOAc/hexane elution) and afforded fractions, A and B

Concentration of the fractions A (R_f = 0.4) gave the *title acyloin* ***67*** (2.0 mg, 60%) as a clear, colorless oil.

^{1}H NMR (400 MHz) δ 3.57 (s, 1H), 2.51 (d, *J* = 2.0 Hz, 1H), 2.07 (m, 1H), 1.82-1.60 (complex m, 4H), 1.52-1.34 (complex m, 3H), 1.15 (m, 1H), 1.05-0.93 (complex m, 1H), 1.01 (d, *J* = 7.2 Hz, 3H), 0.96 (s, 3H), 0.90 (s, 3H), 0.81 (s, 3H).

^{13}C NMR (100 MHz) δ 220.3, 76.2, 51.0, 50.7, 48.6, 38.4, 33.9, 33.1, 30.5, 29.3, 24.7, 22.2, 20.1, 17.9, 14.1.

IR νmax (KBr) 3436, 2949, 2870, 1717, 1462, 1374, 1132, 1021, 794 cm^{-1}.

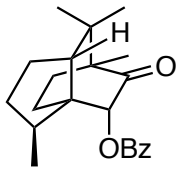
LRESIMS (+ve) *m/z* 259 [$(M + Na)^+$, 100%].

HRESIMS Found: $(M + Na)^+$, 259.1674. $C_{15}H_{24}O_2$ requires 259.1674.

Optical Rotation $[\alpha]_D$ = +38.1 (*c* = 0.7, $CHCl_3$).

Concentration of fraction B (R_f = 0.3) gave less stable colourless oil, which was tentatively identified as regioisomer of **68** (0.3 mg, 5%).

(3*S*,3a*S*,4*R*,6*S*)-3,6,7,7-Tetramethyl-5-oxooctahydro-3a,6-ethanoinden-4-yl benzoate (70)



70

A magnetically stirred solution of acyloin **67** (16 mg, 0.07 mmol) and 4-(*N*,*N*-dimethylamino)pyridine (29 mg, 0.24 mmol) and triethylamine (0.3 mL) in DCM (10 mL) was cooled to 0 °C then treated with benzoyl chloride (0.2 mL, 0.17 mmol). The resulting mixture was allowed to warm to 18 °C and stirred at this temperature for 18 h then treated with HCl (10 mL of a 1 M aqueous solution) and extracted with DCM (4 × 5 mL). The combined organic phases was washed with brine (1 × 15 mL) before being dried (Na_2SO_4), filtered and concentrated under reduced pressure. The resulting light-yellow oil was subjected to flash column chromatography (silica, 1:9 v/v EtOAc/hexane elution) and concentration of the appropriate fractions (R_f = 0.6 in 1:4 v/v EtOAc/hexane) gave the *title keto-ester **70*** (21.0 mg, 88%) as a clear, colourless oil.

^{1}H NMR (400 MHz) δ 8.03 (d, *J* = 8.0 Hz, 2H), 7.56 (m, 1H), 7.44 (t, *J* = 8.0 Hz, 2H), 5.28 (d, *J* = 1.2 Hz, 1H), 2.06 (m, 1H), 1.93–1.47 (complex m, 8H), 1.17 (m, 1H), 1.00 (s, 3H), 0.91 (s, 3H), 0.86 (s, 3H), 0.85 (d, *J* = 7.6 Hz, 3H).

^{13}C NMR (100 MHz) δ 213.0, 165.3, 133.0, 130.1, 129.8, 128.3, 75.2, 51.8, 51.0, 47.7, 39.0, 34.4, 33.8, 29.9, 28.7, 24.4, 23.9, 20.2, 17.4, 14.2.

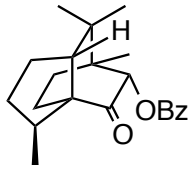
IR ν_{max} (KBr) 2953, 2871, 1734, 1601, 1463, 1451, 1314, 1263, 1103, 1067, 1025, 708 cm^{-1}.

LRESIMS (+ve) *m/z* 363 [$(M + Na)^+$, 100%].

HRESIMS Found: $(M + Na)^+$, 363.1936. $C_{22}H_{28}O_3$ requires 363.1936.

Optical Rotation $[\alpha]_D$ = +122 (*c* = 0.04, $CHCl_3$).

(3*S*,3a*S*,5*S*,6*S*)-3,6,7,7-Tetramethyl-4-oxooctahydro-3a,6-ethanoinden-5-yl benzoate (69)



69

A magnetically stirred solution of the regioisomer of **68** (16 mg, 0.07 mmol) and 4-(*N*,*N*-dimethylamino)pyridine (29 mg, 0.24 mmol) and triethylamine (0.3 mL) in DCM (10 mL) was cooled to 0 °C then treated with benzoyl chloride (0.2 mL, 0.17 mmol). The ensuing mixture was allowed to warm to 18 °C and stirred at this temperature for 18 h then treated with HCl (10 mL of a 1 M aqueous solution) and extracted with DCM (4 × 5 mL). The combined organic phase was washed with brine (1 × 10 mL) before being dried (Na_2SO_4), filtered and concentrated under reduced pressure. The resulting light-yellow oil was subjected to flash column chromatography (silica, 1:9 v/v EtOAc/hexane elution) and concentration of the appropriate fractions (R_f = 0.6 in 1:4 v/v EtOAc/hexane) gave the *title keto-ester **69*** (21.0 mg, 88%) as a clear, colourless oil.

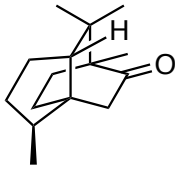
^{1}H NMR (400 MHz) δ 8.09 (d, *J* = 7.2 Hz, 2H), 7.57 (uneven t, *J* = 8.0 Hz, 1H), 7.45 (uneven t, *J* = 7.6 Hz, 2H), 5.72 (d, *J* = 2.4 Hz, 2H), 2.17 (t, *J* = 9.6 Hz, 1H), 2.03-1.84 (m, 3H), 1.83-1.69 (m, 3H), 1.60-1.47 (m, 2H), 1.25 (m, 1H), 1.14 (s, 3H), 1.08 (s, 1.5H), 1.06 (s, 4.5H), 0.89 (s, 3H).

^{13}C NMR (100 MHz) δ 211.5, 166.2, 133.1, 129.9, 128.3, 78.2, 56.3, 45.8, 45.4, 38.0, 35.3, 33.5, 29.9, 27.0, 26.7, 22.1, 21.0, 18.1, 16.3.

LREIMS (70 eV) *m/z* 340 ($M^{+\bullet}$, 32%), 218 (32), 207 (20), 200 (17), 189 (11), 175 (23), 163 (8), 149 (14), 136 (24), 121 (19), 105 (100), 95 (11), 77 (34), 69 (8), 55 (11).

HRESIMS Found: $M^{+\bullet}$, 340.2037 $C_{15}H_{24}O$ requires $M^{+\bullet}$, 340.2038.

(3*S*,3a*S*,6*S*)-3,6,7,7-Tetramethylhexahydro-3a,6-ethanoinden-5(4*H*)-one [(–)-32]



(–)-**32**

A magnetically stirred solution of keto-ester **70** (16 mg, 0.05 mmol) in THF/MeOH (9 mL of a 2:1 v/v mixture) was cooled to –78 °C, then SmI_2 (0.1 M solution in THF) was added dropwise until a bright-blue color persisted (depending on the quality of the reagent up to 5 "equivalents" were required). Once addition was complete, the reaction mixture was allowed to stir at –78 °C for a further 0.25 h, then poured into K_2CO_3 (10 mL of a saturated aqueous solution) and diluted with Et_2O (10 mL). The separated aqueous phase was extracted with Et_2O (2 × 10 mL) and the combined organic fractions were washed with H_2O (1 × 15 mL) and brine (1 × 15 mL) before being dried (Na_2SO_4), filtered and concentrated under reduced pressure. The resulting clear, colorless oil was subjected to flash column chromatography (silica, DCM elution) and concentration of the appropriate fractions (R_f = 0.4) gave the title ketone (–)-**32**[17, 26] (8 mg, 80%) as a clear, colourless oil.

^{1}H NMR (400 MHz) δ 2.16 (d, *J* = 18.0 Hz, 1H), 2.08 (dd, *J* = 18.0 and 2.0 Hz, 1H), 2.05 (m, 1H), 1.76–1.57 (complex m, 4H), 1.56 -1.46 (complex m, 1H), 1.38–1.24 (complex m, 3H), 1.14-1.04 (complex m, 1H), 0.93 (s, 3H), 0.88 (s, 3H), 0.83 (d, *J* = 7.2 Hz, 3H), 0.79 (s, 3H).

^{13}C NMR (100 MHz) δ 218.9, 54.3, 50.2, 46.9, 44.1, 39.2, 34.5, 34.0, 29.4, 28.7, 27.9, 24.3, 19.9, 18.2, 14.0.

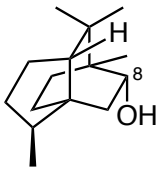
IR ν_{max} (KBr) 2954, 2869, 1718, 1462, 1115, 1072 cm^{-1}.

LREIMS (70 eV) *m/z* 220 ($M^{+\bullet}$, 38%), 205 (32), 177 (32), 135 (36), 105 (36), 83 (84), 69 (67), 57 (100), 55 (67).

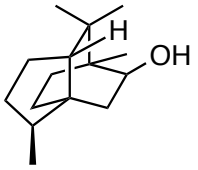
HRESIMS Found: $M^{+\bullet}$, 220.1833 $C_{15}H_{24}O$ requires $M^{+\bullet}$, 220.1827.

Optical Rotation $[\alpha]_D$ = −32.2 (*c* = 0.63, $CHCl_3$), [lit. 17 $[\alpha]_D$ = −42 (*c* = 1.8, $CHCl_3$)].

(3*S*,3a*S*,5*R*,6*S*)-3,6,7,7-Tetramethyloctahydro-3a,6-ethanoinden-5-ol [(–)-19] and (3*S*,3a*S*,6*S*)-3,6,7,7-tetramethyloctahydro-3a,6-ethanoinden-5-ol [(–)-8-*epi*-19]



and



(–)-**19** (–)-8-*epi*-**19**

A magnetically stirred mixture of liquid NH_3 (10 mL), NH_4Cl (40 mg), ketone **32** (6.3 mg 0.03 mmol) and dry THF (3 mL) maintained at –33 °C was treated, in small portions over 0.17 h, with lithium metal (20 mg). The resulting blue solution was stirred for 1 h at –33 to 18 °C after which time any remaining lithium was destroyed by the addition of NH_4Cl. The reaction mixture was then treated with Et_2O (10 mL) and H_2O (10 mL). The separated organic phase was extracted with Et_2O (2 × 5 mL) and the combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a clear, colorless oil. Subjection of this material to flash column chromatography (silica, 1:9 v/v EtOAc/hexane elution) afforded two fractions, A and B.

Concentration of fraction A (R_f = 0.2) gave the title alcohol (–)-**19**[17-18] (3.7 mg, 67%) as a white, crystalline solid, mp = 52-65 °C (lit. 17, mp = 81 °C).

^{1}H NMR (400 MHz) δ 3.97 (m, 1H), 2.08 (m, 1H), 1.95 (m, 1H), 1.60 (m, 1H), 1.47 (m, 2H), 1.39 (m, 1H), 1.28–1.20 (complex m, 3H), 1.14 (complex m, 1H), 1.07 (dd, *J* = 12.6 and 5.4 Hz, 1H), 0.98 (m, 1H), 0.90 (s, 3H), 0.86 (s, 3H), 0.81 (d, *J* = 7.2 Hz, 3H), 0.76 (s, 3H).

^{13}C NMR (150 MHz) δ 71.0, 53.1, 41.3, 40.7, 40.0, 39.8, 35.0, 34.5, 31.0, 26.3, 24.3, 24.2, 21.0, 17.7, 16.2.

IR ν_{max} (KBr) 3386, 2954, 2868, 1457, 1386, 1255, 1084 cm^{-1}.

LREIMS (70 eV) *m/z* 222 ($M^{+\bullet}$, 36%), 204 (12), 189 (14), 177 (95), 161 (27), 151 (28), 133 (25), 119 (50), 107 (46), 95 (55), 91 (46).

HRESIMS Found: $M^{+\bullet}$, 222.1980. $C_{15}H_{26}O$ requires $M^{+\bullet}$, 222.1984.

Optical Rotation $[\alpha]_D$ = −56.5 (*c* = 0.35, $CHCl_3$) [lit. 17 $[\alpha]_D$ = −66 (*c* = 1.4, $CHCl_3$)].

Concentration of fraction B (R_f = 0.3) gave a clear, colourless oil identified as alcohol [(–)-8-*epi*-**19**][17-18] (0.3 mg, 5%).

^{1}H NMR (400 MHz) δ 3.69 (dd, *J* = 9.2 and 2 Hz, 1H), 1.90 (m, 2H), 1.62-1.30 (m, 8H), 1.12 (s, 3H), 1.08 (m, 2H), 0.89 (s, 3H), 0.84 (s, 3H), 0.82 (d, *J* = 7.6 Hz, 3H).

^{13}C NMR (100 MHz) δ 79.6, 53.1, 41.8, 41.6, 40.0, 38.8, 35.7, 34.8, 30.8, 30.4, 29.2, 24.2, 23.0, 18.1, 17.6.

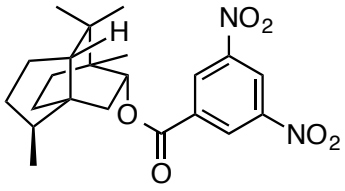
IR ν_{max} (KBr) 3401, 2951, 2868, 1463, 1372, 1043 cm^{-1}.

LREIMS *m/z* 222 [($M^{+\bullet}$), 10], 204 [($M-H_2O)^+$, 14], 189(9), 177(12), 161(12), 151(7), 133(8), 119(26), 107(11), 95(12), 84(100), 69(19), 55(23).

HREIMS Found: $M^{+\bullet}$ = 222.1976. $C_{15}H_{26}O$ requires 222.1984.

Optical Rotation $[\alpha]_D$ = –23.2 (*c* =1.2, $CHCl_3$) [lit. 17 $[\alpha]_D$ = −133 (*c* = 0.78, $CHCl_3$)].

(3*S*,3a*S*,5*R*,6*S*)-3,6,7,7-Tetramethyloctahydro-3a,6-ethanoinden-5-yl 3,5-dinitrobenzoate (71)



71

A magnetically stirred solution of alcohol (–)-**19** (1.6 mg, 0.004 mmol), triethylamine (2 mL, 0.014 mmol) and 4-(*N*,*N*-dimethylamino)pyridine (1.7 mg, 0.014 mmol) in DCM (1.5 mL) maintained at 18 ºC was treated with 3,5-dinitrobenzoyl chloride (2.3 mg, 0.01 mmol). The resulting mixture was stirred at 18 ºC for 16 h then $NaHCO_3$ (3 mL of a saturated aqueous solution) and DCM (2 mL) were added. The separated aqueous phase was extracted with DCM (2 × 3 mL) and the combined organic phases washed with brine (1 × 5 mL) before being dried (Na_2SO_4), filtered and concentrated under reduced pressure. Subjection of the resulting light-yellow oil to flash column chromatography (silica, 1:19 v/v EtOAc/hexane elution) and concentration of the appropriate fractions (R_f = 0.35 in

1:9 v/v EtOAc/hexane) afforded the *title ester **71*** (1.9 mg, 99%) as a white, crystalline solid, mp = 89.3-117.5 ºC.

^{1}H NMR (600 MHz) δ 9.23 (t, *J* = 2.1 Hz, 1H), 9.14 (d, *J* = 2.1 Hz, 2H), 5.42 (m, 1H), 2.33 (m, 1H), 2.00 (m, 1H), 1.79 (m, 1H), 1.63-1.38 (complex m, 5H), 1.33-1.24 (complex m, 3H), 1.05 (m, 1H), 0.99 (s, 3H), 0.96 (s, 3H), 0.83 (d, *J* = 7.2 Hz, 3H), 0.81 (s, 3H).

^{13}C NMR (150 MHz) δ 162.3, 148.6, 134.6, 129.2, 122.1, 78.3, 53.1, 41.3, 39.9, 39.2, 38.2, 34.9, 34.8, 30.5, 26.5, 25.6, 24.2, 20.7, 17.6, 16.6.

IR ν_{max} (KBr) 3101, 2953, 1726, 1627, 1546, 1460, 1343, 1284, 1170, 1075, 972, 721.

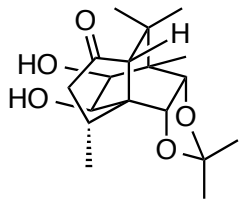
LREIMS (70 eV) *m/z* 416 ($M^{+\bullet}$, 8%), 204 (83), 195 (52), 161 (57), 149 (100), 119 (85).

HREIMS Found: $M^{+\bullet}$, 416.1944. $C_{22}H_{28}N_2O_6$ requires $M^{+\bullet}$, 416.1947

Optical Rotation $[\alpha]_D = -38.0$ (*c* = 1.0, $CHCl_3$).

5.4 Experimental Procedures Associated with Work Described in Chapter Three

(3a*S*,4*R*,8*R*,8a*S*,8b*R*,9*R*,10*S*)-9,10-Dihydroxy-2,2,4,5,5,8-hexamethylhexahydro-8a,4-ethanoindeno[4,5-*d*][1,3]dioxol-6(4*H*)-one (112)



112

Following a protocol defined by Sharpless,[58b] a magnetically stirred solution of alkene **59** (200 mg, 0.69 mmol) and citric acid (357 mg, 1.70 mmol) in acetonitrile/water (8 mL of a 3:1 mixture) was treated with potassium osmate (25 mg, 10 mol %) and 4-methyl-morpholin *N*-oxide (198 mg, 1.70 mmol). The resulting mixture was stirred at room temperature for 72 h then quenched with Na_2SO_3 (10 mL of a saturated aqueous solution) and extracted with EtOAc (3 × 10 mL). The combined organic fractions were washed with brine (1 × 20 mL) before being dried (Na_2SO_4), filtered and concentrated under reduced pressure to give clear, colourless oil. Subjection of this material to flash column chromatography (silica, 3:7 v/v EtOAc/hexane elution) afforded two fractions, A and B.

Concentration of fraction A (R_f = 0.63) afforded the alkene **59** (11.5 mg, 6% recovery) as a clear, colourless oil that was identical, in all respects, with an authentic sample[*].

Concentration of fraction B (R_f = 0.26) afforded *title diol **112*** (140mg, 63% or 78% brsm) as a white solid**,** mp = 195-207 °C.

^{1}H NMR (400 MHz) δ 4.33 (dd, *J* = 8, 2 Hz, 1H), 4.12 (d, *J* = 8 Hz, 1H), 4.01 (d, *J* = 8 Hz, 1H), 3.97 (d, *J* = 8 Hz, 1H), 2.70 (d, *J* = 1.6 Hz, 1H), 2.35 (m, 2H), 2.15 (complex m, 1H), 2.01 (d, *J* =

[*]The synthesis and characterisation of compound **59** has been discussed in Chapter 2.

9.6 Hz, 1H), 1.45 (s, 3H), 1.34 (s, 3H), 1.31 (s, 3H), 1.29 (d, J = 7.2 Hz, 3H), 1.03 (s, 3H), 1.00 (s, 3H).

^{13}C NMR (100 MHz) δ 214.2, 109.1, 82.8, 78.8, 68.5, 65.4, 59.7, 48.6, 46.4, 44.0, 37.7, 33.9, 28.1, 25.7, 23.7, 20.3, 15.0, 11.9.

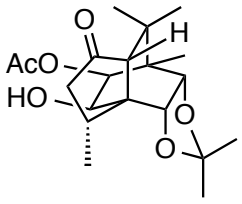
IR ν_{max} (KBr) 3437, 2975, 2936, 2878, 1734, 1458, 1397, 1374, 1266, 1208, 1167, 1089, 1067, 1042, 991, 878, 737 cm^{-1}.

LREIMS (70 eV) *m/z* 324 ($M^{+\bullet}$, 38%), 309 [$(M-CH_3\bullet)^+$, 28%], 291 (12), 266 (36), 248 (31), 233 (30), 219 (28), 205 (34), 191 (46), 177 (37), 163 (42), 151 (53), 147 (62), 139 (100), 128 (47), 121 (45), 109 (35), 97 (56), 95 (37), 83 (53), 69 (64), 59 (29), 55 (45).

HREIMS Found: $M^{+\bullet}$, 324.1938. $C_{18}H_{28}O_5$ requires 324.1937.

Optical Rotation $[\alpha]_D = -100.0$ (c = 0.29, $CHCl_3$).

(3a*S*,4*S*,8*R*,8a*S*,8b*R*,9*R*,10*S*)-9-Hydroxy-2,2,4,5,5,8-hexamethyl-6-oxooctahydro-8a,4-ethanoindeno[4,5-*d*][1,3]dioxol-10-yl acetate (114)



114

A magnetically stirred solution of alcohol **112** (51 mg, 0.17 mmol), acetic anhydride (24.5 μL, 0.26 mmol) and 4-(*N, N*-dimethylamino)pyridine (32 mg, 0.26 mmol) in pyridine (2 mL) was stirred at room temperature for 2 h then quenched with $NaHCO_3$ (5 mL of a saturated aqueous solution). The aqueous layer was extracted with extracted with Et_2O (3 × 5 mL). The combined organic fractions were washed with brine (10 mL) before being dried (Na_2SO_4), filtered and concentrated under reduced pressure to give a clear, colourless oil. Subjection of this material to flash column chromatography (silica, 3:7 v/v EtOAc/hexane elution) afforded, after concentration of appropriate fraction **(**R_f = 0.24 in 3:7 v/v EtOAc/hexane), the *title acetate **114*** as a white, crystalline solid

^{1}H NMR (400 MHz) δ 4.95 (d, *J* = 8 Hz, 1H), 4.54 (dd, *J* = 8, 3.2 Hz, 1H), 4.14 (d, *J* = 8, Hz, 1H), 4.04 (d, *J* = 8 Hz, 1H), 2.33 (d, d, *J* = 10 Hz, 2H), 2.16 (complex m, 1H), 2.09 (s, 3H), 1.70 (d, *J* = 3.6, Hz, 1H), 1.52 (s, 3H), 1.49 (s, 1H), 1.34 (s, 3H), 1.32 (s, 3H), 1.26 (d, *J* = 6.8, Hz, 3H), 1.05 (s, 3H), 0.91 (s, 3H).

^{13}C NMR (100 MHz) δ 214.6, 171.1, 109.6, 82.8, 78.5, 72.0, 64.8, 59.3, 48.7, 46.5, 44.0, 37.8, 34.0, 27.8, 25.7, 24.0, 20.9, 19.8, 14.9, 11.7.

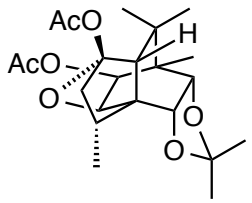
IR ν_{max} (KBr) 3468, 2972, 2918, 2878, 1734, 1383, 1263, 1209, 1166, 1090, 1067 cm^{-1}.

LREIMS (70 eV) *m/z* 366 ($M^{+\bullet}$, 42%), 351 [$(M-CH_3\bullet)^+$, 54%], 324 (15), 308 (10), 291 (7), 266 (44), 248 (69), 231 (59), 220 (17), 206 (58), 191 (50), 179 (25), 161 (44), 147 (44), 133 (33), 122 (33), 97 (100), 91 (23), 83 (34), 69 (48).

HREIMS Found: $M^{+\bullet}$, 366.2043. $C_{20}H_{30}O_6$ requires 366.2042.

Optical Rotation $[\alpha]_D = -145.4$ (*c* = 0.06, $CHCl_3$).

(3a*S*,7*R*,9*R*,9b*R*)-2,2,4,9,11,11-Hexamethylhexahydro-4*H*,7*H*-7,9a,4-(epiethane[1,1,2]triyl)[1,3]dioxolo[4,5-*f*]chromene-5,7-diyl diacetate (116)



116

Following a protocol defined by Pasha,[67] a mixture of alcohol **115** (80 mg, 0.25 mmol), acetyl chloride (87 μL, 1.23 mmol) and zinc dust (1.60 mg, 0.025 mmol) in DCM (2 mL) was stirred magnetically at room temperature for 2 h before being treated with $NaHCO_3$ (5mL of a saturated aqueous solution). The separated aqueous layer was extracted with extracted with Et_2O (3 × 5 mL) and the combined organic phase were washed with brine (1 × 10 mL) before being dried (Na_2SO_4), filtered and concentrated under reduced pressure to give clear, colourless oil. Subjection of this material to flash column chromatography (silica, 3:7 v/v EtOAc/hexane elution) afforded, after

concentration of relevant fractions (R_f = 0.31), the *title acetate* ***117*** (90%) as a white, crystalline solid.

^{1}H NMR (400 MHz) δ 4.93 (d, *J* = 6.4 Hz, 1H), 4.52 (d, *J* = 6.4 Hz, 1H), 4.22 (, *J* = 7.6 Hz, 1H), 4.19 (d, *J* = 6.4 Hz, 1H), 2.56 (t, *J* = 11.6 Hz, 1H), 2.24 (s, 1H), 2.12 (m, 1H), 2.10 (s, 3H), 2.07 (s, 3H), 1.47 (s, 3H), 1.38 (dd, *J* = 12, 5.2 Hz, 1H), 1.29 (s, 3H), 1.18 (d, *J* = 7.2 Hz, 3H), 1.16 (s, 3H), 0.93 (s, 3H), 0.92 (s, 3H).

^{13}C NMR (100 MHz) δ**:** 170.6, 168.7, 110.8, 108.6, 77.8, 75.3, 72.6, 71.3, 54.0, 52.3, 41.9, 41.2, 35.9, 35.3, 27.5, 25.6, 23.8, 21.8, 21.4, 21.0, 16.5, 11.2.

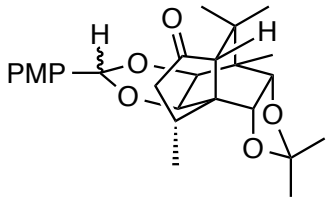
IR ν_{max} (KBr) 2975, 2884, 1742, 1456, 1372, 1301, 1251, 1222, 1205, 1039, 731 cm^{-1}.

LREIMS (70 eV) *m/z* 408 ($M^{+\bullet}$, 4%), 393 [$(M-CH_3\bullet)^+$, 38%], 366 (100), 351 (34), 324 (18), 308 (16), 291 (12), 266 (55), 248 (69), 231 (57), 220 (18), 206 (24), 189 (30), 177 (20), 161 (32), 147 (30), 133 (23), 121 (21), 97 (81), 91 (14), 83 (21), 69 (25), 55 (15).

HREIMS Found: [$(M-CH_3\bullet)^+$], 393.1911. $C_{21}H_{29}O_7$ requires 393.1913.

Optical Rotation $[\alpha]_D$ = –203 (*c* = 0.16, $CHCl_3$).

(3aS,4R,8R,8aS,8bR,9S,13R)-11-(4-methoxyphenyl)-2,2,4,5,5,8-Hexamethylhexahydro-8a,4-[4,5]epidioxoloindeno[4,5-d][1,3]dioxol-6(4H)-one (117)



117

A magnetically stirred solution of the diol **112** (57 mg, 0.18 mmol) and *p*-methoxybenzyldehyde dimethyl acetal (49 mg, 0.27 mmol) in THF (2 mL) was cooled to 0 °C and treated with *p*-tolunesulfonic acid monohydrate (2 mg, 4 mol %). The resulting mixture was stirred at 0 °C for 1.5 h, warmed to 18 °C and stirred for 12 h after which it was quenched with triethylamine (0.5 mL) and concentrated under reduced pressure to give a pale-yellow oil that was dissolved in DCM (5

mL). The resulting solution was treated with NaOH (5 mL of 1 M aqueous solution) and the separated aqueous layer was extracted with DCM (3 × 5 mL). The combine organic phase was washed with brine (1 × 3 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to give a clear, colourless oil. Subjection of this material to flash column chromatography (silica, 1:4 v/v EtOAc/hexane elution) and concentration of appropriate fractions (R_f = 0.27) afforded the *title acetal* ***117*** (61 mg, 77%) as a white, crystalline solid.

^{1}H NMR (400 MHz) δ 7.31 (d, *J* = 9.2 Hz, 2H), 6.87 (d, *J* = 8.4 Hz, 2H), 5.60 (s, 1H), 4.51 (d, *J* = 8.8 Hz, 1H), 4.51 (d, *J* = 8.8 Hz, 1H), 4.33 (d, *J* = 8.8 Hz, 1H), 4.27 (d, *J* = 8 Hz, 1H), 4.13 (d, *J* = 8.8 Hz, 1H), 3.79 (s, 3H), 2.39 (d, *J* = 10.4 Hz, 2H), 2.20 (m, 1H), 1.48 (s, 4H), 1.35 (d, *J* = 6.8 Hz, 3H), 1.33 (s, 3H), 1.22 (s, 3H), 1.15 (s, 3H), 1.00 (s, 3H).

^{13}C NMR (100 MHz) δ 213.4, 162.7, 159.9, 127.9 127.7, 113.6, 109.0, 102.2, 82.2, 79.2, 77.2, 73.3, 60.2, 55.2, 47.8, 46.1, 42.4, 37.1, 34.0, 30.3, 25.5, 23.4, 21.4, 15.3, 13.1.

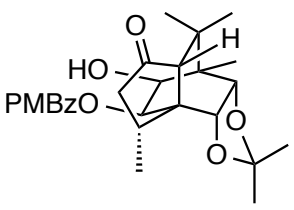
IR ν_{max} (KBr) 2975, 2935, 2878, 2838, 1738, 1615, 1519, 1457, 1402, 1374, 1304, 1252, 1209, 1171, 1119, 1083, 1065, 1033, 1005, 870, 827, 736 cm^{-1}.

LREIMS (70 eV) *m/z* 442 ($M^{+\bullet}$, 52%), 441[$(M-H\bullet)^+$, 38%], 393 [$(M-CH_3\bullet)^+$, 4%], 232 (8), 217 (4), 206 (7), 190 (9), 175 (6), 161 (7), 150 (9), 135 (100), 121 (12), 108 (22), 91 (7), 83 (11), 77 (7), 69 (12).

HREIMS Found: $M^{+\bullet}$, 442.2361. $C_{26}H_{34}O_6$ requires 442.2355.

Optical Rotation $[\alpha]_D$ = –33.9 (*c* =0.27, $CHCl_3$).

(3a*S*,4*R*,8*R*,8a*R*,8b*R*,9*R*,10*S*)-10-Hydroxy-2,2,4,5,5,8-hexamethyl-6-oxooctahydro-8a,4-ethanoindeno[4,5-*d*][1,3]dioxol-9-yl 4-methoxybenzoate (118)



118

A magnetically stirred solution of the acetal **117** (46 mg, 0.10 mmol) in DCM/H_2O (2 mL of a 19:1 mixture) was treated with DDQ (22 mg, 0.10 mmol). After 4 h at 18 °C the mixture was poured into a saturated solution of $NaHCO_3$ (3 mL of saturated aqueous solution). The separated aqueous layer was extracted with DCM (3 × 3 mL). The combined organic phase were washed with brine (1 × 3 mL) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a clear, colourless oil. Subjection of this material to flash column chromatography (silica, 3:7 v/v EtOAc/hexane elution) and concentration of appropriate fractions (R_f = 0.23) afforded the *title alcohol **118*** (37.3 mg, 81%) as a white, crystalline solid.

^{1}H NMR (400 MHz) δ 7.86 (d, *J* = 8.8 Hz, 1H), 4.93 (d, *J* = 9.2 Hz, 1H), 5.68 (d, *J* = 8.4 Hz, 1H), 4.19 (d, *J* = 7.6 Hz, 1H), 4.16 (d, *J* = 8.4 Hz, 1H), 4.09 (d, *J* = 8.0 Hz, 1H), 3.84 (s, 3H), 2.43 (dddd, *J* = 18.4, 9.6, 1.2 Hz, 1H), 2.22 (m, 1H), 2.08 (m, 1H), 1.79 (dd, *J* = 6.0, 2.4 Hz, 1H), 1.68 (brd, *J* = 6.0 Hz, 1H), 1.52 (s, 3H), 1.40 (s, 3H), 1.34 (s, 3H), 1.11 (d, *J* = 6.8 Hz, 1H), 1.10 (s, 3H), 0.99 (s, 3H).

^{13}C NMR (100 MHz) δ 214.6, 166.2, 163.7, 131.9, 121.8, 114.0, 109.5, 83.1, 78.5, 69.4, 67.6, 60.1, 55.4, 47.8, 46.3, 44.3, 37.3, 34.4, 28.0, 25.7, 23.9, 19.9, 15.1, 11.9.

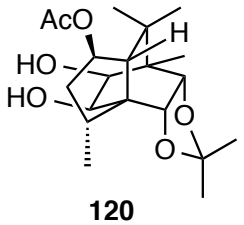
IR ν_{max} (KBr) 3484, 2969, 2936, 2879, 1733, 1606, 1580, 1512, 1459, 1382, 1258, 1209, 1169, 1105, 1069, 1033, 985, 772 cm^{-1}.

LREIMS (70 eV) *m/z* 458 ($M^{+\bullet}$, 3%), 443[$(M-CH\bullet)^+$, 13%], 306 (23), 248 (65), 222 (26), 207 (73), 191 (97), 178 (17), 152 (100), 136 (66), 135 (66), 121 (14), 107 (30), 97 (44), 77 (43), 69 (25).

HREIMS Found: $M^{+\bullet}$, 458.2309. $C_{26}H_{34}O_7$, requires 458.2305.

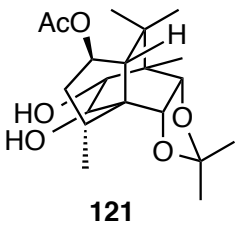
Optical Rotation $[\alpha]_D$ = –5.7 (*c* = 0.07, $CHCl_3$).

(3a*S*,4*R*,6*R*,8*R*,8a*S*,8b*R*,9*R*,10*S*)-9,10-Dihydroxy-2,2,4,5,5,8-hexamethyloctahydro-8a,4-ethanoindeno[4,5-*d*][1,3]dioxol-6-yl acetate (120) and (3a*S*,4*R*,6*R*,8*R*,8a*S*,8b*R*,10*R*)-9,10-dihydroxy-2,2,4,5,5,8-Hexamethyloctahydro-4,8a-ethanoindeno[4,5-*d*][1,3]dioxol-6-yl acetate (121)



120

and



121

Following a protocol defined by Sharpless,[58b] a magnetically stirred solution of olefin **51** (430 mg, 1.29 mmol) and citric acid (540 mg, 2.57 mmol) in acetonitrile/H_2O (10 mL of a 3:1 v/v mixture) maintained at room temperature was treated with potassium osmate (5 mg, 1 mol %) and *N*-methylmorpholin *N*-oxide (539 mg, 2.57 mmol). The ensuing mixture was stirred for 72 h the treated with Na_2SO_3 (5 mL of a saturated aqueous solution) before being extracted with EtOAc (3 × 10 mL). The combined organic fractions were washed with brine (1 × 15 mL) then dried (Na_2SO_4), filtered and concentrated under reduced pressure to give a clear, colourless oil. Subjection of this material to flash column chromatography (silica, 3:7 v/v EtOAc/hexane elution) gave three fractions, A, B and C.

Concentration of fraction A (R_f = 0.65) afforded the alkene **44** (78 mg, 18%) as a clear, colourless oil that was identical, in all respects, with an authentic sample.

Concentration of fraction B (R_f = 0.40) afforded *title diol **121*** (20 mg, 4%) as a white crystalline solid.

^{1}H NMR (400 MHz) δ 5.38 (m, 1H), 4.20 (d, *J* = 7.6 Hz, 1H), 4.13 (d, *J* = 7.6 Hz, 1H), 3.99 (d, *J* = 8.8 Hz, 1H), 3.92 (d, *J* = 8.8 Hz, 1H), 2.72 (m, 1H), 2.24 (m, 2H), 1.53 (d, *J* = 10.8 Hz, 1H), 1.43 (s, 3H), 1.31 (s, 3H), 1.13 (d, *J* = 7.2 Hz, 1H), 1.10 (s, 3h), 1.00 (s, 3H), 0.93 (s, 3H).

^{13}C NMR (100 MHz) δ 170.7, 108.6, 78.5, 76.9, 76.9, 69.6, 68.8, 53.6, 48.0, 43.3, 41.4, 34.0, 32.8, 28.0, 25.7, 23.8, 21.3, 21.0, 18.3, 12.4.

IR ν_{max} (KBr) 3453, 2967, 2935, 1732, 1716, 1458, 1396, 1373, 1247, 1208, 1186, 1090, 1040, 1008, 984, 879 736 cm^{-1}.

LREIMS (70 eV) *m/z* 319 [$(M-CH\bullet)^+$, 10%], 308 (32), 293 (44), 250 (55), 217 (39), 203 (57), 189 (34), 175 (54), 159 (33), 150 (42), 134 (44), 128 (45), 123 (100), 109 (47), 97 (24), 83 (16), 69 (21), 55 (21).

HREIMS Found: $(M-CH_3\bullet)^+$, 353.1957. $C_{19}H_{29}O_6$ requires 353.1964.

Optical Rotation $[\alpha]_D = -5.6$ (*c* = 0.28, $CHCl_3$).

Concentration of fraction C (R_f = 0.28) afforded *title diol* ***120*** (255mg, 55% at 82% conversion) as a white, crystalline solid**,** mp = 166-167 °C.

^{1}H NMR (100 MHz) δ 5.47 (dt, *J* = 8.8 and 3.2 Hz, 1H), 4.20 (d, *J* = 8.4 Hz, 1H), 4.14 (d, *J* = 8.0 Hz, 1H), 3.92 (brd, *J* = 6.8 Hz, 1H), 3.88 (d, *J* = 8.0 Hz, 1H), 2.60 (brs, 1H), 2.26-2.06 (m, 3H), 2.01 (S, 3H), 1.70 (m, 1H), 1.57 (d, *J* = 8.4 Hz, 1H), 1.42 (s, 3H), 1.29 (s, 3H), 1.14 (s, 1.5H), 1.12 (s, 4.5H), 1.00 (s, 3H), 0.92 (s, 3H).

^{13}C NMR (100 MHz) δ 170.9, 108.8, 83.5, 78.8, 77.6, 68.5, 64.8, 56.2, 49.8, 43.3, 42.0, 40.6, 33.2, 28.2, 25.7, 23.7, 21.8, 21.4, 15.0, 12.5.

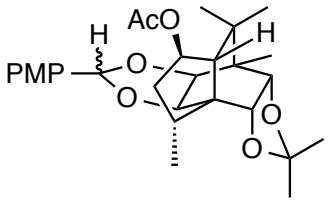
IR ν_{max} (KBr) 3456, 2966, 2936, 2876, 1729, 1713, 1457, 1372, 1263, 1234, 1208, 1187, 1084, 1041 cm^{-1}.

LREIMS (70 eV) *m/z* 353[$(M-CH_3\bullet)^+$, 19], 308 (23), 290 (44), 250 (41), 232 (75), 217 (36), 203 (44), 189 (30), 175 (49), 159 (27), 150 (37), 123 (100), 109 (49), 97 (25), 82 (19), 69 (16), 55 (25).

HREIMS Found: $(M-CH_3\bullet)^+$, 353.1965. $C_{19}H_{29}O_6$ requires 353.1964.

Optical Rotation $[\alpha]_D = -46.8$ (*c* = 1.3, $CHCl_3$).

(3a*S*,4*R*,6*R*,8*R*,8a*S*,8b*R*,9*S*,13*R*)-11-(4-methoxyphenyl)-2,2,4,5,5,8-Hexamethyloctahydro-8a,4-[4,5]epidioxoloindeno[4,5-*d*][1,3]dioxol-6-yl acetate (122)



122

A magnetically stirred solution of the diol **120** (250 mg, 0.69 mmol) and *p*-methoxybenzyldehyde dimethyl acetal (188 mg, 1.03 mmol) in THF (10 mL) was cooled to 0 °C and treated with *p*-tolunesulfonic acid monohydrate (5 mg, 4 mol %). The ensuing mixture was stirred for 12 h then quenched with triethylamine (1 mL) and concentrated under reduced pressure to give a pale-yellow oil. Subjection of this material to flash column chromatography (silica, 1:9 v/v EtOAc/hexane elution) and concentration of appropriate fractions (R_f = 0.12) afforded the *title acetal* ***123*** (261 mg, 78%) as a clear, colourless oil.

^{1}H NMR (400 MHz) δ 7.47 (d, *J* = 8.4 Hz, 2H), 6.92 (d, *J* = 8.4 Hz, 2H), 5.61 (s, 1H), 5.44 (dt, *J* = 9.2, 2.8 Hz, 1H), 4.35 (d, *J* = 8.8 Hz, 1H), 4.28 (d, *J* = 8.4 Hz, 1H), 3.99 (d, *J* = 8.8 Hz, 1H), 3.81 (s, 3H), 2.29-2.04 (m, 2H), 1.99 (s, 3H), 1.74 (m, 1H), 1.57 (d, *J* = 9.2 Hz, 1H), 1.46 (s, 3H), 1.32 (s, 3H), 1.21 (d, *J* = 7.2 Hz, 3H), 0.95 (s, 3H), 0.91 (s, 3H).

^{13}C NMR (100 MHz) δ 170.6, 159.8, 128.3, 127.6, 113.6, 108.7, 101.8, 83.4, 79.3, 77.4, 73.0, 56.2, 55.2, 48.6, 41.8, 41.2, 39.9, 33.0, 30.3, 25.5, 23.4, 22.0, 21.3, 15.2, 13.4.

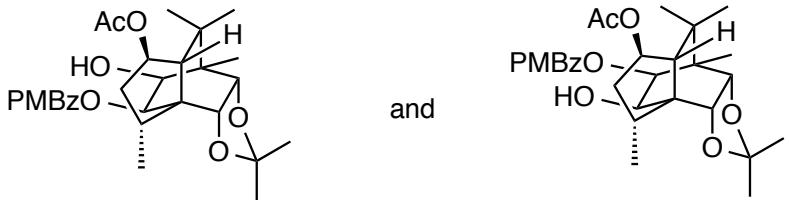
IR ν_{max} (KBr) 2968, 2934, 2878, 1732, 1615, 1518, 1456, 1401, 1373, 1303, 1251, 1209, 1172, 1084, 1043, 873, 830, 780, 735, 617 cm^{-1}.

LREIMS (70 eV) m/z 486 ($M^{+\bullet}$, 69%), 485 [$(M-H\bullet)^+$, 95%], 455 (5), 426 (6), 232 (10), 216 (16), 201 (8), 187 (19), 173 (16), 159 (27), 147 (10), 135 (100), 121 (15), 108 (30), 91 (8), 69 (6), 55 (7)

HREIMS Found: $M^{+\bullet}$, 486.2618. $C_{28}H_{38}O_7$ requires 486.2618.

Optical Rotation $[\alpha]_D$ = –25.0 (*c* = 0.82, $CHCl_3$).

(3a*S*,4*R*,6*R*,8*R*,8a*R*,8b*R*,9*R*,10*S*)-6-Acetoxy-10-hydroxy-2,2,4,5,5,8-hexamethyloctahydro-8a,4-ethanoindeno[4,5-*d*][1,3]dioxol-9-yl 4-methoxybenzoate (123) and (3a*S*,4*S*,6*R*,8*R*,8a*S*,8b*R*,9*R*,10*S*)-6-Acetoxy-9-hydroxy-2,2,4,5,5,8-hexamethyloctahydro-8a,4-ethanoindeno[4,5-*d*][1,3]dioxol-10-yl 4-methoxybenzoate (124)



123 **124**

A magnetically stirred solution of the acetal **122** (240 mg, 0.49 mmol) in DCM/H_2O (10 mL of 19:1 v/v mixture) was treated with DDQ (111 mg, 0.49 mmol). The ensuing mixture was stirred at 18°C for 4 h then treated with $NaHCO_3$ (10 mL of a saturated aqueous solution) and the separated aqueous layer was extracted with DCM (3 × 10 mL). The combine organic phases were washed with brine (1 × 15 mL) before being dried over $MgSO_4$, filtered and concentrated under reduced pressure to give a clear, colourless oil. Subjection of this material to flash column chromatography (silica 1:4 v/v EtOAc/hexane elution) gave two fractions, A and B.

Concentration of fraction A (R_f = 0.41) afforded *alcohol **124*** (12 mg, 8%) as a clear, colourless oil.

^{1}H NMR (400 MHz) δ 7.97 (d, *J* = 8.8 Hz, 2H), 6.92 (d, *J* = 8.8 Hz, 2H), 5.53 (dt, *J* = 9.2, 3.2 Hz, 1H), 5.09 (d, *J* = 8.0 Hz, 1H), 4.50 (dd, *J* = 7.6 Hz, 3.2 Hz, 1H), 4.20 (d, *J* = 8.0 Hz, 1H), 3.96 (d, *J* = 8.0 Hz, 1H), 3.86 (s, 3H), 2.17 (m, 1.5H), 2.02 (s, 3H), 1.75-1.59 (m, 3.5H), 1.33 (s, 3H), 1.12 (d, *J* = 6.4 Hz, 3H), 0.99 (s, 3H).

^{13}C NMR (100 MHz) δ 170.7, 166.6, 163.6, 131.6, 122.2, 113.8, 109.3, 83.5, 78.7, 77.5, 72.6, 64.5, 56.0, 55.4, 50.0, 43.6, 42.1, 40.8, 33.3, 27.9, 25.8, 24.0, 22.0, 21.4, 14.9, 12.6.

IR ν_{max} (KBr) 3469, 2967, 2936, 2877, 1716, 1607, 1512, 1458, 1374, 1261, 1122, 1086, 1040, 994, 953, 846, 756 cm^{-1}.

LREIMS (70 eV) *m/z* 487 [$(M-CH\bullet)^+$, <2%], 442 (2), 427 (4), 384 (2), 342 (2), 324 (3), 290 (6), 275 (2), 232 (6), 209 (3), 209 (3), 190 (6), 175 (6), 152 (4), 135 (100), 107 (3), 107 (3), 92 (2), 77 (3), 55 (2).

HREIMS Found: $(M-CH_3\bullet)^+$, 487.2330. $C_{27}H_{35}O_8$ requires 487.2332.

Optical Rotation $[\alpha]_D = -73.6$ ($c = 0.52$, $CHCl_3$).

Concentration of fraction B ($R_f = 0.30$) afforded *alcohol **123*** (228 mg, 90%) as a white, crystalline solid.

^{1}H NMR (400 MHz) δ 8.10 (d, $J = 9.2$ Hz, 2H), 7.01 (d, $J = 9.2$ Hz, 2H), 5.80 (dt, $J = 9.6$, 4.4 Hz, 1H), 5.47 (d, $J = 8.8$ Hz, 1H), 4.18 (m, 2H), 3.98 (d, $J = 8.0$ Hz, 1H), 3.86 (s, 3H), 2.16 (m, 1H), 2.08 (s, 3H), 1.76 (m, 3H), 1.50 (s, 3H), 1.33 (s, 3H), 1.16 (s, 3H), 1.00 (s, 3H), 0.98 (s, 3H), 0.95 (d, $J = 6.4$ Hz, 3H).

^{13}C NMR (100 MHz) δ 171.0, 167.3, 163.7, 131.8, 121.9, 114.1, 109.2, 83.6, 78.8, 77.0, 69.5, 67.8, 55.8, 55.5, 48.4, 43.7, 41.4, 40.2, 33.5, 28.0, 25.8, 23.9, 21.7, 21.3, 14.9, 12.6.

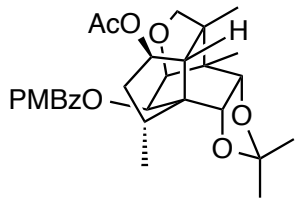
IR ν_{max} (KBr) 3514, 2965, 2936, 2877, 1712, 1606, 1580, 1512, 1458, 1419, 1370, 1283, 1260, 1168, 1111, 1086, 1034, 984, 955, 772 cm^{-1}.

LREIMS (70 eV) *m/z* 487 [$(M-CH\bullet)^+$, 2%], 350 (3), 290 (4), 250 (9), 232 (16), 217 (12), 190 (80), 175 (55), 152 (28), 135 (100), 121 (10), 107 (13), 97 (15), 77 (16), 69 (5).

HREIMS Found: $(M-CH_3\bullet)^+$, 487.2334. $C_{27}H_{35}O_8$ requires 487.2332.

Optical Rotation $[\alpha]_D = -16.1$ ($c = 1.25$, $CHCl_3$).

(3a*S*,7*R*,9*R*,9b*R*)-7-Acetoxy-2,2,3b,6a,9-pentamethyldecahydro-4,9a-methanofuro[3',4':6,7]indeno[4,5-*d*][1,3]dioxol-10-yl 4-methoxybenzoate (125)



125

A solution of the alcohol **123** (74 mg, 0.15 mmol) and $CaCO_3$ (295 mg, 2.95 mmol) in dry DCM (15 mL) was treated with lead tetraacetate (332 mg, 0.49 mmol) and molecular iodine (19 mg, 0.14

mmol). The resulting mixture was sonicated for 4 h at 0-5 °C then treated with $Na_2S_2O_3$ (10 mL of a saturated aqueous solution). The separated aqueous layer was extracted with DCM (3 × 10 mL) and the combined organic phases were washed with brine (1 × 15 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to give a clear, colourless oil. Subjection of this material to flash column chromatography (silica, 1:4 v/v EtOAc/hexane elution) and concentration of appropriate fractions (R_f = 0.13) afforded the *title compound* ***125*** (67 mg, 90%) as a white, crystalline solid, mp =160-167 °C.

^{1}H NMR (300 MHz) δ 8.05 (d, *J* = 9.0 Hz, 2H), 6.98 (d, *J* = 9.0 Hz, 2H), 5.67 (m, 1H), 5.20 (dd, *J* = 6.3, 1.8 Hz, 1H), 4.26 (d, *J* = 6.3 Hz, 1H), 4.12 (d, *J* = 8.1 Hz, 1H), 3.95 (d, *J* = 8.1 Hz, 1H), 3.89 (s, 0.5H), 3.85 (brs, 3.5H), 3.55, (d, *J* = 9.3 Hz, 1H), 2.37-2.20 (m, 2H), 2.07 (s, 3H), 1.85 (m, 1H), 1.77 (dd, *J* = 9.9, 1.8 Hz, 1H), 1.51 (s, 3H), 1.34 (s, 3H), 1.14 (s, 3H), 1.04 (d, *J* = 7.2 Hz, 3H), 0.99 (s, 3H).

^{13}C NMR (100 MHz) δ 170.9, 165.7, 163.4, 131.6, 122.3, 113.9, 108.7, 83.2, 78.3, 77.2, 75.9, 72.8, 71.4, 56.5, 55.4, 49.5, 45.6, 41.9, 40.9, 39.9, 25.9, 23.7, 21.2, 18.7, 16.5, 14.9.

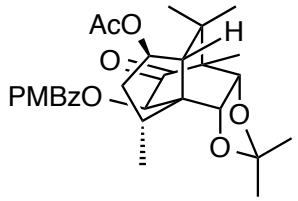
IR ν_{max} (KBr) 2977, 2937, 2881, 1714, 1606, 1580, 1511, 1456, 1419, 1375, 1314, 1277, 1258, 1209, 1166, 1102, 1084, 1057, 1030 1006, 936, 879, 770 cm^{-1}.

LREIMS (70 eV) *m/z* 500 ($M^{+\bullet}$, 5%), 485 [$(M-CH\bullet)^+$, 4%], 440 (3), 393 (6), 366 (20), 351 (6), 324 (4), 288 (6), 266 (11), 248 (19), 231 (17), 206 (5), 189 (8), 161 (8), 135 (100), 107 (8), 97 (22), 84 (11), 69 (9).

HREIMS Found: $M^{+\bullet}$, 500.2419. $C_{28}H_{36}O_8$ requires 500.2410.

Optical Rotation $[\alpha]_D$ = +15.3 (*c* = 1.2, $CHCl_3$).

(3a*S*,4*S*,6*R*,8*R*,8a*R*,8b*R*,9*R*)-6-Acetoxy-2,2,4,5,5,8-hexamethyl-10-oxooctahydro-8a,4-ethanoindeno[4,5-*d*][1,3]dioxol-9-yl 4-methoxybenzoate (126)



126

To a magnetically stirred solution of the alcohol **123** (10 mg, 0.020 mmol) in DCM (1 mL) was added a Dess-Martin periodinane (9.3 mg, 0.022 mmol) in portions. After 2 h of stirring at room temperature the mixture was diluted with DCM (2 mL) and subsequently washed with saturated aqueous NaS_2O_3 (1 × 3 mL) and saturated $NaHCO_3$ (1 × 3 mL) solutions. The combined aqueous layer was extracted once with DCM (1 × 5 mL), and the combined organic extracts were washed with brine (1 × 5 mL) solution, dried ($MgSO_4$) and concentrated under vacuum to give a clear, colourless oil. Subjection of this material to flash column chromatography (silica 1:4 v/v EtOAc/hexane elution) and concentration of appropriate fractions (R_f = 0.12) afforded the *title ketone **126*** (9 mg, 90%) as a clear, colourless oil.

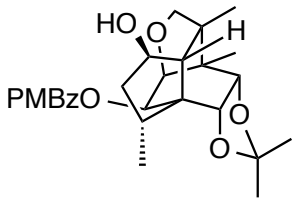
^{1}H NMR (800 MHz) δ 8.04 (d, *J* = 9.6 Hz, 2H), 6.98 (d, *J* = 9.6 Hz, 2H), 5.79 (s, 1H), 5.61 (dt, *J* = 9.6, 4 Hz, 1H), 4.40 (d, *J* = 8 Hz, 1H), 4.24 (d, *J* = 8 Hz, 1H), 3.86 (s, 3H), 2.27 (m, 1H), 2.09 (s, 3H), 2.08 (m, 1H), 1.94 (dd, *J* = 9.6, 1.6 Hz, 1H), 1.77 (m, 1H), 1.47 (s, 3H), 1.35 (s, 3H), 1.11 (s, 3H), 1.10 (s, 3H), 0.96 (d, *J* = 7.2 Hz, 3H), 0.91 (s, 3H).

^{13}C NMR (200 MHz) δ 208.2, 170.7, 164.8, 163.8, 132.0, 121.7, 114.1, 109.3, 82.6, 78.9, 76.2, 109.3, 156.9, 55.9, 55.5, 50.3, 40.8, 39.3, 35.6, 27.8, 25.7, 23.8, 21.3, 21.2, 14.7, 10.5.

IR ν_{max} (KBr) 2976, 2971, 2849, 1738, 1725, 1605, 1511, 1460, 1374, 1315, 1258, 1212, 1167, 1102, 1082, 1052, 1029, 846, 765, 674 cm^{-1}.

HREIMS Found: $M^{+\bullet}$, 485.2179. $C_{27}H_{33}O_8$ requires 485.2175

(3a*S*,7*R*,9*R*,9b*R*)-7-Hydroxy-2,2,3b,6a,9-pentamethyldecahydro-4,9a-methanofuro[3',4':6,7]indeno[4,5-*d*][1,3]dioxol-10-yl 4-methoxybenzoate (127)



127

To a magnetically stirred solution of the acetate **125** (285 mg, 0.57 mmol) in MeOH (10 mL) was treated with K_2CO_3 (100 mg in 1 mL of H_2O). The ensuing mixture was stirred for 12 h after before being filtered through a thin pad of TLC-grade silica gel. The filtrate was concentrated under reduced pressure to give clear, colourless oil that was subjected to flash column chromatography (silica 1:1 v/v EtOAc/hexane elution). Concentration of appropriate fractions (R_f = 0.18) afforded the *title alcohol **127*** (248 mg, 95%) as a white, crystalline solid, mp = 87-106 °C.

^{1}H NMR (400 MHz) δ 7.96 (d, *J* = 8.8 Hz, 2H), 6.94 (d, *J* = 8.8 Hz, 2H), 5.19 (dd, *J* = 6.4 and 1.2 Hz, 1H), 4.81 (m, 1H), 4.25 (d, *J* = 6.4 Hz, 1H), 4.11 (d, *J* = 8.4 Hz, 1H), 3.99 (d, *J* = 9.2 Hz, 1H), 3.96 (d, *J* = 9.2 Hz, 1H), 3.86 (s, 3H), 3.60 (d, d, *J* = 8.4 Hz, 1H), 2.28 (m, 1H), 2.16 (m, 1H), 1.91 (m, 1H), 1.51 (s, 4H), 1.33 (s, 3H), 1.15 (s, 3H), 1.06 (s, 3H), 1.03 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz) δ 165.7, 163.3, 131.4, 122.6, 113.7, 108.6, 83.4, 78.6, 73.4, 72.7, 71.7, 60.0, 55.4, 49.4, 46.1, 44.0, 41.9, 39.7, 25.9, 23.7, 18.9, 16.4, 15.2.

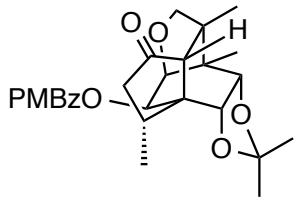
IR ν_{max} (KBr) 3444, 2974, 2936, 2881, 1710, 1606, 1580, 1512, 1456, 420, 1375, 1280, 1259, 1209, 1259, 1209, 1167, 1102, 1074, 1029, 919, 878, 770, 732 cm^{-1}.

LREIMS (70 eV) *m/z* 458 ($M^{+\bullet}$, 7%), 543 [$(M-CH\bullet)^+$, 7%], 358 (1), 328 (3), 323 (3), 306 (3), 248 (3), 206 (7), 173 (3), 152 (3), 135 (100), 119 (3), 107 (6), 97 (6), 91 (3), 77 (7), 55 (3).

HREIMS Found: $(M-CH_3\bullet)^+$, 443.2072. $C_{25}H_{31}O_7$ requires 443.2070.

Optical Rotation $[\alpha]_D$ = +28.2 (*c* = 1.0, $CHCl_3$).

(3a*S*,9*R*,9b*R*)-2,2,3b,6a,9-Pentamethyl-7-oxodecahydro-4,9a-methanofuro[3',4':6,7]indeno[4,5-*d*][1,3]dioxol-10-yl 4-methoxybenzoate (128)



128

A magnetically stirred solution of the alcohol **127** (168 mg, 0.37 mmol) in DCM (5 mL) was treated, in portions, with the Dess-Martin periodinane (170 mg, 0.40 mmol). The ensuing mixture was stirred at room temperature for 2 h then diluted with DCM (5 mL). The resulting solution was washed with NaS_2O_3 (1 × 5 mL of a saturated aqueous solution) and $NaHCO_3$ (1 × 5 mL of a saturated aqueous solution). The combined aqueous phases were extracted once with DCM (1 × 10 mL) and the combined organic phases were washed with brine (1 × 10 mL) before being dried ($MgSO_4$), filtered and concentrated under vacuum to give a clear, colourless oil. Subjection of this material to flash column chromatography (silica 3:7 v/v EtOAc/hexane elution) and concentration of appropriate fractions (R_f = 0.19) afforded the *title ketone* ***129*** (152 mg, 90%) as a white, crystalline solid, mp = 81-93 °C.

^{1}H NMR (400 MHz) δ 7.83 (d, *J* = 8.8 Hz, 2H), 6.93 (d, *J* = 8.8 Hz, 2H), 5.40 (dd, *J* = 6.8, 1.2 Hz, 1H), 4.22 (m, 2H), 4.11 (s, 2H), 3.85 (s, 3H), 3.54 (d, *J* = 10.4 Hz, 1H), 2.54 (m, 1H), 2.33 (m, 2H), 1.81 (m, 1H), 1.53 (s, 3H), 1.35 (s, 3H), 1.18 (d, *J* = 6.8 Hz, 3H), 1.16 (s, 3H), 1.12 (s, 3H).

^{13}C NMR (100 MHz) δ 215.6, 165.5, 163.4, 131.5, 122.1, 113.9, 109.2, 82.8, 77.8, 77.2, 72.9, 71.4, 60.9, 55.4, 50.1, 46.4, 44.9, 41.7, 37.5, 26.0, 23.6, 19.7, 16.0, 14.6.

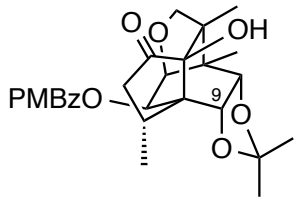
IR ν_{max} (KBr) 2976, 2937, 2884, 1716, 1606, 1580, 1512, 1459, 1382, 1315, 1259, 1210, 1167, 1101, 1086, 1033, 1005, 917, 878, 847, 774, 733, 696 cm^{-1}.

LREIMS (70 eV) *m/z* 456 ($M^{+\bullet}$, 54%), 541 [$(M-CH\bullet)^+$, 27%], 398 (2), 356 (5), 321 (30), 304 (30), 289 (7), 246 (27), 217 (27), 204 (41), 189 (15), 175 (13), 152 (13), 135 (100), 119 (10), 107 (24), 97 (17), 77 (24), 69 (15), 55 (7).

HREIMS Found: $M^{+\bullet}$, 456.2148. $C_{28}H_{36}O_9$ requires 456.2148.

Optical Rotation $[\alpha]_D$ = +28.2 (*c* = 1.0, $CHCl_3$).

(3a*S*,9*R*,9b*R*)-6b-Hydroxy-2,2,3b,6a,9-pentamethyl-7-oxodecahydro-4,9a-methanofuro[3',4':6,7]indeno[4,5-*d*][1,3]dioxol-10-yl 4-methoxybenzoate (130)



130

Step i. A magnetically stirred solution of ketone **128** (110mg, 0.24) in anhydrous Et_2O (5 mL) maintained at 18 °C was treated with triethylamine (0.27 mL, 1.92 mmol) and TMSOTf (0.17 mL, 0.96 mmol). After 32 h the reaction mixture was diluted with Et_2O (10 mL) and washed with $NaHCO_3$ (1 × 10 mL of a saturated aqueous solution) and brine (1 × 10 mL) before being dried (Na_2SO_4), filtered and concentrated under reduced pressure to give the thermodynamically favored silyl enol ether (126 mg, quantitative) as a clear, light-yellow oil. This material was used directly in step ii as described immediately below.

Step ii. A magnetically stirred solution of the above-mentioned enol ether (126 mg, 0.24 mmol) in DCM (5 mL) maintained at −30 °C was treated, in one portion, with *m*-CPBA (54 mg, 0.26 mmol). The resulting mixture was allowed to warm to room temperature over 12 h and then washed with $NaHCO_3$ (1 × 5 mL of a saturated aqueous solution). The separated aqueous phase was extracted with DCM (2 × 5 mL) and the combined organic phases dried (Na_2SO_4), filtered and concentrated under reduced pressure to give a light-yellow oil. This material was dissolved in THF (5 mL) and the ensuing solution treated, at 18 °C, with TBAF. After 1 h the reaction mixture was concentrated under reduced pressure and the residue thus obtained subjected to flash column chromatography (silica 3:7 v/v EtOAc/hexane elution). Concentration of appropriate fractions (R_f = 0.33) afforded the *α-hydroxy ketone **131*** (98 mg, 87%) as a white, crystalline solid.

^{1}H NMR (400 MHz) δ 7.81 (d, *J* = 9.2 Hz, 2H), 6.93 (d, *J* = 9.2 Hz, 2H), 5.51 (d, *J* = 7.2 Hz, 1H), 5.58 (d, *J* = 7.6 Hz, 1H), 4.30 (d, *J* = 7.6 Hz, 1H), 4.19 (d, *J* = 7.6 Hz, 1H), 4.12 (d, *J* = 9.6 Hz,

1H), 3.85 (s, 3H), 3.65 (d, J = 9.6 Hz, 1H), 2.80 (m, 2H), 2.33 (m, 1H), 2.01 (brs, OH), 1.52 (s, 3H), 1.35 (s, 3H), 1.20 (s, 3H), 1.14 (d, J = 6.8 Hz, 3H), 1.11 (s, 3H).

^{13}C NMR (100 MHz) δ 213.3, 165.2, 163.5, 131.5, 121.9, 113.9, 108.9, 83.8, 76.7, 74.7, 69.5, 55.4, 50.2, 47.6, 45.5, 44.8, 34.8, 26.2, 23.7, 16.1, 14.2, 13.8.

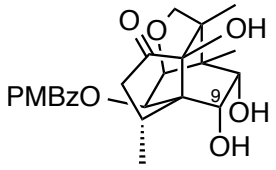
IR ν_{max} (KBr) 3436, 2977, 2938, 1722, 1606, 1581, 1512, 1457, 1375, 1314, 1258, 1209, 1167, 1098, 1077, 1030, 1003, 915, 847, 732 cm^{-1}.

LREIMS (70 eV) *m/z* 472 ($M^{+\bullet}$, 13%), 457 [$(M-CH\bullet)^+$, 16%], 337 (43), 320 (6), 279 (8), 262 (6), 233 (5), 203 (4), 191 (5), 175 (5), 152 (7), 135 (100), 107 (12), 97 (12), 77 (15), 69 (13), 55 (12).

HREIMS Found: $M^{+\bullet}$, 472.2096. $C_{26}H_{32}O_8$ requires 472.2097.

Optical Rotation $[\alpha]_D = -14.2$ (c = 1.0, $CHCl_3$).

(6*R*)-4,5,8a-Trihydroxy-3a,6,8b-trimethyl-8-oxodecahydro-3,5a-methanoindeno[4,5-*c*]furan-9-yl 4-methoxybenzoate (131)



131

A magnetically stirred solution of acetonide **130** (118 mg, 0.25 mmol) in acetic acid/H_2O (5 mL of a 4:1 v/v mixture) was heated to 100 ºC for 24 h. The cooled reaction mixture was quenched with $NaHCO_3$ (5 mL of a saturated aqueous solution) and extracted with EtOAc (4 × 5 mL). The combined organic fractions were washed with brine (1 × 10 mL) before being dried (Na_2SO_4), filtered and concentrated under reduced pressure to give a light-yellow oil. Subjection of this material to flash column chromatography (silica, 3:2 v/v EtOAc/hexane) afforded two fractions, A and B.

Concentration of fractions A (R_f = 0.60 in 3:2 v/v EtOAc/hexane elution) the starting acetonide **130** (49 mg, 41% recovery).

Concentration of fraction B (R_f = 0.34) afforded the *title triol* ***131*** (46 mg, 43% at 59% conversion) as a white, crystalline solid.

^{1}H NMR (400 MHz) δ 7.83 (d, *J* = 8.4 Hz, 2H), 6.94 (d, *J* = 8.4 Hz, 2H), 5.62 (d, *J* = 7.2 Hz, 1H), 4.44 (d, *J* = 8.4 Hz, 1H), 4.26 (d, *J* = 7.2 Hz, 1H), 4.10 (d, *J* = 8.4 Hz, 1H), 4.06 (d, *J* = 10.4 Hz, 1H), 3.85 (s, 3H), 3.62 (d, *J* = 10.4 Hz, 1H), 2.80 (m, 2H), 2.29 (q, *J* = 12.8 Hz, 1H), 1.96 (s, 1H), 1.59 (brs, OH), 1.20 (brs. 6H), 1.08 (s, 3H).

^{13}C NMR (100 MHz) δ 213.4, 165.3, 163.5, 131.5, 121.8, 113.9, 83.0, 76.4, 74.3, 70.1, 69.3, 67.0, 55.4, 50.2, 48.6, 46.5, 45.0, 35.1, 15.9, 14.8, 13.6.

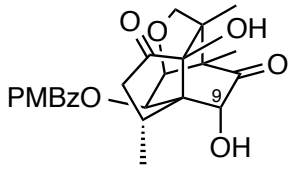
IR ν_{max} (KBr) 3398, 2971, 2936, 2917, 1735, 1723, 1605, 1580, 1512, 1457, 1399, 1343, 1258, 1169, 1101, 1051, 1022, 914, 732 cm^{-1}.

LREIMS (70 eV) *m/z* 432 ($M^{+\bullet}$, 3%), 297 (12), 279 (4), 261 (3), 191 (4), 175 (5), 152 (19), 135 (100), 107 (7), 97 (11), 77 (11), 69 (7), 57 (5).

HREIMS Found: $M^{+\bullet}$, 432.1785. $C_{23}H_{28}O_8$ requires 472.1784.

Optical Rotation $[\alpha]_D = -6.5$ (*c* = 0.44, $CHCl_3$).

(6*R*)-5,8a-Dihydroxy-3a,6,8b-trimethyl-4,8-dioxodecahydro-3,5a-methanoindeno[4,5-*c*]furan-9-yl 4-methoxybenzoate (132)



132

A magnetically stirred solution of the triol **131** (22 mg, 0.051 mmol) in DCM (2 mL) was cooled to 0 °C while a solution of *p*-TsOH•H_2O (26.6 mg, 0.140 mmol) and 4-acetamido-TEMPO (32.6 mg, 0.153 mmol) in DCM (1 mL) was prepared and allowed to stir at 18 °C for 0.5 h. The latter solution was then added to the first over 1.5 h and the ensuing mixture stirred at 18 °C for 48 h before being quenched with $NaHCO_3$ (3 mL of a saturated aqueous solution). The separated aqueous phase was extracted with DCM (3 × 5 mL) and the combined organic fractions were washed with H_2O (1 × 5

mL) and brine (1 × 5 mL) before being dried (Na_2SO_4), filtered and concentrated under reduced pressure to give light-yellow oil. Subjection of this material to flash column chromatography (silica, 2:3 v/v EtOAc/hexane elution) gave two fractions, A and B.

Concentration of fraction A (R_f = 0.39 in 2:3 v/v EtOAc/hexane) afforded *acyloin* ***132*** (15.8 mg, 72% at 89% conversion) white, crystalline solid.

^{1}H NMR (400 MHz) δ 7.86 (d, *J* = 9.2 Hz, 2H), 6.96 (d, *J* = 9.2 Hz, 2H), 5.70 (d, *J* = 7.2 Hz, 1H), 4.35 (s, 1H), 4.31 (d, *J* = 9.6 Hz, 1H), 4.28 (d, *J* = 7.2 Hz, 1H), 3.87 (s, 3H), 3.65 (d, *J* = 9.6 Hz, 1H), 2.88 (m, 2H), 2.50 (brs, OH), 2.40 (m, 1H), 2.08 (s, OH), 1.24 (d, *J* = 6.8 Hz, 3H), 1.21 (s, 3H), 1.14 (s, 3H).

^{13}C NMR (100 MHz) δ 212.5 (2C), 165.1, 163.7, 131.5, 121.6, 114.1, 82.0, 80.0, 74.7, 73.5, 68.7, 58.7, 55.5, 52.0, 49.3, 44.9, 34.3, 14.7 (2C), 12.8.

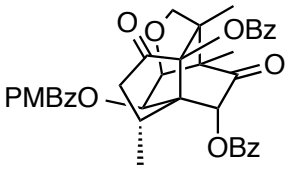
IR ν_{max} (KBr) 3433, 2980, 1718, 1603, 1511, 1461, 1383, 1341, 1258, 1166, 1103, 1024, 937, 846, 736 cm^{-1}.

LREIMS (70 eV) *m/z* 430 ($M^{+\bullet}$, 3%), 278 (7), 250 (1), 204 (2), 191 (3), 151 (3), 135 (100), 107 (4), 97 (4), 84 (7), 77 (5), 69(4), 57 (1).

HREIMS Found: $M^{+\bullet}$, 430.1628. $C_{23}H_{28}O_8$ requires 430.1628.

Concentration of fraction B (R_f = 0.32 in 2:3 v/v EtOAc/hexane) afforded the starting triol **131** (2.5 mg, 11% recovery).

(6*R*)-9-((4-methoxybenzoyl)oxy)-3a,6,8b-trimethyl-4,8-dioxooctahydro-3,5a-methanoindeno[4,5-*c*]furan-5,8a(6*H*)-diyl dibenzoate (133)



133

A magnetically stirred solution of acyloin **132** (16 mg, 0.07 mmol), 4-(*N*,*N*-dimethylamino)pyridine (29 mg, 0.24 mmol) and triethylamine (0.3 mL) in DCM (2 mL) was cooled to 0 °C and treated with benzoyl chloride (0.2 mL, 0.17 mmol). The resulting mixture was allowed to warm to 18 °C and stirred at this temperature for 18 h before treated with HCl (5 mL of 1 M aqueous solution) and extracted with DCM (4 × 5 mL). The combined organic phases were washed with brine (1 × 10 mL) then dried (Na_2SO_4), filtered and concentrated under reduced pressure. The resulting light-yellow oil was subjected to flash column chromatography (silica, 1:9 v/v EtOAc/hexane elution) and concentration of the appropriate fractions (R_f = 0.59 in 1:4 v/v EtOAc/hexane) gave the *titled tri-ester **133*** (21.0 mg, 88%) as a white, crystalline solid.

^{1}H NMR (400 MHz) δ 8.06 (d, *J* = 7.2 Hz, 2H), 7.96 (t, *J* = 9.6 Hz, 4H), 7.63 (quintet, *J* = 7.6 Hz, 2H), 7.51 (m, 4H), 7.01 (d, *J* = 9.2 Hz, 2H), 6.18 (s, 1H), 5.82 (d, *J* = 6.8 Hz, 1H), 4.91 (d, *J* = 10.4 Hz, 2H), 4.53 (d, *J* = 6.8 Hz, 1H), 3.89 (s, 3H), 3.72 (d, *J* = 10.4 Hz, 1H), 3.16 (dd, *J* = 19.2, 10.4 Hz, 1H), 2.93 (m, 1H), 2.41 (dd, *J* = 19.2, 10.4 Hz, 1H), 1.26 (s, 3H), 1.25 (s, 3H), 1.03 (d, *J* = 6.8 Hz, 3H).

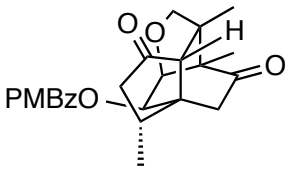
^{13}C NMR (100 MHz) δ 206.9, 206.2, 165.2, 165.1, 164.0,163.9, 134.2, 134.0, 133.7, 131.9, 130.2, 130.1, 130.0, 129.2, 128.8, 128.5, 128.4, 127.9, 121.0, 114.2, 89.1, 79.4, 74.0, 73.9, 68.8, 59.9, 55.5, 54.5, 51.0, 46.1, 33.5, 15.7, 14.3, 12.9.

IR ν_{max} (KBr) 2979, 1727, 1605, 1582, 1512, 1451, 1315, 1259, 1169, 1088, 1066, 1025, 937, 848, 767, 706 cm^{-1}.

HREIMS Found: $M^{+\bullet}$, 661.2050. $C_{37}H_{34}O_{10}$ requires 661.2050.

Optical Rotation $[\alpha]_D$ = –35.2 (*c* = 1.0, $CHCl_3$).

(6*R*)-3a,6,8b-Trimethyl-4,8-dioxodecahydro-3,5a-methanoindeno[4,5-*c*]furan-9-yl 4-methoxybenzoate (135)



135

A magnetically stirred solution of tri-ester **133** (18 mg, 0.017 mmol) in THF/MeOH (3 mL of a 2:1 v/v mixture) was cooled to –78 °C then SmI_2 (0.1 M solution in THF) was added dropwise until the blue color persisted (depending on the quality of the samarium reagent up to 5 equivalents were required). The reaction mixture was allowed to stir at –78 °C for 0.25 h then poured into K_2CO_3 (3 mL of a saturated aqueous solution) and diluted with Et_2O (5 mL). The separated aqueous phase was extracted with Et_2O (4 × 5 mL) and the combined organic fractions were washed with H_2O (1 × 10 mL) and brine (1 × 10 mL) before being dried (Na_2SO_4), filtered and concentrated under reduced pressure. The resulting colourless oil was subjected to flash column chromatography (silica, 3:7 v/v EtOAc/hexane elution) and concentration of the appropriate fractions (R_f = 0.18 in 1:4 v/v EtOAc/hexane) gave the *titled diketone **135*** (10 mg, 90%) as a white, crystalline solid, mp = 90-116 °C.

^{1}H NMR (400 MHz) δ 7.86 (d, *J* = 9.2 Hz, 2H), 6.96 (d, *J* = 9.2 Hz, 2H), 5.08 (dd, *J* = 6.8 and 1.2 Hz, 1H), 4.37 (d, *J* = 9.6 Hz, 1H), 4.26 (d, *J* = 6.8 Hz, 1H), 3.87 (s, 3H), 3.50 (d, *J* = 9.6 Hz, 1H), 2.65-2.50 (complex m, 2H), 2.45-2.05 (complex m, 4H), 1.16 (s, 3H), 1.14 (d, *J* = 7.2 Hz, 3H), 1.12 (s, 3H).

^{13}C NMR (100 MHz) δ 214.3, 210.5, 165.3, 163.8, 131.6, 121.5, 114.1, 78.5, 74.9, 72.5, 62.5, 60.0, 55.5, 49.7, 47.0, 46.0, 43.2, 37.0, 20.5, 13.0, 12.4.

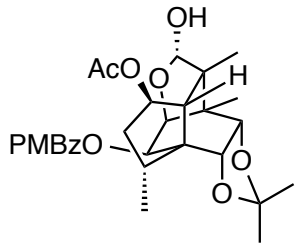
IR ν_{max} (KBr) 2964, 1718, 1605, 1512, 1455, 1382, 1318, 1259, 1168, 1099, 1061, 1030, 927, 848, 765 cm^{-1}.

LREIMS (70 eV) *m/z* 398 ($M^{+\bullet}$, 22), 263 (4), 246 (10), 218 (5), 204 (19), 167 (5), 137 (30), 135 (100), 125 (7), 107 (9), 97 (10), 92 (9), 77 (15).

HREIMS Found: $M^{+\bullet}$, 398.1729. $C_{23}H_{26}O_6$ requires 398.1729.

Optical Rotation $[\alpha]_D = -18.6$ ($c = 0.36$, $CHCl_3$).

(3a*S*,6*S*,7*R*,9*R*,9b*R*)-7-Acetoxy-6-hydroxy-2,2,3b,6a,9-pentamethyldecahydro-4,9a-methanofuro[3',4':6,7]indeno[4,5-*d*][1,3]dioxol-10-yl 4-methoxybenzoate (137)



137

A magnetically stirred solution of bis-ester **125** (4 mg, 0.008 mmol) in acetone (0.2 mL) was treated with freshly prepared DMDO (2 mL of ~ 0.08 M solution in acetone) and the reaction flask was capped, wrapped in aluminum foil (to exclude light) and stirred at room temperature for 72 h. The reaction mixture was then concentrated under reduced pressure to give a clear, colourless oil that was subjected to flash column chromatography (silica, 3:7 v/v EtOAc/hexane elution) and so affording two fractions, A and B.

Concentration of fractions A ($R_f = 0.41$ in 1:1 v/v EtOAc/hexane elution) afforded starting bis-ester **126** (1.6 mg, 40% recovery) as a clear, colourless oil that was identical, in all respects, with an authentic sample.

Concentration of fraction B ($R_f = 0.34$) afforded *hemiacetal **137*** (1.7 mg, 41% at 60% conversion) as a white, crystalline solid.

^{1}H NMR (800 MHz) δ 8.03 (d, $J = 9.6$ Hz, 2H), 6.98 (d, $J = 9.6$ Hz, 2H), 5.72 (m, 1H), 5.34 (s, 1H), 5.17 (dd, $J = 6.4$ and 2.4 Hz, 1H), 4.44 (d, $J = 6.4$ Hz, 1H), 4.12 (d, $J = 8.8$ Hz, 1H), 3.93 (d, $J = 8.8$ Hz, 1H), 3.86 (s, 3H), 2.28 (m, 1H), 2.22 (m, 1H), 2.08 (s, 3H), 1.86 (m, 1H), 1.79 (dd, $J = 9.2$ and 2.4 Hz, 1H), 1.52 (s, 3H), 1.38 (s, 3H), 1.34 (s, 3H), 1.08 (s, 3H), 1.03 (d, $J = 7.2$ Hz, 3H).

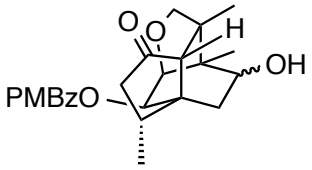
^{13}C NMR (200 MHz) δ 170.9, 165.6, 163.5, 131.8, 122.2, 114.1, 108.6, 101.0, 83.3, 78.6, 74.6, 70.0, 56.3, 55.5, 48.9, 46.0, 45.1, 40.9, 39.8, 25.9, 23.7, 21.2, 17.6, 17.3, 14.7.

IR ν_{max} (KBr) 3436, 2978, 2937, 2883, 1713, 1606, 1580, 1512, 1456, 1376, 1260, 1211, 1167, 1102, 1086, 1056, 1027, 943, 878, 847, 770, 733 cm^{-1}.

LREIMS (70 eV) *m/z* 516 ($M^{+\bullet}$, 2%), 501 [$(M-CH\bullet)^+$, 2%], 455 (4), 410 (2), 276 (4), 246 (2), 218 (20, 200 (6), 173 95), 158 (19), 135 (100), 84 (36), 77 (6).

HREIMS Found: $M^{+\bullet}$, 516.2363. $C_{28}H_{36}O_9$ requires 516.2359

(6*R*)-4-Hydroxy-3a,6,8b-trimethyl-8-oxodecahydro-3,5a-methanoindeno[4,5-*c*]furan-9-yl 4-methoxybenzoate (138)



138

A magnetically stirred solution of ketone **135** (5.0 mg, 0.013 mmol) in MeOH/ DCM (1 mL of a 1:1 v/v mixture) was cooled to −10 ºC and treated with $NaBH_4$ (0.5 mg, 0.014 mmol). After 1 h the reaction mixture was quenched with H_2O (0.2 mL) then concentrated under reduced pressure. The residue thus obtained was partitioned between half-brine (1 mL) and DCM (1 mL) and the separated aqueous phase was extracted with DCM (3 × 1 mL). The combined organic fractions were washed with brine (1 × 2 mL) before being dried (Na_2SO_4), filtered and concentrated under reduced pressure. Subjection of the resulting clear, colourless oil to flash column chromatography (silica, 3:2 v/v EtOAc/hexane) and concentration of the appropriate fractions (R_f = 0.27 in 3:7 v/v EtOAc/hexane) gave *alcohol **138*** (4.7 mg, 90%) as a white, semi solid.

^{1}H NMR (400 MHz) δ 7.84 (d, *J* = 8.8 Hz, 2H), 6.93 (d, *J* = 8.8 Hz, 2H), 4.81 (d, *J* = 6.8 Hz, 1H), 4.15 (d, *J* = 8.8 Hz, 1H), 4.01 (brd, d, *J* = 9.2 Hz, 1H), 4.00 (d, *J* = 6.8 Hz, 1H), 3.85 (s, 3H), 3.48 (d, *J* = 8.8 Hz, 1H), 2.53 (complex m, 1H), 2.45 (s, 1H), 2.38-2.17 (complex m, 3H), 1.7 (brs, OH), 1.52 (dd, *J* = 14.4 and 2.4 Hz, 1H), 1.36 (s, 3H), 1.16 (s, 3H), 1.07 (d, *J* = 6.4 Hz, 3H).

^{13}C NMR (100 MHz) δ 216.9, 165.6, 163.5, 131.6, 121.9, 113.9, 78.7, 75.6, 73.8, 70.5, 61.6, 55.4, 49.4, 46.2, 43.7, 43.5, 41.5, 37.3, 21.6, 17.1, 13.0.

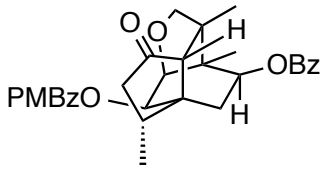
IR ν_{max} (KBr) 3472, 2964, 2878, 1715, 1605, 1580, 1512, 1458, 1259, 1168, 1101, 1064, 1030, 927, 847, 768, 735, 698 cm^{-1}.

LREIMS (70 eV) *m/z* 400 ($M^{+\bullet}$, 7%), 382 [$(M-H_2O)^+$, 16%], 265 (4), 248 (7), 230 (2), 204 (7), 139 (7), 135 (35), 111 (4), 85 (63), 83 (100), 69 (11), 57 (14), 51 (42).

HREIMS Found: $M^{+\bullet}$, 400.1886. $C_{23}H_{28}O_6$ requires 400.1886.

Optical Rotation $[\alpha]_D = -15.4$ (*c* = 0.18, $CHCl_3$).

(6*R*)-4-(benzoyloxy)-3a,6,8b-Trimethyl-8-oxodecahydro-3,5a-methanoindeno[4,5-*c*]furan-9-yl 4-methoxybenzoate (139)



139

A magnetically stirred solution of alcohol **138** (4.7 mg, 0.012 mmol), 4-(*N*,*N*-dimethylamino)pyridine (2.0 mg, 0.017 mmol) and triethylamine (0.005 mL) in DCM (0.5 mL) was cooled to 0 °C and treated with benzoyl chloride (0.002 mL, 0.17 mmol). The resulting mixture was allowed to warm to 18 °C and stirred at this temperature for 1 h, then treated with 1 M HCl (1 mL) and extracted with DCM (4 × 1 mL). The combined organic phase was washed with brine (1 × 1.5 mL) before being dried (Na_2SO_4), filtered and concentrated under reduced pressure. Subjection of this material to flash column chromatography (silica, 3:2 v/v EtOAc/hexane elution) and concentration of the relevant fractions (**R_f** = 0.50) afforded *benzoate ester **139*** (5.2 mg, 86%) as a clear, colourless oil.

^{1}H NMR (400 MHz) δ 8.03 (d, *J* = 8.8 Hz, 2H), 7.86 (d, *J* = 9.2 Hz, 2H), 7.61 (t, *J* = 7.6 Hz, 1H), 7.48 (t, *J* = 8.4 Hz, 2H), 6.95 (d, *J* = 8.8 Hz, 2H), 5.20 (dd, d, *J* = 10 and 2.4 Hz, 1H), 4.92 (dd, *J* = 6.4, 1.2 Hz, 1H), 4.24 (d, *J* = 9.2 Hz, 1H), 4.16 (d, *J* = 6.4 Hz, 1H), 3.57 (d, *J* = 9.2 Hz, 1H), 2.63

(dd, J = 14.8 and 9.6 Hz, 1H), 2.54 (ddd, J = 18.8, 9.2 and 1.2 Hz, 1H), 2.42 (s, 1H), 2.31 (m, 1H), 2.20 (m, 1H), 1.57 (d, J = 2.4 Hz, 0.5H), 1.55 (s, 3H), 1.54 (d, J = 2.4 Hz, 0.5H), 1.52 (s, 3H), 1.17 (s, 3H), 1.08 (d, J = 87.2 Hz, 3H).

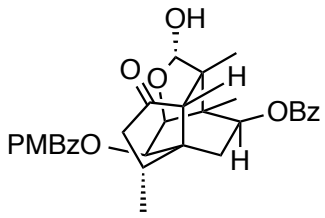
^{13}C NMR (100 MHz) δ 216.2, 166.2, 165.5, 163.6, 133.3, 131.6, 130.0, 129.6, 128.8, 121.8, 114.0, 78.9, 75.2, 73.8, 73.4, 62.2, 55.5, 48.5, 46.1, 43.6, 42.3, 41.5, 37.2, 21.7, 17.1, 12.9.

IR ν_{max} (KBr) 2966, 2934, 2879, 1716, 1605, 1581, 1512, 1451, 1420, 1378, 1314, 1272, 1259, 1168, 1098, 1069, 1026, 1006, 975, 948, 928, 847, 768, 714 cm^{-1}.

LREIMS (70 eV) *m/z* 504 ($M^{+\bullet}$, 17%), 352 (4), 243 (41), 230 (9), 204 (7), 135 (100), 109 (7), 105 (39), 77 (11).

HREIMS Found: $M^{+\bullet}$, 504.2150. $C_{30}H_{32}O_7$ requires 504.2148.

(1*S*,6*R*)-4-(benzoyloxy)-1-Hydroxy-3a,6,8b-trimethyl-8-oxodecahydro-3,5a-methanoindeno[4,5-*c*]furan-9-yl 4-methoxybenzoate (140)



140

A magnetically stirred solution of the acetate **139** (5 mg, 0.009 mmol) in acetone (0.2 mL) was treated with freshly prepared DMDO (2 mL of *ca.* 0.08 M solution in acetone). The reaction flask was capped wrapped in aluminium foil (to exclude light) and stirred at room temperature for 72 h. The reaction mixture was concentrated under reduced pressure to give a colourless oil. Subjection of this material to flash column chromatography (silica, 1:1 v/v EtOAc/hexane elution) resulted in two fractions, A and B.

Concentration of fractions A (R_f = 0.41) afforded starting acetate **139** (3 mg, 66%) as a clear, colourless oil that was identical, in all respects, with an authentic sample.

Concentration of fraction B (R_f = 0.32) afforded *hemiacetal* ***140*** (1.3 mg, 28%) as a clear, colourless oil.

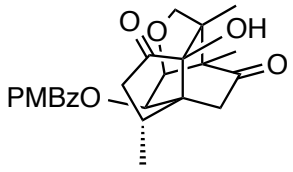
^{1}H NMR (800 MHz) δ 8.05 (d, *J* = 4 Hz, 2H), 7.84 (d, *J* = 8.8 Hz, 2H), 7.61 (uneven t, 1H), 7.50 (uneven q, 2H), 6.95 (d, *J* = 8.8 Hz, 2H), 5.55 (d, *J* = 4.8 Hz, 1H), 5.17 (dd, *J* = 9.6 and 2.4 Hz, 1H), 4.85 (d, *J* = 7.2 Hz, 1H), 4.33 (d, *J* = 7.2 Hz, 1H) (3.86 (s, 3H), 2.68 (AB q, 1H), 2.55 (dd, *J* = 19.2 and 11.2 Hz, 1H), 2.42 (brs, 1H), 2.32 (dd, *J* = 19.2 and 11.2 Hz, 1H), 2.17 (m, 2H), 2.03 (d, *J* = 8 Hz, 1H), 1.57 (s, 3H), 1.36 (s, 3H), 1.08 (d, *J* = 6.4 Hz, 3H).

^{13}C NMR (200 MHz, selected peaks) δ 133.4, 132.1, 131.6, 129.6, 128.7, 114.1, 100.5, 61.8, 55.5, 47.8, 47.2, 46.2, 42.6, 41.9, 37.3, 19.7, 18.1, 12,7.

LREIMS (70 eV) *m/z* 520 ($M^{+\bullet}$, 4%), 385(7), 246(4), 174(4), 152(4), 135(100), 105(25), 77(10), 69(4).

HREIMS Found: $M^{+\bullet}$, 520.2098. $C_{30}H_{32}O_8$ requires 520.2097.

(6*R*)-8a-Hydroxy-3a,6,8b-trimethyl-4,8-dioxodecahydro-3,5a-methanoindeno[4,5-*c*]furan-9-yl 4-methoxybenzoate (142)



142

Step i. A magnetically stirred solution of hydroxyketone **138** (10 mg, 0.024 mmol) in dry Et_2O (1 mL) maintained at 18 °C was treated with triethylamine (0.026 mL, 0.192 mmol) and TMSOTf (0.017 mL, 0.096 mmol). The resulting mixture was stirred at 18 °C for 32 h then diluted with Et_2O (4 mL), washed with $NaHCO_3$ (1 × 4 mL of saturated aqueous solution) and brine (1 × 4 mL) before being dried (Na_2SO_4), filtered and concentrated under reduced pressure to give the anticipated, thermodynamically favored silyl enol ether as a light-yellow oil (in quantitative yield) that was used in step ii described immediately below.

Step ii. A magnetically stirred solution of the enol ether obtained from step i in acetone (1 mL) maintained at 0 °C was treated with freshly prepared DMDO (1 mL). The reaction flash was capped and the mixture was left to 18 °C and then stirred at this temperature for 72 h. The resulting mixture was concentrated under reduced pressure to give a clear, colourless oil that upon subjection to flash column chromatography (silica, 3:2 v/v EtOAc/hexane elution) afforded two fractions, A and B.

Concentration of fractions A (R_f = 0.27) gave the starting hydroxyketone **138** (0.5 mg, 5% recovery).

Concentration of fraction B (R_f = 0.20) afforded *hemiacetal **142*** (5 mg, 90%) as a white, crystalline solid, mp = 203-217 °C.

^{1}H NMR (400 MHz) δ 7.86 (d, *J* = 8.8 Hz, 2H), 6.97 (d, *J* = 8.8 Hz, 2H), 5.16 (d, *J* = 7.2 Hz, 1H), 4.25 (complex t, 2H), 3.87 (s, 3H), 3.62 (d, *J* = 9.6 Hz, 1H), 2.82 (dd, *J* = 19.2 and 9.2 Hz, 1H), 2.75 (d, *J* = 18.4 Hz, 1H), 2.66 (m, 1H), 2.40 (dd, *J* = 19.2 and 9.2 Hz, 1H), 2.19 (d, *J* = 18.4 Hz, 1H), 2.09 (s, 1H), 1.20 (s, 3H), 1.11 (d, *J* = 7.2 Hz, 3H), 1.10 (s, 3H).

^{13}C NMR (100 MHz) δ 212.6, 210.4, 165.0, 163.8, 131.6, 121.3, 114.1, 81.3, 78.4, 74.4, 73.4, 58.9, 55.5, 52.2, 49.9, 44.4, 42.0, 34.3, 14.3, 12.8, 12.7.

IR ν_{max} (KBr) 3435, 2970, 1721, 1605, 1512, 1456, 1258, 1168, 1098, 1064, 1030, 936, 847, 761 cm^{-1}.

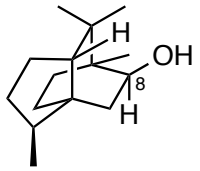
LREIMS (70 eV) *m/z* 414 ($M^{+\bullet}$, 2%), 341(3), 281(10), 152(9), 135(100), 107(5), 77(8).

HREIMS Found: $M^{+\bullet}$, 414.1681. $C_{23}H_{26}O_7$ requires 414.1679.

Optical Rotation $[\alpha]_D$ = –32.2 (*c* = 0.16, $CHCl_3$).

5.3 Experimental Procedures Associated with Work Described in Chapter Four

(3*S*,3a*S*,6*S*)-3,6,7,7-Tetramethyloctahydro-3a,6-ethanoinden-5-ol [(–)-8-*epi*-19]



(–)-8-*epi*-**19**

To magnetically stirred solution of khusione (**32**, 9 mg) in dry MeOH/DCM (1:1, 1 mL) at 0 ºC was added $NaBH_4$ (6 mg). The mixture was stirred for 24 h, quenched with H_2O (100 μL) and diluted with 1 mL MeOH and filtered through a bed of silica (small amount of H_2O is removed in the process) and concentrated under reduced pressure. The resulting colourless oil was subjected to flash column chromatography (silica, 1:9 v/v EtOAc/hexane elution) and concentration of the appropriate fractions gave (–)-8-*epi*-**19** (R_f = 0.40, 7 mg, 77%) as a clear, colourless oil and (–)-khusiol [(–)-**19**] (R_f = 0.27, 0.8 mg, 9%) as a white, crystalline solid.

^{1}H NMR (400 MHz; for *epi*-khusiol) δ 3.69 (dd, *J* = 9.2 and 2 Hz, 1H), 1.90 (m, 2H), 1.62-1.30 (m, 8H), 1.12 (s, 3H), 1.08 (m, 2H), 0.89 (s, 3H), 0.84 (s, 3H), 0.82 (d, *J* = 7.6 Hz, 3H).

^{13}C NMR (100 MHz; for *epi*-khusiol) δ 79.6, 53.1, 41.8, 41.6, 40.0, 38.8, 35.7, 34.8, 30.8, 30.4, 29.2, 24.2, 23.0, 18.1, 17.6.

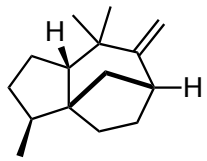
IR ν_{max} (KBr) 3401, 2951, 2868, 1463, 1372, 1043 cm^{-1}.

LREIMS (70 eV) *m/z* 222 [($M^{+\bullet}$), 10%], 204 [($M-H_2O)^+$, 14%], 189(9), 177(12), 161(12), 151(7), 133(8), 119(26), 107(11), 95(12), 84(100), 69(19), 55(23).

HREIMS Found: $M^{+\bullet}$, 222.1976. $C_{15}H_{26}O$ requires 222.1984.

Optical Rotation $[\alpha]_D$ = –23.2 (*c* = 1.2, $CHCl_3$).

(3*S*,3a*S*,6*R*,8a*S*)-3,8,8-Trimethyl-7-methyleneoctahydro-1*H*-3a,6-methanoazulene [(+)-151]



(+)-151

A magnetically stirred solution of (–)-8-*epi*-**19** (13 mg) in dry pyridine (1 mL) at 0 ºC was slowly treated with phosphorus oxychloride ($POCl_3$, 20 μL). The mixture was stirred for 2 h at room temperature, cooled to 0 ºC and quenched slowly with H_2O (2 mL) [CAUTION: $POCl_3$ reacts vigorously with H_2O]. The aqueous phase was extracted with Et_2O (3 × 2 mL). The combined organic phase was washed with brine (3 mL) before being dried (Na_2SO_4), filtered and concentrated under reduced pressure. The resulting colourless oil was subjected to flash column chromatography (silica, neat hexane elution) and concentration of the appropriate fractions (R_f = 0.68 in hexane) gave (+)-prezizaene [(+)-**151**] (10.8 mg, 90%) as a clear, colourless oil.

^{1}H NMR (400 MHz) δ 4.68 (dd, *J* = 18.4 and 2 Hz, 1H), 2.80 (dd, *J* = 6.4 and 4.8 Hz, 1H), 1.96 (m, 2H), 1.81 (m, 2H), 1.55 (m, 5H), 1.23 (brd, *J* = 10.4 Hz, 2H), 1.14 (m, 1H), 1.11 (s, 3H), 1.07 (s, 3H), 0.87 (d, *J* = 7.6 Hz, 3H).

^{13}C NMR (100 MHz) δ 163.1, 105.5 54.3, 53.6, 48.0, 41.1, 40.4, 37.6, 32.6, 32.2, 31.4, 29.9, 27.1, 22.8, 20.0.

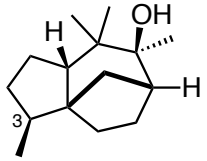
IR ν_{max} (KBr) 3078, 2953, 2869, 1630, 1460, 1380, 1359 cm^{-1}.

LREIMS (70 eV) *m/z* 204 [($M^{+\bullet}$), 46%], 189 [($M\text{-}CH_3$)$^+$, 51%], 175(13), 161(29), 147(20), 133(100), 119(39), 108(53), 91(62), 84(49), 69(20), 55(36).

HREIMS Found: $M^{+\bullet}$, 204.1885. $C_{15}H_{24}$ requires 204.1878.

Optical Rotation $[\alpha]_D$ = +24.6 (*c* =1.0, $CHCl_3$).

(3*S*,3a*S*,6*R*,7*S*,8a*S*)-3,7,8,8-Tetramethyloctahydro-1*H*-3a,6-methanoazulen-7-ol [(+)-153]



(+)-153

A magnetically stirred solution of (–)-khusiol tosylate (**183**) (13 mg) and lithium carbonate (5 mg) in aqueous dioxane (70%, 2 mL) was refluxed for 3 h. The mixture was diluted with H_2O (2 mL) and extracted with Et_2O (3 × 3 mL). The combined organic phase was washed with brine (1 × 5 mL) before being dried (Na_2SO_4), filtered and concentrated under reduced pressure. The resulting colourless oil was subjected to flash column chromatography (silica, 5:95 v/v EtOAc/hexane elution) and concentration of the appropriate fractions gave **(+)**-allokhusiol **153** (R_f = 0.11, 4.8 mg, 55%) as a clear, colourless oil.

^{1}H NMR (400 MHz) δ 2.05 (dd, *J* = 6.8 and 4 Hz, 1H), 1.94 (m, 1H), 1.84-1.64 (m, 4H), 1.60-1.40 (m, 5H), 1.27 (m, 1.5H), 1.16 (s, 3H), 1.09 (m, 1.5H), 0.93 (s, 3H), 0.91 (s, 3H), 0.91(d, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz) δ 77.2, 52.6, 51.7, 50.6, 40.2, 39.7, 35.9, 33.0, 31.9 27.2, 26.2, 23.8, 23.5, 21.3, 19.8.

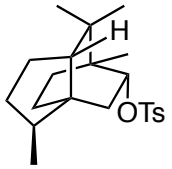
IR ν_{max} (KBr) 3481, 2954, 2868, 1481, 1458, 1391, 1372 cm^{-1}.

LREIMS (70 eV) *m/z* 222 [($M^{+\bullet}$), 77], 207 [$(M\text{-}CH_3)^+$, 19], 204 [$(M\text{-}H_2O)^+$, 46], 189(74), 179(100), 161(56), 147(17), 133(57), 119(56), 109(62), 95(60), 82(55), 71(88), 67(43).

HREIMS Found: $M^{+\bullet}$, 222.1980. $C_{15}H_{26}O$ requires 222.1984.

Optical Rotation $[\alpha]_D$ = +29.2 (*c* = 0.39, $CHCl_3$).

(3*S*,3a*S*,5*R*,6*S*)-3,6,7,7-Tetramethyloctahydro-3a,6-ethanoinden-5-yl 4-methylbenzenesulfonate (183)



khusiol tosylate (**183**)

To magnetically stirred solution of (–)-khusiol [(–)-**19**] (26 mg) in dry pyridine (1 mL) at room temperature was added *p*-toluenesulfonyl chloride. The mixture was stirred for 24 h, quenched with cold H_2O (2 mL) and extracted with Et_2O (3 × 2 mL). The combined ether fraction was washed with HCl (1 × 2 mL of 1 M aqueous solution), $NaHCO_3$ (1 × 2 mL of saturated aqueous solution) and H_2O till neutral before being dried (Na_2SO_4), filtered and concentrated under reduced pressure. The resulting colourless oil was subjected to flash column chromatography (silica, 5:95 v/v EtOAc/hexane elution) and concentration of fractions (R_f = 0.38) gave the khusiol tosylate (**183**) (9.4 mg, 23 % as a clear, colourless oil and starting material (–)-khusiol [(–)-**19**] (R_f = 0.20, 13 mg, 51%).

^{1}H NMR (400 MHz) δ 7.80 (d, *J* = 8.4 Hz, 2H), 7.33 (d, *J* = 8.4 Hz, 2H), 4.76 (ddd, *J* = 7.2, 4.8 and 1.6 Hz, 1H), 2.44 (s, 3H), 1.97 (m, 2H), 1.62-1.10 (m, 9H), 0.96 (m, 1H), 0.84 (s, 3H), 0.79 (s, 3H), 0.73 (d, *J* = 7.6 Hz, 3H), 0.57 (s, 3H).

^{13}C NMR (100 MHz) δ 144.3, 134.6, 129.6, 127.8, 84.2, 52.9, 41.2, 39.9, 39.4, 38.9, 34.8, 34.7, 30.2, 26.4, 24.8, 24.1, 21.6, 20.7, 17.6, 16.4.

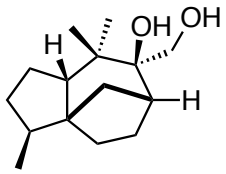
IR ν_{max} (KBr) 2952, 2870, 1598, 1459, 1363, 1187, 1176, 1097, 924, 885 cm^{-1}.

LREIMS (70 eV) *m/z* 376 [($M^{+\bullet}$), 2%], 221(10), 204(94), 189(71), 172(55), 161(71), 147(34), 133(83), 119(100), 107(67), 91(95), 79(40), 69(43), 55(44).

HREIMS Found: $M^{+\bullet}$, 376.2073. $C_{22}H_{32}O_3S$ requires 376.2072.

Optical Rotation $[\alpha]_D$ = –37.7 (*c* = 0.9, $CHCl_3$).

(3*S*,3a*S*,6*R*,7*S*,8a*S*)-7-(hydroxymethyl)-3,8,8-Trimethyloctahydro-1*H*-3a,6-methanoazulen-7-ol (167)



167

A magnetically stirred solution of alkene **151** (5 mg, 0.02 mmol) in pyridine (1 mL) maintained at 18 °C was treated with osmium tetraoxide (7 mg, 0.03 mmol) and the resulting solution stirred for 2 h before being treated with sodium bisulfite (1 mL of a 2 M aqueous solution). The ensuing mixture was then stirred at 18 °C for a further 2 h before being extracted with Et_2O (3 × 1 mL). The combined organic phases were washed with H_2O (2 mL) then dried (Na_2SO_4), filtered and concentrated under reduced pressure to give viscous, yellow oil. Subjection of this material to flash chromatography (silica, EtOAc/hexane elution) and concentration of the relevant fractions afforded a white solid that upon recrystallization (Et_2O/pentane) gave diol **167**[79] (5.2 mg, 90%) as a white, crystalline needles.

^{1}H NMR (400 MHz) δ 3.62 (s, 2H), 2.39 (m, 2H), 1.92 (m, 1H), 1.80-1.40 (complex m, 9H), 1.35 (dd, *J* = 12.0 and 4.0 Hz, 1H), 1.10 (m, 2H), 0.98 (s, 3H), 0.91 (d, *J* = 7.2 Hz, 3H), 0.87 (s, 3H).

^{13}C NMR (100 MHz) δ 77.5, 63.5, 52.6, 52.1, 43.6, 40.1, 38.9, 35.7, 33.0, 31.6, 27.6, 25.7, 22.9, 19.8, 19.2.

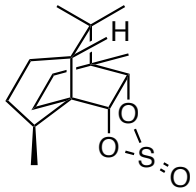
IR ν_{max} (KBr) 3432, 2952, 2868, 1459, 1392, 1180, 1129, 1078, 1060, 1025 cm^{-1}.

LREIMS (70 eV) *m/z* 238 [$M^{+\bullet}$, 16%], 223 (8), 207 (46), 199 (30), 189 (100), 177 (27), 161 (16), 147 (14), 135 (30), 1334(58), 119 (27), 109 (27), 95 (37), 91 (38), 87 (32), 81 (27), 69 (37), 55 (27).

HREIMS Found: $M^{+\bullet}$, 238.1932. $C_{15}H_{26}O_2$ requires 238.1933.

Optical Rotation $[\alpha]_D$ = +23.2 (*c* = 1.2, $CHCl_3$), {lit.[79] $[\alpha]_D$ = –32 (*c* = 0.01, $CHCl_3$)}.

(3a*S*,4*S*,8*S*,8a*S*,8b*R*)-4,5,5,8-Tetramethyloctahydro-4,8a-ethanoindeno[4,5-*d*][1,3,2]dioxathiole 2-oxide (184)



184

To magnetically stirred solution of diol **33** (16 mg) in dry DCM (2 mL) and pyridine (21 μL) at 0 ºC was added thionyl chloride (10 μL). The mixture was stirred for 15 min, quenched with cold H_2O (50 μL) and diluted with DCM (3 mL). The DCM fraction was washed consecutively with HCl (1 × 2 mL of 1 M aqueous solution), $NaHCO_3$ (1 × 5 mL of saturated aqueous solution) and H_2O till neutral before being dried (Na_2SO_4), filtered and concentrated under reduced pressure. The resulting colourless oil was subjected to flash column chromatography (silica, 1:9 v/v EtOAc/hexane elution) and concentration of the appropriate fractions (R_f = 0.60 in 3: 7 v/v EtOAc/hexane) gave an inseparable mixture (1:1) of sulfites **184** (15.9 mg, 84%) as a clear, colourless oil.

^{1}H NMR (400 MHz) partial δ 4.93 (dd, *J* = 8 and 1.2 Hz, 1H), 4.87 (dd, *J* = 8 and 1.2 Hz, H), 4.62 (dd, *J* = 8.8 and 2.4 Hz, 1H), 4.62 (dd, *J* = 8.8 and 2.4 Hz, 1H), 4.57 (dd, *J* = 8.8 and 2.4 Hz, 1H), 2.03 (m, 2H), 1.89 (m, 1H), 1.02 (d, *J* = 7.2 Hz, 3H), 0.99 (d, *J* = 7.6 Hz, 3H), 0.97 (s, 3H), 0.93 (s, 3H), 0.91 (s, 3H), 0.88 (s, 3H), 0.87 (s, 3H), 0.84 (s, 3H).

^{13}C NMR (100 MHz) δ 87.9, 85.4, 84.0, 80.9, 51.4, 51.1, 45.4, 44.5, 39.3, 39.2, 34.8, 34.6, 33.7, 33.5, 26.9, 26.7, 24.8, 24.6, 23.5, 23.3, 21.4, 21.0, 17.7, 17.5, 16.6, 16.3.

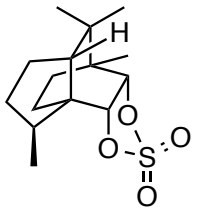
IR ν_{max} (KBr) 2955, 2874, 1469, 1396, 1374, 1210 cm^{-1}.

LREIMS (70 eV) *m/z* 284 [($M^{+\bullet}$), 4%], 220(79), 202(92), 191(23), 177(100), 164(44), 149(31), 132(81), 119(77), 105(41), 95(36), 81(31), 69(47), 55(46).

HREIMS Found: $M^{+\bullet}$, 284.1453. $C_{15}H_{24}O_3S$ requires 284.1446.

Optical Rotation $[\alpha]_D$ = –33.3 (*c* = 0.03, $CHCl_3$).

(3a*S*,4*S*,8*S*,8a*S*,8b*R*)-4,5,5,8-Tetramethyloctahydro-4,8a-ethanoindeno[4,5-*d*][1,3,2]dioxathiole 2,2-dioxide (66)



66

To magnetically stirred solution sulfites **184** (16 mg) in CH_3CN (1 mL) and H_2O (0.5 mL) at room temperature was added sodium periodate (15 mg) and $RuCl_3 \bullet 3H_2O$ (0.1 mg). The mixture was stirred for 2 h, the diluted with EtOAc (4 mL). The solution was washed with sat. $NaHCO_3$ (1 × 3 mL) and brine (1 × 3 mL) before being dried (Na_2SO_4) filtered and concentrated under reduced pressure. The resulting colourless oil was subjected to flash column chromatography (silica, 1:9 v/v EtOAc/hexane elution) and concentration of the appropriate fractions (R_f = 0.52 in 3:7 v/v EtOAc/hexane) gave cyclic sulfate **66** (17.7 mg, 99%) as a white solid (mp = 85-90 ºC).

^{1}H NMR (400 MHz) δ 4.83 (s, 2H), 2.04 (m, 1H), 1.72-1.50 (m, 6H), 1.49-1.33 (m, 2H), 1.20 (ddd, *J* = 8.4, 6.8 and 1.6 Hz, 1H), 1.07 (m, 1H), 0.99 (d, *J* = 7.6 Hz, 3H), 0.96 (s, 3H), 0.90 (s, 3H), 0.86 (s, 3H).

^{13}C NMR (100 MHz) δ 84.6, 81.3, 50.3, 44.4, 39.3, 39.2, 34.7, 34.5, 26.5, 24.5, 23.4, 23.0, 20.9, 17.2, 16.0.

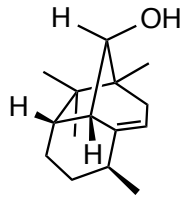
IR ν_{max} (KBr) 2966, 2879, 1462, 1383, 1205, 884 cm^{-1}.

LREIMS (70 eV) *m/z* 300 [($M^{+\bullet}$), 3%], 285 [$(M\text{-}CH_3)^+$, 5], 257(10), 232(6), 215(14), 202(43), 187(45), 177(24), 159(100), 145(45), 132(97), 119(92), 105(61), 91(32), 81(33), 69(55), 55(59)

HREIMS Found: $M^{+\bullet}$, 300.1396. $C_{15}H_{24}O_4S$ requires 300.1395.

Optical Rotation $[\alpha]_D$ = –29.6 (*c* = 0.57, $CHCl_3$).

(1*S*,4*S*,8a*S*)-4,7,9,9-Tetramethyl-1,2,3,4,6,7,8,8a-octahydro-1,7-methanonaphthalen-8-ol (185)



185

A magnetically stirred solution of cyclic sulfate **66** (34 mg) and $NaBH_4$ in dry DMF (1 mL) was under nitrogen for 8 h at 70 ºC. The solvent was then removed under reduced pressure. The residue was suspended in dry THF, and conc. H_2SO_4 (5 μL) and H_2O (5 μL) was added to the stirred suspension. After 20 min excess $NaHCO_3$ was added and the reaction was stirred for further 20 min. Filtration through celite and silica bed and concentration of the filtrate under reduced pressure provided colourless oil. Column chromatography (silica, 1:9 v/v EtOAc/hexane elution) and concentration of the appropriate fractions (R_f = 0.3) gave novel tricyclic *alcohol **185*** (19.4 mg, 70 %) as a white, crystalline solid (mp = 60-66 ºC).

^{1}H NMR (800 MHz) δ 5.27 (d, *J* = 4 Hz, 1H), 3.83 (d, *J* = 4.8 Hz, 1Hz), 2.41 (dd, *J* = 6.4 and 4.8 Hz, 1H), 2.36 (m, 1H), 2.05 (d, *J* = 18.4 Hz, 1H), 1.91 (q, 1H), 1.81 (dd, *J* = 18.4 and 5.6 Hz, 1H), 1.71 (m, 1H), 1.42 (m, 1H), 1.19 (m, 2H), 0.97 (d, *J* = 6.4 Hz, 3H), 0.84 (s, 6H), 0.80 (s, 3H).

^{13}C NMR (200 MHz) δ 143.9, 117.7, 75.4, 48.8, 45.0, 42.2, 41.4, 38.3, 32.8, 32.6, 31.2, 22.3, 21.4, 19.3, 18.6.

IR ν_{max} (KBr) 3370, 2951, 2928, 2868, 1453, 1056 cm^{-1}.

LREIMS (70 eV) *m/z* 220 [($M^{+\bullet}$), 15%], 202 [$(M - H_2O)^+$, 41%], 187(27), 177(8), 159(27), 145(34), 132(100), 119(60), 105(32), 91(32), 83(23), 77(16), 69(24), 55(36).

HREIMS Found: $M^{+\bullet}$, 220.1820. $C_{15}H_{24}O$ requires 220.1827.

Optical Rotation $[\alpha]_D$ = +190 (*c* = 0.22, $CHCl_3$).

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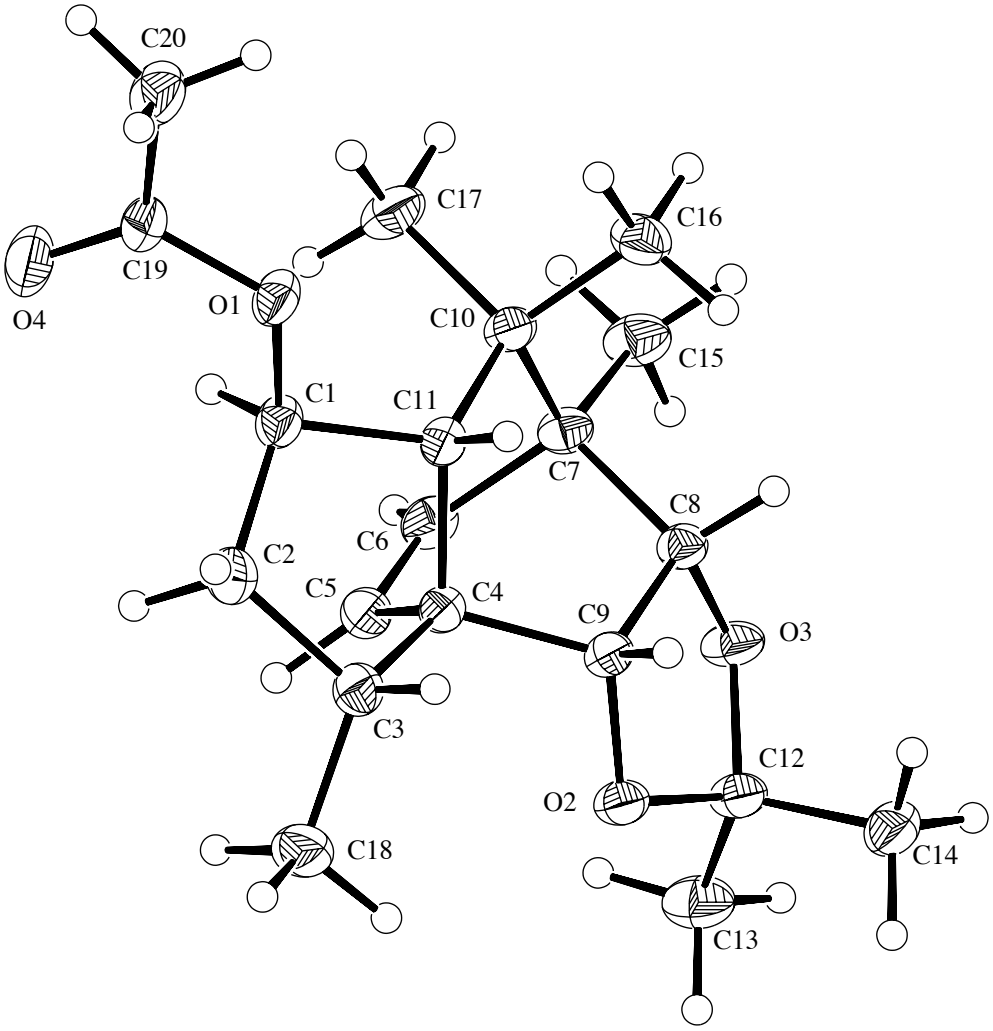
Appendices

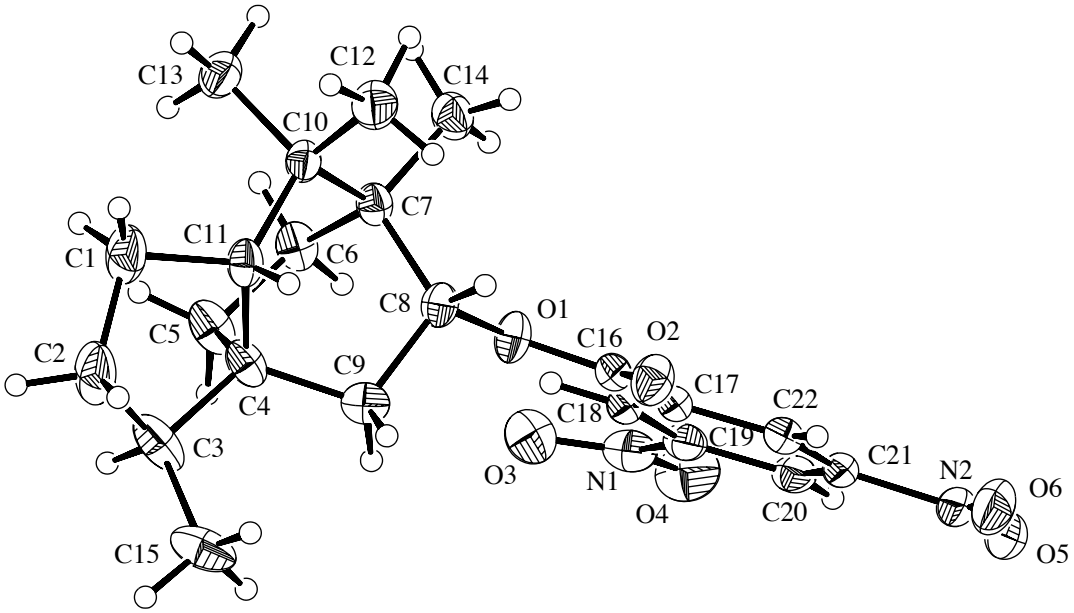
A. 01 X-ray Crystal Structure Data for Compound 44

X-ray crystal structure for compound **44** with labeling of non-hydrogen atoms. Anisotropic displacement ellipsoids display 30% probability levels. Hydrogen atoms are drawn as circles with small radii. Note: A full X-ray crystallographic report for compound **44** is provided in PDF format on the compact disc found on the inside back cover of this thesis.



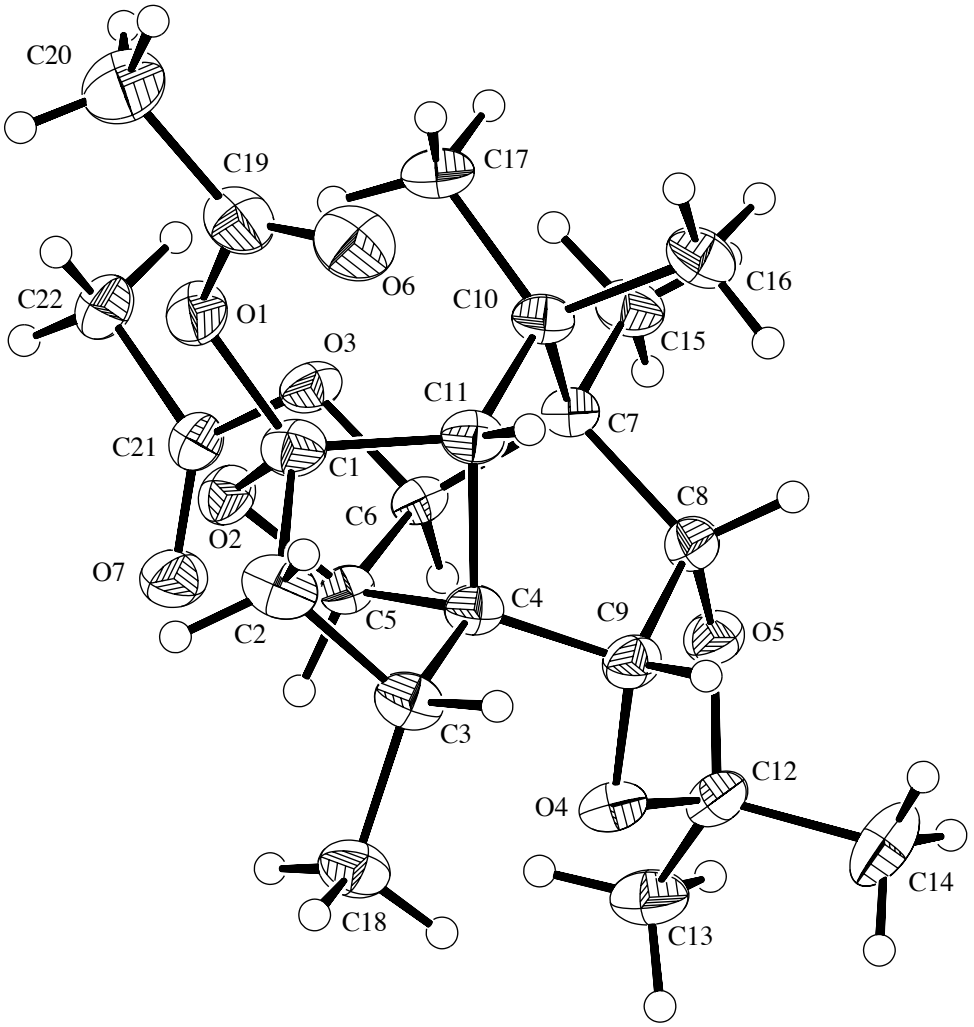
A. 02 X-ray Crystal Structure Data for Compound 71

X-ray crystal structure for compound **71** with labeling of non-hydrogen atoms. Anisotropic displacement ellipsoids display 30% probability levels. Hydrogen atoms are drawn as circles with small radii. Note: A full X-ray crystallographic report for compound **71** is provided in PDF format on the compact disc found on the inside back cover of this thesis.



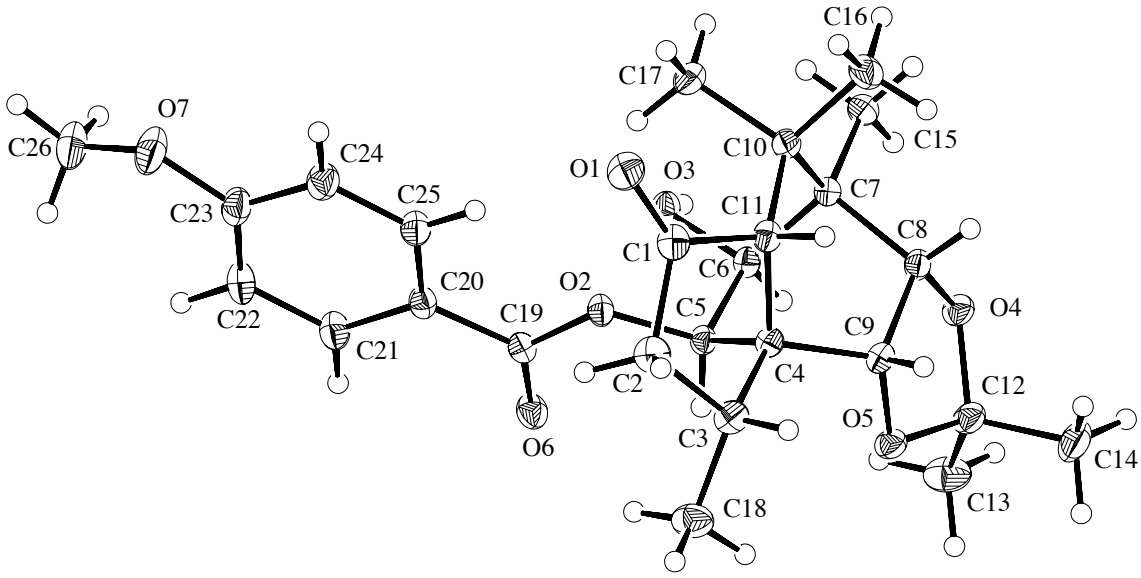
A. 03 X-ray Crystal Structure Data for Compound 116

X-ray crystal structure for compound **116** with labeling of non-hydrogen atoms. Anisotropic displacement ellipsoids display 30% probability levels. Hydrogen atoms are drawn as circles with small radii. Note: A full X-ray crystallographic report for compound **116** is provided in PDF format on the compact disc found on the inside back cover of this thesis.



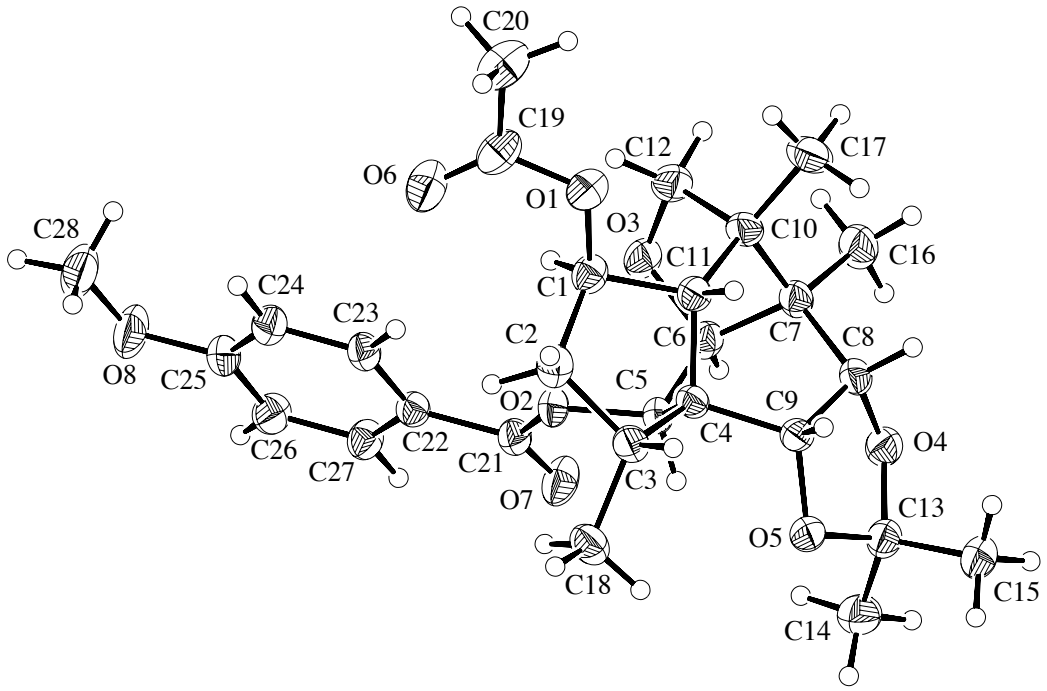
A. 04 X-ray Crystal Structure Data for Compound 118

X-ray crystal structure for compound **118** with labeling of non-hydrogen atoms. Anisotropic displacement ellipsoids display 30% probability levels. Hydrogen atoms are drawn as circles with small radii. Note: A full X-ray crystallographic report for compound **118** is provided in PDF format on the compact disc found on the inside back cover of this thesis.



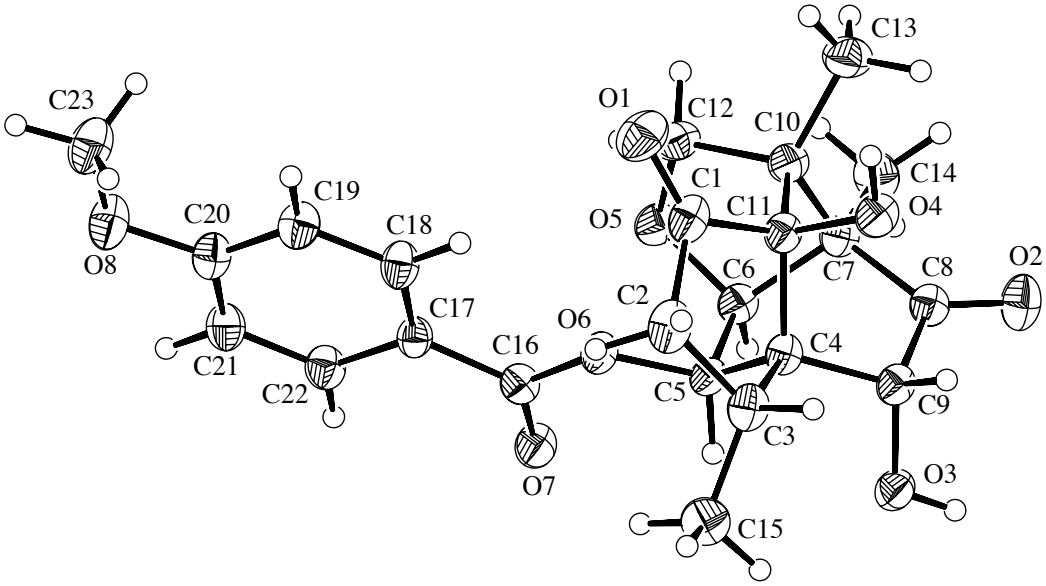
A. 05 X-ray Crystal Structure Data for Compound 125

X-ray crystal structure for compound **125** with labeling of non-hydrogen atoms. Anisotropic displacement ellipsoids display 30% probability levels. Hydrogen atoms are drawn as circles with small radii. Note: A full X-ray crystallographic report for compound **125** is provided in PDF format on the compact disc found on the inside back cover of this thesis.



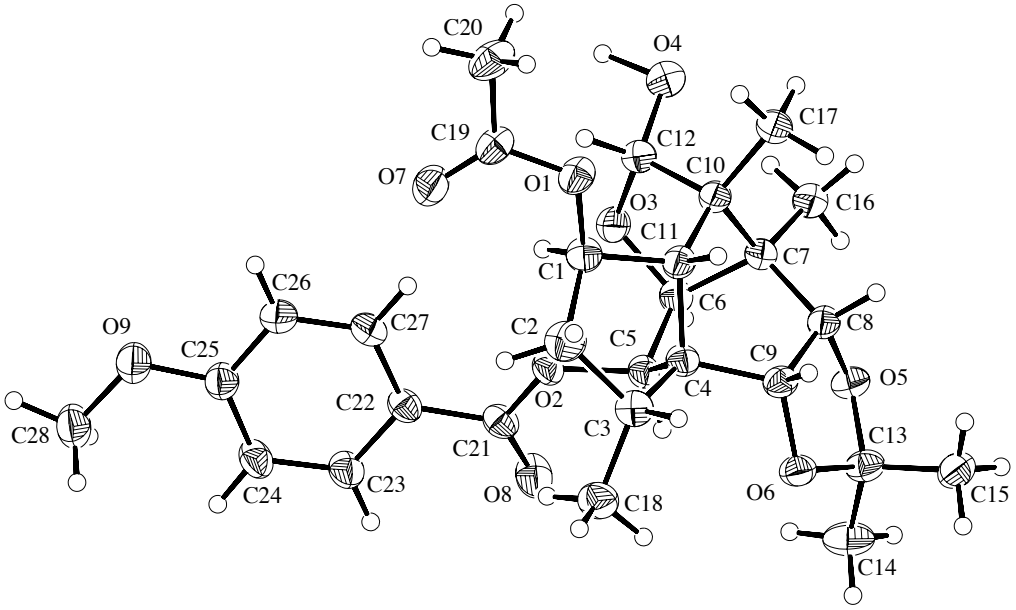
A. 06 X-ray Crystal Structure Data for Compound 132

X-ray crystal structure for compound **132** with labeling of non-hydrogen atoms. Anisotropic displacement ellipsoids display 30% probability levels. Hydrogen atoms are drawn as circles with small radii. Note: A full X-ray crystallographic report for compound **132** is provided in PDF format on the compact disc found on the inside back cover of this thesis.



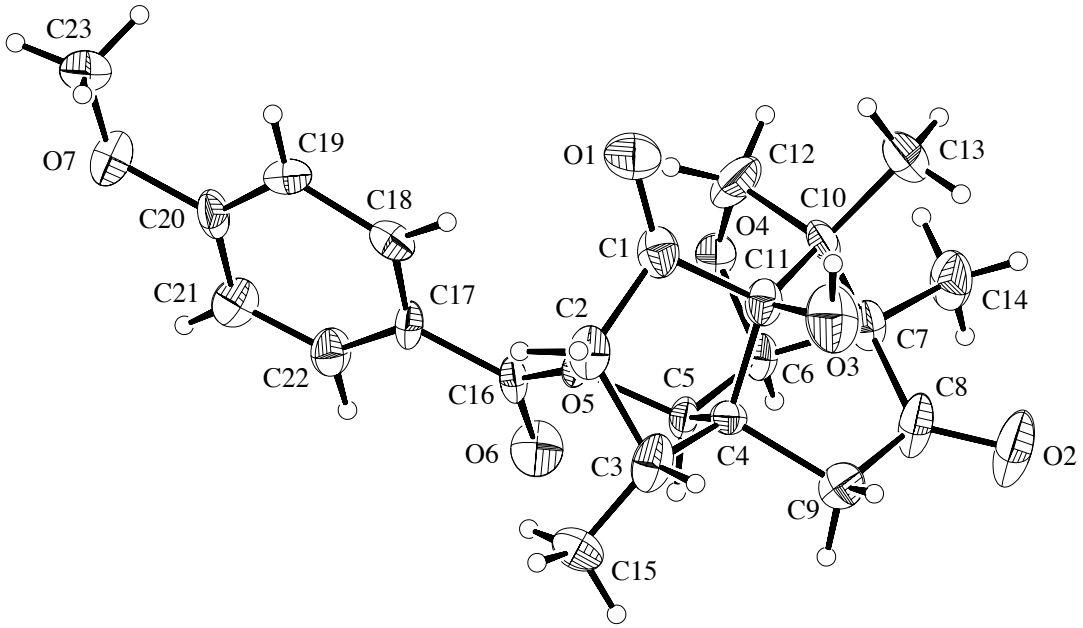
A. 07 X-ray Crystal Structure Data for Compound 136

X-ray crystal structure for compound **136** with labeling of non-hydrogen atoms. Anisotropic displacement ellipsoids display 30% probability levels. Hydrogen atoms are drawn as circles with small radii. Note: A full X-ray crystallographic report for compound **136** is provided in PDF format on the compact disc found on the inside back cover of this thesis.



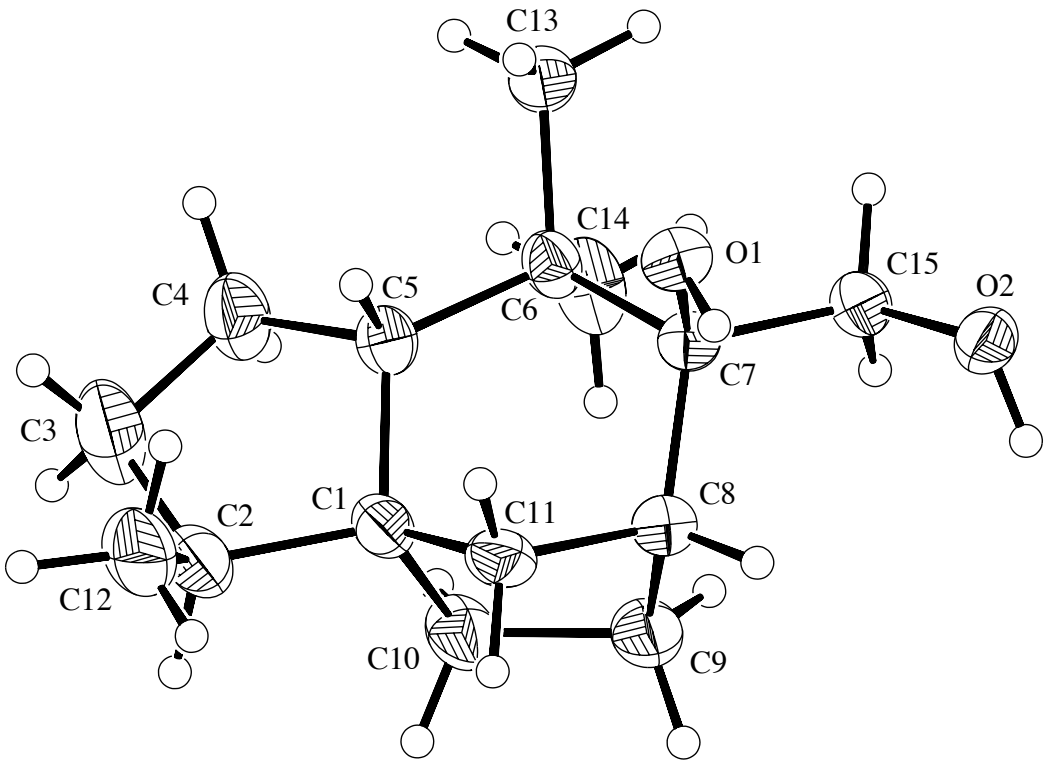
A. 08 X-ray Crystal Structure Data for Compound 142

X-ray crystal structure for compound **142** with labeling of non-hydrogen atoms. Anisotropic displacement ellipsoids display 20% probability levels. Hydrogen atoms are drawn as circles with small radii. Note: A full X-ray crystallographic report for compound **142** is provided in PDF format on the compact disc found on the inside back cover of this thesis.



A. 09 X-ray Crystal Structure Data for Compound 167

X-ray crystal structure for compound **167** with labeling of non-hydrogen atoms. Anisotropic displacement ellipsoids display 30% probability levels. Hydrogen atoms are drawn as circles with small radii. Note: A full X-ray crystallographic report for compound **167** is provided in PDF format on the compact disc found on the inside back cover of this thesis.



A. 10 X-ray Crystal Structure Data for Compound 185

X-ray crystal structure for compound **185** with labeling of non-hydrogen atoms. Anisotropic displacement ellipsoids display 30% probability levels. Hydrogen atoms are drawn as circles with small radii. Note: A full X-ray crystallographic report for compound **185** is provided in PDF format on the compact disc found on the inside back cover of this thesis.