## *Corrigendum*

**Chapter One, Page 5, Line 12:**
*replace* "have" *with* "has".

**Chapter One, Page 13, Line 20 and Page 15, Scheme 1.7:**
*replace* "**25a - e**" *and* "**26a - e**" *with* "**25**" *and* "**26**", *respectively.*

**Chapter One, Page 16, Lines 7 and 8:**
*interchange* "**32**" *and* "**33**".

**Chapter Two, Page 37, Lines 4 and 9:**
*replace* "(**78**)" *with* "[(–)-**78**]".

**Chapter Two, Page 37, Line 7:**
*replace* "five-membered counterpart" *with* "five membered isomer".

**Chapter Three, Page 63, Line 15:**
*replace* "C(4a) is" *with* "C(4a), but not between the protons bonded to C(5) and C(7a), is".

**Chapter Three, Page 64, Line 2:**
*delete* ", but more complex".

**Chapter Three, Page 67, Line 15 and Chapter Four, Page 110, Lines 11 and 13:**
*replace* "acetal" *with* "ketal".

**Chapter Three, Page 69, Line 2:**
*replace* "and ether (δ 96.5," *with* "acetal (δ 96.5) and ether (δ".

**Chapter Four, Page 90, Line 12:**
*replace* "isomeric bicycles" *with* "keto-enol tautomers".

**Chapter Four, Page 91, Scheme 4.6:**
*replace* "60%" *with* "82%".

**Chapter Four, Page 106, caption to Figure 4.10:**
*replace* "***60 and 61***" *with* "***61 and 62***".

**Chapter Six, Page 175, Line 1:**
*replace* "solutiuon" *with* "solution".

**Chapter Six, Page 179, Line 5:**
*replace* "mmol)and" *with* "mmol) and".

# Chemoenzymatic Studies in Sesquiterpene Synthesis

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

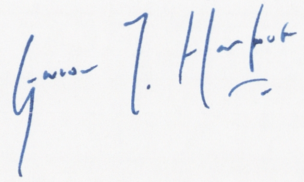
Gwion J. Harfoot


Research School of Chemistry
Canberra, Australia

October, 2004

## *Declaration*

*I declare that the material presented in this Thesis represents the result of original work carried out by the author during the period 2000 – 2004 and has not been submitted for examination for any other degree. This Thesis is less than 100,000 words in length. Established methodologies have been acknowledged, wherever possible, by citation of the original publications from which they derive.*



Gwion J. Harfoot

1st October, 2004

To my parents.

*"We create after Nature"*

Béla Bartók (1881 – 1945)

## *Acknowledgements*

Principally, I would like to thank Prof. Martin Banwell for the supervision of the research presented in this Thesis. Aside from providing me with the opportunity to study at the Australian National University, Martin's professionalism, guidance and organic enthusiasm for chemistry has equipped me with a host of skills, for which I am most appreciative.

The members of the Organic Synthesis and Mechanism group, both past and present are warmly thanked for having made the doctoral experience an enjoyable one. I would especially like to acknowledge those who have shared a laboratory and an extravaganza of chemistry with me, namely Dr. Kate Jolliffe, Dr. Natasha Hungerford, Dr. Markus Vögtle, Dr. David Loong, Dr. Xinghua Ma and Andrew Rea.

I am particularly indebted to the technical staff at the Research School of Chemistry (RSC) for providing expertise on all matters chemical. Especial thanks goes to Dr. Alison Edwards, Chris Blake, Lee Welling, Tony Herlt and Jenny Rothschild, as well as all members of the RSC Workshop. Thanks are also extended to the ever-assiduous Joan Smith and to Christine Sharrad, whose unrivalled particularity for detail cannot be praised enough.

I am ever the stronger for having had the opportunity to experience life with all those friends who have passed through these green years and continually exposed me to its curiosities and pleasures. I am especially appreciative of Magne Sydnes, Satish Chand, Jevon Longdell, Katherine Lilly, Sarah Peck, Jodi Robinson and Fen Bok Yong for their years of steadfast friendship and fun, and without whom life would have been ever so insipid. I am most thankful, however, for the enlightening friendship of Lena Scherfer, whose never-ending support, patience and love are beyond compare.

Finally, but by no means least in my thoughts, I would like to thank my family. My brothers Kieran and Rhodri have proffered, from afar, that peculiar mixture of unconditional love, harassment and adulation which, unbeknownst to them, has seen me through the years. However, it is my parents, Cynthia and Chris, to whom I owe most gratitude. You have not only provided me with encouragement and love, but fuelled my education and pursuit of knowledge, and for this I am eternally grateful.

## *Publications and Presentations*

*The following list details the publications and presentations that have resulted from research performed during the candidature of the Doctor of Philosophy.*

***Publications*:**

i) Banwell, M. G.; Harfoot, G. J., A chemoenzymatic and enantioselective route to the tricyclic frameworks associated with the protoilludane and marasmane classes of sesquiterpene, *Australian Journal of Chemistry*, **2004**, *57*, 895.

ii) Banwell, M. G.; Edwards, A. J.; Harfoot, G. J.; Jolliffe, K. A., A chemoenzymatic synthesis of the linear triquinane (–)-hirsutene and identification of possible precursors to the naturally occurring (+)-enantiomer, *Tetrahedron*, **2004**, *60*, 535.

iii) Banwell, M. G.; Edwards, A. J.; Harfoot, G. J.; Jolliffe, K. A.; McLeod, M. D.; McRae, K. J.; Stewart, S. G.; Vögtle, M., Chemoenzymatic methods for the enantioselective preparation of sesquiterpenoid natural products from aromatic precursors, *Pure and Applied Chemistry*, **2003**, *75*, 223.

iv) Banwell, M. G.; Edwards, A. J.; Harfoot, G. J.; Jolliffe, K. A., A chemoenzymatic synthesis of (–)-hirsutene from toluene, *Journal of the Chemical Society, Perkin Transactions 1*, **2002**, 2439.

***Presentations*:**

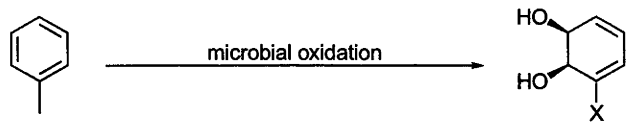
i) Harfoot, G. J., Enzymes and photochemistry: a new and enantioselective route to triquinanes, Conference lecture presentation at: *The New South Wales Southern Highlands Conference on Heterocyclic Chemistry*, Moss Vale, Australia, 1st – 3rd September 2002, p.L4.

ii) Banwell, M. G.; Edwards, A. J.; Harfoot, G. J., Chemoenzymatic approaches to the synthesis of tsugicoline A, Conference paper presentation at: *The New South Wales Southern Highlands Conference on Heterocyclic Chemistry*, Bowral, Australia, 2nd – 4th September 2001, p.P7.

iii) Banwell, M. G.; Edwards, A. J.; Harfoot, G. J., Chemoenzymatic approaches to the synthesis of tsugicoline A, Conference paper presentation at: *World Chemistry Congress 2001: 38th International Union of Pure and Applied Chemistry Congress - Frontiers in Chemistry Division*, Brisbane, Australia, 1st – 6th July 2001, p.PG115.

## *Abstract*

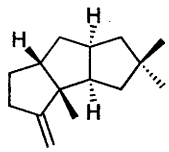
Since the pioneering research of Gibson *et al.* in the mid- to late-1960's, which established that the microbial oxidation of toluene proceeded *via* the intermediacy of *cis*-1,2-dihydrocatechol **1** (X = Me), such metabolites have emerged as useful and versatile synthons for the construction of a diverse range of natural products and their congeners. The ready availability of an ever-increasing range of *cis*-1,2-dihydrocatechols in enantiopure form continually enhances the chiral pool of such materials available to the synthetic chemist.




toluene (**113**) **1** (X = Me)

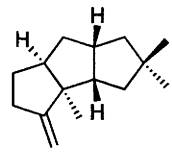
The opening Chapter of this Thesis examines the enzymatic production and synthetic utility of *cis*-1,2-dihydrocatechols, focussing, in particular, on the latent symmetry elements and consequent versatility associated with these metabolites. This Chapter also endeavours to highlight the diastereofacial selectivity achieved when *cis*-1,2-dihydrocatechols engage, as the diene component of reaction, in Diels-Alder cycloaddition processes, with appropriate dienophiles. The Diels-Alder adducts thus formed are considered to be useful scaffolds from which to construct rigid β,γ-unsaturated ketones capable of undergoing photochemically-promoted oxa-di-π-methane rearrangement and [1,3]-acyl shift reactions (the latter process often being accompanied by decarbonylation). Photochemical reactions of β,γ-unsaturated ketones, such as these, are also reviewed in this Chapter in terms of their capacity to form *cis*-fused bicyclic systems resembling those embodied within the linear triquinane, protoilludane and marasmane classes of sesquiterpene. The exploitation of microbial oxidation, Diels-Alder cycloaddition and photochemical reaction steps, to provide synthetic access to each of these classes of natural product, is described in the remaining Chapters.

(+)-Hirsutene [(+)-**54**] belongs to the linear triquinane class of sesquiterpene. Whilst this fungal metabolite, along with its non-natural isomer *ent*-(–)-hirsutene [*ent*-(–)-**54**] exhibits no biological properties, it is considered to be the biogenetic precursor to many of the more highly oxygenated and biologically active linear triquinanes. Consequently, Chapter Two details the search for a protocol providing generic access to the linear triquinane class of sesquiterpenes. Initial synthetic approaches towards *ent*-(–)-hirsutene [*ent*-(–)-**54**] are described, focussing, in particular, on attempts at elaboration of the chiral bicyclo[2.2.2]octenes derived from Diels-Alder cycloaddition reactions of metabolite **1** (X = Me), into the β,γ-unsaturated ketone required for the pivotal photochemical rearrangement.



(+)-Hirsutene

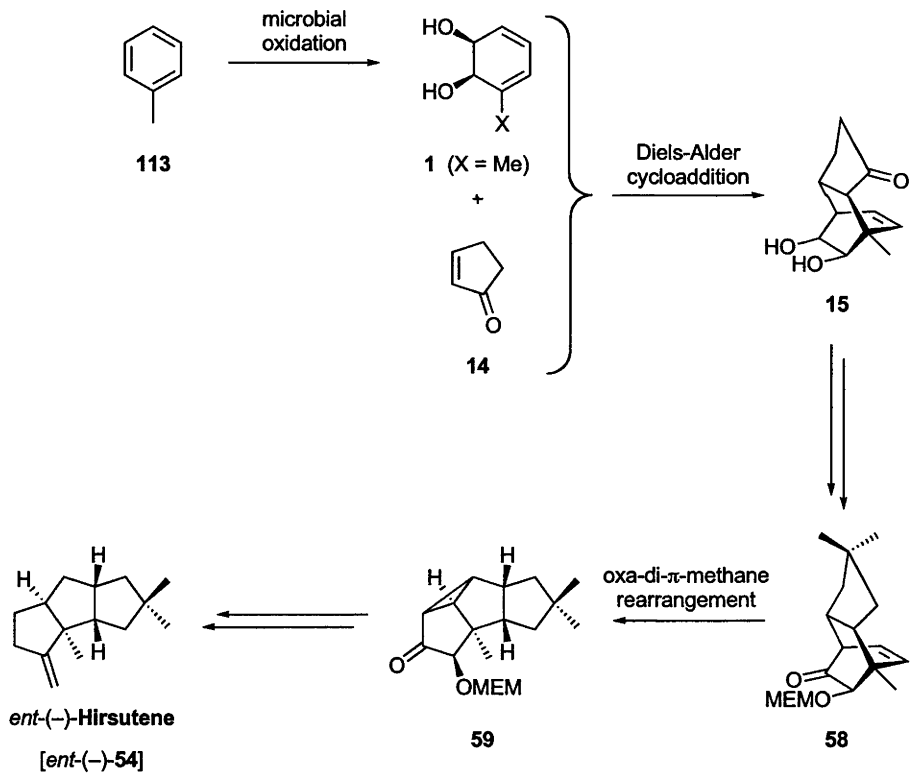
[(+)-54]



*ent*-(–)-Hirsutene

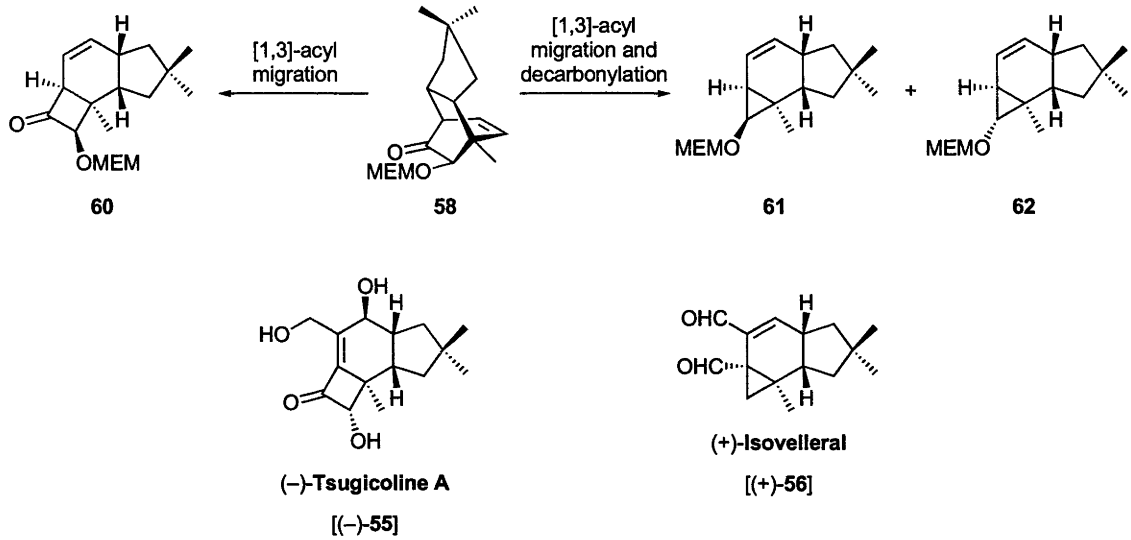
[*ent*-(–)-54]

Chapter Three continues to build upon this theme by delineating the enantioselective total synthesis of *ent*-(–)-hirsutene [*ent*-(–)-**54**] from the *cis*-1,2-dihydrocatechol **1** (X = Me). The strategy described therein exploits the use of this microbial oxidation product in a diastereoselective Diels-Alder cycloaddition reaction to form the chiral bicyclo[2.2.2]octene **15**, which is further elaborated into the β,γ-unsaturated ketone **58**. Subsequent photochemically-promoted oxa-di-π-methane rearrangement furnished the tetracycle **59**, which was then converted into the target triquinane. Since the enantiomer of *cis*-1,2-dihydrocatechol **1** (X = Me) is available, the synthesis described therein also constitutes a formal total synthesis of the natural product (+)-hirsutene [(+)-**54**].




In addition to the formation of tetracycle **59** from β,γ-unsaturated ketone **58** under photochemical reaction conditions, the cyclobutanone **60** and cyclopropyl indenes **61** and **62** were also generated *via* [1,3]-acyl shift and accompanying decarbonylation reactions, respectively. These compounds bear striking similarity to natural products of the protoilludane and marasmane classes of sesquiterpene, and in particular to (–)-tsugicoline A [(–)-**55**] and

(+)-isovelleral [(–)-**56**], respectively. Chapter Four describes the ability to control the outcome of the photochemically-promoted reaction to select for any of the four products and details the elaboration of cyclobutanone **60** into an advanced stage intermediate relevant to the synthesis of (–)-tsugicoline A [(–)-**55**]. The formation of this intermediate and each of the photochemical products **60** – **62** has provided valuable information that can be exploited in the total syntheses of these natural products, using a revised microbial oxidation – Diels-Alder cycloaddition – photochemical reaction sequence, starting instead from *m*-methyl benzyl alcohol.




The research presented in the earlier Chapters exemplifies the capacity for natural products belonging to the linear triquinane, protoilludane and marasmane classes of sesquiterpene to be synthesised from a common precursor *via* three key steps. The versatility of these protocols is further emphasised in Chapter Five, which delineates potential synthetic routes to a variety of sesquiterpene natural products, including the angular triquinanes and [3.3.3]-propellanes. The capacity to enantioselectively construct manifold classes of sesquiterpene, using the microbial oxidation – Diels-Alder cycloaddition – photochemical reaction sequence, is based on the ability to control the selectivity conferred at each of these key steps in the synthesis.

*The following abbreviations have been used throughout this Thesis.*

| | |
|---|---|
| A | absorption |
| Å | Ångstrom |
| Ac | acetyl |
| AIBN | 2,2´-azo*bis*(*iso*butyronitrile) |
| a.k.a. | also known as |
| $[\alpha]_D$ | optical rotation at the sodium D-line, *i.e.* at $\lambda = 589$ nm ($10^{-1}$.deg.cm$^2$.g$^{-1}$) |
| APT | attached proton test (NMR spectroscopy) |
| *aq.* | aqueous |
| Ar | aryl |
| Bn | benzyl |
| *n*-Bu | *n*-butyl |
| *t*-Bu | *tert*-butyl |
| *c* | concentration (mol.L$^{-1}$) |
| *ca.* | *circa* (approximately) |
| *cf.* | *confer* (compare) |
| CIDNP | chemically induced dynamic nuclear polarisation |
| cm | centimetre(s) |
| CNDO-MO | complete neglect of differential overlap – molecular orbital |
| conc. | concentrated |
| COSY | correlation spectroscopy |
| d | doublet |
| DBU | 1,8-diazabicyclo[5.4.0]undec-7-ene |
| DEAD | diethyl azodicarboxylate |
| °C | degrees Celcius |
| Δ | heat (unless used in compound name, where Δ denotes olefin) |
| δ | chemical shift (parts per million, ppm) |
| $\Delta V^{\ddagger}$ | volume of activation (cm$^3$.mol$^{-1}$) |
| DIAD | di*iso*propyl azodicarboxylate |
| DIBAL-H | di*iso*butylaluminium hydride |
| *dig* | *digonal* |
| 2,2-DMP | 2,2-dimethoxypropane |
| E | energy |
| *E* | *entgegen* (opposite) |
| $E^{\oplus}$ | electrophile |
| $\varepsilon_0$ | molar extinction coefficient for UV $\lambda_{max}$ (L.mol$^{-1}$.cm$^{-1}$) |

| | |
|---|---|
| $EC_{50}$ | the statistically-derived median effective concentration (usually molar) of an agent in an environmental medium, expected to produce a certain effect in 50% of test organisms in a given population, under a defined set of conditions. |
| $ED_{50}$ | the statistically-derived median effective dose of a chemical or physical agent expected to produce a certain effect in 50% of test organisms in a given population, or to produce a half-maximal effect in a biological system under a defined set of conditions. |
| e.e. | enantiomeric excess |
| *e.g.* | *exempli gratia* (for example) |
| EI | electron impact (mass spectrometry) |
| ES | electrospray (mass spectrometry) |
| Et | ethyl |
| *et al.* | *et alia* (and others) |
| eV | electron Volt(s) |
| FGI | functional group interconversion(s) |
| FT | Fourier transform |
| g | gram(s) |
| GC | gas chromatographic |
| *gem* | *geminal* |
| h | hour(s) |
| HMBC | heteronuclear multiple-bond correlation |
| HMQC | heteronuclear multiple-quantum coherence |
| *hν* | light |
| HOMO | highest occupied molecular orbital |
| HRMS | high resolution mass spectrometry |
| HSQC | heteronuclear single-quantum coherence |
| Hz | Hertz |
| *ibid.* | *ibidem* (in the same place) |
| IC | internal conversion |
| *i.e.* | *id est* (that is) |
| IR | infra red |
| ISC | intersystem crossing |
| *J* | coupling constant (Hz) |
| kbar | kilobar(s) |
| KHMDS | *N*-potassiohexamethyldisilazide or potassium *bis*(trimethylsilyl)amide |
| L | litre(s) |
| *l* | path length (cm) |
| λ | wavelength (nm) |
| $\lambda_{max}$ | wavelength of maximum absorption (nm) |
| $\lambda_{transmission}$ | wavelength of transmission (nm) |
| LiHMDS | *N*-lithiohexamethyldisilazide or lithium *bis*(trimethylsilyl)amide |
| lit. | literature value |
| LRMS | low resolution mass spectrometry |
| LUMO | lowest occupied molecular orbital |

| | |
|---|---|
| m | multiplet |
| $M^{+\cdot}$ | molecular ion |
| *m*-CPBA | *meta*-chloroperbenzoic acid |
| Me | methyl |
| MEM | (2-methoxyethoxy)methoxy |
| $\mu$g | microgram(s) |
| MHz | mega-Hertz |
| min | minute(s) |
| mL | millilitre(s) |
| $\mu$L | microlitre(s) |
| mm | millimetre(s) |
| mmol | millimole(s) |
| mol | mole(s) |
| m.p. | melting point (°C) |
| MS | mass spectrometry |
| Ms | methanesulfonyl |
| *m/z* | mass-to-charge ratio |
| n | number of monomeric units in an oligomer |
| nm | nanometre(s) |
| NMR | nuclear magnetic resonance |
| nOe | nuclear Overhauser enhancement |
| NOESY | nuclear Overhauser effect and exchange spectroscopy |
| n,$\pi^*$ | electronic transition (promotion) between n (non-bonding) and $\pi^*$ orbitals |
| $\nu_{max}$ | infra red absorption maxima ($cm^{-1}$) |
| p | plasmid |
| PCC | pyridinium chlorochromate |
| Ph | phenyl |
| pH | logarithm of the reciprocal of the hydrogen ion concentration, $-\log_{10}[H^+]$ |
| $\Phi_{ST}$ | quantum yield for singlet – triplet intersystem crossing |
| $\pi$ | denotes double bond |
| $\pi,\pi^*$ | electronic transition (promotion) between $\pi$ and $\pi^*$ orbitals |
| PLC | preparative layer chromatography |
| PMB | *para*-methoxybenzyl |
| PPTS | pyridinium *para*-toluenesulfonate |
| *p*-Ts | *para*-toluenesulfonyl or tosyl |
| q | quartet |
| Ref. | reference |
| ® | registered trademark |
| $R_f$ | retardation factor |
| rpm | revolutions per minute |
| $S_0$ | ground state |
| $S_1$ | first excited singlet state |
| $S_2$ | second excited singlet state |
| $\sigma$ | *sigma* – denotes single bond |

| | |
|---|---|
| s | singlet |
| $S_N^1$ | unimolecular nucleophilic substitution reaction |
| SOI | secondary orbital interaction |
| *sp.* | *species* |
| T | temperature (°C) |
| t | triplet |
| $T_1$ | first excited triplet state |
| $T_2$ | second excited triplet state |
| TBDMS | *tert*-butyldimethylsilyl |
| temp | temperature (°C) |
| TEMPO | 2,2,6,6-tetramethyl-1-piperidinyloxy |
| Tf | trifluoromethanesulfonyl |
| THF | tetrahydrofuran |
| TLC | thin layer chromatography |
| ™ | trademark |
| TMS | trimethylsilyl |
| *trig* | *trigonal* |
| UV | ultra violet (spectroscopy) |
| V | Volt(s) |
| VC | vertical cascade |
| *viz.* | *videlicit* (that is, namely) |
| VP | viewing position |
| *vs.* | *versus* |
| v/v | unit volume per unit volume (ratio) |
| W | Watt(s) |
| w/v | unit weight per unit volume (%) |
| *Z* | *zusammen* (together) |
| > | greater than |
| < | less than |
| → | denotes a transition between electronic states or progressive changes/steps in a procedure |
| ⇨ | denotes a retrosynthetic step or strategic disconnection in a proposed synthetic strategy |
| ‡ | transition state |

## *Table of Contents*

***Appendices***

***Fold-out Schemes, X-ray Crystal Structure Reports and Publications***

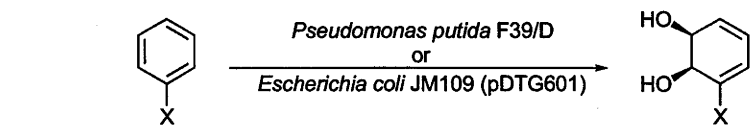
*Chapter One*

# cis-*1,2-Dihydrocatechols, Diels-Alder Cycloadditions and Photochemistry in Sesquiterpene Synthesis*

## 1.1 *cis*-1,2-Dihydrocatechols in synthesis

### 1.1.1 Biocatalytic production of *cis*-1,2-dihydrocatechols

*cis*-1,2-Dihydrocatechols of the general type **1** are a class of compound produced during the early stages of the metabolic pathway by which aromatic hydrocarbons are oxidatively degraded by bacteria (Figure 1.1). This feature of the microbial degradation of aromatic compounds was first recognised in 1968 by Gibson and co-workers at Iowa State University who, in the course of their studies on the soil bacterium *Pseudomonas putida*, isolated the first such metabolic intermediate from a chemically mutated strain of this organism, *viz. P. putida* F39/D.[1,2] Whilst capable of metabolising aromatic compounds to the corresponding *cis*-1,2-dihydrocatechols **1**, *P. putida* F39/D was found to be deficient in the dehydrogenase enzyme responsible for converting dihydroaromatic substrates into the corresponding catechols. As a consequence, significant quantities of *cis*-1,2-dihydrocatechols **1** accumulated, thereby allowing isolation and structural elucidation of this early stage metabolite.[3]




X = H, Me, Cl, Br, I, $CH{=}CH_2$ *etc.* **1**

**Figure 1.1:** *Biocatalytic production of* cis-*1,2-dihydrocatechols of the general type 1.*

---

1 a) Gibson, D. T.; Koch, J. R.; Kallio, R. E., *Biochemistry*, **1968**, *7*, 2653; b) Gibson, D. T.; Koch, J. R.; Schuld, C. L.; Kallio, R. E., *Biochemistry*, **1968**, *7*, 3795.

2 Originally designated *Pseudomonas putida* F1strain 39/D.

3 a) Gibson, D. T.; Hensley, M.; Yoshioka, H.; Mabry, T. J., *Biochemistry*, **1970**, *9*, 1626; b) Gibson, D. T.; Cardini, G. E.; Maseles, F. C.; Kallio, R. E., *Biochemistry*, **1970**, *9*, 1631.

In order to exploit this biocatalytic phenomenon, the genes encoding the enzymes responsible for effecting this biotransformation (collectively known as dioxygenases) were cloned into multi-copy plasmids and subsequently inserted into a variety of hosts.[4] The resulting recombinant microörganisms over-express the dioxygenase enzymes, so that whole-cell recombinants such as *Escherichia coli* JM109 (pDTG601) are capable of generating *cis*-1,2-dihydrocatechols in significant quantity (up to 35 grams of **1** per litre of fermentation broth) and in essentially enantiopure form (>99% e.e.). The absolute stereochemistries of the diols produced in this fashion were determined by single crystal X-ray analyses of the derived Diels-Alder cycloaddition adducts[5] and by chemical degradation[6] and correlation studies[7] which showed that all such diols possess structures of type **1**.

Furthermore, the biotransformation of aromatic compounds to the corresponding *cis*-1,2-dihydrocatechols is a remarkably general process that, through the exploitation of recombinant methods, is applicable to the metabolism of a wide variety of substrates. Indeed, more than two hundred and fifty such metabolites have been produced *via* dioxygenase-mediated biocatalytic conversion and approximately one tenth of these are now commercially available. A selection of representative *cis*-1,2-dihydrocatechols is shown in Figure 1.2.

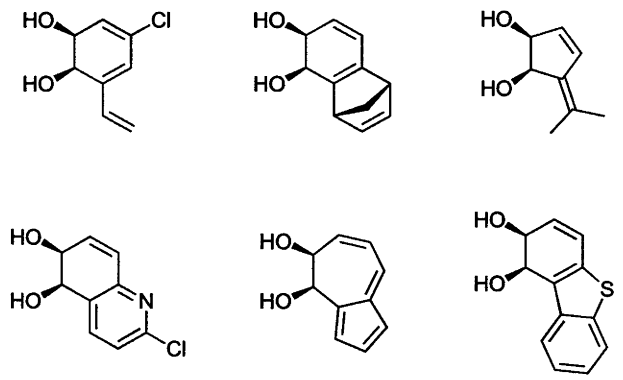



**Figure 1.2:** *A selection of metabolites derived from dioxygenase-mediated* cis-*dihydroxylation of the corresponding aromatic hydrocarbons.*

The microbial oxidation of aromatic compounds has long been recognised as a viable means of degrading these otherwise persistent environmental toxins. For this reason the biotransformation of aromatic compounds into the corresponding *cis*-1,2-dihydrocatechols is considered to be an environmentally benign protocol. Furthermore, since such processes employ only small quantities of organic and little or no (toxic) metal-based species, and because they are performed in aqueous media, such transformations are highly attractive to the chemical

4 Zylstra, G. J.; Gibson, D. T., *J. Biol. Chem.*, **1989**, *264*, 14940.

5 Kobal, V. M.; Gibson, D. T.; Davis, R. E.; Garza, A., *J. Am. Chem. Soc.*, **1973**, *95*, 4420.

6 a) Ziffer, H.; Jerina, D. M.; Gibson, D. T.; Kobal, V. M., *ibid.* 4048; b) Ziffer, H.; Kabuto, C.; Gibson, D. T.; Kobal, V. M.; Jerina, D. M., *Tetrahedron*, **1977**, *33*, 2491.

7 Boyd, D. R.; Dorrity, M. R. J.; Hand, M. V.; Malone, J. F.; Sharma, N. D.; Dalton, H.; Gray, D. J.; Sheldrake, G. N., *J. Am. Chem. Soc.*, **1991**, *113*, 666.

industry.[8] Indeed, the biotransformation of arenes into the corresponding *cis*-1,2-dihydrocatechols has become a routine operation, providing access to a range of chiral substrates for organic synthesis in preparatively useful quantity.

### 1.1.2 General synthetic utility of *cis*-1,2-dihydrocatechols

*cis*-1,2-Dihydrocatechols of the general structure **1** not only contain latent symmetry elements that offer the capacity to control the global chemistry of these compounds, but also possess a remarkable combination of complementary functionalities that facilitate a wide variety of selective bond-forming reactions. In order to examine the latter point in detail, it is first appropriate to discuss the symmetry elements associated with *cis*-1,2-dihydrocatechols, a generic representation of which is presented in Figure 1.3.

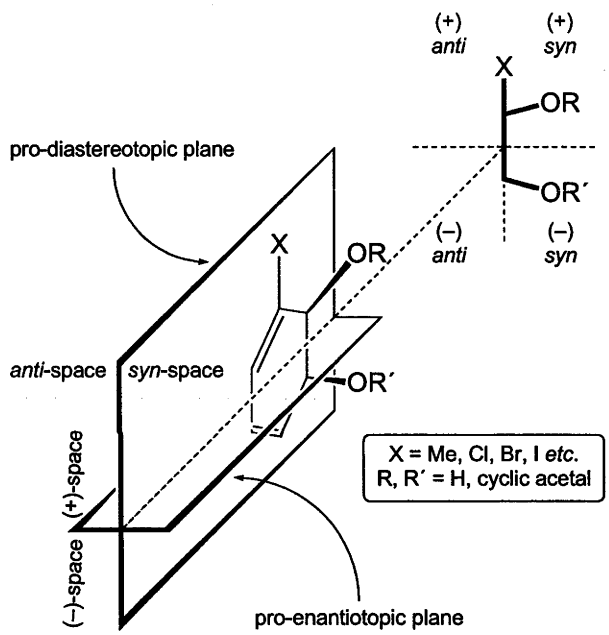



**Figure 1.3:** *Complementary reaction quadrants within* cis*-1,2-dihydrocatechol topology [adapted from Hudlicky, Gonzalez and Gibson (1999)].*[9a]

A bisection of the general structure in the so-called pro-diastereotopic plane results in two distinct faces that occupy either of the *syn*- or *anti*-spaces. The diastereoselectivity of a given reaction may be controlled by the biochemically installed diol functionality that projects into the *syn*-space of the *cis*-1,2-dihydrocatechol, such that specific functionalisation may occur at either the *syn*-face, *via* chelation-control (when R, R′ = H), or at the *anti*-face through steric repulsion (when R, R′ = sterically demanding protecting group).

A bisection of the general structure through the so-called pro-enantiotopic plane results in two sectors that are arbitrarily assigned as (+) and (–) spaces. The presence of the

8 For example, the *cis*-1,2-dihydroxylation of indane is used by Merck to manufacture the anti-HIV drug Indinavir on an annual scale of million kilograms: Zurer, P., *Chem. Eng. News*, **1996**, *74*, 6.

X-substituent in the (+)-domain of the *cis*-1,2-dihydrocatechol may influence two significant aspects of regioselectivity, and hence enantioselectivity, of a given reaction operating on the molecule. Indeed, the regioselectivity of a reaction operating on the diene moiety is largely governed by the extent to which the X-group polarises the diene. In contrast, the regioselectivity of a reaction acting on the diol moiety is predominantly controlled by the steric effect of the X-substituent.

By virtue of the pro-diastereotopic and pro-enantiotopic planes of symmetry bisecting *cis*-1,2-dihydrocatechols of the general structure **1** into the respective *syn*-, *anti*-spaces and (+), (–)-sectors, four complementary quadrants result which encompass the relevant pseudo-symmetry elements of these compounds. The identification of such quadrants helps summarise the predicted stereoselectivity of operations performed on these substrates. The interplay of these features with the complex functionality of the *cis*-1,2-dihydrocatechols disposes these molecules towards a host of specific reactions that have been exploited in various synthetic endeavours.[9]

The multiple functional groups embodied within the compact framework of *cis*-1,2-dihydrocatechols of the general type **1** make it possible for these molecules to undergo a vast number of selective bond-forming reactions (Figure 1.4). As noted earlier, the presence of the X-substituent attached to one terminus (+) of the diene moiety plays a critical rôle in differentiating each of the two olefinic bonds and/or hydroxyl moieties towards reaction, through electronic (polarisation) and steric effects. This feature allows for controlled interaction of the olefin remote from the substituent with an appropriate electrophile and is typically exploited in peripheral oxidative functionalisation of *cis*-1,2-dihydrocatechols. For example when X = Br and R, R′ = cyclic acetal, the olefin remote from the halogen undergoes completely regioselective epoxidation with the electrophilic reagent *m*-CPBA.[10] The remaining olefin may then be subjected to a variety of oxidation reactions including epoxidation, dihydroxylation or, more commonly, ozonolytic cleavage (with reductive workup) to afford the corresponding acyclic compounds. Such differentiation of the olefinic bonds has been exploited in the synthesis of, *inter alia*, simple carbohydrates and cyclitols.[9a] In comparable fashion, the

9 For an excellent review of the rôle of *cis*-1,2-dihydrocatechols in organic synthesis, refer to: a) Hudlicky, T.; Gonzalez, D.; Gibson, D. T., *Aldrichimica Acta*, **1999**, *32*, 35. Other reviews on the chemistry of *cis*-1,2-dihydrocatechols include: b) Carless, H. A. J., *Tetrahedron: Asymmetry*, **1992**, *3*, 795; c) Sheldrake, G. N., *Biologically derived arene* cis*-dihydrodiols as synthetic building blocks*, in *Chirality in Industry*, Collins, A. N.; Sheldrake, G. N.; Crosby, J. (Eds.) John Wiley & Sons: Chichester, England, **1992**, 1, p. 127; d) *Hudlicky*, T.; Brown, S. M., In *Organic Synthesis: Theory and Applications*, Hudlicky, T. (Ed.) JAI Press: Greenwich, Connecticut, U. S. A., **1993**, 2, p. 113; e) Hudlicky, T.; Reed, J. W., In *Advances in Asymmetric Synthesis*, Hassner, A. (Ed.) JAI Press: Greenwich, Connecticut, U. S. A., **1995**, 1, p. 271; f) Hudlicky, T., *Chem. Rev.*, **1996**, *96*, 3; g) Hudlicky, T.; Thorpe, A. J., *Chem. Commun.*, **1996**, 1993; h) Boyd, D. R.; Sheldrake, G. N., *Nat. Prod. Rep.*, **1998**, 309; i) Banwell, M. G., *Chem. Aust.*, **1999**, *66*, 6; j) Bui, V. P.; Hansen, T. V.; Stenstrøm, Y.; Hudlicky, T.; Ribbons, D. W., *New J. Chem.*, **2001**, *25*, 116; k) Endoma, M. A.; Bui, V. P.; Hansen, J.; Hudlicky, T., *Org. Process Res. Dev.*, **2002**, *6*, 525.

10 Hudlicky, T.; Rulin, F.; Tsunoda, T.; Luna, H.; Andersen, C.; Price, J. D., *Isr. J. Chem.*, **1991**, *31*, 229.

steric demands of the X-substituent of a given *cis*-1,2-dihydrocatechol can be used to facilitate selective mono-protection of the less hindered (β-) hydroxyl moiety when, for example, a sterically demanding silylating agent (*e.g.* thexyldimethylsilyl chloride) is employed.[11] An alternative but complementary procedure relies on the steric bulk of the X-substituent to restrict hydride delivery to the (+)-space of an appropriately activated cyclic acetal (*e.g.* *p*-methoxybenzylidene acetal), thereby selectively generating the corresponding α-hydroxy ether (*e.g.* R = PMB, R′ = H).[12] These allylic functionalities, when appropriately substituted, are amenable to Claisen-type sigmatropic rearrangements[13] and, together with the X-substituent, also influence the regioselectivity of Diels-Alder and related cycloaddition reactions.[14] Additionally, in *cis*-1,2-dihydrocatechols where the X-substitutent is a halogen, this moiety may be reductively dehalogenated or undergo metal-for-halogen exchange.[15] Each of these classes of reaction have found utility in the synthesis of a wide variety of natural products. Indeed, regioselective protection protocols and cycloaddition reactions are exploited in the research described in Chapters Two and Three.

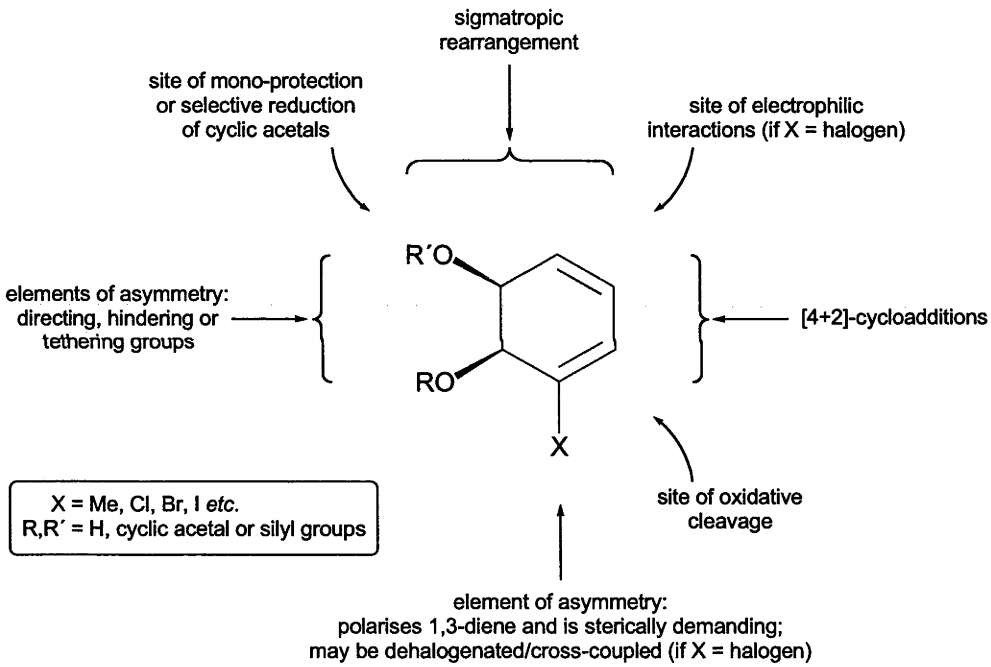



**Figure 1.4:** *Selective bond-forming reaction sites within* cis-*1,2-dihydrocatechols and their derivatives.*

Overall then, the localised bond-forming reactions (described above) that are specific to the various structural features associated with *cis*-1,2-dihydrocatechols allow for a remarkable degree of control during the execution of reactions involving these substrates.

11 Hudlicky, T.; Seoane, G.; Pettus, T., *J. Org. Chem.*, **1989**, *54*, 4239.

12 Banwell, M. G.; McRae, K. J.; Willis, A. C., *J. Chem. Soc., Perkin Trans. 1*, **2001**, 2194.

13 Gonzalez, D.; Schapiro, V.; Seoane, G.; Hudlicky, T.; Abboud, K., *J. Org. Chem.*, **1997**, *62*, 1194.

14 Hudlicky, T.; Olivio, H. F., *Tetrahedron Lett.*, **1991**, *32*, 6077.

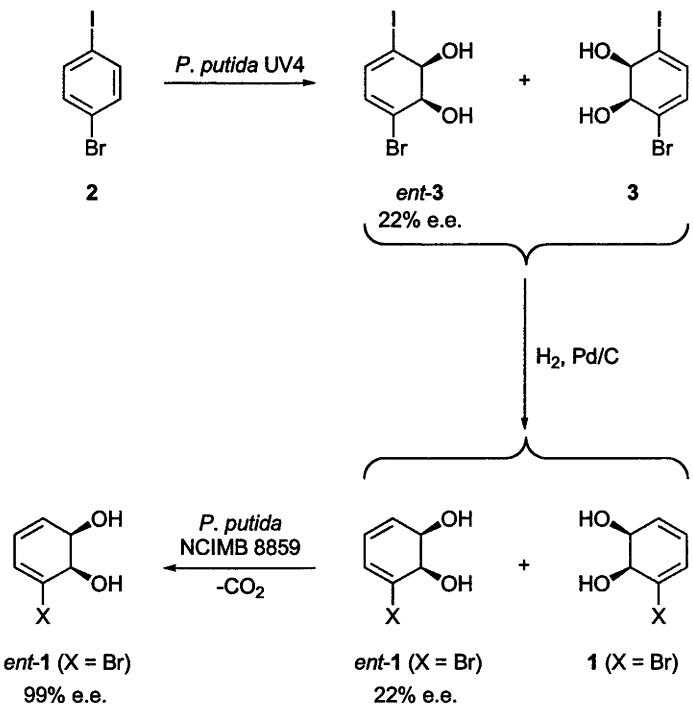
15 a) Boyd, D. R.; Sharma, N. D.; Barr, S. A.; Dalton, H.; Chima, J.; Whited, G.; Seemayer, R., *J. Am. Chem. Soc.*, **1994**, *116*, 1147; b) Allen, C. C. R.; Boyd, D. R.; Dalton, H.; Sharma, N. D.; Brannigan, I.; Kerley, N. A.; Sheldrake, G. N.; Taylor, S. C., *J. Chem. Soc., Chem. Commun.*, **1995**, 117.

### 1.1.3 Chemoenzymatic approaches to dihydrocatechols: enantiomeric-switching and enantiodivergence

In contrast to the purely enzymatic methods of generating dihydrocatechols *via* microbial oxidation, such compounds may also be generated using protocols that additionally incorporate subsequent synthetic (chemical) steps into the procedure. These so-called chemoenzymatic procedures provide access to a greater range of dihydrocatechols than would otherwise be available by purely enzymatic means. One such chemoenzymatic process involves the generation of either enantiomer of a given dihydrocatechol using a procedure described as enantiomeric switching. This technology has found particular utility in organic synthesis due to its ability to provide access to either enantiomeric form of any natural product prepared from dihydrocatechols and, as such, is described below.

Almost invariably, the X-substituent of *cis*-1,2-dihydrocatechols is required in the primal stages of a synthesis so as to direct functionalisation towards the more electron rich olefin and/or the less sterically hindered hydroxyl moiety, and thus preserve the asymmetry of the substrate. In some very elegant science performed by Boyd *et al.* (Scheme 1.1), *p*-iodobromobenzene **2** was enzymatically transformed into the corresponding mixture of *cis*-1,2-dihydrocatechols **3** and *ent*-**3** using *P. putida* UV4.[15b] This mixture was then subjected to hydrogenolytic dehalogenation in which the C–I bond was selectively cleaved to afford a scalemic mixture of the brominated *cis*-1,2-dihydrocatechols **1** and *ent*-**1** (X = Br). The efficiency of this process relies on the ability of toluene dioxygenase to differentiate (on the

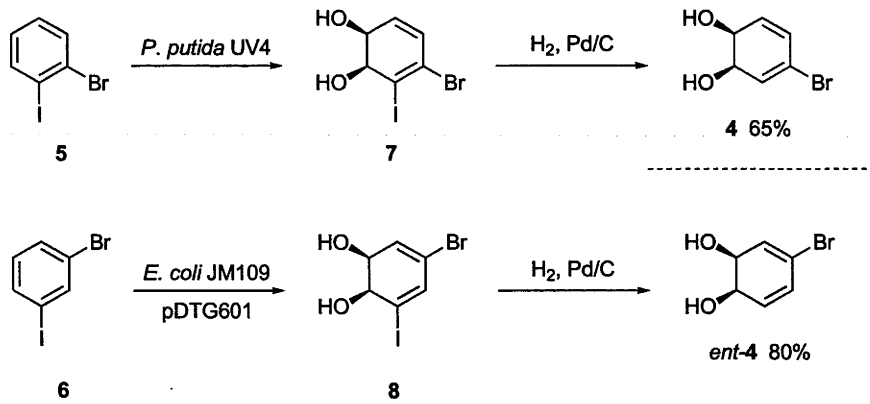
**Scheme 1.1:** *Chemoenzymatic approach to either enantiomer of* ***1*** *(X = Br).*



basis of size) between the iodine and bromine atoms of the substrate during the biotransformation. Due to the relatively small difference in size of the two halogen substituents, the *cis*-1,2-dihydrocatechol *ent*-**3** was obtained in only 22% e.e. Nevertheless, when the mixture of *cis*-1,2-dihydrocatechols **1** and *ent*-**1** (X = Br) was exposed to a second fermentation step using a non-blocked strain *P. putida* NCIMB 8859, the undesired minor isomer **1** (X = Br) was completely metabolised through dehydrogenation, thus allowing *ent*-**1** (X = Br) to accrue in essentially enantiopure (99% e.e.) form and in significant quantity.

This enantiomeric switching methodology has been applied to the synthesis of related dihydrocatechols such as **4** and its enantiomer *ent*-**4** which were synthesised from the respective *ortho*- and *meta*-brominated iodobenzenes **5** and **6** (Scheme 1.2).[15a] In this two-step procedure, the bromo-iodobenzenes were converted *via* microbial dihydroxylation to the corresponding *cis*-1,2-dihydrocatechols **7** and **8** (directed by the steric bulk of the iodo-substituent) which, upon reductive deiodination, afforded the enantiomeric products **4** and *ent*-**4**.

**Scheme 1.2:** *Chemoenzymatic differentiation strategy to effect formation of enantiomeric* cis*-1,2-dihydrocatechols.*




Chemoenzymatic methodology has also been employed to provide access to the related *trans*-1,2-dihydrocatechols *via* two enantiodivergent and complementary diastereomeric-switching strategies developed independently by Boyd *et al.*[16] and Hudlicky *et al.*[17] (Scheme 1.3).[18] Boyd's strategy requires one olefin of the reactive diene moiety within *cis*-1,2-dihydrocatechol **1** (X = Br) to be hydrogenated to afford compound **9**, so as to avoid aromatisation during the Mitsunobu inversion procedure.[19] The product of a Mitsunobu

16 Boyd, D. R.; Sharma, N. D.; Dalton, H.; Clarke, D. A., *Chem. Commun.*, **1996**, 45.

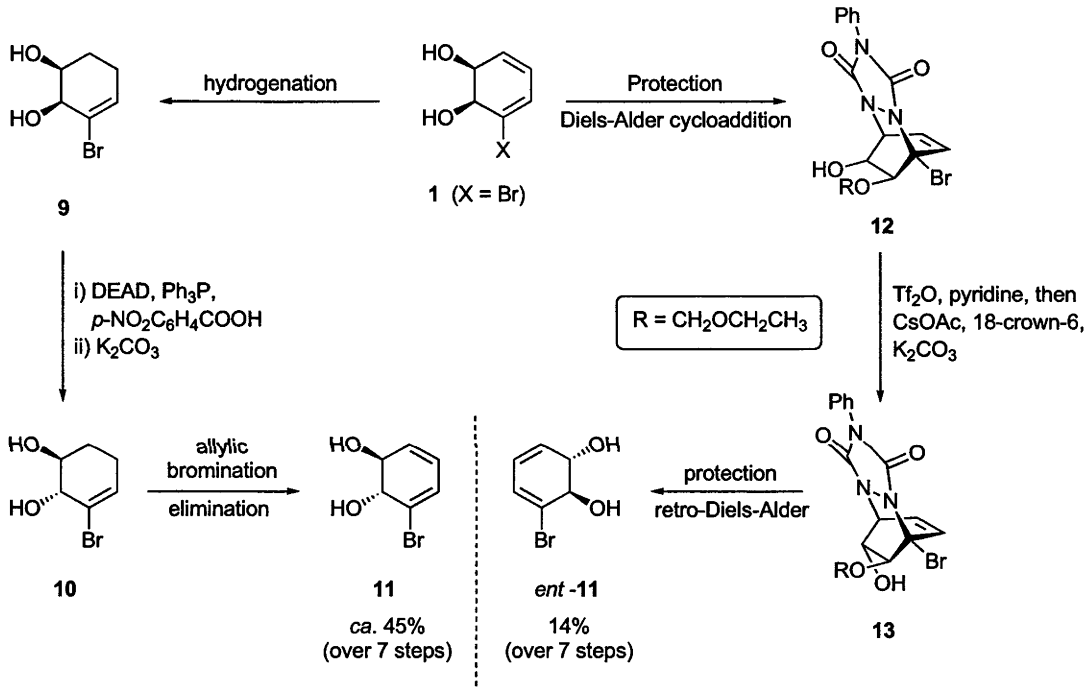
17 McKibben, B. P.; Barnosky, G. S.; Hudlicky, T., *Synlett*, **1995**, 806.

18 More recently, this has been performed by purely enzymatic means from isochorismate, using *Escherischia coli* PBB8 (pDF1): a) Franke, D.; Sprenger, G. A.; Müller, M., *Angew. Chem. Int. Ed.* **2001**, *40*, 555; b) Lorbach, V.; Franke, D.; Sprenger, G. A.; Müller, M., *Chem. Commun.* **2002**, 494; c) Franke, D.; Lorbach, V.; Esser, S.; Dose, C.; Sprenger, G. A.; Halfar, M.; Thömmes J.; Müller, R.; Takors, R.; Müller, M., *Chem. Eur. J.* **2003**, *9*, 4188.

19 Mitsunobu, O., *Synthesis*, **1981**, 1.

esterification reaction, namely compound **10**, was subsequently converted into the *trans*-1,2-dihydrocatechol **11** *via* an allylic bromination – dehydrobromination sequence, which proceeded in approximately 45% yield over seven steps. Hudlicky's strategy likewise masks the reactive diene moiety *via* the formation of a suitably protected Diels-Alder adduct **12** which, when inverted using the Willis procedure[20] (triflate formation, displacement with cesium acetate and hydrolysis), afforded the product **13**. Subsequent retro-Diels-Alder reaction and deprotection furnished the *trans*-1,2-dihydrocatechol *ent*-**11** in 14% overall yield over seven steps.

**Scheme 1.3:** *Complementary enantiodivergent and chemoenzymatic approaches to the enantiomeric* trans-*3-bromo-1,2-dihydrocatechols.*




These enantiomeric switching and enantiodivergence protocols have been applied to a variety of substrates, thereby extending the range of available dihydrocatechol metabolites to include assorted *cis*- and *trans*-isomers. Additionally, these protocols provide access to either enantiomeric form of many such dihydrocatechols, consequently allowing access to either enantiomeric form of any desired natural product target.

20 Willis, C. L., *Tetrahedron Lett.*, **1987**, *28*, 6705.

## 1.2 Diels-Alder cycloaddition reactions in synthesis

### 1.2.1 Selectivity in Diels-Alder cycloaddition reactions

The paramount importance of the Diels-Alder cycloaddition reaction[21] in organic synthesis is largely derived from its ability to generate two carbon-carbon σ-bonds and up to four contiguous stereogenic centres of defined configuration in a single synthetic operation.[22] The stereochemistry at the termini of the new σ-bonds formed during a given Diels-Alder cycloaddition reaction evolves from three principal factors operating upon the reaction which act in concert to dictate the topographic-, regioisomeric- and diastereofacial-selectivities of the process.

The first of these factors concerns the topographic outcome of reaction wherein suprafacial-suprafacial interaction of the reactants *via* pathways involving *endo*- and *exo*-transition states, may occur. In topographic terms, Diels-Alder reactions favour the thermodynamically less-stable *endo*-transition states and this stereoselectivity may be conveniently explained in terms of maximisation of secondary orbital overlap[23] during reaction, leading to the formation of *endo*-products, rather than the corresponding *exo*-isomers.

Secondly, when a plane-nonsymmetrical diene and dienophile react, the formation of *ortho*- and *meta*-type regioisomers is possible. In regiochemical terms, Diels-Alder reactions favour the formation of *ortho*-adducts, rather than the corresponding *meta*-isomers. This selectivity may be explained on the basis of electrostatic interactions between polarised termini of the diene and dienophile preferentially orienting the reactants towards *ortho*-attack, although Frontier Molecular Orbital theory and/or the matching of complimentary reactivity surfaces (orbital coefficients) on the diene and dienophile also offer adequate explanations.[22d]

A further issue of stereoselectivity in the Diels Alder cycloaddition reaction arises when stereogenic centres are associated with either the diene or dienophile, resulting in the possibility

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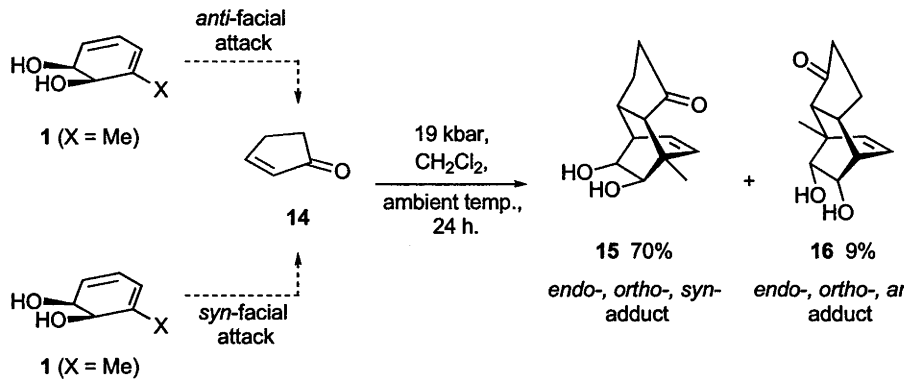
21 Diels, O.; Alder, K., *Justus Liebigs Ann. Chem.*, **1928**, *460*, 98.

22 For useful references concerning the mechanism of the Diels-Alder reaction and its utility in organic synthesis, refer to: a) Fleming, I., *Frontier Orbitals and Organic Chemical Reactions*, John Wiley & Sons: Chichester, England, **1978**, p. 249; b) Carruthers, W., *Cycloaddition Reactions in Organic Synthesis*, Pergamon Press: Oxford, England, **1990**, 8, p. 373; c) Oppolzer, W., In *Comprehensive Organic Synthesis*, Trost, B. M.; Fleming, I. (Eds.), Pergamon Press: Oxford, England, **1991**, 5, p. 315; d) Fringuelli, F.; Taticchi, A., *The Diels-Alder Reaction: selected practical methods*, John Wiley & Sons, Ltd: Chichester, England, **2002**, p. 340.

23 The role of secondary orbital overlap, also known as secondary orbital interaction (SOI), in controlling the selectivity of allowed pericyclic processes is currently disputed in the literature: García, J. I.; Mayoral, J. A.; Salvatella, L., *Acc. Chem. Res.*, **2000**, *33*, 658. In cases where SOI was previously invoked to account for the selectivity of Diels-Alder reactions, a combination of well-known mechanisms (such as solvent effects, steric interactions, hydrogen bonds, electrostatic forces and others) could be used instead to justify such phenomena. Whilst SOI is used to explain the chemistry described in this Thesis, the reader should appreciate that alternate, well-known mechanisms may also account for the outcome of the Diels-Alder reactions.

of formation of *syn-* and *anti*-isomers. Consider, as a didactic exemplar, the participation of *cis*-1,2-dihydrocatechol **1** (X = Me) in a Diels-Alder cycloaddition reaction with the dienophile cyclopenten-2-one (**14**) (Scheme 1.4).[24] The previously enunciated factors governing topographic and regiochemical selectivity suggest that whilst the *endo-*, *ortho*-transition state will predominate, the diastereofacial (π-facial) selectivity is dependent on whether the dienophile adds to the chiral diene in a *syn- or anti*-fashion with respect to the β-hydroxyl groups of the *cis*-1,2-dihydrocatechol **1** (X = Me). In principle then, two Diels-Alder adducts may form: namely the *endo-*, *ortho-*, *syn*-compound **15** and its *endo-*, *ortho-*, *anti*-isomer **16**.

**Scheme 1.4:** *Diels-Alder cycloaddition reaction of* cis-*1,2-dihydrocatechol 1 (X = Me) with cyclopenten-2-one (14).*




Intuitively, the *anti*-isomer **16** would be expected to prevail on steric grounds, but experimental evidence indicates otherwise, since when the *cis*-1,2-dihydrocatechol **1** (X = Me) is reacted with cyclopenten-2-one (**14**) under high-pressure mediated conditions, the *syn*-adduct **15** (70%) predominates over the *anti*-isomer **16** (9%) (Scheme 1.4).[24] From this observation, it is apparent that the diastereofacial selectivity of such Diels-Alder cycloaddition reactions is controlled by several factors. Indeed, numerous interactions have been invoked to account for diastereofacial selectivity in Diels-Alder cycloaddition reactions and in 2000 Mehta and Uma defined a hierarchy of effects that may operate in the stereoelectronic control of such reactions: steric > through-space (electrostatic repulsion/attractive stabilising orbital interactions) > hyperconjugative > ground state orbital distortion (generally in non-polar substrates).[25] Whilst steric interactions are widely accepted as being most influential, it is the precise nature of the non-steric[26] (generally electrostatic) interactions that is often debated, largely due to the lack of predictability in the reaction outcome.

24 Stewart, S. G., *PhD Thesis*, Australian National University, **2001**.

25 Mehta, G.; Uma, R., *Acc. Chem. Res.*, **2000**, *33*, 278.

26 The reader is reminded that steric and electronic effects are not perfectly separable. For example, one of the simplest steric problems, the barrier to rotation in the ethane molecule, may be explained qualitatively and quantitatively in terms of electronic effects by molecular orbital theory. Refer to: Smith, D. W., *J. Chem. Soc., Faraday Trans.*, **1998**, *94*, 3087 and References 17 – 19 therein.

Several theories have been propounded to explain how π-facial selectivity, in Diels-Alder cycloaddition reactions of plane-nonsymmetric dienes, is governed by allylic heteroatoms. Anh,[27] and later Kahn and Hehre,[28] proposed an ostensibly nucleophilic rôle for the heteroatom with respect to the incoming (electrophilic) dienophile: Anh invoked a favourable non-bonded electrostatic interaction between the heteroatom (lone pair) and the dienophile (LUMO) to stabilise the *syn*-transition state, whilst Kahn and Hehre proposed that the more nucleophilic face of a facially-perturbed, electron-rich diene would be more reactive towards an electrophilic dienophile. The theory of Anh was subsequently disputed by Inagaki, Fujimoto and Fukui on the grounds that a non-bonded electrostatic interaction between the heteroatom (lone pair) and dienophile (LUMO) induces an anti-bonding character between the diene (HOMO) and dienophile (LUMO), thereby disfavouring the leading interaction of the Diels-Alder cycloaddition reaction.[29] To explain the origin of *syn*-selectivity Inagaki, Fujimoto and Fukui instead proposed orbital mixing of the heteroatom (lone pair) and the dienophile (HOMO), thus leading to a non-equivalent extension of the resulting π-molecular orbital in the direction of the substituent. However, the results of subsequent *ab initio* computational and photoelectron spectroscopic studies by Werstiuk *et al.* clearly indicate that orbital mixing is insignificant and cannot be the source of the diastereofacial selectivity in Diels-Alder cycloaddition reactions.[30]

Hyperconjugative effects, originally enunciated[31] by Cieplak to explain facial selectivity of carbonyl reactions, were extended to Diels-Alder cycloaddition processes by Turro and le Noble *et al.*, as well as by Macaulay and Fallis.[32] It was proposed that the transition state of Diels-Alder cycloaddition reactions is stabilised by hyperconjugative participation of the *anti*-periplanar σ-bonds into the $\sigma^*$-orbitals of the newly forming bonds. The Cieplak model predicts preferential addition of the dienophile *anti-* to the face of the diene that bears the bond(s) with the greatest σ-donor ability. Given that C–H bonds are more effective σ-donors than are C–O bonds, the *syn*-selectivity associated with Diels-Alder cycloaddition reactions of *cis*-1,2-dihydrocatechol **1** (X = Me) may be rationalised in terms of the Cieplak model by considering the two transition state models **17** and **18** shown in Figure 1.5, where the former is expected to be significantly more stable than the latter.

Recent semi-empirical calculations by Werstiuk and Ma[33] as well as *ab initio* calculations by Poirier *et al.*[34] indicated that the Cieplak effect cannot be significant in Diels-

27 Anh, N. T., *Tetrahedron*, **1973**, *29*, 3227.

28 Kahn, S. D.; Hehre, W. J., *J. Am. Chem. Soc.*, **1987**, *109*, 663.

29 a) Inagaki, S.; Fujimoto, H.; Fukui, K., *ibid.* **1976**, *98*, 4054; b) Ishida, M.; Beniya, Y.; Inagaki, S.; Kato, S., *J. Am. Chem. Soc.*, **1990**, *112*, 8980.

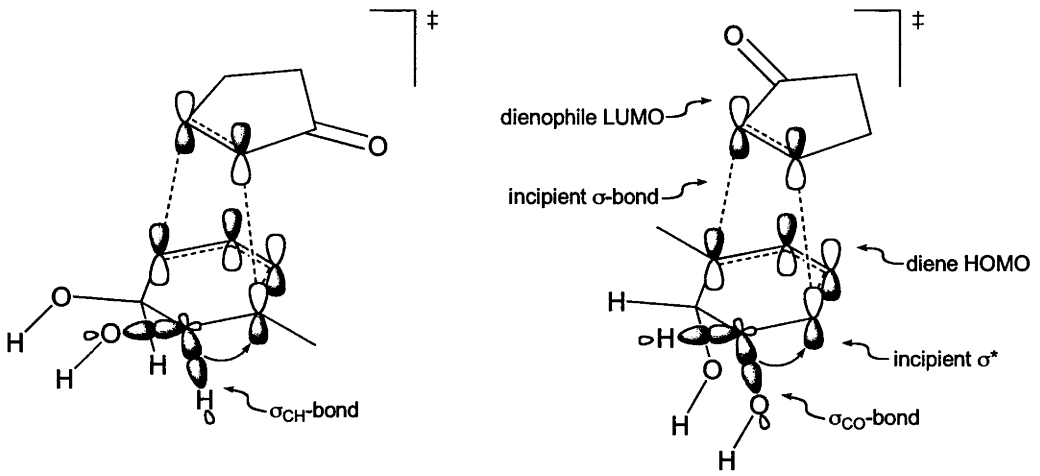
30 Werstiuk, N. H.; Ma, J.; Macaulay, J. B.; Fallis, A. G., *Can. J. Chem.*, **1992**, *70*, 2798.

31 a) Cieplak, A. S., *J. Am. Chem. Soc.*, **1981**, *103*, 4540; b) Cieplak, A. S., *Chem. Rev.*, **1999**, *99*, 1265.

32 a) Chung, W.-S.; Turro, N. J.; Srivastava, S.; Li, H.; le Noble, W. J., *J. Am. Chem. Soc.*, **1988**, *110*, 7882; b) Macaulay, J. B.; Fallis, A. G., *J. Am. Chem. Soc.*, **1990**, *112*, 1136.

33 Werstiuk, N. H.; Ma, J., *Can. J. Chem.*, **1994**, *72*, 2493.

Alder cycloaddition reactions, although Cieplak subsequently[31b] disputed these conclusions, in the belief that the *ab initio* data supports, rather than refutes, the hypothesis of hyperconjugative σ-assistance. Poirier *et al.* alternatively suggested, on the basis of *ab initio* calculations, that the difference in energy required to deform the addends, and in particular the diene, into the *syn*- and *anti*-transition state geometries accounts for most of the difference between activation energies for *syn*- and *anti*-addition.[34b,34c] The remaining difference in activation energies must arise from differences in the interactions between diene and dienophile, but these are relatively insignificant since direct interactions such as steric effects are accounted for by the deformational changes in geometry of the addends at the transition state.[35] This theory accounts for the diastereofacial selectivity observed experimentally in Diels-Alder cycloaddition reactions and is accepted as the most current model for prediction of facial selectivity.




**17**

*endo-, ortho-, syn*-transition state

**18**

*endo-, ortho-, anti*-transition state

**Figure 1.5:** syn- *and* anti-*Diels-Alder cycloaddition transition states 17 and 18 (respectively) for reaction of* cis-*1,2-dihydrocatechol 1 (X = Me) with cyclopenten-2-one (14) (Note: orbitals of only one oxymethine moiety shown for clarity).*

## 1.2.2 Diels-Alder cycloaddition reactions involving *cis*-1,2-dihydrocatechols

The majority of Diels-Alder cycloaddition reactions involving *cis*-1,2-dihydrocatechols **1** employ the corresponding hydroxyl-protected derivatives, rather than the free diols, as the diene component of reaction.[36] Protected *cis*-1,2-dihydrocatechols are invariably more

34 a) Poirier, R. A.; Pye, C. C.; Xidos, J. D.; Burnell, D. J., *J. Org. Chem.*, **1995**, *60*, 2328; b) Xidos, J. D.; Poirier, R. A.; Pye, C. C.; Burnell, D. J., *J. Org. Chem.*, **1998**, *63*, 105; c) Pye, C. C.; Xidos, J. D.; Burnell, D. J.; Poirier, R. A., *Can. J. Chem.*, **2003**, *81*, 14.

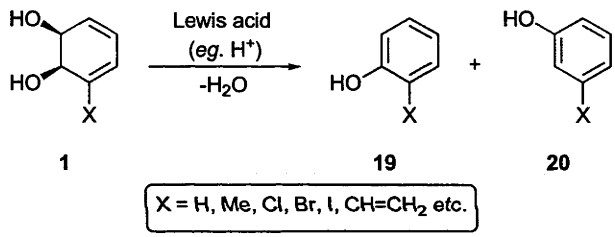
35 Such differences in geometry between the *syn*- and *anti*-transition states are generally manifest in the angles of the heteroatoms about the chiral centres.

36 For recent reviews discussing the use of *cis*-1,2-dihydrocatechols as cycloaddends, refer to: a) Ref. 9a; b) Ref. 9b; c) Ref. 9d. All known examples of cycloaddition reactions of (unprotected) *cis*-1,2-dihydrocatechols are described by: d) Gillard, J. R.; Burnell, D. J., *J. Chem. Soc., Chem. Commun.*, **1989**, 1439; e) Ref. 7; f) Gillard, J. R.; Burnell, D. J., *Can. J. Chem.*, **1992**, *70*, 1296; g) Jenkins, G. N.; Ribbons, D. W.; Widdowson, D. A.; Slawin, A.

thermally stable than the parent diols[36b] and this feature allows them to participate in thermally-promoted Diels-Alder cycloaddition processes without significant decomposition. Furthermore, the steric demands of the – invariably acetal or *bis*-ether – protective moieties of the *cis*-1,2-dihydrocatechols usually prevent *syn*-facial approach of the dienophile and result in the predominant formation of *anti*-adducts.

As implied above, the unprotected *cis*-1,2-dihydrocatechols of type **1** do not generally participate in thermally-promoted Diels-Alder cycloaddition reactions.[36b] Similarly, when Lewis acids are employed in an attempt to catalyse such reactions, rapid dehydration and accompanying aromatisation occurs (Scheme 1.5) to furnish the corresponding *ortho*- and *meta*-substituted phenols **19** and **20**, respectively, as the only isolable products. The phenols thus generated are acidic and may induce further aromatisation of the *cis*-1,2-dihydrocatechols **1**, thereby rendering the elimination process essentially autocatalytic.[36h]

**Scheme 1.5:** *Aromatisation of* cis-*1,2-dihydrocatechol* ***1*** *(X = H, Me, Cl, Br, I, CH=CH$_2$* etc.*) to the corresponding* ortho- *and* meta-*substituted phenols* ***19*** *and* ***20****.*

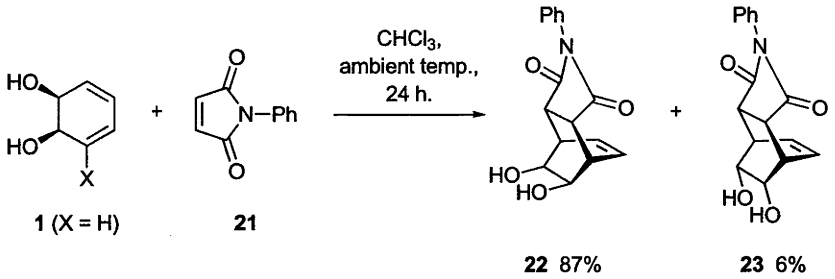



A salient exception to this trend was first reported by Gillard and Burnell who observed that benzene-derived *cis*-1,2-dihydrocatechol **1** (X = H) readily engaged in a Diels-Alder cycloaddition reaction with the potent dienophile *N*-phenylmaleimide (**21**) under mild conditions, to form the respective *syn*- and *anti*-adducts **22** and **23** in a 94:6 ratio and in excellent (93%) yield (Scheme 1.6).[36d] Subsequently, Boyd *et al.* described several, similarly facile, Diels-Alder cycloaddition reactions between *cis*-1,2-dihydrocatechols **1** (X = Me, Et, Cl, $CF_3$, $CH_2OAc$) and the potent dienophile 4-phenyl-1,2,4-triazoline-3,5-dione (**24**), in which the corresponding *syn*-products **25a-e** and *anti*-adducts **26a-e** were produced at ambient temperature in yields of 70 – 80% (Scheme 1.7).[36e] The facial selectivity associated with each

M. Z.; Williams, D. J., *J. Chem. Soc., Perkin Trans. 1*, **1995**, 2647; h) Ref. 27. Representative cycloaddition reactions of protected *cis*-1,2-dihydrocatechols include those reported by: i) Ref. 3a; j) Ref. 5; k) Hudlicky, T.; Luna, H.; Barbieri, G.; Kwart, L. D., *J. Am. Chem. Soc.*, **1988**, *110*, 4735; l) Pittol, C. A.; Pryce, R. J.; Roberts, S. M.; Ryback, G.; Sik, V.; Williams, J. O., *J. Chem. Soc., Perkin Trans. 1*, **1989**, 1160; m) Ley, S. V.; Redgrave, A. J.; Taylor, S. C.; Ahmed, S.; Ribbons, D. W., *Synlett*, **1991**, 741; n) Schürrle, K.; Beier, B.; Piepersberg, W., *J. Chem. Soc., Perkin Trans. 1*, **1991**, 2407; o) Jones, G. R.; Vogel, P., *J. Chem. Soc., Chem. Commun.*, **1993**, 769; p) Hudlicky, T.; McKibben, B. P., *J. Chem. Soc., Perkin Trans. 1*, **1994**, 485; q) Banwell, M. G.; Dupuche, J. R.; Gable, R. W., *Aust. J. Chem.*, **1996**, *49*, 639; r) McRae, K. J., *PhD Thesis*, Australian National University, **2001**; s) Banwell, M. G.; Chun, C.; Edwards, A. J.; Vögtle, M., *Aust. J. Chem.*, **2003**, *56*, 861.

Diels-Alder cycloaddition reaction dramatically favoured the *syn*-products over the *anti*-isomers (at least *ca.* 94:6 in favour of the *syn*-product).[37]

**Scheme 1.6:** *Diels-Alder cycloaddition reaction of* cis-*1,2-dihydrocatechol 1 (X = H) and* N-*phenylmaleimide (21).*




Direct application of the mild reaction conditions described above, to other Diels-Alder cycloaddition reactions involving unprotected *cis*-1,2-dihydrocatechols is precluded by the relatively low reactivity of many dienophiles. However, Diels-Alder cycloaddition reactions where no reaction is observed under conventional conditions (due, for example, to reduced reactivity of the dienophile) can be promoted by the application of high pressure,[38] since such systems possess a large, negative volume of activation, $\Delta V^{\ddagger}$ of between -25 and -45 $cm^3.mol^{-1}$.[39,40] Indeed, recent studies by Stewart have shown that the reduced reactivity of dienophiles such as cyclopenten-2-one (**14**) towards cycloaddition with *cis*-1,2-dihydrocatechols of the general type **1** may be overcome by the use of high-pressure (19 kbar) techniques without significantly promoting the inherent tendency of the diene to aromatise.[24] Nevertheless, the aromatisation of *cis*-1,2-dihydrocatechols of the type **1** (Scheme 1.5) is often competitive with the cycloaddition processes, such that if the application of high-pressure fails to promote any

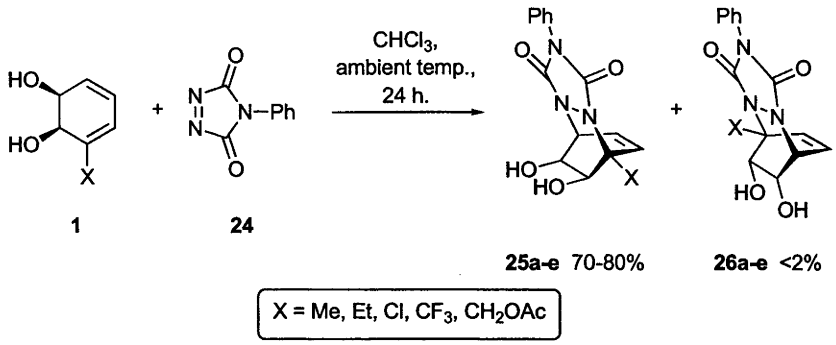
37 Note that when benzene-derived *cis*-1,2-dihydrocatechol **1** (X = H) was protected as the benzylidene acetal derivative the syn-selectivity was reversed.

38 For useful references discussing the utility of high pressure in organic chemistry, refer to: a) Matsumoto, K.; Sera, A.; Uchida, T., *Synthesis*, **1985**, 1; b) Jenner, G., In *Organic High Pressure Chemistry*, le Noble, W. J. (Ed.) Elsevier: New York, U.S.A., **1988**, p. 143; c) Jurczak, J., In *Organic High Pressure Chemistry*, le Noble, W. J. (Ed.) Elsevier: New York, U.S.A., **1988**, p. 304; d) Isaacs, N. S., *Tetrahedron*, **1991**, *47*, 8463; e) Ciobanu, M.; Matsumoto, K., *Leibigs Ann./Recueil*, **1997**, 623; f) Klärner, F.-G.; Diedrich, M. K.; Wigger, A. E., In *Chemistry Under Extreme or Non-Classical Conditions*, van Eldik, R.; Hubbard, C. D. (Eds.), John Wiley & Sons, Inc. and Spektrum Akademischer Verlag: New York, U.S.A., **1997**, p. 103; g) Jurczak, J.; Gryko, D. T., In *Chemistry Under Extreme or Non-Classical Conditions*, van Eldik, R.; Hubbard, C. D. (Eds.), John Wiley & Sons, Inc. and Spektrum Akademischer Verlag: New York, U.S.A., **1997**, p. 163; h) Klärner, F.-G.; Wurche, F., *J. Prakt. Chem.*, **2000**, *342*, 609.

39 McCabe, J. R.; Eckert, C. A., *Acc. Chem. Res.*, **1974**, *7*, 251.

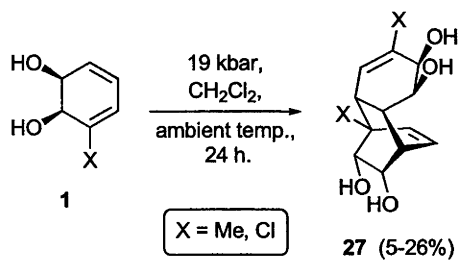
40 The application of high pressure to reaction systems that possess a negative $\Delta V^{\ddagger}$ is widely accepted to significantly increase the rate of reaction (refer to Ref. 34). Additionally, the application of high pressure to some Diels-Alder cycloaddition reactions not only increases the rate of reaction, but may also provide synthetically useful improvements in the diastereoselectivity of these processes: refer to Tietze, L. F.; Henrich, M.; Niklaus, A.; Buback, M., *Chem. Eur. J.*, **1999**, *5*, 297.

**Scheme 1.7:** *Diels-Alder cycloaddition reaction of* cis-*1,2-dihydrocatechol* ***1*** *(X = Me, Et, Cl, $CF_3$, $CH_2OAc$) and 4-phenyl-1,2,4-triazoline-3,5-dione (**24**).*




reaction between the diene **1** and a dienophile, then the former transformation will predominate. Indeed, when iodobenzene-derived *cis*-1,2-dihydrocatechol **1** (X = I) or its bromo-analogue **1** (X = Br) were used in attempts to generate the corresponding Diels-Alder adducts from a variety of dienophiles, only phenolic products were isolated.[24] In addition to aromatisation, a second process competitive with the desired cycloaddition reaction was identified, in which the *cis*-1,2-dihydrocatechols **1** (X = Me, Cl) often underwent dimerisation to form compounds of the general type **27** (X = Me, Cl).[24] Although *cis*-1,2-dihydrocatechols **1** (X = Me, Cl) generally act as the diene component of reaction in cycloaddition processes, the less sterically-demanding olefinic bond of these compounds is partially dienophilic in nature and may react as the 2π-component in Diels-Alder reactions. Thus, Diels-Alder cycloaddition may occur between two *cis*-1,2-dihydrocatechol molecules – one acting as the diene and another as the dienophile – and result in formation of dimers of the general type **27** (X = Me, Cl) in up to 26% yield, depending on the susceptibility of the *cis*-1,2-dihydrocatechol **1** (X = Me, Cl) towards aromatisation and on the reactivity of the dienophile being examined as a potential cycloaddition partner (Scheme 1.8).[24]

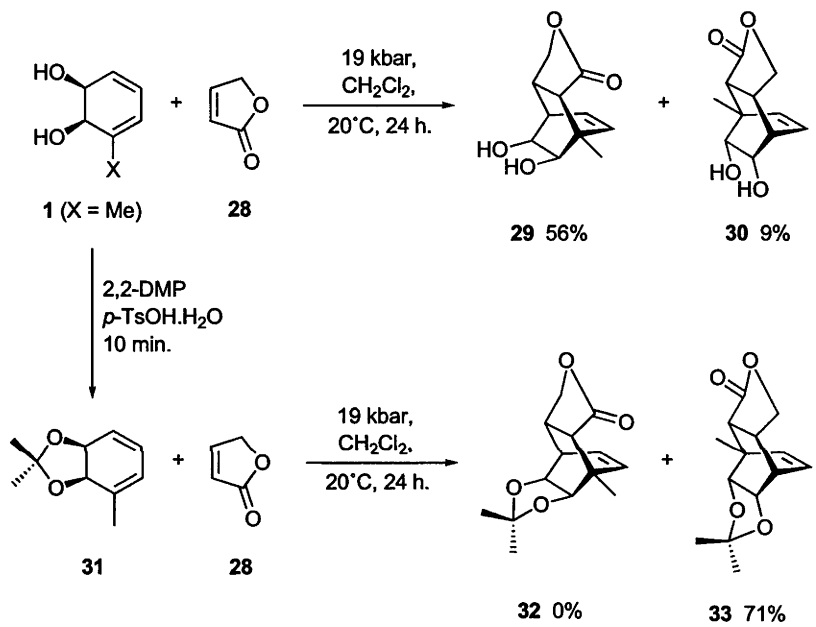
**Scheme 1.8:** *Dimerisation of* cis-*1,2-dihydrocatechols* ***1*** *(X = Me, Cl).*




Despite these competitive aromatisation and dimerisation processes, it has been demonstrated that the *cis*-1,2-dihydrocatechols of type **1** readily participate in diastereofacially selective high pressure-promoted Diels-Alder cycloaddition reactions with a range of

conventional dienophiles so as to produce adducts of synthetic value.[24] By way of example, reaction of the *cis*-1,2-dihydrocatechol **1** (X = Me) with 2(5*H*)-furanone (**28**) under high pressure mediated conditions[41] affords the *endo*-, *ortho*-, *syn*-product **29** in 56% yield, along with the *endo*-, *ortho*-, *anti*-isomer **30** in 9% yield.[24] In contrast, when the *cis*-1,2-dihydrocatechol **1** (X = Me) is protected as the acetonide derivative **31**[36k] and reacted under high pressure-promoted conditions with 2(5*H*)-furanone (**28**), steric factors predominate, such that the sole product of reaction is the *endo*-, *ortho*-, *anti*-adduct **32** (71%): no *endo*-, *ortho*-, *syn*-isomer **33** was observed (Scheme 1.9).[24]

**Scheme 1.9:** *Diels-Alder cycloaddition reactions of* cis*-1,2-dihydrocatechol 1 (X = Me) and the corresponding acetonide 31 with 2(5*H*)-furanone (28).*




The diastereofacial *syn*-selectivity observed for the high pressure-promoted Diels-Alder cycloaddition reactions of *cis*-1,2-dihydrocatechol **1** (X = Me) with 2(5*H*)-furanone (**28**) (Scheme 1.9) and cyclopenten-2-one (**14**) (described earlier, Scheme 1.4), is analogous to that observed for the comparable and pioneering reactions described by Burnell *et al.*[36d] and Boyd *et al.*[36e] (Schemes 1.9 and 1.10, respectively). It is apparent from such observations that, as with conventional conditions, high pressure-promoted Diels-Alder cycloaddition reactions of *cis*-1,2-dihydrocatechols **1** favour the formation of *syn*-adducts, as described theoretically by Cieplak[31] and by Poirier *et al.*[34b, 34c] By virtue of this feature and the additional observation that protected derivatives of *cis*-1,2-dihydrocatechols selectively favour the formation of *anti*-adducts (Scheme 1.9), the diastereoselectivity of such reactions can be controlled. Furthermore, the *syn*- and *anti*-adducts thus generated are pseudo-enantiomeric, such that

41 Typically a solution of the addends in $CH_2Cl_2$ maintained at 19 kbar of pressure and 20°C for 24 h.

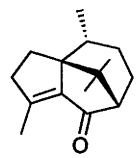
*cis*-1,2-dihydrocatechols may be employed in Diels-Alder cycloaddition reactions to provide enantiodivergent access to chiral bicyclo[2.2.2]octenes from a common precursor.

## 1.3 *cis*-1,2-Dihydrocatechols and Diels-Alder cycloaddition reactions in natural product synthesis

Chiral bicyclo[2.2.2]octenes derived from *cis*-1,2-dihydrocatechols **1** *via* Diels-Alder cycloaddition reactions embody multiple functionalities within rigid frameworks that, when appropriately substituted, are capable of being converted into the skeleta of various natural products. As such, enantiopure bicyclo[2.2.2]octenes are highly valuable chirons. The total synthesis of the sesquiterpene natural product (–)-patchoulenone [(–)-**34**] (Figure 1.6) from *cis*-1,2-dihydrocatechol (**1**, X = Me), presented below, serves to illustrate this point. Particular emphasis is placed on the methods by which the symmetry elements and multiple functionalities of the chiral substrate were exploited as part of the design strategy.

***Banwell, Hockless and McLeod's syntheses of (–)-patchoulenone (1998 and 2003)***

In 1998 Banwell and McLeod communicated[42a] a total synthesis of the sesquiterpene natural product (–)-patchoulenone[43] [(–)-**34**] from the monochiral *cis*-1,2-dihydrocatechol **1** (X = Me), obtained by microbial oxidation of toluene. A subsequent report in 2003 by Banwell, Hockless and McLeod described this chemoenzymatic total synthesis in detail as an eighteen step procedure in which (–)-patchoulenone [(–)-**34**] was produced in 6% overall yield, but, significantly, that a second, more expedient and efficient route to the same product had also been achieved in which the natural product was synthesised over sixteen steps in 7% yield.[42b]




**(–)-Patchoulenone**
**[(–)-34]**

**Figure 1.6:** *The cyperene-type sesquiterpene (–)-patchoulenone [(–)-34].*

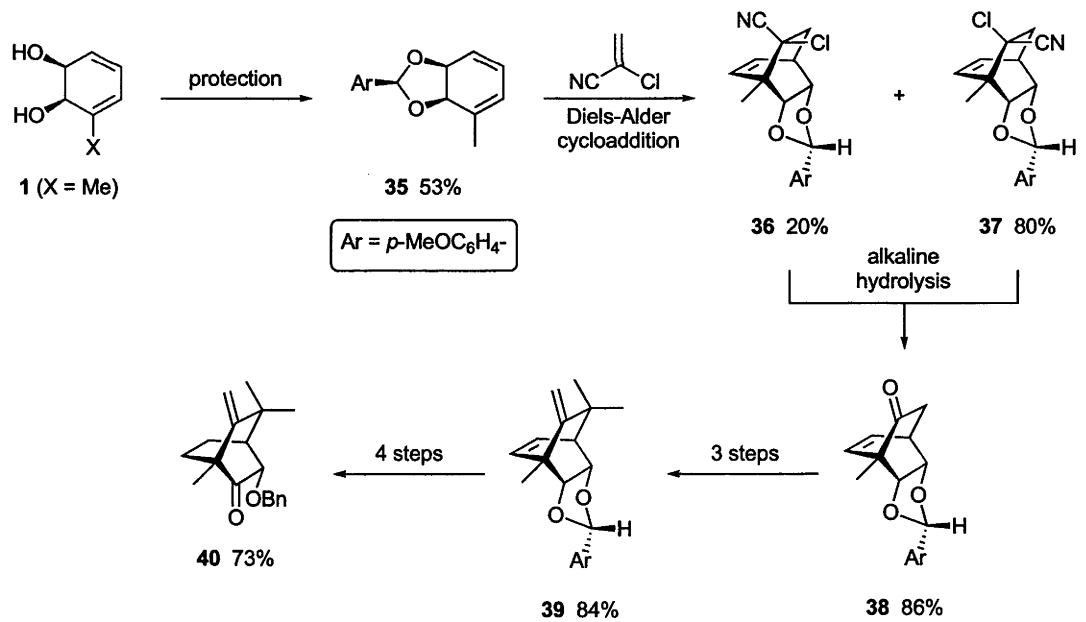
42 a) Banwell, M.; McLeod, M., *Chem. Commun.*, **1998**, 1851; b) Banwell, M. G.; Hockless, D. C. R.; McLeod, M. D., *New J. Chem.*, **2003**, *27*, 50.

43 (–)-Patchoulenone [(–)-**34**] is a member of the cyperene class of sesquiterpenes first isolated from, *inter alia*, the sedge *Cyperus rotundus* L. (Cyperaceae): a) Trivedi, B.; Motl, O.; Herout, V.; Sorm, F., *Collect. Czech. Chem. Commun.*, **1964**, *29*, 1675. The natural product has been found to exhibit, most significantly, *in vitro* activity ($EC_{50}$ $1.08 \times 10^{-4}$ $mol.L^{-1}$) against the malarial parasite *Plasmodium falciparum*; b) Thebtaranonth, C.; Thebtaranonth, Y.; Wanauppathamkul, S.; Yuthavong, Y., *Phytochemistry*, **1995**, *40*, 125.

***First synthesis of (–)-patchoulenone (1998)***

In the first of their two syntheses of (–)-patchoulenone [(–)-**34**], Banwell and McLeod reacted the *cis*-1,2-dihydrocatechol **1** (X = Me), with *p*-methoxybenzaldehyde dimethyl acetal in the presence of an acid catalyst, to afford the *endo*-*p*-methoxybenzylidene acetal **35** in 53% yield (Scheme 1.10).[42a] Subsequent thermally-promoted Diels-Alder cycloaddition reaction between the diene and α-chloroacrylonitrile quantitatively furnished the *endo*- and *exo*-, *ortho*-, *anti*-adducts **36** and **37** in a 1:4 ratio, due to the phenomena discussed in Section 1.2. The resulting mixture of chloronitriles was subjected to alkaline hydrolysis to effect formation of a single ketone product **38** in 86% yield. Ketone **38** was then converted, *via* a series of standard functional group interconversions including *gem*-dimethylation, chemoselective reduction of the olefinic moiety and methylenation, into the *exo*-cyclic alkene **39** in 84% yield, over three steps. Compound **39** was subjected to a series of standard protecting group manipulations, followed by oxidation to obtain the benzyl protected acyloin **40** in 73% yield over four steps. That the acetal **39** is regioselectively cleaved in order for benzyl protection and subsequent oxidation to occur, is evidence that, even at this advanced stage in proceedings, the influence of the methyl sustitutent from the original *cis*-1,2-dihydrocatechol **1** (X = Me), is significant.

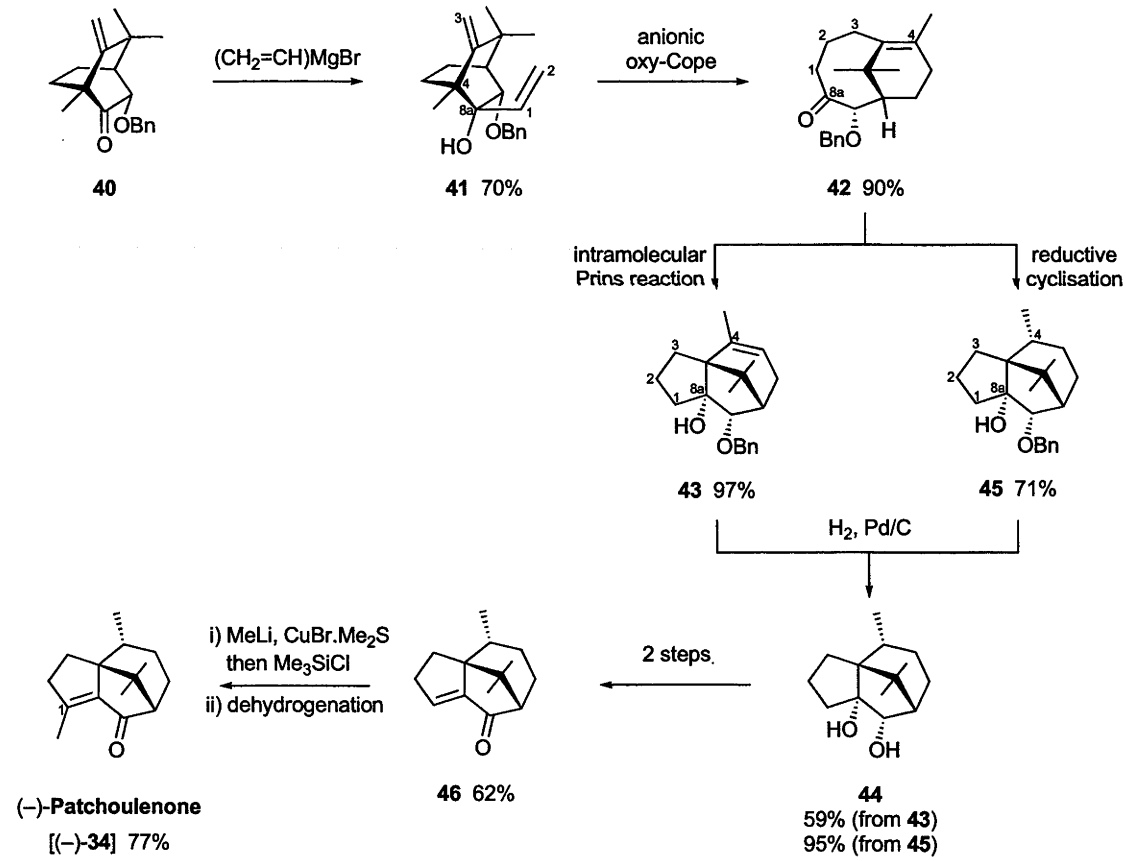
**Scheme 1.10:** *Banwell* et al. *synthesis of protected acyloin synthon.*




In completing the synthesis, acyloin **40** was reacted with vinylmagnesium bromide to effect formation of the 1,5-diene **41** in 70% yield which, upon treatment with sodium hydride in refluxing THF, underwent anionic oxy-Cope rearrangement to form bicyclo[5.3.1]undecanone **42** in 90% yield (Scheme 1.11). As a consequence of the close proximity of the carbonyl and olefinic moieties within bicyclo[5.3.1]undecanone **42**, the molecule readily engages in an acid

catalysed intramolecular Prins reaction to afford the corresponding tricyclic *cis*-diol **43** (97%) which, upon hydrogenation, furnished the saturated *cis*-diol **44** in 59% yield. An alternative and higher yielding approach to compound **44** involved reductive cyclisation of bicyclo[5.3.1]undecanone **42** with samarium (II) diiodide in the presence of thiophenol to furnish the tricyclic alcohol **45** (71%) which, upon hydrogenolytic cleavage, likewise afforded the saturated *cis*-diol **44** in 95% yield. Compound **44** was subjected to a series of standard functional group manipulations including oxidation and dehydration of the respective secondary and tertiary alcohols to form enone **46** in 62% yield over two steps. Enone **46** was then reacted with the Gilman reagent derived from methyllithium and copper (I) bromide-dimethyl sulfide complex and the ensuing enolate anion was trapped as the silylenol ether which, upon dehydrogenation (and concomitant desilylation), afforded (–)-patchoulenone [(–)-**34**] in 77% yield from enone **46**.

**Scheme 1.11:** *Banwell and McLeod synthesis of (–)-patchoulenone [(–)-34].*

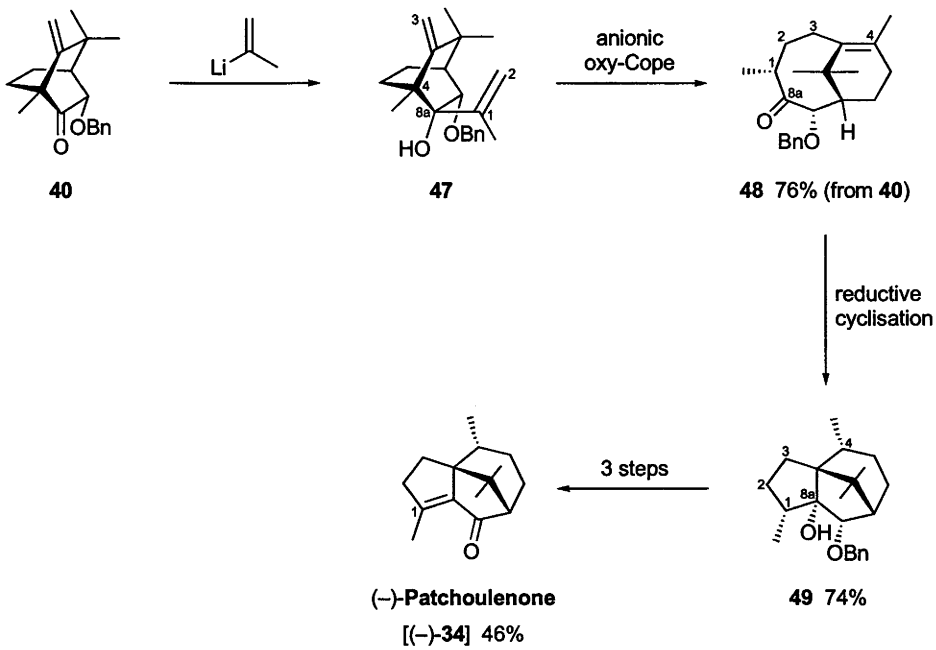



### *Second synthesis of (–)-patchoulenone (2003)*

The second synthesis[42b] of (–)-patchoulenone [(–)-**34**] employed a protocol similar to that reported in the first such procedure, but differed from the first in that the C(1) methyl group of the natural product was installed prior to performing the anionic oxy-Cope reaction (Scheme

1.12). Whilst the early stage methodology is central to both syntheses, the second synthesis diverges from the first upon reaction of the shared acyloin **40** with *iso*propenyl lithium, to form the nucleophilic addition product **47**. Treatment of 1,5-diene **47** with sodium hydride in refluxing THF smoothly effected anionic oxy-Cope rearrangement to form the corresponding bicyclo[5.3.1]undecanone **48** in 76% yield (from acyloin **40**). Reductive cyclisation of bicyclo[5.3.1]undecanone **48** with samarium (II) iodide in the presence of thiophenol furnished the tricylic alcohol **49** (74%). Hydrogenative debenzylation and subsequent oxidation of compound **49** produced the corresponding acyloin which, upon dehydration, generated the natural product (–)-patchoulenone [(–)-**34**] in 46% yield.

**Scheme 1.12:** *Banwell, Hockless and McLeod synthesis of (–)-patchoulenone [(–)-34].*




**40** **47** **48** 76% (from **40**)

**(–)-Patchoulenone** [(–)-**34**] 46% **49** 74%

The influence of the starting *cis*-1,2-dihydrocatechol **1** (X = Me) on the formation of (–)-patchoulenone [(–)-**34**] is evident throughout the total synthesis of this natural product and is of most significance during the Diels-Alder cycloaddition reaction performed in the initial stages of the sequence. In this step, the symmetry of the enantiopure chiral diene addend controls the diastereofacial selectivity observed in the cycloaddition reaction. As a consequence, subsequent manipulation of adducts **36** and **37**, *via* the anionic oxy-Cope and reductive cyclisation reactions, affords the natural product (–)-patchoulenone [(–)-**34**] in single enantiomeric form, thereby demonstrating the utility of *cis*-1,2-dihydrocatechols and Diels-Alder cycloadditions in natural products synthesis.

The sequence of microbial oxidation – Diels-Alder cycloaddition – anionic oxy-Cope rearrangement steps employed in the total synthesis of (–)-patchoulenone [(–)-**34**] has previously been exploited in the formation of advanced intermediates applicable to natural

product synthesis. In this manner, Hudlicky *et al.* have synthesised the BC-ring portion of (–)-morphine,[44] while Banwell *et al.* have synthesised the phomoidride core,[45] steroidal nuclei[46] and the AB ring-systems of taxol.[47] Such exemplary syntheses, along with the formation of (–)-patchoulenone [(–)-**34**],[42] illustrate the utility of chiral bicyclo[2.2.2]octenes and, *ipso facto*, *cis*-1,2-dihydrocatechols in organic synthesis. Whilst these examples additionally expound the use of a specific rearrangement reaction (*viz.* the anionic oxy-Cope reaction) in conjunction with the microbial oxidation – Diels-Alder cycloaddition sequence, there is significant potential for alternative rearrangement processes to be employed in the formation of natural products. Photochemically-promoted reactions of chiral bicyclo[2.2.2]octenones (β,γ-unsaturated ketones) derived from the corresponding bicyclo[2.2.2]octenes are considered as alternative rearrangement processes with synthetic potential. Various possibilities are reviewed in the following Section.

## 1.4 Photochemical reactions in organic synthesis

### 1.4.1 Photochemistry of β,γ-unsaturated ketones

The outcome of photochemical isomerisation reactions of β,γ-unsaturated ketones constrained in a rigid bicyclic framework (*e.g.* compound **50**) has been previously recognised to occur, upon electronic excitation,[48] *via* two predominant rearrangement pathways (Scheme 1.13). Early studies showed that triplet sensitised irradiation of β,γ-unsaturated ketones yielded cyclopropyl ketone isomerisation products resulting from formal [1,2]-acyl migration (*e.g.* compound **51**, Scheme 1.13). This process was later to become commonly known as the oxa-di-π-methane rearrangement process because of its similarity to the well-established di-π-methane or Zimmermann rearrangement. Following extensive studies, (including quenching and sensitisation experiments,[49] CNDO-MO calculations,[50] and phosphorescence

44 a) Hudlicky, T.; Boros, C. H.; Boros, E. E., *Synthesis*, **1992**, 174; b) Butora, G.; Gum, A. G.; Hudlicky, T.; Abboud, K. A., *Synthesis*, **1998**, 275.

45 Banwell, M. G.; McRae, K. J.; Willis, A. C., *J. Chem. Soc., Perkin Trans. 1*, **2001**, 2194.

46 Banwell, M. G.; Hockless, D. C. R.; Holman, J. W.; Longmore, R. W.; McRae, K. J.; Pham, H. T. T., *Synlett*, **1999**, 1491.

47 Banwell, M. G.; Darmos, P.; McLeod, M. D.; Hockless, D. C. R., *ibid.* **1998**, 897.

48 For reviews of this area refer to: a) Houk, K. N., *Chem. Rev.*, **1976**, *76*, 1; b) Schuster, D. I., In *Rearrangements in Ground and Excited States*, de Mayo, P. (Ed.) Academic Press: New York, U.S.A., **1980**, Vol. 3, p. 167; c) Demuth, M.; Schaffner, K., *Angew. Chem., Int. Ed. Engl.*, **1982**, *21*, 820; d) Zimmermann, H. E.; Armesto, D., *Chem. Rev.*, **1996**, *96*, 3065.

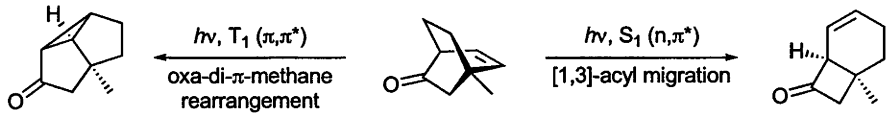
49 a) Ipaktschi, J., *Tetrahedron Lett.*, **1969**, 2153; b) Schuster, D. I.; Sussman, D. H., *Tetrahedron Lett.*, **1970**, 1661; c) Ipaktschi, J., *Chem. Ber.*, **1972**, *105*, 1840; d) Engel, P. S.; Schexnayder, M. A.; Ziffer, H.; Seeman, J. I., *J. Am. Chem. Soc.*, **1974**, *96*, 924; e) Engel, P. S.; Schexnayder, M. A.; Phillips, W. V.; Ziffer, H.; Seeman, J. I., *Tetrahedron Lett.*, **1975**, 1157; f) Riemann, B.; Sadler, D. E.; Schaffner, K., *J. Am. Chem. Soc.*, **1986**, *108*, 5527.

50 Houk, K. N.; Northington, D. J.; Duke, R. E., *J. Am. Chem. Soc.*, **1972**, *94*, 6233.

studies[51]), it was considered that the oxa-di-π-methane rearrangement occurred *via* the alkene $T_1$ (π,π*) excited state.

In contrast to this, direct irradiation of β,γ-unsaturated ketones yielded cyclobutanone isomerisation products resulting from formal [1,3]-acyl migration (*e.g.* compound **52**, Scheme 1.13). This process was not observed to occur on triplet sensitised irradiation and was not inhibited by triplet quenchers.[49b, 49d, 49e] As such, and following nuclear polarisation studies (photo-CIDNP experiments),[52] the observed [1,3]-acyl shift was considered to occur *via* the keto $S_1$ (n,π*) excited state.

**Scheme 1.13:** *Photochemical reaction of β,γ-unsaturated ketone* ***50*** via *triplet and singlet states.*




**51** **50** **52**

Subsequent observations showed that although each of these photochemical reactions is characterised by their respective excited states, the outcome of reactions of β,γ-unsaturated ketones under triplet sensitised or direct irradiative conditions (*i.e.* a given set of reaction conditions) is unable to be generalised: the outcome is dependent not only on the reaction conditions, but also on the structure of the substrate. Indeed, a correlation between excited state-spin multiplicity and electronic configuration with reaction type has been established, such that the oxa-di-π-methane rearrangement (in particular) is now recognised to occur not only from the $T_1$ (π,π*) excited state under triplet sensitised conditions, but also under direct irradiation, emanating from the $S_2$ (π,π*) excited state (Figure 1.7).[53] Likewise, the [1,3]-acyl migration is also recognised to take place from both the $S_1$ (n,π*) and $T_2$ (n,π*) excited states under direct irradiation and triplet sensitised reaction conditions, respectively (Figure 1.7).[52, 54, 55]

51 a) Marsh, G.; Kearns, D. R.; Schaffner, K., *ibid.* **1971**, *93*, 3129; b) Hancock, K. G.; Grider, R. O., *J. Chem. Soc., Chem. Commun.*, **1972**, 580; c) Tegmo-Larsson, I.-M.; Gonzenbach, H.-U.; Schaffner, K., *Helv. Chim. Acta*, **1976**, *59*, 1376; d) Gonzenbach, H.-U.; Tegmo-Larsson, I.-M.; Grosclaude, J.-P.; Schaffner, K., *Helv. Chim. Acta*, **1977**, *60*, 1091.

52 a) Henne, A.; Siew, N. P. Y.; Schaffner, K., *Helv. Chim. Acta*, **1979**, *62*, 1952; b) Henne, A.; Siew, N. P. Y.; Schaffner, K., *J. Am. Chem. Soc.*, **1979**, *101*, 3671.

53 a) Eckersley, T. J.; Parker, S. D.; Rogers, N. A. J., *Tetrahedron*, **1984**, *40*, 3749; b) Eckersley, T. J.; Rogers, N. A. J., *Tetrahedron*, **1984**, *40*, 3759; c) Koppes, M. J. C. M.; Cerfontain, H., *Recl. Trav. Chim. Pays-Bas*, **1988**, *107*, 549.

54 The [1,3]-acyl shift only occurs from the short-lived $T_2$ state of prevalent n,π* character for β,γ-unsaturated ketones possessing a lowest lying $T_1$ (π, π*) state. For more detail, refer to: Ref. 52b.

55 a) Schexnayder, M. A.; Engel, P. S., *Tetrahedron Lett.*, **1975**, 1153; b) Dalton, J. C.; Shen, M.; Snyder, J. J., *J. Am. Chem. Soc.*, **1976**, *98*, 5023; c) Schuster, D. I.; Eriksen, J.; Engel, P. S.; Schexnayder, M. A., *J. Am. Chem. Soc.*, **1976**, *98*, 5025; d) Mirbach, M. J.; Henne, A.; Schaffner, K., *J. Am. Chem. Soc.*, **1978**, *100*, 7127; e) Calcaterra, L. T.; Schuster, D. I., *J. Am. Chem. Soc.*, **1981**, *103*, 2460; f) Schuster, D. I.; Calcaterra, L. T., *J. Am. Chem. Soc.*, **1982**, *104*, 6397; g) Sadler, D. E.; Wendler, J.; Olbrich, G.; Schaffner, K., *J. Am. Chem. Soc.*, **1984**, *106*, 2064.

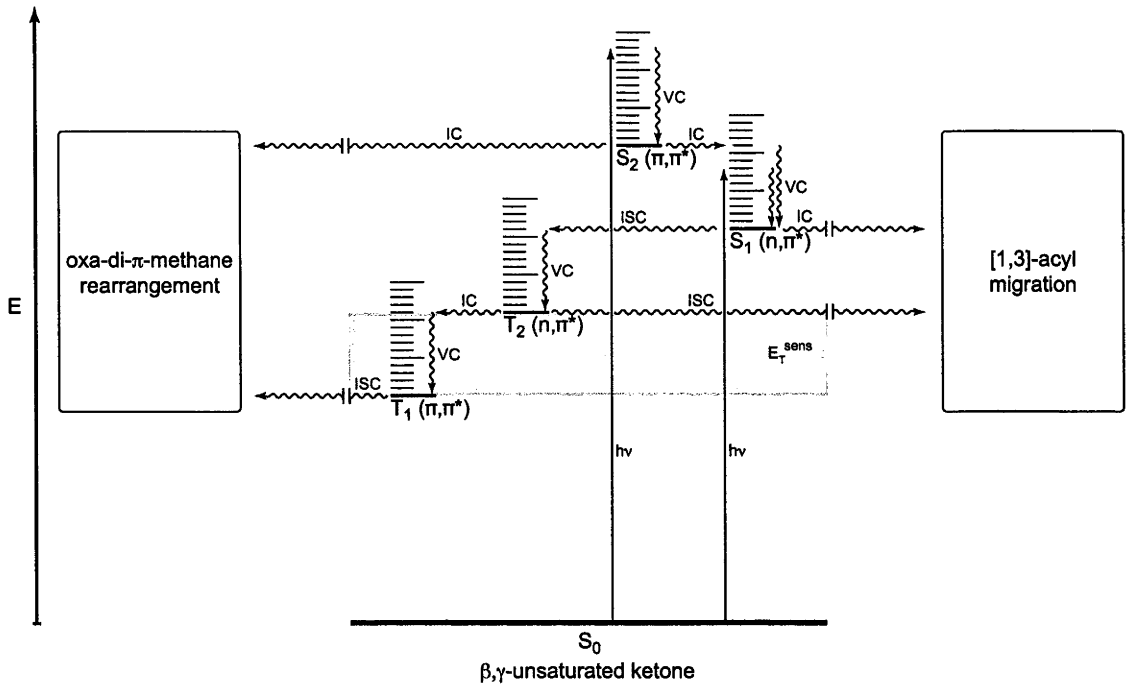
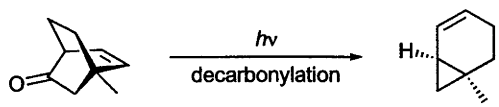



**Figure 1.7:** *Modified Jablonski diagram showing the fates of excited states of a β,γ-unsaturated ketone towards oxa-di-π-methane rearrangement and [1,3]-acyl migration. Optimum range of triplet sensitiser energy ($E_T^{sens}$) for oxa-di-π-methane rearrangement denoted by shading; ISC = intersystem crossing; IC = internal conversion; VC = vertical cascade [adapted from Demuth and Schaffner (1982)].*[48c]

In addition to the oxa-di-π-methane rearrangement and [1,3]-acyl migration reactions, β,γ-unsaturated ketones such as compound **50** that are constrained in a rigid bicyclic framework, have been observed to undergo decarbonylation leading, for example, to compound **53** (Scheme 1.14). Like the above-mentioned reactions, the decarbonylation process is considered to emanate from both triplet sensitised or direct irradiative conditions.

**Scheme 1.14:** *Decarbonylation reaction of β,γ-unsaturated ketone* ***50*** via *triplet and singlet states.*




**50** **53**

## 1.4.2 Mechanisms of photochemical reactions

### *Mechanism of the oxa-di-π-methane rearrangement*

The oxa-di-π-methane rearrangement of, for example, β,γ-unsaturated ketone **50** to the corresponding cyclopropyl ketone **51**, is presumed to arise from the intermediacy of the

biradical species shown in the stepwise mechanism[56] proposed in Figure 1.8. Each biradical intermediate is conformationally restricted by the oligocyclic frameworks within which they are formed, such that no scrambling through rotation of bonds can occur and, *ipso facto*, stereochemistry is not lost at the former α-, β- or γ-carbons of the original β,γ-unsaturated ketone **50**, as it would be in, for example, non-cyclic systems.

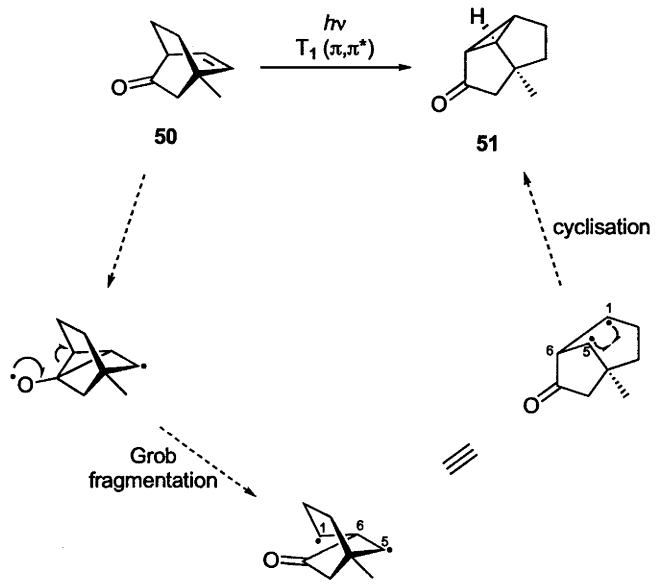



**Figure 1.8:** *Proposed stepwise, biradical mechanism for the oxa-di-π-methane rearrangement.*

It should be noted that each of the proposed processes associated with this mechanistic pathway are, in principle, reversible. By way of example, either of two bonds of the biradical intermediate involved in the Grob fragmentation may cleave, resulting in regeneration of starting material, or in the formation of the second biradical intermediate. Additionally, it should be noted that in some instances, indiscriminate population of the $S_2$ (π,π*) state is considered to result in formation of the oxa-di-π-methane rearrangement product *via* a similar mechanism to that of reactions proceeding from the $T_1$ (π,π*) state,[53c] whilst the $T_2$ (n,π*) or $S_1$ (n,π*) states may lead to the formation of [1,3]-shift and decarbonylation products, as described in the following section.

### *Mechanism of the [1,3]-acyl shift and decarbonylation (α-cleavage) reactions*

Photochemical reactions of cyclic β,γ-unsaturated ketones such as compound **50** involving a formal [1,3]-acyl shift and/or decarbonylation process are generally considered to arise through a common mechanism. The processes are, however, unable to be generalised such that two basic mechanisms of reaction involving either a concerted, symmetry allowed [1,3]-sigmatropic shift or a stepwise radical pair process have been proposed. In essence, the

56 A stepwise mechanism such as proposed here is the most likely mechanism by which the oxa-di-π-methane rearrangements occur. For an extensive discussion of mechanistic proposals, refer to: Ref. 48b.

two mechanisms are intimately linked on a multidimensional reaction surface shown in two dimensions in Figure 1.9 and which may be described in the following manner. Excitation of a β,γ-unsaturated ketone, such as compound **50**, to the carbonyl singlet state, $S_1$ (n,π*), results in distortion of the molecule in the direction of a lengthened α-bond, which is accompanied, to various degrees, by bonding to the γ-carbon. If the distortion is poorly stabilised by γ-bonding the excited state may collapse by internal conversion to the ground state ($S_0$) surface and result in formation of a non-interacting acyl-allyl (caged) radical pair (*i.e.* α-cleavage occurs). Alternatively, if γ-bonding stabilises the distortion, the transition state of a concerted, symmetry-allowed [1,3]-sigmatropic shift forms upon deactivation. Both the non-interacting radical pair and the [1,3]-sigmatropic shift transition state may subsequently collapse *via* their respective stepwise and concerted reaction pathways, to afford either the substrate **50** or the [1,3]-shift product **52**. Given that the [1,3]-sigmatropic shift transition state is of essentially equal stability to the non-interacting radical pair,[57] it can, in principle, also move across the broad, flat maximum of the ground state reaction pathway toward the caged radical pair geometry without a significant change in energy.[58] This description implies that there is little difference between whether the reaction occurs *via* the concerted [1,3]-sigmatropic shift or through the stepwise cleavage/recombination process.[59] In reality, the precise nature of the mechanism depends on the shape and dynamics of movement along the multidimensional $S_1$ (n,π*) and $S_0$ surfaces and the internal conversion between them, all of which are influenced by variations in the reaction conditions, but more significantly, by changes in the structure of the β,γ-unsaturated carbonyl substrate.

Despite these deficiencies just noted, the above-mentioned surface model conveniently explains several general phenomena observed upon direct irradiation of β,γ-unsaturated ketones, including the irreversibility of reaction[60] and decarbonylation. In principle, for that fraction of the first singlet excited state [$S_1$ (n,π*)] deposited upon the ground state surface ($S_0$) in the [1.3]-sigmatropic shift transition state geometry, some dissociation to the caged radical pair may ensue (*vide supra*). Furthermore, with an energy increase to overcome the slight barrier to reaction, escape of the radical pair from the solvent cage may occur, followed by decarbonylation to form bicycles such as **53**. In order for decarbonylation to eventuate, it is

57 The transition state of orbital symmetry forbidden reactions is slightly more stabilised than are the corresponding radical pairs owing to the interaction of "subjacent" orbitals (orbitals of lower energy than the HOMOs of each radical fragment): a) Berson, J. A.; Salem, L., *J. Am. Chem. Soc.*, **1972**, *94*, 8917; b) Berson, J. A., *Acc. Chem. Res.*, **1972**, *5*, 406.

58 However, temperature effects suggest that from the point of initial deposition on the $S_0$ surface, there is essentially no barrier to formation of the [1,3]-shift product: Scharf, H.-D.; Küsters, W., *Chem. Ber.*, **1971**, *104*, 3016.

59 The difference between the α-cleavage/recombination mechanism and a biradical mechanism is regarded as too subtle to experimentally obtain a general solution to: a) Salem, L.; Dauben, W. G.; Turro, N. J., *J. Chim. Phys. Phys.-Chim. Biol.*, **1973**, *70*, 694; b) Salem, L., *J. Am. Chem. Soc.*, **1974**, *96*, 3486.

60 Bicyclo[2.2.2]octenones are regarded as undergoing irreversible reaction by a concerted pathway: Givens, R. S.; Oettle, W. F.; Coffin, R. L.; Carlson, R. G., *J. Am. Chem. Soc.*, **1971**, *93*, 3957.

additionally required that rotation to a geometry that favours alkyl transfer[61] occurs, hence the scope for epimerisation to occur at the original α'-carbon (accompanied by loss of CO).

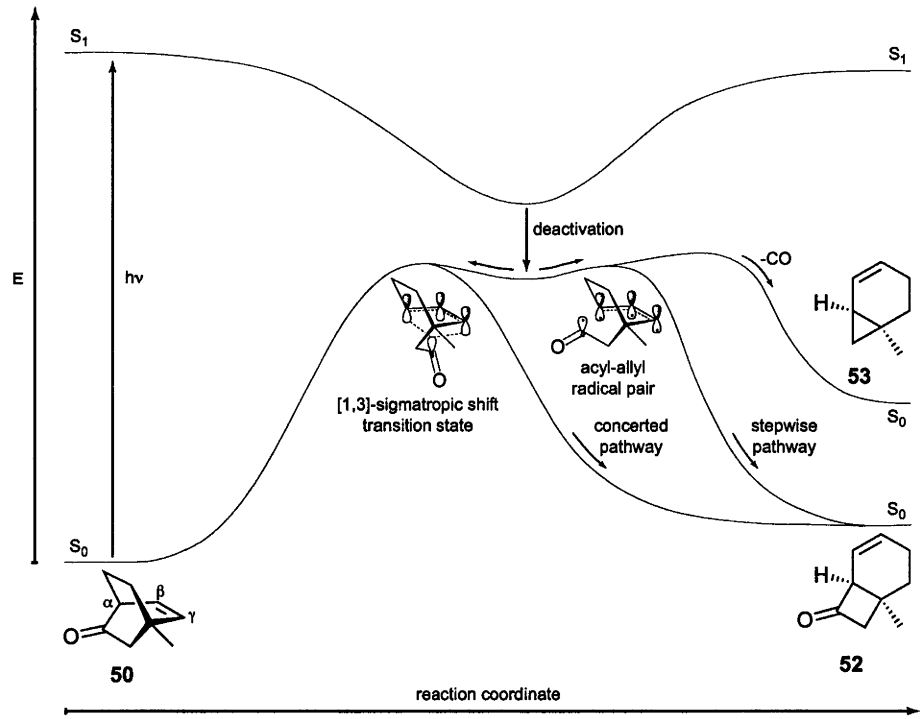



**Figure 1.9:** *Hypothetical singlet potential surfaces [reaction coordinate* vs. *energy (E)] for [1,3]-acyl migration and decarbonylation reactions [adapted from Houk (1976)].*[48a]

It is worth noting with reference to Figure 1.7, that for many β,γ-unsaturated ketones of type **50**, the $S_1$ (n,π*) state undergoes efficient intersystem crossing ($\Phi_{ST} \sim 1$) to the $T_2$ (n,π*) state.[62] The $T_2$ (n,π*) state thus generated may, in turn, either undergo decay to form energetically proximate $T_1$ (π,π*) states or may react to form [1,3]-shift and/or decarbonylation products, **52** and/or **53** respectively. The mechanisms by which the [1,3]-shift and decarbonylation reactions occur are considered to parallel that described (*vide supra*) for the $S_0 \rightarrow S_1$ (n,π*) states. There is, however, some evidence to suggest that the decarbonylation reaction to afford compounds such as **53** may arise from a foiled oxa-di-π-methane rearrangement [which can arise from either the $S_2$ (π,π*) or $T_1$ (π,π*) states, as described in the preceding section], *via* either of the two possible pathways exemplified in Figure 1.10.[48a, 63]

61 H-transfer in the case of β,γ-unsaturated aldehydes.

62 This violates the generally accepted (spin-orbit coupling) rule that $S_1$ (n,π*) → $T_1$ (π,π*) is favoured over $S_1$ (n,π*) → $T_2$ (n,π*), due to the absence of a triplet (π,π*) level between the lowest singlet and the triplet (n,π*) levels: El-Sayed, M. A., *Acc. Chem. Res.*, **1968**, *1*, 8.

63 Note that the intermediates shown do not necessarily correspond to biradical surface minima: the mechanism is essentially concerted and is considered to involve linear and non-linear carbonyl extrusion processes.

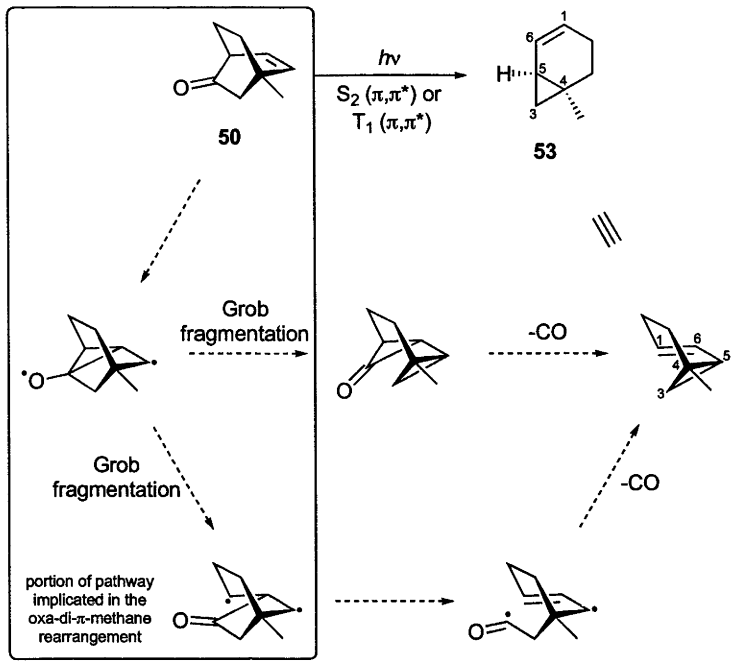



**Figure 1.10:** *Mechanism of decarbonylation arising* via *a foiled oxa-di-π-methane rearrangement.*

There is significant evidence in the literature to indicate that the photochemical [1,3]-acyl shift and decarbonylation processes of any given β,γ-unsaturated ketone may emanate from either or both of the $S_1$ (n,π*) and the $T_2$ (n,π*) states.[64] Furthermore, there are multiple claims in the literature[65] that implicate, but do not substantiate, the $S_1$ (n,π*) state in α-cleavage processes and which are equally compatible with reaction from an excited triplet state.[52] Indeed, this fact suggests that the criteria for identifying the $S_1$ (n,π*) state in ketone photochemistry, in general, need to be re-examined.[48b]

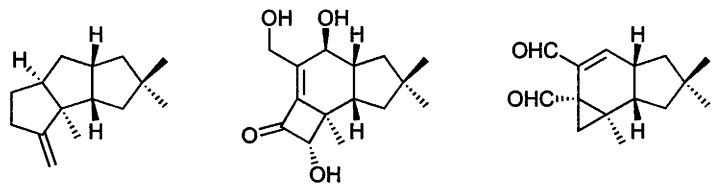
## 1.4.3 Use of photochemistry in the synthesis of natural products

The photochemically-promoted oxa-di-π-methane rearrangement, [1,3]-acyl migration and decarbonylation reactions of β,γ-unsaturated ketones constrained in a rigid bicyclo[2.2.2]octenone system provide access to a variety of *cis*-fused bicyclic systems. Such structures are embodied within the frameworks of a remarkable range of natural products (or their enantiomers) and in particular, those of several sesquiterpenes (Figure 1.11). For example, the 5,5-fused bicyclic system **51** is embodied within the triquinane class of sesquiterpene, of which (+)-hirsutene [(+)-**54**] is a representative member. Equally, compound **51** could be employed to provide access to the corresponding non-natural enantiomer, *ent*-(−)-hirsutene

64 For specific examples, refer to: Ref. 48.

65 a) Yang, N. C.; Feit, E. D., *J. Am. Chem. Soc.*, **1968**, *90*, 504; b) Yang, N. C.; Elliot, S. P.; Kim, B., *J. Am. Chem. Soc.*, **1969**, *91*, 7551; c) Dalton, J. C.; Pond, D. M.; Weiss, D. S.; Lewis, F. D.; Turro, N. J., *J. Am. Chem. Soc.*, **1970**, *92*, 2564; d) Yang, N. C.; Feit, E. D.; Hui, M. H.; Turro, N. J.; Dalton, J. C., *J. Am. Chem. Soc.*, **1970**, *92*, 6974; e) Blank, B.; Henne, A.; Fischer, H., *Helv. Chim. Acta*, **1974**, *57*, 920.

[*ent*-(–)-**54**]. Similarly, members of the protoilludane class of sesquiterpene such as (–)-tsugicoline A [(–)-**55**] incorporate the 6,4-fused ring system **52**, whilst the 6,3-fused bicyclic structure **53** is contained within sesquiterpenes of the marasmane class, such as (+)-isovelleral [(+)-**56**]. It is therefore conceivable that photochemical reaction of an appropriately substituted β,γ-unsaturated ketone (derived, for example, from a cis-1,2-dihydrocatechol *via* Diels-Alder cycloaddition and subsequent manipulation) would allow for divergent and enantioselective accces to the linear triquinane, protoilludane and marasmane classes of sesquiterpene.




*ent*-(–)-**Hirsutene** [*ent*-(–)-**54**] (–)-**Tsugicoline A** [(–)-**55**] (+)-**Isovelleral** [(+)-**56**]

**Figure 1.11:** *Target compounds that embody the ring systems obtained from photochemical reaction of a β,γ-unsaturated ketone such as that constrained within bicyclo[2.2.2]octenone* ***50****.*

## 1.5 Aims of the research described in this Thesis

Based on the foregoing discussions, it would appear that *cis*-1,2-dihydrocatechols of the general type **1** (X = H, Me, Cl, Br, I, $CH{=}CH_2$ *etc.*) offer remarkable potential as starting materials for the synthesis of members of the linear triquinane, protoilludane and marasmane classes of sesquiterpene. The aims of the work described in this Thesis were, therefore, to demonstrate the capacity of the microbial oxidation – Diels-Alder cycloaddition – photochemical reaction sequence to provide synthetic access to the framework of each of the above-mentioned classes of sesquiterpene, and to establish a total synthesis of the non-natural enantiomer of the linear triquinane (+)-hirsutene [(+)-**54**].

Chapter Two describes initial approaches towards *ent*-(–)-hirsutene [*ent*-(–)-**54**], focussing, in particular, on the formation and attempted elaboration of chiral bicyclo[2.2.2]octenes such as compound **57**, to the β,γ-unsaturated ketone **58** required as the substrate for examination of the proposed photochemical rearrangement leading to the linear triquinane framework (Figure 1.12).

Chapter Three delineates the successful enantioselective synthesis of *ent*-(–)-hirsutene [*ent*-(–)-**54**] from *cis*-1,2-dihydrocatechol **1** (X = Me) *via* the Diels-Alder cycloaddition adduct **15** and the photochemically-promoted oxa-di-π-methane rearrangement product **59** (Figure 1.12). Since the enantiomer of *cis*-1,2-dihydrocatechol **1** (X = Me) is also available, the

synthesis described therein constitutes a formal total synthesis of the natural product (+)-hirsutene [(+)-**54**].

Chapter Four details the photochemically-promoted and enantioselective syntheses of the frameworks of cyclobutanone **60** and the epimeric cyclopropyl indenes **61** and **62** associated, respectively, with the protoilludane and marasmane classes of sesquiterpene (Figure 1.12). Elaboration of compound **60** to a key intermediate central to the construction of the protoilludane type sesquiterpene (–)-tsugicoline A [(–)-**55**] is likewise reported.

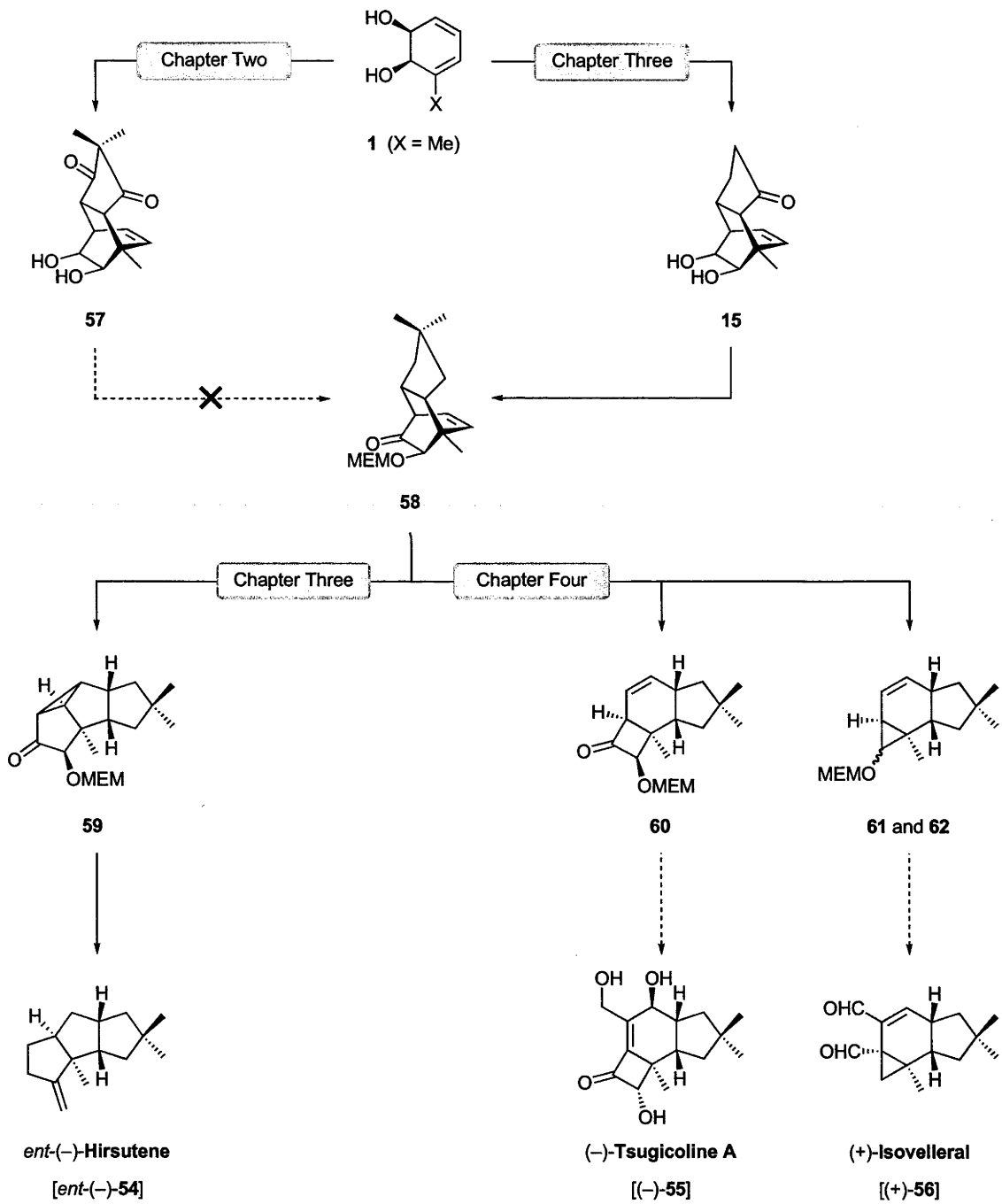



**Figure 1.12:** *Summary of the research presented in Chapters Two to Four.*

Chapter Five outlines the potential for the research described in Chapters Two, Three and Four to be applied to the synthesis of a variety of other sesquiterpene natural products, including those incorporating the angular triquinane and propellane frameworks. The discussion is also extended to the use of modified *cis*-1,2-dihydrocatechols that are customised for specific synthetic targets, and to the generation of synthetically-useful, chiral bicyclo[2.2.2]octenes *via* the application of novel intramolecular Diels-Alder cycloaddition methodologies.

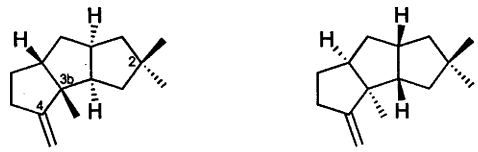
*Chapter Two*

# *Initial Synthetic Approaches to* ent-*(–)-Hirsutene*

## 2.1 Introduction

### 2.1.1 Isolation and structure of (+)-hirsutene

(+)-Hirsutene [(+)-**54**] (Figure 2.1) belongs to the hirsutane class of sesquiterpene fungal metabolites embodying the linear triquinane framework and was isolated by Nozoe *et al.* in 1976[1] from the fermented mycelium of the Basidiomycete *Coriolus consors*.[2]




**(+)-Hirsutene** **[(+)-54]** | ***ent*-(–)-Hirsutene** **[*ent*-(–)-54]**

**Figure 2.1:** *(+)-Hirsutene [(+)-**54**] and the non-natural isomer* ent-*(–)-hirsutene [*ent*-(–)-**54**].*

The structure of this hydrocarbon was established through spectroscopic studies and by comparison with related hirsutanes. Subsequent and numerous synthetic studies served to unequivocally reaffirm the structure. Like other members of this class of sesquiterpene, (+)-hirsutene [(+)-**54**] is composed of three *cis*:*anti*:*cis*-fused pentacyclic rings, in addition to which, it also embodies a *gem*-dimethyl moiety at C(2), an angular methyl at C(3b), and an *exo*-cyclic olefin at C(4). The four contiguous stereocentres associated with the *cis*:*anti*:*cis* ring fusion of the linear triquinane framework are undoubtably the most synthetically challenging

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1 Nozoe, S.; Furukawa, J.; Sankawa, U.; Shibata, S., *Tetrahedron Lett.*, **1976**, 195.

2 *Coriolus consors* (Berk.) Imazeki, is now grouped under the original basionym *Irpex consors* Berkeley: a) Berkeley, M. J., *J. Linn. Soc. London, Bot.*, **1878**, *16*, 51; b) Ko, K. S.; Jung, H. S., *FEMS Microbiol. Lett.*, **1999**, *170*, 181.

feature of hirsutene [(+)-**54**] and this is reflected in the intense synthetic interest afforded this molecule and its non-natural isomer, *viz. ent*-(–)-hirsutene [*ent*-(–)-**54**].

## 2.1.2 Biological properties and proposed biogenesis of (+)-hirsutene

Prior to the isolation of (+)-hirsutene [(+)-**54**], the hydrocarbon was proposed as a hypothetical biogenetic precursor to the linear triquinane class of sesquiterpenes and in particular, to (+)-hirsutic acid C [(+)-**63**],[3] (–)-complicatic acid [(–)-**64**][4] and (–)-coriolin [(–)-**65**], among other, more highly oxygenated, natural products (Figure 2.2).[5] The subsequent isolation of (+)-hirsutene [(+)-**54**], along with humulene (**69**) in the hydrocarbon extract of *C. consors*, lent support to the hypothesis that the hirsutane-type sequiterpenes may arise from a farnesyl precursor.[1] Subsequent biomimetic syntheses of (±)-hirsutene [(±)-**54**] *via* Wagner-

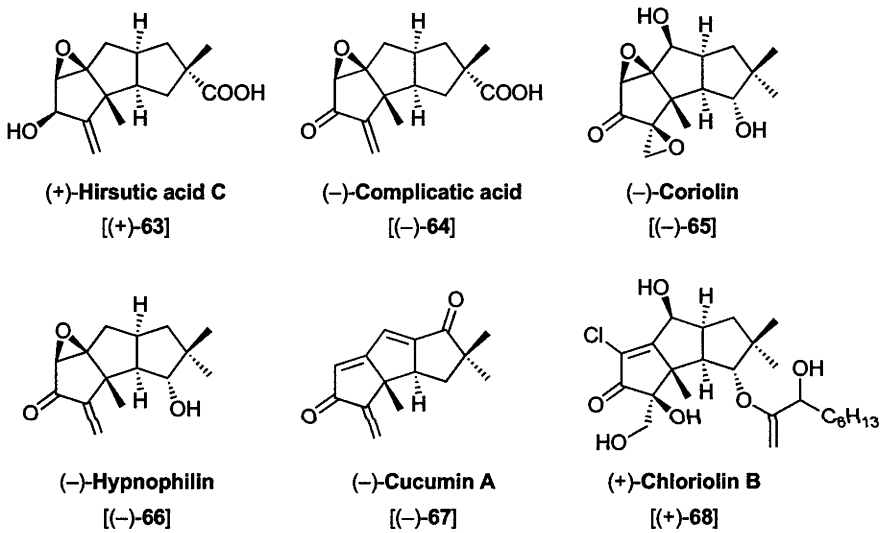



**Figure 2.2:** *A selection of linear triquinane natural products.*

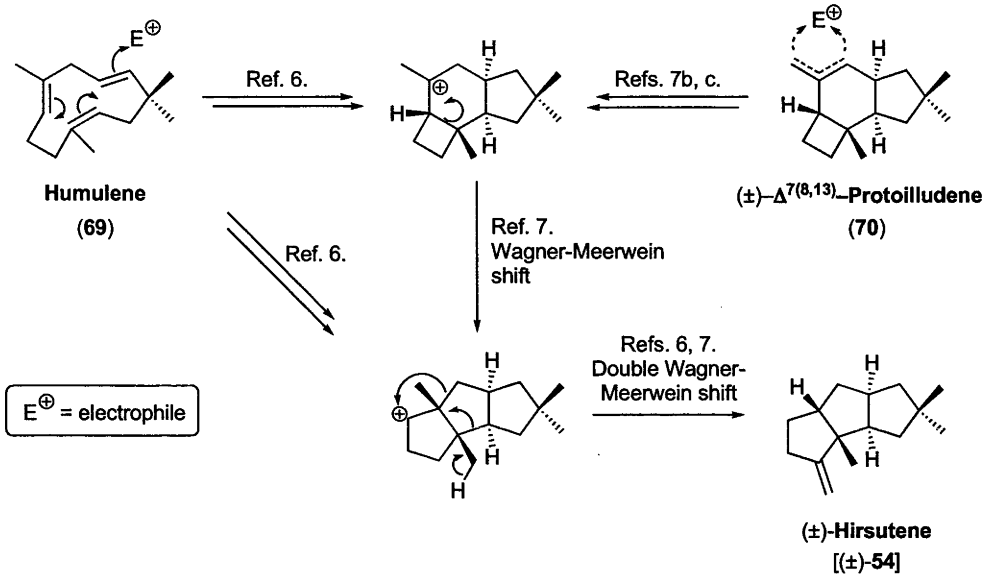
3 (+)-Hirsutic acid C [(+)-**63**] was isolated from what was thought to be the Basidiomycete *Stereum hirsutum* (so named for its hair-like mycelium) thereby providing the name for the hirsutane class of sesquiterpenes: a) Heatley, N. G.; Jennings, M. A.; Florey, H. W., *Br. J. Exp. Pathol.*, **1947**, *28*, 35. Later attempts to reisolate (+)-hirsutic acid C [(+)-**63**, then simplified to "hirsutic acid"] from this culture were unsuccessful: b) Comer, F. W.; McCapra, F.; Qureshi, I. H.; Scott, A. I., *Tetrahedron*, **1967**, *23*, 4761. Subsequently, (+)-hirsutic acid C [(+)-**63**] was isolated from *Stereum complicatum*: c) Mellows, G.; Mantle, P. G.; Feline, T. C.; Williams, D. J., *Phytochemistry*, **1973**, *12*, 2717. No biological activity has been reported.

4 (–)-Complicatic acid [(–)-**64**] was isolated from *Stereum complicatum* and characterised by Mellows *et al.* (Ref. 3c) who postulate that the incompletely characterised compound, hirsutic acid N, isolated from *Stereum hirsutum* {along with (+)-hirsutic acid C [(+)-**63**]}, by Heatley, Jennings and Florey (Ref. 3a) is, in fact, (–)-complicatic acid [(–)-**64**]. The natural product exhibits antibacterial activity.

5 (–)-Coriolin [(–)-**65**] was isolated from cultures of *Coriolus consors* (Basidiomycetes) {the same species from which (+)-hirsutene [(+)-**54**] was isolated}: a) Takeuchi, T.; Iinuma, H.; Iwanaga, J.; Takahashi, S.; Takita, T.; Umezawa, H., *J. Antibiot.*, **1969**, *22*, 215; b) Takahashi, S.; Naganawa, H.; Iinuma, H.; Takita, T.; Maeda, K.; Umezawa, H., *Tetrahedron Lett.*, **1971**, 1955; c) Nakamura, H.; Takita, T.; Umezawa, H.; Kunishima, M.; Nakayama, Y.; Iitaka, Y., *J. Antibiot.*, **1974**, *27*, 301. (–)-Coriolin [(–)-**65**] is purported to exhibit antitumour and antibacterial activities, in addition to which it inhibits growth of *Trichomonas vaginalis* TV1099 and is non-cytotoxic towards murine (mammalian) cell lines.

Meerwein rearrangement processes, from both humulene (**69**)[6] and (±)-$\Delta^{7(8,13)}$-protoilludene (**70**),[7] further implicate the rôle of hirsutene in the biosynthesis of the linear triquinane class of sesquiterpenes (Scheme 2.1).

**Scheme 2.1:** *Biomimetic syntheses of (±)-hirsutene [(±)-54]* via *(proposed) Wagner-Meerwein rearrangement processes.*




Unlike (+)-hirsutene [(+)-**54**], many of the more highly oxygenated natural products belonging to the linear triquinane class of sesquiterpene (Figure 2.2) exhibit significant biological properties.[8] For example, the fungal metabolite (–)-hypnophilin [(–)-**66**] is recognised to possess antitumour activity and shows an ability to inhibit growth of both Gram-positive and Gram-negative bacteria, as well as a range of fungi.[9] Presumably the presence of the Michael acceptor on the A-ring of (–)-hypnophilin [(–)-**66**] is responsible for this biological activity. Highly conjugated fungal metabolites, such as (–)-cucumin A [(–)-**67**] are highly cytotoxic towards leukaemia cells and also exhibit significant antimicrobial activity against diverse bacteria and fungi.[10] (+)-Chloriolin B [(+)-**68**] – which is novel in that it is not only oxygenated but also chlorinated – was found to exhibit marked activity against two human

6 Misumi, S.; Matsushima, H.; Shirahama, H.; Matsumoto, T., *Chem. Lett.*, **1982**, 855.

7 a) Ohfune, Y.; Shirahama, H.; Matsumoto, T., *Tetrahedron Lett.*, **1976**, 2795; b) Hayano, K.; Ohfune, Y.; Shirahama, H.; Matsumoto, T., *Tetrahedron Lett.*, **1978**, 1991; c) Hayano, K.; Ohfune, Y.; Shirahama, H.; Matsumoto, T., *Helv. Chim. Acta*, **1981**, *64*, 1347.

8 Most hirsutanes exhibit weak antibiotic activity, in addition to other, more significant, biological properties.

9 (–)-Hypnophilin [(–)-**66**] was isolated from mycelial cultures of *Pleurotellus hypnophilus* (Berk.) Sacc. (Agaricales): a) Kupka, J.; Anke, T.; Giannetti, B.-M.; Steglich, W., *Arch. Microbiol.*, **1981**, *130*, 223; b) Steglich, W., *Pure Appl. Chem.*, **1981**, *53*, 1233; c) Giannetti, B.-M.; Steffan, B.; Steglich, W.; Kupka, J.; Anke, T., *Tetrahedron*, **1986**, *42*, 3587.

10 (–)-Cucumin A [(–)-**67**] was isolated from cultures of *Macrocystidia cucumis* (Pers. *ex* Fr.) (Agaricales): Hellwig, V.; Dasenbrock, J.; Schumann, S.; Steglich, W.; Leonhardt, K.; Anke, T., *Eur. J. Org. Chem.*, **1998**, 73.

tumour cell lines. The vinylogous α-chloro functionality is postulated to be the pharmacophore responsible for this activity.[11]

In view of the aforementioned biological properties, various members of the hirsutane class of linear triquinanes have some potential as therapeutic agents. The limited availability of such compounds from natural sources has fuelled research into their synthesis. The desire to access such compounds synthetically, and preferentially *via* a single route, has meant that (+)-hirsutene [(+)-**54**] (as the simple biogenetic precursor) has served as a prototypical target for the synthesis of the *cis*:*anti*:*cis*-fused tricyclopentanoid skeleton associated with the hirsutane family of sesquiterpenes.

## 2.2 Previous syntheses of hirsutene

### 2.2.1 Overview

Since the isolation of (+)-hirsutene [(+)-**54**] in 1976 there have been extensive efforts to synthesise the natural product that are described in more than thirty procedures, of which twenty have culminated in total syntheses.[12] Such research efforts have generally focussed on the use

11 (+)-Chloriolin B [(+)-**68**] was isolated from cultures of an unidentified fungus found growing on the Indo-Pacific sponge *Jaspis* aff. *johnstoni*: Cheng, X.-C.; Varoglu, M.; Abrell, L.; Crews, P.; Lobkovsky, E.; Clardy, J., *J. Org. Chem.*, **1994**, *59*, 6344.

12 Selected synthesis reviews of hirsutene (**54**): a) Mehta, G.; Srikrishna, A., *Chem. Rev.*, **1997**, *97*, 671; b) Singh, V.; Thomas, B., *Tetrahedron*, **1998**, *54*, 3647. Total syntheses: c) Ref. 1; d) Ref. 7 (biomimetic); e) Tatsuta, K.; Akimoto, K.; Kinoshita, M., *J. Am. Chem. Soc.*, **1979**, *101*, 6116; f) Hudlicky, T.; Kutchan, T. M.; Wilson, S. R.; Mao, D. T., *J. Am. Chem. Soc.*, **1980**, *102*, 6351 and Hudlicky, T.; Koszyk, F. F.; Kutchan, T. M.; Sheth, J. P., *J. Org. Chem.*, **1980**, *45*, 5020; g) Mehta, G.; Reddy, A. V., *J. Chem. Soc., Chem. Commun.*, **1981**, 756 and Mehta, G.; Murthy, A. N.; Reddy, D. S.; Reddy, A. V., *J. Am. Chem. Soc.*, **1986**, *108*, 3443; h) Ref. 6 (biomimetic); i) Magnus, P.; Quagliato, D. A., *Organometallics*, **1982**, *1*, 1243 and Magnus, P.; Quagliato, D., *J. Org. Chem.*, **1985**, *50*, 1621; j) Wender, P. A.; Howbert, J. J., *Tetrahedron Lett.*, **1982**, *23*, 3983 and Wender, P. A.; Howbert, J. J., *Tetrahedron Lett.*, **1983**, *24*, 5325; k) Ley, S. V.; Murray, P. J., *J. Chem. Soc., Chem. Commun.*, **1982**, 1252 and Ley, S. V.; Murray, P. J.; Palmer, B. D., *Tetrahedron*, **1985**, *41*, 4765; l) Curran, D. P.; Rakiewicz, D. M., *J. Am. Chem. Soc.*, **1985**, *107*, 1448 and Curran, D. P.; Rakiewicz, D. M., *Tetrahedron*, **1985**, *41*, 3943; m) Hua, D. H.; Sinai-Zingde, G.; Venkataraman, S., *J. Am. Chem. Soc.*, **1985**, *107*, 4088 and Hua, D. H.; Venkataraman, S.; Ostrander, R. A.; Sinai, G. Z.; McCann, P. J.; Coulter, M. J.; Xu, M. R., *J. Org. Chem.*, **1988**, *53*, 507 and Hua, D. H., *Adv. Carbanion Chem.*, **1992**, *1*, 249; n) Disanayaka, B. W.; Weedon, A. C., *J. Chem. Soc., Chem. Commun.*, **1985**, 1282 and Disanayaka, B. W.; Weedon, A. C., *J. Org. Chem.*, **1987**, *52*, 2905; o) Cossy, J.; Belotti, D.; Pete, J. P., *Tetrahedron Lett.*, **1987**, *28*, 4547 and Cossy, J.; Belotti, D.; Pete, J. P., *Tetrahedron*, **1990**, *46*, 1859; p) Sternbach, D. D.; Ensinger, C. L., *J. Org. Chem.*, **1990**, *55*, 2725; q) Moriarty, K. J.; Shen, C. C.; Paquette, L. A., *Synlett*, **1990**, 263 and Paquette, L. A.; Moriarty, K. J.; Shen, C. C., *Isr. J. Chem.*, **1991**, *31*, 195; r) Ramig, K.; Kuzemko, M. A.; McNamara, K.; Cohen, T., *J. Org. Chem.*, **1992**, *57*, 1968 and Cohen, T.; McNamara, K.; Kuzemko, M. A.; Ramig, K.; Landi, J. J., Jr.; Dong, Y., *Tetrahedron*, **1993**, *49*, 7931; s) Weinges, K.; Reichert, H.; Huber-Patz, U.; Irngartinger, H., *Liebigs Ann. Chem.*, **1993**, 403; t) Oppolzer, W.; Robyr, C., *Tetrahedron*, **1994**, *50*, 415; u) Singh, V.; Vedantham, P.; Sahu, P. K., *Tetrahedron Lett.*, **2002**, *43*, 519 and Singh, V.; Vedantham, P.; Sahu, P. K., *Tetrahedron*, **2004**, *60*, 8161; v) Lee, H.-Y.; Kim, Y., *J. Am. Chem. Soc.*, **2003**, *125*, 10156. Formal syntheses: w) Greene, A. E., *Tetrahedron Lett.*, **1980**, *21*, 3059; x) Little, R. D.; Muller, G. W., *J. Am. Chem. Soc.*, **1981**, *103*, 2744 and Little, R. D.; Muller, G. W.; Venegas, M. G.; Carroll, G. L.; Bukhari, A.; Patton, L.; Stone, K., *Tetrahedron*, **1981**, *37*, 4371 and Little, R. D.; Higby, R. G.; Moeller, K. D., *J. Org. Chem.*, **1983**, *48*, 3139; y) Dawson, B. A.; Ghosh, A. K.; Jurlina, J. L.; Stothers, J. B., *J. Chem. Soc., Chem. Commun.*, **1983**, 204 and Dawson, B. A.; Ghosh, A.

of efficient and increasingly novel methodologies to synthesise racemic modifications of the *cis*:*anti*:*cis* tricyclopentanoid skeleton associated with the linear triquinane family of sesquiterpenes. Remarkably, only one enantioselective total synthesis of (+)-hirsutene [(+)-**54**] has been achieved,[12m] although others[12ee, 12hh] have claimed formal enantioselective preparations of the linear triquinane. Likewise, only one enantioselective total synthesis of the non-natural isomer *ent*-(–)-hirsutene [*ent*-(–)-**54**] is extant.[12s]

By way of example, both of the aforementioned enantioselective total syntheses are described below, along with several exemplary syntheses of racemic material that are notable for the use of novel cycloaddition and photochemical reaction methodologies.[13]

## 2.2.2 Total syntheses

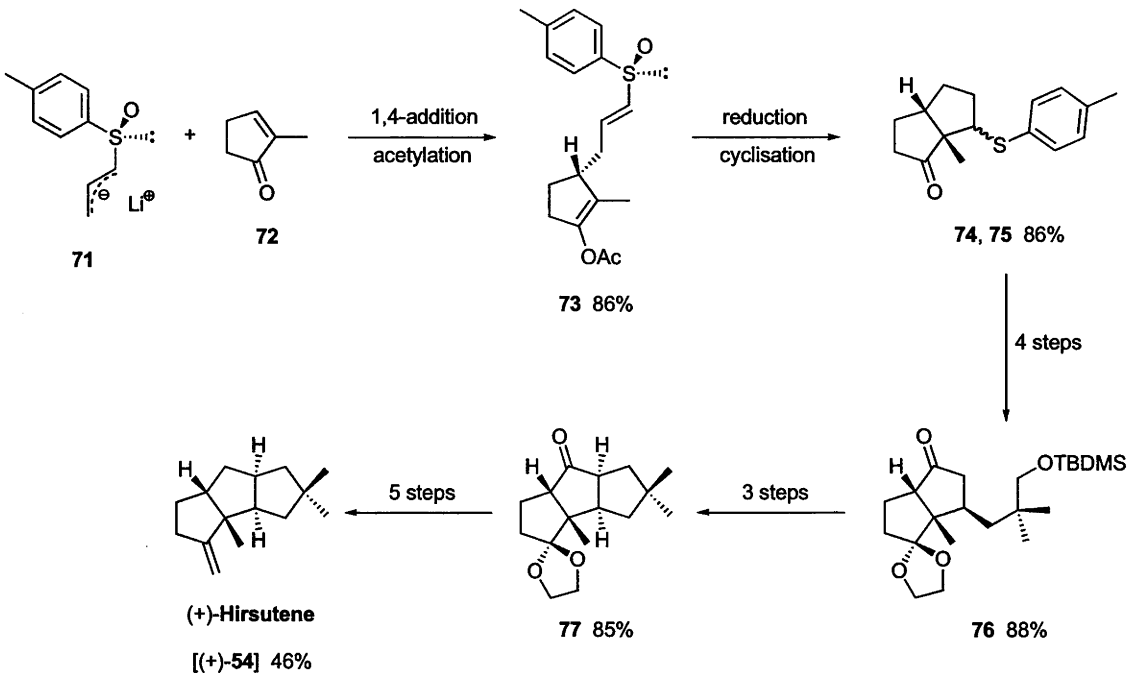
### *Hua's synthesis of (+)-hirsutene (1985)*

The only enantioselective total synthesis of the natural isomer (+)-hirsutene [(+)-**54**] reported to date is that described by Hua *et al.* in 1985 (Scheme 2.2).[12m] This sixteen step synthesis of the natural product employs the chiral sulfinylallyl anion **71** to control successive, stepwise assembly of each ring of the tricyclic framework in an enantioselective fashion. The sequence proceeded in 16% overall yield.

K.; Jurlina, J. L.; Ragauskas, A. J.; Stothers, J. B., *Can. J. Chem.*, **1984**, *62*, 2521; z) Funk, R. L.; Bolton, G. L., *J. Org. Chem.*, **1984**, *49*, 5021 and Funk, R. L.; Bolton, G. L.; Daggett, J. U.; Hansen, M. M.; Horcher, L. H. M., *Tetrahedron*, **1985**, *41*, 3479; aa) Hewson, A. T.; MacPherson, D. T., *J. Chem. Soc., Perkin Trans. 1*, **1985**, 2625; bb) Iyoda, M.; Kushida, T.; Kitami, S.; Oda, M., *J. Chem. Soc., Chem. Commun.*, **1986**, 1049; cc) Franck-Neumann, M.; Miesch, M.; Lacroix, E., *Tetrahedron Lett.*, **1989**, *30*, 3529 and Franck-Neumann, M.; Miesch, M.; Lacroix, E.; Metz, B.; Kern, J. M., *Tetrahedron*, **1992**, *48*, 1911; dd) Sarkar, T. K.; Ghosh, S. K.; Rao, P. S. V. S.; Mamdapur, V. R., *Tetrahedron Lett.*, **1990**, *31*, 3465 and Sarkar, T. K.; Ghosh, S. K.; Rao, P. S. V. S.; Satapathi, T. K.; Mamdapur, V. R., *Tetrahedron*, **1992**, *48*, 6897; ee) Castro, J.; Sorensen, H.; Riera, A.; Morin, C.; Moyano, A.; Pericas, M. A.; Greene, A. E., *J. Am. Chem. Soc.*, **1990**, *112*, 9388; ff) Shono, T.; Kise, N.; Fujimoto, T.; Tominaga, N.; Morita, H., *J. Org. Chem.*, **1992**, *57*, 7175; gg) Toyota, M.; Nishikawa, Y.; Motoki, K.; Yoshida, N.; Fukumoto, K., *Tetrahedron Lett.*, **1993**, *34*, 6099 and Toyota, M.; Nishikawa, Y.; Motoki, K.; Yoshida, N.; Fukumoto, K., *Tetrahedron*, **1993**, *49*, 11189; hh) Inoue, T.; Hosomi, K.; Araki, M.; Nishide, K.; Node, M., *Tetrahedron: Asymmetry*, **1995**, *6*, 31; ii) Rawal, V. H.; Fabré, A.; Iwasa, S., *Tetrahedron Lett.*, **1995**, *36*, 6851; jj) Anger, T.; Graalmann, O.; Schroder, H.; Gerke, R.; Kaiser, U.; Fitjer, L.; Noltemeyer, M., *Tetrahedron*, **1998**, *54*, 10713; kk) Leonard, J.; Bennett, L.; Mahmood, A., *Tetrahedron Lett.*, **1999**, *40*, 3965; ll) Wang, J.-C.; Krische, M. J., *Angew. Chem. Int. Ed.*, **2003**, *42*, 5855.

13 The selection presented here is in no way representative of the scope of the total and/or formal syntheses of hirsutene (**54**), but was chosen (with the exception of the enantioselective syntheses) to reflect syntheses that employ Diels-Alder and photochemical methodologies, akin to the research presented in this thesis. It is worth noting that existing synthetic approaches to the ABC tricyclopentane framework of hirsutene (**54**) may be crudely classified into five categories: i) successive annelation of five-membered rings onto a cyclopentane derivative (*i.e.* A → AB → ABC or B → AB → ABC *etc.*); ii) simultaneous annelation of two rings onto a cyclopentane derivative (*i.e.* A → ABC or B → ABC *etc.*); iii) annelation of two linked cyclopentane derivatives to form a central five-membered ring (*i.e.* AC → ABC); iv) simultaneous formation of all three five-membered rings, and; v) miscellaneous methods that defy simple classification, such as the syntheses of Mehta *et al.* (Ref. 12g), Iyoda and Oda *et al.* (Ref. 12bb), Rawal, Fabré and Iwasa (Ref. 12ii), and Singh, Vedantham and Sahu (Ref. 12u) described here (*vide infra*).

**Scheme 2.2:** *Hua's synthesis of (+)-hirsutene [(+)-54].*



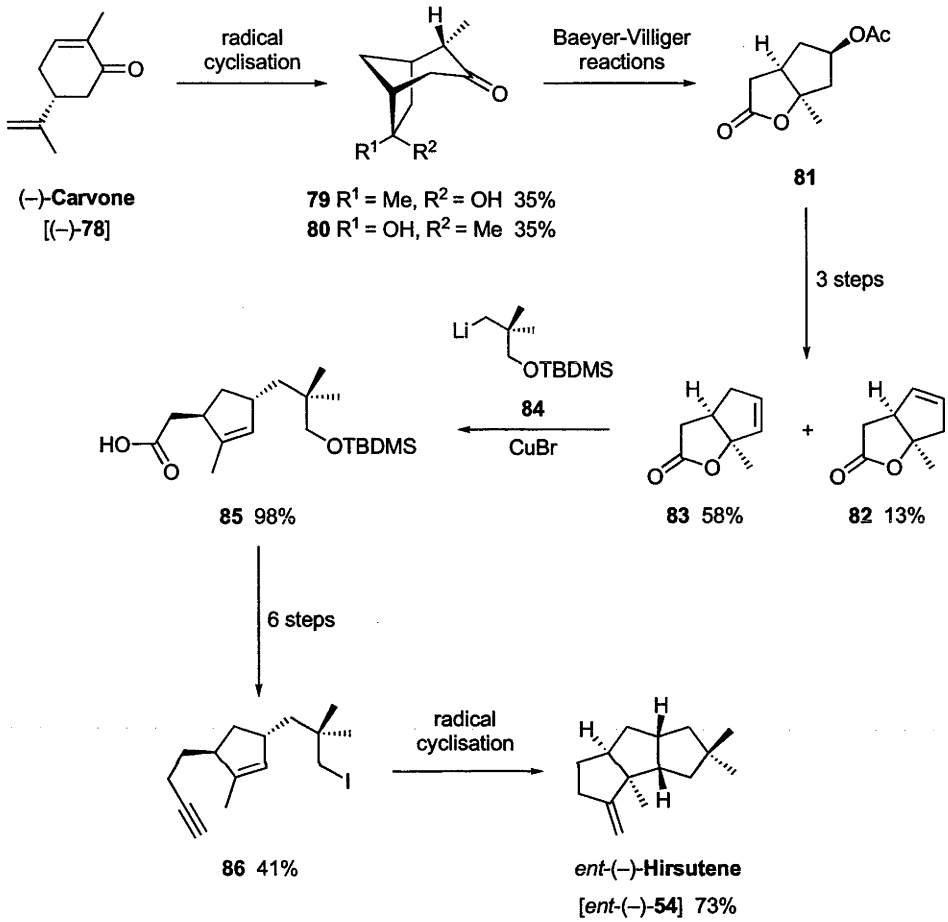

The synthesis commenced upon treatment of (–)-*S*-allyl *p*-tolyl sulfoxide with LDA. Reaction of the ensuing chiral sulfinylallyl anion **71** with 2-methyl-2-cyclopentenone (**72**), followed by *O*-acetylation, furnished the 1,4-adduct **73** enantioselectively and in 86% yield. Having served its purpose in directing the stereoselectivity of the reaction, the chiral sulfoxide was reduced to the corresponding vinylic sulfide that subsequently underwent cyclisation with the enol acetate moiety in the presence of titanium tetrachloride to afford the epimeric sulfides **74** (17%) and **75** (69%). Compounds **74** and **75** were committed to a series of standard functional group manipulations, including dehydrosulfenylation and allylic oxidation, before subjecting the resulting α,β-enone to organocupration so as to yield the *exo*-adduct **76** (88%) which was contaminated with small amounts (5%) of the corresponding *endo*-adduct. The *exo*-adduct **76** was cyclised to the tricyclic ketone **77** (85%) after desilylation and tosylation of the pendant hydroxyl moiety. Ionic deoxygenation of the ketone **77**, followed by deprotection, afforded the norketone which was smoothly methylenated to produce (+)-hirsutene [(+)-**54**] in 46% yield over these final five steps.

### *Weinges' synthesis of* ent-*(–)-hirsutene (1992)*

The only enantioselective total synthesis of non-natural, or *ent*-(–)-hirsutene [*ent*-(–)-**54**] to have been reported to date is that performed by Weinges *et al.*[12s] Their convergent twelve-step synthesis (Scheme 2.3) starts from the naturally abundant (–)-carvone [(–)-**78**] and involves initial construction of the central or B-ring of the target molecule, to which two side-chains were subsequently appended. These pendant side-chains were then

simultaneously coupled to form the A- and C-rings *via* a tandem radical cyclisation strategy, first developed by Curran,[121] thus furnishing *ent*-(–)-hirsutene [*ent*-(–)-**54**].

**Scheme 2.3:** *Weinges' synthesis of* ent-*(–)-hirsutene [*ent-*(–)-**54**].*



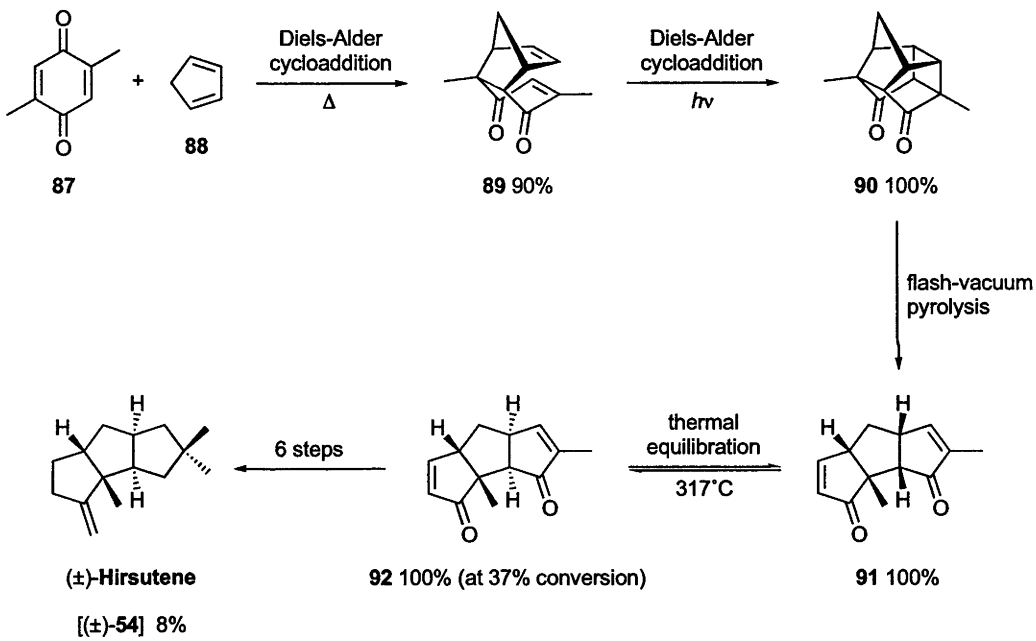

The synthesis commenced with a mercuric acetate-promoted radical cyclisation of (–)-carvone (**78**) to afford a 1:1 and chromatographically-separable mixture of the diastereoisomeric ketones **79** and **80**. Upon treatment with *meta*-chloroperbenzoic acid, ketone **79** smoothly underwent Baeyer-Villiger reaction to afford a seven membered lactone that subsequently rearranged to afford its more stable five-membered counterpart. Oxidation of the newly released secondary alcohol, followed by a further Baeyer-Villiger reaction, furnished lactone **81** in 30% yield from (–)-carvone (**78**). Lactone **81** was converted, through a series of standard functional group interconversions, into the cyclopentenes **82** (13% from **81**) and **83** (58% from **81**), the latter being an intermediate in Curran's synthesis[121] of (±)-hirsutene [(±)-**54**]. Upon organocupration with the reagent derived from reaction of **84** and CuBr, compound **83** afforded the $S_N^1$ product **85** in 98% yield. Compound **85** was subsequently subjected to several functional group interconversions before installing the alkynyl moiety, and then converting the pendant hydroxyl moiety of the saturated side chain into iodide **86** which was obtained in 41% overall yield. Iodide **86** embodies the stereochemistry necessary for formation of the *cis*:*anti*:*cis*

triquinane framework of target *ent*-(–)-**54** by virtue of the stereochemistry of the substrate, (–)-carvone [(–)-**78**]. Upon treatment with tri-*n*-butyltin hydride, the iodide **86** underwent intramolecular tandem 5-*exo*-*trig* and 5-*exo*-*dig* radical cyclisation reactions to afford *ent*-(–)-hirsutene [*ent*-(–)-**54**] [in 73% yield from **86** and in 4% overall yield].

### *Mehta's synthesis of (±)-hirsutene (1985)*

In 1985 Mehta *et al.* reported a total synthesis of (±)-hirsutene [(±)-**54**] involving a novel, stepwise, photo-thermal metathetic sequence using methodology generally applicable to the synthesis of other linearly fused *cis*:*anti*:*cis* triquinane frameworks.[12g] The target compound was obtained in ten steps and 7% overall yield (Scheme 2.4).

**Scheme 2.4:** *Mehta's synthesis of (±)-hirsutene [(±)-54].*




Thus, following procedures developed by Cookson *et al.*,[14] a thermally-promoted Diels-Alder [4 + 2]-cycloaddition reaction between 2,5-dimethyl-*p*-benzoquinone (**87**) and cyclopentadiene (**88**) furnished *endo*-adduct **89** which, upon irradiation, underwent [2 + 2]-cycloaddition to form the caged adduct **90** in 90% yield over two steps. Flash vacuum pyrolysis of compound **90** effected quantitative formation of the linearly fused *cis*:*syn*:*cis* tricyclopentanoid framework **91**. Thermal equilibration at 317°C partially isomerised the *cis*:*syn*:*cis* skeleton into the more thermodynamically stable *cis*:*anti*:*cis* tricyclopentanoid framework **92** in near quantitative yield (at 37% conversion). Thus, by employing only heat and light it was possible to rapidly access the required triquinane framework. Subsequent

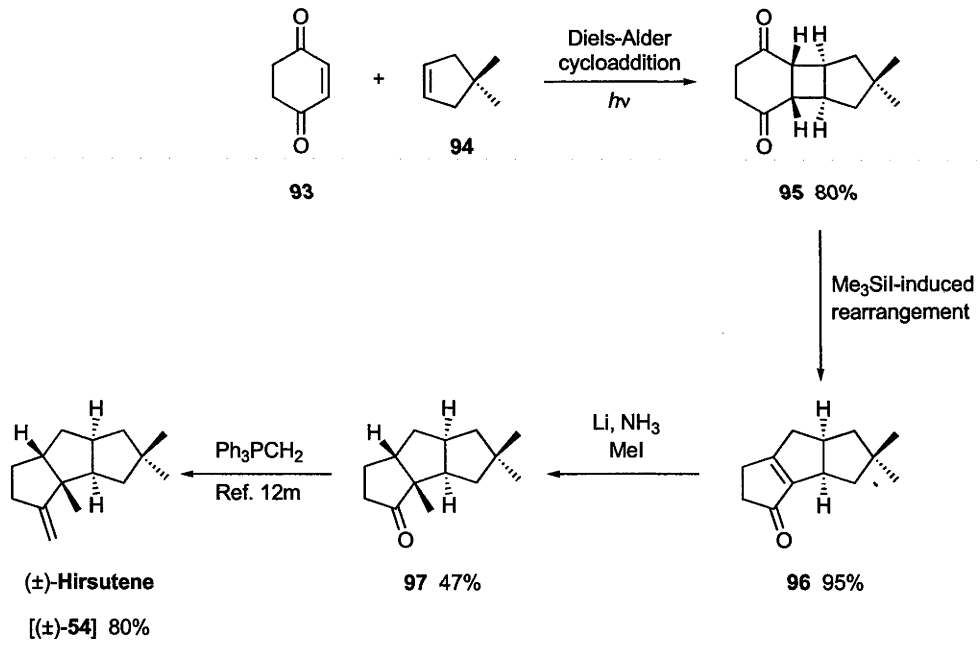
14 Cookson, R. C.; Crundwell, E.; Hill, R. R.; Hudec, J., *J. Chem. Soc.*, **1964**, 3062.

hydrogenation, alkylation, olefination and deoxygenation steps afforded (±)-hirsutene [(±)-**54**] in 8% yield over six steps.

### *Iyoda and Oda's synthesis of (±)-hirsutene (1986)*

Remarkable brevity is shown in the four-step synthesis of (±)-hirsutene [(±)-**54**] published by Iyoda and Oda *et al.* in 1986 (Scheme 2.5).[12bb] This expedient synthesis expands on a related concept first exploited by Tatsuta, Akimoto and Kinoshita in their 1979 synthesis of (±)-hirsutene [(±)-**54**], for which the key step involved rearrangement of a *cis*:*anti*:*cis* fused 6:4:5-tricycle (produced by the de Mayo reaction) to a *cis*:*anti*:*cis* tricyclopentanoid framework.[12e] Paquette, Moriarty and Shen later exploited an analogous stereocontrolled 1,2-Wagner-Meerwein shift within a *cis*:*anti*:*cis* fused 4:6:5-tricycle (produced by sequential thermal and photochemical Diels-Alder cycloaddition reactions) to similar effect in their 1990 synthesis of (±)-hirsutene [(±)-**54**].[12q]

**Scheme 2.5:** *Iyoda and Oda's synthesis of (±)-hirsutene [(±)-54].*

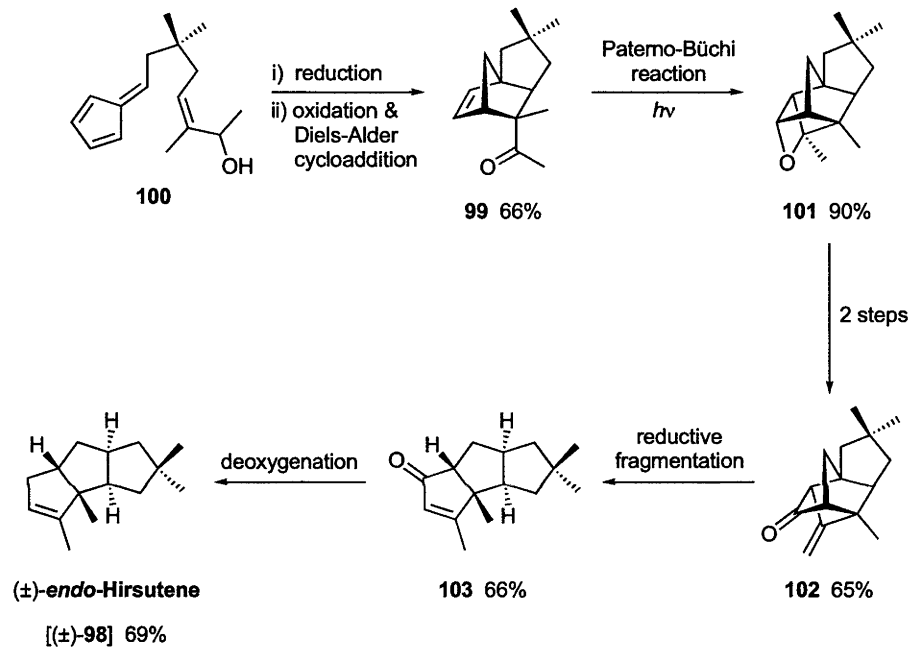



Photochemically-promoted [2 + 2]-cycloaddition of cyclohex-2-ene-1,4-dione (**93**) to 4,4-dimethylcyclopentene (**94**) afforded the *cis*:*anti*:*cis* adduct **95** in 80% yield. Iodotrimethylsilane-induced deoxygenative rearrangement of compound **95** furnished the enone **96** (95%) which, upon stereoselective dissolving metal reduction with lithium in ammonia and trapping of the enolate with methyl iodide, produced the norketone **97** bearing the *cis*:*anti*:*cis* tricyclopentanoid framework in 47% yield. The synthesis of norketone **97** constitutes a formal synthesis of (±)-hirsutene [(±)-**54**] (in 34% overall yield) by analogy with the final methylenation step reported in several previous total syntheses.[1, 12m]

***Rawal, Fabré and Iwasa's synthesis of* (±)-endo-*hirsutene* (1995)**

The formal synthesis of (±)-hirsutene [(±)-**54**] reported by Rawal, Fabré and Iwasa in 1995,[12ii] like the synthesis described by Mehta *et al.* (Scheme 2.4),[12g] incorporates novel Diels-Alder and photochemical methodologies into an ostensibly linear synthesis to construct, in this case, *endo*-(±)-hirsutene [(±)-**98**] in 18% yield over seven steps (Scheme 2.6). By virtue of a previously reported synthesis of (±)-hirsutene [(±)-**54**] from the *endo*-isomer, the formation of compound [(±)-**98**] constitutes a formal preparation of the natural product.[7]

**Scheme 2.6:** *Rawal, Fabré and Iwasa's synthesis of* (±)-endo-*hirsutene [(±)-98].*

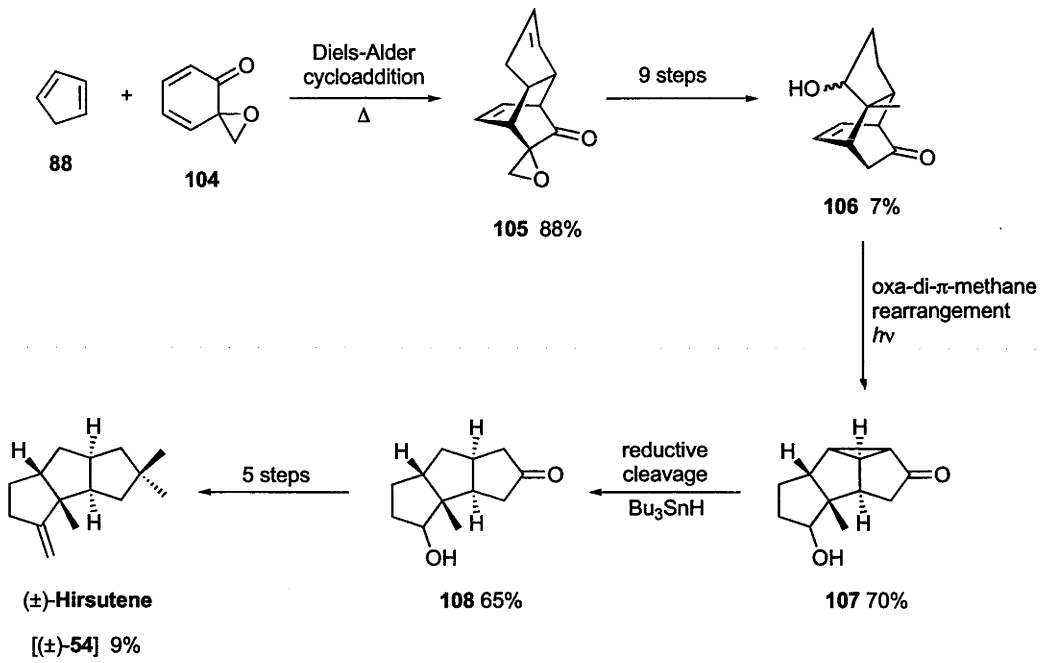



Using methodology modified from that originally developed by Sternbach and Ensinger[12p] in their total synthesis of the same target {(±)-hirsutene [(±)-**54**]}, the Diels-Alder adduct **99** was synthesised from fulvene **100**. Thus, reduction of fulvene **100** to afford the corresponding cyclopentadiene, followed by oxidation of the pendant allylic alcohol to the corresponding enone under Oppenauer conditions, effected smooth formation of the [4 + 2]-cycloaddition product **99** in 66% yield. Irradiation of compound **99** smoothly effected Paterno-Büchi reaction to form the oxetane **101** (90%), which was then cleaved to the homoallylic alcohol and subsequently oxidised to the β,γ-unsaturated ketone **102**. Reductive fragmentation of the strained ketone **102**, using lithium di-*tert*-butylbiphenylide, furnished the enone **103** embodying the *cis*:*anti*:*cis* tricyclopentanoid framework in 39% yield over four steps. Enone **103** was subsequently deoxygenated in a single step upon treatment with sodium borohydride in a solution of trifluoroacetic acid, dichloromethane and acetonitrile to form (±)-*endo*-hirsutene [(±)-**98**] in 69% yield.

***Singh, Vedantham and Sahu's synthesis of (±)-hirsutene (2002)***

The synthesis of (±)-hirsutene [(±)-**54**] reported by Singh, Vedantham and Sahu in 2002[12u] exploits a concept first enunciated by Demuth and Schaffner twenty years earlier in which a stereoselective and photochemically-induced oxa-di-π-methane rearrangement of an appropriate β,γ-unsaturated ketone produced the corresponding *cis*:*anti*:*cis* fused tricyclopentanoid framework of the target triquinane.[15] This synthesis of (±)-hirsutene [(±)-**54**] furnished the natural product in less than 1% yield over sixteen steps (Scheme 2.7) and bears close resemblance to the enantioselective approach associated with the research described in this Thesis.

**Scheme 2.7:** *Singh, Vedantham and Sahu's synthesis of (±)-hirsutene [(±)-54].*




Thus, reaction of cyclopentadiene (**88**) with the diene **104**, derived from oxidative cyclisation of saligenin, furnished the Diels-Alder cycloaddition product **105** in 88% yield. The tricyclic ketoepoxide **105** was subjected to a series of standard functional group interconversions to remove the oxirane ring and selectively install the hydroxyl and methyl moieties present on the cyclopentane ring of the β,γ-unsaturated ketone **106** which was obtained in 7% yield over nine steps. Triplet sensitised photochemically-induced oxa-di-π-methane rearrangement of this β,γ-unsaturated ketone **106** stereoselectively furnished the tetracyclic intermediate **107** in 70% yield, the peripheral cyclopropane bond of which underwent *O*-stannyl ketyl-promoted ring scission to form the tricyclopentanoid framework **108** in 65% yield. The

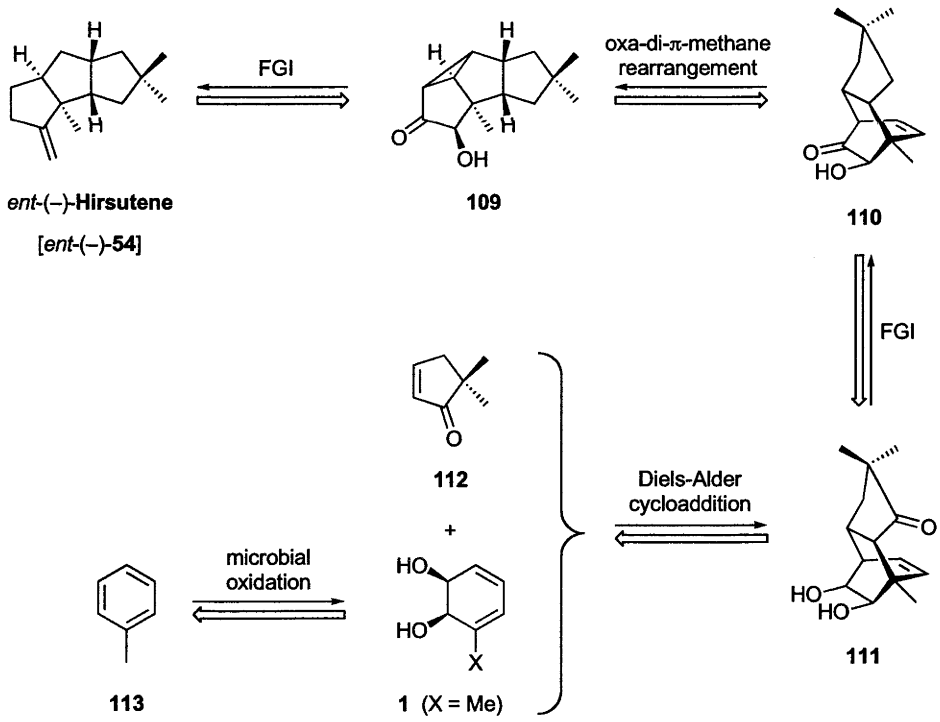
15 Demuth, M.; Schaffner, K., *Angew. Chem., Int. Ed. Engl.*, **1982**, *21*, 820.

now redundant carbonyl functionality was converted into a *gem*-dimethyl moiety over three steps, whilst several additional, but standard, functional group interconversions were employed to finally secure (±)-hirsutene [(±)-**54**] in 9% yield.

## 2.3 Retrosynthetic analysis and strategy

Given that the *cis*:*anti*:*cis*-stereochemistry of linear triquinane natural products such as (+)-hirsutene [(+)-**54**] is thermodynamically favoured, the control of ring junction stereochemistry presents only a modest challenge to the synthetic chemist and instead syntheses have generally focussed on the development of rapid and increasingly novel, yet specific, cyclopentannulation protocols. Relatively little effort has been made, however, to develop generally applicable enantioselective syntheses of such triquinanes. The approach to *ent*-(–)-hirsutene [*ent*-(–)-**54**] described herein redresses this issue and utilises chemoenzymatic, Diels-Alder cycloaddition and photochemically-promoted rearrangement steps as key features of the synthesis, as described in the retrosynthetic analysis shown below (Scheme 2.8).

**Scheme 2.8:** *Retrosynthetic analysis of* ent-*(–)-hirsutene [*ent-*(–)-**54**].




Thus, it was anticipated that *ent*-(–)-hirsutene [*ent*-(–)-**54**] could be accessed from the tetracycle **109** through a series of standard functional group interconversions including cleavage of the cyclopropyl bond peripheral to the tricyclopentanoid framework. Tetracycle **109** is the projected product from oxa-di-π-methane rearrangement of the β,γ-unsaturated ketone **110**. In the synthetic direction, subjection of compound **110** to triplet sensitised photochemical reaction

conditions should result in the stereoselective formation of the requisite tetracycle **109** that embodies the tricyclopentanoid framework of the target molecule. It was envisaged that the oxa-di-π-methane rearrangement precursor **110** could be assembled from compound **111** through another series of functional group interconversions. The synthetic origin of compound **111** may be traced to precursors **1** (X = Me) and **112** through a Diels-Alder disconnection. Drawing on previous experience within the Banwell Group (as discussed in Chapter One), it is well established that *cis*-1,2-dihydrocatechols (and their derivatives) readily participate, as the 4π component, in Diels-Alder cycloaddition reactions with suitably activated dienophiles such as the cyclopentenone **112**. The *cis*-1,2-dihydrocatechol **1** (X = Me) was employed as the 4π addend for its ability to engage in diastereofacially selective cycloaddition reactions and because of its ready availability in enantiopure and preparatively useful quantity from toluene (**113**).

It is anticipated that the methyl group of toluene (**113**) will serve a three-fold purpose in directing the selectivity required at each of the key microbial oxidation, Diels-Alder cycloaddition and photochemically-promoted rearrangement steps described in the retrosynthetic analysis. Based on the results of previous studies, detailed in Chapter One, it has been established that the methyl group will not only direct the position of *cis*-1,2-dihydroxylation during the microbial oxidation step, but also control the regioselectivity conferred on the Diels-Alder cycloaddition reaction. Furthermore, the methyl group should dictate (by virtue of steric demand) which of the hydroxyl moieties of the original *cis*-1,2-dihydrocatechol is oxidised to form the β,γ-unsaturated ketone **110** necessary for the photochemically-promoted oxa-di-π-methane rearrangement. Having served its purpose in conferring selectivity on the synthesis in this manner, the methyl group of toluene (**113**) will eventually form the angular methyl moiety situated at C(3b) of *ent*-(–)-hirsutene [(–)-**54**].

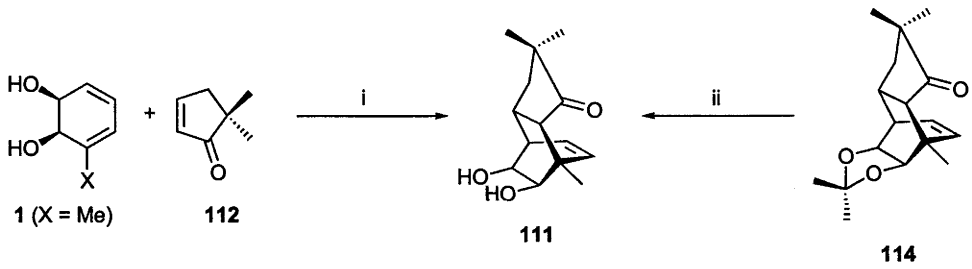
## 2.4 Towards the synthesis of *ent*-(–)-hirsutene

### 2.4.1 Synthesis of Diels-Alder adducts

The general retrosynthetic strategy described in Scheme 2.8 (above) is predicated upon the successful union of the *cis*-1,2-dihydrocatechol **1** (X = Me), as a diene, with an appropriate cyclopentyl dienophile to afford the corresponding Diels-Alder cycloaddition product **111**, necessary for elaboration to the key intermediate acyloin **110**. It was considered that since this step is highly convergent, it would be prudent to install as much of the functionality required for the key intermediate on either of the diene or dienophile prior to performing the cycloaddition reaction itself.

To this end, the *gem*-dimethylated dienophile **112** was synthesised from dimethyl ketene dimer and allyl alcohol using established methodology.[16] It was anticipated that this dienophile would react with the diene **1** (X = Me) efficiently and in a *syn*-selective manner, in accordance with the related Diels-Alder cycloaddition reactions performed by Stewart.[17] However, when reacted with *cis*-1,2-dihydrocatechol **1** (X = Me) in dichloromethane over 24 h at ambient temperature under high-pressure (19 kbar)-promoted reaction conditions, the Diels-Alder adduct **111** was obtained in only 2% yield (at 49% conversion) (Scheme 2.9). In addition to unreacted *cis*-1,2-dihydrocatechol **1** (X = Me), considerable quantities of the *o*- and *m*-cresols, produced by dehydration and concomitant aromatisation of the diol **1** (X = Me), were observed. It is worth noting that the Diels-Alder cycloaddition product **111** was also synthesised *via* another, more preparatively useful route in order to confirm its structure: the acetonide **114** (refer to Chapter 3) was deprotected to afford the corresponding diol (in 87% yield at 97% conversion) and found to be identical, in all respects, with material obtained *via* the more direct route.

**Scheme 2.9:** *Synthesis of Diels-Alder adduct **111**.*




*Reagents and conditions*: i) 19 kbar, $CH_2Cl_2$, ambient temp. 24 h; ii) HCl (1.0 mol.$L^{-1}$ solution in THF/water, 1:1), ambient temp. 20 h.

The most significant features in the $^1$H NMR spectrum of cycloaddition product **111** (Figure 2.3) were the resonances associated with the newly installed olefin which appear as a triplet and doublet at δ 6.01 (*J* 7.5 Hz) and 5.87 (*J* 8.5 Hz) respectively. In addition, the two oxymethine protons appear as a multiplet at δ 3.79 – 3.76 and as a doublet of doublets at δ 3.26 (*J* 9.0 and 5.0 Hz). The one-proton multiplet in the region δ 2.77 – 2.74 is a characteristic feature associated with the $^1$H NMR spectra of many such structures described herein and is assigned to the bridgehead methyne proton. Likewise, the one-proton doublet centred at δ 2.75 (*J* 11.0 Hz; partly overlapping with the above resonance) and the multiplet at δ 3.04 – 2.98, are

16 Kopecky, K. R.; Levine, C., *Can. J. Chem.*, **1981**, *59*, 3273. Tetramethylcyclobutane-1,3-dione was cracked to afford dimethyl ketene, which was reacted with the sodium alkoxide of allyl alcohol. The ester, thus formed, subsequently underwent Claisen rearrangement to afford 2,2-dimethyl-4-pentenoic acid, the acid chloride of which was cyclised in the presence of aluminium trichloride, to furnish 5,5-dimethyl-2-cyclopentenone (**112**).

17 Stewart, S. G., *PhD Thesis*, Australian National University, **2001**.

also diagnostic features of the $^{1}H$ NMR spectra of such structures and may be ascribed to the ring-junction methine protons. The $^{13}C$ NMR spectrum of compound **111** displays the expected fourteen carbon resonances, while the presence of strong bands at 3401 and 1732 $cm^{-1}$ in the IR spectrum confirm the presence of both the diol moiety and the carbonyl functionality, respectively, thus implying union of diene and dienophile. This was further evidenced by the presence of a molecular ion at *m/z* 236 in the EI mass spectrum, for which an accurate mass measurement, in conjunction with microanalytical data, established the molecular formula as $C_{14}H_{20}O_3$. The stereochemistry of the product was determined through use of single crystal X-ray analysis which showed (Figure 2.4) the cyclopentanone ring to be both *endo*-disposed to that portion of the molecule derived from the diene, while also *syn*-related to the diol moiety. Additionally, the Diels-Alder adduct **111** was observed to contain the bridgehead methyl substituent and carbonyl moiety in an *ortho*-relationship.

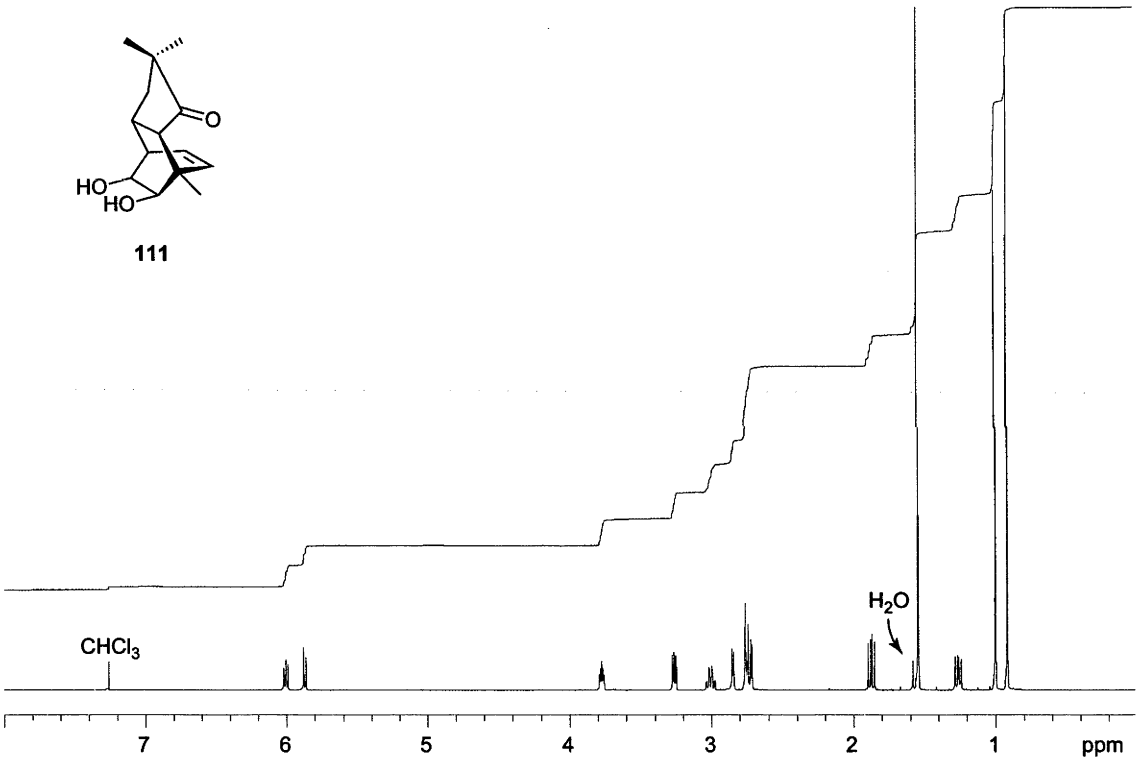


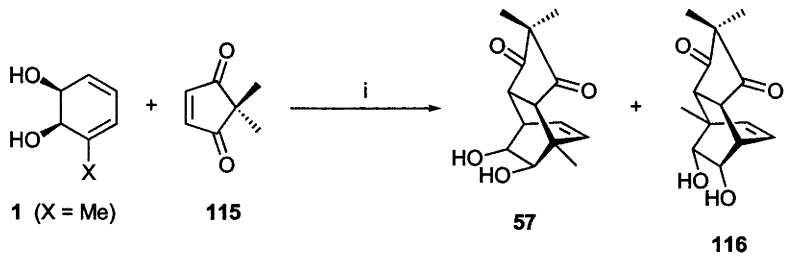

**Figure 2.3:** *500 MHz $^{1}H$ NMR spectrum of Diels-Alder adduct* ***111*** *in $CDCl_3$.*

The low yield of the Diels-Alder cycloaddition product **111** almost certainly arises from the steric demand of the dienophile, and in particular, the *gem*-dimethyl moiety, offsetting the activation provided by the single carbonyl moiety.[18] It was considered that the introduction of a second carbonyl moiety would increase the activation sufficiently as to overcome this steric hindrance and, thus, the low yield, while adding no extra steps to the synthesis.

18 Interestingly the *syn*-isomer remains favoured (*cf.* the less sterically demanding *anti*-isomer): orbital interactions between $\sigma(C-O)$ of the diene and $\pi^*$ of the dienophile are sufficiently attractive to direct the facial selectivity.

To this end, the dienophile 2,2-dimethylcyclopent-4-ene-1,3-dione (**115**) was synthesised according to literature procedures from 2-methylcyclopentane-1,3-dione by methylation at the position α- to both ketones,[19] followed by dehydrogenation with copper (II) bromide to install the olefinic bond.[20] The Diels-Alder cycloaddition reaction was thus performed by reacting compound **115** with *cis*-1,2-dihydrocatechol **1** (X = Me) under high-pressure conditions (as before) to afford two isomeric products: the *syn*-isomer **57** in 73% yield and the *anti*-isomer **116** in 9% yield (Scheme 2.10).

**Scheme 2.10:** *Synthesis of Diels-Alder adducts 57 and 116.*




*Reagents and conditions*: i) 19 kbar, $CH_2Cl_2$, ambient temp., 24 h.

Both isomers exhibited a fragment ion at *m/z* 250 associated with loss of 1,2-dihydroxyethane through a retro-Diels-Alder reaction and for which accurate mass measurements, augmented with microanalytical data, established the molecular formulae, *viz.* $C_{14}H_{18}O_4$. Both the $^1H$ and $^{13}C$ NMR spectra of each isomer, which were fully assigned using a variety of connectivity experiments, exhibit the expected number and chemical shifts of resonances. For example, the most significant features in the $^{13}C$ NMR spectrum of the *syn*-isomer **57** are the resonances associated with the oxymethine carbons of the diol functionality at δ 69.9 and 64.9, as well as signals attributed to the carbonyl carbons of the dione moiety at δ 220.8 and 219.7 which, together, imply union of the original diene and dienophile. Accordingly, the IR spectra of both the *syn*- and *anti*-isomers **57** and **116** feature absorption bands attributed to stretching frequencies of the two non-equivalent carbonyl moieties at 1757, 1718 $cm^{-1}$ and 1757, 1715 $cm^{-1}$, respectively. The relative stereochemistry, including the *endo*-disposed nature of the *syn*-isomer **57**, was revealed by single crystal X-ray crystallographic analysis (Figure 2.4). The stereochemistry of the *endo*-,*anti*-isomer **116** was similarly deduced through a combination of spectral assignment and comparison of the outcome of this reaction with that of related systems.

19 Agosta, W. C.; Smith, A. B., *J. Org. Chem.*, **1970**, *35*, 3856.

20 Kreiser, W.; Wiggermann, A.; Krief, A.; Swinnen, D., *Tetrahedron Lett.*, **1996**, *37*, 7119.

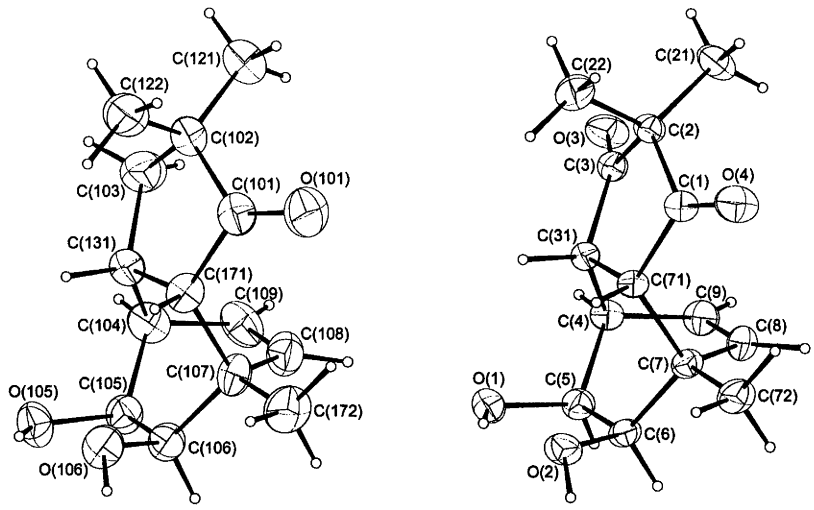



**Figure 2.4:** *Displacement Ellipsoid Plots (50%) derived from single crystal X-ray analyses of Diels-Alder adducts **111*** and ***57***.

## 2.4.2 Attempted deoxygenation of the cyclopentane ring: initial investigations

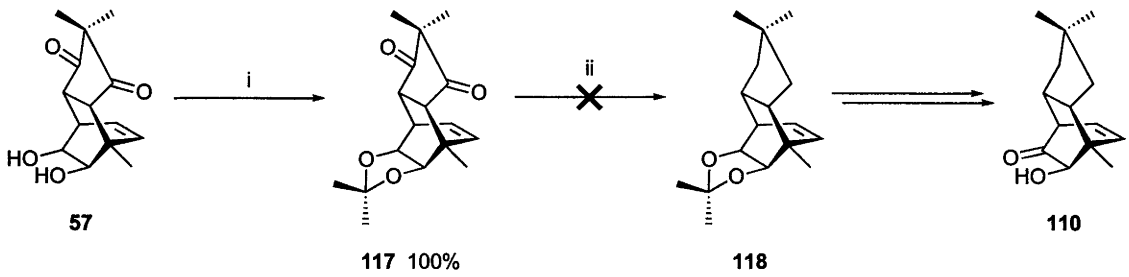
In principle, the Diels-Alder adduct **57** incorporates the carbon skeleton and functionality appropriate for elaboration to the key β,γ-unsaturated ketone intermediate **110** (Scheme 2.8). The most notable of the functional group interconversions required to achieve such ends would involve deoxygenation of the two now-redundant 1,3-related carbonyl moieties present on the cyclopentane ring. In order to allow for selective deoxygenation of the cyclopentane ring, it was considered necessary to mask the vicinal diol functionality using a protecting group inert to the conditions required for deoxygenation and which could then (ideally) be removed under specific reaction conditions. To this end, the *syn*-isomer **57** was reacted, according to a standard protocol, with 2,2-dimethoxypropane in the presence of an acid catalyst to form the corresponding acetonide **117** in quantitative yield (Scheme 2.11).

The EI mass spectrum of the acetonide **117** features a molecular ion at *m/z* 290, for which an accurate mass measurement and microanalytical data established the expected elemental composition as $C_{17}H_{22}O_4$, consistent with the increased mass provided by the protecting group. Additionally, a prominent signal characteristic of an acetonide and associated with loss of a methyl radical from the molecular ion was also observed in the EI mass spectrum at *m/z* 275. That protection has occurred is also manifest in the marked absence of any peaks in the IR spectrum at between 3700 – 3100 $cm^{-1}$ attributed to the free (or H-bonded) hydroxyl stretches. Likewise, an absence of resonances in the $^1H$ NMR spectrum, that may be attributed to the hydroxyl protons of the vicinal diol moiety, along with the presence of two additional three-proton singlets at δ 1.48 and 1.33 arising from the methyl groups of the acetonide, indicate that protection has occurred. The $^{13}C$ NMR spectrum also exhibits resonances attributed to the

abovementioned structural features, in addition to which, the prominent signal at δ 112.5 arising from the $sp^3$-hybridised acetal carbon is observed.

Although a variety of reductive procedures such as the Wolff-Kishner[21] (or Huang-Minlon modification[22]) and Clemmensen[23] reactions exist to directly deoxygenate ketones, such methodologies were not successfully employed in the conversion of the substrate **117** into compound **118**, presumably due to the extreme basicity and acidity of the respective reactions (Scheme 2.11). Similarly, attempts to derivatise the carbonyl moieties of compound **117** as the dithioketals were unsuccessful, thereby eliminating the capacity to make use of subsequent desulfurisation methodologies.[24]

**Scheme 2.11:** *Attempted direct deoxygenation of protected Diels-Alder adduct 117.*




*Reagents and conditions*: i) 2,2-DMP, *p*-TsOH.$H_2O$, $CH_2Cl_2$, ambient temp., 24 h; ii) Numerous methods (see text).

## 2.4.3 Formation of diols

It was considered that the capacity for deoxygenation would be greatly increased if the 1,3-dione was converted to the corresponding diol, since this would allow for a variety of derivatives, such as the corresponding pseudohalides, to be synthesised, which should, in principle, be readily deoxygenated. To this end, the dione **117** was reduced under kinetically controlled conditions using di*iso*butylaluminium hydride to afford a single diastereomeric diol **119** in quantitative yield (Scheme 2.12; Table 2.1, Entry 1).

Consistent with the reduction of two carbonyl moieties, the EI mass spectrum of diol **119** features a molecular ion four mass units greater than that of the substrate at *m/z* 294 and for

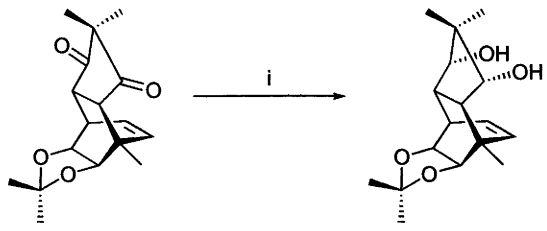
21 For a review, refer to: Todd, D., *Org. React.*, **1948**, *4*, 378.

22 Huang-Minlon, *J. Am. Chem. Soc.*, **1946**, *68*, 2487.

23 For a review, refer to: Vedejs, E., *Org. React.*, **1975**, *22*, 401.

24 For a review on the deoxygenation of carbonyl compounds, including experimental procedures, refer to: Reusch, W., In *Reduction: Techniques and Applications in Organic Synthesis*, Augustine, R. L. (Ed.) Marcel Dekker Inc.: New York, U.S.A., **1968**, p. 171.

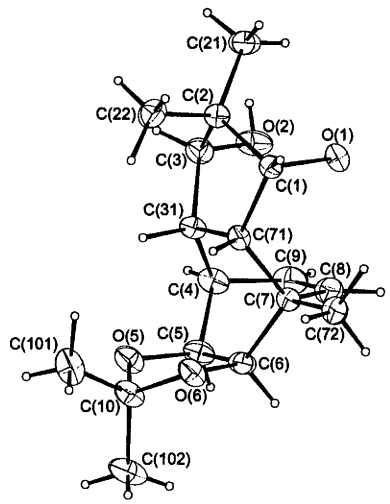
**Scheme 2.12:** *Towards deoxygenation: synthesis of diol **119** under kinetically controlled conditions.*




**117** **119** 100%

*Reagents and conditions*: i) DIBAL-H in hexanes, THF, -78°C to ambient temp., 6 h.

which an accurate measurement, in conjunction with microanalytical data, confirmed the molecular composition, *viz.* $C_{17}H_{26}O_4$. As expected, the IR spectrum is devoid of any absorption bands attributed to carbonyl stretches, but a broad absorption arising from the hydroxyl groups is observed at 3288 $cm^{-1}$. Similarly, the appearance, in the $^1H$ NMR spectrum, of a two-proton multiplet at δ 3.72 – 3.66 attributed to the oxymethine protons of the diol moiety is in accordance with the proposed structure. The relative stereochemistry of the diol **119** was determined by single crystal X-ray analysis, which showed both of the newly formed hydroxyl moieties to be α-oriented (Figure 2.5). It is postulated that the steric bulk of the hydride donor prevents it from attacking the more sterically hindered α-face of the carbonyl groups, such that hydride delivery occurs from the β-face, thereby directing the resulting α-hydroxyl moieties into the cleft formed between the ethylene bridge and the cyclopentane ring.



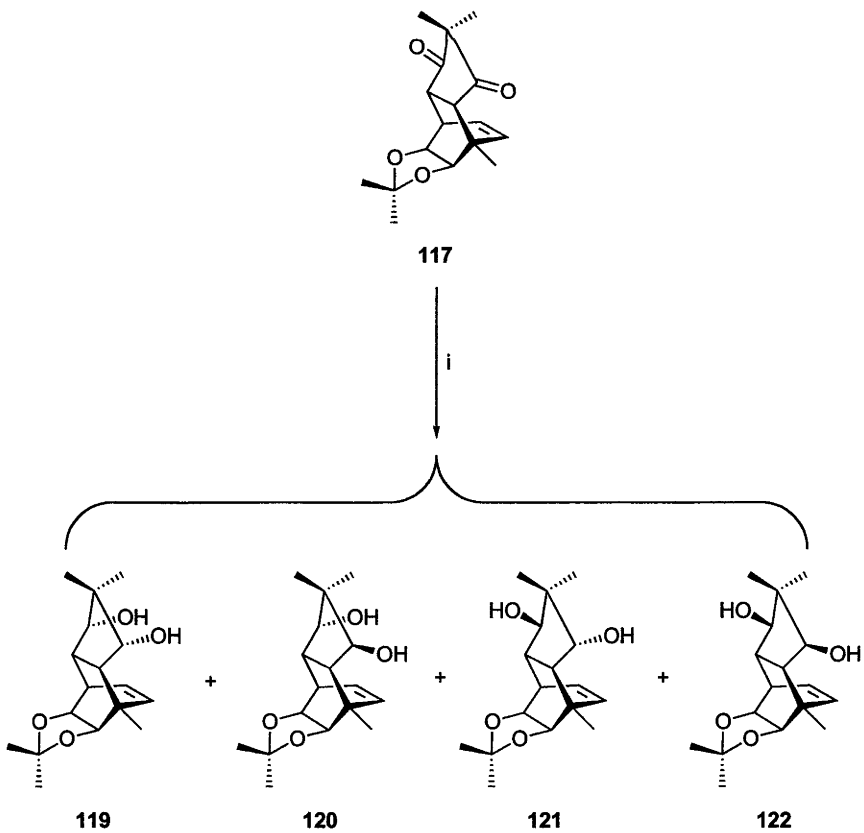

**119**

**Figure 2.5:** *Displacement Ellipsoid Plot (50%) derived from single crystal X-ray analysis of diol **119**.*

Interestingly, reduction of dione **117** using lithium aluminium hydride in refluxing ether or THF (Table 2.1, Entries 2 and 3, respectively) afforded the remaining three possible diastereoisomeric diols **120** – **122**, in addition to the diol **119** (Scheme 2.13). Although the two

newly formed diols **120** and **121**, and the previously described isomer **119**, were readily isolable from the mixture containing the four diastereoisomers, diol **122** was unable to be separated completely from diol **121**. Nevertheless, the mixture containing diol **122** was analysed by IR spectroscopy to furnish, as expected, a spectrum that featured absorption bands closely matched to those of the other three diols. The $^{1}H$ NMR spectra of each of the compounds **120** and **121**, like the spectrum of compound **119**, featured resonances characteristic of the newly formed diol moiety, while the $^{13}C$ NMR spectra each displayed the expected seventeen carbon resonances. The EI mass spectra of compounds **120** and **121** showed molecular ions at *m/z* 294 for which accurate mass measurements and microanalytical data confirmed the expected elemental composition as $C_{17}H_{26}O_4$. Whilst the stereochemistry of diol **119** has been confirmed by single crystal X-ray analysis, the diastereoisomeric structures of the diols **120** – **122** were tentatively assigned based on relative $R_f$ values. It is postulated that diols possessing sterically hindered hydroxyl groups (such as **119**, $R_f$ 0.4 in 1:1 v/v ethyl acetate-hexane) will be prevented from H-bonding to the silica stationary phase and elute more rapidly during chromatography than will diols bearing less crowded hydroxyl groups [such as **122**, $R_f$ 0.1(7)]. However, this argument is speculative and, as such, the stereochemistry assigned to diols **120** – **122** has yet to be independently verified.

**Scheme 2.13:** *Towards deoxygenation: synthesis of diols 119 – 122 under thermodynamically controlled conditions.*




*Reagents and conditions*: i) $LiAlH_4$, THF, ambient temp. to reflux, 48 h.

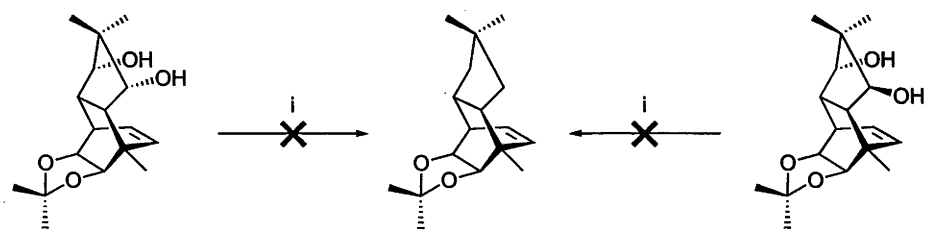
| *Entry* | *Reductant and Conditions* | *Yields* (%) | | | |
|---|---|---|---|---|---|
| | | **119** | **120** | **121** | **122** |
| *1* | DIBAL-H, THF, -78°C | 100 | 0 | 0 | 0 |
| *2* | $LiAlH_4$, $Et_2O$, Δ | 28 | 31 | 26 | 10 |
| *3* | $LiAlH_4$, THF, Δ | 10 | 75 | 5 | 9 |

**Table 2.1:** *Product distributions from reduction of dione 117 under various conditions.*

### 2.4.4 Attempted deoxygenation of the cyclopentane ring: ionic protocols

With the diols **119** and **120** available in preparatively useful quantities *via* the protocols described above, subsequent efforts focussed on methods of deoxygenation of the C(5) and C(7) centres, with a view to forming the tetracycle **118**. Initial investigations centred around direct (one-pot) methods of deoxygenation of the hydroxyl moieties within each of **119** and **120**, although all such procedures failed to afford the required product **118** (Scheme 2.14). For example, treatment of diol **119** with the sulfur trioxide-pyridine complex and subsequently with lithium aluminium hydride[25] or lithium triethylborohydride, produced a complex mixture of products.

**Scheme 2.14:** *Attempted deoxygenation of diols 119 and 120 using direct (one-pot) methods.*




**119** **118** **120**

*Reagents and conditions*: i) Numerous methods (see text).

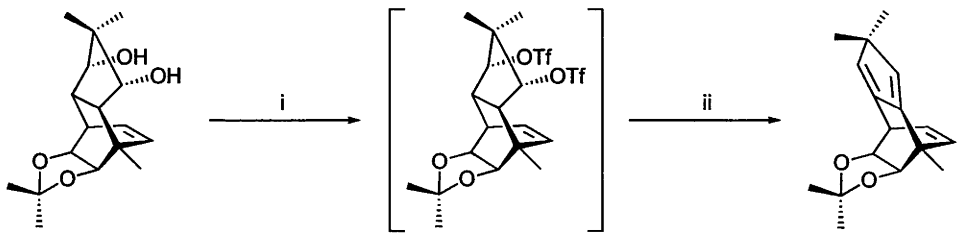
Subsequent investigations focussed on forming halide or pseudohalide derivatives of the diol **119**, prior to performing a reductive step. Several attempts at conversion of diol **119** into the corresponding dibromide were not successful.[26] Such reactions tended to afford a complex mixture of high molecular weight products invariably lacking the olefinic bond and for

25 Corey, E. J.; Achiwa, K., *J. Org. Chem.*, **1969**, *34*, 3667.

26 a) Hutchins, R. O.; Masilamani, D.; Maryanoff, C. A., *ibid.* **1976**, *41*, 1071; b) Olah, G. A.; Gupta, B. G. B.; Malhotra, R.; Narang, S. C., *J. Org. Chem.*, **1980**, *45*, 1638; c) Wagner, A.; Heitz, M.-P.; Mioskowski, C., *Tetrahedron Lett.*, **1989**, *30*, 1971.

which GCMS analysis failed to demonstrate the presence of any bromine isotopes, thereby suggesting that polymerisation had occurred. In contrast, however, when diol **119** was reacted with triflic anhydride in the presence 2,6-lutidine,[27] the elimination product **123** was produced in 42% yield, indicating that derivatisation of the diol had, indeed, occurred (Scheme 2.15).

**Scheme 2.15:** *Synthesis of triene 123* via *the* bis-*triflate.*




**119** **123** 42%

*Reagents and conditions*: i) $Tf_2O$, 2,6-lutidine, $CH_2Cl_2$, 0°C to ambient temp., 48 h; ii) $NEt_3$, aqueous workup.

The $^1H$ NMR spectrum of triene **123** (Figure 2.6) features four prominent resonances at δ 6.25, 5.96, 5.77 and 5.68 that are attributed to the four olefinic protons, while the $^{13}C$ NMR spectrum exhibits resonances at δ 144.7, 141.0, 139.3, 135.0, 133.7 and 132.7 that are assigned

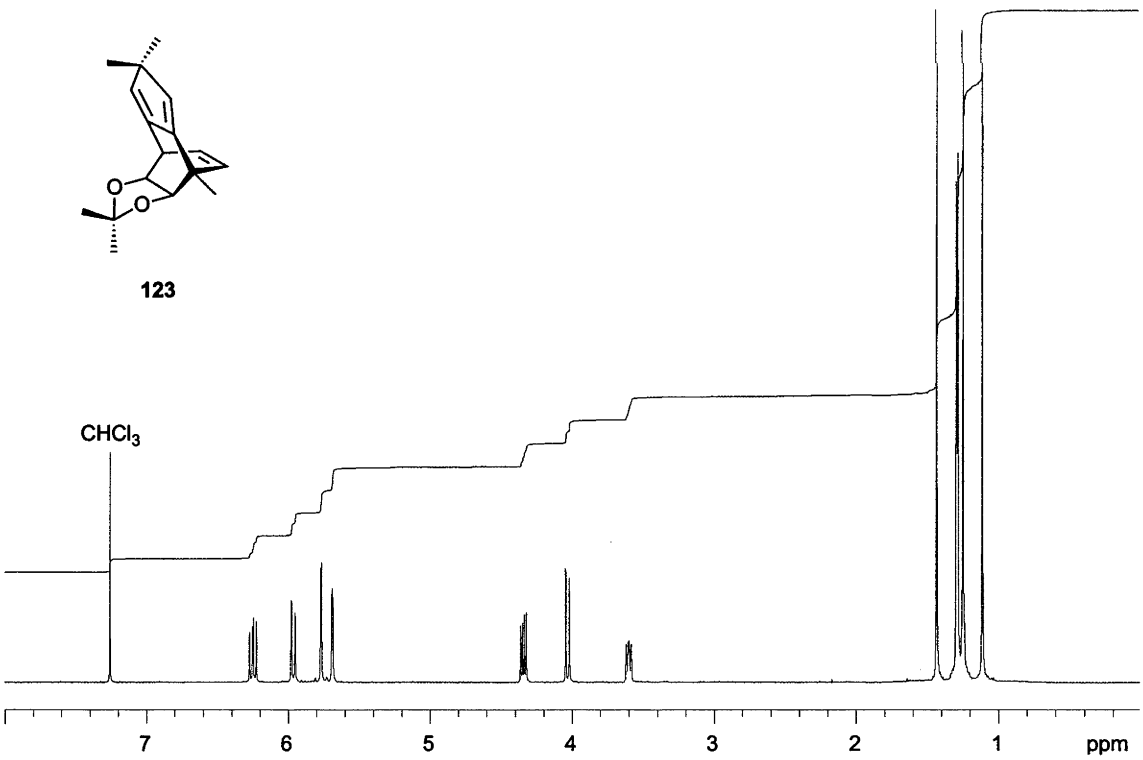


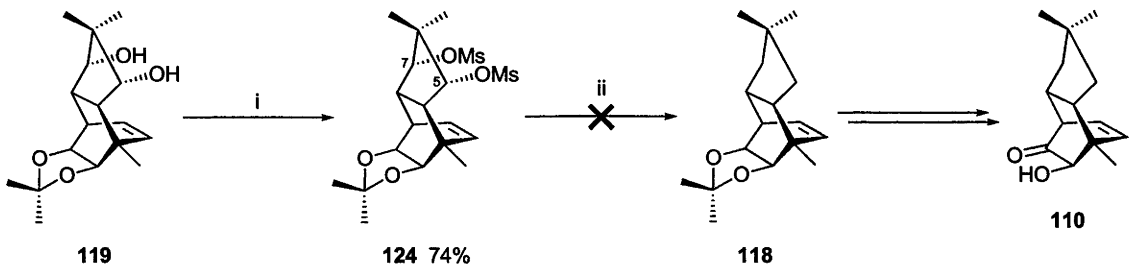

**Figure 2.6:** *300 MHz $^1H$ NMR spectrum of triene 123 in $CDCl_3$.*

27 a) Stang, P. J.; Treptow, W., *Synthesis*, **1980**, 283; b) Ambrose, M. G.; Binkley, R. W., *J. Org. Chem.*, **1983**, *48*, 674.

to the six olefinic carbons. The asymmetric conjugated diene moiety of the triene **123** exhibits two absorption bands in the IR spectrum attributed to C=C stretching at 1740 and 1701 $cm^{-1}$. The presence of an ion at *m/z* 258 in the EI mass spectrum, for which an accurate mass measurement established the molecular formula as $C_{17}H_{22}O_2$, is consistent with the assigned structure. It should be recognised that although the formation of triene **123** effectively constitutes a formal deoxygenation procedure, the restricted synthetic utility of this material and the difficulties associated with obtaining it in preparative yields, preclude its use in the research described here.

In contrast to the above derivatisation reactions, which afforded polymeric or elimination products, the reaction of diol **119** with methanesulfonyl chloride in the presence of triethylamine and pyridine[28] afforded the stable *bis*-mesylate **124** in 74% yield (Scheme 2.16). The EI mass spectrum of this pseudohalide featured an ion at *m/z* 450, consistent with the formation of two mesyl esters and for which an accurate mass measurement established the molecular formula as $C_{19}H_{30}O_8S_2$. In keeping with expectations, nineteen carbon resonances were observed in the $^{13}C$ NMR spectrum, while the $^1H$ NMR spectrum exhibited two resonances at δ 4.94 and 4.76 attributed to the two oxymethine protons, along with the two singlets at δ 3.05 and 2.99 derived from the methyl protons of the sulfonyl ester moieties.

**Scheme 2.16:** *Synthesis of* bis-*mesylate* ***124.***



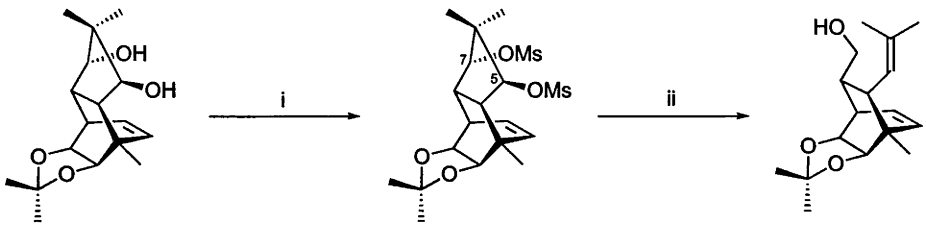

*Reagents and conditions*: i) MsCl, pyridine, $NEt_3$, $CH_2Cl_2$, 0°C to ambient temp., 73 h; ii) Numerous methods (see text).

Analogous reaction of diol **120** (which, like diol **119**, is available in preparatively useful quantities) with methanesulfonyl chloride afforded the corresponding *bis*-mesylate **125** in 75% yield (Scheme 2.17). The EI mass spectrum of *bis*-mesylate **125** features an ion at *m/z* 450 for which an accurate mass measurement confirmed the molecular composition, *viz.* $C_{19}H_{30}O_8S_2$. Remaining spectroscopic data were, likewise, in agreement with the expected structure and closely matched those of the diastereomerically related *bis*-mesylate **124**.

28 Crossland, R. K.; Servis, K. L., *J. Org. Chem.*, **1970**, *35*, 3195.

Numerous attempts to reductively deoxygenate the C(5) and/or C(7) positions of the *bis*-mesylates **124** and **125** by ionic means,[29] using, for example, lithium aluminium hydride or di*iso*butyl aluminium hydride, failed, yielding only the unreacted substrate, the corresponding diol or a complex mixture of products. Although the highly nucleophilic reducing agent, lithium triethylborohydride,[30] was also unable to effect deoxygenation of the *bis*-mesylates **124** and **125**, the latter underwent fragmentation to afford product **126** in quantitative yield (Scheme 2.17).

**Scheme 2.17:** *Synthesis of the fragmentation product 126.*




*Reagents and conditions*: i) MsCl, pyridine, $NEt_3$, $CH_2Cl_2$, 0°C to ambient temp., 73 h; ii) $LiEt_3BH$, THF, ambient temp. to reflux, 4 h.

The $^1H$ NMR spectrum of compound **126** features resonances at δ 6.14, 5.86 and 4.92 associated with the two olefinic protons of the bicyclo[2.2.2]octane skeleton and with the newly formed double bond, respectively (Figure 2.7). Additionally, two one-proton resonances were observed at δ 3.43 and 3.24 and these are attributed to the two diastereotopic protons of the hydroxymethylene moiety. The $^{13}C$ NMR spectrum exhibited the expected seventeen signals, with the newly formed olefinic resonances present at δ 135.2 and 124.5, while the peak at δ 64.7 is attributed to the hydroxymethylene carbon, thereby implying, *ipso facto*, that the two mesylate groups of the substrate have been removed. This was further reflected in the EI mass spectrum, which featured an ion at *m/z* 278, for which an accurate mass measurement was obtained, and which proved consistent with the molecular formula, *viz.* $C_{17}H_{26}O_3$.

Presumably fragmentation product **126** is formed from compound **125** *via* a retro-Prins reaction, followed by reduction of the resulting aldehydic portion to the primary alcohol. As with the formation of triene **123**, the retro-Prins reaction involves elimination of an electrofuge to establish unsaturation (and hence, partial deoxygenation), thus accentuating the intrinsic instability of such systems to elimination/fragmentation under ionic deoxygenative conditions.

29 Holder, R. W.; Matturro, M. G., *ibid.* **1977**, *42*, 2166.

30 The $[Et_3BH]^-$ anion of lithium triethylborohydride (Super Hydride®) is considered to be approximately 40 times more nucleophilic than the $[AlH_4]^-$ anion of lithium aluminium hydride: Krishnamurthy, S.; Brown, H. C., *ibid.* **1983**, *48*, 3085.

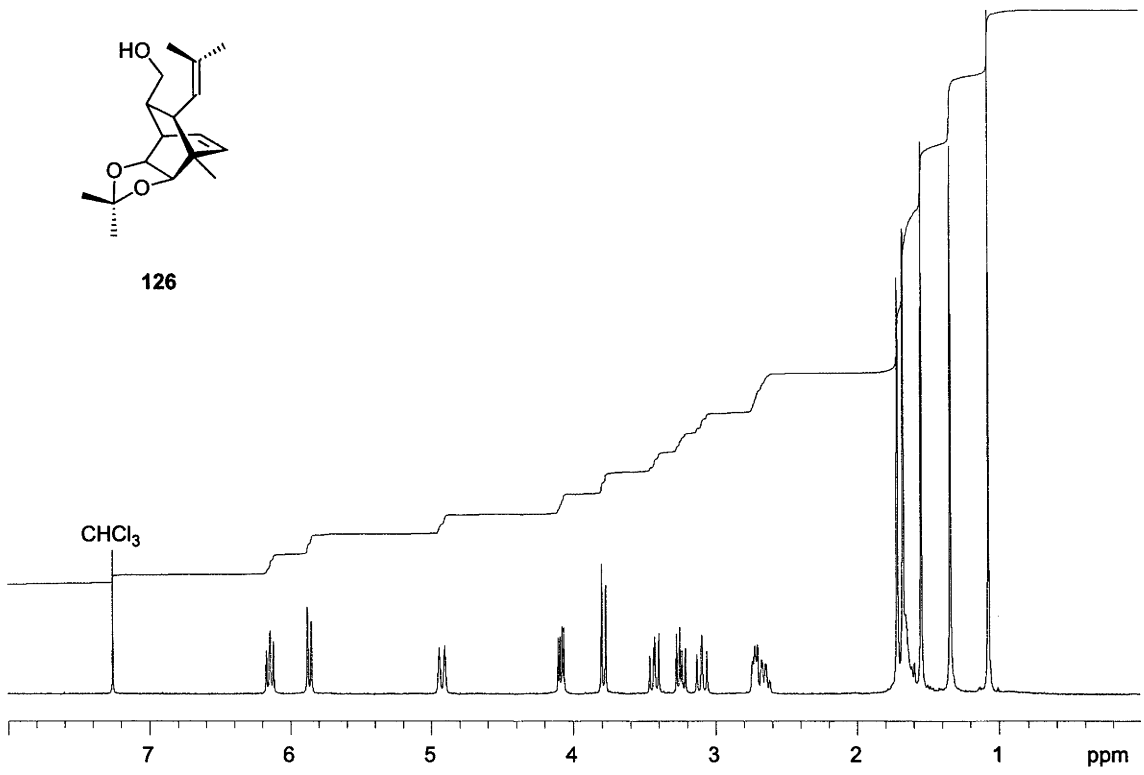



**Figure 2.7:** *300 MHz $^1H$ NMR spectrum of fragmentation product* ***126*** *in $CDCl_3$.*

### 2.4.5 Attempted deoxygenation of the cyclopentane ring: radical protocols

As an alternative to the failed attempts at deoxygenation that employed ionic methods, radical based protocols were subsequently investigated. Initial studies focussed, without success, on one-pot conversion[31] of the *bis*-mesylate **124** into the corresponding diiodide followed by radical dehalogenation with either Zn[31a] or tri-*n*-butyltin hydride.[31b] Given that methanesulfonic esters are considered better leaving groups than are halides, further derivatisation was not attempted and instead *bis*-mesylate **124** was directly subjected to radical-based methods of deoxygenation. However, no reaction was observed when the pseudohalide **124** was treated with a solution of the single electron transfer reagent samarium diiodide,[32] while dissolving-metal reduction using sodium in ammonia[33] afforded the corresponding diol **119** in quantitative yield.

As a last resort, the diol **119** was successfully converted into the *bis*-*S*-methyl xanthate ester **127** in 91% yield, by reacting the corresponding disodium *bis*-alkoxide of the diol with

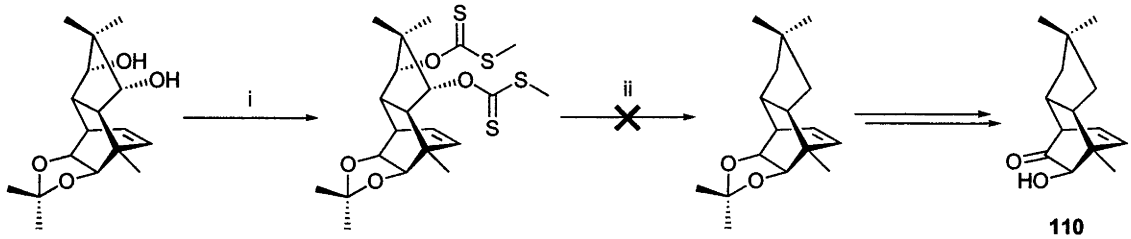
31 a) Fujimoto, Y.; Tatsuno, T., *Tetrahedron Lett.*, **1976**, *37*, 3325; b) Ueno, Y.; Tanaka, C.; Okawara, M., *Chem. Lett.*, **1983**, 795. Although the iodination procedures are ionic, subsequent dehalogenation is recognised as a radical process.

32 The mechanisms by which samarium diiodide reductively cleaves halides and psuedohalides may involve either ionic or radical species: a) Girard, P.; Namy, J. L.; Kagan, H. B., *J. Am. Chem. Soc.*, **1980**, *102*, 2693; b) Kagan, H. B.; Namy, J. L.; Girard, P., *Tetrahedron*, **1981**, *37*, 175.

33 Cuvigny, T.; Larchevêque, M., *J. Organomet. Chem.*, **1974**, *64*, 315.

carbon disulfide and then with methyl iodide (Scheme 2.18).[34] The $^1$H NMR spectrum of the *bis*-*S*-methyl xanthate ester **127** exhibits four one-proton resonances in the region δ 6.19 – 5.84 which are attributed to the two oxymethine protons of the esters and to the two olefinic protons. Characteristic singlets at δ 2.62 and 2.59 were assigned to the methyl protons of each ester moiety. The $^{13}$C NMR spectrum likewise exhibits resonances associated with the newly formed *bis*-xanthate esters, including the signals at δ 216.4 and 215.4 arising from each of the thiocarbonyl carbons. Further evidence for the formation of the *bis*-ester is derived from the EI mass spectrum which exhibits a molecular ion at *m/z* 474 for which an accurate mass measurement confirmed the molecular composition as $C_{21}H_{30}O_4S_4$.

**Scheme 2.18:** *Synthesis of* bis-S-*methyl xanthate ester* ***127*** *from diol* ***119***.




*Reagents and conditions*: i) NaH, imidazole, THF, ambient temp., 1 h, then $CS_2$, ambient temp., 1 h, then MeI, ambient temp., 16 h; ii) *n*-$Bu_3SnH$, AIBN, toluene, ambient temp. to reflux, 18 h.

Subsequent treatment of the *bis*-*S*-methyl xanthate ester **127** with either tri-*n*-butyltin hydride[34] or *tris*-trimethylsilyl silane[35] (in the presence of AIBN as a radical initiator) in refluxing toluene failed to effect deoxygenation, instead affording a complex mixture of high-molecular weight products. In contrast to the situation involving ionic methods of deoxygenation (Section 2.4.4), in which *bis*-pseudohalides underwent elimination to form the triene **123** and fragmentation product **126**, the radical conditions employed herein did not induce the *bis*-*S*-methyl xanthate ester **127** to undergo the corresponding Chugaev elimination reaction.

It is apparent from the outcome of the numerous attempts at deoxygenation of compounds **117**, **119** and **120** (and derivatives thereof), that such reactions are remarkably difficult because these substrates embody a 1,3-oxygenated cyclopentane ring. Substrates in which two donor oxygen atoms are separated by three carbon atoms, are susceptible to

34 a) Barton, D. H. R.; McCombie, S. W., *J. Chem. Soc., Perkin Trans. 1*, **1975**, 1574; b) Iacono, S.; Rasmussen, J., *Org. Synth.*, **1986**, *64*, 57; c) Barton, D. H. R.; Ferreira, J. A.; Jaszberenyi, J. C., In *Preparative Carbohydrate Chemistry*, Hanessian, S. (Ed.) Marcel Dekker: New York, U.S.A., **1997**, p. 151.

35 a) Chatgilialoglu, C.; Griller, D.; Lesage, M., *J. Org. Chem.*, **1988**, *53*, 3641; b) Ballestri, M.; Chatgilialoglu, C.; Clark, K. B.; Griller, D.; Giese, B.; Kopping, B., *J. Org. Chem.*, **1991**, *56*, 678.

fragmentation under a variety of conditions, particularly when the nucleofuge is either a free hydroxyl group or an ester moiety.[36] Indeed, sulfonate esters such as compounds **124** and **125** are widely employed as substrates for achieving controlled fragmentation in organic synthesis and the facility by which such processes occur is illustrated (Scheme 2.17) with the formation of compound **126** from *bis*-mesylate **125** *via* a retro-Prins reaction. Whilst compound **126** was the only fragmentation product to be isolated during the attempted deoxygenation procedures detailed above, it is considered that similar bond fission processes (perhaps with accompanying polymerisation) may also account for the outcome of reactions where no identifiable products were isolated.

## 2.5 Conclusion

An efficient Diels-Alder cycloaddition reaction of *cis*-1,2-dihydrocatechol **1** (X = Me) with the *gem*-dimethylated dienophile **115** has been developed and shown to result in formation of the *syn*-adduct **57** in preparatively useful yield. The *syn*-isomer **57** was used to generate several bicyclo[2.2.2]octene derivatives (**117**, **119** – **122**) which could, in principle, be employed to target non-natural enantiomers of more highly oxygenated members of the triquinane class of sesquiterpene, such as (–)-coriolin [(–)-**65**]. However, in order to synthesise *ent*-(–)-hirsutene [*ent*-(–)-**54**] it was necessary to deoxygenate the cyclopentane ring of the Diels-Alder adduct, and whilst a number of different ionic and radical methods of deoxygenation were investigated, none were met with success.

A new synthetic strategy was required that would take advantage of the discoveries made in this Chapter: such a strategy is detailed in Chapter Three.

36 For a review of fragmentation reactions occurring within 1,3-oxygenated systems, refer to: Ho, T.-L., *Heterolytic Fragmentation of Organic Molecules*, John Wiley & Sons, Inc., **1993**, p. 326.

*Chapter Three*

# *Total Synthesis of* ent-*(–)-Hirsutene*

## 3.1 Introduction

In light of the results detailed in Chapter Two, a revised approach to the synthesis of *ent*-(–)-hirsutene [*ent*-(–)-**54**] was pursued. The new synthetic approach to *ent*-(–)-hirsutene [*ent*-(–)-**54**] still employs microbial oxidation, Diels-Alder cycloaddition and photochemically-promoted rearrangement steps as key features and essentially, simply focusses on an alternative means of attaining the requisite β,γ-unsaturated ketone **110**.

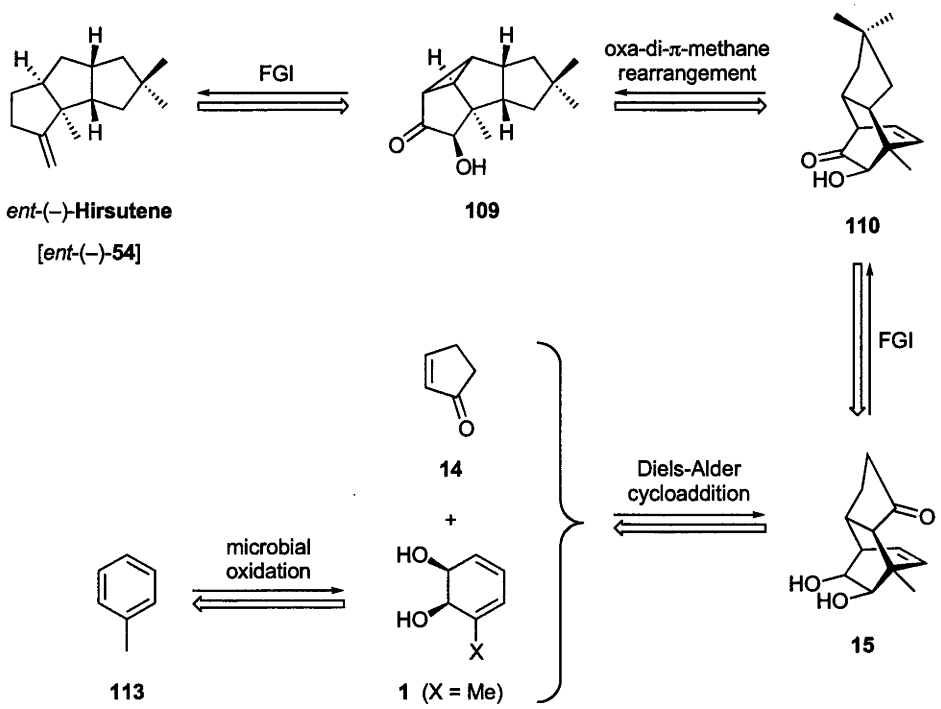
## 3.2 Revised retrosynthetic analysis

The new synthetic approach to *ent*-(–)-hirsutene [*ent*-(–)-**54**] is summarised in Scheme 3.1. In keeping with the retrosynthetic analysis described in Chapter Two (Scheme 2.8), it was anticipated that *ent*-(–)-hirsutene [*ent*-(–)-**54**] could be accessed from the tetracycle **109** through a series of standard functional group interconversions including cleavage of the cyclopropyl bond peripheral to the tricyclopentanoid framework. Tetracycle **109** is the projected product from triplet sensitised photochemically-promoted oxa-di-π-methane rearrangement of the β,γ-unsaturated ketone **110**. It was envisaged that the oxa-di-π-methane rearrangement precursor **110** could be assembled from compound **15** through an additional series of functional group interconversions, including *gem*-dimethylation. The origin of compound **15** may be traced to precursors **1** (X = Me) and **14** through a Diels-Alder disconnection. Indeed, the *cis*-1,2-dihydrocatechol **1** (X = Me) and dienophile **14** have been previously reacted in a high pressure-promoted Diels-Alder reaction by Stewart who demonstrated that the *cis*-1,2-dihydrocatechol **1** (X = Me) participates in a diastereofacially selective cycloaddition to preferentially furnish the *syn*-adduct **15**.[1] In turn, and as detailed in Chapter One, the

1 Stewart, S. G., *PhD Thesis*, Australian National University, **2001**.

*cis*-1,2-dihydrocatechol **1** (X = Me) is readily availabile in enantiopure form and preparatively useful quantity *via* microbial oxidation of toluene (**113**).

**Scheme 3.1:** *Revised retrosynthetic analysis of* ent-*(–)-hirsutene [*ent-*(–)-54].*




Thus, the new synthetic approach to *ent*-(–)-hirsutene [*ent*-(–)-**54**] retains the central elements of the retrosynthetic analysis enunciated in Chapter Two, and whilst less highly convergent than that conceived earlier, it should, if successful, be generally applicable to the enantioselective synthesis of linear triquinanes. The key benefit of the new approach is that it circumvents the issues presented in Chapter Two, that arose from attempts to deoxygenate the 1,3-dione functionality (required for installation of the *gem*-dimethyl moiety through a Diels-Alder process), by delaying the installation of the *gem*-dimethyl moiety until after the pivotal Diels-Alder cycloaddition reaction.

## 3.3 Total synthesis of *ent*-(–)-hirsutene

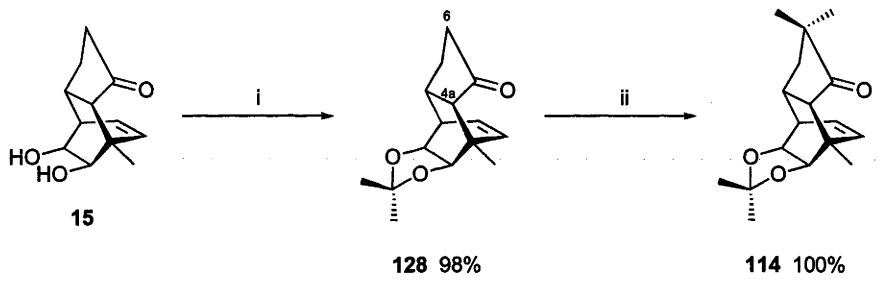
### 3.3.1 Installation of the *gem*-dimethyl moiety

The revised retrosynthetic strategy described in Scheme 3.1 (above) has its inception in the high pressure-promoted Diels-Alder cycloaddition reaction of *cis*-1,2-dihydrocatechol **1** (X = Me) with cyclopenten-2-one (**14**) first described by Stewart in 1999 (refer to Chapter One, Scheme 1.4).[1] The diastereofacial selectivity of this reaction, and indeed other cycloaddition reactions of *cis*-1,2-dihydrocatechol **1** (X = Me, derived from microbial oxidation of toluene),

was found to favour the *endo*-, *ortho*-, *syn*-adduct **15** which was furnished in 70% yield, along with small amounts (9%) of the *endo*-, *ortho*-, *anti*-isomer **16**.

The *syn*-Diels-Alder adduct **15** embodies the skeleton and functionality appropriate for elaboration to the key β,γ-unsaturated ketone intermediate **110**. The requirement of being able to perform selective manipulations – notably *gem*-dimethylation and deoxygenation – of the five-membered ring within this framework and to then smoothly reveal the vicinal diol moiety at a later stage, governed the decision to mask the vicinal diol moiety within compound **15** as the corresponding acetonide. Consequently, substrate **15** was subjected to facile, acid-catalysed protection conditions to afford the corresponding acetonide **128** in 98% yield (Scheme 3.2). The marked absence of any peaks at between 3700 – 3100 $cm^{-1}$ in the IR spectrum indicates that the vicinal diol moiety has been protected. In addition, the EI mass spectrum exhibits the expected molecular ion at *m/z* 248, for which an accurate mass measurement, in conjunction with microanalysis established the molecular formula as $C_{15}H_{20}O_3$.

**Scheme 3.2:** *Installation of the* gem-*dimethyl moiety to form compound* ***114***.




*Reagents and conditions*: i) 2,2-DMP, *p*-TsOH.$H_2O$, $CH_2Cl_2$, 0°C to ambient temp., 75 h; ii) LiHMDS, THF, 0°C to ambient temp., 2 h, then MeI, 0°C to ambient temp., 2 h.

With the acetonide **128** in hand, it was necessary to install the *gem*-dimethyl functionality at C(6). In order to avoid alkylation at the more sterically hindered C(4a) position and to favour *C*-alkylation over *O*-alkylation, the lithium salt of the hindered base *bis*(trimethylsilyl)amine was used to selectively deprotonate the substrate at C(6). The resulting anion was trapped with methyl iodide and the ensuing mono-methylated product(s) (not isolated) were sequentially reacted with further equivalents of base and methyl iodide to smoothly effect formation of the *gem*-dimethylated product **114** in quantitative yield (Scheme 3.2). No compounds in which alkylation had occurred at C(4a) were observed. The EI mass spectrum of the product **114** exhibits an ion at *m/z* 276 for which an accurate mass measurement established the expected molecular formula as $C_{17}H_{24}O_3$. The $^1H$ NMR spectrum of the product **114** was fully assigned using a variety of connectivity experiments and features resonances at δ 1.01 and 0.91 (as shown in Figure 3.1) which are associated with the *gem*-dimethyl

functionality. The corresponding resonances at δ 26.8 and 22.5 in the $^{13}C$ NMR spectrum are, likewise, consistent with *geminal* alkylation.

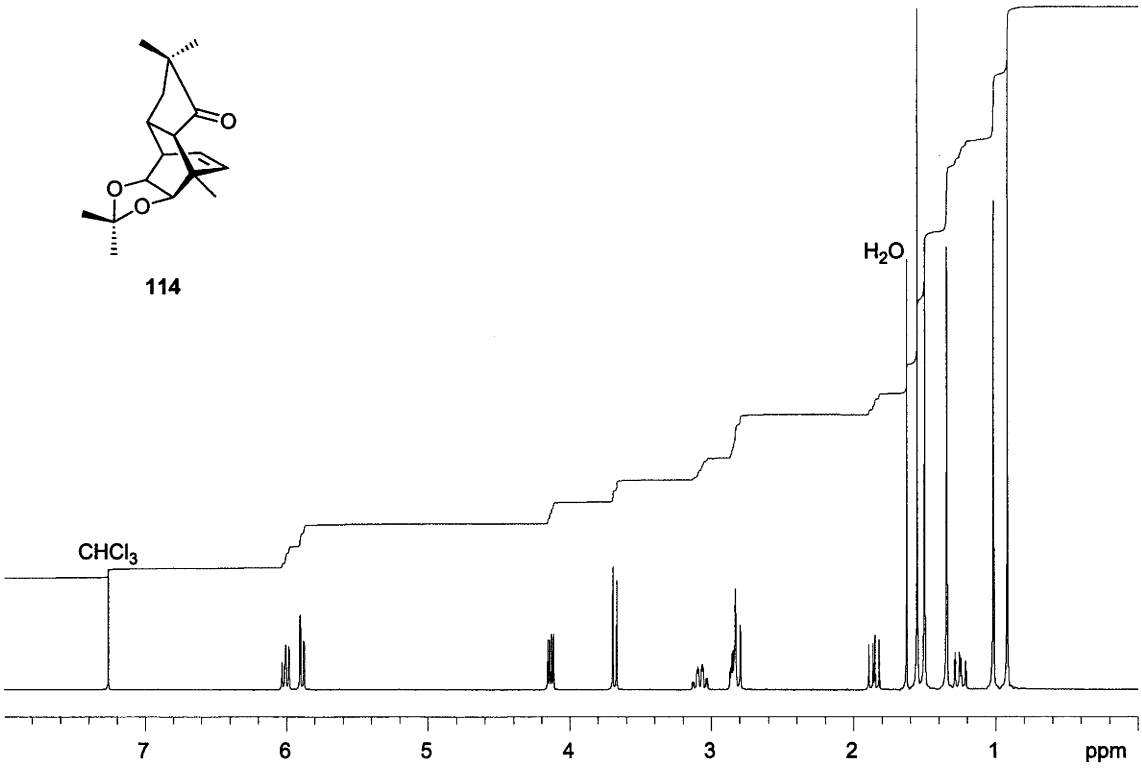


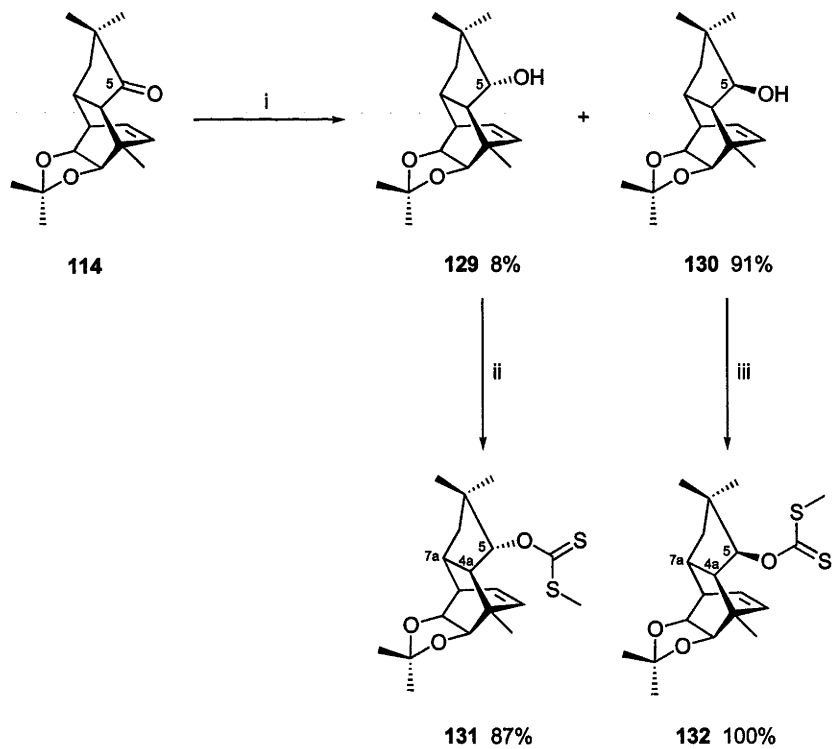

**Figure 3.1:** *300 MHz $^1H$ NMR spectrum of* gem*-dimethylated compound **114** in $CDCl_3$.*

### 3.3.2 Deoxygenation of the cyclopentane ring

The carbonyl moiety having served a two-fold purpose – once in activating the dienophile and directing the diastereofacial selectivity of the Diels-Alder reaction, and once in directing *gem*-dialkylation – was now redundant and methodology directed towards its deoxygenation was employed. To this end, the ketone **114** was reduced with lithium aluminium hydride to afford a 1:9 mixture of the chromatographically separable epimers **129** and **130** of the corresponding alcohol (99% combined yield) (Scheme 3.3). Both the minor α-epimeric (**129**) and major β-epimeric (**130**) forms of the alcohol exhibit IR bands at 3494 and 3500 $cm^{-1}$, respectively, which, along with an absence of peaks attributable to carbonyl stretches in both spectra, indicate that reduction of the ketone has occurred. The $^1H$ and $^{13}C$ NMR spectra of each epimeric product were consistent with the expected structures and completely assigned using a variety of NMR connectivity experiments. Although described above as the respective α- and β-epimers, nOe proximity experiments provided insufficient evidence to be of use in assigning stereochemistry to the C(5) oxymethine carbon centres of each product: the stereochemistry of each epimer was, instead, retrospectively assigned after analysis of the derived xanthate esters.

Barton-McCombie-type deoxygenation procedures[2] were employed to deoxygenate the C(5) position of each of the α- and β-epimeric alcohols **129** and **130**. This two-step procedure first required conversion of each alcohol into the corresponding *S*-methyl xanthate esters *via* reaction of the individual sodium alkoxides with carbon disulfide and, subsequently, with methyl iodide (Scheme 3.3). After separation by flash chromatography from the polysulfide by-products of each reaction mixture, the α- and β-epimeric *S*-methyl xanthate esters **131** and **132** were isolated in 87% and 100% yields, respectively. The EI mass spectra of these compounds each feature a parent ion at *m/z* 368, for which accurate mass measurements, in conjunction with microanalytical data, established the molecular formulae, *viz.* $C_{19}H_{28}O_3S_2$. The $^1H$ and $^{13}C$ NMR spectra of each *S*-methyl xanthate ester were completely assigned using a variety of connectivity experiments and noted to exhibit resonances consistent with the structures of the expected products **131** and **132**, the most significant of which are, arguably, the peaks at δ 216.3 and 216.1 derived from the respective thiocarbonyl moieties. The C(5) stereochemistry of each xanthate ester was assigned using nOe experiments. An enhancement between the resonances attributed to the protons attached to C(5) and C(4a) is, among other evidence, the simplest and

**Scheme 3.3:** *Formation of* S*-methyl xanthate esters **131** and **132**.*



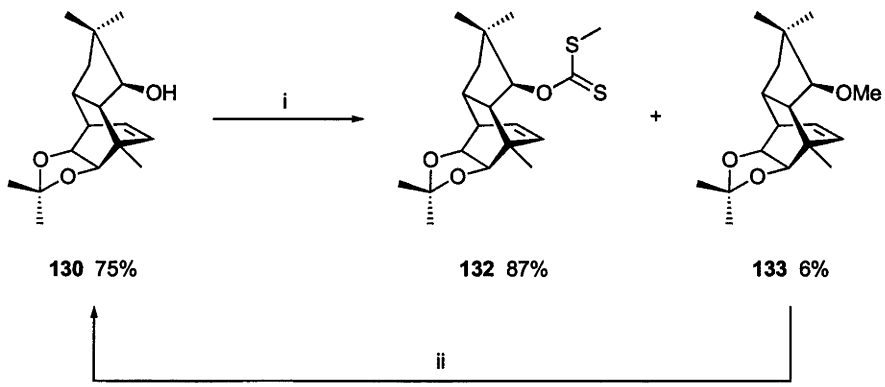

*Reagents and conditions*: i) $LiAlH_4$, THF, 0°C to 50°C, 24 h; ii) NaH, THF, 0°C to reflux, 20 h, then $CS_2$, ambient temp. to reflux, 18 h, then MeI, ambient temp. to reflux, 8 h; iii) NaH, THF, 0°C to reflux, 6 h, then $CS_2$, ambient temp. to reflux, 13 h, then MeI, ambient temp. to reflux, 8 h.

2 a) Barton, D. H. R.; McCombie, S. W., *J. Chem. Soc., Perkin Trans. 1*, **1975**, 1574; b) Iacono, S.; Rasmussen, J., *Org. Synth.*, **1986**, *64*, 57; c) Barton, D. H. R.; Ferreira, J. A.; Jaszberenyi, J. C., In *Preparative Carbohydrate Chemistry*, Hanessian, S. (Ed.) Marcel Dekker: New York, U.S.A., **1997**, p. 151.

most convincing argument that the stereochemistry at C(5) of the *S*-methyl xanthate ester **132** is of the β-epimeric form. Similar, but more complex arguments can be used to rationalise the stereochemistry at C(5) of the α-epimeric *S*-methyl xanthate ester **131**.

It should be noted that on several occasions the formation of *S*-methyl xanthate ester **132** was accompanied by concomitant formation of the corresponding methyl ether **133** in 6% yield (Scheme 3.4). The EI mass spectrum of this by-product features a parent ion at *m/z* 292 for which an accurate mass measurement was obtained that, together with microanalytical data, established the molecular formula as $C_{18}H_{28}O_3$. The $^1$H NMR spectrum of compound **133** exhibits a resonance at δ 3.41 which, along with the signal at δ 59.1 in the $^{13}$C NMR spectrum, is diagnostic of a methyl ether. Reaction of the methyl ether by-product **133** with trimethylsilyl iodide (generated *in situ* according to the method of Olah *et al.*) regenerated the original β-epimeric alcohol **130** in 75% yield.[3]

**Scheme 3.4:** *Synthesis of methyl ether by-product **133** and regeneration of diol **130**.*



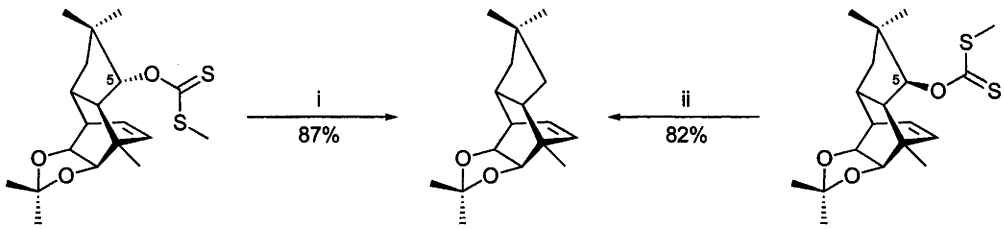

*Reagents and conditions*: i) NaH, THF, 0°C to reflux, 8 h, then $CS_2$, 0°C to reflux, 2 h, then MeI, 0°C to reflux, 4 h; ii) TMSCl, NaI, MeCN, ambient temp. to reflux, 80 h.

The second stage of the Barton-McCombie-type deoxygenation procedure was effected by separately reacting each *S*-methyl xanthate ester with tri-*n*-butyltin hydride (in the presence of AIBN as a radical initiator) in refluxing toluene.[2] After appropriate workup, deoxygenated product **118** was isolated in 87% yield from the α-epimeric substrate **131** and 82% yield from the β-epimeric substrate **132** (Scheme 3.5). Evidence for C(5) deoxygenation of tetracycle **118** was established from the $^1$H NMR spectrum (Figure 3.2) which, along with the $^{13}$C NMR spectrum, was completely assigned using a variety of connectivity experiments. The EI mass spectrum of compound **118** featured a fragment ion at *m/z* 247 consistent with loss of a methyl

3 a) Jung, M. E.; Lyster, M. A., *J. Org. Chem.*, **1977**, *42*, 3761; b) Olah, G. A.; Husain, A.; Gupta, B. G. B.; Narang, S. C., *Angew. Chem., Int. Ed. Engl.*, **1981**, *20*, 690.

radical from the acetonide moiety and for which an accurate mass measurement,[4] in conjunction with microanalytical data, established the molecular formula as $C_{17}H_{26}O_2$.

**Scheme 3.5:** *Deoxygenation of the* S*-methyl xanthate esters* ***131*** *and* ***132****.*




**131** **118** **132**

*Reagents and conditions*: i) *n*-$Bu_3SnH$, AIBN, toluene, ambient temp. to reflux, 3 h; ii) *n*-$Bu_3SnH$, AIBN, toluene, ambient temp. to reflux, 18 h.

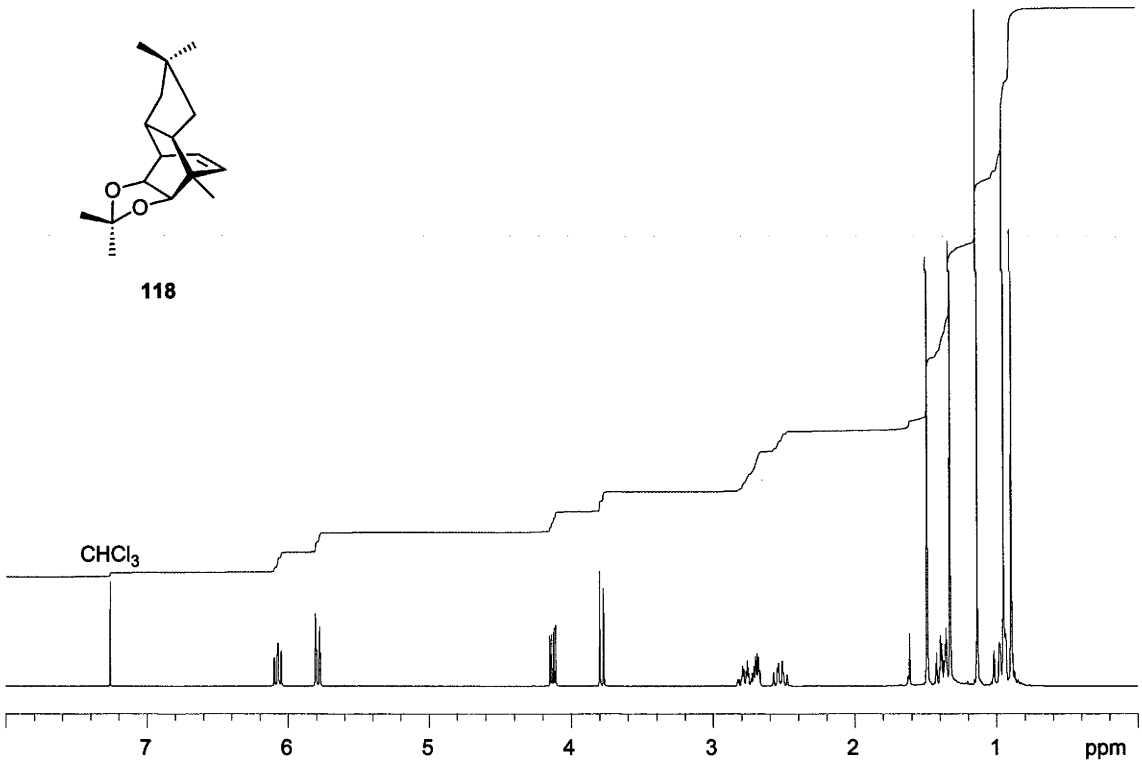



**Figure 3.2:** *300 MHz* $^1$*H NMR spectrum of deoxygenated compound* ***118*** *in* $CDCl_3$*.*

4 Molecules bearing an acetonide moiety typically exhibit an $[M - CH_3^{\cdot}]^+$ fragment ion under EI conditions.

### 3.3.3 Formation of the β,γ-unsaturated ketone substrate for the photochemically-promoted oxa-di-π-methane rearrangement

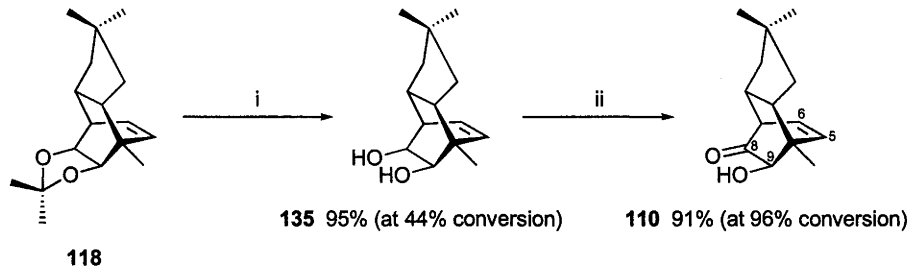
The successful formation of tetracycle **118** from *cis*-1,2-dihydrocatechol **1** (X = Me) *via* Diels-Alder cycloaddition, alkylation and deoxygenation protocols, meant subsequent steps were directed towards elaboration of this material into the β,γ-unsaturated ketone **110** required for the pivotal, photochemically-promoted oxa-di-π-methane rearrangement reaction.

Acid-catalysed removal of the acetonide protecting group from the deoxygenated compound **118** proved to be difficult, although when forcing conditions were employed over extended reaction times, the substrate **118** was efficiently, albeit incompletely, converted into the corresponding diol **135** (95% at 44% conversion) (Scheme 3.6). The EI mass spectrum of **135** displays a fragment ion at *m/z* 162, consistent with loss of 1,2-dihydroxyethylene from the molecular ion *via* a retro-Diels-Alder process and for which an accurate mass measurement, in conjunction with microanalytical data, established the expected molecular formula, *viz.* $C_{14}H_{22}O_2$. All other derived spectroscopic data were likewise consistent with the structure of diol **135**, with the IR spectrum, in particular, exhibiting an intense peak associated with H-bonded O–H stretching at 3344 $cm^{-1}$.

Oxidation of the less hindered of the two hydroxyl moieties within the diol **135** was effected using the sterically demanding oxoammonium ion derived from reaction of 4-acetamido-TEMPO with *p*-toluenesulfonic acid (Scheme 3.6).[5] The acyloin **110** thus generated (91% at 96% conversion) was found to display two prominent IR absorption bands at 1734 and 1722 $cm^{-1}$ which may be attributed to the intermolecularly H-bonded asymmetric and intramolecular H-bonded carbonyl stretches, respectively. The EI mass spectrum features a molecular ion at *m/z* 220 consistent with a mass decrease of two units and the oxidative nature of the reaction. An accurate mass measurement on this ion, when combined with microanalytical data for the acyloin **110**, confirmed the molecular formula as $C_{14}H_{20}O_2$. Using connectivity and proximity experiments, the $^1H$ and $^{13}C$ NMR spectra of acyloin **110** were completely assigned and consistent with the expected structure. In particular, the $^1H$ NMR spectrum features a prominent doublet at δ 3.39 (*J* 1.8 Hz) attributed to the C(9) oxymethine proton, the multiplicity of which arises from coupling to the hydroxyl proton. The $^{13}C$ NMR spectrum features a resonance at δ 74.7 attributed to the C(9) oxymethine carbon atom, in addition to signals at δ 127.8, 140.4 and 213.7 associated with C(5), C(6) and C(8), respectively, of the β,γ-unsaturated ketone framework.

5 a) Ma, Z.; Bobbitt, J. M., *J. Org. Chem.*, **1991**, *56*, 6110; b) Banwell, M. G.; Bridges, V. S.; Dupuche, J. R.; Richards, S. L.; Walter, J. M., *J. Org. Chem.*, **1994**, *59*, 6338.

**Scheme 3.6:** *Synthesis of acyloin* ***110****.*




**118** **135** 95% (at 44% conversion) **110** 91% (at 96% conversion)

*Reagents and conditions*: i) $CH_3COOH$:$H_2O$ 3:2, THF, 60°C, 48 h; ii) 4-AcNH-TEMPO, *p*-TsOH.$H_2O$, $CH_2Cl_2$, 0°C to ambient temp., 23 h.

The acyloin **110** was found to be remarkably unstable and readily decomposed to afford a complex mixture of products. Subsequent studies demonstrated that when acyloin **110** was dissolved in ethyl acetate and allowed to stand for a period of 4 weeks or more, a white semi-crystalline precipitate formed. This process was facilitated by the addition of silica gel to the solution. ES mass analysis of a methanolic solution of the precipitate showed signals in the negative ion spectrum at *m/z* 475, 695, 915, 1135 and 1355 consistent with the chloride ion addends of the cyclic dimer, trimer, tetramer, pentamer and hexamer, respectively. In addition, the positive ion ES mass spectrum also exhibits a peak at *m/z* 1783 which is indicative of the sodium ion addend of the octamer. No higher order oligomers were observed for the polymerisation process which occurred in yields of 80% at 45% conversion. All such oligomers would appear to possess $C_n$ symmetry,[6] given that the $^1H$ and $^{13}C$ NMR spectra of the oligomeric mixture feature a set of signals consistent with a single monomeric unit. Furthermore, oligomerisation would appear to involve the oxygenated centre at C(8), since there is a complete absence of features associated with the carbonyl moiety in both the $^{13}C$ and IR spectra, with the former instead displaying a resonance at δ 98.7 characteristic of an acetal carbon [C(8)]. Indeed, the remaining spectroscopic data are consistent with the structure of the oligmeric species **136** (n = 1, 2, 3, 4, 5 and 7) that are composed of a $C_n$-symmetric system of hemiacetal-linked monomers (Scheme 3.7).

Although other modes of oligomerisation are possible,[7] there is a modest literature precedent for the formation of oligomers (usually dimers) similar to that of type **136**.[8] Indeed,

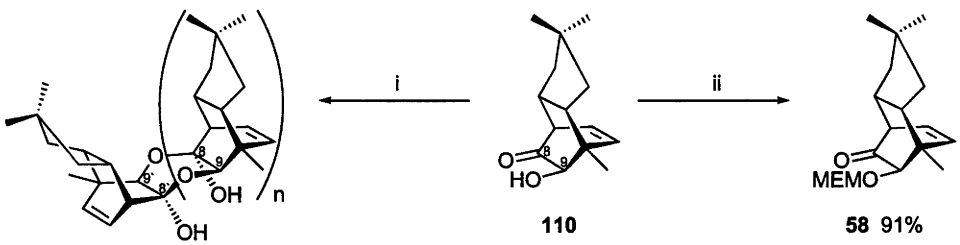
6 Note that in this situtation, "n" refers not only to the number of rotational symmetry operations but also to the number of monomeric units making up the oligocycle.

7 An additional mode of oligmerisation in which the oxygenated connections between monomeric units involve C(8) alone, would be expected to form cyclic acetals in a similar manner to the trimerisation of acetaldehyde to paraldehyde. However, there is no literature precedent for non-activated ketones such as acyloin **110** to react in this fashion, with the exception of adamantone which, upon exposure to γ-radiation, dimerised: a) Sharipov, G. L.; Voloshin, A. I.; Kazakov, V. P.; Tolstikov, G. A., *Mendeleev Commun.*, **1991**, 124. On the other hand, activated ketones tethered in methane(tri-α-haloacetone) molecules readily cyclise to form tri(halomethyl)-2,4,9-trioxaadamantanes: b) Stetter, H.; Stark, H., *Chem. Ber.*, **1959**, *92*, 732; c) Herranz, E.;

the innocuous reaction conditions reported here are consistent with these reports, which indicate that such reactions may occur spontaneously[8a] and can also be assisted by traces of acid[8b, 8c, 8e] or base[8b, 8c, 8f] (although under strongly acidic conditions, the reaction may be reversible[8d]).

In order to circumvent the problems associated with the instability of the naked acyloin **110** towards decomposition and/or oligomerisation, the hydroxyl moiety was protected with a photochemically inert, non-hindered protecting group, *viz.* the (2-methoxyethoxy)methyl group. This was achieved by reacting the acyloin **110** with (2-methoxyethoxy)methylene chloride, in the presence of Hünig's base, to afford the desired β,γ-unsaturated ketone **58** in 91% yield (Scheme 3.7). Compound **58** was completely inert to oligomerisation. The EI mass spectrum of this material exhibits a molecular ion at *m/z* 308, consistent with an increase in mass attributed to the protecting group. An accurate mass measurement on this ion, in conjunction with microanalytical data established the expected molecular formula ($C_{18}H_{28}O_4$) for compound **58**. The IR spectrum displays a characteristic stretch attributed to the carbonyl moiety at 1736 $cm^{-1}$ and indicates a complete absence of the free (unprotected) hydroxyl functionality. The $^1H$ NMR spectrum (Figure 3.3) displays all the resonances attributed to features of the acyloin precursor **110**, with the exception of the hydroxyl proton, in addition to which are the resonances attributed to the protecting group at δ 3.84, 3.78, 3.58 and 3.39, as well as the peaks at δ 5.11 and 4.11 arising from each of the diastereotopic protons. The $^{13}C$ NMR spectrum (Figure 3.4) of the β,γ-unsaturated ketone **58** was also completely assigned

**Scheme 3.7:** *Formation of oligomers of type* ***136*** *(n=1, 2, 3, 4, 5 and 7) and β,γ-unsaturated ketone* ***58****.*




80% polymerisation
(at 45% conversion)

**136** n = 1,2,3,4,5 and 7.

**110**

**58** 91%

*Reagents and conditions*: i) silica gel, EtOAc, ambient temp., 4 weeks; ii) MEM-Cl, Hünig's base, $CH_2Cl_2$, ambient temp., 16 h.

Serratosa, F., *Tetrahedron*, **1977**, *33*, 995. An alternative mode of H-bonded oligomerisation such as that displayed during the self-organisation of lactates, should also be possible. However, such conformations involve the formation of cooperative OH ··· OH and strong OH ··· O=C bonds which are unlikely to exist for the oligomers described above due to the absence of a (blue-shifted) carbonyl stretch in the IR spectrum: d) Borho, N.; Suhm, M. A., *Org. Biomol. Chem.*, **2003**, *1*, 4351.

8 a) Sheehan, J. C.; O'Neill, R. C.; White, M. A., *J. Am. Chem. Soc.*, **1950**, *72*, 3376; b) Arvai, G.; Fattori, D.; Vogel, P., *Tetrahedron*, **1992**, *48*, 10621; c) Jauch, J., *Tetrahedron*, **1994**, *50*, 12903; d) Rozen, S.; Bareket, Y., *Chem. Commun.*, **1996**, 627; e) Boutoute, P.; Mousset, G.; Veschambre, H., *New J. Chem.*, **1998**, 247; f) Drew, M. G. B.; Harwood, L. M.; Macías-Sánchez, A. J.; Scott, R.; Thomas, R. M.; Uguen, D., *Angew. Chem., Int. Ed. Engl.*, **2001**, *40*, 2311.

featuring, most significantly, resonances attributed to the carbonyl (δ 210.3), olefinic (δ 140.3 and 128.5) and ether (δ 96.5, 72.0, 67.7 and 59.3) carbon atoms.

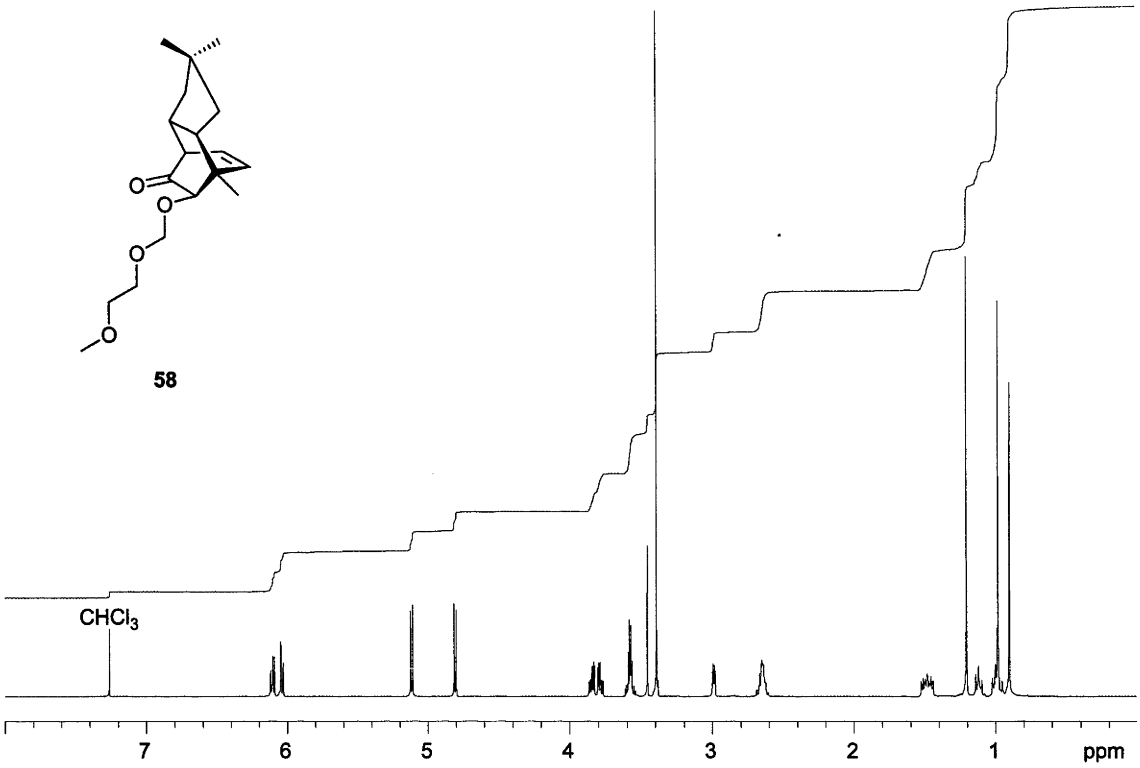



**Figure 3.3:** *500 MHz $^{1}H$ NMR spectrum of β,γ-unsaturated ketone 58 in $CDCl_3$.*

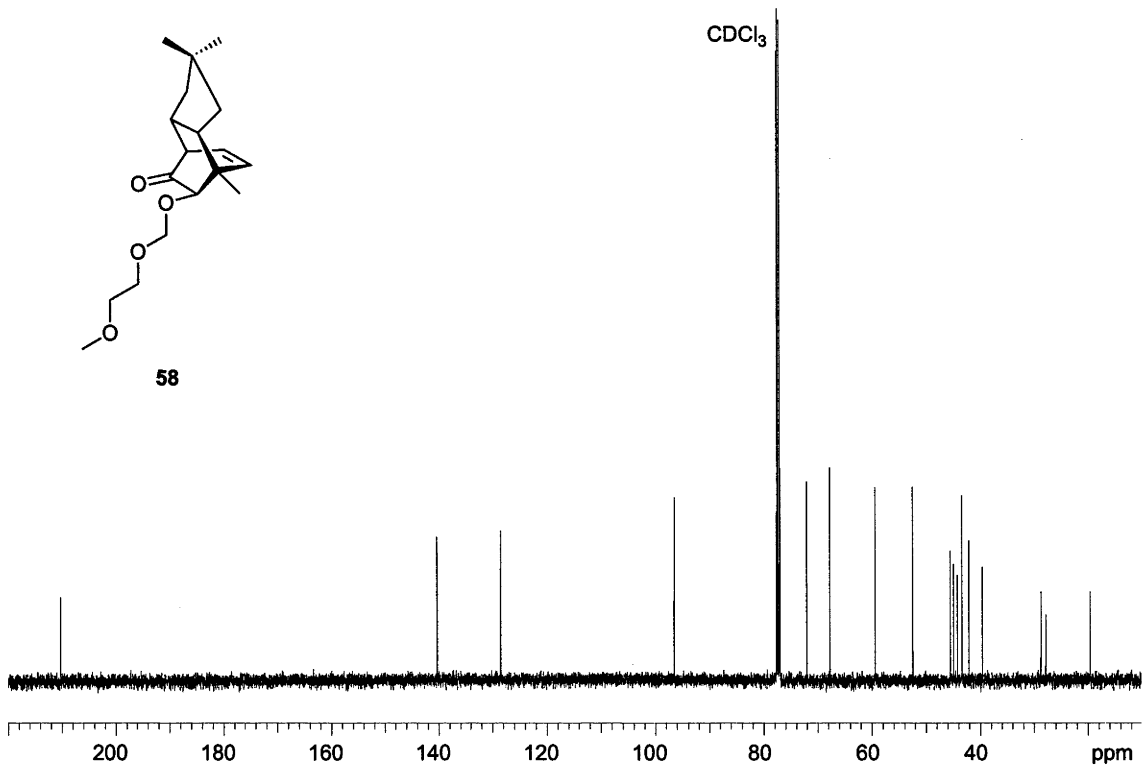
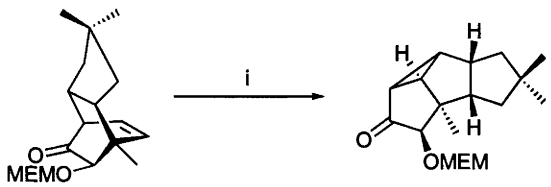



**Figure 3.4:** *126 MHz $^{13}C$ NMR spectrum of β,γ-unsaturated ketone 58 in $CDCl_3$.*

### 3.3.4 Photochemically-promoted oxa-di-π-methane rearrangement

Based on the analysis presented in Chapter One in which key photochemical reactions of β,γ-unsaturated ketones were detailed, compound **58** was irradiated under triplet sensitised reaction conditions,[9] according to the methods described by Demuth (1994).[10] After irradiation over prolonged periods of up to 32 h, the oxa-di-π-methane rearrangement product **59**, embodying the linear triquinane framework of *ent*-(–)-hirsutene [*ent*-(–)-**54**], was formed, in 80% isolated yield (at 71% conversion) (Scheme 3.8).[11] The EI mass spectrum exhibits a

**Scheme 3.8:** *Photochemically-promoted oxa-di-π-methane rearrangement of β,γ-unsaturated ketone **58** to cyclopropyl ketone **59**.*




**58** **59** 80% (at 71% conversion)

*Reagents and conditions*: i) *hν* (125 W Philips HPL-N lamp), UV filter [$\lambda_{transmission}$ >340 nm, thickness >10 mm, NaBr 750 $gL^{-1}$, $Pb(NO_3)_2$ 8 $gL^{-1}$], acetone, acetophenone, 0°C to 10°C, 32 h.

molecular ion at *m/z* 308 and an accurate mass measurement established the expected molecular formula of the product as $C_{18}H_{28}O_4$, thereby providing evidence to support the oxa-di-π-methane rearrangement. The $^1H$ and $^{13}C$ NMR spectra of the cyclopropyl ketone (Figures 3.5 and 3.6, respectively) were completely assigned through connectivity and proximity experiments. These $^1H$ and $^{13}C$ NMR analyses feature significant differences from those of the starting β,γ-unsaturated ketone (Figures 3.3 and 3.4, respectively), the most prominent of which concern the absence of peaks attributed to olefinic resonances in the spectra of the product. The structure of cyclopropyl ketone **59** was additionally verified by single crystal X-ray analysis (Figure 3.7).

9 Using acetone/acetophenone as a triplet sensitiser and Pyrex and an aqueous filter solution to select for wavelengths >340 nm whilst irradiating with a high-pressure (Philips 125 W HPL-N) mercury arc lamp.

10 Demuth, M., In *Photochemical Key Steps in Organic Synthesis: an Experimental Course Book*, Mattay, J.; Griesbeck, A. G. (Eds.), VCH Verlagsgesellschaft mbH: Weinheim, Germany, **1994**, p. 73.

11 Greater yields of up to 98% at 86% conversion were obtained when reactions were performed on a smaller scale, over 25 h. It was determined that one of the factors most influencing yields and reaction times was the rate of magnetic stirring. Indeed, it has been demonstrated that photochemical reactions only occur within the first few mm of the solution to which "active" wavelengths of light penentrate, hence the need for excellent mixing. This phenomenon has been recognised by other researchers, hence the move in industry towards continuous flow photoreactors which lead to high local concentrations of excited states (and which also maximise heat and mass transfer rates whilst minimising the quantity of solvent required for reaction): a) Horspool, W. M., In *Synthetic Organic Photochemistry*, Horspool, W. M. (Ed.) Plenum Press: New York, U.S.A., **1984**, p. 489; b) Ref. 10].

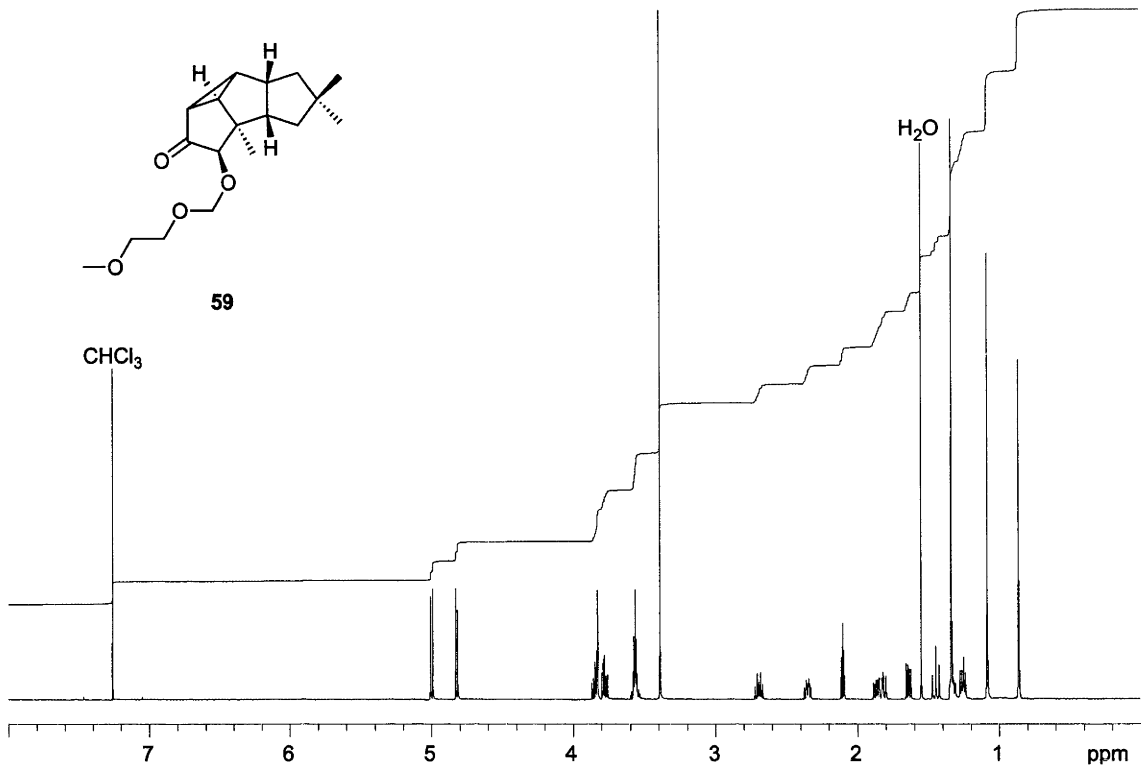



**Figure 3.5:** *500 MHz $^{1}H$ NMR spectrum of cyclopropyl ketone* ***59*** *in $CDCl_3$.*

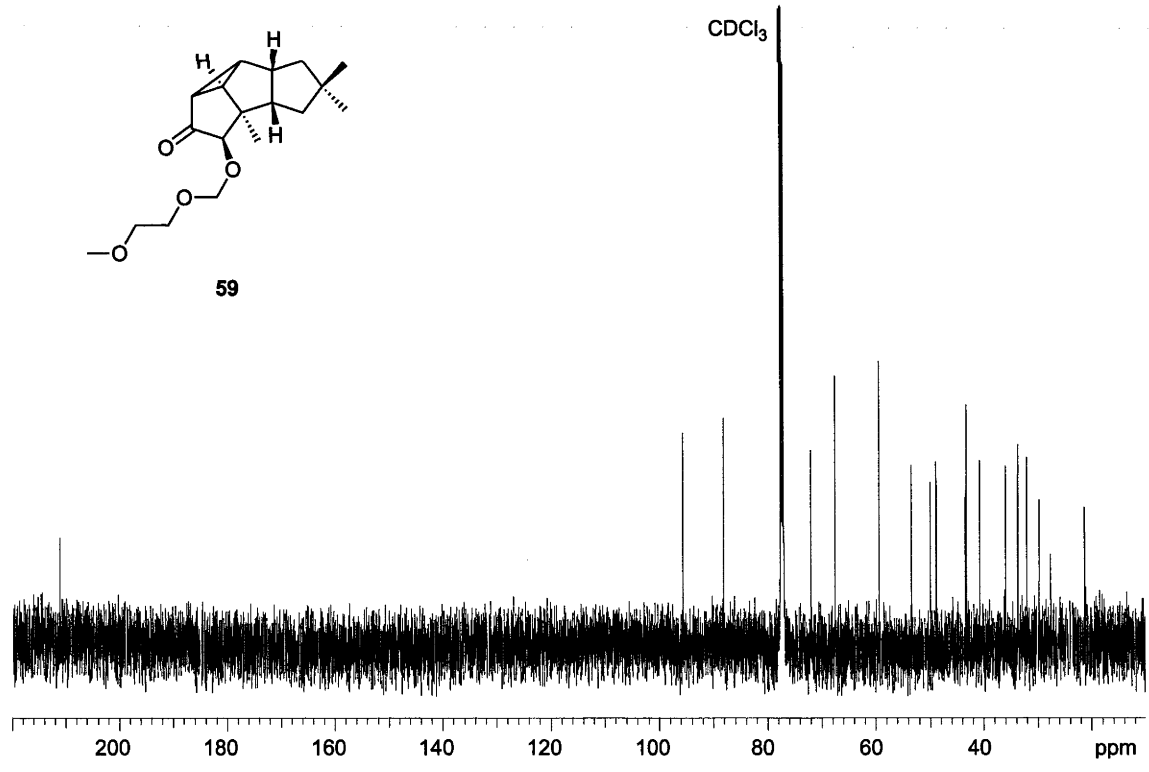
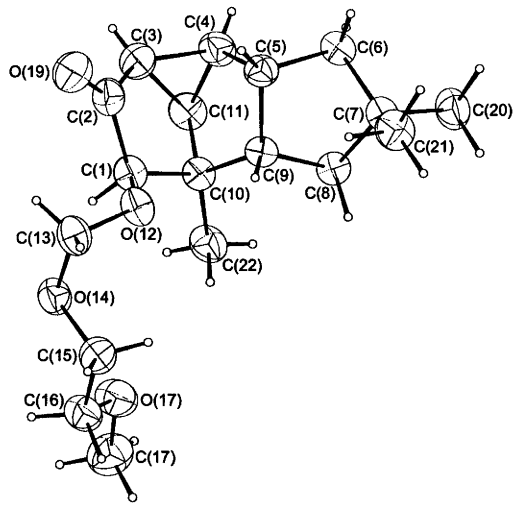



**Figure 3.6:** *126 MHz $^{13}C$ NMR spectrum of cyclopropyl ketone* ***59*** *in $CDCl_3$.*




**59**

**Figure 3.7:** *Displacement Ellipsoid Plot (50%) of cyclopropyl ketone* ***59*** *derived from single crystal X-ray analysis.*

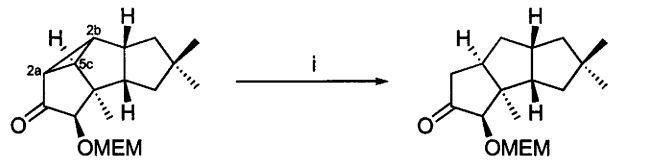
In addition to the cyclopropyl ketone **59**, three other minor products were also isolated from the reaction mixture. However, for the purposes of simplicity, the only photochemical reaction discussed in this Chapter is the triplet sensitised oxa-di-π-methane rearrangement proposed to occur *via* the $T_1$ ($\pi,\pi^*$) excited state. Side-reactions occurring under triplet sensitised conditions through the $T_2$ ($n,\pi^*$) excited state and reactions performed under direct irradiative reaction conditions are discussed in Chapter Four.

### 3.3.5 *O*-Stannyl ketyl-promoted cyclopropane ring scission

With the cyclopropyl ketone **59** in hand, it was necessary to cleave the peripheral C(2a) – C(2b) bond of the cyclopropane moiety, as required for the targeted natural product. Using a method successfully employed by Singh, Vedantham and Sahu (2002) in their recently reported synthesis of (±)-hirsutene,[12] the tetracycle **59** was subjected to *O*-stannyl ketyl-promoted cyclopropane scission by reaction with tri-*n*-butyltin hydride (in the presence of AIBN as a radical initiator) which effected, after reflux, cleavage of the peripheral C(2a) – C(2b) bond to form tricyclic ketone **137** (Scheme 3.9). The EI mass spectrum of the product reveals a parent ion at *m/z* 310, for which an accurate mass measurement established the molecular formula to be $C_{18}H_{30}O_4$, consistent with a mass increase of two hydrogen atoms and, hence, the reductive nature of the reaction. The $^1$H NMR spectrum of **137** (Figure 3.8) was fully assigned using a variety of connectivity experiments and, as expected, does not exhibit any of the features associated with the cyclopropane moiety of the starting material. Indeed, these data, along with the $^{13}$C NMR spectrum and other spectroscopic and analytical data, are in complete agreement with the proposed structure.

12 Singh, V.; Vedantham, P.; Sahu, P. K., *Tetrahedron Lett.*, **2002**, *43*, 519.

**Scheme 3.9:** *Peripheral cyclopropane ring scission of tetracycle* ***59*** *to form tricyclic ketone* ***137****.*




**59** **137** 87% (at 81% conversion)

*Reagents and conditions*: i) *n*-$Bu_3SnH$, AIBN, benzene, ambient temp. to reflux, 9 h.

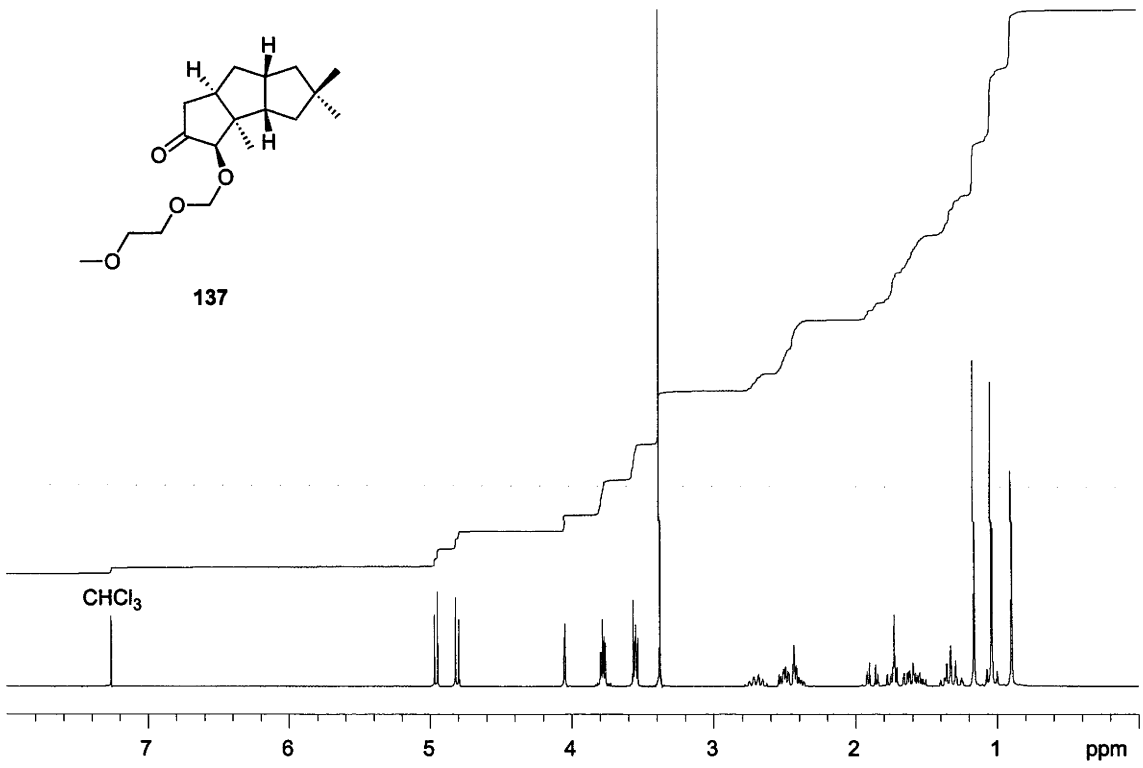



**Figure 3.8:** *300 MHz $^1H$ NMR spectrum of tricyclic ketone* ***137*** *in $CDCl_3$.*

The formation of tricycle **137** (87% at 81% conversion) from tetracycle **59** *via* *O*-stannyl ketyl-promoted cyclopropane ring scission may be rationalised with reference to the mechanism shown in Figure 3.9 (path i). From this Figure it can be seen that, in addition to **137**, a second product **138** may also be expected to form *via* cleavage of the C(2a) – C(5c) bond (Figure 3.9, path ii) of the ketyl radical intermediate common to both pathways. The formation of **137** as the sole product, may be explained by stereoelectronic effects, whereby overlap of the $sp^2$-like (*p*) orbital of the ketyl radical with the orbitals of the peripheral C(2a) – C(2b) bond is greater than with the orbitals of the internal C(2a) – C(5b) bond, to which the same $sp^2$-like

orbital is almost orthogonal,[13] as shown in Figure 3.9 (inset). This phenomenon has been demonstrated in the synthesis of a variety of sesquiterpene natural products, including (–)-acorenone B[14] and (±)-sinularene.[15]

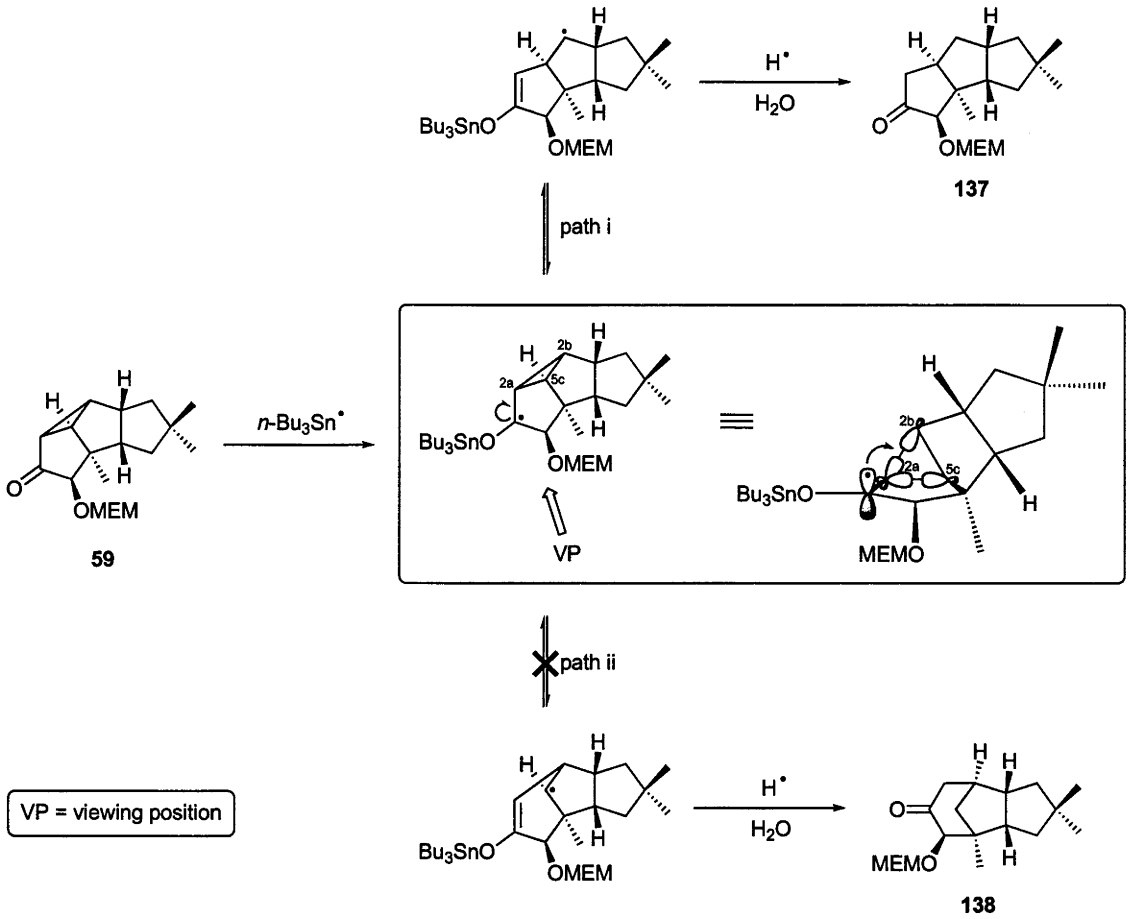



**Figure 3.9:** *Mechanism of* O*-stannyl ketyl-promoted cyclopropane ring scission and (inset) stereoelectronic relationship of the ketyl radical to the cyclopropane σ-bonds.*

### 3.3.6 Completion of the total synthesis of *ent*-(–)-hirsutene

With the acquisition of the *epi*-triquinane skeleton of the tricycle formed using the methods just described, attention was now focussed on that series of functional group interconversions required to transform this compound into the target *ent*-(–)-hirsutene [*ent*-(–)-**54**].

Given that the now redundant carbonyl moiety had served its purpose in promoting the oxa-di-π-methane rearrangement and, subsequently, in directing cleavage of the peripheral bond of the cyclopropane, it was deoxygenated using methods similar to those employed earlier (Section 3.3.2). To this end, the tricyclic ketone **137** was reduced to the corresponding alcohol

13 a) Beckwith, A. L. J.; Easton, C. J.; Serelis, A. K., *J. Chem. Soc., Chem. Commun.*, **1980**, 482; b) Beckwith, A. L. J., *Tetrahedron*, **1981**, *37*, 3073.

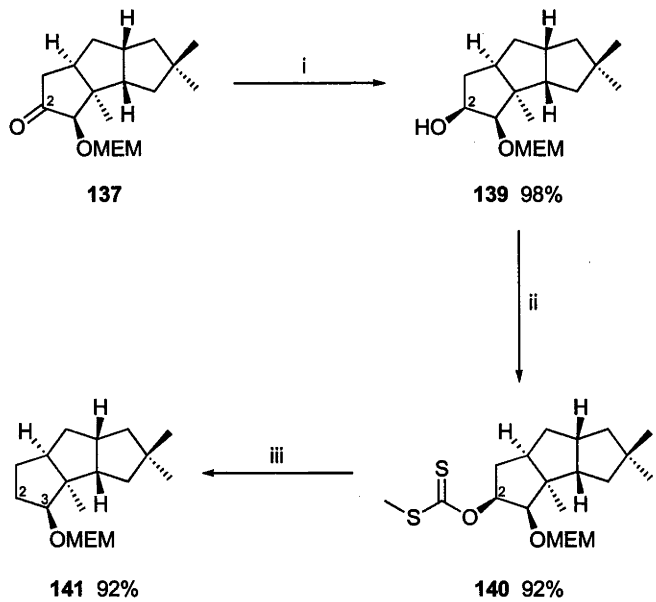
14 White, J. D.; Ruppert, J. F.; Avery, M. A.; Torii, S.; Nokami, J., *J. Am. Chem. Soc.*, **1981**, *103*, 1813.

15 Attah-Poku, S. K.; Antczak, K.; Alward, S. J.; Fallis, A. G., *Can. J. Chem.*, **1984**, *62*, 1717.

**139** upon exposure to sodium borohydride in methanol, thereby affording a single diastereoisomeric product in close to quantitative yield (Scheme 3.10). The derived $^{13}C$ NMR spectral data not only feature a signal at δ 72.9 associated with the C(2) carbon of the secondary alcohol moiety, but, *ipso facto*, complete absence of a resonance associated with the quaternary carbon of the carbonyl moiety of the precursor. This evidence is corroborated in the $^{1}H$ NMR spectrum of compound **139**, which exhibits a series of resonances in the form of a multiplet at δ 4.15 – 4.07 attributed to the presence of an oxymethine proton [H(2)] at C(2). NOESY experiments indicate a strong correlation between H(2) and protons on adjacent carbon atoms [H(1α), H(1β) and H(3)], while the C(2) hydroxyl proton only correlates to H(1β), suggesting that hydride delivery has occurred from the lower (α-) face of the molecule (as drawn), probably due to the steric hindrance of the MEM-ether preventing β-facial attack. The remaining spectroscopic and microanalytical data were fully consistent with the assigned structure.

Barton-McCombie-type deoxygenation procedures[2] were subsequently employed to deoxygenate the C(2) position of alcohol **139**, again using the two-step methodology similar to that successfully adopted in Section 3.2.2. To this end, the sodium alkoxide of alcohol **139** was reacted with carbon disulfide and subsequently with methyl iodide, to form the corresponding *S*-methyl xanthate ester **140** in 92% yield (Scheme 3.10).

**Scheme 3.10:** *Transformation of ketone 137 into compound 141 through deoxygenation at C(2).*




*Reagents and conditions*: i) $NaBH_4$, ambient temp., 3 h; ii) NaH, THF, reflux, 3 h, then $CS_2$, 0°C to reflux, 3 h, then MeI, 0°C to reflux, 3 h; iii) *n*-$Bu_3SnH$, AIBN, toluene, ambient temp. to reflux, 2 h.

The second stage of the Barton-McCombie-type deoxygenation procedure was effected by reacting the *S*-methyl xanthate ester **140** with the stannyl radical derived from tri-*n*-butyltin hydride in refluxing toluene, to afford deoxygenated product **141** in 92% yield (Scheme 3.10). Despite a marked absence of functionality on the essentially hydrocarbon skeleton making interpretation difficult, the $^{1}H$ and $^{13}C$ NMR spectra of the product ether **141** were able to be completely assigned through use of connectivity experiments. In both of the $^{1}H$ and $^{13}C$ NMR spectra, the only signals attributable to oxygenated functionality were those associated with the (2-methoxyethoxy)methoxy ether at C(3), thereby indicating that deoxygenation at C(2) was successful. Furthermore, the EI mass spectrum of compound **141** exhibits a molecular ion at *m/z* 296, for which an accurate mass measurement, when augmented with microanalytical data, established the expected molecular formula, *viz.* $C_{18}H_{32}O_3$.

Devoid of functionality other than the masked hydroxyl at C(3), the ether **141** is poised to selectively entertain those functional group interconversions necessary for installation of the final [C(3) methylene] carbon required for construction of the triquinane target, *ent*-(–)-hirsutene [*ent*-(–)-**54**]. To this end, deprotection of the ether **141** was achieved according to the conditions specified by Monti *et al.*[16] to cleanly afford the alcohol **142** in 76% yield (Scheme 3.11), which by comparison with previously reported total syntheses of racemic material,[17] constitutes a formal enantioselective synthesis of *ent*-(–)-hirsutene [*ent*-(–)-**54**]. Indeed, the $^{1}H$ NMR and IR spectroscopic properties for this material were in complete accord with those reported in the literature, with the exception of EI mass spectral analysis, which features a molecular ion at *m/z* 208 (*cf.* the reported fragment ion at *m/z* 206).[17f] Nevertheless, an accurate mass measurement was obtained on this ion, which was found to be consistent with both the microanalytical data and the expected molecular formula, namely $C_{14}H_{24}O$.

Subsequent oxidation of alcohol **142** to the corresponding norketone *ent*-**97** was effected in 71% yield, following a literature procedure that employed PCC as the oxidant (Scheme 3.11). The spectroscopic properties of the norketone *ent*-**97**, thus produced, were fully consistent with those reported in the asymmetric synthesis of *ent*-(–)-hirsutene [*ent*-(–)-**54**] by Weinges *et al.*[18] Although the optical rotation of the norketone *ent*-**97** {$[\alpha]_D^{19}$ –55.9 (c 0.37,

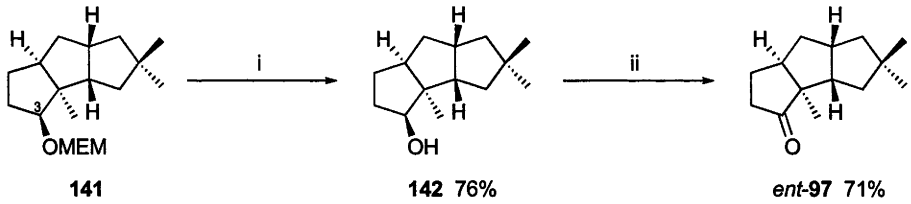
16 Monti, H.; Léandri, G.; Klos-Ringuet, M.; Corriol, C., *Synth. Commun.*, **1983**, *13*, 1021.

17 Racemic alcohol **142** is reported variously in the literature: a) Ref. 12; b) Tatsuta, K.; Akimoto, K.; Kinoshita, M., *J. Am. Chem. Soc.*, **1979**, *101*, 6116; c) Tatsuta, K.; Akimoto, K.; Kinoshita, M., *Koen Yoshishu - Tennen Yuki Kagobutsu Toronkai, 22nd Conference Proceedings*, **1979**, Department of Chemistry, Kyushu University, Fukuoka, Japan, 456; d) Franck-Neumann, M.; Miesch, M.; Lacroix, E., *Tetrahedron Lett.*, **1989**, *30*, 3529; e) Franck-Neumann, M.; Miesch, M.; Lacroix, E.; Metz, B.; Kern, J. M., *Tetrahedron*, **1992**, *48*, 1911; f) Toyota, M.; Nishikawa, Y.; Motoki, K.; Yoshida, N.; Fukumoto, K., *Tetrahedron Lett.*, **1993**, *34*, 6099; g) Toyota, M.; Nishikawa, Y.; Motoki, K.; Yoshida, N.; Fukumoto, K., *Tetrahedron*, **1993**, *49*, 11189. For References a), b), c), e), f) and g) the stereochemistry at C(3) is consistent with that described here: limited spectroscopic data are reported. References d) and e) do not define stereochemistry at C(3), but state respectively that "un seul épimère obtenu" and "un seul diastéréoisomère [...] obtenu".

18 Weinges, K.; Reichert, H.; Huber-Patz, U.; Irngartinger, H., *Liebigs Annalen der Chemie*, **1993**, 403.

$CHCl_3$)} differed in magnitude from that reported {$[\alpha]_{598}^{20}$ –81.5 (c 0.5, *n*-hexane)},[19] presumably due to solvent, concentration and/or temperature effects, the sign was consistent. Indeed, the microanalytical data obtained on the white, crystalline solid were consistent with the expected molecular formula of norketone *ent*-**97**, *viz.* $C_{14}H_{22}O$.

**Scheme 3.11:** *Synthesis of norketone* ent-**97**.




**141** **142** 76% *ent*-**97** 71%

*Reagents and conditions*: i) PPTS, *t*-BuOH, reflux, 8 h; ii) PCC, $CH_2Cl_2$, ambient temp., 16 h.

Like its precursor, the norketone *ent*-**97** was noted to be a volatile solid (m.p. 23 – 24°C) that readily sublimed *in vacuo*, confounding conventional handling techniques. Given this inherent characteristic of alcohol **142** (m.p. 44 – 46°C) and norketone *ent*-**97** it was considered that by minimising the number of steps involving manipulations of these two intermediates, loss of material due to volatility could be avoided by performing multiple reactions within one step. It should be noted that the subsequent (and yet to be discussed) methylenation of norketone *ent*-**97** to form *ent*-hirsutene [*ent*-(–)-**54**], using a non-stabilised ylid was considered unlikely to be trivial in the presence of an oxidant[20] and was therefore discounted from such a one-pot, multi-step sequence. It was, however, considered feasible to effect both the deprotection and subsequent oxidation steps in a single process. To this end, and in accord with the conditions specifed earlier, the ether **141** was deprotected, then cooled to 0°C and subsequently treated with an excess of Dess-Martin periodinane (Scheme 3.12). In order to homogenise the system, the reaction mixture was gently warmed to 32°C which had unforeseen consequences on the reaction outcome. In addition to the norketone *ent*-**97** (43%), modest yields of the α,β-unsaturated ketone **143** (41%) were also obtained, the spectroscopic properties of which are in accord with those described for the previously reported racemate.[21] This phenomenon, in which a ketone is dehydrogenated to the corresponding α,β-unsaturated ketone by single electron transfer processes using excess hypervalent iodine reagents at elevated

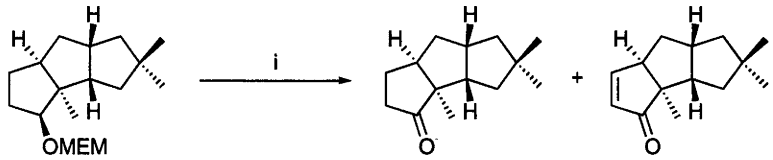
19 Note that the optical rotation of norketone *ent*-**97**, as reported in Ref. 18, was measured at a wavelength of 598 nm: all other optical rotation measurements in the same reference were recorded at 589 nm (the D-line of Na).

20 *In situ* primary alcohol oxidation – Wittig olefination using non-stabilised ylids has been recently reported: Blackburn, L.; Pei, C.; Taylor, R. J. K., *Synlett*, **2002**, *2*, 215.

21 Sternbach, D. D.; Ensinger, C. L., *J. Org. Chem.*, **1990**, *55*, 2725.

temperatures, has recently been exploited by Nicolaou *et al.*[22] However, since both the norketone *ent*-**97** and α,β-unsaturated ketone **143** were, in this case, formed in only modest yield[23] {the latter has previously been converted *via* a one-pot, two step procedure into *ent*-(–)-hirsutene [*ent*-(–)-**54**][24]}, it was considered prudent to return to conventional methodologies to complete the synthesis.

**Scheme 3.12:** *One-pot deprotection-oxidation protocol.*




**141** *ent*-**97** 43% **143** 41%

*Reagents and conditions*: i) PPTS, *t*-BuOH, reflux, 8 h, then *tris*-acetoxyperiodinane, 0°C to 32°C, 16 h.

The synthesis of *ent*-(–)-hirsutene [*ent*-(–)-**54**] was completed by reacting the coveted norketone *ent*-**97** with the phosphorane ylid generated by reaction of methyl triphenylphosphonium bromide with LiHMDS in deoxygenated toluene, according to modified literature procedures (Scheme 3.13).[25] Like its precursors **142** and *ent*-**97**, *ent*-(–)-hirsutene [*ent*-(–)-**54**] proved to be highly volatile but was isolated in 100% yield (at 32% conversion). The $^{1}$H NMR and $^{13}$C NMR spectra of *ent*-(–)-hirsutene [*ent*-(–)-**54**] (Figures 3.10 and 3.11, respectively) displayed all of the expected features and are in complete accord with the data reported by Weinges *et al.*, as well as that reported for the natural isomer. Likewise, the EI mass spectrum displays a molecular ion at *m/z* 204, while an accurate mass measurement on this species confirmed the expected molecular formula of $C_{15}H_{24}$. The specific rotation of $[\alpha]_D^{22}$ –26.0 (c 0.22, $CDCl_3$) observed for *ent*-(–)-hirsutene [*ent*-(–)-**54**] is of the opposite sign, but of similar magnitude as that observed for the natural product [(+)-**54**] {$[\alpha]_D^{22}$ +48 (c 0.35, pentane)}, and is in good agreement with that reported by Weinges for the non-natural isomer *et al.* {$[\alpha]_D^{20}$ –29.4 (c 1.0, *n*-pentane)}.[18]

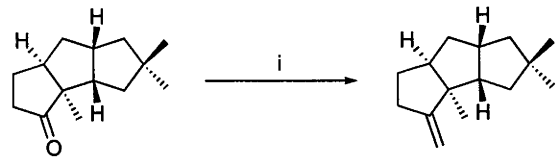
22 Refer to: Nicolaou, K. C.; Montagnon, T.; Baran, P. S., *Angew. Chem., Int. Ed. Engl.*, **2002**, *41*, 1386 and references 3 – 13 cited therein.

23 By controlling the amount of oxidant and using reduced temperatures, it is conceivable that the reaction outcome could be controlled to afford only one product. This possibility was not investigated because of the limited amounts of material available.

24 Involving Pt-catalysed hydrogenation, then Wittig methylenation, according to the procedure detailed in Ref. 21.

25 a) Hua, D. H.; Sinai-Zingde, G.; Venkataraman, S., *J. Am. Chem. Soc.*, **1985**, *107*, 4088; b) Hua, D. H.; Venkataraman, S.; Ostrander, R. A.; Sinai, G. Z.; McCann, P. J.; Coulter, M. J.; Xu, M. R., *J. Org. Chem.*, **1988**, *53*, 507; c) Hua, D. H., *Adv. Carbanion Chem.*, **1992**, *1*, 249; d) Nozoe, S.; Furukawa, J.; Sankawa, U.; Shibata, S., *Tetrahedron Lett.*, **1976**, 195.

**Scheme 3.13:** *Final step associated with the total synthesis of* ent-*(–)-hirsutene [*ent-*(–)-**54**].*




*ent*-**97** *ent*-(–)-**Hirsutene**

[*ent*-(–)-**54**] 100% (at 32% conversion)

*Reagents and conditions*: i) $Ph_3PMe$, KHMDS, toluene, 0°C to ambient temp., 2 h, then *ent*-**97** in toluene, 0°C to reflux, 1.5 h.

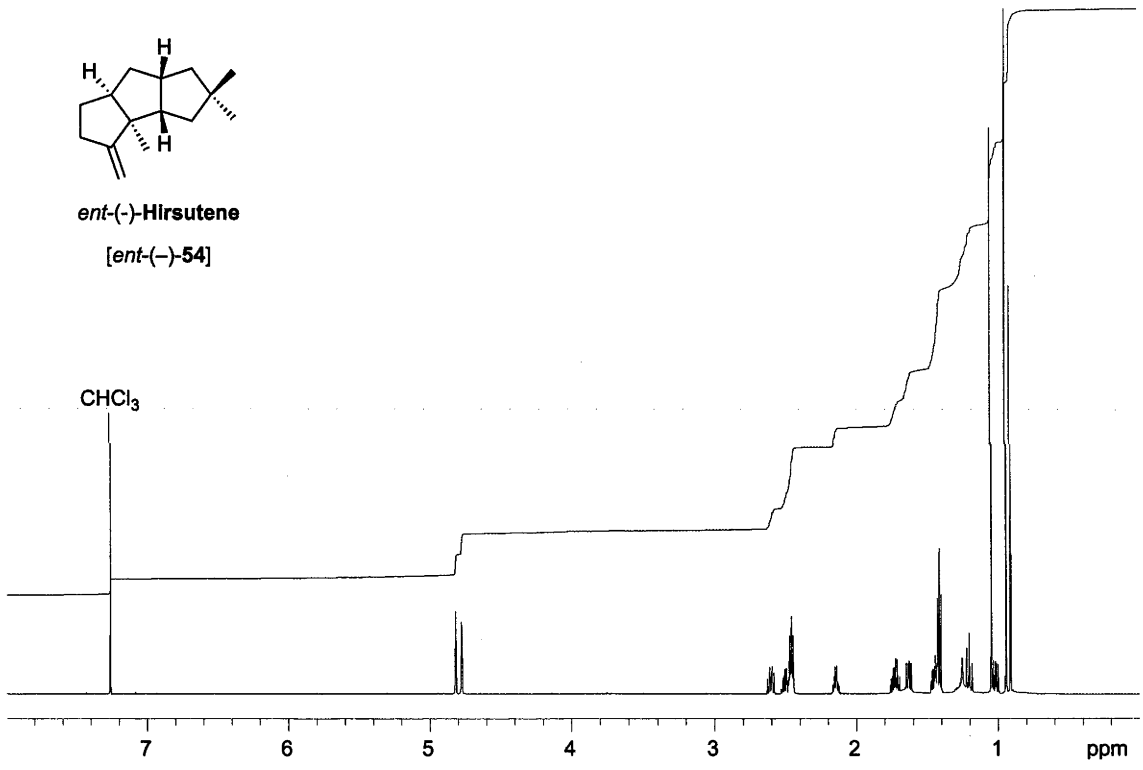



**Figure 3.10:** *600 MHz $^1H$ NMR spectrum of synthetic* ent-*(–)-hirsutene [*ent-*(–)-**54**] in $CDCl_3$.*

## 3.4 Enantiomeric switching and enantiodivergence: formal synthesis of (+)-hirsutene

One noteworthy feature of the above-mentioned synthesis of *ent*-(–)-hirsutene [*ent*-(–)-**54**], is that the enantiospecific outcome is ostensibly dictated by the chirality of the *cis*-1,2-dihydrocatechol **1** (X = Me). Since the enantiomer *ent*-**1** (X = Me) of *cis*-1,2-dihydrocatechol **1** (X = Me) is accessible from *p*-iodotoluene (**144**), *via* compound **145**,

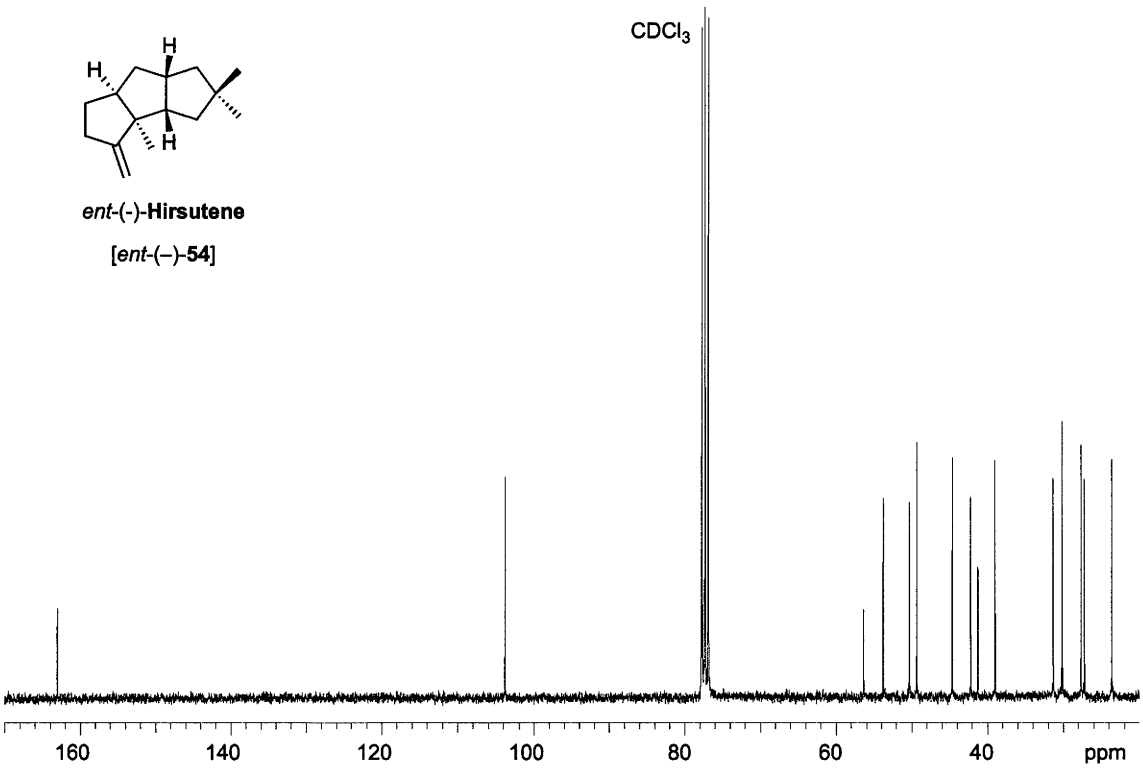



**Figure 3.11:** *75 MHz $^{13}C$ NMR spectrum of synthetic* ent-*(–)-hirsutene [*ent-*(–)-**54**] in $CDCl_3$.*

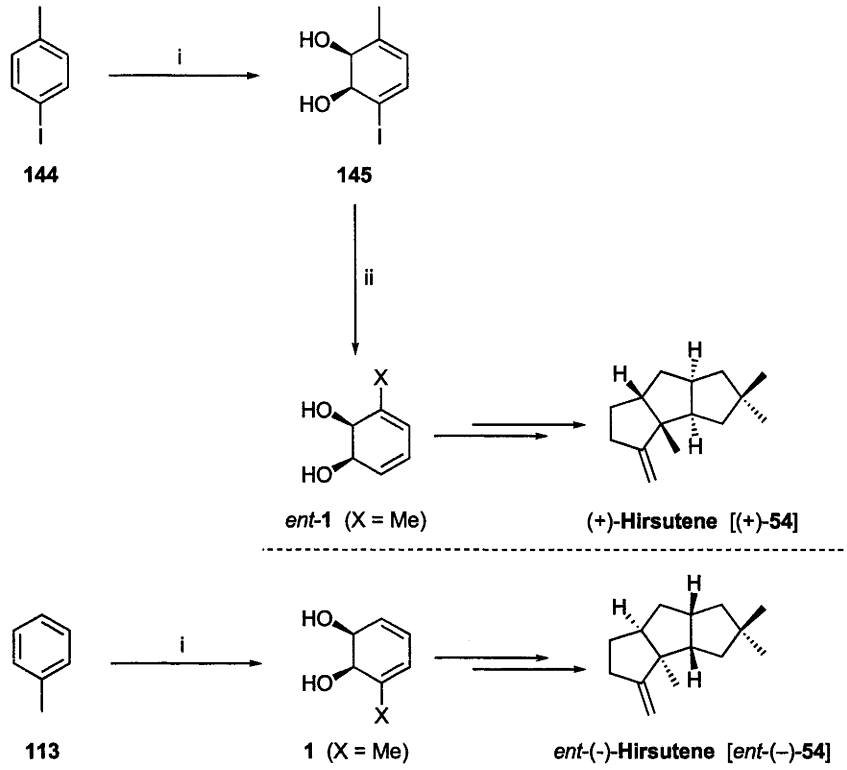
by virtue of a phenomenon known as enantiomeric switching (described in Chapter One),[26] the synthesis detailed above therefore also constitutes a formal total synthesis of the natural product (+)-hirsutene [(+)-**54**] (Scheme 3.14).

In addition to this feature of the synthesis, there is also the potential to access (+)-hirsutene from *cis*-1,2-dihydrocatechol **1** (X = Me) itself. In the synthesis discussed above, *cis*-1,2-dihydrocatechol **1** (X = Me) engages in a high pressure-promoted Diels-Alder cycloaddition reaction with cyclopenten-2-one (**14**) to afford the *syn*-product **15** in 70% yield, which was then converted into the non-natural enantiomer *ent*-(–)-hirsutene [*ent*-(–)-**54**]. It has been demonstrated that by protecting the *cis*-1,2-dihydrocatechol **1** (X = Me) as the corresponding acetonide **31** (85%),[27] prior to performing the high pressure-promoted Diels-Alder cycloaddition reaction, the diastereofacial selectivity of this reaction is reversed, such that an *anti*-adduct **146** is produced in 56% yield (Scheme 3.15).[1] This product incorporates a skeletal core which is related enantiomerically to that of the *syn*-product **15** (and is essentially identical to the *anti*-by-product **16** produced from the same reaction). By virtue of the use of the protected or non-protected variants of *cis*-1,2-dihydrocatechol **1** (X = Me) to control the facial selectivity, it is therefore possible to access either of these pseudo-enantiomers through a

26 Boyd, D. R.; Sharma, N. D.; Barr, S. A.; Dalton, H.; Chima, J.; Whited, G.; Seemayer, R., *J. Am. Chem. Soc.*, **1994**, *116*, 1147.

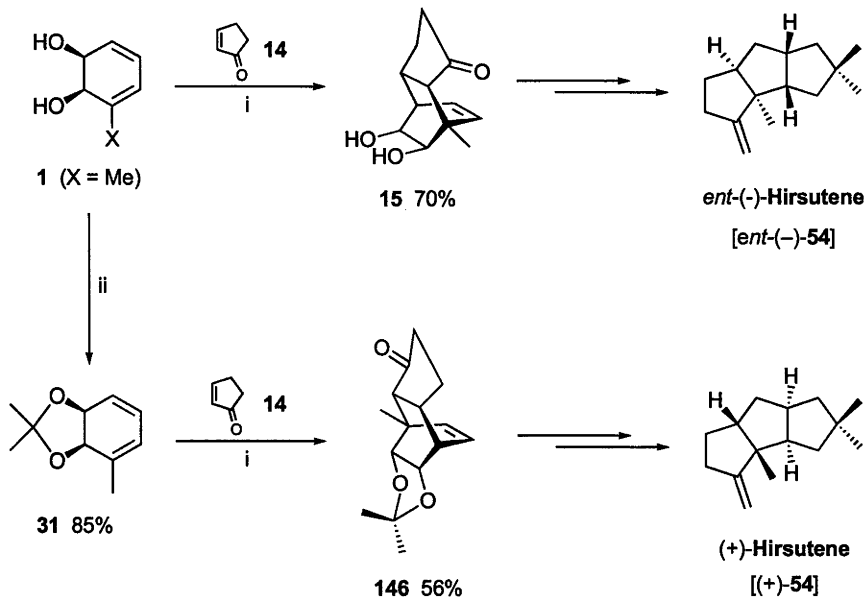
27 Hudlicky, T.; Luna, H.; Barbieri, G.; Kwart, L. D., *ibid.* **1988**, *110*, 4735.

**Scheme 3.14:** *Formal synthesis of (+)-hirsutene [(+)-54]* via *enantiomeric switching.*




*Reagents and conditions*: i) *E. coli* JM109 (pDTG601A); ii) $H_2$, Pd/C, MeOH.

**Scheme 3.15:** *Enantiodivergent approach to (+)-hirsutene [(+)-54].*




*Reagents and conditions*: i) 19 kbar, $CH_2Cl_2$, 20°C, 24 h; ii) 2,2-DMP, *p*-TsOH, $CH_2Cl_2$,

phenomenon that may be regarded as enantiodivergence. Based on this premise and considering the application of the chemistry defined earlier in this Chapter, it is reasonable to anticipate that the *anti*-pseudo-enantiomer **146** would be able to be converted through a similar series of pseudo-enantiomeric intermediates, to the natural product (+)-hirsutene [(+)-**54**] (Scheme 3.15).

## 3.5 Conclusion

In the synthesis detailed above, the Diels-Alder cycloaddition adduct **15** has been converted into the non-natural enantiomer [*ent*-(–)-**54**] of the natural product (+)-hirsutene [(+)-**54**]. The seventeen-step synthesis leading to *ent*-(–)-hirsutene [*ent*-(–)-**54**] from *cis*-1,2-dihydrocatechol **1** (X = Me) is completely enantioselective and proceeds in an overall yield of 14%.

The chemistries described not only in this Chapter, but also in Chapter Two, should, in principle, lend themselves to the synthesis of more highly oxygenated linear triquinane-type natural products. This feature, coupled with the capacity to obtain either enantiomeric form of the linear triquinane skeleton associated with the natural product (+)-hirsutene [(+)-**54**] by virtue of enantiomeric switching and enantiodivergence phenomena, should render the chemistries and strategies employed in this synthesis particularly powerful methods for synthesising linear triquinanes.

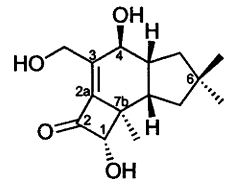
*Chapter Four*

# *Towards the Synthesis of (–)-Tsugicoline A and (+)-Isovelleral*

## 4.1 Introduction

### 4.1.1 Isolation and structure of (–)-tsugicoline A

(–)-Tsugicoline A [(–)-**55**] (Figure 4.1) belongs to the protoilludane class of sesquiterpene fungal metabolites and was isolated by Nasini *et al.* in 1995 from the Basidiomycete *Laurilia tsugicola* (Henn. and Shirai) [*Echinodontium tsugicola*] (CBS 248.51), a decay agent found on trees of the genus *Tsuga* and *Abies*.[1]




**(–)-Tsugicoline A**

**[(–)-55]**

**Figure 4.1:** *Structure and associated numbering system of (–)-tsugicoline A [(–)-55].*

The structure of this sesquiterpene was elucidated through spectroscopic studies that revealed (–)-tsugicoline A [(–)-**55**] to be composed of a tricyclic core in which cyclobutyl and cyclopentyl rings are *anti*-fused to adjacent pairs of atoms of a central cyclohexenyl system. Unlike the majority of protoilludanes,[2] (–)-tsugicoline A [(–)-**55**] features a carbonyl moiety at the C(2) position of the cyclobutyl ring. This ketone moiety is conjugated with the olefinic

1 Arnone, A.; Brambilla, U.; Nasini, G.; Vajna de Pava, O., *Tetrahedron*, **1995**, *51*, 13357.

2 Protoilludanes are often referred to as $\Delta^{6(7)}$-protoilludanes, to denote the alkene ($\Delta$) at the 6-position of the sesquiterpene framework, in accordance with IUPAC convention. For the purposes of simplicity and consistency, the $\Delta^{6(7)}$-prefix has been omitted (unless specified) when referring to such protoilludanes in this Thesis, since the ACS nomenclature employed herein does not follow this notation or numbering system.

bond originating at the C(2a) ring junction and terminating at C(3). Additionally, C(3) features a hydroxymethylene substituent, which, along with the *gem*-dimethyl moiety present at C(6) and the α-oriented angular methyl at C(7b), constitute the remaining atoms associated with the fifteen-carbon framework of the protoilludane skeleton. Two hydroxyl moieties (in addition to that of the hydroxymethylene) are also present: one α-oriented at C(1) and a second β-oriented at C(4).

### 4.1.2 Biological properties and proposed biogenesis of (–)-tsugicoline A

(–)-Tsugicoline A [(–)-**55**] is reported to be biologically inactive against a variety of microörganisms, including several common bacteria and fungi, but does inhibit germination of the cress *Lepidium sativum*, a property which may be attributed to the presence of the strained enone moiety acting as a Michael acceptor.[1] (–)-Tsugicoline A [(–)-**55**] is produced by a fungal pathogen of pine trees of the genera *Tsuga* (hemlock) and *Abies* (spruce), and since the natural product is phytotoxic, it may have potentially useful applications in the forestry industry.

Perhaps the most significant biological rôle of (–)-tsugicoline A [(–)-**55**] is its intermediacy in the biosynthesis of other protoilludane sesquiterpenes.[3] (–)-Tsugicoline A [(–)-**55**] is the first reported sesquiterpene of protoilludane origin with two oxidated carbons in the cyclobutyl ring and, as such, is proposed to be a common intermediate in the biosynthesis of the representative selection of protoilludanes shown in Figure 4.2, including (–)-stearoyldelicone [(–)-**147**],[4] (–)-coprinolone [(–)-**148**],[5] (–)-sulcatine B [(–)-**149**][6] and (–)-lentinellic acid [(–)-**150**].[7]

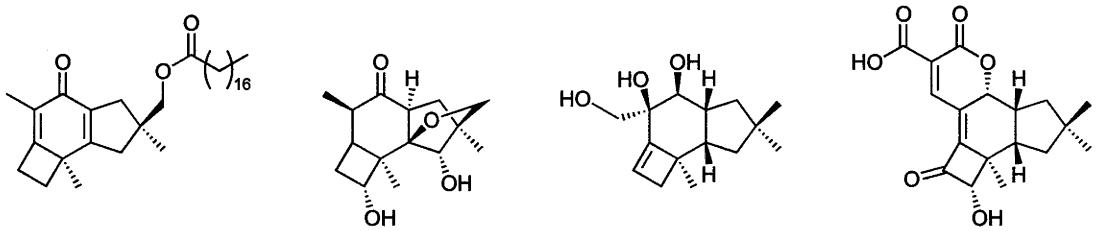



**Figure 4.2:** *A selection of protoilludane natural products.*

3 Ayer, W. A.; Browne, L. M., *Tetrahedron*, **1981**, *37*, 2199.

4 (–)-Stearoyldelicone [(–)-**147**] was isolated from the Basidiomycete *Russula delica* and is biologically inactive: Clericuzio, M.; Pan, F.; Han, F.; Pang, Z.; Sterner, O., *Tetrahedron Lett.*, **1997**, *38*, 8237.

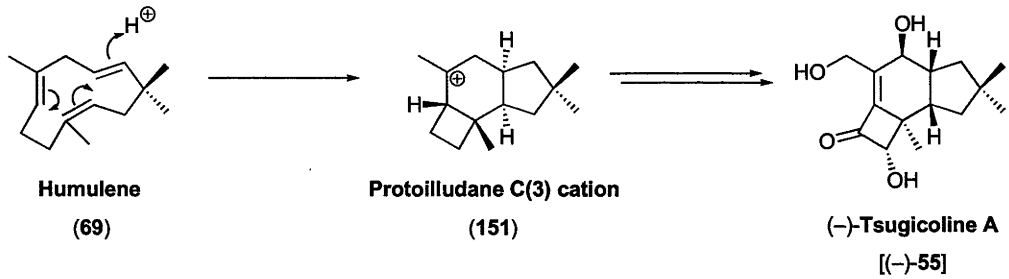
5 (–)-Coprinolone [(–)-**148**] was isolated from the Basidiomycete *Coprinus psychromorbidus* and is biologically inactive: Starratt, A. N.; Stothers, J. B.; Ward, E. W. B., *J. Chem. Soc., Chem. Commun.*, **1988**, 590.

6 (–)-Sulcatine B [(–)-**149**] was isolated from the rare Basidiomycete *Laurilia sulcata* (Burt) Pouzar and exhibits antifungal properties: Arnone, A.; Nasini, G.; Assante, G.; van Eijk, G. W., *Phytochemistry*, **1992**, *31*, 2047.

7 (–)-Lentinellic acid [(–)-**150**] was isolated from cultures of *Lentinellus omphalodes* (Fr.) P. Karst. and *L. ursinus* (Fr.) Kühn. The natural product is cytotoxic and exhibits broad-spectrum antibacterial and antifungal properties: Stärk, A.; Anke, T.; Mocek, U.; Steglich, W.; Kirfel, A.; Will, G., *Z. Naturforsch., C: Biosci.*, **1988**, *43*, 177.

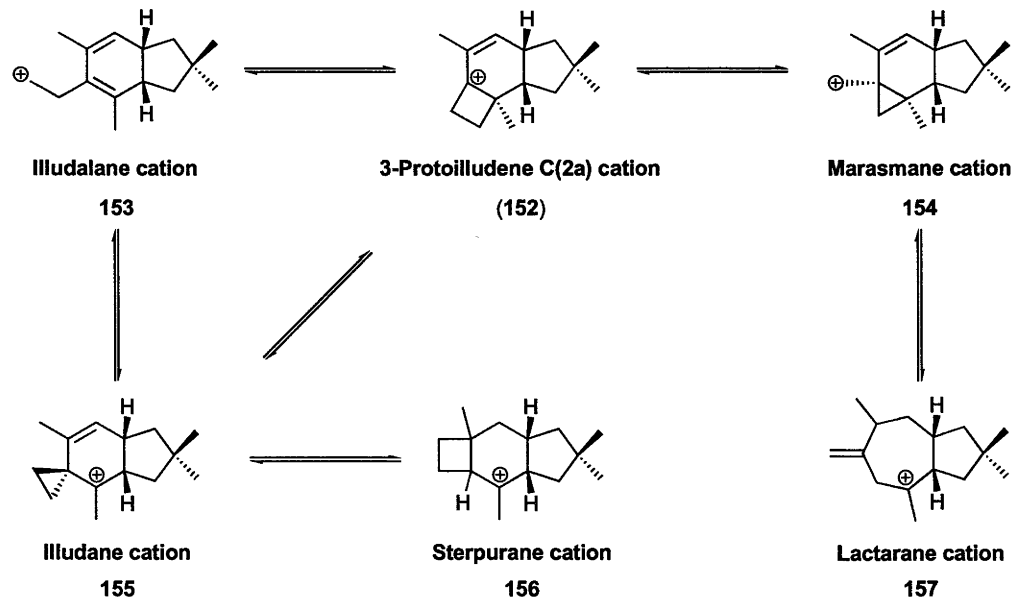
Additionally, (–)-tsugicoline A [(–)-**55**] is considered to belong to the cyclohumulanoid group of sesquiterpenes that are biogenetically derived from humulene (**69**) *via* a protoilludane C(3) cation (**151**) (Scheme 4.1).[1]

**Scheme 4.1:** *Possible pathway associated with the biogenetic synthesis of (–)-tsugicoline A [(–)-55] from humulene (69).*




Extensive biomimetic studies suggest that protoilludanes such as tsugicoline A (**55**) may, in turn, be precursors to 3-protoilludene C(2a) cations of the general type **152** which can, in turn, lead to the isomeric cations (**153** – **157**, shown in Scheme 4.2) that are implicated in the biosynthesis of the illudane, illudalane, marasmane, sterpurane and lactarane classes of sesquiterpene, respectively.[3, 8]

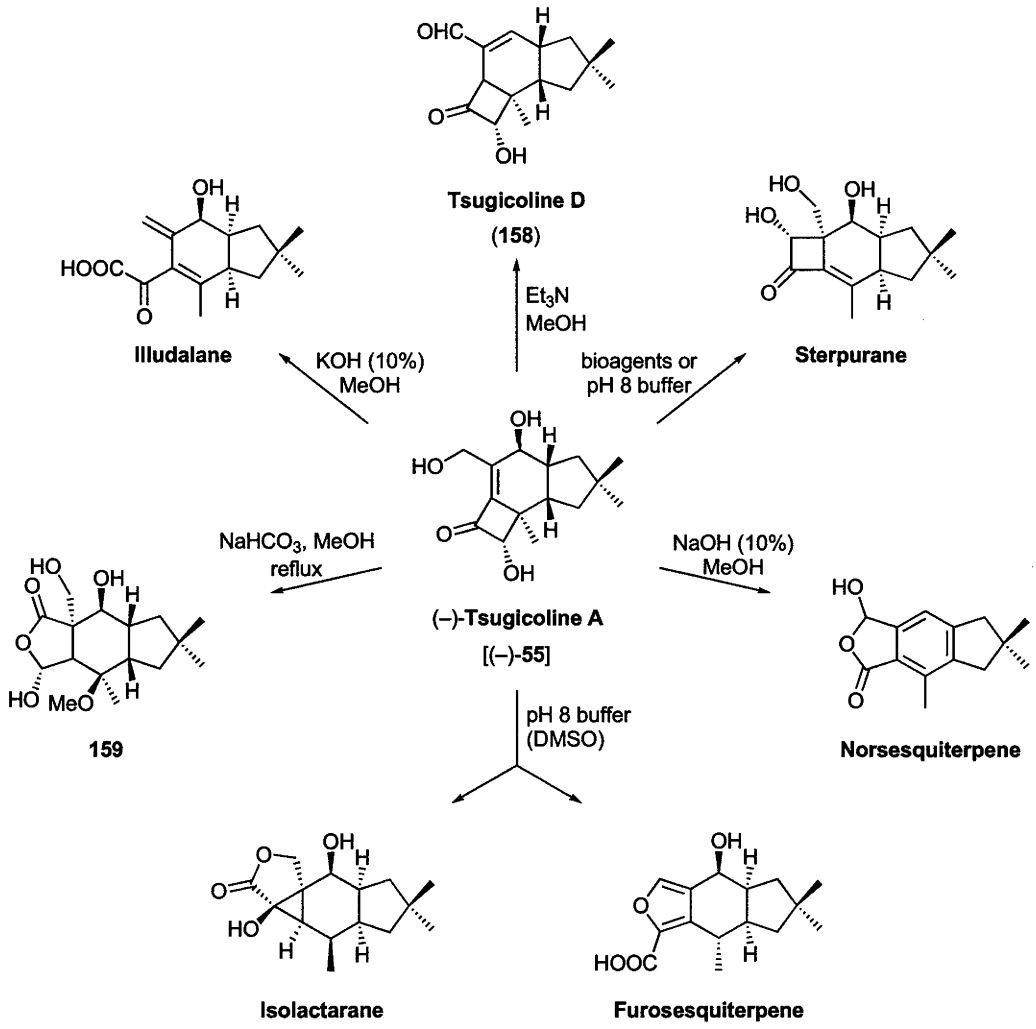
**Scheme 4.2:** *Biogenetic synthesis of illudane, illudalane, marasmane, sterpurane and lactarane classes of sesquiterpene from 3-protoilludene C(2a) cations of the general type 152.*




8 a) Morisaki, N.; Furukawa, J.; Kobayashi, H.; Iwasaki, S.; Itai, A.; Nozoe, S.; Okuda, S., *Chem. Pharm. Bull.*, **1985**, *33*, 2783; b) Morisaki, N.; Furukawa, J.; Kobayashi, H.; Iwasaki, S.; Nozoe, S.; Okuda, S., *Chem. Pharm. Bull.*, **1987**, *35*, 2678. Note that 3-protoilludene C(2a) cations of the type **152** are constitutionally heterotopic with 2a-protoilludene C(4) cations.

In fact, compounds embodying the framework of the illudalane and sterpurane classes of sesquiterpene can be generated biomimetically from tsugicoline A (Scheme 4.3).[9, 10] (–)-Tsugicoline A [(–)-**55**] can also be converted into related protoilludane [*i.e.* tsugicoline D (**158**)],[1] furosesquiterpene, norsesquiterpene and isolactarane skeleta,[10b] each of which is embodied within various natural products. Base-induced isomerisation of (–)-tsugicoline A [(–)-**55**] also affords the lactone **159**, the novel structure of which remains to be observed amongst natural products.[10b] Such observations have implications regarding the biogenetic pathways so far accepted for the formation of sesquiterpenes of protoilludane origin.

**Scheme 4.3:** *Biomimetic formation of various sesquiterpene frameworks from (–)-tsugicoline A [(–)-55].*

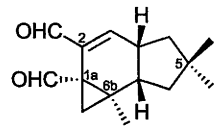



9 Although (–)-tsugicoline A [(–)-**55**] has not been isomerised into marasmane-type or illudane-type structures, synthetic protoilludanes have been converted, *via* 3-protoilludene C(2a) cations of the type **152**, into the corresponding marasmanes and illudanes.

10 a) Arnone, A.; De Gregorio, C.; Nasini, G.; De Pava, O. V., *J. Chem. Soc., Perkin Trans. 1*, **1997**, 1523; b) Arnone, A.; De Gregorio, C.; Mele, A.; Nasini, G.; Vajna de Pava, O., *J. Chem. Soc., Perkin Trans. 1*, **2000**, 745.

### 4.1.3 Isolation and structure of (+)-isovelleral

(+)-Isovelleral [(+)-**56**] belongs to the marasmane class of sesquiterpene fungal metabolites first isolated[11] in 1969 from the Basidiomycete *Lactarius vellereus* by List and Hackenberg, but later identified[12] in damaged tissues of both *L. vellereus* and *L. pergamenus* by Magnusson, Thorén and Wickberg who assigned a preliminary structure to the natural product (Figure 4.3). The relative stereochemistry of (+)-isovelleral [(+)-**56**] was assigned by Camazine *et al.* who isolated the natural product from another source, the Basidiomycete *Lentinellus ursinus*.[13] The enantioselective total synthesis of (+)-isovelleral [(+)-**56**] reported by Bergman *et al.* in 1990 unequivocally established the absolute stereochemistry of the natural isomer,[14] supporting earlier, and tentative, biogenetic assignments[15] that the absolute configuration matched that of related marasmane sesquiterpenes.




**(+)-Isovelleral**

**[(+)-56]**

**Figure 4.3:** *Structure and associated numbering system of (+)-isovelleral [(+)-56].*

Like other members of the marasmane class of sesquiterpene, (+)-isovelleral [(+)-**56**] consists of a *cis*:*anti*:*cis*-fused 3:6:5 cyclopropa[*e*]indene skeleton in which the olefinic bond is situated between the carbon atoms of the cyclohexyl ring that are not engaged in ring fusion.[16] Additionally, (+)-isovelleral features a *gem*-dimethyl moiety at C(5), methyl functionality at the cyclopropyl ring junction C(6b) and an aldehyde moiety at each of the opposing cyclopropyl ring junction C(1a) and at the adjacent terminus of the olefinic bond at C(2).

### 4.1.4 Biological properties and proposed biogenesis of (+)-isovelleral

The unsaturated dialdehyde functionality prominent within the cyclopropa[*e*]indene framework of (+)-isovelleral [(+)-**56**] represents a highly electrophilic substructure that is considered to be the origin of the natural product's novel biological activity.[13] First recognised as an active principle in the pungent sap of various *Lactarius sp.*, (+)-isovelleral [(+)-**56**] was

11 List, P. H.; Hackenberg, H., *Arch. Pharm. (Weinheim, Ger.)*, **1969**, *2*, 125.

12 Magnusson, G.; Thorén, S.; Wickberg, B., *Tetrahedron Lett.*, **1972**, 1105.

13 Camazine, S. M.; Resch, J. F.; Eisner, T.; Meinwald, J., *J. Chem. Ecol.*, **1983**, *9*, 1439.

14 Bergman, R.; Hansson, T.; Sterner, O.; Wickberg, B., *J. Chem. Soc., Chem. Commun.*, **1990**, 865.

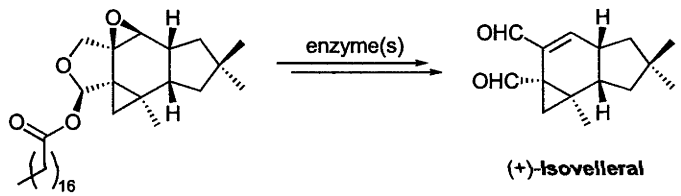
15 Kihlberg, J.; Bergman, R.; Nilsson, L.; Sterner, O.; Wickberg, B., *Tetrahedron Lett.*, **1983**, *24*, 4631.

16 The ivaxillaranes – a very small class of sesquiterpenes - also embody the cyclopropa[*e*]indene framework: a) Herz, W.; Sudarsanam, V.; Schmid, J. J., *J. Org. Chem.*, **1966**, *31*, 3232; b) Romo, J.; de Vivar, A. R.; Nathan, P. J., *Tetrahedron*, **1967**, *23*, 29; c) Benesová, V.; Sedmera, P.; Herout, V.; Sorm, F., *Tetrahedron Lett.*, **1971**, 2679; d) Benesová, V.; Sedmera, P.; Herout, V.; Sorm, F., *Collect. Czech. Chem. Commun.*, **1973**, *38*, 1084.

isolated[11] as a pungent and peppery-tasting compound that acts as an antifeedant in mammals.[13] (+)-Isovelleral [(+)-**56**] also exhibits antibacterial and antifungal properties,[17] in addition to which, it is phytotoxic[17c, 17d] as well as being cytotoxic towards mammalian cells (through lysis).[17c, 17d] The natural product exhibits potent mutagenic activity in bacterial and mammalian cells[17] and also displays affinity for the dopamine D1 and vanillanoid nerve cell receptors.[17d]

It is currently believed that (+)-isovelleral [(+)-**56**] is generated from unstable fatty acid esters of the marasmane velutinal *via* enzymatic hydrolysis, ring opening and elimination reactions which are initiated upon physical damage to the mycotic tissues from which (+)-isovelleral [(+)-**56**] is isolated (Scheme 4.4).[18] This response to injury is considered to constitute a chemical defence system against parasites.[17b] Whilst esters such as stearoylvelutinal (**160**) are otherwise biologically inactive, these natural products are formed from humulene (**69**) (and stearoic acid) *via* protoilludane sesquiterpenes such as (–)-tsugicoline A [(–)-**55**] and are considered to be the biogenetic precursors to both the marasmane and lactarane family of sesquiterpenes (Scheme 4.2).[19]

**Scheme 4.4:** *Enzymatic production of (+)-isovelleral [(+)-56] from stearoylvelutinal (160).*




**Stearoylvelutinal**

**(160)**

**(+)-Isovelleral**

**[(+)-56]**

17 a) Sterner, O.; Bergman, R.; Kesler, E.; Magnusson, G.; Nilsson, L.; Wickberg, B.; Zimerson, E., *Mutat. Res.*, **1982**, *101*, 269; b) Sterner, O.; Bergman, R.; Kihlberg, J.; Wickberg, B., *J. Nat. Prod.*, **1985**, *48*, 279; c) Anke, H.; Hillen-Maske, E.; Steglich, W., *Z. Naturforsch., C: Biosci.*, **1989**, *44*, 1; d) Jonassohn, M.; Hjertberg, R.; Anke, H.; Dekermendjian, K.; Szallasi, A.; Thines, E.; Witt, R.; Sterner, O., *Bioorg. Med. Chem.*, **1997**, *5*, 1363.

18 Hansson, T.; Sterner, O., *Tetrahedron Lett.*, **1991**, *32*, 2541.

19 *In vivo* studies indicate that marasmanes and lactaranes are produced *via* independent, parallel pathways from stearoylvelutinal esters: a) Hansson, T.; Pang, Z.; Sterner, O., *Acta Chem. Scand.*, **1993**, *47*, 403, although biomimetic studies show that marasmanes may be isomerised into lactaranes directly: b) De Bernardi, M.; Vidari, G.; Vita-Finzi, P.; Fiasson, K. G., *Tetrahedron Lett.*, **1982**, *23*, 4623.

## 4.2 Previous studies on the synthesis of (–)-tsugicoline A

### 4.2.1 Overview

To date no total syntheses of (–)-tsugicoline A [(–)-**55**] have been reported, although several methods for the formation of protoilludane natural products embodying the cyclobuta[*e*]indene framework associated with this sesquiterpene have been developed, particularly in connection with the synthesis of simpler (*i.e.* less highly oxygenated) protoilludanes such as illudol,[20] pteridanone[21] and 6-protoilludene.[22] The three total syntheses of racemic illudol [(±)-**161**] extant in the literature,[20b - 20d] are representative of the current state of research into the total synthesis of protoilludane natural products and, as such, are described below.[23]

### 4.2.2 Total syntheses of (±)-illudol

***Matsumoto's synthesis of (±)-illudol (1971)***

The synthesis of (±)-illudol [(±)-**161**] reported[20b] by Matsumoto *et al.* in 1971 was based on the earlier observation[24] that diquinanes react with 1,1-dialkoxyethylene molecules under photochemical conditions to form *cis*:*anti*:*cis*-fused 4:5:5 tricyclic structures. Provided these tricycles incorporate a pendant carbon atom and diol moiety peripheral to the inner ring, central ring-expansion could be effected, *via* oxidative cleavage and concomitant aldol condensation, to furnish 4:6:5 tricylic structures resembling the protoilludane framework.[25]. In this synthesis, (±)-illudol [(±)-**161**] is produced in less than 1% yield over nineteen steps (Scheme 4.5).

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20 Isolation: a) McMorris, T. C.; Nair, M. S. R.; Anchel, M., *J. Am. Chem. Soc.*, **1967**, *89*, 4562. Synthesis: b) Matsumoto, T.; Miyano, K.; Kagawa, S.; Yu, S.; Ogawa, J.; Ichihara, A., *Tetrahedron Lett.*, **1971**, 3521; c) Semmelhack, M. F.; Tomoda, S.; Hurst, K. M., *J. Am. Chem. Soc.*, **1980**, *102*, 7567; d) Semmelhack, M. F.; Tomoda, S.; Nagaoka, H.; Boettger, S. D.; Hurst, K. M., *J. Am. Chem. Soc.*, **1982**, *104*, 747; e) Semmelhack, M. F., In *Strategies and Tactics in Organic Synthesis*, Lindberg, T. (Ed.) Academic Press: London, England, **1984**, p. 201; f) Johnson, E. P.; Vollhardt, K. P. C., *J. Am. Chem. Soc.*, **1991**, *113*, 381.

21 Isolation: a) Castillo, U. F.; Sakagami, Y.; Alonso-Amelot, M.; Ojika, M., *Tetrahedron*, **1999**, *55*, 12295. Partial synthesis: b) Mehta, G.; Ghosh, P.; Sreenivas, K., *ARKIVOC (Gainesville, FL, U. S.)*, **2003**, 92.

22 Isolation: a) Nozoe, S.; Kobayashi, H.; Urano, S.; Furukawa, J., *Tetrahedron Lett.*, **1977**, 1381; b) Hannsen, H.-P.; Sprecher, E.; Abraham, W.-R., *Phytochemistry*, **1986**, *25*, 1979. Synthesis: c) Furukawa, J.; Morisaki, N.; Kobayashi, H.; Iwasaki, S.; Nozoe, S.; Okuda, S., *Chem. Pharm. Bull.*, **1985**, *33*, 440; d) Oppolzer, W.; Nakao, A., *Tetrahedron Lett.*, **1986**, *27*, 5471.

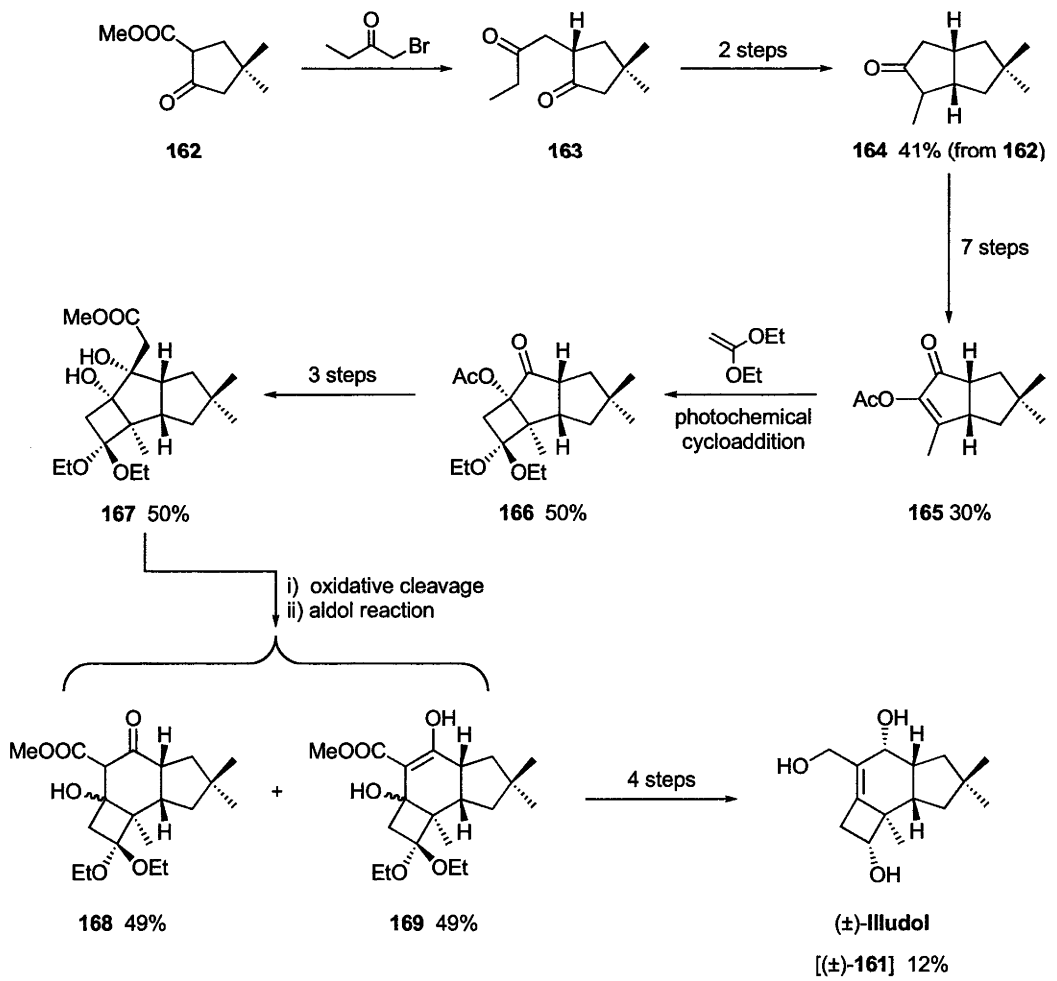
23 Indeed, the three total syntheses of (±)-illudol [(±)-**161**] (Refs. 20b – 20d) and the two total syntheses of 6-protoilludene (Refs. 22c – 22d) constitute the entirety of total syntheses of protoillud-2a-ene natural products (a.k.a. $\Delta^6$-protoilludanes).

24 Kagawa, S.; Matsumoto, S.; Nishida, S.; Yu, S.; Morita, J.; Ichihara, A.; Shirahama, H.; Matsumoto, T., *Tetrahedron Lett.*, **1969**, 3913.

25 These two key features of Matsumoto's synthesis were later exploited by Morisaka *et al.* in their 1985 syntheses of the natural products (±)-6-protoilludene (Ref. 22c) and 8-hydroxy-6-protoilludene, the latter being a biosynthetic precursor of cyclohumulanoid sesquiterpenes: Morisaki, N.; Furukawa, J.; Kobayashi, H.; Iwasaki, S.; Itai, A.; Nozoe, S.; Okuda, S., *Chem. Pharm. Bull.*, **1985**, *33*, 2783.

The synthesis commenced upon treatment of a mixture of the methyl ester of 4,4-dimethyl-2-keto-cyclopentanecarboxylic acid (**162**) and bromomethyl ethyl ketone, with sodium hydride. Subsequent reaction with perchloric acid afforded the diketone **163** which, upon base-promoted cyclisation and catalytic hydrogenation, formed the bicycle **164** (41% from **162**). The latter compound was converted, through a series of standard functional group interconversions, into the olefinic diquinane **165** (30% over seven steps) which, when irradiated in the presence of 1,1-diethoxyethylene, furnished the *cis*:*anti*:*cis*-fused photo-adduct **166** in 50% yield.[23] Compound **166** was subjected to a series of standard functional group interconversions, to effect two carbon homologation *exo*- to the central ring and simultaneously install the *cis*-diol functionality **167**. This sequence proceeded in 50% yield over the three steps. Oxidative cleavage of compound **167** with sodium periodate and concomitant aldol condensation furnished a 1:1 mixture of isomeric bicycles **168** and **169** in 98% yield. Subjection of the isomers **168** and **169** to a further series of standard functional group interconversions, including two reduction steps, then afforded (±)-illudol [(±)-**161**] in 12% yield over the final four steps.

**Scheme 4.5:** *Matsumoto's synthesis of (±)-illudol [(±)-161].*

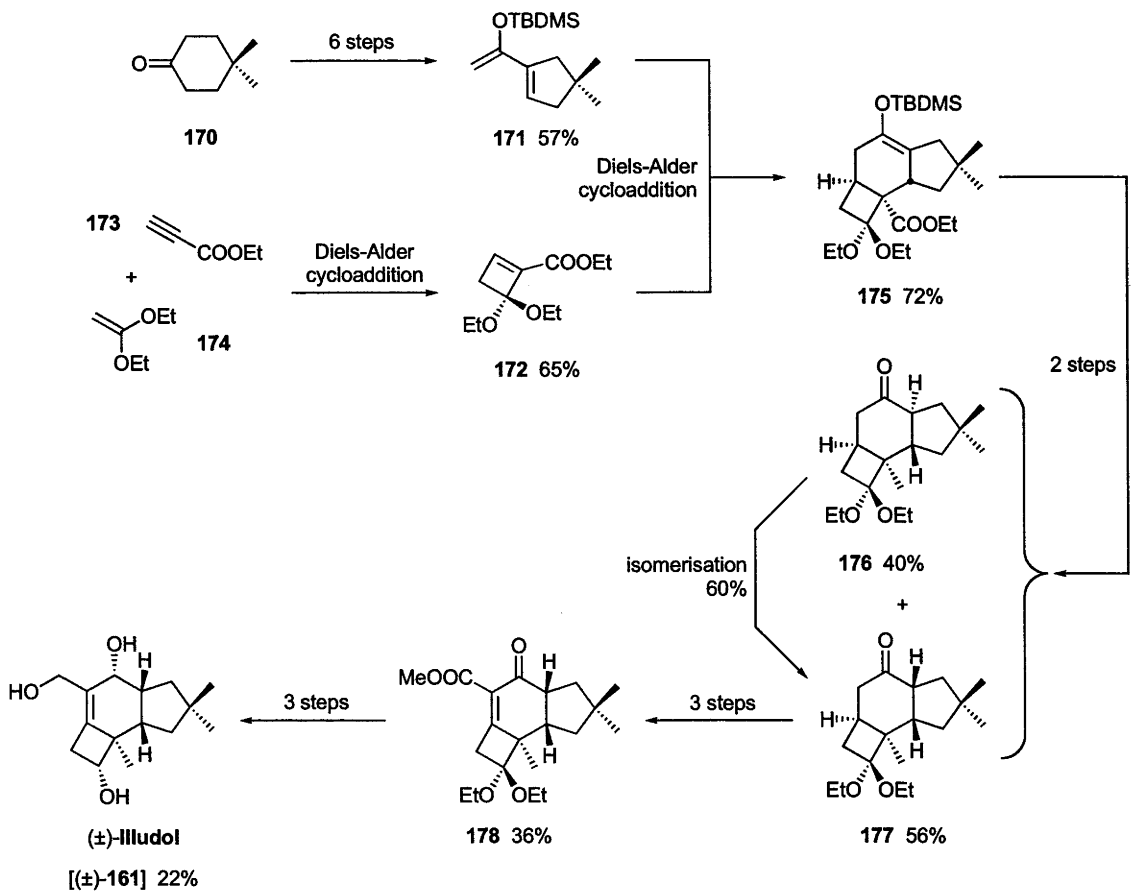


***Semmelhack, Tomoda and Hurst's synthesis of (±)-illudol (1980)***

The synthesis of (±)-illudol [(±)-**161**] reported by Semmelhack, Tomoda and Hurst afforded the natural product in 11% yield over sixteen steps (as the longest linear sequence) from 4,4-dimethylcyclohexanone (**170**).[20c - 20e] Key features of the synthesis include the use of an intramolecular Diels-Alder cycloaddition reaction, hydrolysis of an enone moiety to afford the *cis*:*anti*:*cis*-fused cyclobuta[*e*]indene framework of illudol, and sequential installation of the hydroxymethyl and olefinic moieties at C(3). The complete reaction sequence is described in Scheme 4.6.

The synthesis was initiated upon treatment of 4,4-dimethylcyclohexanone (**170**) with methylmagnesium bromide, which produced the corresponding alcohol. Upon dehydration of this material to the olefin and subsequent ozonolysis, 3,3-dimethyl-6-oxoheptanal was obtained. Acid-catalysed aldol condensation and accompanying dehydration produced an acetylcyclopentene which was reacted with lithium di*iso*propylamide and the ensuing enolate was trapped as the silyl ether **171** (in 58% overall yield) to reveal the 4π-component necessary for Diels-Alder cycloaddition reaction. Diene **171**, was reacted with the substituted dienophilic cyclobutene **172** [derived from thermal reaction of ethyl propiolate (**173**) with

**Scheme 4.6:** *Semmelhack, Tomoda and Hurst's synthesis of (±)-illudol [(±)-**161**].*



1,1-diethoxyethylene (**174**)], to furnish the tricyclic Diels-Alder adduct **175** in 75% yield and >95% regioselectivity. The carboxymethyl ester moiety of Diels-Alder adduct **175** was then converted into the corresponding methyl moiety using Ireland's protocol[26] and subsequent desilylation of the resulting product afforded the isomeric *trans*- and *cis*-fused indenes **176** and **177**, respectively. The *trans*-isomer **176** was converted into the *cis*-isomer **177** under basic conditions and in 65% overall yield from **175**. The ketone moiety associated with compound **177** was employed twice in the generation of the corresponding enolates: first to install the pendant carboxymethyl ester by reaction with carbon dioxide and diazomethane, and subsequently to install the olefinic bond, thereby resulting in formation of the α,β-enone **178** in 36% yield from **177**. Generation of the α,β-enone **178** constitutes a formal synthesis of (±)-illudol since it intersects with a late stage intermediate formed in the synthesis[20b] reported by Matsumoto *et al.* Thus, the synthesis was completed by subjecting intermediate **178** to a series of standard functional group interconversions to afford racemic (±)-illudol [(±)-**161**] in 22% yield (from **178**).

***Johnson and Vollhardt's synthesis of (±)-illudol (1991)***

The synthesis of (±)-illudol [(±)-**161**] performed by Johnson and Vollhardt[20f] differs from the two previous strategies[20b - 20e] in that it does not involve a stepwise approach to tricycle construction, instead using a stereoselective [2 + 2 + 2]-cyclisation process to form the requisite cyclobut[*e*]indene framework directly. The eighteen step synthesis, which is illustrated in Scheme 4.7, affords racemic illudol [(±)-**161**] in <1% overall yield. A similar strategy was later employed[27] by Malacria *et al.* in their 2000 synthesis of *epi*-illudol.

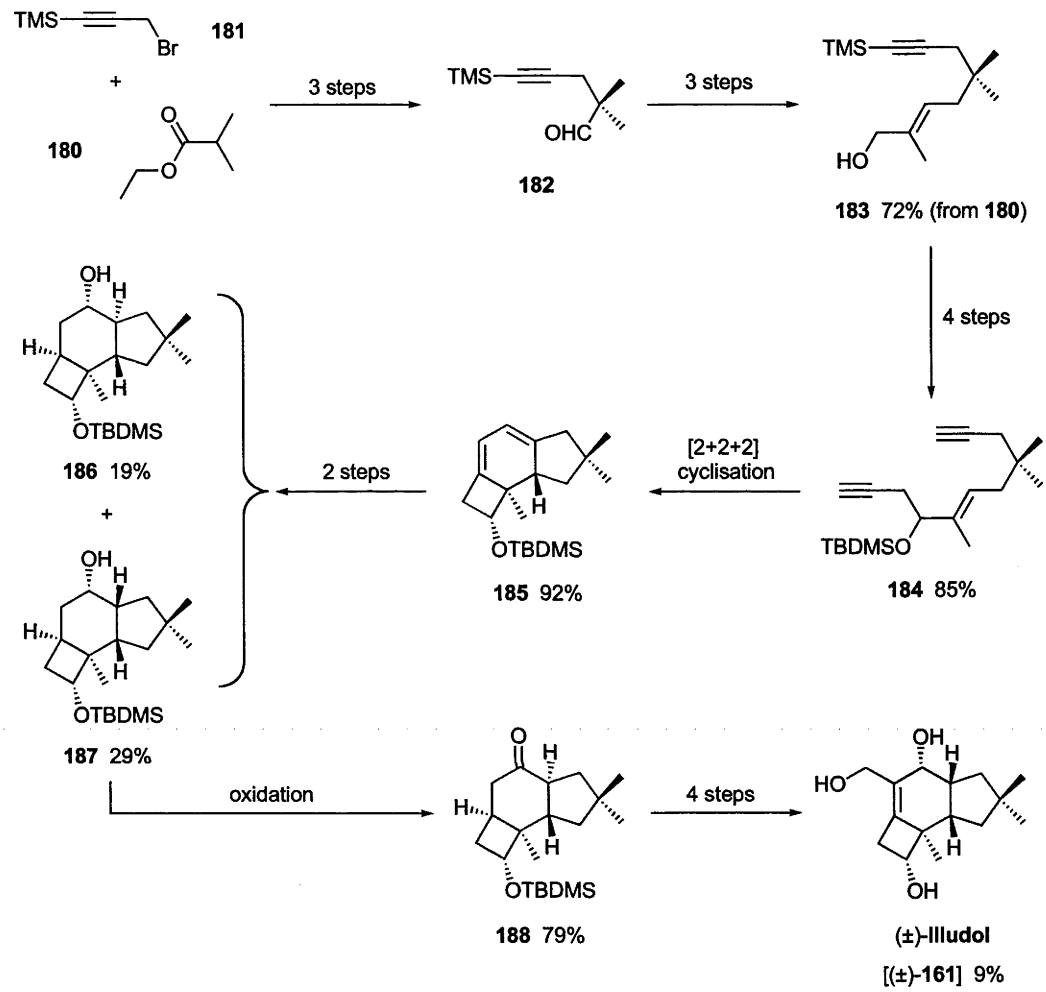
The synthesis began with alkylation of the enolate of ethyl-2-methylpropanoate (**180**) using 3-bromo-1-(trimethylsilyl)propyne (**181**), followed by reduction of the ester to the corresponding alcohol and subsequent oxidation, to afford the aldehyde **182**. One-carbon homologation of aldehyde **182**, *via* Wittig olefination and sequential hydrolysis of the enol ether product, furnished a second aldehyde that was subjected to a second Wittig olefination reaction to afford predominantly (>95%) *E*-configured alcohol **183** in 72% yield from **180**. The alcohol **183** was then elaborated, *via* a series of standard functional group interconversions, to the enediyne **184** in 85% yield. Enedyne **184** underwent stereoselective [2 + 2 + 2]-cyclisation, upon treatment with catalytic amounts of cyclopentadienyl cobalt dicarbonyl, to afford the diene **185** as a single diastereoisomer in 92% yield. Dissolving metal reduction of the C(2a)=C(3) olefinic bond and regiospecific hydroboration of the remaining C(4)=C(4a) olefinic bond, generated two diastereoisomeric alcohols **186** and **187** (in a 2:3 ratio, 48%), the latter of which was oxidized to the ketone **188** in 79% yield. The lithium enolate of ketone **188** provided a means for installation of the pendant hydroxymethyl functionality and also served to introduce

26 Ireland, R. E.; Muchmore, D. C.; Hengartner, U., *J. Am. Chem. Soc.*, **1972**, *94*, 5098.

27 Rychlet Elliot, M.; Dhimane, A.-L.; Hamon, L.; Malacria, M., *Eur. J. Org. Chem.*, **2000**, 155.

the olefinic moiety, the product of which was reduced and deprotected to afford (±)-illudol [(±)-**161**] (in 9% yield from **188**).

**Scheme 4.7:** *Johnson and Vollhardt's synthesis of (±)-illudol [(±)-**161**].*




## 4.3 Previous studies on the synthesis of isovelleral

### 4.3.1 Overview

A considerable amount of research has been devoted to the synthesis of marasmane sesquiterpenes, not only because of the novel biological activities these natural products exhibit, but also due to the challenge they present to the synthetic chemist. Indeed, the complexity of the *cis*:*anti*:*cis*-fused cyclopropa[*e*]indene framework associated with the marasmanes has seen particular emphasis placed on the development of increasingly efficient methodologies to

construct simpler, less highly functionalised members of this class of sesquiterpene, such as (+)-isovelleral [(+)-**56**].[28]

The first total synthesis of isovelleral to be reported was enantioselective and delivered the natural or (+)-isomer [(+)-**56**].[28a] A second total synthesis of racemic (±)-isovelleral [(±)-**56**] was reported[28b] shortly thereafter. The latter synthesis was gainfully employed, in 1997, to generate a racemic mixture of a late-stage synthetic intermediate, which was subsequently chemically resolved and reacted further, to culminate in the first total synthesis of the non-natural isomer (–)-isovelleral [*ent*-(–)-**56**].[28d] A second, as well as shorter and higher-yielding, enantioselective total synthesis of (+)-isovelleral [(+)-**56**] was reported recently.[28e] Each of the aforementioned total syntheses is described below, with the exception of the enantioselective synthesis of (–)-isovelleral [*ent*-(–)-**56**] due to its similarity with the synthesis of racemic material.

## 4.3.2 Total syntheses

***Wickberg's synthesis of (+)-isovelleral (1990)***

In 1990, Wickberg *et al.* reported the first total and enantioselective synthesis of (+)-isovelleral [(+)-**56**] *via* a diastereoselective intramolecular Diels-Alder cycloaddition reaction of a chiral intermediate derived from *D*-ribonolactone.[28a] The total synthesis of (+)-isovelleral [(+)-**56**], thus described, proceeded in 7% yield over thirteen steps (Scheme 4.8). The work also constitutes a formal synthesis of its probable biosynthetic precursor, stearoylvelutinal (**160**).[29]

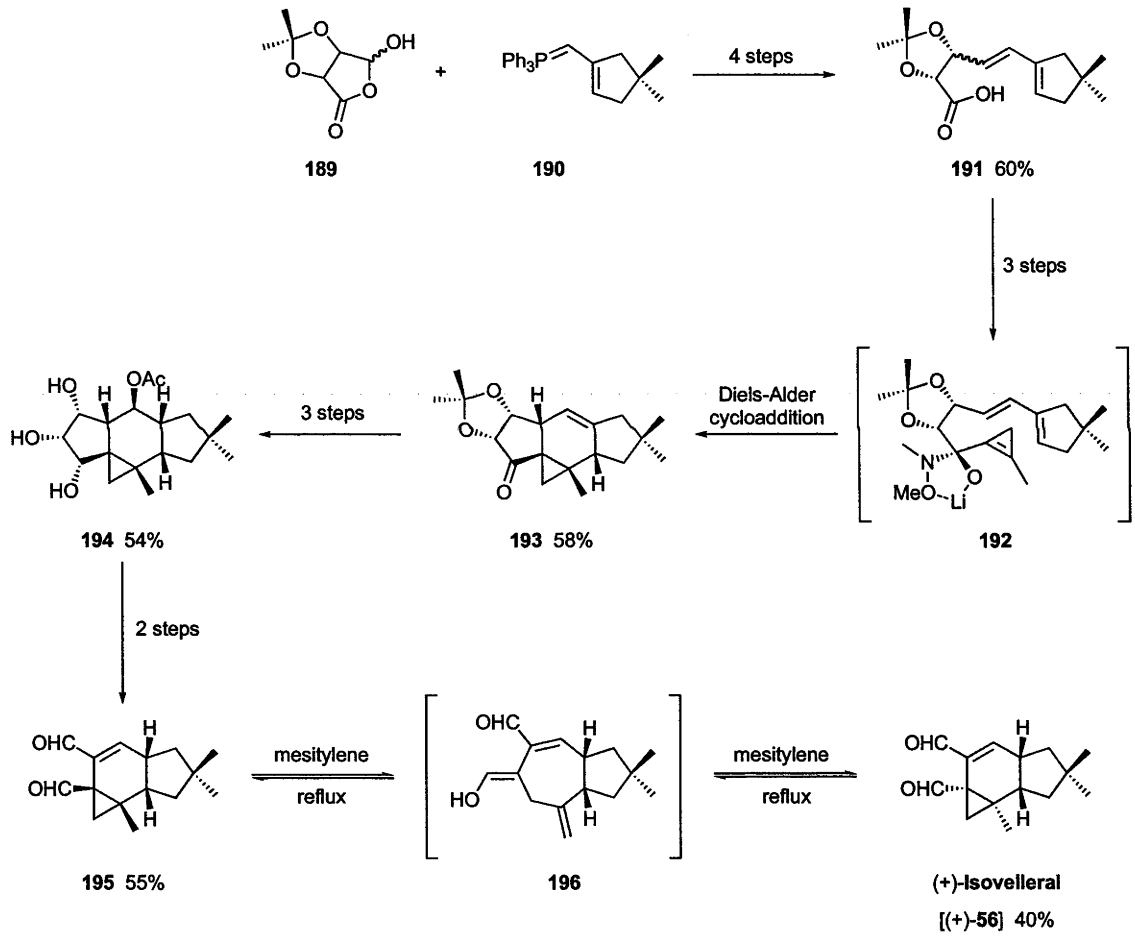
The synthesis commenced upon reaction of the aldehyde derived from the ring-opened form of 2,3-*O*-*iso*propylidene-*L*-erythrouronic acid (**189**) with phosphorane **190**, to afford a 2:3 mixture of inseparable *E*- and *Z*-diene carboxylic acids **191**. Mercuric acetate-catalysed *cis*- – *trans*-isomerisation ultimately increased the ratio to 19:1 in favour of the *trans*-isomer of compound **191**, which was then separated from the *cis*-isomer. The *trans*-isomer of acid **191** (formed in 60% yield over four steps) was converted into the corresponding Weinreb amide and treated with methylcyclopropenyl lithium to generate the transient species **192**, which spontaneously underwent a diastereoselective and intramolecular Diels-Alder reaction to furnish the cycloaddition product **193** in 58% yield over the four steps. The Diels-Alder adduct **193**, embodying the marasmane framework, was then converted to triol **194** (54%) *via* three standard functional group interconversions, namely hydroboration, protection and deprotection steps.

28 a) Bergman, R.; Hansson, T.; Sterner, O.; Wickberg, B., *J. Chem. Soc., Chem. Commun.*, **1990**, 865; b) Thompson, S. K.; Heathcock, C. H., *J. Org. Chem.*, **1990**, *55*, 3004; c) Thompson, S. K.; Heathcock, C. H., *J. Org. Chem.*, **1992**, *57*, 5979; d) Jonassohn, M.; Hjertberg, R.; Anke, H.; Dekermendjian, K.; Szallasi, A.; Thines, E.; Witt, R.; Sterner, O., *Bioorg. Med. Chem.*, **1997**, *5*, 1363; e) Bell, R. P. L.; Wijnberg, J. B. P. A.; de Groot, A., *J. Org. Chem.*, **2001**, *66*, 2350.

29 Sterner, O.; Bergman, R.; Wickberg, B., *Finn. Chem. Lett.*, **1984**, 116.

Triol **194** was subjected to periodate oxidation to form the desired dialdehydic moiety required for the natural product, and subsequent elimination of acetic acid installed the similarly necessary olefinic bond, thereby generating the diastereoisomer **195** of (+)-isovelleral in 55% yield over two steps. Previous studies have shown that (+)-isovelleral [(+)-**56**] may be thermally rearranged to the optically active pyrovellerofuran **196**. Under similar conditions, it was found that the diastereoisomer **195** established thermal equilibrium with (+)-isovelleral [(+)-**56**] and provided these two compounds in a 3:2 ratio. After separation, unreacted compound **195** was recycled, under thermal reaction conditions, to afford (+)-isovelleral [(+)-**56**] in 71% yield after five cycles.

**Scheme 4.8:** *Wickberg's synthesis of (+)-isovelleral [(+)-56].*



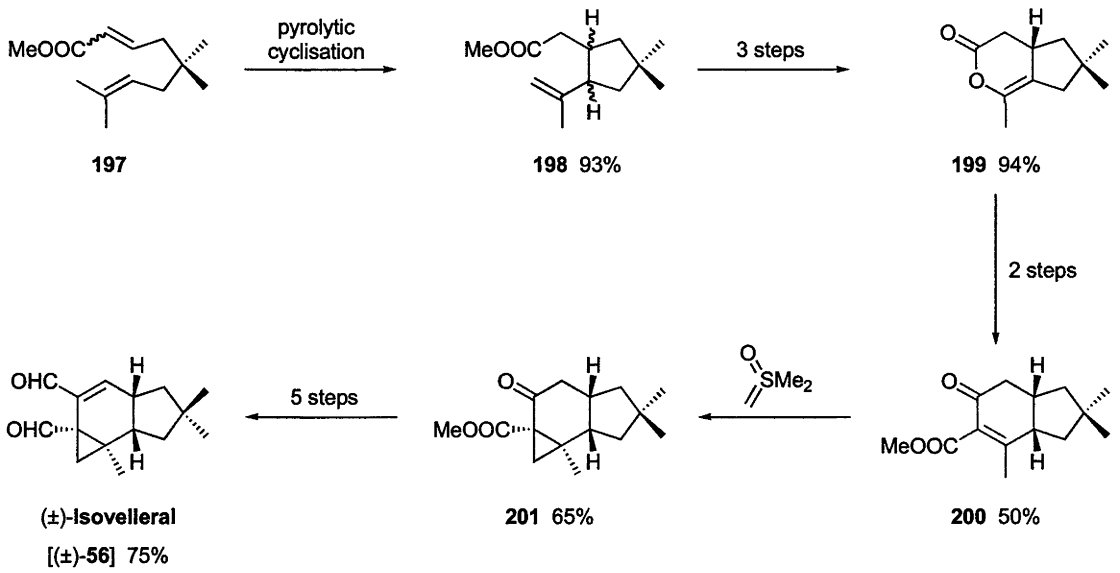

***Thompson and Heathcock's synthesis of (±)-isovelleral (1990)***

Concomitant with the enantioselective synthesis of (+)-isovelleral [(+)-**56**] described by Wickberg *et al.*,[28a] an additional synthesis of racemic (±)-isovelleral [(±)-**56**] was reported by Thompson and Heathcock.[28b, 28c] This fourteen step synthesis (Scheme 4.9) generates the *cis*:*anti*:*cis*-fused 3:6:5 cyclopropa[*e*]indene framework of (±)-isovelleral [(±)-**56**] in 15%

overall yield (from 3-methyl-but-2-enal) using pyrolytic cyclisation, intramolecular aldol and cyclopropanation reactions as key steps, as detailed below.

Pyrolytic cyclisation of the diene ester **197** (generated as a 20:1 mixture of *E*- and *Z*-isomers from 3-methyl-but-2-enal) furnished a 7:3 mixture of *cis*- and *trans*-isomers **198** in 93% yield. Saponification of the ester and ozonolytic cleavage of the olefinic moiety quantitatively yielded the keto acid, which was cyclized to afford the lactone **199** in 94% yield over three steps. Lactone **199** was treated with the lithium enolate of methyl acetate and then reacted with methanesulfonic acid to obtain the unsaturated β-keto ester **200**, which embodies the *cis*-fused indene framework associated with (+)-isovelleral [(+)-**56**]. The olefinic portion of **200** underwent reaction with the Corey-Chaykovsky dimethyloxosulfonium ylide reagent,[30] thereby generating the desired *cis*:*anti*:*cis*-fused 3:6:5 cyclopropa[*e*]indene framework as a single diastereoisomer **201** in 65% yield. The ketone **201** was converted into the corresponding enol triflate which was then subjected to palladium catalysed methoxycarbonylation, followed by a standard reduction-oxidation protocol, to furnish racemic (±)-isovelleral [(±)-**56**] in 75% yield over five steps.

**Scheme 4.9:** *Thompson and Heathcock's synthesis of (±)-isovelleral [(±)-56].*




***Bell, Wijnberg and de Groot's synthesis of (+)-isovelleral (2001)***

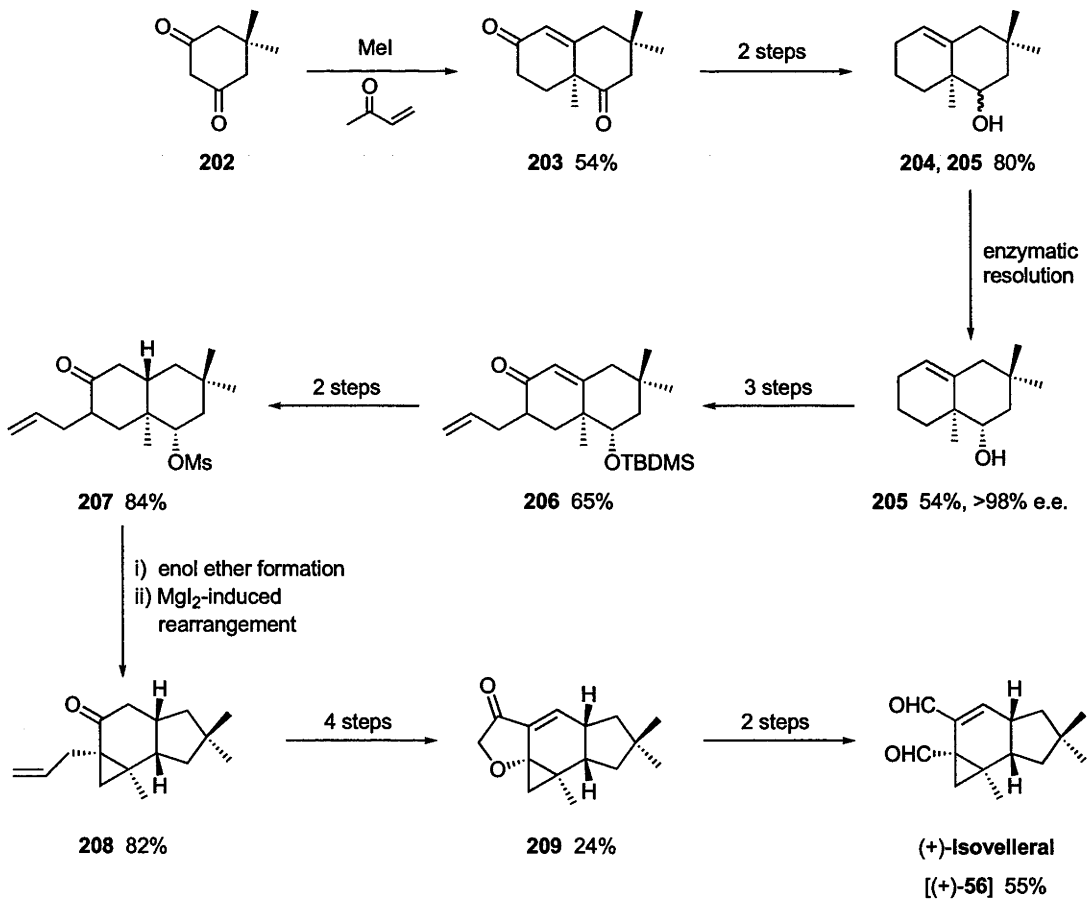
The enantioselective synthesis of (+)-isovelleral [(+)-**56**] reported by Bell, Wijnberg and de Groot draws on the availability of an enantiopure starting material (produced *via*

30 Corey, E. J.; Chaykovsky, M., *J. Am. Chem. Soc.*, **1965**, *87*, 1353.

enzymatic resolution[31] of a previously synthesised,[32] racemic bicycle) and a tandem rearrangement – cyclopropanation reaction, to construct the natural product as described below and in Scheme 4.10.[28e]

Thus, *gem*-dialkylation of 5,5-dimethyl-cyclohexan-1,3-dione (**202**) at the position between the carbonyl moieties, first with methyl iodide and subsequently with methyl vinyl ketone, furnished the dialkylated product which was then cyclised, with accompanying dehydration, *via* the Robinson annulation sequence, to form the racemic enone **203** in 54% yield.[32a] The carbonyl moiety of the α,β-unsaturated ketone **203** was selectively protected as the dithioacetal which, upon dissolving metal reduction, was desulfurised with accompanying reduction of the remaining ketone moiety. In this fashion, a separable 1:10 mixture of alcohols **204** and **205** was obtained.[32b] The major, (+)-β-hydroxy bicycle **205** was subsequently resolved (54%, >98% e.e.) from the mixture using a lipase-mediated esterification reaction.[31] Protection of the free alcohol **205**, followed by allylic oxidation, afforded the corresponding

**Scheme 4.10:** *Bell, Wijnberg and de Groot's synthesis of (+)-isovelleral [(+)-56].*




31 Franssen, M. C. R.; Jongejan, H.; Kooijman, H.; Spek, A. L.; Bell, R. P. L.; Wijnberg, J. B. P. A.; de Groot, A., *Tetrahedron: Asymmetry*, **1999**, *10*, 2729.

32 a) Heathcock, C. H.; Gray, D., *Tetrahedron*, **1971**, *27*, 1239; b) Orru, R. V. A.; Wijnberg, J. B. P. A.; Bouwman, C. T.; de Groot, A., *J. Org. Chem.*, **1994**, *59*, 374.

α,β-unsaturated enone which was alkylated at the α′-position with allyl bromide to form bicycle **206** in 65% yield. Bicycle **206** was then converted, *via* two functional group interconversions, into the ketone **207** (84%). The ketone **207** was, in turn, transformed into the unstable silyl enol ether and subsequently subjected to a magnesium diiodide-induced tandem rearrangement – cyclopropanation reaction, which smoothly afforded the tricycle **208** in 82% yield over two steps. Tricycle **208** embodies the *cis*:*anti*:*cis*-fused 3:6:5 cyclopropa[*e*]indene framework associated with (+)-isovelleral [(+)-**56**]. Isomerisation of the olefinic bond in ketone **208** furnished a 10:1 mixture of *E*- and *Z*-isomers, respectively, in which the ketone moiety was converted to the corresponding enol triflate. Ozonolytic cleavage of the pendant olefin, followed by reductive workup and subsequent palladium-catalysed one-carbon homologation with carbon monoxide, afforded the lactone **209** (24% over four steps), which was subjected to a standard two-step reduction-oxidation protocol to furnish (+)-isovelleral [(+)-**56**] in 55% yield. The natural product was produced in approximately 10% yield over twelve steps from the enantiopure (+)-β-hydroxy bicycle **205**.

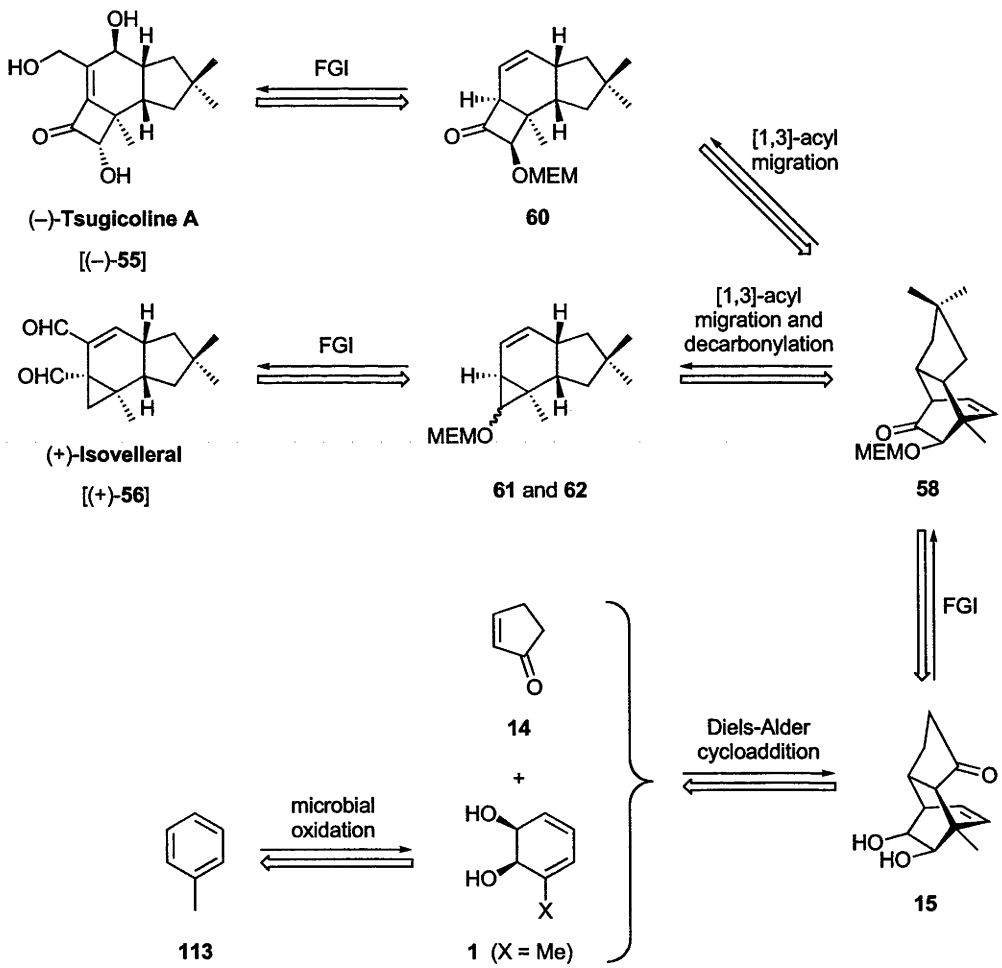
## 4.4 Retrosynthetic analysis and strategy

Few syntheses of cyclohumulanoid sesquiterpenes provide enantioselective access to multiple classes of sesquiterpene *via* a common synthetic intermediate, despite such sesquiterpene natural products {*e.g.* (–)-tsugicoline A [(–)-**55**] and (+)-isovelleral [(+)-**56**]} being biogenetically related, albeit distantly. Relatively little effort has also been made to develop enantioselective syntheses that are generally applicable to multiple members of a given class of sesquiterpene. The synthetic approaches to (–)-tsugicoline A [(–)-**55**] and (+)-isovelleral [(+)-**56**], described herein, attempt to redress this deficiency in synthetic methodology and feature photochemically-promoted rearrangements of an intermediate also common to the synthesis of *ent*-(–)-hirsutene [*ent*-(–)-**54**] (as described in Chapters Two and Three) as key steps in the retrosynthetic analyses (Scheme 4.11). By virtue of this fact, chemoenzymatic and Diels-Alder cycloaddition reactions are also featured as key steps in the retrosynthetic analyses of these sesquiterpene natural products.

It was anticipated that the protoilludane (–)-tsugicoline A [(–)-**55**] could be accessed from the tricycle **60** through a series of standard functional group interconversions, including installation of the hydroxymethylene moiety peripheral to the cyclobut[*e*]indene framework. Likewise, the marasmane (+)-isovelleral [(+)-**56**] was expected to be formed from the tricyclic intermediates **61** and **62** embodying the cyclopropa[*e*]indene framework of the natural product *via* a series of standard functional group interconversions, including installation of the two adjacent aldehydic moieties. The requisite tricyclic compounds **60**, **61** and **62** are the anticipated products from 1,3-acyl rearrangement and, in the case of the latter two epimers, accompanying decarbonylation reactions of the β,γ-unsaturated ketone **58**. In the synthetic direction, subjection of compound **58** to direct-irradiative (singlet-sensitised) photochemical

reaction conditions should result in the stereoselective formation of the requisite tricycles **60** – **62** that embody the framework of each target molecule.[33] The β,γ-unsaturated ketone **58** is recognisable from the research presented in Chapter Three, as the precursor to the oxa-di-π-methane rearrangement product **59** generated under triplet sensitised photochemical reaction conditions, and which was subsequently converted over several steps into *ent*-(–)-hirsutene [*ent*-(–)-**54**]. Consequently, β,γ-unsaturated ketone **58** could be assembled from toluene (**113**), *via* a series of steps including microbial oxidation and Diels-Alder cycloaddition reactions as detailed in Chapter Three.

**Scheme 4.11:** *Retrosynthetic analyses of (–)-tsugicoline A [(–)-55] and (+)-isovelleral [(+)-56].*



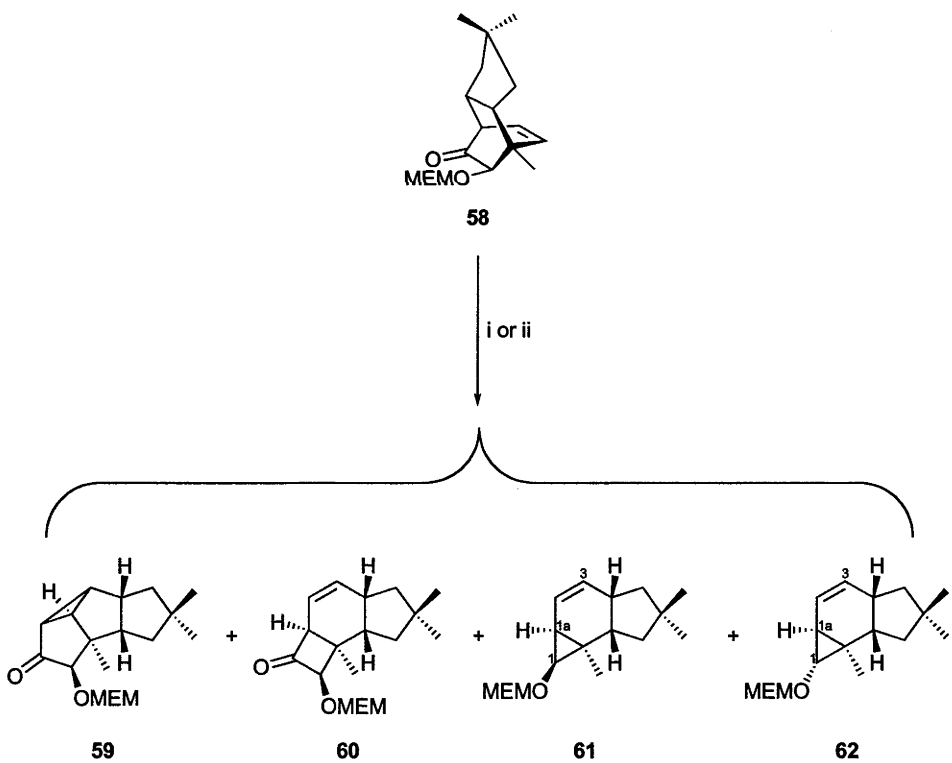

33 For a review of the photochemistry of β,γ-unsaturated carbonyl compounds, refer to: Houk, K. N., *Chem. Rev.*, **1976**, *76*, 1.

## 4.5 Towards the synthesis of (–)-tsugicoline A and (+)-isovelleral

### 4.5.1 Photochemical synthesis of frameworks associated with the protoilludane and marasmane classes of sesquiterpene

In Chapter Three, the β,γ-unsaturated ketone **58** {synthesised from the *cis*-1,2-dihydrocatechol **1** (X = Me) through a Diels-Alder cycloaddition reaction and elaboration of the bicyclo[2.2.2]octene framework} was converted into the cyclopropyl ketone **59** in 80% yield (at 71% conversion) *via* a triplet sensitised photochemically-promoted oxa-di-π-methane rearrangement reaction that was proposed to emanate from the $T_1$ (π,π*) excited state. During the course of these studies, three minor products were also isolated from the reaction mixture, which were identified as the cyclobutanone **60** and the C(1)-epimeric cyclopropylindenes **61** and **62** (Scheme 4.12).

**Scheme 4.12:** *Photochemically-promoted reactions of β,γ-unsaturated ketone 58 under direct irradiative and triplet sensitised reaction conditions.*




For yields, refer to Table 4.1 and Chapter Four text

*Reagents and conditions*: i) *hν* (125 W Philips HPL-N lamp), UV filter [$\lambda_{transmission}$ >340 nm, thickness >10 mm, NaBr 750 $gL^{-1}$, $Pb(NO_3)_2$ 8 $gL^{-1}$], acetone, acetophenone, 0°C to 10°C, 32 h; ii) *hν* (125 W Philips HPL-N lamp), benzene, 6°C – 10°C, 5 min – 10 h.

Cyclobutanone **213** was isolated chromatographically from the triplet sensitised photochemical reaction mixtures in 18% yield (at 71% conversion; Table 4.1, Entry 1).[34]

| *Entry* | *Conditions* | *Time* | *Percentage yields: actual and (adjusted[i])* | | | |
|---|---|---|---|---|---|---|
| | | | **59** | **60** | **61** and **62** | **58**[iv] |
| *1* | Triplet sensitised [ii] | 32 h | 57 (80) | 13 (18) | 2 (3) | 29 |
| *2* | Direct irradiative [iii] | 5 min | 2 (10) | 20 (80) | 3 (10) | 75 |
| *3* | Direct irradiative [iii] | 10 h | 13 - | 0 - | 52 - | 0 |

Shading denotes product selected for under specified reaction conditions and duration of irradiation.

i) Adjusted yields (in brackets) based on percentage conversion of starting material.

ii) *hν* (125 W Philips HPL-N lamp), aqueous UV filter solution [$\lambda_{transmission}$ >340 nm, thickness >10 mm, $NaBr_{(aq.)}$ 750 $gL^{-1}$, $Pb(NO_3)_{2\,(aq.)}$ 8 $gL^{-1}$], acetone, acetophenone, 0°C to 10°C.

iii) *hν* (125 W Philips HPL-N lamp), benzene, 6°C – 10°C.

iv) Percentage recovery of unreacted starting material.

**Table 4.1:** *Actual and adjusted yields (%) of photoproducts produced upon irradiation of β,γ-unsaturated ketone 58 under triplet sensitised and direct irradiative conditions.*

The EI mass spectrum of cyclobutanone **60** features a parent ion at *m/z* 308, for which an accurate mass measurement established the molecular composition, *viz.* $C_{18}H_{28}O_4$. This formula is consistent with the microanalytical data and indicative of an isomerisation product of the substrate **58**. The presence of a cyclobutanone carbonyl moiety was established by examination of both the IR spectrum, which exhibits a highly characteristic absorption at 1780 $cm^{-1}$, and the UV spectrum, which features $\lambda_{max}$ 315 nm ($\varepsilon_0$ 99.1 $L.mol^{-1}.cm^{-1}$). The $^1H$ NMR spectrum (Figure 4.4) features a two-proton multiplet at δ 5.72 – 5.70, attributed to the olefinic protons, whilst a one-proton doublet at δ 4.47 (*J* 3.5 Hz) is assigned to the oxymethine proton. Additionally, a multiplet observed at δ 3.24 – 3.16 is attributed to the ring-junction methine proton situated adjacent (α-) to the ketone. The remaining resonances are all fully consistent with the expected structure. The associated $^{13}C$ NMR spectrum is shown in Figure 4.5 and was fully assigned using a variety of connectivity experiments. The expected eighteen resonances were observed, the most diagnostic of these being the one at δ 208.4 which is assigned to the cyclobutanone carbonyl. Additionally, the olefinic carbons give rise to signals at δ 137.0 and 120.5, while the oxymethine carbon features a resonance at δ 92.3.

In addition to the cyclobutanone **60**, the two C(1)-epimeric cyclopropyl indene systems **61** and **62** were isolated by column chromatography, as a diastereoisomeric mixture, in yields of

34 As noted in Chapter Three, greater yields of the requisite cyclopropyl ketone **59** of up to 98% at 86% conversion over 25 h were obtained when reactions were performed on a smaller scale (<10 mL), particularly when rapid rates (>500 rpm) of magnetic stirring were also employed. Accordingly, the yields of the cyclobutanone **60** and cyclopropyl indenes **61** and **62** each diminish to <1% (at 86% conversion).

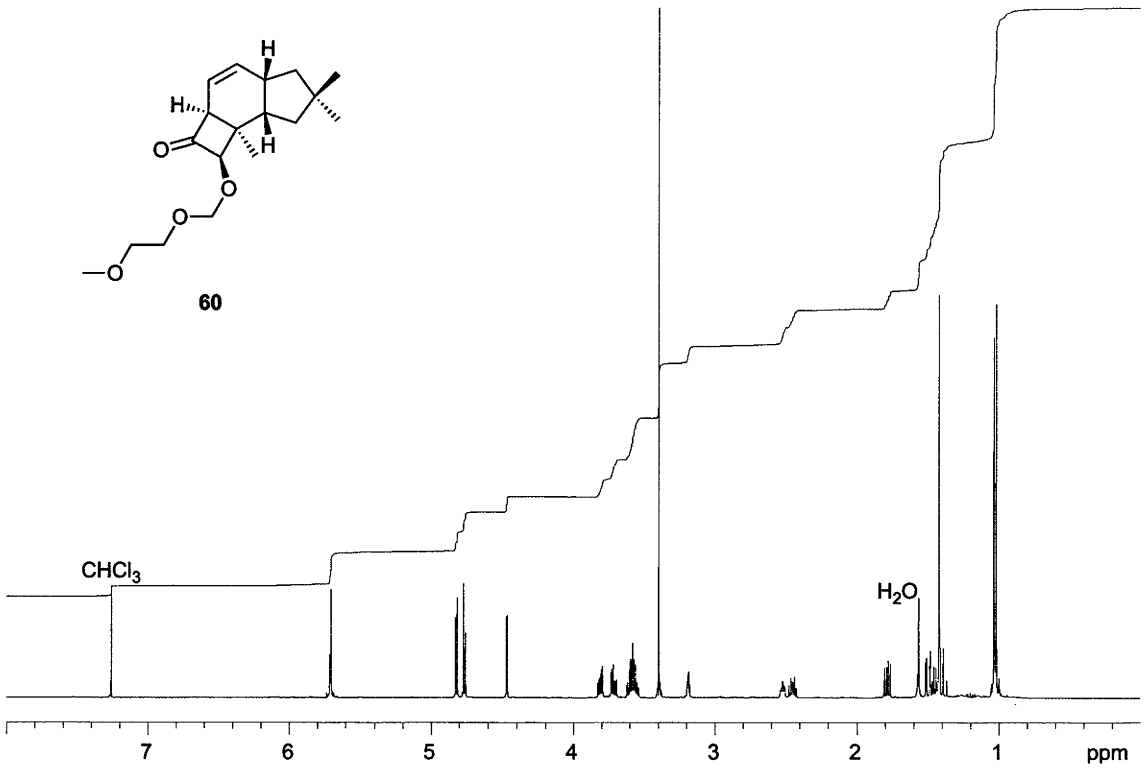



**Figure 4.4:** *500 MHz $^{1}H$ NMR spectrum of cyclobutanone **60** in $CDCl_3$.*

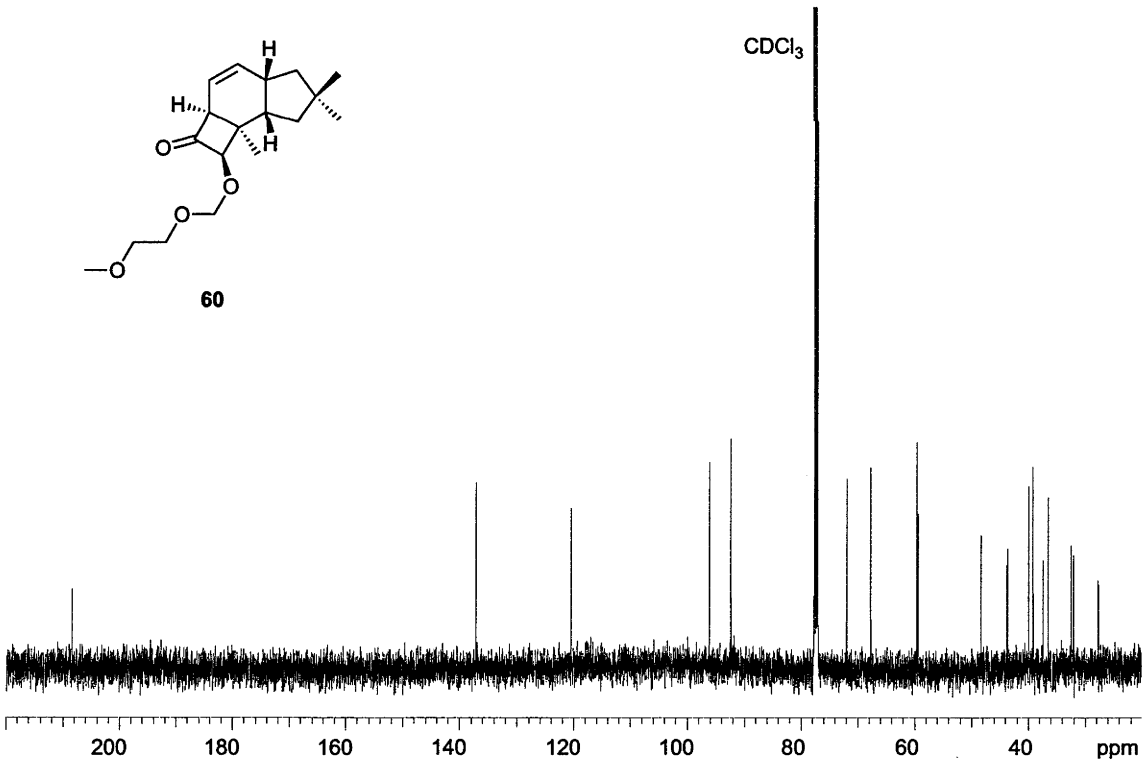



**Figure 4.5:** *126 MHz $^{13}C$ NMR spectrum of cyclobutanone **60** in $CDCl_3$.*

2 and 1% (at 71% conversion), respectively (Table 4.1, Entry 1).[34] Fractional decomposition of the mixture of compounds **61** and **62** was induced by exposing an ethyl acetate solution of these materials to light for a duration of three weeks, so as to afford the major diastereoisomer **61**, in

46% yield. An EI mass spectrum of cyclopropyl indene **61** features a molecular ion at *m/z* 280, for which an accurate mass measurement, in conjunction with microanalytical data, established the molecular composition to be $C_{17}H_{28}O_3$, indicative of photodecarbonylation. The absence of signals associated with a carbonyl moiety in both the IR and $^{13}C$ NMR spectra, is also consistent with loss of carbon monooxide from the substrate. Indeed, the $^{13}C$ NMR spectrum of compound **61** displays the expected seventeen resonances, whilst the $^{1}H$ NMR spectrum features, most significantly, a set of signals associated with the two olefinic protons at δ 5.66 and 5.24. Complete assignment of the $^{1}H$ and $^{13}C$ NMR spectra (Figures 4.6 and 4.7) was facilitated by connectivity and proximity experiments. The stereochemistry of the product was evinced, from nOe experiments, as that possessing *endo*-stereochemistry for the protected hydroxyl moiety. Indeed, enhancements were observed between the olefinic C(3) proton at δ 5.66 and one of the diastereotopic dioxymethylene protons of the 2-(methoxyethoxy)methoxy protecting group at δ 4.49. No such enhancement was observed between the olefinic C(3) proton and the oxymethine C(1) proton at δ 3.38.

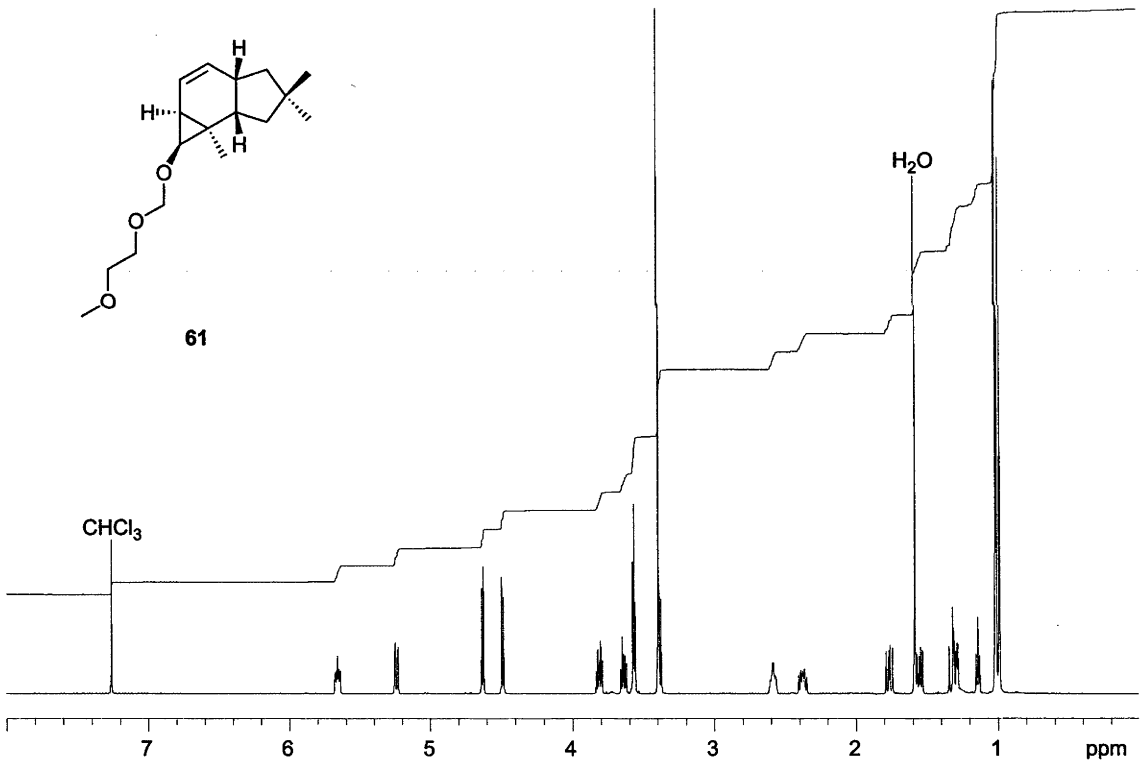



**Figure 4.6:** *500 MHz $^{1}H$ NMR spectrum of cyclopropyl indene **61** in $CDCl_3$.*

It follows that the minor diastereoisomer **62** is that in which the protected hydroxyl moiety is in an *exo*-orientation. Although this minor epimeric product **62** was not isolated free of the major diastereoisomer, the spectroscopic (for example, the $^{1}H$ NMR spectrum, Figure 4.8) and microanalytical data, thus obtained for the mixture, are consistent with the proposed structure.

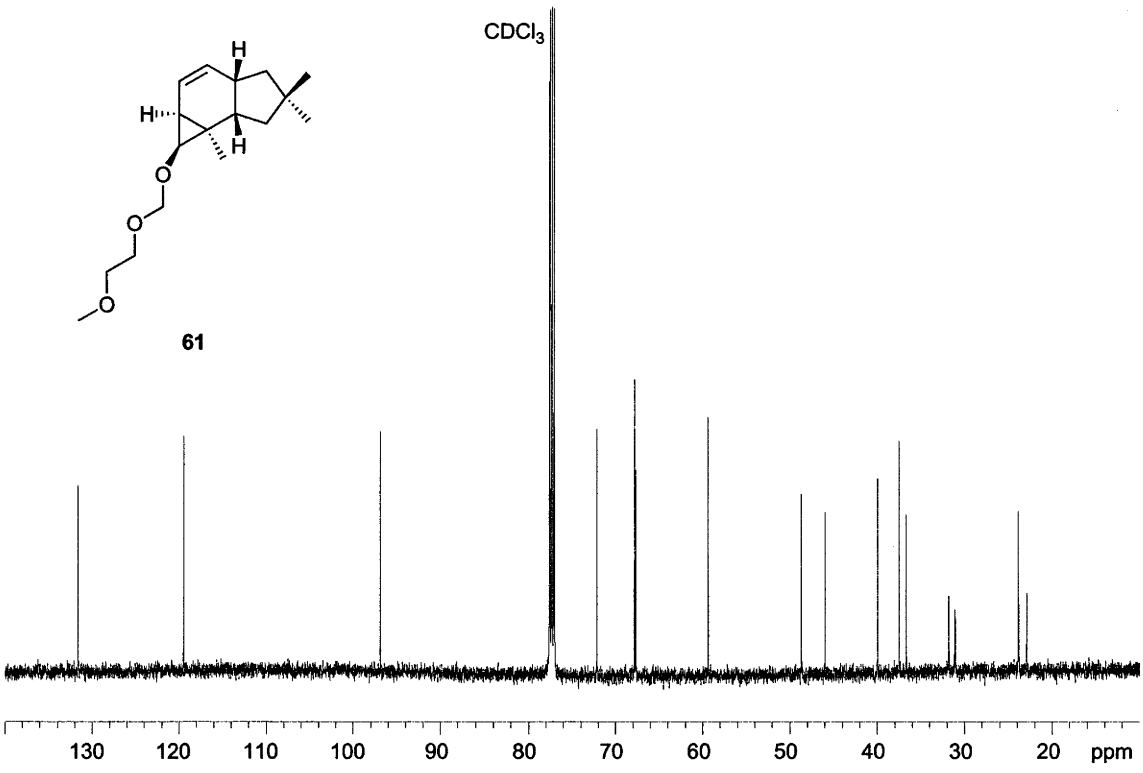



**Figure 4.7:** *126 MHz $^{13}C$ NMR spectrum of cyclopropyl indene **61** in $CDCl_3$.*

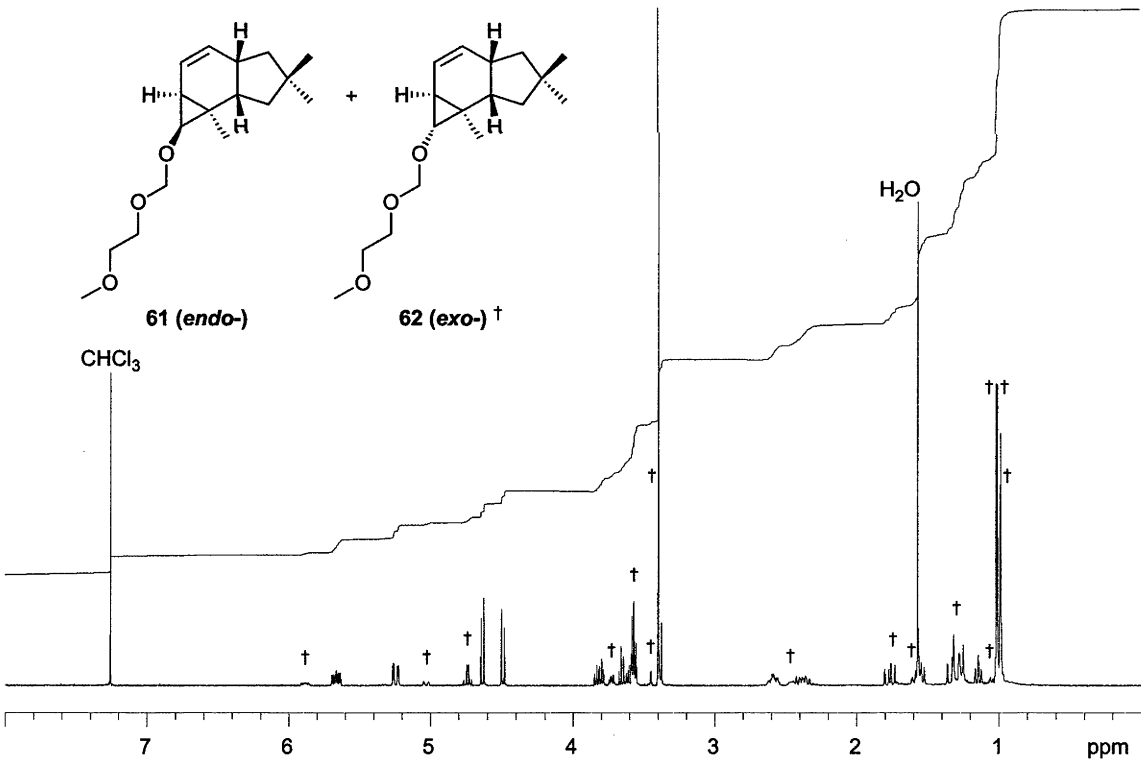



**Figure 4.8:** *300 MHz $^1H$ NMR spectrum of the 9:1 mixture of* endo- *and* exo-*cyclopropyl indenes **61** and **62** in $CDCl_3$.*

Based on the commentary presented in Chapter One, the cyclobutanone **60** and the C(1)-epimeric cyclopropylindenes **61** and **62** observed under the conditions described above, are considered to arise from the $T_2$ (n,π*) excited state *via* [1,3]-acyl migration and accompanying

decarbonylation reactions [although the latter isomers may also result from a foiled oxa-di-π-methane rearrangement reaction emanating from the $T_1$ ($\pi,\pi^*$) state]. It was considered that the same three products **60**, **61** and **62** could be generated in significant quantity and at the expense of the cyclopropyl ketone product **59**, provided that irradiation conditions favouring the singlet state were employed. Indeed, when a degassed solution of β,γ-unsaturated ketone **58** in benzene was subjected to direct irradiation over five minutes at between 6 and 10°C, the cyclobutanone **60** was isolated (Table 4.1, Entry 2) in 80% yield (at 25% conversion), along with small amounts of the diastereoisomeric cyclopropylindenes (**61** and **62**, (10% at 25% conversion, 4:6 ratio) and the cyclopropyl ketone **59** (10% at 25% conversion).

It is worth noting that the product distribution resulting from direct irradiation of the β,γ-unsaturated ketone **58** varies considerably with time, as presented graphically in Figure 4.9. These results show direct irradiative reaction[35] times of between five and fifteen minutes duration to be optimal for the formation of cyclobutanone **60** in maximum yield (albeit at modest conversion, as defined above), while minimising formation of the remaining products **59**, **61** and **62**. If, however, longer reaction times are employed, the β,γ-unsaturated ketone **58** is eventually entirely consumed, along with the transient cyclobutanone **60**. Instead, the cyclopropyl indenes **61** and **62** predominate and were, on one occasion, isolated in 52% yield (7:3 ratio), together with small amounts (13%) of the cyclopropyl ketone **59** (Table 4.1, Entry 3).

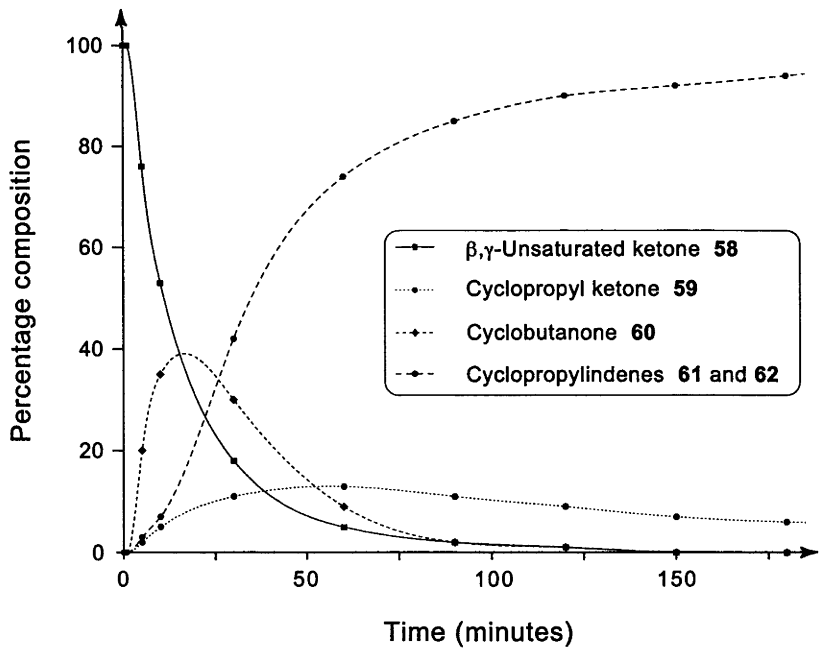



**Figure 4.9:** *Graph of Percentage composition* vs. *Time (minutes) for β,γ-unsaturated ketone 58 and associated products 59, 60, 61 and 62 formed under direct irradiative reaction conditions.*

35 Irradiation performed on a solution of substrate (conc. 2.0 $gL^{-1}$) in benzene, using *hν* (125 W Philips HPL-N lamp), 6°C – 10°C, 500 rpm magnetic-stirring rate. Slower rates of stirring extend the graphs along the x-axis (Time).

It is considered that the [1,3]-acyl migration and accompanying decarbonylation reactions resulting from the direct irradiation of β,γ-unsaturated ketone **58** emanate from the $S_1$ (n,π*) excited state, while the oxa-di-π-methane rearrangement is assumed to arise from the $S_2$ (π,π*) excited state. In principle, indiscriminate population of the $T_1$ (π,π*) and $T_2$ (n,π*) excited states, may also lead to formation of the oxa-di-π-methane and [1,3]-acyl migration/decarbonylation products, respectively, but this is unlikely since reactions performed in deoxygenated benzene were not influenced to a significant degree (with respect to yield) by the presence of triplet quenchers (specifically, biphenyl and cyclohexadiene) in solution.

From the above results, it is apparent that the decarbonylation and (to a lesser extent) oxa-di-π-methane rearrangement reactions act as irreversible sinks, to form the cyclopropyl indenes **61** and **62** and cyclopropyl ketone **59**, respectively.[36] That decarbonylation is an irreversible process (*i.e.* the step involving loss of carbon monooxide is not rate-limiting) was further confirmed by the observation that irradiation of a solution of β,γ-unsaturated ketone **58** in benzene under one atmosphere of carbon monooxide gas did not afford diminished yields of the cyclopropyl indenes **61** and **62**. Whether the decarbonylation reaction arises directly from the β,γ-unsaturated ketone **58** or *via* the ephemeral cyclobutanone **60** is unclear. Certainly, irradiation of a solution of isolated cyclobutanone **60** in benzene afforded the expected decarbonylation products **61** and **62**, in addition to which the β,γ-unsaturated ketone **58** and cyclopropyl ketone **59** were also formed (Figure 4.10).[35] The protected acyloin **58** was eventually consumed upon prolonged irradiation, along with the substrate cyclobutanone **60**, in

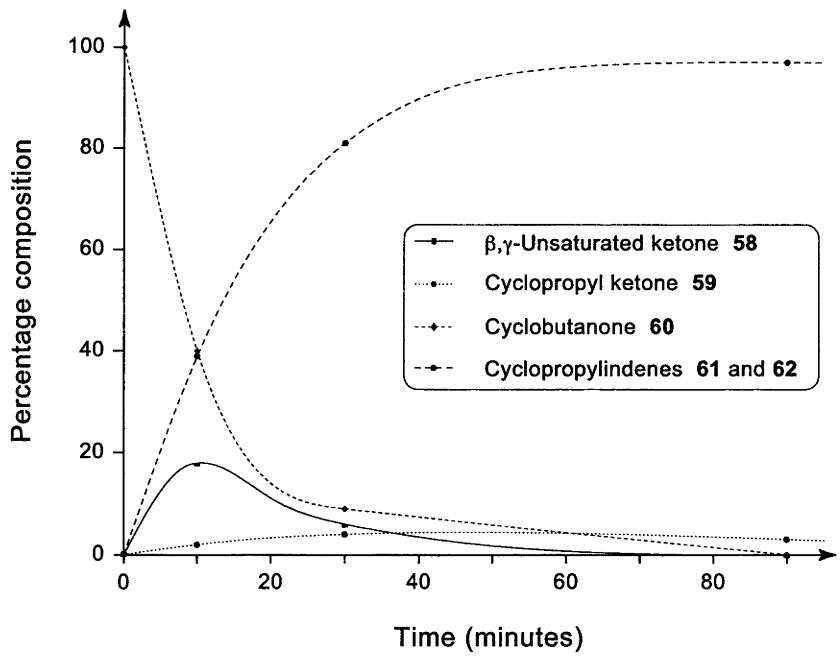



**Figure 4.10:** *Graph of Percentage composition* vs. *Time (minutes) for cyclobutanone **60** and associated products (**58**, **59**, **60** and **61**) formed under direct irradiative reaction conditions.*

36 Note, however, that the slight decrease in percentage of cyclopropyl ketone **59** present in the reaction mixtures after prolonged irradiation may be attributed to a small degree of reversibility of reaction.

the ultimate formation of the cyclopropyl indenes **61** and **62** (isolated in 55% yield and in a 7:3 ratio), whilst traces of the latter triquinane-type compound **59** remained.[37]

The results presented in Figure 4.10 demonstrate the reversibility of the [1,3]-acyl migration reaction and imply that under direct irradiative reaction conditions, the photochemical reaction mixture is comprised of a set of two compounds **58** and **60** in equilibrium with one another (and with the decarbonylative and, to a lesser extent, oxa-di-π-methane rearrangement reactions acting as irreversible sinks to form compounds **61** and **62**, and **59**, respectively).[38]

The significance of these observations is that direct irradiative reaction conditions of short duration may be used to select for the cyclobutanone **60**, whilst the irreversibility of the decarbonylation process may be exploited through use of sustained irradiation to selectively favour the formation of the two diastereoisomeric cyclopropyl indenes **61** and **62**. The ability to control the outcome of reactions of β,γ-unsaturated ketone **58** performed under direct irradiative conditions, for either of the cyclobutanone **60** or cyclopropyl indenes **61** and **62**, complements the selective production of the cyclopropyl ketone **59**, from the same substrate, under triplet sensitised reaction conditions. The similarity of each of the cyclobutanone **60**, cyclopropyl indenes **61** and **62** and cyclopropyl ketone **59** to the frameworks associated with the protoilludane, marasmane and linear triquinane classes of sesquiterpene, respectively, is striking. Indeed, the utility of the latter compound in the synthesis of *ent*-(–)-hirsutene [*ent*-(–)-**54**] has already been demonstrated in Chapter Three. In the remainder of the present Chapter the potential utility of cyclobutanone **60** and cyclopropylindenes **61** and **62** in the respective syntheses of the protoilludane (–)-tsugicoline A [(–)-**55**] and the marasmane (+)-isovelleral [(+)-**56**], will be examined.

### 4.5.2 Elaboration of the cyclobutanone towards the synthesis of (–)-tsugicoline A

Cyclobutanone **60** bears a marked similarity to the protoilludene class of sesquiterpenes,[39] of which (–)-tsugicoline A [(–)-**55**] is a member. Indeed, the cyclobutanone framework **60**, generated *via* Diels-Alder cycloaddition and photochemically-promoted [1,3]-acyl migration reactions from *cis*-1,2-dihydrocatechol **1** (X = Me), differs from (–)-tsugicoline A [(–)-**55**] only with respect to the functionality present along the C(1) – C(4) periphery of the molecule. The similarity of the cyclobutanone **60** ring-system to that embodied within (–)-tsugicoline A [(–)-**55**] would suggest that it is possible, at least in principle, to convert this photo-product into the protoilludene.

37 A similar control experiment with cyclopropyl ketone **59** under triplet sensitised reaction conditions was not performed.

38 The position of equilibrium may be controlled by optical pumping. For a review of the chemical applications of optical pumping, see: Bersohn, R., *Acc. Chem. Res.*, **1972**, *5*, 200.

39 Most resemblance is, in fact, borne to the protoillud-3-ene (a.k.a. $\Delta^7$-protoilludene) class of sesquiterpene.

With the cyclobutanone **60** in hand, studies directed towards the synthesis of (–)-tsugicoline A [(–)-**55**] were performed. Particular emphasis was placed on installation of the C(4) hydroxyl functionality and on shifting the olefinic moiety into conjugation with the ketone at C(2). To this end, cyclobutanone **60** was reacted with dimethyldioxirane in acetone/dichloromethane and the resulting epoxide **210** was isolated as the sole diastereoisomeric product in 53% yield (Scheme 4.13).[40]

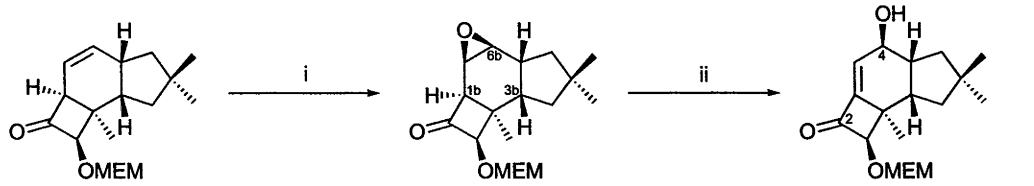
The most conspicuous feature of the $^{1}H$ and $^{13}C$ NMR spectra of epoxide **210** was a lack of resonances attributable to the olefinic bond of the substrate. Instead, the $^{1}H$ NMR spectrum of epoxide **210** displays two resonances at δ 3.33 and 3.07, while the $^{13}C$ NMR spectrum exhibits peaks at δ 51.8 and 56.9, associated with the C(1a) and C(6b) oxymethine protons and carbons of the epoxide moiety, respectively. The remaining resonances were consistent with the expected structure, for which the $^{1}H$ and $^{13}C$ NMR spectra were completely assigned using a combination of connectivity and proximity experiments to deduce the stereochemistry of the product. Indeed, NOESY experiments imply through-space interactions between the proton on C(1b) and the proton on C(6b), but an absence of such phenomena between C(1b) and C(3b). By virtue of these and similar enhancements, the diastereoisomer is assigned as that in which the epoxide ring is situated on the same (β-) face of the cyclohexyl ring as the cyclobutanone ring. The EI mass spectrum exhibits a parent ion at *m/z* 324, for which an accurate mass measurement, in conjunction with microanalytical data, confirmed the expected molecular formula as $C_{18}H_{28}O_5$.

The epoxide **210** was subsequently treated with lithium hexamethyldisilazide under kinetically controlled conditions to afford the corresponding allylic alcohol **211** in 69% yield (at 77% conversion, Scheme 4.13). Allylic alcohol **211** was determined to be a ring-opened isomer of the substrate epoxide **210** by EI mass spectral analysis which featured a fragment ion at *m/z* 279 corresponding to loss of the 2-(methoxyethoxy)methoxy ether from the molecular ion, the composition of which ($C_{18}H_{28}O_5$) was confirmed by an accurate mass measurement. The IR spectrum displays absorption maxima at 3472 and 1774 $cm^{-1}$ which are attributed to the hydroxyl and carbonyl stretches of the allylic alcohol and cyclobutyl ketone moieties, respectively. The most significant feature of the $^{1}H$ NMR spectrum (Figure 4.11) is the doublet ($J$ = 6.5 Hz) at δ 7.15 which arises from the olefinic methine proton of the α,β-unsaturated ketone moiety. Additionally, the oxymethine protons of the protected cyclobutanol and allylic hydroxyl moieties are displayed as signals at δ 5.38 and 4.44 – 4.41, respectively. One of the doublets ($J$ = 7.0 Hz) arising from the diastereotopic protons of the methylene acetal is shifted considerably downfield (to δ 5.06),[41] which suggests that the newly-formed free hydroxyl

40 The other diastereoisomer of epoxide **210** was also observed, but in insufficient quantities as to be characterised.

41 Such a downfield shift is not unusual for many compounds described in this thesis, but compared to other compounds **60** and **210** embodying the protoilludane structure and which also feature resonances arising from the

**Scheme 4.13:** *Formation of allyl alcohol **211** from cyclobutanone **60**.*




**60** **210** 53% **211** 69% (at 77% conversion)

*Reagents and conditions*: i) dimethyldioxirane (~0.1 molL$^{-1}$ in acetone), $CH_2Cl_2$, -10°C – 0°C, 6 h; ii) LiHMDS, THF, -78°C – 0°C, 6 h.

moiety is interacting, in a through space manner, with this proton. This phenomenon is also reflected in the $^{13}C$ NMR spectrum, whereby the methylene acetal is shifted downfield to δ 105.7. The $^{13}C$ NMR spectrum is otherwise consistent with the expected structure, exhibiting eighteen signals in total, including those at δ 209.6, 139.7, 137.0 and 65.0 associated with the C(2) – C(4) γ-hydroxy α,β-unsaturated ketone envelope.

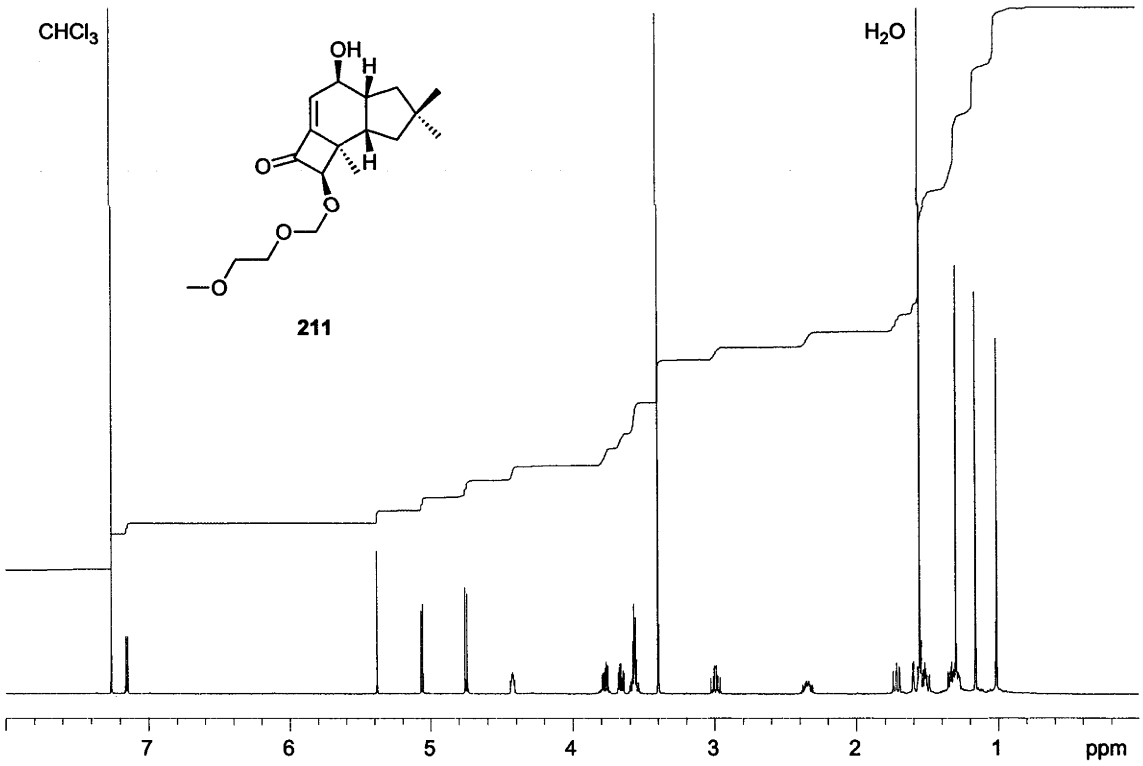


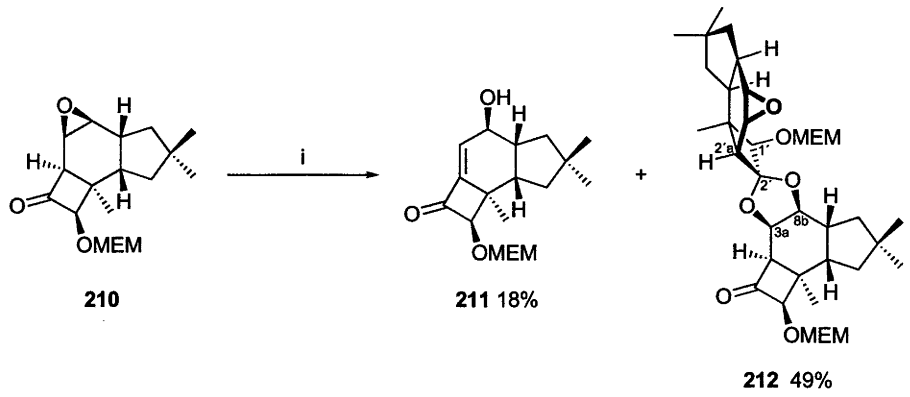

**Figure 4.11:** *500 MHz $^1H$ NMR spectrum of allyl alcohol **211** in $CDCl_3$.*

In order to improve the conversion, and hence yield, of the ring opening reaction it was considered necessary to effect complete deprotonation of the epoxide **210** using greater than one

diastereotopic methylene acetal protons of the MEM-ether in the $^1H$ NMR spectrum at between δ 4.82 – 4.63, this disparity is significant.

equivalent of base. However, if two or more equivalents of base were used, allyl alcohol **211** was produced in only 18% yield, and was now accompanied by a second product **212**, that was formed in 49% yield (Scheme 4.14) and which exhibited a parent ion at *m/z* 648 in the EI mass spectrum. An accurate mass measurement, in conjunction with microanalytical data, established the molecular formula, as $C_{36}H_{56}O_{10}$, indicative of a dimeric species. Extensive NMR analysis of the product **212** showed this to be a heterodimer. The $^{1}H$ NMR (Figure 4.12) and $^{13}C$ NMR spectra of each monomeric unit were completely assigned using a variety of connectivity experiments and found to embody the structure of the epoxide substrate **210**. However, one unit was noted to feature two oxymethine moieties [C(3a) and C(8b)] associated with ring-opening of the parent epoxide, while the other lacked the [C(2')] cyclobutanone carbonyl, instead featuring a resonance in the $^{13}C$ NMR spectrum at δ 105.0 and indicative of an acetal. Connectivity experiments further demonstrated that the monomers were linked through the spiro-fused C(2') acetal centre of one monomer *via* the oxygen atoms of the C(3a) and C(8b) oxymethine moieties of the other. Proximity experiments established the stereochemistry of the system as that embodied within structure **212**. In particular, evidence in support of this structure derives from nOe experiments which revealed interactions between C(1')–H (δ 3.65) and each of C(3a)–H and C(8b)–H (δ 4.06 and 4.03, respectively). No such enhancements were observed between C(2'a)–H (δ 2.61) and each of C(3a)–H and C(8b)–H. The remaining spectroscopic data are consistent with the proposed structure of heterodimer **212**.

**Scheme 4.14:** *Formation of allyl alcohol **211** and heterodimer **212**.*




*Reagents and conditions*: i) LiHMDS (≥2 eq.), THF, -78°C – 0°C, 6 h.

Presumably heterodimer **212** forms from addition of the alkoxide of allylic alcohol **211** (produced by base-promoted epoxide ring opening) to the cyclobutanone carbonyl of a second molecule of substrate. The hydroxyl moiety of the resulting hemiacetal, or its conjugate base, may then engage in an intramolecular 5-*exo-trig* Michael addition reaction with the latent enone to produce the spiro-fused acetal **212**. It is proposed that formation of this dimer could be suppressed through *in situ* trapping of the product of epoxide ring-opening with an appropriate

organochlorosilane, thereby preventing the subsequent dimerisation reaction from occurring. In such a fashion, it should be possible to optimise the reaction so as to selectively generate the allyl alcohol **211** as an advanced intermediate in the synthesis of (–)-tsugicoline A [(–)-**55**].

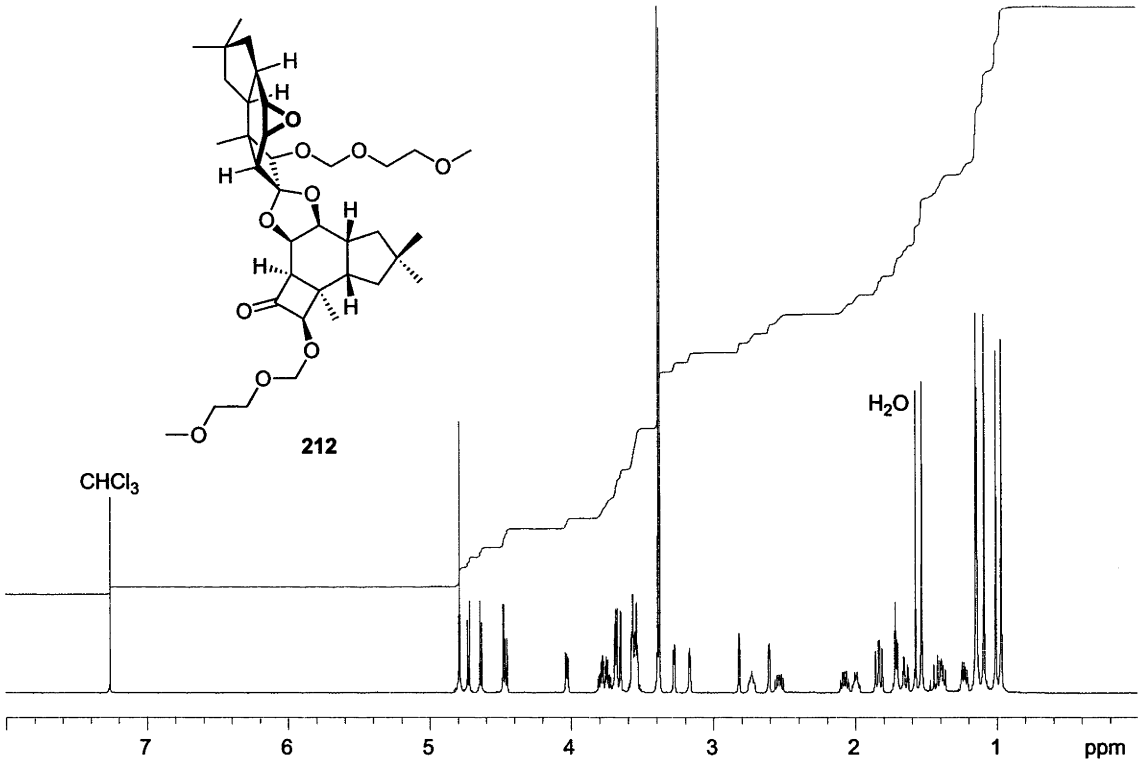



**Figure 4.12:** *500 MHz $^1H$ NMR spectrum of the* spiro-*cyclic heterodimer 212 in $CDCl_3$.*

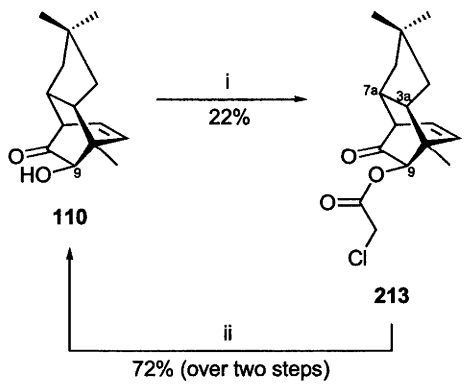
### 4.5.3 Ongoing research towards the synthesis of (–)-tsugicoline A and (+)-isovelleral

Formation of (–)-tsugicoline A [(–)-**55**] from the cyclobutanone **60**, or of (+)-isovelleral [(+)-**56**] from cyclopropyl indenes **61** and **62**, requires that a series of functional group interconversions are performed upon each of the photochemical products to install the requisite functionality associated with each target sesquiterpene. Whilst no success has yet been achieved in further elaborating the cyclopropyl indenes **61** and **62** to (+)-isovelleral [(+)-**56**], several functional group interconversions of cyclobutanone **60**, relevant to the synthesis of (–)-tsugicoline A [(–)-**55**], were presented in the previous Section 4.5.2.

The formation of (–)-tsugicoline A [(–)-**55**] from allyl alcohol **211** (or cyclobutanone **60**) requires inversion of stereochemistry at C(1). Whilst no efforts have been made directly in this regard, attempts to indirectly effect inversion of C(1) in cyclobutanone **60** through inversion at the corresponding C(9) oxymethine of the β,γ-unsaturated ketone **110**, and prior to

performing the photochemical 1,3-acyl shift, were investigated using Mitsunobu protocols.[42] Although acyloin **110** was smoothly converted into a chloroacetate ester by such methods (Scheme 4.15), this was not accompanied by inversion of stereochemistry at C(9). Rather, the non-inverted chloroacetate **213** was obtained. As expected, the IR spectrum of ester **213** displays absorption maxima associated with the two carbonyl stretches at 1769 and 1744 $cm^{-1}$, while the EI mass spectrum features two molecular ions at *m/z* 298 (2%) and *m/z* 296 (6%) which correspond to those for a chlorinated compound. An accurate mass measurement on the latter ion established the molecular composition as $C_{16}H_{21}O_3{}^{35}Cl$, consistent with microanalytical data. Complete assignment of the $^1H$ and $^{13}C$ NMR spectra was facilitated by extensive connectivity and proximity analyses including the use of NOESY experiments which showed enhancements between the methylene protons of the ester at δ 4.16 and the C(3a)-H and C(7a)-H ring-junction methane protons (δ 2.68 – 2.56). No such enhancements were observed between the oxymethine C(9)-H protons (δ 4.92) and the same C(3a)-H and C(7a)-H ring-junction methane protons, thereby indicating that esterification had proceeded without inversion.

**Scheme 4.15:** *Attempted Mitsunobu inversion of acyloin **110**.*




*Reagents and conditions*: i) $ClCH_2COOH$, $PPh_3$, DIAD, toluene, ambient temp., 6 h; ii) $NH_{3\ (aq.)}$, MeOH, ambient temp., 3 h.

In order to further confirm this observation, and to avoid difficulties associated with purification of the chloroacetate ester,[43] a one-pot esterification-saponification procedure was developed. Thus, acyloin **110** was esterified according to the Mitsunobu procedure described above and once all starting material was consumed, the crude chloroacetate ester **213** was subsequently hydrolysed to afford product **110**, identical with the acyloin substrate and in 72% yield. To assist with characterisation, the product was protected as the

42 a) Lipshutz, B. H.; Miller, T. A., *Tetrahedron Lett.*, **1990**, *31*, 5253; b) Saïah, M.; Bessodes, M.; Antonakis, K., *Tetrahedron Lett.*, **1992**, *33*, 4317.

43 The chloroacetate ester **213** was observed to hydrolyse significantly to acyloin **110** on exposure to silica gel during flash column chromatography: a phenomenon observed by: Pozsgay, V., *J. Am. Chem. Soc.*, **1995**, *117*, 6673.

2-(methoxyethoxy)methoxy ether and subjected to direct irradiation under photochemical reaction conditions. That inversion was not successful during the Mitsunobu esterification procedure was implicit in the nature of the four photochemical products **59** – **62**, thus obtained, each being identical, in every respect, with those described earlier in this Chapter and in Chapter Three.

The formation of (+)-isovelleral [(+)-**56**] from cyclopropyl indenes **61** and **62** requires the installation of two formyl groups at C(1a) and C(2), in addition to the deletion of the protected hydroxyl moiety at C(1). It is considered that conversion of the C(1) protected hydroxyl moiety to an appropriate leaving group and subsequent elimination with a strong base would allow for concomitant introduction of a formyl group (or a nucleophilic equivalent thereof) at C(1a).[44]

Whilst chemical methods for the introduction of a hydroxymethyl group at C(3) of allyl alcohol **211**[45] and of a formyl group at C(2) of cyclopropyl indenes **61** and **62** {as required for (–)-tsugicoline A [(–)-**55**] and (+)-isovelleral [(+)-**56**] respectively} could probably be devised, a more attractive approach would involve incorporation of such moieties, from the beginning of the synthesis. Thus, revised retrosynthetic strategies (detailed below) were formulated for (–)-tsugicoline A [(–)-**55**] and (+)-isovelleral [(+)-**56**] to fulfil this objective.

## 4.6 Revised retrosynthetic strategies

Based on the analysis presented in Chapter One, it is anticipated that dihydroxylation of *m*-methylbenzyl alcohol **214** (or an equivalent thereof), using toluene dioxygenase in a whole-cell mediated biotransformation, would afford the novel *cis*-1,2-dihydrocatechol **215**. The *cis*-1,2-dihydrocatechol **215** should, when carried forward *via* Diels-Alder cycloaddition and photochemically-promoted rearrangement reactions, afford hydroxymethylated synthetic intermediates that could be converted to (–)-tsugicoline A [(–)-**55**] and (+)-isovelleral [(+)-**56**]. These protocols are described below in the revised retrosynthetic analyses (Scheme 4.16) of these sesquiterpene natural products.[46]

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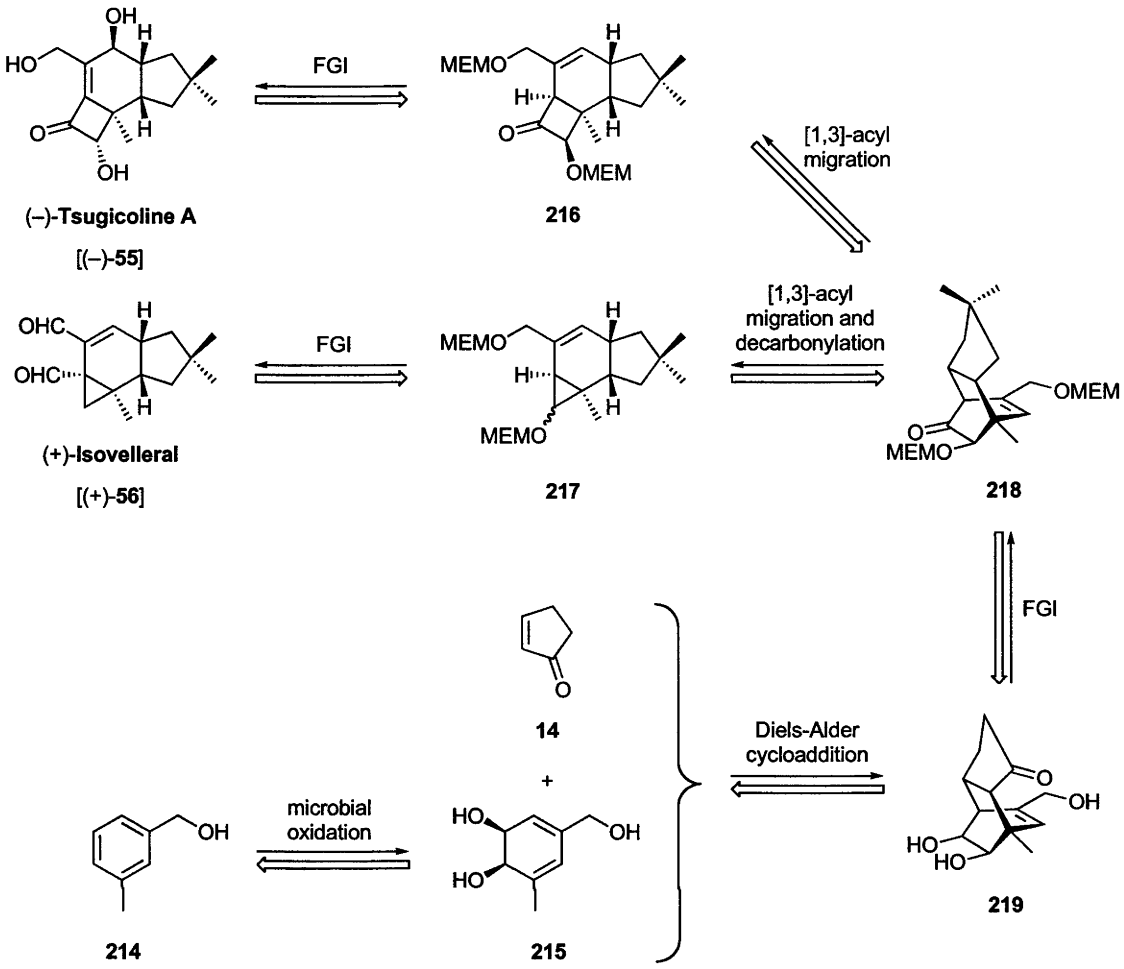
44 Banwell, M. G.; Reum, M. E., *Adv. Strain Org. Chem.*, **1991**, *1*, 19.

45 Using methodology analogous to that developed to install the C(1) methyl group in the first (1998) synthesis of (–)-patchoulenone [(–)-**34**] (detailed in Chapter One): a) Banwell, M.; McLeod, M., *Chem. Commun.*, **1998**, 1851; b) Banwell, M. G.; Hockless, D. C. R.; McLeod, M. D., *New J. Chem.*, **2003**, *27*, 50.

46 Additionally, an appropriately substituted isochorismate, when subjected to a whole-cell mediated biotransformation with *Escherichia coli* strains AN193 or H1882 (engineered with plasmid pJF*entBC*) may be expected to afford the corresponding *trans*-1,2-dihydrocatechol: a) Franke, D.; Sprenger, G. A.; Müller, M., *Angew. Chem., Int. Ed. Engl.*, **2001**, *40*, 555; b) Franke, D.; Lorbach, V.; Esser, S.; Dose, C.; Sprenger, G. A.; Halfar, M.; Thömmes, J.; Müller, R.; Takors, R.; Müller, M., *Chem. Eur. J.*, **2003**, *9*, 4188. Although the production of preparatively useful quantities of *trans*-1,2-dihydrocatechols is still in its inception, such a metabolite could be carried forward through a similar series of steps to that described above to deliver a C(1)-inverted analogue of cyclobutanone **60**, as required for the synthesis of (–)-tsugicoline A [(–)-**55**]. In a similar manner, it should be possible to install the requisite C(1a) formyl group of (+)-isovelleral [(+)-**56**] through reaction of the known

**Scheme 4.16:** *Revised retrosynthetic analyses of (–)-tsugicoline A [(–)-55] and (+)-isovelleral [(+)-56].*




Thus, it was anticipated that (–)-tsugicoline A [(–)-**55**] and (+)-isovelleral [(+)-**56**] could be accessed from the respective tricycles **216** and **217**, through a series of standard functional group interconversions. Each of the respective tricyclic compounds **216** and **217** are the projected products from 1,3-acyl rearrangement and, in the latter case, accompanying decarbonylation reaction of the β,γ-unsaturated ketone **218**. In the synthetic direction, subjection of compound **218** to direct-irradiative (singlet-sensitised) photochemical reaction conditions should generate the tricycles **216** and **217** that embody the framework of each target molecule.[47] The β,γ-unsaturated ketone **218** could be assembled from compound **219** through another series of functional group interconversions. The synthetic origin of compound **219** may be traced to precursors **215** and **14** through a Diels-Alder disconnection. Indeed, the *cis*-1,2-dihydrocatechol **215** would be expected to readily participate, as the 4π component, in Diels-Alder cycloaddition reactions with a suitably activated dienophile such as cyclopentenone

*cis*-1,2-dihydrocatechol derived from microbial oxidation of di-*t*-butyl phthalate with *Micrococcus sp.* 12B: c) Eaton, R. W.; Ribbons, D. W., *Bacteriol.*, **1982**, *151*, 48.

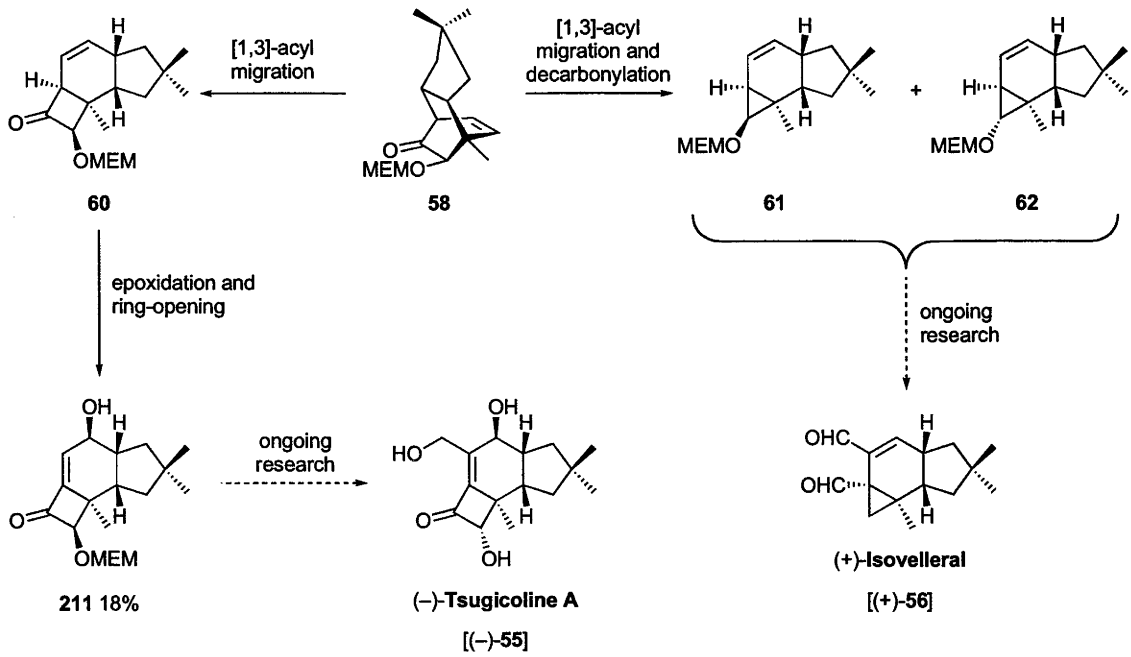
47 For a review of the photochemistry of β,γ-unsaturated carbonyl compounds, refer to: Houk, K. N., *Chem. Rev.*, **1976**, *76*, 1.

**14**. It is anticipated that dihydroxylation of *m*-methylbenzyl alcohol **214** (or an equivalent thereof), using toluene dioxygenase in a whole-cell mediated biotransformation, would afford enantiopure *cis*-1,2-dihydrocatechol **215**. While this particular metabolite has not been reported previously, many related *cis*-1,2-dihydrocatechols derived from *meta*-disubstituted benzenes have been described.[48]

## 4.7 Conclusion

In the research detailed herein and summarised in Scheme 4.17, the β,γ-unsaturated ketone **58** was converted *via* photochemically-promoted reactions into the cyclobutanone **60** and cyclopropyl indenes **61** and **62**. The cyclobutanone **60** was further transformed *via* several functional group interconversions into the allyl alcohol **211**. Each of cyclobutanone **60** and allyl alcohol **211**, along with cyclopropyl indenes **61** and **62**, bear significant resemblance to the frameworks embodied within the protoilludane and marasmane classes of sesquiterpene, respectively. Whilst it may be possible to devise total syntheses of (–)-tsugicoline A [(–)-**55**] and (+)-isovelleral [(+)-**56**] from these intermediates, an alternative retrosynthetic strategy has been proposed in which the key microbial oxidation, Diels-Alder cycloaddition and photochemical rearrangement steps of the synthesis are retained. The new strategy would employ the novel *cis*-1,2-dihydrocatechol metabolite **215** potentially derived from microbial oxidation of *m*-methyl benzyl alcohol **214**, to install the functionality required for the target natural products. Research focussed along these lines will commence shortly.

**Scheme 4.17:** *Summary of research towards the synthesis of (–)-tsugicoline A [(–)-55] and (+)-isovelleral [(+)-56].*




48 Boyd, D. R.; Sheldrake, G. N., *Nat. Prod. Rep.*, **1998**, 309.

*Chapter Five*

# *Future Research*

## 5.1 Introduction

The research presented in Chapters Two, Three and Four of this Thesis exemplifies the capacity for natural products belonging to the linear triquinane, protoilludane and marasmane classes of sesquiterpene to be synthesised from a common precursor. Indeed, the methodologies used in the total synthesis of *ent*-(–)-hirsutene [*ent*-(–)-**54**], and in significant advances towards the formation of (–)-tsugicoline A [(–)-**55**] and (+)-isovelleral [(+)-**56**], employed a three-step *cis*-1,2-dihydroxylation – Diels-Alder cycloaddition – photochemical rearrangement sequence, which diverged only at the latter step, to enantioselectively generate the skeleta associated with each of the targeted compounds. Whilst it is recognised that these methods should also find utility in the synthesis of other members of the linear triquinane, protoilludane and marasmane classes of sesquiterpene, the versatility of these protocols is further highlighted when unified with complimentary approaches to other structurally distinct sesquiterpenes.

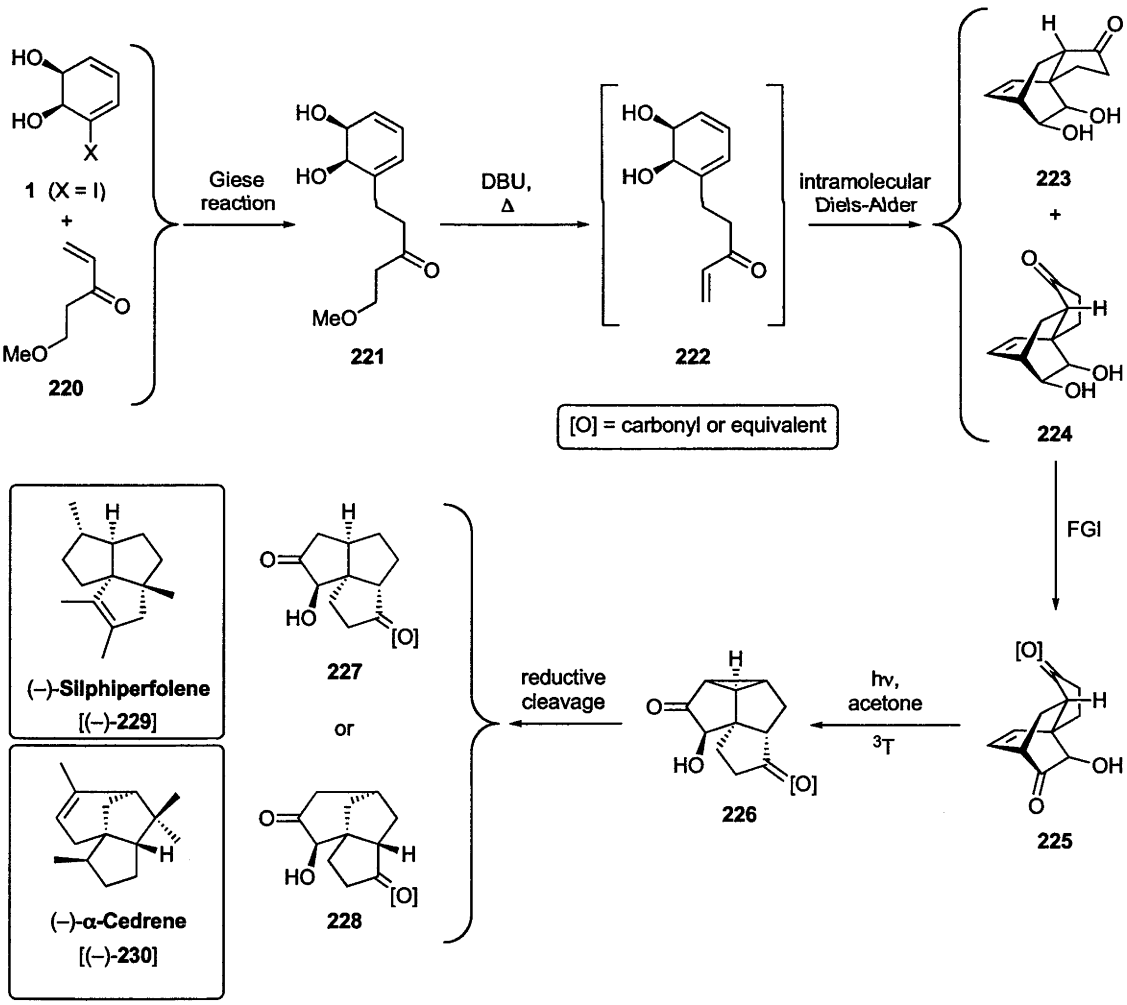
## 5.2 Proposed sesquiterpene syntheses

In the present Chapter, enantioselective synthetic approaches to the angular triquinane and [3.3.3]-propellane classes of natural product, as well as various other types of sesquiterpene are proposed. Many of these compounds have not been synthesised previously and their absolute stereochemistries and biological properties remain unknown. The proposed syntheses are broadly grouped into two categories, depending on the general strategies employed to synthesise the frameworks associated with the various classes of sesquiterpene. The approaches evolve from the research presented in Chapters Two, Three and Four, and champion the combination of microbial oxidation, Diels-Alder cycloaddition and photochemically-promoted rearrangement processes, amongst others, as key steps in each synthesis. Specific examples of the potential application of such reaction sequences are provided in the following Sections.

### 5.2.1 Proposed access to angular triquinanes and other classes of sesquiterpene

Engaging the iodinated *cis*-1,2-dihydrocatechol **1** (X = I) in a Giese reaction[1] with the vinyl ketone **220** would be expected to deliver the conjugate **221** (Scheme 5.1). Treatment of compound **221** with a mild base, such as DBU, should result in an elimination reaction and generate the unstable enone **222** which would be expected to undergo subsequent *syn*-selective intramolecular Diels-Adler cycloaddition and generate the adducts **223** and **224** (with the latter *endo*-isomer likely to predominate over the former *exo*-isomer). It was envisaged that elaboration of the *endo*-adduct **224** to the β,γ-unsaturated ketone **225** *via* a series of standard functional group interconversions and subsequent irradiation of this compound under triplet sensitised photochemical reaction conditions should effect formation of the oxa-di-π-methane rearrangement product **226**. In principle, reductive cleavage of the cyclopropyl ketone **226** can be selectively effected at either of two bonds, to generate the tricycles **227** or **228**. These reduced products **227** and **228** bear marked similarity to the sesquiterpenes

**Scheme 5.1:** *Proposed access to the angular triquinane and cedrane classes of sesquiterpene.*




1 Giese, B., *Angew. Chem., Int. Ed. Engl.*, **1983**, *95*, 771.

(–)-silphiperfolene[2] [(–)-**229**] and (–)-α-cedrene[3] [(–)-**230**], respectively. In principle, each of these natural products could be synthesised *via* a similar sequence of steps from the appropriately functionalised precursors.

In a related manner, it is anticipated (Scheme 5.2) that the installation of sterically demanding protecting groups onto the free hydroxyl moieties of the iodinated *cis*-1,2-dihydrocatechol **1** (X = I) to form diene **231**, would allow the corresponding enone **232** to be generated (*via* compound **233**). Intramolecular Diels-Alder cyclisation of compound **232**, should selectively favour formation of the *anti*-adducts **234** and **235**, rather than the *syn*-isomers. Reaction of the *endo*-, *anti*-Diels-Alder adduct **235** in a similar fashion to that described for the *endo*-, *syn*-adduct **224** in Scheme 5.1, would be expected to smoothly deliver the protected acyloin **236**. The β,γ-unsaturated ketone **236**, when subjected to direct irradiative photochemical reaction conditions, should, in turn, afford the cyclobutanone **237** and/or the cyclopropane **238** depending on the duration of the reaction. Each of these photoproducts **237** and **238** closely resemble the tricyclic frameworks assigned to the as yet unsynthesised novel sesquiterpenes (+)-viridianol[4] [(+)-**239**] and (–)-tamariscene[5] [(–)-**240**], respectively.

It is worth noting that by extending the length of the tether between the diene and dienophile moieties of compound **241**, the size of the rings that form upon Diels-Alder cycloaddition (compounds **242** and **243**) and subsequent photochemical reaction (compounds **244** and **245**) may be increased. This could provide the opportunity to enantioselectively access natural products such as (+)-madreporanone[6] [(+)-**246**] and (–)-thujopsene[7] [(–)-**247**] using similar routes to those described above for (–)-silphiperfolene [(–)-**229**] and (–)-tamariscene [(–)-**240**], respectively (Scheme 5.3).[8]

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2 (–)-Silphiperfolene [(–)-**229**] was isolated from the roots of *Silphium perfoliatum*: Bohlmann, F.; Jakupovic, J., *Phytochemistry*, **1980**, *19*, 259. No biological properties have been reported.

3 (–)-α-Cedrene [(–)-**230**] was first isolated as a mixture with the (+)-β-cedrene isomer from wood oil of the cedar *Juniperus virginiana*: a) Walter, P., *Annalen*, **1841**, *39*, 247. Structural elucidation was performed independently by: b) Stork, G.; Breslow, R., *J. Am. Chem. Soc.*, **1953**, *75*, 3291; c) Plattner, P. A.; Fürst, A.; Eschenmoser, A.; Keller, W.; Kläui, H.; Meyer, S.; Rosner, M., *Helv. Chim. Acta*, **1953**, *36*, 1845. No biological properties, other than the natural product's fragrance have been reported.

4 (+)-Viridianol [(+)-**239**] was isolated from the red seaweed *Laurencia viridis*: Norte, M.; Fernández, J. J.; Souto, M. L., *Tetrahedron Lett.*, **1994**, *35*, 4607. No biological properties have been reported.

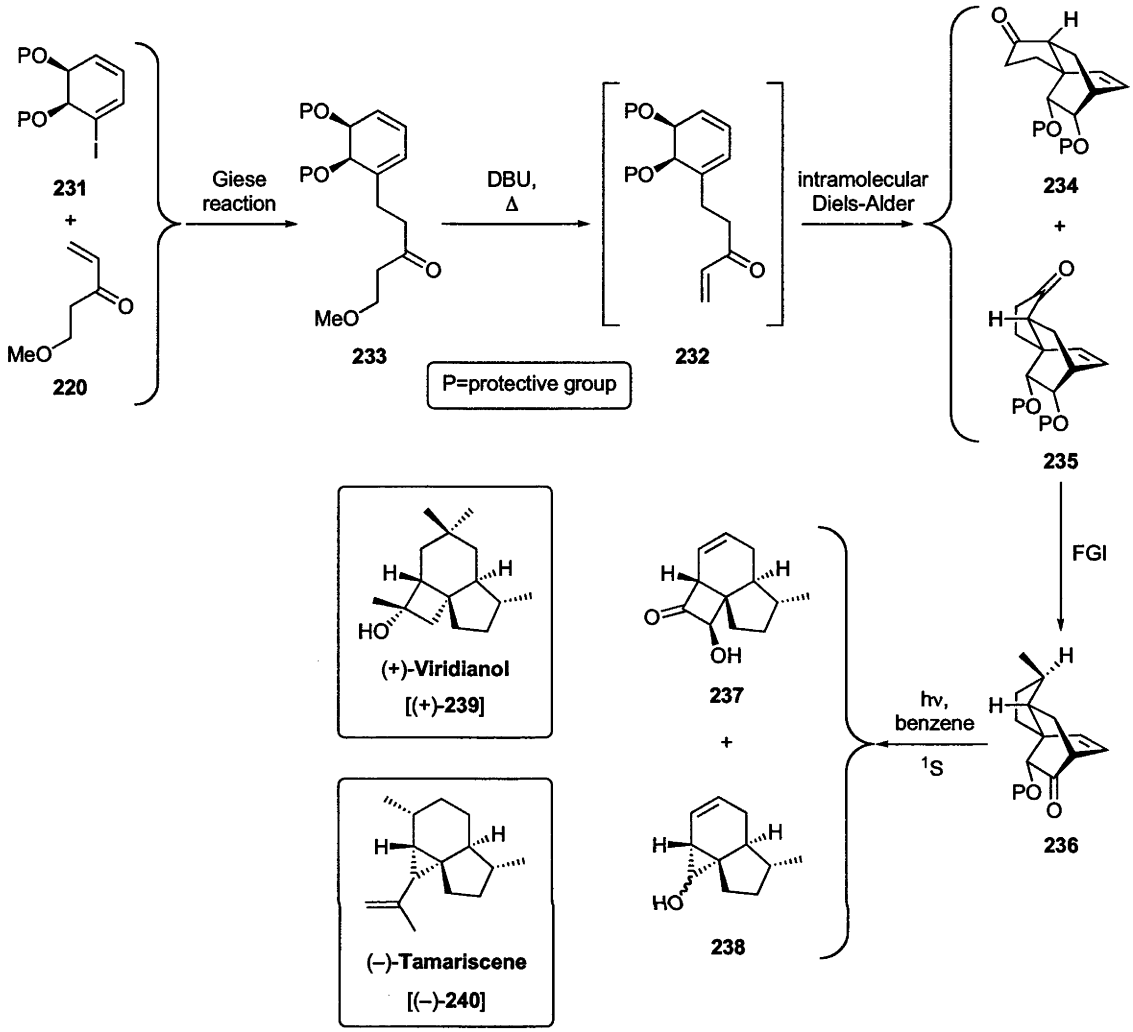
5 (–)-Tamariscene [(–)-**240**] was isolated from the liverworts *Frullania tamarisci* and *F. fragifolia* (Tayl.), whilst the opposite enantiomer, (+)-tamariscene [(+)-**240**] was isolated from the medicinal plant *Valeriana officinalis* L.: Paul, C.; König, W. A.; Muhle, H., *Phytochemistry*, **2001**, *57*, 307. No biological properties have been reported.

6 (+)-Madreporanone [(+)-**246**] was isolated from the Chilean plant *Azorella madreporica*: Loyola, L. A.; Bórquez, J.; Morales, G.; San-Martín, A.; Darias, J., *Tetrahedron Lett.*, **2002**, *43*, 6359. No biological properties have been reported.

7 (–)-Thujopsene [(–)-**247**], also known as widdrene, was first isolated from the oil of Japanese hiba (*Thujopsis dolabrata*): a) Yano, M., *J. Soc. Chem. Ind., Jpn.*, **1913**, *16*, 443. Structural elucidation was performed by: b) Erdtman, H.; Norin, T., *Chem. Ind. (London)*, **1960**, 622. No biological properties, other than the natural product's fragrance have been reported.

8 The methodology described to access (–)-tamariscene [(–)-**240**] is, however, for the opposite enantiomeric series to that required for (–)-thujopsene [(–)-**247**].

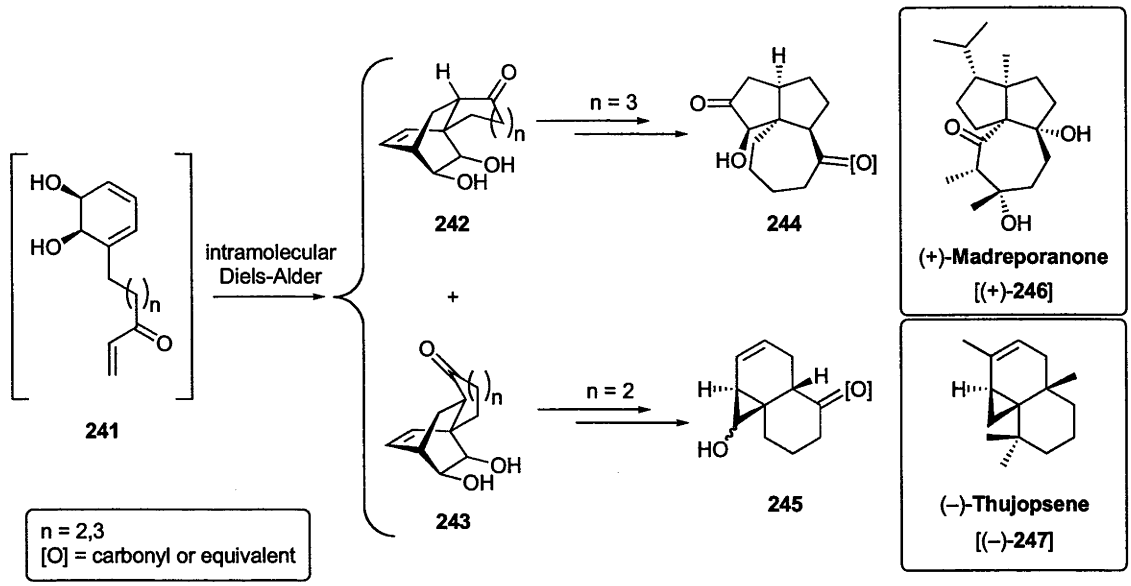
**Scheme 5.2:** *Proposed access to (+)-viridianol [(+)-239] and (–)-tamariscene [(–)-240].*



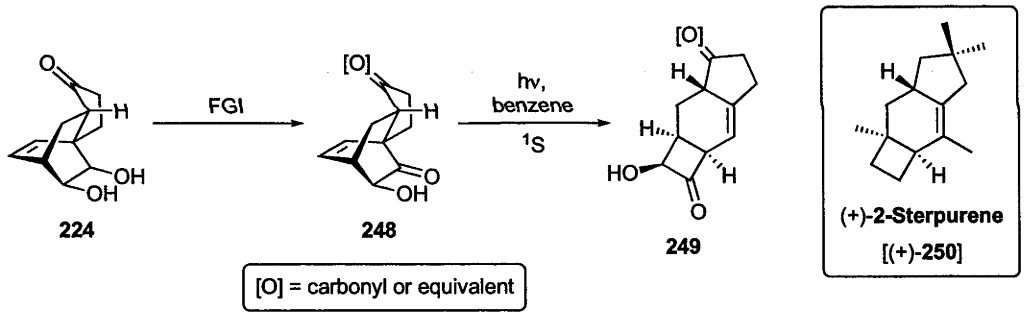

In addition to the selectivity conferred at each of the key steps mentioned above, control is also possible in the oxidation step to furnish the β,γ-unsaturated ketone, thereby further exemplifying the versatility of the protocols delineated in this Thesis. Thus, if the more sterically hindered of the two hydroxyl moieties within diol **224** is oxidised (rather than that remote from the fused cyclopentyl group), then the β,γ-unsaturated ketone **248**, rather than the isomer **225** would be obtained (Scheme 5.4). Subjection of β,γ-unsaturated ketone **248** to direct irradiative photochemical reaction conditions of short duration should result in the formation of the cyclobutanone **249**, which incorporates the tricyclic skeleton associated with the sterpurane classs of sesquiterpenes, of which (+)-2-sterpurene[9] [(+)-**250**] is a representative member.

9 (+)-2-Sterpurene [(+)-**250**] was (first) isolated from the pathogenic fungus *Stereum purpureum* and is considered to be a metabolite responsible for "silvering" plants afflicted with silver-leaf disease: Ayer, W. A.; Saeedi-Ghomi, M. H., *Can. J. Chem.*, **1981**, *59*, 2536.

**Scheme 5.3:** *Proposed access to (+)-madreporanone [(+)-246] and (–)-thujopsene [(–)-247].*




**Scheme 5.4:** *Proposed access to the sterpurane class of sesquiterpene.*



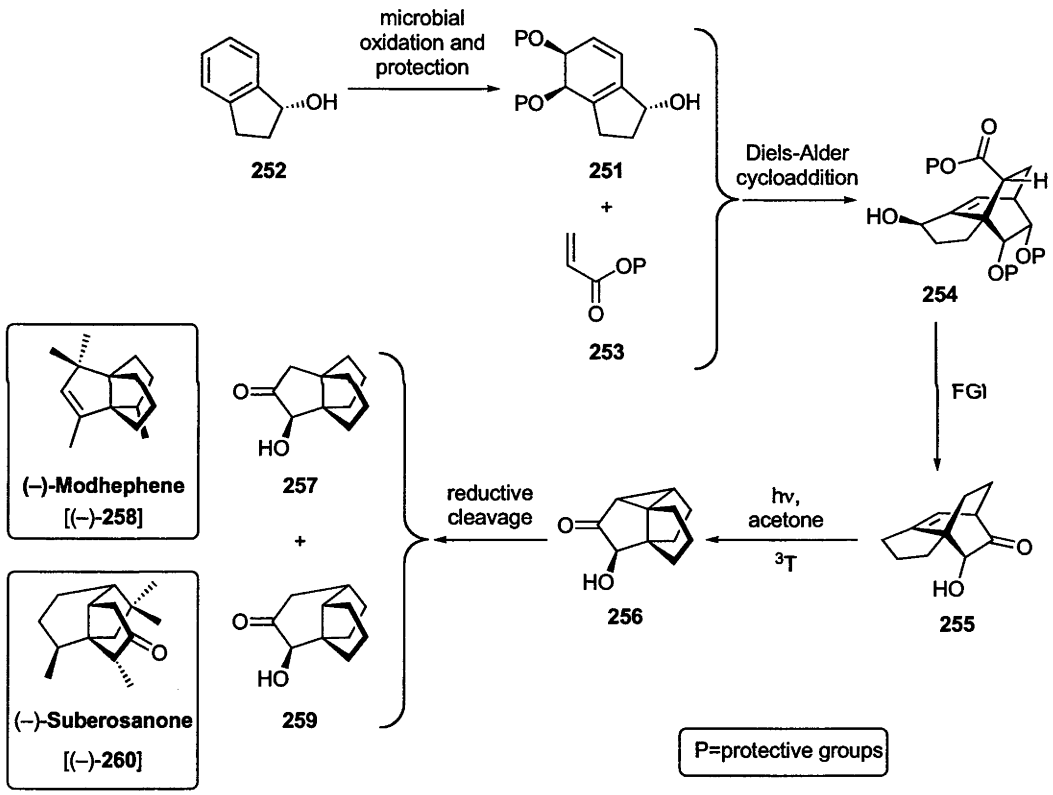

## 5.2.2 Proposed access to [3.3.3]-propellanes and other classes of sesquiterpene

In a similar manner to that reported previously, hydroxyl-protected dienes such as the acetonide derivative of *cis*-1,2-dihydrocatechol **251** obtained from (*R*)-indan-1-ol (**252**),[10] would be expected to engage in *anti*-selective Diels-Alder cycloaddition reactions with simple and appropriately activated dienophiles such as **253** to afford adducts of type **254** (Scheme 5.5). Application of a series of functional group interconversions similar to those detailed previously

10 Bowers, N. I.; Boyd, D. R.; Sharma, N. D.; Goodrich, P. A.; Groocock, M. R.; Blacker, A. J.; Goode, P.; Dalton, H., *J. Chem. Soc., Perkin Trans. 1*, **1999**, 1453. Although *cis*-1,2-dihydrocatechol **251** can be generated by purely enzymatic means, it could also be synthesised using a chemoenzymatic approach in which a 1,2-dihalogenated aromatic is first converted to the corresponding *cis*-1,2-dihydrocatechol and this metabolite is subsequently converted to the required material (*i.e.* compound **251**) using chemical means.

would be expected to deliver the β,γ-unsaturated ketone **255** which, under triplet sensitised photochemical reaction conditions should furnish the oxa-di-π-methane rearrangement product **256**. Reductive cleavage of the peripheral cyclopropane bond within tetracycle **256**, would afford the tricycle **257** which embodies the framework of the [3.3.3]-propellane class of sesquiterpenes, of which (–)-modhephene[11] [(–)-**258**] is a representative member. Alternatively, reductive cleavage of the internal cyclopropyl bond within compound **256** would afford the corresponding tricycle **259** which closely resembles the framework embodied within natural products such as (–)-suberosanone[12] [(–)-**260**]. It is anticipated that these natural products and, indeed, more complex members of each class, could be synthesised from intermediates such as **257** and **259**, or appropriately substituted variants thereof.

**Scheme 5.5:** *Proposed access to the [3.3.3]-propellane and suberosane classes of sesquiterpene.*




11 (–)-Modhephene [(–)-**258**] was first isolated from the leaves and stems of the toxic plant *Isocoma wrightii*: Zalkow, L. H.; Harris, R. N.; Van Derueer, D., *J. Chem. Soc., Chem. Commun.*, **1978**, 420. No biological properties have been reported.

12 (–)-Suberosanone [(–)-**260**] was isolated from the gorgonian *Isis hippuris* and exhibits $ED_{50}$ values of $<5.0 \times 10^{-6}$ $\mu g.mL^{-1}$ against P-388 and HT-29 cancer cell lines: Sheu, J.-H.; Hung, K.-C.; Wang, G.-H.; Duh, C.-Y., *J. Nat. Prod.*, **2000**, *63*, 1603.

## 5.3 Conclusion

A unified approach to the construction of multiple classes of structurally distinct and biologically active sesquiterpene natural products has been proposed, based on the total synthesis of *ent*-(–)-hirsutene [*ent*-(–)-**54**] and on the significant advances towards (–)-tsugicoline A [(–)-**55**] and (+)-isovelleral [(+)-**56**], presented in Chapters Two, Three and Four of this Thesis. The potential for the construction of manifold classes of sesquiterpene is provided by the capacity to control the selectivity conferred on individual steps in the proposed syntheses and in particular, on the microbial oxidation, Diels-Alder cycloaddition and photochemically-promoted rearrangement reactions. It is this combination of three key steps that renders the protocols presented in this Thesis of considerable significance in the synthesis of sesquiterpene natural products.

*Chapter Six*

# *Experimental Procedures for Chapters Two to Four*

## 6.1 General experimental procedures

### 6.1.1 Materials and methods

Starting materials and reagents were generally available from the Sigma-Aldrich, Merck, TCI, or Lancaster Chemical Companies and were used as supplied or, on occasion, simply recrystallised or distilled. *cis*-1,2-Dihydrocatechol **1** (X = Me) was generously provided by Prof. T. Hudlicky[1] of Brock University (Ontario, Canada) and Dr G. Whited[2] of Genencor International Inc. (Palo Alto, California, U.S.A.). Similarly, 4-Acetamido-TEMPO was kindly supplied by Prof. J. M. Bobbitt[3] of the University of Connecticut (Connecticut, U.S.A.). Inorganic salts were purchased from Sigma-Aldrich, AJAX, BDH or Unilab Chemical Companies.

Tetrahydrofuran (THF), diethyl ether and benzene were distilled from sodium benzophenone ketyl and the latter solvent was stored over 4 Å molecular sieves. Methanol was distilled from magnesium *bis*(methoxide). Toluene was distilled, through a Vigreux column, from molten sodium metal. Dichloromethane, acetonitrile, *t*-butanol, pyridine, triethylamine, *N,N*-di*iso*propylethylamine (Hünig's base) and 2,6-di-*t*-butyl-4-methylpyridine were all distilled through Vigreux columns from calcium hydride. *t*-Butanol, pyridine and triethylamine were stored over 4 Å molecular sieves, while *N,N*-di*iso*propylethylamine (Hünig's base) was stored over calcium hydride. Acetone was agitated with anhydrous $CaSO_4$ for 24 h before being decanted and distilled through an efficient Hempel column (packed with Fenske rings) from

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3 bobbitt@nucleus.chem.uconn.edu

fresh quantities of anhydrous $CaSO_4$. Hexane, ethyl acetate and water were each purified by rapid distillation through Vigreux columns.

Glassware was soaked in a base bath (Pyroneg® in water) before being rinsed, first with distilled water, then acetone, and subsequently oven-dried at 120°C. Assembled apparatus was evacuated (<1.0 mm Hg) and flushed three times with dry (oxygen-free) nitrogen, prior to use. All reaction mixtures were manipulated using standard Schlenk techniques and, unless otherwise specified, were magnetically stirred.

Temperatures higher than ambient (generally 15 – 25°C) were attained using thermostated oil baths. To attain temperatures lower than ambient, a cooled, water-circulating bath was used (10 – 0°C), as were constant temperature baths (ice/water slush, 0°C; chloroform slush, –63°C; dry-ice/acetone, –78°C). Liquid nitrogen (–196°C) was used when temperatures lower than those quoted above were required.

Deoxygenated solvents or solutions were obtained by subjecting these to three repeated cycles of freezing (to –196°C), evacuation (to <1.0 mm Hg) and thawing, or, in the case of NMR samples, by bubbling nitrogen through the solution for 15 min.

High pressure-promoted reactions were performed using a PSIKA Pressure Systems Ltd. 20 kbar Pressure Reaction System apparatus. Reaction mixtures were prepared (as solutions in dichloromethane, under a nitrogen atmosphere) in a compressible reaction vessel manufactured from Teflon® which was immersed in a castor oil/methanol mixture (85:15) contained in a cavity within the reactor and subjected to 19 kbar pressure at ambient temperature.

Photochemical reactions were performed using a Philips 125 W HPL-N Hg arc lamp housed in a quartz water-cooled jacket. Reaction mixtures were prepared as deoxygenated solutions in a Pyrex™ reaction vessel under a nitrogen atmosphere and magnetically stirred at 500 rpm.

Organic solutions (extracts) obtained from the aqueous work-up of reaction mixtures were dried with magnesium sulfate ($MgSO_4$) or sodium sulfate ($Na_2SO_4$) before filtration and concentration under reduced pressure on a rotary evaporator equipped with a water aspirator and, unless otherwise specified, with the water bath temperature generally not exceeding 50 °C.

Flash (column) chromatography was performed according to the method of Still, Khan and Mitra,[4] using silica gel 60 (230 – 400 mesh, 0.040 – 0.0063 mm) as supplied by Merck.

4 Still, W. C.; Kahn, M.; Mitra, A., *J. Org. Chem.*, **1978,** *43,* 2923.

Analytical thin layer chromatography (TLC) was performed on self-indicating aluminium-backed silica gel 60 $GF_{254}$ (0.2 mm thick) plates, as supplied by Merck. Similarly, preparative layer chromatography (PLC) was performed on self-indicating glass-backed silica gel 60 $GF_{254}$ (1.0 mm thick) plates, as supplied by Merck. All chromatographic elutions were performed using distilled hexane and/or ethyl acetate in a variety of ratios, as indicated. Eluted TLC and PLC plates were visualised by physical [UV irradiation ($\lambda$ = 254 nm)] and/or chemical means [treatment with either a) phosphomolybdic acid : ceric sulfate : sulfuric acid (conc.) : water (37.5 g : 7.5 g : 37.5 g : 720 mL), or with b) anisaldehyde : sulfuric acid (conc.) : ethanol (3 mL : 4.5 mL : 200 mL)].

### 6.1.2 Instrumentation

NMR spectra were recorded on either a Varian Inova 500 spectrometer operating at 500 MHz for proton ($^1H$) and 126 MHz for carbon ($^{13}C$) nuclei, or a Varian Mercury 300 spectrometer, operating at 300 MHz for proton and 75 MHz for carbon nuclei. In one instance, a Varian Inova 600 spectrometer, operating at 600 MHz for proton nuclei, was used. Unless otherwise specified, spectra were acquired at 25°C in deuterochloroform ($CDCl_3$) which had been filtered through granular, basic alumina immediately prior to use. Signals arising from the residual protio- and predominant deuterio-forms of the solvent[5] were used as the internal reference standard for proton and carbon NMR spectra, respectively. Proton NMR spectral data are recorded as follows: chemical shift ($\delta$) [multiplicity, coupling constant(s) ($J$, Hz), relative integral], where multiplicity is denoted as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) or combinations of the above. Carbon NMR spectral data are recorded as follows: chemical shift ($\delta$, ppm) [protonicity], where protonicity is denoted as C (quaternary), CH (methine), $CH_2$ (methylene) or $CH_3$ (methyl). The assignment of signals observed in proton and carbon NMR spectra was assisted by conducting complementary connectivity and/or proximity experiments. Connectivity experiments used include the attached proton test (APT), homonuclear ($^1H/^1H$) correlation spectroscopy (COSY) and/or heteronuclear ($^1H/^{13}C$) correlation spectroscopy [heteronuclear multiple-quantum coherence (HMQC), heteronuclear single-quantum coherence (HSQC) and/or heteronuclear multiple-bond correlation (HMBC)]. Proximity experiments include one- or two-dimensional nuclear Overhauser effect and exchange spectroscopy (NOESY) experiments. Invariably, the gradient forms of two-dimensional experiments were used (*eg.* g-COSY, g-HMBC).

Infrared spectra ($\nu_{max}$) were recorded on a Perkin–Elmer 1800 Series FTIR Spectrometer and samples were analysed as thin (crystalline or liquid) films on NaCl disks under a dry nitrogen atmosphere.

5 Formed from protio-deuterio exchange with (residual) moisture present in the sample.

Low and high resolution electron impact (EI) mass spectra were obtained on either a VG Fisons AutoSpec M series three sector (E/B/E) double focussing mass spectrometer (located at the Australian National University, Canberra, Australia), a VG ZAB-2SEQ hybrid sector (BEqQ) instrument (located at the Australian National University), or a Kratos Analytical Concept ISQ mass spectrometer (located at the University of Tasmania, Hobart, Australia). Low resolution electrospray (ES) mass spectra were obtained on either a VG Quattro II triple quadrupole MS instrument (located at the Australian National University) or a Micromass-Waters LC-ZMD single quadrupole liquid chromatograph-MS instrument (located at the Australian National University) operating in either positive and/or negative ionisation modes and at capilliary and cone voltages of 3.5 and 30 V, respectively. Gas chromatographic (GC) analysis and mass spectrometry were performed using respective Varian 3400 Gas Chromatograph and Agilent/HP 6890-5973 instruments fitted with a polydimethylsiloxane capillary column. Peaks were detected using a flame ionisation detector operating at 300 °C and helium was employed as the carrier gas (flow rate *ca.* 35 $cm.s^{-1}$) with a temperature program of 50°C (3 min) – 250°C (2 min) at a rate of $10°C.min^{-1}$.

Elemental analyses were performed by the Australian National University's Microanalytical Services Unit based at the Research School of Chemistry, Canberra, Australia, using a Carbo Erba EA 1106 CHN-O automatic Elemental analyser (for CHN analysis). A Dionex Ion Chromatography analyser was used for sulfur analysis while chlorine analysis was determined by titration with standardised mercuric nitrate.

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

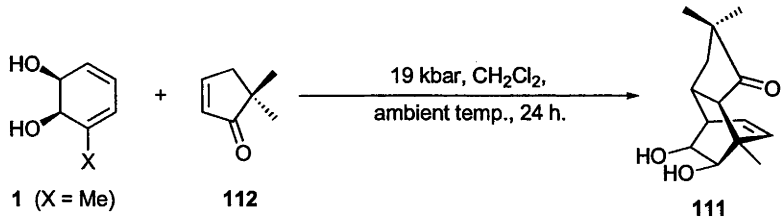
Ultraviolet-Visible (UV-Vis) spectra were obtained using a Shimadzu UV-2101PC UV-Vis scanning spectrophotometer, for a range of concentrations ($c$, $mol.L^{-1}$). Absorbtion (A) measurements were performed at 20°C in a cell with a path length ($l$) of 1.0 cm, using spectroscopic grade acetonitrile as solvent. Molar absorptivities ($\varepsilon_0$) were calculated for a given wavelength ($\lambda_{max}$, nm) using the equation $\varepsilon_0 = A/(c.l)$ and are given in $L.mol^{-1}.cm^{-1}$.

Melting points were measured on a Reichert hot-stage microscope apparatus and are uncorrected.

## 6.2 Experimental procedures for Chapter Two

**(3a*S*,4*S*,7*S*,7a*S*,8*S*,9*R*)-1,2,3a,4,7,7a-Hexahydro-8,9-dihydroxy-2,2,4-trimethyl-4,7-ethano-3*H*-indene-3-one (111)**

*Method A:*




A solution of *cis*-1,2-dihydrocatechol **1** (X = Me) (100 mg, 0.79 mmol) and 5,5-dimethyl-2-cyclopentenone[6] (**112**) (178 mg, 1.62 mol) in dichloromethane (1 mL) was prepared in a Teflon® high-pressure reaction vessel under a nitrogen atmosphere and subsequently subjected to 19 kbar pressure at ambient temperature for 24 h. The system was then restored to atmospheric pressure and concentrated under reduced pressure. Subjection of the ensuing brown oil to flash chromatography (silica, 1:1 → 1:0 v/v ethyl acetate – hexane gradient elution) afforded two fractions, A and B.

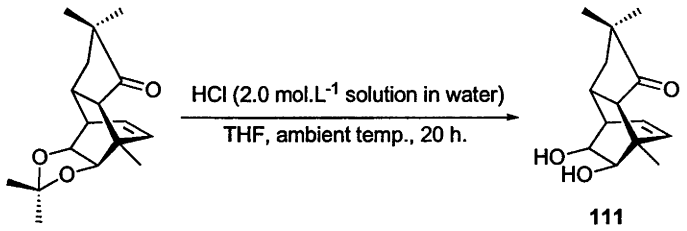
Concentration of fraction A ($R_f$ 0.3, 1:1 v/v ethyl acetate – hexane elution, phosphomolybdic acid visualisation) afforded the *title compound **111*** (2 mg, 2% at 49% conversion) as a white crystalline solid, m.p. 80 – 82°C.

**$^1$H NMR** (500 MHz) δ 6.01 (t, *J* 7.5 Hz, 1H), 5.87 (d, *J* 8.5 Hz, 1H), 3.79-3.76 (m, 1H), 3.26 (dd, *J* 9.0 and 5.0 Hz, 1H), 3.04-2.98 (m, 1H), 2.85 (d, *J* 4.5 Hz, 1H), 2.77-2.74 (m, partially obscured, 1H), 2.75 (d, *J* 11.0 Hz, 1H), 2.72 (d, *J* 5.0 Hz, 1H), 1.87 (dd, *J* 13.0 and 9.0 Hz, 1H), 1.55 (s, 3H), 1.26 (dd, *J* 13.0 and 9.0 Hz, 1H), 1.00 (s, 3H), 0.91 (s, 3H).
**$^{13}$C NMR** (126 MHz) δ 224.3 (C), 138.8 (CH), 131.9 (CH), 71.0 (CH), 66.0 (CH), 46.7 (CH), 46.1 (C), 42.6 (CH), 42.2 (C), 40.7 ($CH_2$), 29.0 (CH), 26.7 ($CH_3$), 22.5 ($CH_3$), 19.6 ($CH_3$).
**IR** $\nu_{max}$ 3401, 3041, 2961, 2928, 2868, 1732, 1454, 1381, 1364, 1274, 1250, 1112, 1054, 1008, 937, 897, 833, 733, 704 $cm^{-1}$.
**Mass Spectrum** (EI, 70 eV) *m/z* 236 ($M^{+\cdot}$, 3%), 218 {[M – $H_2O$]$^{+\cdot}$, 1%}, 176 {[M – HOCH=CHOH]$^{+\cdot}$, 100%}, 161 (20), 148 (26), 133 (17), 119 (10), 105 (60), 92 (77), 91 (28) 77 (28), 56 (32).
**HREIMS** Found: $M^{+\cdot}$, 236.1405. Calculated for $C_{14}H_{20}O_3$ $M^{+\cdot}$, 236.1412.
**Elemental Analysis** Found: C, 71.22; H, 8.76. $C_{14}H_{20}O_3$ requires C, 71.16; H, 8.53%.
**Optical Rotation** $[\alpha]_D^{25}$ –95.6 (*c* 0.04).

6 Prepared from tetramethylcyclobutan-1,3-dione and allyl alcohol according to the methods of: Kopecky, K. R.; Levine, C., *Can. J. Chem.*, **1981,** *59,* 3273.

Concentration of fraction B ($R_f$ 0.2, 1:1 v/v ethyl acetate – hexane elution, UV and phosphomolybdic acid visualisation) afforded unreacted *cis*-1,2-dihydrocatechol **1** (X = Me) (51 mg, 51% recovery) which proved identical, in all respects, with authentic material.

*Method B:*



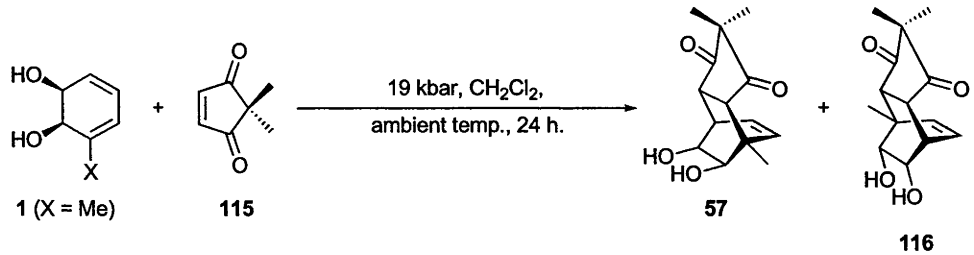

**114** **111**

A solution of acetonide **114** (8.6 mg, 0.03 mmol, generated according to the procedure detailed in Section 6.2, page 144) in THF (2.5 mL) was treated with aqueous HCl (2.5 mL of a 2 mol.L$^{-1}$ solution in water, 5.00 mmol) and allowed to stand at ambient temperature for 20 h. After this time, solvents and gaseous HCl were removed under reduced pressure. Subjection of the ensuing light-yellow oil to flash chromatography (silica, 3:7 → 1:1 v/v ethyl acetate – hexane gradient elution) afforded two fractions, A and B.

Concentration of fraction A ($R_f$ 0.7, 1:1 v/v ethyl acetate – hexane elution, phosphomolybdic acid visualisation) afforded a white crystalline solid which proved identical, in all respects, with unreacted acetonide **114** (0.3 mg, 3% recovery).

Concentration of the fraction B ($R_f$ 0.3, 1:1 v/v ethyl acetate – hexane elution, phosphomolybdic acid visualisation) afforded the *title compound **111*** (6.2 mg, 87% at 97% conversion) identical, in all respects, with material obtained *via Method A*.

**(3a*S*,4*S*,7*R*,7a*S*,8*S*,9*R*)-1,3,3a,4,7,7a-Hexahydro-8,9-dihydroxy-2,2,4-trimethyl-4,7-ethano-2*H*-indene-1,3-dione (57)** and **(3a*R*,4*R*,7*S*,7a*R*,8*S*,9*R*)-1,3,3a,4,7,7a-hexahydro-8,9-dihydroxy-2,2,4-trimethyl-4,7-ethano-2*H*-indene-1,3-dione (116)**




A solution of *cis*-1,2-dihydrocatechol **1** (X = Me) (1.01 g, 8.0 mmol) and 2,2-dimethyl-4-cyclopenten-1,3-dione[7] (**115**) (2.00 g, 16.2 mmol) in dichloromethane (9 mL) was prepared in a Teflon® high-pressure reaction vessel under a nitrogen atmosphere and subsequently subjected to 19 kbar pressure at ambient temperature for 24 h. The system was then restored to atmospheric pressure and concentrated under reduced pressure. Subjection of the ensuing brown oil to flash chromatography (silica, 3:7 → 4:1 v/v ethyl acetate – hexane gradient elution) afforded two fractions, A and B.

Concentration of fraction A ($R_f$ 0.2, 1:1 v/v ethyl acetate – hexane elution, phosphomolybdic acid visualisation) afforded the *title compound 57* (1.47 g, 73%) as a white crystalline solid, m.p. 119 – 121°C.

**$^1$H NMR** (300 MHz) δ 6.02 (dd, *J* 8.4 and 6.3 Hz, 1H), 5.83 (dd, *J* 8.4 and 1.2 Hz, 1H), 3.77 (dd, *J* 9.0 and 3.6 Hz, 1H), 3.70 – 3.34 (broad s, 2H), 3.51 (dd, *J* 10.2 and 3.0 Hz, 1H), 3.29 (d, *J* 8.7 Hz, 1H), 3.30 – 3.26 (m, partially obscured, 1H), 3.21 (d, *J* 10.2 Hz, 1H), 1.58 (s, 3H), 1.06 (s, 3H), 0.92 (s, 3H).

**$^{13}$C NMR** (75 MHz) δ 220.8 (C), 219.7 (C), 138.7 (CH), 131.5 (CH), 69.9 (CH), 64.9 (CH), 54.7 (C), 47.6 (CH), 45.0 (CH), 42.8 (C), 39.8 (CH), 23.5 ($CH_3$), 20.3 ($CH_3$), 16.8 ($CH_3$).

**IR** $\nu_{max}$ 3442, 2970, 2930, 2874, 1757, 1718, 1462, 1379, 1360, 1286, 1204, 1143, 1113, 1051, 1021, 701 $cm^{-1}$.

**Mass Spectrum** (EI, 70 eV) *m/z* 250 ($M^{+\cdot}$, 8%), 190 {[M – HOCH=CHOH]$^{+\cdot}$, 59}, 162 (4), 119 (14), 105 (10), 91 (23), 70 (100).

**HREIMS** Found: $M^{+\cdot}$, 250.1203; [M – HOCH=CHOH]$^{+\cdot}$, 190.0992. Calculated for $C_{14}H_{18}O_4$ $M^{+\cdot}$, 250.1205; [M – HOCH=CHOH]$^{+\cdot}$, 190.0994.

**Elemental Analysis** Found: C, 66.79; H, 6.93. $C_{14}H_{18}O_4$ requires C, 67.18; H, 7.25%.

**Optical Rotation** $[\alpha]_D^{27}$ +34.1 (*c* 0.67).

7 Synthesised from 2-methyl-cyclopentan-1,3-dione *via* 2,2-dimethylcyclopentan-1,3-dione using the methods of: a) Agosta, W. C.; Smith, A. B., *J. Org. Chem.*, **1970,** *35,* 3856; b) Kreiser, W.; Wiggermann, A.; Krief, A.; Swinnen, D., *Tetrahedron Lett.*, **1996,** *37,* 7119.

Concentration of fraction B ($R_f$ 0.1, 1:1 v/v ethyl acetate – hexane elution, phosphomolybdic acid visualisation) afforded the *title compound* ***116*** (0.19 g, 9%) as a white crystalline solid, m.p. 124 – 125°C.

**$^1$H NMR** (300 MHz) δ 6.08 (t, *J* ~8.1 Hz, 1H), 5.87 (d, *J* 8.4 Hz, 1H), 4.04 (dd, *J* 7.2 and 1.8 Hz, 1H), 3.54 (d, *J* 7.5 Hz, 1H), 3.42 – 3.38 (m, 1H), 3.24 – 2.76 (broad s, 2H), 3.02 (dd, *J* 10.2 and 3.0 Hz, 1H), 2.65 (d, *J* 10.2 Hz, 1H), 1.61 (s, 3H), 1.03 (s, 3H), 0.93 (s, 3H).

**$^{13}$C NMR** (75 MHz) δ 217.8 (C), 216.8 (C), 137.0 (CH), 131.1 (CH), 74.0 (CH), 69.8 (CH), 54.4 (C), 51.4 (CH), 48.2 (CH), 43.1 (C), 39.1 (CH), 23.4 ($CH_3$), 19.3 ($CH_3$), 17.0 ($CH_3$).

**IR** $\nu_{max}$ 3494, 2987, 2954, 2937, 2889, 1757, 1715, 1453, 1408, 1374, 1334, 1286, 1199, 1143, 1123, 1081, 1055, 1010, 1029, 829, 732 $cm^{-1}$.

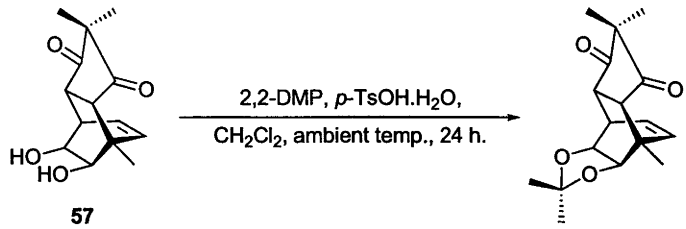
**Mass Spectrum** (EI, 70 eV) *m/z* 250 ($M^{+\cdot}$, 1%), 190 {[M – HOCH=CHOH]$^{+\cdot}$, 81}, 162 (2), 119 (8), 105 (3), 91 (11), 70 (100).

**HREIMS** Found: $M^{+\cdot}$, 250.1205; [M – HOCH=CHOH]$^{+\cdot}$, 190.0995. Calculated for $C_{14}H_{18}O_4$ $M^{+\cdot}$, 250.1205; [M – HOCH=CHOH]$^{+\cdot}$, 190.0994.

**Elemental Analysis** Found: C, 67.22; H, 6.99. $C_{14}H_{18}O_4$ requires C, 67.18; H, 7.25%.

**Optical Rotation** $[\alpha]_D^{27}$ –2.3 (*c* 0.77).

**(3a*R*,4*S*,4a*S*,7a*S*,8*R*,8a*S*)-3a,4a,5,6,7,7a,8,8a-Octahydro-2,2,4,6,6-pentamethyl-4,8-etheno-4*H*-indeno[5,6-*d*]-1,3-dioxole-5,7-dione (117)**




57 117

A magnetically stirred solution of diol **57** (1.07 g, 4.27 mmol) and 2,2-dimethoxypropane (7.5 mL, 61.00 mmol) in dichloromethane (7.5 mL) was maintained at ambient temperature and treated with *p*-TsOH.$H_2O$ (12 mg, 0.06 mmol). After 24 h the reaction mixture was concentrated under reduced pressure. Subjection of the ensuing deep-red oil to flash chromatography (silica, 1:4 v/v ethyl acetate – hexane elution) afforded, after concentration of the appropriate fractions ($R_f$ 0.9, 1:1 v/v ethyl acetate – hexane elution, phosphomolybdic acid visualisation), the *title compound **117*** (1.24 g, 100%) as a clear, colourless oil.

**$^1$H NMR** (300 MHz) δ 6.03 (dd, *J* 8.4 and 6.6 Hz, 1H), 5.82 (d, *J* 8.4 Hz, 1H), 4.11 (dd, *J* 8.1 and 3.9 Hz, 1H), 3.69 (d, *J* 8.4 Hz, 1H), 3.53 (dd, *J* 10.2 and 3.0 Hz, 1H), 3.43 – 3.39 (m, 1H), 3.22 (d, *J* 10.2 Hz, 1H), 1.58 (s, 3H), 1.48 (s, 3H), 1.33 (s, 3H), 1.06 (s, 3H), 0.91 (s, 3H).

**$^{13}$C NMR** (75 MHz) δ 220.3 (C), 219.6 (C), 138.7 (CH), 132.1 (CH), 112.5 (C), 80.8 (CH), 75.0 (CH), 54.5 (C), 47.9 (CH), 45.3 (CH), 42.0 (C), 37.3 (CH), 26.8 ($CH_3$), 24.7 ($CH_3$), 23.5 ($CH_3$), 20.4 ($CH_3$), 16.8 ($CH_3$).

**IR** $\nu_{max}$ 2976, 2930, 1759, 1720, 1460, 1375, 1265, 1206, 1163, 1109, 1065, 1049, 880, 710 $cm^{-1}$.

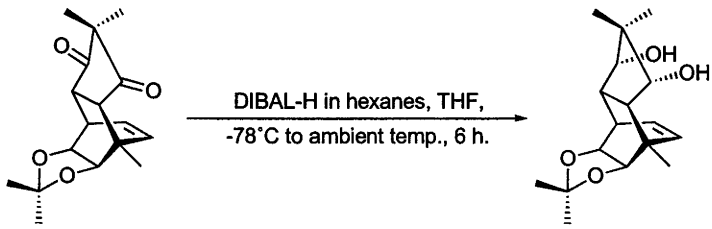
**Mass spectrum** (EI, 70 eV) *m/z* 290 ($M^{+\cdot}$, 11%), 275 {[M – $CH_3\cdot$]$^+$, 15%}, 261 {[M – CO – H·]$^+$, 12%}, 232 {[M – $(CH_3)_2CO]^{+\cdot}$, 27}, 189 (28), 161 (87), 134 (100), 105 (88), 100 (75), 70 (98).

**HRIEMS** Found: $M^{+\cdot}$, 290.1524. $C_{17}H_{22}O_4$ requires $M^{+\cdot}$, 290.1518.

**Optical Rotation** $[\alpha]_D^{22}$ +29.3 (*c* 0.20).

**(3aR,4S,4aS,5R,7S,7aS,8R,8aS)-3a,4a,5,6,7,7a,8,8a-Octahydro-2,2,4,6,6-pentamethyl-4,8-etheno-4H-indeno[5,6-d]-1,3-dioxole-5,7-diol (119)**, **(3aR,4S,4aS,5S,7S,7aS,8R,8aS)-3a,4a,5,6,7,7a,8,8a-octahydro-2,2,4,6,6-pentamethyl-4,8-etheno-4H-indeno[5,6-d]-1,3-dioxole-5,7-diol (120)**, **(3aR,4S,4aS,5R,7R,7aS,8R,8aS)-3a,4a,5,6,7,7a,8,8a-octahydro-2,2,4,6,6-pentamethyl-4,8-etheno-4H-indeno[5,6-d]-1,3-dioxole-5,7-diol (121)** and **(3aR,4S,4aS,5S,7R,7aS,8R,8aS)-3a,4a,5,6,7,7a,8,8a-octahydro-2,2,4,6,6-pentamethyl-4,8-etheno-4H-indeno[5,6-d]-1,3-dioxole-5,7-diol (122)**

*Method A*:[8]




**117** **119**

DIBAL-H (1.55 mL of a 1 mol.$L^{-1}$ solution in hexane, 0.155 mmol) was added, dropwise, to a magnetically stirred solution of dione **117** (102.6 mg, 0.35 mmol) in THF (1.7 mL) maintained at –78°C. After 3 h the reaction mixture was warmed to ambient temperature and allowed to stand for a further 3 h, before being treated with $NH_4Cl$ (10 mL of a saturated aqueous solution) and diluted with water (10 mL) and diethyl ether (10 mL). The resulting biphasic mixture was extracted with diethyl ether (4 × 10 mL) and the combined organic phases washed with brine (1 × 10 mL), then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a pale-yellow solid. Recrystallisation (ethyl acetate) of this material afforded the *title compound **119*** (103 mg, 99%) as a white, crystalline solid, m.p. 106 – 107°C (with sublimation).

**$^1$H NMR** (300 MHz) δ 6.08 (dd, *J* 8.1 and 6.6 Hz, 1H), 5.88 (d, *J* 8.1 Hz, 1H), 4.11 (dd, *J* 8.1 and 3.9 Hz, 1H), 3.75 (d, *J* 8.4 Hz, 1H), 3.72 – 3.66 (m, 2H), 3.10 (ddd, *J* 11.4, 6.0 and 2.4 Hz, 1H), 2.95 – 2.90 (m, 1H), 2.81 (dd, *J* 11.4 and 5.7 Hz, 1H), 1.95 (d, *J* 8.1 Hz, 1H), 1.89 (d, *J* 6.9 Hz, 1H), 1.47 (s, 3H), 1.36 (s, 3H), 1.34 (s, 3H), 1.12 (s, 3H), 0.92 (s, 3H).

**$^{13}$C NMR** (75 MHz) δ 138.5 (CH), 131.7 (CH), 112.2 (C), 84.2 (CH), 83.3 (CH), 81.9 (CH), 76.8 (CH), 49.8 (C), 47.6 (CH), 43.3 (CH), 40.8 (C), 36.7 (CH), 26.9 ($CH_3$), 24.8 ($CH_3$), 24.6 ($CH_3$), 20.4 ($CH_3$), 17.8 ($CH_3$).

**IR** $\nu_{max}$ 3288, 2946, 2890, 1455, 1378, 1257, 1208, 1160, 1061, 1030, 979, 876 $cm^{-1}$.

**Mass spectrum** (EI, 70 eV) *m/z* 294 ($M^{+\cdot}$, 2%), 279 {$[M - CH_3\cdot]^+$, 12%}, 265 {$[M - CHO\cdot]^+$, 64}, 251 (15), 236 {$[M - (CH_3)_2CO]^{+\cdot}$, 18}, 194 (89), 147 (42), 135 (93), 134 (92), 105 (68), 92 (53), 91 (44), 84 (100).

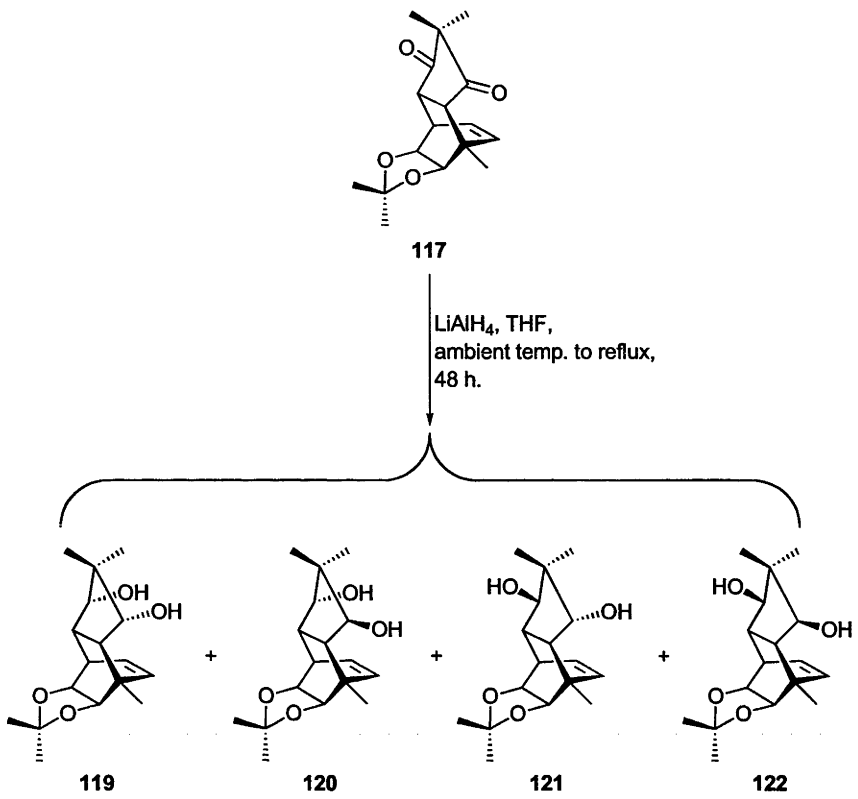
**HREIMS** Found: $M^{+\cdot}$, 294.1826.[9] Calculated for $C_{17}H_{26}O_4$ $M^{+\cdot}$, 294.1831.

8 Only diol **119** is generated using *Method A*.

**Elemental Analysis** Found: C, 69.36; H, 8.90. $C_{17}H_{26}O_4$ requires C, 69.02; H, 9.03%.

**Optical Rotation** $[\alpha]_D^{28}$ +45.1 (*c* 0.78).

*Method B:*




Powdered $LiAlH_4$ (*ca.* 1.00 g, 26.7 mmol) was added, portionwise, to a magnetically stirred solution of dione **117** (103 mg, 0.35 mmol) in THF (20 mL) maintained at ambient temperature. The resulting mixture was heated at reflux for 48 h, then cooled to ambient temperature and treated with $NH_4Cl$ (10 mL of a saturated aqueous solution). The resulting biphasic mixture was extracted with diethyl ether (4 × 10 mL) and the combined organic phases were washed with brine (1 × 10 mL), then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a light-yellow oil. Subjection of this material to flash chromatography (silica, 1:4 → 3:7 v/v ethyl acetate – hexane gradient elution) afforded three fractions, A – C.

Concentration of fraction A ($R_f$ 0.4, 1:1 v/v ethyl acetate – hexane elution, phosphomolybdic acid visualisation) afforded the *title compound **119*** (10 mg, 10%) identical, in all respects, with material obtained *via Method A*.

9 Recorded on the Kratos Analytical Concept ISQ mass spectrometer (located at the University of Tasmania).

Concentration of fraction B [$R_f$ 0.2(3), 1:1 v/v ethyl acetate – hexane elution, phosphomolybdic acid visualisation] afforded a clear, colourless glass tentatively assigned as the *title compound* ***120*** (78 mg, 75%).

**$^1$H NMR** (300 MHz) δ 6.30 (dd, *J* 8.1 and 6.6 Hz, 1H), 5.83 (dt, *J* 8.1 and 0.9 Hz, 1H), 4.11 (dd, *J* 8.4 and 4.2 Hz, 1H), 3.78 (d, *J* 8.1 Hz, 1H), 3.67 (dd, *J* 8.4 and 6.9 Hz, 1H), 3.44 (d, *J* 9.0 and 6.9 Hz, 1H), 3.09 (ddd, *J* 11.1, 6.6 and 2.4 Hz, 1H), 2.88 – 2.83 (m, 1H), 2.38 – 2.31 (m, 1H), 1.48 (s, 3H), 1.36 (s, 3H), 1.34 (s, 3H), 0.98 (s, 3H), 0.89 (s, 3H).
**$^{13}$C NMR** (75 MHz) δ 137.3 (CH), 135.2 (CH), 112.3 (C), 81.7 (CH), 81.3 (CH), 80.8 (CH), 76.5 (CH), 48.7 (CH), 46.1 (C), 41.3 (C), 40.4 (CH), 37.3 (CH), 26.8 ($CH_3$), 24.7 ($CH_3$), 20.7 ($CH_3$), 20.4 ($CH_3$), 20.1 ($CH_3$).
**IR** $\nu_{max}$ 3467, 2958, 2930, 2873, 1457, 1381, 1371, 1262, 1207, 1160, 1061, 1032, 876, 725, 710 cm$^{-1}$.
**Mass Spectrum** (EI, 70 eV)[9] *m/z* 294 ($M^{+\cdot}$, <1%), 279 (7), 265 {[M – CHO·]$^+$, 15}, 236 {[M – $(CH_3)_2CO]^{+\cdot}$, 28}, 194 (100), 172 (37), 134 (73), 105 (39), 84 (94).
**HREIMS** Found: $M^{+\cdot}$, 294.1826.[9] Calculated for $C_{17}H_{26}O_4$ $M^{+\cdot}$, 294.1831.
**Elemental Analysis** Found: C, 69.30; H, 9.20. $C_{17}H_{26}O_4$ requires C, 69.36; H, 8.90%.
**Optical Rotation** $[\alpha]_D^{22}$ –8.6 (*c* 0.23).

Concentration of fraction C [$R_f$ 0.1(7), 1:1 v/v ethyl acetate – hexane elution, phosphomolybdic acid visualisation] afforded an oily semi-solid (15 mg) tentatively identified as a *ca.* 4:1 mixture of the *title compounds* ***121*** and ***122*** (14%).

**IR** $\nu_{max}$ 3434, 2959, 2930, 2873, 1464, 1381, 1372, 1263, 1207, 1164, 1155, 1082, 1045, 882, 731 cm$^{-1}$.

The semi-solid obtained on concentration of fraction C was triturated (ethyl acetate) to afford the *title compound* ***121*** (11.6 mg, 11%) as a white crystalline mass, m.p. 107 – 108°C (with sublimation).

**$^1$H NMR** (300 MHz) δ 6.16 (t, *J* 7.5 Hz, 1H), 5.90 (dm, *J* 8.1 Hz, 1H), 4.15 (dd, *J* 8.1 and 4.2 Hz, 1H), 3.76 (d, *J* 8.1 Hz, 1H), 3.22 – 3.13 (complex m, 2H), 2.98 – 2.93 (m, 1H), 2.55 – 2.47 (m, 1H), 2.24 (dd, *J* 11.4 and 8.7 Hz, 1H), 1.47 (s, 3H), 1.33 (s, 3H), 1.31 (s, 3H), 1.27 (dd, *J* 7.5 and 4.2 Hz, 1H), 0.96 (s, 3H), 0.84 (s, 3H).
**$^{13}$C NMR** (75 MHz) δ 139.7 (CH), 133.6 (CH), 112.1 (C), 81.1 (CH), 80.9 (CH), 80.7 (CH), 76.2 (CH), 46.5 (CH), 44.0 (C), 43.9 (CH), 41.7 (C), 37.4 (CH), 26.7 ($CH_3$), 24.7 ($CH_3$), 24.3 ($CH_3$), 20.4 ($CH_3$), 14.8 ($CH_3$).
**IR** $\nu_{max}$ 3335, 2974, 2936, 2873, 1460, 1381, 1369, 1297, 1262, 1205, 1158, 1059, 1040, 880, 748 cm$^{-1}$.

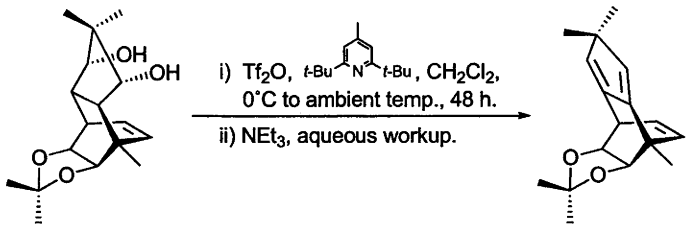
**Mass Spectrum** (EI, 70 eV) *m/z* 294 ($M^{+\cdot}$, <1%), 279 {[M – $CH_3\cdot$]$^+$, 17}, 265 {[M – CHO·]$^+$, 5}, 236 {[M – $(CH_3)_2CO]^{+\cdot}$, 56}, 194 (100), 147 (58), 135 (80), 134 (72), 105 (70), 91 (49), 84 (79).

**HREIMS** Found: $M^{+\cdot}$, 294.1837. Calculated for $C_{17}H_{26}O_4$ $M^{+\cdot}$, 294.1831.

**Elemental Analysis** Found: C, 69.05; H, 8.98. $C_{17}H_{26}O_4$ requires C, 69.36; H, 8.90%.

**Optical Rotation** $[\alpha]_D^{22}$ +26.7 (*c* 0.11).

**(3a*R*,4*S*,8*R*,8a*S*)-3a,4,8,8a-Tetrahydro-2,2,4,6,6-pentamethyl-4,8-etheno-6*H*-indeno[5,6-*d*]-1,3-dioxole (123)**




**119** **123**

Triflic anhydride (64 μL, 0.38 mmol) was added, dropwise, to a magnetically stirred solution of diol **119** (50.4 mg, 0.17 mmol) and 2,6-di-*tert*-butyl-4-methylpyridine (169 mg, 0.82 mmol) in dichloromethane (3 mL) maintained at 0°C. The reaction mixture was subsequently allowed to warm to ambient temperature and, after 48 h, was treated with triethylamine (1 mL), then water (10 mL) and dichloromethane (10 mL). The separated aqueous phase was then extracted with dichloromethane (4 × 10 mL) and the combined organic phases were washed with brine (1 × 5 mL) before being dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. The light-brown residue thus obtained was subjected to flash chromatography (silica, 0:1 → 1:19 v/v ethyl acetate – hexane gradient elution) and concentration of the appropriate fractions ($R_f$ 0.9, 1:1 v/v ethyl acetate – hexane elution, UV and phosphomolybdic acid visualisation) afforded the *title compound **123*** (18.6 mg, 42%) as a clear, colourless oil.

**$^1$H NMR** (300 MHz) δ 6.25 (dd, *J* 7.8 and 6.3 Hz, 1H), 5.96 (dd, *J* 8.1 and 0.9 Hz, 1H), 5.77 (d, *J* 2.1 Hz, 1H), 5.68 (dd, *J* 1.8 and 0.9 Hz, 1H), 4.34 (dd, *J* 7.8 and 4.2 Hz, 1H), 4.03 (d, *J* 7.8 Hz, 1H), 3.62 – 3.58 (m, 1H), 1.43 (s, 3H), 1.29(4) (s, 3H), 1.28(5) (s, 3H), 1.25 (s, 3H), 1.11 (s, 3H).

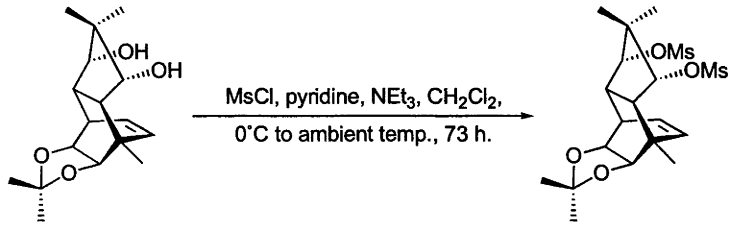
**$^{13}$C NMR** (75 MHz) δ 144.7 (CH), 141.0 (CH), 139.3 (CH), 135.0 (CH), 133.7 (CH), 132.7 (CH), 112.3 (C), 82.0 (CH), 77.6 (CH), 55.5 (CH), 43.5 (C), 40.1 (CH), 26.5 ($CH_3$), 24.8 ($CH_3$), 23.3 ($CH_3$), 23.2 ($CH_3$), 17.3 ($CH_3$).

**IR** $\nu_{max}$ 2978, 2931, 1740, 1701, 1461, 1381, 1266, 1239, 1207, 1161, 1102, 1064, 706 $cm^{-1}$.

**Mass Spectrum** (EI, 70 eV) *m/z* 258 ($M^{+\cdot}$, 6%), 243 {[M – $CH_3^{\cdot}$]$^+$, 8}, 200 {[M – $(CH_3)_2CO$]$^{+\cdot}$, 8}, 185 (6), 183 (7), 171 (89), 158 (100), 156 (46), 143 (33), 141 (24), 128 (19), 115 (13).

**HREIMS** Found: $M^{+\cdot}$, 258.1620. Calculated for $C_{17}H_{22}O_2$ $M^{+\cdot}$, 258.1620.

**(3a*R*,4*S*,4a*S*,5*R*,7*S*,7a*S*,8*R*,8a*S*)-3a,4a,5,6,7,7a,8,8a-Octahydro-2,2,4,6,6-pentamethyl-4,8-etheno-4*H*-indeno[5,6-*d*]-1,3-dioxole-5,7-diol *bis*-methanesulfonate (124)**




**119** **124**

Methanesulfonyl chloride (23 μL, 0.30 mmol) was added to a magnetically stirred solution of diol **119** (40 mg, 0.14 mmol), triethylamine (42 μL, 0.30 mL) and pyridine (1 mL) in dichloromethane (1.4 mL) maintained at 0°C. After 1 h the reaction mixture was warmed to ambient temperature and allowed to stand for 72 h, then concentrated under reduced pressure. The residue, thus obtained, was partitioned between ethyl acetate (5 mL) and water (5 mL) and the separated aqueous phase was extracted with ethyl acetate (5 × 5 mL). The combined organic phases were dried ($Na_2SO_4$), filtered and concentrated under reduced pressure and the ensuing light-brown oil subjected to flash chromatography (silica, 1:1 v/v ethyl acetate – hexane elution). Concentration of the appropriate fractions ($R_f$ 0.5, 1:1 v/v ethyl acetate – hexane elution, phosphomolybdic acid visualisation) gave the *title compound **124*** (45 mg, 74%) as a clear, light-yellow oil.

**$^1$H NMR** (300 MHz) δ 6.05 (dd, *J* 8.1 and 6.6 Hz, 1H), 5.86 (d, *J* 8.1 Hz, 1H), 4.94 (d, *J* 6.0 Hz, 1H), 4.76 (dd, *J* 6.6 and 0.9 Hz, 1H), 4.09 (dd, *J* 8.4 and 3.9 Hz, 1H), 3.76 (d, *J* 8.4 Hz, 1H), 3.30 (ddd, *J* 11.4, 6.6 and 2.1 Hz, 1H), 3.05 (s, 3H), 3.05 – 2.97 (m, partially obscured, 2H), 2.99 (s, 3H), 1.45 (s, 3H), 1.41 (s, 3H), 1.33 (s, 3H), 1.23 (s, 3H), 1.10 (s, 3H).

**$^{13}$C NMR** (75 MHz) δ 137.3 (CH), 130.6 (CH), 112.4 (C), 91.9 (CH), 91.4 (CH), 81.4 (CH), 76.1 (CH), 50.0 (CH), 47.7 (CH), 41.9 (CH), 40.4 (C), 39.9 ($CH_3$), 38.8 (C), 36.7 ($CH_3$), 27.0 ($CH_3$), 25.4 ($CH_3$), 24.7 ($CH_3$), 20.4 ($CH_3$), 19.9 ($CH_3$).

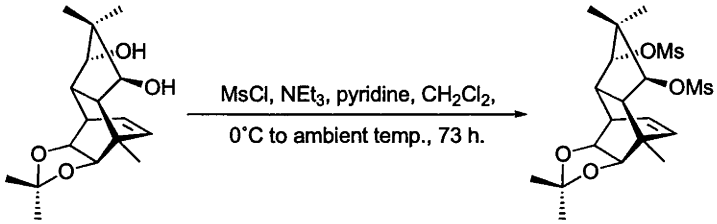
**IR** $\nu_{max}$ 2980, 2936, 2883, 1373, 1334, 1263, 1207, 1170, 1063, 1033, 972, 932, 894, 834, 730, 520 $cm^{-1}$.

**Mass Spectrum** (EI, 70 eV) *m/z* 450 ($M^{+\cdot}$, 1%), 435 {$[M - CH_3\cdot]^+$, 6}, 421 {$[M - CHO\cdot]^+$, 26}, 392 {$[M - (CH_3)_2CO]^{+\cdot}$, 13}, 350 (20), 296 (15), 200 (100), 185 (40), 171 (46), 158 (28), 105 (29), 100 (45).

**HREIMS** Found: $M^{+\cdot}$, 450.1381. Calculated for $C_{19}H_{30}O_8S_2$ $M^{+\cdot}$, 450.1382.

**Optical Rotation** $[\alpha]_D^{22}$ +47.0 (*c* 0.68).

**(3a*R*,4*S*,4a*S*,5*S*,7*S*,7a*S*,8*R*,8a*S*)-3a,4a,5,6,7,7a,8,8a-Octahydro-2,2,4,6,6-pentamethyl-4,8-etheno-4*H*-indeno[5,6-*d*]-1,3-dioxole-5,7-diol *bis*-methanesulfonate (125)**




120 125

Methanesulfonyl chloride (15 μL, 0.19 mmol) was added to a magnetically stirred solution of diol **120** (26 mg, 0.09 mmol), triethylamine (27 μL, 0.30 mL) and pyridine (1 mL) in dichloromethane (1.0 mL) maintained at 0°C. After 1 h the reaction mixture was warmed to ambient temperature and allowed to stand for 72 h, before being concentrated under reduced pressure. The residue, thus obtained, was partitioned between ethyl acetate (5 mL) and water (5 mL) and the separated aqueous phase was extracted with ethyl acetate (5 × 5 mL). The combined organic phases were dried ($Na_2SO_4$), filtered and concentrated under reduced pressure and the ensuing light-brown oil was subjected to flash chromatography (silica, 1:4 v/v ethyl acetate – hexane elution). Concentration of the appropriate fractions ($R_f$ 0.6, 1:4 v/v ethyl acetate – hexane elution, phosphomolybdic acid visualisation) gave the *title compound* ***125*** (29 mg, 75%) as a clear, light-yellow oil.

**$^1$H NMR** (300 MHz) δ 6.28 (dd, *J* 8.1 and 6.6 Hz, 1H), 5.79 (d, *J* 8.4 Hz, 1H), 4.74 (d, *J* 6.9 Hz, 1H), 4.66 (d, *J* 9.3 Hz, 1H), 4.08 (dd, *J* 8.1 and 3.9 Hz, 1H), 3.79 (d, *J* 8.1 Hz, 1H), 3.29 (ddd, *J* 11.4, 6.9 and 2.4 Hz, 1H), 3.07 (s, 3H), 3.00 (s, 3H), 3.00 – 2.96 (m, 1H), 2.72 – 2.65 (m, 1H), 1.48 (s, 3H), 1.34 (s, 3H), 1.33 (s, 3H), 1.19 (s, 3H), 1.08 (s, 3H).

**$^{13}$C NMR** (75 MHz) δ 135.7 (CH), 134.7 (CH), 112.4 (C), 89.3 (CH), 88.3 (CH), 81.5 (CH), 76.0 (CH), 46.1 (CH), 45.8 (C), 40.5 (C), 39.8 ($CH_3$), 39.0 (CH), 38.9 ($CH_3$), 37.2 (CH), 26.8 ($CH_3$), 24.6 ($CH_3$), 21.1 ($CH_3$), 21.0 ($CH_3$), 20.6 ($CH_3$).

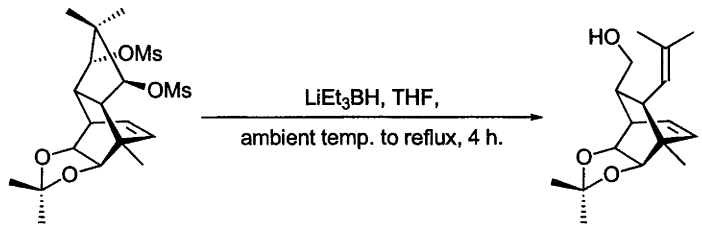
**IR** $\nu_{max}$ 2981, 2937, 1373, 1336, 1207, 1173, 1059, 933, 904, 881, 860, 844, 527 $cm^{-1}$.

**Mass Spectrum** (EI, 70 eV) *m/z* 450 ($M^{+\cdot}$, 2%), 435 {$[M - CH_3\cdot]^+$, 6}, 421 {$[M - CHO\cdot]^+$, 6}, 392 {$[M - (CH_3)_2CO]^{+\cdot}$, 9}, 350 (5), 296 (5), 200 (100), 185 (34), 171 (52), 158 (43), 105 (23), 100 (53), 91 (18), 85 (19).

**HREIMS** Found: $M^{+\cdot}$, 450.1380. Calculated for $C_{19}H_{30}O_8S_2$ $M^{+\cdot}$, 450.1382.

**Optical Rotation** $[\alpha]_D^{23}$ +35.8 (*c* 0.32).

**(3a*R*,4*S*,7*R*,7a*S*,8*R*,9*S*)-3a,4,7,7a-Tetrahydro-8-(hydroxymethyl)-2,2,4-trimethyl-9-(2-methyl-1-propenyl)-4,7-ethano-1,3-benzodioxole (126)**




**125** **126**

$LiEt_3BH$ (178 μL of a 1 $mol.L^{-1}$ solution in THF, 0.18 mmol) was added to a magnetically stirred solution of the *bis*-mesylate **125** (20 mg, 0.05 mmol) in THF (3 mL) maintained at ambient temperature. The reaction mixture was heated at reflux for 4 h, then cooled and quenched with $NH_4Cl$ (5 mL of a saturated aqueous solution). The resulting mixture was extracted with ethyl acetate (4 × 10 mL) and the combined organic phases were washed with brine (1 × 2 mL), then dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. Subjection of the ensuing light-brown oil to flash chromatography (silica, 1:4 v/v ethyl acetate – hexane elution) afforded, after concentration of the appropriate fractions ($R_f$ 0.7, 2:3 v/v ethyl acetate – hexane elution, phosphomolybdic acid visualisation), the *title compound* ***126*** (12.4 mg, 100%) as a clear, colourless oil.

**$^1$H NMR** (300 MHz) δ 6.14 (t, *J* 7.5 Hz, 1H), 5.86 (d, *J* 8.1 Hz, 1H), 4.92 (dt, *J* 11.4 and 1.2 Hz, 1H), 4.08 (dd, *J* 8.4 and 3.9 Hz, 1H), 3.78 (d, *J* 8.4 Hz, 1H), 3.43 (d, *J* 11.4 and 8.7 Hz, 1H), 3.24 (dd, *J* 11.4 and 6.6 Hz, 1H), 3.10 (t, *J* 10.8 Hz, 1H), 2.74 – 2.60 (complex m, 2H), 1.71 (d, *J* 0.9 Hz, 3H), 1.71 – 1.63 (m, partially obscured, 1H), 1.67 (d, *J* 1.2 Hz, 3H), 1.55 (s, 3H), 1.34 (s, 3H), 1.07 (s, 3H).

**$^{13}$C NMR** (75 MHz) δ 138.7 (CH), 135.2 (C), 132.1 (CH), 124.5 (CH), 112.0 (C), 80.7 (CH), 76.2 (CH), 64.7 ($CH_2$), 42.6 (C), 39.0 (CH), 38.5 (CH), 37.8 (CH), 26.6 ($CH_3$), 26.2 ($CH_3$), 24.8 ($CH_3$), 20.5 ($CH_3$), 18.5 ($CH_3$).

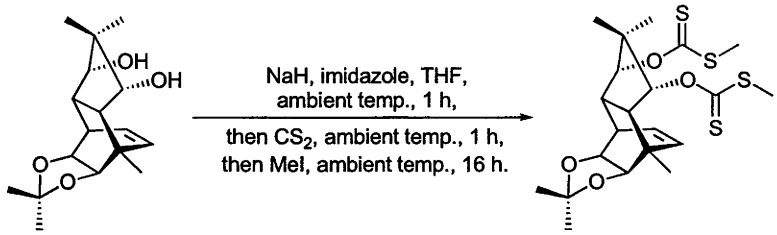
**IR** $\nu_{max}$ 3436, 2963, 2927, 1452, 1373, 1262, 1207, 1165, 1061, 1045, 875, 711 $cm^{-1}$.

**Mass Spectrum** (EI, 70 eV) *m/z* 278 ($M^{+\cdot}$, 1%), 263 {$[M - CH_3\cdot]^+$, 11}, 249 {$[M - CHO\cdot]^+$, 4}, 220 {$[M - (CH_3)_2CO]^{+\cdot}$, 31}, 202 (11), 189 (16), 171 (17), 159 (25), 147 (32), 131 (24), 128 (29), 118 (29), 112 (100), 109 (63), 108 (51), 105 (56), 97 (54), 94 (91), 79 (46), 69 (38), 56 (60).

**HREIMS** Found: $[M - CH_3\cdot]^+$ 263.1640. Calculated for $C_{17}H_{26}O_3$ $[M - CH_3\cdot]^+$, 263.1647.

**Optical Rotation** $[\alpha]_D^{22}$ +23.6 (*c* 0.35).

**(3a*R*,4*S*,4a*S*,5*R*,7*S*,7a*S*,8*R*,8a*S*)-3a,4a,5,6,7,7a,8,8a-Octahydro-2,2,4,6,6-pentamethyl-4,8-etheno-4*H*-indeno[5,6-*d*]-1,3-dioxole-5,7-diol *bis*-*S*-methyl xanthate (127)**




**119** **127**

A magnetically stirred mixture of diol **119** (14.4 mg, 0.05 mmol), NaH (5.8 mg of a 60% dispersion in mineral oil, 0.15 mmol) and imidazole (two crystals) in THF (1 mL) was maintained at ambient temperature. After 1 h, $CS_2$ (18 μL, 0.30 mmol) was added and the mixture was allowed to stand for an additional 1 h, before treating with methyl iodide (11 μL, 0.18 mmol). The resulting mixture was allowed to stand for a further 16 h and then quenched with acetic acid (glacial, 20 μL) before being diluted with water (10 mL) and ethyl acetate (10 mL). The separated aqueous phase was extracted with ethyl acetate (3 × 10 mL) and the combined organic phases were washed with $NaHCO_3$ (1 × 5 mL of a saturated aqueous solution), then dried ($MgSO_4$), filtered and concentrated under reduced pressure. The ensuing yellow oil was subjected to flash chromatography (silica, 1:9 v/v ethyl acetate – hexane elution) and concentration of the appropriate fractions ($R_f$ 0.9, 1:4 v/v ethyl acetate – hexane elution, phosphomolybdic acid visualisation) gave the *title compound* ***127*** (21.1 mg, 91%) as colourless crystals, m.p. 124 – 126°C.

**$^1$H NMR** (300 MHz) δ 6.19 (d, *J* 6.3 Hz, 1H), 6.03 – 5.98 (complex m, 2H), 5.84 (d, *J* 8.1 Hz, 1H), 4.06 (dd, *J* 8.4 and 4.2 Hz, 1H), 3.73 (d, *J* 8.4 Hz, 1H), 3.39 (ddd, *J* 11.4, 6.6 and 2.4 Hz, 1H), 3.10 (dd, *J* 11.4 and 6.3 Hz, 1H), 2.99 – 2.95 (m, 1H), 2.62 (s, 3H), 2.59 (s, 3H), 1.47 (s, 3H), 1.32 (s, 3H), 1.17(1) (s, 6H), 1.16(6) (s, 3H).

**$^{13}$C NMR** (75 MHz) δ 216.4 (C), 215.4 (C), 137.6 (CH), 130.3 (CH), 112.3 (C), 93.2 (CH), 91.9 (CH), 81.3 (CH), 76.3 (CH), 51.0 (CH), 46.7 (CH), 42.6 (C), 40.5 (C), 36.2 (CH), 26.9 ($CH_3$), 25.2 ($CH_3$), 24.7 ($CH_3$), 20.4 ($CH_3$), 19.4 ($CH_3$), 19.2 ($CH_3$), 18.1 ($CH_3$).

**IR** $\nu_{max}$ 2966, 2931, 1369, 1261, 1236, 1220, 1205, 1184, 1058, 1034, 878, 735 cm$^{-1}$.

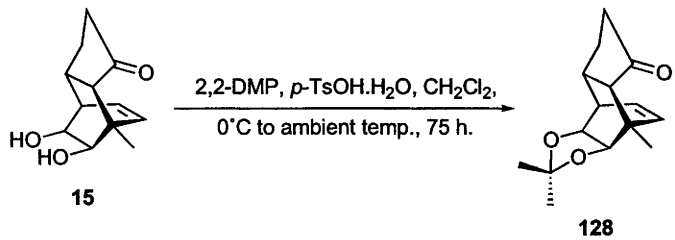
**Mass Spectrum** (EI, 70 eV) *m/z* 474 ($M^{+\cdot}$, 5%), 427 {[M – $CH_3\cdot$]$^+$, 12}, 383 {[M – $CH_3S(S)C\cdot$]$^+$, 15}, 309 (11), 259 (6), 201 (43), 173 (16), 159 (64), 91 (100).

**HREIMS** Found: $M^{+\cdot}$, 474.1024. Calculated for $C_{21}H_{30}O_4S_4$ $M^{+\cdot}$, 474.1027.

**Optical Rotation** $[\alpha]_D^{22}$ +49.5 (*c* 0.14).

## 6.3 Experimental procedures for Chapter Three

**(3a*R*,4*S*,4a*S*,7a*S*,8*S*,8a*S*)-3a,4,4a,6,7,7a,8,8a-Octahydro-2,2,4-trimethyl-4,8-etheno-5*H*-indeno[5,6-*d*]-1,3-dioxol-5-one (128)**




**15** **128**

2,2-Dimethoxypropane (10 mL, 81.3 mmol) was added to a magnetically stirred solution of diol **15** (2.38 g, 11.5 mmol; generated according to the procedure described by Stewart[10]) and *p*-TsOH.$H_2O$ (24.6 mg, 0.1 mmol) in dichloromethane (20 mL) maintained at 0°C. After 3 h the resulting mixture was warmed to ambient temperature and maintained at this temperature for 72 h. The reaction mixture was then concentrated under reduced pressure and the ensuing deep-red residue subjected to flash chromatography (silica, 1:4 → 3:7 v/v ethyl acetate – hexane gradient elution). Concentration of the appropriate fractions ($R_f$ 0.7, 1:1 v/v ethyl acetate – hexane elution, phosphomolybdic acid visualisation) afforded the *title compound **128*** (2.80 g, 98%) as a clear, colourless oil.

**$^1$H NMR** (300 MHz) δ 6.17 (dd, *J* 8.1 and 6.6 Hz, 1H), 5.84 (dd, *J* 8.1 and 0.9 Hz, 1H), 4.07 (dd, *J* 8.1 and 3.9 Hz, 1H), 3.70 (d, *J* 8.1 Hz, 1H), 3.13 – 3.05 (m, 1H), 2.89 – 2.85 (m, 1H), 2.55 (d, *J* 9.3 Hz, 1H), 2.15 – 1.95 (complex m, 3H), 1.62 – 1.45 (complex m, partially obscured, 1H), 1.49 (s, 3H), 1.45 (s, 3H), 1.33 (s, 3H).

**$^{13}$C NMR** (75 MHz) δ 222.5 (C), 138.5 (CH), 132.1 (CH), 112.2 (C), 80.9 (CH), 76.2 (CH), 49.9 (CH), 42.3 (C), 41.4 (CH), 39.7 ($CH_2$), 32.8 (CH), 26.7 ($CH_3$), 25.1 ($CH_2$), 24.8 ($CH_3$), 19.9 ($CH_3$).

**IR** $\nu_{max}$ 3043, 2987, 2962, 2933, 2904, 2880, 1731, 1458, 1381, 1372, 1261, 1207, 1165, 1067, 1050, 1034, 879, 715 $cm^{-1}$.

**Mass Spectrum** (EI, 70 eV) *m/z* 248 ($M^{+\cdot}$, 5%), 233 {[M – $CH_3^{\cdot}$]$^+$, 20}, 219 {[M – CO – $H^{\cdot}$]$^+$, 10}, 190 {[M – $(CH_3)_2CO]^{+\cdot}$, 46}, 173 (21), 161 (58), 148 (41), 134 (67), 119 (55), 105 (100), 100 (95), 91 (76), 75 (75).

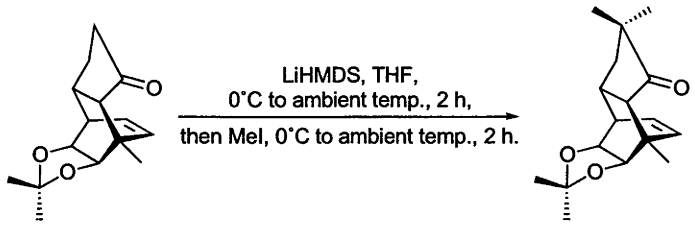
**HREIMS** Found: $M^{+\cdot}$, 248.1412. Calculated for $C_{15}H_{20}O_3$ $M^{+\cdot}$, 248.1412.

**Elemental Analysis** Found: C, 72.61; H, 8.13. $C_{15}H_{20}O_3$ requires C, 72.55; H, 8.12%.

**Optical Rotation** $[\alpha]_D^{24}$ –122.0 (*c* 0.60).

10 Stewart, S. G., *PhD Thesis*, Australian National University, **2001**.

**(3a*R*,4*S*,4a*S*,7a*S*,8*S*,8a*S*)-3a,4,4a,6,7,7a,8,8a-Octahydro-2,2,4,6,6-pentamethyl-4,8-etheno-5*H*-indeno[5,6-*d*]-1,3-dioxol-5-one (114)**




128 114

LiHMDS (11.7 mL of a 1 mol.L$^{-1}$ solution in THF, 11.7 mmol) was added dropwise, over 5 min, to a magnetically stirred solution of the ketone **128** (2.77 g, 11.2 mmol) in THF (20 mL) maintained at 0°C. After 45 min the reaction mixture was warmed to ambient temperature over 75 min, then re-cooled to 0°C and treated, dropwise, with MeI (0.73 mL, 11.73 mmol). After 45 min at 0°C, the reaction mixture was again warmed to ambient temperature over a period of 75 min. The reaction mixture was then re-cooled to 0°C and sequentially treated with further aliquots of LiHMDS (11.7 mL of a 1 mol.L$^{-1}$ solution in THF, 11.7 mmol) and MeI (0.73 mL, 11.73 mmol) using the warming and cooling regimen described above. This process was repeated a third time and then the reaction mixture was quenched, at ambient temperature, with $NH_4Cl$ (20 mL of a saturated aqueous solution) and $Na_2S_2O_3$ (20 mL of a saturated aqueous solution). The separated aqueous phase was extracted with ethyl acetate (4 × 30 mL) and the combined organic phases were dried ($Na_2SO_4$), filtered and concentrated under reduced pressure to give a dark-yellow oil. This material was subjected to flash chromatography (silica, 1:4 → 2:3 v/v ethyl acetate – hexane gradient elution) and concentration of the appropriate fractions ($R_f$ 0.8, 1:1 v/v ethyl acetate – hexane elution, phosphomolybdic acid visualisation) afforded the *title compound **114*** (3.08 g, 100%) as a white crystalline solid, m.p. 70 – 72°C.

**$^1$H NMR** (300 MHz) δ 6.00 (broad t, *J* 7.5 Hz, 1H), 5.89 (dd, *J* 8.4 and 0.9 Hz, 1H), 4.14 (dd, *J* 8.1 and 3.9 Hz, 1H), 3.68 (d, *J* 8.4 Hz, 1H), 3.08 (ddd, *J* 19.8, 9.0 and 2.1 Hz, 1H), 2.87 – 2.82 (complex m, partially obscured, 1H), 2.81 (d, *J* 10.8 Hz, 1H), 1.85 (dd, *J* 12.9 and 9.0 Hz, 1H), 1.55 (s, 3H), 1.50 (s, 3H), 1.34 (s, 3H), 1.25 (dd, *J* 12.9 and 9.3 Hz, 1H), 1.01 (s, 3H), 0.91 (s, 3H).

**$^{13}$C NMR** (75 MHz) δ 223.9 (C), 138.9 (CH), 132.0 (CH), 112.0 (C), 81.8 (CH), 76.0 (CH), 47.1 (CH), 46.1 (C), 41.6 (C), 40.4 ($CH_2$), 40.2 (CH), 29.6 (CH), 26.8 (two $CH_3$ signals overlapping), 24.8 ($CH_3$), 22.5 ($CH_3$), 19.9 ($CH_3$).

**IR** $\nu_{max}$ 2987, 2961, 2933, 2899, 269, 1736, 1464, 1454, 1381, 1373, 1263, 1207, 1164, 1063, 1052, 1024, 881, 711 cm$^{-1}$.

**Mass Spectrum** (EI, 70 eV) *m/z* 276 ($M^{+\cdot}$, 4%), 261 {[M – $CH_3\cdot$]$^+$, 10}, 218 {[M – $(CH_3)_2CO]^{+\cdot}$, 26}, 189 (19), 176 (53), 134 (66), 105 (100), 91 (37), 75 (57).

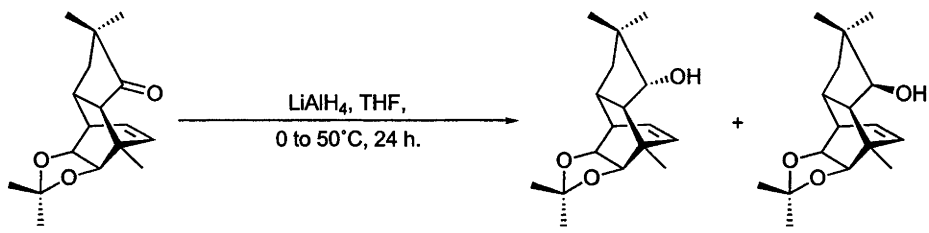
**HREIMS** Found: $M^{+\cdot}$, 276.1724. Calculated for $C_{17}H_{24}O_3$ $M^{+\cdot}$, 276.1725.

**Elemental Analysis** Found: C, 73.51; H, 8.47. $C_{17}H_{24}O_3$ requires C, 73.88; H, 8.75%.

**Optical Rotation** $[\alpha]_D^{24}$ –47.1 (*c* 0.65).

**(3a*R*,4*S*,4a*S*,5*S*,7a*S*,8*S*,8a*S*)-3a,4,4a,6,7,7a,8,8a-Octahydro-2,2,4,6,6-pentamethyl-4,8-etheno-5*H*-indeno[5,6-*d*]-1,3-dioxol-5-ol (129)** and **(3a*R*,4*S*,4a*S*,5*R*,7a*S*,8*S*,8a*S*)-3a,4,4a,6,7,7a,8,8a-octahydro-2,2,4,6,6-pentamethyl-4,8-etheno-5*H*-indeno[5,6-*d*]-1,3-dioxol-5-ol (130)**

*Method A:*




**114** **129** **130**

A solution of ketone **114** (6.07 g, 22.0 mmol) in THF (60 mL) was added dropwise, over 4 h, to a magnetically stirred solution of lithium aluminium hydride (852 mg, 22.4 mmol) in THF (80 mL) maintained at 0°C. After a further 2 h at 0°C the reaction mixture was heated at 50°C for 18 h, then cooled to 0°C and treated, dropwise, with Glauber's salt (3 mL). The resulting grey-white precipitate was removed by filtration and washed with ethyl acetate (multiple small washings to a total volume of 250 mL). The combined filtrate was concentrated under reduced pressure to give a clear, colourless oil. Subjection of this material to flash chromatography (silica, 1:4 → 2:3 v/v ethyl acetate – hexane elution) afforded two fractions, A and B.

Concentration of fraction A ($R_f$ 0.5, 3:7 v/v ethyl acetate – hexane elution, phosphomolybdic acid visualisation), afforded the α-epimeric form of the *title compound **129*** (502 mg, 8%) as a white, crystalline solid, m.p. 61 – 62°C.

**$^1$H NMR** (300 MHz) δ 6.13 – 6.05 (complex m, 2H), 4.09 (dd, *J* 8.1 and 3.9 Hz, 1H), 3.72 (d, *J* 8.1 Hz, 1H), 3.56 (dd, *J* 10.5 and 6.0 Hz, 1H), 2.93 – 2.82 (m, 1H), 2.78 – 2.70 (m, partially obscured, 1H), 2.72 (dd, *J* 10.8 and 6.0 Hz, 1H), 1.48 (s, 3H), 1.44 – 1.35 (m, partially obscured, 1H), 1.37 (s, 3H), 1.34 (s, 3H), 1.12 (d, *J* 10.8 Hz, 1H), 1.08 (t, *J* 11.7 Hz, 1H), 0.96 (s, 3H), 0.93 (s, 3H).

**$^{13}$C NMR** (75 MHz) δ 141.4 (CH), 131.6 (CH), 112.1 (C), 83.0 (CH), 81.3 (CH), 76.9 (CH, overlapping with the $CDCl_3$ resonance[11]), 47.1 (CH), 43.9 (C), 41.6 (C), 41.0 ($CH_2$), 39.0 (CH), 37.2 (CH), 26.8 ($CH_3$), 26.2 ($CH_3$), 24.9 ($CH_3$), 23.0 ($CH_3$), 20.6 ($CH_3$).

**IR** $\nu_{max}$ 3500, 2985, 2935, 2902, 2873, 1464, 1380, 1371, 1261, 1207, 1081, 1056, 1028, 880, 710 cm$^{-1}$.

11 Specifically, overlapping with the upfield peak of the 1:1:1 triplet attributed to the $CDCl_3$ resonance.

**Mass Spectrum** (EI, 70 eV) *m/z* 279 {[M + H·]$^+$, 2%}, 278 (M$^{+\cdot}$, <1), 263 {[M – $CH_3$·]$^+$, 5}, 249 {[M – CHO·]$^+$, 15}, 220 {[M – $(CH_3)_2CO$]$^{+\cdot}$, 23}, 178 (42), 106 (48), 105 (37), 93 (39), 75 (100).

**HREIMS** Found: M$^{+\cdot}$, 278.1884; [M – $CH_3$·]$^+$, 263.1648. Calculated for $C_{17}H_{26}O_3$ M$^{+\cdot}$, 278.1882; [M – $CH_3$·]$^+$, 263.1647.

**Elemental Analysis** Found: C, 72.97; H, 9.18. $C_{17}H_{26}O_3$ requires C, 73.35; H, 9.41%.

**Optical Rotation** $[\alpha]_D^{24}$ +75.1 (*c* 0.22).

Concentration of fraction B ($R_f$ 0.4, 3:7 v/v ethyl acetate – hexane elution, phosphomolybdic acid visualisation), afforded the β-epimeric form of the *title compound* ***130*** (5.54 g, 91%) as a white, crystalline solid, m.p. 88 – 89°C.

**$^1$H NMR** (300 MHz) δ 6.10 (broad t, *J* 7.5 Hz, 1H), 5.87 (dt, *J* 8.1 and 0.9 Hz, 1H), 4.11 (dd, *J* 8.1 and 3.9 Hz, 1H), 3.77 (d, *J* 8.1 Hz, 1H), 3.25 (t, *J* 8.4 Hz, 1H), 2.83 – 2.72 (m, 1H), 2.67 – 2.62 (m, 1H), 2.17 (dd, *J* 10.5 and 9.0 Hz, 1H), 1.51 – 1.44 (m, partially obscured, 1H), 1.48 (s, 3H), 1.33 (s, 3H), 1.32 (s, 3H), 1.24 (d, *J* 7.2 Hz, 1H), 0.99-0.89 (m, partially obscured, 1H), 0.93 (s, 3H), 0.89 (s, 3H).

**$^{13}$C NMR** (75 MHz) δ 139.1 (CH), 133.5 (CH), 111.9 (C), 83.5 (CH), 81.2 (CH), 76.7 (CH), 47.9 (CH), 41.9 ($CH_2$), 41.6 (C), 40.6 (C), 39.7 (CH), 33.9 (CH), 26.7 ($CH_3$), 26.6 ($CH_3$), 24.8 ($CH_3$), 21.5 ($CH_3$), 20.6 ($CH_3$).

**IR** $\nu_{max}$ 3494, 2986, 2948, 2930, 2898, 2872, 1457, 1380, 1371, 1263, 1205, 1064, 1053, 1038, 877, 729, 711 cm$^{-1}$.

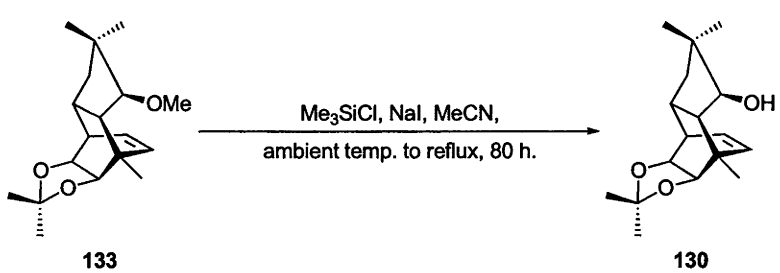
**Mass Spectrum** (EI, 70 eV) *m/z* 279 {[M + H·]$^+$, 2%}, 278 (M$^{+\cdot}$, <1%), 263 {[M – $CH_3$·]$^+$, 10}, 249 {[M – CHO·]$^+$, 3}, 220 {[M – $(CH_3)_2CO$]$^{+\cdot}$, 23}, 202 (21), 187 (25), 178 (100), 148 (20), 134 (23), 119 (35), 106 (60), 105 (42), 91 (35).

**HREIMS** Found: [M – $CH_3$·]$^+$, 263.1648. Calculated for $C_{17}H_{26}O_3$ [M – $CH_3$·]$^+$, 263.1647.

**Elemental Analysis** Found: C, 73.40; H, 9.25. $C_{17}H_{26}O_3$ requires C, 73.35; H, 9.41%.

**Optical Rotation** $[\alpha]_D^{24}$ +18.3 (*c* 0.37).

*Method B:*[12]

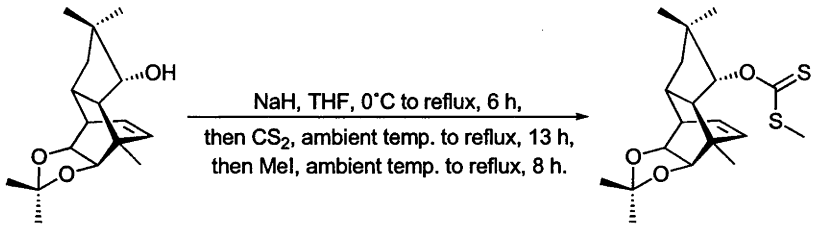



**133** **130**

12 Note that only alcohol **130** is generated using *Method B*.

A solution of methyl ether **133** (334 mg, 1.2 mmol; generated according to the procedure detailed in Section 6.3, page 150) in acetonitrile (3 mL) was added to a magnetically stirred solution of sodium iodide (363 mg, 2.4 mmol) and trimethylsilyl chloride (0.31 mL, 2.4 mmol) in acetonitrile (3 mL) maintained at ambient temperature. The reaction mixture turned brown immediately and was allowed to stand for 76 h. After this time, an additional solution of sodium iodide (363 mg, 2.4 mmol) and trimethylsilyl chloride (0.31 mL, 2.4 mmol) in acetonitrile (3 mL) was added to the reaction mixture, which was then heated at reflux for 4 h and quenched by addition of $Na_2S_2O_3$ (3 mL of a saturated aqueous solution). The resulting mixture was then extracted with ethyl acetate (5 × 10 mL) and the combined organic phases were dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. The ensuing pale-yellow oil was subjected to flash chromatography (silica, 0:4 → 1:9 v/v ethyl acetate – hexane gradient elution) and afforded, upon concentration of the appropriate fractions ($R_f$ 0.4, 3:7 v/v ethyl acetate – hexane elution, phosphomolybdic acid visualisation), the *title compound* ***130*** (254 mg, 75%) identical in all respects, with that obtained *via Method A*.

**(3a*R*,4*S*,4a*S*,5*S*,7a*S*,8*S*,8a*S*)-3a,4,4a,6,7,7a,8,8a-Octahydro-2,2,4,6,6-pentamethyl-4,8-etheno-5*H*-indeno[5,6-*d*]-1,3-diox-ol-5-ol *S*-methyl xanthate (131)**




**129** **131**

Sodium hydride (147 mg of a 60% dispersion in mineral oil, 3.68 mmol) was added to a magnetically stirred solution of alcohol **129** (204 mg, 0.73 mmol) in THF (10 mL) maintained at 0°C. The resulting mixture was then warmed to ambient temperature and, after 18 h, was heated at reflux for 2 h, before being cooled to ambient temperature and treated with carbon disulfide (884 μL, 14.70 mmol). After 16 h the reaction mixture was again heated at reflux for 2 h, before being cooled to ambient temperature and treated with methyl iodide (914 μL, 14.68 mmol). The reaction mixture was allowed to stand at this temperature for 2 h, then heated at reflux for 6 h, cooled to ambient temperature and quenched by dropwise treatment with acetic acid (0.5 mL). The resulting mixture was filtered through a short pad of Celite® and the solids thus retained were washed with ethyl acetate (4 × 10 mL). The combined filtrates were washed with $NaHCO_3$ (2 × 10 mL of a saturated aqueous solution), then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a yellow oil. Subjection of this material to flash chromatography (silica, 0:4 → 1:4 v/v ethyl acetate – hexane gradient elution) and concentration of the appropriate fractions ($R_f$ 0.4, 1:9 v/v ethyl acetate – hexane elution, phosphomolybdic acid visualisation) afforded the *title compound **131*** (235 mg, 87%) as a clear, colourless oil.

**$^1$H NMR** (300 MHz) δ 6.00 – 5.92 (complex m, 3H), 4.14 (dd, *J* 8.1 and 3.9 Hz, 1H), 3.72 (d, *J* 8.1 Hz, 1H), 2.94 – 2.83 (complex m, 2H), 2.81 – 2.76 (m, 1H), 2.57 (s, 3H), 1.48 (s, 3H), 1.44 – 1.31 (complex m, partially obscured, 2H), 1.33 (s, 3H) 1.12 (s, 3H), 1.02 (s, 3H), 0.89 (s, 3H).

**$^{13}$C NMR** (75 MHz) δ 216.3 (C), 140.6 (CH), 128.6 (CH), 112.0 (C), 92.9 (CH), 81.4 (CH), 76.6 (CH), 45.9 (CH), 45.0 (C), 42.4 ($CH_2$), 40.9 (C), 38.4 (CH), 36.6 (CH), 26.8 ($CH_3$), 25.8 ($CH_3$), 24.7 ($CH_3$), 22.8 ($CH_3$), 20.5 ($CH_3$), 19.3 ($CH_3$).

**IR** $\nu_{max}$ 2962, 2932, 1456, 1380, 1369, 1261, 1233, 1224, 1207, 1185, 1163, 1050, 1029, 965, 879, 713 cm$^{-1}$.

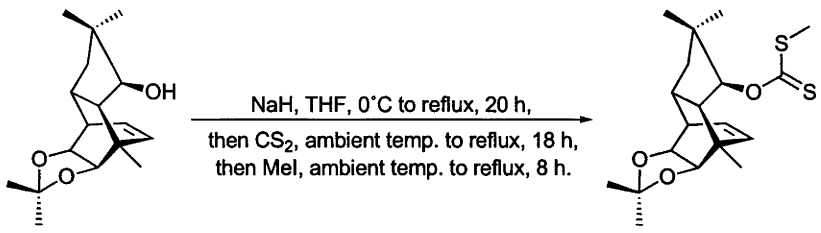
**Mass Spectrum** (EI, 70 eV) *m/z* 368 ($M^{+\cdot}$, 18%), 353 {$[M - CH_3\cdot]^+$, 12}, 339 {$[M - CHO\cdot]^+$, 3}, 310 {$[M - (CH_3)_2CO]^{+\cdot}$, 2}, 261 {$[M - CH_3SC(S)O\cdot]^+$, 54}, 203 {$[M - (CH_3)_2CO - CH_3SC(S)O\cdot]^+$, 95}, 185 (50), 160 (42), 105 (47), 95 (100).

**HREIMS** Found: $M^{+\cdot}$, 368.1487. Calculated for $C_{19}H_{28}O_3S_2$ $M^{+\cdot}$, 368.1480.

**Elemental Analysis** Found: C, 61.66; H, 7.86, S, 17.49. $C_{19}H_{28}O_3S_2$ requires C, 61.92; H, 7.66; S, 17.40%.

**Optical Rotation** $[\alpha]_D^{22}$ +18.5 (*c* 0.26).

**(3aR,4S,4aS,5R,7aS,8S,8aS)-3a,4,4a,6,7,7a,8,8a-octahydro-2,2,4,6,6-pentamethyl-4,8-etheno-5H-indeno-[5,6-d]-1,3-dioxol-5-ol *S*-methyl xanthate (132)**




**130** **132**

THF (10 mL) was cooled to 0°C and treated with alcohol **130** (407 mg, 1.46 mmol) and sodium hydride (298 mg of a 60% dispersion in mineral oil, 7.44 mmol). The resulting mixture was subsequently heated at reflux for 6 h, then cooled to ambient temperature and treated with carbon disulfide (880 μL, 14.6 mmol). After 11 h the reaction mixture was heated at reflux for 2 h, then cooled to ambient temperature and treated with methyl iodide (1.00 mL, 16.08 mmol). The reaction mixture was maintained at this temperature for 2 h, then heated at reflux for 6 h, cooled to ambient temperature and subsequently quenched with acetic acid (0.5 mL). The resulting mixture was filtered through a short pad of Celite® and the solids, thus retained, were washed with ethyl acetate (4 × 10 mL). The combined filtrates were washed with $NaHCO_3$ (2 × 10 mL of a saturated aqueous solution), then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a yellow oil. Subjection of this material to flash chromatography (silica, 0:1 → 1:4 v/v ethyl acetate – hexane gradient elution) and concentration of the appropriate fractions ($R_f$ 0.4, 1:9 v/v ethyl acetate – hexane elution, phosphomolybdic acid visualisation) afforded the *title compound **132*** (538 mg, 100%) as a clear, colourless oil.

**$^1$H NMR** (300 MHz) δ 6.17 (broad t, *J* 7.5 Hz, 1H), 5.94 (d, *J* 8.4 Hz, 1H), 5.66 (d, *J* 8.7 Hz, 1H), 4.11 (dd, *J* 8.1 and 3.9 Hz, 1H), 3.78 (d, *J* 8.4 Hz, 1H), 2.97 – 2.86 (m, 1H), 2.71 – 2.64 (m, 2H), 2.56 (s, 3H), 1.58 – 1.52 (m, partially obscured, 1H), 1.52 (s, 3H), 1.33 (s, 3H), 1.17 (s, 3H), 1.17 – 1.09 (m, partially obscured, 1H), 1.00 (s, 3H), 0.96 (s, 3H).

**$^{13}$C NMR** (75 MHz) δ 216.1 (C), 139.1 (CH), 133.5 (CH), 112.0 (C), 91.9 (CH), 81.2 (CH), 76.4 (CH), 45.2 (CH), 42.6 (C), 42.1 ($CH_2$), 41.2 (C), 39.7 (CH), 33.7 (CH), 27.0 ($CH_3$), 26.8 ($CH_3$), 24.7 ($CH_3$), 23.0 ($CH_3$), 20.3 ($CH_3$), 19.2 ($CH_3$).

**IR** $\nu_{max}$ 2985, 2957, 2932, 2904, 2874, 1460, 1380, 1370, 1258, 1224, 1206, 1054, 1027, 878, 714 $cm^{-1}$.

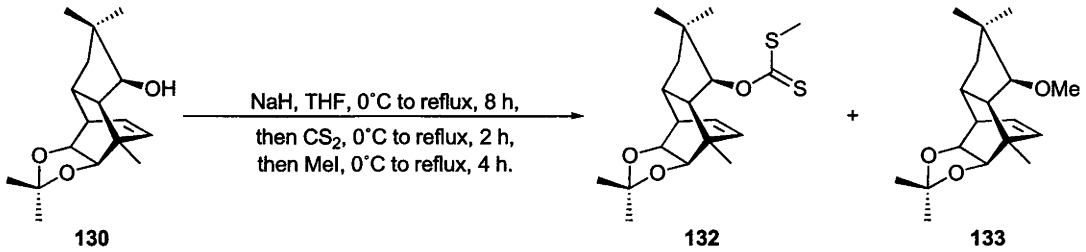
**Mass Spectrum** (EI, 70 eV) *m/z* 368 ($M^{+\cdot}$, <1%), 353 {[M – $CH_3\cdot$]$^+$, 11}, 260 {[M – $CH_3SC(S)O\cdot$ – H·]$^+$, 71}, 231 (35), 203 {[M – $(CH_3)_2CO$ – $CH_3SC(S)O\cdot$]$^+$, 72}, 202 (62), 187 (65), 185 (45), 160 (71), 145 (48), 105 (43), 95 (100).

**HREIMS** Found: $M^{+\cdot}$, 368.1484. Calculated for $C_{19}H_{28}O_3S_2$ $M^{+\cdot}$, 368.1480.

**Elemental Analysis** Found: C, 61.33; H, 7.86, S, 17.25. $C_{19}H_{28}O_3S_2$ requires C, 61.92; H, 7.66; S, 17.40%.

**Optical Rotation** $[\alpha]_D^{21}$ +77.1 (*c* 0.23).

**(3a*R*,4*S*,4a*S*,5*S*,7a*S*,8*S*,8a*S*)-3a,4a,5,6,7,7a,8,8a-Octahydro-5-methoxy-4,6,6-trimethyl-4,8-etheno-4*H*-indeno[5,6-*d*]-1,3-dioxole (133)**




**130** **132** **133**

A solution of alcohol **130** (5.50 g, 19.8 mmol) in THF (60 mL) was added, dropwise, over 2 h, to a magnetically stirred mixture of sodium hydride (3.95 g of a 60% dispersion in mineral oil, 98.8 mmol) in THF (60 mL) maintained at 0°C. The reaction mixture was subsequently heated at reflux for 6 h, then cooled to 0°C and treated with carbon disulfide (11.9 mL, 197.9 mmol). After being heated at reflux again for a further 1 h, the resulting yellow solution was then cooled to 0°C and treated with methyl iodide (12.5 mL, 200.8 mmol). The reaction mixture was then heated at reflux for 2 h, cooled to 0°C and treated, sequentially, with additional aliquots of carbon disulfide (11.9 mL, 197.9 mmol) and methyl iodide (12.5 mL, 200.8 mmol), using the heating and cooling regimen described above. The reaction mixture was subsequently quenched by dropwise treatment with acetic acid (5 mL). The resulting mixture was diluted with $NH_4Cl$ (20 mL of a saturated aqueous solution) and extracted with ethyl acetate (5 × 50 mL). The combined extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure to yield a yellow-brown oil. Subjection of this material to flash chromatography (silica, 0:4 → 1:4 v/v ethyl acetate – hexane gradient elution) afforded two fractions, A and B.

Concentration of fraction A ($R_f$ 0.4, 1:9 v/v ethyl acetate – hexane elution, phosphomolybdic acid visualisation) afforded the *S*-methyl xanthate ester **132** (235 mg, 87%), identical, in all respects with authentic material obtained as detailed earlier (Section 6.3, page 149).

Concentration of fraction B ($R_f$ 0.5, 3:7 v/v ethyl acetate – hexane elution, phosphomolybdic acid visualisation) afforded the *title compound **133*** (387 mg, 6%) as a clear, colourless, hygroscopic oil.

**$^1$H NMR** (300 MHz) δ 6.10 (t, *J* 7.2 Hz, 1H), 5.87 (dt, *J* 8.1 and 0.9 Hz, 1H), 4.11 (dd, *J* 8.1 and 3.9 Hz, 1H), 3.76 (d, *J* 8.4 Hz, 1H), 3.41 (s, 3H), 2.87 (d, *J* 8.4 Hz, 1H), 2.73 (tdd, *J* 10.8, 8.1 and 2.7 Hz, 1H), 2.62 (dddd, *J* 6.6, 3.9, 2.7 and 0.9 Hz, 1H), 2.30 (dd, *J* 10.8 and 8.7 Hz, 1H), 1.46 (s, 3H), 1.38 (dd, *J* 12.3 and 8.1 Hz, 1H), 1.31 (s, 3H), 1.24 (s, 3H), 1.06 (s, 3H), 1.05 – 0.92 (m, partially obscured, 1H), 0.94 (s, 3H).

**$^{13}$C NMR** (75 MHz) δ 139.3 (CH), 133.5 (CH), 111.9 (C), 93.4 (CH), 81.3 (CH), 76.6 (CH), 59.1 ($CH_3$), 46.6 (CH), 43.2 ($CH_2$), 41.7 (C), 41.0 (C), 39.7 (CH), 33.5 (CH), 28.6 ($CH_3$), 26.7 ($CH_3$), 24.9 ($CH_3$), 22.2 ($CH_3$), 20.4 ($CH_3$).

**IR** $\nu_{max}$ 2959, 2947, 2932, 2900, 2871, 2825, 1454, 1380, 1370, 1264, 1222, 1206, 1185, 1164, 1119, 1114, 1063, 1054, 1027, 973, 877, 729, 712 $cm^{-1}$.

**Mass Spectrum** (EI, 70 eV) *m/z* 292 ($M^{+\cdot}$, 2%), 277 {$[M - CH_3\cdot]^+$, 10}, 260 (27), 238 (20), 234 (20), 202 (90), 192 (100), 187 (47), 173 (37), 160 (70), 147 (42), 134 (34), 119 (42), 105 (84), 91 (35), 87 (59), 85 (40), 61 (54).

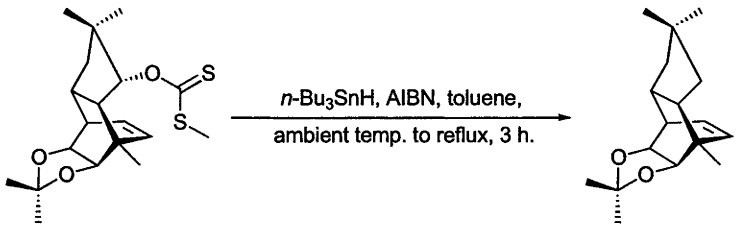
**HREIMS** Found: $M^{+\cdot}$, 292.2041. Calculated for $C_{18}H_{28}O_3$ $M^{+\cdot}$, 292.2038.

**Elemental Analysis** Found: C, 71.58; H, 9.11. $C_{18}H_{28}O_3.0.5H_2O$ requires C, 71.73; H, 9.70%.

**Optical Rotation** $[\alpha]_D^{18}$ +0.8 (*c* 0.37).

**(3a*R*,4*R*,4a*S*,7a*R*,8*S*,8a*S*)-3a,4a,5,6,7,7a,8,8a-Octahydro-2,2,4,6,6-pentamethyl-4,8-etheno-4*H*-indeno[5,6-*d*]-1,3-dioxole (118)**

*Method A:*




131 118

Tri-*n*-butyltin hydride (360 μL, 1.34 mmol) was added to a magnetically stirred solution of the *S*-methyl xanthate ester **131** (246 mg, 0.67 mmol) and AIBN (4.3 mg, 0.03 mmol) in toluene (20 mL) maintained at ambient temperature and the resulting mixture was subsequently heated at 100°C for 1 h. The cooled reaction mixture was treated with additional tri-*n*-butyltin hydride (360 μL, 1.34 mmol) and AIBN (4.0 mg, 0.02 mmol) and the resulting mixture heated at reflux for 1 h. The cooled reaction mixture was, once more, treated with additional tri-*n*-butyltin hydride (180 μL, 0.67 mmol) and AIBN (3.7 mg, 0.02 mmol) and the resulting mixture was heated at reflux for 1 h, after which time metallic tin globules had precipitated. Solvent and carbonyl sulfide were removed from the cooled reaction mixture under reduced pressure and the was residue subjected to flash chromatography (silica, 0:1 → 1:19 v/v ethyl acetate – hexane gradient elution). Concentration of the relevant fractions ($R_f$ 0.7, 3:7 v/v ethyl acetate – hexane elution, phosphomolybdic acid visualisation) afforded a solid. Recrystallisation (ethyl acetate) of this material afforded the *title compound **118*** (152 mg, 87%) as a white, crystalline solid, m.p. 65 – 66°C.

**$^1$H NMR** (300 MHz) δ 6.07 (broad t, *J* 7.2 Hz, 1H), 5.79 (dt, *J* 8.4 and 0.9 Hz, 1H), 4.13 (dd, *J* 8.4 and 3.9 Hz, 1H), 3.79 (d, *J* 8.1 Hz, 1H), 2.83 – 2.67 (complex m, 2H), 2.58 – 2.49 (m, 1H), 1.50 (s, 3H), 1.44 – 1.34 (complex m, partially obscured, 2H), 1.34 (s, 3H), 1.15 (s, 3H), 1.03 – 0.91 (m, partially obscured, 2H), 0.96 (s, 3H), 0.91 (s, 3H).

**$^{13}$C NMR** (75 MHz) δ 139.0 (CH), 132.9 (CH), 111.8 (C), 81.0 (CH), 76.9 (CH, overlapping with the $CDCl_3$ resonance[9]), 45.3 ($CH_2$), 44.1 ($CH_2$), 42.1 (C), 41.0 (CH), 39.7 (CH), 38.5 (C), 36.7 (CH), 29.0 ($CH_3$), 28.1 ($CH_3$), 26.7 ($CH_3$), 24.9 ($CH_3$), 20.7 ($CH_3$).

**IR** $\nu_{max}$ 2988, 2951, 2934, 2898, 2872, 2853, 1457, 1380, 1370, 1274, 1262, 1223, 1206, 1164, 1064, 1053, 1025, 881, 714 cm$^{-1}$.

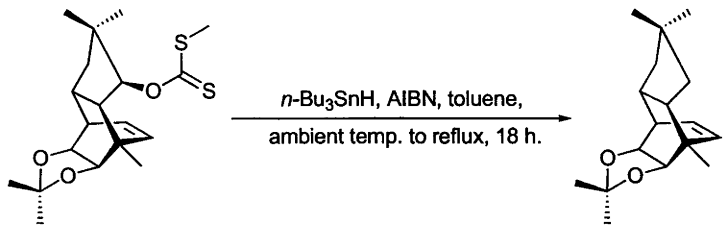
**Mass Spectrum** (EI, 70 eV) *m/z* 247 {[M – $CH_3$·]$^+$, 9%}, 204 {[M – $(CH_3)_2CH$·]$^+$, 58}, 189 {[M – $(CH_3)_2CO$]$^{+\cdot}$, 21}, 175 (18), 162 (100), 147 (22), 119 (23), 105 (36), 91 (41).

**HREIMS** Found: [M – $CH_3$·]$^+$, 247.1697. Calculated for $C_{17}H_{26}O_2$ [M – $CH_3$·]$^+$, 247.1698.

**Elemental Analysis** Found: C, 77.53; H, 9.98. $C_{17}H_{26}O_2$ requires C, 77.82; H, 9.99%.

**Optical Rotation** $[\alpha]_D^{24}$ +39.0 (*c* 0.43).

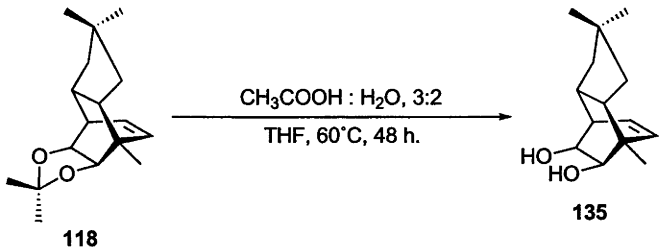
*Method B:*




**132** **118**

Tri-*n*-butyltin hydride (1.20 mL, 4.46 mmol) was added to a magnetically stirred solution of the *S*-methyl xanthate ester **132** (538 mg, 1.46 mmol) and AIBN (3.4 mg, 0.02 mmol) in toluene (20 mL) maintained at ambient temperature and the resulting mixture was heated at 100°C for 17 h. The cooled reaction mixture was then treated with additional tri-*n*-butyltin hydride (0.80 mL, 2.97 mmol) and AIBN (5.0 mg, 0.03 mmol) and the resulting mixture was heated at reflux for 1 h, after which time a black precipitate had formed. Solvent and carbonyl sulfide were removed from the cooled reaction mixture under reduced pressure and the residue was subjected to flash chromatography (silica, 0:1 → 1:19 v/v ethyl acetate – hexane gradient elution). Concentration of the relevant fractions ($R_f$ 0.7, 3:7 v/v ethyl acetate – hexane elution, phosphomolybdic acid visualisation) afforded a solid. Recrystallisation (ethyl acetate) of this material afforded the *title compound **118*** (266 mg, 82%) identical, in all respects, with that obtained *via Method A*.

**(3a*S*,4*R*,7*S*,7a*R*,8*S*,9*R*)-2,3,3a,4,7,7a-Hexahydro-2,2,4-trimethyl-4,7-ethano-1*H*-indene-8,9-diol (135)**




**118** **135**

A magnetically stirred emulsion of acetonide **118** (1.37 g, 5.2 mmol) in acetic acid (20 mL of a 60% v/v solution in water) and THF (5 mL) was maintained at 60°C for 48 h. The cooled reaction mixture was subsequently treated with $NaHCO_3$ (18 g, 214 mmol) and water (20 mL). After carbon dioxide evolution had ceased, the separated aqueous phase was extracted with ethyl acetate (5 × 50 mL) and the combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure. Subjection of the ensuing light-yellow oil to flash chromatography (silica, 5:95 → 30:70 v/v ethyl acetate – hexane gradient elution) afforded two fractions, A and B.

Concentration of fraction A ($R_f$ 0.7, 3:7 v/v ethyl acetate – hexane elution, phosphomolybdic acid visualisation) afforded unreacted acetonide **118** (772 mg, 56% recovery) which proved identical, in all respects, with authentic material.

Concentration of fraction B ($R_f$ 0.3, 3:7 v/v ethyl acetate – hexane elution, phosphomolybdic acid visualisation) afforded a light-yellow solid. Recrystallization (ethyl acetate) of this material afforded the *title compound **135*** (483 mg, 95% at 44% conversion) as a white crystalline solid, m.p. 91 – 92°C.

**$^1$H NMR** (300 MHz) δ 6.06 (broad t, *J* 7.8 Hz, 1H), 5.77 (broad d, *J* 8.4 Hz, 1H), 3.76 – 3.70 (m, 1H), 3.34 (dd, *J* 8.7 and 5.4 Hz, 1H), 2.97 (d, *J* 5.1 Hz, 1H), 2.79 (d, *J* 5.7 Hz, 1H), 2.72 – 2.57 (complex m, 2H), 2.46 – 2.36 (m, 1H), 1.45 – 1.33 (complex m, 2H), 1.14 (s, 3H), 1.03 (d, *J* 11.1 Hz, 1H), 0.96 (s, 3H), 0.95 (d, *J* 11.1 Hz, 1H), 0.89 (s, 3H).

**$^{13}$C NMR** (75 MHz) δ 138.7 (CH), 132.5 (CH), 70.2 (CH), 66.5 (CH), 45.6 ($CH_2$), 44.2 ($CH_2$), 42.7 (C), 41.9 (CH), 40.5 (CH), 38.6 (C), 36.1 (CH), 29.0 ($CH_3$), 28.1 ($CH_3$), 20.4 ($CH_3$).

**IR** $\nu_{max}$ 3344, 2949, 2930, 2867, 2853, 1456, 1365, 1069, 1053, 1012, 1003, 711 $cm^{-1}$.

**Mass Spectrum** (EI, 70 eV) *m/z* 162 {[M – HOCH=CHOH]$^{+\cdot}$, 100%}, 147 {[M – HOCH=CHOH – $CH_3\cdot$]$^+$, 38}, 119 (4), 118 (15), 106 (34), 91(33).

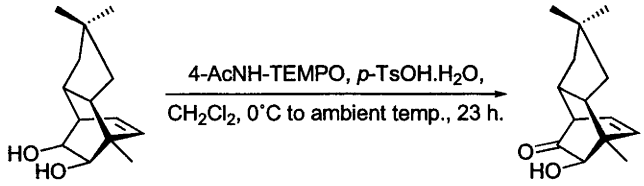
**HREIMS** Found: [M – HOCH=CHOH]$^{+\cdot}$, 162.1410. Calculated for $C_{14}H_{22}O_2$ [M – HOCH=CHOH]$^{+\cdot}$, 162.1409.

**Elemental Analysis** Found: C, 75.36; H, 9.83. $C_{14}H_{22}O_2$ requires C, 75.63; H, 9.97%.

**Optical Rotation** $[\alpha]_D^{24}$ +55.7 (*c* 0.44).

**(3a*S*,4*R*,7*S*,7a*R*,9*R*)-2,3,3a,4,7,7a-Hexahydro-9-hydroxy-2,2,4-trimethyl-4,7-ethano-1*H*-indene-8-one (110)**

*Method A:*




**135** **110**

4-Acetamido-TEMPO (922 mg, 4.32 mmol) was added, portionwise, over 1 h, to a magnetically stirred solution of diol **135** (457 mg, 2.06 mmol) and *p*-TsOH.$H_2O$ (822 mg, 4.32 mmol) in dichloromethane (40 mL) maintained at 0°C. The resulting pale-orange mixture was stirred at 0°C for 6 h, then gradually warmed to ambient temperature over 2 h. After 14 h at ambient temperature, the reaction mixture was treated with $NaHCO_3$ (20 mL of a saturated aqueous solution). The separated aqueous phase was extracted with dichloromethane (4 × 20 mL and the combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure. Subjection of the ensuing orange oil to flash chromatography (silica, 0:1 → 4:6 v/v ethyl acetate – hexane gradient elution) afforded two fractions, A and B.

Concentration of fraction A ($R_f$ 0.4, 3:7 v/v ethyl acetate – hexane elution, phosphomolybdic acid visualisation) afforded the *title compound **110*** (395 mg, 91% at 96% conversion) as a clear, colourless oil.

**$^1$H NMR** (300 MHz) δ 6.14 – 6.05 (complex m, 2H), 3.39 (d, *J* 1.8 Hz, 1H), 3.10 – 3.07 (m, 1H), 2.70 – 2.51 (complex m, 3H), 1.68 – 1.67 (broad m, 1H), 1.54 – 1.45 (complex m, 2H), 1.25 (s, 3H), 1.17 (dd, *J* 11.7 and 9.9 Hz, 1H), 1.10 (dd, *J* 12.6 and 10.5 Hz, 1H), 0.99 (s, 3H), 0.90 (s, 3H).

**$^{13}$C NMR** (75 MHz) δ 213.7 (C), 140.4 (CH), 127.8 (CH), 74.7 (CH), 51.3 (CH), 45.9 (C), 45.5 (CH), 44.8 ($CH_2$), 44.2 ($CH_2$), 41.3 (CH), 39.9 (C), 28.8 ($CH_3$), 27.9 ($CH_3$), 19.1 ($CH_3$).

**IR** $\nu_{max}$ 3442, 2952, 2931, 2855, 1734, 1722, 1456, 1366, 1128, 1074, 788, 767, 707 $cm^{-1}$.

**Mass Spectrum** (EI, 70 eV) *m/z* 220 ($M^{+\cdot}$, 100%), 205 {$[M - CH_3\cdot]^+$, 42}, 192 {$[M - CO]^{+\cdot}$, 20}, 191 {$[M - CO - H\cdot]^+$, 17}, 177 (13), 163 (65), 161 (70), 147 (31), 107 (35), 105 (47), 91 (61).

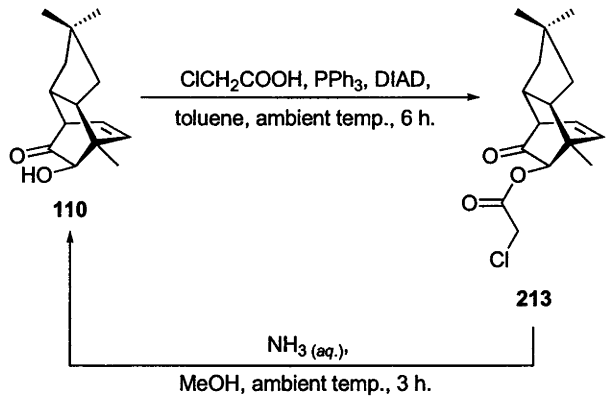
**HREIMS** Found: $M^{+\cdot}$, 220.1464. Calculated for $C_{14}H_{20}O_2$ $M^{+\cdot}$, 220.1463.

**Elemental Analysis** Found: C, 76.09; H, 9.01. $C_{14}H_{20}O_2$ requires C, 76.33; H, 9.15%.

**Optical Rotation** $[\alpha]_D^{18}$ –34.3 (*c* 0.40).

Concentration of fraction B ($R_f$ 0.3, 3:7 v/v ethyl acetate – hexane elution, phosphomolybdic acid visualisation) afforded the unreacted diol **135** (18 mg, 4% recovery) which was identical, in all respects, with authentic material.

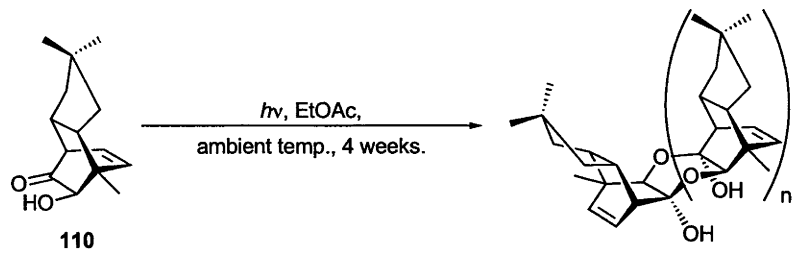
*Method B*:[13]




DIAD (136 $\mu$L of a 95% solution, 0.66 mmol) was added, dropwise, to a magnetically stirred solution of acyloin **110** (72 mg, 0.33 mmol), chloroacetic acid (276 mg, 2.92 mmol) and triphenyl phosphine (259 mg, 0.99 mmol) in toluene (16 mL) maintained at ambient temperature. After 2h the colourless solution was treated in a dropwise fashion with an additional aliquot of DIAD (136 $\mu$L of a 95% solution, 0.66 mmol) and again, after a further 2 h, with an additional 1.0 mole equivalent of DIAD (68 $\mu$L of a 95% solution, 0.33 mmol). The reaction was monitored using analytical TLC (3:7 v/v ethyl acetate – hexane elution, phosphomolybdic acid visualisation) which indicated that all starting material ($R_f$ 0.4) had been consumed (presumably to form ester **213**; see Section 6.4, page 174) 2 h after the final addition of DIAD (6 h total). The solution was then concentrated under reduced pressure and the resulting clear, colourless oil was redissolved in an ammoniacal solution of methanol (2.0 mL of a 2.0 mol.L$^{-1}$ $NH_{3\ (aq.)}$ solution in MeOH, 4.00 mmol). Reaction was monitored by TLC (as above), which indicated that after 3 h all of the ester ($R_f$ 0.5) was hydrolysed. Solvent and excess $NH_3$ were removed under reduced pressure and the resulting clear, pale-yellow oil was subjected to flash column chromatography (silica; 1:9 → 3:7 ethyl acetate – hexane gradient elution) to afford (in addition to unreacted triphenylphosphine, triphenylphosphine oxide, DIAD and chloroacetic acid), after concentration of the appropriate fractions ($R_f$ 0.4, 3:7 v/v ethyl acetate – hexane elution, phosphomolybdic acid visualisation) *title compound* **110** (52 mg, 72%), which was identical, in all respects, with authentic material.

13 *Method B* was discussed in Chapter Four but is grouped in this Section, with *Method A* (discussed in Chapter Three), for convenience.

**Poly{oxy-8,9-[(3a*S*,4*R*,7*S*,7a*R*,8*S*,9*R*)-2,3,3a,4,7,7a-Hexahydro-8-hydroxy-2,2,4-trimethyl-4,7-ethano-1*H*-indenediyl]oxy} (136)**




**110**

n = 1, 2, 3, 4, 5 and 7.

**136**

A solution of acyloin **110** (33 mg, 0.15 mmol) in ethyl acetate was treated with several grains of silica gel and maintained at ambient temperature. After 4 weeks, a white precipitate had formed and subsequent filtration of the reaction mixture afforded a white solid. Recrystallisation of the filtrand (ethyl acetate) afforded a mixture of the oligomeric *title compounds* ***136*** (n = 1, 2, 3, 4, 5 and 7; 12 mg, 80% polymerisation at 45% conversion).

**$^1$H NMR** (500 MHz, $CD_3OD$) δ 6.14 (dd, *J* 8.0 and 7.0, 1H), 5.82 (d, *J* 8.5, 1H), 3.23 (s, 1H), 2.92 - 2.85 (m, 1H), 2.65 - 2.59 (m, 1H), 2.57 (dd, *J* 3.5 and 2.5, 1H), 1.43 (ddd, *J* 12.0, 8.0 and 2.5, 1H), 1.37 (ddd, *J* 12.0, 7.5 and 2.5, 1H), 1.18 (s, 3H), 1.05 (t, partially obscured, *J* 11.0, 1H), 1.00 (t, partially obscured, *J* 11.0, 1H), 0.99 (s, 3H), 0.93 (s, 3H).

**$^{13}$C NMR** (126 MHz, $CD_3OD$) δ 138.8 (CH), 134.6 (CH), 98.7 (C), 77.0 (CH), 49.1 (CH), 46.7 ($CH_2$), 45.5 ($CH_2$), 45.0 (C), 42.9 (CH), 41.7 (CH), 40.7 (C), 29.8 ($CH_3$), 29.0 ($CH_3$), 21.2 ($CH_3$).

**IR** $\nu_{max}$ 3230, 3051, 2952, 2855, 1453, 1364, 1307, 1265, 1203, 1140, 1112, 1098, 1046, 1014, 995, 963, 812, 764, 713 $cm^{-1}$.

**Mass Spectrum** (ES, +ve ion mode) *m/z* 463 {$[M_2 + Na]^+$, 100%}, 903 {$[M_4 + Na]^+$, 45}, 1343 {$[M_6 + Na]^+$, 3}, 1783 {$[M_8 + Na]^+$, <1}.

(ES, -ve ion mode) 475 {$[M_2 + Cl]^-$, 100%}, 695 {$[M_3 + Cl]^-$, 1}, 915 {$[M_4 + Cl]^-$, 5}, 1135 {$[M_5 + Cl]^-$, <1}, 1355 {$[M_6 + Cl]^-$, <1}.

(EI, 70 eV) *m/z* 440 {$[M_2]^{+\cdot}$, 1%}, 422 {$[M_2 - H_2O]^{+\cdot}$, 5}, 278 (15), 220 [$M^{+\cdot}$, 100], 205 (28), 203 (82), 192 (22), 175 (69), 163 (69), 162 (37), 161 (65), 147 (33), 119 (29), 107 (45), 106 (37), 105 (80), 91 (77), 77 (36).

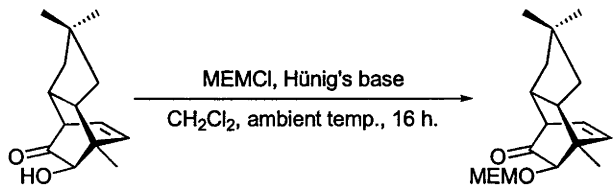
**HREIMS** Found: $M^{+\cdot}$, 440.2927. Calculated for $C_{16}H_{21}O_3$ $M^{+\cdot}$, 440.2927.

**Elemental Analysis** Found: C, 75.59; H, 9.57. $C_{16}H_{21}O_3$ requires C, 76.33; H, 9.15%.

**Optical Rotation** $[\alpha]_D^{23}$ +180.1 (*c* 0.03, $CH_3OH$).

Subjection of the filtrate to flash chromatography (silica, 0:1 → 3:7 v/v ethyl acetate – hexane gradient elution), afforded, upon concentration of the appropriate fractions ($R_f$ 0.4, 3:7 v/v ethyl acetate – hexane elution, phosphomolybdic acid visualisation), unreacted *acyloin* **110** (18 mg, 55% recovery).

**(3a*S*,4*R*,7*S*,7a*R*,9*R*)-2,3,3a,4,7,7a-Hexahydro-9-[(2-methoxyethoxy)methoxy]-2,2,4-trimethyl-4,7-ethano-1*H*-indene-8-one (58)**




**110** **58**

MEM-Cl (360 μL, 3.15 mmol) was added, dropwise, over 15 min, to a solution of acyloin **110** (347 mg, 1.57 mmol) and Hünig's base (690 μL, 3.96 mmol) in dichloromethane (3.5 mL) maintained at ambient temperature. The resulting mixture was allowed to stand for 16 h and then quenched with $NaHCO_3$ (2 mL of a saturated aqueous solution). The separated aqueous phase was extracted with dichloromethane (5 × 10 mL) and the combined organic phases were washed with water (1 × 50 mL), then dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. Subjection of the ensuing light-brown oil to flash chromatography (silica, 0:99:1 → 20:79:1 v/v/v ethyl acetate – hexane – triethylamine gradient elution) afforded, after concentration of the appropriate fractions ($R_f$ 0.4, 3:7 v/v ethyl acetate – hexane elution, phosphomolybdic acid visualisation), the *title compound 58* (444 mg, 91%) as a clear, colourless oil.

**$^1$H NMR** (500 MHz) δ 6.11 (dd, *J* 8.0 and 6.0 Hz, 1H), 6.04 (broad d, *J* 8.0 Hz, 1H), 5.11 (d, *J* 6.5 Hz, 1H), 4.81 (d, *J* 7.0 Hz, 1H), 3.84 (ddd, *J* 10.5, 5.5 and 4.0 Hz, 1H), 3.78 (ddd, *J* 10.5, 5.5 and 4.0 Hz, 1H), 3.58 (dt, *J* 5.5 and 3.5 Hz, 2H), 3.45 (s, 1H), 3.39 (s, 3H), 2.99 ( broad d, *J* 6.0 Hz, 1H), 2.69 – 2.60 (m, 2H), 1.53 – 1.44 (m, 2H), 1.21 (s, 3H), 1.12 (dd, *J* 12.0 and 10.0 Hz, 1H), 1.02 – 0.95 (m, partially obscured, 1H), 0.98 (s, 3H), 0.90 (s, 3H).

**$^{13}$C NMR** (126 MHz) δ 210.3 (C), 140.3 (CH), 128.5 (CH), 96.5 ($CH_2$), 76.9 (CH), 72.0 ($CH_2$), 67.7 ($CH_2$), 59.3 ($CH_3$), 52.5 (CH), 45.5 (C), 44.9 ($CH_2$), 44.2 ($CH_2$), 43.4 (CH), 42.0 (CH), 39.5 (C), 28.7 ($CH_3$), 27.8 ($CH_3$), 19.5 ($CH_3$).

**IR** $\nu_{max}$ 2951, 2931, 2898, 2872, 1736, 1457, 1366, 1128, 1110, 1050, 1036, 988, 970, 708 $cm^{-1}$.

**Mass Spectrum** (EI, 70 eV) *m/z* 308 ($M^{+\cdot}$, 6%), 279 {$[M - CO - H\cdot]^+$, 5}, 219 {$[M - CH_3O(CH_2)_2OCH_2\cdot]^+$, 5}, 175 {$[M - CO - CH_3O(CH_2)_2OCH_2\cdot]^+$, 47}, 162 (20), 161 (18), 108 (50), 105 {$[CH_3O(CH_2)_2OCH_2O\cdot]^+$, 29}, 89 {$[CH_3O(CH_2)_2OCH_2\cdot]^+$, 100}, 59 (93).

**HREIMS** Found: $M^{+\cdot}$, 308.1986. Calculated for $C_{18}H_{28}O_4$ $M^{+\cdot}$, 308.1988.

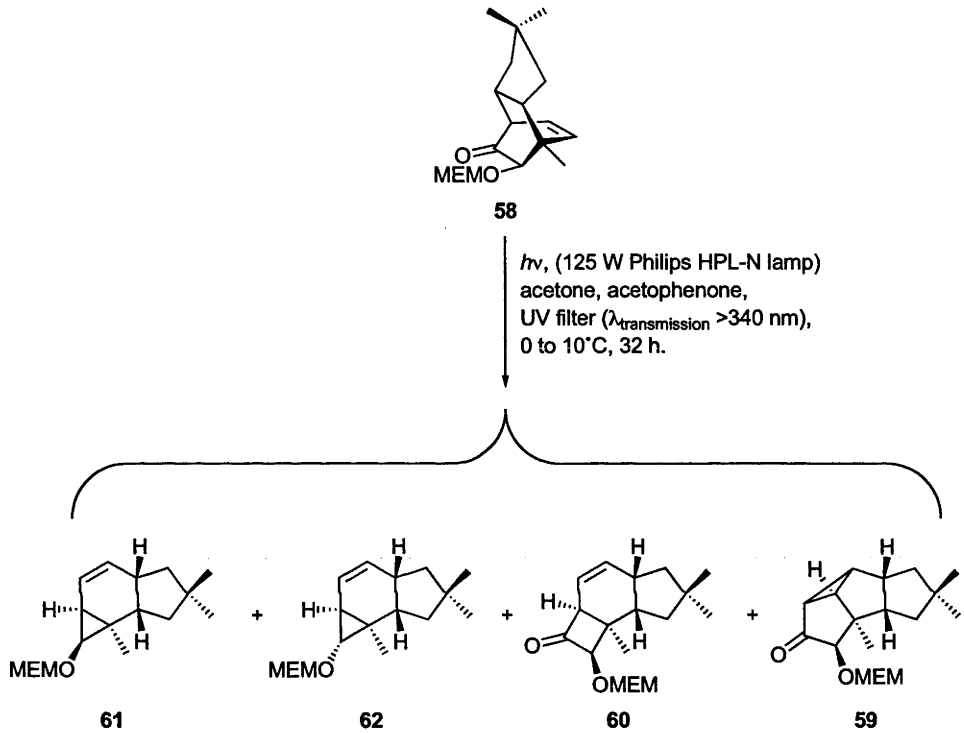
**Elemental Analysis** Found: C, 69.80; H, 8.75. $C_{18}H_{28}O_4$ requires C, 70.10; H, 9.15%.

**Optical Rotation** $[\alpha]_D^{23}$ +28.1 (*c* 0.39).

**UV** $\lambda_{max}$ 313 nm ($\varepsilon_0$ 111.4 $L.mol^{-1}.cm^{-1}$).

**(1*S*,1a*S*,3a*S*,6a*S*,6b*R*)-1,1a,3a,4,5,6,6a,6b-Octahydro-1-[(2-methoxyethoxy)methoxy]-5,5,6b-trimethyl-cycloprop[*e*]indene (61)** and **(1*R*,1a*S*,3a*S*,6a*S*,6b*R*)-1,1a,3a,4,5,6,6a,6b-octahydro-1-[(2-methoxyethoxy)methoxy]-5,5,6b-trimethyl-cycloprop[*e*]indene (62)**, **(1*R*,2a*S*,4a*S*,7a*S*,7b*R*)-2,2a,4a,5,6,7,7a,7b-octahydro-1-[(2-methoxyethoxy)methoxy]-6,6,7b-trimethyl-1*H*-cyclobut[*e*]indene-2-one (60)** and **(1*R*,2a*S*,2b*S*,2c*S*,5a*S*,5b*R*,5c*R*)-decahydro-1-[(2-methoxyethoxy)methoxy]-4,4,5b-trimethyl-2*H*-cyclopenta[*a*]cyclopropa[*cd*]pentalen-2-one (59)**

*Method A:*




A deoxygenated, magnetically stirred (500 rpm) solution of β,γ-unsaturated ketone **58** (254 mg, 0.82 mmol) and acetophenone (240 μL, 2.06 mmol) in acetone (120 mL) was prepared in a Pyrex™ vessel jacketed by an aqueous UV filter solution[14] and maintained at between 0 and 10°C. The reaction mixture was irradiated for 32 h, using a Philips 125 W HPL-N lamp, and was subsequently concentrated under reduced pressure. Subjection of the ensuing clear, colourless oil to flash chromatography (silica, 0:1 → 3:7 v/v ethyl acetate – hexane gradient elution), afforded four major fractions, A – D.

14 $\lambda_{transmission}$ >340 nm, thickness >10 mm, NaBr $_{(aq.)}$ 750 $gL^{-1}$, $Pb(NO_3)_2$ $_{(aq.)}$ 8 $gL^{-1}$, prepared according to the methods of: Mattay, J.; Griesbeck, A. G., *Photochemical Key Steps in Organic Synthesis: an Experimental Course Book*, in *Photochemical Key Steps in Organic Synthesis: an Experimental Course Book*, J. Mattay and A.G. Griesbeck, Editors. 1994, VCH Verlagsgesellschaft mbH: Weinheim, Germany. p. 1.

Concentration of fraction A ($R_f$ 0.5, 3:7 ethyl acetate – hexane elution, phosphomolybdic acid visualisation) afforded the *title compounds* ***61*** and ***62*** (7:3 mixture of epimers at C1, 5 mg, 3% at 71% conversion) as a clear, colourless oil.

**$^1$H NMR** (300 MHz) δ 5.88 (ddd, *J* 10.0, 6.0 and 2.5 Hz, 1H, *exo*-), 5.66 (ddd, *J* 9.5, 6.0 and 3.0 Hz, 1H, *endo*-), 5.24 (dd, *J* 9.5 and 2.0 Hz, 1H, *endo*-), 5.03 (d, *J* 9.5 Hz, 1H, *exo*-), 4.75 (d, *J* 6.5 Hz, 1H, *exo*-), 4.72 (d, *J* 6.5 Hz, 1H, *exo*-), 4.63 (d, *J* 6.5 Hz, 1H, *endo*-), 4.49 (d, *J* 6.5 Hz, 1H, *endo*-), 3.81 (dt, *J* 11.0 and 4.5 Hz, 1H, *endo*-), 3.74 – 3.72 (m, 2H, *exo*-), 3.66 - 3.62 (m, 1H, *endo*-), 3.57 (t, *J* 4.5 Hz, 2H, *endo*- and t, *J* 4.5 Hz, 2H, *exo*-), 3.45 (d *J* 2.1 Hz, 1H, *exo*-), 3.40 (s, 3H, *endo*- and s, 3H, *exo*-), 3.38 (d, *J* 6.5 Hz, 1H, *endo*-), 2.61 - 2.56 (m, 1H, *endo*-), 2.48 – 2.42 (complex m, 2H, *exo*-), 2.38 (dt, *J* 12.5 and 7.6 Hz, 1H, *endo*-), 1.77 (dd, *J* 13.3 and 8.8 Hz, 1H, *endo*-), 1.74 – 1.67 (partially obscured m, 1H, *exo*-), 1.60 – 1.54 (partially obscured m, 1H, *exo*-), 1.55 (dd, *J* 12.0 and 6.5 Hz, 1H, *endo*-), 1.35 – 1.19 (complex m, 2H, *endo*- and complex m, 2H, *exo*-), 1.14 (t, *J* 6.3 Hz, 1H, *endo*-), 1.05 (dd, *J* 6.0 and 2.0 Hz, 1H, *exo*-), 1.02 (s, 3H, *endo*- and s, 3H, *exo*-), 1.01 (s, 3H, *endo*- and s, 3H, *exo*-), 0.99 (s, 3H, *endo*- and s, 3H, *exo*-).

**$^{13}$C NMR** (75 MHz) δ 131.6 (CH, *endo*-), 128.8 (CH, *exo*-), 125.2 (CH, *exo*-), 119.4 (CH, *endo*-), 96.9 ($CH_2$, *endo*-), 96.2 ($CH_2$, *exo*-), 72.1 ($CH_2$, *endo*- and *exo*-), 67.8 ($CH_2$, *endo*-), 67.7 ($CH_2$, *exo*-), 67.6 (CH, *endo*-), 66.6 (CH, *exo*-), 59.3 ($CH_3$, *endo*- and *exo*-), 48.6 ($CH_2$, *endo*-), 48.5 ($CH_2$, *exo*-), 45.9 ($CH_2$, *endo*-), 45.1 ($CH_2$, *exo*-), 40.0 (CH, *exo*-), 39.9 (CH, *endo*-), 39.1 (CH, *exo*-), 37.5 (CH, *endo*-), 37.3 (C, *exo*-), 36.6 (C, *endo*-), 32.3 ($CH_3$, *exo*-), 32.0 ($CH_3$, *exo*-), 31.8 ($CH_3$, *endo*-), 31.1 ($CH_3$, *endo*-), 26.7 (CH, *exo*-), 24.4 ($CH_3$, *exo*-), 23.8 (C and $CH_3$ signals overlapping, *endo*-), 22.8 (CH, *endo*-), 16.9 (CH, *exo*-).

**IR** $\nu_{max}$ 3022, 2951, 2927, 2864, 1462, 1363, 1200, 1173, 1128, 1097, 1077, 1050, 999, 982, 851, 756 $cm^{-1}$.

**Mass Spectrum** (EI, 70 eV) *m/z* 280 ($M^{+\cdot}$, <1%), 205 ({[M – $CH_3O(CH_2)_2O\cdot]^+$, 5}, 204 {[M – H· – $CH_3O(CH_2)_2O\cdot]^+$, 4}, 176 {[M – H· – $CH_3O(CH_2)_2OCH_2O\cdot]^+$, 39}, 175 {[M – $CH_3O(CH_2)_2OCH_2O\cdot]^+$, 43}, 161 (33), 147 (14), 119 (20), 107 (17), 106 (16), 105 {[$CH_3O(CH_2)_2OCH_2O\cdot]^+$, 41}, 91 (37), 89 {[$CH_3O(CH_2)_2OCH_2\cdot]^+$, 100}, 59 (97).

**HREIMS** Found: $M^{+\cdot}$, 280.2038. Calculated for $C_{17}H_{28}O_3$ $M^{+\cdot}$, 280.2038.

**Elemental Analysis** Found: C, 71.87; H, 9.28. $C_{17}H_{28}O_3$ requires C, 72.82; H, 10.06%.

Concentration of fraction B ($R_f$ 0.4, 3:7 v/v ethyl acetate – hexane elution, phosphomolybdic acid visualisation) afforded unreacted β,γ-unsaturated ketone **58** (73 mg, 29% recovery) which proved identical, in all respects, with authentic material.

Concentration of fraction C ($R_f$ 0.3, 3:7 ethyl acetate – hexane elution, phosphomolybdic acid visualisation) afforded the *title compound* ***60*** (32 mg, 18% at 71% conversion) as a clear, colourless oil.

**$^1$H NMR** (500 MHz) δ 5.72 - 5.70 (m, 2H), 4.82 (d, *J* 7.0 Hz, 1H), 4.76 (d, *J* 7.0 Hz, 1H), 4.47 (d, *J* 3.5 Hz, 1H), 3.81 (ddd, *J* 11.0, 5.5 and 3.0 Hz, 1H), 3.71 (ddd, *J* 11.0, 6.5 and 3.5 Hz, 1H), 3.60 (ddd, partially obscured, *J* 11.0, 6.0 and 3.5 Hz, 1H), 3.56 (ddd, partially obscured, *J* 11.0, 6.0 and 3.5 Hz, 1H), 3.40 (s, 3H), 3.24 – 3.16 (m, 1H), 2.54 – 2.50 (m, partially obscured, 1H), 2.45 (dt, *J* 12.0 and 7.0 Hz, 1H), 1.78 (dd, *J* 13.0 and 7.0 Hz, 1H), 1.50 (dd, *J* 13.0 and 2.5 Hz, 1H), 1.47 – 1.37 (m, partially obscured, 2H), 1.42 (s, 3H), 1.03 (s, 3H), 1.02 (s, 3H).

**$^{13}$C NMR** (126 MHz) δ 208.4 (C), 137.0 (CH), 120.5 (CH), 96.0 ($CH_2$), 92.3 (CH), 71.9 ($CH_2$), 67.6 ($CH_2$), 59.5 (CH), 59.3 ($CH_3$), 48.3 ($CH_2$), 43.7 ($CH_2$), 39.9 (CH), 39.2 (CH), 37.4 (C), 36.5 (C), 32.3 ($CH_3$), 32.0 ($CH_3$), 27.7 ($CH_3$).

**IR** $\nu_{max}$ 2950, 2930, 2866, 1780, 1451, 1364, 1126, 1098, 1074, 1039, 1012, 846 $cm^{-1}$.

**Mass Spectrum** (EI, 70 eV) *m/z* 308 ($M^{+\cdot}$, <1%), 279 {$[M - CO - H^{\cdot}]^+$, <1}, 219 {$[M - CH_3O(CH_2)_2OCH_2^{\cdot}]^+$, 2}, 204 {$[M- CO - CH_3O(CH_2)_2O^{\cdot} - H^{\cdot}]^+$, 2}, 201 (2), 175 {$[M - CO - CH_3O(CH_2)_2OCH_2O^{\cdot}]^+$, 30}, 162 {$[M - CH_3O(CH_2)_2OCH_2OCH{=}CO]^{+\cdot}$, 25}, 161 {$[M - CH_3O(CH_2)_2OCH_2OCH{=}CO - H^{\cdot}]^+$, 22}, 147 {$[CH_3O(CH_2)_2OCH_2OCH{=}CO + H^{\cdot}]^+$, 17}, 119 {$[CH_3O(CH_2)_2OCH_2OCH^{\cdot} + H^{\cdot}]^+$, 14}, 105 {$[CH_3O(CH_2)_2OCH_2O^{\cdot}]^+$, 33}, 91 (33), 89 $CH_3O(CH_2)_2OCH_2^{\cdot}]^+$, 99}, 59 {$[CH_3O(CH_2)_2^{\cdot}]^+$, 100}.

**HREIMS** Found: $M^{+\cdot}$, 308.1986; $[M - CO - H^{\cdot}]^+$, 279.1957. Calculated for $C_{18}H_{28}O_4$ $M^{+\cdot}$, 308.1988; $[M - CO - H^{\cdot}]^+$, 279.1960.

**Elemental Analysis** Found: C, 70.02; H, 9.05. $C_{18}H_{28}O_4$ requires C, 70.10; H, 9.15%.

**Optical Rotation** $[\alpha]_D^{19}$ +284.4 (*c* 0.22).

**UV** $\lambda_{max}$ 315 nm ($\varepsilon_0$ 99.1 $L.mol^{-1}.cm^{-1}$).

Concentration of fraction D ($R_f$ 0.2, 3:7 v/v ethyl acetate – hexane elution, phosphomolybdic acid visualisation) afforded a pale-yellow solid solid which was recrystallized (ethyl acetate) thus affording the *title compound* ***59*** (145 mg, 80% at 71% conversion) as a white crystalline solid, m.p. 78 – 79°C.

**$^1$H NMR** (500 MHz) δ 5.00 (d, *J* 6.5 Hz, 1H), 4.82 (d, *J* 6.5 Hz, 1H), 3.85 (ddd, *J* 11.0, 5.5 and 4.0 Hz, 2H), 3.83 (d *J* 1.5 Hz, 1H), 3.57 (ddd, *J* 5.5, 4.0 and 1.5 Hz, 2H), 3.39 (s, 3H), 2.68 (dt, *J* 12.0 and 7.5 Hz, 1H), 2.35 (dt, *J* 9.0 and 6.5 Hz, 1H), 2.10 (t, *J* 5.5 Hz, 1H), 1.87 (ddd, *J* 10.5, 5.0 and 1.5 Hz, 1H), 1.82 (ddd, *J* 13.5, 9.5 and 2.0 Hz, 1H), 1.64 (dd, *J* 10.5 and 6.0 Hz, 1H), 1.45 (t, *J* 12.0 Hz, 1H), 1.35 – 1.31 (complex m, partially obscured, 1H), 1.34 (s, 3H), 1.26 (dd, *J* 8.0 and 6.0 Hz, 1H), 1.08 (s, 3H), 0.86 (s, 3H).

**$^{13}$C NMR** (126 MHz) δ 211.0 (C), 95.6 ($CH_2$), 88.1 (CH), 72.0 ($CH_2$), 67.5 ($CH_2$), 59.4 ($CH_3$), 53.3 (CH), 49.9 (C), 48.8 ($CH_2$), 43.4 ($CH_2$), 43.3 (CH), 40.7 (C), 35.9 (CH), 33.6 (CH), 32.0 (CH), 29.7 ($CH_3$), 27.6 ($CH_3$), 21.3 ($CH_3$).

**IR** $\nu_{max}$ 2971, 2956, 2933, 2869, 1731, 1453, 1173, 1126, 1110, 1055, 1047, 1034, 1010, 991, 961, 854, 846 $cm^{-1}$.

**Mass Spectrum** (EI, 70 eV) *m/z* 308 ($M^{+\cdot}$, 4%), 279 {$[M - CO - H^{\cdot}]^+$, 7}, 233 {$[M - CH_3O(CH_2)_2O^{\cdot}]^+$, 14}, 219 {$[M - CH_3O(CH_2)_2OCH_2^{\cdot}]^+$, 47}, 204

{[M – $CH_3O(CH_2)_2OCH_2O\cdot$ – H·]$^+$, 27}, 189 {[M – CO – $CH_3O(CH_2)_2O\cdot$]$^+$, 14}, 175 {[M – CO – $CH_3O(CH_2)_2OCH_2\cdot$]$^+$, 10}, 173 (13), 163 (9), 147 (20), 108 (57), 105 {[$CH_3O(CH_2)_2OCH_2O\cdot$]$^+$, 24}, 89 {[$CH_3O(CH_2)_2OCH_2\cdot$]$^+$, 88}, 59 (100).

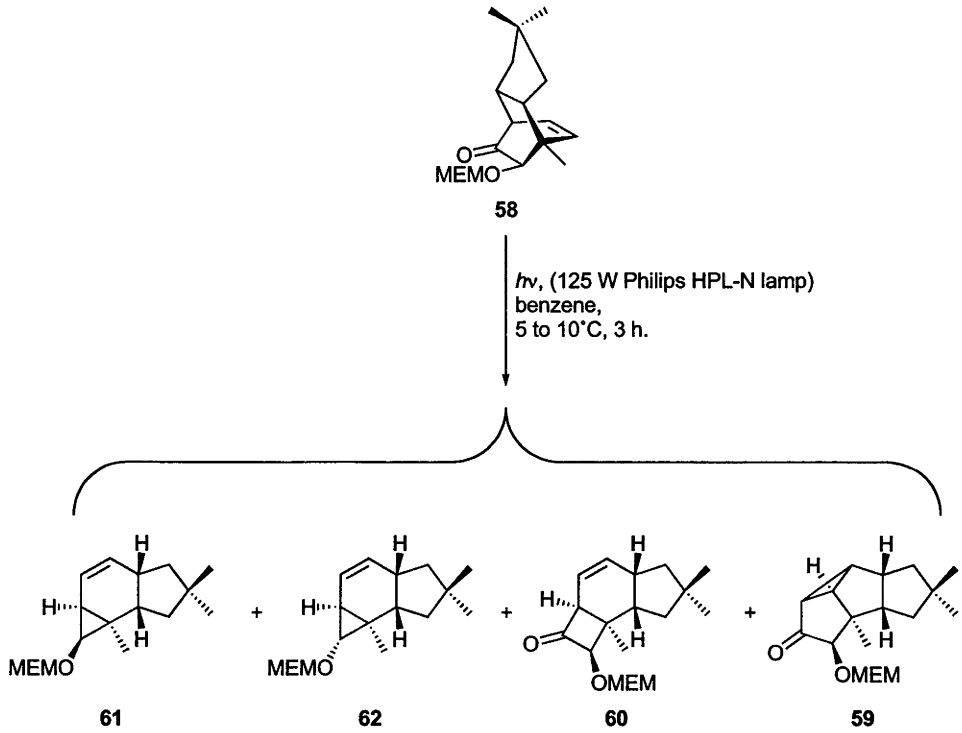
**HREIMS** Found: $M^{+\cdot}$, 308.1988; [M – $CH_3O(CH_2)_2OCH_2\cdot$]$^+$, 219.1384. Calculated for $C_{18}H_{28}O_4$ $M^{+\cdot}$, 308.1988; [M – $CH_3O(CH_2)_2OCH_2\cdot$]$^+$, 219.1385.

**Elemental Analysis** Found: C, 70.05; H, 8.86. $C_{18}H_{28}O_4$ requires C, 70.10; H, 9.15%.

**Optical Rotation** $[\alpha]_D^{19}$ +101.9 (*c* 0.22).

**UV** $\lambda_{max}$ 280 nm ($\varepsilon_0$ 47.4 L.mol$^{-1}$.cm$^{-1}$).

*Method B*:[15]




A deoxygenated, magnetically stirred (500 rpm) solution of β,γ-unsaturated ketone **58** (58 mg, 0.19 mmol) in benzene (25 mL) was prepared in a Pyrex™ vessel and maintained at between 5 and 10°C. The reaction mixture was irradiated for 5 min, using a Philips 125 W HPL-N lamp, and was subsequently concentrated under reduced pressure. Subjection of the ensuing clear, colourless oil to flash chromatography (silica, 0:1 → 3:7 v/v ethyl acetate – hexane gradient elution), afforded four major fractions, A - D.

Concentration of fraction A ($R_f$ 0.5, 3:7 ethyl acetate – hexane elution, phosphomolybdic acid visualisation) afforded the *title compounds* ***61*** and ***62*** (7:3 mixture of

15 *Methods B*, *C* and *D* were discussed in Chapter Four but are grouped in this Section, with *Method A* (discussed in Chapter Three), for convenience.

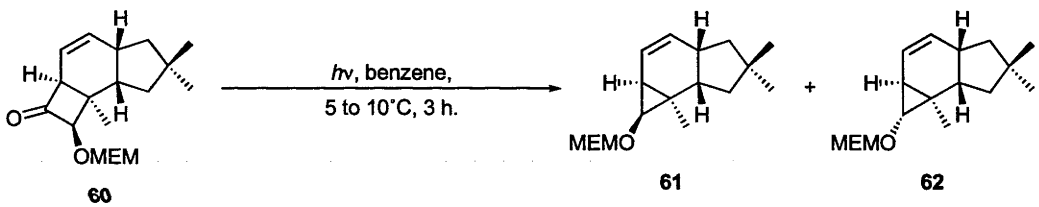
epimers at C1, 2 mg, 10% at 25% conversion) identical, in all respects, with material obtained *via Method A* .

Concentration of fraction B ($R_f$ 0.4, 3:7 v/v ethyl acetate – hexane elution, phosphomolybdic acid visualisation) afforded unreacted β,γ-unsaturated ketone **58** (44 mg, 75% recovery) which proved identical, in all respects, with authentic material.

Concentration of fraction C ($R_f$ 0.3, 3:7 v/v ethyl acetate – hexane elution, phosphomolybdic acid visualisation) afforded the *title compound **60*** (12 mg, 80% at 25% conversion) identical, in all respects, with material obtained *via Method A.*

Concentration of fraction D ($R_f$ 0.2, 3:7 v/v ethyl acetate – hexane elution, phosphomolybdic acid visualisation) afforded the *title compound **59*** (1 mg, 10% at 25% conversion) identical, in all respects, with material obtained *via Method A.*

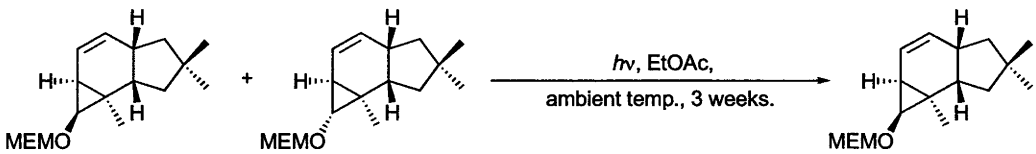
*Method C*:[15, 16]




A deoxygenated, magnetically stirred (500 rpm) solution of cyclobutanone **60** (12.1 mg, 0.04 mmol) in benzene (6 mL) was prepared in a Pyrex™ vessel and maintained at between 5 and 10°C. The reaction mixture was irradiated for 3 h, using a Philips 125 W HPL-N lamp, and was subsequently concentrated under reduced pressure. Subjection of the ensuing clear, colourless oil to flash chromatography (silica, 0:1 → 3:7 v/v ethyl acetate – hexane gradient elution), afforded, upon concentration of the appropriate fractions ($R_f$ 0.5, 3:7 v/v ethyl acetate – hexane elution, phosphomolybdic acid visualisation), a 7:3 mixture of the *title compounds **61*** and ***62*** (6.1 mg, 55 %), identical, in all respects, with that obtained *via Method A.*

16 Note that only cyclopropanes **61** and **62** are generated using *Method C.*

*Method D*:[15, 17]




A 3:7 *exo-*/*endo*-mixture of the cyclopropyl indenes **61** and **62** (112 mg, 40 mmol) dissolved in ethyl acetate (5 mL) and contained in a Pyrex™ vessel was maintained at ambient temperature and exposed to natural light. After three weeks, solvent was removed under reduced pressure and the resulting pale-yellow oil was subjected to flash column chromatography (silica; 0:1 → 1:9 ethyl acetate – hexane gradient elution). Concentration of the appropriate fractions ($R_f$ 0.5, 3:7 v/v ethyl acetate – hexane elution, phosphomolybdic acid visualisation) afforded a clear, colourless oil which was redissolved in ethyl acetate (2 mL). The solution was subsequently treated with activated charcoal (100 mg) and refluxed gently. After 5 min the mixture was cooled to ambient temperature, filtered and concentrated under reduced pressure to afford the single diastereomeric *title compound* ***61*** (25 mg, 22%) as a clear, colourless oil.

**$^1$H NMR** (500 MHz) δ (500 MHz) 5.66 (ddd, *J* 9.5, 6.0 and 3.0, 1H), 5.24 (dd, *J* 9.5 and 2.0, 1H), 4.63 (d, *J* 6.5, 1H), 4.49 (d, *J* 6.5, 1H), 3.81 (dt, *J* 11.0 and 4.5, 1H), 3.66 - 3.62 (m, 1H), 3.57 (t, *J* 4.5, 2H), 3.40 (s, 3H), 3.38 (d, *J* 6.5, 1H), 2.61 - 2.56 (m, 1H), 2.38 (dt, *J* 12.5 and 7.5, 1H), 1.77 (dd, *J* 13.5 and 9.0, 1H), 1.55 (dd, *J* 12.0 and 6.5, 1H), 1.32 (t, *J* 12.5, 1H), 1.30 (dd, *J* 13.0 and 3.0, 1H), 1.14 (t, *J* 6.5, 1H), 1.02 (s, 3H), 1.01 (s, 3H), 0.99 (s, 3H).

**$^{13}$C NMR** (126 MHz) δ 131.6 (CH), 119.4 (CH), 96.9 ($CH_2$), 72.1 ($CH_2$), 67.8 ($CH_2$), 67.6 (CH), 59.3 ($CH_3$), 48.6 ($CH_2$), 45.9 ($CH_2$), 39.9 (CH), 37.5 (CH), 36.6 (C), 31.8 ($CH_3$), 31.1 ($CH_3$), 23.8 (C and $CH_3$ signals overlapping), 22.8 (CH).

**IR** $\nu_{max}$ 3022, 2951, 2928, 2866, 1450, 1364, 1200, 1172, 1127, 1078, 1050, 999, 982, 853, 756 $cm^{-1}$.

**Mass Spectrum** (EI, 70 eV) *m/z* 280 ($M^{+\cdot}$, <1%), 205 {[M – $CH_3O(CH_2)_2O^{\cdot}]^+$, 4}, 204 (3), 176 {[M - H$^{\cdot}$ – $CH_3O(CH_2)_2OCH_2O^{\cdot}]^+$, 33}, 175 {[M – $CH_3O(CH_2)_2OCH_2O^{\cdot}]^+$, 36}, 161 (23), 105 {[$CH_3O(CH_2)_2OCH_2O^{\cdot}]^+$, 36}, 91 (33), 89 {[$CH_3O(CH_2)_2OCH_2^{\cdot}]^+$, 100}, 59 (96).

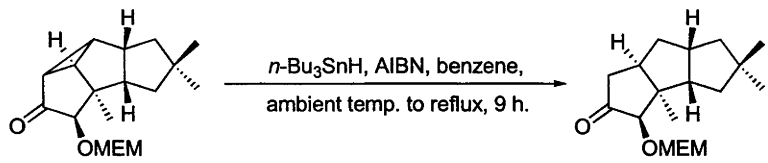
**HREIMS** Found: $M^{+\cdot}$, 280.2038. Calculated for $C_{17}H_{28}O_3$ $M^{+\cdot}$, 280.2038.

**Elemental Analysis** Found: C, 72.57; H, 10.18. $C_{17}H_{28}O_3$ requires C, 72.82; H, 10.06%.

**Optical Rotation** $[\alpha]_D^{22}$ +212.5 (*c* 0.23).

17 Note that only cyclopropane **61** is generated using *Method D*.

**(3*R*,3a*S*,3b*S*,6a*R*,7a*R*)-Decahydro-3-[(2-methoxyethoxy)methoxy]-3a,5,5-trimethyl-2*H*-cyclopenta[*a*]pentalen-2-one (137)**




**59** **137**

Tri-*n*-butyltin hydride (254 μL, 0.94 mmol) was added, dropwise, to a magnetically stirred solution of cyclopropyl ketone **59** (145 mg, 0.47 mmol) and AIBN (3.4 mg, 0.02 mmol) in benzene (15 mL) maintained at ambient temperature. The resulting mixture was allowed to stand for 1 h, before being heated at reflux for an additional 1 h. The reaction mixture was subsequently cooled to ambient temperature and treated with additional aliquots of tri-*n*-butyltin hydride (254 μL, 0.94 mmol) and AIBN (5.9 mg, 0.04 mmol) before being heated at reflux for a further 2 h. The cooled reaction mixture was again treated with additional amounts of AIBN (2.3 mg, 0.01 mmol) and tri-*n*-butyltin hydride (254 μL, 0.94 mmol), then heated at reflux for a further 5 h, such that the total reflux time was 8 h. The reaction mixture was then cooled to ambient temperature and concentrated under reduced pressure. The ensuing light-yellow oil was subjected to flash chromatography (silica, 0:1 → 3:7 v/v ethyl acetate – hexane elution), thus affording two fractions, A and B.

Concentration of fraction A ($R_f$ 0.3, 3:7 v/v ethyl acetate – hexane elution, phosphomolybdic acid visualisation) afforded the *title compound **137*** (104 mg, 87% at 81% conversion) as a clear, colourless oil.

**$^1$H NMR** (300 MHz) δ 4.95 (d, *J* 6.9 Hz, 1H), 4.80 (d, *J* 6.9 Hz, 1H), 4.05 (d, *J* 1.8 Hz, 1H), 3.80 – 3.76 (m, 2H), 3.57 – 3.53 (m, 2H), 3.38 (s, 3H), 2.78 – 2.62 (m, 1H), 2.54 – 2.37 (complex m, 3H), 1.88 (dd, *J* 17.7 and 5.4 Hz, 1H), 1.78 – 1.70 (m, partially obscured,[18] H), 1.66 – 1.50 (complex m, 2H), 1.40 – 1.24 (complex m, 2H), 1.16 (s, 3H), 1.07 – 1.00 (m, partially obscured, 1H), 1.04 (s, 3H), 0.90 (s, 3H).

**$^{13}$C NMR** (75 MHz) δ 216.6 (C), 95.6 ($CH_2$), 88.4 (CH), 72.0 ($CH_2$), 67.3 ($CH_2$), 59.3 ($CH_3$), 50.6 (C), 49.2 ($CH_2$), 47.1 (CH), 46.6 (CH), 44.8 (C), 43.9 (CH), 42.2 ($CH_2$), 39.4 ($CH_2$), 37.1 ($CH_2$), 29.6 ($CH_3$), 27.4 ($CH_3$), 22.9 ($CH_3$).

**IR** $\nu_{max}$ 2949, 2867, 2818, 1752, 1466, 1365, 1177, 1134, 1111, 1098, 1044, 1004, 982, 849 $cm^{-1}$.

**Mass Spectrum** (EI, 70 eV) *m/z* 310 ($M^{+\cdot}$, 1%), 221 {[M – $CH_3O(CH_2)_2OCH_2\cdot]^+$, 35}, 206 {[M – CO – H· – $CH_3O(CH_2)_2O\cdot]^+$, 13}, 161 (34), 149 (25), 109 (29), 107 (22), 96 (80), 89 {$[CH_3O(CH_2)_2OCH_2\cdot]^+$, 84}, 59 {$[CH_3O(CH_2)_2\cdot]^+$, 100}.

18 Due to overlap of multiplet with singlet resonance attributed to residual $H_2O$.

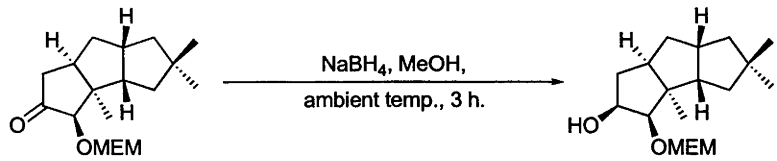
**HREIMS** Found: $M^{+\cdot}$, 310.2141. Calculated for $C_{18}H_{30}O_4$ $M^{+\cdot}$, 310.2144.

**Elemental Analysis** Found: C, 69.64; H, 9.66. $C_{18}H_{30}O_4$ requires C, 69.64; H, 9.74%.

**Optical Rotation** $[\alpha]_D^{22}$ +19.6 (*c* 0.45).

Concentration of fraction B ($R_f$ 0.2, 3:7 v/v ethyl acetate – hexane elution, phosphomolybdic acid visualisation) afforded unreacted cyclopropyl ketone **59** (27 mg, 19% recovery) which was identical, in all respects, with authentic material.

**(2*S*,3*R*,3a*S*,3b*S*,6a*R*,7a*R*)-Decahydro-3-[(2-methoxyethoxy)methoxy]-3a,5,5-trimethyl-2*H*-cyclopenta[*a*]pentalen-2-ol (139)**




**137** **139**

$NaBH_4$ (28 mg, 0.73 mmol) was added to a magnetically stirred solution of ketone **137** (100 mg, 0.33 mmol) in methanol (15 mL) maintained at ambient temperature. Hydrogen gas evolution occurred upon dissolution, but ceased rapidly and after 4 h the reaction mixture was diluted with ethyl acetate (2 mL), then treated with water (15 mL). The separated aqueous phase was extracted with ethyl acetate (5 × 15 mL) and the combined organic phases were then dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. Subjection of the ensuing clear, colourless oil to flash chromatography (silica, 1:9 → 1:4 v/v ethyl acetate – hexane gradient elution) afforded, after concentration of the appropriate fractions ($R_f$ 0.2, 3:7 v/v ethyl acetate – hexane elution, phosphomolybdic acid visualisation), the *title compound **139*** (100 mg, 98%) as a clear, colourless oil.

**$^1$H NMR** (300 MHz) δ 4.86 (d, *J* 6.9 Hz, 1H), 4.76 (d, *J* 6.9 Hz, 1H), 4.15 – 4.07 (m, 1H), 3.86 – 3.79 (complex m, 1H), 3.77 – 3.70 (complex m, 1H), 3.57 (d, *J* 4.8 Hz, 1H), 3.53 (dd, *J* 11.4 and 5.4 Hz, 2H), 3.38 (s, 3H), 3.01 (d, *J* 6.0 Hz, 1H), 2.81 – 2.65 (complex m, 2H), 2.12 (dd, *J* 13.2, 8.7 and 7.2 Hz, 1H), 1.96 (dd, *J* 16.8, 7.5 and 2.1 Hz, 1H), 1.68 – 1.57 (complex m, 2H), 1.50 – 1.21 (complex m, partially obscured, 4H), 1.10 (dd, *J* 12.9 and 5.7, 1H), 1.04 (s, 3H), 1.00 (s, 3H), 0.93 (s, 3H).

**$^{13}$C NMR** (75 MHz) δ 97.4 ($CH_2$), 91.3 (CH), 72.9 (CH), 72.0 ($CH_2$), 68.1 ($CH_2$), 59.3 ($CH_3$), 53.4 (C), 50.0 (CH), 48.4 (CH), 47.7 ($CH_2$), 44.3 (CH), 42.8 ($CH_2$), 42.3 (C), 39.9 ($CH_2$), 39.2 ($CH_2$), 30.9 ($CH_3$), 29.1 ($CH_3$), 24.9 ($CH_3$).

**IR** $\nu_{max}$ 3479, 2930, 2865, 1462, 1381, 1364, 1313, 1249, 1200, 1170, 1097, 1036, 849 $cm^{-1}$.

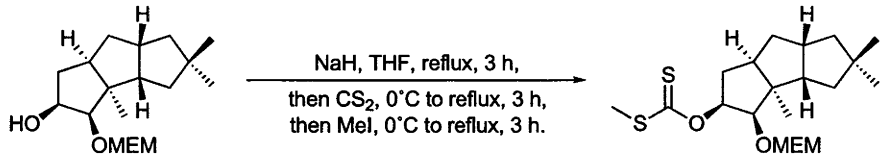
**Mass Spectrum** (EI, 70 eV) *m/z* 313 {[M + H·]$^+$, 1%}, 312 ($M^{+\cdot}$, <1), 236 {[M – H· – $CH_3O(CH_2)_2O$·]$^+$, 24}, 223 {[M – $CH_3O(CH_2)_2OCH_2$·]$^+$, 20}, 206 {[M – H· – $CH_3O(CH_2)_2OCH_2O$·]$^+$, 22}, 179 (39), 161 (54), 149 (51), 89 {[$CH_3O(CH_2)_2OCH_2$·]$^+$, 78}, 59 {[$CH_3O(CH_2)_2$·]$^+$, 100}.

**HREIMS** Found: $M^{+\cdot}$, 312.2298; [M + H·]$^+$, 313.2375. Calculated for $C_{18}H_{32}O_4$ $M^{+\cdot}$, 312.2301; [M + H·]$^+$, 313.2379.

**Elemental Analysis** Found: C, 68.96; H, 10.10. $C_{18}H_{32}O_4$ requires C, 69.19; H, 10.32%.

**Optical Rotation** $[\alpha]_D^{17}$ +11.7 (*c* 0.61).

**(2*S*,3*R*,3a*S*,3b*S*,6a*R*,7a*R*)-decahydro-3-[(2-methoxyethoxy)methoxy]-3a,5,5-trimethyl-2*H*-cyclopenta[a]pentalen-2-ol *S*-methyl xanthate (140)**




**139** **140**

A magnetically stirred solution of alcohol **139** (96 mg, 0.31 mmol) and sodium hydride (64 mg of a 60% dispersion in mineral oil, 1.60 mmol) in THF (15 mL) was heated at reflux for 3 h and subsequently cooled to 0°C before being treated, dropwise, with carbon disulfide (192 μL, 3.19 mmol). After 0.5 h, the resulting mixture was heated at reflux for 2.5 h, before being cooled to 0°C and treated with methyl iodide (1.00 mL, 16.08 mmol). The reaction mixture was subsequently heated at reflux for 3 h, then cooled to 0°C and quenched with acetic acid (1.0 mL). Excess acid was neutralised by the addition of $NaHCO_3$ (10 mL of a saturated aqueous solution) and the system was diluted with ethyl acetate (5 mL). The separated aqueous phase was extracted with ethyl acetate (5 × 10 mL) and the combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a pale-yellow oil. Subjection of this material to flash chromatography (silica, 1:19 → 1:4 v/v ethyl acetate – hexane gradient elution) and concentration of the appropriate fractions ($R_f$ 0.4, 1:4 v/v ethyl acetate – hexane elution, phosphomolybdic acid visualisation) afforded the *title compound **140*** (118 mg, 92%) as a clear, colourless oil.

**$^1$H NMR** (300 MHz) δ 5.84 (dt, *J* 6.9 and 5.1 Hz, 1H), 4.73 (dd, *J* 11.4 and 6.9 Hz, 2H), 3.83 (d, *J* 5.1 Hz, 1H), 3.80 – 3.65 (complex m, 2H), 3.53 (t, *J* 5.1 Hz, 2H), 3.37 (s, 3H), 3.01 – 2.91 (m, 1H), 2.79 – 2.65 (m, 1H), 2.56 (s, 3H), 2.33 (ddd, *J* 14.4, 9.6 and 6.9 Hz, 1H), 2.09 – 2.02 (m, 1H), 1.72 – 1.58 (complex m, partially obscured,[18] 3H), 1.50 (ddd, *J* 12.9, 10.2 and 7.2 Hz, 1H), 1.37 – 1.25 (m, 2H), 1.15 – 1.06 (m, 1H), 1.08 (s, 3H), 1.06 (s, 3H), 0.96 (s, 3H).

**$^{13}$C NMR** (75 MHz) δ 215.4 (C), 96.2 ($CH_2$), 86.7 (CH), 84.3 (CH), 72.0 ($CH_2$), 67.6 ($CH_2$), 59.3 ($CH_3$), 53.4 (C), 49.7 (CH), 47.7 [(CH) and ($CH_2$): two signals overlapping], 44.2 (CH), 43.0 (C), 42.8 ($CH_2$), 40.4 ($CH_2$), 36.0 ($CH_2$), 30.6 ($CH_3$), 28.7 ($CH_3$), 24.5 ($CH_3$), 19.3 ($CH_3$).

**IR** $\nu_{max}$ 2949, 2933, 2864, 2815, 1464, 1364, 1220, 1176, 1134, 1115, 1098, 1062, 853 cm$^{-1}$.

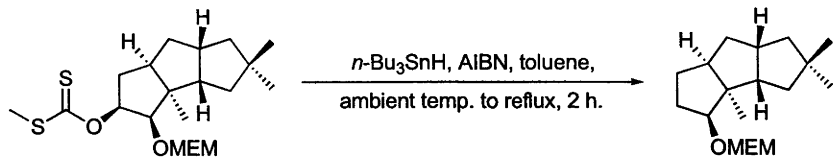
**Mass Spectrum** (EI, 70 eV) *m/z* 369 {[M – HS·]$^+$, 6%}, 355 {[M – $CH_3S$·]$^+$, 5}, 190 {[M – $CH_3O(CH_2)_2OCH_2O$ – $CH_3SC(S)O$·]$^+$, 8}, 149 {[M – $CH_3O(CH_2)_2OCH_2OCH$=$CHOC(S)SCH_3$ – $CH_3$·]$^+$, 12}, 107 {[$CH_3SC(S)O$·]$^+$, 8}, 105 {[$CH_3O(CH_2)_2OCH_2O$·]$^+$, 10}, 89 {[$CH_3O(CH_2)_2OCH_2$·]$^+$, 100}, 59 {[$CH_3O(CH_2)_2$·]$^+$, 95}.

**HREIMS** Found: [M – HS·]$^+$, 369.2100; [M – $CH_3S$·]$^+$, 355.1940. Calculated for $C_{20}H_{34}O_4S_2$ [M – HS·]$^+$, 369.2100; [M – $CH_3S$·]$^+$, 355.1943.

**Elemental Analysis** Found: C, 59.82; H, 8.68, S, 15.64. $C_{20}H_{34}O_4S_2$ requires C, 59.67; H, 8.51; S, 15.93%.

**Optical Rotation** $[\alpha]_D^{19}$ +45.0 (*c* 0.41).

**(3a*S*,3b*S*,4*S*,6a*S*,7a*R*)-Decahydro-3-[(2-methoxyethoxy)methoxy]-2,2,3b-trimethyl-1*H*-cyclopenta[*a*]pentalene (141)**




**140** **141**

Tri-*n*-butyltin hydride (152 μL, 0.57 mmol) was added to a magnetically stirred solution of *S*-methyl xanthate **140** (114 mg, 0.28 mmol) and AIBN (3.6 mg, 0.02 mmol) in toluene (15 mL) maintained at ambient temperature. The resulting mixture was allowed to stand for 10 min prior to being heated at reflux for 2 h, after which time metallic tin precipitates mirrored the inside of the reaction vessel. Solvent and carbonyl sulfide were then removed under reduced pressure to afford a colourless oil which was subjected to column chromatography (silica, 0:1 → 1:9 v/v ethyl acetate – hexane gradient elution). Concentration of the appropriate fractions ($R_f$ 0.2, 1:9 v/v ethyl acetate – hexane elution, phosphomolybdic acid visualisation) afforded the *title compound* ***141*** (77 mg, 92%) as a clear, colourless oil.

**$^1$H NMR** (300 MHz) δ 4.75 (d, *J* 6.9 Hz, 1H), 4.70 (d, *J* 6.9 Hz, 1H), 3.72 – 3.65 (complex m, 3H), 3.57 – 3.54 (complex m, 2H), 3.39 (s, 3H), 2.69 (dd, *J* 19.2 and 9.6 Hz, 1H), 2.62 – 2.48 (m, 1H), 2.07 – 2.00 (m, 1H), 1.98 – 1.86 (m, 1H), 1.76 – 1.56 (complex m, 3H), 1.64 (d *J* 0.6 Hz, 1H), 1.45 (ddd, *J* 12.6, 8.7 and 7.2 Hz, 1H), 1.38 – 1.25 (m, 1H), 1.29 (d, *J* 9.6 Hz, 2H), 1.10 – 1.03 (m, partially obscured, 1H), 1.05 (s, 3H), 0.99 (s, 3H), 0.94 (s, 3H).

**$^{13}$C NMR** (75 MHz) δ 95.3 ($CH_2$), 88.1 (CH), 72.1 ($CH_2$), 66.9 ($CH_2$), 59.3 ($CH_3$), 54.2 (C), 51.7 (CH), 48.5 ($CH_2$), 47.9 (CH), 44.8 (CH), 43.5 ($CH_2$), 42.5 (C), 40.9 ($CH_2$), 31.2 ($CH_2$), 30.5 ($CH_3$), 28.5 ($CH_3$), 28.3 ($CH_2$), 23.8 ($CH_3$).

**IR** $\nu_{max}$ 2949, 2869, 1464, 1381, 1373, 1364, 1200, 1156, 1136, 1111, 1045, 982, 852 cm$^{-1}$.

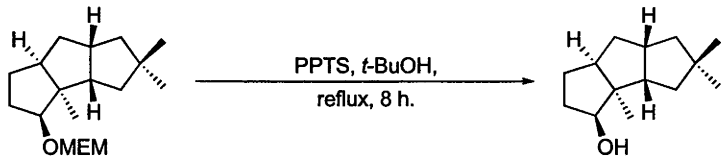
**Mass Spectrum** (EI, 70 eV) *m/z* 296 ($M^{+\cdot}$, <1%), 220 {[M – H· – $CH_3O(CH_2)_2O\cdot$]$^+$, 60}, 207 {[M – $CH_3O(CH_2)_2OCH_2\cdot$]$^+$, 50}, 190 {[M – H· – $CH_3O(CH_2)_2OCH_2O\cdot$]$^+$, 44}, 189 {[M – $CH_3O(CH_2)_2OCH_2O\cdot$]$^+$, 49}, 163 (37), 121 (30), 107 (45), 89 {[$CH_3O(CH_2)_2OCH_2\cdot$]$^+$, 100}.

**HREIMS** Found: $M^{+\cdot}$, 296.2337. Calculated for $C_{18}H_{32}O_3$ $M^{+\cdot}$, 296.2351.

**Elemental Analysis** Found: C, 72.75; H, 11.27. $C_{18}H_{32}O_3$ requires C, 72.93; H, 10.88%.

**Optical Rotation** $[\alpha]_D^{25}$ +32.0 (*c* 0.68).

**(3*S*,3a*S*,3b*S*,6a*R*,7a*S*)-Decahydro-3a,5,5-trimethyl-1*H*-cyclopenta-[*a*]pentalen-3-ol (142)**




**141** **142**

A magnetically stirred solution of the MEM-ether **141** (9.5 mg, 0.032 mmol) and PPTS (17 mg, 0.068 mmol) in *t*-butanol (2 mL) was heated at reflux for 4 h. The reaction mixture was then cooled to ambient temperature and subsequently treated with additional PPTS (4.1 mg, 0.016 mmol), before being heated at reflux for a further 4 h. After this time, the resulting mixture was cooled to 30°C and concentrated under a gentle stream of nitrogen gas. Subjection of the ensuing light-brown oil to flash chromatography (silica, 0:1 → 1:4 v/v ethyl acetate – hexane gradient elution) afforded, after concentration of the appropriate fractions ($R_f$ 0.2, 1:9 v/v ethyl acetate – hexane elution, phosphomolybdic acid visualisation), the *title compound **142*** (5.1 mg, 76%) as a white, crystalline solid, m.p. 44 – 46°C.

**$^1$H NMR** (300 MHz) δ 3.78 (t, *J* 6.6 Hz, 1H), 2.66 – 2.51 (complex m, 2H), 2.12 – 2.04 (m, 1H), 2.01 – 1.91 (complex m, 1H), 1.80 – 1.25 (complex m, 9H), 1.12 – 1.05 (m, partially obscured, 1H), 1.06 (s, 3H), 0.98 (s, 3H), 0.95 (s, 3H).

**$^{13}$C NMR** (75 MHz) δ 83.2 (CH), 55.0 (C), 51.7 (CH), 48.5 ($CH_2$), 47.6 (CH), 44.9 (CH), 43.6 ($CH_2$), 42.5 (C), 40.9 ($CH_2$), 33.8 ($CH_2$), 30.4 ($CH_3$), 28.3 ($CH_3$), 28.2 ($CH_2$), 23.3 ($CH_3$).

**IR** $\nu_{max}$ 3376, 2949, 2932, 2864, 1464, 1374, 1364, 1313, 1136, 1075, 1033, 1003 cm$^{-1}$.

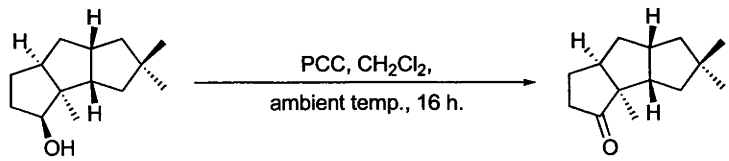
**Mass Spectrum** (EI, 70 eV) *m/z* 208 ($M^{+\cdot}$, 50%), 190 {[M – $H_2O$]$^{+\cdot}$, 14}, 175 {[M – $H_2O$ – $CH_3\cdot$]$^+$, 11}, 162 (20), 149 (100), 123 (30), 107 (55), 93 (35), 81 (28).

**HREIMS** Found: $M^{+\cdot}$, 208.1830. Calculated for $C_{14}H_{24}O$ $M^{+\cdot}$, 208.1827.

**Elemental Analysis** Found: C, 80.65; H, 11.43. $C_{14}H_{24}O$ requires C, 80.71; H, 11.61%.

**Optical Rotation** $[\alpha]_D^{26}$ +36.4 (*c* 0.11).

**(3a*S*,3b*S*,6a*R*,7a*S*)-Decahydro-3a,5,5-trimethyl-3*H*-cyclopenta[*a*]pentalen-3-one** (*ent*-**97**)




**142** *ent*-**97**

PCC (68.7 mg, 0.32 mmol) was added to a magnetically stirred solution of alcohol **142** (33.2 mg, 0.159 mmol) in dichloromethane (10 mL) maintained at ambient temperature. The resulting orange-yellow mixture was allowed to stand for 16 h, after which time it had turned red-brown. Solvent was subsequently removed under a stream of nitrogen and the residue subjected to flash chromatography (silica, 5:95 v/v ethyl acetate – pentane elution). Concentration of the appropriate fractions ($R_f$ 0.5, 1:4 v/v ethyl acetate – pentane elution, phosphomolybdic acid visualisation) afforded the title compound *ent*-**97** (23 mg, 71%) as a white crystalline solid, m.p. 23 – 24°C.

**$^1$H NMR** (300 MHz) δ 2.79 (dt, *J* 11.1 and 8.4 Hz, 1H), 2.51 (ttd, *J* 9.0, 9.0 and 3.3 Hz, 1H), 2.44 – 2.21 (complex m, 3H), 2.00 (dddd, *J* 13.2, 9.9, 8.4 and 6.3 Hz, 1H), 1.72 (dddd, *J* 12.9, 9.0, 3.9 and 2.1 Hz, 1H), 1.64 (ddd, partially obscured,[18] *J* 12.0, 8.1 and 2.7 Hz, 1H), 1.57 (dd, *J* 8.1 and 3.6 Hz, 1H), 1.48 – 1.34 (complex m, 2H), 1.17 (t, *J* 11.1 Hz, 1H), 1.04 (s, 3H), 0.99 (dd, *J* 12.6 and 9.3 Hz, 1H), 0.94 (s, 3H), 0.90 (s, 3H).

**$^{13}$C NMR** (75 MHz) δ 224.8 (C), 59.7 (C), 49.2(0) (CH), 49.1(8) ($CH_2$), 47.0 (CH), 43.7 ($CH_2$), 42.2 (CH), 41.5 (C), 37.9 ($CH_2$), 34.6 ($CH_2$), 29.6 ($CH_3$), 26.9 ($CH_3$), 22.7 ($CH_2$), 17.7 ($CH_3$).

**IR** $\nu_{max}$ 2933, 2866, 1739, 1464, 1409, 1383, 1365, 1208, 1151, 1092, 1070, 1043, 1008 $cm^{-1}$.

**Mass Spectrum** (EI, 70 eV) *m/z* 206 ($M^{+\cdot}$, 100%), 191 {$[M - CH_3\cdot]^+$, 9}, 188 (7), 178 {$[M - CO]^{+\cdot}$, 7}, 162 (46), 150 (39), 149 (36), 123 (24), 107 (56), 95 (46), 94 (46), 93 (45), 79 (38).

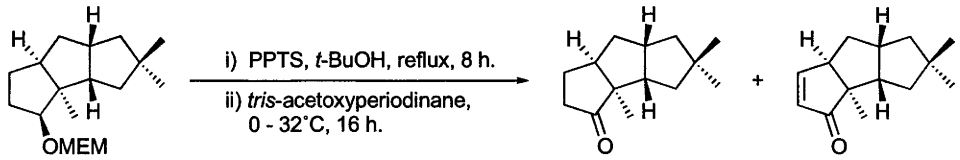
**HREIMS** Found: $M^{+\cdot}$, 206.1671. Calculated for $C_{14}H_{22}O$ $M^{+\cdot}$, 206.1671.

**Elemental Analysis** Found: C, 81.72; H, 11.10. $C_{14}H_{22}O$ requires C, 81.50; H, 10.75%.

**Optical Rotation** $[\alpha]_D^{19}$ –55.9 (*c* 0.37) {lit.[19] $[\alpha]_{598}^{20}$ –81.5 (*c* 0.5, *n*-hexane)}.

19 Weinges, K.; Reichert, H.; Huber-Patz, U.; Irngartinger, H., *Liebigs Ann. Chem.*, **1993**, 403.

**(3a*S*,3b*S*,6a*R*,7a*R*)-3a,3b,4,5,6,6a,7,7a-Octahydro-3a,5,5-trimethyl-3*H*-cyclopenta[*a*]pentalene-3-one (143)**




**141** *ent*-**97** **143**

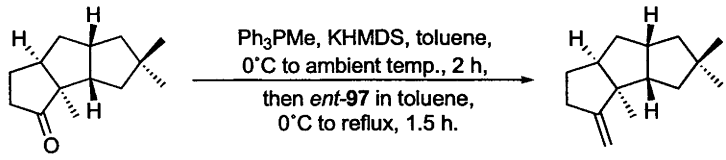
A magnetically stirred solution of MEM-ether **141** (99 mg, 0.33 mmol) and PPTS (210 mg, 0.84 mmol) in *t*-BuOH (10 mL) was heated at reflux for 8 h. The reaction mixture was subsequently cooled to 0°C and, upon solidification, treated with *tris*-acetoxyperiodinane (570 mg, 1.34 mmol), before warming to 30 – 32°C. After 16 h, the reaction mixture was concentrated under reduced pressure to afford a pale-yellow semi-solid. The semi-solid was subjected to flash chromatography (silica, 0:1 → 3:17 v/v ethyl acetate – hexane gradient elution) to afford two fractions, A and B.

Concentration of fraction A ($R_f$ 0.5, 1:4 v/v ethyl acetate – hexane elution, phosphomolybdic acid visualisation) afforded the ketone *ent*-**97** (30 mg, 43%) as a white crystalline solid, m.p. 23 – 24°C, identical, in all respects, with material obtained as detailed earlier (Section 6.3, page 171).

Concentration of fraction B ($R_f$ 0.5, 1:4 v/v ethyl acetate – hexane elution, phosphomolybdic acid visualisation) afforded the *title compound* ***143*** (28 mg, 41%) as a white crystalline solid, m.p. 80 – 82°C.

**$^1$H NMR** (300 MHz) δ 7.46 (q, *J* 2.7 Hz, 1H), 6.09 (dd, *J* 5.7 and 1.8 Hz, 1H), 2.98 – 2.93 (m, 1H), 2.51 (dt, *J* 11.4 and 7.5 Hz, 1H), 2.19 (dtd, *J* 18.9, 7.8 and 2.4 Hz, 1H), 1.81 – 1.66 (m, partially obscured, 2H), 1.60 (ddd, *J* 13.5, 8.1 and 0.3 Hz, 1H), 1.45 (broad s, 1H), 1.42 (d, *J* 4.8 Hz, 1H), 1.28 (dd, *J* 13.8 and 2.7 Hz, 1H), 1.10 (s, 6H), 0.93 (s, 3H).
**$^{13}$C NMR** (75 MHz) δ 216.4 (C), 166.8 (CH), 132.0 (CH), 56.7 (C), 56.0 (CH), 51.3 (CH), 45.8 ($CH_2$), 42.7 ($CH_2$), 42.4 (CH), 40.8 (C), 36.5 ($CH_2$), 31.9 ($CH_3$), 30.6 ($CH_3$), 18.9 ($CH_3$).
**IR** $\nu_{max}$ 2940, 2895, 2867, 1694, 1585, 1451, 1374, 1370, 1363, 1354, 1207, 840 cm$^{-1}$.
**Mass Spectrum** (EI, 70 eV) *m/z* 204 ($M^{+\cdot}$, 90%), 189 {[M – $CH_3\cdot$]$^+$, 100}, 149 (30), 133 (22), 119 (25), 108 (86), 105 (37), 95 (28), 91 (41), 81 (28), 79 (27), 77 (31), 55 (33).
**HREIMS** Found: $M^{+\cdot}$, 204.1517. Calculated for $C_{14}H_{20}O$ $M^{+\cdot}$, 204.1514.
**Elemental Analysis** Found: C, 81.65; H, 10.31. $C_{14}H_{20}O$ requires C, 82.30; H, 9.87%.
**Optical Rotation** $[\alpha]_D^{20}$ –90.5 (*c* 0.15).

**(3a*S*,3b*S*,6a*S*,7a*R*)-Decahydro-2,2,3b-trimethyl-4-methylene-1*H*-cyclopenta[*a*]pentalene [*ent*-(–)-hirsutene, *ent*-(–)-54]**




*ent*-97 *ent*-(–)-Hirsutene [*ent*-(–)-54]

KHMDS (297 μL of a 15% w/v solution in toluene, 0.197 mmol) was added, dropwise, to a magnetically stirred solution of methyl triphenylphosphonium bromide (68.9 mg, 0.19 mmol) in freshly distilled toluene (10 mL) maintained at 0°C. The resulting yellow solution was stirred for 1 h, then warmed to ambient temperature over an additional 1 h and immediately re-cooled to 0°C. A deoxygenated solution of ketone *ent*-**97** (19.8 mg, 0.096 mmol) in toluene (5 mL) was subsequently added, dropwise, to the reaction mixture, which was then heated at reflux for 1.5 h. The solvent was then removed from the cooled reaction mixture under a stream of nitrogen. Subjection of the ensuing light-yellow oil to flash chromatography (silica, pentane elution) afforded two fractions, A and B.

Concentration of fraction A ($R_f$ 0.6, pentane elution, anisaldehyde visualisation) afforded the title compound [*ent*-(–)-**54**][19] (6.3 mg, 100% at 32% conversion) as a clear, colourless oil.

**$^1$H NMR** (600 MHz) δ 4.82 – 4.81 (dddd, *J* 1.2, 1.2, 1.2 and 1.2 Hz, 1H), 4.78 – 4.76 (broad t, *J* 2.4 Hz, 1H), 2.60 (dt, *J* 11.4 and 8.4 Hz, 1H), 2.50 (ddt, partially obscured, *J* 15.0, 7.8 and 7.8 Hz, 1H), 2.46 (ddt, *J* 9.0, 6.6 and 2.4 Hz, 2H), 2.15 (ddd, *J* 14.4, 8.4 and 2.4 Hz, 1H), 1.73 (dtd, *J* 12.6, 9.0 and 6.0 Hz, 1H), 1.63 (ddd, *J* 20.4, 16.8 and 3.6 Hz, 1H), 1.48 – 1.43 (m, 1H), 1.42 (t, *J* 7.8 Hz, 2H), 1.25 (broad s, 1H), 1.20 (t, *J* 22.8 Hz, 1H), 1.05 (s, 3H), 1.02 (dd, *J* 25.2 and 15.6 Hz, 1H), 0.94 (s, 3H), 0.91 (s, 3H).

**$^{13}$C NMR** (75 MHz) δ 163.0 (C), 103.8 ($CH_2$), 56.3 (C), 53.8 (CH), 50.3 (CH), 49.3 ($CH_2$), 44.6 ($CH_2$), 42.2 (CH), 41.3 (C), 39.0 ($CH_2$), 31.3 ($CH_2$), 30.1 ($CH_3$), 27.6 ($CH_3$), 27.2 ($CH_2$), 23.6 ($CH_3$).

**IR** $\nu_{max}$ 3068, 2931, 2865, 1649, 1464, 1382, 1370, 1364, 876 cm$^{-1}$.

**Mass Spectrum** (EI, 70 eV) *m/z* 204 ($M^{+\cdot}$, 9%), 189 {[M – $CH_3^{\cdot}$]$^+$, 3}, 147 (4), 107 (4), 94 (100), 79 (34), 77 (9), 67 (4), 55 (4).

**HREIMS** Found: $M^{+\cdot}$, 204.1876. Calculated for $C_{15}H_{24}$ $M^{+\cdot}$, 204.1878.

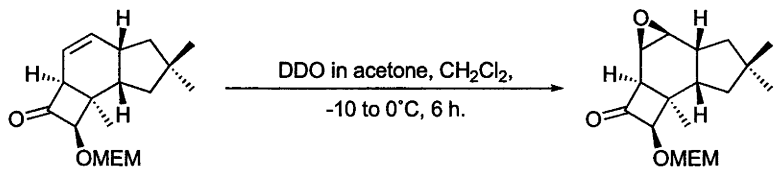
**Elemental Analysis** Found: C, 87.07; H, 12.62. $C_{15}H_{24}$ requires C, 88.16; H, 11.84%.

**Optical Rotation** $[\alpha]_D^{22}$ –26.0 (*c* 0.22, $CDCl_3$) {lit.[19] $[\alpha]_D^{20}$ –29.4 (*c* 1.0, *n*-pentane)}.

Concentration of fraction B ($R_f$ 0.1, pentane elution, anisaldehyde visualisation) afforded unreacted ketone *ent*-**97** (13.5 mg, 68% recovery) which was identical with material obtained as detailed earlier (Section 6.3, page 171)..

## 6.4 Experimental procedures for Chapter Four[20]

**(1a*R*,1b*R*,3*R*,3a*R*,3b*S*,6a*R*,6b*S*)-1a,1b,3,3a,3b,4,5,6,6a,6b-Decahydro-3-[(2-methoxyethoxy) methoxy]-3a,5,5-trimethyl-2*H*-cyclobut[6,7]indeno[4,5-*b*]oxirene-2-one (210)**




**60** **210**

Dimethyldioxirane (3.0 mL of an ~0.1 mol $L^{-1}$ solution in acetone, ~0.3 mmol)[21] was added in three 1.0 mL aliquots over 4 h to a magnetically stirred solution of cyclobutanone **60** (24.4 mg, 0.079 mmol) in $CH_2Cl_2$ (4 mL) maintained at between -10 – 0°C (dry ice - acetone). After a further 2 h the reaction mixture was concentrated under reduced pressure to afford a clear, colourless oil that was then subjected to flash column chromatography (silica; 2:23 → 1:4 ethyl acetate – hexane gradient elution). Concentration of the appropriate fractions ($R_f$ 0.2, 3:7 v/v ethyl acetate – hexane elution, phosphomolybdic acid visualisation) afforded the *title compound **210*** (13.6 mg, 53%) as a clear, colourless oil.[22]

**$^1$H NMR** (500 MHz) δ 4.81 (d, *J* 7.0 Hz, 1H), 4.73 (d, *J* 7.0 Hz, 1H), 4.41 (d, *J* 3.0 Hz, 1H), 3.80 (ddd, *J* 11.0, 5.5 and 3.0 Hz, 1H), 3.70 (ddd, *J* 11.0, 6.5 and 3.0 Hz, 1H), 3.61 - 3.53 (complex m, 2H), 3.39 (s, 3H), 3.33 (t, *J* 4.0 Hz, 1H), 3.19 (t, *J* 4.0 Hz, 1H), 3.07 (dd, *J* 4.5 and 1.5 Hz, 1H), 2.45 - 2.41 (complex m, 1H), 2.32 (dt, *J* 12.5 and 7.5 Hz, 1H), 1.84 (dd, *J* 13.5 and 9.0 Hz, 1H), 1.74 (t, *J* 12.5 Hz, 1H), 1.65 (dd, *J* 14.0 and 4.0 Hz, 1H), 1.37 (partially obscured dd, *J* 11.5 and 7.5 Hz, 1H), 1.36 (s, 3H), 1.13 (s, 3H), 1.02 (s, 3H).

**$^{13}$C NMR** (126 MHz) δ 207.0 (C), 96.1 ($CH_2$), 92.3 (CH), 71.9 ($CH_2$), 67.7 ($CH_2$), 59.3 ($CH_3$), 58.6 (CH), 56.9 (CH), 51.8 (CH), 45.8 ($CH_2$), 45.5 ($CH_2$), 37.4 (CH), 37.0 (C), 36.0 (C and CH signals overlapping), 31.5 ($CH_3$), 30.7 ($CH_3$), 28.5 ($CH_3$).

**IR** $\nu_{max}$ 2952, 2933, 2891, 2868, 2819, 1780, 1450, 1364, 1242, 1199, 1171, 1129, 1101, 1075, 1054, 1031, 1013, 970, 889, 851, 832 $cm^{-1}$.

**Mass Spectrum** (EI, 70 eV) *m/z* 324 ($M^{+\cdot}$, <1%), 309 {$[M - CH_3\cdot]^+$, <1%}, 217 (11), 161 (15), 107 (11), 105 {$[CH_3O(CH_2)_2OCH_2O\cdot]^+$, 13}, 95 (18), 89 {$[CH_3O(CH_2)_2OCH_2\cdot]^+$, 98}, 59 {$[CH_3O(CH_2)_2\cdot]^+$, 100}, 55 (12).

**HREIMS** Found: $M^{+\cdot}$, 324.1931. Calculated for $C_{18}H_{28}O_5$ $M^{+\cdot}$, 324.1937.

**Elemental Analysis** Found: C, 66.31; H, 8.62. $C_{18}H_{28}O_5$ requires C, 66.64; H, 8.70%.

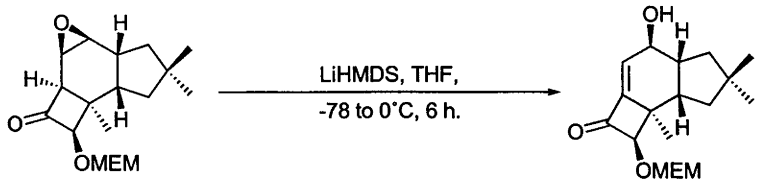
**Optical Rotation** $[\alpha]_D^{22}$ +134.6 (*c* 0.06).

20 Protocols for compounds shared in common by both Chapters Three and Four are detailed in Section 6.3.

21 Prepared according to the procedure of Adam, W.; Bialas, J.; Hadjiarapoglou, L., *Chem. Ber.*, **1991,** *124* 2377.

22 Traces of the other diastereoisomeric isomer of epoxide **210** were also detected, although not in sufficient quantities to allow for characterisation.

**(1*R*,4*S*,4a*R*,7a*S*,7b*R*)-1,4,4a,5,6,7,7a,7b-Octahydro-4-hydroxy-1-[(2-methoxyethoxy) methoxy]-6,6,7b-trimethyl-2*H*-cyclobut[*e*]indene-2-one (211)**




**210** **211**

LiHMDS (21 $\mu$L of a 1.0 mol $L^{-1}$ solutiuon in THF, 0.02 mmol) was added to a magnetically stirred solution of epoxide **210** (6.1 mg, 0.02 mmol) in THF (2 mL) maintained at -78°C. The resulting mixture was allowed to stand at this temperature for 2 h and then gradually warmed to 0°C over 4 h. The reaction mixture was subsequently quenched by the dropwise addition of $NH_4Cl$ (0.5 mL of a saturated aqueous solution) which caused LiCl to precipitate. The salt was redissolved by addition of $H_2O$ (0.5 mL) and the biphasic system was diluted with ethyl acetate (2 mL). The separated aqueous phase was then extracted with ethyl acetate (5 × 2 mL) and combined organic phases were dried ($Na_2SO_4$), filtered and concentrated under reduced pressure to afford a clear, colourless oil. This material was subjected to preparative layer chromatography (silica; 1:9 v/v ethyl acetate – hexane elution, phosphomolybdic acid visualisation) to afford two bands, A and B.

Extraction of band A ($R_f$ 0.2, 3:7 v/v ethyl acetate – hexane elution, UV and phosphomolybdic acid visualisation) with ethyl acetate (5 × 2 mL) and concentration of the filtrate afforded unreacted epoxide **210** (1.4 mg, 23% recovery) identical, in all respects, with authentic material.

Extraction of band B ($R_f$ 0.1, 3:7 v/v ethyl acetate – hexane elution, UV and phosphomolybdic acid visualisation) with ethyl acetate (5 × 2 mL) and concentration of the filtrate afforded the *title compound **211*** (3.3 mg, 69% at 77% conversion) as a clear, colourless oil.

**$^1$H NMR** (500 MHz) δ 7.15 (d, *J* 6.5 Hz, 1H), 5.38 (s, 1H), 5.06 (d, *J* 7.0 Hz, 1H), 4.75 (d, *J* 7.0 Hz, 1H), 4.44 – 4.41 (m, 1H), 3.77 (ddd, *J* 11.0, 5.5 and 3.5 Hz, 1H), 3.66 (ddd, *J* 11.0, 5.5 and 3.5 Hz, 1H), 3.60 – 3.53 (m, 2H), 3.40, (s, 3H), 2.99 (td, *J* 12.5 and 7.5 Hz, 1H), 2.38 – 2.31 (m, 1H), 1.72 (dd, *J* 12.5 and 10.0 Hz, 1H), 1.60 – 1.50 (m, partially obscured, 1H), 1.51 (ddd, *J* 12.5, 8.5 and 2.0 Hz, 1H), 1.36 – 1.28 (complex m, partially obscured, 1H), 1.30 (s, 3H), 1.16 (s, 3H), 1.01 (s, 3H) ppm (signal due to OH not observed).
**$^{13}$C NMR** (126 MHz) δ 209.6 (C), 139.7 (C), 137.0 (CH), 105.7 ($CH_2$), 93.4 (CH), 71.8 ($CH_2$), 68.1 ($CH_2$), 65.0 (CH), 59.4 ($CH_3$), 44.7 (C), 43.1(4) ($CH_2$), 43.0(6) ($CH_2$), 41.0 (C), 40.2 (CH), 36.7 (CH), 30.0 ($CH_3$), 27.7 ($CH_3$), 24.0 ($CH_3$).

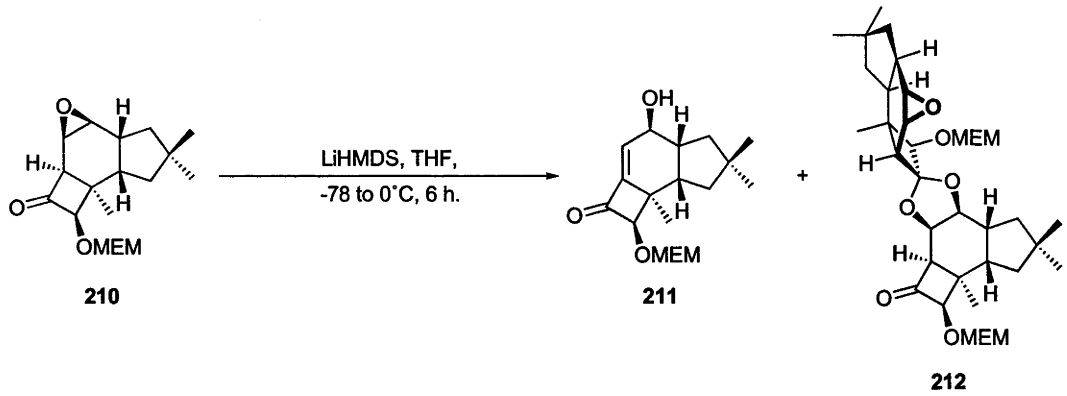
**IR** $\nu_{max}$ 3472, 2953, 2918, 2869, 2849, 1774, 1464, 1312, 1221, 1173, 1119, 1098, 1051, 1028, 977, 925, 875, 734 $cm^{-1}$.

**Mass Spectrum** (EI, 70 eV) *m/z* 279 {[M – $CH_3OCH_2\cdot]^+$, 7%}, 235 {[M – $CH_3O(CH_2)_2OCH_2\cdot]^+$, 25}, 206 {[M – $CH_3O(CH_2)_2OCH_2OCH\cdot]^+$, 100}, 191 (37), 161 (20), 150 (20), 149 (20), 138 (36), 122 (21), 121 (18), 89 {$[CH_3O(CH_2)_2OCH_2\cdot]^+$, 68}, 59 {$[CH_3O(CH_2)_2\cdot]^+$, 80}.

**HREIMS** Found: [M – $CH_3O(CH_2)_2OCH_2\cdot]^+$, 235.1341; [M – $CH_3O(CH_2)_2OCH_2OCH\cdot]^+$, 206.1307. Calculated for $C_{18}H_{28}O_5$ [M – $CH_3O(CH_2)_2OCH_2\cdot]^+$, 235.1334;
[M – $CH_3O(CH_2)_2OCH_2OCH\cdot]^+$, 206.1307.

**Optical Rotation** $[\alpha]_D^{26}$ +278.2 (*c* 0.03).

**(1'a*R*,1'b*R*,2*R*,3'*R*,3a*R*,3'a*R*,3b*R*,3'b*S*,5*R*,5a*R*,5b*S*,6'a*R*,6'b*S*,8a*R*,8b*S*)-1'a,1'b,3',3a,3'a,3b,3'b,4',5,5',5a,5b,6,6',6'a,6'b,7,8,8a,8b-Dodecahydro-3',5-*bis*[(2-methoxyethoxy)methoxy]-3'a,5',5',5a,7,7-hexamethyl-spiro{4*H*-cyclobut[6,7]indeno[4,5-*b*]-1,3-dioxole-2,2'-(2*H*)-cyclobut[6,7]indeno[4,5-*b*]oxirane}-4-one (212)**




**210** **211** **212**

LiHMDS (88 $\mu$L of a 1.0 mol $L^{-1}$ solutiuon in THF, 0.09 mmol) was added to a magnetically stirred solution of epoxide **210** (11.8 mg, 0.04 mmol) in THF (4 mL) maintained at -78°C. The resulting mixture was allowed to stand at this temperature for 2 h and then gradually warmed to 0°C over 4 h. The system was subsequently quenched by the dropwise addition of $NH_4Cl$ (0.5 mL of a saturated aqueous solution) which caused LiCl to precipitate. The salt was redissolved by dropwise addition of $H_2O$ (0.5 mL) and the biphasic system was diluted with ethyl acetate (2 mL). The separated aqueous phase was then extracted with ethyl acetate (5 × 2 mL) and combined organic phases were dried ($Na_2SO_4$), filtered and concentrated under reduced pressure to afford a clear, colourless oil. This material was subjected to preparative layer chromatography (silica; 1:9 v/v ethyl acetate – hexane elution, phosphomolybdic acid visualisation) to afford two bands, A and B.

Extraction of band A ($R_f$ 0.1, 3:7 v/v ethyl acetate – hexane elution, phosphomolybdic acid visualisation) with ethyl acetate (5 × 2 mL) and concentration of the filtrate afforded the allylic alcohol **211** (2.1 mg, 18%) identical, in all respects, with material obtained as detailed earlier (Section 6.4, page 177).

Extraction of band B ($R_f$ 0.3, 1:1 v/v ethyl acetate – hexane elution, UV and phosphomolybdic acid visualisation) with ethyl acetate (5 × 2 mL) and concentration of the filtrate afforded the *title compound 212* (2.9 mg, 49%) as a clear, colourless oil.

**$^1$H NMR** (500 MHz) δ 4.79 (s, 2H), 4.73 (d, *J* 7.0 Hz, 1H), 4.63 (d, *J* 7.0 Hz, 1H), 4.48 (d, *J* 2.5 Hz, 1H), 4.46 (d, *J* 6.5 Hz, 1H), 4.03 (q, *J* 3.5 Hz, 1H), 3.81 - 3.72 (complex m, 2H), 3.68 (dd, *J* 5.5 and 4.0 Hz, 2H), 3.65 (d, *J* 3.0 Hz, 1H), 3.58 - 3.53 (complex m, 4H), 3.39 (s, 3H), 3.38 (s, 3H), 3.28 (dd, *J* 4.0 and 2.0 Hz, 1H), 3.17 (t, *J* 3.5 Hz, 1H), 2.82 (d, *J* 2.0 Hz, 1H), 2.76 - 2.71 (complex m, 1H), 2.61 (t, *J* 2.5 Hz, 1H), 2.54 (ddd, *J* 13.5, 9.0 and 7.0 Hz, 1H), 2.10 - 2.04 (m, 1H), 2.02 - 1.97 (m, 1H), 1.83 (dd, *J* 14.0 and 11.0 Hz, 2H), 1.72 (s, 1H), 1.70 (d, *J* 3.0 Hz, 1H),

1.64 (dd, *J* 13.5 and 4.0 Hz, 1H), 1.53 (s, 3H), 1.47 - 1.37 (m, 2H), 1.23 (dd, *J* 11.5 and 6.5 Hz, 1H), 1.15 (s, 3H), 1.14 (s, 3H), 1.09 (s, 3H), 1.01 (s, 3H), 0.97 (s, 3H).

**$^{13}$C NMR** (126 MHz) δ 202.8 (C), 105.0 (C), 96.0 ($CH_2$), 95.6 ($CH_2$), 92.1 (CH), 88.5 (CH), 75.3 (CH), 71.9(2) ($CH_2$), 71.8(7) ($CH_2$), 71.7 (CH), 67.9 ($CH_2$), 67.6 ($CH_2$), 60.4 (CH), 59.4 ($CH_3$), 58.4 (CH), 53.7 (CH), 47.2 (CH), 45.5(1) ($CH_2$), 45.4(5) ($CH_2$), 45.2 ($CH_2$), 43.8 ($CH_2$), 39.5 (CH), 36.7 (C), 36.4 (CH), 36.1 (C), 35.8 (C), 35.7(0) (C), 35.6(9) (CH), 33.3 (CH), 30.9 ($CH_3$), 30.6 ($CH_3$), 30.5 ($CH_3$), 30.0 ($CH_3$), 27.2 ($CH_3$), 27.0 ($CH_3$).

**IR** $\nu_{max}$ 2952, 2932, 2868, 2819, 1779, 1466, 1380, 1365, 1286, 1266, 1240, 1192, 1130, 1100, 1063, 1025, 1007, 954, 935, 861, 819 $cm^{-1}$.

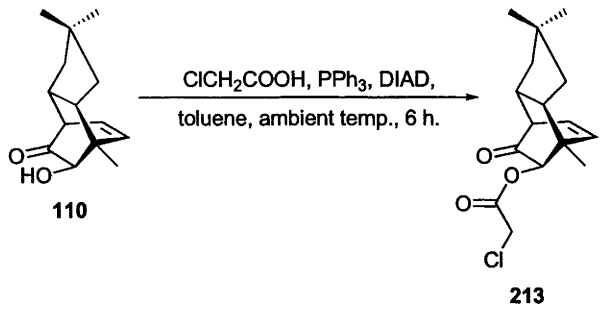
**Mass Spectrum** (EI, 70 eV) *m/z* 648 ($M^{+\cdot}$, <1%), 559 {[M – $CH_3O(CH_2)_2OCH_2\cdot]^+$, <1}, 543 {[M – $CH_3O(CH_2)_2OCH_2O\cdot]^+$, <1}, 374 (6), 331 (27), 289 (80), 191 (22), 163 (19), 161 (18), 117 (34), 89 {$[CH_3O(CH_2)_2OCH_2\cdot]^+$, 100}, 73 (33), 59 {$[CH_3O(CH_2)_2\cdot]^+$, 93}.

**HREIMS** Found: $M^{+\cdot}$, 648.3892. Calculated for $C_{36}H_{56}O_{10}$ $M^{+\cdot}$, 648.3873.

**Elemental Analysis** Found: C, 66.60; H, 8.49. $C_{36}H_{56}O_{10}$ requires C, 66.64; H, 8.70%.

**Optical Rotation** $[\alpha]_D^{23}$ +84.8 (*c* 0.21).

**(3a*S*,4*R*,7*S*,7a*R*,9*R*)-2,3,3a,4,7,7a-Hexahydro-2,2,4-trimethyl-8-oxo-4,7-ethano-1*H*-indene-9-chloroacetic acid ester (213)**




110 213

DIAD (62 μL of a 95% solution, 0.30 mmol) was added, dropwise, to a magnetically stirred solution of acyloin **110** (33 mg, 0.15 mmol), chloroacetic acid (125 mg, 1.33 mmol) and triphenyl phosphine (117 mg, 0.45 mmol) in toluene (7.5 mL) maintained at ambient temperature. After 2 h the colourless solution was treated, dropwise, with an additional aliquot of DIAD (62 μL of a 95% solution, 0.30 mmol)and again, after a further 2 h, with a third aliquot of DIAD (31 μL of a 95% solution, 0.15 mmol). After a further 2 h, the reaction mixture was concentrated under reduced pressure to afford a clear, colourless oil. Subjection of this material to flash chromatography on silica (1:9 - 1:4 ethyl acetate – hexane elution) caused significant decomposition of the ester,[23] as indicated by analytical TLC (3:7 v/v ethyl acetate – hexane elution, phosphomolybdic acid visualisation). Nevertheless, concentration of the appropriate fractions ($R_f$ 0.5) afforded spectroscopically-pure samples of the *title compound **213*** (10 mg, 22%) as a clear, colourless oil.

**$^1$H NMR** (500 MHz) δ 6.21 – 6.18 (m, 1H), 6.12 (broad d, *J* 8.5 Hz, 1H), 4.92 (s, 1H), 4.16 (s, 2H), 3.11 (ddd, *J* 6.5, 2.5 and 1.5 Hz, 1H), 2.68 – 2.56 (complex m, 2H), 1.55 (ddd, *J* 12.5, 7.5 and 2.5 Hz, 1H), 1.50 (ddd, *J* 12.5, 8.0 and 2.0 Hz, 1H), 1.16 (dd, partially obscured, *J* 12.0 and 10.5 Hz, 1H), 1.14 (s, 3H), 1.03 – 0.98 (m, partially obscured, 1H), 1.00 (s, 3H), 0.92 (s, 3H).
**$^{13}$C NMR** (126 MHz) δ 205.7 (C), 167.4 (C), 139.3 (CH), 129.1 (CH), 75.5 (CH), 51.7 (CH), 45.0 (C), 44.7 ($CH_2$), 44.1 ($CH_2$), 44.0 (CH), 42.3 (CH), 41.0 ($CH_2$), 39.6 (C), 28.6 ($CH_3$), 27.8 ($CH_3$), 18.9 ($CH_3$).
**IR** $\nu_{max}$ 3041, 2954, 2934, 2856, 1769, 1744, 1461, 1411, 1383, 1366, 1330, 1302, 1283, 1259, 1164, 1130, 1091, 1031, 1017, 937, 793, 707 $cm^{-1}$.
**Mass Spectrum** (EI, 70 eV) *m/z* 298 {$[C_{16}H_{21}O_3{}^{37}Cl]^{+\cdot}$, 2%}, 296 {$[C_{16}H_{21}O_3{}^{35}Cl]^{+\cdot}$, 6}, 283 {$[C_{16}H_{21}O_3{}^{37}Cl - CH_3\cdot]^+$, <1}, 281 {$[C_{16}H_{21}O_3{}^{35}Cl - CH_3\cdot]^+$, 2}, 220 (9), 207 (31), 202 (38), 174 (61), 162 (100), 159 (56), 147 (35), 118 (32), 106 (46), 105 (38), 96 (28), 91 (55), 81 (77), 80 (53).

23 Cleavage of chloroacetate (with accompanying migration) has been observed before during chromatography on silica: Pozsgay, V., *J. Am. Chem. Soc.*, **1995**, *117*, 6673.

**HREIMS** Found: $[C_{16}H_{21}O_3{}^{35}Cl]^{+\cdot}$, 296.1193. Calculated for $C_{16}H_{21}ClO_3$ $[C_{16}H_{21}O_3{}^{35}Cl]^{+\cdot}$, 296.1179.

**Elemental Analysis** Found: C, 65.06; H, 7.22, Cl, 11.89. $C_{16}H_{21}ClO_3$ requires C, 64.75; H, 7.13; Cl, 11.95%.

**Optical Rotation** $[\alpha]_D^{25}$ +38.4 (*c* 0.97).

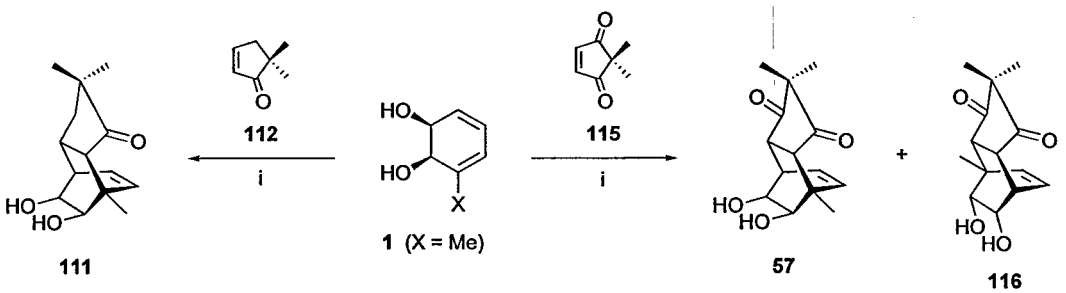
## A.1 Appendix one

*Appendices*

# *Fold-out Schemes, X-ray Crystal Structure Reports and Publications*

## A.1 Appendix one

**Fold-out Scheme 1:** *Initial synthetic approaches to* ent-*(–)-hirsutene [*ent-*(–)-54]: Diels-Alder cycloaddition studies.*

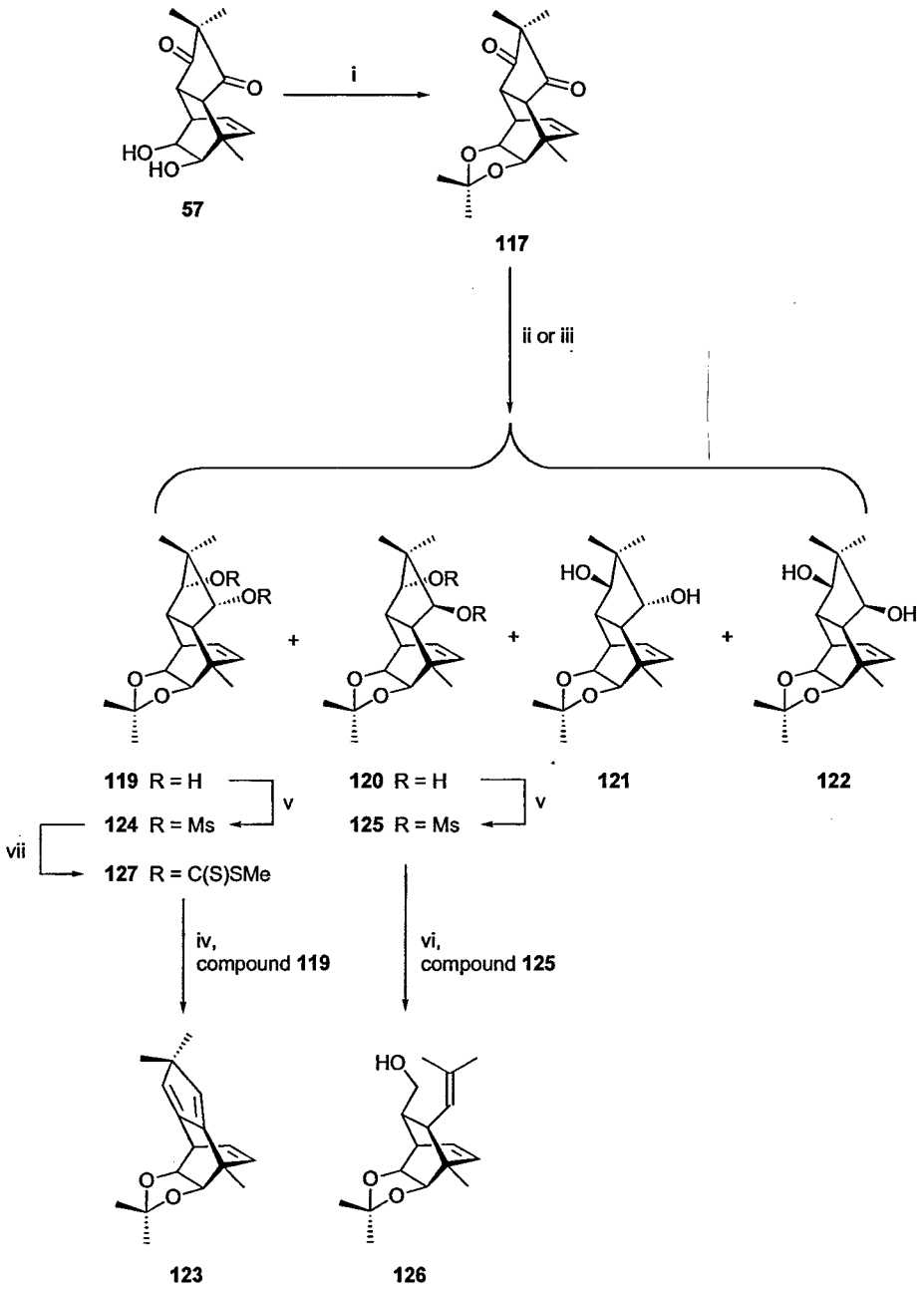



*Reagents and conditions*: i) 19 kbar, $CH_2Cl_2$, ambient temp., 24 h.

## A.2 Appendix two

## A.2 Appendix two

**Fold-out Scheme 2:** *Initial synthetic approaches to* ent-*(–)-hirsutene [*ent-*(–)-54]: attempted methods of deoxygenation.*

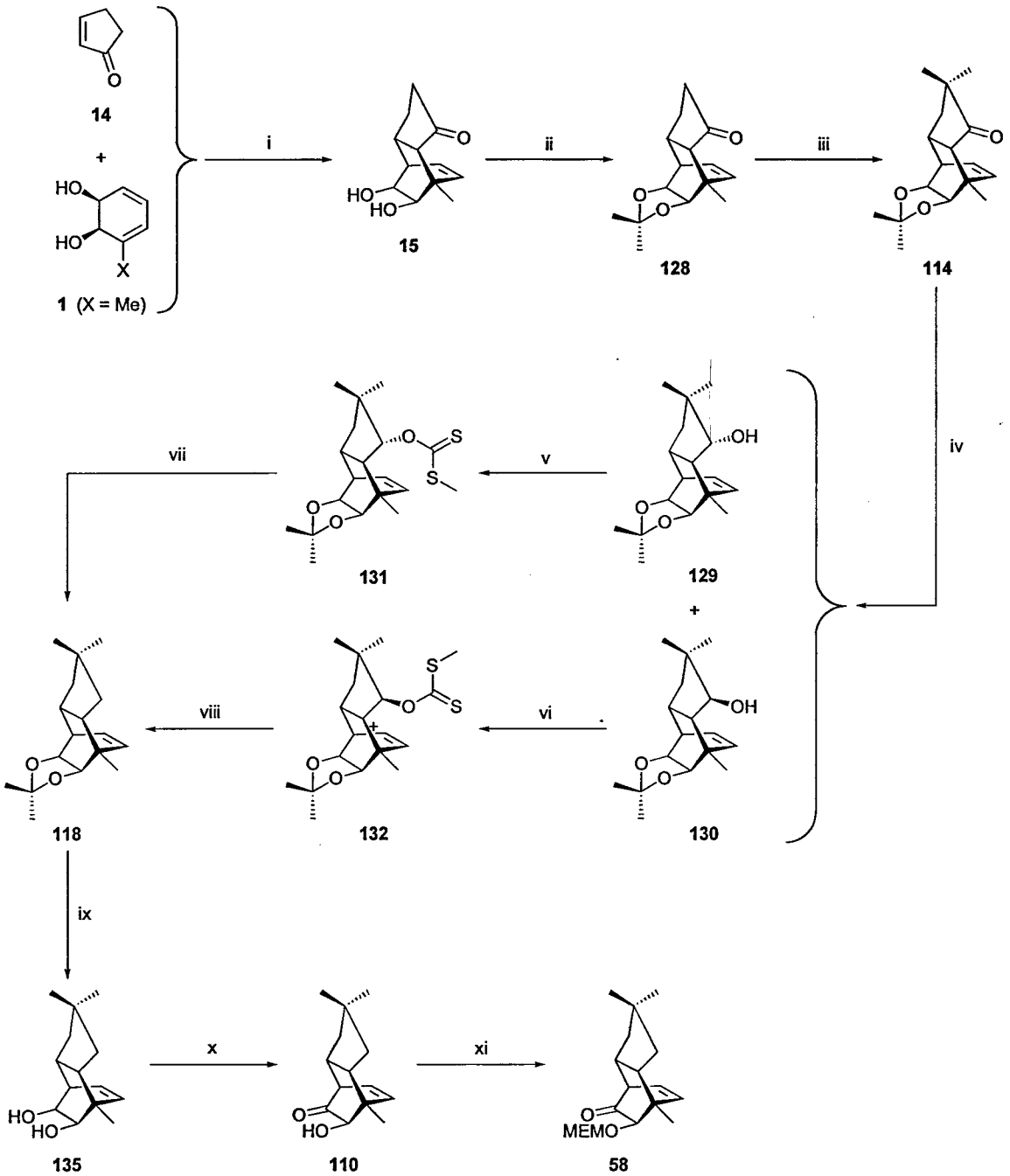



*Reagents and conditions*: i) 2,2-DMP, *p*-TsOH.$H_2O$, $CH_2Cl_2$, ambient temp., 24 h; ii) DIBAL-H in hexanes, THF, -78°C to ambient temp., 6 h; iii) $LiAlH_4$, THF, ambient temp. to reflux, 48 h; iv) $Tf_2O$, 2,6-lutidine, $CH_2Cl_2$, 0°C to ambient temp., 48 h, then $NEt_3$, aqueous workup.; v) MsCl, pyridine, $NEt_3$, $CH_2Cl_2$, 0°C to ambient temp., 73 h; vi) $LiEt_3BH$, THF, ambient temp. to reflux, 4 h; vii) NaH, imidazole, THF, ambient temp., 1 h, then $CS_2$, ambient temp., 1 h, then MeI, ambient temp., 16 h.

## A.3 Appendix three

## A.3 Appendix three

**Fold-out Scheme 3:** *Initial stages of the total synthesis of* ent-*(–)-hirsutene [*ent-*(–)-**54**].*

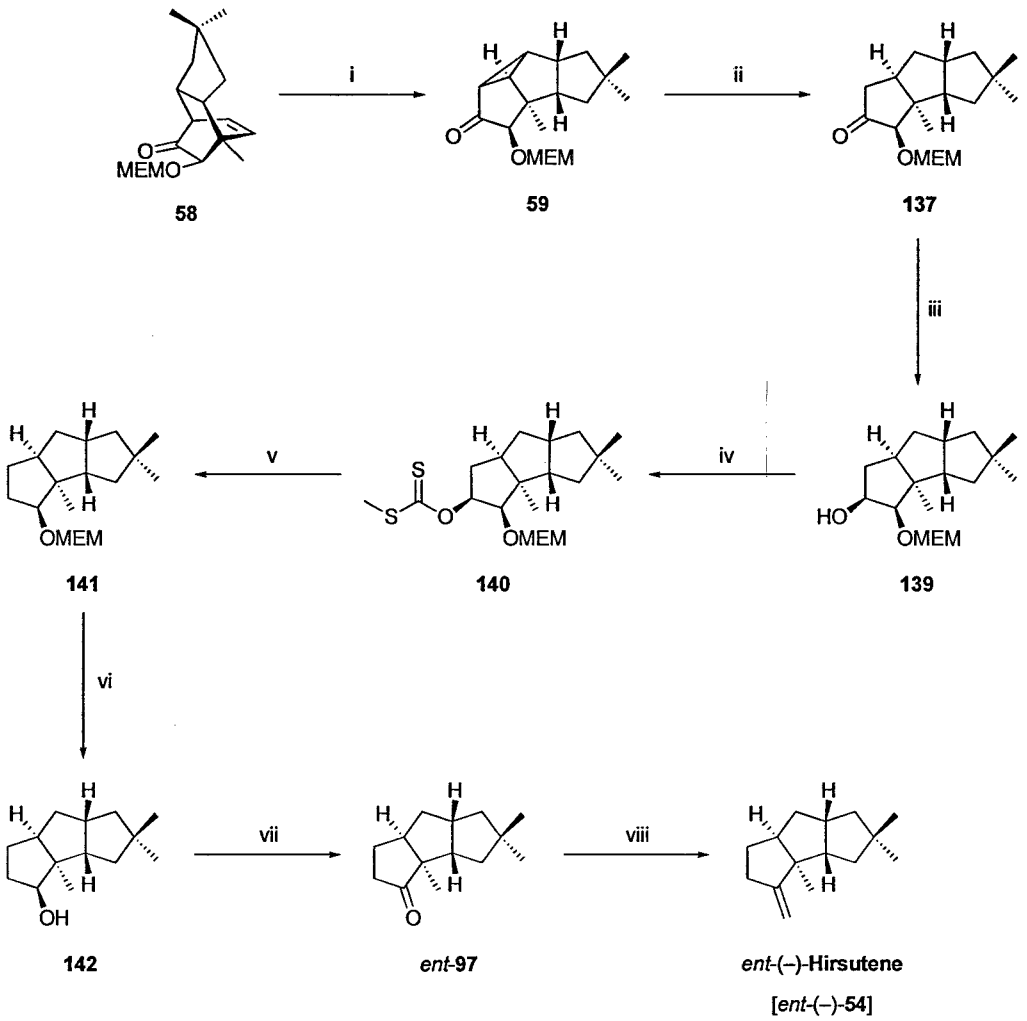



*Reagents and conditions*: i) 19 kbar, $CH_2Cl_2$, ambient temp. 24 h; ii) 2,2-DMP, *p*-TsOH.$H_2O$, $CH_2Cl_2$, 0°C to ambient temp., 75 h; iii) LiHMDS, THF, 0°C to ambient temp., 2 h, then MeI, 0°C to ambient temp., 2 h; iv) $LiAlH_4$, THF, 0°C to 50°C, 24 h; v) NaH, THF, 0°C to reflux, 20 h, then $CS_2$, ambient temp. to reflux, 18 h, then MeI, ambient temp. to reflux, 8 h; vi) NaH, THF, 0°C to reflux, 6 h, then $CS_2$, ambient temp. to reflux, 13 h, then MeI, ambient temp. to reflux, 8 h; vii) *n*-$Bu_3SnH$, AIBN, toluene, ambient temp. to reflux, 3 h; viii) *n*-$Bu_3SnH$, AIBN, toluene, ambient temp. to reflux, 18 h; ix) $CH_3COOH$:$H_2O$ 3:2, THF, 60°C, 48 h; x) 4-AcNH-TEMPO, *p*-TsOH.$H_2O$, $CH_2Cl_2$, 0°C to ambient temp., 23 h; xi) MEM-Cl, Hünig's base, $CH_2Cl_2$, ambient temp., 16 h.

## A.4 Appendix four

# A.4 Appendix four

**Fold-out Scheme 4:** *Final stages of the total synthesis of* ent-*(–)-hirsutene [*ent-*(–)-54].*

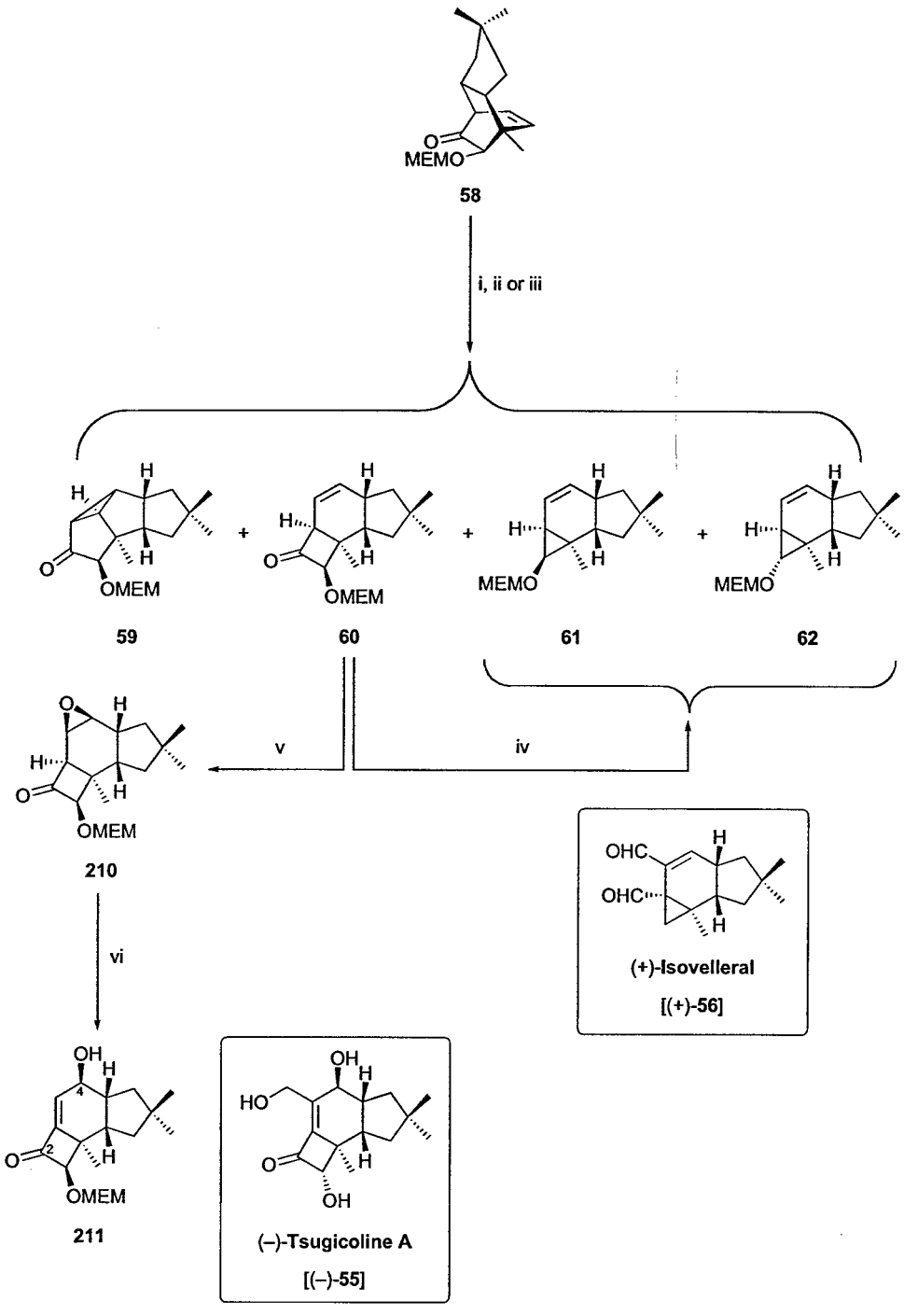



*Reagents and conditions*: i) *h*ν (125 W Philips HPL-N lamp), UV filter [$\lambda_{transmission}$ >340 nm, thickness >10 mm, NaBr 750 $gL^{-1}$, $Pb(NO_3)_2$ 8 $gL^{-1}$], acetone, acetophenone, 0°C to 10°C, 32 h; ii) *n*-$Bu_3SnH$, AIBN, benzene, ambient temp. to reflux, 9 h; iii) $NaBH_4$, ambient temp., 3 h; iv) NaH, THF, reflux, 3 h, then $CS_2$, 0°C to reflux, 3 h, then MeI, 0°C to reflux, 3 h; v) *n*-$Bu_3SnH$, AIBN, toluene, ambient temp. to reflux, 2 h; vi) PPTS, *t*-BuOH, reflux, 8 h; vii) PCC, $CH_2Cl_2$, ambient temp., 16 h; viii) $Ph_3PMe$, KHMDS, toluene, 0°C to ambient temp., 2 h, then *ent*-**97** in toluene, 0°C to reflux, 1.5 h.

## A.5 Appendix five

## A.5 Appendix five

**Fold-out Scheme 5:** *Towards the synthesis of (–)-tsugicoline A [(–)-55] and (+)-isovelleral [(+)-56].*



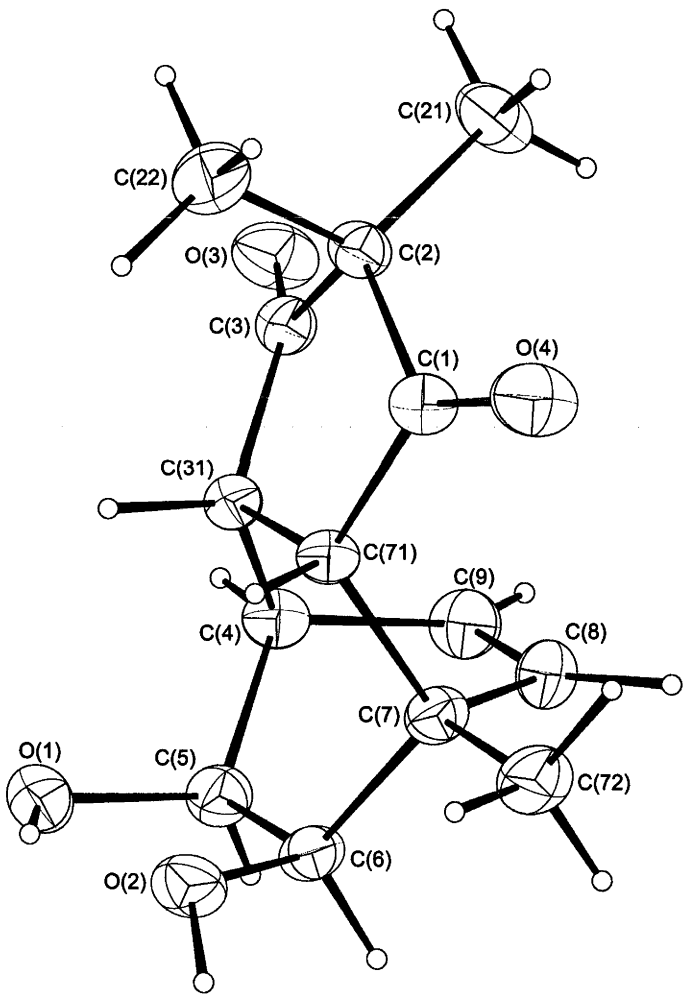

*Reagents and conditions*: i) *hν* (125 W Philips HPL-N lamp), UV filter [$\lambda_{transmission}$ >340 nm, thickness >10 mm, NaBr 750 $gL^{-1}$, $Pb(NO_3)_2$ 8 $gL^{-1}$], acetone, acetophenone, 0°C to 10°C, 32 h; ii) *hν* (125 W Philips HPL-N lamp), benzene, 6°C – 10°C, 5 min.; iii) *hν* (125 W Philips HPL-N lamp), benzene, 6°C – 10°C, 10 h; iv) *hν* (125 W Philips HPL-N lamp), benzene, 6°C – 10°C, 3 h; v) dimethyldioxirane (~0.1 $molL^{-1}$ in acetone), $CH_2Cl_2$, -10°C – 0°C, 6 h; vi) LiHMDS, THF, -78°C – 0°C, 6 h.

# A.6 Appendix six

## X-ray crystal structure report for compound 57

*A full X-ray crystallographic report for compound 57 (as compiled by Dr. A. J. Edwards of the Australian National University) is provided in PDF-format[1] on the compact-disc found on the inside back-cover of this Thesis.*

X-ray report 57.pdf



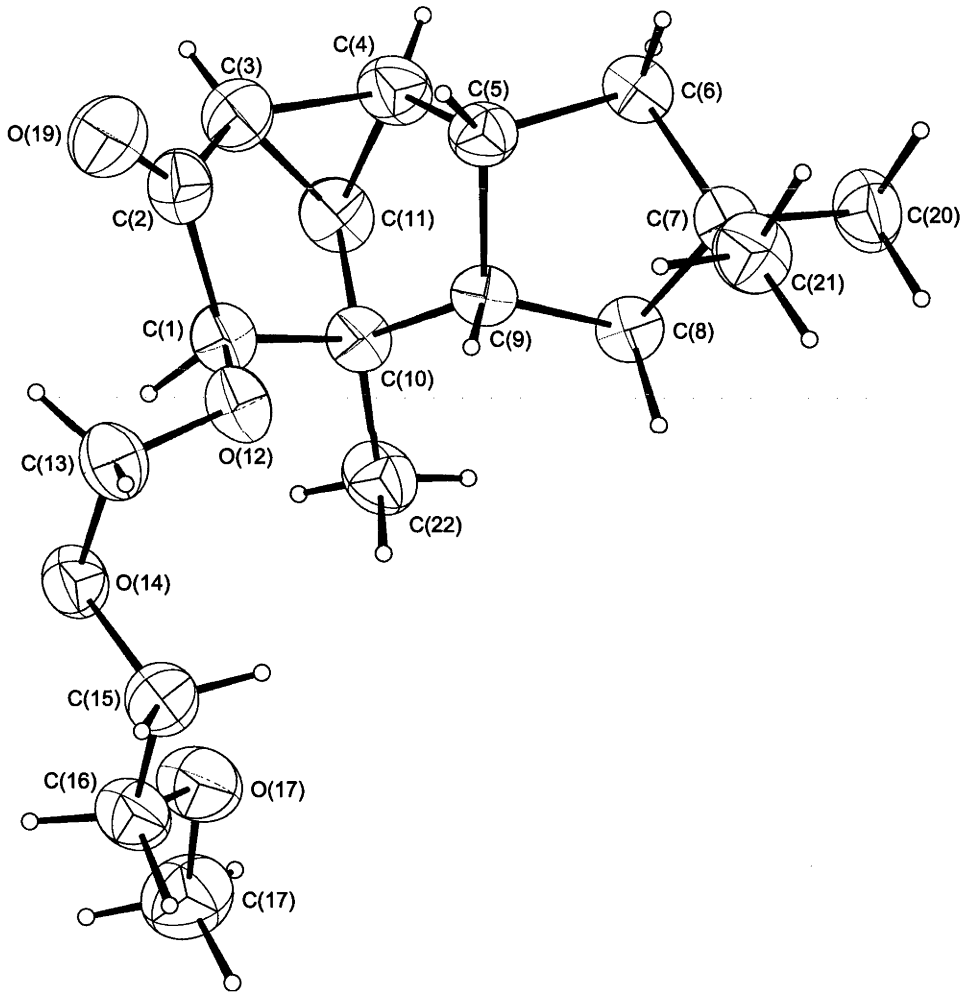

1 PDF-format files can be viewed on most major operating systems using Adobe Acrobat Reader 6.0, which is free software available online at http://www.adobe.com/products/acrobat/readstep2.html.

## A.7 Appendix seven

### X-ray crystal structure report for compound 59

*A full X-ray crystallographic report for compound **59** (as compiled by Dr. A. J. Edwards of the Australian National University) is provided in PDF-format[1] on the compact-disc found on the inside back-cover of this Thesis.*

X-ray report 59.pdf

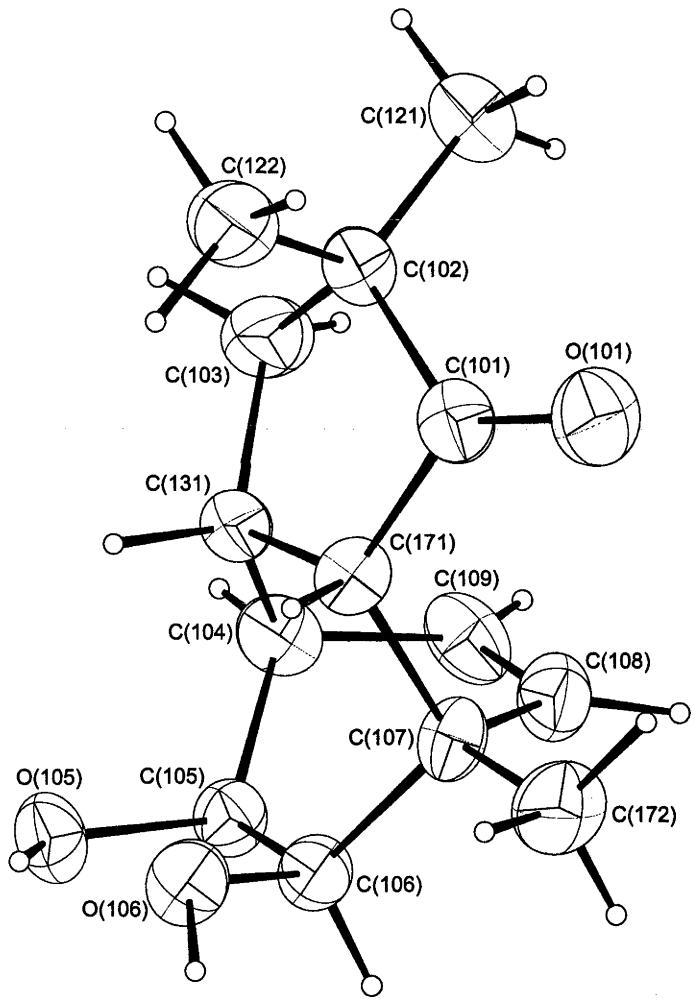


# A.8 Appendix eight

## X-ray crystal structure report for compound 111

*A full X-ray crystallographic report for compound **111** (as compiled by Dr. A. J. Edwards of the Australian National University) is provided in PDF-format[1] on the compact-disc found on the inside back-cover of this Thesis.*

X-ray report 111.pdf

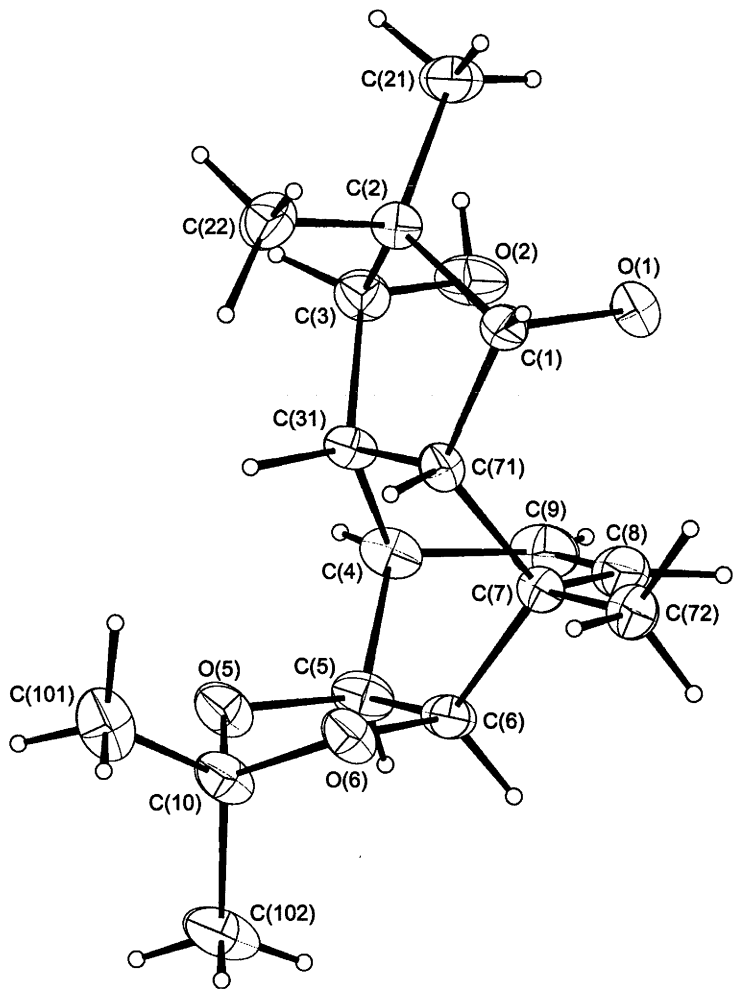


# A.9 Appendix nine

## X-ray crystal structure report for compound 119

*A full X-ray crystallographic report for compound **119** (as compiled by Dr. A. J. Edwards of the Australian National University) is provided in PDF-format[1] on the compact-disc found on the inside back-cover of this Thesis.*

X-ray report 119.pdf



# A.10 Appendix ten

## Publications

*The following list chronologically details the publications that have resulted from research performed during the candidature of the Doctor of Philosophy. Full copies of each of the publications are provided in PDF-format[1] on the compact-disc found on the inside back-cover of this Thesis.*

Publication 01.pdf — Banwell, M. G.; Edwards, A. J.; Harfoot, G. J.; Jolliffe, K. A., A chemoenzymatic synthesis of (–)-hirsutene from toluene, *Journal of the Chemical Society, Perkin Transactions 1*, **2002**, 2439.

Publication 02.pdf — Banwell, M. G.; Edwards, A. J.; Harfoot, G. J.; Jolliffe, K. A.; McLeod, M. D.; McRae, K. J.; Stewart, S. G.; Vögtle, M., Chemoenzymatic methods for the enantioselective preparation of sesquiterpenoid natural products from aromatic precursors, *Pure and Applied Chemistry*, **2003**, *75*, 223.

Publication 03.pdf — Banwell, M. G.; Edwards, A. J.; Harfoot, G. J.; Jolliffe, K. A., A chemoenzymatic synthesis of the linear triquinane (–)-hirsutene and identification of possible precursors to the naturally occurring (+)-enantiomer, *Tetrahedron*, **2004**, *60*, 535.

Publication 04.pdf — Banwell, M. G.; Harfoot, G. J., A chemoenzymatic and enantioselective route to the tricyclic frameworks associated with the protoilludane and marasmane classes of sesquiterpene, *Australian Journal of Chemistry*, **2004**, *57*, 895.