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Studies towards the total synthesis of dictyoxetane

by

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To Denise & Denise-Eleni

Abstract

Dictyoxetane, a structurally novel diterpene isolated from the brown algae, *Dictyota dichotoma*, is related to the dollabellane class of natural products. Dictyoxetane contains a dioxatricyclic subunit that has never been encountered in any other natural product. This thesis describes studies towards a first total synthesis of dictyoxetane, based on a proposed intramolecular Paternò-Büchi [2+2] photocyclisation reaction between a ketone and a cyclic enol ether to generate the oxetane heterocycle of the natural product.

Chapter 1 introduces the dolabellanes, their proposed biosynthesis and biological activities. The isolation, structure and proposed biosynthesis of dictyoxetane are discussed, along with existing synthetic studies towards the core dioxatricyclic ring system. Key aspects of the Paternò-Büchi reaction of alkenes with carbonyl compounds are presented.

In Chapter 2 a model system, designed to test the key Paternò-Büchi [2+2] photocyclisation reaction, is proposed, based on the use of isopulegol as a readily available starting material. A number of strategies are investigated for the overall conversion of the double bond of isopulegol into a six-membered ring enol ether. A successful route based on epoxide ring-opening and intramolecular addition of a tertiary alcohol across a triple bond allows for preliminary studies into the photocyclisation reaction to be performed.

Chapter 3 describes studies towards the synthesis of the [4.3.0]-*trans*-hydrindane ring system contained within dictyoxetane, a structural feature that has yet to be addressed in the literature. γ-Functionalisation of the enone in **241** is achieved through acetal protection with concomitant double bond migration. Stereoselective hydroboration, epoxidation and dihydroxylation of the resulting double bond are demonstrated in approaches towards installation of the *trans*-ring junction. An alternative approach to an appropriately functionalized *trans*-hydrindane, based on conjugate addition-enolate trapping of 3-methylcyclopentenone, is also described.

Chapter 4 contains the experimental procedures and analytical data of all compounds prepared during the course of this study.

Abbreviations

α	observed optical rotation in degrees
Å	angstrom(s)
Ac	acetyl
acac	acetylacetonate
AIBN	2,2′-azobisisobutyronitrile
anhyd	anhydrous
AO	atomic orbital
ap	apparent
aq	aqueous
Ar	aryl
atm	atmosphere(s)
9-BBN	9-borabicyclo[3.3.1]nonyl
Bn	benzyl
bp	boiling point
br	broad (spectral)
BR	birdical
Bu, *n*-Bu	normal (primary) butyl
^{t}Bu	*tert*-butyl
Bz	benzoyl (not benzyl)
°C	degrees Celsius
calcd	calculated

cat	catalytic
Cbz	benzyloxycarbonyl
cm	centimeter(s)
cm–1	wavenumber(s)
m-CPBA	*meta*-chloroperoxybenzoic acid
Cy	cyclohexyl
δ	chemical shift in parts per million
d	doublet (spectral)
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DIBAL-H	diisobutylaluminum hydride
DMAP	4-(*N*,*N*-dimethylamino)pyridine
DMDO	dimethyldioxirane
DMF	dimethylformamide
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-
DMSO	dimethyl sulfoxide
dr	diastereomeric ratio
E	energy
E^+	electrophile
ED50	dose effective in 50% of test subjects
EDG	electron donating group
EDTA	ethylenediaminetetraacetic acid
EI	electron impact
ee	enantiomeric excess
eq	equivalent

ESI	electrospray ionization
Et	ethyl
EWG	electron withdrawing group
Fmoc	9-fluorenylmethoxycarbonyl
FT	Fourier transform
g	gram(s)
GC	gas chromatography
h	hour(s)
HMBC	heteronuclear multiple bond correlation
HMPA	hexamethylphosphoric triamide, (hexamethylphosphoramide)
HMQC	heteronuclear multiple quantum correlation
HOMO	highest occupied molecular orbital
HPLC	high-performance liquid chromatography
HPW	Hajos Parrish Wiechert
HRMS	high-resolution mass spectrometry
HSQC	heteronuclear single quantum correlation
Hz	hertz
IBX	2-iodoxybenzoic acid
IR	infrared
ISC	inter system crossing
J	coupling constant (in NMR spectrometry)
K	kelvin(s) (absolute temperature)
L	liter(s)

LA	Lewis acid
LAH	lithium aluminum hydride
LD50	dose that is lethal in 50% of test subjects
LDA	lithium diisopropylamide
LHMDS	lithium hexamethyldisilazane, lithium bis(trimethylsilyl)amide
lit	literature value
LUMO	lowest unoccupied molecular orbital
μ	micro
m	multiplet (spectral)
M	molar (moles per liter)
M+	parent molecular ion
MALDI	matrix-assisted laser desorption ionization
max	maximum
Me	methyl
Mes	2,4,6-trimethylphenyl (mesityl)
MHz	megahertz
min	minute(s)
MO	molecular orbital
mol	mole(s)
mmol	millimole(s)
MOM	methoxymethyl
mp	melting point
Ms	methylsulfonyl (mesyl)
MS	mass spectrometry, molecular sieves

m/*z*	mass-to-charge ratio
MVK	methyl vinyl ketone
NBS	*N*-bromosuccinimide
nm	nanometer(s)
NMO	*N*-methylmorpholine-*N*-oxide
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
NOESY	nuclear Overhauser effect spectroscopy
Nu	nucleophile
obs	observed
o/n	over night
PCC	pyridinium chlorochromate
Ph	phenyl
piv	pivaloyl
pm	picometer(s)
PMB	*para*-methoxybenzyl
ppm	part(s) per million
Pr	propyl
^{i}Pr	isopropyl
py	pyridine
q	quartet (spectral)
RCM	ring-closure metathesis
Rf	retention factor (in chromatography)
rt	room temperature

s	singlet (spectral)
SET	single electron transfer
SM	starting material
S_N1	unimolecular nucleophilic substitution
S_N2	bimolecular nucleophilic substitution
SOC	spin orbital coupling
SOMO	single-occupied molecular orbital
t	triplet (spectral)
TBAB	tetrabutylammonium bromide
TBAF	tetrabutylammonium fluoride
TBDMS	*tert*-butyldimethylsilyl
TCE	trichloroethylene
Temp	temperature
TES	triethylsilyl
Tf	trifluoromethanesulfonyl (triflyl)
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
THP	tetrahydropyran-2-yl
TIPS	triisopropylsilyl
TLC	thin-layer chromatography
TMEDA	*N*,*N*,*N*′,*N*′-tetramethyl-1,2-ethylenediamine
TMS	trimethylsilyl; tetramethylsilane
Tol	tolyl

TPAP	tetrapropylammonium perruthenate
Tr	triphenylmethyl (trityl)
p-TSA	*para*-toluenesulfonic acid
*t*R	retention time (in chromatography)
Ts	*para*-toluenesulfonyl (tosyl)
UV	ultraviolet
vis	visible
vol	volume
v/v	volume per unit volume (volume-to-volume ratio)
W	watt(s)
wt	weight
w/w	weight per unit weight (weight-to-weight ratio)

Contents

Chapter 1

Introduction

1.1 Dolabellanes

Chemical investigations of different species of Dictyotales (brown algae) indicated an exceptionally rich source of secondary metabolites. More than 300 diterpenes belonging to a number of structural classes from at least 35 algae species collected from all over the world have been analysed.[1] Analysis established a correlation between geographic distribution of the species and structural variation of their associated diterpenes. Among the wide list of terpenoids, the class of dolabellanes represents one of the principal groups. Even though dolabellanes are mainly produced by marine organisms (seaweeds, molluscs, corals), they are also found in territorial sources (fungi, moss, higher plants).[2]

In 1975, Borschberg reported the discovery of *β*-araneosene, a novel diterpene isolated from the terrestrial mould *Sordaria araneosa* (Figure 1).[3] There was no precedent for this bicyclic skeleton which was later called "dolabellane" when, in 1976, Faulkner and Ireland isolated a series of related diterpenoids from the sea hare *Dolabella californica*.[4]

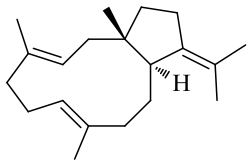
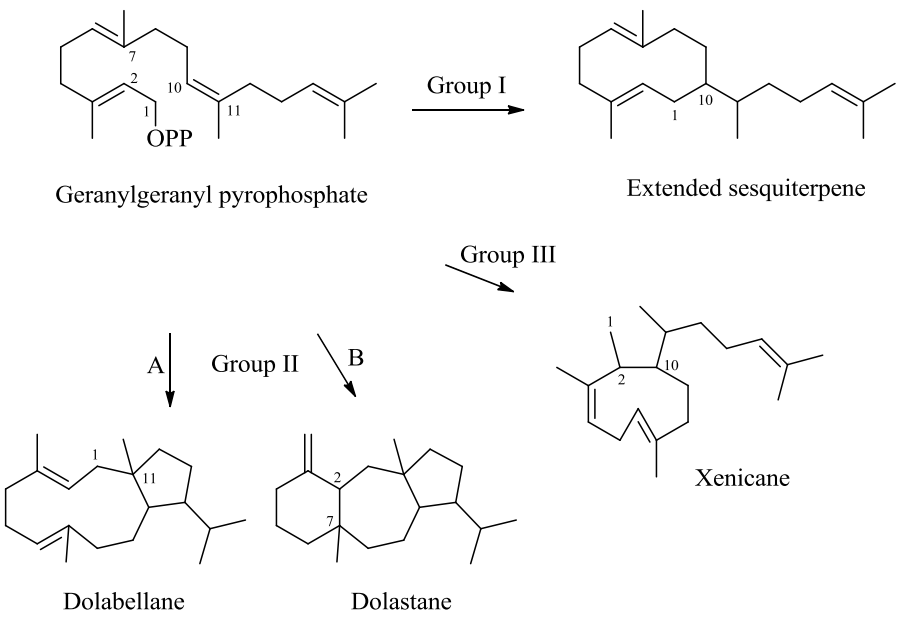


Figure 1 *β*-araneosene

In a review published in 1998, Rodríguez discussed the isolation, total syntheses, reactivity and biological activity of about 140 different dolabellanes.[2] An update on the chemistry of dolabellanes was published by Hiersemann in 2005.[5] In recent years, the number of isolated dolabellane natural products has continued to grow steadily.

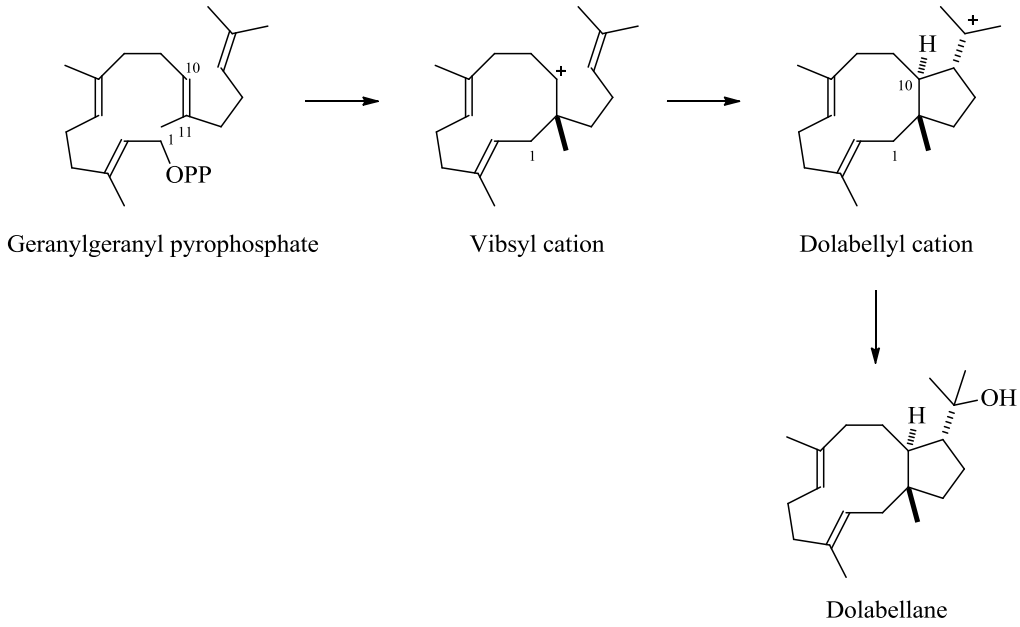
Naturally occurring diterpene compounds isolated from populations of Dictyotaceae species are assumed to be biosynthesised by an anabolic pathway that employs the achiral

geranylgeranyl pyrophosphate precursor. They have been organized into three chemical groups depending on the first normal cyclisation of the geranylgeranyl diphosphate (Scheme 1).[6]



Scheme 1 Cyclisation of geranylgeranyl diposphate

Compounds from group I result from a cyclisation between positions 1 and 10 and are mainly prenylated derivatives of known sesquiterpene skeletons. Compounds from group III arise from cyclisation between positions 2 and 10, resulting in a xenicane type skeleton. Finally, dolabellanes are the result of cyclisation between positions 1 and 11. It is assumed that geranylgeranyl diphosphate is first ionised (Scheme 2). The first cyclisation generates the vibsyl cation which undergoes a second cyclisation to give the dolabellyl cation. The loss of a proton or nucleophilic attack by water provides the dolabellane skeleton. A 5-*exo*-trig cyclisation would be favoured over a 6-*endo*-trig type cyclisation, avoiding formation of bicyclo [9.4.0] tetradecane derivatives. The methyl group and the proton at the ring junction are also in an *trans* relationship. Consequently the ring system of dolabellanes is characterised by an unusual *trans*-bicyclo [9.3.0] tetradecane framework.

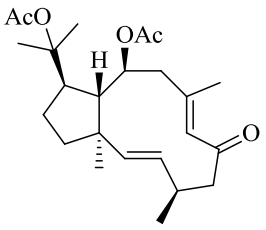


Scheme 2 Proposed biogenesis for dolabellanes

Group II also includes dolastane diterpenes (Scheme 1). Indeed dolabellanes may be considered to be their biogenetic precursors through transannular cyclisations.

Of great interest is the observation that most of the dolabellanes studied to date exhibit a wide array of biological activity, such as cytotoxic, antibacterial, antifungal, antiviral, antimalarial, molluscicidal, ichthyotoxic or phytotoxic activity.[2] The list is too exhaustive to discuss all of them, and two examples are listed below.

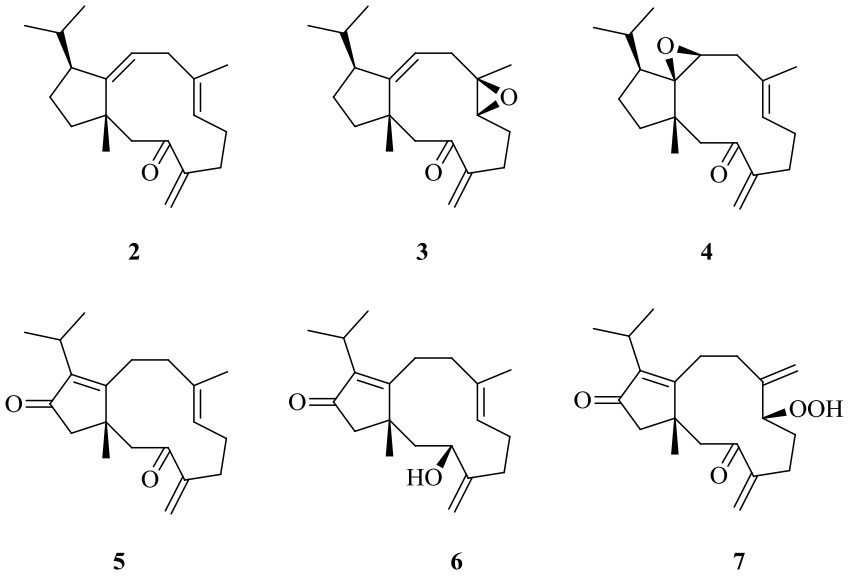
The dolabellane **1** has been extracted from the marine sponge *Sigmosceptrella quadrilobata* collected along the coast of the (Comorian archipelago) (Figure 2). It is cytotoxic against four cancer cell lines with an IC_{50} between 7.7 and 17.2 mg/mL.[7]



1

Figure 2 Dolabellane **1**

Six dolabellanes **2-7** were isolated from the soft coral *Clavularia inflata* collected at Orchid Island located off Taiwan's southeast coast (Figure 3).[8] They are cytotoxic against the cell lines A549 (human, lung carcinoma), HT-29 (human, colon carcinoma) and P388 (mouse, leukaemia). Hydroperoxide **7** proved to be the most potent compound with ED_{50} values of 0.56, 0.31 and 0.052 mg/mL respectively.



2 **3** **4**

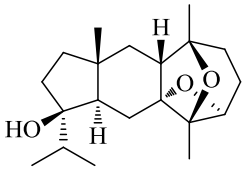
5 **6** **7**

Figure 3 Dolabellanes **2-7**

These fascinating natural structures represent challenging target molecules for total synthesis. As natural products they are very difficult to obtain in any significant quantity and it is not surprising that many research groups have reported the total and enantioselective synthesis of a large number of dolabellanes, and that advances in this field are still being published.[9]

1.2 Dictyoxetane

Studies of a specimen of the brown algae *Dictyota dichotoma* (Hudson) Lamouroux,[10] collected by hand at Kursadai Island, Gulf of Mannar in India, have proved it to be a prolific source of diterpenes. The algae contains some fifteen new dolabellanes, a dolastane derivative and a new dictyoxetane **8** structurally related to the class of dolabellanes (Figure 4).[11] In 1985, Pullaiah and co-workers reported the structural determination of this dictyoxetane by single-crystal X-ray analysis, but to date the absolute configuration remains unknown.[12]



8

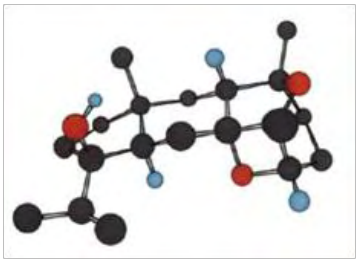
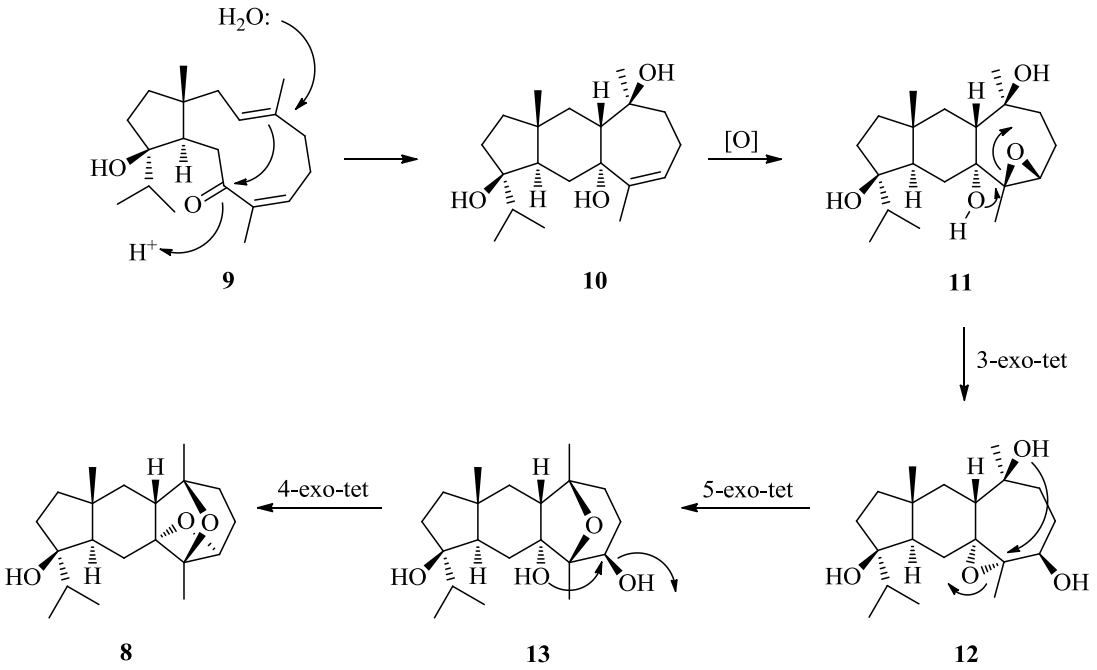


Figure 4 Dictyoxetane **8**

This intricate dioxatricyclic framework had never been encountered in any other natural product. This unusual diterpene embodies within its tricarbocyclic skeleton a highly strained novel 2,7-dioxatricyclo[4.2.1.0]nonane ring system. It is a compact molecule containing a small ring ether (n=4), three normal ring ether (n=5-7) and a medium 1,4-dioxacyclooctane medium ring ether (n=8).

As yet, very little is known about the biogenetic origin of dictyoxetane. In 1995, Hoffmann and co-workers proposed the following hypothetical biogenesis (Scheme 3).[13]



Scheme 3 Proposed biosynthesis for dictyoxetane

The known dolabellane metabolite **9** is proposed to undergo a transannular cyclisation. Attack of water would occur preferentially from the *exo* face leading to a tricyclic triol **10**. Stereoselective epoxidation followed by epoxide rearrangement would generate a new epoxide which could then be opened to give a tetrahydrofuran ring **13**. Formation of the oxetane ring could then occur *via* a 4-*exo*-tet cyclisation to deliver dictyoxetane.

There are as yet no reports outlining biological activity data for dictyoxetane although naturally occurring oxetane-containing compounds show important bioactivity (Figure 5).[14]

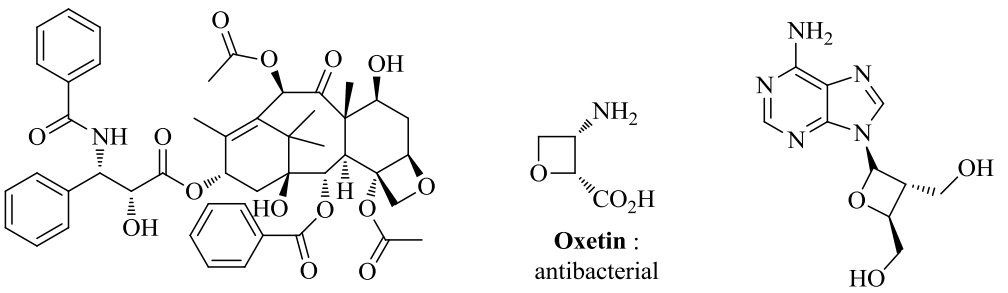
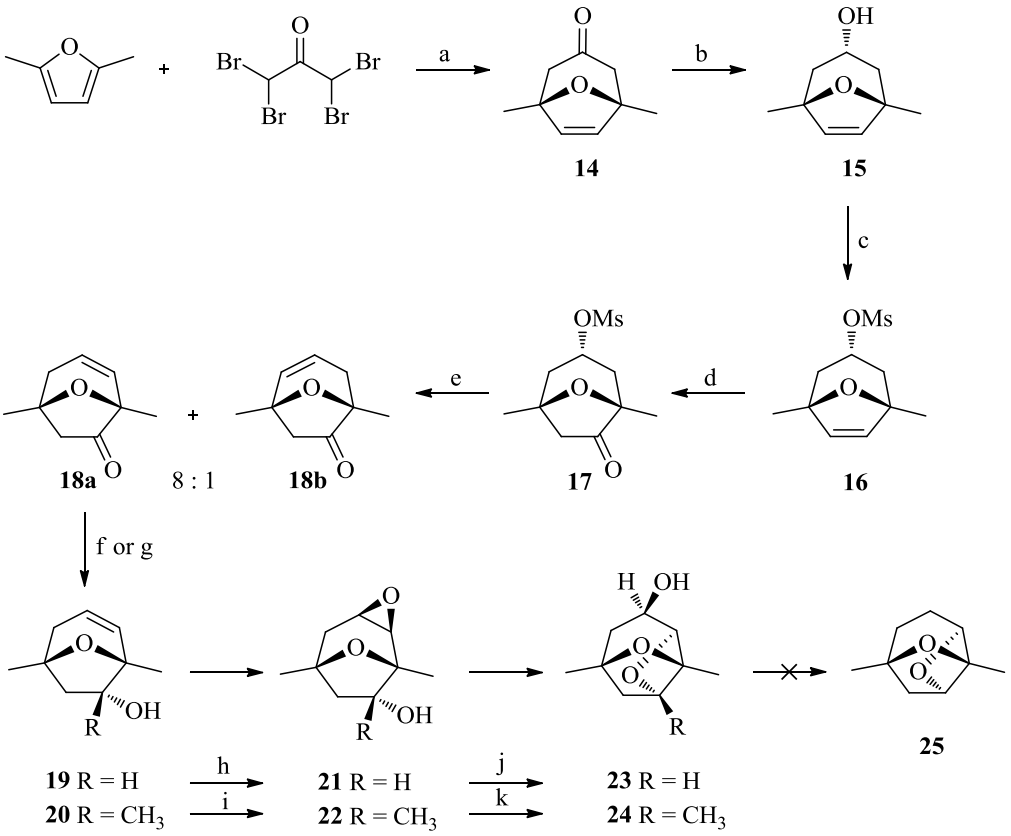


Figure 5 Naturally occurring bioactive oxetanes

A total synthesis of dictyoxetane has yet to be reported. However the interesting dioxatricyclic core has been studied and syntheses have been described by two groups.

In 1995 Hoffmann and Reinecke presented the first synthetic attempts towards the key four-membered oxetane ring by using a stereoelectronically favourable intramolecular nucleophilic displacement reaction (Scheme 4).[13]

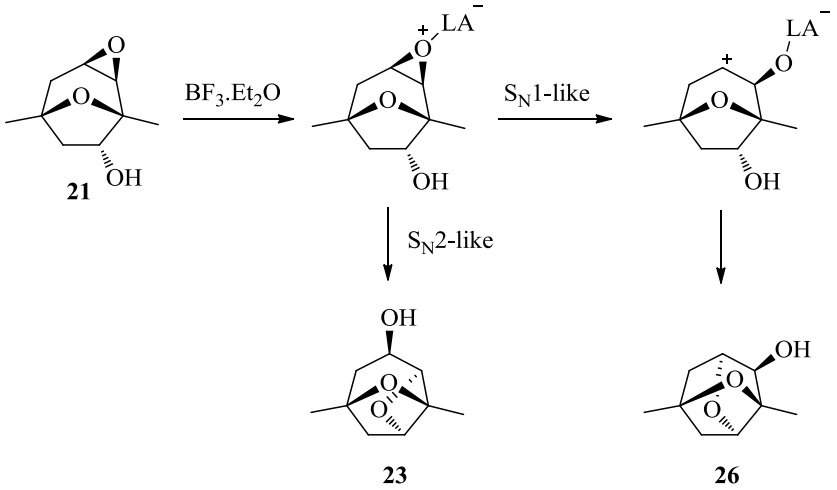


Conditions: a) Zn, $B(OEt)_3$, THF, rt, then Zn, CuCl, NH_4Cl, MeOH, 15 °C→rt, 59%; b) DIBAL-H, THF, -78 °C→rt, 88%; c) CH_3SO_2Cl, Et_3N, 0 °C, 73%; d) BH_3, THF, 0 °C, then PCC, CH_2Cl_2, rt, 79%; e) DBU, CH_3CN, reflux, 79% combined yield; f) DIBAL-H, THF, -78 °C→-10 °C, 94%; g) CH_3MgBr, THF, -78 °C, 55%; h) *m*-CPBA, CH_2Cl_2, 0 °C→rt, 75%; i) *m*-CPBA, CH_2Cl_2, 0 °C, 58%; j) KOH, DMSO/H_2O, rt, 82%; k) KOH, DMSO/H_2O, rt, 80%.

Scheme 4 Synthesis of oxetanes **23** and **24**

First, bicyclic enone **14** was prepared through the method of Hoffmann and Iqbal.[15] Triethyl borate was used as a Lewis acid to generate an allyl cation from tetrabromoacetone which

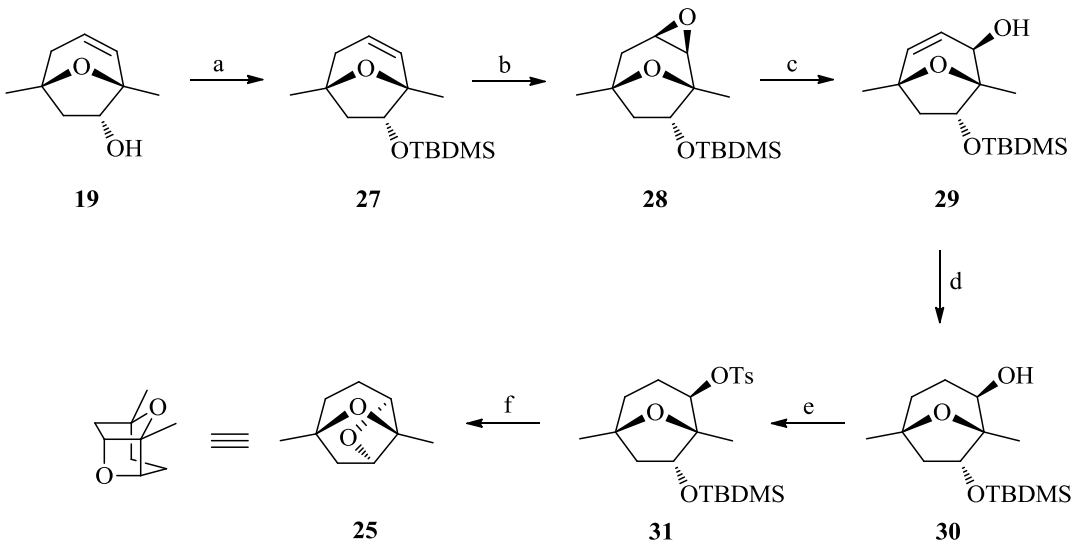
underwent cycloaddition with 2,5-dimethylfuran. Stereoselective reduction of the ketone with DIBAL-H gave the unsaturated *endo* alcohol **15**. Mesylation of the secondary alcohol followed by a combined hydroboration/oxidation furnished the ketomesylate **17** with desymmetrisation of the bridged bicycle. The regiochemistry of the functionalisation of the three-carbon bridge in **17** was expected to be controlled by the *σ*-acceptor effect of the carbonyl. Therefore a base-mediated elimination afforded keto olefin **18a** as the major product (**18a:18b** 8:1). Stereoselective reduction of the ketone with DIBAL-H or alkylation with methyl magnesium bromide gave homoallylic alcohols **19** and **20**. Again attack proceeded *via* the *exo* face. Stereoselective epoxidation of the double bond with *m*-CPBA led to epoxy alcohols **21** and **22**, which upon treatment with base delivered the tricyclic oxetanes in very good yields. Hydroxyoxetane **23** was also obtained under Lewis acid catalysis. In this case, isomeric bistetrahydrofuran **26** was also formed (**23**:**26** 2:1) probably *via* an S_N1-like cyclisation (Scheme 5).



Scheme 5 Formation of oxetanes **23** and **26**

Unfortunately, subsequent attempts to remove the hydroxyl group in **23** in a radical process failed (Scheme 4). Therefore they developed an alternative route to the dioxatricycle **25**

(Scheme 6). Starting from the pure stereoisomer alcohol **19**, protection as a silyl ether followed by epoxidation afforded *exo* epoxide **28**. This was converted under basic conditions to allylic alcohol **29**. Hydrogenation of the double bond and tosylation led to **31**. Silyl ether **31** was deprotected and cyclised in one pot using TBAF, delivering the desired oxetane.

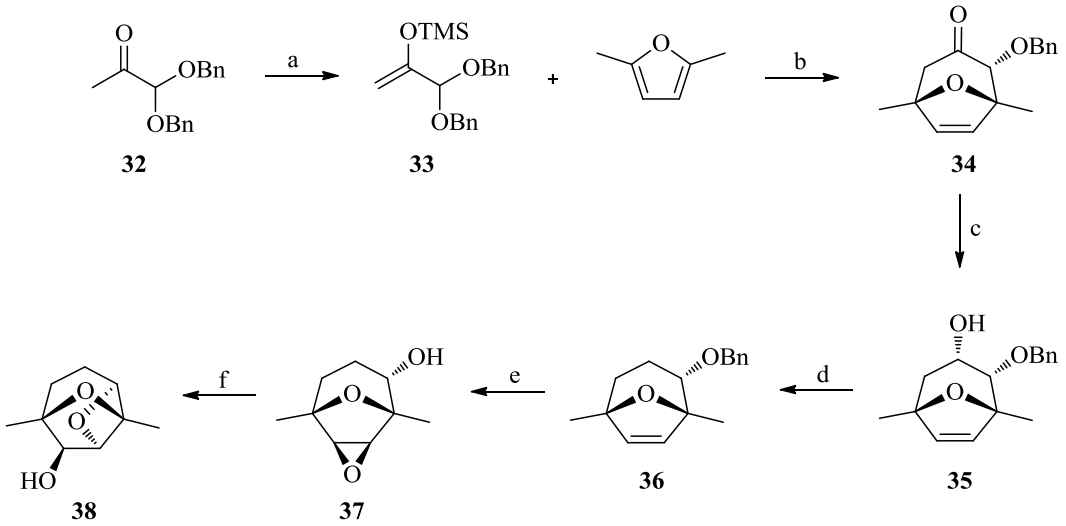


Conditions: a) TBDMSOTf, Et_3N, CH_2Cl_2, 0 °C, 86%; b) *m*-CPBA, CH_2Cl_2, 0 °C, 93%; c) LDA, DMPU, Et_2O, rt, 94%; d) H_2, Pd/C, EtOH, 99%; e) *n*-BuLi, THF, TsCl, -78 °C→rt, 97%; f) TBAF, THF, rt→reflux, 39%.

Scheme 6 Cyclisation to oxetane **25**

In continuation of this work, Hoffmann published progress on the functionalisation of the dioxatricyclic structure, and reported the biological activities of these oxetanes.[16]

Ketone **32** was converted into the silyl enol ether **33** and was submitted to trimethylsilyl triflate-catalysed [4+3] cycloaddition with 2,5-dimethylfuran (Scheme 7). Diastereoselective reduction of the bicyclic adduct **34** gave *endo* alcohol **35**. Barton-McCombie deoxygenation afforded oxabicycle **36**, which was further epoxidised and deprotected. Finally, cyclisation with boron trifluoroetherate furnished tricyclic hydroxy oxetane **38**.

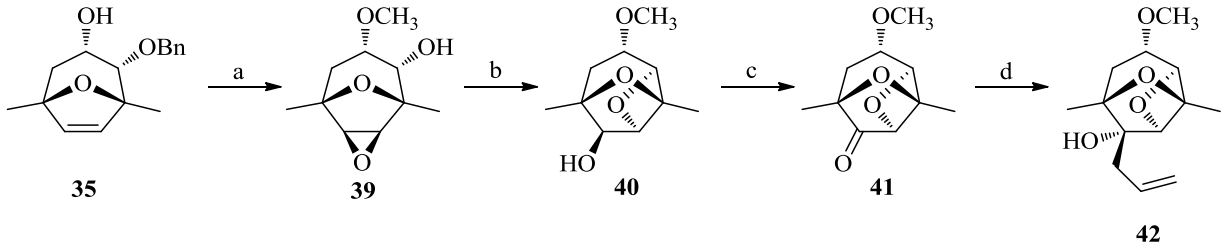


32 **33** **34** **35** **36** **37** **38**

Conditions: a) LDA, TMSCl, THF, -78 °C→rt; b) TMSOTf cat., CH_2Cl_2, -78 °C, 53% over 2 steps; c) DIBAL-H, THF, -78 °C, 94%; d) i) NaH, CS_2, CH_3I, THF, 0 °C→rt, 77%, ii) Bu_3SnH, AIBN, toluene, 95 °C, 92%; e) i) *m*-CPBA, CH_2Cl_2, 0 °C→rt, 85%, ii) H_2, Pd/C, MeOH, 85%; f) $BF_3{\cdot}Et_2O$, CH_2Cl_2, 0 °C, 72%.

Scheme 7 Synthesis of hydroxy oxetane **38**

Alcohol **35** was also used as a precursor for the creation of bisoxygenated oxetanes **40**, **41** and **42** (Scheme 8).



35 **39** **40** **41** **42**

Conditions: a) i) NaH, CH_3I, THF, 0 °C→rt, 100%, ii) *m*-CPBA, CH_2Cl_2, 0 °C, 97%, iii) H_2, Pd/C, MeOH, AcOH, 80% over 3 steps; b) ^{t}BuOK, THF, rt, 85%; c) DMSO, $(COCl)_2$, CH_2Cl_2, Et_3N, -78 °C→rt, yield not given; d) allylMgBr, Et_2O, -30 °C→-10 °C, 70%.

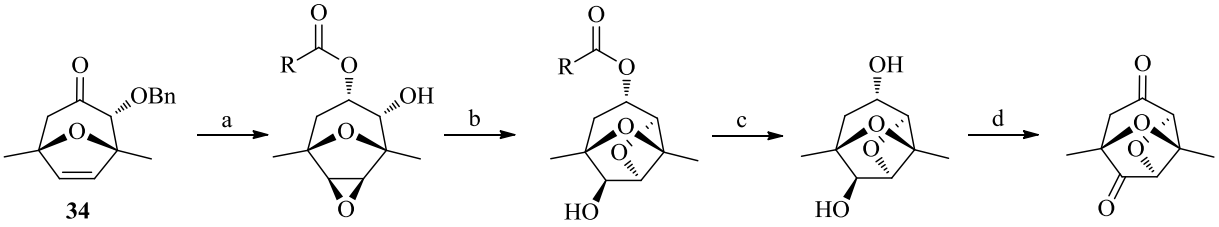
Scheme 8 Synthesis of oxygenated oxetanes **40**, **41** and **42**

O-Methylation, epoxidation and debenzylation of **35** gave **39**. Subsequent treatment with base furnished alcohol **40**. Swern oxidation provided the expected keto oxetane **41**. The stability of the oxetane ring towards Grignard reagents was indicated with the stereoselective formation

of the *endo* tertiary homoallylic alcohol **42** when ketone **41** was treated with allylmagnesium bromide.

Cytostatic and cytotoxic activites of **38**, **40**, **41** and **42** were investigated *in vitro, via* the HMO2 (human gastric carcinoma) and the HEP G2 (human heptocellular carcinoma) cell lines.[16,17] All four oxetanes showed cytostatic activity. The most potent **41** towards the HMO2 cell line inhibited cell growth by 68% at 1 μmol/l.

In 2002 Hoffmann and co-workers presented further functionalised dictyoxetane subunits.[18] Starting from *rac*-**34**, a sequence of reduction, protection and epoxidation delivered epoxy alcohols **43** and **44** necessary for the cyclisation (Scheme 9). Cyclisation was carried out under Lewis acid conditions and the ester group in **45** was then reductively cleaved to give tricyclic diol **47**. One pot double oxidation of diol **47** gave diketone **48**.



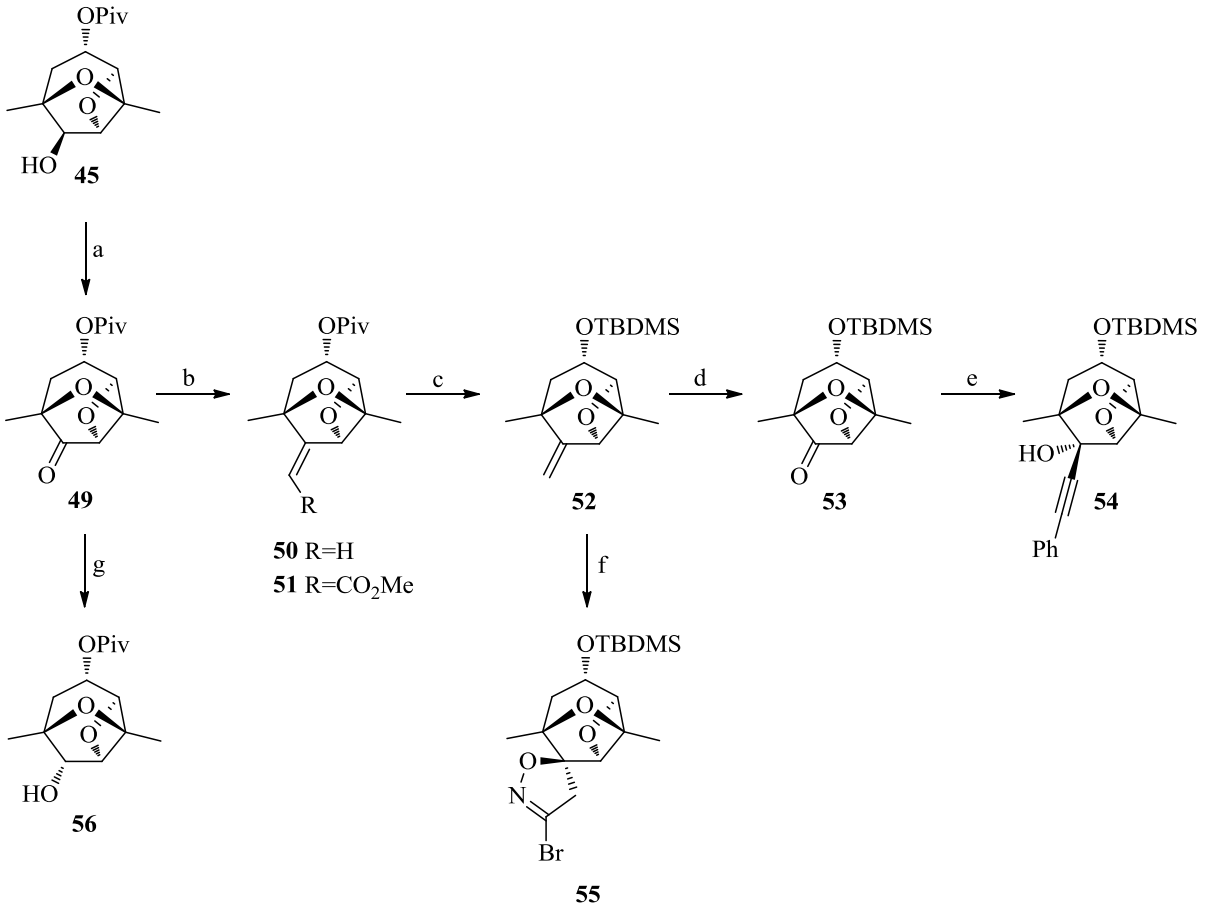
Conditions: a) i) DIBAL-H, THF, -78 °C→0 °C, 94%, ii) RCOCl, Py, DMAP, THF, 0 °C→rt, **43** 90%, iii) *m*-CPBA, CH_2Cl_2, 0 °C→rt, **43** 89%, iv) Pd/C, H_2, EtOAc, AcOH, rt, **43** and **44** 90%; b) $BF_3 \cdot Et_2O$, CH_2Cl_2, 0 °C, **45** 71% and **46** 69%; c) DIBAL-H, THF, -78 °C, Na, K-tartrate, 98% from **45**; d) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C→rt, 50%.

Scheme 9 Formation of diketo oxetane **48**

Diketone **48** could be used for further transformations of the dioxatricyclic framework.

An alternative route to different functionalised oxetanes started with oxidation of **45** to keto ester **49** which was reduced to epimeric alcohol **56** (Scheme 10). Wittig olefination of keto ester **49** furnished exocyclic olefins **50** and **51**. The ester group in **51** adopts selectively the

less hindered *E*-configuration. A subsequent sequence of deprotection of **50**, reprotection and oxidative cleavage gave ketone **53** which underwent reaction with a Grignard reagent with total stereoselectivity. The exocyclic double bond in **52** also acted as a dipolarophile in a nitrile oxide cycloaddition with complete π-facial selectivity (**55**).[19] This indicated that nucleophilic addition to the carbonyl and the pericyclic reaction proceeded selectively from the *exo* face, *trans* to the oxetane oxygen.

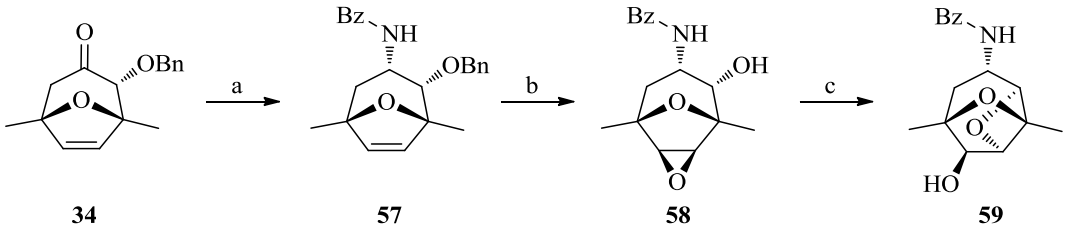


Conditions: a) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C→rt, 77%; b) Ph_3P=CHR, CH_2Cl_2, rt, **50** 53% and **51** 82%; c) i) DIBAH, THF, -78 °C, 66% from **50**, ii) TBDMSCl, CH_2Cl_2, imidazole, rt, 98%; d) i) O_3, CH_2Cl_2, -78 °C, ii) PPh_3, 81% over 2 steps; e) Phenylacetylene, ^{t}BuMgCl, THF, -20 °C→rt, 81%; f) Br_2C=N-OH, DBU, acetonitrile, 0 °C→rt, 20%; g) $NaBH_3CN$, MeOH, rt, 50%.

Scheme 10 Creation of functionalised oxetanes

A series of aminated oxetanes were prepared *via* reductive amination[20] of oxabicyclic ketone **34** followed by protection as an *N*-benzamide to give the aminated bicyclic olefin **57**.

Epoxidation of the double bond and deprotection of the alcohol gave precursor **58**, which was cyclised to oxetane **59** (Scheme 11).



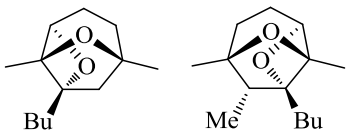
34 **57** **58** **59**

Conditions: a) i) NH_4OAc, $NaBH_3CN$, MeOH, rt, ii) BzCl, Py, DMAP, 0 °C, 65-80% over 2 steps; b) i) *m*-CPBA, CH_2Cl_2, 0 °C→rt, 82%, ii) Pd/C, H_2, MeOH, AcOH, 49% over 2 steps; c) LiH, ^tBuOK, THF, 0 °C→rt, 18%.

Scheme 11 Formation of aminated oxetane **59**

The dioxatricyclic ester *rac*-**51** did show cytostatic but no cytotoxic activity towards tumor cells (cell lines: HepG 7, MCF 7), and it has been suggested that the presence of the C3 hydroxyl group appeared to be essential to maintain the anti-tumor activity.

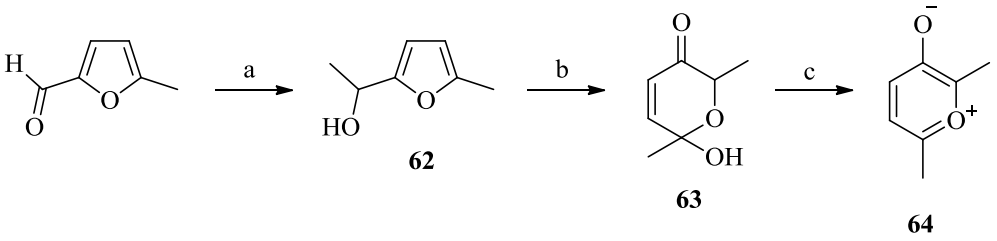
In parallel to Hoffmann's work, Heathcock and co-workers also studied a new synthetic method to prepare the dictyoxetane core structure.[21] In 1996 they reported a synthesis of heterocycles **60** and **61** (Figure 6) using a known dipolar cycloaddition of a 3-oxidopyrylium salt[22] to create the carbon skeleton and an intramolecular S_N2 displacement to obtain the oxetane ring.



60 **61**

Figure 6 Oxetanes **60** and **61** prepared by Heathcock et *al.*

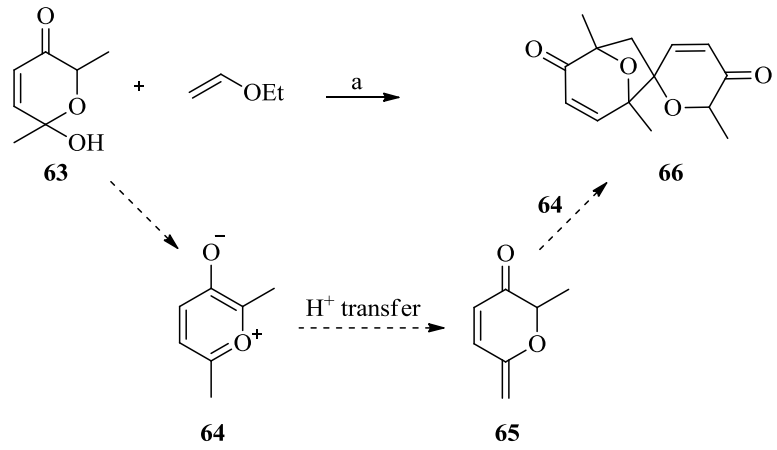
Methylation of commercially available 5-methylfurfural gave 2-furylcarbinol **62**, which was rearranged, by treatment with *m*-CPBA, to the enone **63** (Scheme 12). Pyrylium betaine **64** could then be obtained *via* reaction of **63** with methanesulfonyl chloride and triethylamine.



Conditions: a) MeLi, THF, -78 °C, 100%; b) *m*-CPBA, CH_2Cl_2, 85%; c) MsCl, Et_3N, CH_2Cl_2.

Scheme 12 Formation of 3-oxidopyrylium betaine **64**

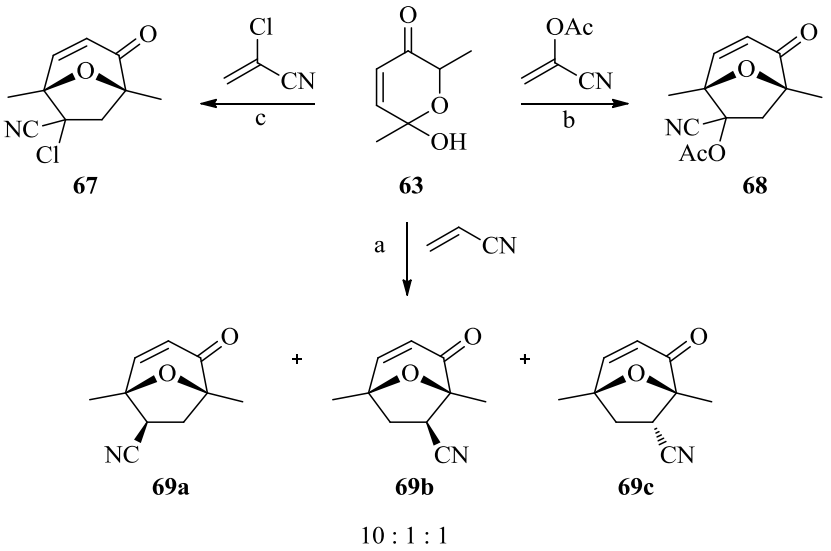
Reaction of the 1,3-dipole with different dipolarophiles was then investigated. Initial attempts using ethyl vinyl ether yielded only dimer **66**, probably as a result of 1,3-dipolar cycloaddition of the ylide **64** with dienone **65**, obtained *via* an internal proton transfer (Scheme 13).



Conditions: a) MsCl, Et_3N, CH_2Cl_2, 52%.

Scheme 13 Formation of dimer **66**

These results showed that electron rich dipolarophiles (ethyl vinyl ether, vinyl acetate and ketene thioacetals) generally did not undergo cycloaddition with **63**, and only dimerisation or degradation was observed. However more reactive dipolarophiles underwent cycloaddition and offered different cycloadducts (Scheme 14).



Conditions: a) MsCl, (^{i}Pr)$_2$EtN, CH_3CN, 140 °C, 45%; b) MsCl, (^{i}Pr)$_2$EtN, CH_3CN, 140 °C, 48%; c) MsCl, (^{i}Pr)$_2$EtN, CH_3CN, 110 °C, 30%.

Scheme 14 Cycloaddition with different polarophiles

The use of acrylonitrile as the dipolarophile gave a 10:1:1 mixture of regioisomers and diastereoisomers. Reactions with chloroacrylonitrile and acetoxyacrylonitrile resulted in single cycloadducts **67**and **68** in moderate yields. At this stage, the stereochemistry was not determined because these stereocentres would be destroyed upon later conversion to a carbonyl group. On the other hand, the regiochemistry observed in cycloadducts **67** and 6**8** did not turn out to be the required one, which would be where the two functions are proximal, directly situated for the closure of the oxetane (Figure 7).

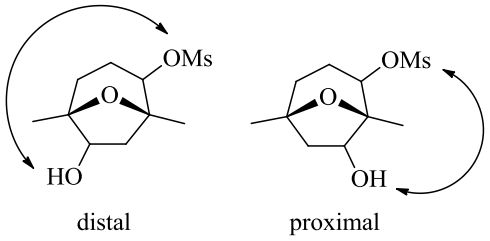
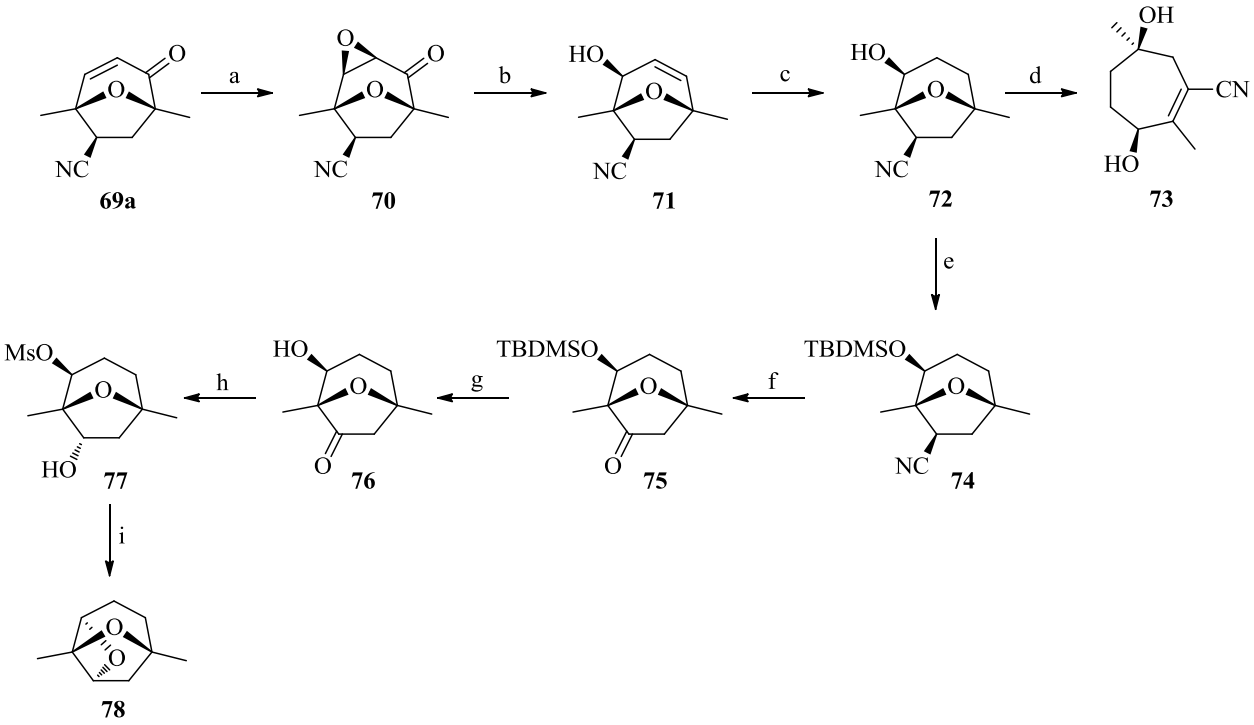


Figure 7 Position of the substituents for cyclisation

Nevertheless Heathcock suggested that **69a** might be employed by using a Wharton enone transposition (Scheme 15).[23] Epoxidation followed by reductive elimination furnished allylic alcohol **71**, albeit in low yield. Hydrogenation of the double bond gave the saturated cyano alcohol **72** which did not undergo oxidative decyanation[24] as expected but instead gave cycloheptanol **73**. **73** was envisaged to be obtained through simple *β*-elimination of the intermediate nitrile-stabilized anion.

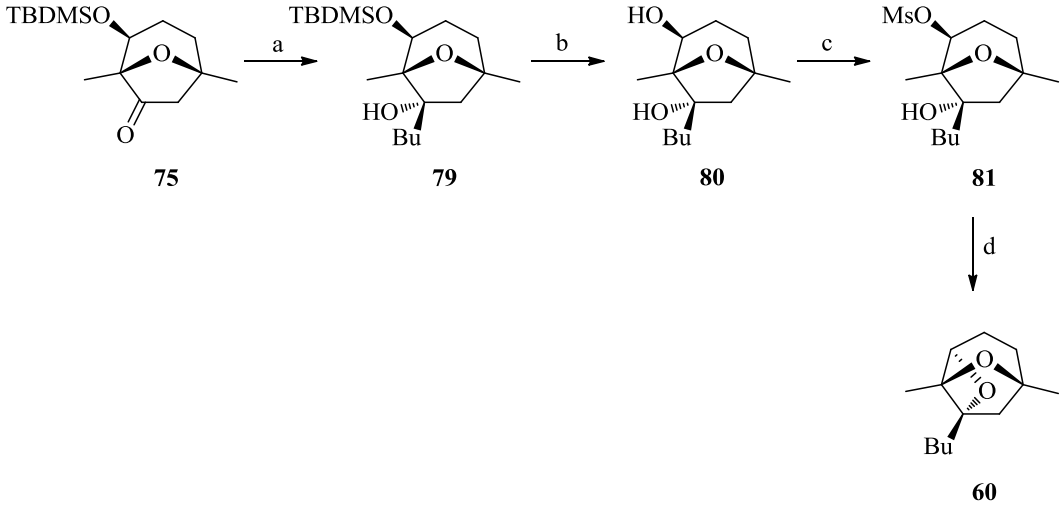


Conditions: a) ^{t}BuOOH, Na_2CO_3, MeOH, H_2O, 40%; b) i) H_2NNH_2, ii) AcOH, 30% over 2 steps; c) H_2, Pd/C, THF, 100%; d) i) LDA, THF, ii) O_2, iii) $SnCl_2$, 56% over 3 steps; e) TBDMSCl, imidazole, DMF, 90%; f) i) LDA, THF, -78 °C, ii) O_2, iii) $SnCl_2$, 62% over 3 steps; g) 2% HF in CH_3CN, 100%; h) i) MsCl, Et_3N, CH_2Cl_2, ii) $NaBH_4$, MeOH, 68% over 2 steps; i) NaH, THF, yield not given.

Scheme 15 Cyclisation to oxetane **78**

Suppression of *β*-elimination was attempted by protecting the secondary alcohol as the silyl ether. Oxidative decyanation did then occur to give **75** along with 20% of the elimination product. A sequence of deprotection, mesylation and reduction of the keto mesylate delivered the cyclisation precursor **77**. Treatment with base appeared to lead to the formation of the

oxetane **78** as evidenced by ^{1}H NMR analysis. However, this product was too volatile to easily handle and they decided to synthesise a heavier analogue by adding an alkyl chain. Reaction of ketone **75** with butyllithium allowed introduction of a butyl substituent (Scheme 16). Deprotection of the silyl ether and selective mesylation of the secondary alcohol gave **81**, which underwent smooth oxetane cyclisation. Oxetane **60** still appeared to be somewhat volatile but was more convenient to handle than **78**.



75 **79** **80** **81** **60**

Conditions: a) *n*-BuLi, THF, -78 °C; b) 2% HF, CH_3CN, 84%; c) MsCl, Et_3N, CH_2Cl_2, 0 °C, 93%; d) NaH, THF, reflux, 77%.

Scheme 16 Formation of butyl oxetane **60**

Two model oxetanes **60** and **78** were successfully synthesised *via* a method based on a dipolar cycloaddition and an intramolecular S_N2 displacement. However this route displayed several disadvantages. First, the sequence epoxidation/Wharton rearrangement was low yielding, and secondly *β*-elimination was competing with the oxidative decyanation. Heathcock intended to bypass those problems by accomplishing carbonyl transposition in the two-carbon bridge instead of in the three-carbon bridge (Figure 8).

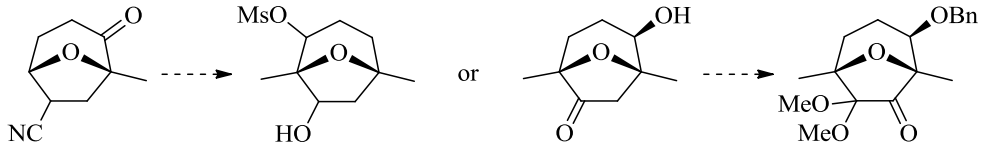
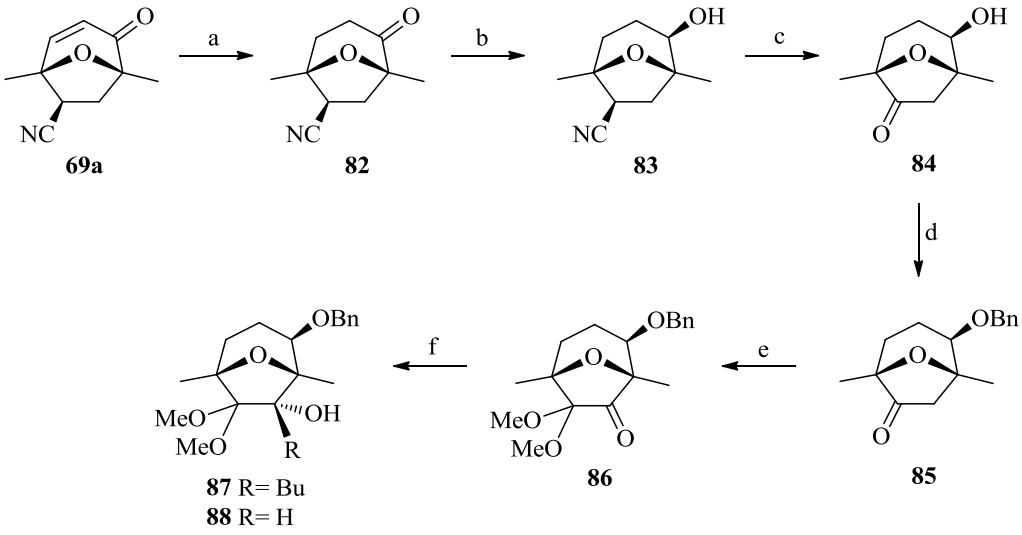


Figure 8 Function transposition on the 3 or 2 carbon bridge

Cycloadduct **69a** was converted to hydroxy ketone **84** *via* hydrogenation, selective reduction and oxidative decyanation, and the obtained alcohol was then protected as the benzyl ether **85** (Scheme 17). $PhI(OAc)_2$ in methanolic KOH has been reported to oxidise cyclic ketones to the corresponding α-hydroxy ketones.[25] Attempts to oxidise ketone **85** at the α-position under those conditions led to the unexpected dimethoxy ketone **86**. With the ketone in place and the acetal protected carbonyl, introduction of the butyl group in this case occurred together with 20% of the reduction product **88**.

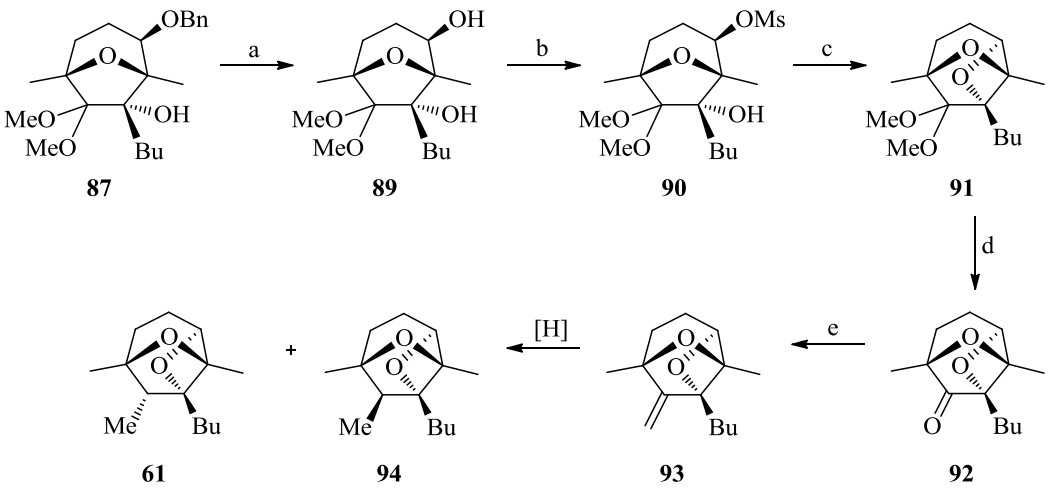


Conditions: a) H_2, Pd/C, 85%; b) L-Selectride, THF, -78 °C, 80%; c) i) LDA, THF, -78 °C, ii) O_2, iii) $SnCl_2$, 77% over 3 steps; d) BnBr, NaH, THF, 88%; e) $PhI(OAc)_2$, KOH, MeOH, 0 °C→rt, 66%; f) *n*-BuLi, TMEDA, THF, -20 °C, **101** 65%, **102** 20%.

Scheme 17 Transposition of the carbonyl on the 2 carbon bridge

Benzyl ether **87** was then deprotected and directly mesylated. **90** was cyclised into oxetane **91** using the same conditions as for **60** and in an improved yield (Scheme 18). The acetal was hydrolysed under acidic conditions to afford **92** without affecting the oxetane moiety. Wittig

olefination of ketone **92** afforded alkene **93**. Finaly, hydrogenation of the exocyclic double bond was investigated. Standard conditions, H_2 over Pd/C, gave a mixture of products, presumably due to insertion of palladium into the allylic oxetane which would form a π-allyl complex and open the four-membered ring.[26] When the reaction was performed with H_2 over Rh/Al_2O_3,[27] a 1:3 mixture of diastereomers **61**:**94** was isolated. It was assumed that rhodium would coordinate to the oxygen of the oxetane, thus directing hydrogenation from underneath the ring system to give the *exo* methyl. To prevent this facial selectivity, hydrogenation was attempted using diimide, which would not coordinate to oxygen. H_2 was delivered to the less sterically hindered face and furnished essentially isomeric product **61**.



Conditions: a) H_2, $Pd(OH)_2$, EtOAc, 100%; b) MsCl, Et_3N, CH_2Cl_2, 0 °C, 92%; c) NaH, THF, reflux, 88%; d) TFA, $CHCl_3$, H_2O, rt, 92%; e) $Ph_3P{=}CH_2$, THF, reflux, 93%; [H]: H_2, Rh/Al_2O_3, 1:3 **61**:**94**, 84% or tosyl hydrazide, NaOAc, >15:1 **61**:**94**, 89%.

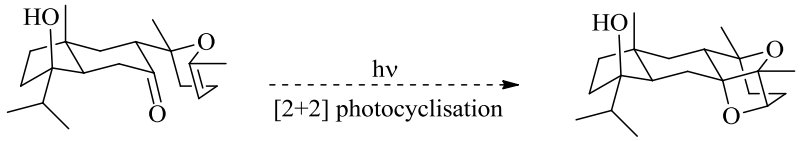
Scheme 18 Carrying the oxetane through the synthesis

In summary, studies towards the synthesis of dictyoxetane have led to the successful preparation of a number of novel dioxatricyclic ring systems. Hoffmann's strategy towards the oxetane ring is based on an intramolecular nucleophilic attack of a hydroxyl group onto an epoxide.[13,16,18] Heathcock, on the other hand, developed an S_N2 reaction of an alcohol on a mesylate, and proved that oxetanes were stable to acid-catalysed conditions, suggesting that

oxetane formation may not need to be the last step in a synthesis.[21] Hoffmann's work also showed the dioxatricyclic ring system to be stable to a variety of conditions, including acids, phosphonium ylides and hydrogenation.

1.3 Aims and objectives

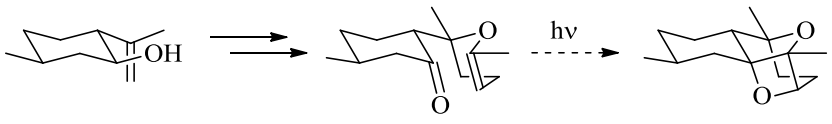
The aim of our research is to investigate a new approach to the total synthesis of dictyoxetane **8** and to establish the absolute configuration of the natural product. The dioxatricyclic ring system is proposed to be obtained *via* an intramolecular Paternò-Büchi [2+2] photocyclisation reaction between a ketone and a cyclic enol ether (Scheme 19).



95 **8**

Scheme 19 Proposed Paternò-Büchi [2+2] photocyclisation to form dictyoxetane **8**

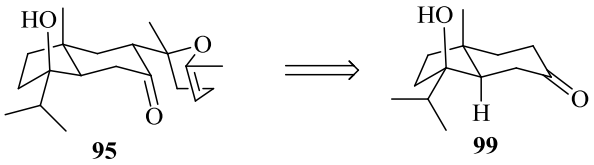
Studies have been focused on the creation on a model system **97** designed to probe the intended photocyclisation (Scheme 20). Commercially available isopulegol **96** was chosen as a starting material towards the formation of a dihydropyran ring system (Chapter 2).



96 **97** **98**

Scheme 20 Model system to test cyclisation

The second aim of this project was to investigate the formation of the *trans*-hydrindane type core structure of the natural product precursor **99** (Scheme 21). Several approaches are discussed (Chapter 3).



Scheme 21 *Trans*-hydrindane system

1.4 The Paternò-Büchi reaction

The Paternò-Büchi reaction is named after Emanuele Paternò and George Hermann Büchi and is the photochemical [2+2] cyclisation of carbonyl compounds and alkenes.[28-30] It is a simple and convenient route for the formation of functionalized oxetane rings and can generate up to three stereogenic centres.[31] The first intermolecular photocycloaddition of benzaldehyde to 2-methyl-2-butene was reported by Paternò in 1908.[28] It was only in 1950 that the oxetane structure of the main product was confirmed when Büchi and co-workers reinvestigated the reaction.[29]

In Paternò-Büchi reactions, it is generally the carbonyl which undergoes photoexcitation.[32] The wavelength absorption band for alkanones appears at 280-300 nm and involves excitation of a non bonding lone pair electron from the oxygen resulting in a $n \rightarrow \pi^*$ transition (Figure 9). This excitation is formally forbidden since the two orbitals are orthogonal and the lone pairs lie in the node of the π-system. Yet, excitation occurs and because the two singly occupied orbitals are orthogonal, the two radical centres behave independently.

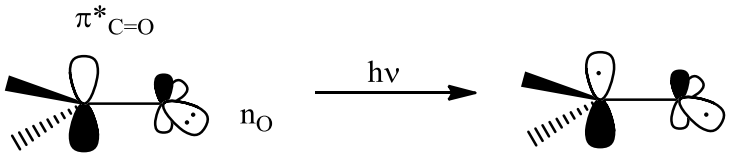
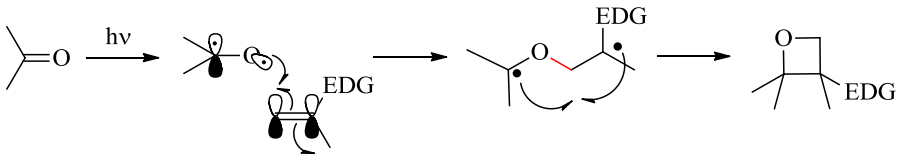


Figure 9 Carbonyl excitation

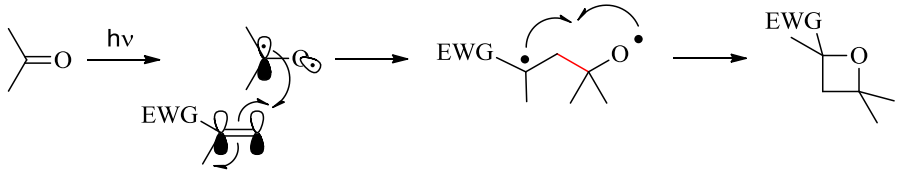
Considering orbital interactions between a n,π^* excited carbonyl and an alkene, a 1,4-biradical intermediate may be generated through two possible pathways.[33]

Following excitation, the more electrophilic half-filled oxygen n-orbital can interact with the empty π^*-orbital of an electron-rich alkene, perpendicular to the π-plane. Formation of the C-O bonded biradical is called the "perpendicular approach" (Scheme 22).



Scheme 22 Perpendicular approach

Alternatively, attack of the more nucleophilic half-filled π^*-orbital of the carbonyl towards the empty π^*-orbital of an electron-deficient alkene may occur parallel to the π-plane (Scheme 23). Such orientation is called the "parallel approach" and creates a C-C bonded biradical.



Scheme 23 Parallel approach

Thus, in these two mechanisms, addition of the carbonyl is directed by the electronic nature of the alkene and the most stable 1,4-biradical intermediate is formed.[34]

The n,π^* transition forms the corresponding singlet state S_1 (approximate lifetime: 1-2 ns) with paired electron spins. However most Paternò-Büchi reactions occur from the carbonyl triplet state T_1, having unpaired electron spins, which can be accessed by intersystem crossing (ISC) (Figure 10).[35]

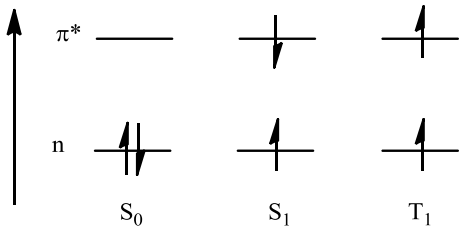
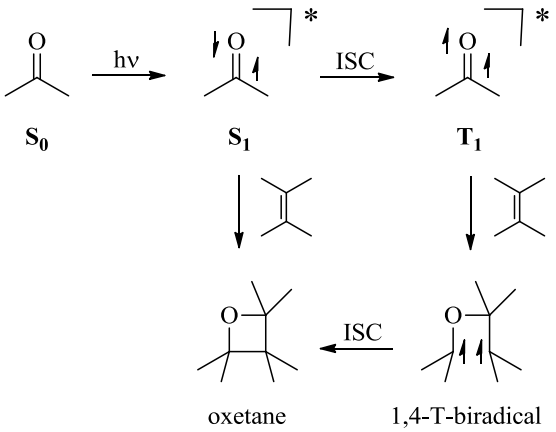


Figure 10 ISC from S_1 to T_1

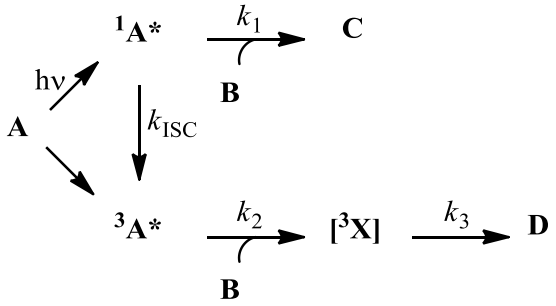
Nevertheless, with a large excess of alkene, it has been observed that the singlet excited state **S_1** can add to the double bond before ISC occurs (Scheme 24). In fact, since **S_1** has two radical electrons possessing opposite spin, the radical electron from the carbonyl couples with the radical electron of opposite spin from the alkene. The two remaining radical electrons are also of opposite spin and thus quickly bond to close the oxetane ring.[36]

On the other hand, ring-closure takes longer for the triplet excited state. In **T_1**, the two radical electrons possess the same spin (Scheme 24). When the radical electron from the carbonyl couples with the radical anion of opposite spin from the alkene, the key 1,4-biradical intermediate is formed. The two radical electrons are of the same spin and thus cannot form a bond. To progress from this triplet state to the ground state singlet product, spin-inversion is necessary and ISC occurs. The lifetime of the 1,4-biradical is remarkably increased and is determined by the ISC rate ($\tau_{BR}= 1/k_{ISC}$). As the spin flips, the bond can then be formed to close the system.



Scheme 24 Oxetane formation *via* $\mathbf{S_1}$ or $\mathbf{T_1}$

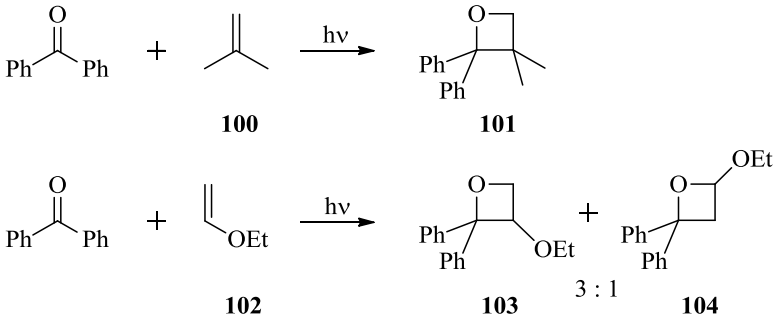
Control of the regioselectivity and stereoselectivity of the oxetanes formed during the nucleophilic attack (*via* a perpendicular approach) of an excited carbonyl to an electron-rich alkene is a challenge for organic chemistry. The advantage of the Paternò-Büchi reaction is that both the singlet (^{1}A*) and the triplet (^{3}A*) states of the excited carbonyl can take part in the reaction to deliver oxetane (Scheme 25). In the most common cases of unsymmetrical alkenes, **C** and **D** represent therefore different regio- and stereoisomers.



Scheme 25 Formation of regio- and stereoisomers

Regioselectivity in the oxetane product may be predicted with the formation of the transitional 1,4-biradical. However, the radical stability is not the only factor determining the geometry of the final oxetanes. Stereochemical, electronic and steric factors should also be considered. In the example below, oxetanes **101**, **103** and **104** are obtained from the Paternò-Büchi reaction

of benzophenone with 1,1-disubsituted alkene **100** and 1-monosubstituted alkene **102** (Scheme 26). Addition of **100** gives **101** as the only product,[37,38] however cyclisation with enol ether **102**[38] is not completely selective, giving a 3:1 mixture of regioisomers **103** and **104**.



Scheme 26 Regiochemistry in the formation of oxetanes

For 1,2-disubstituted alkenes, the question of stereochemistry arises. If the photocyclisation occurs from the singlet state (high concentration of alkene), the reaction is expected to be stereospecific, thus conserving the relative configuration of the alkene (conformational memory).[39] However, in the triplet state reactions, the stereochemistry is scrambled in the process and the information is largely lost during oxetane formation. Whether *cis*- or *trans*-2-butene reacts with benzophenone, the same mixture of oxetanes **105** and **106** is obtained (**105**:**106** 6:1) (Figure 11).[40]

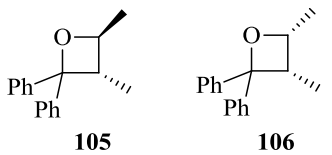
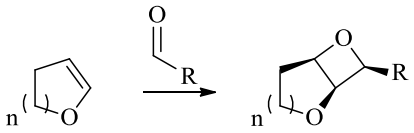


Figure 11 Stereochemistry in the formation of oxetanes

Generally, Paternò-Büchi reactions of alkenes within five and six-membered rings are reported to lead to *cis* products.[41] The stereoselectivity of reactions of alkenes in larger rings and acyclic alkenes depends upon whether reaction proceeds *via* the singlet or triplet

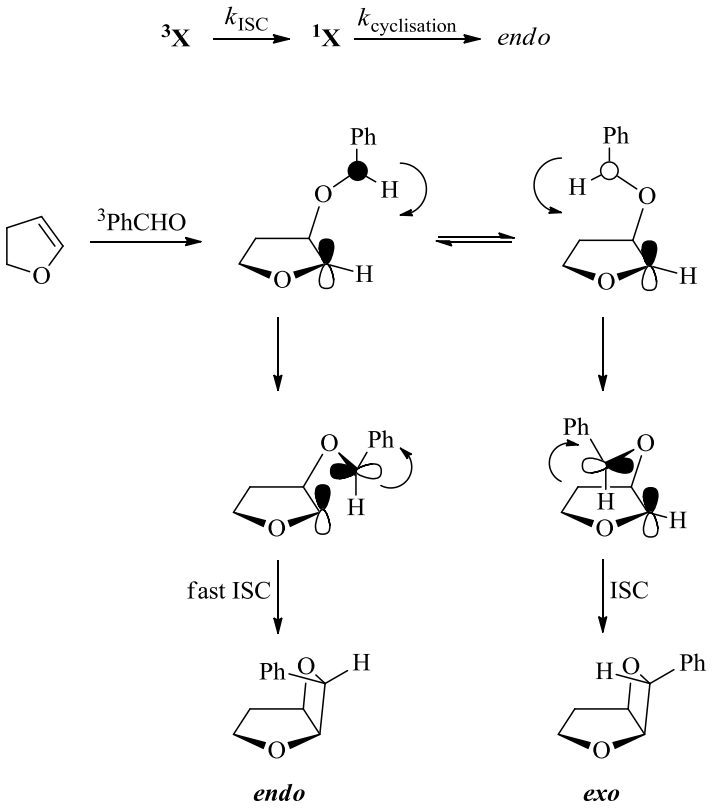
pathway.[42] For cyclic monoalkenes, formation of the thermodynamically less favoured *endo*-oxetanes has been observed. The Paternò-Büchi reaction of 2,3-dihydrofuran with triplet excited state benzaldehyde was reported to give oxetane with perfect regioselectivity and to strongly favour the *endo* product (Table 1).[43] Very good selectivity was also observed with cyclisation with 2,3-dihydropyran (*endo*:*exo* 9:1), and with an aliphatic aldehyde such as propionaldehyde, good *endo* selectivity is obtained (75%) when the concentration of alkene is kept low (< 0.1 M). The selectivity in the benzaldehyde cycloaddition is due to the the rapid ISC rate of aromatic aldehydes.



n	R	[alkene]	*Endo* %
1	Ph	-	100
1	Et	< 0.1 M	85
2	Ph	-	90
2	Et	< 0.1 M	75

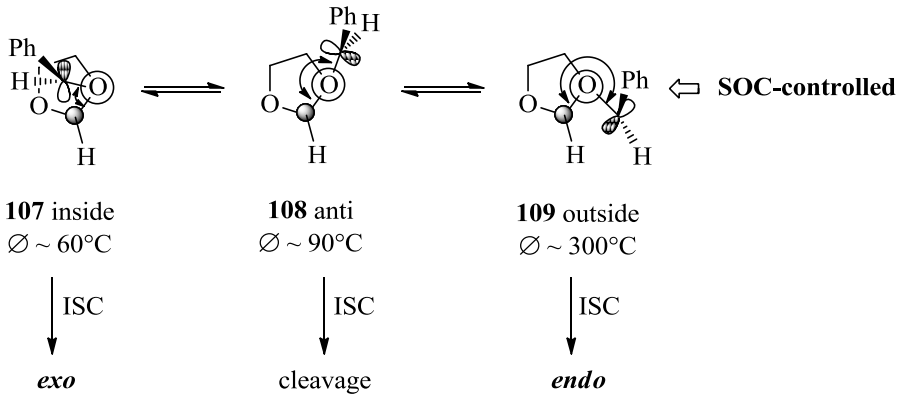
Table 1 Endo selectivity

To explain this selectivity, Griesbeck has proposed that the stereochemistry in the product would be induced by the preferred geometry in the triplet 1,4-biradical, which is prone to rapid ISC to the singlet state due to optimal spin-orbit coupling (SOC) (Scheme 27).



Scheme 27 Endo selectivity and SOC

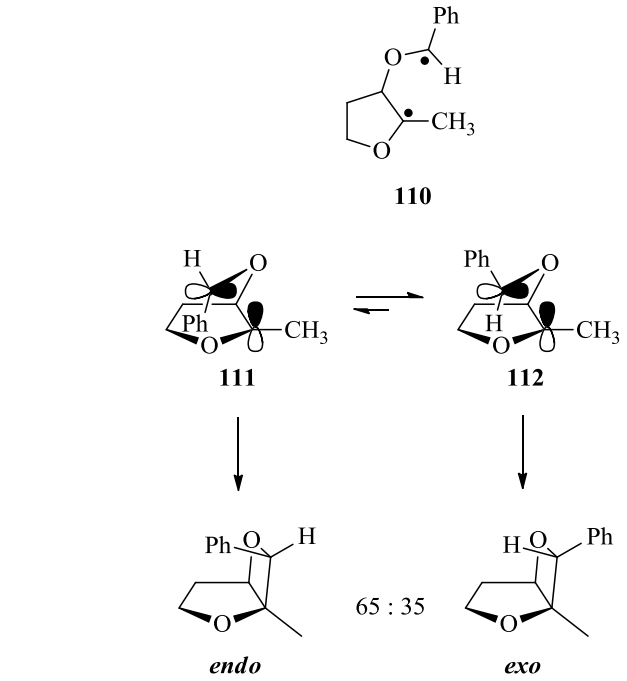
Favourable SOC geometry is provided by the phenyl ring being positioned perpendicular to the dihydropyran ring, such that the axes of the *p*-orbitals at the radical centres are oriented perpendicular to each other. Furthermore SOC is proportional to the distance between the two radical centres and the dihedral angle ϕ between the *p*-orbitals situated on these positions (Salem rules) (Scheme 28).[44]



Scheme 28 Dihedral angle for *endo*/*exo* selectivity

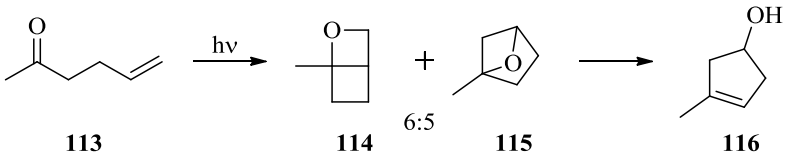
The two conformers **107** and **109** possess the appropriate geometry for effective SOC, but minimisation of interactions are greater in **109** which therefore favours the *endo* conformer. ISC from *anti* conformer **108** leads to cleavage of the singlet biradical and formation of starting material.

In the case of substituted cycloalkenes, the *endo*:*exo* ratio dropped significantly (Scheme 29). For instance, methyl dihydrofuran biradical **110** gave a 65:35 ratio of *endo*:*exo* bicycles. The methyl group plays a stabilising effect on the adjacent radical, leading to a high level of regioselectivity in the addition step. However, biradical **110** suffers from interactions between the methyl and the *β*-alkoxy substituents.[45] Conformers **111** and **112** have to be considered, and for steric reasons, **112** is preferably converted to the *exo* cycloproduct.



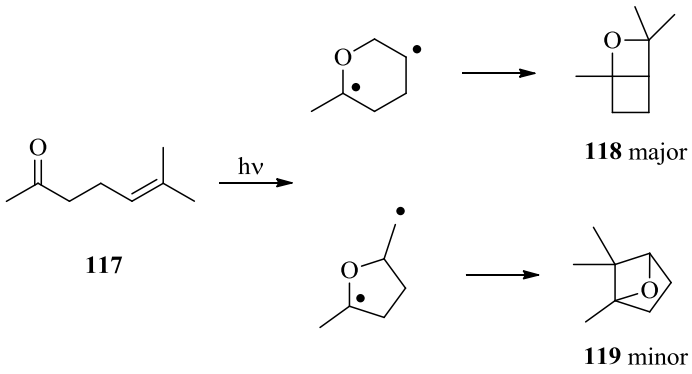
Scheme 29 Effect of substitution on the *endo*/*exo* ratio

The first intramolecular Paternò-Büchi reaction was published by Srinivasan in 1960.[46] Hex-5-en-2-one **113** was cyclised to form 2-oxabicyclo[2.2.0]hexane **114** along with regioisomer **115**, which degenerated to cyclopentenol **116** during purification (Scheme 30).



Scheme 30 Intramolecular Paternò-Büchi reaction

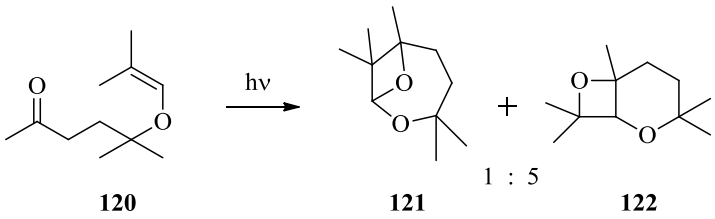
They suggested that the observed regioselectivity could be explained by the stability of the intermediate biradicals (Scheme 31).



Scheme 31 Biradical and selectivity

Major oxetane **118** was obtained *via* formation of the most stable biradical intermediate, while, minor product **119** arose from closure of a five-membered ring biradical.

A very interesting example of an intramolecular Paternò-Büchi reaction has been reported between a ketone and the double bond of an enol ether (Scheme 32).[47] Irradiation of **120** in benzene gave a mixture of adducts **121** and **122** where a *8-endo-trig* is favoured over a *7-exo-trig* mode of cyclisation.



Scheme 32 Cyclisation of an enol ether system

In general, however, the regio- and stereochemical outcome of the intramolecular Paternò-Büchi reaction is hard to predict, and each system should be considered independently.

Chapter 2

Synthesis of a photocyclisation precursor model system

In order to probe the possibility of synthesising dictyoxetane *via* a key Paternò-Büchi reaction, a model system **97** was proposed (Figure 12). It was envisioned that the keto enol ether **97** could be prepared from isopulegol **96**. The ketone functionality could be obtained by oxidation of the secondary alcohol in isopulegol, whereas the dihydropyran ring could be elaborated from the disubstituted alkene.

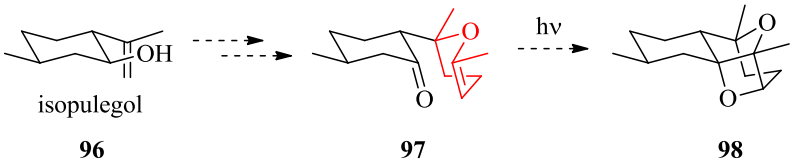


Figure 12 Proposed model system

A comparison can be made between model system **97** and the proposed photoprecursor to dictyoxetane **95** (Figure 13).

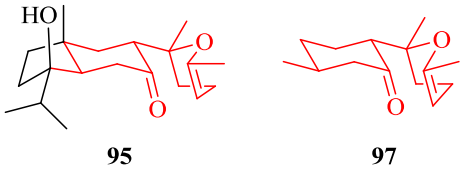
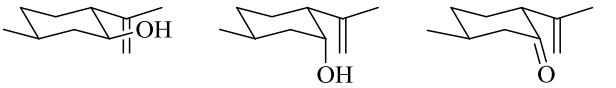


Figure 13 Comparing the photoprecursor to the model system

In **95**, the [5,6]-fused bicycle is a conformationaly "locked" structure, where the substituents on the six-membered ring are equatorial. The six-membered ring in **97** was anticipated to adopt a stable chair conformation, where the two alkyl substituents, and most importantly the dihydropyran ring, would be expected to be equatorial. Therefore, isopulegol is an ideal structure for further elaborations into a model photocyclisation precursor.

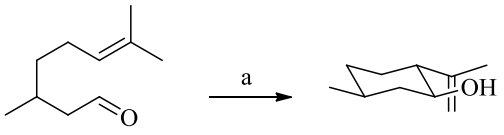
Racemic isopulegol **96** is commercially available in technical grade, also containing neo-isopulegol isomer **123** and isopulegone **124** (Figure 14). However, it could be purified by column chromatography.



isopulegol **96** neo-isopulegol **123** isopulegone **124**

Figure 14 Technical grade isopulegol

Isopulegol could also be obtained *via* a carba-ene reaction.[48] Cyclisation of citronellal with zinc bromide provided isopulegol in 84% yield (Scheme 33).



Citronellal **96**

Conditions: a) $ZnBr_2$, toluene, rt, 84%.

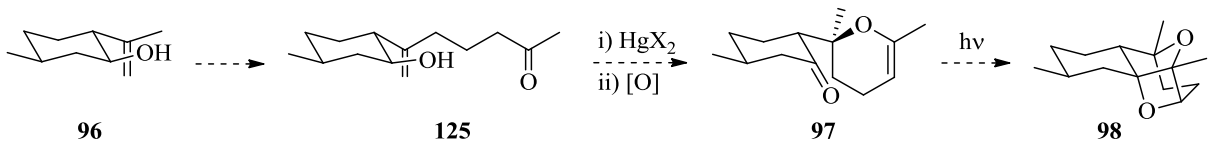
Scheme 33 Cyclisation of citronellal

Because technical grade isopulegol was more expensive than citronellal and required purification, fresh isopulegol was cyclised when needed.

From isopulegol, several approaches were investigated to construct the dihydropyran ring system.

2.1 Hg^{2+} catalysed cyclisation

The initial approach investigated was based on cyclisation of *δ,ε*-unsaturated ketone **125** into a six-membered ether ring using a mercury salt (Scheme 34).

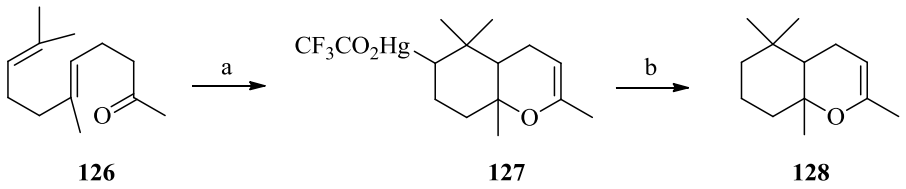


96 **125** **97** **98**

Scheme 34 Proposed cyclisation using mercury(II)

A study published in 1972 presented electrophilic cyclisation of isoprenoids using mercury salts as initiators.[49] Geranylacetone **126** gave rise to a bicyclic product **128** through

mercuration of the double bond and reduction of the organo-mercurial intermediate **127** (Scheme 35).

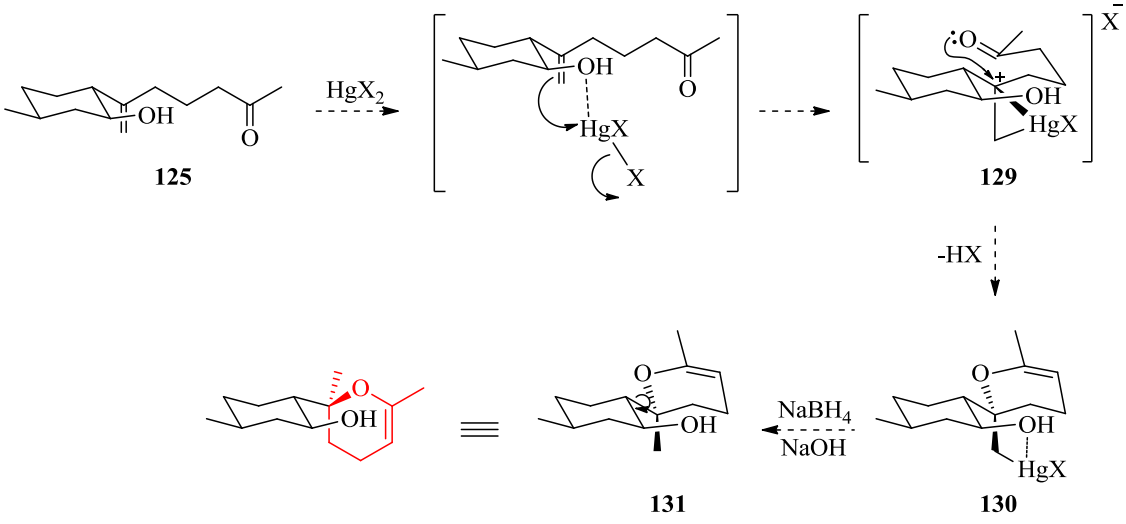


126 **127** **128**

Conditions: a) $Hg(CO_2CF_3)_2$, CH_3NO_2, -20 °C; b) $NaBH_4$, 62% over 2 steps.

Scheme 35 Mercury-mediated cyclisation of geranylacetone

Towards the formation of the dihydropyran ring system **131**, it was expected that addition of mercury onto the double bond in **125** would be directed by the presence of the oxygen of the adjacent alcohol (Scheme 36). Formation of the new stereocentre would therefore be controlled as mercuration of the double bond would occur from the top face and subsequent nucleophilic attack of the carbonyl from the opposite face in **129**.

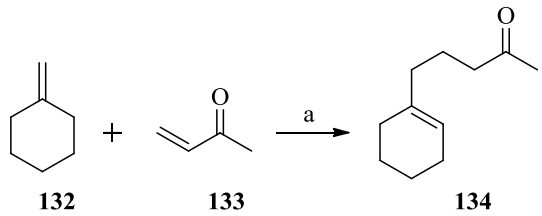


125 **129** **131** **130**

Scheme 36 Proposed directed mercuration and cyclisation

This approach necessitated access to olefinic ketone **125**. Starting from isopulegol, formation of a carbon-carbon bond could be achieved *via* a Lewis acid promoted intermolecular ene reaction with methyl vinyl ketone (MVK) **133**. Snider *et al.* have reported the ene reaction of

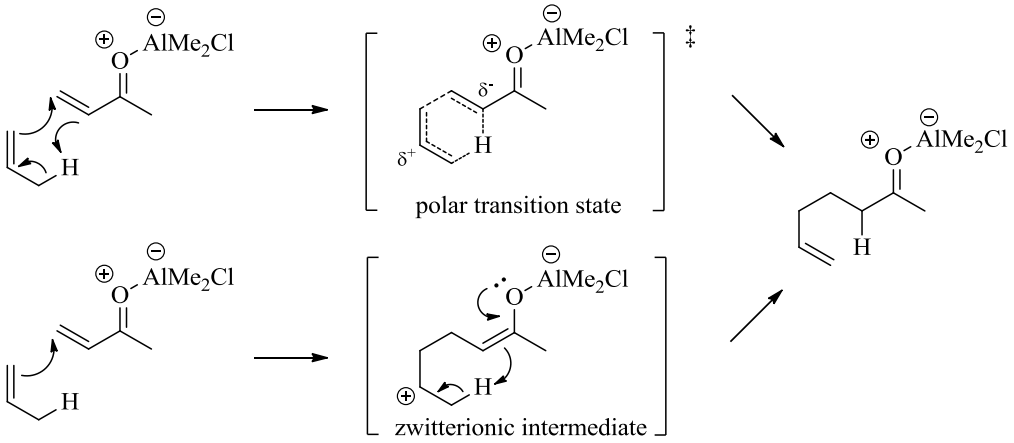
α,β-unsaturated ketones in the presence of alkylaluminium halides to generate *δ,ε*-unsaturated ketones (Scheme 37).[50]



Conditions: a) Me_2AlCl, CH_2Cl_2, -20 °C, 39%.

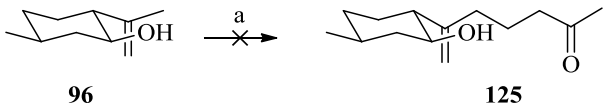
Scheme 37 Ene reaction

The Lewis acid catalysed ene reaction is a pericyclic reaction between an alkene possessing an allylic hydrogen (ene) and a compound containing a double or triple bond (enophile).[51] It proceeds either *via* a concerted mechanism with a polar transition state or a stepwise mechanism with a zwitterionic intermediate (Scheme 38). It is often difficult to distinguish between the two mechanisms, and it has been suggested that the energies are similar and that the lower energy process is substrate and catalyst dependant. The initial compound (ene) must possess a transferable allylic hydrogen, and the enophile should be electron deficient. The choice of the Lewis acid depends of the enophile as it is required to "activate" the system. Thus the reaction of the reactive 4 π-electron system MVK **133** with **96** could in principle be achieved with mild Me_2AlCl.



Scheme 38 Ene reaction mechanism

However, attempted ene reaction between isopulegol and MVK using Me_2AlCl failed to produce ketone **125**, and only starting material was recovered (Scheme 39).[52]

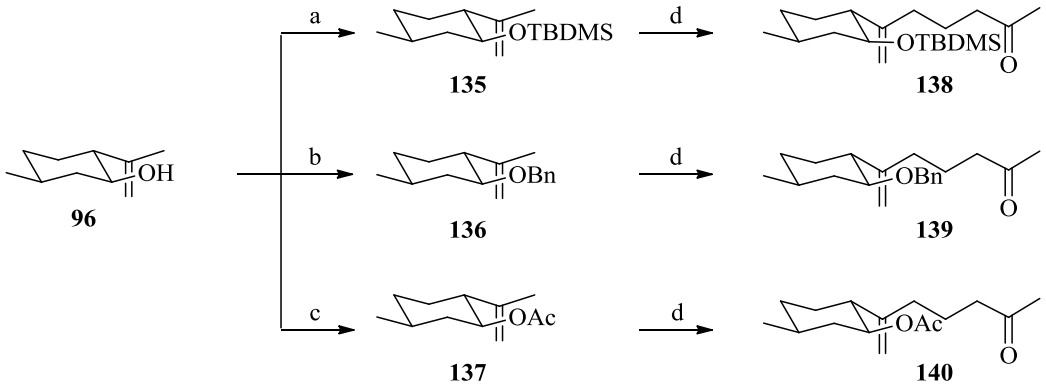


96 **125**

Conditions: a) MVK, Me_2AlCl, CH_2Cl_2, -20 °C.

Scheme 39 Ene reaction on isopulegol

Interactions between the free alcohol in **96** and the Lewis acid may possibly inhibit the reaction. Therefore the secondary alcohol was protected with different protecting groups, which could also potentially direct the subsequent cyclisation (*vide infra*). Silyl ether **135**, benzyl ether **136** and acetate ester **137** were obtained in 89, 94 and 52% yields respectively (Scheme 40). With these substrates in hand, ene reactions using equimolar amount of MVK and aluminium catalyst were performed under Snider's conditions.[53]

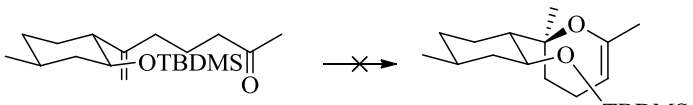


Conditions: a) TBDMSCl, imidazole, DMF, rt, 89%; b) BnBr, NaH, DMF, rt, 94%; c) Ac_2O, pyridine, toluene, rt, 52%; d) MVK, Me_2AlCl, CH_2Cl_2, -20 °C, **138** 41%, **139** 14%, **140** 27%.

Scheme 40 Ene reaction on protected isopulegol

The three unsaturated ketones **138**, **139** and **140** were obtained in modest yields. In each case, starting material was recovered and by products were also obtained but not characterised. Silyl ether proved to be the most efficient substrate in this reaction and so compound **138** was used to test the proposed cyclisation.

Triflate and acetate mercury salts were tested under several conditions (Table 2).[54]



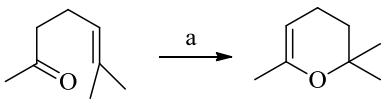
138 **141**

Entry	Conditions	Results
1	i) $Hg(OAc)_2$ 1.5 eq CH_3CN, 0 °C, 3 h ii) $NaBH_4$	not obtained
2	i) $Hg(CO_2CF_3)_2$ 1.5 eq CH_3NO_2, 0 °C→rt, o/n ii) $NaBH_4$	not obtained
3	i) $Hg(CO_2CF_3)_2$ 1.5 eq CH_3CN, 0 °C, 3 h ii) $NaBH_4$	not obtained
4	i) $Hg(CO_2CF_3)_2$ 1.5 eq, CH_3CN, 0 °C→rt, o/n ii) $NaBH_4$	not obtained
5	i) $Hg(CO_2CF_3)_2$ 2 eq, CH_3CN, -20 °C, 20 min ii) $NaBH_4$	not obtained

Table 2

All reactions gave complex mixtures which were difficult to purify. Unfortunately the desired heterocycle **141** was never obtained *via* this method.

An alternative approach was considered, using acidic conditions. Desmaële reported the acid-catalysed cyclisation of 6-methylhept-5-en-2-one **142** to 2,2,6-trimethyl-3,4-dihydropyran **143** (Scheme 41).[55]

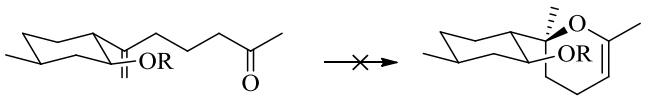


142 **143**

Conditions: a) H_2SO_4, 0 °C→20 °C, Amberlite® IR 120, rt, 85%.

Scheme 41 Acid-catalysed cyclisation

The acid-catalysed cyclisation conditions were applied to ketones **139** and **138**. (Table 3).



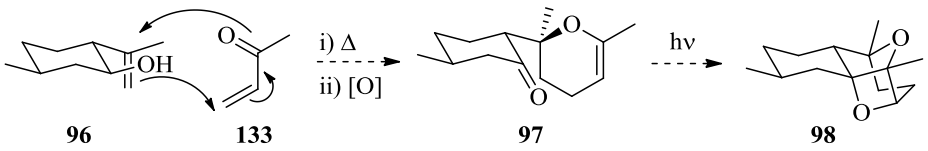
Entry	Substrate	Conditions	Results
1	**139** R= Bn	H_2SO_4 40%, rt	not obtained
2	**139** R= Bn	H_2SO_4 40%, reflux	not obtained
3	**139** R= Bn	H_2SO_4 40%, rt Amberlite® IR 120	not obtained
4	**139** R= Bn	$ClSO_3H$ 5 eq, nitropropane -78 °C→rt	not obtained
5	**138** R=TBDMS	*p*-TSA 0.2 eq, CH_2Cl_2 reflux	not obtained
6	**138** R=TBDMS	*p*-TSA 0.4 eq, CH_2Cl_2 reflux	not obtained

Table 3

Unfortunately, when the acid-catalysed cyclisation conditions were applied to ketones **138** and **139** none of the desired cyclisation product was observed. Starting materials were recovered in most cases with formation of small amounts of products. Analyses did not match with the required structure.

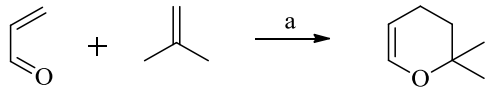
2.2 Diels-Alder cycloaddition

A second approach towards the six-membered cyclic enol ether **97** was a thermal hetero [4+2] cycloaddition between isopulegol and MVK (Scheme 42).



Scheme 42 Proposed hetero Diels-Alder cycloaddition

It has been shown that nonactivated mono olefins undergo thermal cycloaddition with acrolein as a diene.[56] In 1971, Joyce *et al.* reported the Diels-Alder addition of isobutylene to acrolein (Scheme 43).[57]

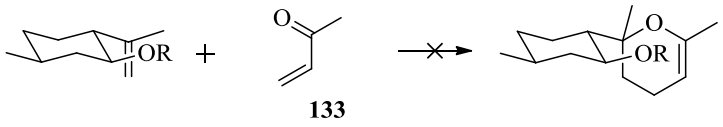


Conditions: a) 300 °C in a pressure vessel, 21%.

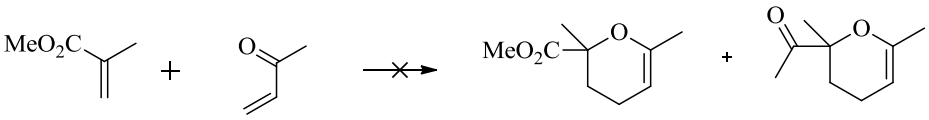
Scheme 43 [4+2] cycloaddition of acrolein

For the synthesis of **97**, MVK would be the diene and the dienophile would be the olefin of isopulegol.

Diels-Alder cycloaddition of MVK with isopulegol **96** and benzyl ether **136** was investigated at different temperatures and reaction times (Table 4). The use of three equivalents of dienophile has been reported to limit polymerisation.[58] However, in most cases polymers were obtained due to the ease of polymerisation of MVK. Analysis of the isolated products after column chromatography never proved the formation of the desired structure. The Diels-Alder reaction between MVK and the activated olefin methyl methacrylate **146** has been reported to give a mixture of pyran **144** and dimer **145**.[58] Attempts to achieve this reaction failed to give the cyclised compounds and again polymerisation was observed.



133



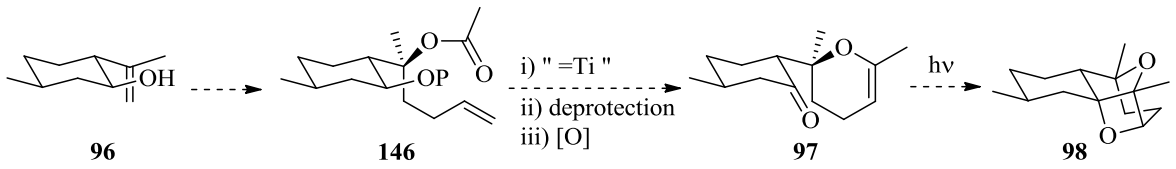
146 **133** **144** **145**

Entry	Substrates	Solvent	Temperature	Time	Results
1	R= H, **96**:**133** 3:1	toluene	80 °C	20 h	not obtained
2	R= H, **96**:**133** 3:1	toluene	165 °C	3 h	not obtained
3	R= H, **96**:**133** 3:1	toluene	250 °C	20 min	not obtained
4	R= H, **96**:**133** 3:1	toluene	300 °C	1 h	not obtained
5	R= Bn, **136**:**133** 3:1	toluene	80 °C	o/n	not obtained
6	**146**:**133** 3:1	toluene	200 °C in a sealed tube	1 h	not obtained
7	**146**:**133** 3:1	toluene	100 °C in a sealed tube	1 h	not obtained
8	**146**:**133** 3:1	toluene	230 °C in a sealed tube	2 h	not obtained
9	**146**:**133** 3:1	benzene	180 °C in a sealed tube	2 h	not obtained

Table 4

2.3 Takai-Utimoto metathesis

A third approach towards the cylic enol ether involved cyclisation of an olefinic ester using the Takai-Utimoto titanium alkylidene (Scheme 44).



Scheme 44 Proposed Takai-Utimoto metathesis

In 2006, Rainer *et al.* reported the total synthesis of Gambierol, a marine toxin containing eight ether rings and eighteen stereocentres (Figure 15).[59]

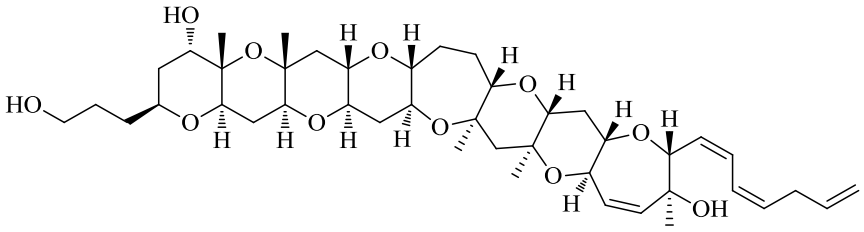
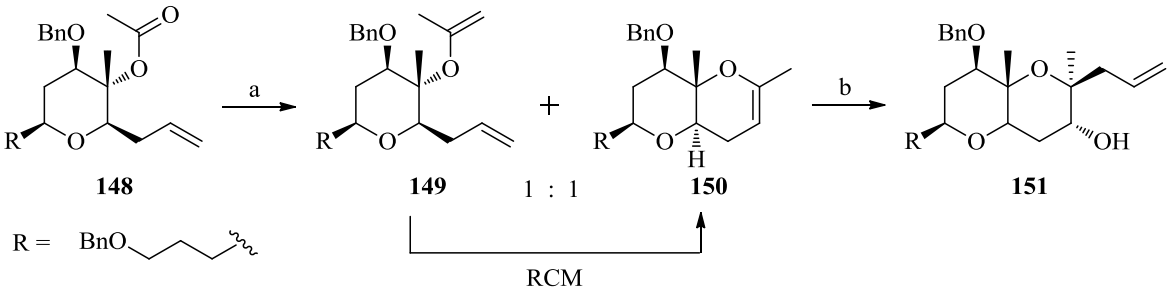


Figure 15 Gambierol

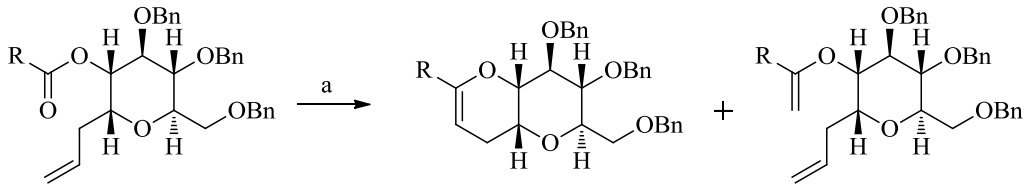
Their strategy towards the fused tetrahydropyran rings relied on the formation of cyclic enol ethers using the Takai-Utimoto reagent (Scheme 45).[60] When olefinic acetate **148** was subjected to titanium alkylidene conditions, a 1:1 mixture of cyclic **149** and acyclic **150** products was obtained. The mixture could then be submitted to Grubbs II catalyst to cyclise the remaining acyclic material.[61] Subsequent epoxidation and ring opening with allyl Grignard reagent furnished C-ketoside **151** which could then be subjected to the same conditions after acetylation.



Conditions: a) $TiCl_4$, CH_2Br_2, $PbCl_2$, TMEDA, Zn, THF, CH_2Cl_2; subsequent RCM with 2nd generation Grubbs catalyst, 80%; b) DMDO, CH_2Cl_2, allyl magnesium chloride, 50%.

Scheme 45 Takai-Utimoto strategy

In his study of methods of generating the cyclic enol ether, Rainer chose the Takai-Utimoto reagent over Tebbe or Petasis reagents because of its *in situ* preparation and its lower Lewis acidity. He also showed that formation of a cyclic enol ether was the result of an olefin metathesis-carbonyl olefination sequence, and was dependent on the steric environment of both the ester and olefin (Scheme 46).[62]



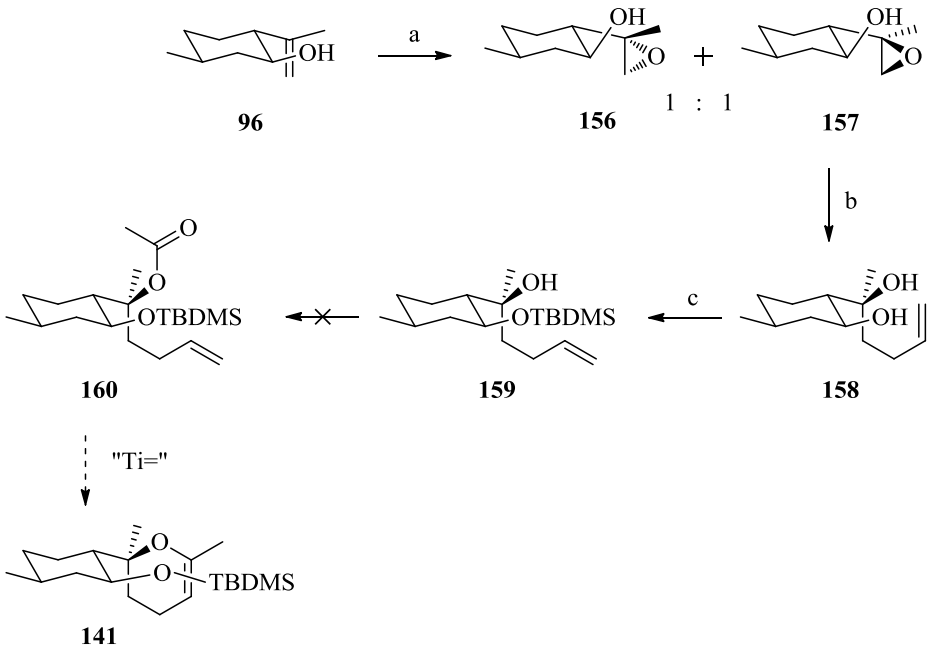
Ester	**154** : **155**	Yield (%)
152	1: 2.8	84
153	> 95 : 5	70

Conditions: a) $TiCl_4$, Zn, $PbCl_2$, CH_2Br_2, THF, TMEDA, CH_2Cl_2, 65 °C.

Scheme 46 Selectivity in Takai-Utimoto olefination

Creation of the required olefinic ester system **147** was investigated. Starting from isopulegol, epoxidation of the double bond with *m*-CPBA gave a 1:1 mixture of epoxides **156** and **157** (Scheme 47). Epoxidation of isopulegol has been reported by Kim *et al.*[63] They were unable to improve the stereoselectivity of this homoallylic epoxidation reaction. Epoxide stereochemistries were determined by comparison with the literature data. Opening of epoxide

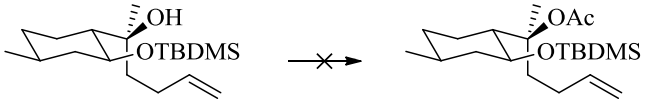
157 with commercially available allyl magnesium bromide gave diol **158** in a 74% yield. Addition of CuI did not improve the yield of this process.[63] With the desired stereochemistry in place, selective protection of the secondary alcohol gave silyl ether **159** in 89% yield.



Conditions: a) *m*-CPBA, CH_2Cl_2, 0 °C→rt, 58% combined yield; b) allylMgBr, Et_2O, -40 °C→rt, 74%; c) TBDMSCl, imidazole, DMF, rt, 89%.

Scheme 47 Proposed route to the olefinic ester

The desired olefinic ester **160** would then be obtained by acetylation of the tertiary alcohol. Several conditions were tested including the use of different acylating agents, bases, additives, solvents, and different temperatures and reaction times (Table 5). However, acetylation of the tertiary alcohol was not observed in any case.



159 **160**

Entry	Acetate (eq)	Base (eq)	DMAP (eq)	Solvent	Temp	Time	Results
1[64]	Ac_2O (1.5)	Py (1.5)	-	toluene	rt	o/n	SM
2	Ac_2O (1.5)	Py (1.5)	0.1	toluene	70 °C	2 h	SM
3[65]	Ac_2O (10)	Et_3N (10)	1	CH_2Cl_2	rt	22 h	SM
4	Ac_2O (71)	Et_3N (96)	0.1	-	50 °C	o/n	X
5	Ac_2O (71)	Py (165)	0.1	-	50 °C	5 days	X
6[66]	AcCl (1.1)	*n*-BuLi (1.1)	-	THF	reflux	1 h	SM
7	AcCl (1.1)	*n*-BuLi (1.1)	-	THF	reflux	o/n	X
8	AcCl (2)	*n*-BuLi (1.1)	-	THF	reflux	4 days	X
9[67]	Ac_2O (5)	TMSOTf (5%)	-	CH_2Cl_2	-78 °C→rt	o/n	X
10	Ac_2O (5)	TMSOTf (5%)	-	CH_2Cl_2	0 °C→rt	o/n	X
11	Ac_2O (5)	TMSOTf (5%)	-	CH_2Cl_2	0 °C	1 h	X

X: not obtained

Table 5

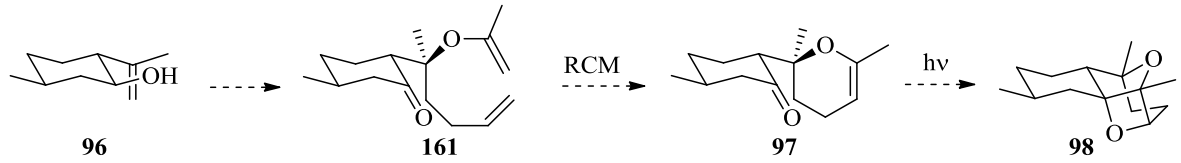
Although TMS-protection of a related tertiary alcohol has been reported,[63] it appeared that alcohol **159** was unreactive under any of the conditions tested, with only starting material observed under mildly basic conditions or short reaction times (entries **1**, **2**, **3** and **6**). Under more forcing conditions, complex mixtures were formed (entries **4**, **5**, **7** and **8**). Formation of

several products was observed when catalytic TMSOTf was used, but analysis did not indicate formation of an acetate.

This failure to introduce the ester functionality meant it was impossible to test the Takai-Utimoto reagent and subsequent cyclisation. Consequently, a related strategy was investigated.

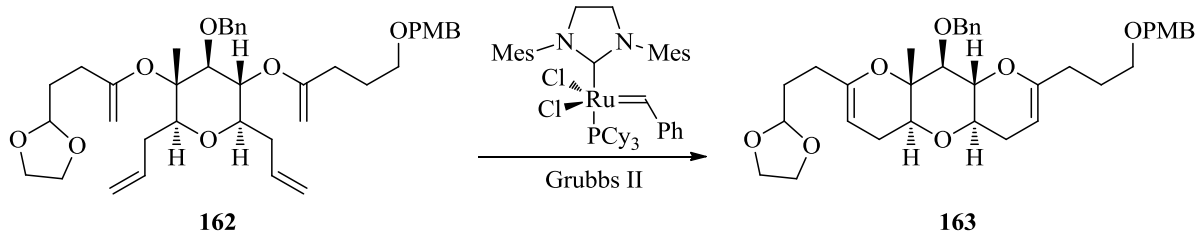
2.4 Ring Closing Metathesis approach

In a fourth approach, access to the cyclic enol ether was envisaged *via* a ring closing metathesis (RCM) of an olefinic acyclic enol ether **161** (Scheme 48).



Scheme 48 Proposed RCM

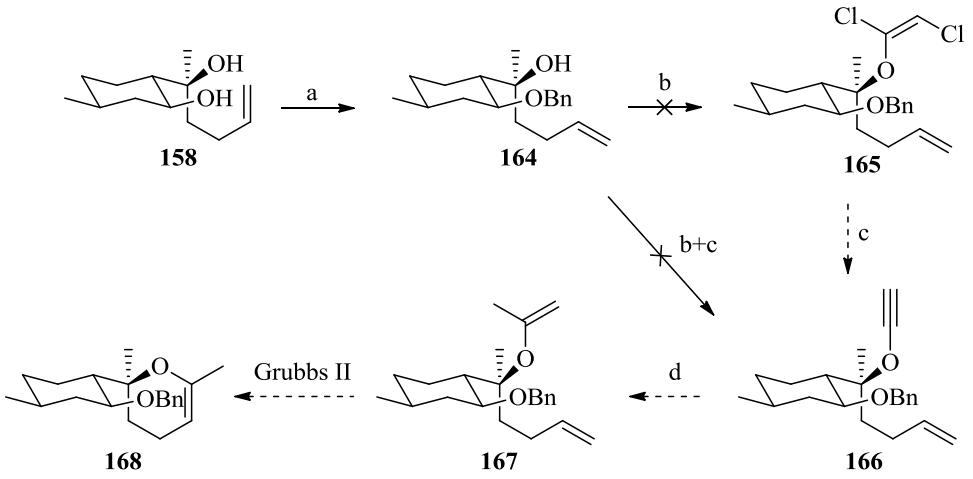
In 2005, Clark reported a simultaneous double RCM in the synthesis of gambieric acids.[68] Tricycle **163** was obtained in excellent yield when bis(enol ether) **162** was subjected to RCM by treatment with Grubbs II ruthenium catalyst.



Scheme 49 Double RCM, formation of two cyclic enol ethers

Towards the formation of enol ether **161**, secondary alcohol **158** was first selectively protected as the benzyl ether in 69% yield (Scheme 50).[69] Tertiary alcohol in **164** was then intended to be converted to alkynyl ether **166** following a method developed by Green *et al.*[70]

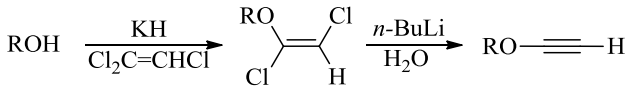
Enol ether **167** could subsequently be obtained by treatment of the triple bond with a methyl Grignard reagent.



Conditions: a) BnBr, TBAB, KOH, CH_2Cl_2, rt, 69%; b) KH, trichloroethylene, CH_2Cl_2, **165** never observed; c) *n*-BuLi, **166** never observed; d) conditions never tried: MeMgBr.

Scheme 50 Proposed route to olefinic enol ether

Greene and co-workers showed that *O*-alkynylation could be achieved in a one- or two-pot transformation by treatment of an alkoxide, obtained by treatment of the corresponding alcohol with KH, with trichloroethylene (TCE).[71] The dichloroenol ether intermediate could be converted to the acetylenic ether upon treatment with *n*-BuLi (Scheme 51).



Scheme 51 Formation of acetylenic ether

There are no studies and no rules that could indubitably predict the configuration of the dichloroenol ether. However, X-ray structures obtained from enol ethers derived from Stericol® and *trans*-phenylcyclohexanol showed a *trans* relationship between the two chlorines (Figure 16).[72]

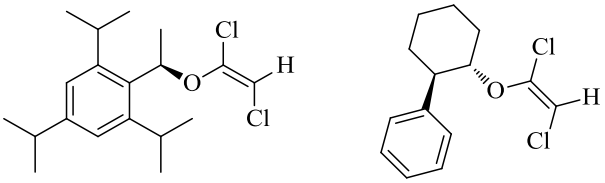
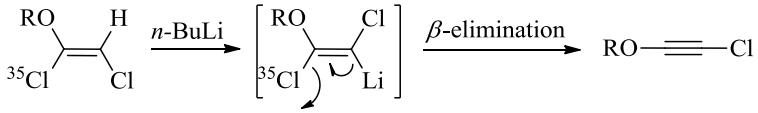


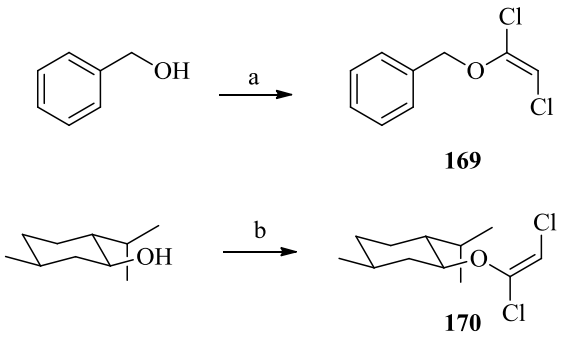
Figure 16 *Trans* dichloroenol ether

The ynol ether is subsequently available by treatment of the dichloroenol ether with *n*-BuLi. A very recent study of the mechanism confirmed the formation of a lithio-chloro carbenoid intermediate, obtained through vinylic proton abstraction. Also, by replacement of an atom of chlorine by an isotopically enriched one, *cis* β-elimination was exclusively proved to give the corresponding chloroynol ether (Scheme 52).



Scheme 52 *cis* β-elimination

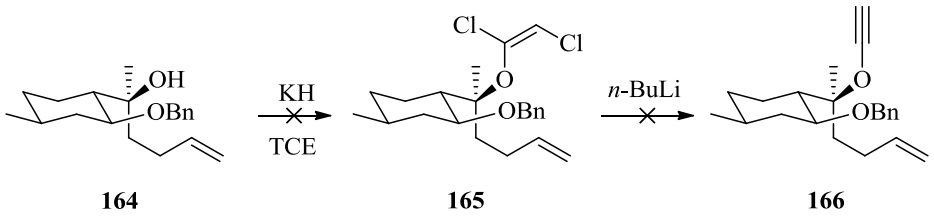
Greene's methodology was initially tested on simpler systems. Dichloroenol ethers **169**[73] and **170**[72] were obtained quantitatively from benzyl alcohol and menthol respectively (Scheme 53). **170** was reported in 94% yield as the (*Z*)-dichloroenol ether.



Conditions: a) KH, TCE, THF, -78 °C→rt, quant.; b) KH, TCE, THF, rt, quant.

Scheme 53 Formation of dichloroenol ethers

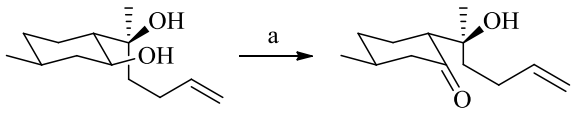
Initial formation of dichloroenol ether **165** was carried out on benzyl ether **164** under several conditions (Table 6). Conversion to the acetylenic ether **166** using *n*-BuLi was also tested (Scheme 54).



164 **165** **166**

Scheme 54 Attempts in formation of 165 and 166

As the equatorial benzyl ether may hinder this transformation, ketone **171** was prepared by TPAP-mediated oxidation of alcohol **158** in 65% yield (Scheme 55).[63]

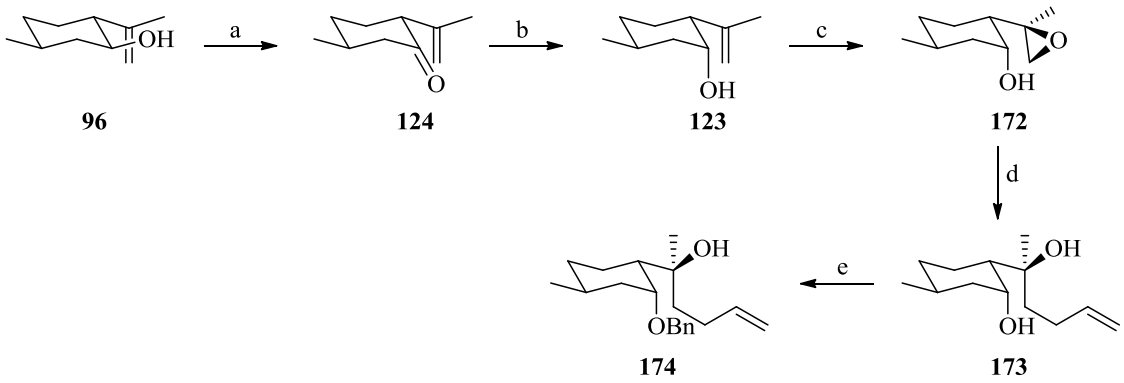


158 **171**

Conditions: a) TPAP, NMO, MS 4 Å, CH_2Cl_2, rt, 65%.

Scheme 55 Oxidation of diol **158**

Axial benzyl ether **174** was also prepared to investigate the transformation. Neoisopulegol **123** contained in technical grade isopulegol could be obtained by column chromatography. However, Kocienski reported a more convenient oxidation-reduction sequence.[74] Jones oxidation of isopulegol followed by stereoselective reduction with L-Selectride gave the axial alcohol **123**. Subsequent directed epoxidation using *tert*-butyl hydroperoxide in the presence of a catalytic amount of $VO(acac)_2$ led to a mixture of products, and gave after purification 27% of the desired (*R*)-epoxide **172**. Grignard addition of the allyl moiety occurred in 60% yield, and following protection of the secondary alcohol delivered benzyl ether **174.**



Conditions: a) PCC, CH_2Cl_2, rt, 82%; b) L-selectride, THF, -78 °C, 57%; c) ^{t}BuOOH, $VO(acac)_2$, toluene, rt, 27%; d) allylMgCl, CuI, THF, -30 °C, 60%; e) BnBr, TBAB, KOH, CH_2Cl_2, rt, 35%.

Scheme 56

Entry	Substrate R= Bn	KH eq	TCE eq	Additive (eq)	Temperature	Time	Results
1[75]	**164**	20	1.2	-	-78 °C→rt	5 h	SM
2	**164**	5	1.2 neat	-	0 °C→rt	40 min	SM
3	**164**	15	1.2 neat	-	0 °C→rt	o/n	SM
4[76]	**164**	2.3	1.2 neat	-	rt	2.5 h	SM
5	**164**	1.5	1.2	-	-78 °C→reflux	1 day	SM
6	**164**	1.5	1.2	-	reflux	1 day	SM
7	**164**	1.5	1.2	*n*-BuLi (3)	rt	1 day	SM
8	**171**	5	2 neat	-	0 °C→rt	o/n	SM
9	**171**	3	5 neat	18-c-6 (1.2)	rt	o/n	SM
10	**164**	10	10 neat	-	0 °C→rt	5 days	by product
11	**164**	2 (NaH)	10 neat	-	rt	o/n	SM
12	**164**	2	1.2	-	-78 °C→rt	o/n	SM
13	**174**	2	5 neat	-	rt	o/n	SM
14	**174**	1.5	1.2	*n*-BuLi (3)	-78 °C→rt	o/n	SM

Table 6

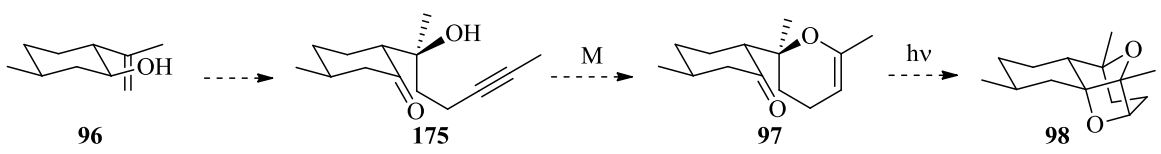
Unfortunately, all the tested conditions did not lead to the desired dichloroenol ether, with starting material being recovered in most cases (Table 6). However, in entry **10**, formation of a product, whose structure corresponds to transformation of the terminal alkene, was observed. ^{13}C NMR analyses showed disappearance of the terminal alkene CH_2 group (ca. 140 ppm). Appearance of an extra ethylenic CH peak (ca. 125 ppm) and shift of the ethylenic CH from ca. 140 to 126 ppm might correspond to a *trans* conformation of a double bond. Appearance of a CH_3 group (ca. 1.3 ppm) was also observed, and supposed to be the alkene substituent. However, the structure of this by product has not been fully elucidated but did not correspond to the desired enol ether.

Deprotonation of the tertiary alcohol occurred, since gas was released upon treatment with base (KH or NaH), indicating that nucleophilic attack by the alkoxide was the limiting step.

Changing the configuration of the secondary alcohol, and thus the level of steric hindrance, did not improve the reactivity of the tertiary alcohol. In light of these results, and those of acetylation above, further approaches based on intermolecular transformations of the tertiary alcohol were assumed unsuccessful. Consequently, an alternative synthesis was considered wherein the tertiary alcohol would be functionalised intramolecularly.

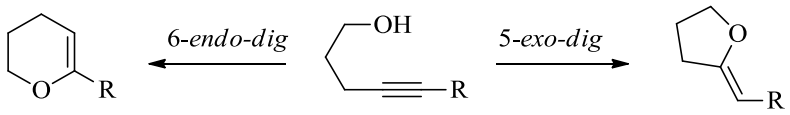
2.5 Transition metal-mediated cycloisomerisation of alkynol

A new approach to **97** was based on an intramolecular addition of the tertiary alcohol to the alkyne in **175** (Scheme 57).



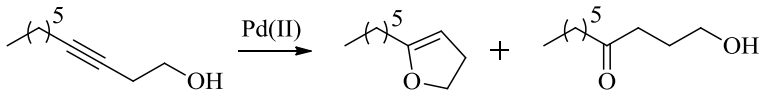
Scheme 57 Proposed metal-mediated cycloisomerisation

The metal-catalysed cycloisomerisation of alkynols has been reported to generate oxygen-containing heterocycles. It was anticipated that the main problem would be competition between the two modes of cyclisation: *exo-dig* versus *endo-dig*.[77]



Scheme 58 *exo-dig* and *endo-dig*

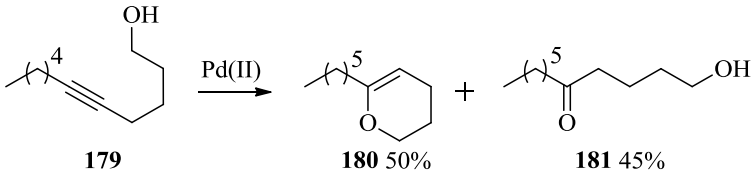
Palladium (II) species have been found to be effective in promoting the intramolecular addition of hydroxyl across acetylenes. The regioselectivity in the cyclisation of alkynol systems using $PdCl_2(PhCN)_2$ has been reported. Cyclisation of 3-decynol **176** gave the 5-*endo-dig* cyclisation product dihydrofuran **177**, alongside hydrolysed product **178 (**Scheme 59). Reaction under $PdCl_2$, aq. CH_3CN conditions gave exclusively the open hydrolysed product.



176 **177** 60% **178** 30%

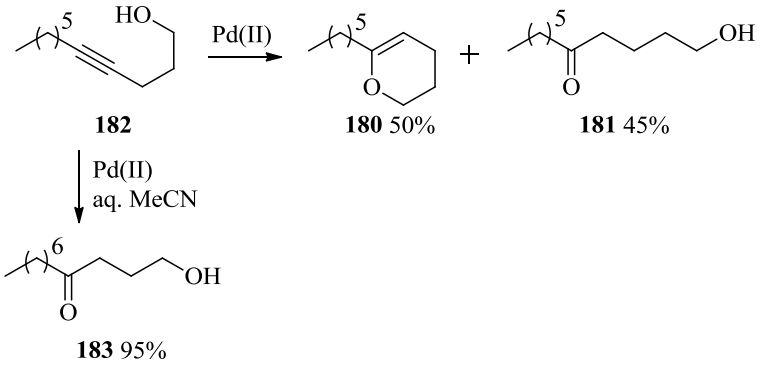
Scheme 59 Pd(II)-mediated 5-*endo-dig* cyclisation

5-Undecynol **179** cyclised in a 6-*exo-dig* manner to give dihydropyran **180** along with hydrolysed hydroxy ketone **181** (Scheme 60). Reaction under $PdCl_2$, aq. CH_3CN conditions led again to the open hydrolysed product.



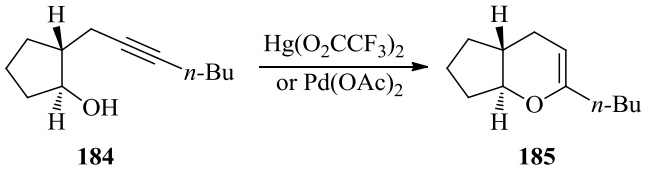
Scheme 60 Pd(II)-mediated 6-*exo-dig* cyclisation

In comparison, 4-undecynol **182** cyclised in a 6-*endo-dig* fashion to give the same results as previously (Scheme 61). However, with $PdCl_2$, aq. CH_3CN, 5-*endo-dig* cyclisation was preferred, giving the hydrolysed product, opened hydroxy ketone **183**.



Scheme 61 5-*endo-dig* cyclisation

Riediker and Schwartz have shown that alkynol **184** underwent cycloisomerisation to the dihydropyran product **185** under mercury (II)- or palladium (II)-promoted reaction conditions (Scheme 62).[78]



Scheme 62 Hg(II)- or Pd(II)-mediated dihydropyran cyclisation

Therefore, both substrates substitution patterns and the reaction conditions have been shown to direct the catalytic process towards a given mode of cyclisation. Therefore it was not possible to easily predict which way cyclisation would occur in the system of interest.

From isopulegol, different approaches were investigated to create the alkynol system (Figure 17).

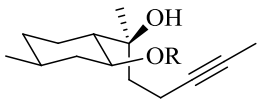
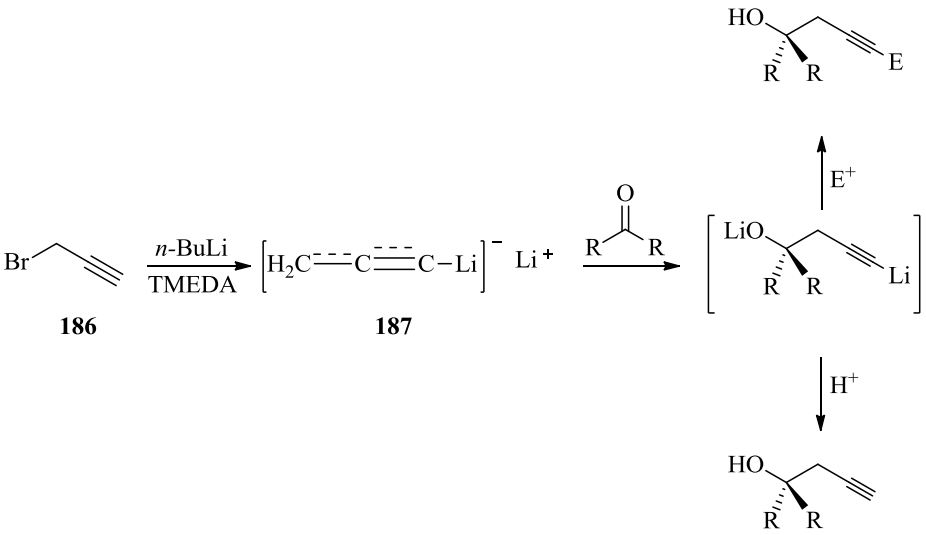


Figure 17 Alkynol system

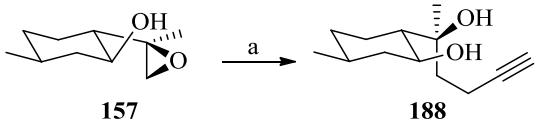
Dilithiation of propargyl bromide **186** with two equivalents of *n*-BuLi and TMEDA is reported to generate the 1,3-dilithiopropyne dianion **187**, which could react with carbonyls to produce homopropargyl alcohols in high yields (Scheme 63).[79]



Scheme 63 Formation of 1,3-dilithiopropyne dianion

The dilithium specie was first generated *via* lithium-halogen exchange and deprotonation of propargyl bromide with two equivalents of *n*-BuLi in the presence of TMEDA at -78 °C. After 40 min, a white precipitate was observed. Subsequent reaction with epoxide **157**

afforded diol **188** in 45% yield (the stability of this compound is discussed later) (Scheme 64). Because of the presence of the alcohol function, which would first be deprotonated, four equivalents of propargyl bromide and eight equivalents of butyllithium were employed.

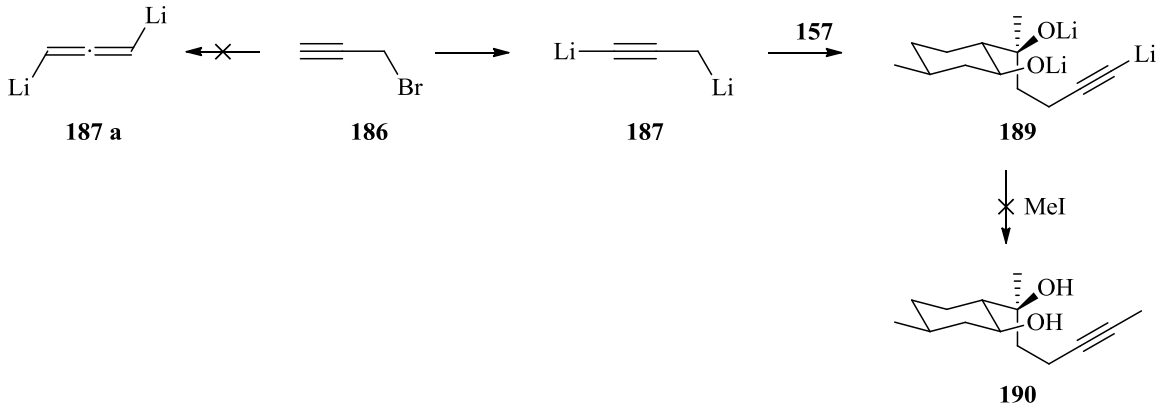


157 **188**

Conditions: a) propargyl bromide, *n*-BuLi, TMEDA, Et_2O, hexane, -78 °C→rt, 45%.

Scheme 64 Opening of epoxide with dilithium reagent

Propargyl and allenyl organometallic reagents are powerful nucleophiles which can exist in equilibrium with each other.[79] Presumably the potential formation of allenyl dianion **187 a** was in the present case disfavoured (dianion destabilised) over generation of the propargylic dianion **187**, since addition occurred with high regioselectivity. However, attempts at *in-situ* trapping of the lithium intermediate **189** with MeI failed to give **190** (Scheme 65).

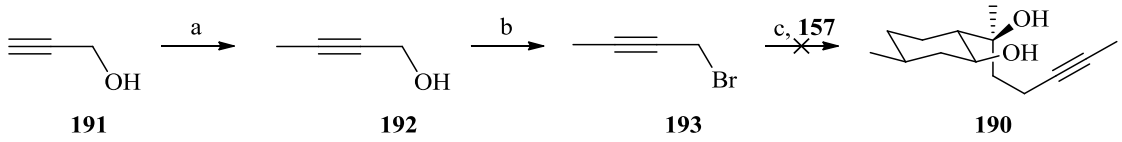


187 a **186** **187** **189** **190**

Scheme 65 Allenyl and propargylic dianions

In order to directly install the terminal methyl group, it was decided to synthesize a methyl-substituted propargyl lithium anion. Methylation of propargyl alcohol **191** was carried out with lithium amide and MeI,[80] and gave after distillation 26% w/w of a 20:1 mixture of alkylated **192** and non-alkylated **191** compounds, along with 36% w/w of a 6:1 mixture. As

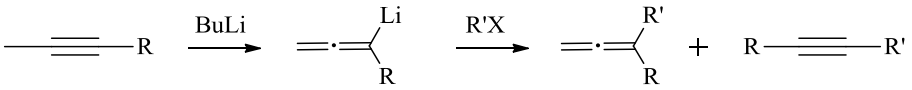
the two compounds display very close boiling points and could not be easily further purified, the first fraction was used for subsequent investigations. Methylated propargyl alcohol **192** was converted to bromide **193**, which was used without further purification (Scheme 66). Subsequent treatment of **193** with one equivalent of *n*-BuLi was expected to undergo lithium-halogen exchange only. Reaction with epoxide **157** resulted in a complex mixture of products, from which the desired product **190** could not be isolated.



Conditions: a) Li, liq. NH_3, $Fe(NO_3)_3$, MeI, Et_2O, -78 °C→rt; b) PBr_3, py, Et_2O, -40 °C, 91% crude; c) *n*-BuLi, TMEDA, Et_2O, hexane, -78 °C.

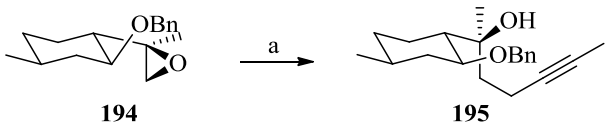
Scheme 66 Addition of but-2-ynyl anion

It has been demonstrated that 2-alkynes may be metallated by *n*-BuLi (Scheme 67). Regiospecific deprotonation led to "3-metallated 1,2-dienes" and reaction with electrophiles would give both acetylenic and allenic derivatives.



Scheme 67 Acetylenic and allenic adducts from2-butyne

Although a mixture of products was expected, it was decided to test this method using 2-butyne and **157**. Unfortunately no reaction occurred, and starting material was recovered. When the reaction was carried out with benzyl ether **194** (*vide infra*), formation of a complex mixture of products was observed. However, formation of the desired product **195** was confirmed by TLC analysis but was not isolated (Scheme 68).

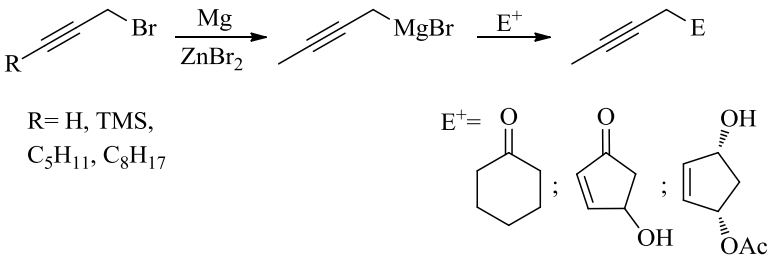


194 **195**

Conditions: a) 2-butyne, TMEDA, *n*-BuLi, Et_2O, -25 °C→10 °C, yield not recorded.

Scheme 68 Reaction of 2-butyne anion on epoxide **194**

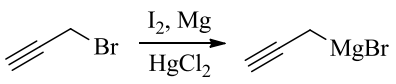
Addition of Grignard reagents to epoxide systems was also investigated. An interesting study, published in 2007, dealt with the preparation and reactions of propargyl and substituted propargyl Grignard reagents, catalysed by $ZnBr_2$ so avoiding the commonly used mercury salts (Scheme 69).[81]



Scheme 69 $ZnBr_2$-catalysed reaction of propargyl Grignard reagents

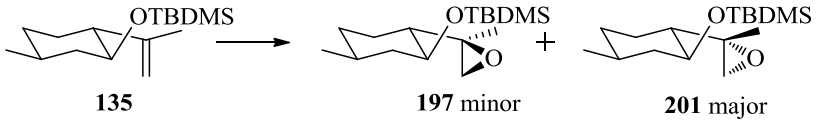
However, attempts at preparing Grignard reagents under these conditions (4% mol $ZnBr_2$) with propargyl bromide or methyl-propargyl bromide failed. Titration (phenanthroline and methyl orange) was unsuccessful and attempted reactions on epoxide **157** resulted only in recovery of starting material.

Subsequent efforts focused on the preparation of propargyl magnesium bromide using a mercury catalyst (Scheme 70). As no reliable method of titration could be found, a large excess of Grignard reagent was prepared prior to reaction with different epoxides.[82]



Scheme 70 Propargyl Grignard reagent

Initially, alcohol **157** was protected under standard conditions as the benzyl ether **194** (84% yield), and as silyl ethers **196** and **197** (57 and 75% yield respectively). Silyl protection occurred in lower yields compared to benzylation, probably due to steric hindrance. Efforts to optimise these yields by protecting isopulegol with TBDMSCl and epoxidising the silyl ether product resulted however in the undesired diastereomeric (*S)*-epoxide **201** as the major product (ratio not recorded) (Scheme 71).

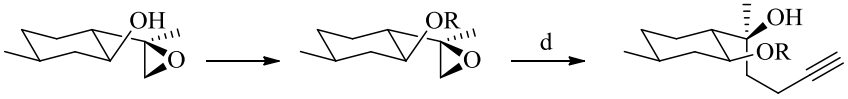


135 **197** minor **201** major

Conditions: a) *m*-CPBA, CH_2Cl_2, rt, 98% of a mixture of epoxides.

Scheme 71 Formation of major (*R)*-epoxide

A 10:1 ratio of propargyl magnesium bromide:epoxide was used, and Grignard addition was investigated on several epoxides (Scheme 72).



157

a **194**, R= Bn
b **196**, R= TES
c **197**, R= TBDMS

188, R= H
198, R= Bn
199, R= TES
200, R= TBDMS

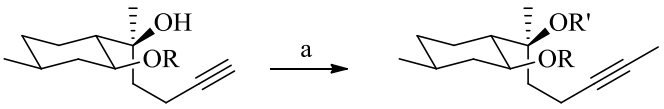
Conditions: a) BnBr, NaH, DMF, 0 °C→rt, **194** 84%; b) TESCl, imidazole, DMF, rt, **196** 57%; c) TBDMSCl, imidazole, DMF, rt, **197** 75%; d) Propargyl bromide, Mg, I_2, $HgCl_2$, Et_2O, 0 °C→rt, **188** 84%, **198** 76%, **199** 70%, **200** 92%.

Scheme 72 Grignard reaction on epoxides

The desired alkynol systems were obtained in varying yields. Consumption of starting material was observed in all cases and the difference in yields was due to the formation of greater or lesser amounts of by products and the complexity of purifications. Even though formation of diol **188** was achieved in one case in 84% yield, this proved irreproducible and the diol was obtained in poor yields in most cases. This was due to numerous by products

being formed during the reaction process, which rendered purification complicated. Also, fast degradation of the product was observed even when kept under nitrogen at low temperature. Consequently diol **188** needed to be used immediately after formation.

Methylation of the terminal triple bond with *n*-BuLi and MeI was thus carried out on protected compounds **198**, **199** and **200**. However *O*-methylation of the tertiary alcohols was observed in some cases and the yields consequently decreased (Scheme 73).



198 R= Bn
199 R= TES
200 R= TBDMS

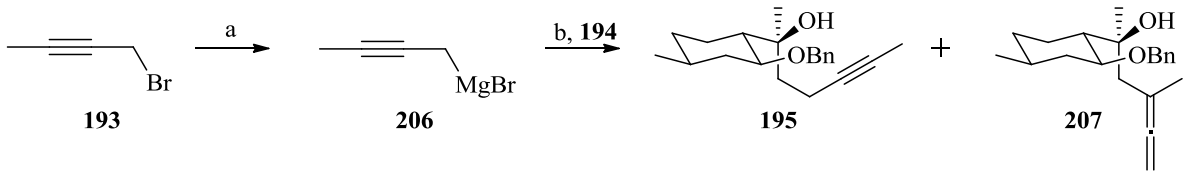
195 R= Bn, R'= H, 84%
203 R= TES, R'= Me, 35%
204 R= TBDMS, R'= H, 43%
205 R= TBDMS, R'= Me, 25%

Conditions: a) *n*-BuLi, MeI, THF, -78 °C→rt.

Scheme 73 *C*- and *O*-methylation

When benzyl ether **198** was subjected to methylation, alkylated alkyne **195** was obtained in 84% yield. However, triethylsilyl ether **199** gave a complex mixture of products and starting material (65%), where di-methylated product **203** was isolated in 35% yield. The product of single methylation of the alkyne was not isolated. *O*-Methylation was also observed with the *tert*-butyl dimethylsilyl ether **200**, where mono- **204** and di-methylated **205** products were obtained in 43 and 25% respectively.

To avoid this *O*-methylation problem, methyl propargyl Grignard was prepared from propargyl alcohol. The Grignard reagent **206** was prepared as described previously and reacted with benzyl ether epoxide **194**. Formation of the desired propargylic alcohol **195** was observed but was not isolated, alongside allenic product **207**, which was otained in 30% yield (Scheme 74). Due to the difficulties in purification, this route was abandoned.

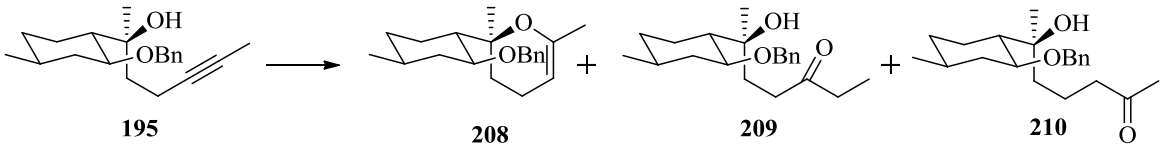


193 **206** **195** **207**

Conditions: a) Mg, I_2, $HgCl_2$, Et_2O, 0 °C; b) Et_2O, 0 °C→rt, **195** yield no recorded, **207** 30%.

Scheme 74 Methyl propargyl Grignard addition

As the *C*-methylated benzyl ether propargyl **195** was obtained in better yields, cyclisation was first tested on this substrate. Reactions were usually carried out in CH_2Cl_2 at rt, in the presence of molecular sieves (3 Å) and a cyclisation catalyst (Table 7). In every case, the cyclic enol ether **208** was obtained *via* a 6-*endo*-*dig* cyclisation, along with two hydrolysed forms **209** and **210**.



195 **208** **209** **210**

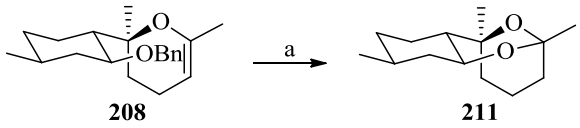
Entry	Catalyst (eq)	Conditions	**208**	**209**	**210**
1	$Pd(OAc)_2$ (0.65)	AcOH	observed	28%	observed
2	$Pd(CH_3CN)_2Cl_2$ (0.1)	CH_3CN	observed	observed	28%
3	$Pd(OAc)_2$ (0.65)	AcOH	42%	23%	observed
4	$PtCl_4$ (5% mol)	-20 °C	minor	observed	observed
5	Au (I)		3 products observed but SM remained		
6	Au (III)		3 products observed but SM remained		
7	$Pd(OAc)_2$ (0.65)	SM, dried[a]	34%	9%	observed
8	$Pd(OAc)_2$ (0.65)	SM, dried[a] extra MS 3 Å	47%	6%	observed

[a] Starting material was dried from water by azeotrope evaporation with toluene prior to reaction (× 3)
Au (I)= [bis(trifluoromethanesulfonyl)-imidate] (triphenylphosphine) gold
Au (III)= dichloro(2-pyridine carboxylate) gold

Table 7

The desired cyclic enol ether **208** was formed in 34-47% yield, but degraded quickly, mainly to its open form **210**, and also under acidic conditions (silica). The best 47% yield was obtained when the starting material was first evaporated with toluene and more molecular sieves were added (2 × mass SM). However, formation of ring-opened products was impossible to avoid. Hydroxy ketone **209** was presumably formed by hydrolysis of the 5-*exo*-*dig* cyclisation product, although this intermediate has never been isolated.

At this stage, deprotection of the secondary alcohol was necessary. Benzyl enol ether **208** was deprotected *via* dissolving metal reduction. However after reaction with Li/liq. NH_3 and acidic work up, acetal **211** was formed in 77% yield as a single product (Scheme 75).

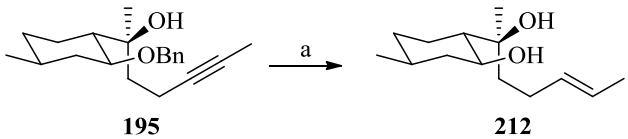


208 **211**

Conditions: a) Li, liquid NH_3, THF, EtOH, -78 °C→rt, 77%.

Scheme 75 Deprotection of **208** and acetal formation

It seemed that the cyclic enol ether would be too sensitive and would not survive strongly basic or acidic deprotection conditions, so it was decided to deprotect the secondary alcohol before cyclisation. Unfortunately, attempted deprotection of **195** also resulted in reduction of the triple bond, affording alkene diol **212** quantitatively (Scheme 76).

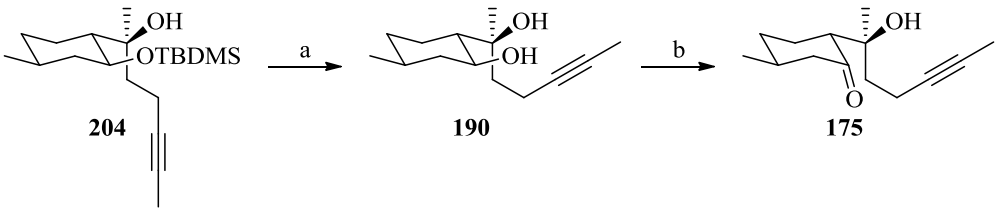


195 **212**

Conditions: a) Li, liquid NH_3, THF, EtOH, -78 °C→rt, 97%.

Scheme 76 Deprotection of **195** and reduction of triple bond

Silyl ether **204** was deprotected under TBAF conditions, leading to diol **190** in 91% yield. The secondary alcohol was oxidised with TPAP/NMO to give ketone **175** in 88% (Scheme 77).



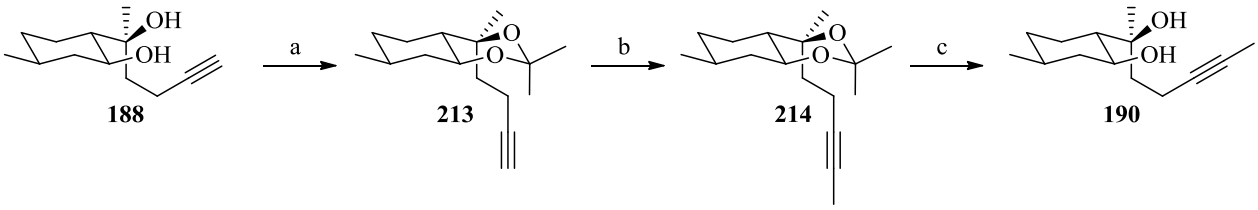
Conditions: a) TBAF, THF, rt, 91%; b) TPAP, NMO, MS 4 Å, CH_2Cl_2, 88%.

Scheme 77 Formation of ketone **175**

To summarise, benzyl ether **198** did undergo methylation of the terminal triple bond and subsequent cyclisation, but could not be converted into the keto-cyclic enol ether precursor of the oxetane target. Methylation of the alkyne in silyl ether **199** could not be accomplished without competing *O*-methylation and formation of by products. Alkylation of silyl ether **200** was a cleaner reaction but *O*-methylation could not be avoided. However, subsequent oxidation of the secondary alcohol provided an alternative substrate **175** to test the cyclisation into a cyclic enol ether.

A different route to **175** was therefore investigated to circumvent these troublesome steps.

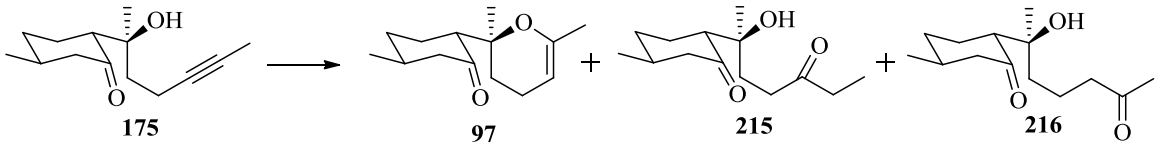
The two alcohols in alkynol **188** were simultaneously protected as an acetonide **213** in 85% yield (Scheme 78). Methylation of the terminal alkyne occurred in 92% yield and subsequent deprotection of the acetal in AcOH delivered diol **190** in 88% yield.



Conditions: a) dimethoxypropane, *p*-TSA, Et_3N, THF, rt, 85%; b) *n*-BuLi, MeI, THF, -78 °C→rt, 92%; c) aqueous 60% AcOH, rt, 88%.

Scheme 78 Formation of **190**

Cyclisation was attempted with keto alkynol **175** (Table 8).



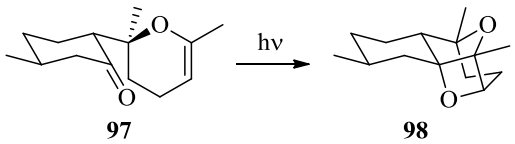
Entry	Catalyst (eq)	Conditions	**97**	**215**	**216**
1	$Pd(OAc)_2$ (0.1) + addition until disappearance of SM	MS, dried[a] extra MS 3 Å	34%	observed	observed
2	$Pd(OCOCF_3)_2$ (0.1)	SM, dried[a]		by product	
3	$Pd(OAc)_2$ (0.3) + addition until disappearance of SM	SM, dried[a]	57%	observed	observed

[a] Starting material was dried of water by azeotrope evaporation with toluene prior to reaction (× 3)

Table 8

At best, keto enol ether **97** was achieved in 57% yield. Once again, formation of hydrolysis products is observed during the reaction and the purification process. Cyclisation with $Pd(OCOCF_3)_2$ led to the formation of a rearrangement product whose structure has not been fully determined.

2.6 Photocyclisation results



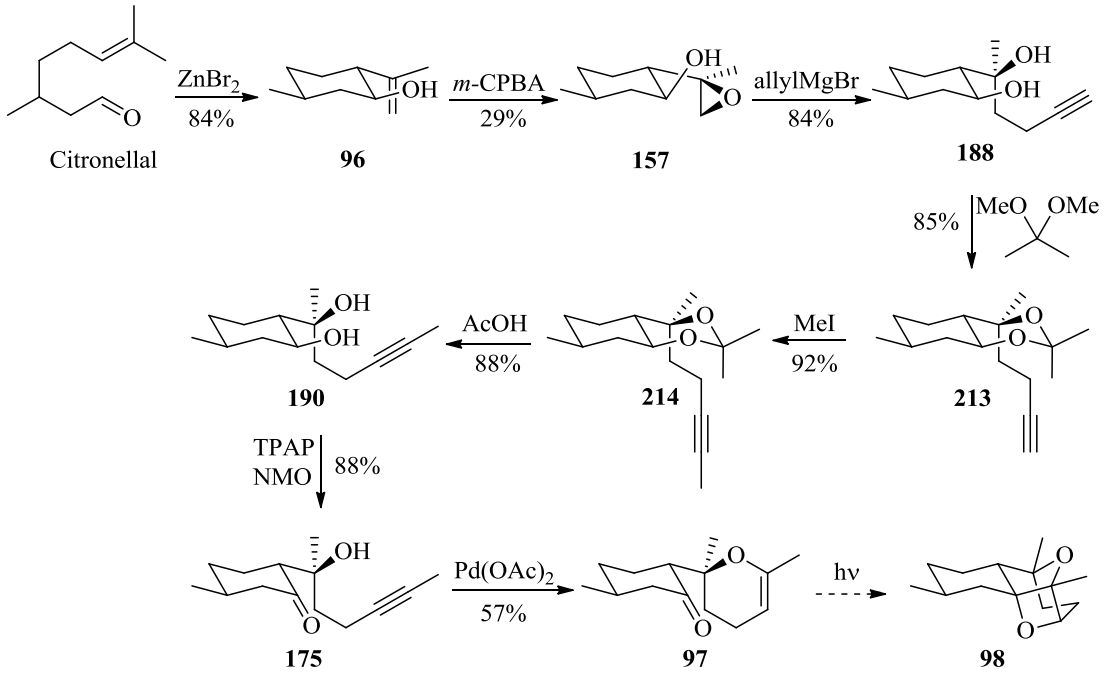
97 **98**

Scheme 79 Photocyclisation

Photocyclisation was attempted on the model system **97** (Scheme 79). **97** was irradiated in a solution of hexane (0.005 M) using a 250 W medium pressure Hg-arc lamp. Evolution of the reaction was very slow and led to a complex mixture of products with starting material remaining. Purification by column chromatography followed by HPLC purification of the main product gave 1 mg of a new compound having the right mass. Further analyses could not be carried out on such a low amount of material.

2.7 Summary

A successful route to the model photocyclisation precursor keto enol ether **97** has been developed in a 7% overall yield starting from citronellal (Scheme 80). Attempted photocyclisation of **97** was unsuccessful, although this reaction needs to be repeated and investigated further. The concentration of the solution, the reaction solvent and the temperature may be parameters to study. The power of the lamp may be also important.


ZnBr2
84%
m-CPBA
29%
allylMgBr
84%
Citronellal
96
157
188
85%
MeO
OMe
AcOH
88%
MeI
92%
190
214
213
TPAP
NMO
88%
Pd(OAc)2
57%
hν
175
97
98

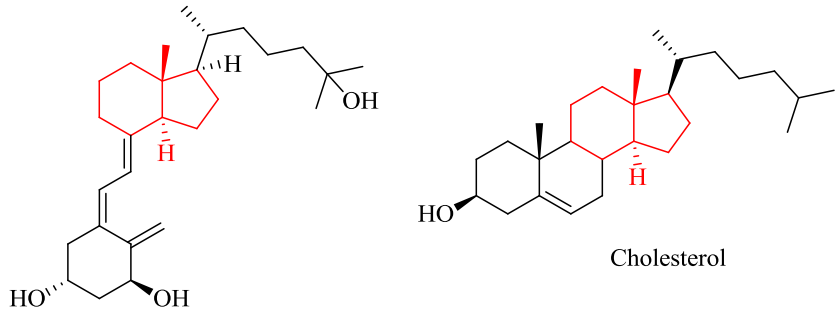
Scheme 80

Chapter 3

Studies towards the synthesis of a *trans*-hydrindane

3.1 Introduction

The *trans*-hydrindane system represents a key substructure in several classes of bioactive natural products including terpenes, steroids[83] and vitamin D[84] (Figure 18).



Calcitrol = 1,25-dihydroxyvitamin D_3

Figure 18 Naturally occurring *trans*-hydrindanes

In the synthesis of these elaborate molecules, creation of a *trans*-ring junction in the [4.3.0]-fused bicycle can be problematic since the relative stability of *cis*- and *trans*-hydrindanes is dependent on the substitution pattern of the two rings.

Allinger and Tribble reported the conformational analysis of the hydrindane ring system.[85] Calculations of the torsion angles in [5,6]-fused bicycles showed that the *trans* isomer is more strained than the *cis* compound. In the *trans*-ring junction model, the six-membered ring is supposed to adopt a chair conformation, where the three-carbon chain of the five-membered ring is forced to twist to fit the equatorial positions (Figure 19). The *cis* isomer on the other hand is flatter, with one carbon in an equatorial- and the other carbon in an axial-like position on the six-membered ring.

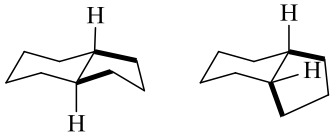


Figure 19 *Trans*- and *cis*-hydrindane conformations

They also calculated the difference of energy between *cis*- and *trans*-fused hydrindanes (Figure 20) and hydrindanones (Figure 21). When a methyl group is placed at the bridgehead, the bicyclic skeleton tends to rigidify.

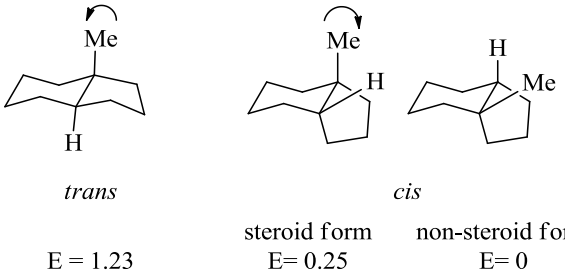


Figure 20 Calculated energies for *trans* and *cis*-hydrindane

For the *trans* isomer, the methyl group is necessarily axial to the six-membered ring and therefore the energy of the molecule increases (Figure 20). For the *cis* isomer, there were two possible conformations. In the "non-steroid form", the methyl group is positioned on the equatorial bridgehead position and the obtained conformation was more stable than the *trans*. However, in the "steroid" form, the methyl group is in an axial position with regard to the six-membered ring, and the energy is higher than the non-steroid one. So in general, the presence of a methyl group tends to stabilize the *cis* hydrindane relative to the *trans* structure even with two axial substituents (steroid form). This was because in the *cis* conformation, the methyl group is twisted away from the six-membered ring but is pushed back into the cyclohexane ring in the *trans* isomer.

Calculations showed that the stability order is also different for methylhydrindanones (Figure 21). Within the three ketones, the *trans* isomer is the highest in energy due to the same strain effects discussed before. For the *cis* conformations, the steroid form is the most stable. This is due to the methyl and the carbonyl groups being approximately eclipsed, while in the non-steroid form the carbonyl is approximately eclipsing the hydrogen.

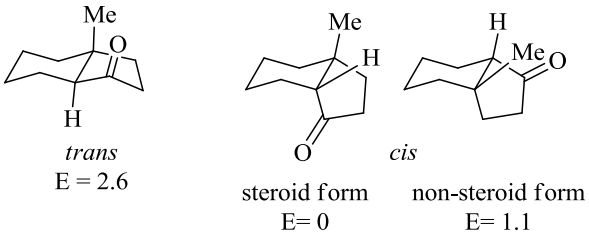


Figure 21 Calculated energies for hydrindanones

Other calculations provided the energy differences in bicycle[m,3,0]alkanes and hydrindanones derivatives, with m= 3,4,5 and 6, with and without angular methyl group. For m= 4, the calculated energies showed that the *trans*-hydrindane is the most stable and therefore more abundant in a 6:4 ratio (Figure 22).[86]

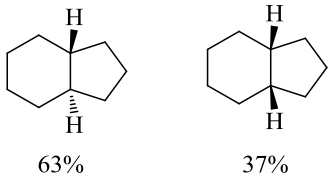


Figure 22 Major *trans*-hydrindane

In the presence of a carbonyl and a methyl group on the bridge-head position, the *cis* isomer is significantly favoured (regardless the position of the carbonyl) (Figure 23). To explain this preferred conformation, the *cis*-fusion is suggested to minimise 1,3-diaxial interactions between the methyl group and the hydrogens from the cyclohexane ring.

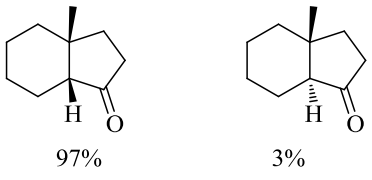


Figure 23 Major *cis*-hydrindanone

However, synthetic routes for the preparation of *trans*-hydrindane systems were reported. Reduction of the double bond at the ring junction of Hajos-Parrish-Wiechert (HPW) type ketones is well known (Figure 24).

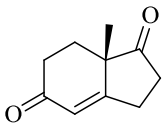
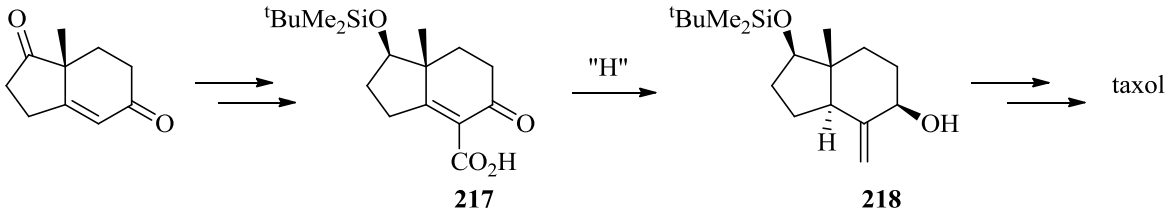


Figure 24 HPW diketone

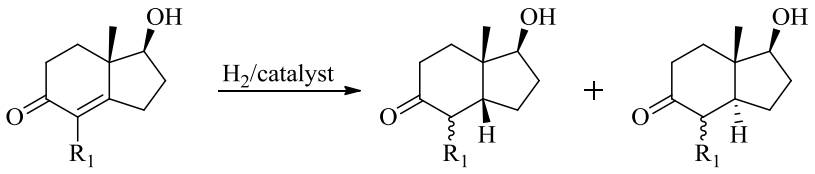
In the synthesis of Taxol®, Danishefsky and co-workers have reported the use of the HPW ketone as a precursor for the creation of the *trans*-hydrindane intermediate **218** (Scheme 81).[87,88] They showed that catalytic hydrogenation of the double bond gave selectively the *trans*-fused bicycle.



Conditions: H_2/Pd-$BaSO_4$; CH_2O, piperidine, DMSO; $NaBH_4$, $CeCl_3$, 57%.

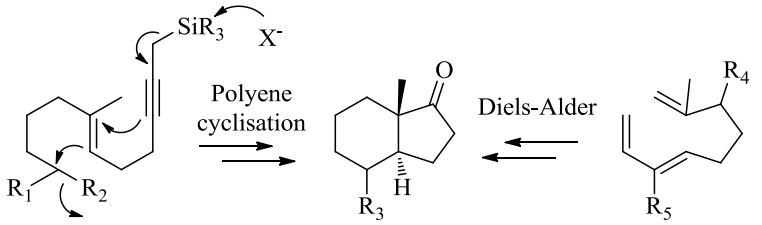
Scheme 81 HPW ketone precursor of *trans*-hydrindane system

However, hydrindane-related unsaturated ketones have been shown to undergo stereoselective hydrogenation depending on the stereoelectronic features of the substituents. Exclusive formation of *cis*- or *trans*-product can be achieved by varying the substituent adjacent to the ketone (Scheme 82).[88]



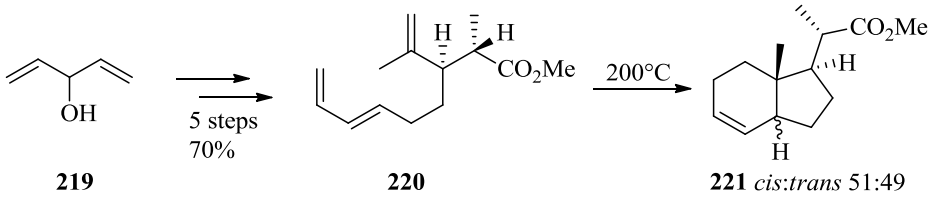
Scheme 82 Effect of alkene substitution on selectivity of reduction

Construction of the *trans*-hydrindane skeleton from acyclic precursors can be performed in one-step, either by polyene cyclisation or by an intramolecular Diels–Alder reaction (Scheme 83).



Scheme 83 Polyene and Diels-Alder cyclisation

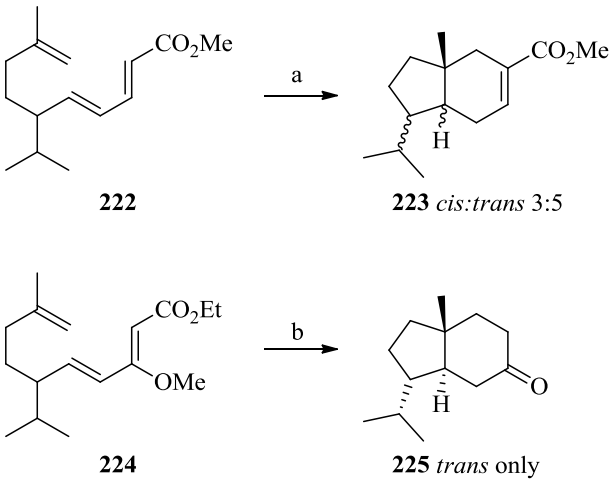
Towards the synthesis of vitamin D, Parker and Iqbal reported the intramolecular [4+2] cycloaddition of triene **220** (Scheme 84).[89] Under thermal conditions the hydrindane fragment **221** was formed *via* Diels-Alder reaction. However, they observed no selectivity and an equal amount of *cis* and *trans* isomers was formed.



Scheme 84 Formation of hydrindane **221** by cycloaddition

Again, the substitution pattern in the substrates may have an important influence on the outcome of the reaction. A 3:5 mixture of isomers **223** was obtained from Diels-Alder

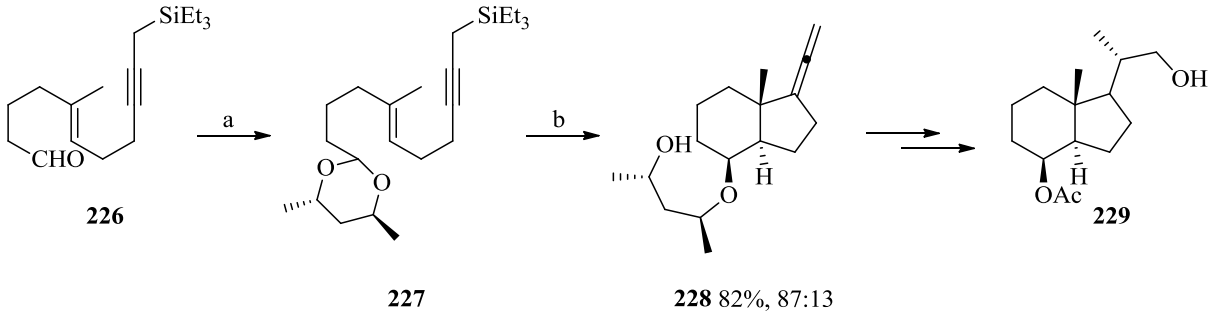
reaction of triene **222** and after isomerisation of the double bond. In contrast, methoxy triene **224** cyclised selectively in a *trans* fashion, and the corresponding ketone **225** was obtained after hydrolysis and decarboxylation (Scheme 85).[90]



Conditions: a) 173 °C, 96%; NaOH, MeOH; b) 173 °C, 80%; HCl; LiCl, Me_2SO, H_2O.

Scheme 85 Effect of the substitution on the selectivity

In a proposed synthesis of vitamin D, hydrindane intermediate **229** was achieved from aldehyde **226** (Scheme 86). The corresponding optically active acetal **227** underwent biomimetic acid-catalysed cyclisation to deliver *trans*-hydrindane **228** in a 82% yield and a 87:13 ratio with the *cis* product predominating. Alcohol **229**, precursor of vitamin D, was further obtained upon simple transformations.[91]

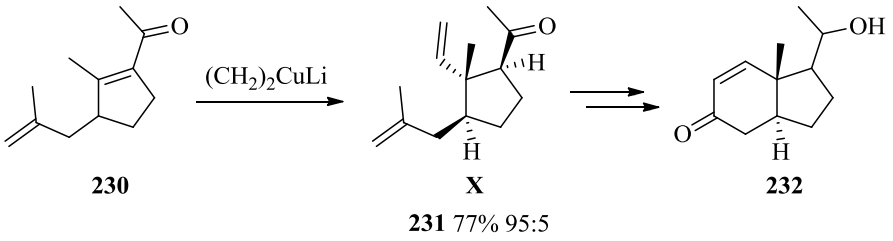


226 **227** **228** 82%, 87:13 **229**

Conditions: a) (2*S*,4*S*)-pentane-diol, $(CO_2H)_2$, 48%; b) $TiCl_4$, 2,4,6-trimethyl-pyridine, CH_2Cl_2, 82%.

Scheme 86 Simultaneous carbon-carbon bond formation

A conjugate addition-enolate trapping technique has also been used for the construction of *trans*-hydrindanes, and proven to be highly diastereoselective. For instance, conjugate addition of vinyllithiumcuprate to *α,β*-unsaturated ketone **230** yielded **231** in high diastereoselectivity (95:5) (Scheme 87).[92] Subsequent transformations gave *trans*-hydrindane derivative **232**, which was employed in cortisone synthesis.

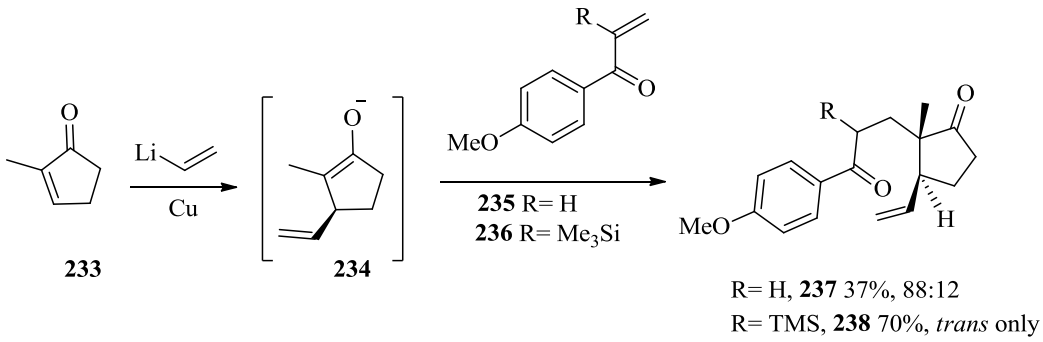


230 **X** **232**

231 77% 95:5

Scheme 87 Conjugate addition for hydrindane formation

In the enantioselective synthesis of estrone developed by Quinkert *et al*., two Michael additions were used to furnish *trans*-hydrindane precursors **237** and **238**.[93] Enolate **234** obtained from 2-methylcyclopentenone was reacted with *α,β*-unsaturated ketones **235** and **236**. By increasing the steric environment in **236**, they showed that yield and selectivity can both be greatly improved (Scheme 88).



Scheme 88 *Trans* selectivity induced by enolate trapping

3.2 Aims and objectives

Dictyoxetane **8** contains a *trans*-fused hydrindane core structure where the five-membered ring adopts an envelope conformation and the six-membered ring is in a chair conformation (Figure 25).[12] The axial methyl group and the proton at the ring junction are *trans* to each other.

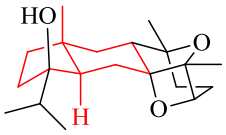
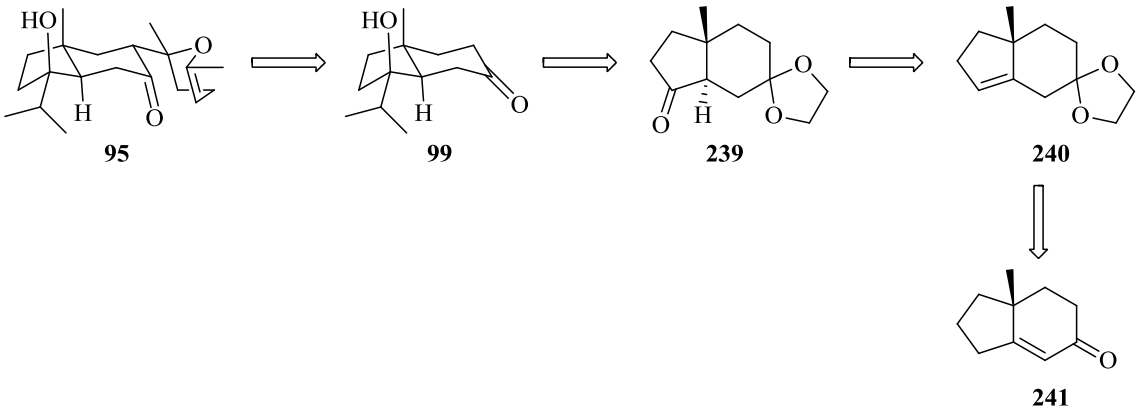


Figure 25 Dictyoxetane **8**

To investigate the use of photocyclisation as a means to synthesise dictyoxetane, hydrindanone **99** was proposed as a suitable precursor. **99** was envisaged to be accessed starting from the known enone **241** (Scheme 89).



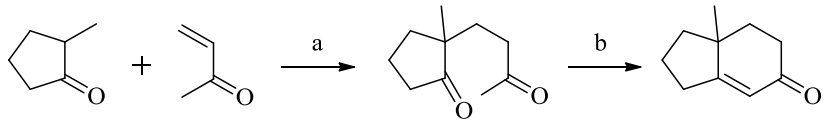
Scheme 89 Proposed retrosynthesis of photocyclisation precursor **95**

In the forward direction, *γ*-functionalization of **241** would be achieved through ketone protection with simultaneous double bond migration. Regio- and stereoselective manipulations of alkene **240** would give ketone **239**. Facial-selective attack of a nucleophilic isopropyl moiety on ketone **239** would give a tertiary alcohol, which upon acetal deprotection would give **99**.

3.3 Results and Discussion

3.3.1 Manipulation of 7a-methylhexahydroinden-5-one

Several conditions have been investigated to create the starting bicyclic ketone **241**. A method developed by Caine *et al*. reported the formation of the 5,6-fused-bicyclic enone **241** under basic conditions in 57% yield.[94] Using this method, Michael addition of the commercially available 2-methylcyclopentanone on MVK furnished diketone **242**. Subsequent aldol condensation using ethanolic KOH, yielded fused cyclohexenone ring **241** in only 2% yield, the rest of the material being decomposition or side-products (Scheme 89).

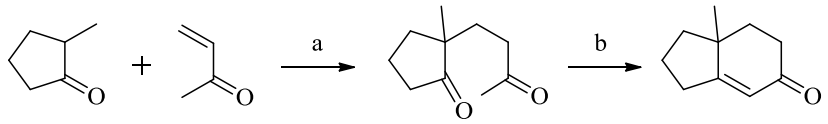


242 **241**

Conditions: a) KOH, EtOH, Et_2O; b) 10% KOH, EtOH, 2% over 2 steps.

Scheme 89 Michael addition-aldol condensation under basic conditions

Rao *et al*. reported a two-step synthesis of **241** through Robinson annelation.[95] Initial conjugate addition of 2-methylpentanone with MVK under acidic conditions was followed by a base-mediated intramolecular aldol condensation and dehydration. Following this technique, hexenone **241** was prepared in an improved yield of 38% (Scheme 90).

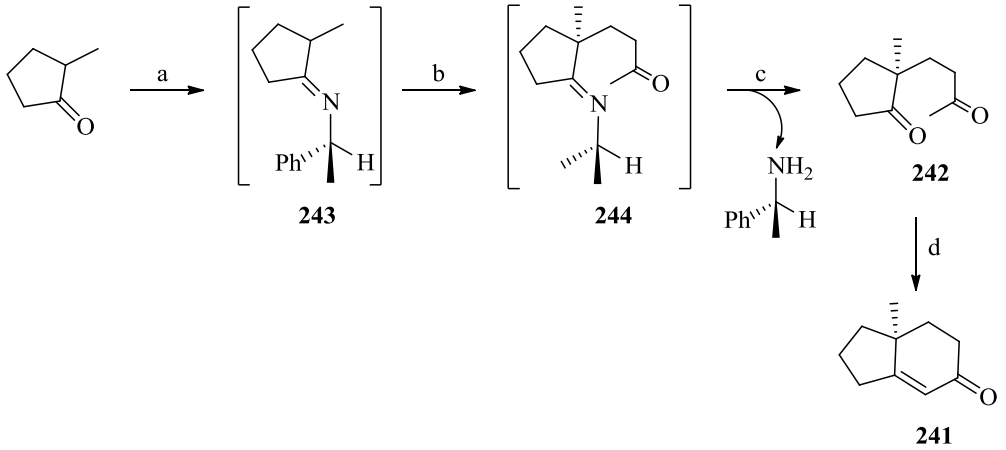


242 **241**

Conditions: a) H_2SO_4 conc., toluene, reflux; b) KOH, EtOH, 38% over 2 steps.

Scheme 90 Michael addition under acidic conditions

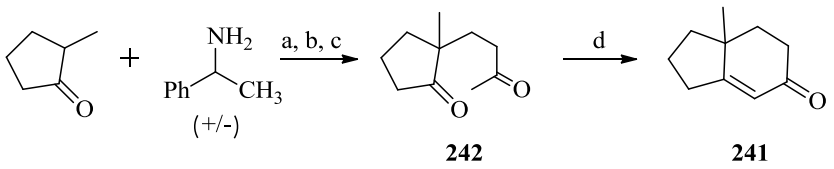
An efficient asymmetric synthesis of bicyclic ketone **241** was reported by Revial and Pfau, based on the initial condensation of α-methylbenzylamine with a 2-methylcyclopentanone (Scheme 91).[96] The imine intermediate **243** undergoes Michael addition with MVK, and further hydrolysis under acidic conditions gives diketone **242**. After cyclisation, they obtained ketone **241** in 89% ee.



Conditions: a) (*S*)-(-)-methylbenzylamine; b) MVK, reflux; c) AcOH, H_2O; d) NaOH, MeOH.

Scheme 91 Asymmetric synthesis of ketone **241**

This method was attempted using racemic *α*-methylbenzylamine. Diketone **242** was not purified, but IR analysis of the crude reaction confirmed the presence of two carbonyls (1737, 1714 cm^{-1}). Intramolecular aldol condensation and alcohol elimination in ethanolic KOH delivered racemic bicyclic ketone **241** in 44% yield (Scheme 92).

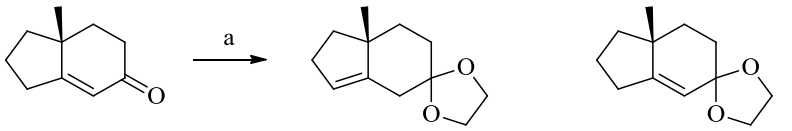


Conditions: a) (+/-)-*α*-methylbenzylamine, toluene, reflux; b) MVK, reflux; c) AcOH, H_2O, rt; d) KOH, EtOH, reflux, 44% over 4 steps.

Scheme 92 Methylbenzylamine-mediated formation of diketone

The stereochemistry presented in the following synthesis is arbitrarily chosen.

The *α,β*-unsaturated carbonyl moiety **241** was transformed into an acetal *via* the well-established method of protection using ethylene glycol and *p*-TSA. Acetal **240** was obtained in 77% yield with the expected double bond migration to the *β,γ*-position (Scheme 93).



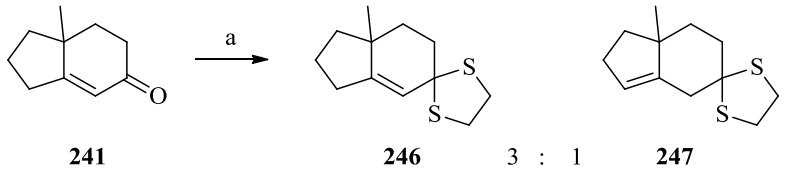
241 **240** **245** not observed

Conditions: a) ethylene glycol, *p*-TSA, toluene, reflux, 77%.

Scheme 93 Acetal protection with simultaneous double bond migration

The fact that the enone double bond can migrate upon ketalisation was first reported in 1937 by Fernholz and Stavely, and has subsequently been applied in natural product synthesis.[97] Olefin isomerisation was reported to be favoured by the use of strong acid such as *p*-TSA (pKa < 1) when the use of acid of lower acidity (pKa ~ 3) does not to cause the double bond migration. Migration of the olefin was evidenced by HMBC analysis of **240** and consideration of the alternative product **245**. No correlation was observed between the quaternary carbon of the acetal and the olefinic proton. Migration of the double bond was here imperative since it would allow further transformation to the requisite carbonyl **99**.

Ketone **241** was also transformed into the corresponding dithioacetal, but formation of two inseparable isomers was observed (Scheme 94).[98] The two structures, **246**, with no migration of the double bond, and **247**, with migration, were proposed, as ^{1}H NMR analysis showed two peaks in the ethylenic region, in a 3:1 ratio. A doublet at 5.47 ppm possesses a small coupling constant of 1.3 Hz, and was assumed to represent the ethylenic proton in compound **246**. The second signal at 5.33 ppm has a more complex multiplicity and was attributed to the ethylenic proton in structure **247**. All the other signals were overlapped.

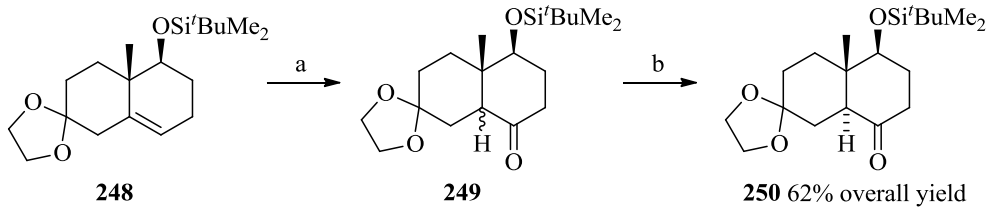


241 **246** 3 : 1 **247**

Conditions: a) ethane 1,2-dithiol, *p*-TSA, toluene, reflux, 84%.

Scheme 94 Thioacetal protection

The first strategy investigated towards formation of *trans*-bicycle **239** was a sequence of hydroboration-oxidation of the double bond and further oxidation of the secondary alcohol. The example below shows that, upon hydroboration-oxidation and subsequent oxidation, acetal **248** gave ketone **249** as a mixture of isomers (Scheme 95). Although the ratio of isomers was not determined in **249**, the *trans* product **250** predominated after epimerisation of the mixture of ketones.[99]

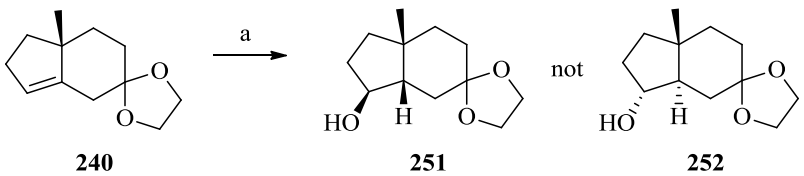


248 **249** **250** 62% overall yield

Conditions: a) i) B_2H_6·THF, ii) H_2O_2/NaOH, iii) TPAP, NMO, CH_2Cl_2; b) NaOH/MeOH.

Scheme 95 Hydroboration-oxidation-isomerisation to *trans*-decalone

Treatment of alkene **240** with 9-BBN followed by oxidation of the boron intermediate with hydrogen peroxide afforded the less substituted secondary alcohol as a single isomer in 65% yield (Scheme 96).[100]

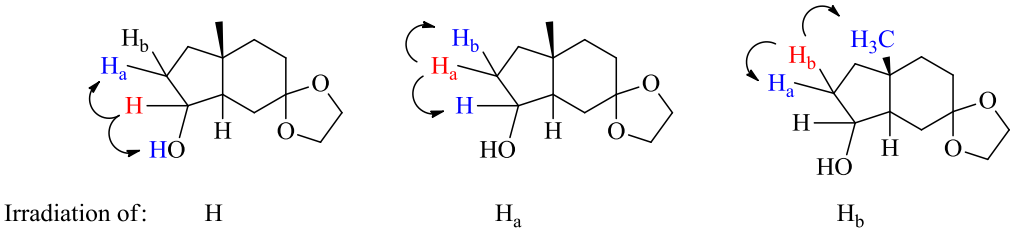


240 **251** **252**

Conditions: a) i) 9-BBN, THF, rt, ii) H_2O_2/NaOH, rt, 65% over 2 steps.

Scheme 96 Hydroboration-oxidation

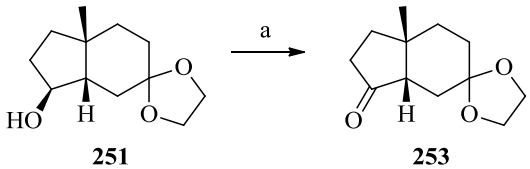
At this stage, nOe studies were undertaken to determine the stereochemistry.



Scheme 97 nOe studies of secondary alcohol

Irradiation of the proton adjacent to the ring junction on the five-membered ring showed an nOe to the hydrogen from the alcohol and to a vicinal proton H_a (Scheme 97). Importantly, no nOe was observed with the methyl group. When H_a was irradiated, expected nOe's with H and germinal H_b were observed. Again, no nOe was detected with the methyl group. Irradiation of H_b gave nOe's to H_a and the methyl group. Also, when irradiating of the methyl group, an nOe were observed in the NMR signal region of the proton at the ring junction, but due to signals overlapping, it was not possible to confirm the exact correlation. nOe's between the adjacent protons on the five-membered ring tend to prove that hydroboration occurred from the *exo* face.

Oxidation of the alcohol with IBX afforded ketone **253** in 91% yield (Scheme 98).



Conditions: a) IBX, DMSO, rt, 91%.

Scheme 98 Formation of *cis*-hydrindanone **253**

X-ray analysis of the crystal structure confirmed the *cis*-hydrindanone structure (Figure 26).

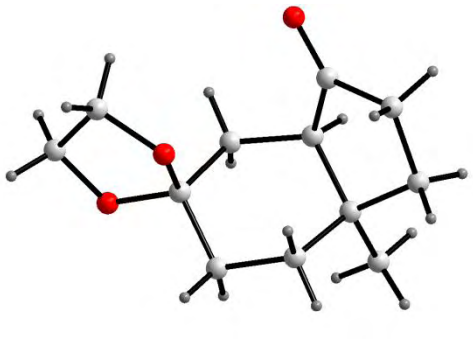
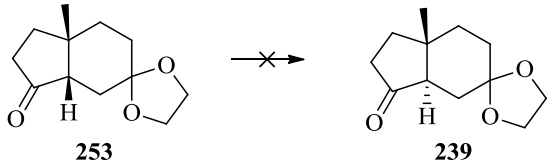


Figure 26 X-ray structure of *cis*-hydrindanone **253** by B. Kariuki

With the *cis* compound in hand, efforts were focused on the epimerisation of the stereocentre adjacent to the carbonyl (Scheme 99).

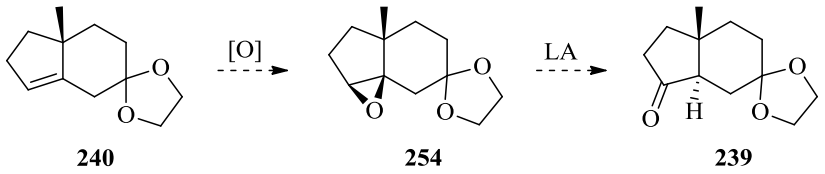


Conditions: 0.05 M NaOMe, MeOH, reflux; 5% NaOH, THF, reflux; or DBU, toluene, reflux.

Scheme 99 Failed epimerisation

Reaction with NaOMe gave mainly starting material and a mixture of degradation products after several days. Epimerisation with NaOH or DBU only resulted exclusively in starting material. This demonstrated that the *cis*-hydrindanone **253** system is thermodynamically stable and that the *trans* system **239** could not be obtained by epimerisation of the *cis*-ring junction product.

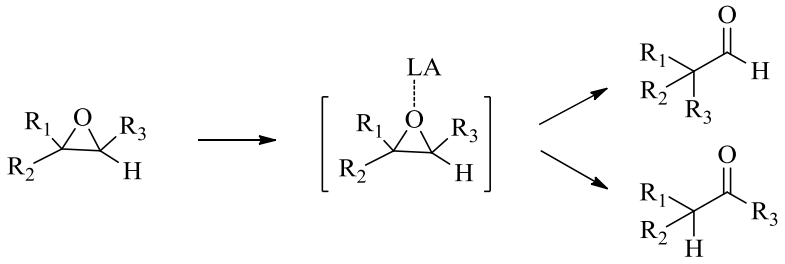
In a second approach, the *trans*-ring junction in **239** was proposed to be generated *via* a Lewis acid-mediated rearrangement of an epoxide (Scheme 100).



240 **254** **239**

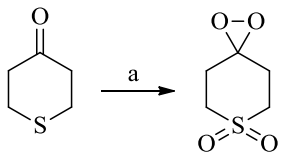
Scheme 100 Proposed epoxide rearrangement

The rearrangement of an epoxide to a ketone under Lewis acid conditions is known, and is still widely investigated in order to improve its efficiency and its selectivity (Scheme 101).[101]



Scheme 101 Epoxide rearrangement

Epoxidation of the double bond in **240** was first investigated. Initial attempts were undertaken using catalytic tetrahydrothiopyran-4-one and stoichiometric Oxone®, maintaining the pH of the reaction at 7.0-7.5 with sodium bicarbonate to prevent decomposition of epoxides sensitive to acids or bases. Oxone® converts the thiopyranone to dioxirane **255** in situ, which then functions as the oxidant (Scheme 102).



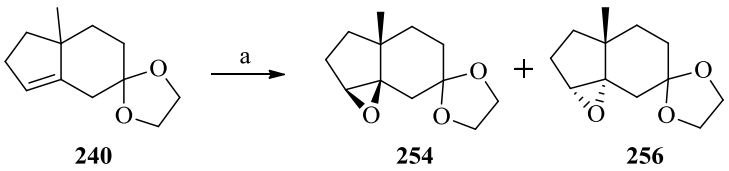
255

Conditions:a) Oxone®, $NaHCO_3$, CH_3CN.

Scheme 102 Formation of dioxirane **255**

Two epoxides were obtained: *cis*-epoxide **254**, where the epoxide and the methyl group at the ring junction are on the same face, and *trans*-epoxide **256**, where the epoxide resides on the

opposite face, *trans* to the methyl group at the ring junction, in a ratio **254**:**256** 6:4 and in a combined 82% yield (Scheme 103).



Conditions: a) Oxone®, tetrahydrothiopyran-4-one, Na_2.EDTA, $NaHCO_3$, CH_3CN, rt, 82%.

Scheme 103 Formation of two epoxides

The NMR data of the two epoxides were clearly different and nOe studies were necessary to determine their stereochemistry. In *cis*-epoxide **254** (for numbering see Figure 27), irradiation of the methyl group indicated equal nOe's to both C_3 protons. It also showed an nOe to the axial C_7 and C_9 protons and to the equatorial C_{10} proton. No nOe was observed between the methyl group and the C_5 proton. Irradiation of the C_5 proton showed an nOe to the equatorial C_7 proton and two equal nOe's for both C_4 protons. In addition an nOe to the acetal protons was detected. This analysis was consistent with the epoxide being *cis* to the methyl group and was considered sufficient to confirm the stereochemistry of compound **254**.

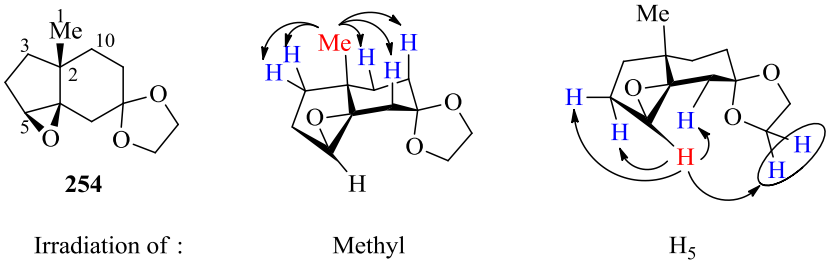
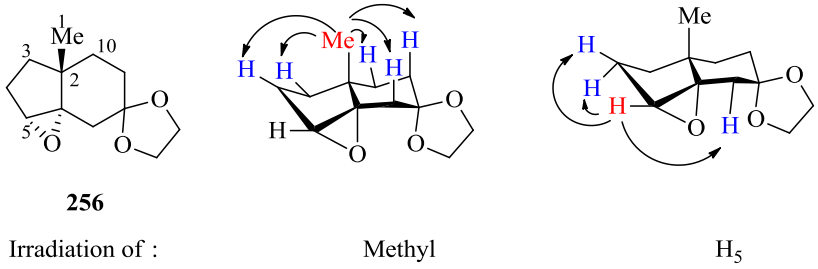


Figure 27 nOe studies of epoxide **254**

In *trans*-epoxide **256**, irradiation of the methyl group showed an nOe to the axial C_7 and C_9 protons, the equatorial C_{10} proton and to one each of the C_3 and C_4 protons (Figure 28). No nOe was observed to the C5 proton. Irradiation of the C_5 proton showed an nOe to the

equatorial C7 proton and two equal nOe's for both C_4 protons. No nOe was observed with C_3 protons. Consequently, this analysis was consistent with distortion of the five-membered ring and indicated that the epoxide was *trans* to the methyl group.



256

Irradiation of : Methyl H_5

Figure 28 nOe studies of epoxide **256**

Having determined the stereochemistry of the two compounds, epoxidation was also investigated using *m*-CPBA as the oxidant. This method afforded both epoxides in a combined 81% yield, but with an inverse ratio of isomers **254**:**256** 4:6. This ratio can be explained by the peracid reacting preferentially on the more hindered *endo* face through H-bonding to give the *trans*-epoxide **256** as the major compound (Figure 29). Epoxidation using **255** favoured the *cis* diastereomer through approach from the less hindered *exo* face.

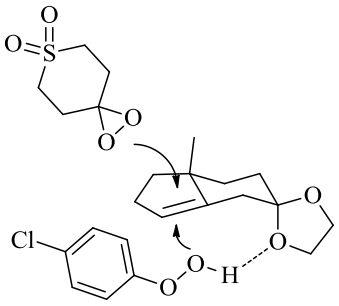
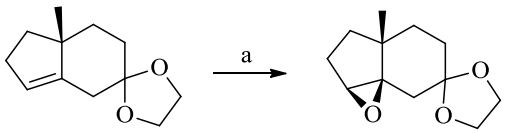


Figure 29 Facial selectivity in epoxidation

In a final examination of epoxidation of the double bond, the use of DMDO proved to be the most selective oxidising agent as it delivered the desired *cis* epoxide **254** in 86% yield as a single stereoisomer (Scheme 104).[102]

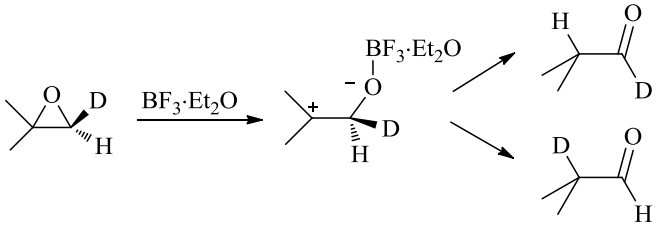


240 **254**

Conditions: a) DMDO, acetone, rt, 86%.

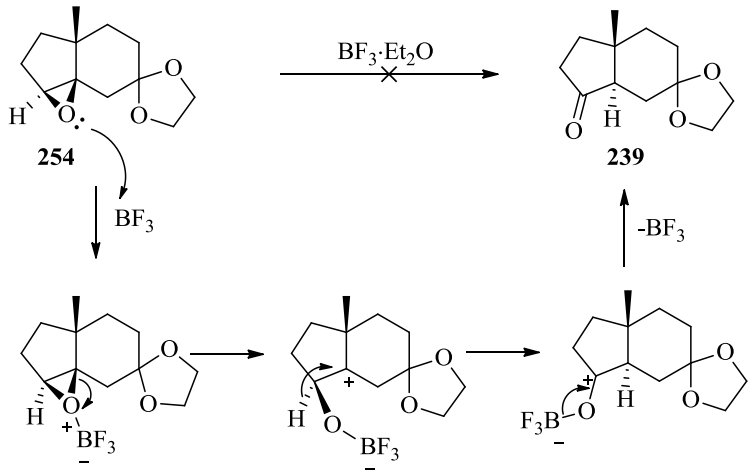
Scheme 104 Selective formation of **254**

cis-Epoxide **254** was required for the rearrangement to the *trans*-hydrindanone system, since selective Lewis acid-mediated rearrangement of epoxides has been reported with hydride shift. Coxon and co-workers have studied the boron trifluoride catalysed rearrangement of deuterated dimethyloxirane to a cationic intermediate, and described a mechanism involving a 1,2-shift of the hydride (Scheme 105).[103]



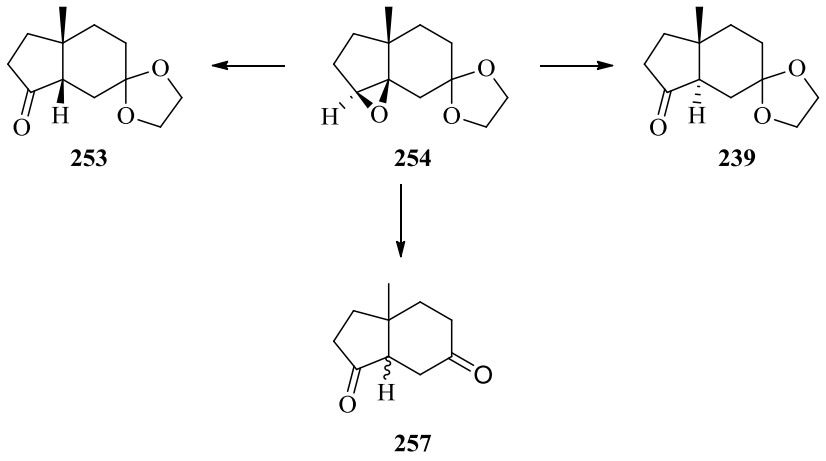
Scheme 105 Rearrangement with hydride shift

Rearrangement of the trisubstituted epoxide was therefore expected to occur *via* the mechanism described in Scheme 106: activation of the epoxide by complexation of the oxygen to the Lewis acid would lead to ring-opening by cleavage of the C-O bond to give the more stable carbocation, a 1,2-hydride shift would occur with retention of configuration, and loss of the Lewis acid would lead to the formation of the desired ketone.



Scheme 106 Proposed mechanism for formation of **239**

Unfortunately, rearrangement experiments proved to be inconsistent and irreproducible. Both *cis*- and *trans*-bicycles **253** and **239** were isolated (Table 9). Rearrangement with simultaneous deprotection of the acetal was also observed in 85% yield (entry **2**), with **257** obtained as a single isomer of undetermined stereochemistry (Scheme 107).



Scheme 107 Epoxide rearrangement results

$BF_3{\cdot}Et_2O$ proved to be a very active catalyst and the transformation usually occurred within one hour at room temperature (entry **1**). Attempts to slow down the reaction by lowering the temperature did not improve the selectivity of the reaction. Other Lewis acids have been tested (entries **4**, **6** and **10**). No reaction occurred with $BF_3{\cdot}Et_2O$ in THF (entries **7** and **10**).

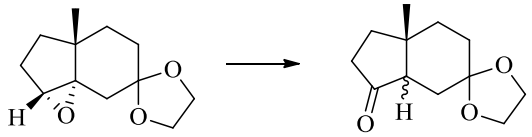
Entry	Lewis acid (eq)	Solvent	Conditions	Results[a]
1[104]	$BF_3{\cdot}Et_2O$ (0.1)	CH_2Cl_2	rt, 1 h	37% *cis* **253**
2	$BF_3{\cdot}Et_2O$ (0.1)	CH_2Cl_2	rt, 10 min	85% **257**
3[105]	$BF_3{\cdot}Et_2O$ (0.5)	CH_2Cl_2	0 °C→rt 1h	62% *cis* **253** 26% **257**
4	$LiClO_4$ (0.8)	toluene	80 °C 5 days	32% *cis* **253**
5	$BF_3{\cdot}Et_2O$ (1)	toluene	rt, 20 min	14% *trans* **239** 8% *cis* **253**
6	$ZnCl_2$ (1)	CH_2Cl_2	rt, 3 days	Product impossible to characterise
7	$BF_3{\cdot}Et_2O$ (1.13)	THF	0 °C→rt 3 days	No reaction
8	$BF_3{\cdot}Et_2O$ (1.13)	CH_2Cl_2	0 °C→rt 20 min	13% *trans* **239** 19% **257**
9	$ZnCl_2$ (2)	THF	rt, 2 days	No reaction
10	$MgCl_2$ (10)	THF	rt, 2 days	No reaction

[a] isolated yields after column chromatography

Table 9

Purification was extremely difficult due to the similar polarity of **239** and **253**. At best, *trans*-hydrindanone **239** was obtained in 14% yield and *cis*-hydrindanone **253** was isolated in 32% yield.

Attempts to rearrange the *trans*-epoxide **256** also led to a complex mixture of products, from which 23% of *cis*-hydrindanone **253** was isolated (Table 10).



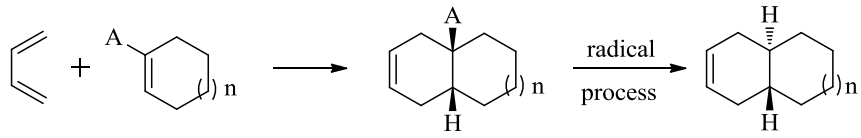
256

Entry	LA (eq)	Solvent	Conditions	Results
1	$BF_3.Et_2O$ (0.1)	CH_2Cl_2	rt, 1 h	18% *cis* **253**
2	$BF_3.Et_2O$ (0.8)	CH_2Cl_2	0 °C→rt 1 h	23% *cis* **253**
3	$BF_3.Et_2O$ (0.5)	CH_2Cl_2	-78 °C→rt 2h	same results as entry **2** by TLC analysis

Table 10

Although formation of the *trans*-ring junction has been observed, rearrangement of *cis*-epoxide **254** was not a reliable or efficient method of synthesizing *trans*-hydrindanone **239**.

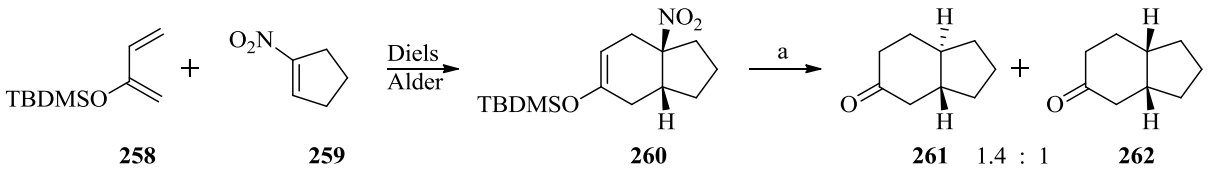
An alternative approach to the *trans*-ring junction was envisaged through a radical process. In his studies towards the development of a "*trans* Diels-Alder" methodology, Danishefsky reported the free radical-mediated formation of *trans*-ring junctions in bicycles (Scheme 108).[106] Cycloadditions were carried out with substituted (otherwise unreactive) dienophiles, where the activating group is able to subsequently generate free radical intermediates. The resulting *cis*-fused structure could thus be converted to the *trans* isomer by removal of the activating moiety and its controlled replacement.



A = DA activating group
n = 0, 1

Scheme 108 Radical formation of *trans*-hydrindane

As a result, he reported the cycloaddition of a functionalised diene **258** with nitrocyclopentene (Scheme 109). The obtained *cis* cycloadduct **260** underwent radical denitration with Bu_3SnH and AIBN, and after hydrolysis of the silyl ether, a 1.4:1 ratio of *trans*- to *cis*-hydrindanone was reported.



Conditions: a) Bu_3SnH, AIBN.

Scheme 109 selective radical formation of *trans*-hydrindane

It was proposed that this ratio may reflect a low *trans*/*cis* preference in the tertiary bridgehead radical intermediate. However, the overall reaction demonstrated that a *trans*-hydrindane could be obtained from a bridgehead radical intermediate (Figure 30).

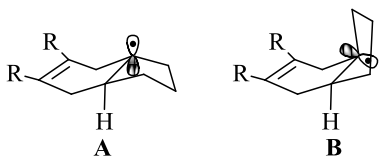
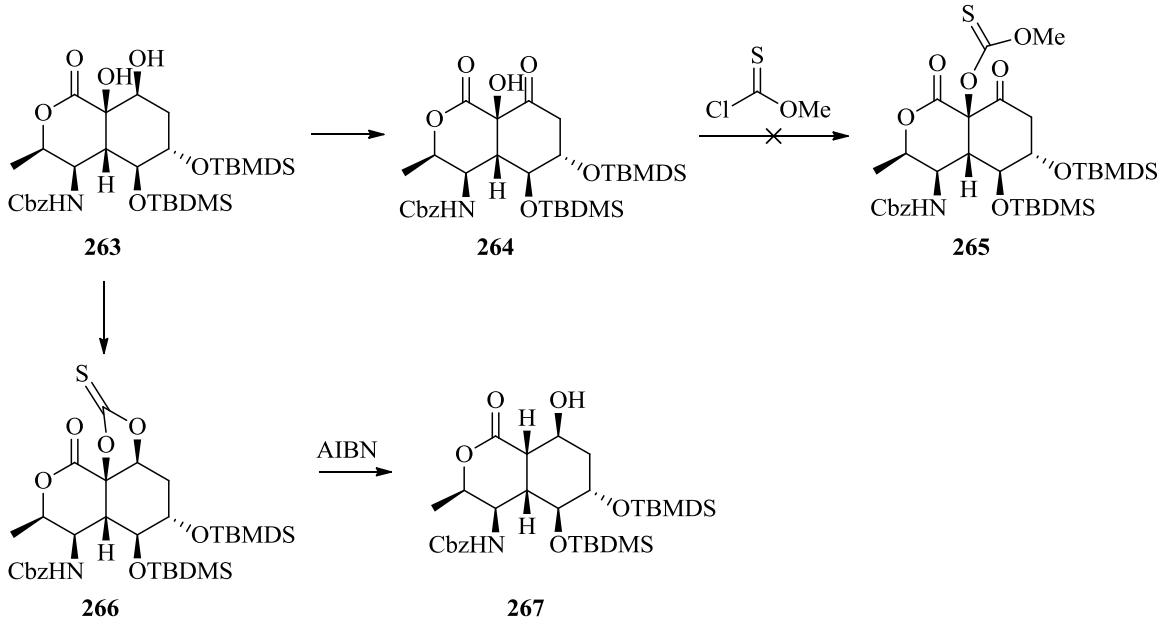


Figure 30 Radical intermediate

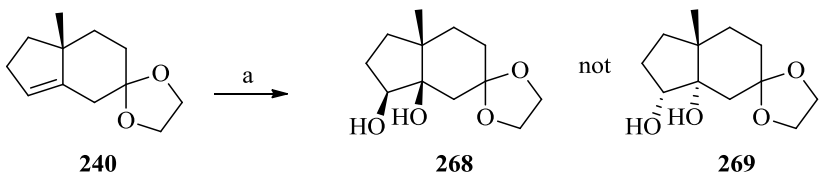
An alternative approach to the requisite *trans*-ring junction was therefore envisaged through deoxygenation of a tertiary alcohol situated at the ring junction. It has been reported that a direct Barton deoxygenation reaction on a tertiary alcohol at a bicycle ring junction was

unsuccessful as the required xanthate ester **265** could not be obtained due to steric inaccessibility of the tertiary alcohol group (Scheme 110).[107] Radical deoxygenation by tin hydride reduction of the thiocarbonate derivative of the diol **266** selectively led to the rupture of the tertiary carbon-oxygen bond to form the more stable tertiary radical. In this example however, a *trans* selectivity has been observed.



Scheme 110 Radical formation of hydrindane from thiocarbonate

To investigate this approach, dihydroxylation of alkene **240** was carried out under Upjohn conditions to give the corresponding diol in 77% yield as a single isomer (Scheme 111).



Conditions: a) OsO_4, NMO, THF/H_2O/^{t}BuOH, rt, 77%.

Scheme 111 Dihydroylation under Upjohn conditions

To determine the stereochemistry of the diol, nOe studies were necessary (Figure 31).

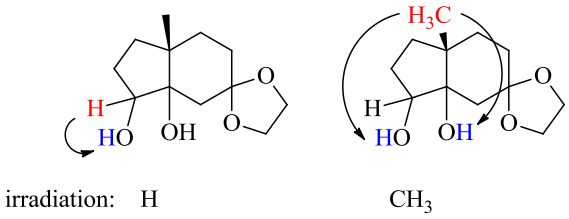


Figure 31 nOe analysis of diol

Irradiation of H showed a single nOe to the germinal proton from the alcohol, and no nOe was observed between H and the methyl group. When the methyl group was irradiated, nOe with both alcoholic protons were observed, and no nOe with H was detected. These analyses are consistent with structure **268**.

Synthesis of cyclic thiocarbonate **270** was achieved by reaction with thiophosgene and DMAP in 16% yield (Scheme 112). The poor yield of this transformation is due difficulties in the purification and the formation of two other products, the structures of which could not be determined. However, X-ray analysis of the crystal structure confirmed the stereochemistry in **270** (Figure 32).

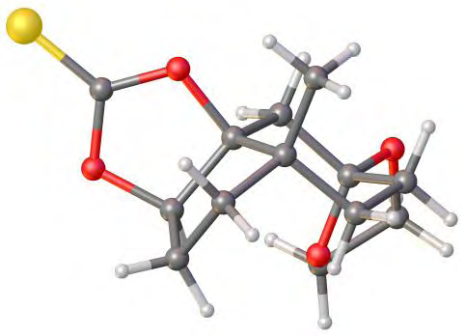
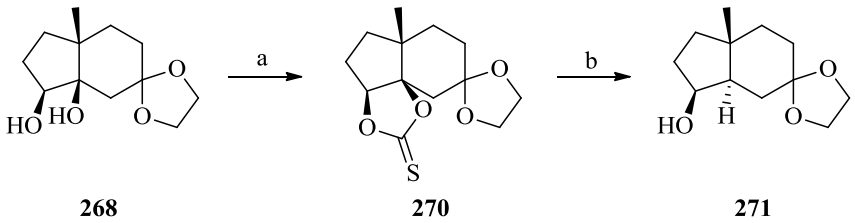


Figure 32 X-ray structure of *cis*-thiocarbonate **270** by L. Male

Attempted deoxygenation of **270** was carried out with Bu_3SnH and AIBN, but mainly starting material was recovered (Scheme 112). Formation of a tiny amount of a unique product was observed by TLC analysis after two days of reaction, but this was not sufficient for full

characterisation. This reaction needs to be repeated and investigated further, but the low yield in the thiocarbonate formation hampers this approach.



268 **270** **271**

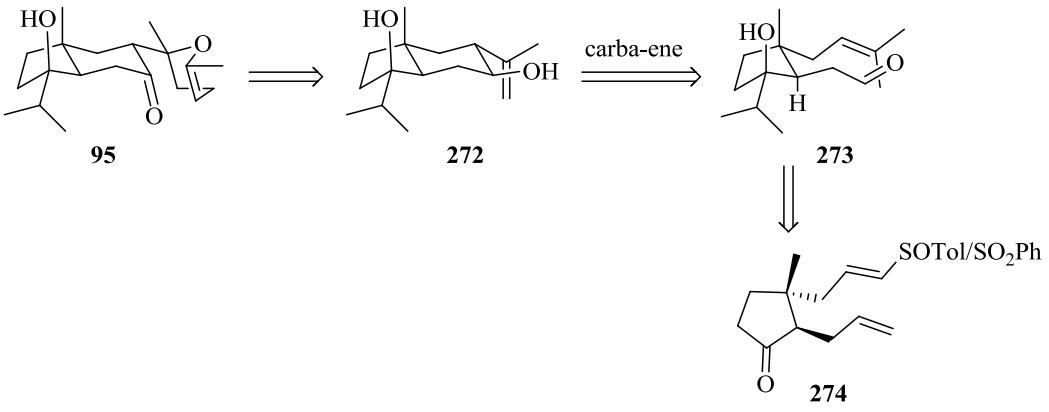
Conditions: a) thiophosgene, DMAP, CH_2Cl_2, rt, 16%; b) Bu_3SnH, AIBN, toluene, reflux, to repeat.

Scheme 112 Radical deoxygenation

Following the lack of success in the formation of a *trans*-hydrindanone structure from a [4.3.0] bicyclic system, a complementary approach was undertaken.

3.3.2 Conjugate addition to 3-methylcyclopenten-2-one

As discussed in Chapter 2, isopulegol was formed *via* an intramolecular ene cyclisation between an aldehyde and an allylic group.[108] It was envisaged that the same strategy could be applied in this system to synthesize *trans*-hydrindane **272** through cyclisation between the *trans*-vicinal prenyl and carbonyl groups in **273** (Scheme 113).



95 **272** **273** **274**

Scheme 113 Proposed formation of hydrindane **272**

To obtain the required *trans* substituted cyclopentane **274** a nucleophilic 1,4-addition on the commercially available conjugated ketone, 3-methylcyclopentanone, followed by trapping of the resulting enolate was proposed.(Figure 33),

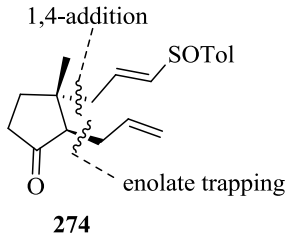
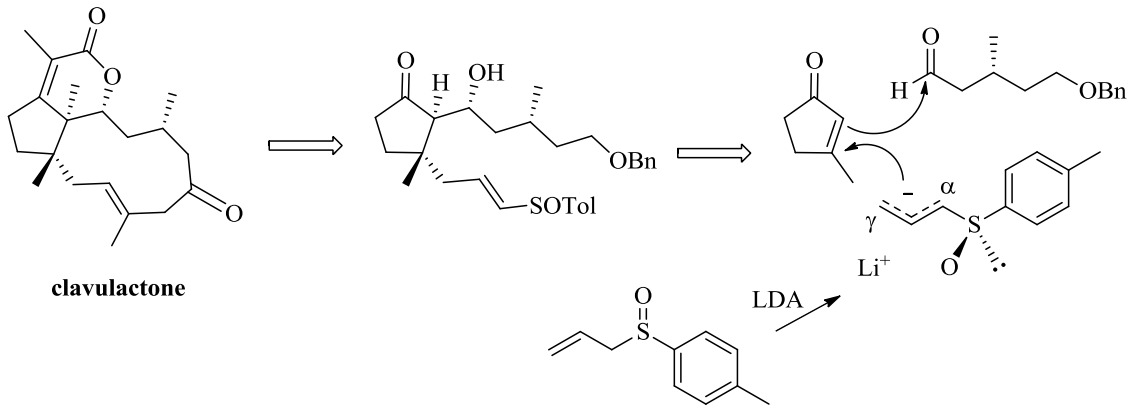


Figure 33 Conjugate addition-enolate trapping strategy

The synthesis of the *trans*-ring junction of the 5,11-bicyclic core of clavulactone, a dolabellane diterpene isolated from *Clavularia viridis*, was reported. In this case the requisite *trans* stereochemistry was obtained through a key three-component strategy which involved allyl *p*-tolyl sulfoxide anion as the appropriate nucleophile (Scheme 114).[109]



Scheme 114 Michael-aldol strategy to clavulactone

Lithiated allylsulfoxide carbanions were shown to be generated upon treatment with LDA, and to undergo regioselective addition from the *γ*-position to Michael acceptors, such as unsaturated ketones, to give the 1,4-enolate adduct. Aldol reaction of an aldehyde with the resulting lithium enolate led to a one-pot construction of a *trans* skeleton. The *trans*

configuration was explained as being a consequence of 1,2-asymmetric induction. The selectivity of the addition of sulfinyl allyl anions to unsaturated ketones has been explained by postulating a ten-membered cyclic "chair-chair" transition state, responsible for the 1,4-γ-selectivity (Figure 34).[110]

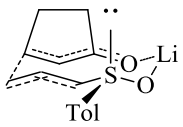
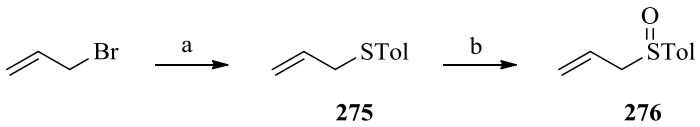


Figure 34 Proposed transition state

Allyl *p*-tolyl sulfide **275** was prepared quantitatively from allyl bromide, *p*-mercaptan toluene and dissolved sodium. It was then oxidised with sodium periodate to deliver the racemic allylic sulfoxide **276** in 61% yield (Scheme 115).

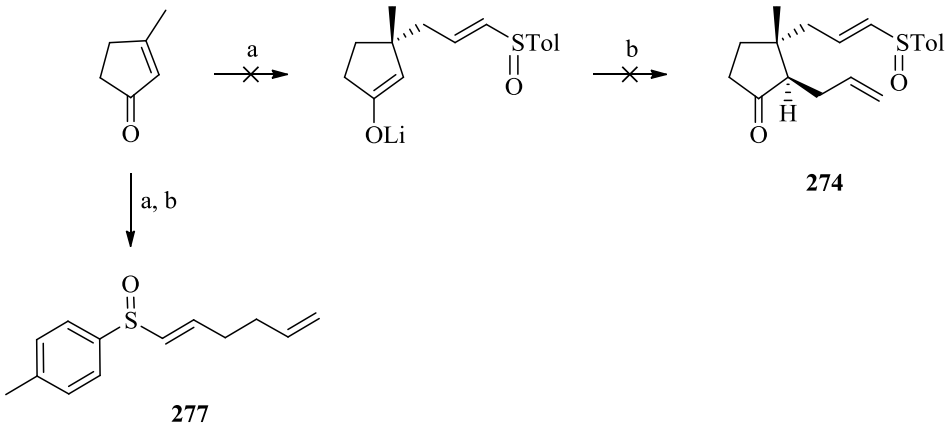


275 **276**

Conditions: a) TolSH, Na, EtOH, 0 °C→rt, quant.; b) $NaIO_4$, MeOH, 61%.

Scheme 115 Synthesis of sulfoxide **276**

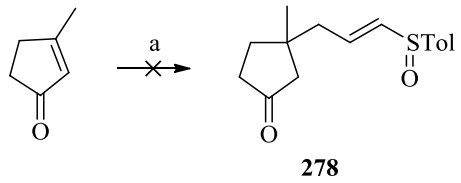
The carbanion of **276** was produced by treatment with LDA and reacted with 3-methylcyclopentenone (Scheme 116). The enolate was then trapped with allyl bromide. This tandem conjugate addition-enolate trapping reaction, however, yielded a complex mixture of products, from which vinyl sulfoxide **277** was isolated as the major product. The formation of **277** shows that deprotonation of sulfoxide **276** occurred, but addition of the resulting anion to the cyclopentenone has not.



Conditions: a) i) diisopropylamine, *n*-BuLi, THF, -30 °C, ii) sulfoxide **276**, THF, -78 °C; b) allyl bromide, -78 °C.

Scheme 116 Failed conjugate addition

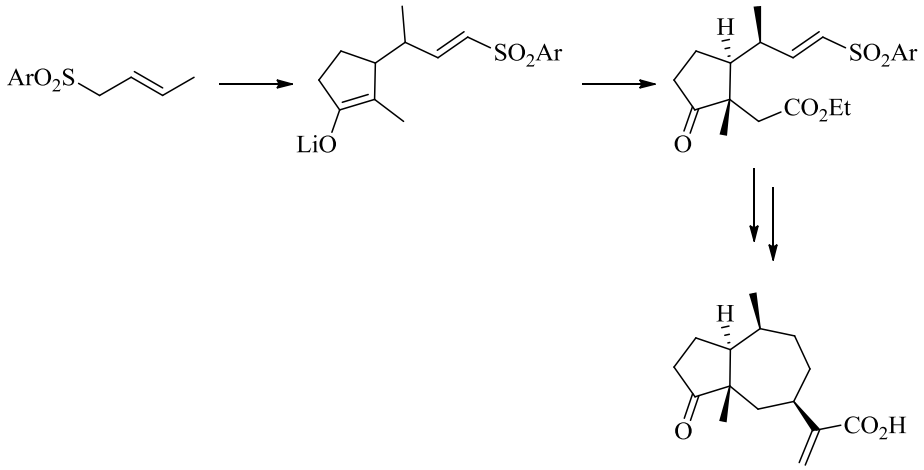
The simple 1,4 addition of the sulfoxide **276** to the cyclopentenone, which has been reported to proceed in 80% yield, was also attempted but the 1,4-adduct **278** was not formed (Scheme 117).[111]



Conditions: a) i) diisopropylamine, *n*-BuLi, THF, -30 °C, ii) sulfoxide **276**, THF, -78 °C, iii) methylcyclopentenone, -78 °C.

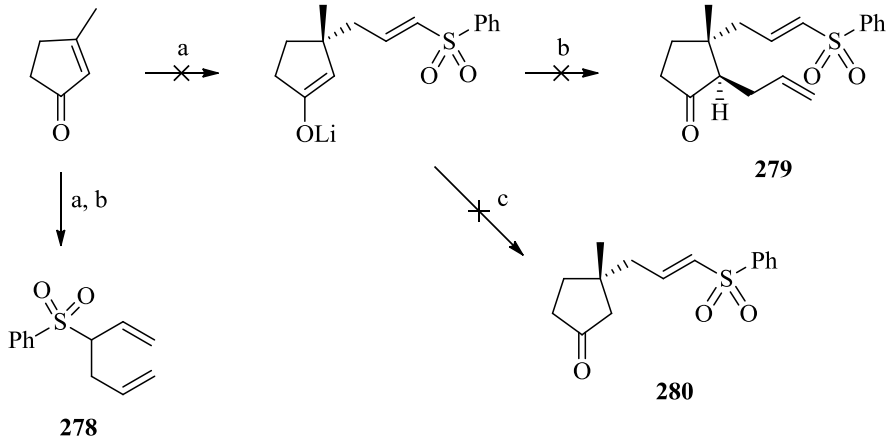
Scheme 117 Failed 1,4-addition

Conjugate addition of lithiated alkylallylic sulfones to cyclic enones has also been used for the construction of *trans*-hydrindanes and *trans*-perhydroazulenes (Scheme 118).[112]



Scheme 118 Synthesis of a *trans*-perhydroazulene

This reaction was attempted by generating the carbanion of commercially available phenyl allyl sulfone and subsequent trapping of the enolate with allyl bromide. In this case, by-product **278** was obtained as the major product. Simple 1,4-addition of the sulfone was also carried out but again the desired product **280** was not observed (Scheme 119).

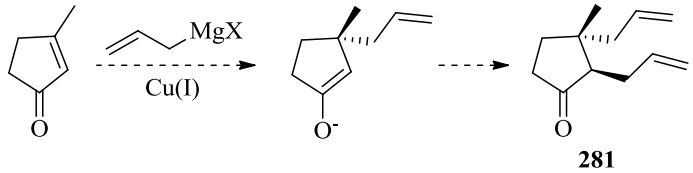


Conditions: a) i) *n*-BuLi, allyl phenyl sulfone, THF, -78 °C; b) allyl bromide, -78 °C, **278** 21%, c) AcOH.

Scheme 119 Failed conjugate additions of sulfone anion

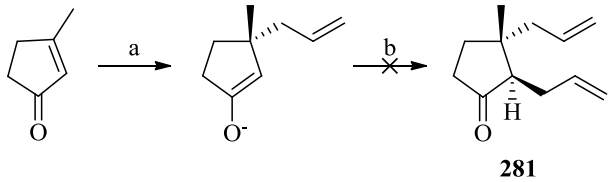
Using the same conjugate addition-enolate trapping strategy, the 1,4-addition reaction of allylic copper species derived from Grignard reagents has also been investigated (Scheme

120).[113,114] The expected *trans* orientation would here again be obtained *via* 1,2-asymmetric induction.



Scheme 120 Proposed Cu-mediated conjugate addition

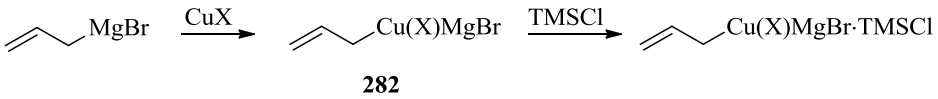
Initial attempts at the 1,4-addition of allyl magnesium bromide on 3-methylcyclopentenone, mediated by $CuBr \cdot Me_2S$, followed by addition of allyl bromide led to a complex mixture of products (Scheme 121). The major fraction was isolated and GC/MS analysis showed it to be a mixture of two compounds: the major one probably being an over alkylated by-product (structure not determined) alongside 6% of a product of the correct molecular weight, but the structure **281** has never been confirmed. Also, 1,2- and 1,4-addition adducts were noticeable (*vide infra*).



Conditions: a) $CuBr \cdot Me_2S$, allyl magnesium bromide, THF, -40 °C→rt; b) allyl bromide, rt.

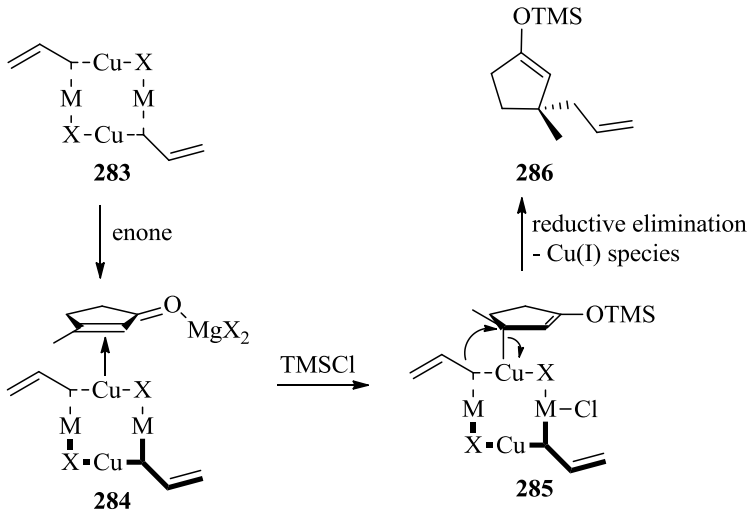
Scheme 121 Failed conjugate addition

Copper catalysed 1,4-addition of Grignard reagents on 3-methylcyclopentenone and trapping of the enolate as a silyl enol ether has also been reported.[115,116] The combination of RMgX (R= allyl) and CuX was proposed to form species such as halocuprate **282** (Scheme 122).[114]



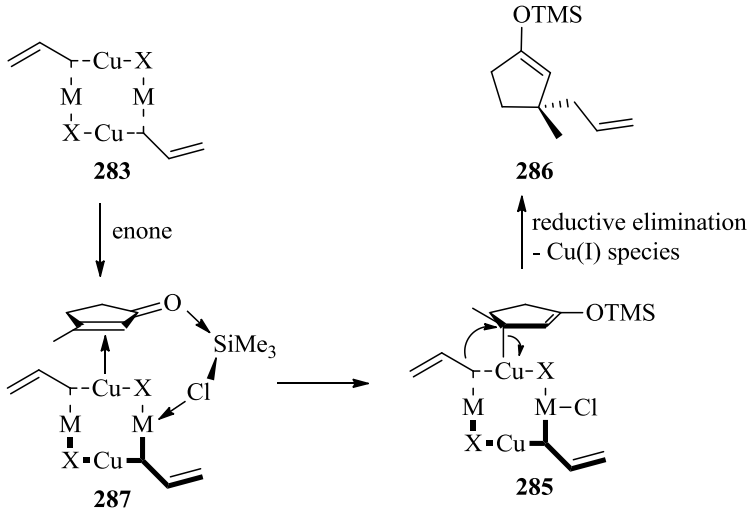
Scheme 122 Formation of halocuprate reagent

In addition to its role of trapping the enolate, TMSCl has been showed to accelerate the copper-catalysed conjugate addition of Grignard reagents and to significantly enhance yields of 1,4-adducts.[117] In terms of mechanistic interpretations, an initial π-complex **284** was suggested (Scheme 123).[114] Oxidation to the Cu(III) is presumed to be assisted by TMS enol ether **285** formation, and reductive elimination probably led to addition product **286**.[118]



Scheme 123 Proposed copper-catalysed Grignard addition mechanism

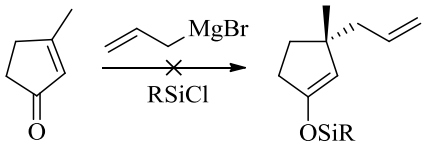
Another possibility could involve TMSCl acting as a Lewis base, complexing *via* the chloride ion to the metal (M= MgBr) in **287**, leading to the TMS-activated enone π-complex (Scheme 124).



Scheme 124 TMS activation of enone system

Addition of HMPA was shown to further improve the yield.[119] To avoid the use of extremely toxic HMPA, DMPU was used instead. TMEDA, which has also been demonstrated to facilitate conjugate additions of RCu to enones, might serve to stabilize and solubilise copper reagents and at the same time to increase the reactivity of the silyl halide.[120] It was also investigated as an additive (Table 11).

Copper mediated conjugate addition of allyl Grignard followed by trapping of the enolate as a silyl enol ether was attempted using different sources of copper and silyl reagents (Table 11).



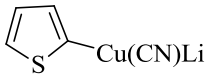
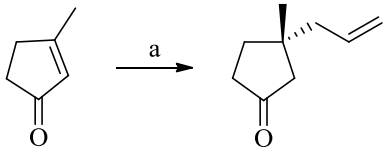
Entry	Copper	Silyl	Additive	Results
1[121]	CuI (I)	TMSCl/Et_3N 1:1 v:v	TMEDA	not observed, mainly SM
2[122]		TMSCl	Et_3N	small amount of product observed along with SM and by products, did not survive purification conditions
3	CuBr·Me_2S	TMSCl	-	large mixture of products
4[123]	CuBr·Me_2S	TMSCl	DMPU, Et_3N	large mixture of products
5[115]	CuI	TMSCl	LiBr, +/- Et_3N	not observed
6	CuBr·Me_2S	TMSCl	LiCl	not observed
7	CuBr·Me_2S	TIPSOTf	-	not observed
8	CuBr·Me_2S	TBDMSCl	-	not observed
9	CuBr·Me_2S	TBDMSOTf	-	not observed

Table 11

CuI and CuBr·Me_2S have been widely used in 1,4-additions, and thienyl(cyano) copper lithium has been found to be very stable and easy to handle copper source.[124] Starting material was mainly recovered in entries **1**, **5** and **6**. In entry **2**, starting material remained along with a mixture of products, but analysis of the crude material by ^{1}H NMR did not show any sign of the enol proton. In entries **2** and **4**, all the starting material was consumed but again, among

the numerous products formed, formation of the trimethyl silyl enol ether was not observed. Because the TMS group is very sensitive and labile, more robust silyl groups were also investigated to attempt to trap the enolate. In entries **7**, **8** and **9**, 1,4-addition product (*vide infra*) were detected, but not the desired silyl enol ethers.

As formation of *β*-allyl substituted ketone **288** has previously been observed as an undesired product, the simple conjugated addition was investigated. Allyl ketone **288** was obtained in 87% yield using CuBr.Me_2S as additive (Scheme 125).



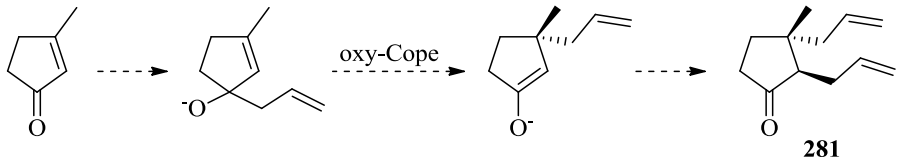
288

Conditions: a) allyl magnesium chloride, CuBr·Me_2S, THF, -40°C→rt, 87%.

Scheme 125 Copper-mediated 1,4-addition

Under these conditions however, it was not possible to trap out the enolate in situ.

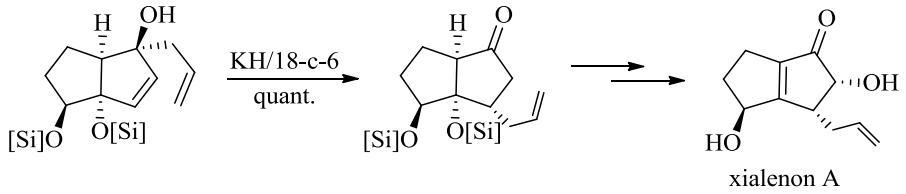
An alternative 1,2-addition followed by an oxy-Cope rearrangement was also envisaged (Scheme 126).



281

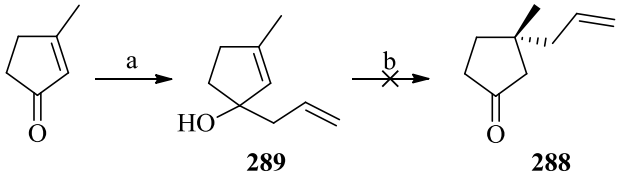
Scheme 126 Proposed oxy-Cope rearrangement

In the synthesis of xialenon A, a 1,2-addition of an allyl group followed by an oxy-Cope rearrangement was used in order to circumvent problems in the 1,4-addition reaction (Scheme 127).[125]



Scheme 127 Oxy-Cope strategy in the synthesis of Xialenon A

Methylcyclopentenone was treated with allyl Grignard reagent to give the expected 1,2-addition product **289** in 76% yield (Scheme 128). However the allylic alcohol did not undergo desired [3,3] sigmatropic rearrangement when treated with KH and 18-crown-6. Only starting material or degradation was observed.



Conditions: a) allylMgCl, THF, -78°C→rt, 76%; b) KH, 18-c-6, THF, -10°C→rt.

Scheme 128 1,2-addition-oxy-Cope rearrangement

3.4 Conclusion and future work

Two approaches to the *trans*-hydrindane ring system of dictyoxetane have been investigated. The first approach, based on γ-functionalisation of enone **241** has proved more successful than the second, where tandem conjugate addition and enolate trapping of 3-methylcyclohexenone could not be achieved.

The successful acetal protection with concomitant double bond migration of **241** has allowed studies into the regio- and stereoselective functionalisation of alkene **240**. Hydroboration and dihydroxylation of **240** are highly stereoselective, favouring attack on the same side as the

bridgehead methyl, whereas the stereoselectivity of epoxidation has been shown to be dependant on the reagent used. Attempts to access the trans-ring junction through epoxide rearrangement or epimerization of a *cis*-hydrindanone have so far proved ineffective.

Radical-mediated deoxygenation of thiocarbonate **270** should be investigated further. This route is currently hampered by the low yield of **270**, but if this can be overcome, then a study into the selectivity of hydrogen abstraction at the bridgehead carbon radical can be undertaken, which may possibly be influenced by the nature of the hydrogen donor.

Chapter 4

Experimental

General experimental

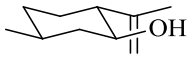
1H and 13C NMR data were recorded on a Bruker AC300, Bruker AV300, Bruker AMX400 or a Bruker DRX500 spectrometer. Spectra were recorded in C_6D_6 referenced to residual C_6H_6 (1H, 7.16 ppm; 13C, 128.06 ppm), CD_3CN referenced to residual CH_3CN (1H, 1.92 ppm 13C, 1.2 ppm) and $CDCl_3$ referenced to residual $CHCl_3$ (1H, 7.26 ppm; 13C, 77.0 ppm). Chemical shifts (δ) are reported in ppm and coupling constants (J) are reported in Hz. The following abbreviations are used to describe multiplicity; s-singlet, d-doublet, t-triplet, q quartet, m-multiplet, ap. apparent. All coupling constants are reported as observed and not averaged. Mass spectra were recorded on a LCT spectrometer utilising electrospray ionisation (recorded in the positive mode) with a methanol mobile phase, or electron impact ionisation, and are reported as (*m/z* (%)). HRMS were recorded on a LCT spectrometer using lock mass incorporated into the mobile phase. IR spectra were recorded neat, from nujol or as KBr disks on a Perkin Elmer 1600 series FT-IR, Perkin Elmer FT-IR Paragon 1000 or a Perkin Elmer 100-series FT-IR spectrometer. HPLC was carried out on a DIONEX summit P580 quaternary low pressure gradient pump with a built-in vacuum degasser using a Summit UVD 170s UV/Vis multi-channel detector with analytical flow cell and Chromeleon software and HPLC grade solvents. Analytical separations used a flow rate of 1 mL/min and semi-preparative used a flow rate of 3 mL/min. Melting points were determined using open glass capillaries on a Gallenkamp melting point apparatus and are uncorrected. Analytical TLC was carried out on Merck 60 F245 aluminium-backed silica gel plates. Short wave UV (245 nm), anisaldehyde was used to visualise components. Compounds were purified by flash column chromatography using Merck silica gel 60, basic alumina (Brockmann I, standard grade, ~150 mesh 58 Å), florisil® (60-100 U.S. mesh) or Bio-Beads (S-X8 beads,

200 - 400 mesh). Single crystal data collection at room temperature and structural solutions were performed by Dr Benson Kariuki and Dr Louise Male at the University of Birmingham. Solvents and reagents were purified as follows:

Solvents were degassed by bubbling argon through a needle immersed in the solvent for 15 min. *n*-BuLi was purchased as either 2.5 M or 1.6 M solutions in hexanes and the solutions were titrated with menthol in the presence of 1-(biphenyl-4-yl)-3-phenyl-2-azapropene ("BLUE"). TMEDA was distilled from calcium hydride. TCE was washed with HCl (2 M aqueous solution), K_2CO_3 (2 M aqueous solution), dried with K_2CO_3 and $CaCl_2$. Diethyl ether and hexane were distilled from sodium. Tetrahydrofuran was distilled from sodium and benzophenone. *m*CPBA was purified by washing with a pH 7 phosphate buffer unless otherwise stated: A buffer solution was prepared from 0.1 M NaOH (154 mL) and 0.2 M KH2PO4 (94 mL) and made up to 376 mL with distilled water. *m*CPBA (77% w/w, 10 g) was dissolved in diethyl ether (100 mL) and washed four times with the buffer solution. The organic extract was dried over MgSO4 and carefully evaporated under reduced pressure to yield pure *m*CPBA (7.3 g).

All other reagents and solvents were purchased from Aldrich, Alfa Aesar, Fisher Scientific, Merck or TCI Europe and were used as received. The following cooling baths were used: 0 °C (ice/water) and -78 °C (dry ice/acetone). All reactions in non-aqueous solvents were carried out under argon in oven-dried or flame-dried glassware.

***rac*-Isolpulegol 96**[126]



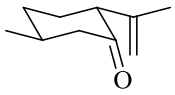
$ZnBr_2$ (1.65 g, 1.13 mmol) was added portionwise to a solution of (+/-) citronellal (1.16 mL, 6.48 mmol) in toluene (10 mL) at 0 °C. After 90 min the solution was filtered and evaporated. The residue was dissolved in Et_2O and washed with water (2 × 20 mL) and $NaHCO_3$ (10 mL of a saturated aqueous solution). The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (9:1 petrol:Et_2O) gave **96** (0.84 g, 84%) as a colourless oil. Rf 0.18 (4:1 petrol: Et_2O); υ_{max}(neat)/cm^{-1} 3415, 3072, 2921, 2949, 2868, 1645, 1448, 1374, 1026 and 884; δ_H(300 MHz; $CDCl_3$) 0.85-0.96 (2 H, m), 0.93 (3 H, d, *J* 6.5, CHC*H*$_3$), 1.24-1.40 (1 H, m), 1.40-1.57 (1 H, m), 1.62-1.72 (5 H, m), 1.83-1.93 (2 H, m), 2.00-2.08 (1 H, m), 3.46 (1 H, ap. td, *J* 10.4 and 4.4, C*H*OH), 4.86 (1 H, s, C=C*H*$_2$) and 4.90 (1 H, s, C=C*H*$_2$); δ_C(75 MHz; $CDCl_3$) 19.2 (CH_3), 22.3 (CH_3), 29.6 (CH_2), 31.4 (CH), 34.3 (CH_2), 42.6 (CH_2), 54.1 (CH), 70.3 (CH), 112.8 (CH_2) and 146.6 (C); *m/z* (EI) 154.1355 (M^+, $C_{10}H_{18}O$ requires 154.1358), 254.1 (39%), 136.1 (74), 121.1 (100), 95.1 (59) and 81.1 (44).

***rac*-Neoisolpulegol 123**[74]

L-selectride (13.14 mL of a 1.0 M solution in THF, 13.14 mmol) was slowly added to a solution of isopulegone **124** (1.00 g, 6.57 mmol) in THF (20 mL) at -78 °C and the reaction was allowed to warm to rt. After 24 h the mixture was quenched with H_2O_2 (5 mL) and NaOH (5 mL of a 15% aqueous solution). The solution was partially evaporated and extracted with

Et_2O (2 × 20 mL). The combined organic layers were washed with HCl (10 mL of a 1 M aqueous solution), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (12:1 petrol:Et_2O) gave **123** (0.58 g, 57%) as a colourless oil.Rf 0.72 (2:1 petrol: Et_2O), υ_{max}(neat)/cm^{-1} 3476, 2945, 2923, 2877, 1715, 1455, 1376 and 1031; δ_H(300 MHz; $CDCl_3$) 0.84-0.98 (1 H, m), 0.88 (3 H, d, *J* 6.5, CHC*H*$_3$), 1.07-1.18 (1 H, m), 1.39-1.53 (2 H, m), 1.67-1.76 (3 H, m), 1.79 (3 H, s, C*H*$_3$), 1.93-2.02 (2 H, m), 3.99 (1 H, d, *J* 1.8, C*H*OH), 4.78 (1 H, s, C=C*H*$_2$) and 4.95 (1 H, s, C=C*H*$_2$); δ_C(75 MHz; $CDCl_3$) 22.8 (CH_3), 23.1 (CH_3), 23.9 (CH_2), 25.8 (CH), 34.7 (CH_2), 40.9 (CH_2), 48.4 (CH), 66.3 (CH), 111.3 (CH_2) and 147.1 (C); *m/z* (EI) 154.1359 (M^+, $C_{10}H_{18}O$ requires 154.1358), 254.1 (27%), 136.1 (69), 121.1 (100), 93.1 (56), 81.1 (50) and 81.1 (44).

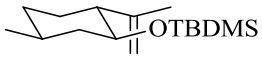
***rac*-Isopulegone 124**[74]



PCC (15.75 g, 73.06 mmol) was added to a solution of isopulegol **96** (7.50 g, 48.7 mmol) in CH_2Cl_2 (230 mL) at rt. The mixture was stirred for 12 h and filtered through a pad of silica and celite eluting with CH_2Cl_2. The solution was concentrated *in vacuo* and purified by column chromatography (12:1 petrol:Et_2O) to give ketone **124** (6.06 g, 82%) as a colourless oil. υ_{max}(neat)/cm^{-1} 2953, 2927, 2870, 1709, 1455, 1375, 1125 and 889; δ_H(400 MHz; $CDCl_3$) 1.00 (3 H, d, *J* 6.3, CHC*H*$_3$), 1.33-1.45 (1 H, m), 1.71 (3 H, s, CC*H*$_3$), 1.75 (1 H, dd, *J* 13.0 and 3.4), 1.79-1.94 (2 H, m), 1.97-2.06 (2 H, m), 2.36 (1 H, ddd, *J* 13.3, 3.8 and 2.2), 2.92 (1 H, dd, *J* 13.0 and 5.4, CH_2CH_2CHC), 4.67-4.69 (1 H, m, C=C*H*$_2$) and 4.88-4.90 (1 H, m,

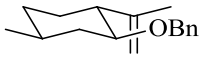
C=CH_2); δ_C(75 MHz; $CDCl_3$) 21.3 (CH_3), 22.2 (CH_3), 31.1 (CH_2), 33.8 (CH_2), 35.2 (CH), 50.5(CH_2), 57.6 (CH), 112.7 (CH_2), 143.4 (C) and 210.1 (C).

rac-(1_S_,2_R_,5_S_)-1-_tert_-Butyldimethylsiloxy-2-isopropenyl-5-methylcyclohexane 135



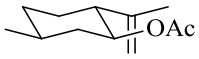
TBDMSCl (0.11 g, 0.73 mmol) was added to a solution of isopulegol **96** (0.10 g, 0.65 mmol) and imidazole (0.08 g, 1.29 mmol) in DMF (2 mL) at rt. The reaction was stirred for 12 h, after which the mixture was quenched with water (30 mL) and extracted with Et_2O (2 × 30 mL). The combined organic layers were washed with brine (30 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (9:1 petrol:Et_2O) gave silyl ether **135** (0.15 g, 89%) as a colourless oil. R_f 0.36 (8:2 petrol:Et_2O); υ_{max}(neat)/cm^{-1} 2954, 1643 , 1360 , 1265 , 1104 and 906; δ_H(300 MHz; $CDCl_3$) -0.02 (3 H, s, SiCH_3), 0.01 (3 H, s, SiCH_3), 0.85 (9 H, s, C(CH_3)$_3$), 0.91 (3 H, d, *J* 6.5, CHCH_3), 0.92-1.06 (1 H, m), 1.21-1.49 (2 H, m), 1.55-1.66 (3 H, m), 1.67 (3 H, s, CH_2=CCH_3), 1.79-1.94 (2 H, m), 3.45 (1 H, ap. td, *J* 10.2, *J* 4.4, C*H*O) and 4.65-4.75 (2 H, m, C=CH_2); δ_C(75 MHz; $CDCl_3$) -4.8 (CH_3, Si*C*H_3), -3.9 (CH_3, Si*C*H_3), 18.1 (C, *C*(CH_3)$_3$), 20.9 (CH_3), 22.0 (CH_3, CH_2=C*C*H_3), 25.5 (3 × CH_3, C(*C*H_3)$_3$), 30.5 (CH_2), 31.7 (CH), 34.4 (CH_2), 45.2 (CH_2), 53.3 (CH), 73.6 (CH, *C*HO), 111.0 (CH_2, C=*C*H_2) and 149.9 (C, *C*=CH_2); *m/z* (EI) 268.2228 (M^+, $C_{16}H_{32}OSi$ requires 268.2222), 268.2 (1%), 211.2 (100), 185.2 (5), 169.2 (76) and 75.0 (16).

***rac*-(1*S*,2*R*,5*S*)-1-Benzyloxy-2-isopropenyl-5-methylcyclohexane 136**



NaH (0.28 g of a 60% dispersion in mineral oil, 7.10 mmol) was added portionwise to a solution of isopulegol **96** (1.00 g, 6.50 mmol) and benzyl bromide (0.85 mL, 7.10 mmol) in DMF (10 mL) at 0 °C and the reaction was allowed to warm at rt. The mixture was stirred for 10 h after which the reaction was quenched with MeOH (5 mL). After 1 h, the solution was evaporated and the residue was dissolved in CH_2Cl_2 (10 mL) and water (10 mL), and extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were washed with brine (10 mL), water (10 mL), dried ($MgSO_4$) and the solution was concentrated *in vacuo*. Purification by column chromatography (4:1 petrol:Et_2O) gave benzyl ether **136** (0.67 g, 94%) as a colourless oil. R_f 0.80 (2:1 petrol:Et_2O), υ_{max}(neat)/cm^{-1} 2951 (CH), 1713 (C=C) and 1598 (C=C Ar); δ_H(300 MHz; $CDCl_3$) 0.89 (3 H, d, *J* 6.5, CH*C*H_3), 0.92-0.99 (2 H, m), 1.17-1.45 (2 H, m), 1.53-1.62 (2 H, m), 1.63 (3 H, s, CH_2=CC*H*$_3$), 1.97-2.16 (2 H, m), 3.24 (1 H, ap. td, *J* 10.5 and 4.1, C*H*O), 4.37 (1 H, d, *J* 11.7, C*H*$_2$Ph), 4.55 (1 H, d, *J* 11.7, C*H*$_2$Ph), 4.75 (2 H, s, C=C*H*$_2$) and 7.14-7.35 (5 H, m, Ar); δ_C(75 MHz; $CDCl_3$) 20.0 (CH_3), 22.3 (CH_3), 31.1 (CH_2), 31.5 (CH, *C*HCH_3), 34.4 (CH_2), 40.2 (CH_2), 45.4 (CH), 51.8 (CH_2, *C*H_2Ph), 70.4 (C), 72.1 (CH, *C*HO), 110.9 (CH_2, C=*C*H_2), 127.2 (CH, Ar), 127.6 (2 × CH, Ar), 127.7 (CH, Ar), 128.1 (CH, Ar), 128.3 (C, Ar) and 147.8 (C, *C*=CH_2); *m/z* (EI) 244.1831 (M^+, $C_{17}H_{24}O$ requires 244.1827), 244 (0.1%), 138 (42), 109 (20), 91 (100) and 69 (20).

***rac*-(1*S*,2*R*,5*S*)-1-Acetoxy-2-isopropenyl-5-methylcyclohexane 137**

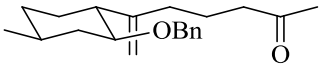


A solution of isopulegol **96** (0.50 g, 3.24 mmol), acetic anhydride (0.30 mL, 3.24 mmol) and pyridine (0.26 mL, 3.24 mmol) in toluene (5 mL) was stirred for 1 day at rt. The mixture was quenched with water (10 mL) and HCl (5 mL of a 1 M aqueous solution), and extracted with Et_2O (2 × 20 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and the solution was concentrated *in vacuo*. Purification by column chromatography (12:1 petrol:Et_2O) gave **137** (0.33 g, 52%) as a pale yellow oil. R_f 0.38 (8:1 petrol:Et_2O); υ_{max}(neat)/cm^{-1} 2951, 1720, 1648, 1360 and 1265; δ_H(300 MHz; $CDCl_3$) 0.87 (3 H, d, *J* 6.5, CHC*H*$_3$), 0.89-1.17 (4 H, m), 1.22-1.41 (1 H, m), 1.42-1.56 (1 H, m), 1.60 (3 H, s, CH_2=CC*H*$_3$), 1.91 (3 H, s, COC*H*$_3$), 1.94-2.09 (2 H, m), 4.66 (2 H, s, C=C*H*$_2$) and 4.74 (1 H, ap. td, *J* 10.9 and 4.4, C*H*O); δ_C(75 MHz; $CDCl_3$) 19.3 (CH_3, CO*C*H$_3$), 20.9 (CH_3, CH_2=C*C*H$_3$), 21.9 (CH_3, CH*C*H$_3$), 30.2 (CH_2), 31.2 (CH, *C*HCH$_3$), 33.9 (CH_2), 40.3 (CH_2), 50.6 (CH), 73.3 (CH, *C*HO), 111.5 (CH_2, C=*C*H$_2$), 146.0 (CH_2, *C*=CH$_2$) and 170.2 (C, *C*O); *m/z* (EI) 196.1456 (M^+, $C_{12}H_{20}O_2$ requires 196.1463), 196 (2%), 136 (100), 121 (78), 107 (60), 93 (61), 81 (48) and 67 (26).

***rac*-(1*S*,2*R*,5*S*)-1-*tert*-Butyldimethylsiloxy-2-(hept-6'-en-2'-on-6'-yl)-5-methylcyclo hexane 138**

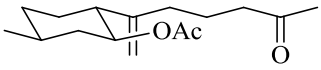
Me_2AlCl (0.64 mL of a 1.0 M solution in hexanes, 0.64 mmol) was added to a solution of olefin **135** (0.20 g, 0.75 mmol) and MVK (0.06 mL, 0.68 mmol) in CH_2Cl_2 (10mL) at -20 °C. The reaction was stirred at -20 °C for 2 h and allowed to warm at rt. After 12 h, the mixture was quenched with water (10 mL) and extracted with Et_2O (2 × 20 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and the solution was concentrated *in vacuo*. Purification by column chromatography (9:1 petrol: Et_2O) gave **138** (0.10 g, 41%) as a colourless oil. R_f 0.37 (8:2 petrol:Et_2O); υ_{max}(neat)/cm^{-1} 1719, 1643, 1360, 1265, 1104 and 835; δ_H(300 MHz; $CDCl_3$) -0.17 (3 H, s, SiCH_3), -0.12 (3 H, s, SiCH_3), 0.81 (9 H, s, C(CH_3)$_3$), 0.88 (3 H, d, *J* 6.6, CHCH_3), 0.91-1.03 (2 H, m), 1.11-1.29 (1 H, m), 1.35-1.51 (1 H, m), 1.52-1.87 (6 H, m), 2.00 (2 H, t, *J* 7.7, CH_2=CCH_2), 2.10 (3 H, s, COCH_3), 2.41 (2 H, t, *J* 7.4, CH_2CO), 3.46 (1 H, ap. td, *J* 10.3 and 4.3, C*H*O) and 4.73-4.77 (2 H, m, C=CH_2); δ_C(75 MHz; $CDCl_3$) -4.8 (CH_3, Si*C*H_3), -4.1 (CH_3, Si*C*H_3), 17.9 (C, *C*(CH_3)$_3$), 21.7 (CH_2), 22.2 (CH_3, CH*C*H_3), 25.8 (3 × CH_3, C(*C*H_3)$_3$), 29.8 (CH_3, CO*C*H_3), 31.6 (CH, *C*HCH$_3$), 31.7 (CH_2), 34.4 (CH_2), 36.2 (CH_2, CH_2=C*C*H_2), 43.4 (CH_2, *C*H_2CO), 45.3 (CH_2), 51.7 (CH), 75.1 (CH, *C*HO), 108.6 (CH_2, C=*C*H_2), 152.1 (C, *C*=CH_2) and 208.9 (C, *C*O); *m/z* (ESI) 361.2551 ($[M+Na]^+$, $C_{20}H_{38}NaO_2Si$ requires 361.2539), 361 (100%).

***rac*-(1*S*,2*R*,5*S*)-1-Benzyloxy-2-(hept-6'-en-2'-on-6'-yl)-5-methylcyclohexane 139**



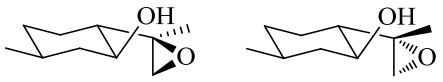
Me_2AlCl (4.47 mL of a 1.0 M solution in hexanes, 4.47 mmol) was added to a solution of olefin **136** (1.27 g, 5.20 mmol) and MVK (0.40 mL, 4.73 mmol) in CH_2Cl_2 (20mL) at -78°C. The reaction was allowed to warm at rt o/n, quenched with water (10 mL) and extracted with Et_2O (2 × 30 mL). The combined organic layers were washed with water (20 mL) and brine (20 mL), dried ($MgSO_4$) and the solvent was removed *in vacuo*. Purification by column chromatography (4:1 petrol:Et_2O) gave **139** (0.21 g, 14%) as a colourless oil. R_f 0.39 (5:1 petrol:Et_2O); υ_{max}(neat)/cm^{-1} 2923 (CH), 1715 (C=C) and 1644 (CO); δ_H(300 MHz; $CDCl_3$) 0.89 (3 H, d, *J* 6.5, CHC*H*$_3$), 0.92-1.06 (2 H, m), 1.31-1.43 (1 H, m, C*H*CH_3), 1.53-1.73 (5 H, m), 1.88-1.97 (3 H, m), 1.99 (3 H, s, COC*H*$_3$), 2.07-2.16 (1 H, m), 2.33 (2 H, t, *J* 7.9, C*H*$_2$CO), 3.26 (1 H, ap. td, *J* 10.9 and 4.5, C*H*O), 4.32 (1 H, m, C*H*$_2$Ph), 4.54 (1 H, d, *J* 11.6, C*H*$_2$Ph), 4.73-4.81 (2 H, m, C=C*H*$_2$) and 7.15-7.27 (5 H, m, Ar); δ_C(75 MHz; $CDCl_3$) 21.2 (CH_2), 21.8 (CH_3, CH*C*H_3), 29.4 (CH_3, CO*C*H_3), 31.1 (CH, *C*HCH_3), 31.6 (CH_2), 34.1 (2 × CH_2), 40.0 (CH_2), 42.7 (CH_2, *C*H_2CO), 49.9 (CH), 70.2 (CH_2, *C*H_2Ph), 80.5 (CH, *C*HO), 108.5 (CH_2, C=*C*H_2), 126.8 (CH, Ar), 127.1 (2 × CH, Ar), 127.7 (2 × CH, Ar), 138.7 (C, Ar), 151.3 (C, *C*=CH_2) and 208.8 (C, *C*O); *m/z* (ESI) 337.2145 ($[M+Na]^+$, $C_{21}H_{30}NaO_2$ requires 337.2143), 337.2 (100%).

***rac*-(1*S*,2*R*,5*S*)-1-Acetoxy-2-(hept-6'-en-2'-on-6'-yl)-5-methylcyclohexane 140**



Me_2AlCl (0.65 mL of a 1.0 M solution in hexanes, 0.65 mmol) was added to a solution of olefin **137** (0.15 g, 0.76 mmol) and MVK (0.06 mL, 0.70 mmol) in CH_2Cl_2 (10mL) at -20 °C. The reaction was allowed to warm to rt and stirred for 3 h. The mixture was quenched with water (10 mL) and extracted with Et_2O (2 × 20 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and the solvent was removed *in vacuo*. Purification by column chromatography (10:1 petrol:Et_2O) gave **140** (0.05 g, 27%) as a pale yellow oil. R_f 0.31 (10:1 petrol:Et_2O); υ_{max}(neat)/cm^{-1} 2948, 1717, 1644 (CO) and 1352 (-CO-CH_3); δ_H(300 MHz; $CDCl_3$) 0.90 (3 H, d, *J* 6.5, CHC*H*$_3$), 0.92-1.05 (2 H, m), 1.15-1.47 (7 H, m), 1.54-1.59 (3 H, m), 1.62 (3 H, s, COC*H*$_3$), 1.95 (3 H, s, OCOC*H*$_3$), 2.07 (2 H, t, *J* 7.8, C*H*$_2$CO), 4.76 (1 H, ap. td, *J* 10.6 and 4.1, C*H*O) and 4.82-4.90 (2 H, m, C=C*H*$_2$); δ_C(75 MHz; $CDCl_3$) 19.1 (CH_3, CH*C*H$_3$), 20.7 (CH_2), 21.6 (CH_3, OCO*C*H$_3$), 29.9 (CH_3, CO*C*H$_3$), 30.9 (CH_2), 31.1 (CH, *C*HCH$_3$), 33.6 (CH_2), 34.1 (CH2), 40.0 (CH_2), 43.2 (CH_2, *C*H$_2$CO), 50.2 (CH), 73.1 (CH, *C*HO), 111.2 (CH_2, C=*C*H$_2$), 145.8 (C, *C*=CH$_2$), 170.1 (C, O*C*O) and 208.8 (C, *C*O); *m/z* (ESI) 289.1783 ([M+Na]$^+$, $C_{16}H_{26}NaO_3$ requires 289.1780), 289 (100%).

***rac*-(1*S*,2*S*,5*S*)-2-((2'*R*)-2'-Methyloxiran-2'-yl)-5-methylcyclohexanol 157 and *rac*-(1*S*,2*S*,5*S*)-2-((2'*S*)-2'-methyloxiran-2'-yl)-5-methylcyclohexanol 156**



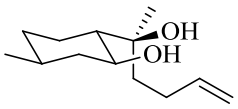
m-CPBA (1.69 g, 9.78 mmol) was added portionwise to a solution of isopulegol **96** (1.37 g, 8.89 mmol) in CH_2Cl_2 (35 mL) at 0 °C and the reaction was allowed to warm up to rt. The mixture was stirred for 12 h and quenched with $NaHCO_3$ (20 mL of a saturated aqueous solution). The mixture was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic layers were washed with water (20 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give after chromatography (1.5:1 petrol:Et_2O) epoxide **157** (0.47 g, 31%) and epoxide **156** (0.42, 27%).

157 was obtained as a white solid. R_f 0.21 (1:1 petrol:Et_2O); mp 40-41 °C (lit[63] 34-35 °C); υ_{max}(neat)/cm^{-1} 3429, 2949, 2922, 2868, 1729, 1450, 1376, 1284, 1450, 1095, 1049, 1028, 904 and 806; δ_H(300 MHz; $CDCl_3$) 0.83-1.00 (3 H, m), 0.91 (3 H, d, *J* 6.6, CHC*H*$_3$), 1.11-1.25 (1 H, m), 1.30 (3 H, s, CC*H*$_3$), 1.34-1.52 (1 H, m), 1.60-1.73 (2 H, m), 1.97-2.06 (1 H, m), 2.53 (1 H, d, *J* 4.6, C*H*$_2$O), 2.58 (1 H, d, *J* 4.6, C*H*$_2$O), 2.86 (1 H, s, O*H*) and 3.71 (1 H, ap. dt, *J* 10.4 and 4.4, C*H*O); δ_C(75 MHz; $CDCl_3$) 16.8 (CH_3), 21.8 (CH_3), 27.4 (CH_2), 30.8 (CH_2), 33.8 (CH_2), 43.4 (CH), 51.1 (CH), 53.0 (CH_2, C*H*$_2$O), 59.1 (C) and 71.3 (CH, C*H*O); *m/z* (EI) 170.1310 (M^+, $C_{10}H_{18}O_2$ requires 170.1310), 169.1 (4%), 152.1 (41), 123.1 (50), 108.1 (54), 93.1 (56), 81.1 (100) and 67.1 (38).

156 was obtained as white solid. R_f 0.13 (1:1 petrol:Et_2O); mp 51-52 °C (lit[63] 54-55 °C); υ_{max}(neat)/cm^{-1} 3428, 2921, 2868, 1726, 1449, 1376, 1286, 1050, 1025, 1003, 867 and 810;

δ_H(300 MHz; $CDCl_3$) 0.78-0.98 (2 H, m), 0.88 (3 H, d, *J* 6.5, CHC*H*$_3$), 0.99-1.14 (1 H, m), 1.32 (3 H, s, CC*H*$_3$), 1.34-1.46 (2 H, m), 1.59-1.69 (1 H, m), 1.78-1.93 (2 H, m), 2.63 (1 H, d, *J* 4.2, C*H*$_2$O), 2.88 (1 H, d, *J* 4.1, C*H*$_2$O), 3.25 (1 H, ap. dt, *J* 10.4 and 4.4, C*H*O) and 3.41 (1 H, s, O*H*); δ_C(75 MHz; $CDCl_3$) 20.8 (CH_3), 23.8 (CH_3), 27.6 (CH_2), 31.2 (CH), 33.8 (CH_2), 42.8 (CH_2), 48.9 (CH), 52.2 (CH), 60.3 (C) and 70.5 (CH, C*H*O); *m/z* (EI) 170.1310 (M^+, $C_{10}H_{18}O_2$ requires 170.1310), 169.1 (4%), 152.1 (41), 123.1 (50), 108.1 (54), 93.1 (56), 81.1 (100) and 67.1 (38).

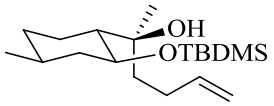
rac-(1*S*,2*S*,5*S*)-2-((2'*S*)-2'-Hydroxyhex-5'-en-2'-yl)-5-methylcyclohexanol 158



A solution of allyl magnesium bromide (5.32 mL of a 1.0 M solution in Et_2O, 5.32 mmol) was added over 30 min to a solution of epoxide **157** (0.15 g, 0.89 mmol) in Et_2O (10 mL) at -30 °C. The mixture was stirred for 1h at -30 °C and was allowed to warm to rt. After 2 h the reaction was poured into a mixture of NH_4Cl (5 mL of a saturated aqueous solution) and HCl (5 mL of a 1 M aqueous solution). The aqueous layer was extracted with Et_2O (3 × 15 mL) and the combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography (2:1 petrol:Et_2O) to give **158** (0.14 g, 74%) as a colourless oil. R_f 0.36 (1:2 petrol:Et_2O); υ_{max}(neat)/cm^{-1} 3283, 3090, 2948, 2921, 2868, 1641, 1454, 1375, 1003 and 909; δ_H(400 MHz; $CDCl_3$) 0.83-0.92 (2 H, m), 0.88 (3 H, d, *J* 6.5, CHC*H*$_3$), 1.01 (1 H, ap. td, *J* 12.1 and 11.0, ax. CHC*H*$_2$CH), 1.16 (3 H, s, CC*H*$_3$), 1.34-1.66 (6 H, m), 1.87-1.94 (1 H, m, eq. CHC*H*$_2$CH), 2.02-2.25 (2 H, m, C*H*$_2$CH=CH$_2$), 3.72 (1 H, ap. td, *J* 10.3 and 4.2, C*H*OH), 3.98 (2 H, s, 2 × O*H*), 4.90-5.03 (2

H, m, CH=CH_2) and 5.75-5.86 (1 H, m, CH=CH_2); δ_C(75 MHz; $CDCl_3$) 22.2 (CH_3, CHCH_3), 23.2 (CH_3, CCH_3), 26.8 (CH_2), 27.2 (CH_2), 31.5 (CH), 34.7 (CH_2), 40.6 (CH_2), 44.9 (CH_2, CHCH_2CH), 50.6 (CH), 72.7 (CH, CHOH), 76.5 (C), 114.6 (CH_2, CH=CH$_2$) and 139.3 (CH, CH=CH_2); *m*/*z* (ESI) 235.1668 ([M+Na]$^+$, $C_{13}H_{24}O_2Na$ requires 235.1674), 235.2 (100%).

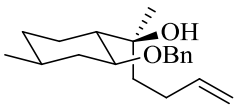
rac-(2*S*)-2-((1'*S*,2'*S*,4'*S*)-2'-((*tert*-Butyldimethylsilyl)oxy)-4'-methylcyclohexyl)hex-5-en-2-ol 159



Imidazole (0.77 g, 5.69 mmol) and TBDMSCl (1.29 g, 8.54 mmol) were added to a solution of diol **158** (1.21, 5.69 mmol) in DMF (14 mL) at rt. The reaction was stirred for 2 days before being quenched with water (10 mL). The aqueous layer was extracted with Et_2O (3 × 20 mL) and the combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography (5:1 petrol:Et_2O) to give silyl ether **159** (1.66 g, 89%) as a colourless oil. R_f 0.25 (8:1 petrol:Et_2O); υ_{max}(neat)/cm^{-1} 3488, 2927, 2858, 1640 (C=C), 1456, 1372, 1258, 1053 and 863; δ_H(400 MHz; $CDCl_3$) 0.13 (6 H, d, *J* 5.4, Si(CH_3)$_2$), 0.83-0.92 (14 H, m), 1.03-1.14 (1 H, m), 1.12 (3 H, s, CCH_3), 1.34-1.54 (4 H, m), 1.58-1.69 (2 H, m), 1.85-1.93 (1 H, m), 1.98-2.11 and 2.19-2.31 (2 H, 2 × m, CH_2), 3.45 (1 H, ap. td, *J* 10.4 and 3.9, CHO), 4.84-5.04 (3 H, m, CH=CH_2 and OH) and 5.75-5.87 (1 H, m, CH=CH_2); δ_C(75 MHz; $CDCl_3$) -4.6 (CH_3, SiCH_3), -2.9 (CH_3, SiCH_3), 17.9 (C, SiC), 22.1 (CH_3), 23.5 (CH_3), 25.9 (3 × CH_3), 26.7 (CH_2), 27.0 (CH_2), 31.7 (CH), 34.4 (CH_2), 40.4 (CH_2), 45.4 (CH_2), 50.7 (CH), 74.3 (C), 75.6 (CH, CHO), 113.8

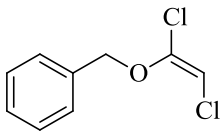
(CH_2, CH=*C*H_2) and 139.6 (CH, *C*H=CH_2); *m*/*z* (ESI) 349.2540 ($[M+Na]^+$, $C_{19}H_{38}O_2SiNa$ requires 349.2539), 349.5 (100%).

rac-(2*S*)-2-((1'*S*,2'*S*,4'*S*)-2'-(Benzyloxy)-4'-methylcyclohexyl)hex-5-en-2-ol 164



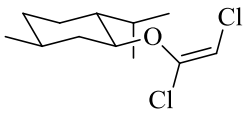
To a solution of diol **158** (0.16 g, 0.78 mmol), TBAB (0.09 g, 0.28 mmol) and BnBr (0.37 mL, 3.11 mmol) in CH_2Cl_2 (35 mL), was added KOH (35 mL of a 50% aqueous solution) at rt with vigorous stirring. After being stirred o/n, water (10 mL) and CH_2Cl_2 (10 mL) were added to the reaction and the aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography (5:1 petrol:Et_2O) to give benzyl ether **164** (0.16 g, 69%) as a colourless oil. R_f 0.62 (1:1 petrol:Et_2O); υ_{max}(neat)/cm^{-1} 3451, 3069, 2949, 2924, 2868, 1714, 1451, 1267, 1094, 1026, 910 and 712; δ_H(300 MHz; $CDCl_3$) 0.85-0.99 (2 H, m), 0.96 (3 H, d, *J* 6.5, CHC*H*$_3$), 0.99-1.09 (1 H, m), 1.10 (3 H, s, CC*H*$_3$), 1.35-1.57 (3 H, m), 1.58-1.75 (3 H, m), 1.99-2.14 (1 H, m, C*H*$_2$CH=CH_2), 2.18-2.33 (2 H, m), 3.60 (1 H, ap. td, *J* 10.4 and 3.8, C*H*O), 4.42 (1 H, d, *J* 10.9, C*H*$_2$Ph), 4.72 (1 H, d, *J* 10.9, C*H*$_2$Ph), 4.88-4.94 (1 H, m, CH=C*H*$_2$), 4.96-5.05 (1 H, m, CH=C*H*$_2$), 5.06 (1 H, s, O*H*), 5.76-5.91 (1 H, m, C*H*=CH_2) and 7.27-7.36 (5 H, m, C*H*$_{Ar}$); δ_C(75 MHz; $CDCl_3$) 22.1 (CH_3, CH*C*H$_3$), 23.8 (CH_3, C*C*H$_3$), 27.0 (2 × *C*H_2), 31.4 (CH, *C*HCH$_3$), 34.4 (CH_2), 39.5 (CH_2), 40.2 (CH_2), 49.5 (CH, *C*HC), 70.1 (CH_2, *C*H$_2$Ph), 74.2 (C, *C*OH), 81.1 (CH, *C*HO), 113.8 (CH_2, CH=*C*H_2), 127.9 (CH, Ar), 128.1 (2 × CH, Ar), 128.5 (2 × CH, Ar), 137.4 (C, Ar) and 139.5 (CH, *C*H=CH_2); *m*/*z* (ESI) 325.2146 ($[M+Na]^+$, $C_{20}H_{30}O_2Na$ requires 325.2144), 325.2 (100%).

(E)-(((1,2-Dichlorovinyl)oxy)methyl)benzene 169[73]



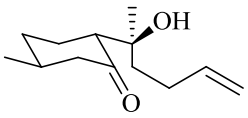
Benzyl alcohol (0.1 g, 0.93 mmol) in THF (1.4 mL) was added dropwise to a solution of washed KH (0.18 g, 1.39 mmol) in THF (0.8 mL) at rt. When the gas has stopped evolving, the white slurry solution was cooled to -78 °C and a solution of trichloroethylene (0.15 g, 1.11 mmol) in THF (0.5 mL) was added over 10 min. The reaction was allowed to warm to rt and stirred for 90 min. The resulting dark brown solution was partitioned with water (3 mL) and Et_2O (3 mL). The mixture was washed with water (10 mL) and extracted with hexane (3 × 15 mL). The combined organic layers were washed with brine (20 mL) and dried ($MgSO_4$). Concentration of the solvent *in vacuo* yielded dichloroenol ether **169** (0.19 g, 100%) as a colourless oil, which was used without any further purification. R_f 0.76 (1:1 petrol:Et_2O); υ_{max}(neat)/cm^{-1} 3034, 2956, 1752, 1455, 1307, 1165 and 697; δ_H(300 MHz; $CDCl_3$) 5.05 (2 H, s, CH_2), 5.51 (1 H, s, C=CH) and 7.35-7.47 (5 H, m, CH_{Ar}); δ_C(100 MHz; $CDCl_3$) 73.4 (CH_2), 98.9 (CH), 128.5 (2 × CH, Ar), 128.6 (2 × CH, Ar), 128.8 (CH, Ar), 134.6 (C, Ar) and 143.3 (C); *m/z* (EI) 201.9955 (M^+, $C_9H_8Cl_2O$ requires 201.9952), 200 (37%), 181 (31), 166 (0),138 (100) and 130 (75).

(1*R*,2*S*,4*S*)-2-(((*E*)-1',2'-Dichlorovinyl)oxy)-1-isopropyl-4-methylcyclohexane 170[72]



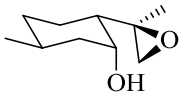
Menthol (0.1 g, 0.64 mmol) in THF (1.4 mL) was added dropwise to a solution of washed KH (0.13 g, 0.96 mmol) in THF (0.8 mL) at rt. When the gas has stopped evolving, the white slurry solution was cooled to -78 °C and a solution of trichloroethylene (0.07 mL, 0.77 mmol) in THF (0.5 mL) was added over 10 min. The reaction was allowed to warm up to rt and stirred for 100 min. The dark brown solution was quenched with water (5 mL) and partitioned with 10 mL each of water and hexane. The mixture was washed with brine (20 mL) and extracted with hexane (3 × 20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* to yield dichloro enol ether **170** (0.16 g, 100%) as a colourless oil, which was used without any further purification. R_f 0.45 (1:1 petrol:Et_2O); υ_{max}(neat)/cm^{-1} 2955, 2925, 2871, 1626, 1278, 1081 and 825; δ_H(400 MHz; $CDCl_3$) 0.81 (3 H, d, *J* 6.9, CHC*H*$_3$), 0.84-0.91 (1 H, m), 0.93 (6 H, t, *J* 7.1, 2 × C*H*$_3$), 0.96-1.05 (1 H, m), 1.10 (1 H, ap. td, *J* 12.2 and 11.1, ax. CHC*H*$_2$CH), 1.34-1.46 (1 H, m), 1.46-1.55 (1 H, m), 1.64-1.74 (2 H, m), 2.01-2.08 (1 H, m, eq. CHC*H*$_2$CH), 1.15-1.24 (1 H, m, C*H*), 4.08 (1 H, ap. td, *J* 10.8 and 4.4, C*H*O) and 5.52 (1 H, s, C*H*Cl); δ_C(100 MHz; $CDCl_3$) 15.9 (CH_3), 20.7 (CH_3), 22.1 (CH_3), 23.2 (CH_2), 25.5 (CH), 31.5 (CH), 34.1 (CH_2), 39.9 (CH_2), 47.1 (CH), 81.7 (CH, C*H*O), 97.9 (CH, C*H*Cl) and 142.7 (C); *m*/*z* (ESI) $[M+Na]^+$, 375.3 (100%).

***rac*-(2*R*,5*S*)-2-((2'*S*)-2'-Hydroxyhex-5'-en-2'-yl)-5-methylcyclohexanone 171**



TPAP (0.01 g, 0.03 mmol) was added in one portion to a stirred mixture of diol **158** (0.10 g, 0.47 mmol), NMO (0.08 g, 0.71 mmol) and powdered 4 Å MS (0.24 g) in CH_2Cl_2 (0.9 mL) at rt. The mixture was stirred o/n at rt, filtered through a pad of silica eluting with EtOAc, and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography (4:1 petrol:Et_2O) to give **171** (64 mg, 65%) as a colourless oil. R_f 0.27 (3:1 petrol:Et_2O); υ_{max}(neat)/cm^{-1} 3432, 3100, 2927, 1708 and 1378; δ_H(400 MHz; $CDCl_3$) 1.01 (3 H, d, *J* 6.2, CHC*H*$_3$), 1.18 (3 H, s, CC*H*$_3$), 1.27-1.60 (4 H, m), 1.80-1.95 (2 H, m), 1.96-2.05 (1 H, m), 2.05-2.18 (3 H, m), 2.33-2.43 (2 H, m), 4.03 (1 H, s, CO*H*), 4.90-5.06 (2 H, m, CH=C*H*$_2$) and 5.75-5.89 (1 H, m, C*H*=CH_2); δ_C(75 MHz; $CDCl_3$) 22.2 (CH_3, CH*C*H_3), 23.6 (CH_3, C*C*H_3), 27.6 (CH_2), 28.4 (CH_2), 33.9 (CH_2), 35.3 (CH), 39.6 (CH_2), 51.5 (CH_2), 56.7 (CH), 72.9 (C), 114.3 (CH_2, CH=*C*H_2), 139.0 (CH, *C*H=CH_2) and 215.5 (C, *C*=O); *m*/*z* (EI) 210.1611 (M^+, $C_{13}H_{22}O_2$ requires 210.1620), 210 (3%), 195 (8), 155 (23), 112 (41), 97 (15), 70 (26), 55 (25) and 43 (100).

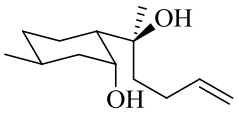
***rac*-(1*R*,2*S*,5*S*)-2-((2'*R*)-2'-Methyloxiran-2'-yl))-5-methylcyclohexanol 172**[74]



^{t}BuOOH (1.13 mL of a 70% solution in water, 8.27 mmol) and $VO(acac)_2$ (0.03 g, 0.12mmol) were added to a solution of neoisopulegol **123** (0.91 g, 5.87 mmol) in toluene (10.5 mL). The

4r e action was stirred o/n at rt before being dissolved with Et_2O (10 mL) and water (10 mL). The mixture was extracted with Et_2O (3 × 30 mL) and the combined organic layers were washed with $NaHCO_3$ (20 mL of a saturated aqueous solution), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography (2:1 petrol/Et_2O) to give epoxide **172** (0.27 g, 27%) as a colourless oil. R_f 0.30 (2:1 petrol/Et_2O); υ_{max}(neat)/cm^{-1} 3414, 2923, 2851, 1730, 1261 and 800; δ_H(400 MHz; $CDCl_3$) 0.77-0.93 (2 H, m), 0.81 (3 H, d, *J* 6.5, CHC*H*$_3$), 0.94-1.06 (1 H, m), 1.35 (3 H, s, CC*H*$_3$), 1.40-1.52 (2 H, m), 1.64-1.87 (3 H, m), 2.45 (1 H, d, *J* 4.5, C*H*$_2$O), 2.70 (1 H, s, O*H*), 2.77 (1 H, d, *J* 4.5, C*H*$_2$O) and 4.26 (1 H, br. s, C*H*OH); δ_C(100 MHz; $CDCl_3$) 21.6 (CH_3, CC*H*$_3$), 22.1 (CH_3, CHC*H*$_3$), 22.2 (CH_2), 25.4 (CH), 34.4 (CH_2), 41.9 (CH_2), 44.3 (CH), 51.3 (CH_2, *C*H$_2$O), 60.1 (C) and 67.7 (CH, *C*HOH).

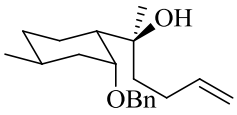
rac-(1*R*,2*S*,5*S*)-2-((2'*S*)-2'-Hydroxyhex-5'-en-2'-yl)-5-methylcyclohexanol 173



A solution of epoxide **172** (0.27 g, 1.57 mmol) and CuI (0.02 g, 0.08 mmol) in THF (20 mL) was cooled to -30 °C and allyl magnesium chloride (4.70 mL of a 2.0 M solution in THF, 9.41 mmol) was added dropwise. The reaction was allowed to warm to rt and stirred for 3 h, after which NH_4Cl (20 mL of a saturated aqueous solution) was added carefully. The aqueous layer was extracted with Et_2O (3 × 15 mL) and the combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography (5:1 petrol/Et_2O) to give **173** (0.20 mg, 60%) as a colourless oil. R_f 0.37 (1:1 petrol/Et_2O); υ_{max}(neat)/cm^{-1} 3325, 2946, 2918, 1645, 1458, 1376, 1144 and 914; δ_H(300

MHz; $CDCl_3$) 0.82-0.94 (5 H, m), 1.00-1.16 (1 H, m), 1.18-1.29 (1 H, m), 1.33 (3 H, s, CC*H*$_3$), 1.48-1.72 (3 H, m), 1.74-1.88 (3 H, m), 1.96-2.14 (4 H, m), 4.36-4.41 (1 H, m, C*H*OH), 4.92-5.09 (2 H, m, CH=C*H*$_2$) and 5.75-5.90 (1 H, m, C*H*=CH$_2$); δ_C(100 MHz; $CDCl_3$) 19.8 (CH_2), 22.2 (CH_3), 25.5 (CH_3), 25.7 (CH), 28.6 (CH_2), 34.8 (CH_2), 40.1 (CH_2), 42.6 (CH_2), 46.0 (CH), 68.2 (CH, *C*HOH), 75.3 (C), 114.5 (CH_2, CH=*C*H$_2$) and 138.5 (CH, *C*H=CH$_2$); *m*/*z* (ESI) 235.1674 ([M+Na]$^+$, $C_{13}H_{24}O_2Na$ requires 235.1665), 235.1 (100%).

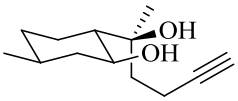
rac-(2*S*)-2-((1'*S*,2'*R*,4'*S*)-2'-(Benzyloxy)-4'-methylcyclohexyl)hex-5-en-2-ol 174



KOH (40 mL of a 50% aqueous solution) was added with vigorous stirring to a solution of diol **173** (0.20 g, 0.94 mmol), TBAB (0.11 g, 0.34 mmol) and BnBr (0.45 mL, 3.77 mmol) in CH_2Cl_2 (40 mL). The mixture was stirred o/n at rt and partitioned with water (20 mL) and CH_2Cl_2 (40 mL). The solution was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography (10:1 petrol:Et_2O) to give **174** (0.10 g, 35%) as a colourless oil. R_f 0.60 (5:1 petrol/Et_2O); υ_{max}(neat)/cm^{-1} 3377, 2926, 2039, 1712 and 1413; δ_H(400 MHz; $CDCl_3$) 0.84-1.01 (2 H, m), 0.90 (3 H, d, *J* 6.5, CHC*H*$_3$), 1.21 (3 H, s, CC*H*$_3$), 1.25-1.31 (1 H, ddd, *J* 12.5, 3.7 and 2.5, CC*H*), 1.57 (2 H, t, *J* 8.5, CC*H*$_2$CH$_2$), 1.62-1.70 (1 H, m), 1.71-1.87 (3 H, m), 1.91-1.09 (2 H, m, C*H*$_2$), 2.16-2.24 (1 H, m), 3.94 (1 H, s, O*H*), 4.12 (1 H, m, C*H*O), 3.36 (1 H, d, *J* 11.1, C*H*$_2$Ph), 4.66 (1 H, d, *J* 11.2, C*H*$_2$Ph), 4.91-5.06 (2 H, m, CH=C*H*$_2$), 5.77-5.89 (1 H, m, C*H*=CH$_2$) and 7.26-7.38 (5 H, m, C*H*$_{Ar}$); δ_C(75 MHz; $CDCl_3$) 20.7 (CH_2, *C*H$_2$CH=CH$_2$), 22.3 (CH_3, CH*C*H$_3$), 25.9 (CH), 26.2 (CH_3, C*C*H$_3$),

28.5 (CH_2), 34.8 (CH_2), 37.1 (CH_2), 39.1 (CH_2), 46.6 (CH), 69.7 (CH_2), 76.1(CH, *C*HO), 114.1 (CH_2, CH=*C*H_2), 127.8 (Ar), 128.5 (Ar) and 139.0 (CH, *C*H=CH_2); *m*/*z* (ESI) 325.2136 ($[M+Na]^+$, $C_{20}H_{30}O_2Na$ requires 325.2136), 325.3 (100%).

***rac*-(1*S*,2*S*,5*S*)-2-((2'*S*)-2'-hydroxyhex-5'-yn-2'-yl)-5-methylcyclohexanol 188**



Method 1

Propargyl bromide (0.26 mL, 2.35 mmol) and TMEDA (0.18 mL, 1.17 mmol) were added to a solution of *n*-BuLi (3.26 mL of a 1.4 M solution in hexane, 4.70 mmol) in Et_2O (3.5 mL) and hexane (2 mL) at -78 °C. A solution of epoxide **157** (0.10 g, 0.59 mmol) in Et_2O (0.7 mL) was added dropwise and the mixture was allowed to warm to rt. After 12 h the solution was quenched with NH_4Cl (20 mL of a saturated aqueous solution), extracted with Et_2O (3 × 15 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography (3:1 petrol/Et_2O) to give **173** (0.06 mg, 45%)

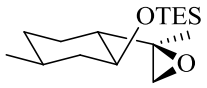
Method 2

Magnesium turnings (0.45 g, 18.89 mmol) were flame-dried under vacuum, flushed with argon (× 3), then suspended in Et_2O (2.5 mL). A crystal of I_2 was introduced and the solution was stirred until the colour has discharged. $HgCl_2$ (0.02 g, 0.94 mmol) was added and after 10 min the solution was cooled to 0°C. Subsequent addition of propargyl bromide (1.73 mL, 15.74 mmol) was very exothermic with an induction time. The solution was maintained at 0 °C by keeping the addition very slow. After the addition was complete, the mixture was

stirred for an additional 1 h at the same temperature, after which the dark grey solution was decanted. The propargyl Grignard solution was added to a solution of epoxide **157** (0.27 g, 1.58 mmol) in Et_2O (10 mL) at -78 °C. The reaction was allowed to warm to rt and stirred for 2.5 h, poured into NH_4Cl (100 mL of a saturated aqueous solution) and the aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with brine (30 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography (2:1 petrol/Et_2O) to give **188** (0.28 g, 84%) as a colourless oil. R_f 0.43 (2:1 petrol/Et_2O); υ_{max}(neat)/cm^{-1} 3306, 2949, 2920, 2869, 2177, 2115, 1978, 1454, 1375, 1047 and 1004; δ_H(300 MHz; $CDCl_3$) 0.80-0.96 (2 H, m), 0.90 (3 H, d, *J* 6.5, CHC*H*$_3$), 1.04 (1 H, ap. dt, *J* 12.1 and 11.0, ax. CHC*H*$_2$CH), 1.19 (3 H, s, CC*H*$_3$), 1.34-1.49 (2 H, m, 2 × C*H*), 1.60-1.84 (4 H, m), 0.88-0.98 (1 H, m, eq. CHC*H*$_2$CH), 1.96 (1 H, t, *J* 2.7, C≡CC*H*$_3$), 2.20-2.43 (2 H, m, C*H*$_2$C≡CH), 3.75 (1 H, ap. td, *J* 10.4 and 4.1, C*H*OH) and 3.86 (2 H, br. s, 2 × O*H*); δ_C(100 MHz; $CDCl_3$) 12.2 (CH_2, *C*H_2C≡CH), 21.9 (CH_3, CH*C*H_3), 22.8 (CH_3, C*C*H_3), 26.6 (CH_2), 31.3 (CH, *C*HCH$_3$), 34.3 (CH_2), 39.7 (CH_2), 44.7 (CH_2, CH*C*H_2CH), 50.1 (CH, C*C*H), 68.3 (CH, C≡*C*H), 72.3 (CH, *C*HOH), 75.9 (C, *C*CH_3) and 85.0 (C, *C*≡CH); *m*/*z* (EI) 210.1620 (M^+, $C_{13}H_{22}O_2$ requires 210.1622), 210.2 (9%), 192.2 (27), 154.1 (23), 149.1 (29), 121.1 (24), 115.1 (100), 108.1 (23), 97.1 (40), 93.1 (29) and 81.1 (34).

***rac*-Triethyl(((1*S*,2*S*,5*S*)-2-((2'*R*)-2'-methyloxiran-2'-yl)-5-methylcyclohexyl)oxy)silane**

196

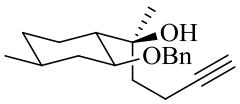


TESCl (0.29 g, 1.94 mmol) was added to a solution of epoxide **157** (0.30 g, 1.76 mmol) and imidazole (0.24 g, 3.52 mmol) in DMF (16 mL) at rt. The reaction was stirred o/n and concentrated in vacuo. The residue was taken in Et_2O (20 mL) and water (15 mL) and the aqueous layer was extracted with Et_2O (3 × 15 mL) The combined organic layers were washed with water (15 mL) and brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography (25:1 petrol:Et_2O) to give **196** (0.29 g, 57%) as a colourless oil. R_f 0.28 (10:1 petrol/Et_2O); υ_{max}(neat)/cm^{-1} 2926, 2867, 1973, 1453, 1064, 825 and 750; δ_H(400 MHz; $CDCl_3$) 0.55-0.66 (6 H, m, 3 × C*H*$_2$), 0.74-0.83 (1 H, m), 0.86 (3 H, d, *J* 6.6, CHC*H*$_3$), 0.94 (9 H, t, *J* 7.9, 3 × C*H*$_3$), 0.98-1.07 (2 H, m), 1.10-1.19 (1 H, m, C*H*), 1.27 (3 H, s, C*H*$_3$), 1.29-1.37 (1 H, m, C*H*), 1.54-1.68 (2 H, m), 1.80-1.87 (1 H, m, eq. CHC*H*$_2$CH), 2.43 (1 H, d, *J* 4.9, C*H*$_2$O), 2.46 (1 H, d, *J* 4.9, C*H*$_2$O) and 3.49 (1 H, ap. td, *J* 10.3 and 4.2, C*H*O); δ_C(100 MHz; $CDCl_3$) 5.4 (3 × CH_2), 6.8 (3 × CH_3), 19.6 (CH_3), 22.0 (CH_3, CH*C*H$_3$), 27.2 (CH_2), 31.3 (CH), 33.8 (CH_2), 44.9 (CH_2, CH*C*H$_2$CH), 50.6 (CH), 52.8 (CH_2, *C*H$_2$O), 58.3 (C) and 72.8 (CH, *C*HO); *m*/*z* (EI) 284.2172 (M^+, $C_{16}H_{32}O_2Si$ requires 284.2173), 284.2 (10%), 255.2 (100), 237.2 (64), 197.1 (24) and 103.1 (28).

***rac-tert*-Butyldimetyl(((1*S*,2*S*,5*S*)-2-((2'*R*)-2'-methyloxiran-2'-yl)-5-methylcyclohexyl) oxy)silane 197**

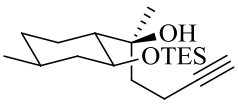
TBDMSCl (0.23 g, 1.51 mmol) was added to a solution of epoxide **157** (0.21 g, 1.26 mmol) and imidazole (0.10 g, 1.51 mmol) in DMF (13 mL) at rt. The reaction was stirred o/n and quenched with water (10 mL). The aqueous layer was extracted with Et_2O (3 × 15 mL) and the combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography (16:1 petrol:Et_2O) to give **197** (0.27 g, 75%) as a colourless oil. R_f 0.59 (3:1 petrol/Et_2O); υ_{max}(neat)/cm^{-1} 2953, 2927, 2865, 1463, 1366, 1249, 1071, 834 and 775; δ_H(300 MHz; $CDCl_3$) 0.08 (3 H, s, SiCH_3), 0.09 (3 H, s, SiCH_3), 0.73-0.81 (1 H, m), 0.81-0.87 (3 H, m, CHCH_3), 0.87-0.92 (9 H, m, (CH_3)$_3$), 0.93-1.11 (2 H, m), 1.13-1.23 (1 H, m, C*H*), 1.28 (3 H, s, CH_3), 1.30-1.45 (1 H, m, C*H*), 1.54-1.69 (2 H, m), 1.80-1.89 (1 H, ddd, *J* 12.4, 4.1 and 1.9, eq. CHCH_2CH), 2.44 (1 H, d, *J* 4.9, CH_2O), 2.47 (1 H, d, *J* 4.9, CH_2O) and 3.40-3.53 (1 H, m, C*H*O); δ_C(100 MHz; $CDCl_3$) -4.6 (CH_3, SiCH_3), -3.2 (CH_3, SiCH_3), 18.0 (C, C(CH_3)$_3$), 20.0 (CH_3), 22.1 (CH_3), 25.9 (3 × CH_3, C(CH_3)$_3$), 27.3 (CH_2), 31.4 (CH), 34.0 (CH_2), 45.0 (CH_2, CHCH_2CH), 50.6 (CH), 51.3 (CH_2, CH_2O), 58.5 (C) and 73.1 (CH, *C*HO); *m*/*z* (ESI) 307.2070 ($[M+Na]^+$, $C_{16}H_{32}O_2NaSi$ requires 307.2069), 307.3 (100%).

***rac*-(2*S*)-2-((1'*S*,2'*S*,4'*S*)-2'-(benzyloxy)-4'-methylcyclohexyl)hex-5-yn-2-ol 198**



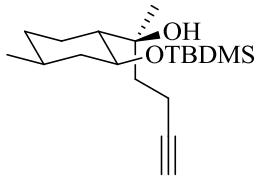
Magnesium turnings (0.14 g, 5.76 mmol) were flame-dried under vacuum, flushed with argon (× 3) and suspended in Et_2O (1 mL). A crystal of I_2 was introduced and the solution was stirred until the colour has disappeared. $HgCl_2$ (0.01 g, 0.03 mmol) was added and after 10 min the solution was cooled to 0 °C. Propargyl bromide (0.43 mL, 3.84 mmol) was added slowly at 0 °C and the mixture was stirred for an additional 1 h at the same temperature, after which the dark grey solution was decanted. The propargyl magnesium bromide solution was added to a solution of epoxide **194** (0.10 g, 0.38 mmol) in Et_2O (1.5 mL) at -30 °C. After 2 h the reaction was poured into NH_4Cl (10 mL of a saturated aqueous solution) and the aqueous layer was extracted with Et_2O (3 ×15 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography (8:1 petrol:Et_2O) to give **198** (87 mg, 76%) as a white solid. R_f 0.76 (1:1 petrol:Et_2O); mp 55 °C; υ_{max}(neat)/cm^{-1} 3472, 2950, 2923, 2868, 2132, 1455, 1405, 1374, 1056 and 696; δ_H(400 MHz; C_6D_6) 0.47-0.65 (2 H, m), 0.68-0.87 (1 H, m), 0.78 (3 H, d, *J* 6.5, CHC*H*$_3$), 0.98 (3 H, s, CC*H*$_3$), 1.01-1.11 (1 H, m), 1.29-1.37 (1 H, m), 1.40-1.51 (2 H, m), 1.69-1.78 (2 H, m), 1.80 (1 H, t, *J* 2.7, C≡C*H*), 1.86-1.94 (1 H, m), 2.39-2.61 (2 H, m, C*H*$_2$C≡CH), 3.21 (1 H, ap. td, *J* 10.4 and 4.0, C*H*O), 4.01 (1 H, d, *J* 11.2, C*H*$_2$Ph), 4.29 (1 H, d, *J* 11.2, C*H*$_2$Ph), 5.00 (1 H, s, O*H*) and 6.99-7.20 (5 H, m, *H*Ar); δ_C(100 MHz; C_6D_6) 12.7 (CH_2, *C*H$_2$C≡CH), 22.2 (CH_3, CH*C*H$_3$), 23.6 (CH_3, C*C*H$_3$), 27.1 (CH_2), 31.4 (CH), 34.5 (CH_2), 39.7 (CH_2), 40.7 (CH_2), 50.2 (CH), 68.3 (CH, C≡*C*H), 70.1 (CH_2, *C*H$_2$Ph), 73.5 (C, *C*OH), 81.1 (CH, *C*HO), 85.8 (C, *C*≡CH), 128.1 (2 × CH, Ar), 128.2 (2 × CH, Ar) and 128.8 (CH, Ar) and 138.1 (C, Ar); *m*/*z* (EI) 300.2090 (M^+, $C_{20}H_{28}O_2$ requires 300.2089), 300 (3%), 136 (16), 91 (100) and 81 (4).

***rac*-(2*S*)-2-((1'*S*,2'*S*,4'*S*)-2'-((triethylsilyl)oxy)-4'-methylcyclohexyl)hex-5-yn-2-ol 199**



Magnesium turnings (0.37 g, 15.03 mmol) were flame-dried under vacuum, flushed with argon (× 3), and suspended in Et_2O (2.5 mL). A crystal of I_2 was introduced and the solution was stirred until the colour has disappeared. $HgCl_2$ (0.02 g, 0.08 mmol) was introduced and after 10 min the solution was cooled to 0 °C. Propargyl bromide (1.12 mL, 10.02 mmol) was added slowly and the mixture was stirred for an additional 1 h at 0 °C, after which a solution of epoxide **196** (0.28 g, 1.00 mmol) in Et_2O (5 mL) was added dropwise. After 30 min the reaction was poured into NH_4Cl (80 mL of a saturated aqueous solution) and the aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with brine (15 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography (100:1 petrol:Et_2O) to give **199** (0.23 g, 70%) as a colourless oil. R_f 0.76 (2:1 petrol:Et_2O); υ_{max}(neat)/cm^{-1} 3412, 2950, 2924, 2872, 1718, 1456, 1376, 1191, 1030 and 884, δ_H(400 MHz; $CDCl_3$) 0.63 (6 H, q, *J* 7.8, 3 × C*H*$_2$), 0.80-0.91 (2 H, m), 0.89 (3 H, d, *J* 6.5, CHC*H*$_3$), 0.95 (9 H, t, *J* 7.9, 3 × C*H*$_3$), 1.04-1.15 (1 H, m), 1.11 (3 H, s, CC*H*$_3$), 1.33-1.47 (2 H, m), 1.56-1.75 (4 H, m), 1.84-1.92 (1 H, m), 1.87 (1 H, t, *J* 2.6, C≡C*H*), 2.18-2.40 (2 H, m, C*H*$_2$C≡CH), 3.77-3.85 (1 H, ap. td, *J* 10.3 and 3.8, C*H*O) and 5.13 (1 H, s, O*H*); δ_C(100 MHz; $CDCl_3$) 5.5 (3 × *C*H$_2$), 6.8 (3 × *C*H$_3$), 12.0 (CH$_2$, *C*H$_2$C≡CH), 22.0 (CH$_3$, CH*C*H$_3$), 23.0 (CH$_3$, C*C*H$_3$), 26.6 (CH$_2$), 31.6 (CH), 34.2 (CH$_2$), 39.9 (CH$_2$), 45.2 (CH$_2$), 50.6 (CH), 67.4 (CH, C≡*C*H), 73.8 (C, *C*OH), 75.2 (CH, *C*HO) and 85.5 (C, *C*≡CH); *m*/*z* (EI) 324.2481 (M^+, $C_{19}H_{36}O_2Si$ requires 324.2485), 324.2 (8%), 295.2 (66), 277.2 (39), 185.1 (27), 103.1 (100) and 75.0 (67).

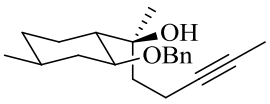
***rac*-(2*S*)-2-((1'*S*,2'*S*,4'*S*)-2'-((*tert*-Butyldimethylsilyl)oxy)-4'-methylcyclohexyl)hex-5-yn-2-ol 200**



Magnesium turnings (0.36 g, 14.71 mmol) were flame-dried under vacuum, flushed with argon (× 3) and suspended in Et_2O (2.5 mL). A crystal of I_2 was introduced and the solution was stirred until the colour has disappeared. $HgCl_2$ (0.08 g, 0.29 mmol) was added and after 10 min the solution was cooled to 0°C. Propargyl bromide (1.09 mL, 9.81 mmol) was added and the mixture was stirred for an additional 1 h at 0 °C. A solution of epoxide **197** (0.28 g, 0.98 mmol) in Et_2O (2.5 mL) was then introduced dropwise and the reaction was allowed to warm to rt. After 90 min, the mixture was poured into NH_4Cl (50 mL of a saturated aqueous solution) and the aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography (30:1 petrol:Et_2O) to give silyl ether **200** (0.29 g, 92%) as a colourless oil. R_f 0.53 (9:1 petrol:Et_2O); υ_{max}(neat)/cm^{-1} 3478, 3314, 2953, 2929, 2859, 2100, 1457, 1373, 1258, 1055 and 832; δ_H(400 MHz; $CDCl_3$) 0.12 (3 H, s, SiC*H*$_3$), 0.13 (3 H, s, SiC*H*$_3$), 0.83-0.91 (14 H, m), 1.02-1.09 (1 H, m), 1.09-1.14 (3 H, s, CC*H*$_3$), 1.33-1.49 (2 H, m), 1.56-1.75 (4 H, m), 1.84-1.92 (2 H, m), 2.17-2.41 (2 H, m, C*H*$_2$), 3.81 (1 H, ap. td, *J* 10.4 and 3.9, C*H*O) and 5.05 (1 H, s, O*H*); δ_C(100 MHz; $CDCl_3$) -4.7 (CH_3, Si*C*H$_3$), -2.9 (CH_3, Si*C*H$_3$), 12.0 (CH_2, *C*H$_2$C≡CH), 17.8 (C, *C*(CH$_3$)$_3$), 22.0 (CH_3, CH*C*H$_3$), 23.2 (CH_3, C*C*H$_3$), 25.8 (3 × CH_3, C(*C*H$_3$)$_3$), 26.7 (CH_2), 31.6 (CH), 34.2 (CH_2), 39.9 (CH_2), 45.3 (CH_2), 50.7 (CH), 67.4 (CH, C≡*C*H), 73.8 (C), 75.4 (CH, *C*HO) and 85.5 (C,

C≡CH); *m*/*z* (EI) 324.2485 (M^+, $C_{19}H_{36}O_2Si$ requires 324.2488), 324.2 (100%), 309.2 (93), 305.2 (11), 292.2 (13) and 291.2 (58).

rac-(2*S*)-2-((1'*S*,2'*S*,4'*S*)-2'-(benzyloxy)-4'-methylcyclohexyl)hept-5-yn-2-ol 195



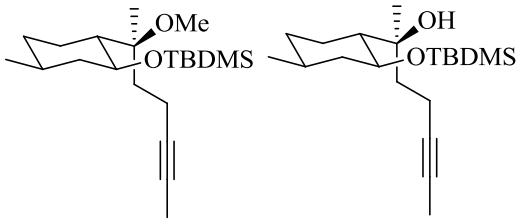
n-BuLi (3.21 mL of a 1.7 M solution in hexane, 5.29 mmol) was added dropwise to a solution of alkyne **198** (0.79 g, 2.65 mmol) in THF (20 mL) at -78 °C. After 30 min, MeI (0.20 mL, 3.18 mmol) was added at -78 °C and the reaction was allowed to warm to rt o/n. The solution was quenched with NH_4Cl (20 mL of a saturated aqueous solution) and extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with brine (20 mL) and water (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography (5:1 petrol:Et_2O) to give **195** (0.70 g, 84%) as a colourless oil. R_f 0.32 (5:1 petrol:Et_2O); υ_{max}(neat)/cm^{-1} 2949, 2924, 1453, 1372, 1060, 1027 and 713; δ_H(300 MHz; $CDCl_3$) 0.50-0.58 (2 H, m), 0.72-0.88 (1 H, m), 0.80 (3 H, d, *J* 6.4, CHC*H*$_3$), 0.94-1.04 (1 H, m), 1.07 (3 H, s, CC*H*$_3$), 1.28-1.40 (1 H, m), 1.45-1.59 (2 H, m), 1.61 (3 H, t, *J* 2.6, C≡CC*H*$_3$), 1.74-1.96 (3 H, m), 2.43-2.79 (2 H, m, C*H*$_2$C≡C), 3.25 (1 H, ap. td, *J* 10.4 and 3.8, C*H*O), 4.04 (1 H, d, *J* 11.2, C*H*$_2$Ph), 4.32 (1 H, d, *J* 11.2, C*H*$_2$Ph), 5.07 (1 H, s, O*H*) and 7.00-7.24 (5 H, m, Ar); δ_C(100 MHz; C_6D_6) 3.3 (CH_3, C≡C*C*H_3), 12.8 (CH_2, *C*H_2C≡C), 21.9 (CH_3, CH*C*H_3), 23.5 (CH_3, C*C*H_3), 26.9 (CH_2), 31.2 (CH), 34.3 (CH_2), 39.4 (CH_2), 41.1 (CH_2), 49.9 (CH), 69.8 (CH_2), 73.4 (C), 74.6 (C), 80.4 (C), 80.8 (CH, *C*HO), 127.5 (2 × CH, Ar), 127.7 (2 × CH, Ar), 128.0 (CH, Ar) and 137.8 (C, Ar); *m*/*z* (EI) 314.2246 (M^+, $C_{21}H_{30}O_2$ requires

314.2240), 314.2 (1%), 281.2 (8), 219.2 (11), 160.1 (16) and 119.1 (16), 91.0 (100) and 81.1 (21).

rac-Triethyl(((1*S*,2*S*,5*S*)-2-((2'*S*)-2'-methoxyhept-5'-yn-2'yl)-5-methylcyclohexyl)oxy) silane 203

n-BuLi (0.26 mL of a 2.4 M solution in hexane, 0.62 mmol) was added dropwise to a solution of alkyne **199** (0.10 g, 0.31 mmol) in THF (6 mL) at -78 °C. After 30 min, MeI (0.02 mL, 0.37 mmol) was added at -78 °C and the reaction was allowed to warm to rt o/n. The solution was quenched with NH_4Cl (10 mL of a saturated aqueous solution) and extracted with Et_2O (3 × 15 mL). The combined organic layers were washed with brine (10 mL) and water (10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography (100:1 petrol:Et_2O) to give **203** (0.04 g, 35%) as a colourless oil. R_f 0.74 (5:1 petrol:Et_2O); υ_{max}(neat)/cm^{-1} 2951, 2948, 2875, 2015, 1455, 1102, 1007 and 721, δ_H(400 MHz; $CDCl_3$) 0.56-0.68 (6 H, m, 3 × Si(C*H*$_2$CH$_3$)$_3$), 0.73-0.87 (2 H, m), 0.89-1.02 (12 H, m, C*H*$_3$ and 3× Si(CH$_2$C*H*$_3$)$_3$), 1.03-1.16 (1 H, m), 1.32-1.43 (5 H, m), 1.54-1.61 (1 H, m), 1.62-1.76 (2 H, m, C*H*$_2$), 1.76-1.81 (3 H, m, C≡CC*H*$_3$), 1.87-1.98 (1 H, m), 2.11-2.35 (3 H, m), 3.04-3.13 (1 H, m, C*H*O) and 3.30 (3 H, s, OC*H*$_3$); δ_C(100 MHz; $CDCl_3$) 3.5 (CH$_3$, C≡C*C*H$_3$), 7.0 (3 × CH$_2$, Si(*C*H$_2$CH$_3$)$_3$), 7.3 (3 × CH$_3$, Si(CH$_2$*C*H$_3$)$_3$), 13.9 (CH$_2$, *C*H$_2$C≡C), 22.1 (CH$_3$, CH*C*H$_3$), 25.6 (CH$_3$, C*C*H$_3$), 28.9 (CH$_2$), 31.6 (CH), 34.7 (CH$_2$), 38.9 (CH$_2$), 40.0 (CH$_2$), 52.6 (CH$_3$, O*C*H$_3$), 55.4 (CH), 74.7 (CH, *C*HO), 76.9 (C), 80.3 (C) and 80.8 (C); *m*/*z* (ESI) 375.2695 ([M+Na]$^+$, $C_{21}H_{40}O_2NaSi$ requires 375.2697), 375.3 (100%).

***rac*-*tert*-Butyl(((1*S*,2*S*,5*S*)-2-((2'*S*)-2'-methoxyhept-5'-yn-2'-yl)-5-methylcyclohexyl)oxy) dimethylsilane 204 and *rac*-(2*S*)-2-((1'*S*,2'*S*,4'*S*)-2'-((*tert*-Butyldimethylsilyl)oxy)-4'-methylcyclohexyl)hept-5-yn-2-ol 205**



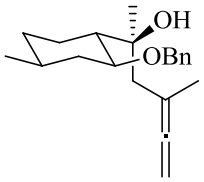
n-BuLi (0.42 mL of a 2.3 M solution in hexane, 0.97 mmol) was added dropwise to a solution of alkyne **200** (0.16 g, 0.48 mmol) in THF (5 mL) at -78 °C. After 1 h, MeI (0.04 mL, 0.97 mmol) was added at -78 °C and the reaction was allowed to warm to rt. After 2 h, the solution was quenched with NH_4Cl (10 mL of a saturated aqueous solution) and extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with brine (10 mL) and water (10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography (40:1 petrol:Et_2O) to give first **205** (0.04 g, 25%) followed by **204** (0.07 g, 43%) as two colourless oils.

205: R_f 0.65 (5:1 petrol:Et_2O); υ_{max}(neat)/cm^{-1} 2950, 2927, 2857, 1472, 1456, 1071 and 832; δ_H(400 MHz; $CDCl_3$) 0.08 (6 H, 2 s, Si(CH_3)$_2$), 0.74-0.85 (1 H, m), 0.86-0.92 (12 H, m, CHCH_3 and C(CH_3)$_3$), 0.93-1.06 (2 H, m), 1.25 (3 H, s, CCH_3), 1.30-1.41 (1 H, m, C*H*), 1.53-1.67 (2 H, m), 1.67-1.74 (2 H, m, CH_2), 1.74-1.79 (4 H, m), 1.83-1.90 (1 H, m), 2.06-2.27 (2 H, m, CH_2C≡C), 3.08 (3 H, s, OCH_3) and 3.60 (1 H, ap. td, *J* 10.1 and 3.9, C*H*O); δ_C(100 MHz; $CDCl_3$) -3.9 (CH_3, SiCH_3), -3.6 (CH_3, SiCH_3), 3.5 (CH_3, C≡CCH_3), 12.9 (CH_2, CH_2C≡C), 18.1 (C, C(CH_3)$_3$), 22.2 (CH_3, CHCH_3), 22.8 (CH_3, CCH_3), 25.4 (CH_2), 26.1 (3 × CH_3, C(CH_3)$_3$), 31.9 (CH), 34.7 (CH_2), 35.3 (CH_2), 46.6 (CH_2), 48.4 (CH_3, OCH_3), 50.3

(CH), 72.9 (CH, *C*HO), 74.8 (C), 77.2 (C) and 80.2 (C); *m*/*z* (ESI) 375.2691 ($[M+Na]^+$, $C_{21}H_{40}O_2NaSi$ requires 375.2695), 375.3 (100%).

204: R_f 0.48 (5:1 petrol:Et_2O); υ_{max}(neat)/cm^{-1} 3486, 2952, 2927, 2858, 2015, 1718, 1457, 1036, and 832; δ_H(400 MHz; $CDCl_3$) 0.12 (3 H, s, SiCH_3), 0.14 (3 H, s, SiCH_3), 0.83-0.92 (14 H, m), 1.03-1.14 (4 H, m), 1.32-1.51 (2 H, m, 2 × C*H*), 1.53-1.68 (3 H, m), 1.68-1.78 (4 H, m), 1.85-1.92 (1 H, m), 2.12-2.35 (2 H, m, CH_2C≡C), 3.81 (1 H, ap. td, *J* 10.4 and 3.9, C*H*O) and 5.01 (1 H, s, O*H*); δ_C(100 MHz; $CDCl_3$) -4.6 (CH_3, Si*C*H_3), -2.9 (CH_3, Si*C*H_3), 3.5 (CH_3, C≡C*C*H_3), 12.3 (CH_2, *C*H_2C≡C), 17.9 (C, *C*(CH_3)$_3$), 22.1 (CH_3, CH*C*H_3), 23.2 (CH_3, C*C*H_3), 25.8 (3 × CH_3, C(*C*H_3)$_3$), 26.8 (CH_2), 31.6 (CH), 34.3(CH_2), 40.5 (CH_2), 45.3 (CH_2), 50.5 (CH), 73.9 (C), 74.9 (C), 75.5 (CH, *C*HO)and 80.0 (C); *m*/*z* (EI) 338.2641 (M^+, $C_{20}H_{38}O_2Si$ requires 338.2633), 337.3 (3%), 263.2 (98), 189.2 (28), 169.1 (83), 125.1 (83) and 75.0 (100).

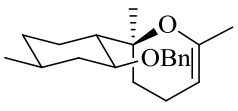
***rac*-(2*S*)-2-((1'*S*,2'*S*,4'*S*)-2'-(benzyloxy)-4'-methylcyclohexyl)-4-methylhexa-4,5-dien-2-ol 207**



Magnesium turnings (0.14 g, 5.76 mmol) were flame-dried under vacuum, flushed with argon (× 3) and suspended in Et_2O (1 mL). A crystal of I_2 was introduced and the solution was stirred until the colour has discharged. $HgCl_2$ (0.01 g, 0.03 mmol) was added and after 10 min the solution was cooled to 0 °C. Bromobutyne (0.35 mL, 3.80 mmol) was added and the mixture was stirred for an additional 1 h at 0 °C. A solution of epoxide **194** (0.10 g, 0.38 mmol) in Et_2O (1 mL) was introduced dropwise and the reaction was allowed to warm to rt.

After 3 h, the mixture was poured into NH_4Cl (10 mL of a saturated aqueous solution) and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography (12:1 petrol:Et_2O) to give **207** (34 mg, 30%) as a colourless oil. R_f 0.47 (5:1 petrol:Et_2O); υ_{max}(neat)/cm^{-1} 3030, 2923, 2865, 2033, 1602, 1497, 1454, 1376, 1346, 1107 and 1068; δ_H(400 MHz; C_6D_6) 0.60-0.72 (1 H, m), 0.74-0.92 (2 H, m), 0.83 (3 H, d, *J* 6.5, CHC*H*$_3$), 1.05-1.15 (1 H, m), 1.17 (3 H, s, CC*H*$_3$), 1.43-1.50 (1 H, m), 1.80-1.90 (2 H, m), 1.94-2.01 (1 H, m), 2.13 (3 H, t, *J* 3.2, C*H*$_3$), 2.15-2.32 (2 H, m, C*H*$_2$), 3.33 (1 H, ap. td, *J* 10.4 and 3.8, C*H*O), 4.08 (1 H, d, *J* 11.2, C*H*$_2$Ph), 4.35 (1 H, d, *J* 11.2, C*H*$_2$Ph), 4.59 (2 H, m, C*H*$_2$), 5.20 (1 H, s, O*H*) and 7.02-7.24 (5 H, m, Ar); δ_C(100 MHz; C_6D_6) 20.9 (CH_3), 22.1 (CH_3,CHC*H*$_3$), 24.6 (CH_3, CC*H*$_3$), 27.5 (CH_2), 31.5 (CH), 34.4 (CH_2), 39.7 (CH_2), 44.9 (CH_2), 49.9 (CH), 70.0 (CH_2), 71.8 (C), 75.9 (C), 81.3 (CH), 96.5 (C), 127.6 (2 × CH, Ar), 127.8 (2 × CH), 128.1 (C, Ar), 137.9 (C) and 208.8 (C); *m*/*z* (EI) 314.2246 (M^+, $C_{21}H_{30}O_2$ requires 314.2255), 314.2 (6%), 242.2 (7), 208.2 (10), 163.1 (14), 110.1 (19), 91.1 (100) and 77.0 (11).

rac-(2*S*)-2-((1'*S*,2'*S*,4'*S*)-2'-(benzyloxy)-4'-methylcyclohexyl)-2,6-dimethyl-3,4-dihydropyran 208

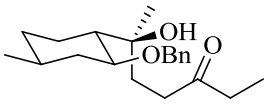


Alkyne **195** was dissolved in toluene and evaporated (× 3) before use. $Pd(OAc)_2$ (0.05 g, 0.21 mmol) was added to a solution of alkyne **195** (0.10 g, 0.32 mmol) in CH_2Cl_2 (4 mL) containing molecular sieves (0.20 g, MS 3 Å) at rt and the reaction was stirred o/n. The

mixture was then filtered, evaporated and the residue was purified by column chromatography (12:1 petrol:Et_2O) to give **208** (0.05 g, 47%) as a colourless oil. R_f 0.47 (5:1 petrol:Et_2O); υ_{max}(neat)/cm^{-1} 2949, 2924, 2869, 1453, 1372, 1095, 1060 and 1027; δ_H(400 MHz; C_6D_6) 0.74-1.08 (3 H, m), 0.86 (3 H, d, *J* 6.5, CHC*H*$_3$), 1.13-1.26 (1 H, m, C*H*), 1.36-1.44 (1 H, m), 1.52 (3 H, s, C*H*$_3$), 1.55-1.63 (1 H, m), 1.67-1.75 (1 H, m), 1.77 (3 H, s, C*H*$_3$), 1.84-1.96 (2 H, m), 1.99-2.14 (2 H, m), 2.14-2.25 (1 H, m), 3.21 (1 H, ap. td, *J* 10.4 and 4.1, C*H*O), 4.18 (1 H, d, *J* 11.5, C*H*$_2$Ph), 4.48 (1 H, d, *J* 11.4, C*H*$_2$Ph), 7.07-7.39 (5 H, m, Ar); δ_C(100 MHz; C_6D_6) 19.0 (CH_2), 21.6 (CH_3, CHC*H*$_3$), 22.9 (CH_3), 25.2 (CH_3), 26.2 (CH_2), 27.6 (CH_2), 32.4 (CH), 35.5 (CH_2), 41.5 (CH_2), 52.3 (CH), 70.7 (CH_2), 78.1 (C), 79.8 (CH, C*H*O), 93.4 (CH), 128.3 (2 × CH, Ar), 128.5 (2 × CH, Ar), 128.8 (CH, Ar), 140.2 (C) and 149.7 (C); *m*/*z* (EI) 314.2246 (M^+, $C_{21}H_{30}O_2$ requires 314.2244), 314.2 (24%), 208.2 (23), 165.1 (35), 150.1 (41), 121.1 (44), 91.1 (100) and 81.1 (44).

***rac*-(6*S*)-6-((1'*S*,2'*S*,4'*S*)-2'-(benzyloxy)-4'-methylcyclohexyl)-6-hydroxyheptan-3-one**

209

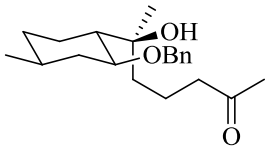


209 was obtained as a pale yellow oil. R_f 0.42 (2:1 petrol:Et_2O); υ_{max}(neat)/cm^{-1} 3474, 2950, 2921, 1713, 1454, 1405, 1056 and 698; δ_H(400 MHz; $CDCl_3$) 0.85-0.98 (2 H, m), 0.95 (3 H, d, *J* 6.5, CHC*H*$_3$), 0.99-1.06 (1 H, m), 1.03 (3 H, t, *J* 7.4, CH_2C*H*$_3$), 1.08 (3 H, s, CC*H*$_3$), 1.35-1.47 (1 H, m, C*H*), 1.52-1.60 (1 H, m, C*H*), 1.61-1.75 (4 H, m), 2.24-2.32 (1 H, m), 2.38-2.48 (3 H, m), 2.56-2.67 (1 H, m), 3.59 (1 H, ap. td, *J* 10.5 and 3.9, C*H*O), 4.41 (1 H, d, *J* 10.9, C*H*$_2$Ph), 4.71 (1 H, d, *J* 10.9, C*H*$_2$Ph), 5.10 (1 H, s, O*H*), 7.26-7.36 (5 H, m, Ar); δ_C(100

MHz; $CDCl_3$) 7.9 (CH_3, CH_2CH_3), 22.1 (CH_3, $CHCH_3$), 23.4 (CH_3, CCH_3), 26.9 (CH_2), 31.4 (CH), 34.4 (CH_2), 34.5 (CH_2), 35.9 (CH_2), 36.0 (CH_2), 39.6 (CH_2), 50.1 (CH), 70.1 (CH_2, CH_2Ph), 73.9 (C), 81.0 (CH, *C*HO), 128.0 (CH, Ar), 128.1 (2 × CH, Ar), 128.6 (2 × CH, Ar), 137.4 (C, Ar) and 212.4 (C, *C*=O); *m*/*z* (ESI) 355.2248 ($[M+Na]^+$, $C_{21}H_{32}O_3Na$ requires 355.2249), 355.1 (100%).

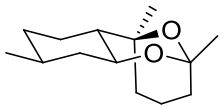
rac-(6*S*)-6-((1'*S*,2'*S*,4'*S*)-2'-(benzyloxy)-4'-methylcyclohexyl)-6-hydroxyheptan-2-one

210



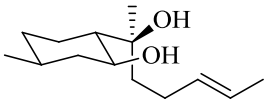
210 was obtained as a pale yellow oil. R_f 0.22 (2:1 petrol:Et_2O); υ_{max}(neat)/cm^{-1} 3474, 2950, 2921, 1713, 1454, 1371, 1056 and 698; δ_H(400 MHz; $CDCl_3$) 0.85-1.04 (3 H, m), 0.96 (3 H, d, *J* 6.5, $CHCH_3$), 1.07 (3 H, s, CCH_3), 1.22-1.31 (1 H, m), 1.34-1.51 (2 H, m), 1.54-1.80 (5 H, m), 2.11 (3 H, s, CH_3), 2.23-2.31 (1 H, m), 1.31-1.50 (2 H, m, CH_2), 3.58 (1 H, ap. td, *J* 10.5 and 3.8, C*H*O), 4.41 (1 H, d, *J* 10.9, CH_2Ph), 4.71 (1 H, d, *J* 10.9, CH_2Ph), 5.05(1 H, s, O*H*), 7.27-7.37 (5 H, m, Ar); δ_C(100 MHz; $CDCl_3$) 17.2 (CH_2), 22.1 (CH_3, $CHCH_3$), 27.0 (CH_3, CCH_3), 29.8 (CH_3), 34.5 (CH), 39.6 (CH_2), 40.3 (CH_2), 44.3 (CH_2), 49.3 (CH), 70.1 (CH_2, CH_2Ph), 74.5 (C), 81.1 (CH, *C*HO), 127.9 (CH, Ar), 128.1 (2 × CH, Ar), 128.6 (2 × CH, Ar), 137.4 (C, Ar) and 209.5 (C, *C*=O); *m*/*z* (ESI) 355.2252 ($[M+Na]^+$, $C_{21}H_{32}O_3Na$ requires 355.2249), 355.2 (100%).

(2*R*,6*S*,6a*S*,9*S*,10a*S*)-2,6,9-trimethyldecahydro-2,6-epoxybenzo-oxocine 211



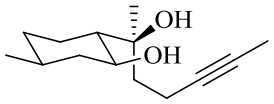
A flame-dried flask equipped with a dry ice condenser was charged with liquid ammonia (ca. 3 mL) and Li (0.01g, 1.49 mmol) was added. Cyclic enol ether **208** (0.04 g, 0.11 mmol) in a mixture of THF (5 mL) and EtOH (0.4 mL) was then added slowly. After ca. 35 min, NH_4Cl (10 mL of a saturated aqueous solution) was carefully added and the flask was stirred opened to the air to let the ammonia to evaporate. The mixture was taken in water (10 mL) and Et_2O (10 mL). The aqueous layer was extracted with Et_2O (3 × 10 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography (5:1 petrol:Et_2O) to give **211** (0.02 mg, 77%) as a colourless oil. R_f 0.43 (5:1 petrol:Et_2O); υ_{max}(neat)/cm^{-1} 2940, 1713, 1457, 1369 and 1061; δ_H(400 MHz; $CDCl_3$) 0.82-0.90 (1 H, m), 0.93 (3 H, d, *J* 6.6, CHC*H*$_3$), 0.98-1.09 (1 H, m), 1.12 (3 H, s, C*H*$_3$), 1.24-1.31 (1 H, m), 1.28 (3 H, m, C*H*$_3$), 1.31-1.40 (3 H, m), 1.44-1.56 (4 H, m), 1.56-1.63 (1 H, m), 1.65-1.73 (1 H, m), 1.88-1.95 (1 H, m), 2.03-2.17 (1 H, m) and 3.44 (1 H, ap. td, *J* 10.6 and 3.9, C*H*O); δ_C(100 MHz; $CDCl_3$) 15.4 (CH_2), 22.2 (CH_3, CH*C*H$_3$), 25.1 (CH_3), 26.3 (CH_2), 27.8 (CH_3), 31.4 (CH), 34.1 (CH_2), 35.1 (CH_2), 37.1 (CH_2), 40.9 (CH_2), 47.8 (CH), 68.9 (CH, *C*HO), 73.1 (C) and 98.0 (C, O*C*O); *m*/*z* (EI) 224.1778 (M^+, $C_{14}H_{24}O_2$ requires 224.1776), 224.2 (3%), 164.2 (100), 149.1 (30), 136.1 (47), 121.1 (59), 111.1 (49), 107.1 (28) and 81.1 (37).

***rac*-(1*S*,2*S*,5*S*)-2-((2'*S*)-(*E* or *Z*)-2'-Hydroxyhept-5'-en-2'-yl)-5-methylcyclohexanol 212**



A flame-dried flask equipped with a dry ice condenser was charged with liquid ammonia (ca. 14 mL) and Li (0.05g, 6.61 mmol) was added. Benzyl ether **195** (0.16 g, 0.51 mmol) in a mixture of THF (1.85 mL) and EtOH (0.06 mL) was then added slowly. After 3 h, the reaction was stirred opened to the air to let the ammonia to evaporate and the residue was taken up in water (10 mL) and Et_2O (10 mL). The aqueous layer was extracted with Et_2O (3 × 10 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. to give without purification **212** (0.11 g, 97%) as a white solid. R_f 0.38 (2:1 petrol:Et_2O); υ_{max}(neat)/cm^{-1} 3190, 3018, 2917, 2850, 1433, 1002 and 967; mp 50-52 °C; δ_H(400 MHz; $CDCl_3$) 0.82-0.94 (2 H, m), 0.88 (3 H, d, *J* 6.6, CHC*H*$_3$), 1.00 (1 H, ap. dt, *J* 12.1 and 11.1, ax. CHC*H*$_2$CH), 1.14 (3 H, s, C*H*$_3$), 1.33-1.56 (4 H, m), 1.56-1.65 (5 H, m), 1.87-1.93 (1 H, m, eq. CHC*H*$_2$CH), 1.95-2.16 (2 H, m, C*H*$_2$), 3.44 (1 H, ap. td, *J* 10.4and 4.1, C*H*O), 4.21 (1 H, s, O*H*), 4.75 (1 H, s, O*H*) and 5.34-5.48 (2 H, m, C*H*=C*H*); δ_C(100 MHz; $CDCl_3$) 17.8 (CH_3), 21.9 (CH_3, CHC*H*$_3$), 25.6 (CH_3, CC*H*$_3$), 26.5 (CH_2), 31.2 (CH_2), 34.4 (CH), 41.0 (CH_2), 44.5 (CH_2), 50.2 (CH_2), 72.3 (CH), 76.3 (CH,C*H*O), 124.8 (CH) and 131.4 (CH); *m*/*z* (ESI) 249.1831 ([M+Na]$^+$, $C_{14}H_{26}O_2Na$ requires 249.1841), 249.2 (100%).

***rac*-(1*S*,2*S*,5*S*)-2-((*S*)-2'-Hydroxyhept-5'-yn-2'-yl)-5-methylcyclohexanol 190**



Method 1

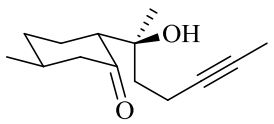
TBAF (0.23 mL of a 1.0 M solution in THF, 0.23 mmol) was added to a solution of silyl ether **204** (0.08 g, 0.23 mmol) in THF (2.3 mL). The solution was stirred for 5 h at rt, after which the mixture was washed with water (20 mL) and extracted with Et_2O (2 × 20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography (1:1 petrol:Et_2O) to give **190** (0.05 g, 91%).

Method 2

Acetonide **214** (0.17 g, 0.65 mmol) was stirred in AcOH (15 mL of a 60% aqueous solution) for 2 h. The reaction was then treated with $NaHCO_3$ (15 mL of a saturated aqueous solution) and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (2:1 petrol/Et_2O) gave **190** (0.13 g, 88 %) as a white solid. R_f 0.12 (2:1 petrol/Et_2O); mp 87°C; υ_{max}(neat)/cm^{-1} 3300, 2949, 2920, 2220, 1974, 1454, 1376, 1051 and 1003; δ_H(400 MHz; $CDCl_3$) 0.80-0.94 (2 H, m), 0.90 (3 H, d, *J* 6.5, CHC*H*$_3$), 1.03 (1 H, ap. dt, *J* 12.5 and 11.5, ax. CHC*H*$_2$CH), 1.18 (3 H, s, CC*H*$_3$), 1.36-1.50 (2 H, m, 2 × C*H*), 1.58-1.68 (3 H, m), 1.69-1.74 (1 H, m), 1.76 (3 H, t, *J* 2.5, C≡CC*H*$_3$), 1.94 (1 H, ap. ddt, *J* 12.3, 3.8 and 1.9, eq. CHC*H*$_2$CH), 2.16-2.34 (2 H, m, C*H*$_2$C≡C), 3.74 (1 H, ap. td, *J* 10.3 and 2.9, C*H*OH) and 3.90 (2 H, s, 2 × O*H*); δ_C(100 MHz; $CDCl_3$) 3.4 (CH_3, C≡C*C*H$_3$), 12.4 (CH_2, *C*H$_2$C≡C), 21.9 (CH_3,

$CHCH_3$), 22.7 (CH_3, CCH_3), 26.7 (CH_2), 31.3 (CH), 34.4 (CH_2), 39.8 (CH_2), 44.6 (CH_2, $CHCH_2CH$), 50.1 (CH), 72.3 (CH, *C*HOH), 76.5 (C), 76.6 (C) and 79.3 (C, C≡*C*CH_3); *m*/*z* (EI) 224.1777 (M^+, $C_{14}H_{24}O_2$ requires 224.1777), 224.2 (1%), 157.1 (26), 139.1 (19), 111.1 (100) and 81.1 (38).

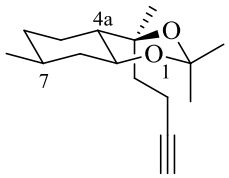
rac-(2*R*,5*S*)-2-((2'*S*)-2'-Hydroxyhept-5-yn-2-yl)-5-methylcyclohexanone 175



TPAP (0.01 mg, 0.03 mmol) was added to a solution of diol **190** (0.12 g, 0.52 mmol) and NMO (0.09 g, 0.78 mmol) containing molecular sieves (0.51 g, MS 4 Å) in CH_2Cl_2 (2.5 mL) at rt. After being stirred for 1 day, the reaction was filtered through a pad of silica, eluted with EtOAc, and concentrated *in vacuo*. Purification by column chromatography (2:1 petrol:Et_2O) gave **175** (0.10 g, 88 %) as a colourless oil. R_f 0.49 (2:1 petrol:Et_2O); υ_{max}(neat)/cm^{-1} 3507, 2954, 2927, 2150, 2040, 2023 and 1695; δ_H(400 MHz; $CDCl_3$) 1.01 (3 H, d, *J* 6.3, $CHCH_3$), 1.16 (3 H, s, CCH_3), 1.28-1.40 (1 H, m, CH_2CH_2CHC), 1.50 (1 H, ap. qd, *J* 13.1 and 3.2, ax. CH_2CH_2CHC), 1.63-1.73 (2 H, m, $CH_2CH_2C{\equiv}C$), 1.76 (3 H, t, *J* 2.6, C≡CCH_3), 1.80-1.95 (2 H, m, $CHCH_3$ and CH_2CH_2CHC), 2.00 (1 H, dt, *J*.13.0 and 1.2, ax. CH_2CHCH_3), 2.10-2.32 (3 H, m, eq. CH_2CH_2CHC and $CH_2C{\equiv}C$), 2.36 (1 H, dt, *J* 13.1, 3.7 and 2.4, eq. CH_2CHCH_3) and 2.48 (1 H, ddd, *J* 13.1, 5.5and 1.1, C*H*C); δ_C(100 MHz; $CDCl_3$) 3.5 (CH_3, C≡CCH_3), 12.9 (CH_2, $CH_2C{\equiv}C$), 22.2 (CH_3, $CHCH_3$), 23.6 (CH_3, CCH_3), 28.4 (CH_2, CH_2CH_2CHC), 33.8 (CH_2, CH_2CH_2CHC), 35.3 (CH, $CHCH_3$), 39.4 (CH_2, $CH_2CH_2C{\equiv}C$), 51.5 (CH_2, CH_2CHCH_3), 56.4 (CH, CH_2CH_2CHC), 72.6 (C), 75.3 (C), 79.6 (C) and 215.3 (C, *C*=O); *m*/*z* (ESI) 245.1521 ($[M+Na]^+$, $C_{14}H_{26}O_2Na$ requires 245.1517), no LRMS obtained.

***rac*-(4*S*,4a*S*,7*S*,8a*S*)-4-(But-3'-yn-1-yl)-2,2,4,7-tetramethylhexahydrobenzo[1,3]dioxane**

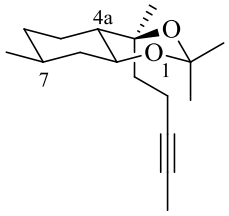
213



To a solution of diol **188** (0.05 g, 0.24 mmol) and *p*-TSA.H_2O (1.35 mg, 0.01 mmol) in THF (0.5 mL) was added 2-2-dimethoxypropane (0.03 mL, 0.28 mmol) and the mixture was stirred at rt for 48 h. The reaction was then neutralised with Et_3N (0.6 mL) and concentrated *in vacuo*. The residue was purified by column chromatography (100:5 petrol:Et_2O) to give **213** (0.05 g, 85%) as a colourless oil. R_f 0.91 (3:1 petrol:Et_2O); υ_{max}(neat)/cm^{-1} 3311 (≡CH), 2989, 2926, 2862, 2118 (C≡C), 1453, 1375, 1196 (COC) and 1144; δ_H(400 MHz; $CDCl_3$) 0.80-0.95 (2 H, m), 0.92 (3 H, d, *J* 6.6, CHC*H*$_3$), 1.01 (1 H, ap. td, *J* 12.2 and 10.7, ax. CHC*H*$_2$CH), 1.19 (3 H, s, CC*H*$_3$), 1.31 (3 H, s, C*H*$_3$), 1.33-1.40 (1 H, m, C*H*), 1.42 (3 H, s, C*H*$_3$), 1.45-1.53 (1 H, m, C*H*), 1.54-1.60 (1 H, m), 1.61-1.76 (3 H, m), 1.84-1.88 (1 H, m, eq. CHC*H*$_2$CH), 1.89 (1 H, t, *J* 2.6, C≡C*H*), 2.19-2.37 (2 H, m, C*H*$_2$C≡CH) and 6.64 (1 H, ap. dt, *J* 10.4 and 4.3, C*H*O); δ_C(100 MHz; $CDCl_3$) 12.3 (CH_2, *C*H_2C≡CH), 22.2 (CH_3, CH*C*H_3), 23.1 (CH_3, C*C*H_3), 24.8 (CH_3), 24.8 (CH_2), 31.1 (CH, *C*HCH$_3$), 31.7 (CH_3), 34.3 (CH_2), 40.8 (CH_2), 41.3 (CH_2, CH*C*H_2CH), 45.5 (CH), 67.4 (CH, *C*HO), 67.5 (CH, C≡*C*H), 74.5 (C), 85.4 (C, *C*≡CH) and 97.8 (C, *C*$(CH_3)_2$); *m*/*z* (ESI) 273.1831 ($[M+Na]^+$, $C_{16}H_{26}O_2Na$ requires 273.1827), 273.1 (100%).

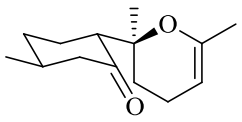
***rac*-(4*S*,4a*S*,7*S*,8a*S*)-4-(Pent-3'-yn-1-yl)-2,2,4,7-tetramethylhexahydrobenzo[1,3]dioxane**

214



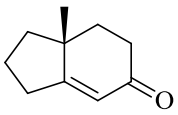
n-BuLi (0.11 mL of a 2.1 M solution in THF, 0.24 mmol) was added dropwise to a solution of acetonide **213** (0.03 g, 0.12 mmol) in THF (15 mL) at -78°C. After 30 min, MeI (0.03 mL, 4.79 mmol) was added at -78 °C and the reaction was left to warm up to rt and stirred for 3 h. The solution was then quenched with NH_4Cl (10 mL of a saturated aqueous solution) and the aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with brine (20 mL), water (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (2:1 petrol:Et_2O) gave **214** (30 mg, 92%) as a colourless oil. R_f 0.85 (1:1 petrol:Et_2O); υ_{max}(neat)/cm^{-1} 2989, 2924, 2860, 2361 (C≡C), 2339, 1449, 1375, 1195 (COC), 1145 and 1080; δ_H(400 MHz; $CDCl_3$) 0.84-1.07 (3 H, m), 0.92 (3 H, d, *J* 6.6, CHC*H*$_3$), 1.18 (3 H, s, CC*H*$_3$), 1.32 (3 H, C*H*$_3$), 1.34-1.39 (1 H, m, C*H*), 1.40-1.50 (1 H, m, C*H*), 1.43 (3 H, s, C*H*$_3$), 1.55-1.72 (4 H, m), 1.76 (3 H, t, *J* 2.5, C≡CC*H*$_3$), 1.84-1.91 (1 H, m), 2.13-2.31 (2 H, m, C*H*$_2$C) and 3.65 (1 H, ap. td, *J* 10.4 and 4.3, C*H*O); δ_c(100 MHz; $CDCl_3$) 3.4 (CH_3, C≡C*C*H$_3$), 12.5 (CH_2, *C*H$_2$C≡C), 22.2 (CH_3, CH*C*H$_3$), 23.2 (CH_3, C*C*H$_3$), 24.8 (CH_3), 24.9 (CH_2), 31.2 (CH), 31.8 (CH_3), 34.4 (CH_2), 41.1 (CH_2), 41.4 (CH_2), 45.5 (CH), 67.4 (CH), 74.7 (C), 74.8 (C), 80.0 (C, *C*≡CCH$_3$) and 97.8 (C, *C*(CH$_3$)$_2$); *m*/*z* (ESI) 287.1983 ([M+Na]$^+$, $C_{17}H_{28}O_2Na$ requires 287.1987), 287.2 (100%).

(*2R*,5*S*)-2-((2'*S*)-2',6'-Dimethyl-3'-4'-dihydro-2*H*-pyran-2-yl)-5-methylcyclohexanone 97



Alkynyl alcohol **175** was dried of water by evaporation from toluene (× 2) before reaction. $Pd(OAc)_2$ (0.09 g, 0.35 mmol) was added to a solution of alkynyl alcohol **175** (0.12 g, 0.54 mmol) in CH_2Cl_2 (1.2 mL) containing MS 3 Å (0.12 g) at rt. After 5 h, the mixture was filtered through a pad of silica eluting with CH_2Cl_2 and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography (5:1 petrol:Et_2O) to give **97** (0.07 g, 57%) as a colourless oil. R_f 0.91 (1:1 petrol:Et_2O); υ_{max}(neat)/cm^{-1} 2926, 2872, 1713, 1681, 1447, 1373, 1314, 1300, 1246, 1199, 1138, 1069 and 1010; δ_H(300 MHz; C_6D_6) 0.63 (3 H, d, *J* 6.1, CHC*H*$_3$), 0.79-1.02 (1 H, m), 1.20-1.32 (1 H, m), 1.38-1.61 (4 H, m), 1.51 (3 H, s, C*H*$_3$), 1.74 (3 H, s, C*H*$_3$), 1.79-1.91 (1 H, m), 2.00-2.11 (1 H, m), 2.12-2.28 (3 H, m), 2.45 (1 H, dd, *J* 13.1 and 4.6, CC*H*C) and 4.43-4.49 (1 H, m, C*H*=C); δ_c (100 MHz; C_6D_6) 18.2 (CH_2, *C*H_2CH=C), 20.9 (CH_3), 22.0 (CH_3), 22.2 (CH_3), 25.6 (CH_2), 27.7 (CH_2), 34.3 (CH_2), 36.1 (CH), 51.8 (CH_2), 59.8 (CH), 76.5 (C, *C*CH_3), 94.5 (CH, *C*H=C), 148.8 (C, CH=*C*) and 128.5 (C, *C*=O); *m*/*z* (EI) 222.1623 (M^+, $C_{14}H_{22}O_2$ requires 222.1620), 222.2 (100 %), 204.1 (39), 161.1 (56), 111.1 (55) and 105.1 (18).

***rac*-(7a*R*)-7a-Methylhexahydro-inden-5-one 241**



Method 1

A solution of KOH (0.10 g, 1.83 mmol) in Et_2O (7.5 mL) and EtOH (0.7 mL) was cooled to 0°C and 2-methylcyclopentanone (1.00 g, 10.19 mmol) was added, followed by a solution of MVK (0.33 g, 4.67 mmol) in Et_2O (1.8 mL). The mixture was stirred for 45 min at 0°C and a further 45 min at rt, after which HCl (7.5 mL of a 10% aqueous solution) was added. The solution was extracted with Et_2O (3 ×15 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography (7:3 petrol:Et_2O) to give **241** (35 mg, 2%).

Method 2

A solution of 2-methylcyclopentanone (0.50 g, 5.09 mmol), MVK (0.36 g, 5.14 mmol) and concentrated H_2SO_4 (1 drop) in toluene (10 mL) was refluxed for 12 h. The cooled reaction mixture was quenched with water (10 mL) and the mixture was extracted with Et_2O (2 × 20 mL). The combined organic layers were washed with water (10 mL), $NaHCO_3$ (10 mL of a saturated aqueous solution) and brine (2 x 10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo* to give diketone**242**, IR (neat)/cm^{-1} 1713-1736. The crude diketone (0.53 g) was taken up in KOH (7.5 mL of a 10% solution in EtOH) and refluxed for 30 min. The cooled reaction mixture was acidified to pH=6 with AcOH. The solution was evaporated and the residue was diluted with Et_2O (10 mL) and water (10 mL),

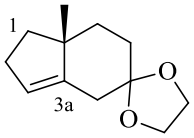
and was extracted with Et_2O (3 x 10 mL). The combined organic layers were washed successively with water (10 mL), $NaHCO_3$ (10 mL of a saturated aqueous solution) and brine (2 × 10 mL). The solution was dried (Na_2SO_4) and the solvent was removed *in vacuo*. Purification by column chromatography (4:1 petrol:Et_2O) gave **241** (0.29 g, 38%).

Method 3

A solution of 2-methylcyclopentanone (5.00 g, 50.94 mmol) and (+/-)-methylbenzylamine (6.17 g, 50.94 mmol) in toluene (50 mL) was equipped with a Dean-Stark apparatus and refluxed o/n. MVK (3.75 g, 53.49 mmol) was added to the cooled solution of imine and the mixture was stirred at 40°C for ca. 12h. The solution was allowed to cool to rt and water (3 mL) and AcOH (3 mL) were added. After being stirred for 2h, the mixture was washed with brine (5 mL) and water (8 mL), and extracted with petrol:Et_2O (5 × 10 mL of a 50:50 mixture). The combined organic layers were washed successively with HCl (5 mL of a 10% aqueous solution), water (5 mL) and brine (2 × 5 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give diketone **242**. The crude diketone (ca. 13 g) was dissolved in KOH (100 mL of a 10% solution in EtOH) and refluxed for 30 min. The cooled reaction mixture was acidified to pH=6 with AcOH. The solution was evaporated and the residue was diluted with Et_2O (50 mL) and water (30 mL), and was extracted with Et_2O (3 × 20 mL). The combined organic layers were washed successively with water (20 mL), $NaHCO_3$ (20 mL of a saturated aqueous solution) and brine (20 mL). The solution was dried ($MgSO_4$) and the solvent was removed *in vacuo*. Purification by column chromatography (7:3 petrol:Et_2O) gave **241** (3.40 g, 44%) as a yellow oil. R_f 0.17 (4:1 petrol:Et_2O); υ_{max}(neat)/cm^{-1} 2925, 1659 and 1422 (C=C); δ_H(300 MHz; $CDCl_3$) 0.94 (3 H, s, C*H*$_3$), 1.15-1.33 (1 H, m), 1.47-1.66 (4 H, m), 1.76-1.85 (1 H, m), 2.03-2.15 (1 H, m), 2.17-2.38 (2 H, m), 2.40-2.55 (1 H, m) and 5.52 (1 H, s, C*H*); δ_C(75 MHz;

$CDCl_3$) 20.6 (CH_2), 21.8 (CH_3), 30.2 (CH_2), 33.3 (CH_2), 35.5 (CH_2), 40.3 (CH_2), 42.1 (C, *C*CH_3), 120.7 (CH), 177.9 (C, *C*CH), 198.7 (C, *C*=O); *m/z* (EI) 150.1049 (M^+, $C_{10}H_{14}O$ requires 150.1044), 150 (41%), 122 (100), 108 (46), 93 (20) and 79 (30).

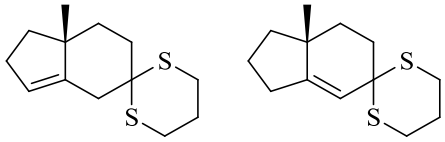
rac-(7a*R*)-7a-Methylhexahydro-5-spiro([1',3']dioxolane)indene 240



Ethylene glycol (6.90 g, 0.11 mmol) and *p*-TSA (0.38 g, 2.00 mmol) were added to a solution of enone **241** (3.00 g, 0.20 mol) in toluene (50 mL). The reaction was equipped with a Dean-Stark apparatus and refluxed for 3 h after which the solution was cooled and evaporated. The residue was taken up in ether (10 mL) and water (10 mL), and the aqueous layer was extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with $NaHCO_3$ (10mL of a saturated aqueous solution) and water (10 mL), dried (Na_2SO_4) and the solvent was removed *in vacuo*. Purification by flash column chromatography (10:1 petrol:Et_2O) gave **240** (0.14 g, 70%) as a yellow oil. R_f 0.54 (4:1 petrol:Et_2O); υ_{max}(neat)/cm^{-1} 1265 (C-O), 1727 (C=C) and 2986 (CH); δ_H(500 MHz; $CDCl_3$) 1.04 (3 H, s, C*H*$_3$), 1.52 (1 H, td, *J* 13.5 and 4, $CCH_2CH_2CCH_3$), 1.61-1.69 (3 H, m, $CCH_2CH_2CCH_3$, $CCH_2CH_2CCH_3$ and $CH_3CCH_2CH_2CH$), 1.75-1.85 (2 H, m, $CCH_2CH_2CCH_3$ and $CH_3CCH_2CH_2CH$), 2.23-2.35 (3 H, m, 1 × CCH_2C and $CHCH_2$), 2.42 (1 H, dd, *J* 13.6 and 2.4, CCH_2C), 3.90-3.95 (4 H, m, OCH_2CH_2O) and 5.27 (1 H, d, *J* 1.9, C*H*); δ_C(126 MHz; $CDCl_3$) 22.1 (*C*H_3), 30.3 (CH_2, $CHCH_2$), 31.7 (CH_2), 36.0 (CH_2, CCH_2C), 37.5 (CH_2), 40.1 (CH_2, $CH_3CCH_2CH_2CH$), 44.9 (C, *C*CH_3), 64.3 (CH_2, OCH_2), 64.4 (CH_2, OCH_2), 109.6 (O*C*O), 122.3 (*C*H) and 146.2

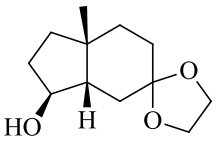
(*C*CH); *m/z* (EI) 194.1312 (M^+, $C_{12}H_{18}O_2$ requires 194.1307), 194 (3%), 99 (100), 91 (4) and 55 (14).

rac-(7a_R_)-7a-Methylhexahydro-5-spiro([1',5']dithiane)-3-indene 247 and (7a_R_)-7a-methylhexahydro-5-spiro([1',5']dithiane)-3a-indene 246



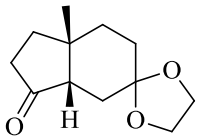
Propane dithiol (0.40 mL, 4.00 mmol) and *p*-TSA (0.01 g, 0.07 mmol) were added to a solution of enone **241** (0.10 g, 0.67 mmol) in toluene (10 mL). The reaction was equipped with a Dean-Stark apparatus and refluxed for 12 h after which the solution was cooled and quenched with NaOH (12 mL of a 1 M solution). The mixture was extracted with Et_2O (3 x 20 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (20:1 petrol:Et_2O) gave a 3:1 mixture of **246**:**247** (0.14 g, 84%) as a colourless oil. R_f 0.70 (9:1 petrol:Et_2O); **246**: δ_H(400 MHz; $CDCl_3$) 5.47 (1 H, d, *J* 1.3, C*H*); *m/z* (EI) 240.1004 (M^+, $C_{13}H_{20}S_2$ requires 240.1006), 240.1 (43%), 207.1 (11), 166.1 (100), 151.1 (20) and 133.1 (16); and **247**: δ_H(400 MHz; $CDCl_3$) 5.32-5.35 (1 H, m, C*H*); *m/z* (EI) 240.1002 (M^+, $C_{13}H_{20}S_2$ requires 240.1006), 240.1 (18%) and 145.0 (100).

***rac*-(3*S*,3a*S*,7a*R*)-7a-Methyloctahydro-5-spiro([1',3']dioxolane)inden-3-ol 251**



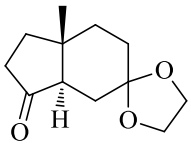
A solution of 9-BBN (2 mL of a 0.5 M in THF, 1.10 mmol) was added to olefin **240** (0.10 g, 0.52 mmol) and the reaction mixture was stirred for 30 min at rt. The reaction was then oxidised with NaOH (0.27 mL of a 3M aqueous solution) and H_2O_2 (0.22 mL of a 27% aqueous solution). After 1 h, water (10 mL) was added, and the mixture was extracted with Et_2O (2 × 20 mL). The combined organic layers were washed with $NaHCO_3$ (10 mL of a saturated aqueous solution) and brine (10 mL), dried (Na_2SO_4) and the solvent was removed *in vacuo*. Purification by column chromatography (3:2 Et_2O:petrol) gave **251** (0.07 g, 65%) as a colourless oil. R_f 0.21 (1:1 petrol:Et_2O); υ_{max}(neat)/cm^{-1} 1708 (C=C), 2950 (CH) and 3416 (OH); δ_H(300 MHz; CD_3CN) 1.08 (3 H, s, C*H*$_3$), 1.25-1.34 (1 H, m), 1.39-1.59 (7H, m, 1 × $CH_3CCH_2CH_2CH$, 1 × CCH_2CH_2C, $CH_3CCH_2CH_2CH$, CCH_2CH_2C, CCH_2CH), 1.66 (2 H, d, *J* 5.4, $CHCH_2C$), 2.00-2.10 (1 H, m, $CH_3CCH_2CH_2CH$), 2.71 (1 H, d, *J* 4.4, O*H*), 3.79-3.94 (4 H, m, OCH_2CH_2O) and 4.21-4.29 (1 H, m, $CH_3CCH_2CH_2CH$); δ_C(75 MHz; $CDCl_3$) 26.7 (CH_3), 31.5 (CH_2, CCH_2CH_2C), 32.5 (CH_2, $CHCH_2C$), 32.6 (CH_2, $CH_3CCH_2CH_2CH$), 33.6 (CH_2, CCH_2CH_2C), 37.8 (CH_2, $CH_3CCH_2CH_2CH$), 39.4 (CH_3, CH_3C), 54.5 (CH, CCH_2CHCH), 64.3 (CH_2, OCH_2), 64.8 (CH_2, OCH_2), 76.6 (C, $CH_3CCH_2CH_2CH$) and 109.6 (C, OCO); *m/z* (EI) 212.1424 (M^+, $C_{12}H_{20}O_3$ requires 212.1412), 212 (3%), 150 (3), 99 (100), 86 (10) and 55 (6).

(3a*S*,7a*R*)-7a-Methylhexahydro-5-spiro([1',3']dioxolane)inden-3-one 253



A solution of alcohol **251** (0.14 g, 0.68 mmol) and IBX (0.38 g, 1.36 mmol) in DMSO (3.4 mL) was stirred for 12 h at rt, after which the mixture was quenched with water (4 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with water (10 mL) and brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (4:1 petrol:Et_2O) gave **253** (0.13 g, 91%) as a white solid. R_f 0.21 (1:1 petrol:Et_2O); mp 49-51; υ_{max}(neat)/cm^{-1}; δ_H(300 MHz; C_6D_6) 0.78 (3 H, s, CH_3), 0.95-1.08 (1 H, m), 1.09-1.17 (1 H, m), 1.26-1.35 (1 H, m), 1.45-1.57 (3 H, m), 1.58-1.70 (2 H, m), 1.88-2.00 (1 H, m), 2.10-2.21 (1 H, m), 2.25-2.34 (1 H, m) and 3.42-3.69 (4 H, m, OCH_2CH_2O); δ_C(75 MHz; $CDCl_3$) 26.2 (CH_3), 29.4 (CH_2), 31.7 (CH_2), 32.1 (CH_2), 34.3 (CH_2), 35.4 (CH_2), 37.1 (C), 55.4 (CH), 63.7 (CH_2, CH_2O), 64.5 (CH_2, CH_2O), 108.0 (C), 216.2 (C, *C*=O); *m*/*z* (EI) 210.1259 ($C_{12}H_{18}O_3$ requires 210.1256), 210.1 (11%), 295.1 (13), 99 (100), and 86.0 (21).

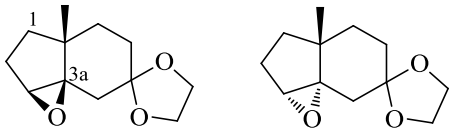
(3a*R*,7a*R*)-7a-Methylhexahydro-5-spiro([1',3']dioxolane)inden-3-one 239



A solution of **254** (0.10 g, 0.47 mmol) in toluene (5 mL) was treated with $BF_3 \cdot Et_2O$ (0.07 g, 0.47 mmol). After 20 min, the mixture was extracted with Et_2O (2 × 20 mL). The combined

organic layers were washed with brine (20 mL), NaOH (15 mL of a 4% aqueous solution), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (4:1 petrol:Et_2O) to give **239** (14 mg, 14%) as a white solid, followed by **253** (8 mg, 8%). R_f 0.59 (2:1 petrol:Et_2O); υ_{max}(neat)/cm^{-1} 2951, 1741, 1459, 1365, 1162, 1109, 1022 and 945; δ_H(300 MHz; C_6D_6) 0.50 (3 H, s, CH_3), 1.06-1.18 (1 H, m), 1.26-1.40 (2 H, m), 1.44-1.52 (1 H, m), 1.53-1.60 (1 H, m), 1.60-1.64 (1 H, m), 1.71-1.83 (1 H, m), 1.87-1.94 (2 H, m), 2.13-2.25 (2 H, m) and 1.38-1.52 (4 H, m OCH_2CH_2O); δ_C(100 MHz; C_6D_6) 16.6 (CH_3), 30.6 (CH_2), 32.2 (CH_2), 35.4 (CH_2), 35.6 (CH_2), 36.1 (CH_2), 38.4 (C), 57.0 (CH), 64.2 (CH_2, OCH_2), 64.5 (CH_2, OCH_2), 109.7 (C) and 213.5 (C, *C*=O); *m*/*z* (EI) 210.1264 ($C_{12}H_{18}O_3$ requires 210.1256), 210 (28%), 181 (24), 154 (15), 112 (10), 99 (100), 86 (74) and 55 (22).

rac-(3*S*,3a*R*,7a*R*)-7a-Methyl-3,3a-epoxyhexahydro-5-spiro([1',3']dioxolane)indene 254 and _rac_-(3*R*,3a*S*,7a*R*)-7a-methyl-3,3a-epoxyhexahydro-5-spiro([1',3']dioxolane)indene 256



Method 1

Tetrahydrothiopyran-4-one (0.01 g, 0.05 mmol) was added to a solution of olefin **240** (0.10 g, 0.52 mmol) in acetonitrile (2.5 mL) at rt, followed by Na_2.EDTA (1.5 mL of a 4.10^{-4} M solution). A mixture of oxone® monopersulfate (0.48 g, 0.77 mmol) and $NaHCO_3$ (0.20 g, 2.40 mmol) was then introduced portion-wise over a period of 3 h. The reaction was stirred at

rt for a further 3 h and the mixture was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried (Na_2SO_4) and the solvent was removed under reduced pressure. Purification by column chromatography (8:1 petrol:Et_2O) gave first epoxide **254** (55 mg, 50%), followed by epoxide **256** (35 mg, 32%)

Method 2

m-CPBA (0. 40 g, 2.32 mmol) was added to a solution of olefin **240** (0.20 g, 1.03 mmol) in CH_2Cl_2 (10 mL) and the reaction was stirred for 10 min at rt. The mixture was then quenched with NaOH (5 mL of a 5% aqueous solution) and extracted with Et_2O (3 × 10 mL). The combined organic layers were dried (Na_2SO_4) and the solvent was removed *in vacuo*. Purification by column chromatography (2:1 petrol:Et_2O) gave epoxide **254** (65 mg, 30%) and epoxide **256** (0.11 g, 51%).

Method 3

DMDO was prepared from a procedure from A. Sherlock Ph.D. thesis, University of Nottingham, 2006.and used directly:

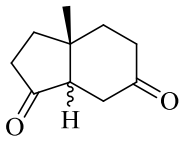
A two neck 3 L round bottom flask was equipped with a condenser fitted with a dry-ice mantle and connected to a two neck 500 mL round bottom receiving flask cooled at -78 °C. The two neck 500 mL flask was connected to a vacuum pump. The 3 L flask was charged with water (254 mL), acetone (192 mL) and $NaHCO_3$ (58 g, 0.69 mol) and cooled to between 5-10 °C. Oxone® (120 g, 0.20 mol) was added in one portion with vigorous stirring and after 20 min the cooling bath was removed. Suction was applied and the slightly yellow DMDO solution was distilled into the cooled receiving flask. After ca. 30 min the distillation was stopped, and the two neck flask containing DMDO was fitted with a stopper and a septum, kept at low temperature and flushed with argon.

DMDO was added to a solution of **240** (0.50 g, 2.58 mmol) in acetone (10 mL) at rt until disappearance of starting material was observed by TLC monitoring, and the solution was concentrated *in vacuo*. The residue was purified by column chromatography (4:1 petrol:Et_2O) to give **254** (0.47 g, 86 %).

254 was obtained as a pale yellow oil. Rf 0.28 (4:1 petrol:Et_2O); υ_{max}(neat)/cm^{-1} 1265 (CO epoxide) and 2936 (CH); δ_H(500 MHz; $CDCl_3$) 1.06 (3 H, s, C*H*$_3$), 1.28-1.33 (2 H, m, C*H*$_2$CH$_2$CH), 1.33-1.39 (1 H, m), 1.48-1.56 (2 H, m), 1.61-1.67 (1 H, m), 1.69-1.81 (2 H, m), 1.86-1.93 (1 H, dt, *J* 14.2 and 4.6), 2.18 (1 H, d, *J* 13.1), 3.28 (1 H, s, C*H*) and 3.89-3.95 (4 H, m, OC*H*$_2$C*H*$_2$O); δ_C(126 MHz; $CDCl_3$) 18.2 (CH_3), 25.0 (CH_2, *C*H$_2$CH), 31.3 (CH_2), 31.8 (CH_2), 34.6 (CH_2), 35.6 (CH_2, C*C*H$_2$C), 39.2 (C, *C*CH$_3$), 64.3 (CH_2, O*C*H$_2$), 64.4 (CH_2, O*C*H$_2$), 64.4 (CH), 68.7 (C, *C*CH) and 109.7 (C, O*C*O); *m*/*z* (ESI) 233.1254 ([M+Na]$^+$, $C_{12}H_{18}O_3$ requires 233.1256), 233.1 (100%).

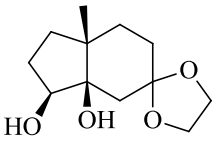
256 was obtained as a pale yellow oil. Rf 0.11 (4:1 petrol:Et_2O); υ_{max}(neat)/cm^{-1} 1265 (CO epoxide) and 2957 (CH); δ_H(500 MHz; $CDCl_3$) 1.00 (3 H, s, C*H*$_3$), 1.13-1.29 (2 H, m, C*H*$_2$CH$_2$CH), 1.55-1.62 (2 H, m), 1.65-1.72 (1 H, m), 1.73-1.90 (3 H, m), 1.95 (1 H, dd, *J* 13.8 and 7.6), 2.38 (1 H, d, *J* 13.8), 3.33 (1 H, s, C*H*) and 3.86-4.06 (4 H, m, OC*H*$_2$C*H*$_2$O); δ_C(126 MHz; $CDCl_3$) 20.6 (CH_3), 26.3 (CH_2, *C*H$_2$CH), 31.1 (CH_2), 31.4 (CH_2), 32.7 (CH_2, *C*H$_2$CH$_2$CH), 34.3 (CH_2, C*C*H$_2$C), 38.6 (C, *C*CH$_3$), 59.1 (CH), 64.3 (CH_2, O*C*H$_2$), 64.6 (CH_2, O*C*H$_2$), 69.7 (C, *C*CH) and 109.9 (C, O*C*O); *m*/*z* (EI) 210.1243 (M$^+$, $C_{12}H_{18}O_3$ requires 210.1256), 210 (2%), 195 (4), 99 (100), 86 (18) and 55 (7).

***rac*-(3aS)-3a-Methylhexahydroinden-1,6-dione 257**



257 was obtained as a pale yellow oil. υ_{max}(neat)/cm^{-1} 2959, 2926, 2861, 1655, 1452 and 1201; δ_H(400 MHz; C_6D_6) 0.75 (3 H, s, C*H*$_3$), 0.90-0.98 (2 H, m, C*H*$_2$), 1.03-1.13 (2 H, m, C*H*$_2$), 1.13-1.23 (1 H, m), 1.53-1.58 (1 H, m, C*H*), 1.81-1.97 (3 H, m) and 2.71-2.77 (2 H, m, C*H*$_2$CH); δ_C(75 MHz; C_6D_6) 24.7 (CH_3), 32.9 (CH_2), 33.7 (CH_2), 34.3 (CH_2), 35.7 (CH_2, CHC*H*$_2$), 36.9 (CH_2), 37.2 (C), 56.0 (CH), 206.4 (C, *C*O) and 214.9 (C, *C*O); *m*/*z* (ESI) ([M+Na]$^+$), 189.1 (100%).

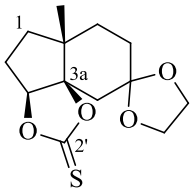
(3*S*,3a*R*,7a*R*)-7a-Methyloctahydro-5-spiro([1',3']dioxolane)inden-3,3a-diol 268



A crystal of OsO_4 was added to a solution of NMO (0.07 g, 0.57 mmol) and olefin **240** (0.10 g, 0.52 mmol) in THF (0.5 mL), ^{t}BuOH (1.8 mL) and water (0.2 mL) at rt. The reaction was stirred for 2 days and quenched with sodium metabisulfite (0.16 g). After 1h, the mixture was extracted with EtOAc (3 × 20 mL) and the combined organic layers were washed with HCl (15 mL of a 1 M aqueous solution) and brine (15 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (2:1 petrol:Et_2O) gave diol **268** (0.09 g, 77%) as a white solid. Rf 0.11 (4:1 Et_2O:petrol); mp 70-72 °C; δ_H(400 MHz; $CDCl_3$) 1.08 (3 H, s, C*H*$_3$), 1.42-1.77 (9 H, m), 2.03-2.14 (1 H, m), 2.39 (1 H, d, *J* 3.8, CHO*H*), 2.94 (1 H, s,

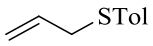
CO*H*), 3.88-4.02 (4 H, m, 2 × C*H*$_2$O) and 4.14-4.22 (1 H, m, C*H*OH); δ_c(100 MHz; $CDCl_3$) 21.5 (CH_3), 28.7 (CH_2), 30.3 (CH_2), 32.4 (CH_2), 33.9 (CH_2), 40.2 (CH_2), 42.3 (C, *C*CH_3), 64.2 (CH_2, *C*H_2O), 64.4 (CH_2, *C*H_2O), 76.6 (CH, *C*HOH), 80.1 (C, *C*OH) and 109.1 (C); *m*/*z* (EI) 228.1362 (M^+, $C_{12}H_{18}O_3$ requires 228.1354), 228.1 (12%), 210.1 (11), 99.0 (100) and 86.0 (24).

rac-(3*S*,3a*R*,5a*R*)-5a-Methylhexahydro-5-spiro([1',3']dioxolane)inden-3,3a-([1',3']dioxo-2'-thione) 270



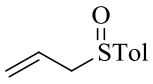
A solution of thiophosgene (0.11 mL, 1.39 mmol) in CH_2Cl_2 (3 mL) was added to a solution of diol **268** (0.16 g, 0.70 mmol) and DMAP (0.43 g, 3.48 mmol) in CH_2Cl_2 (12 mL) at rt. After 6 h, silica was added and the mixture was concentrated *in vacuo*. Purification by column chromatography (1:1 petrol:Et_2O) gave **270** (0.03 g, 16 %) as a white crystal. R_f 0.35 (2:1 petrol:Et_2O); υ_{max}(neat)/cm^{-1} 2964, 1805, 1367, 1167 (C=S) and 1022; δ_H(400 MHz; $CDCl_3$) 1.19 (3 H, s, C*H*$_3$), 1.40-1.49 (1 H, m), 1.54-1.65 (3 H, m), 1.68-1.77 (1 H, m), 1.78-1.88 (1 H, m), 1.91-1.99 (1 H, m), 2.06-2.26 (3 H, m), 3.87-3.97 (4 H, m, 2 × C*H*$_2$O) and 5.30 (1 H, d, *J* 7.1, C*H*); δ_C(100 MHz; $CDCl_3$) 18.9 (CH_3), 29.4 (CH_2), 30.0 (CH_2), 31.4 (CH_2), 36.4 (CH_2), 37.1 (CH_2), 44.4 (C, *C*CH_3), 64.3 (CH_2, *C*H_2O), 64.6 (CH_2, *C*H_2O), 90.6 (CH, *C*HO), 101.3 (C), 108.1 (C) and 191.0 (C, *C*=S); *m*/*z* (EI) 270.0926 (M^+, $C_{13}H_{18}O_4S$ requires 270.0920), 271.1 (14%), 254.1 (6) and 99.0 (100).

Allyl-*p*-tolyl sulfide 275



4-Methylphenylthiol (1.00 g, 8.05 mmol) was added to a solution of sodium (0.20 g, 8.50 mmol) in absolute EtOH (7.5 mL) and the solution was cooled to 0 °C. Allylbromide (1.13 mL, 13.04 mmol) was added dropwise and the solution was stirred for 1 h at rt. EtOH was then evaporated and the residue was dissolved in Et_2O (20 mL) and water (20 mL) and extracted with Et_2O (2 × 20 mL). The combined organic layers were washed with water (15 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give crude sulfide **275** (1.27 g, 96%). Rf 0.93 (1:1 petrol:Et_2O; υ_{max}(neat)/cm^{-1} 2919, 2143, 2023, 1594, 1491, 1144 and 810; δ_H(300 MHz; $CDCl_3$) 2.32 (3 H, s, C*H*$_3$), 3.40-3.60 (2 H, m, SC*H*$_2$), 4.95-5.25 (2 H, m, CH=C*H*$_2$), 5.60-6.20 (1 H, m, C*H*=CH_2) and 7.02-7.24 (4 H, m, Ar); δ_c(100 MHz; $CDCl_3$) 21.0 (CH_3), 37.8 (CH_2, S*C*H_2), 117.3 (CH_2, CH=*C*H_2), 129.5 (2 × CH, Ar), 130.6 (2 × CH, Ar), 132.0 (C, Ar), 133.8 (CH, C*H*=CH_2) and 136.3 (C, *C*CH_3); *m*/*z* (EI) 164.0 (53%), 149.0 (22), 131.1 (28), 123.0 (50), 91.0 (33), 77.0 (37), 65.0 (22), 51.0 (25) and 45.0 (100).

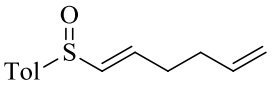
Allyl-*p*-sulfoxide 276



A solution of allyl-*p*-tolyl sulfide **275** (1.27 g, 7.74 mmol) in MeOH (7 mL) was quickly added to a solution of sodium metaperiodate (1.65 g, 7.74 mmol) in water (5 mL), and the reaction was stirred for 16 h at rt. The mixture was then filtered and extracted with Et_2O (3 × 20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*.

Purification by column chromatography (3:1 petrol:Et_2O) gave sulfoxide **276** (0.86 g, 61%) as a colourless oil. δ_H(300 MHz; $CDCl_3$) 2.41 (3 H, s, CH_3), 3.45-3.67 (2 H, m, SCH_2), 5.17-5.40 (2 H, m, CH=CH_2), 5.61-5.80 (1 H, m, CH=CH_2) and 7.35-7.60 (4 H, m, Ar); δ_c(100 MHz; $CDCl_3$) 19.3 (CH_3), 58.7 (CH_2, SCH_2), 121.6 (CH_2, CH=CH_2), 122.3 (2 × CH, Ar), 123.4 (CH, CH=CH_2), 127.7 (2 × CH, Ar), 135.4 (C) and 136.8 (C).

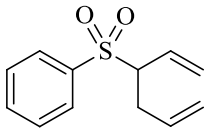
(*E*)- or (*Z*)-1-(hexa-1,5-dien-1-ylsulfinyl)-4-methylbenzene 277



LDA was prepared from *n*-BuLi (3.88 mL of a 1.5 M solution in hexane, 2.60 mmol) and diisopropylamine (0.36 mL, 2.60 mmol) in THF (4 mL) at -30 °C, and the solution was cooled at -78 °C. The solution of LDA was added to a solution of allyl-*p*-tolyl sulfoxide **276** (0.45 g, 2.50 mmol) in THF (8 mL) at -78 °C. After 1 h at this temperature, 3-methylcyclopentanone (0.25 mL, 2.50 mmol) was added. The mixture was stirred for 5 min and treated with NH_4Cl (20 mL of a saturated aqueous solution). The aqueous layer was extracted with Et_2O (3 × 20 mL), and the combined organic layers were washed with brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (3:1 petrol:Et_2O) gave by-product **277** (mass not recorded) as a colorless oil. Rf 0.31 (1:1 Et_2O:petrol); υ_{max}(neat)/cm^{-1} 2976, 2922, 1640, 1495, 1082, 1041 and 1014; δ_H(300 MHz; $CDCl_3$) 2.16-2.37 (4 H, m 2 × CH_2), 2.40 (3 H, s, CH_3), 4.96-5.07 (2 H, m, CH=CH_2), 5.69-5.83 (1 H, m, CH=CH_2), 6.21 (1 H, dt, *J* 15.2 and 1.4, SOCH), 6.57 (1 H, dt, *J* 15.2 and 6.6, SOCH=CH), 7.27-7.33 (m, 2 H, 2 × CH_{Ar}) and 7.46-7.52 (m, 2 H, CH_{Ar}); δ_c(100 MHz; $CDCl_3$) 21.4 (CH_3), 31.7 (CH_2), 32.1 (CH_2), 115.7 (CH_2), 124.6 (CH_{Ar}), 129.9 (CH_{Ar}), 135.5

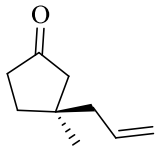
(CH), 136.8 (CH), 139.6 (CH), 140.9 (C) and 141.4 (C); *m*/*z* (ESI) 243.0829 ($[M+Na]^+$, $C_{13}H_{16}ONaS$ requires 243.0820), 243.1 (100%).

(Hexa-1,5-dien-3-ylsulfonyl)benzene 278



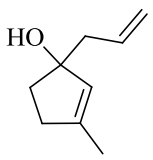
n-BuLi (2.85 mL of a 1.8 M solution in hexane, 5.24 mmol) was added dropwise to a solution of allyl-*p*-tolyl sulfone (0.78 mL, 5.09 mmol) in THF (20 mL) at -78 °C. 3-Methylcyclopentanone (0.50 mL, 5.09 mmol) was added followed 15 min later by allybromide (2.20 mL, 25.48 mmol). The mixture was stirred for 30 min and treated with NH_4Cl (25 mL of a saturated aqueous solution). The aqueous layer were extracted with Et_2O (3 × 20 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (3:1 petrol:Et_2O) gave by-product **278** (0.24 g, 21%) as a colorless oil. Rf 0.69 (1:1 petrol:Et_2O); υ_{max}(neat)/cm^{-1} 3068, 1447, 1306, 1146, 1084 and 689; δ_H(300 MHz; $CDCl_3$) 2.35-2.49 (1 H, m, C*H*$_2$), 2.81-2.91 (1 H, m, C*H*$_2$), 3.49-3.59 (1 H, m, C*H*), 4.96-5.31 (4 H, m, 2 × CH=C*H*$_2$), 5.55-5.71 (2 H, m, 2 × C*H*=CH_2), 7.49-7.86 (5 H, m, C*H*$_{Ar}$); δ_c(75 MHz; $CDCl_3$) 31.6 (CH_2), 69.3 (CH), 118.4 (CH_2, CH=*C*H_2), 123.8 (CH_2, CH=*C*H_2), 128.8 (2 × CH, *C*HAr), 129.3 (2 × CH, *C*HAr), 129.8 (CH, *C*HAr), 132.8 (CH, *C*H=CH_2), 133.7 (CH, *C*H=CH_2); *m*/*z* (ESI) 245.2937 ($[M+Na]^+$, $C_{12}H_{14}NaO_2S$ requires 245.2931), 245.0 (100%).

3-Ally-3-methylcyclopentanone 288



$CuBr_2 \cdot SMe_2$ was flame-dried under vacuum and flushed with argon (× 3) before reaction. Allyl magnesium bromide (8.32 mmol of a 2.0 M solution in THF, 4.16 mL) was added dropwise to a solution of 3-methylcyclopenten-1-one (0.20 g, 2.08 mmol) and $CuBr_2 \cdot SMe_2$ (1.71 g, 8.32 mmol) in THF (50 mL) at -40 °C. The reaction was allowed to warm to rt and stirred for 4h. The solution was quenched with NH_4Cl (10 mL of a saturated aqueous solution) and extracted with Et_2O (2 × 20 mL). The combined organic layers were washed with water (15 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (5:1 petrol:Et_2O) gave **288** (0.25 g, 87%) as a colourless oil. Rf 0.50 (3:1 petrol:Et_2O); υ_{max}(neat)/cm^{-1} 2955, 1738, 1639, 1455, 1405, 1169, 994 and 914; δ_H(300 MHz; $CDCl_3$) 1.05 (3 H, s, C*H*$_3$), 1.67-1.76 (1 H, m), 1.80-1.87 (1 H, m), 1.93-2.01 (1 H, m), 2.07-2.15 (3 H, m), 2.23-2.30 (2 H, m, C*H*$_2$), 4.99-5.09 (2 H, m, CH=C*H*$_2$) and 5.72-5.84 (1 H, m, C*H*=CH_2); δ_c(100 MHz; $CDCl_3$) 25.5 (CH_3), 34.6 (CH_2), 36.7 (CH_2), 39.4 (C), 45.6 (CH_2), 51.5 (CH_2), 117.9 (CH=*C*H_2), 134.4 (*C*H=CH_2) and 219.5 (*C*=O); *m*/*z* (EI) 138.1044 (M^+, $C_9H_{14}O$ requires 138.1045), 138.1 (29%), 97.1 (100) and 69.1 (43).

1-Allyl-3-methylcyclopent-2-enol 289



A solution of allyl magnesium chloride (11.44 mL of a 2.0 M solution in THF, 22.89 mmol) was added dropwise to a solution of methylcyclopentenone (2.00 g, 20.81 mmol) in THF (40 mL) at -78 °C. After 1 h the reaction was quenched with with NH_4Cl (25 mL of a saturated aqueous solution) and extracted with Et_2O (2 × 20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Distillation of the crude material gave **288** (2.18 g, 76%) as a colourless oil. Rf 0.87 (1:1 petrol:Et_2O); υ_{max}(neat)/cm^{-1} 3405, 2931, 1703, 1363, 1223, 1165 and 1050; δ_H(300 MHz; $CDCl_3$) 1.70 (3 H, s, C*H*$_3$), 1.78-1.86 (1 H, m), 1.98-2.06 (2 H, m), 2.07-2.17 (1 H, m), 2.32 (2 H, d, *J* 7.2, C*H*$_2$CH), 2.34-2.41 (1 H, m), 5.03-5.10 (2 H, m, C*H*$_2$=CH), 5.26-5.30 (1 H, m, C*H*=C) and 5.74-5.86 (1 H, m, CH_2=C*H*); δ_c(100 MHz; $CDCl_3$) 16.6 (CH_3), 35.1 (CH_2), 38.0 (CH_2), 45.5 (CH_2), 85.2 (C), 117.8 (CH_2), 130.1 (CH), 134.3 (CH) and 143.9 (C); *m*/*z* (EI) 138.1043 (M^+, $C_9H_{14}O$ requires 138.1045), 138.1 (33%), 97.1 (100) and 69.1 (76).

Appendix

Table 1. Crystal data and structure refinement for **253**.

Empirical formula	C12 H18 O3	
Formula weight	210.26	
Temperature	296(2) K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	P21/n	
Unit cell dimensions	a = 7.11(3) Å	α= 90°.
	b = 14.86(6) Å	β= 101.6(2)°.
	c = 11.69(4) Å	γ = 90°.
Volume	1210(8) $Å^3$	
Z	4	
Density (calculated)	1.155 Mg/m^3	
Absorption coefficient	0.662 mm^{-1}	
F(000)	456	
Crystal size	0.34 x 0.30 x 0.20 mm^3	
Theta range for data collection	4.87 to 62.21°.	
Index ranges	-7<=h<=7, -15<=k<=17, -12<=l<=12	
Reflections collected	5422	
Independent reflections	1641 [R(int) = 0.0426]	
Completeness to theta = 62.21°	85.6 %	
Max. and min. transmission	0.8790 and 0.8062	
Refinement method	Full-matrix least-squares on F^2	

Data / restraints / parameters	1641 / 0 / 137
Goodness-of-fit on F^2	1.025
Final R indices [I>2sigma(I)]	R1 = 0.0502, wR2 = 0.1248
R indices (all data)	R1 = 0.0805, wR2 = 0.1445
Largest diff. peak and hole	0.182 and -0.130 e.$Å^{-3}$

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **253**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	12114(4)	4562(2)	8973(2)	75(1)
C(2)	12692(4)	5299(2)	8170(2)	67(1)
C(3)	10428(4)	4318(2)	7061(2)	57(1)
C(4)	10489(4)	3661(2)	6044(2)	70(1)
C(5)	9132(3)	2837(2)	6095(2)	63(1)
C(6)	6993(3)	3123(1)	6000(2)	48(1)
C(7)	5812(4)	2319(2)	6417(2)	61(1)
C(8)	6112(4)	2389(2)	7779(2)	74(1)
C(9)	6698(3)	3379(2)	8078(2)	60(1)
C(10)	6837(3)	3888(1)	6924(2)	49(1)
C(11)	8348(4)	4662(2)	7033(2)	60(1)
C(12)	6114(4)	3415(2)	4713(2)	75(1)
O(1)	11201(2)	3866(1)	8166(1)	69(1)

O(2)	11687(3)	5084(1)	6997(2)	87(1)
O(3)	6970(3)	3720(2)	9076(2)	91(1)

Table 3. Bond lengths [Å] and angles [°] for **253**.

C(1)-O(1)	1.462(5)
C(1)-C(2)	1.550(6)
C(1)-H(1A)	0.9700
C(1)-H(1B)	0.9700
C(2)-O(2)	1.449(6)
C(2)-H(2A)	0.9700
C(2)-H(2B)	0.9700
C(3)-O(2)	1.459(5)
C(3)-O(1)	1.462(5)
C(3)-C(4)	1.545(5)
C(3)-C(11)	1.559(7)
C(4)-C(5)	1.567(6)
C(4)-H(4A)	0.9700
C(4)-H(4B)	0.9700
C(5)-C(6)	1.561(7)
C(5)-H(5A)	0.9700
C(5)-H(5B)	0.9700
C(6)-C(12)	1.570(6)
C(6)-C(10)	1.588(5)

C(6)-C(7)	1.593(5)
C(7)-C(8)	1.567(7)
C(7)-H(7A)	0.9700
C(7)-H(7B)	0.9700
C(8)-C(9)	1.550(7)
C(8)-H(8A)	0.9700
C(8)-H(8B)	0.9700
C(9)-O(3)	1.251(5)
C(9)-C(10)	1.567(6)
C(10)-C(11)	1.561(5)
C(10)-H(10)	0.9800
C(11)-H(11A)	0.9700
C(11)-H(11B)	0.9700
C(12)-H(12A)	0.9600
C(12)-H(12B)	0.9600
C(12)-H(12C)	0.9600

O(1)-C(1)-C(2)	104.2(3)
O(1)-C(1)-H(1A)	110.9
C(2)-C(1)-H(1A)	110.9
O(1)-C(1)-H(1B)	110.9
C(2)-C(1)-H(1B)	110.9
H(1A)-C(1)-H(1B)	108.9
O(2)-C(2)-C(1)	106.1(3)

O(2)-C(2)-H(2A)	110.5
C(1)-C(2)-H(2A)	110.5
O(2)-C(2)-H(2B)	110.5
C(1)-C(2)-H(2B)	110.5
H(2A)-C(2)-H(2B)	108.7
O(2)-C(3)-O(1)	106.2(3)
O(2)-C(3)-C(4)	110.0(3)
O(1)-C(3)-C(4)	109.0(3)
O(2)-C(3)-C(11)	109.3(3)
O(1)-C(3)-C(11)	110.8(3)
C(4)-C(3)-C(11)	111.4(3)
C(3)-C(4)-C(5)	110.6(3)
C(3)-C(4)-H(4A)	109.5
C(5)-C(4)-H(4A)	109.5
C(3)-C(4)-H(4B)	109.5
C(5)-C(4)-H(4B)	109.5
H(4A)-C(4)-H(4B)	108.1
C(6)-C(5)-C(4)	112.5(3)
C(6)-C(5)-H(5A)	109.1
C(4)-C(5)-H(5A)	109.1
C(6)-C(5)-H(5B)	109.1
C(4)-C(5)-H(5B)	109.1
H(5A)-C(5)-H(5B)	107.8
C(5)-C(6)-C(12)	109.7(3)

C(5)-C(6)-C(10)	110.3(2)
C(12)-C(6)-C(10)	112.7(3)
C(5)-C(6)-C(7)	109.9(3)
C(12)-C(6)-C(7)	111.6(2)
C(10)-C(6)-C(7)	102.5(3)
C(8)-C(7)-C(6)	106.8(2)
C(8)-C(7)-H(7A)	110.4
C(6)-C(7)-H(7A)	110.4
C(8)-C(7)-H(7B)	110.4
C(6)-C(7)-H(7B)	110.4
H(7A)-C(7)-H(7B)	108.6
C(9)-C(8)-C(7)	105.5(2)
C(9)-C(8)-H(8A)	110.6
C(7)-C(8)-H(8A)	110.6
C(9)-C(8)-H(8B)	110.6
C(7)-C(8)-H(8B)	110.6
H(8A)-C(8)-H(8B)	108.8
O(3)-C(9)-C(8)	125.3(2)
O(3)-C(9)-C(10)	125.7(3)
C(8)-C(9)-C(10)	109.0(3)
C(11)-C(10)-C(9)	116.5(3)
C(11)-C(10)-C(6)	116.3(3)
C(9)-C(10)-C(6)	105.4(3)
C(11)-C(10)-H(10)	105.9

C(9)-C(10)-H(10)	105.9
C(6)-C(10)-H(10)	105.9
C(3)-C(11)-C(10)	113.2(3)
C(3)-C(11)-H(11A)	108.9
C(10)-C(11)-H(11A)	108.9
C(3)-C(11)-H(11B)	108.9
C(10)-C(11)-H(11B)	108.9
H(11A)-C(11)-H(11B)	107.8
C(6)-C(12)-H(12A)	109.5
C(6)-C(12)-H(12B)	109.5
H(12A)-C(12)-H(12B)	109.5
C(6)-C(12)-H(12C)	109.5
H(12A)-C(12)-H(12C)	109.5
H(12B)-C(12)-H(12C)	109.5
C(3)-O(1)-C(1)	106.5(3)
C(2)-O(2)-C(3)	108.3(2)

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$). The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2 a^{*2} U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	77(2)	87(2)	58(2)	-5(2)	7(1)	-12(2)
C(2)	67(2)	60(2)	72(2)	-14(1)	6(1)	-6(1)
C(3)	60(2)	57(1)	52(2)	9(1)	4(1)	-15(1)

C(4)	53(2)	92(2)	68(2)	-8(2)	19(1)	-6(1)
C(5)	63(2)	61(2)	66(2)	-18(1)	17(1)	2(1)
C(6)	54(1)	46(1)	44(1)	-4(1)	8(1)	-5(1)
C(7)	65(2)	52(1)	64(2)	-2(1)	9(1)	-10(1)
C(8)	87(2)	70(2)	65(2)	10(1)	14(1)	-20(2)
C(9)	57(2)	76(2)	47(2)	-6(1)	11(1)	-3(1)
C(10)	48(1)	45(1)	53(1)	-3(1)	7(1)	4(1)
C(11)	68(2)	43(1)	65(2)	-1(1)	5(1)	-3(1)
C(12)	83(2)	86(2)	51(2)	1(1)	1(1)	-19(2)
O(1)	69(1)	66(1)	66(1)	12(1)	-3(1)	-11(1)
O(2)	90(1)	96(1)	69(1)	16(1)	-1(1)	-51(1)
O(3)	103(2)	118(2)	55(1)	-21(1)	22(1)	-20(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3)

	x	y	z	U(eq)
H(1A)	13235	4327	9502	90
H(1B)	11224	4799	9428	90
H(2A)	12317	5889	8399	81
H(2B)	14070	5295	8216	81
H(4A)	11794	3451	6091	84
H(4B)	10089	3973	5307	84

H(5A)	9219	2428	5461	75
H(5B)	9564	2518	6823	75
H(7A)	4459	2371	6064	73
H(7B)	6278	1745	6194	73
H(8A)	4934	2243	8038	89
H(8B)	7114	1981	8152	89
H(10)	5583	4173	6655	59
H(11A)	7982	5070	6379	72
H(11B)	8334	4999	7743	72
H(12A)	6852	3903	4492	112
H(12B)	4810	3606	4663	112
H(12C)	6144	2915	4197	112

Table 1. Crystal data and structure refinement for **270**.

Empirical formula	C_{13} H_{18} O_4 S	
Formula weight	270.33	
Temperature	120(2) K	
Wavelength	1.54178 Å	
Crystal system	?	
Space group	?	
Unit cell dimensions	a = 10.0570(2) Å	α= 90°.
	b = 10.53490(10) Å	β= 100.6450(10)°.
	c = 12.3103(2) Å	γ = 90°.
Volume	1281.82(4) $Å^3$	
Z	4	
Density (calculated)	1.401 Mg/m^3	
Absorption coefficient	2.299 mm^{-1}	
F(000)	576	

Crystal size	0.28 x 0.22 x 0.16 mm^3
Theta range for data collection	6.71 to 66.46°.
Index ranges	-8<=h<=8, -12<=k<=12, -13<=l<=10
Reflections collected	4349
Independent reflections	1506 [R(int) = 0.0410]
Completeness to theta = 66.46°	66.7 %
Max. and min. transmission	0.7099 and 0.5654
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1506 / 0 / 164
Goodness-of-fit on F^2	1.165
Final R indices [I>2sigma(I)]	R1 = 0.0772, wR2 = 0.2539
R indices (all data)	R1 = 0.0841, wR2 = 0.2853
Largest diff. peak and hole	0.555 and -0.525 e.$Å^{-3}$

The hydrogen atoms were fixed as riding models.

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3). U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	2159(6)	4630(4)	4731(4)	27(2)
C(2)	3725(6)	3030(4)	5069(4)	27(2)
C(3)	4653(7)	2923(5)	4239(4)	35(2)
C(4)	3703(6)	2633(4)	3142(4)	27(2)
C(5)	2554(5)	1815(4)	3459(4)	20(2)
C(6)	2329(6)	2463(4)	4533(4)	21(2)
C(7)	1572(6)	1694(4)	5267(4)	24(2)
C(8)	2193(6)	365(4)	5485(4)	26(2)
C(9)	2210(6)	-308(4)	4406(4)	23(2)
C(10)	3103(6)	450(4)	3725(4)	25(2)
C(11)	1297(6)	1800(5)	2564(4)	29(2)
C(12)	2332(7)	-818(6)	7077(5)	40(2)
C(13)	3467(7)	148(6)	7220(4)	37(2)
O(1)	3400(4)	4353(3)	5271(3)	30(1)
O(2)	1529(4)	3627(3)	4238(3)	28(1)
O(3)	1415(4)	-321(3)	6146(3)	28(1)

O(4)	3534(4)	420(3)	6113(3)	26(1)
S(1)	1510(2)	6059(1)	4701(1)	31(1)

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