UNIVERSITY OF SUSSEX

STUDIES TOWARDS THE TOTAL SYNTHESIS OF ASTERISCANOLIDE

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I dedicate this thesis to my wonderful parents, Rosa Martha Barrera Bravo and Francisco Javier Jiménez Villarreal, with love and eternal gratitude for their guidance, constant belief, and endless support that made me the person I am today.

"I am among those who think that science has great beauty. A scientist in his laboratory is not only a technician: he is also a child placed before natural phenomena which impress him like a fairy tale."

Marie Sklodowska Curie

STATEMENT

The work described in this thesis was carried out in the Department of Chemistry at the University of Sussex between October 2006 and the present date. Unless otherwise stated, it is the work of the author and has not been submitted in support of any other degree at this, or any other University.

Signature:

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Rosa Martha Jiménez Barrera

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ABBREVIATIONS AND SYMBOLS

Å	Angstrom
ABCN	1,1'-Azobis(cyclohexanecarbonitrile)
Ac	Acetyl
AIBN	2,2'-Azobis(2-methylpropionitrile)
Amberlite® IRA-900-NO_2^-	Styrene-divinylbenzene ammonium anion-exchange resin
Amberlyst® A-21	Styrene-divinylbenzene tertirary amino anion-exchange resin
aq	Aqueous solution
Bn	Benzyl
B. P.	Boiling point
br	Broad
Bu	Butyl
ºC	Degrees Celsius
calc.	Calculated
cat	Catalytic amount
CBS	Corey-Bakshi-Shibata catalyst
Conc.	Concentrated
cm	Centimetre
CM	Cross metathesis
COD	Cyclooctadiene
Cp	Cyclopentadienyl
CSA	Camphorsulfonic acid
d	Doublet
Darvon	4-Dimethylamino-3-methyl-1,2-diphenyl-2-butanol
dba	Dibenzylideneacetone
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DIBAL-H	Diisobutylaluminium hydride
DIEA	Diisopropylethylamine
DMAP	*N*,*N*-Dimethylaminopyridine
DME	Dimethyl ether

DMF	*N*,*N*-Dimethylformamide
DMP	Dess-Martin Periodinane
DMSO	Dimethyl sulfoxide
Dowex® 50W-X8	Polystyrene sulfonic acid cation-exchange resin
d.r.	Diastereomeric ratio
d.s.	Diastereomeric selectivity
E	German; entgegen = opposite
ee	Enantiomeric excess
EI	Electron impact
EIMS	Electron impact mass spectrometry
eq	Number of molar equivalents
ESI	Electro-spray ionization
Et	Ethyl
g	Gram(s)
gem-	*geminal*-
h	Hour(s)
HOMO	Highest occupied molecular orbital
HMPA	Hexamethylphosphoramide
HRMS	High resolution mass spectrometry
Hz	Hertz
HWE	Horner-Wadsworth-Emmons reaction
hν	Irradiation
i-	*iso*-
IBX	*o*-Iodoxybenzoic acid
INOC	Intramolecular nitrile oxide-olefin cycloaddition
ISOC	Intramolecular silyl nitronate-olefin cycloaddition
IR	Infrared spectroscopy
J	Coupling constant
KHMDS	Potassium bis(trimethylsilyl)amide
LA	Lewis acid
LAH	Lithium aluminium hydride

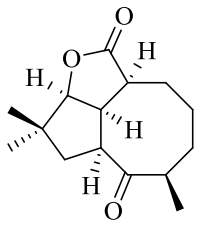
LDA	Lithium diisopropylamide
LHMDS	Lithium bis(trimethylsilyl)amide
LICA	Lithium cyclohexylisopropylamide
LRMS	Low resolution mass spectrometry
LUMO	Lowest unoccupied molecular orbital
m	Multiplet
m-	*meta*- Substituted
M	Molar concentration
m-CPBA	*m*-Chloroperbenzoic acid
Me	Methyl
mg	Milligram(s)
MHz	Megahertz
min	Minute(s)
mL	Millilitre(s)
mol	Mole(s)
mol%	Mole percent
mmol	Millimole(s)
MMPP	Magnesium monoperoxyphthalate
M. P.	Melting point
Ms	Methanesulfonyl
MS	Molecular sieves
MW	Microwave reactor
n- / N	Normal
N/A%	Not applicable percent yield
NMO	*N*-Methylmorpholine-*N*-oxide
NMR	Nuclear magnetic resonance
Oxone®	Potasium peroxymonosulfate
p-	*para*- Substituted
PCC	Pyridinium chlorochromate
Ph	Phenyl
pH	Potential hydrogen

PMB	*p*-Methoxybenzyl
ppm	Parts per million
Pr	Propyl
Proton-sponge®	1,8-Bis(dimethylamino)naphthalene
psi	Pounds per square inch
p-TSA	*p*-Toluenesulfonic acid
py	Pyridine
q	Quartet
quant.	Quantitative yield
RaNi	Raney Nickel
RCM	Ring-closing metathesis
Red-Al®	Sodium bis(2-methoxyethoxy)aluminium hydride
ROM	Ring-opening metathesis
RT	Room temperature
s	Singlet
s-	*sec*-
SEM	2-(Trimethylsilyl)ethoxymethyl
SM	Starting material
SOMO	Singly occupied molecular orbital
t	Triplet
t- / *tert*-	Tertiary
TBAF	Tetra-*n*-butylammonium fluoride
TBAT	Tetra-*n*-butylammonium (triphenylsilyl)difluorosilicate
TBS	*tert*-Butyldimethylsilyl
TBTH	Tributyltin hydride
TES	Triethylsilyl
Tf	Trifluoromethanesulfonyl
TFAA	Trifluoroacetic anhydride
TFE	Trifluoroethanol
THF	Tetrahydrofuran
THPA	Tetrahydrophthalic anhydride

TLC	Thin layer chromatography
TMEDA	*N*, *N*, *N*', *N*'-Tetramethylethylenediamine
TMS	Trimethylsilyl
Tol	Toluene (ligand)
TPAP	Tetra-*n*-propylammonium perruthenate
trig	Trigonal
Ts	Toluene sulfonyl
w	Weak
W	Watts
Z	German; zusammen = together
μL	Microlitre(s)
δ	Chemical shift
Δ	Heat under reflux

SUMMARY

The cyclooctane sesquiterpene lactone, asteriscanolide **1** (**Figure 1**), has attracted considerable interest in the chemical literature since San Feliciano and colleagues[1] first reported its isolation from *Asteriscus aquaticus L.* To date, no pharmaceutical applications have been found for **1**. However, the challenge offered by the construction of its cyclooctanoid core represents an important target for the development of methods directed towards the preparation of other related eight-membered ring-containing terpenoids with more interesting biological properties.



1

Figure 1. Asteriscanolide.

This thesis illustrates an investigation into the total synthesis of natural product asteriscanolide **1**. Following up on the previous work established by Marsh,[2] an approach to **1** was designed, seeking to build a suitable framework for an intramolecular [3 + 2] nitrile oxide-olefin cycloaddition (INOC) as the pivotal synthetic step to assemble the medium-sized ring.

The INOC strategy was extensively investigated. As this remained unsuccessful, the investigation was extended to various other intramolecular strategies, including intramolecular [3 + 2] silyl nitronate-olefin cycloaddition (ISOC), samarium(II) iodide-mediated cyclisation, radical-mediated cyclisation, and nitronate anion-epoxide cyclisation, which identified certain limitations that would hinder further progress. To this end, a second generation towards **1** incorporating ring-closing metathesis (RCM) and intermolecular nitronate anion-epoxide addition was designed. A detail discussion of the results is contained within.

CHAPTER 1

INTRODUCTION

1.1 Natural Products

Over the centuries, the scientific community have always been searching for natural products with biological activities that can contribute in the discovery and design of potential drugs for the treatment or prevention of life-threatening human diseases.[3,4]

Natural compounds can be obtained from tissues of both terrestrial and marine sources, including plants, bacteria, fungi, vertebrates, and invertebrates.[4,5] Thanks to the biodiversity of nature, a wide variety of natural products have been found, each of them with unique molecular architecture.[3,6]

The separation methodology of the components of a mixture has been practised since the beginning of chemical science.[7] However, the isolation and purification of natural origin products by traditional methods are frequently limited by a number of factors. Firstly, extraction of highly complex materials often involves expensive and time-consuming procedures. Secondly, unstable molecules may be sensitive to air, thermal, light or pH conditions. Finally, large-scale production of natural products is constrained due insufficient natural resources.[7,8]

Organic chemistry plays a fundamental role in the study of synthesising naturally occurring products and their related analogues. Nonetheless, it was not until the 1950s when medicinal synthetic compounds were equally competing with their natural counterparts.[8] Recent studies have revealed that the key for discovering new drugs is to explore and understand nature at a molecular level, and combine it with the knowledge of organic synthesis, creating chemical concepts and implementing theoretical principles.[8,9]

Although remarkable progress has been made, many of these natural products and their derivatives are currently in screening or clinical testing.[6] Attention must be paid in the development of novel synthetic tools to obtain important bioactive molecules.

1.2 Cyclooctanoids

1.2.1 The Synthetic Challenge of Cyclooctanoid Systems

Great interest and activity in the synthesis of compounds bearing medium-sized rings in their structure, particularly cyclooctanoids, has increased considerably during the last three decades due to their presence found in many biologically active natural products.[10-12] The construction of eight-membered rings from acyclic precursors is considered to be an interesting challenge for synthetic organic chemistry since it involves several aspects that should be taken into consideration.[10-17] In terms of the ring size, the ring closure of cyclooctanes by intramolecular cycloaddition reactions has demonstrated to be often more difficult to prepare than smaller or even larger cycles.[11,14] This can be attributed to the high degree of strain and the transannular interactions develop unfavourable entropic and enthalpic effects, thus impeding the cyclisation to occur.[15-18] Consequently, the synthetic strategies commonly used for the formation of other ring sizes, cannot always be applied on eight-membered ring systems.[10,11] Indeed, the current synthetic methodology that has been developed for eight-membered ring compounds has only been aimed for specific targets, but a general pattern for their preparation still remains a mystery.[18]

1.2.2 Conformations of Eight-Membered Rings

There are various possible energetically stable conformations of the eight-membered ring (**Figure 2**). The interconversion of these forms depends directly on the nature of the substituents.[11,18]

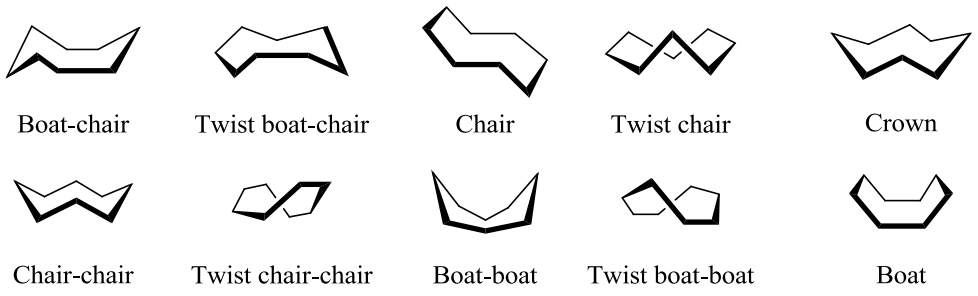
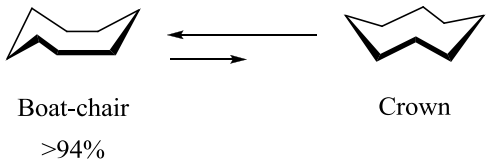


Figure 2. Conformations of eight-membered rings.

After exhausting studies with different molecules containing the eight-membered ring system, including spectroscopic methods, X-ray crystallography, and molecular mechanics calculations, it has been clear that the most stable conformation is predominately the boat-chair conformation, which is in equilibrium with the crown conformation (**Scheme 1**).[11,20] The boat-chair conformation, which bears two eclipsed ethane linkages, tends to reduce the transannular nonbonded repulsions, and has the lowest-energy torsional strain.[11,19]



Scheme 1. Equilibrium of the eight-membered ring.

1.2.3 Strategies for the Formation of Cyclooctanoids

There are several strategies that can be used for the synthesis of eight-membered carbocycles. These strategies fall into three main categories according to the chemical transformation in which ring is generated: fragmentation, ring expansion, and C-C bond formation reactions.[11] Among these synthetic strategies, C-C bond formation reactions offers the possibility of creating a new ring in one step, while fragmentation and ring expansion reactions already requires a pre-existing ring. The direct formation of cyclooctanoid compounds can be accomplished through C_1-C_8 ring closure cyclisations, cycloadditions, and coupling reactions.[10,11]

Cycloaddition reactions, especially higher-order cycloaddition reactions, are one of the most attractive and versatile methods for the synthesis of carbocyclic systems.[10] These types of reactions have become an efficient route to obtain complex cyclooctanoids with extensive functionality and good control of stereocentres in a single step.[12,18]

1.2.4 The Occurrence of Cyclooctanoids in Nature

Frequently, naturally occuring cyclooctanoids present the eight-membered ring fused or bridged to other smaller rings, and can also contain double bonds or other

group functionalities. The majority of these polycyclic cyclooctanes are located in the natural class of the terpenes, lignans, and some pigments.[10,11] In nature, there are over a hundred products that contain the eight-membered ring.[10,13] These have been found and isolated from terrestrial plants, marine organisms, pathogenic fungi, and insects.[10] Illustrative examples of selected cyclooctanoids widely distributed in nature are shown in **Table 1**[I]. Terpene ceroplastol **2** is found in the wax secreted by certain species of scale insect *Ceroplastes* to avoid desiccation.[21] Most cyclooctanoid lignans are found in plants, like schizandrin **3**, a dibenzocyclooctadiene lignan isolated from the fruit seeds of *Schizandra chinensis* Baill.[22] In the class of pigments, a unique cyclooctadiene red indole chlorophyte pigment, caulerpin **4**, can be obtained from the green algal genus *Caulerpa*.[23]

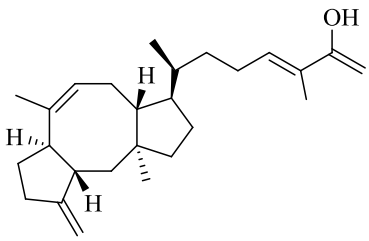
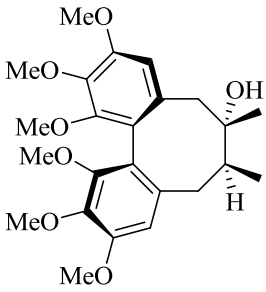
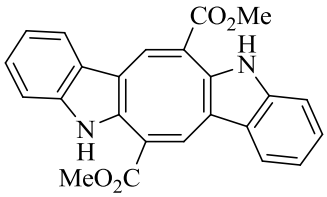
Terpene	**Lignan**	**Pigment**
		
Ceroplastol **2**	Schizandrin **3**	Caulerpin **4**
		
Ceroplastes rusci	*Schizandra chinensis*	*Caulerpa racemosa*

Table 1. Selected examples of terpene, lignan, and pigment cylooctanoids in nature.

[I] Image sources: In order from left to right http://test2macroinstantes.blogspot.com/2007/04/cochinilla.html, http://www.dinophoto.sk/medicinal.htm, and http://www.reefcorner.com/SpecimenSheets/caulerpa.htm Used with kind permission of photographers Javier Gállego, Dionyz Dugas, and Ken Hahn, respectively.

1.3 Terpenes

1.3.1 Terpene Definition and the Isoprene Rule

Terpenes, also referred as isoprenoids, are a large class of cyclic and acyclic natural products, and their basic structure is based on the repetition of isoprene (2-methyl-1,3-butadiene) units (**Figure 3**). Following the isoprene rule,[24] terpenoids are divided into families depending on the number of isoprene residues from which they are biologically derived; sometimes certain atoms can be added or lost.[25] The general molecular formula is $(C_5H_8)_n$ where n is the number of linked isoprene units. For example, C_5-hemiterpenes are made from one isoprene unit, C_{10}-monoterpenes consist of two isoprene units, C_{15}-sesquiterpenes contain three, C_{20}-diterpenes four, C_{25}-sesterterpenes five, C_{30}-triterpenes six, C_{40}-tetraterpenes have eight, and molecules with more than eight isoprene units are named polyterpenes.

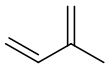


Figure 3. Isoprene.

1.3.2 Ring Systems of Cyclooctanoid Terpenes

The most notable cyclooctanoid terpene ring systems in the category of the sesquiterpenoids are precapnellane **5**, asteriscane **6**, and neolemnane **7**. From the family of the diterpenoids, taxane **8** has received the most attention while rare C_{20}-diterpene systems such as basmane **9** and crenulane **10** have also been identified. In addition, there are numerous types of diterpenes from the polycyclic fusicoccane **11**, and many can be found in higher plants. Members of the sesteterpenoid group mainly have structures characterised by functionalised 5-8-5 tricycle ring system. The ophiobolane **12** skeleton belongs to the family of the C_{25}-sesteterpenoids. Numbering sequence of these ring systems are shown (**Figure 4**).[11]

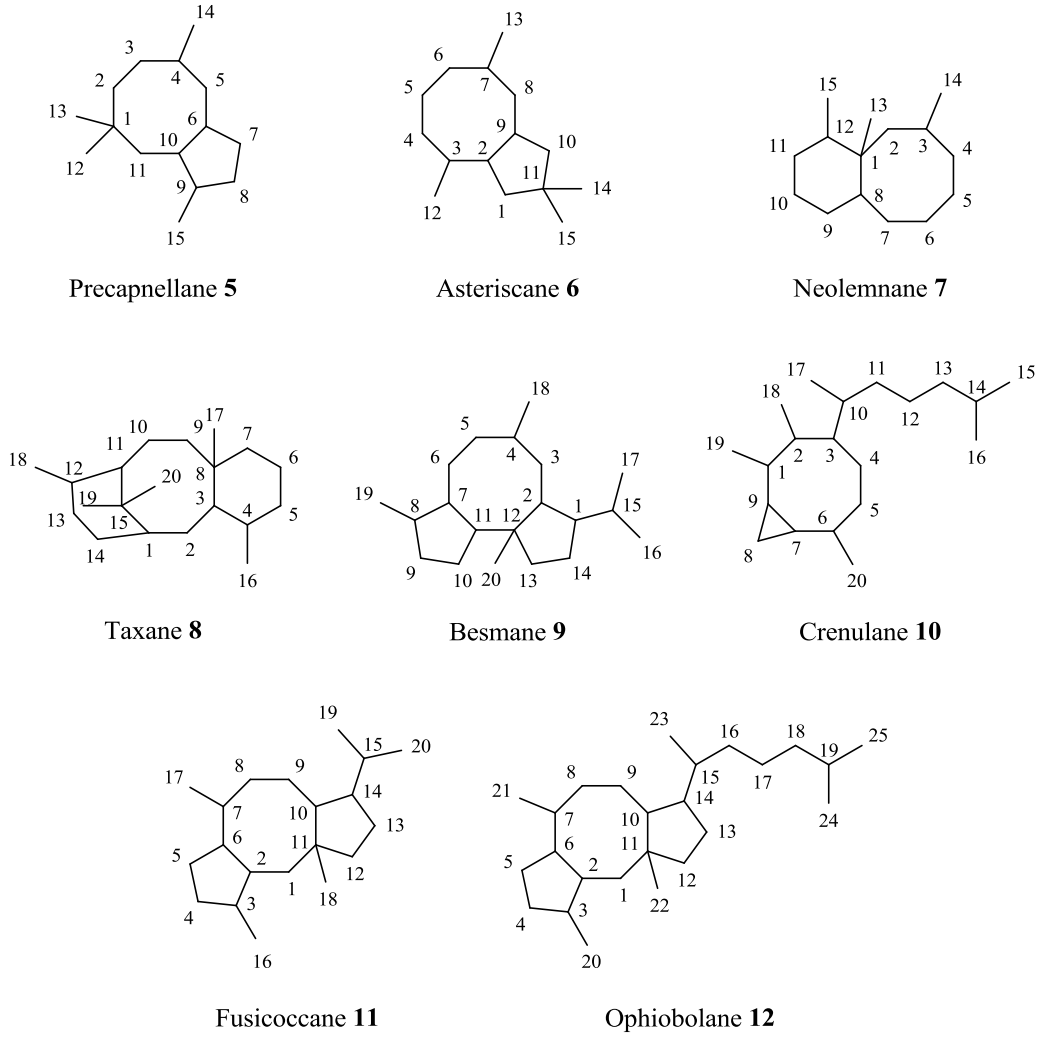


Figure 4. Common ring systems of cyclooctanoid terpenes.

1.3.3 Biological Activities of Cyclooctanoid Terpenes

Presently, many terpenoids possessing the eight-membered carbocycle in their molecular system exhibit potential biological applications, from anticancer agents, to anti-fungal and antibiotics. Many are utilised in the agricultural and pharmaceutical industry, and others have been very useful as product targets for a significant number of synthetic endeavours. **Table 2** provides a list of important biological activities found on different cyclooctanoid terpenes.

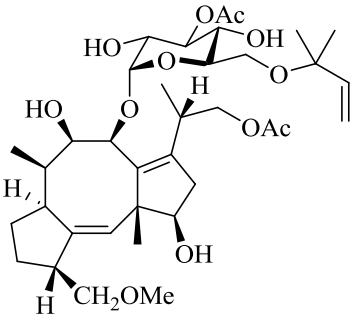
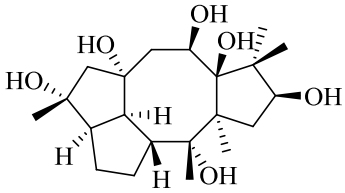
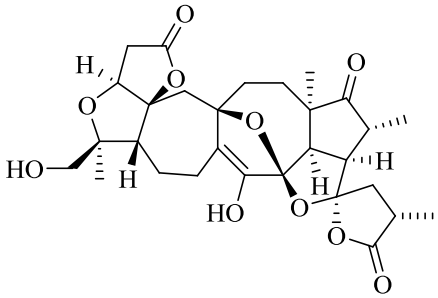
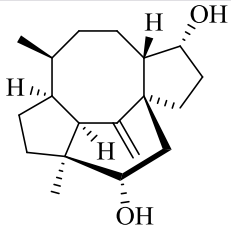
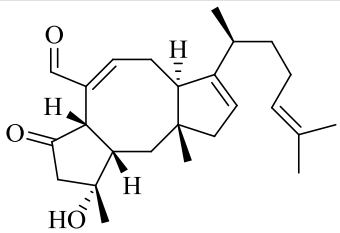
Terpene family	Cyclooctanoid terpene	Biological activity
Diterpene	 Fusicoccin A **13**	Phytotoxic[26]
Diterpene	 Kalmanol **14**	Cardiotoxic[27]
Triterpene	 Lancifodilactone G **15**	Anti-HIV[28]
Diterpene	 Longipenol **16**	Termite defence secretion[29]
Sesteterpene	 Ophiobolin M **17**	Nematocidal[30]

Table 2. Biological activities of selected cyclooctanoid terpenes.

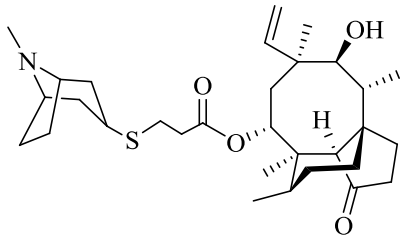
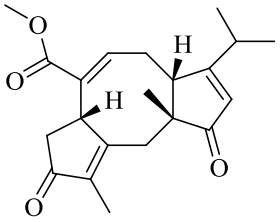
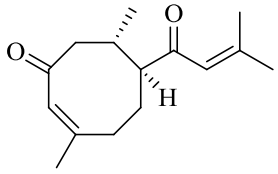
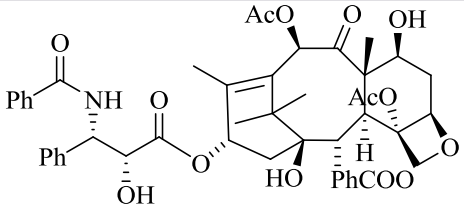
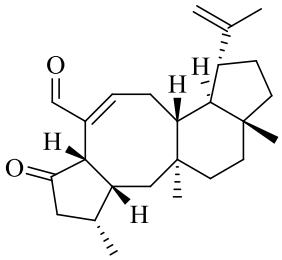
Diterpene	 Retapamulin **18**	Antibacterial[31]
Diterpene	 Serpendione **19**	Antihypertensive[32]
Sesquiterpene	 Spartidienedione **20**	Antiinflamatory and antipyretic[33]
Diterpene	 Taxol® **21**	Anticancer[34]
Sesteterpene	 Variecolin **22**	Angiotensin II antagonist and immunosuppressive[35]

Table 2. Biological activities of selected cyclooctanoid terpenes (continuation).

1.4 Cyclooctane Sesquiterpenoids

1.4.1 Fused Ring Systems of Cyclooctane Sesquiterpenoids

Most of the natural sesquiterpenes bearing eight-membered rings have been isolated from marine sources. Their molecular structure generally presents fused cyclooctanes, in many cases incorporating bicyclic 5,8-fused ring systems. Dactylol **23**,[36,37] poitediol **24**,[38] and precapnelladiene **25**[39] are among the first to be synthesised of this kind of cyclooctanoid sesquiterpenes. More recently, less common 6,8-fused ring systems such as neolemnalyl acetate **26**,[40] and parvifoline **27**[41] have also been synthesised (**Figure 5**).

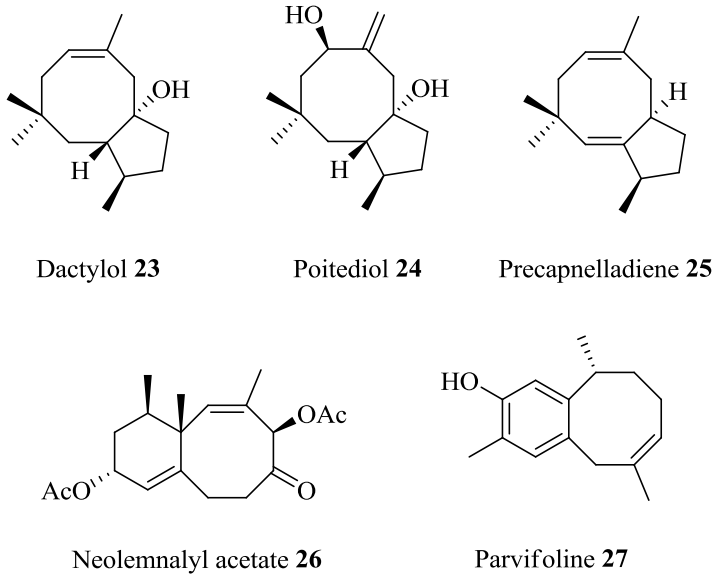


Figure 5. Synthesised cyclooctane sesquiterpenoids.

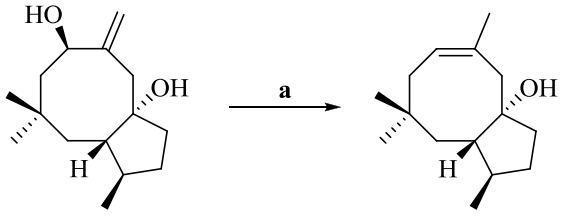
1.4.2 Selected Synthesis of 5,8-Fused Ring System Sesquiterpenes

1.4.2.1 Dactylol **23**

Dactylol **23** was first isolated from the Caribbean sea hare known as *Aplysia dactylomela*[42] (**Figure 6**[II]) and later in the red seaweed *Laurencia poitei*.[43]

Figure 6. *Aplysia dactylomela.*

In 1985, Gadwood[36] converted (±)-dactylol **23** from synthetic poitediol **24** under Birch conditions[44] (**Scheme 2**).



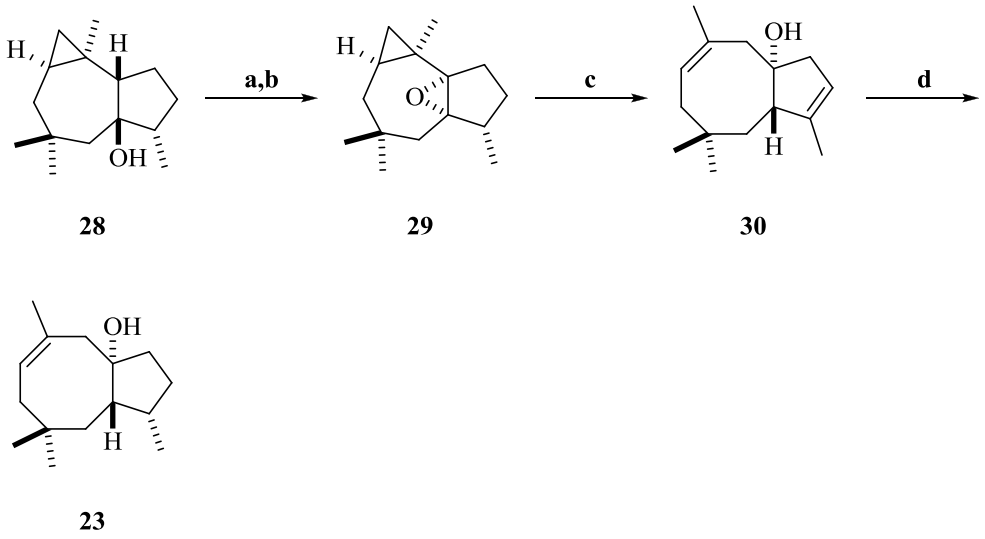
24 **23**

Reagents and conditions: **(a)** Na-liquid NH_3, EtOH, 70%.

Scheme 2. Gadwood's conversion of poitediol **24** to dactylol **23**.

[II] Image source: http://seaslugs.free.fr/nudibranche/a_aply_dactylomela.htm Used with kind permission of Philibert Bidgrain.

During the same year, Matsumoto's group[37] converted africanol **28** to sesquiterpene **23** through a formal 1,2-shift of a methyl group (**Scheme 3**). Dehydration of **28**, followed by epoxidation of the resultant mixture of two tetrasubstituted olefins gave oxirane **29**, which was subsequently treated with boron trifluoride diethyl etherate to afford *trans*-fused alcohol **30**. Finally, selective hydrogenation on the five-membered ring formed dactylol **23**.

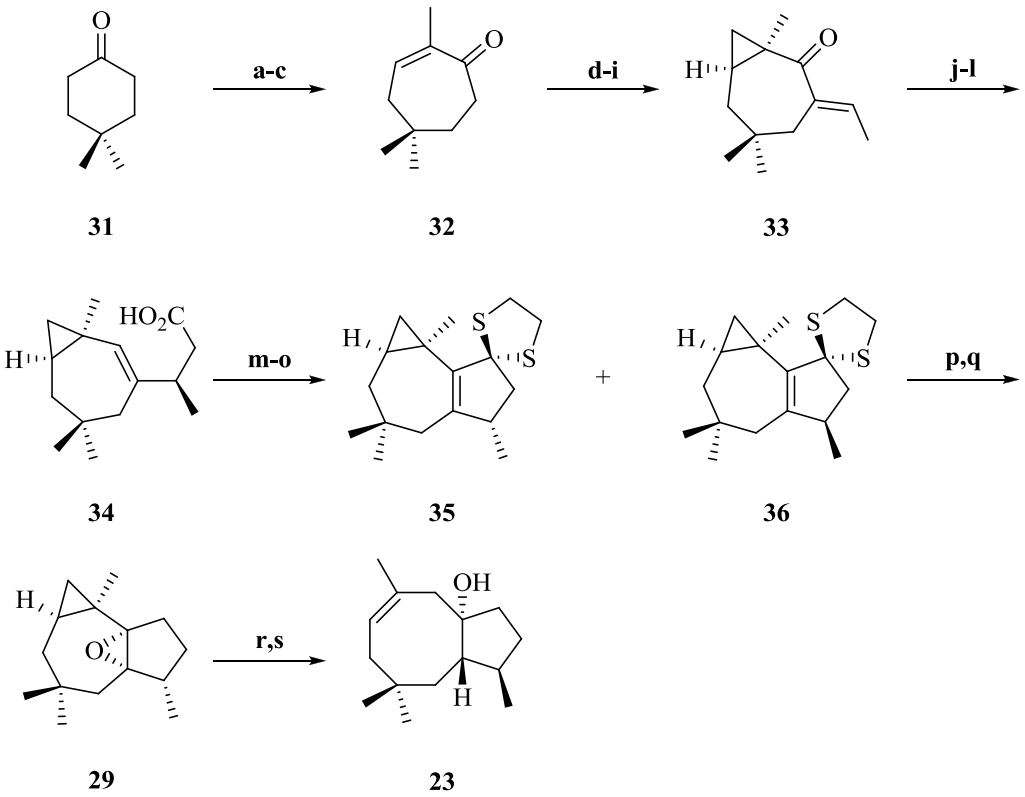


28 **29** **30** **23**

Reagents and conditions: **(a)** $POCl_3$, py, 70 ºC → 90 ºC, 1 h, (1:1); **(b)** *m*-CPBA, CH_2Cl_2, RT, 5 min, 42% (over two steps); **(c)** $BF_3{\cdot}OEt_2$, -10 ºC, 30 min, 18%; **(d)** H_2/PtO_2, EtOH, RT, 9 h, 90%.

Scheme 3. Matsumoto's conversion of africanol **28** to dactylol **23**.

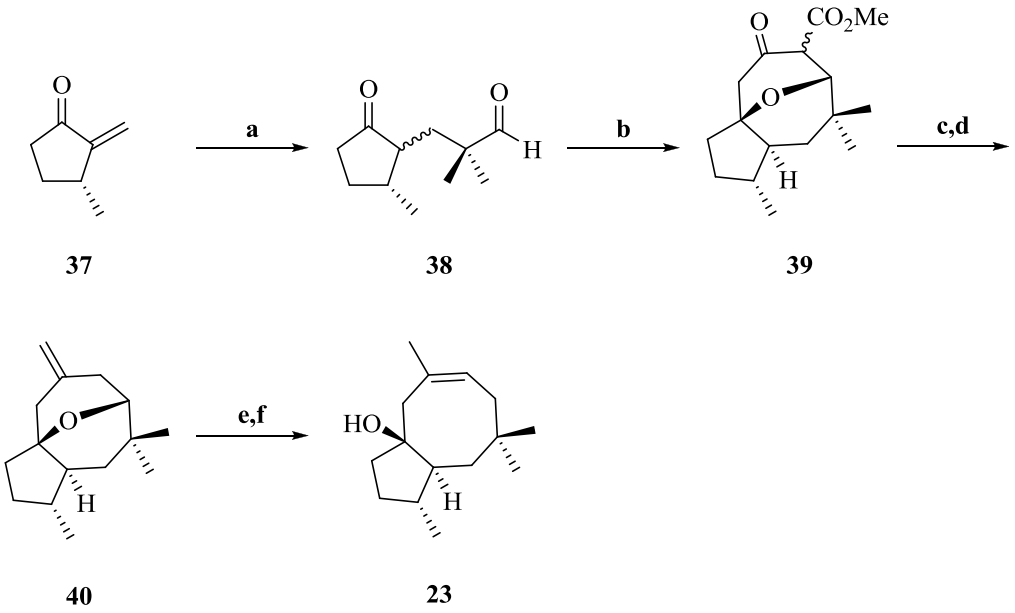
Later that year Paquette and colleagues[45] published a formal total synthesis of C_{15}-dactylol **23** (**Scheme 4**). Ring expansion of cyclohexanone **31** by the Saegusa method[46] gave rise to cycloheptenone **32**, which was subjected to a Simmons-Smith cyclopropanation.[47,48] Aldol condensation, acetylation, and β-elimination afforded **33**. Reduction of **33** with the Luche reagent[49] and subsequent heating of the resulting β-alcohol with triehtylorthoacetate, followed by saponification produced carboxylic acid **34**. The corresponding acid chloride was prepared and exposed to stannic chloride, generating a mixture of cyclopentenones, which under standard dithioketalisation procedure, gave a favorable ratio of **35** and **36**. Sequential Raney nickel desulfurization and epoxidation was performed to yield key intermediate **29**, as synthesised by Matsumoto's research group.[37]



Reagents and conditions: **(a)** Et_3N, TMSCl; **(b)** *n*-BuLi, Cl_2CHCH_3; **(c)** PhMe, Δ, 71% (over three steps); **(d)** $HOCH_2CH_2OH$, H^+, 83%; **(e)** C_2H_5ZnI, CH_2I_2, 92%; **(f)** H_3O^+, quant.; **(g)** LICA, CH_3CHO, 79%; **(h)** Ac_2O, Et_3N, 96%; **(i)** DBU, PhH, Δ, 93%; **(j)** $NaBH_4$, $CeCl_3{\cdot}7H_2O$; **(k)** $CH_3C(OC_2H_5)_5$, propionic acid, Δ, 72%; **(l)** KOH; **(m)** $(COCl)_2$; **(n)** $SnCl_4$, $ClCH_2CH_2Cl$, 0 ºC, 96%; **(o)** $HSCH_2CH_2SH$, TsOH, **35**/**36** (83:17); **(p)** RaNi, EtOH; **(q)** *m*-CPBA, 27% (over three steps); **(r)** $BF_3{\cdot}Et_2O$, 0 ºC; **(s)** H_2, PtO_2, EtOH.

Scheme 4. Paquette's total synthesis of dactylol **23**.

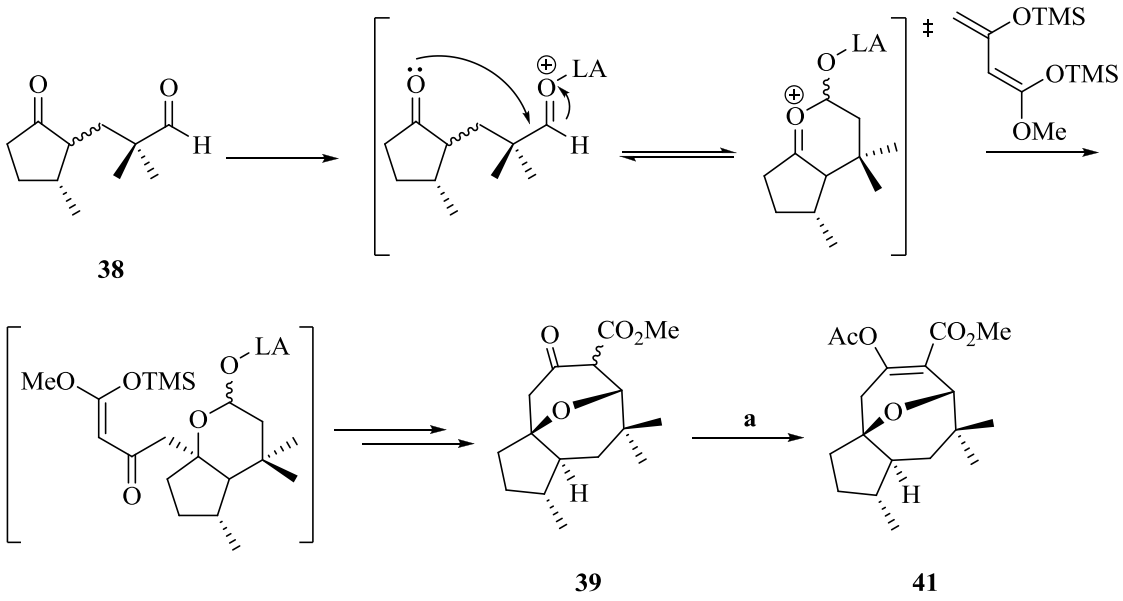
Molander and Eastwood[50] developed the total synthesis of (+)-dactylol **23** *via* a Novel [3 + 5] annulation (**Scheme 5**). Cyclopentenone **37** with a trimethylsilyl enol ether in the presence of a mixed Lewis acid system formed the dicarbonyl compound **38**. Annulation of **38** using β-dicarbonyl-1,3-dianionic equivalent led to a mixture of keto-enol tautomers of **39**. Decarboxylation of **39** and a subsequent methylenation with Tebbe's reagent[51] gave access to **40**, which was subjected to an isomerisation procedure. Target (+)-dactylol **23** was obtained when mixed olefins were treated with a dissolving metal reduction.



Reagents and conditions: **(a)** $(CH)_2C{=}CHOSiMe_3$, $TiCl_4$, $Ti(O\textit{i}\text{-}Pr)_4$, CH_2Cl_2, -95 ºC, 83%; **(b)** $CH_2{=}C(OTMS)CH{=}C(OTMS)OMe$, $TrSbCl_6$, CH_2Cl_2, -78 ºC, 77%; **(c)** NaCl, DMSO, H_2O, 140 ºC, 84%; **(d)** $Cp_2TiClCH_2Al\ Me_2$, THF, 0 ºC, 92%; **(e)** $RhCl_3{\cdot}3H_2O$, 70 ºC, 96%; **(f)** Li, $H_2N(CH_2)_2NH_2$, DME, 40 ºC, 25%.

Scheme 5. Molander and Eastwood's total synthesis of dactylol **23**.

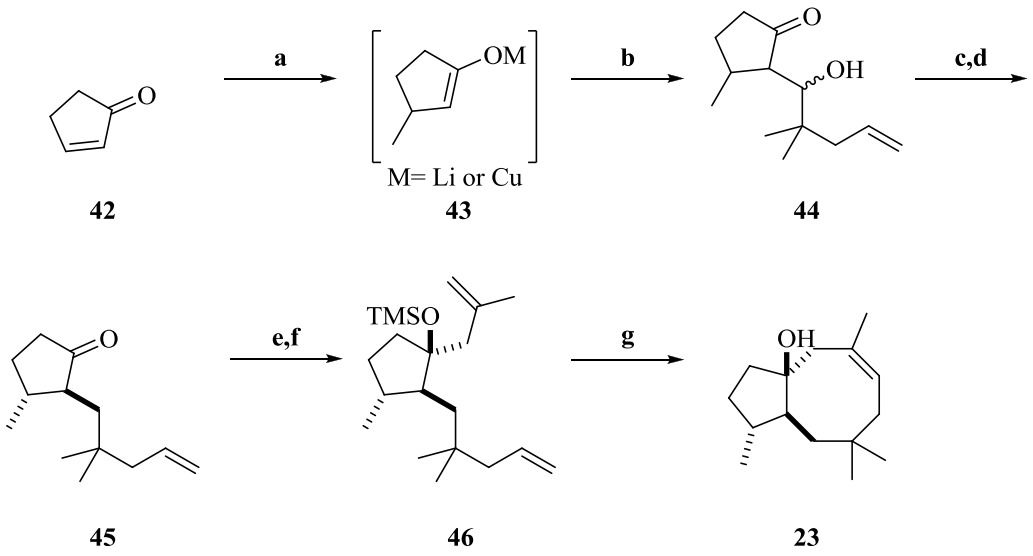
The stereoselectivity of this annulation reaction can be explained by the unprecedented neighboring group participation mechanism, involving a cylic oxocarbenium ion intermediate that served as a template for diastereoselective carbon-carbon bond formation. Confirmation of the complete regio- and stereoselectivity was demonstrated by the functionalisation of **39** to furnish the single enol acetate **41** (**Scheme 6**).



Reagents and conditions: **(a)** Ac_2O, DMAP, py, 90%.

Scheme 6. Molander and Eastwood's synthesis of precursors **39** and **41**.

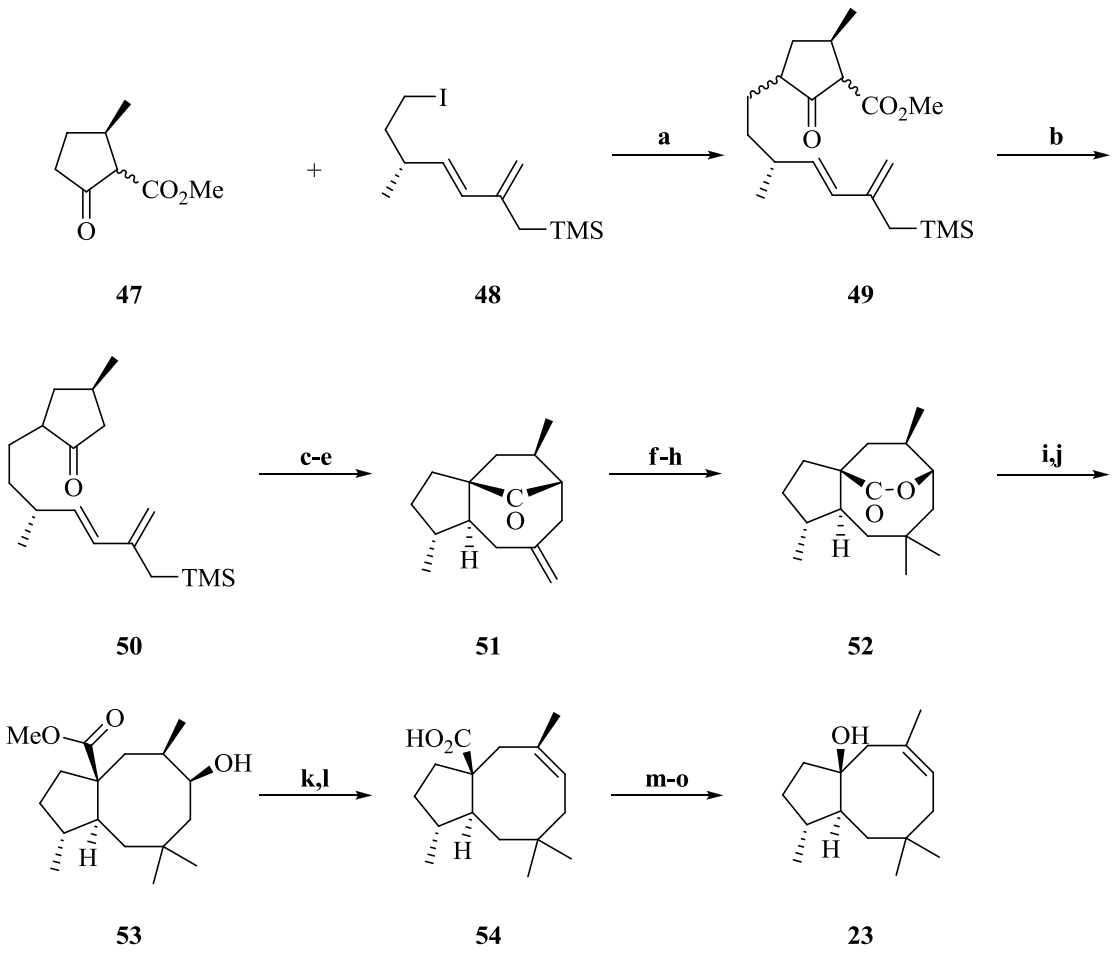
Fürstner and Langemann[52] developed a concise total synthesis of racemic dactylol **23** featuring a ring-closing metathesis as the key step for the preparation of the eight-membered ring (**Scheme 7**). Reaction of cyclopentenone **42** with lithium dimethyl cuprate, followed by the addition of commercially available 2,2-dimethyl-4-pentenal in order to trap nonequilibrating enolate **43**, gave **44**. Dehydration, and a subsequent chemo- and diastereoselective hydrogenation led to 1,2-*trans*-ketone **45**, which was converted to the protected tertiary alcohol **46** bearing a methallyl side chain. Cyclisation of the silylated alcohol **46** by RCM was accomplished using Schrock's catalyst.[53] Workup of **46** with an aqueous solution of tetra-*n*-butylammonium fluoride gave access to (±)-dactylol **23** in 17% overall yield.



Reagents and conditions: **(a)** MeLi, CuI, Bu_3P, Et_2O, -78 ºC (1 h) → -40 ºC (2.5 h); **(b)** CH_2=$CHCH_2C(CH_3)_2CHO$, -78 ºC → RT, 77%; **(c)** CH_3SO_2Cl, DMAP, CH_2Cl_2, 35 ºC, 18 h, 85%; **(d)** Bu_3SnH, $ZnCl_2$, $Pd(PPh_3)_4$, THF, RT, 20 min, 83%; **(e)** methallyl bromide, Mg-graphite, THF, 65 ºC, 30 min; $CeCl_3$, -78 ºC, 2 h, 80%; **(f)** $(Me_3Si)_2NH$, acetyl chloride, DMAP, 93%; **(g)** molybdenum carbene (3 mol%), hexane, 55 ºC, 3 h; aq TBAF, THF, 50 ºC, 3 h, 92%.

Scheme 7. Fürstner and Langemann's total synthesis of dactylol **23**.

In 2000, Harmata and Rashatasakhon[54] illustrated the synthesis of (+)-**23** incorporating an intramolecular [4 + 3] cycloaddition reaction (**Scheme 8**). Alkylation of the enantiomerically pure ketoester **47** with iododiene **48** gave the cycloaddition precursor **49**. Removal of the carbomethoxy group *via* a Krapcho procedure[55,56] afforded ketone **50**. Chlorination of the lithium enolate of **50** with triflyl chloride, exposure of the resultant chloroketone to triethylamine in a 1:1 mixture of trifluoroethanol and diethyl ether, and addition of tosic acid afforded cycloadduct **51**. The major isomer of **51** underwent a cyclopropanation using the Simmons-Smith methodology,[47,48] which after a Baeyer-Villiger reaction[57] and hydrogenation procedure formed **52**. Hydrolysis of **52** and esterification of the corresponding hydroxy acid generated hydroxy ester **53**. The bicylic ester **54** was obtained after installation of the double bond, followed by saponification. Completion of the synthesis of (+)-**23** was achieved through reduction of the resulting acid chloride of **54**.



Reagents and conditions: **(a)** NaH; *n*-BuLi, 70%; **(b)** KCN, DMSO, Δ, 94%; **(c)** LDA, TfCl; **(d)** Et_3N: TFE/Et_2O (1:1); **(e)** *p*-TSA, (25:1), 74% (over three steps); **(f)** CH_2I_2, Et_2Zn, 95%; **(g)** MMPP, DMF, 84%, **(h)** H_2/PtO_2, (4:1), 98%; **(i)** KOH; **(j)** CH_2N_2; **(k)** $POCl_3$, HMPA, py; **(l)** KOH, 84% (over four steps); **(m)** $COCl_2$, DMF; **(n)** *m*-CPBA, py, DMAP; **(o)** LAH, Et_2O, 50% (over three steps).

Scheme 8. Harmata and Rashatasakhon's total synthesis of dactylol **23**.

1.4.2.2 Poitediol **24**

In 1978, sesquiterpene poitediol **24** was isolated along with dactylol **23** from the ethanol extracts of the red seaweed *Laurencia poitei*[43] (**Figure 7**[III]).

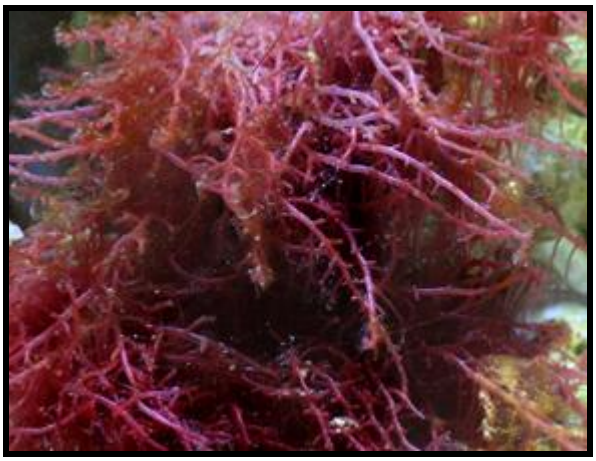
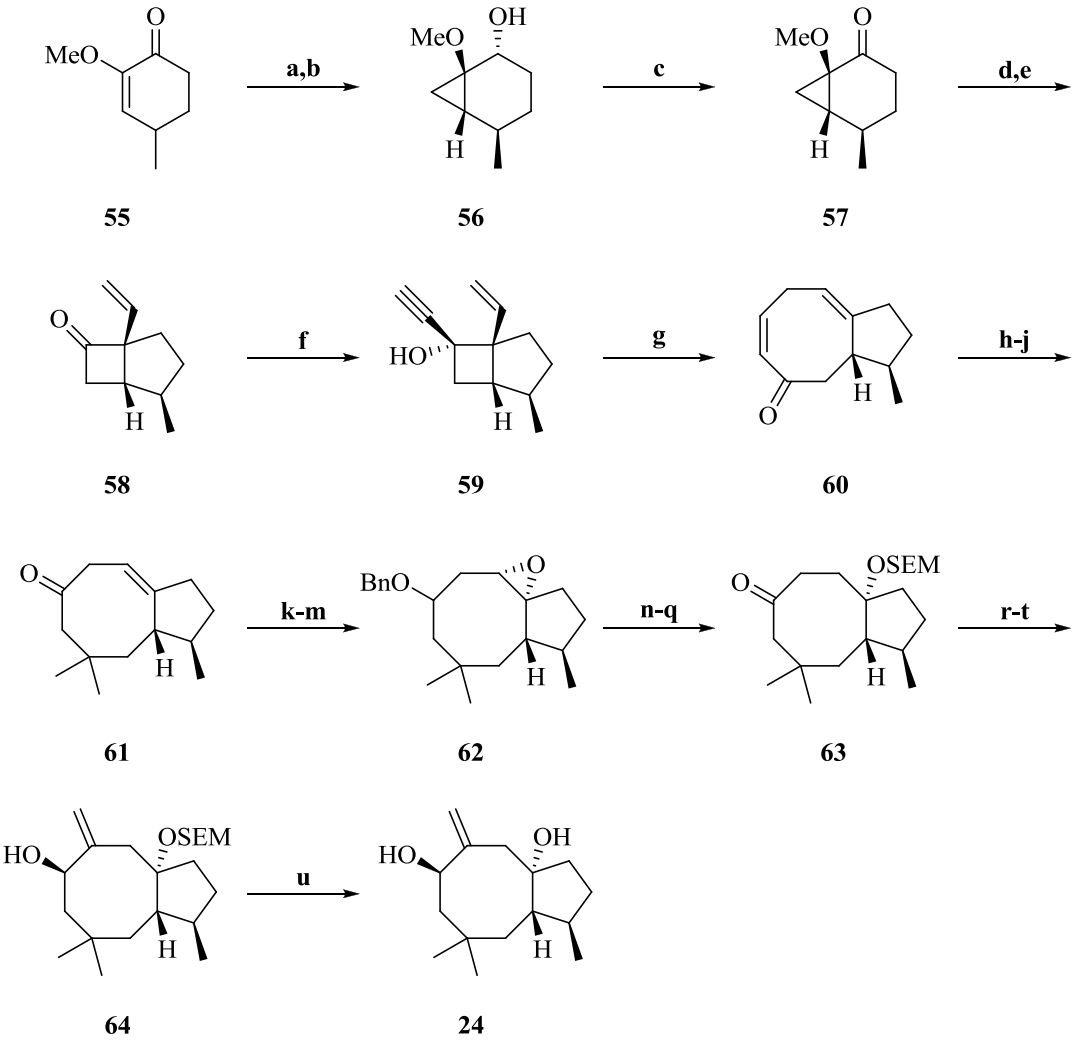


Figure 7. *Laurencia poitei*.

Gadwood *et al*.[58] published the total synthesis of poitediol **24** in a racemic form employing an anionic oxy-Cope rearrangement[59] as the strategic step (**Scheme 9**). The stereoselective reduction of enone **55** gave *trans*-norcaranol **56**, which after oxidation was converted to **57**, followed by the addition of vinylmagnesium bromide and boron trifluoride etherate to form cyclobutanone **58**. Reaction of **58** with lithium acetylide generated **59**. A subsequent oxy-Cope rearrangement of **59** furnished cyclooctadienone **60** upon heating under neutral conditions. Sequential treatment of **60** with methyl-lithium, oxidative rearrangement with pyridinium chlorochromate, and reaction with lithium dimethyl cuprate provided cyclooctadienone **61**. Formation of the α-epoxide **62** was accomplished by reduction, benzylation, and epoxidation conditions. Addition of lithium triethylborohydride to **62**, followed by protection of the alcohol, debenzylation, and Swern oxidation[60] yielded ketone **63**. Introduction of the α-methylene group and subsequent reduction gave **64**. The synthesis of (±)-poitediol **24** was achieved after the desilylation of alcohol **64**.

[III] Image sources: http://www.lionfishlair.com/ourtanks/100gvolitan.shtml Used with kind permission of photographer Renee Coles-Hix.

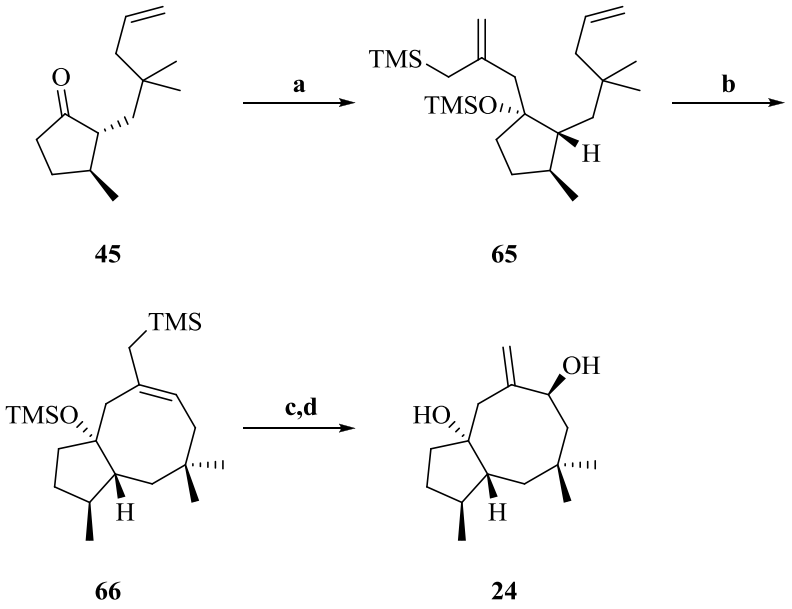


Reagents and conditions: **(a)** DIBAL-H, Et_2O, -100 ºC; **(b)** Et_2Zn, CH_2I_2, O_2; **(c)** PCC, CH_2Cl_2, 69% (over three steps); **(d)** CH_2=CHMgBr, PhH; **(e)** $BF_3{\cdot}Et_2O$, Et_2O, 54% (over two steps); **(f)** LiC≡CH, THF, -30 ºC, 5 min; **(g)** 50 ºC, 3 h, 50% (over two steps); **(h)** MeLi, Et_2O, -78 ºC; **(i)** PCC, CH_2Cl_2; **(j)** $LiMe_2Cu$, Et_2O, 53% (over three steps); **(k)** LAH, Et_2O, -78 ºC; **(l)** KH, $PhCH_2Br$, Bu_4NI, THF; **(m)** *m*-CPBA, CH_2Cl_2; **(n)** $LiEt_3$, BH, THF, 50 ºC, 66% (over four steps); **(o)** SEMCl, *i*-Pr_2NEt, THF, 50 ºC; **(p)** Na, NH_3; **(q)** ClCOCOCl, Me_2SO, -78 ºC; *i*-Pr_2NEt, 79% (over three steps); **(r)** LDA, THF; CH_2O; **(s)** MsCl, *i*-Pr_2NEt, 46% (over two steps); **(t)** *i*-Bu_3Al, hexane, 25 ºC, 41%; **(u)** 0.1 M HCl in MeOH, 76%.

Scheme 9. Gadwood's total synthesis of poitediol **24**.

It was not until 2009 when Vanderwal and co-workers[61] synthesise (+)-poitediol **24** by employing allylsilane ring-closing metathesis and electrophilic desilylation as the pivotal operation for the construction of the eight-membered ring (**Scheme 10**). The synthesis of **45** was adapted from the previous dactylol synthesis reported by Fürstner and Langemann.[52] Indium-mediated allylation of ketone **45** with [2-(iodomethyl)allyl]trimethylsilane and a

subsequent *in situ* silylation afforded diene **65**, which was treated with Grubbs (2nd generation) catalyst[62] to produce cylooctene **66**, followed by stereoselective epoxidation. The corresponding silyl epoxide was decomposed upon fluoride-mediated elimination with concomitant silyl ether cleavage to complete the synthesis of (+)-**24** in 18% overall yield.



Reagents and conditions: **(a)** $ICH_2C(CH_2)CH_2Si(CH_3)_3$, In^0, DMF, 0 ºC, 1.5 h; TMSCl, DMAP, imidazole, 0 ºC → RT, 4 h, 55%; **(b)** Grubbs (2nd generation) catalyst, CH_2Cl_2, Δ, 7 h; **(c)** *m*-CPBA, 0 ºC, 1 h; **(d)** TBAF, THF, 30-33 ºC, 18 h, 46% (over three steps).

Scheme 10. Vanderwal's total synthesis of poitediol **24**.

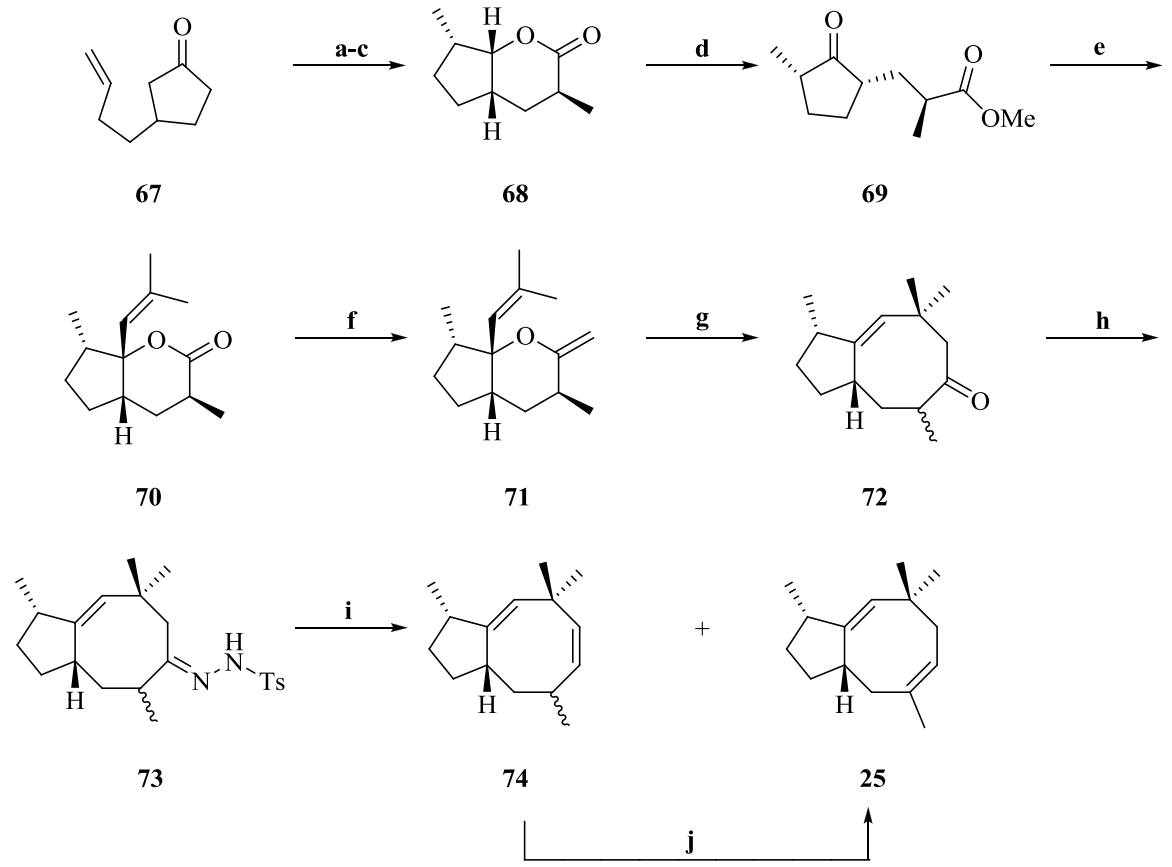
1.4.2.3 Precapnelladiene **25**

Cyclooctanoid sesquiterpene precapnelladiene **25** was isolated from the non-polar extracts of the soft coral *Capnella imbricata*[63] (**Figure 8**[IV]).

Figure 8. *Capnella imbricata*.

In 1985, Paquette *et al*[64] described a stereocontrolled total synthesis of (±)-**25** using a Claisen rearrangement[65,66] as the key transformation of the medium-sized ring (**Scheme 11**). Thermal ene cyclisation of **67** has been demonstrated previously by Conia's group.[67] The resulting bicycled ketone was subjected to a Baeyer-Villiger oxidation,[57] followed by methylation to afford **68**, which was treated with substoichiometric quantities of methoxide ion with buffered PCC to afford epimerically pure keto ester **69**. Treatment of **69** with 2-methylpropen-1-yllithium produced **70**. Addition of Tebbe's reagent[51] gave **71**. Thermolysis of **71** led to key intermediate **72**. Regiocontrolled conversion of the carbonyl group in **72** to a double bond was prepared to access tosylhydrazone **73**. Decomposition gave mainly less-substituted olefin **74** and **25** as the minor component. Subsequent rhodium trichloride-promoted isomerisation allowed the formation of (±)-**25**.

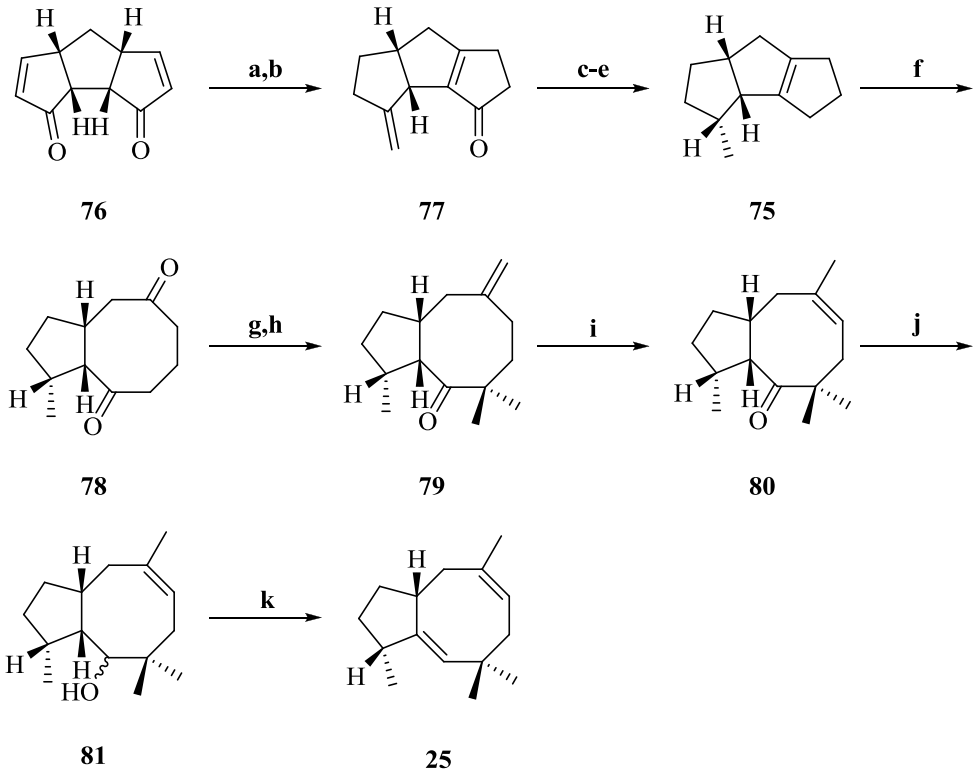
[IV] Image source: http://www.pbase.com/the_underwater_world/image/68566250 Used with kind permission of photographer Danielle Caceres-Bricheno.



Reagents and conditions: **(a)** 325 ºC, 1.5 h; **(b)** *m*-CPBA, CH_2Cl_2, 76%; **(c)** DIPA, THF, *n*-BuLi, CH_3I, 87%; **(d)** $NaOCH_3$, MeOH; PCC, NaOAc, 71%; **(e)** $LiCH{=}C(CH_3)CH_3$, Et_2O, -78 ºC, 58%; **(f)** Tebbe's reagent, PhMe; **(g)** 200 ºC, 48 h, 67% (over two steps); **(h)** tosylhidrazine, MeOH, HCl, 96%; **(i)** *n*-BuLi, diglyme, Δ, **74**/**25** (3:1), 94%; **(j)** $RhCl_3$, EtOH, Δ, 45%.

Scheme 11. Paquette's total synthesis of precapnelladiene **25**.

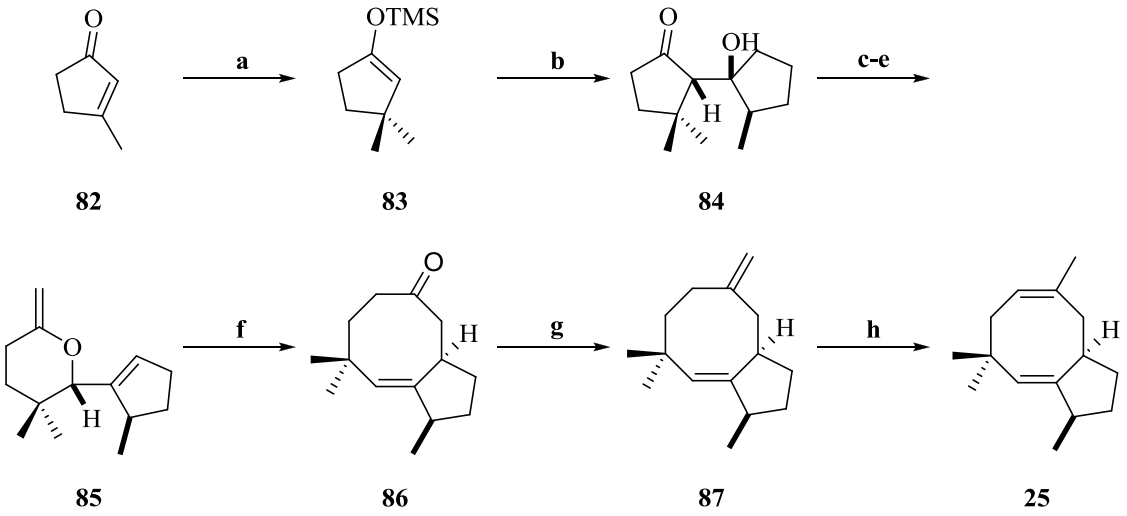
Mehta's and colleagues[68] synthesised (±)-sesquiterpene **25** from triquinane precursor **75** (**Scheme 12**). Subjecting the readily available tricyclic bis-enone **76** to relocation of one of the enone moieties, partial hydrogenation, and selective Wittig olefination[69] gave rise to **77**, which after stereoselective hydrogenation over rhodium-carbon catalyst, thiacetalization, and desulfurization to deoxygenate formed olefin **75**. Catalytic ruthenium dioxide oxidation employing Sharpless conditions[70] gave biclyclic dione **78**, which was subjected to chemoselective Wittig olefination, followed by two successive regioselective methylations to access **79**. Isomerisation was achieved with a rhodium catalyst to produce **80**. Sequential metal hydride reduction and dehydration of the resulting **81** yielded (±)-**25**.



Reagents and conditions: **(a)** $RhCl_3 \cdot 3H_2O$, EtOH, 70%; H_2-10%, Pd/C, EtOAc, quant.; **(b)** $Ph_3P^+MeI^-$, NaO-*t*-C_5H_{11}, PhMe, 85%; **(c)** H_2-5%, Rh/C-EtOH, 90%; **(d)** $HSCH_2CH_2SH$-*p*-$MeC_6H_4SO_3H$, PhH, 80%; **(e)** Na-liquid NH_3, 65%; **(f)** RuO_2, $NaIO_4$, CCl_4, MeCN, H_2O, 80%; **(g)** $(Me_2Si)_2NH$, *n*-BuLi, MeI, -78 ºC, THF, 92%; **(h)** $(i\text{-}Pr)_2NH$, *n*-BuLi, MeI, -78 ºC, THF, 67%; **(i)** $RhCl_3 \cdot H_2O$, EtOH, 80%; **(j)** LAH, Et_2O, 80%; **(k)** $POCl_3$, DBU, py, 70%.

Scheme 12. Mehta's total synthesis of precapnelladiene **25**.

Another Claisen rearrangement[65,66] strategy was employed in 1990 by Petasis and Patane[71] for the total synthesis of racemic **25** (**Scheme 13**). The synthesis commenced with the conjugate addition of **82** with lithium dimethylcuprate, affording the silyl enol ether **83**, which was subjected to a Mukaiyama aldol reaction[72] to give precursor **84**. Formation of the enol ether **85** was accomplished when **84** was treated under Baeyer-Villiger reaction conditions,[57] dehydration, and methylenation conditions. Thermolysis of **85** led to cyclooctanone **86**. Methylenation of **85** with dimethyl titanocene gave access to diene **87**. Synthesis of (±)-precapnelladiene **25** was completed after catalytic isomerisation.



Reagents and conditions: **(a)** Me_2CuLi, TMSCl, THF, TMEDA, 89%; **(b)** $TiCl_4$, CH_2Cl_2, (±)-2-methylcyclopentanone, 93%; **(c)** *m*-CPBA, $NaHCO_3$, CH_2Cl_2, quant.; **(d)** MsCl, Et_3N, DMAP; **(e)** Cp_2TiMe_2, THF, 60 ºC; **(f)** PhMe, 185 ºC, 45%; **(g)** Cp_2TiMe_2, THF, 60 ºC, 92%; **(h)** $RhCl_3$, EtOH, 50 ºC.

Scheme 13. Petasis and Patane's total synthesis of precapnelladiene **25**.

The Claisen rearrangement of **85** occurred with high stereoselectivity. The chair-chair transition state was favored over the chair-boat transition state (**Figure 9**).

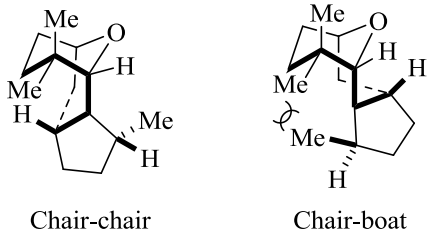
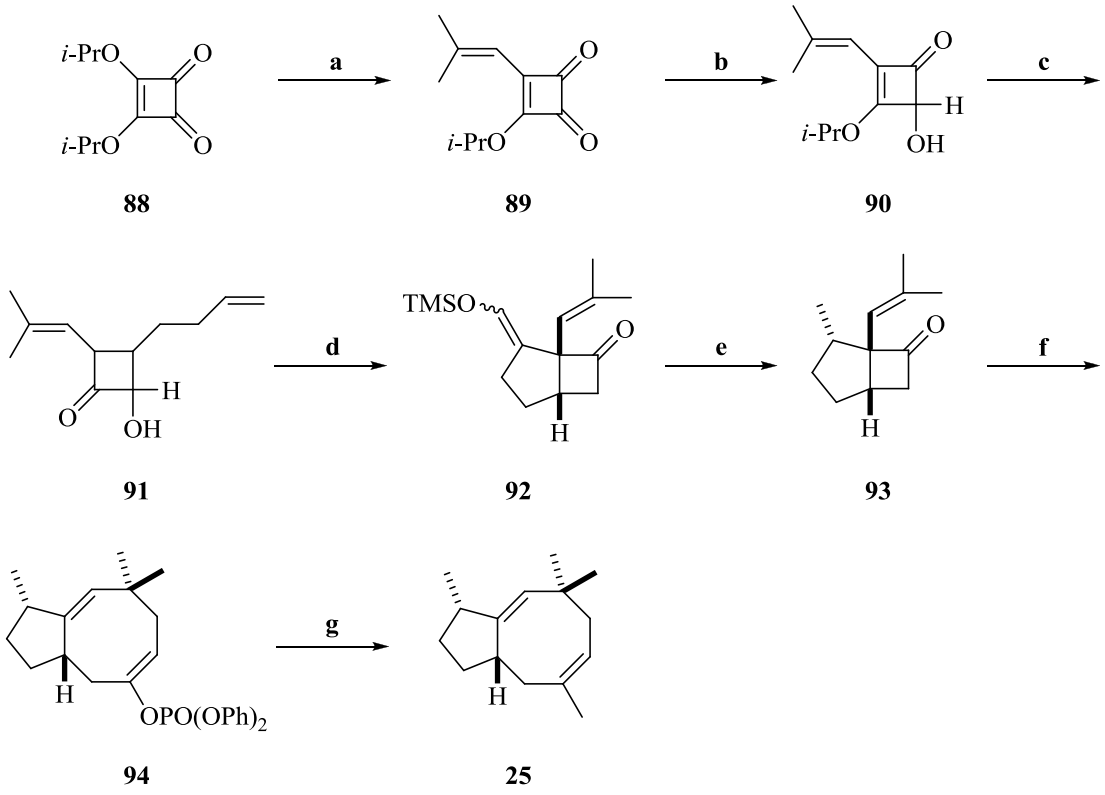


Figure 9. Petasis and Patane's transitions states of precursor **85**.

Moore's research group[73] published an alternative to synthesise (±)-sesquiterpene **25** *via* a tandem anionic oxy-Cope[74] rearrangement (**Scheme 14**). Treatment of diisopropyl squarate **88** with 1-lithio-2-methylpropene, followed by TFAA and aqueous workup afforded **89**. Selective reduction of the more electrophilic carbonyl group produced **90**. The precursor **91** was obtained in one-pot operation by the addition of 4-lithio-1-butene to the vinylogous ester in **90** and acid hydrolysis of the resulting β-hydroxyl enol ether. Trimethylsilylation and thermal rearrangement formed bicyclo[3.2.0]heptanone **92**, which was then treated with aqueous acid, chemoselective thioacetalization, and desulfurization conditions to

generate **93**. The subsequent addition of vinyllithium induced the oxy-Cope expansion in a regioselective manner, trapping the resultant enolate with diphenyl chlorophosphate to form **94**. Subjecting **94** to trimethylaluminium in the presence of substoichiometric amount of $Pd[PPh_3]_4$ completed the synthesis of (±)-**25** with an overall yield of 12%.

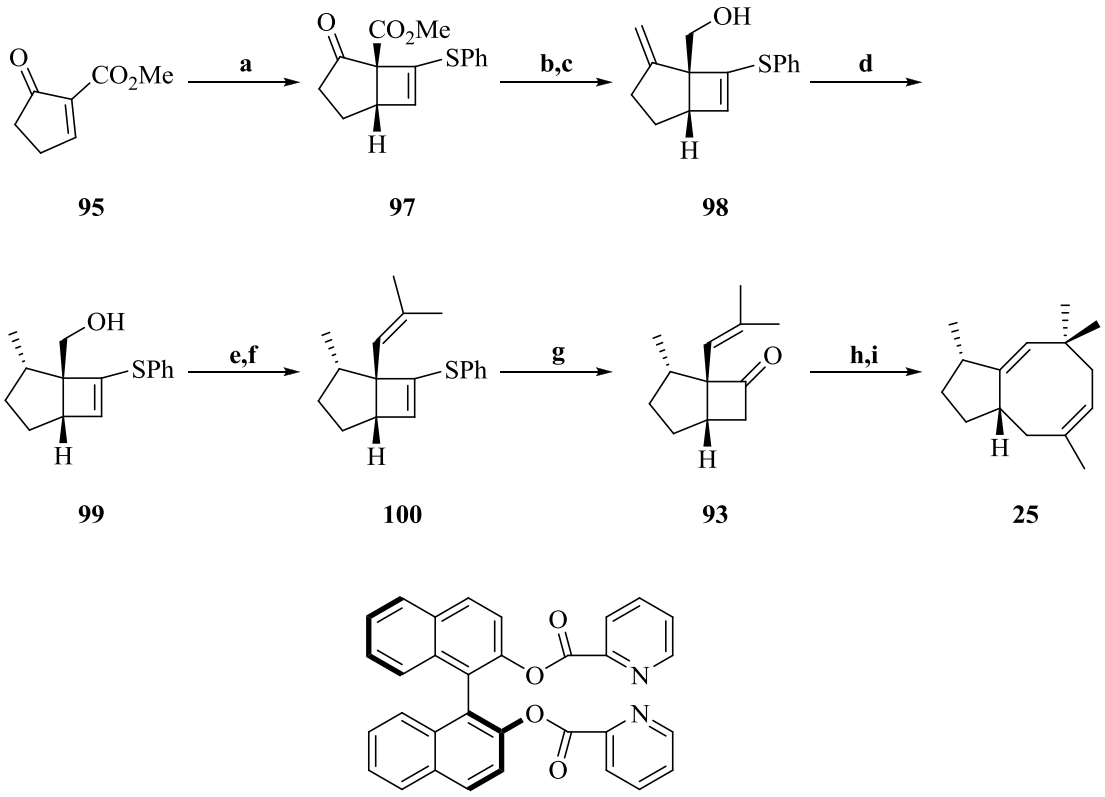


Reagents and conditions: **(a)** $LiCH=C(CH_3)CH_3$; TFAA; $NaHCO_3$, H_2O, 94%; **(b)** LiAlH-(*t*-OBu)$_3$, 93%; **(c)** $CH_2=CHCH_2CH_2Li$; 1 M HCl, 80%; **(d)** TMSCl, Et_3N; 138 ºC, 76%; **(e)** TBAF, H_2O; $HS(CH_2)_3SH$; RaNi (W-2), 57%; **(f)** $LiCH=CH_2$, -78 ºC → RT; $ClPO(OPh)_2$, 47%; **(g)** $Pd[P(Ph)_3]_4$, $AlMe_3$, 78%.

Scheme 14. Moore's total synthesis of precapnelladiene **25**.

Ito and Iguchi[75] have more recently developed an enantioselective formal synthesis of (+)-**25** (**Scheme 15**). Chiral copper-catalysed enantioselective [2 + 2] cycloaddition reaction of **95** with a bis-pyridine lignan **96** gave compound **97**. Subsequent introduction of the methyl group was accomplished in a stereoselective manner by treating **97** with a Wittig reagent,[69] followed by reductive conditions to obtain the corresponding alcohol **98**. Coordination of the hydroxyl group at the angular position with the Wilkinson catalyst[76] for hydrogenation of **98** access compound **99** with high diastereoselectivity. Oxidation of the hydroxyl group using Dess-Martin periodinane,[77] followed by the Wittig reaction of the resultant aldehyde

produced **100**, which was hydrolysed to generate precursor **93**, identical to that reported by Moore's group.[73]



Lignan **96**

Reagents and conditions: **(a)** HC≡CSPh, **96**, $CuCl_2$, $AgSbF_6$, CH_2Cl_2, -78 ºC, 73%, 68% *ee*; **(b)** methyltriphenylphosphonium bromide, *n*-BuLi, Et_2O, 0 ºC, 76%; **(c)** LAH, Et_2O, 0 ºC, 98%; **(d)** $Rh(PPh_3)_3Cl$, H_2, CH_2Cl_2, RT, 66%, (11:1); **(e)** DMP, $NaHCO_3$, CH_2Cl_2, RT, 88%; **(f)** isopropyltriphenylphosphonium iodide, *n*-BuLi, THF, -78 ºC, 86%; **(g)** $HgCl_2$, MeCN, H_2O, 70 ºC, 20%; **(h)** $LiCH{=}CH_2$, -78 ºC → RT; $ClPO(OPh)_2$; **(i)** $Pd[P(Ph)_3]_4$, $AlMe_3$.

Scheme 15. Ito and Iguchi's total synthesis of precapnelladiene **25**.

1.5 Asteriscanolide **1**

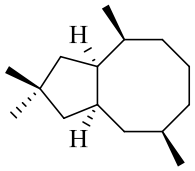
1.5.1 Isolation and Structural Elucidation of Asteriscanolide **1**

In 1985, San Feliciano and co-workers[1] published the isolation of cyclooctane sesquiterpene lactone asteriscanolide **1** from the hexane extract of a plant known as *Asteriscus aquaticus L* (**Figure 10**[V]), a sweet fragrant plant from the Compositae family, commonly named as golden star that grows annually in the Mediterranean territory.

Figure 10. *Astericus aquaticus*.

Although several synthetic substances possessing an identical carbon framework of **1** were reported before in the literature,[78,79] up to that time, no natural product had appeared with that specific skeletal arrangement. San Feliciano called the bicyclic compound asteriscane **6** (**Figure 11**).

[V] Image source: http://www.planetefleurs.fr/Systematique/Asteraceae/Asteriscus_aquaticus.htm Used with kind permission of photographer Christian Bravard.

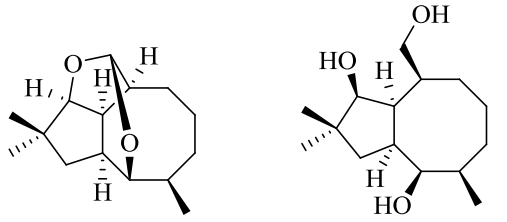


6

Figure 11. Asteriscane.

The natural product asteriscanolide **1**, was isolated as a crystalline solid (mp 178 ºC; $[\alpha]_D$ 12.1º ($CHCl_3$)) of the (+)-enantiomer by repeated chromatography of a methanol defatted hexane extract of the aforementioned. The structural elucidation of **1** was performed by IR, EIMS, NMR, and X-ray experiments.

The EIMS study displayed M^+ at m/z= 250, corresponding to the formula $C_{15}H_{22}O_3$, and the IR spectrum showed absorption of γ-lactone and ketone groups (1770, 1705 cm^{-1}). Confirmation of the structure was supported by the data from several detailed 2D-NMR studies. The relative stereochemistry of ring junctions was deduced from the values of proton coupling constants, being all *cis*, which was proved by analysis of reduction products. Treatment of **1** with an excess of lithium aluminum hydride gave rise to the formation of asteriscaneacetal **101**, as well as the expected asteriscanetriol **102** (**Figure 12**).



Asteriscaneacetal **101** Asteriscanetriol **102**

Figure 12. San Feliciano's reduction products from asteriscanolide **1**.

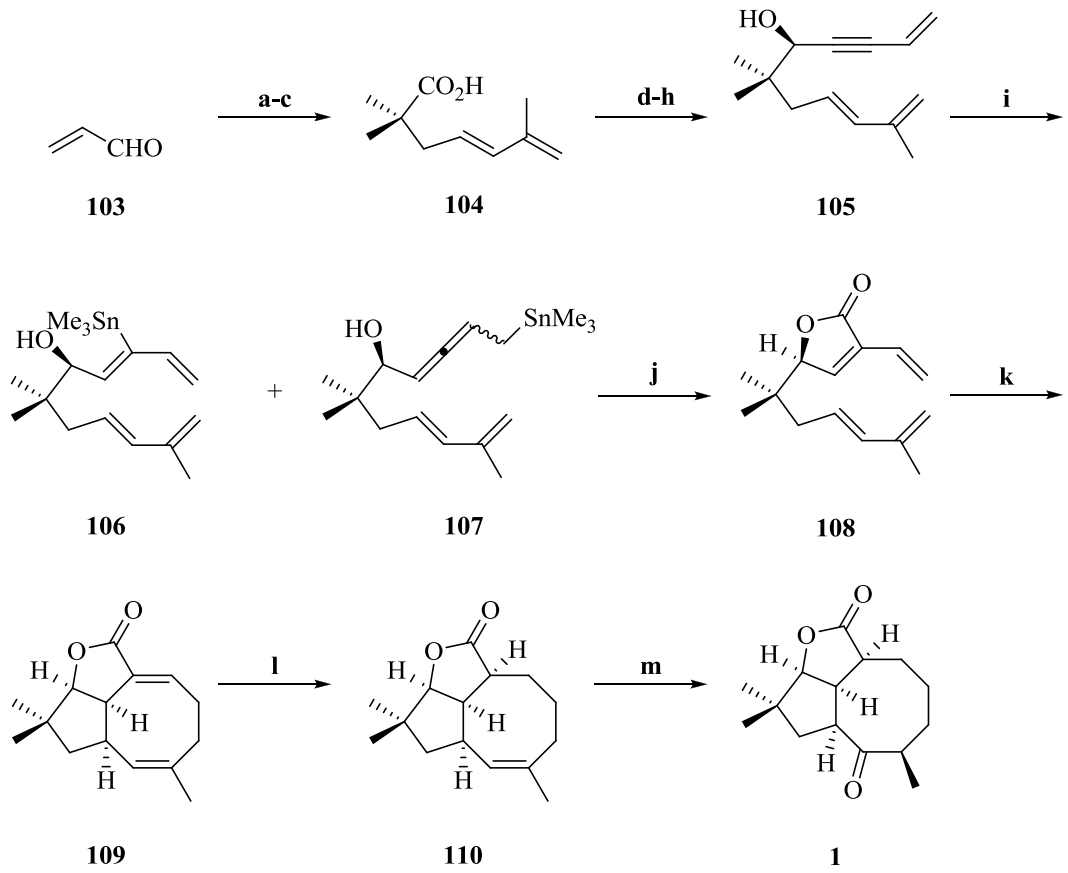
Final structural assignment and absolute configuration of **1** were determined by a single crystal X-ray diffraction experiment. Molecule **1** consisted of five stereocentres, four of which were contiguous, and a bicyclo[6.3.0]undecane ring system bridged by a butyrolactone ring fragment. The cyclooctane ring adopted an almost boat conformation and the pentagonal rings displayed envelope conformations typical of such rings.

1.5.2 Previous Total Syntheses of Asteriscanolide **1**

1.5.2.1 Wender's Synthesis

In 1988, Wender *et al.*[80] reported the first total synthesis of sesquiterpene lactone (+)-asteriscanolide **1** based on a nickel-catalysed intramolecular [4 + 4] cycloaddition reaction[14,81] as the strategic step for the formation of the eight-membered ring.

The thirteen-step sequence started with acrolein **103**, which was treated with isopropenyl lithium, followed by esterification with isobutyric anhydride, and subsequent regio- and stereoselective enolate Claisen rearrangement[82] to afford diene acid **104**. Conversion of the carboxylic acid to the aldehyde functionality was accomplished using LAH, followed by Swern oxidation procedure.[83] It was after the addition of lithium vinylacetylide and an additional Swern oxidation when the introduction of asymmetry was facilitated by an enantioselective reduction of the resultant propargyl ketone employing a Darvon alcohol modified lithium hydride reagent[84] to form the corresponding alcohol **105**. Hydroalumination of the alkyne in **105** with Red-Al® and stannylation of the resultant vinylaluminate furnished the mixture of stannanes **106** and **107**. Transmetallation of mixed products **106** and **107** utilising *n*-butyllithium, followed by carboxylation and acidic workup yielded the desired cycloaddition precursor **108**. The formation of cyclooctadiene **109** was performed by treating bis-diene lactone **108** with $Ni(COD)_2$ in the presence of triphenylphosphine with high stereoselectivity; less than 5% of [4 + 2] cycloadducts were observed. Selective conjugate reduction of **109** gave precursor **110**. The introduction of the C-7 stereocentre was realised by face-selective hydroboration of **110** and *in situ* oxidation of the resulting borane with pyridinium chlorochromate giving access to (+)-**1** in 2.7% overall yield (**Scheme 16**).



Reagents and conditions: **(a)** isopropenyl Grignard, 57%; **(b)** isobutyric anhydride, 99%; **(c)** LDA, -78 ºC → 0 ºC, 69%; **(d)** LAH, 93%; **(e)** DMSO, $(COCl)_2$, Et_3N, 88%; **(f)** LiC≡CCH=CH_2, 88%; **(g)** DMSO, $(COCl)_2$, Et_3N, 89%; **(h)** LAH/Darvon, 95%, >98% *ee*; **(i)** Red-Al®; Me_3SnCl, 83%; **(j)** *n*-BuLi; CO_2, 56%; **(k)** $Ni(COD)_2$, Ph_3P, 90 ºC, 67%; **(l)** Red-Al®, CuBr, 74%; **(m)** BH_3·THF; PCC, 48%.

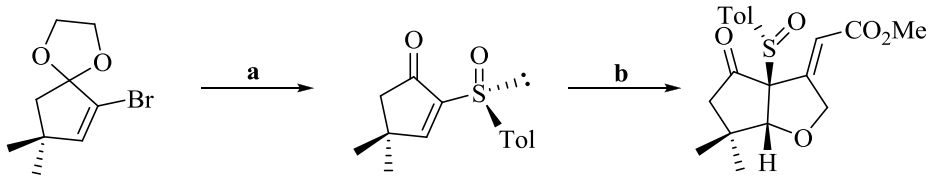
Scheme 16. Wender's total synthesis of asteriscanolide **1**.

1.5.2.2 Paquette's Synthesis

In 2000, Paquette and colleagues[85] became the second group to develop a successful enantioselective total synthesis of (+)-**1** using unprecedented Michael-Michael reaction sequence[86] and ring-closing metathesis as the key bond-forming operations.

The synthesis initiated with the lithium-halogen exchange of known bromoketal **111**, followed by condensation of the vinyllithium reagent with (*S*)-(-)-menthyl *p*-toluenesulfinate to give cyclopentenone **112**. The preparation of bicyclic ester **113** was elaborated by chirality transfer from the enantiodefined sulfoxide substituent of **112** and subsequent Michael reaction with methyl 4-hydroxy-2-butynoate and potassium carbonate.

The Michael addition of the heteroatom-centred appeared to be asymmetrically inducted and the initial product of the 1,4-conjugate addition proved to be capable of subsequent intramolecular addition to the triple bond. Hence, the one-step fully controlled conversion of **112** to **113** set up two of the stereocentres of (+)-**1** in a novel tandem process in modest yield (**Scheme 17**).

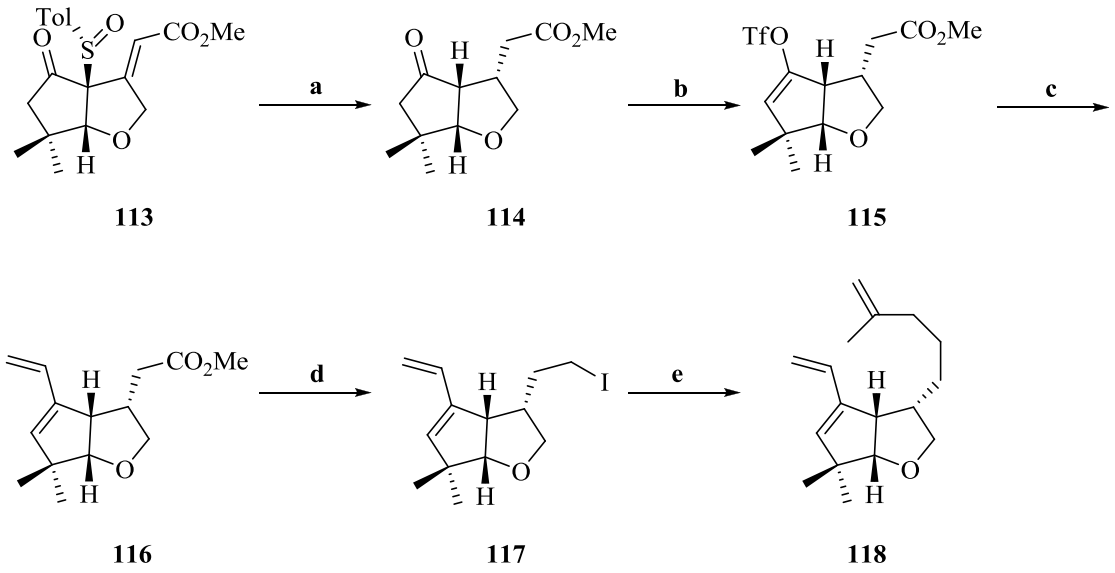


111 **112** **113**

Reagents and conditions: **(a)** *n*-BuLi; (*S*)-(-)-menthyl *p*-toluenesulfinate; CSA, aq acetone, 77%; **(b)** methyl 4-hydroxy-2-butynoate, K_2CO_3, THF, 38%.

Scheme 17. Paquette's synthesis of precursor **113**.

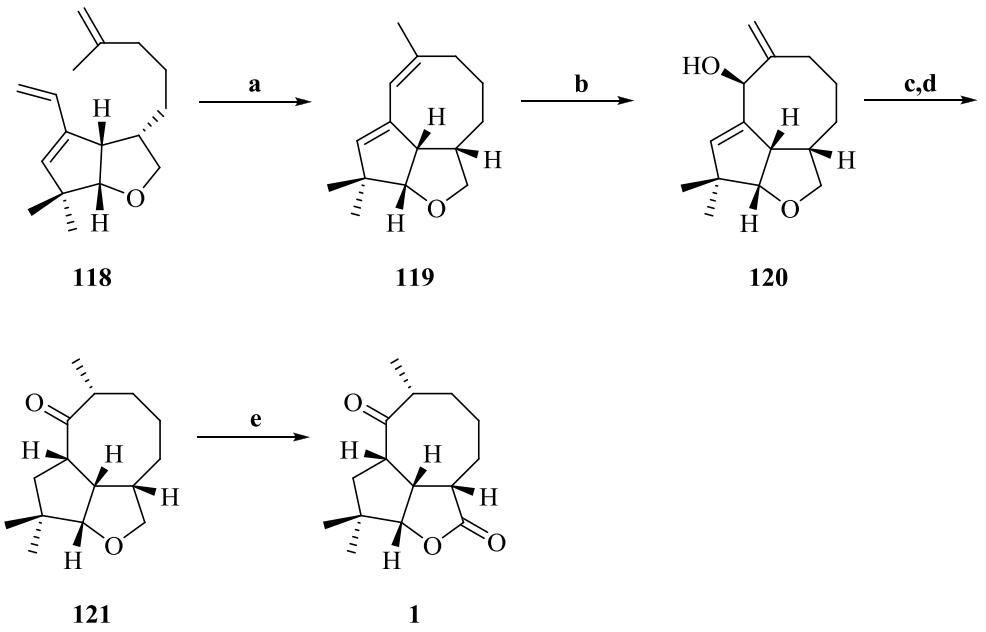
The carbon-sulfur bond cleavage and saturation of the olefinic linkage of **113** were accomplished in a one-pot face-selective hydrogenation with Raney nickel to afford keto-ester **114**, which was converted into triflate **115** in almost quantitative yield. Subjection of **115** into a Stille coupling reaction[87] gave diene **116** in good yield. After reduction and iodination conditions, the resulting iodide **117** was exposed to a copper-catalysed substitution with methallylmagnesium chloride to form triene **118** (**Scheme 18**).



Reagents and conditions: **(a)** H_2, RaNi (150 psi), MeOH, 88%; **(b)** KHMDS, $PhNTf_2$, THF, -78 ºC, 98%; **(c)** $Bu_3SnCHCH_2$, $Pd_2(dba)_3$, $CHCl_3$, LiCl, THF, 95%; **(d)** LAH, 94%; MsCl, Et_3N; NaI, 79%; **(e)** $CH_3C(CH_2)CH_2MgCl$, CuI, THF, 0 ºC, 98%.

Scheme 18. Paquette's synthesis of precursor **118**.

The RCM reaction produced cyclooctane **119** in high yield; subsequent photooxygenation of **119** in dicholoromethane and reduction of the resultant hydroperoxide gave diallylic alcohol **120**. Dess-Martin oxidation,[77] followed by hydrogenation of the resulting dienone afforded **121**. The introduction of the final stereogenic centre by this hydrogenation was confirmed by the regioselective ruthenium tetraoxide oxidation to yield crystalline (+)-asteriscanolide **1** (**Scheme 19**).



Reagents and conditions: **(a)** Grubbs (1st generation) catalyst, CH_2Cl_2, Δ, 93%; **(b)** O_2, TTP, CH_2Cl_2, hν; LAH, 61%; **(c)** DMP, CH_2Cl_2; **(d)** H_2, 10% Pd/C (300 psi), EtOH, 67% (over two steps); **(e)** $RuCl_3$, $NaIO_4$, MeCN, CCl_4, H_2O, RT, 63%.

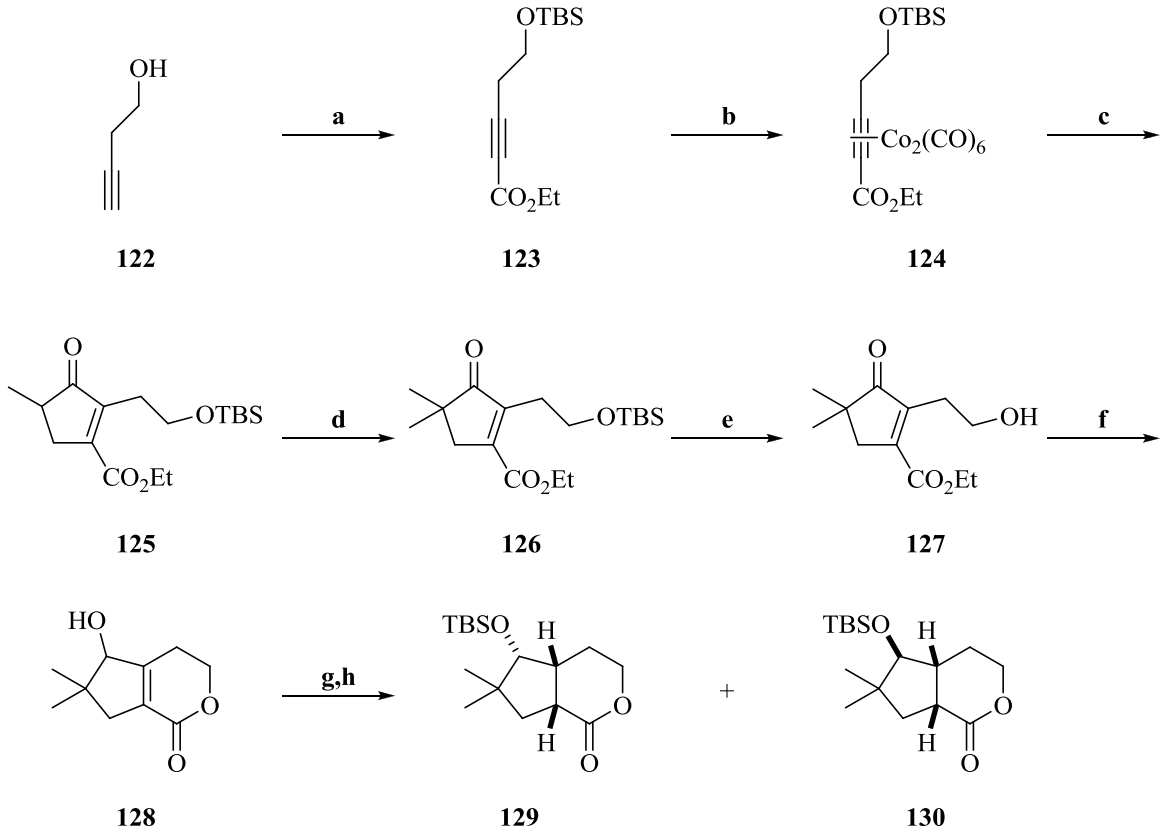
Scheme 19. Paquette's total synthesis of asteriscanolide **1**.

1.5.2.3 Krafft's Synthesis

During the same year as Paquette's synthesis, Krafft's research group[88] published the total synthesis of (±)-asteriscanolide **1** and also presented a detailed account of the synthetic studies a year after.[89] The synthetic route was achieved by an intermolecular Pauson-Khand [2 + 2 + 1] cycloaddition reaction[90] and a ring-closing metathesis as the key transformations. The strategy incorporates the cyclooctane stereogenic centre C-7 prior to the ring formation.

Protection of the hydroxyl group in 3-butyn-1-ol **122**, followed by formation of lithio alkyne with *s*-BuLi in THF and addition of ethyl chloroformate gave alkynoate **123**. Treatment of alkynoate **123** with dicobalt octacarbonyl in petroleum ether produced dicobalt hexacarbonyl complexed alkyne **124**, the cycloaddition precursor. Incremental addition of NMO to **124** with propene in dichloromethane led to cyclopentenone **125**. Deprotonation of **125** using LHMDS/HMPA, followed by quenching the resultant HMPA-complexed lithium enolate with methyl iodide afforded *gem*-dimethyl cyclopentenone **126**.

Fluoride ion-mediated desilylation gave primary alcohol **127**. Luche reduction[49] and a subsequent acid-catalysed lactonisation afforded hydroxyl lactone **128**. The protection of the hydroxyl group to the corresponding TBS ether improved facial selectivity, which after hydrogenation yielded the desired all-*cis* diastereoisomer **129** and isomer **130** (**Scheme 20**).

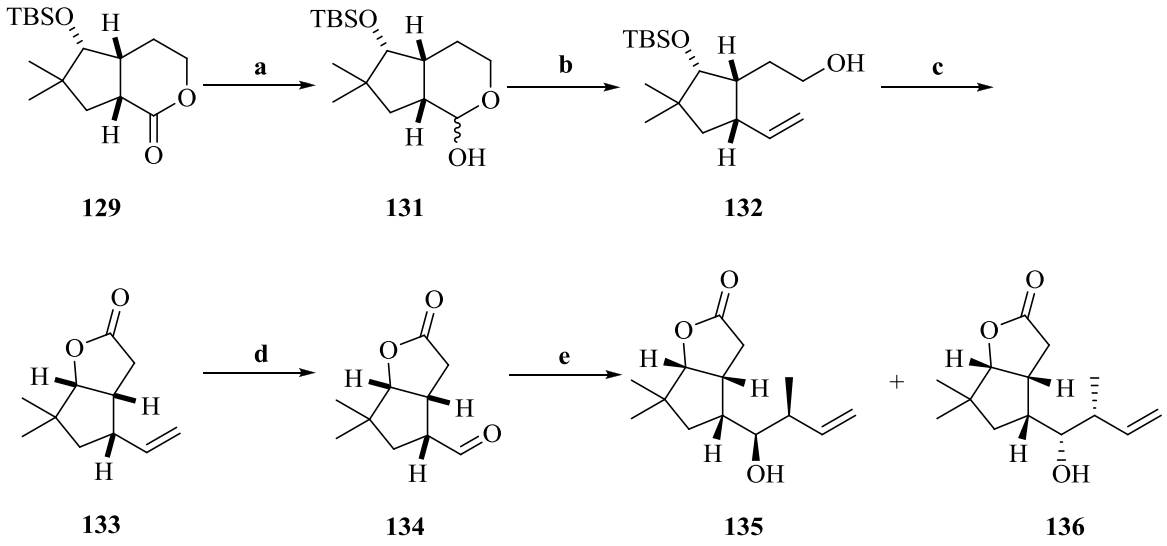


Reagents and conditions: **(a)** TBSCl, Et_3N, DMAP, 95%; *s*-BuLi, THF, -78 ºC, EtOCOCl, 70%; **(b)** $Co_2(CO)_8$, 0 ºC, petroleum ether, quant.; **(c)** NMO·H_2O, propene/CH_2Cl_2 (1:1), 92%; **(d)** LHMDS, -78 ºC, THF, HMPA; MeI, 94%; **(e)** HF/py, MeCN, quant.; **(f)** $NaBH_4$/$CeCl_3$·$7H_2O$; 2 M HCl/acetone (1:1), 88%; **(g)** TBSOTf, py, 0 ºC, quant.; **(h)** H_2, Pd/C (20 psi), EtOH, 4 h, **129**/**130** (9:1), quant.

Scheme 20. Krafft's synthesis of precursors **129** and **130**.

The reduction of lactone **129** using DIBAL-H, followed by Wittig olefination[69] of the resultant lactol **131** provided poly-substituted cyclopentane **132**. Conversion of primary alcohol **132** to the corresponding carboxylic acid was accomplished under Jones oxidation conditions,[91] which after desilylation of the secondary alcohol, followed by reflux with acid chloride in acetone and spontaneous intramolecular lactonisation gave bicylic lactone **133**. Ozonolysis with a reductive workup using Me_2S formed aldehyde **134** without

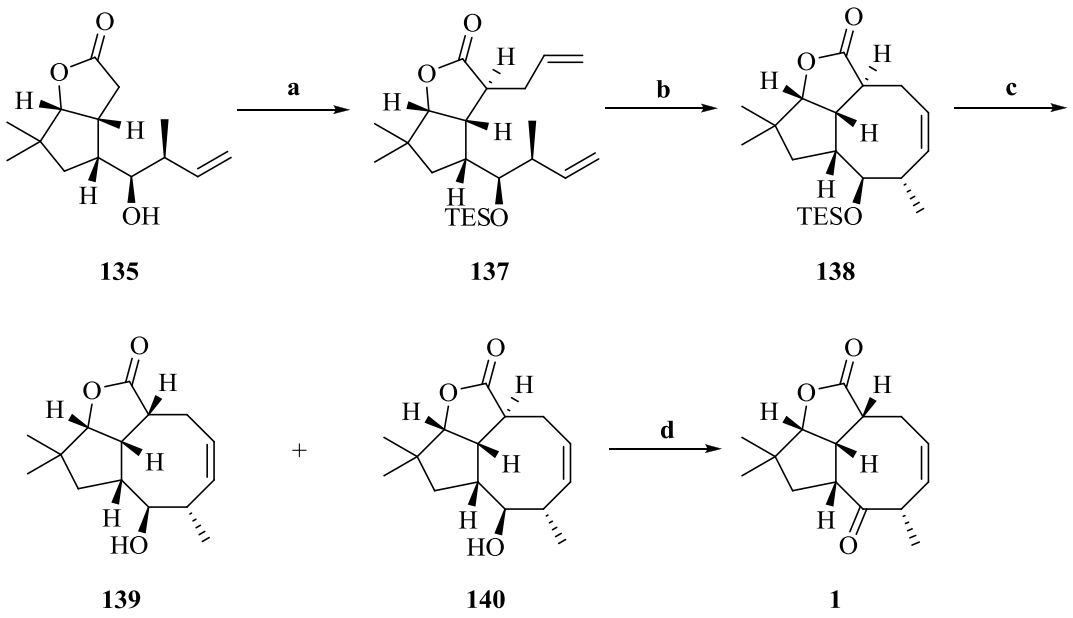
epimerization. The stereoselective introduction of the C-7 methyl group was accomplished through a Lewis acid-catalysed stanylation, yielding homoallylic alcohol **135** and isomer **136** (**Scheme 21**).



Reagents and conditions: **(a)** DIBAL-H, PhMe, -78 ºC, quant.; **(b)** CH_3PPh_3Br, *n*-BuLi, THF, Δ, 88%; **(c)** CrO_3, H_2SO_4, acetone; 2 M HCl/acetone (1:1), Δ, 89%; **(d)** O_3, CH_2Cl_2, -78 ºC; SMe_2, quant.; **(e)** $CH_3CHCHCH_2SnBu_3$, $BF_3{\cdot}OEt_2$, CH_2Cl_2, -78 ºC, **135**/**136** (8:1), 74%.

Scheme 21. Krafft's synthesis of precursors **135** and **136**.

The elaboration of **135** to the corresponding TES ether, followed by the alkylation of the lactone, trapping the lithium enolate with allyl bromide in the presence of HMPA generated diene **137** in high yield. The ring-closing metathesis of **137** with a substoichiometric amount of Grubbs (2^{nd} generation) catalyst[62] under reflux gave the so called "inside-outside" tricycle **138** bearing the C-7 methyl group with the correct orientation. Treatment of **138** with TBAT and acetonitrile under reflux formed a mixture of separable alcohols **139** and **140**. After hydrogenation and oxidation reaction conditions, a mixture of enantiomers of **1** was obtained with an overall yield of 12% (**Scheme 22**).



135 **137** **138**

139 **140** **1**

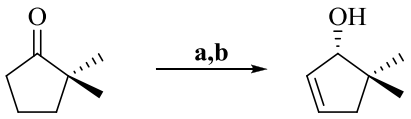
Reagents and conditions: **(a)** TESOTf, py, 87%; LHMDS, HMPA, THF, -78 ºC; allyl bromide, 90%; **(b)** Grubbs (2nd generation) catalyst (50 mol%), CH_2Cl_2, Δ, 92%; **(c)** TBAT, MeCN, Δ, **139**/**140** (2:1); **(d)** H_2, Pd/C (20 psi), EtOH, 93%; TPAP, NMO, CH_2Cl_2, quant.

Scheme 22. Krafft's total synthesis of asteriscanolide **1**.

1.5.2.4 Snapper's Synthesis

An efficient synthesis of (+)- and (-)-asteriscanolide **1** was developed by Snapper's group[92] in the year 2000, featuring a novel intramolecular cyclobutadiene cycloaddition reaction, ring-opening metathesis (ROM), and subsequent Cope rearrangement[93] as the key transformations.

The successful route begins with the reduction of commercially available ketone **141** to form the nonracemic allylic alcohol **142**. The Saegusa oxidation[46] of the silyl enol ether derived from ketone **141**, followed by (*S*)-B-Me-CBS-catalysed enantioselectitve reduction[94] of the resultant enone generated (*S*)-dimetylcyclopentenol **142**. While this configuration of **142** led to natural product (+)-**1**, the use of (*R*)-B-Me-CBS catalyst in the reduction gave the antipode of **142**, which was used to prepare (-)-asteriscanolide **1** (**Scheme 23**).

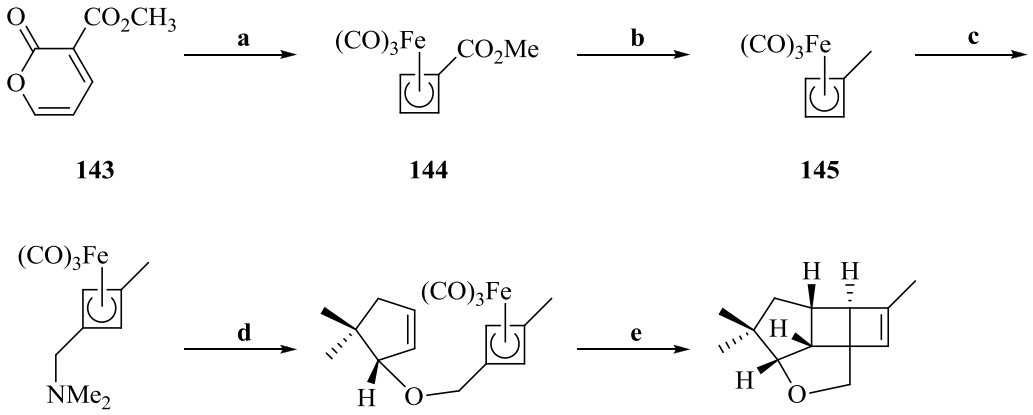


141 **142**

Reagents and conditions: **(a)** LDA, TMSCl, Et_3N; $Pd(OAc)_2$ (10 mol%), benzoquinone, 60%; **(b)** $BH_3{\cdot}OEt_2$, THF, (*S*)-B-Me-CBS (10 mol%), 56%, 94% *ee*.

Scheme 23. Snapper's synthesis of precursor **142**.

Mild heating of the photolysis product of commercially available α-pyrone **143** with $Fe_2(CO)_9$ achieved the iron-complexed cyclobutadiene ester **144**. Reduction of the ester functionality to a methyl group using LAH and boron trifluoride diethyl etherate gave **145**. Subsequent functionalisation of the cyclobutadiene moiety was accomplished by an electrophilic aminomethylation to provide *p*-substituted cyclobutadiene complex **146**, which after *in situ* methylation and etherification using the sodium alkoxide of homochiral **142** generated cycloaddition precursor **147**. Cycloadduct **148** was obtained upon heating **147** with trimethylamine *N*-oxide in acetone (**Scheme 24**).



143 **144** **145**

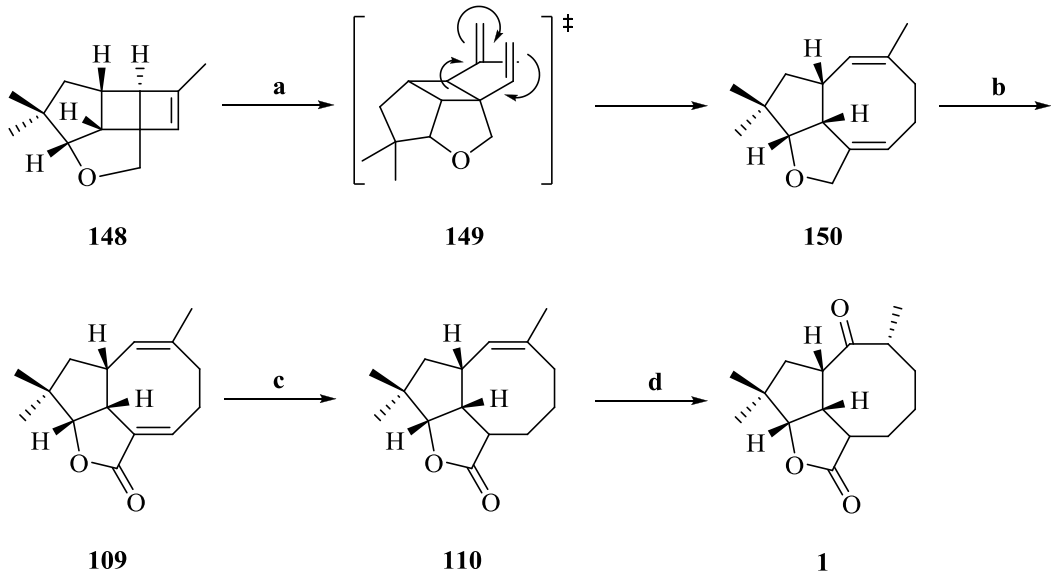
146 **147** **148**

Reagents and conditions: **(a)** hν, PhH; $Fe_2(CO)_9$, 50 ºC, 64%; **(b)** LAH, $BF_3{\cdot}OEt_2$, 93%; **(c)** $Me_2NCH_2NMe_2$, H_3PO_4, AcOH, 100 ºC, 67%; **(d)** MeI, THF; NaH, **142**, THF/DMF, 50%; **(e)** Me_3NO, acetone, 56 ºC, 63%.

Scheme 24. Snapper's synthesis of precursor **148**.

Treatment of **148** with Grubbs (2^{nd} generation) catalyst[62] in benzene under ethylene atmosphere induced a ring-opening metathesis and proceeded with a Cope rearrangement of the resulting ring-opened species, dialkenyl cyclobutane **149**, with relatively mild

reaction conditions to generate cyclooctadiene **150**. The allylic oxidation of **150** with pyridinium chlorochromate in dichloromethane gave Wender's intermediate,[80] cyclooctadiene **109**. The further elaboration of intermediate **110** to the target natural compound (+)-**1** was accomplished following Wender's synthetic sequence: Selective 1,4-reduction of the unsaturated lactone **109** using copper hydride, hydroboration of the remaining olefin **110**, and PCC oxidation of the resulting alkyl borane. The BH_3 reduction conveniently installed the required C-7 ketone (**Scheme 25**).



Reagents and conditions: **(a)** Grubbs (2nd generation) catalyst (5 mol%), ethylene, PhH, Δ, 50-80 ºC, 74%; **(b)** PCC, py, 4Å MS, CH_2Cl_2, 79%; **(c)** Red-Al®, CuBr, AcOH, THF, 89%; **(d)** $BH_3{\cdot}OEt_2$, Et_2, THF; PCC, py, 4Å MS, CH_2Cl_2, 60%.

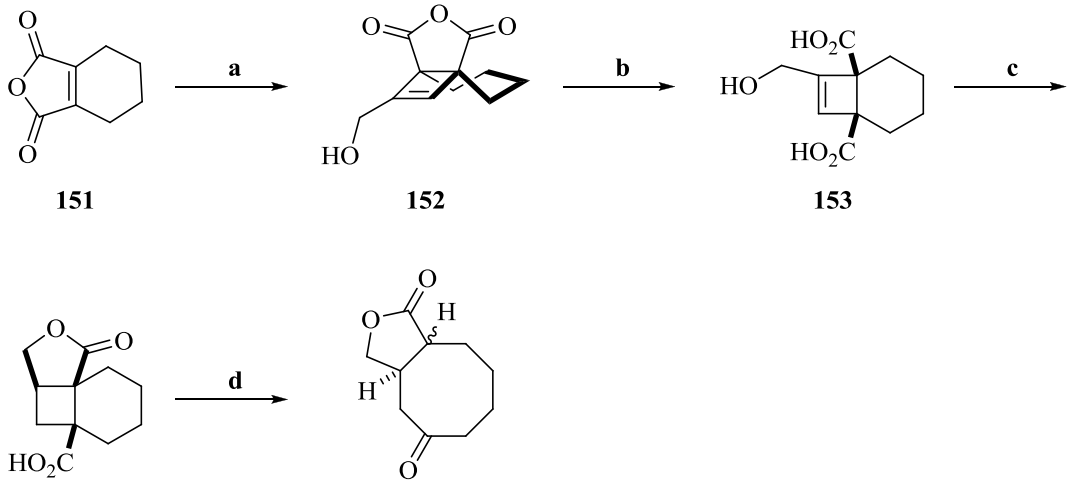
Scheme 25. Snapper's total synthesis of asteriscanolide **1**.

1.5.3 Previous Synthetic Approaches to Asteriscanolide **1**

1.5.3.1 Booker-Milburn's Approach

In 1994, Booker-Milburn and co-workers[95] described their first approach towards the synthesis of asteriscanolide **1**. The strategy involved a novel aza-de Mayo fragmentation[96,97] of a cyclobutane carboxylic acid, which was prepared by an efficient [2 + 2] photocycloaddition of tetrahydrophthalic anhydride (THPA) to propargyl alcohol.

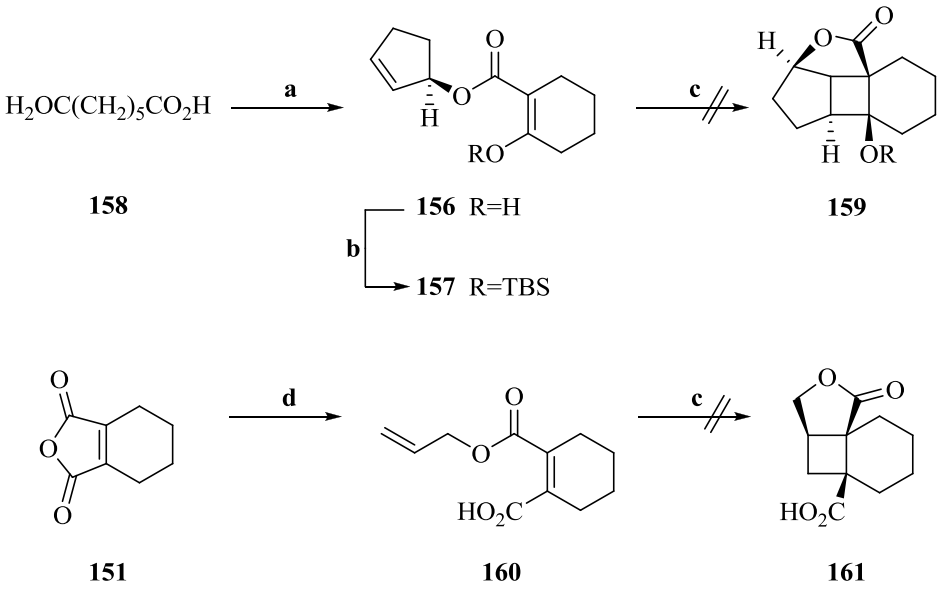
Irradiation of a solution of THPA **151** in acetonitrile with propargyl alcohol gave cyclobutene anhydride **152**. Subsequent hydrolysis employing aqueous tetrahydrofuran afforded hydroxyl diacid **153**. Hydrogenation, followed by acid-catalysed lactonisation produced the desired cyclobutane-carboxylic acid **154**. Conversion of the acid to the isocyanate was accomplished by treating **154** with diphenylphosphoryl azide, which was hydrolysed *in situ* to the amine and subsequently fragmented to access cylooctanone lactone **155** in good yield (**Scheme 26**).



Reagents and conditions: **(a)** propargyl alcohol, hν, MeCN, 1 h, 77%; **(b)** THF/H_2O, 85%; **(c)** H_2, Pd/C (1 atm), MeOH; *p*-TSA (cat), dioxane, Δ, 60%; **(d)** $(PhO)_2PON_3$, Et_3N, dioxane, Δ; 2 M HCl, *cis*/*trans* (2.8:1), 61%.

Scheme 26. Booker-Milburn's synthesis of precursor **155**.

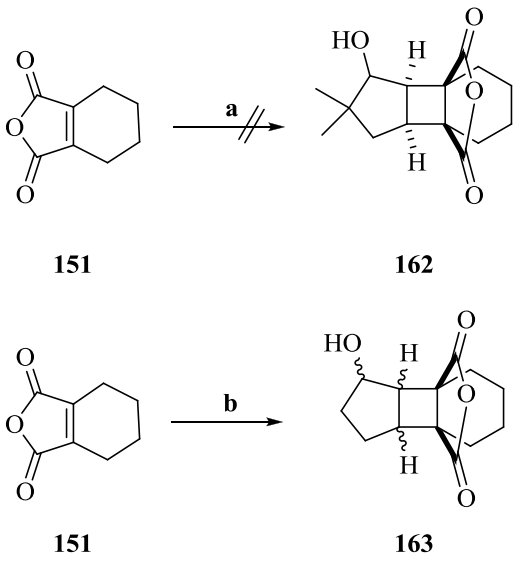
The initial strategy was abandoned as esters **156** and **157**, previously sythesised from **158**, were found to be inert to photolysis conditions; none of the intramolecular [2 + 2] photoadducts **159** were obtained. The failure of the reaction was rationalised on the basis of electronic grounds, and therefore, the photochemistry of more electron deficient acid-ester **160**, derived from THPA **151**, was investigated finding also to be inert to form photoadduct **161**. The problem was partly explained by the argument that esters have a conformational preference governed by electronic factors that prevent the adoption of the necessary conformation for the intramolecular cycloaddition (**Scheme 27**).



Reagents and conditions: **(a)** $(COCl)_2$, CH_2Cl_2; 2-cyclopentenol, Et_3N, CH_2Cl_2; NaH, PhMe, 59%; **(b)** NaH, TBSCl, THF, 91%; **(c)** hν, cyclohexane, MeCN or acetone; **(d)** allyl alcohol, Et_3N, DMPA, CH_2Cl_2, 85%.

Scheme 27. Booker-Milburn's attempt to precursors **159** and **161**.

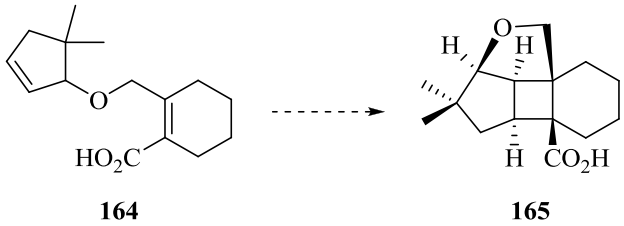
In the following two years, Booker-Milburn *et al.*[98] extended the investigation towards the synthesis of natural product **1** by an intermolecular [2 + 2] photocycloaddition between THPA **151** and racemic 5,5-dimethyl-2-cyclopentenol **142**,[99] but unfortunately, no [2 + 2] photoadducts **162** were observed. This was probably the result of unfavourable steric hindrance induced by the *gem*-dimethyl groups, as photolysis of THPA **151** and 2-cyclopentenol readily underwent to give photoadduct **163** (**Scheme 28**).



Reagents and conditions: **(a)** 5,5-dimethyl-2-cyclopentenol **142**, hν, MeCN, 48 h; **(b)** 2-cyclopentenol, hν, MeCN, 10 h, 70%.

Scheme 28. Booker-Milburn's attempt to precursor **162** and synthesis of precursor **163**.

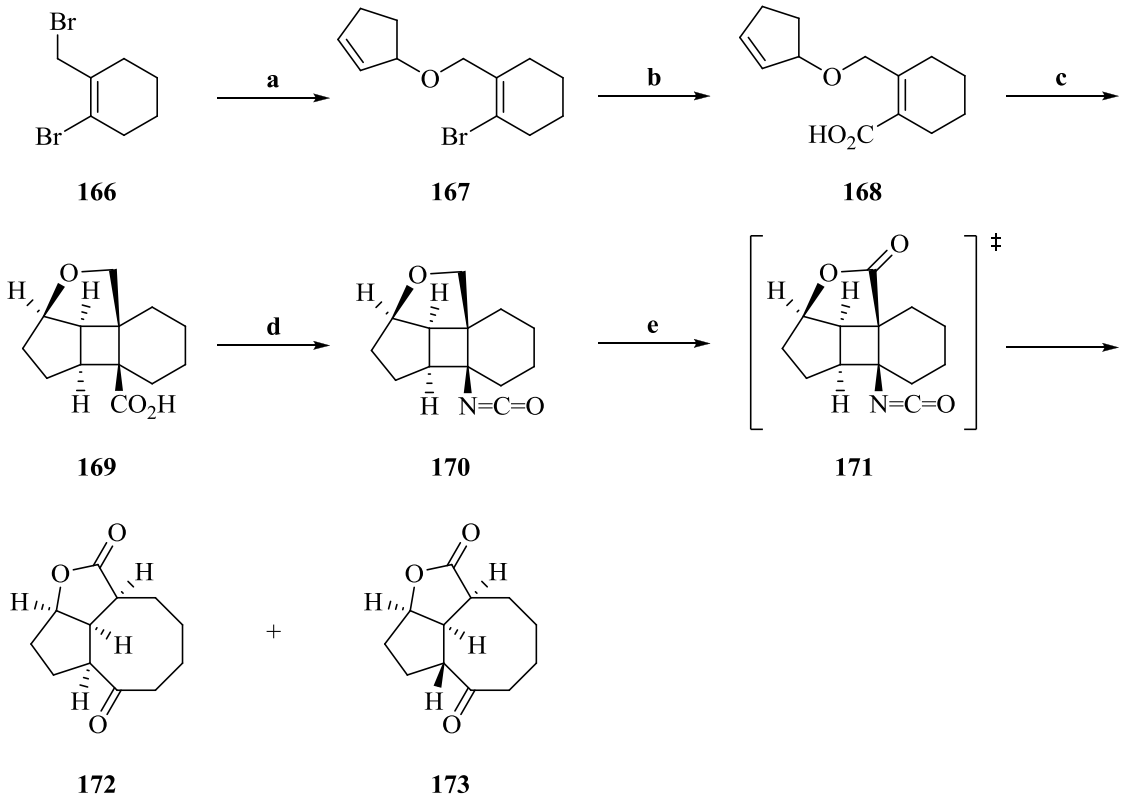
Furthermore, a more favourable acid-ether **164** was designed as a key intermediate towards **165**, assuming the carbonyl group was now absent and the sp^3-hybridised centre should allow a much greater degree of conformational flexibility during the cycloaddition step (**Scheme 29**).



Scheme 29. Booker-Milburn's proposal for synthesis of precursor **165**.

Thus, treatment of allylic bromide **166** with the sodium alkoxide of 2-cyclopentenol gave the required ether **167**. The preparation of the photocyloaddition precursor **168** was achieved by lithium-halogen exchange and quenching the resultant vinyllithium species with solid carbon dioxide. Photolysis of **168** in acetone afforded cyclobutane **169**, which was subjected to a Curtius rearrangement[100] to give isocyanate **170**. This isocyanate proved to be remarkably stable in both acid hydrolysis and chromatography. Hence, an unconventional protecting group was adopted in the following steps. Oxidation of **170** with

ruthenium tetraoxide led to the labile isocyanate-lactone **171**, which underwent the aza-de Mayo fragmentation *in situ* upon hydrolysis in aqueous acid followed by basification to yield cyclooctanone **172** in conjunction with the corresponding epimer **173** (**Scheme 30**).



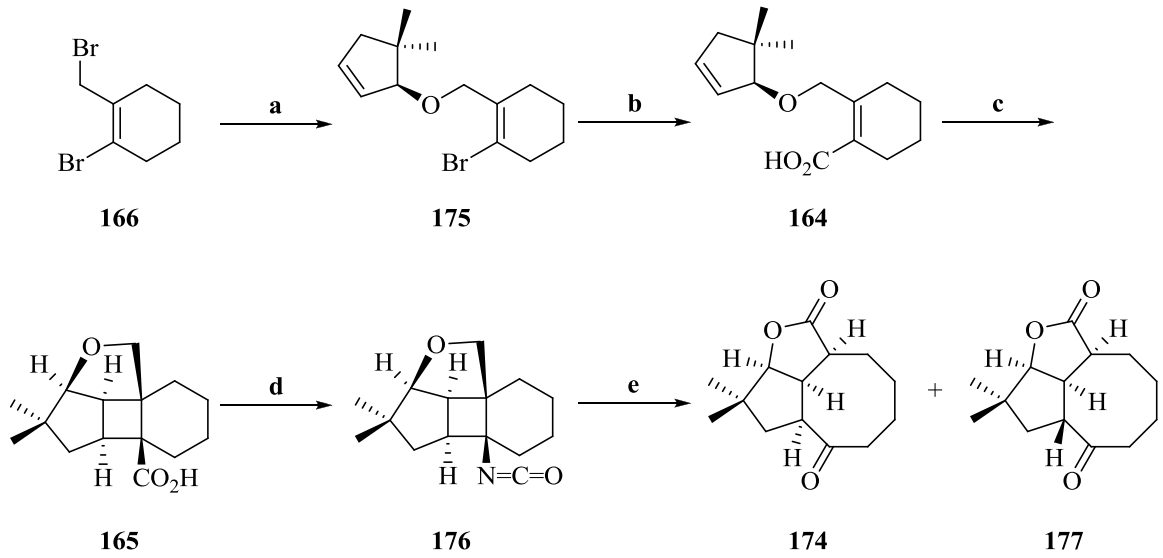
Reagents and conditions: **(a)** NaH, 2-cyclopentenol, DMF, 0 ºC, 73%; **(b)** *t*-BuLi, THF, -78 ºC; CO_2, 83%; **(c)** hν, acetone, 4 h, 75%; **(d)** $(PhO)_2PON_3$, Et_3N, dioxane, Δ, 89%; **(e)** RuO_2, $NaIO_4$, CCl_4, H_2O, MeCN; 2 M H_2SO_4; $NaHCO_3$, **172**/**173** (1:2), 55%.

Scheme 30. Booker-Milburn's synthesis of precursors **172** and **173**.

Booker-Milburn's strategy illustrated an elegant route towards asteriscanolide **1** *via* intramolecular [2 + 2] photocycloaddition and a Curtius rearrangement/ruthenium tetraoxide fragmentation sequence. This approach provides access to **172**, the core skeleton of **1**, which lacks the *gem*-dimethyl groups and the essential methyl group at C-7.

In 1997, final attempts to extend Booker-Milburn's model studies to the actual system of **1** were reported using the aforementioned synthetic route with 5,5-dimethyl-2-cyclopentenol **142**, leading to the eventual synthesis of 7-desmethylasteriscanolide **174**.[101]

Starting material dibromide **166** was treated with the sodium alkoxide of 5,5-dimethyl-2-cyclopentenol **142** to generate ether **175**. Metal-halogen exchange, followed by quenching the resulting vinyllithium with solid carbon dioxide furnished the α,β-unsaturated carboxylic acid **164**. Irradiation of **164** in acetonitrile with acetophenone as a sensitiser led to photoadduct **165**, which after a Curtius rearrangement with diphenylphosphoryl azide in toluene afforded the stable isocyanate **176**. As described before, ruthenium tetraoxide-mediated oxidation and subsequent hydrolysis of the corresponding isocyanate lactone formed a separable mixture of **174** and the 9-H epimer **177** (**Scheme 31**).

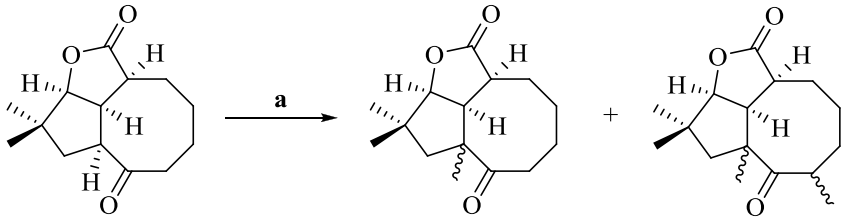


Reagents and conditions: **(a)** NaH, 5,5-dimethyl-2-cyclopentenol **142**, DMF, 0 ºC, 75%; **(b)** *t*-BuLi, THF, -78 ºC; CO_2, 81%; **(c)** hν, MeCN, PhCOMe, 3 h, 51%; **(d)** $(PhO)_2PON_3$, Et_3N, PhMe, 89%; **(e)** RuO_2, $NaIO_4$, CCl_4, H_2O, MeCN; 2 M H_2SO_4; dioxane, 100 ºC, **174**/**177** (1:1), 56%.

Scheme 31. Booker-Milburn's synthesis of precursors **174** and **177**.

At this stage, attention was focused on the introduction of the methyl group at C-7 in order to culminate **1**, which was initiated using a standard enolate protocol (**Scheme 32**). However, treatment of **174** with LDA and alkylation with methyl iodide was unsuccessful. The result was the undesired mixture of methylated product **178** and dimethylated **179**. Deprotonation of **174** gave the more substituted enolate at C-9, which underwent methylation to give **178**, rather than the expected kinetic enolate at C-7. Compound **179** arises from further alkylation of **178**. The deprotonation preference of the asteriscanolide **1** skeleton was confirmed, as a number of reaction conditions were applied without

improvement. The application of enamine chemistry to introduce the C-7 methyl group was equally unsuccessful giving either unreacted ketones or complex reaction mixtures.

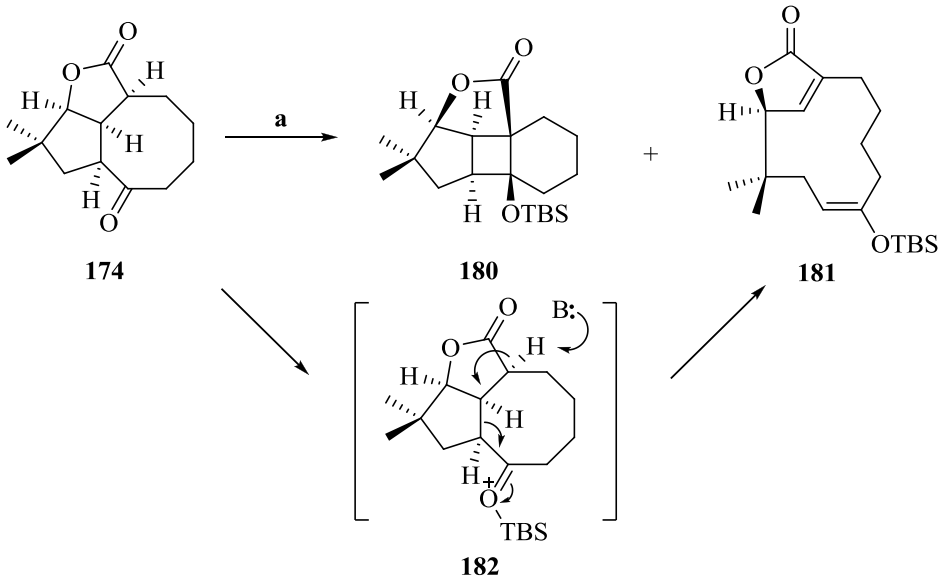


174 **178** **179**

Reagents and conditions: **(a)** LDA, THF, -78 ºC; MeI, **178**/**179** (1:1), 24%.

Scheme 32. Booker-Milburn's synthesis of precursors **178** and **179**.

An alternative approach towards **1** was proposed *via* TBS enol ether of **174** with TBSOTf in a basic media.[102] Unfortunately, none of the expected enol ethers were obtained, and the only products isolated were cyclobutane **180** and fragmented enol ether **181**. Cyclobutane **180** was derived by a transannular cyclisation,[103] ironically the exact reverse of the fragmentation used to form the starting material **174**. The second product, silyl enol ether **181**, was produced by a base-catalysed retro-Michael fragmentation of **182** (**Scheme 33**).

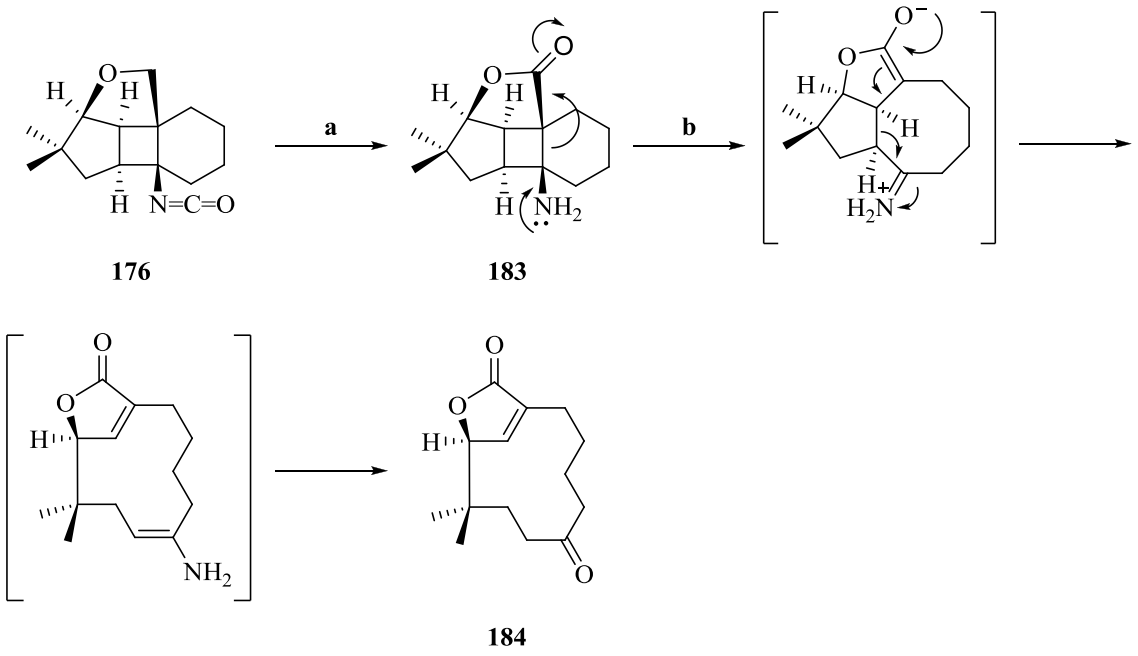


174 **180** **181** **182**

Reagents and conditions: **(a)** TBSOTf, Et_3N, CH_2Cl_2, RT, 1 h, **180**/**181** (1:1), 30%.

Scheme 33. Booker-Milburn's synthesis of precursors **180** and **181**.

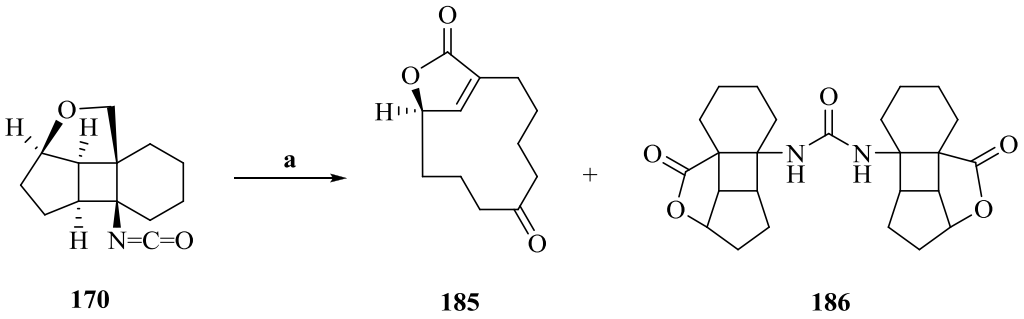
A related fragmentation sequence was also observed during the oxidation/hydrolysis of **176** after a polar intermediate **183** was isolated from the reaction mixture, which underwent a similar reaction to form **184** (**Scheme 34**).



Reagents and conditions: **(a)** RuO_2, $NaIO_4$, CCl_4, H_2O, MeCN; 4 M H_2SO_4, dioxane, 100 ºC, 15 min; **(b)** aq dioxane, 100 ºC, 2.5 h, 36% (over two steps).

Scheme 34. Booker-Milburn's synthesis of precursor **184**.

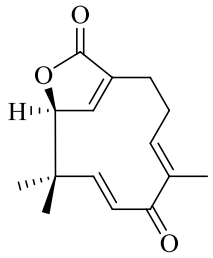
In the same manner, oxidation of **170**, followed by hydrolysis of the isocyanate induced the same fragmentation ring system **185** and dimerisation product **186** (**Scheme 35**).



Reagents and conditions: **(a)** RuO_2, $NaIO_4$, CCl_4, H_2O, MeCN; H_2O/dioxane, 100 ºC, **185** (2%), **186** (28%).

Scheme 35. Booker-Milburn's synthesis of precursors **185** and **186**.

These fragmentations gave rise to an identical butenolide-fused undecane skeleton found in naturally occurring asteriscunolide C **187** (**Figure 13**), and as structures related to **1** have been isolated from the same natural source of the astericunolides (*Astericus graveolens*), Booker-Milburn proposed that it is possible for the two skeletal arrangements to be biosynthetically related *via* the aforementioned retro-Michael fragmentation.



187

Figure 13. Asteriscunolide C.

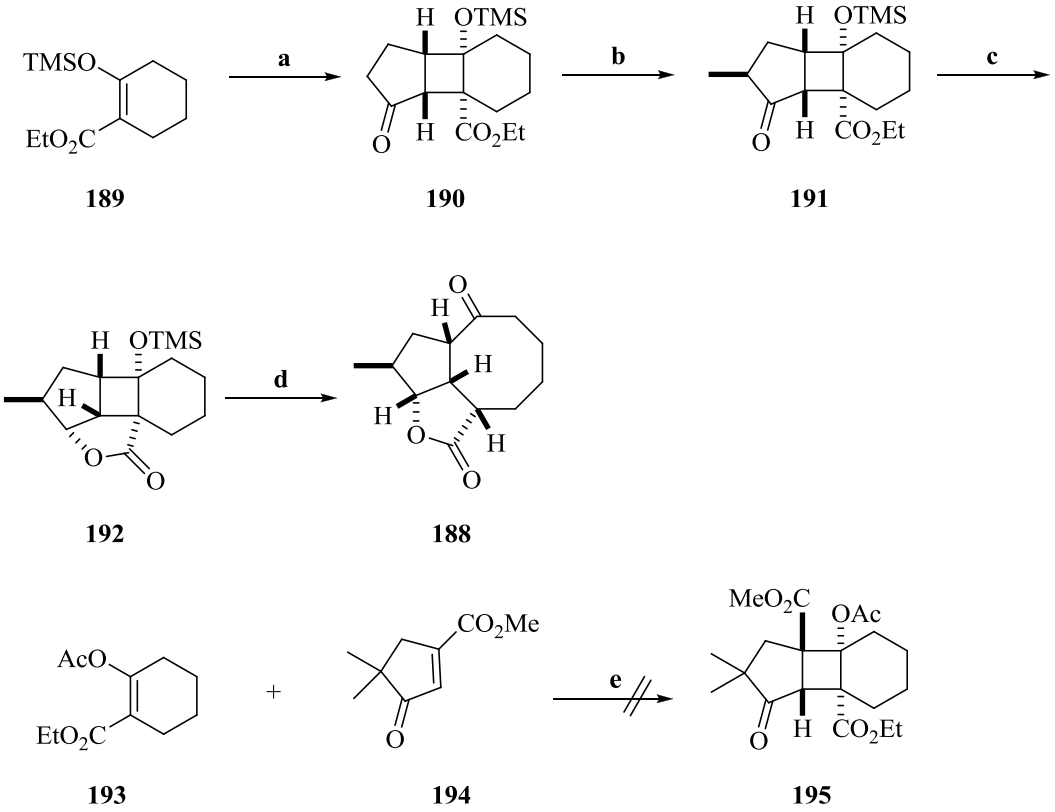
In summary, Booker-Milburn's laboratory revealed that **174** is prone to fragmentation, and the attempted methylation of **174** *via* enolate formation is in competition with the potential retro-Michael sequence previously mentioned. This would explain the reason why mono-alkylation at C-9 was observed rather than at C-7 and the apparent necessity to introduce the methyl group at C-7 prior to the formation of the eight-membered ring. A five step strategy for the synthesis of 7-desmethylasteriscanolide **174** has been described, highlighting an intramolecular [2 + 2] photocycloaddition-fragmentation (aza-de Mayo) sequence as the key transformation.

1.5.3.2 Lange's Approach

In 1996, Lange and Organ[104] published the synthesis of (±)-norasteriscanolide **188**, featuring a very similar route to that reported by Booker-Milburn *et al*.[95,98,101]

Irradiation of trimethylsilyl enol ether **189** in the presence of cyclopentenone formed photoadduct **190**, which was treated with LDA and methyl iodide to access mono-methyl product **191**. Treatment of **190** with an excess of these reagents failed to give desired *gem*-dimethyl group at C-11, resulting only in methylation at the 2-position, which would have involved an enolate double bond *exo*-cyclic to the cyclobutane ring. Reduction of **191** with

sodium borohydride, followed by *in situ* lactonisation produced **192**. Fluoride-ion mediated desilylation and subsequent spontaneous retro-aldol fragmentation yielded (±)-**188** in four steps. In addition, in their attempt to circumvent the methylation problem, the initial photoaddition was conducted using **193** and dimethylated enone **194**, but no desired photoadduct **195** was observed (**Scheme 36**).



Reagents and conditions: **(a)** cyclopentenone, hν, CH_2Cl_2, 15 h, 35%; **(b)** LDA, THF, -78 ºC; MeI, 95%; **(c)** $NaBH_4$, MeOH, 0 ºC, 70%; **(d)** TBAF, THF, 0 ºC, 90%; **(e)** hν.

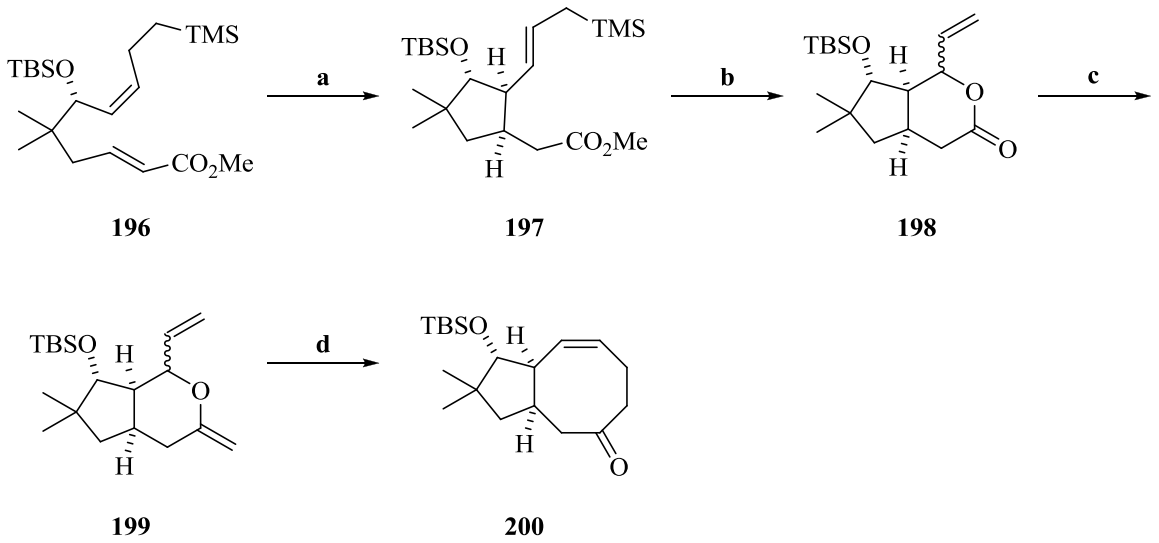
Scheme 36. Lange's synthesis of precursor **188** and attempt to precursor **195**.

Although Lange's approach shows to be efficient, as 5,8 ring system skeleton of **1** was prepared in a very stereoselective manner in only four steps, two methyl groups were still missing and the yield of the intermolecular photocycloaddition is significantly poor in comparison with Booker-Milburn's [2 + 2] photocycloaddtion,[101] who also had the *gem*-dimethyl groups installed prior to cycloaddition.

1.5.3.3 Sarkar's Approach

Sarkar and colleagues[105] reported an efficient route to the *cis* 5,8-fused bibyclic carbon framework of **1** in a four-step sequence. The strategy comprises the use of thermal ene cyclisation, lactonisation, and [3,3] sigmatropic rearrangement as the key bond-forming operations.

From the preparation of 1,6-diene **196**, previously described by Sarkar,[106] thermal 3-(3,4) ene cyclisation of **196** gave allylsilane **197**, which was exposed to *m*-CPBA, followed by stirring with silica gel in dicholomethane to generate **198**. Methylation of **198** with dimethyltitanocene gave the extremely labile enol ether **199**, which was subjected to thermolysis in a tube coated with sodium hydroxide to afford cyclooctane **200** in modest yield (**Scheme 37**).



196 **197** **198** **199** **200**

Reagents and conditions: **(a)** PhMe, 235 ºC, 18 h, 96%; **(b)** *m*-CPBA, Na_2HPO_4, CH_2Cl_2, RT; SiO_2, CH_2Cl_2, RT, 46%; **(c)** Cp_2TiMe_2, THF, 65 ºC, 24 h, 65%; **(d)** 180 ºC, PhMe, 24 h, 36%.

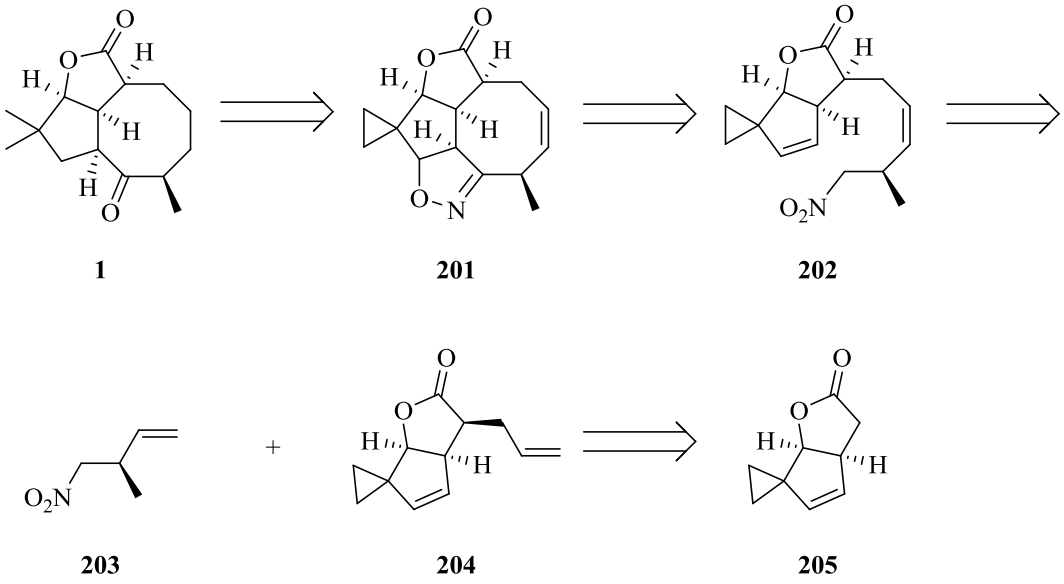
Scheme 37. Sarkar's synthesis of precursor **200**.

Sarkar's approach is a short and effective route for the construction of the 5,8-fused carbocyclic core of **1**. In general, the strategy operates in low yields, however, is an attractive alternative approach to **1**. More importantly, the synthetic procedure offers a

potential application to a number of terpenoid natural products with similar molecular structures.

1.5.3.4 Parsons' Approach

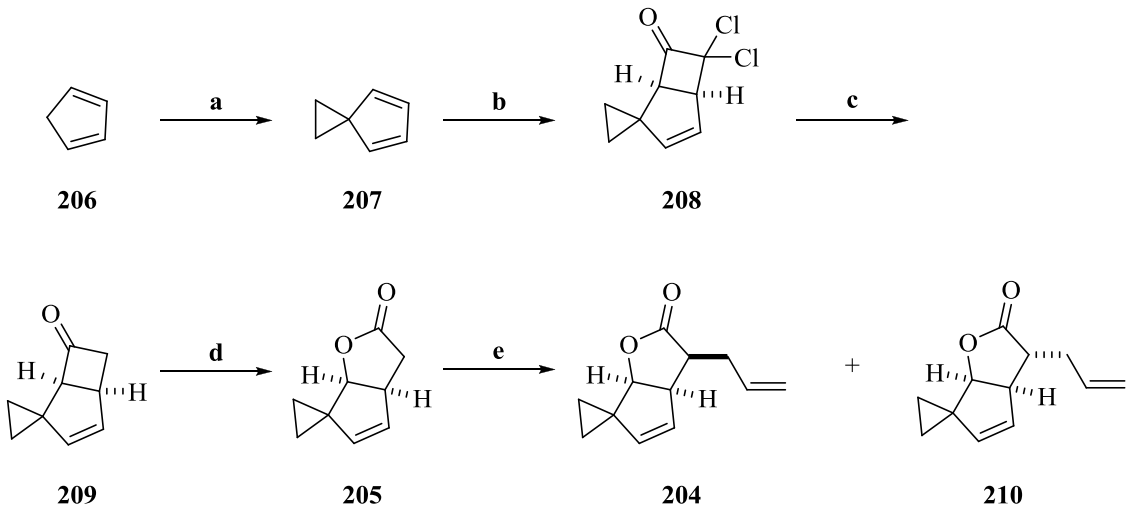
Recent synthetic investigations towards asteriscanolide **1** had been carried in our group by Parsons and Marsh.[2] The original synthetic approach aimed to prepare **1** *via* a global hydrogenation procedure and an acidic catalysed hydrolysis sequence of isoxazoline **201**. The key intermediate **201** could potentially be accessed through an intramolecular [3 + 2] nitrile oxide cycloaddition reaction of a nitrile oxide, which would be prepared *in situ* from nitro compound **202**. Alkene cross metathesis (CM) of nitroalkene **203** with allylic lactone **204** could provide cyclisation precursor **202**. Allyl lactone **204** might be assessed *via* the allylation of known lactone **205**[107] (**Scheme 38**).



Scheme 38. Parsons' first proposal for synthesis of asteriscanolide **1**.

Lactone **205** was readily prepared from commercially available cyclopentadiene **206** in a four-step sequence. A mixture of **206** with 1,2-dibromoethane was added to a suspension of sodium hydride in tetrahydrofuran, giving access to spirocyclic diene **207**. Addition of dichloroacetyl chloride to triethylamine in dichloromethane formed dichlorocyclobutanone **208** *via* a [2 + 2] ketene-olefin cycloaddition with dichloroketene.[108] Subsequent exposure

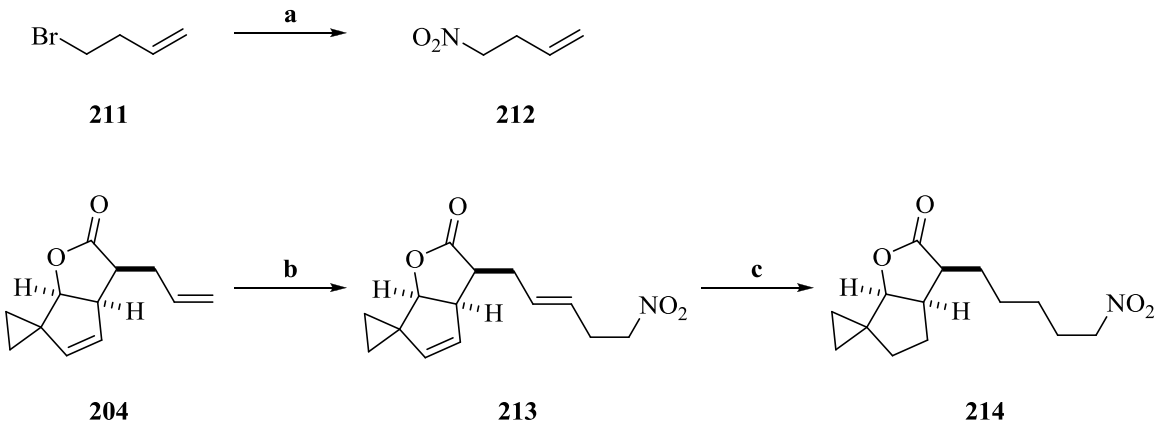
of **208** to zinc dust and ammonium chloride in methanol gave cyclobutanone **209**.[109] Baeyer-Villiger oxidation[57] of **209** gave lactone **205**.[107] Alkylation of **205** was accomplished using LHMDS and quenching the resultant enolate with allyl bromide to obtain a separable mixture of **204** and **210** in modest yield. Further attempts to enhance the yield and facial selectivity were unsuccessful (**Scheme 39**).



Reagents and conditions: **(a)** NaH, 1,2-dibromoethane, THF, 0 ºC, 70%; **(b)** $Cl_2CHCOCl$, Et_3N, CH_2Cl_2, 0 ºC, 71%; **(c)** Zn (4.8 eq), NH_4Cl (12 eq), MeOH, RT, 83%; **(d)** H_2O_2, AcOH, 0 ºC → RT, 18 h, 64%; **(e)** LHMDS, THF, -78 ºC; allyl bromide, -78 ºC → RT, **204**/**210** (1:1.1), 62%.

Scheme 39. Parsons' synthesis of precursors **204** and **210**.

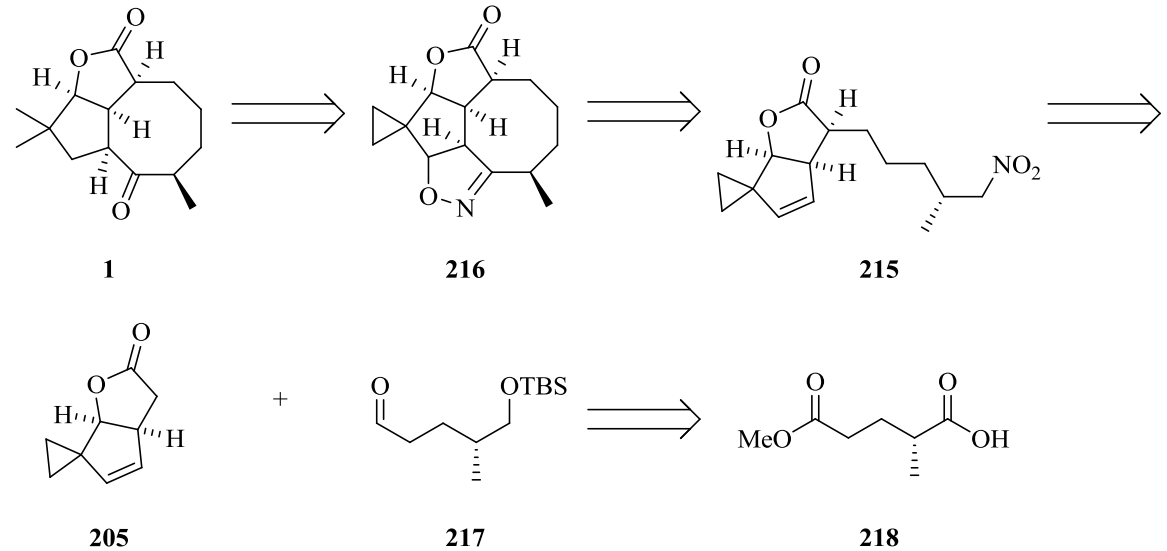
Cross metathesis of the diastereomerically pure allyl lactone **204** was performed utilising a readily available nitro olefin as a model to assess the viability of the construction of eight-membered ring through an intramolecular nitrile oxide-olefin cycloaddition. Bromide **211** was converted to the corresponding nitro product **212** by reaction with sodium nitrite in DMF.[110] Subsequent CM with **204** and 4-nitrobut-1-ene **212** gave olefin **213** in high yield, but only the *E*-configuration was obtained. Unfortunately, this geometrically restrictive *E*-alkene would not allow the INOC to occur. As such, attempted regioselectivity hydrogenation of the newly formed double bond in **213** using diimide[111] was not successful as only the fully saturated system **214** was isolated (**Scheme 40**).



Reagents and conditions: **(a)** $NaNO_2$, DMF, RT, 2 h, 43%; **(b) 212**, Grubbs (2^{nd} generation) catalyst (5 mol%), CH_2Cl_2, Δ, 18 h, 95%; **(c)** $H_2NNH_2{\cdot}H_2O$, 1 M aq $CuSO_4$ (cat), air, EtOH, Δ, 16 h, 75%.

Scheme 40. Parsons' synthesis of precursors **212** and **214**.

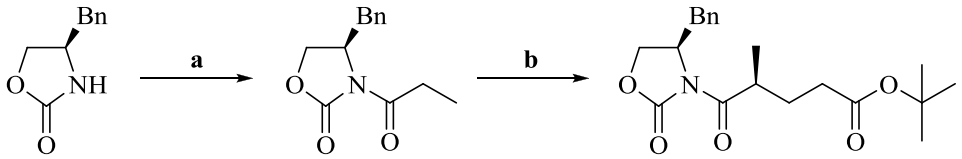
Parsons and Marsh illustrated another nitrile oxide cycloaddition alternative towards **1**, this time from nitroalkane **215** to generate isoxazoline **216**. This requires a suitable precursor, aldehyde **217**, which can be prepared from the known acid-ester **218**[112] with the aim to utilise aldol protocol to couple **205** with **217** (**Scheme 41**).



Scheme 41. Parsons' second proposal for synthesis of asteriscanolide **1**.

Due to the commercial unavailability of **218**, an alternative to construct the framework required for **217** was investigated using the chiral oxazolidionone chemistry. Commercially available (*R*)-4-benzyl-2-oxazolidinone **219** was subjected to *N*-acylation[113] to give the

desired chiral auxiliary **220**. Sequential conjugate addition of the titanium enolate of **220** to the *tert*-butyl acrylate[114] afforded oxazolidinone **221** (**Scheme 42**).

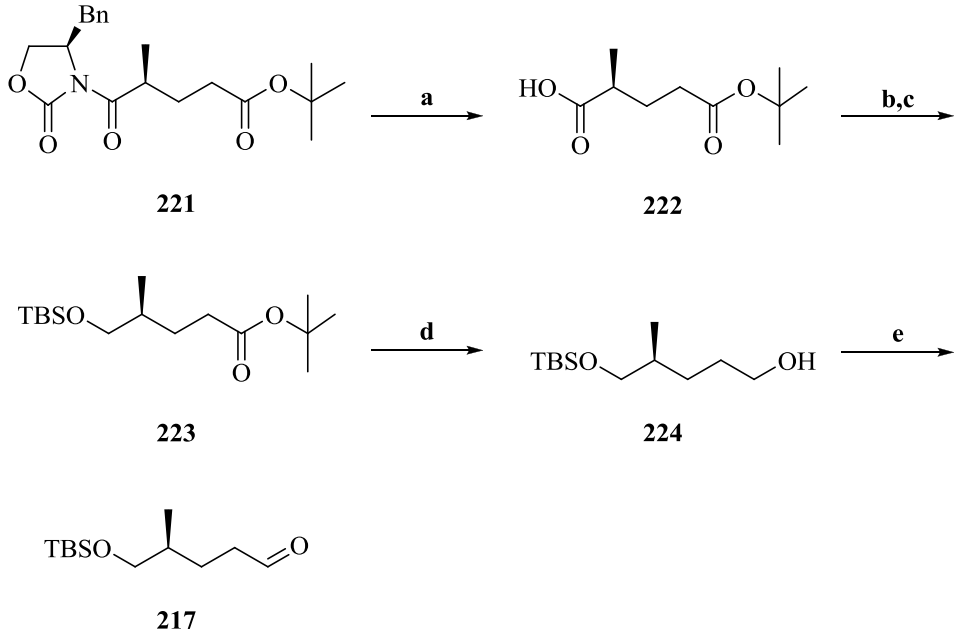


219 **220** **221**

Reagents and conditions: **(a)** Propionoic anhydride, LiCl, Et_3N, THF, -10 ºC → RT, 20 h, quant.; **(b)** Ti(O*i*-Pr)$_4$, $TiCl_4$, DIEA, CH_2Cl_2, 0 ºC, 2 h; *t*-butyl acrylate, 0 ºC → RT, 18 h, 89%.

Scheme 42. Parsons' synthesis of precursor **221**.

Cleavage of the auxiliary[115] in **221** gave carboxylic acid **222**, which was exposed to chemoselective reduction conditions, followed by protection of the resulting alcohol to form **223**. DIBAL-H reduction of the ester functionality and subsequent treatment of the corresponding alcohol **224** with IBX in refluxing acetone[116] afforded aldol precursor **217** (**Scheme 43**).

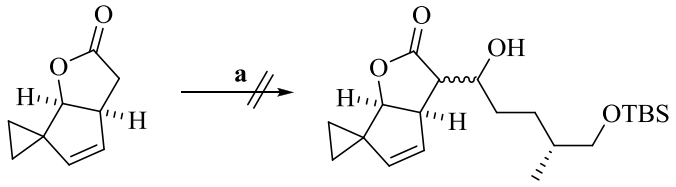


221 **222** **223** **224** **217**

Reagents and conditions: **(a)** H_2O_2, LiOH, THF, 0 ºC, 2 h, 92%; **(b)** $BH_3 \cdot SMe_2$, THF, 0 ºC, 4 h, 76%; **(c)** TBSOTf, 2,6-lutidine, RT, 18 h, 88%; **(d)** DIBAL-H, CH_2Cl_2, -78 ºC, 3 h, 89%; **(e)** IBX, acetone, Δ, 4 h, 87%.

Scheme 43. Parsons' synthesis of aldehyde **217**.

Disappointingly, the aldol reaction between precursors **205** and **217** did not give the expected β-hydroxylactone **225**. The reaction was originally tried treating **205** with LDA at low temperature and quenching the resulting enolate with the aldehyde **217**. However, only the starting material and some decomposition were observed (**Scheme 44**).



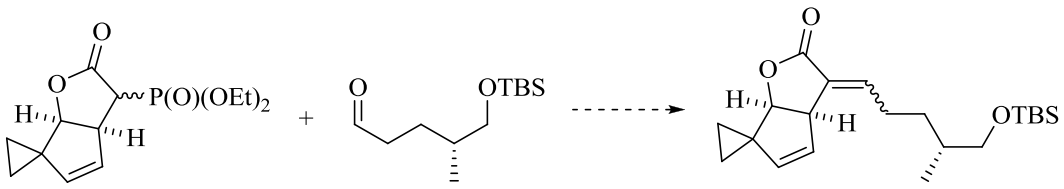
205 **225**

Reagents and conditions: **(a)** LDA, THF, -78 ºC; HMPA, **217**, -78 ºC → 0 ºC.

Scheme 44. Parsons' attempt to precursor **225**.

In addition, a series of reactions were undertaken, varying the base, the presence of a coordinating co-solvent, and the temperature during the formation of the enolate but unfortunately, no desired aldol product was obtained. Two possible explanations were rationalised, the first was concerned with the inability to generate the enolate, which standing against this, is the synthesis of **1** reported by Krafft group,[88,89] alkylation of the lactone was achieved in good yield under standard conditions to produce the RCM precursor, allyl lactone **137**, and the second, and most probable theory, attributed to the basicity of the enolate, meaning that if the enolate was more basic than nucleophilic, the lack of product and regeneration of the starting material could be justified.

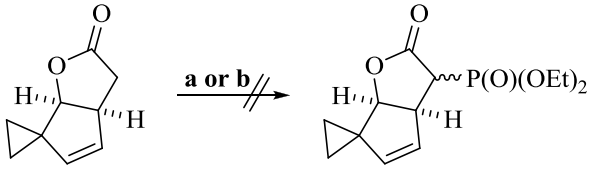
As a result of the unsuccessful aldol reaction, Parsons and Marsh illustrated a viable and efficient alternative using the Horner-Wadsworth-Emmons reaction (HWE).[117] The condensation of α-phosphonated lactone **226** and aldehyde **217** could led to the α,β-unsaturated product **227** (**Scheme 45**).



226 **217** **227**

Scheme 45. Parsons' proposal for synthesis of olefin **227**.

Treatment of **205** with LDA in tetrahydrofuran at low temperature, followed by addition of diethyl chlorophosphite and exposure to air did not generate the required phosphonate **226**.[118] In a similar manner, use of diethyl chlorophosphate and a second equivalent of base did not give rise to the desired phosphonated lactone **226** (**Scheme 46**).



205 **226**

Reagents and conditions: **(a)** LDA, THF, -78 ºC; $ClP(OEt)_2$, -78 ºC → RT; air; **(b)** LDA, THF, -78 ºC; $ClP(O)(OEt)_2$, -78 ºC; LDA, -78 ºC → RT.

Scheme 46. Parsons' attempt to phosphonated lactone **226**.

In summary, Parsons and Marsh described an attractive route for the synthesis of asteriscanolide **1** *via* an intramolecular [3 + 2] nitrile oxide cycloaddition reaction of isoxazoline **201** as the key step for the construction of the eight-membered ring. This approach provides a synthetic procedure to generate lactone **205** with a significant part of the required molecular architecture. However, only the synthesis of geometrically unfavorable INOC precursor, nitro *E*-olefin **213**, and fully saturated nitroalkene **214** were obtained. Furthermore, exhausting attempts for installing the carbon chain bearing the important homochiral methyl group in butyrolactone **205** have been carried without any success, and modifications in the strategy have also failed to approach **1**.

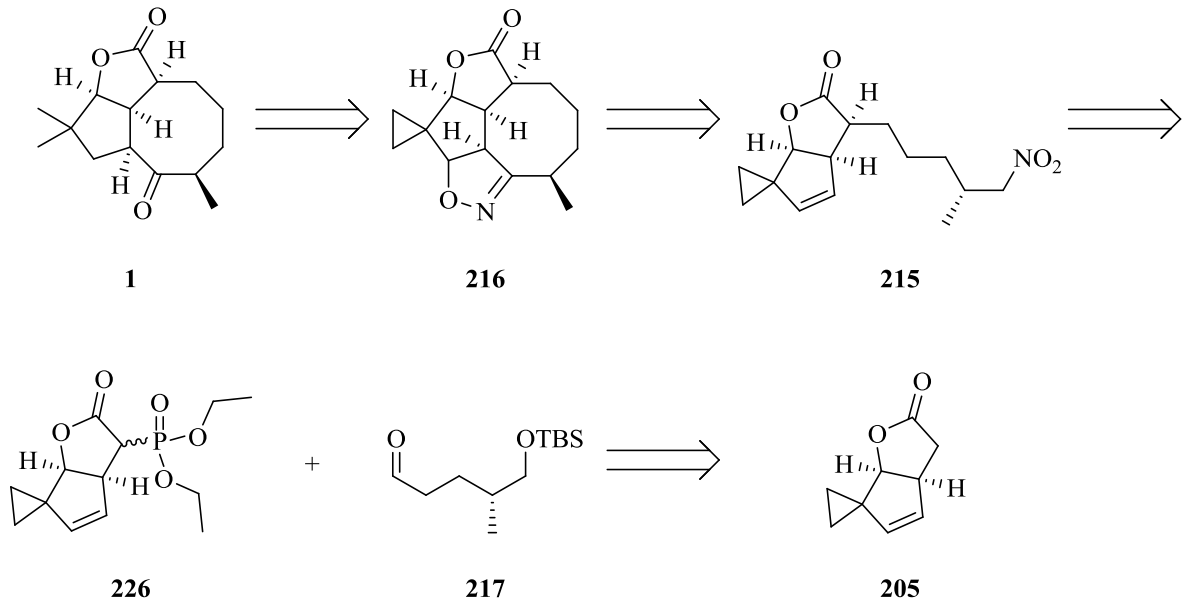
Consequently, further research in Parsons' laboratory has been taken place following this attractive approach towards natural product asteriscanolide **1**.

CHAPTER 2

RESULTS AND DISCUSSION

2.1 Retrosynthetic Analysis

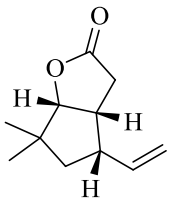
Following Marsh's work,[2] initial disconnective approach identified isoxazoline **216** as a suitable precursor that can potentially give access to asteriscanolide **1** in one synthetic operation with a global hydrogenation and an acidic workup sequence. The hydrogenation of **216** would potentially cleave the cyclopropane ring to form the *gem*-dimethyl function[119] and the N-O bond. Carrying out this reaction in the presence of acetic acid would conduct to the hydrolysis of the resultant imine to provide the required ketone, and hopefully, would also led to the dehydration of the β-hydroxyl group, which is necessary for the completion of the synthesis of natural product **1**. The isoxazoline precursor **216**, could potentially be prepared *via* an intramolecular [3 + 2] nitrile oxide-olefin cycloaddition reaction, with the required nitrile oxide being generated *in situ* by dehydration of nitro compound **215** using the Mukaiyama-Hoshino procedure.[120] The nitroalkene intermediate **215**, bearing the important enantiodefined methyl group, is to be assessed through a HWE olefination[117] of aldehyde **217** and phosphonated lactone **226**, followed by a selective conjugate reduction of the α,β-unsaturated carbonyl group and simple functional group manipulation. In turn, **226** should be accessible by phosphorylation of the well known lactone **205**[107] (**Scheme 47**).



Scheme 47. Retrosynthetic analysis.

2.2 Synthesis of Lactone **205**

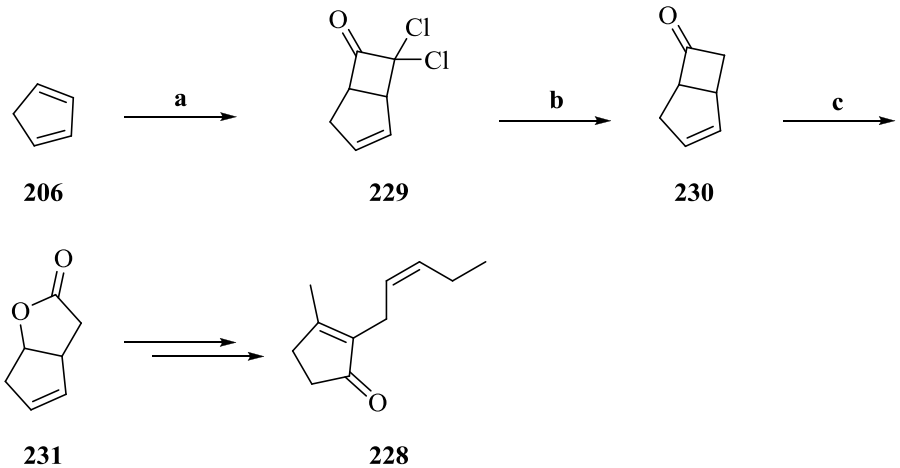
In our retrosynthetic analysis, the initial goal was to synthesise **205**[107] in an efficient multi-gram scale synthesis. The construction of the *cis*-fused bicyclic ring system **205** was a key step in our strategy, as it bears a significant part of target molecule **1**. However, a very similar fragment had also been of interest to another research group. As described before (see section 1.5.2.3), Krafft's[88,89] synthesis of **1** incorporates the design of lactone **133** in a twelve-step sequence prior to the formation of the cyclooctane ring (**Figure 14**).



133

Figure 14. Krafft's lactone.

In 1972, Grieco[121] reported the synthesis of *cis*-jasmone **228** employing the cycloaddition of dichloroketene to cyclopentadiene **206** in order to form **229**, followed by dechlorination to generate **230** and subsequent Baeyer-Villiger oxidation[57] to provide a related lactone **231** to that required in our synthetic plan (**Scheme 48**).



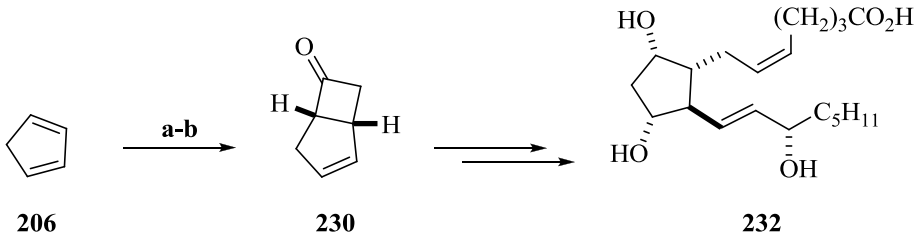
206 **229** **230**

231 **228**

Reagents and conditions: **(a)** $Cl_2CHCOCl$, Et_3N, hexane, 0 ºC, 85%; **(b)** Zn (6 eq), AcOH, RT, 95%; **(c)** H_2O_2, AcOH, 0 ºC → RT, 24 h, 90%.

Scheme 48. Grieco's synthesis of *cis*-jasmone **228**.

Another example of the conversion of cyclopentadiene **206** to bicyclic **230** was reported by Newton and Roberts[122] for the synthesis of prostaglandin-$F_{2\alpha}$ **232** (**Scheme 49**).

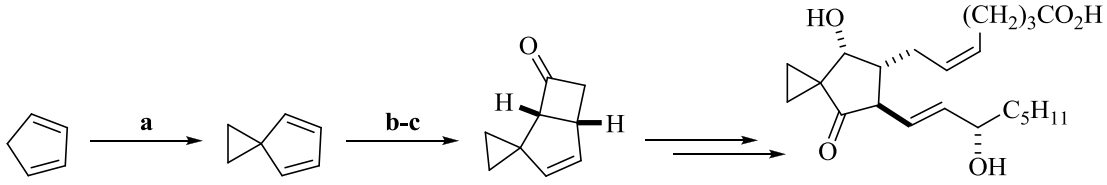


206 **230** **232**

Reagents and conditions: **(a)** $Cl_2CHCOCl$; **(b)** Zn, AcOH, 85% (over two steps).

Scheme 49. Newton and Robert's synthesis of prostaglandin-$F_{2\alpha}$ **232**.

More importantly, Newton and colleagues[109] have also published the synthesis of a cyclopropyl analogue of prostaglandin D_2 **233**, where the tricyclic ketone **209**, our required compound towards lactone **205**, was prepared in modest yield (**Scheme 50**).

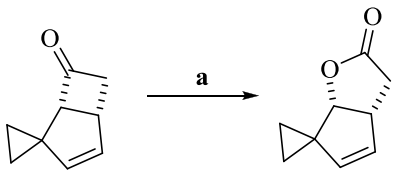


206 **207** **209** **233**

Reagents and conditions: **(a)** NaH, 1,2-dibromoethane, $Et_3(PhCH_2)NCl$, NaOH, RT; **(b)** $Cl_2CHCOCl$, Et_3N, hexane, 0 ºC, 60% (over two steps); **(c)** Zn (9.3 eq), NH_4Cl (4.2 eq), MeOH, RT, 16 h, 75%.

Scheme 50. Newton's synthesis of prostaglandin D_2 **233**.

Jaworski *et al.*[107] prepared cyclopropyl ketone **209** for the formation of analogues of prostaglandins, which was then treated under Baeyer-Villiger conditions[57] to give the desired lactone **205** in modest yield (**Scheme 51**).

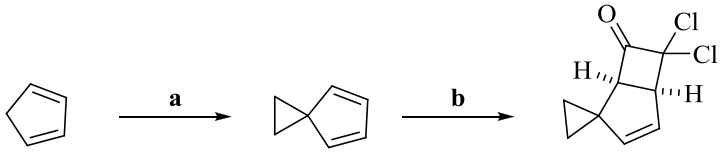


209 **205**

Reagents and conditions: **(a)** H_2O_2, AcOH, 35 h, 54%.

Scheme 51. Jaworski's synthesis of lactone **205**.

Following the procedure described by Green *et al.*,[108] a cooled mixture of freshly cracked and distilled cyclopentadiene **206** and 1,2-dibromoethane was added to a suspension of sodium hydride in tetrahydrofuran, giving spirocyclic diene **207**. Further to this, a solution of **207** and triethylamine in dichloromethane was exposed to dichloroacetyl choride, giving rise to **208** through a [2 + 2] cycloaddition reaction with dichloroketene (**Scheme 52**).

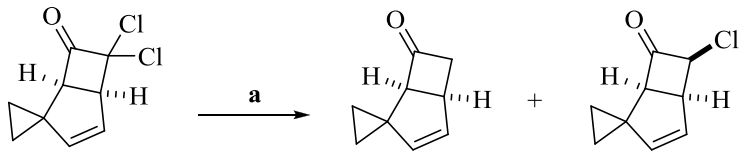


206 **207** **208**

Reagents and conditions: **(a)** NaH, 1,2-dibromoethane, THF, 0 ºC, 70%; **(b)** $Cl_2CHCOCl$, Et_3N, CH_2Cl_2, 0 ºC, 74%.

Scheme 52. Synthesis of precursor **208**.

With **208** in hand, we turn to the dechlorination methodology reported by Newton's group.[109] Dichlorocyclobutanone **208** was treated with zinc dust and ammonium chloride in methanol to give cyclobutanone **209** in 70% yield. In addition, a small quantity of the mono-chloride cyclobutanone **234** was also isolated (**Scheme 53**).

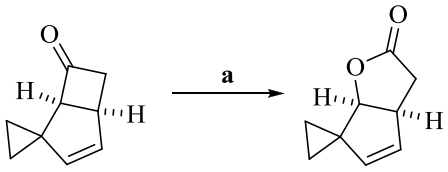


208 **209** **234**

Reagents and conditions: **(a)** Zn (4 eq), NH_4Cl (10 eq), MeOH, RT, 24 h, **209** (70%), **234** (5%).

Scheme 53. Synthesis of precursors **209** and **234**.

As described by Jaworski,[107] it was pleasing to find that oxidation of **209** employing Baeyer-Villiger[57] conditions was repeatable in our hands. Treatment of **209** with hydrogen peroxide in acetic acid gave rise to the expected lactone **205** in good yield, which was recrystallised to give a crystalline solid (**Scheme 54** and **Figure 15**).



209 **205**

Reagents and conditions: **(a)** H_2O_2, AcOH, 16 h, 0 ºC → RT, 84%.

Scheme 54. Synthesis of lactone **205**.

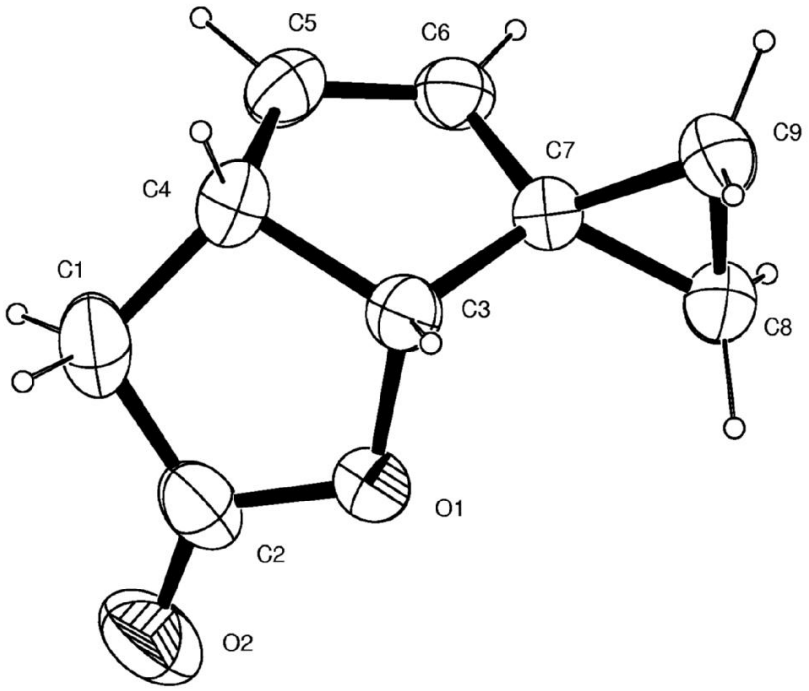
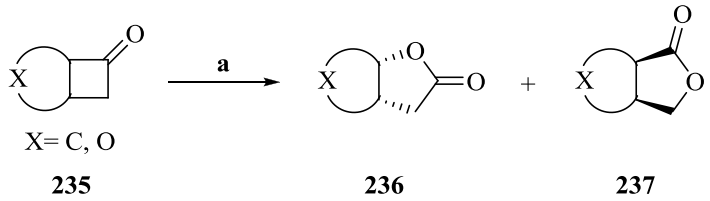


Figure 15. X-ray crystal structure of lactone **205**.

Hopefully, the introduction of the chiral C-7 methyl group into racemic lactone **205** would enable the isolation of (+)-asteriscanolide **1**. It was also reasoned that optically pure **205** could potentially be prepared by two different methodologies:

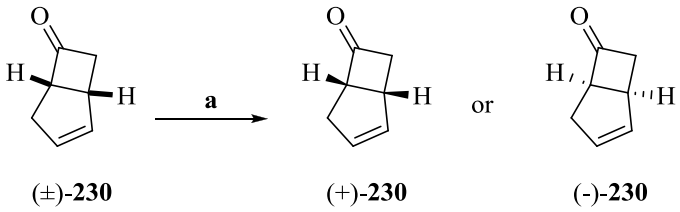
In 2004, Mihovilovic *et al.*[123] reported a series of stereoselective Baeyer-Villiger oxidations[57] of fused bicyclic ketones with a cyclobutanone structural motif **235** to give the corresponding regioisomeric lactones **236** and **237** using a biocatalyst (**Scheme 55**).



Reagents and conditions: **(a)** Recombinant *Escherichia coli*/whole-cells from *Brevibacterium*.

Scheme 55. Regiodivergent biooxidation of racemic bicycle ketone **235**.

On the other hand, Wallis and co-workers[124] from the Glaxo group research applied α-methylbenzylamine/bisulfite addition complex to racemic **230** (**Scheme 56**). This could be used in our project for the resolution of racemic **209**.

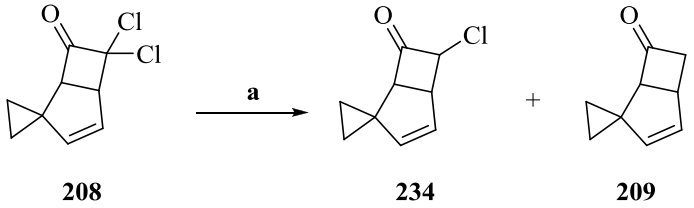


Reagents and conditions: **(a)** D-(+) or L-(-) 1-phenylethanamine, SO_2, H_2O, CH_2Cl_2; Na_2CO_3, H_2O.

Scheme 56. Wallis' resolution of racemic ketone **230**.

2.3 Synthesis of Lactone **238**

The partial dechlorination of **208** has also been observed by Hassner and co-workers,[125] where reduction of **208** with zinc dust (previously activated by treatment with 10% hydrochloric acid) and acetic acid in diethyl ether gave mainly chloroketone **234** and a minor quantity of cyclobutanone **209** (**Scheme 57**).

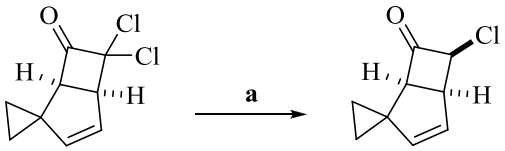


208 **234** **209**

Reagents and conditions: **(a)** Zn (1.3 eq), AcOH, Et_2O, RT, N/A%.

Scheme 57. Hassner's synthesis of precursors **209** and **234**.

Having efficiently prepared **209**, it was decided to investigate and optimize the conditions for the preparation of the mono-chloride ketone **234** in order to provide an alternative for the synthesis of the α-phosphonated lactone **226**. Hence, dechlorination of **208** was performed using three equivalents of zinc dust and ammonium chloride in methanol at 0 ºC for eight hours, and further stirred at room temperature for additional seven hours. This resulted with only the formation of **234** as a crystalline solid in good yield (**Scheme 58** and **Figure 16**).



208 **234**

Reagents and conditions: **(a)** Zn (3 eq), NH_4Cl (10 eq), MeOH, 0 ºC (8 h) → RT (7 h), 82%.

Scheme 58. Synthesis of precursor **234**.

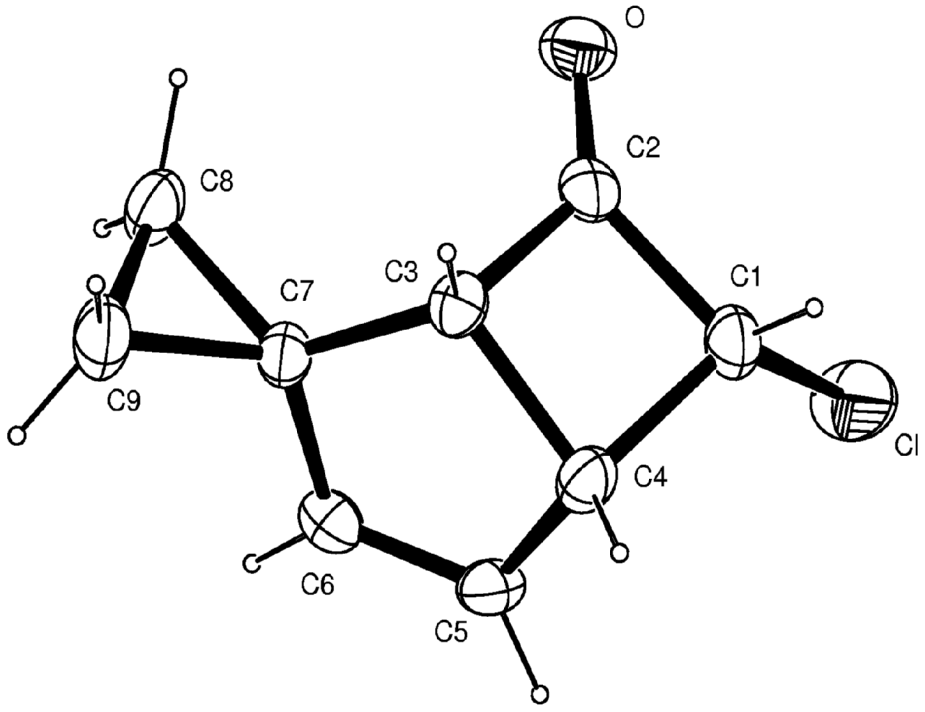
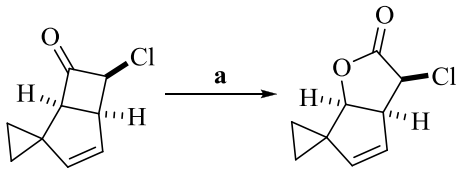


Figure 16. X-ray crystal structure of precursor **234**.

In the same manner as **209**, mono-chloride ketone **234** underwent a Baeyer-Villiger oxidation[57] with hydrogen peroxide in acetic acid, forming exclusively the mono-chloride lactone **238** as a crystalline solid in excellent yield (**Scheme 59** and **Figure 17**).



234 **238**

Reagents and conditions: **(a)** H_2O_2, AcOH, 16 h, 0 ºC → RT, 99%.

Scheme 59. Synthesis of lactone **238**.

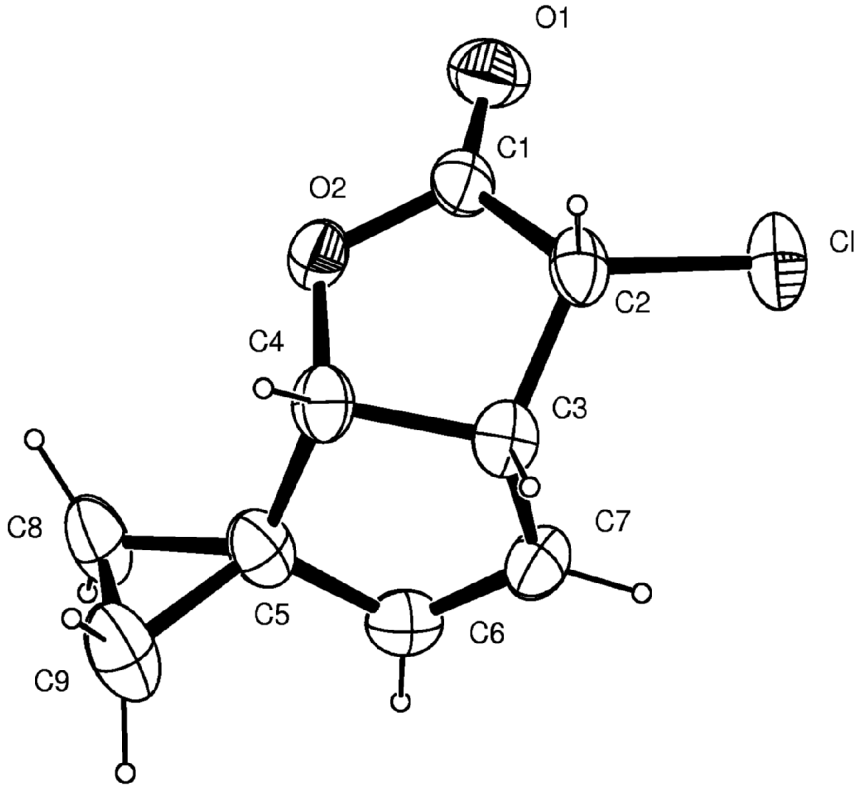


Figure 17. X-ray crystal structure of lactone **238**.

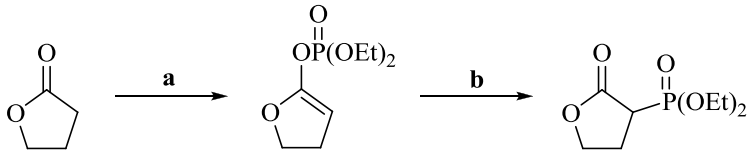
Up to this point, both lactones **205** and **238** represent viable precursors towards the phosphonated lactone **226**, one of the partners for the HWE condensation[117] strategy. The chemistry for the construction of **205** and **238** was easy to scale up and isolated as crystalline solids, thus providing direct structural evidence.

2.4 Synthesis of Phosphonated Lactone **226**

2.4.1 Subjecting Lactone **205** to Phosphonation Conditions

Having isolated lactones **205** and **238**, we first focused our attention on the conversion of **205** into the corresponding phosphonate compound **226**. With regards to the α-phosphonation of similar lactone systems, Wiemer *et al.*[118,126,127] have reported two different phosphonation methods of γ-butyrolactone **239** for the use as a precursor to the HWE[117] reaction.

The first route was based upon a 1,3-phosphorus migration in dialkyl vinyl phosphate **240** to produce the desired α-phosphono compound **241**[126,127] (**Scheme 60**).

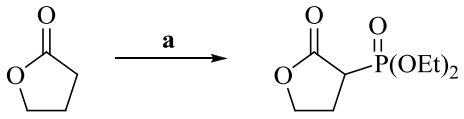


239 **240** **241**

Reagents and conditions: **(a)** LDA, THF; $ClP(O)(OEt)_2$, HMPA; **(b)** LDA, 68% (over two steps).

Scheme 60. Wiemer's phosphonation: First method.

An alternative strategy employs the reaction of an enolate with diethyl phosphorochloridite, followed by aerial oxidation to afford **241**[118] (**Scheme 61**).



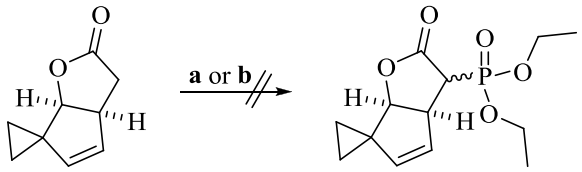
239 **241**

Reagents and conditions: **(a)** LDA, THF; $ClP(OEt)_2$; **(b)** air, 69% (over two steps).

Scheme 61. Wiemer's phosphonation: Second method.

Whilst there is no report of the synthesis of phosphonated bicyclic lactone **226**, we decided to apply Wiemer's methodology on our lactone **205**. Thus, treatment of **205** with lithium diisopropylamide in tetrahydrofuran at low temperature, followed by the addition of diethyl

chlorophosphate in hexamethylphosphoramide as a co-solvent and a second equivalent of base did not allow the formation of **226**. This only led to the decomposition of **205**. Likewise, treating **205** with lithium diisopropylamide, addition of diethyl chlorophosphite, and subsequent exposure to air did not give rise to the desired phosphono product **226**. Only decomposition was observed (**Scheme 62**).



205 **226**

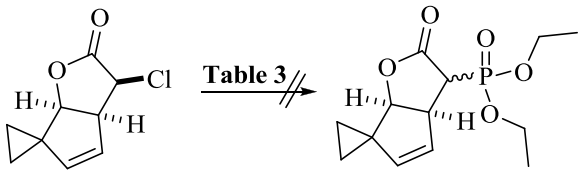
Reagents and conditions: **(a)** LDA, THF, -78 ºC; $ClP(O)(OEt)_2$, HMPA, -78 ºC; LDA, -78 ºC → RT; **(b)** LDA, THF, -78 ºC; $ClP(OEt)_2$, -78 ºC → RT; air.

Scheme 62. Attempt to phosphonation of lactone **205**.

2.4.2 Subjecting Lactone **238** to Phosphonation Conditions

In light of the unsuccessful generation of **226** utilising lactone **205**, we turn to investigate the possibility of forming a carbon-phosphorous bond on the mono-chlorinated lactone **238**. For this, attempts to synthesise dialkyl phosphonated lactone **226** were carried out using various chemical pathways including Michaelis-Arbuzov's reaction,[128] Michaelis-Becker's reaction,[129] and an organometallic reaction.[130,131]

Thus, lactone **238** was first subjected to a Michaelis-Arbuzov rearragement[128] (**Scheme 63**). **Table 3** summarises the variety of the reaction conditions used.



238 **226**

Scheme 63. Attempt to phosphonation of lactone **238**.

Entry	$P(OEt)_3$ (eq)	Solvent	Heating conditions	Time (h)	Product
1	1.1	-	Δ	48	SM + **226** (traces)
2	7	-	MW 150 W (130 ºC)	2.5	SM + **226** (traces)
3	1.1	-	MW 150 W (200 ºC)	2	Decomposition
4	1.1	PhMe	Δ	8	SM

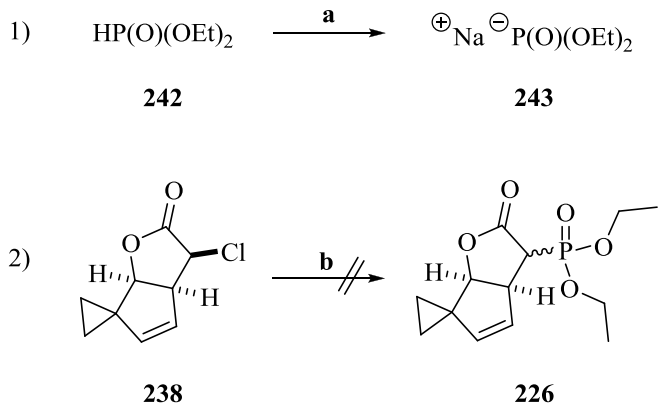
Table 3. Phosphonation approach of lactone **238** utilising Michaelis-Arbuzov reaction.

Initially we used triethyl phosphite (**Entry 1**). The reaction mixture was monitored by TLC when heating to reflux for two days, but only starting material **238** and traces of **226** were obtained.

The use of microwaves[132] in this type of reaction (150 W, 130 ºC) for two and a half hours provided trace amounts of **226** together with the starting material **238** (**Entry 2**), but higher heating with microwaves (150 W, 200 ºC) for two hours led to the total decomposition of the starting material **238** (**Entry 3**).

Solvents are not generally used in the Michaelis-Arbuzov transformation, but occasionally can control the reaction.[128] Therefore, the presence of a hydrocarbon solvent such as toluene[133] in this reaction was employed (**Entry 4**). The reaction was left to stir for eight hours in refluxing toluene. Unfortunately, only starting material **238** was isolated.

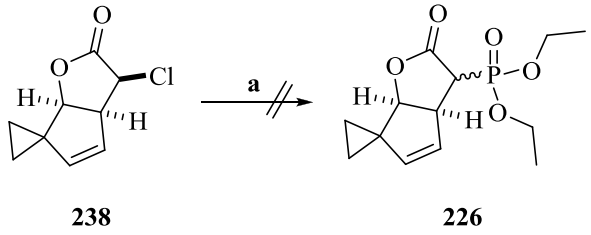
In a second approach to generate **226**, a Michaelis-Becker reaction[129] was performed. The first step was based on the treatment of diethyl phosphite **242** and sodium hydride in tetrahydrofuran at low temperature to give the phophonic salt **243**. The second step involved adding **243** to the mono-chloride lactone **238**. However, only traces of **226** were generated and the starting material was recovered (**Scheme 64**).



Reagents and conditions: **(a)** NaH, THF, 0 ºC, 5 min; **(b) 243**, 0 ºC → RT, 16 h.

Scheme 64. Attempt to phosphonation of lactone **238** utilising Michaelis-Becker reaction.

Finally, an altenative route was executed *via* an organometallic reaction.[130,131] Formation of a lithium compound from treating lactone **238** with *t*-butyllithium and subsequent addition of diethyl chlorophosphate at low temperature in tetrahydrofuran did not furnish **226**. Only the starting material **238** and some decomposition material were observed (**Scheme 65**).

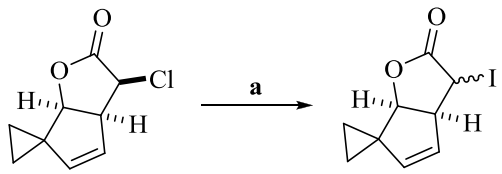


Reagents and conditions: **(a)** *t*-BuLi (2 eq), THF, -78 ºC, 2 h; $ClPO(OEt)_2$ (10 eq), -78 ºC, THF, 1 h.

Scheme 65. Attempt to phosphonation of lactone **238** utilising organometallic reaction.

2.4.3 Applying the Finkelstein Reaction to Lactone **238**

After the unsuccessful synthesis of α-phosphonated lactone **226**, an alternative strategy was investigated. In order to increase the reactivity of lactone **238**, we decided to convert **238** to the corresponding iodide **244** through the Finkelstein halogen exchange reaction.[134] This was achieved by treating **238** with sodium iodide in the presence of acetone under reflux for two days, giving **244** as a 24:1 mixture of diastereoisomers in 70% yield, where convex face selectivity was favoured (**Scheme 66** and **Figure 18**).



238 **244**

Reagents and conditions: **(a)** NaI (15 eq), acetone, Δ, 48 h, convex/concave face selectivity (24:1), 70%.

Scheme 66. Halogen exchange of lactone **238** utilising Finkelstein reaction.

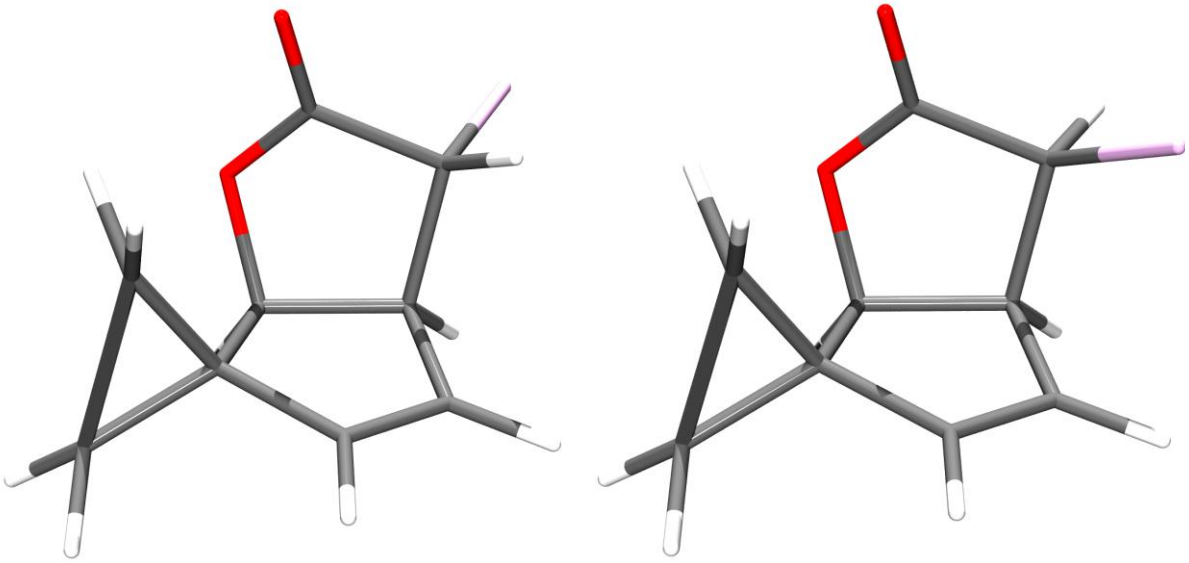
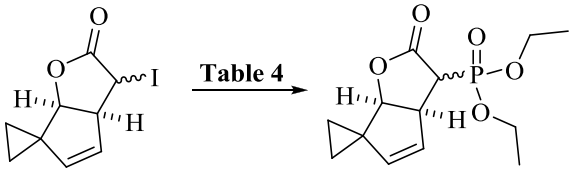


Figure 18. Favoured convex face selectivity (left) and disfavoured concave face selectivity (right) of the nucleophilic substitution of lactone **238**.

2.4.4 Subjecting Lactone **244** to Phosphonation Conditions

We next focused our attention towards the application of the Michaelis-Arbuzov reaction[128] to new mono-halogenated intermediate **244** (**Scheme 67**). **Table 4** summarises the variety of the reaction conditions used.



244 **226**

Scheme 67. Phosphonation of lactone **244** using $P(OEt)_3$.

Entry	$P(OEt)_3$ (eq)	Heating conditions	Time (h)	Yield (%)	Face selectivity[a] (convex:concave)
1	1.2	Δ	16	20	5:1
2	1.2	MW 150 W (200 ºC)	0.03	21	4:1
3	2	MW 150 W (125 ºC)	1	40	6:1
4	6	MW 150 W (130 ºC)	1.5	50	6:1
5	7	MW 150 W (130 ºC)	2.5	60	5:1
6	7.5	MW 150 W (135 ºC)	3	60	5:1

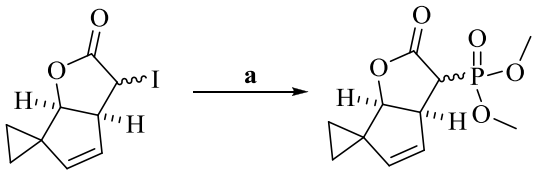
[a]Ratio determined by ^{1}H NMR analysis.

Table 4. Phosphonation of lactone **244** utilising Michaelis-Arbuzov reaction.

It was pleasing to find that treatment of **244** with triethyl phosphite under reflux for sixteen hours finally afforded the desired α-phosphonated precursor **226** as an inseparable 5:1 mixture of diastereoisomers in 20% yield with the expected phosphonate substituent on the convex face as the major product (**Entry 1**).

Microwave irradiation[132] with the same equivalents of the phosphonation reagent for two minutes increased the yield (**Entry 2**). We also observed a significant improvement on the formation of **226** (**Entry 3** to **6**) with a 60% of optimum yield (**Entry 5** and **6**) when using MW and increasing the number of equivalents of $P(OEt)_3$, reaction time, and temperature.

In addition, compound **244** was exposed to microwaves using trimethyl phosphite for three hours, affording **245** as an inseparable 3:1 mixture of diastereoisomers in 10% yield, favouring the phosphonate ester placed on the convex face of the system (**Scheme 68**).



244 **245**

Reagents and conditions: **(a)** $P(OMe)_3$ (7 eq), MW 150 W (105 ºC), 3 h, convex/concave face selectivity (3:1), 10%.

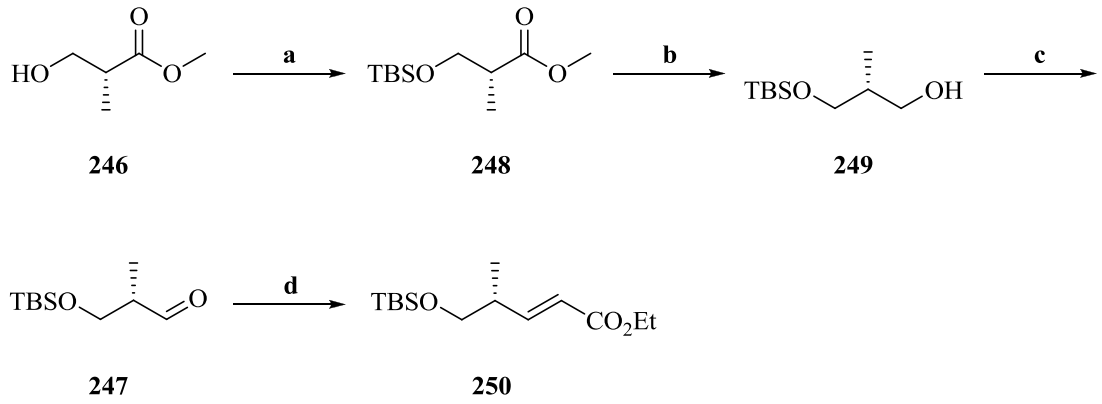
Scheme 68. Phosphonation of lactone **244** using $P(OMe)_3$.

2.5 Synthesis of Aldehyde **217**

In an initial investigation by Marsh[2] it was found that chiral aldehyde **217** could be synthesised by the use of a chiral auxiliary.[113-115] However, an alternative strategy for the construction of **217** was envisaged.

The commercially available (2*R*)-(-)-(3)-hydroxy-2-methylpropionate **246**, whose chiral carbon potentially represented the C-7 methyl group of asteriscanolide **1**, was chosen as a starting material for the synthesis of aldehyde **217**.

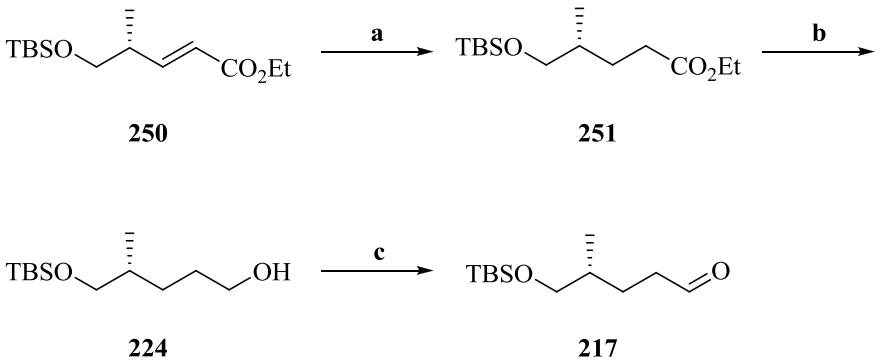
Due to the presence of the aldehyde functionality **247** adjacent to the asymmetric centre, it was necessary to apply a methodology that did not affect the optical purity.[135] The Wittig chiral aldehyde **247** was prepared according to the literature previously described by a number of research groups,[136-138] with slight modifications.[139] The free hydroxyl group of Roche ester **246** was protected as the TBS ether **248**, followed by reduction of the ester with 2.2 equivalents of diisobutylaluminium hydride to furnish alcohol **249**. The use of one equivalent of DIBAL-H to form directly aldehyde **247** was unreliable as the desired aldehyde **247** was formed in only 50% yield. As such, a two-step sequence was used. Reduction of **248** afforded the corresponding alcohol **249** in 94% yield. Subsequent Parikh-Doering oxidation[140] using sulfur trioxide pyridine complex in dimethyl sulfoxide and dichloromethane generated aldehyde **247** in 84% yield, which was stored in the freezer at -30 ºC to reduce the possibility of racemisation of a potentially thermally sensitive α-chiral stereocentre. Aldehyde **247** underwent a two carbon homologation employing a Wittig ylide, (carbethoxymethylene)triphenylphosphorane in dichloromethane at room temperature, giving the *E*-alkene of α,β-ester **250** as a single isomer in excellent yield (**Scheme 69**).



Reagents and conditions: **(a)** TBSCl (1.4 eq), imidazole (1.4 eq), DMPA (10 mol%), CH_2Cl_2, 0 ºC → RT (16 h), 96%; **(b)** DIBAL-H (2.2 eq), CH_2Cl_2, - 78 ºC → RT (16 h); $NaKC_4H_4O_6$, 16 h, 94%; **(c)** SO_3·py (4 eq), Et_3N (5 eq), Me_2SO, CH_2Cl_2, 0 ºC → RT (16 h), 84%; **(d)** $Ph_3P{=}CHCO_2Et$ (1 eq), CH_2Cl_2, RT, 16 h, 99%.

Scheme 69. Synthesis of precursor **250**.

Alkene **250** was then treated with substoichiometric amounts of platinum oxide in ethyl acetate under hydrogen gas for twenty four hours to give ester **251** in 97% yield. Marshall and co-workers,[141] however, utilised palladium on carbon as the hydrogenation catalyst, where they reported that the use of ethyl acetate was important, as the choice of ethanol led to the complete loss of the TBS ether. We decided to prepare aldehyde **217** in a similar two-step sequence for the same reason than aldehyde **247**. Although elaboration of **251** to the corresponding alcohol **224** has been accomplished by using DIBAL-H[137,141] or LiCl-$NaBH_4$,[138] we used instead lithiumaluminium hydride in tetrahydrofuran at low temperature, which furnished **224** in excellent yield. It was found that Nicoalou[142] and Marshall[143] had synthesised aldehyde **217** by exposing alcohol **224** to Swern oxidation conditions.[83] On the other hand, Marsh[2] used IBX in acetone.[116] In our project, aldehyde **217** was prepared from alcohol **224** under Parikh-Doering conditions[140] with sulfur trioxide pyridine complex in dimethyl sulfoxide and dichloromethane to give rise to **217** in 92% yield (**Scheme 70**).



Reagents and conditions: **(a)** H_2, PtO_2 (10 mol%), EtOAc, 24 h, 97%; **(b)** $LiAlH_4$ (1.1 eq), THF, 0 ºC, 3 h, 99%; **(c)** SO_3·py (4 eq), Et_3N (5 eq), Me_2SO, CH_2Cl_2, 0 ºC → RT (16 h), 92%.

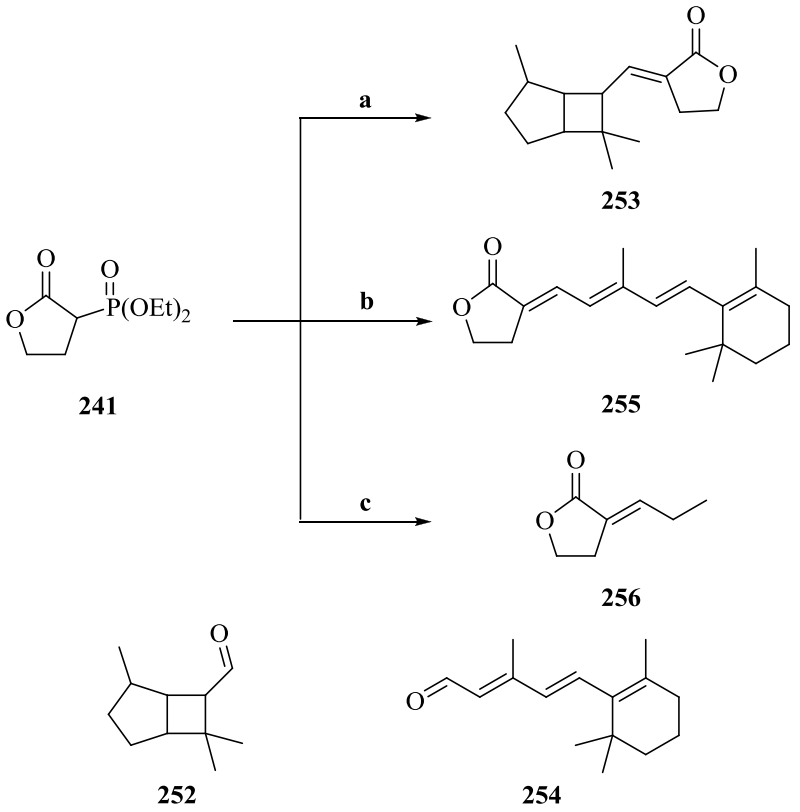
Scheme 70. Synthesis of aldehyde **217**.

This strategy demonstrated to be a reliable route for the construction of aldehyde **217**, which incorporates the enantiodefined C-7 methyl group.

2.6 Synthesis of Nitroalkene **215**

2.6.1 The Horner-Wadsworth-Emmons Approach

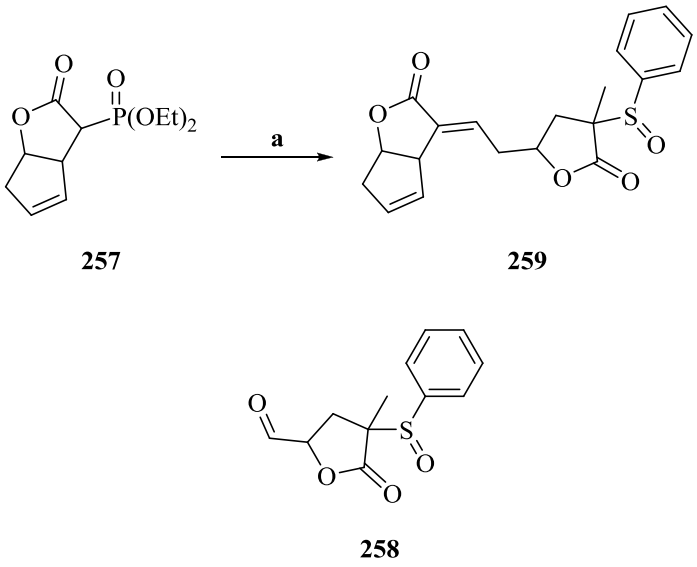
In search of a viable and efficient route for the construction of alkene **227** *via* the HWE reaction,[117] we found that **241** has been extensively studied and employed as a parter for the HWE reaction. Sodium hydride,[144,145] nitrogenated bases in the presence of LiCl,[146,147] and potassium hexamethyldisilazane[118,148] are among the basic conditions used. To illustrate, Rosini and colleagues[146] published the condensation of γ-butyrolactone **241** with aldehyde **252** to give **253** using DBU with LiCl. Mathies *et al.*[144] reported the condensation of lactone **241** with aldehyde **254** to form **255** using sodium hydride. Additionally, Weimer and co-workers[118] described the selective synthesis of *E*-propylidene lactone **256** from **241** and propionaldehyde using KHMDS (**Scheme 71**).



Reagents and conditions: **(a)** LiCl, DBU, THF; **252**, THF, *Z*/*E* (3:2), 72%; **(b)** NaH, THF, 0 ºC; **254**, THF, 96%; **(b)** KHMDS, 18-crown-6, THF, -78 ºC; propionaldehyde, THF, 75%.

Scheme 71. Examples of HWE condensation of γ-butyrolactone **241**.

In 1994, Kishimba[148] published the condensation of γ-butyrolactone **257** with aldehyde **258** employing sodium hydride in tetrahydrofuran to give *E*-olefin **259** in poor yield (**Scheme 72**).



257 **259**

258

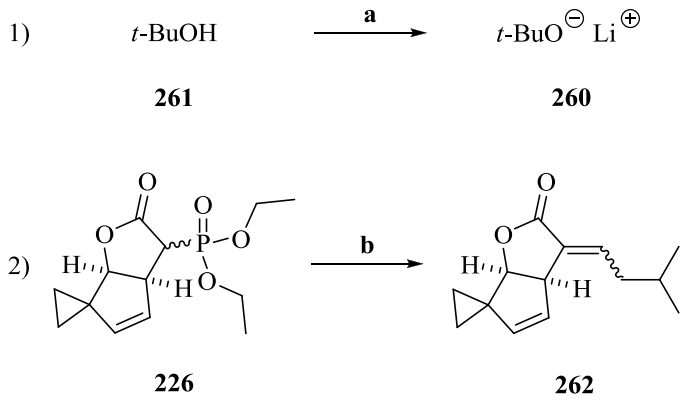
Reagents and conditions: **(a)** NaH, THF; **258**, 12%.

Scheme 72. Kishimba's condensation of γ-butyrolactone **257**.

So far, in the chemistry literature, there has been no report of a bicylic lactone such as **205** participating in a HWE process. In spite of this, it was reasoned that the HWE condensation could potentially be an efficient key step towards the synthesis of nitroalkene **215**.

2.6.1.1 Model Study

To investigate the plausibility of the HWE[117] approach to phosphonated lactone **226** with an aldehyde, a brief model study was conducted. For this investigation, the condensation was performed in two steps and commercially available isovaleraldehyde was used to represent the HWE partner. Thus, compound **226** was exposed to lithium *tert*-butoxide **260**, prepared *in situ* by subjecting *tert*-butanol **261** to *n*-butyllithium at low temperature in tetrahydrofuran, followed by the addition of isovaleraldehyde. It was pleasing to discover that condensation of **226** did actually take place, giving rise to the alkene **262** as a 1:1.1 mixture of *Z*/*E* geometric isomers in 45% yield (**Scheme 73**).

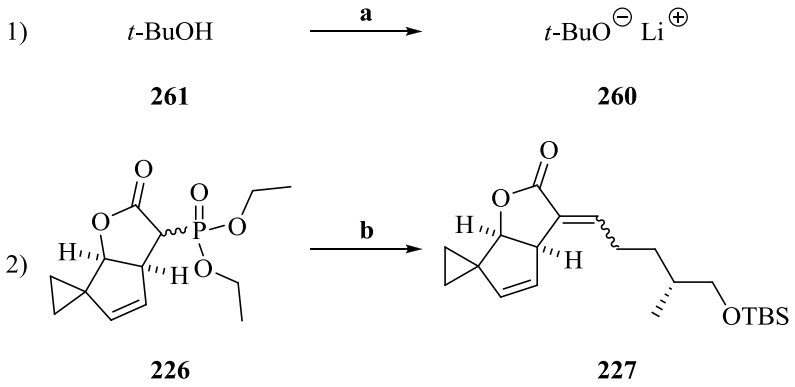


Reagents and conditions: **(a)** *n*-BuLi (1.1 eq), THF, -70 ºC, 10 min; **(b) 260**, -50 ºC, 15 min; isovaleraldehyde, THF, -70 ºC (2 h) → RT (16 h), *Z*/*E* (1:1.1), 45% (over two steps).

Scheme 73. Horner-Wadsworth-Emmons condensation: Model study.

2.6.1.2 Synthesis of Olefin **227**

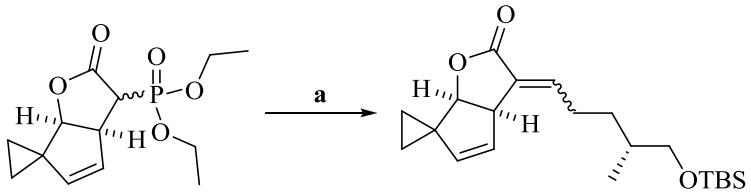
Having successfully synthesised **262**, the HWE condensation[117] step could now be applied in our strategy. In the same manner as previously described in the model study, phosphonate precursor **226** was added to a solution of *tert*-butoxide **260**, prepared *in situ* from *tert*-butanol **261**, followed by the addition of homochiral aldehyde **217**. We were pleased to discover that formation of the highly desired olefin **227** was achieved as a separable 1.1:1 mixture of *Z*/*E* isomers in 66% yield (**Scheme 74**).



Reagents and conditions: **(a)** *n*-BuLi (1.1 eq), THF, -70 ºC, 10 min; **(b) 260**, -50 ºC, 15 min; **217**, THF, -70 ºC (2 h) → RT (16 h), *Z*/*E* (1.1:1), 66% (over two steps).

Scheme 74. Synthesis of olefin **227**: First method.

Furthermore, the triumphal application of the HWE reaction was extended. This time, condensation of phosphonate **226** with aldehyde **217** was executed by the presence of aqueous solution of potassium carbonate.[149] This route gave alkene **227** as a separable 1.2:1 mixture of the *Z*/*E* geometric isomers in 80% yield (**Scheme 75**).



226 **227**

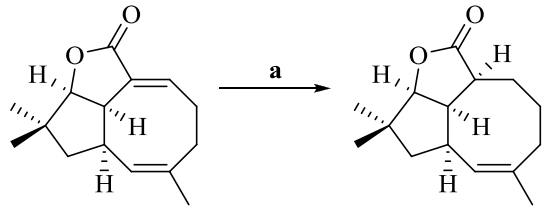
Reagents and conditions: **(a)** aq K_2CO_3 (96 eq), **217**, THF, -10 ºC → RT (7 days), *Z*/*E* (1.2:1), 80%.

Scheme 75. Synthesis of olefin **227**: Second method.

2.6.2 Subjecting Olefin **227** to Selective Conjugate Reduction

A wide variety of synthetic methods have been developed for the selective conjugate reduction of α,β-unsaturated carbonyl compounds by using metal-base reagents.[150] Hydrogenation involving copper complex as a transition metal catalyst has demonstrated to be useful tool for the chemoselective conjugate 1,4 reduction, where isolated alkenes and most functional groups do not interfere usually.[151,152]

Lending credibility to this potential approach, in their total synthesis of asteriscanolide **1**, Wender's group[80] accomplished the conjugate reduction of the unsaturated lactone utilising copper hydride and selective kinetic protonation of the resultant enolate from the *exo*-face produced **110** in 74% isomeric purity (**Scheme 76**).

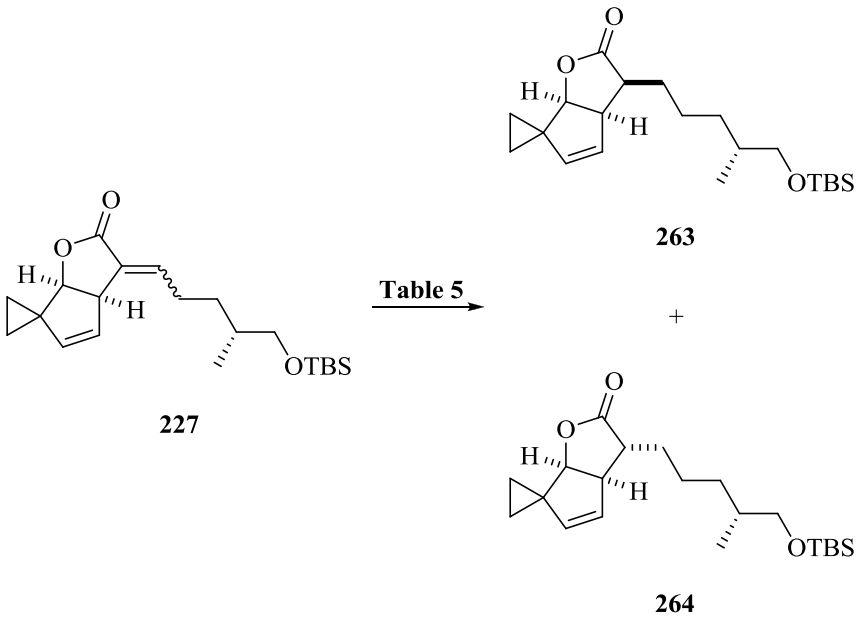


109 **110**

Reagents and conditions: **(a)** Red-Al®, CuBr, 74%.

Scheme 76. Wender's selective conjugate reduction.

In our synthetic plan, the saturation of olefin **227** (**Scheme 77**) was envisaged by the hydride transfer using copper and magnesium reagents. The results are summarised in **Table 5**.



Scheme 77. Synthesis of precursors **263** and **264**.

Entry	Hydrogenation reagent	Solvent	T (ºC)	Time (h)	Product
1	Red-Al® (4eq), CuBr (4 eq)	THF	-78 to -10	3	**263** (20%) + **264** (50%)
2	$[Ph_3P(CuH)]_6$ (0.24 eq)	PhH/H_2O	RT	16	Decomposition
3	Mg turnings (10 eq)	MeOH	RT	16	**263** (40%) + **264** (40%)

Table 5. Selective conjugate reduction of olefin **227**.

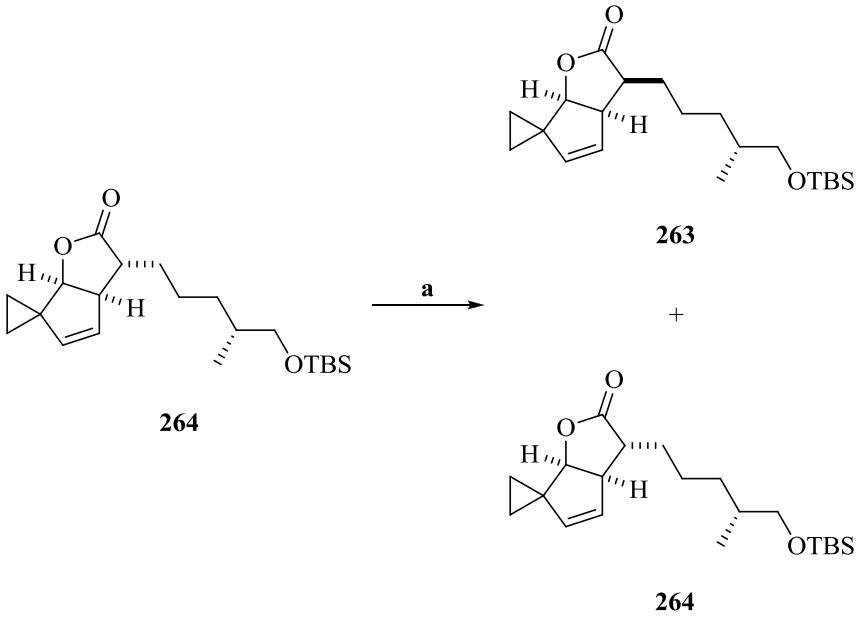
Olefin **227** was treated with Red-Al® in the presence of cuprous bromide in tetrahydrofuran,[151,153] giving rise to a separable mixture of diastereoisomers **263** and **264** in 20% and 50% yield, respectively (**Entry 1**).

In a second approach we investigated using a stable copper(I) hydride cluster, hexa-μ-hydrohexakis(triphenylphosphine) hexacopper (Stryker's reagent)[152,154] in the presence of

water at room temperature. Disappointingly, all the starting material **227** decomposed (**Entry 2**).

Alternatively, the use of other metals had also been explored. Treatment of olefin **227** with magnesium turnings in the presence of methanol[155,156] at room temperature successfully gave in a 1:1 ratio both expected diastereoisomers **263** and **264** in 80% yield. This operation supported a Birch-type radical anion formation,[44] followed by additional electron incorporation and protonation (**Entry 3**).

At this stage, partial kinetic protonation of isolated **264** occurred under basic conditions when employing lithium diisopropylamide in tetrahydrofuran at low temperature and quenching with *tert*-butyl bromide. The reverse addition method changed the ratio to 5:1 in favour to **263** and each diastereoisomer was isolated (**Scheme 78**).

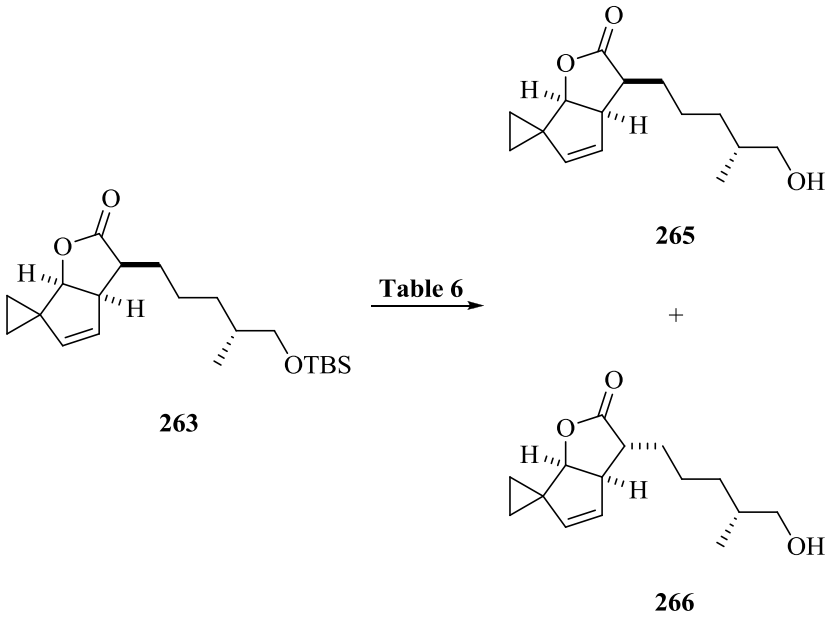


Reagents and conditions: **(a)** LDA (1.1 eq), THF, -78 ºC; *t*-BuBr (10 eq), THF, -78 ºC (3 h) → RT (16 h), **263**/**264** (5:1).

Scheme 78. Partial kinetic protonation of precursor **264**.

2.6.3 Functional Group Transformation Towards Nitroalkene **215**

To continue this investigation, we envisaged performing a simple functional group manipulation from precursor **263** to nitroalkene **215**. For this, cleavage of alcohol **263** was required (**Scheme 79**). **Table 6** describes the basic and acid-based desilylation procedures performed.



Scheme 79. Synthesis of precursors **265** and **266**.

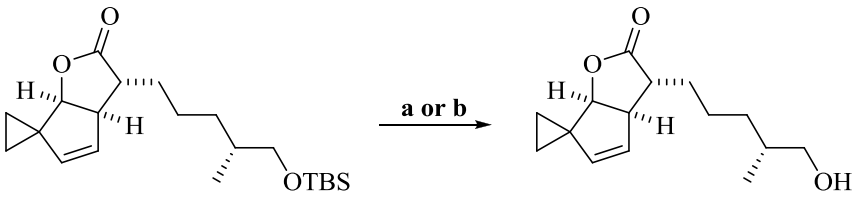
Entry	Reaction Conditions	T (ºC)	Time (h)	Product
1	TBAF, THF	0	6	**265** (75%) + **266** (25%)
2	2 M HCl in EtOH	0 to RT	4	**265** (99%)

Table 6. Silyl deprotection of precursor **263**.

Initial attempt for the removal of the TBS group was achieved using tetrabutylammonium fluoride in tetrahydrofuran[157] to give alcohol **265** in 75% yield. Unfortunately, during the reaction, we observed that fluoride itself was acting as a base, and therefore, epimerization took place affording unwanted alcohol **266** in 25% yield (**Entry 1**).

In a second attempt, silyl deprotection of **263** was accomplished by using acid hydrolysis.[158,159] Treatment of **263** with a 2 M solution of hydrochloric acid in ethanol exclusively gave unprotected alcohol **265** in excellent yield (**Entry 2**).

On the other hand, TBS cleavage of **264** using the same desilylation methods as in **263** led only to the formation of alcohol **266** (**Scheme 80**).

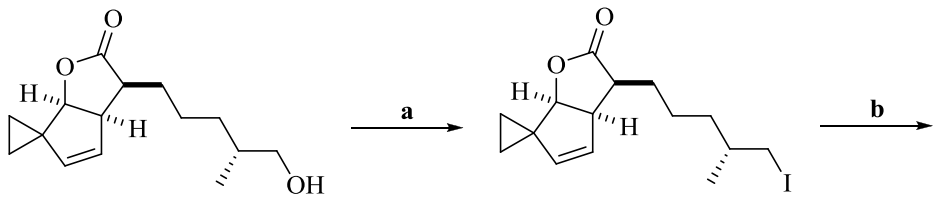


264 **266**

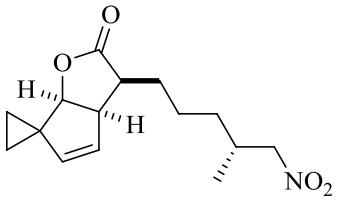
Reagents and conditions: **(a)** TBAF (1.4 eq), THF, 0 ºC, 6 h, 99%; **(b)** 2 M HCl in EtOH, 0 ºC, 4 h, 99%.

Scheme 80. Synthesis of precursor **266**.

We next sought a method for the conversion of the hydroxyl-group to primary iodide **267**. Following the iodination methodology described by Garegg[160] alcohol **265** was treated with iodine, triphenyl phosphine, and imidazole in dicholoromethane. The iodinated lactone **267** was fortuitously obtained in 95% yield. Subsequent conversion of the iodo moiety **267** into the desired nitro functionality **215** was performed by the use of nitrite ion bounded to macroporous quaternary ammonium Amberlite® resin (IRA-900-NO_2^-) in refluxing benzene.[161] This efficient procedure generated the desired nitroalkene precursor **215** in 80% yield (**Scheme 81**).



265 **267**

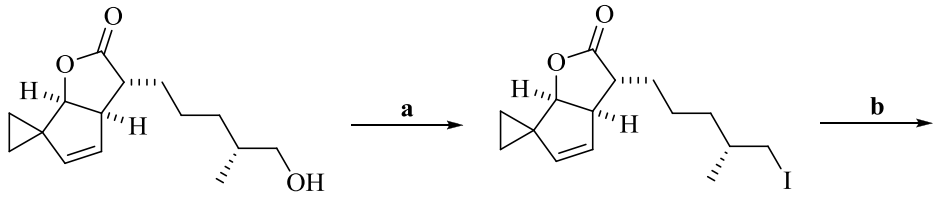


215

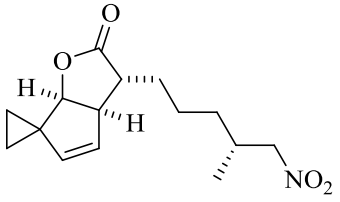
Reagents and conditions: **(a)** I_2 (2 eq), PPh_3 (2 eq), imidazole (2 eq), 0 ºC (20 min) → RT (16 h), 95%; **(b)** Amberlite® IRA-900-NO_2^- (11.1 eq), PhH, Δ, 48 h, 80%.

Scheme 81. Synthesis of nitroalkene **215**.

The functional group transformation was further extended to **266**. In a similar manner, iodination of **266** by Garegg's method[160] gave **268** in 74% yield, followed by nitration with Amberlite® IRA-900-NO_2^- in refluxing benzene[161] led to **269** in 60% yield (**Scheme 82**).



266 **268**



269

Reagents and conditions: **(a)** I_2 (2 eq), PPh_3 (2 eq), imidazole (2 eq), 0 ºC (20 min) → RT (16 h), 74%; **(b)** Amberlite® IRA-900-NO_2^- (8.2 eq), PhH, Δ, 48 h, 60%.

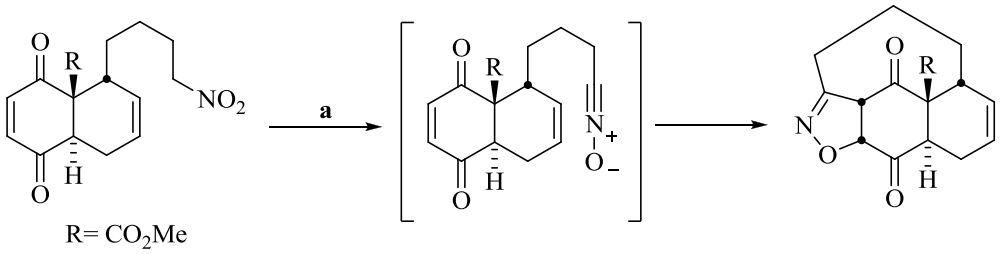
Scheme 82. Synthesis of nitroalkene **269**.

2.7 Approaches Towards the Formation of Cyclooctanoid Systems

2.7.1 Intramolecular [3 + 2] Nitrile Oxide-Olefin Cycloaddition

The nitrile oxide-olefin cycloaddition reaction is a powerful synthetic method for the construction of fused five-membered ring heterocyclics.[162] Since the discovery of intramolecular nitrile oxides cycloadditions to the alkene function,[163] many extensions and applications for the synthesis of natural and unnatural products have been developed. There are a number of methods for the preparation of nitrile oxides. The most common and easy way is the *in situ* technique, which includes the Huisgen and Mack's[164] method using hydroximoyl chlorides, and the dehydration of nitro compounds employing either the Mukaiyama-Hoshino procedure[120] or Shimizu's modification.[165]

Formation of eight-membered rings utilising the INOC reaction have been observed in the chemical literature by few scientific groups. To exemplify, Kozikowski *et al.*[166] described an unexpected fused cyclooctane **270** instead of the less-strained six-membered ring while subjecting *p*-naphthoquinone derivative **271** to Mukaiyama-Hoshino conditions.[120] The resultant course of this cycloaddition reflects the effect of the electron-withdrawal in the enedione moiety, thereby increasing the reactivity (**Scheme 83**).



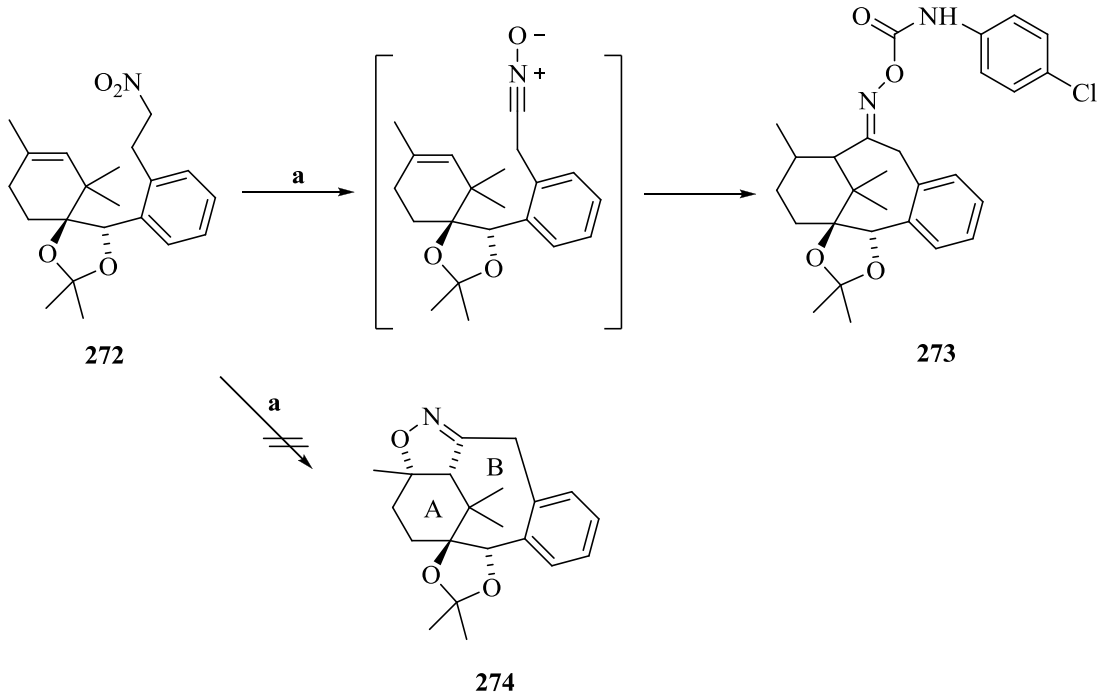
271 **270**

Reagents and conditions: **(a)** *p*-ClC_6H_4NCO, Et_3N, PhH, Δ, 15 h, 58%.

Scheme 83. Kozikowski's cyclooctanoid synthesis: INOC conditions.

In a different manner, Nagaoka and colleague[167] apply the INOC procedure for the synthesis of the A/B ring system of taxane **8** by treating nitroalkene **272** under Mukaiyama conditions.[120] However, the reaction gave rise to the oxime derivative **273** and the expected isoxazoline **274** was not detected. This result was attributed to the fact that cyclisation was

vertically orientated with respect to the double bond of the A ring and not to the in-plane approach (**Scheme 84**).

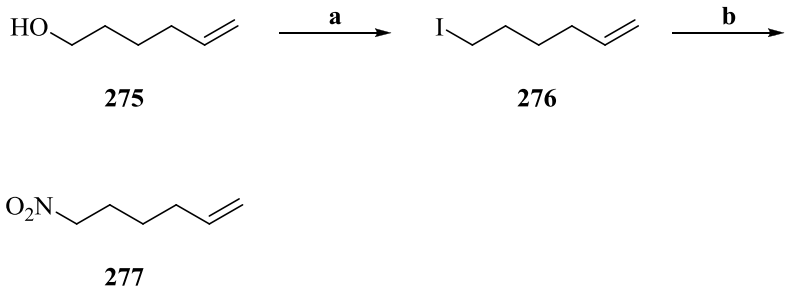


Reagents and conditions: **(a)** *p*-ClC_6H_4NCO, Et_3N, PhH, 70 ºC, 10 h, 94%.

Scheme 84. Nagaoka's cyclooctanoid synthesis: INOC conditions.

2.7.1.1 Model Study

Confident of the potential application of the INOC reaction to our synthetic strategy, an initial simple model study was carried out to establish the ease of preparation isoxazolines from nitrile oxides.[168,169] To represent the nitroalkene, commercially available hex-5-en-1-ol **275** was treated under iodination conditions[160] with iodine, triphenyl phosphine, and imidazole in dicholoromethane affording iodinated compound **276** in 80% yield. The synthesis of niroalkene **277** was undertaken by treatment of **276** with sodium nitrite in DMF.[110] Displacement of the iodide occurred in 49% yield (**Scheme 85**).

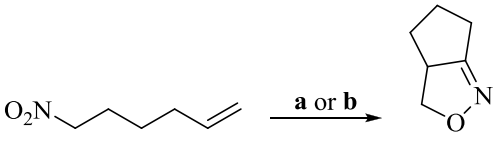


Reagents and conditions: **(a)** I_2 (1.4 eq), PPh_3 (1.4 eq), imidazole (1.4 eq), 0 ºC (20 min) → RT (16 h), 80%; **(b)** $NaNO_2$ (1.1 eq), DMF, RT, 3 h, 49%.

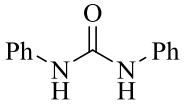
Scheme 85. Synthesis of nitroalkene **277**: Model study.

Having nitroalkene **277** in hand, we proceed to investigate the *in situ* preparation of the nitrile oxide group, which will hopefully generate the corresponding isoxazoline **278**.

In the first attempt, nitroalkene **277** was dehydrated by the Mukaiyama-Hoshino's technique[120] using phenyl isocyanate in the presence of triethylamine. The desired isoxazoline **278** was successfully made by this method. However, the *N,N'*-diphenyl urea by-product **279** was precipitated from the 1,3-dipolar cycloaddition solution, which was impossible to separate from the desired isoxazoline **278** due to similar solubilities. Further purification by flash column chromatography did not separate isoxazoline **278** from the by-product **279**. The second attempt employed the Shimizu's procedure,[165] where nitroalkene **277** was treated with *p*-toluenesulfonyl chloride and triethylamine in dichloromethane furnishing isoxazoline **278** in 52% yield. This methodology proved to be more suitable as purification of the isoxazoline **278** was accomplished without any difficulties (**Scheme 86**).



277 **278**



279

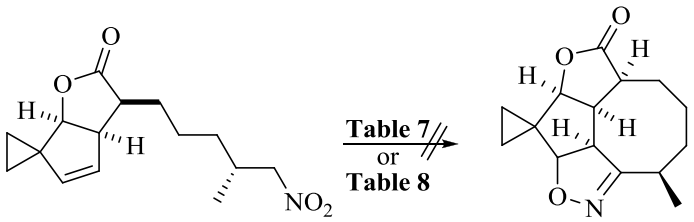
Reagents and conditions: **(a)** PhNCO (2 eq), Et_3N (2 eq), PhH, RT, 16 h, N/A%; **(b)** *p*-TsCl (2 eq), Et_3N (2 eq), CH_2Cl_2, 0 ºC → RT, 52%.

Scheme 86. Intramolecular [3 + 2] nitrile oxide-olefin cycloaddition: Model study.

2.7.1.2 Subjecting Nitroalkene **215** to INOC Conditions

Having succesfully isolated the key nitro-alkene intermediate **215**, we now focused our attention on the synthesis of **216** *via* the INOC reaction strategy.

In the first attempt, nitrile oxide from **215** was prepared *in situ* using the procedure described by Shimizu[165] (**Scheme 87**). However, problems occurred when attempting to synthesise isoxazoline **216**. **Table 7** summarises our efforts in forming precursor **216**.



215 **216**

Scheme 87. Attempt to isoxazoline **216**: Shimizu and Mukaiyama-Hoshino conditions.

Entry	Reaction Conditions	Solvent	Conc. (m/L)	T (ºC)	Time (h)	Product
1	*p*-TsCl (2 eq), Et_3N (2 eq)	CH_2Cl_2	0.0279	0 to RT	16	SM + **280** (81%)
2	*p*-TsCl (2 eq), Et_3N (2 eq)	CH_2Cl_2	0.0035	0 to RT	16	SM
3	*p*-TsCl (2.5 eq), Et_3N (2.5 eq)	CH_2Cl_2	0.0179	0 to RT	16	SM + **280**
4	*p*-TsCl (2 eq), Et_3N (2 eq)	CH_2Cl_2	0.0085	0 to RT	48	SM + **280**
5	*p*-TsCl (2 eq), Et_3N (2 eq)	PhH	0.0095	Δ	6	SM + **280**
6	*p*-TsCl (3 eq), Et_3N (3 eq)	PhH	0.0029	75[a]	3	SM + **280**
7	*p*-TsCl (3 eq), Et_3N[b] (3 eq)	CH_2Cl_2	0.0059	0 to RT	72	SM + **280** + decomposition
8	*p*-TsCl (3 eq), Et_3N[b] (3 eq)	PhH	0.0029	Δ	48	SM + **280** + decomposition
9	*p*-TsCl (3 eq), Et_3N[b] (3 eq)	PhMe	0.0029	Δ	48	SM + **280** + decomposition

[a]The reaction was carried out using MW 150 W.
[b]Triethylamine was added slowly over 24 hours using a syringe pump and stirred for the time indicated.

Table 7. Subjecting nitroalkene **215** to Shimizu conditions.

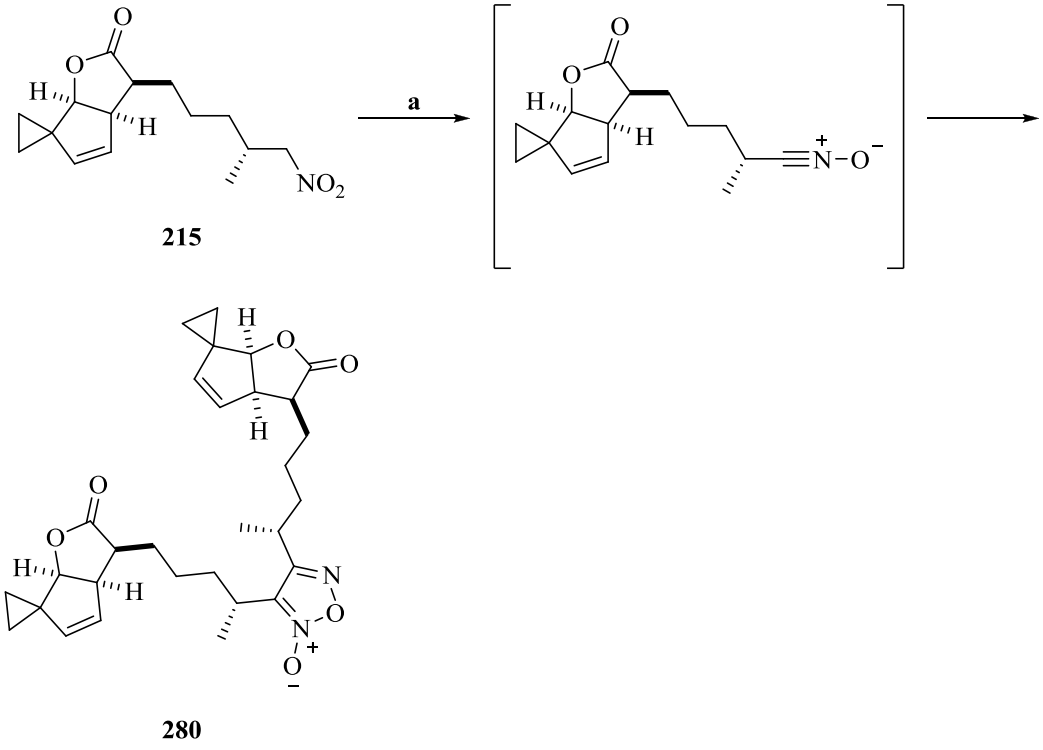
We can attribute the failure of the reaction to the formation of the dimer product, furoxan **280** (**Scheme 88**). Treatment of nitroalkene **215** with *p*-toluenesulfonyl chloride and triethylamine in dichloromethane led to unwanted dimer **280** in 81% yield, the recovery of starting material **215**, and a compound that we were unable to identify by proton NMR because of the small amount obtained. This latter compound gave a mass ion by HRMS of 284.1258 ((*calc.* 284.1257) $C_{15}H_{19}NO_3Na$ $(M + Na)^+$). This could correspond to cycloaddition product **216** or possible dehydration of INOC precursor **215** (**Entry 1**).

At this point, we rationalised that coupling of the reactive nitrile oxide groups placed on the end of the molecules occurred in preference to the intramolecular cycloaddition. As such, the reaction was conducted using Shimizu's conditions[165] with more dilute solutions (**Entry 2**, **3**, and **4**). Unfortunately, we did not observed the desired isoxazoline **216** using the high-dilution technique and only furoxan **280** was obtained as a product (**Entry 3** and **4**).

Alternatively, benzene was used as the solvent, but neither under reflux (**Entry 5**) or microwave irradiation (**Entry 6**) could furnish **216**, and only dimer **280** was produced together with unreacted starting material **215**.

Since nitrile oxides are quite unstable and can easily dimerize and produce 1,2,5-oxadiazole-2-oxides, commonly known as furoxans or furazan oxides,[170,171] we decided that in order to avoid this problem, the generation of nitrile oxide should be performed slowly.[162] Thus, to a very diluted solution of nitroalkene **215** and *p*-toluenesulfonyl chloride in dichloromethane was added triethylamine in a dropwise manner over twenty four hours using a syringe pump (**Entry 7**). Disappointingly, only found unreacted **215**, furazan oxide **280**, and decomposition material was found.

The use of benzene (**Entry 8**) or toluene (**Entry 9**) by Shimizu's method with slow addition of triethylamine led only to the starting material **215**, dimer **280**, and decomposed material.



Reagents and conditions: **(a)** *p*-TsCl (2 eq), Et_3N (2 eq), CH_2Cl_2, 0 ºC → RT, 81%.

Scheme 88. Synthesis of furoxan **280**.

Undeterred, a second attempt to isoxazoline **216** was investigated, but this time INOC reaction was performed using the Mukaiyama-Hoshino technique.[120] The results of this investigation are summarised in **Table 8**.

Nitroalkene **215** was dehydrated with phenyl isocyanate in the presence of triethylamine in benzene at room temperature. Unfortunately, this led to the formation of the corresponding furazan oxide **280** and unreacted compound **215** (**Entry 1**).

In a similar manner, subjecting **215** to Mukaiyama-Hoshino conditions[120] under reflux did not give rise to desirable **216**. Only starting material **215** and **280** were observed (**Entry 2**).

Disappointingly, the slow formation of the nitrile oxide by adding triethylamine in a slow fashion using phenyl isocyanate in refluxing benzene (**Entry 3**) or toluene (**Entry 4**) for four days proved to be unfruitful. The substitution of phenyl isocyanate for *p*-clorophenyl isocyanate in refluxing toluene led only to **215**, furoxan **280**, and decomposition (**Entry 5**).

Entry	Reaction conditions	Solvent	Conc. (m/L)	T (ºC)	Time (h)	Product
1	PhCNO (2 eq), Et_3N (2 eq)	PhH	0.0358	RT	16	SM + **280**
2	PhCNO (2 eq), Et_3N (2 eq)	PhH	0.0358	Δ	16	SM + **280**
3	PhCNO (10 eq), Et_3N[a] (10 eq)	PhH	0.0029	Δ	96	SM + **280** + decomposition
4	PhCNO (10 eq), Et_3N[a] (10 eq)	PhMe	0.0029	Δ	96	SM + **280** + decomposition
5	ClPhCNO (10 eq), Et_3N[a] (10 eq)	PhMe	0.0034	Δ	72	SM + **280** + decomposition

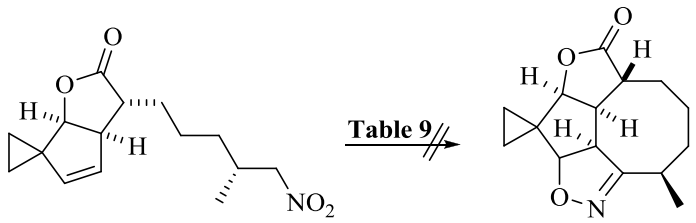
[a]Triethylamine was added slowly over 24 hours using a syringe pump and stirred for the time indicated.

Table 8. Subjecting nitroalkene **215** to Mukaiyama-Hoshino conditions.

2.7.1.3 Subjecting Nitroalkene **269** to INOC Conditions

As a final attempt it was hoped that the investigation of the intramolecular nitrile oxide-olefin cycloaddition reaction on analogue nitroalkene **269** would be more geometrically

favoured in terms of the nitrile oxide unit with respect to the double bond, thus forming isoxazoline **281** (**Scheme 89**). The results are summarised in **Table 9**.



269 **281**

Scheme 89. Attempt to isoxazoline **281**: Shimizu and Mukaiyama-Hoshino conditions.

Entry	Reaction Conditions	Solvent	Conc. (m/L)	T (ºC)	Time (h)	Product
1	*p*-TsCl (2 eq), Et_3N (2 eq)	CH_2Cl_2	0.0194	0 to RT	16	SM + **282** (64%)
2	*p*-TsCl (2eq), Et_3N[a] (2 eq)	CH_2Cl_2	0.0029	0 to RT	96	SM + **282**
3	PhCNO (eq), Et_3N[a] (3 eq)	PhH	0.0029	Δ	96	SM + **282** + decomposition
4	PhCNO (10 eq), Et_3N[a] (10 eq)	PhMe	0.0034	Δ	96	SM + **282** + decomposition

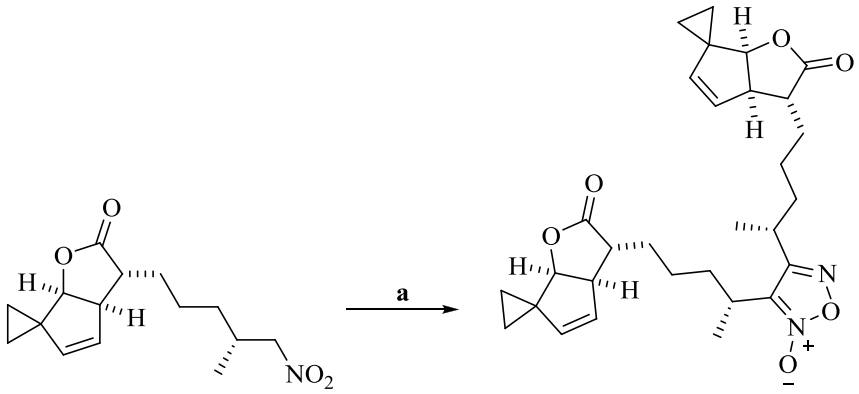
[a]Triethylamine was added slowly over 24 hours using a syringe pump and stirred for the time indicated.

Table 9. Subjecting nitroalkene **269** to Shimizu and Mukaiyama-Hoshino conditions.

Treatment of INOC precursor **269** under Shimizu conditions[165] with *p*-toluenesulfonyl chloride in the presence of triethylamine was unsuccessful, as the reaction led to undesired furoxan **282** in 64% yield (**Scheme 90**), some recovered nitroalkene **269**, and a small compound unable to identify by proton NMR due to the lack of material obtained. This latter compound gave a mass ion by HRMS of 284.1268 ((*calc.* 284.1257) $C_{15}H_{19}NO_3Na$ $(M + Na)^+$). This could correspond to cycloaddition product **281** or dehydration of nitroalkene **269** (**Entry 1**).

The slow *in situ* generation of the nitrile oxide group by the dropwise addition of triethylamine into the Shimizu procedure[165] did not help to give **281** (**Entry 2**).

At this late stage, the employment of the Mukaiyama-Hoshino technique[120] by treating **269** with phenyl isocyanate and triethylamine in refluxing benzene (**Entry 3**) or toluene (**Entry 4**) proved to be unsuccessful, as dimer **282** was obtained and **281** was not isolated.



269 **282**

Reagents and conditions: **(a)** *p*-TsCl (2 eq), Et_3N (2 eq), CH_2Cl_2, 0 ºC → RT, 64%.

Scheme 90. Synthesis of furoxan **282**.

To conclude this investigation employing nitroalkene precursors **215** and **269**, we examined the use of an intramolecular nitrile oxide-olefin cycloaddition reaction and neither set of conditions, Shimizu[165] or Mukaiyama-Hoshino[120] resulted in the formation of any isoxazoline product **216** or **281**, respectively. Only the corresponding furazan oxides **280** and **282** were formed, and part of the starting material was recovered. This result was disappointing, as the INOC would have been a rapid approach to the required isoxazoline precursors.

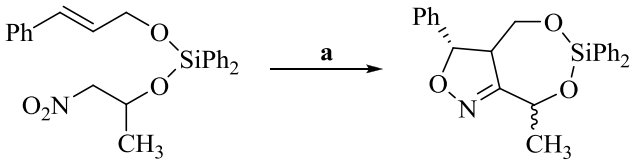
As this extensive investigation remained fruitless, alternatives for the intramolecular cycloaddition reaction were now considered.

2.7.2 Intramolecular [3 + 2] Silyl Nitronate-Olefin Cycloaddition

Silyl nitronates can be considered as synthetic equivalents of nitrile oxides in 1,3-dipolar cycloaddition reactions.[172] In their reaction with olefins, the *N*-[(silyl)oxy]isoxazolidines formed are readily transformed into 2-isoxazolines upon heating[173] or treatment with acid or tetrabutylammonium fluoride.[174] However, intramolecular [3 + 2] silyl nitronate-olefin

cycloadditions are much more rarely used than the related INOC reactions.[175] This can be explained to the fact that silyl nitronates are thermolabile, sensitive to humidity, and there are much less reactive than nitrile oxides.[172] Starting from nitro compounds, the most common method for the preparation of silyl nitronates is the use of trimethylsilyl chloride in the presence of a base.[160]

Although no report actually exist in the literature concerning the generation of an eight-membered ring using the ISOC procedure, Breau's *et al.*[176] achieved the cycloaddition of silaketal **283** to obtain a seven-membered ring tether **284** in 45% yield (**Scheme 91**).



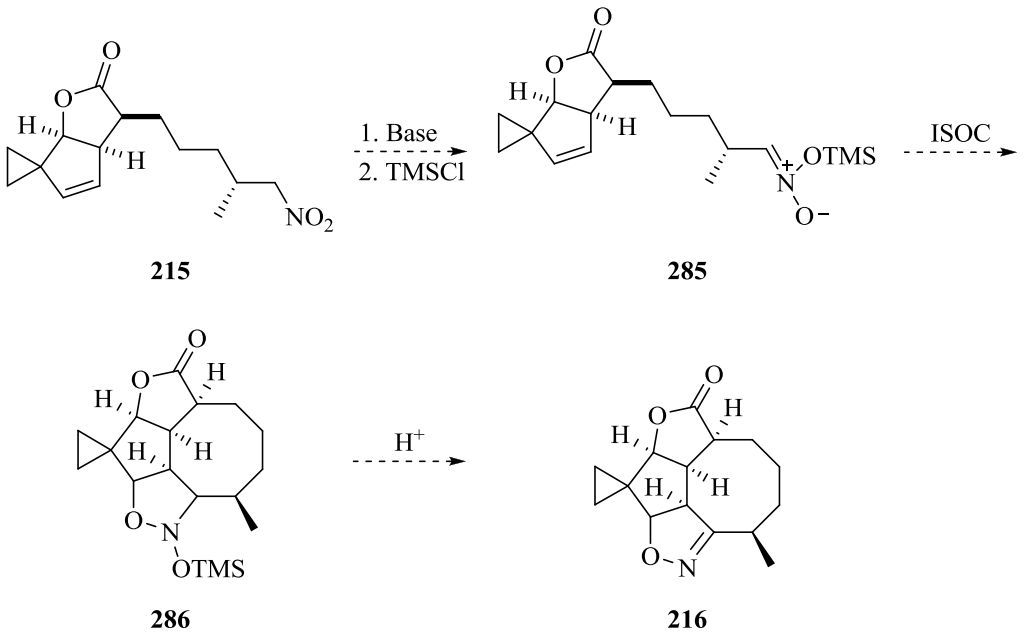
283 **284**

Reagents and conditions: **(a)** TMSCl (2 eq per day), Et_3N (2 eq per day), PhH, Δ, 12 days, 45%.

Scheme 91. Breau's cyclooctanoid synthesis: ISOC conditions.

2.7.2.1 Subjecting Nitroalkene **215** to ISOC Conditions

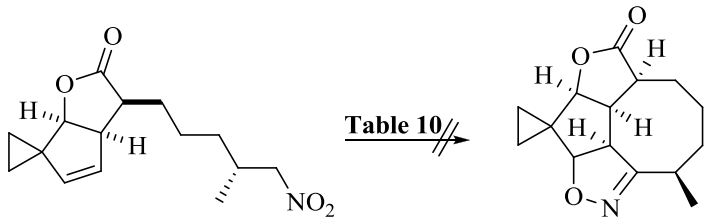
With **215** in hand, intramolecular silyl nitronate-olefin cycloaddition was viewed as another alternative to access the formation of the eight-membered carbocycle. It was reasonable to assume that the problematic dimerization of **215** using INOC conditions could be solved by the influence of the silyl group on nitronate **285**. Treatment of **285** under ISOC conditions could potentially give *N*-[(silyl)oxy]isoxazolidine **286** and subsequently form **216** after a desilylation process (**Scheme 92**).



215 **285** **286** **216**

Scheme 92. Proposal for synthesis of isoxazoline **216** utilising ISOC conditions.

During this investigation all attempts were unsuccessful, despite using standard conditions, the intramolecular cycloaddition towards **216** could not be accomplished (**Scheme 93**). Various bases and conditions were investigated. The results are summarised in **Table 10**.



215 **216**

Scheme 93. Attempt to isoxazoline **216**: ISOC conditions.

Entry	Reaction conditions	Solvent	T (ºC)	Time (h)	Product
1	TMSCl[a] (1.1 eq), Et_3N (1.2 eq)	PhH	0 to RT	72	SM
2	TMSCl[a] (1.1 eq), Et_3N (1.2 eq)	PhH	Δ	24	SM
3	TMSCl[a] (10 eq), Et_3N (11 eq)	PhH	Δ	72	SM
4	TMSCl[a] (2.5 eq), DBU(1.2 eq)	CH_2Cl_2	0 to RT	24	SM
5	TMSCl[a] (5 eq), DBU (2.4 eq)	CH_2Cl_2	0 to RT	72	SM + decomposition
6	TMSCl[a] (1.3 eq), Et_3N (1.3 eq), NaI (1.3 eq)	CH_3CN	0 to RT	72	SM + decomposition
7	TMSCl[a] (3.9 eq), Et_3N (3.9 eq), NaI (3.9 eq)	CH_3CN	0 to RT	72	Decomposition

[a]Trimethylsilyl chloride was added 30 minutes after the addition of the base.

Table 10. Subjecting nitroalkene **215** to ISOC conditions.

In an initial attempt, silylation of nitro-olefin **215** was performed using trimethylsilyl chloride and triethylamine in benzene at room temperature, but disappointingly, only unreacted material **215** was isolated (**Entry 1**). As a result, the reagents used were rigorously purified and dried. A similar procedure was used under reflux but following workup only induced to the recovery of **215** (**Entry 2**). The same misfortune happen when the equivalents of the reagents were increased (**Entry 3**).

It was then decided to use a stronger base. As such, deprotonation of nitro compound **215** was attempted with 1,8-diazabicyclo(5.4.0)undec-7-ene in dichloromethane (**Entry 4**). Unfortunately, we were unable to obtain isoxazoline **216**.

Furthermore, increasing the number of equivalents of DBU and TMSCl only led to the isolation of unreacted starting material **215**, decomposition, and a compound that we were unable to identify by proton NMR due to the lack of available material (**Entry 5**). This latter compound gave a mass ion by HRMS of 284.1257 ((*calc.* 284.1257) $C_{15}H_{19}NO_3Na$ $(M + Na)^+$). This could correspond to the ISOC product **216**.

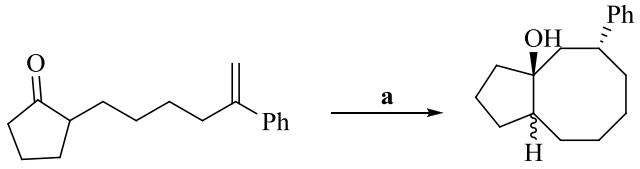
We then envisaged silylation of **215** *via* a variant procedure using trimethylsilyl chloride, triethylamine, sodium iodide, and acetonitrile.[177] It was reasoned that the addition of the sodium iodide into the reaction could potentially facilitate the desilylation process. Disappointingly, the application of this method to our system failed, having only recovered material and some decomposition (**Entry 6**). Also, increasing the number of equivalents of the silylation reagents consumed all the starting material **215** and none of the products corresponded to the desired cycloadduct **216** (**Entry 7**).

After several unsuccessful avenues, alternative conditions for an intramolecular cyclisation were investigated. Thus, synthesis of appropriate precursors was also required.

2.7.3 Samarium(II) Iodide-Mediated Intramolecular Cyclisation

Samarium(II) iodide-mediated reductive cyclisations have found considerable application in the construction of eight-membered rings.[10] One of the most important SmI_2-promoted reaction is the carbonyl-alkene/alkyne reaction.[178] The carbonyl group is initially reduced to generate a ketyl radical anion, which then attacks the unsaturated system. The carbonyl-alkene/alkyne coupling could be accomplished with both activated and unactivated alkenes and alkynes.

Molander's group[16] illustrated that unsaturated ketone **287** cyclise to form bicyclic 5,8-fused alcohol **288** through a ketyl radical-alkene intramolecular cyclisation in the SmI_2-HMPA milieu (**Scheme 94**).



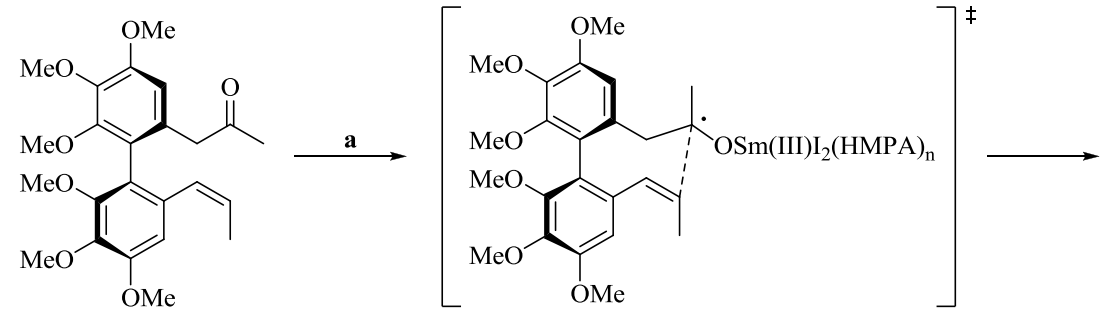
287 **288**

Reagents and conditions: **(a)** SmI_2 (2.2 eq), *t*-BuOH **261** (2 eq), HMPA, THF, 1.5 h, 78%, d.s. 1:1.

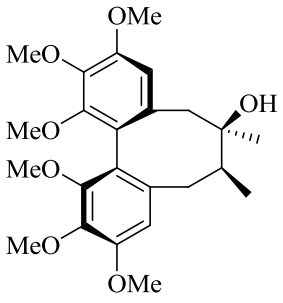
Scheme 94. Molander's cyclooctanoid synthesis: SmI_2 cyclisation conditions.

In 2003, Molander *et al.*[179] published the total synthesis of (+)-isoschizandrin **289** *via* a samarium diiodide-promoted 8-*endo-trig* carbonyl-alkene cyclisation as the final step. The

ketyl-olefin coupling assembled the medium-sized ring when **290** was treated with SmI_2, *t*-butanol **261**, and hexamethylphosphoramide affording **289** in good yield. The presence of the biaryl motif enhances this ring closure by lowering the SOMO/LUMO energy gap and reducing the entropic effects by ordering at least four of the ring's eight carbons (**Scheme 95**).



290



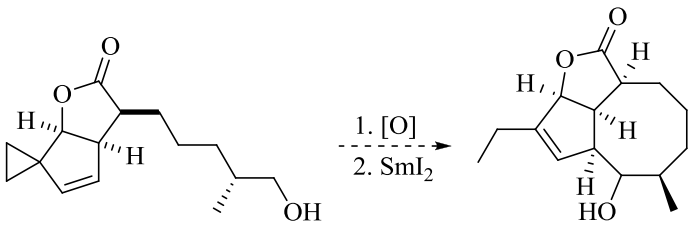
289

Reagents and conditions: **(a)** SmI_2 (2.2 eq), *t*-BuOH **261** (2 eq), HMPA, THF, 85%, d.r. >18:1.

Scheme 95. Molander's synthesis of isoschizandrin **289** *via* SmI_2-mediated cyclisation.

2.7.3.1 Subjecting Aldehyde **291** to SmI_2 Cyclisation Conditions

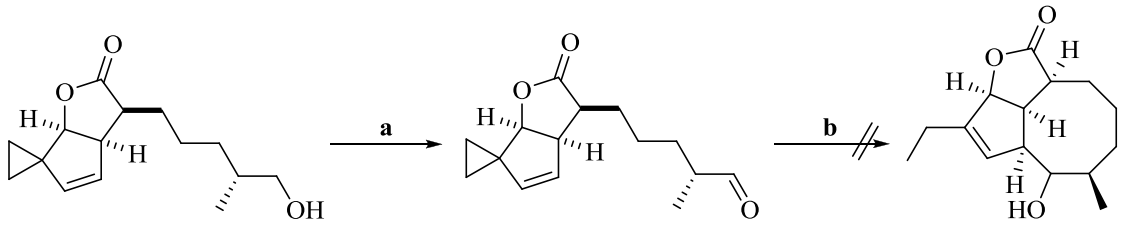
Whilst there is precedent for preparing eight-membered carbocycles using the samarium(II) iodide-mediated cyclisation reaction, the possibility of generating modified precursor cyclooctanol **292** by an 8-*exo-trig* radical cyclisation process from precursor **265** appeared to be an attractive option. We were encouraged by the benefit that if **292** was formed, subsequent oxidation to the corresponding ketone at C-8 could provide an alternative route to asteriscanolide **1** (**Scheme 96**).



265 **292**

Scheme 96. Proposal for synthesis of precursor **292** utilising SmI_2 cyclisation conditions.

For this investigation aldehyde **291** was prepared initially from the primary alcohol precursor **265** using tetrapropylammonium perruthenate.[180] Disappointingly, exposure of unsaturated aldehyde **291** to samarium diiodide reductive cyclisation conditions did not afford the desired product **292** and only reduction to the alcohol **265** was observed (**Scheme 97**).



265 **291** **292**

Reagents and conditions: **(a)** TPAP, NMO, 4 Å MS, CH_2Cl_2, 75%; **(b)** SmI_2 (2.2 eq), *t*-BuOH **261** (2 eq), HMPA, THF.

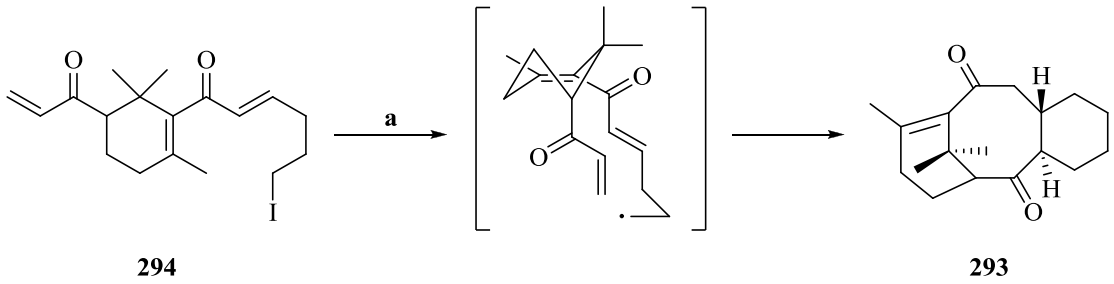
Scheme 97. Attempt to precursor **292**: SmI_2 cyclisation conditions.

We postulated that ring-strain associated with the desired transition state was responsible for the failure of the cycloaddition. Due to time constraints and lack of any evidence of the desired product, this route was not investigated further. Alternatively, a radical-mediated intramolecular cyclisation could be envisaged as another method to create an eight-membered ring in our system.

2.7.4 Radical-Mediated Intramolecular Cyclisation

Free radical-induced cyclisations have emerged as a versatile methodology for the synthesis of carbocyclic ring systems.[10] There are few examples of the use of radical cyclisation reactions leading to cyclooctane ring formation. Among the different reducing agents tributyltin hydride (TBTH) in the presence of a substoichiometric amount of radical initiator has been the most commonly used.[181]

Pattenden *et al.*[182] have described the formation of an eight-membered ring fragment of taxanes **293** based on a cascade radical-mediated macrocyclisation-transannulation strategy. Treatment of bis-enone **294** with Bu_3SnH and 2,2'-azobis(2-methylpropionitrile) (AIBN) led to **293** as a result of the 12-*endo-trig* cyclisation in a single operation (**Scheme 98**).

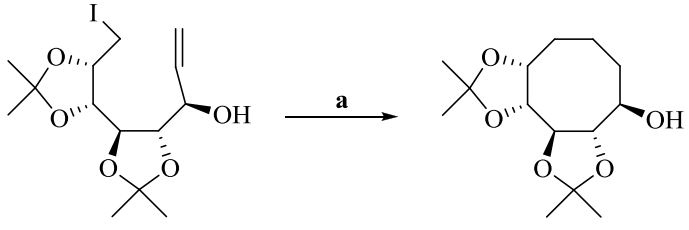


294 **293**

Reagents and conditions: **(a)** Bu_3SnH, AIBN (cat), PhH, Δ, 25%.

Scheme 98. Pattenden's cyclooctanoid synthesis: Radical cyclisation conditions.

Another example involving a TBTH-promoted carbocyclisation for the construction of a cyclooctane ring has been reported by Marco-Contelles and colleague.[183] The 8-*endo-trig* radical reaction of primary alkyl precursor **295** provided **296** in 50% yield (**Scheme 99**).



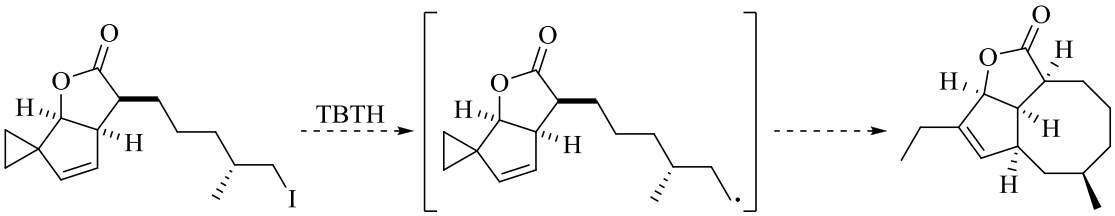
295 **296**

Reagents and conditions: **(a)** Bu_3SnH (1.5 eq), AIBN (10 mol%), PhH, Δ, 50%.

Scheme 99. Marco-Contelles' cyclooctanoid synthesis: Radical cyclisation conditions.

2.7.4.1 Subjecting Iodoalkene **267** to Radical Cyclisation Conditions

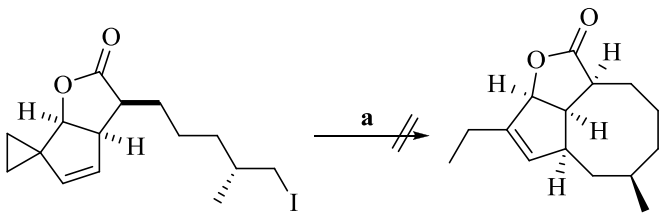
An alternative new approach employing free radical-promoted cyclisation technique was investigated in our real system. It was hoped that previously prepared iodoalkene **267** could potentially give access to cyclooctanoid lactone **297**. Despite that **297** change totally our retrosynthetic analysis; the intention was to explore the possibility of the formation of the eight-membered ring by the use of this methodology (**Scheme 100**).



267 **297**

Scheme 100. Proposal for synthesis of precursor **297** utilising radical cyclisation conditions.

Attempt was then made when iodoalkene **267** was treated slowly with Bu_3SnH and 1,1'-azobis(cyclohexanecarbonitrile) (ABCN) in refluxing benzene. Unfortunately, only decomposition products were isolated. Proton NMR experiments and HRMS analyses of the products isolated indicated that the radical reduction actually took place, but no cyclisation products were obtained (**Scheme 101**).



267 **297**

Reagents and conditions: **(a)** Bu_3SnH (2.2 eq), ABCN (10 mol%), PhH, Δ, 96 h.

Scheme 101. Attempt to precursor **297**: Radical cyclisation conditions.

This brief investigation, although not yielding the desired cyclooctanoid **297**, provides further evidence showing that intramolecular cyclisation could be geometrically

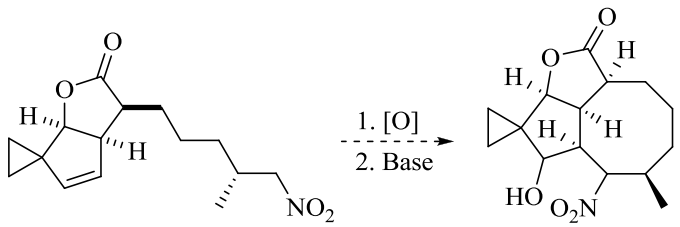
disfavoured in terms of the peripheral functional group in the chain with respect to the unsaturated system. Therefore, focusing once more on alternative methods for the pivotal cyclisation step was necessary.

2.7.5 Intramolecular Nitronate Anion-Epoxide Cyclisation

The ring opening reactions of epoxides with nucleophiles are considered as a very useful approach in organic synthesis.[184] In a similar manner to the Henry reaction,[185] β-nitroalcohols can be prepared by the nucleophilic addition of nitronate anions to oxirane rings. While no substantial research has been conducted, these reactions are usually carried out under basic conditions and several methods have been reported.[186-188] However, so far there is no precedent involving intramolecular cleavage of epoxides by nitronate species for the formation of eight-membered rings.

2.7.5.1 Subjecting Nitroepoxide **298** to Cyclisation Conditions

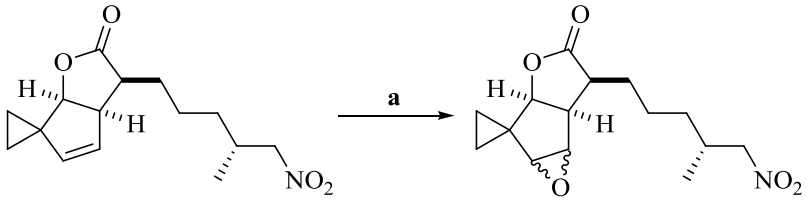
At this late stage of the project, synthetic efforts were now directed towards functionalisation of the unsaturated fragment of our system. Although we had limited material of precursor **215** available, in our study we aim to utilise **215** for an intramolecular nitronate anion addition to an epoxide in order to form the key C-C bond, and thus complete the tricyclic framework **299** of target molecule **1** (**Scheme 102**).



215 **299**

Scheme 102. Proposal for synthesis of precursor **299** utilising nitronate anion-epoxide cyclisation conditions.

To investigate this new synthetic route, nitroalkene **215** was first converted to epoxide **298**. Treating **215** with Oxone® in a two-phase system with ethyl acetate and water gave **298** as a separable 1.7:1 mixture of *endo*/*exo* diastereoisomers in excellent yield (**Scheme 103**).[189]

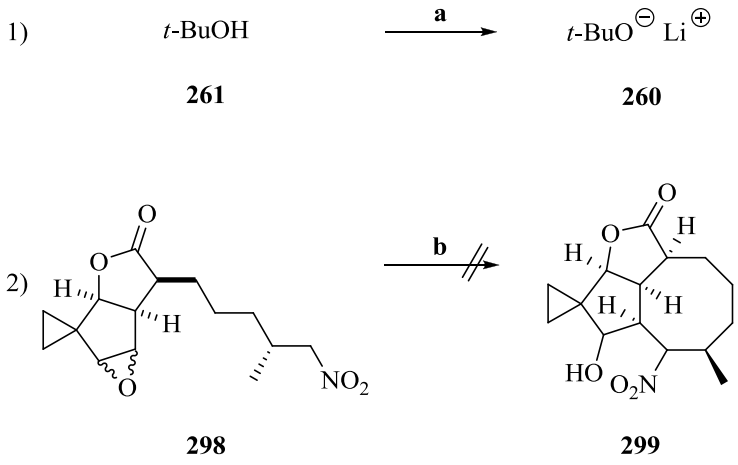


215 **298**

Reagents and conditions: **(a)** Oxone® (1 eq), $NaHCO_3$ (5 eq), acetone (10 eq), EtOAc, H_2O, RT, 16 h, *endo*/*exo* epoxidation (1.7:1), 99%.

Scheme 103. Synthesis of nitroepoxide **298**.

In the attempt to cyclisation, nitroepoxide **298** was exposed to lithium *tert*-butoxide **260**, previously prepared from *t*-BuOH **261** and *n*-BuLi at low temperature in tetrahydrofuran. Unfortunately, only **298** and decomposition material were observed (**Scheme 104**).



261 **260**

298 **299**

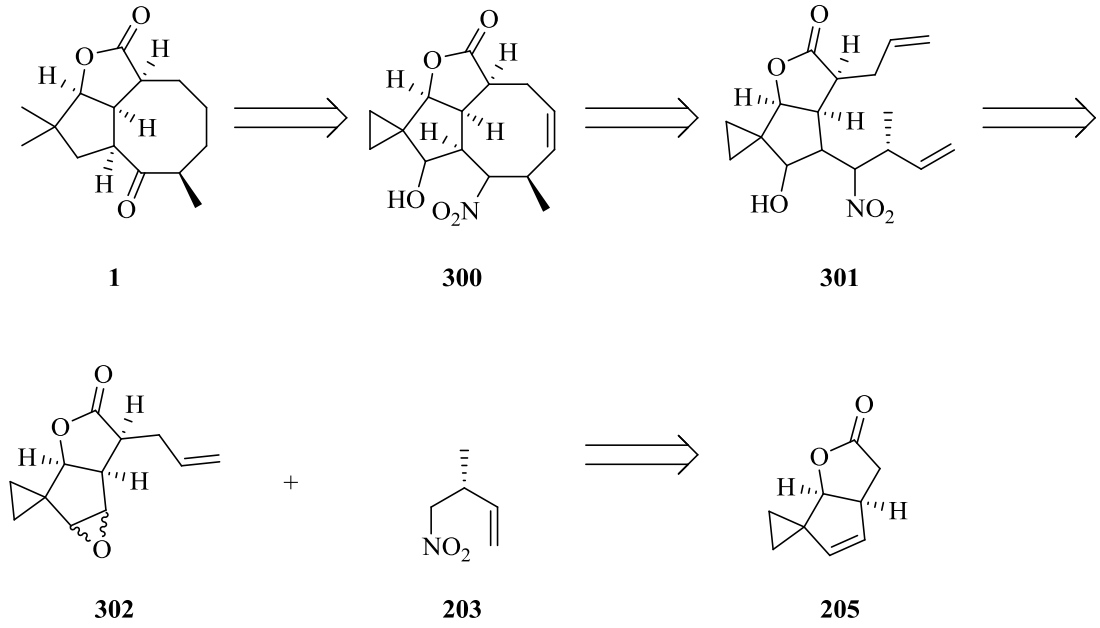
Reagents and conditions: **(a)** *n*-BuLi (1.1 eq), THF, -70 ºC, 10 min; **(b) 260**, THF, -70 ºC (2 h) → RT (16 h).

Scheme 104. Attempt to precursor **299**: Intramolecular nitronate anion-epoxide cyclisation conditions.

Due to the challenging nature of our system, a second generation retrosynthetic approach was identified.

2.8 Second Generation Retrosynthetic Analysis

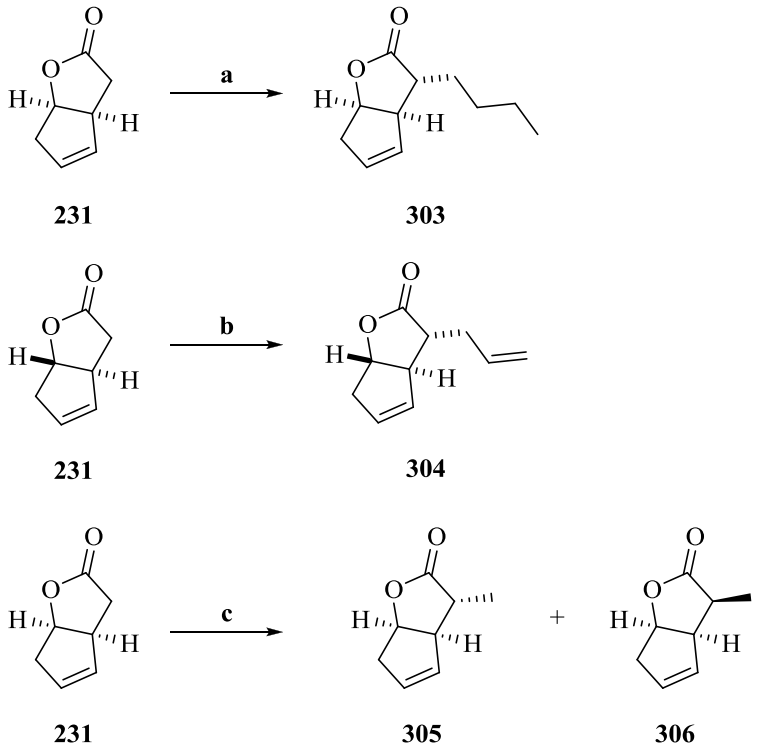
In this new approach, it was hoped that generation of β-nitroalcohol **300**, a suitable substitute of isoxazoline **216**, could be obtained by a ring-closing metathesis of diene **301**. This could be prepared *via* nucleophilic ring-opening of the oxirane ring of compound **302** with nitroalkene **203** under basic conditions. Alkylation of the well known lactone **205**,[107] followed by oxidation of the olefin moiety should provide epoxide precursor **302** (**Scheme 105**).



Scheme 105. Retrosynthetic analysis reviewed.

2.9 Synthesis of Epoxide **302**

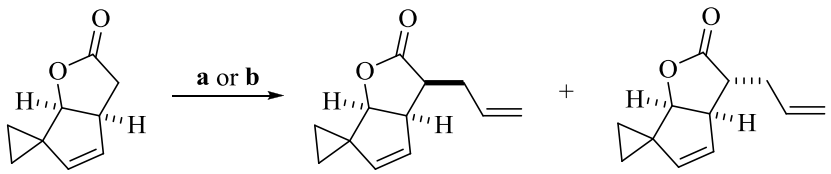
The alkylation of bicyclic γ-lactones bearing a similar framework to precursor **205** has been reported to give diastereoisomer products (**303**[190] and **304**[191]) under standard conditions where the alkyl substituent was placed on the convex face of the bicyclic system. In contrast, a mixture of lactones **305** and **306**[192] was obtained when a smaller electrophile was used (**Scheme 106**).



Reagents and conditions: **(a)** LDA, HMPA, THF, hexane, -78 ºC; 1-iodobutane, -40 ºC → -18 ºC, 42%; **(b)** LHMDS, THF, -90 ºC; allyl iodide, 79%; **(c)** LHMDS, THF, -65 ºC; MeI, -65 ºC → -20 ºC, 68% (**305**), 9% (**306**).

Scheme 106. Examples of alkylation of bicyclic γ-butyrolactone **231**.

Following Marsh's protocol[2] treatment of **205** with lithium diisopropylamide in tetrahydrofuran at low temperature and quenching of the resulting enolate with allyl bromide afforded a separable 1:1.5 mixture of lactone **204** and undesired diastereoisomer **210** in modest yield. Improvement of the facial selectivity was observed when lithium bis(trimethylsilyl)amide and allyl bromide were used (**Scheme 107**).

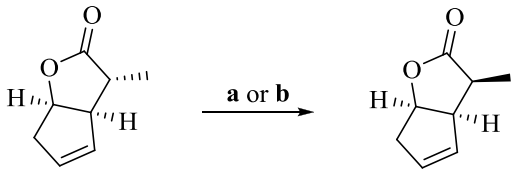


205 **204** **210**

Reagents and conditions: **(a)** LDA (1.1 eq), THF, -78 ºC, 1 h; allyl bromide (2 eq), -78 ºC (2 h) → RT (16 h), **204**/**210** (1:1.5), 52%; **(b)** LHMDS (1.1 eq), THF, -78 ºC, 1 h; allyl bromide (2 eq), -78 ºC (2 h) → RT (16 h), **204**/**210** (1:1.1), 74%.

Scheme 107. Synthesis of precursors **204** and **210**.

Carnell and colleagues,[192] who reported the preparation of **305** and **306**,[192] also developed the conversion of **305** to **306**. Thus, re-formation of the enolate with LHMDS and quenching with methanol gave a small amount of **306**. Moreover, Olivo *et al.*[193] from the University of Iowa published a similar epimerization step. This time, kinetic protonation of the lithium enolate of lactone **305** gave the thermodynamically unfavored methyl lactone **306** by using LHMDS, followed by workup procedure with a saturated solution of ammonium chloride in 78% yield (**Scheme 108**).

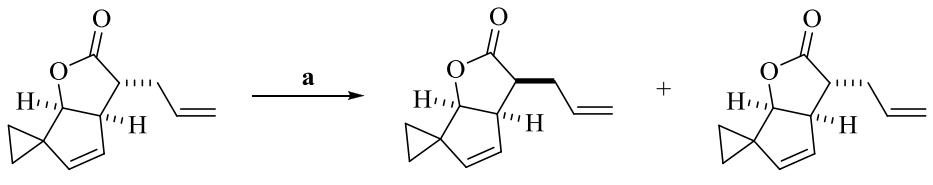


305 **306**

Reagents and conditions: **(a)** LHMDS, THF, -65 ºC; MeOH, -65 ºC → -20 ºC, 15%; **(b)** LHMDS, -78 ºC, 2 h; aq NH_4Cl, 78%.

Scheme 108. Epimerization procedures of bicyclic γ-butyrolactone **305**.

As reported by Marsh,[2] quenching the lithium enolate of **210** with *tert*-butyl bromide changed the ratio to 2.3:1 in favour of the desired diastereosisomer **204** bearing the allyl group on the concave face. The use of *tert*-butyl bromide enabled protonation from the least sterically encumbered face (**Scheme 109**).

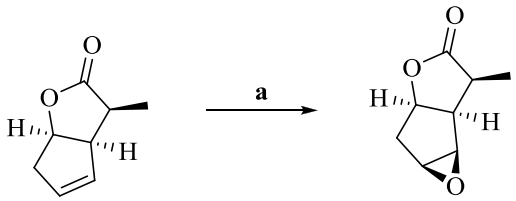


210 **204** **210**

Reagents and conditions: **(a)** LDA (1.1 eq), THF, -78 ºC; *t*-BuBr (10 eq), THF, -78 ºC (3 h) → RT (16 h). **204**/**210** (2.3:1).

Scheme 109. Partial kinetic protonation of precursor **210**.

Olivo's group[193] reported the stereoselective epoxidation of the analogous unsaturated bicyclic lactone **306** employing peracetic acid in a mixture of sodium acetate-acetic acid giving preferentially the *endo*-epoxide **307** in 89% yield (**Scheme 110**).

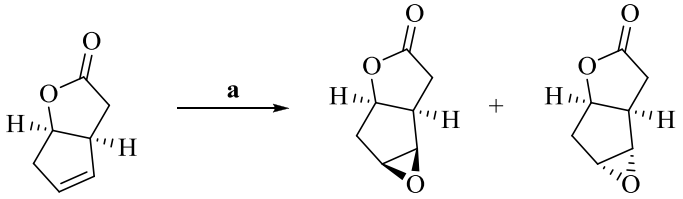


306 **307**

Reagents and conditions: **(a)** AcOOH (1.5 eq), NaOAc (2 eq), AcOH, RT, 48 h, 89%.

Scheme 110. Olivo's epoxidation of bicyclic γ-butyrolactone **306**.

Likewise, the Furstoss' group[194] also obtained diastereofacial selectivity when treating lactone **231** with *m*-chloroperbenzoic acid, which afforded a mixture of diastereomeric epoxides **308** and **309** in 80% and 6% yield, respectively, favouring the *endo*-epoxide **308** (**Scheme 111**).

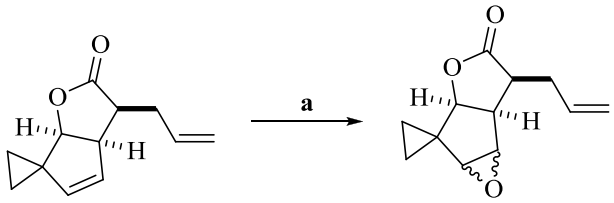


231 **308** **309**

Reagents and conditions: **(a)** *m*-CPBA (1.1 eq), CH_2Cl_2, 0 ºC → RT, 12 h, 80% (**308**), 6% (**309**).

Scheme 111. Furstoss' epoxidation of bicyclic γ-butyrolactone **231**.

In our case, it was decided to perform the olefin epoxidation of lactone **204** using *m*-CPBA in dichloromethane. This produced the desired oxirane ring lactone **302** as a separable 3.5:1 mixture of *endo*/*exo* diastereoisomers in 73% yield (**Scheme 112**). The expected minor product, *exo*-epoxide diastereoisomer **302**, was isolated a crystalline solid (**Figure 19**).



204 **302**

Reagents and conditions: **(a)** *m*-CPBA (1.1 eq), $NaHCO_3$ (1.1 eq), CH_2Cl_2, 0 ºC → RT, 48 h, *endo*/*exo* epoxidation (3.5:1), 73%.

Scheme 112. Synthesis of epoxide **302**.

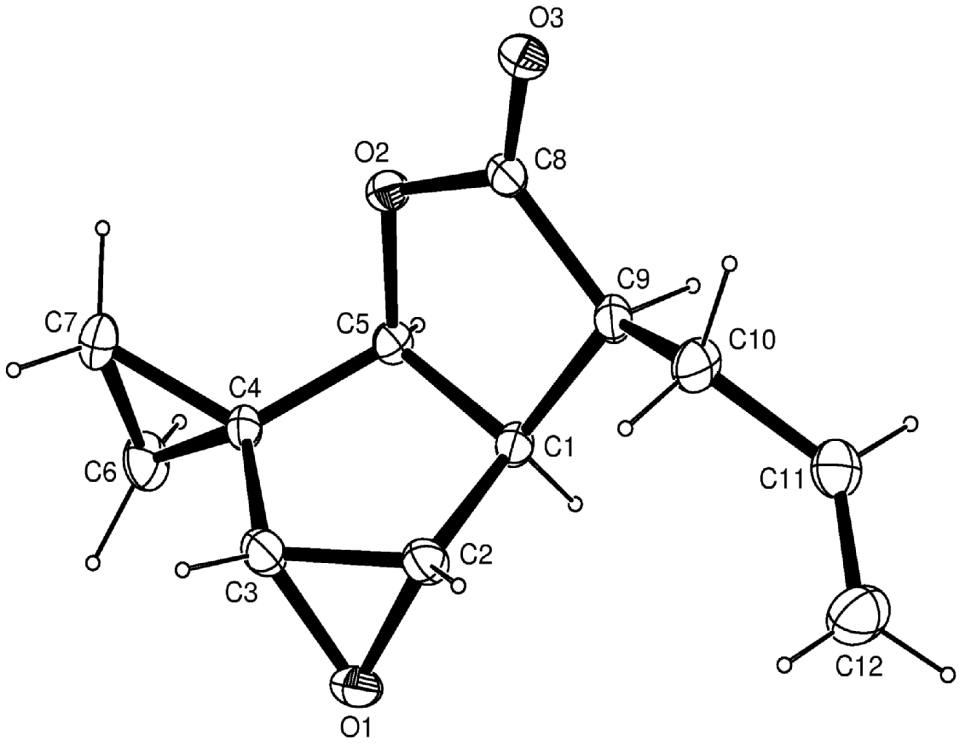
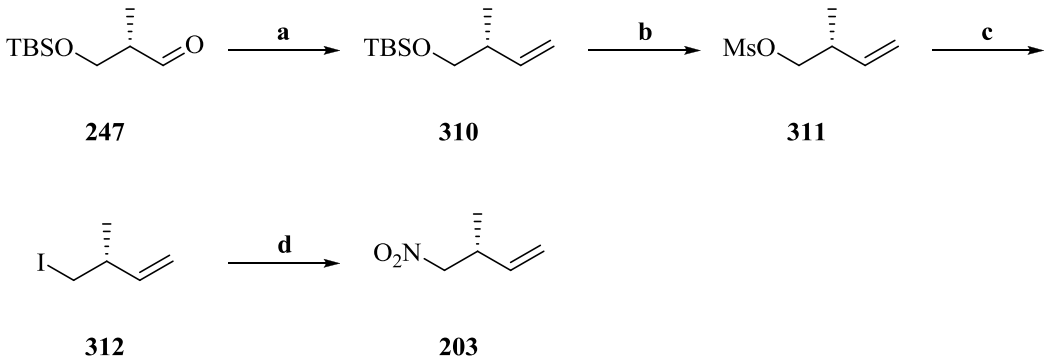


Figure 19. X-ray crystal structure of *exo*-epoxide **302**.

2.10 Synthesis of Nitroalkene **203**

Attention was focused towards the preparation of chiral nitroalkene **203**. Marsh[2] initially envisaged that **203** could be synthesised by regioselective 'Me^-' nucleophile addition to butadiene oxide.[195] However, a more reliable strategy was investigated in this project.

To commence the study, aldehyde **247** was chosen as the point of departure. Formation of alkene **310** was prepared according to the literature[196] with slight modifications.[2] Treatment of precursor **247** with methyltriphenylphosphonium bromide in tetrahydrofuran gave olefin **310** in good yield. Deprotection of the hydroxyl group with Dowex® 50W-X8[197] (cation-exchange resin) in dichloromethane, followed by mesylation and subsequent iodide replacement of the corresponding mesylate **311** led to iodide **312**.[198] Finally, nitration of **312** with Amberlite® resin in refluxing benzene[161] furnished nitroalkene **203** in 67% yield (**Scheme 113**).



Reagents and conditions: **(a)** $Ph_3P(Me)Br$ (2 eq), *n*-BuLi (2.5 eq), THF, 0 ºC → RT, 16 h, 81%; **(b)** Dowex® 50W-X8, CH_2Cl_2, 48 h; MsCl (1.1 eq), NEt_3 (1.1 eq), DMAP (cat), CH_2Cl_2, 0 ºC → RT, 16 h, 75%; **(c)** NaI (10 eq), acetone, Δ, 16 h, 71%; **(d)** Amberlite® IRA-900-NO_2^- (4.5 eq), PhH, Δ, 48 h, 67%.

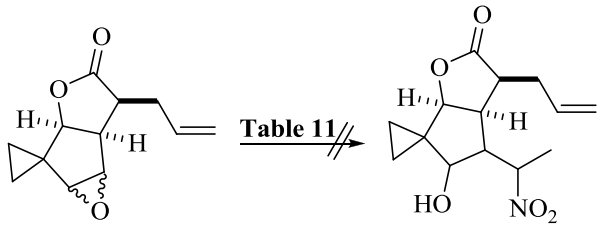
Scheme 113. Synthesis of nitroalkene **203**.

Having successfully prepared at least small quantities of key nitroalkene **203** in four steps from aldehyde **247**, the synthesis of the potential ring-closing metathesis precursor **302** could now be investigated.

2.11 Intermolecular Nitronate Anion-Epoxide Addition Approach

2.11.1 Model Study

To test the approach in principle, the reaction was attempted on epoxide **302** with commercially available nitroethane. Unfortunately, nitroethane in the presence of a base and subsequent nitronate anion addition to epoxide **302** failed to give any of the desired β-nitroalcohol product **313** (**Scheme 114**). Several bases, including some commonly used for the Henry reaction[185] were investigated for the deprotonation of the nitro compound and the results are summarised in **Table 11**.



302 **313**

Scheme 114. Intermolecular [3 + 2] nitrile oxide-olefin cycloaddition: Model study.

Entry	Reaction conditions	Solvent	T (ºC)	Time (h)	Product
1	$EtNO_2$ (10 eq), Proton-sponge® (10 eq)	CH_2Cl_2	RT	120	SM
2	$EtNO_2$ (10 eq), DIEA (10 eq)	CH_2Cl_2	RT	120	SM
3	$EtNO_2$ (10 eq), DBU (10 eq)	CH_2Cl_2	RT	168	SM + decomposition
4	$EtNO_2$ (10 eq), Amberlyst® A-21 (10 eq)	CH_2Cl_2	RT	168	SM + decomposition
5	$EtNO_2$ (10 eq), *t*-BuOK (10 eq)	*t*-BuOH **261** THF (1:1)	RT	168	SM + decomposition
6	$EtNO_2$ (1.1 eq), *t*-BuOLi **260** (1.1 eq)	THF	-78 to RT	16	SM

[a]The starting material **302** was added 1 hour after the addition of the base.

Table 11. Subjecting epoxide **302** to nitronate anion-epoxide addition conditions.

Ring-opening of epoxide **302** was first attempted using proton-sponge® and nitroethane in dichloromethane at room temperature. The reaction mixture was left for five days, but this indicated only the presence of the starting material (**Entry 1**).

Next was investigated the nucleophilic addition of **302** using nitroethane and DIEA, also known as Hünig's base in dichloromethane at room temperature. However, after five days of stirring only unreacted **302** was isolated (**Entry 2**).

Literature precedent has shown that there are many deprotonating agents that can be used for the Henry reaction[185] such as DBU,[199] Amberlyst A-21 resin,[200] and potassium *tert*-butoxide.[201] An investigation using these bases was carried out in our real system.

The employment of an excess of DBU[199] as the deprotonation source and nitroethane in dichloromethane at ambient temperature for one week led only the recovery of **302** and some decomposed material (**Entry 3**).

An excess of resin Amberlyst® A-21[200] (**Entry 4**) was investigated. This was added to a mixture of nitroethane and epoxide **302** in dichloromethane and left to stir for seven days. These conditions only resulted in the isolation of the starting material **302** and decomposition material.

The application of a stronger base such as potassium *tert*-butoxide[201] in a 1:1 mixture of tetrahydrofuran and *tert*-butanol **261** at room temperature for one week did not give access to the desired nitroalcohol **313**. Only starting material **302** and decomposition were observed (**Entry 5**). In addition, when **302** was exposed to lithium *tert*-butoxide **260** in tetrahydrofuran at low temperature no desired nitroalcohol **313** was formed and only starting material **302** was observed (**Entry 6**).

Unfortunately, time constrains and lack of material prevented any further investigations at this point. However, the results obtained and the syntheses of a number of intermediates towards asteriscanolide **1** justify additional investigation in the future.

2.12 Conclusions

Intensive synthetic studies towards asteriscanolide **1** have been undertaken using a novel strategy. The diverse disconnections have allowed the preparation of synthetically useful intermediates that had been subjected to our initial synthetic plans.

The synthesis of lactone **205** and mono-chlorinated lactone **238** was successfully achieved in a four-step procedure, starting from commercially available cyclopentadiene **206**, providing a significant part of our target molecule **1**.

Attempts to introduce the phosphonate ester in key lactone **205** under standard conditions failed. However, a promising result for the elaboration of α-phosphonated lactone **226** was observed when using chloro-lactone **238**. Alternatively, formation of mono-iodinated lactone **244** from the halogen exchange of **238** resulted to be a reliable and scaleable strategy for the construction of the HWE precursor **226**.

An efficient route for the synthesis of the HWE parter **217** incorporating the important homochiral C-7 methyl group was accomplished in a seven-step sequence starting from commercially available Roche ester **246**.

Efforts to combine the two necessary fragments α-phosphonated lactone **226** and aldehyde **217** led to the completion of the entire carbon framework **227** *via* a HWE condensation.

Preparation of the required INOC precursor **215** and the corresponding diastereoisomer **269** were synthesised *via* the functional group manipulation of the advanced olefin **227**. However, failure was experienced in trying to form the eight-membered ring under both Mukaiyama-Hoshino and Shimizu conditions, resulting only in dimerization products **280** and **282**.

Alternative strategies to device the ring closure were extensively investigated. Further approaches using the ISOC reaction, samarium(II) iodide-mediated cyclisation, radical-mediated cyclisation, and nitronate anion-epoxide cyclisation remained fruitless. Further work is required to investigate the intramolecular route.

A second generation approach was envisaged with a RCM manoeuvre as the pivotal step. For this, the application of an epoxide-opening operation was necessary. Although intermediates epoxide **302** and nitroalkene **203** were made in a relatively efficient manner, a model study has not yet been realised. Future work using this chemistry would be required.

CHAPTER 3

EXPERIMENTAL

3.1 General Experimental Procedures

All the reactions were performed under a nitrogen atmosphere unless otherwise stated, using oven-dried glassware. Reactions requiring anhydrous conditions were conducted by using flame-dried glassware. Microwave reactions were carried out with a CEM Discover SP microwave synthesis series.

Anhydrous diethyl ether and tetrahydrofuran were distilled from sodium in the presence of benzophenone. Dichloromethane, benzene, toluene, *N*,*N*-dimethylformamide, triethylamine, and ethyl acetate were distilled from calcium hydride prior to use. Methanol and ethanol were distilled from activated Magnesium turnings using a crystal of iodine. Phenyl isocyanate was distilled from P_2O_5 and stored over flame-dried 3Å molecular sieves. All other grade solvents were used as received for routine purposes from Fischer scientific. Chemical reagents were commercially available and used without further purification unless otherwise stated.

All reactions were monitored, where appropriate, by analytical thin layer chromatography (TLC) using Merck glass backed plates pre-coated with 0.25 mm layer of silica gel 60 F_{254} containing a fluorescent indicator. Visualisation was achieved with ultra violet florescence radiation (254 nm), and/or by staining with alkaline potassium permanganate, vanillin, or phosphomolybdic acid dips. Purification by flash column chromatography was carried according to Still procedure[202] using Fisher Scientific silica 60A (35-70 mesh).

Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded using a Varian VNMRS operating at 500 MHz, or a Bruker Advance AC-300 operating at 300 MHz. Samples were run at ambient probe temperature using deuteriochloroform as the solvent, unless otherwise stated. Residual isotopic solvent ($CHCl_3$, δ_H = 7.27 ppm) was used as the internal reference. Chemical shifts (δ) are quoted in parts per million (ppm), and coupling constants (*J*) are measured in Hertz (Hz). The following abbreviations are used to describe the multiplicity of a given signal: s, singlet; d, doublet; t, triplet; m, multiplet; dd, doublet of doublets; ddd, double doublet of doublets; dt, doublet of triplets; br, broad singlet.

Carbon nuclear magnetic resonance spectra (^{13}C NMR) were recorded using a Varian VNMRS operating at 125 MHz, or a Bruker Advance AC-300 operating at 75 MHz and proton decoupled. Samples were run at ambient probe temperature using deuteriochloroform as the solvent, unless otherwise stated. Residual isotopic solvent ($CHCl_3$, δ_C = 77.00 ppm) was used as the internal reference. Chemical shifts (δ) are quoted in parts per million (ppm). Carbon spectra assignments are supported by DEPT and correlation experiments. The following abbreviations are use to describe the multiplicity of a given signal: C, quaternary; CH, methane; CH_2, methylene, CH_3, methyl.

The numbering of all the compounds mentioned in this section is arbitrary, with the sole intention to aid in the assignment of protons and carbons in the relevant spectra. As such, they do not necessarily correspond with that of the I.U.P.A.C. system.

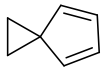
Infrared spectra (IR) were recorded on a Perkin-Elmer FT-IR 298 (1710) spectrometer, with absorption maxima (ν_{max}) measured in cm^{-1}. Some samples were prepared as either a thin film (liquids) or a solution in dichloromethane (solids) between sodium chloride plates, and other samples were directly placed on a universal attenuated total reflectance sampling accessory. The following abbreviations are used in reference to the intensity of absorption: s, strong; m, medium; w, weak; br, broad.

Mass spectrometry data were recorded by Dr. Alaa Abdul-Sada on a Bruker Daltronics Apex III 4.7T using positive electro-spray ionization (+'ve ESI), and a Fisons Instrument VG Autospec using positive electron impact (+'ve EI), with methanol as the solvent. Only molecular ions, fractions from molecular ions and other major peaks are reported as mass/charge (m/z) ratios. The following abbreviations are used to describe the experiment: HRMS, high resolution mass spectrometry; LRMS, low resolution mass spectrometry. GC MS analyses were carried out on a Quattro micro GC using HP-5MS fused silica (30 m × 0.25 i. d. × 0.25 μm). The carried gas used was helium at a flow rate of 1 mL/min.

Optical rotations were recorded using a Bellingham-Stanley ADP440 polarimeter with a 1 cm-path length cell. Optical rotation $[\alpha]_D$ data are given in units $10^{-1}degcm^2g^{-1}$, and solution concentrations are given in g/100 cm^{-3}.

3.2 Synthesis of Lactone **205**

Spiro[2.4]hepta-4,6-diene **207**



Following the modified procedure reported by Green *et al.*[108]: To a stirred suspension of sodium hydride (52.70 g, 1.32 mol, 60% dispersion in mineral oil) in tetrahydrofuran (250 mL) at 0 ºC was added a mixture of freshly cracked and distilled cyclopentadiene **206** (50.00 mL, 0.61 mol), and 1,2-dibromoethane (50.20 mL, 0.58 mol) in a dropwise manner. The reaction mixture was allowed to warm slowly to ambient temperature, and was left to stir for 16 hours before being treated with methanol (100 mL) in a dropwise fashion. Once the excess of sodium hydride has decomposed, water (200 mL) was added with pentane (3 × 150 mL), and the combined organic extracts were dried over anhydrous magnesium sulphate, filtered, and concentrated under reduced pressure. Distillation of the crude product afforded the title compound **207**[VI] as a colourless oil (37.60 g, 70%).

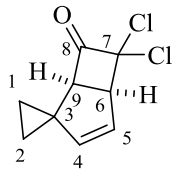
B. P.: 116-118 ºC, 760 mm Hg.

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.56 (2H, d, *J* = 6.6 Hz), 6.17 (2H, d, *J* = 6.6 Hz), 1.69 (4H, s).

^{13}C NMR (75 MHz, $CDCl_3$): δ 139.3 (CH), 129.1 (CH), 37.8 (C), 12.7 (CH_2).

[VI] Spectral data concurrent with the literature: Baretta, A.; Chong, K. S.; Cloke, F. G. N.; Feigenbaum, A.; Green, M. L. H. *J. Chem. Soc., Dalton Trans.* **1983**, 861-864.

6,6-Dichlorospiro[bicyclo[3.2.0]heptane-2,1'-cyclopropane]-3-en-7-one **208**

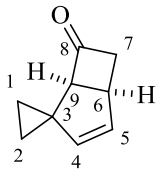


Following the modified procedure reported by Newton and colleagues[109]: To a stirred solution of spiro[2.4]hepta-4,6-diene **207** (5.00 mL, 49.92 mmol), and triethylamine (7.60 mL, 54.91 mmol) in dichloromethane (125 mL) at 0 °C was added dichloroacetyl chloride (5.04 mL, 52.41 mmol) in a dropwise manner. The reaction mixture was left to stir for 16 h at ambient temperature. The resultant dark brown solution was treated with pentane (5 × 100 mL), and the extracts were filtered. The filter cake was well washed with pentane, and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography, eluting with petroleum ether, afforded the title compound **208**[VII] as a colourless oil (7.50 g, 74%).

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 5.73 (1H, dd, *J* = 5.5, 2.6 Hz, H-5), 5.55 (1H, dd, *J* = 5.7, 1.5 Hz, H-4), 4.34-4.15 (1H, m, H-6), 3.73 (1H, d, *J* = 7.6 Hz, H-9), 1.30-1.24 (1H, m, cyclopropyl), 0.97-0.87 (1H, m, cyclopropyl), 0.85-0.73 (2H, m, cyclopropyl).
^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 196.5 (C-8), 143.6 (C-4), 125.5 (C-5), 76.7 (C-7), 64.9 (C-6), 60.0 (C-9), 32.2 (C-3), 13.6 (C-1), 8.9 (C-2).
HRMS (+'ve ESI): calculated for $C_9H_8Cl_2ONa^+$ 224.9844 $(M + Na)^+$, found 224.9845.
IR ν_{max} (neat, cm^{-1}): 3083 (w), 3006 (w), 2964 (w), 1801 (s), 1597 (w), 1425 (w), 1278 (w), 1184 (w), 963 (m), 748 (s), 679 (m), 588 (m).

[VII] Spectral data concurrent with the literature: Jones, S. W.; Middlemiss, D.; Newton, R. F.; Scheinmann, F.; Wakefield, B. J. *J. Chem. Res., Miniprint* **1988**, 12, 3001-3027.

Spiro[bicyclo[3.2.0]heptane-2,1'-cyclopropane]-3-en-7-one **209**



Following the modified procedure reported by Newton and colleagues[109]: To a stirred solution of zinc dust (7.08 g, 108.00 mmol), and ammonium chloride (14.50 g, 271.00 mmol) in methanol (140 mL) was added a solution of 6,6-dichlorospiro[bicyclo[3.2.0]heptane-2,1'-cyclopropane]-3-en-7-one **208** (5.50 g, 27.00 mmol) in methanol (25 mL) in a dropwise manner, keeping the temperature below 40 ºC. The reaction mixture was stirred at room temperature for 24 hours before being filtered. The filter cake was well washed with methanol, and the filtrate was concentrated under reduced pressure. The residue was partitioned between water (75 mL) and dichloromethane (75 mL), and the organic phase was separated. The aqueous component was extracted with dichloromethane (3 × 50 mL), and the combined organic extracts were dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. Purification by flash column chromatography, eluting with 5% diethyl ether/petroleum ether, afforded the title compound **209**[VIII] as a colourless oil (2.51 g, 70%).

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 5.83 (1H, dd, *J* = 5.5, 2.4 Hz, H-5), 5.30 (1H, d, *J* = 5.4 Hz, 1H, H-4), 3.66-3.56 (1H, m, H-6), 3.37-3.27 (2H, m, H-7), 2.80 (1H, dt, *J* = 17.6, 3.5 Hz, H-9), 1.24-1.09 (1H, m, cyclopropyl), 0.81-0.73 (1H, m, cyclopropyl), 0.73-0.62 (2H, m, cyclopropyl).

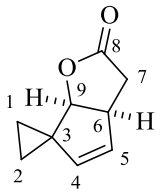
^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 210.9 (C-8), 139.1 (C-4), 130.5 (C-5), 67.9 (C-6), 54.5 (C-7), 36.9 (C-9), 31.2 (C-3), 13.9 (C-1), 8.9 (C-2).

LRMS (+'ve EI): *m/z* 134 (M, 15%), 105 (47), 93 (46), 78 (100), 65 (51).

[VIII] Spectral data concurrent with the literature: Jones, S. W.; Middlemiss, D.; Newton, R. F.; Scheinmann, F.; Wakefield, B. J. *J. Chem. Res., Miniprint* **1988**, 12, 3001-3027.

IR ν_{max} (neat, cm^{-1}): 3079 (w), 3006 (w), 2953 (w), 1771 (s), 1599 (w), 1425 (w), 1390 (w), 1222 (w), 1081 (m), 959 (m), 744 (m).

3a,6a-Dihydrospiro[cyclopenta[*b*]furan-6,1'-cyclopropan]-2(3*H*)-one **205**



Following the modified procedure reported by Marsh[2]: To a stirred solution of spiro[bicyclo[3.2.0]heptane-2,1'-cyclopropane]-3-en-7-one **209** (0.15 g, 1.20 mmol) in 90% aqueous acetic acid (5 mL) at 0 °C was added a mixture hydrogen peroxide (0.23 mL, 2.66 mmol, 35 wt.% solution in water) in 90% aqueous acetic acid (6 mL) in a dropwise manner. The reaction mixture was stirred at 0 °C for 16 hours, before being added very slowly to a saturated aqueous solution of sodium hydrogen carbonate (100 mL). The product was extracted with diethyl ether (4 × 50 mL), and the combined organic extracts were washed successively with a 10 % aqueous sodium sulfite solution (50 mL), and a saturated aqueous sodium hydrogen carbonate solution (2 × 50 mL) before being dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. Purification by flash column chromatography, eluting with 50% diethyl ether/hexane, afforded a white solid, which was recrystallised[IX] from diethyl ether to give the title compound **205** as white monoclinic crystals (0.14 g, 84%).

M. P.: 52-54 ºC.

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 5.54 (1H, dd, *J* = 5.6, 1.7 Hz, H-5), 5.34 (1H, dd, *J* = 5.6, 2.0 Hz, H-4), 4.57 (1H, d, *J* = 6.3 Hz, H-9), 3.78-3.65 (1H, m, H-6), 2.81 (1H, dd, *J* = 18.0, 9.9 Hz, H-7$_{a\ or\ b}$), 2.51 (1H, dd, *J* = 18.0, 2.0 Hz, H-7$_{a\ or\ b}$), 1.22-1.17 (1H, m, cyclopropyl), 0.98-0.89 (2H, m, cyclopropyl), 0.82-0.77 (1H, m, cyclopropyl).

^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 176.6 (C-8), 136.9 (C-4), 129.0 (C-5), 89.4 (C-9), 45.0 (C-6), 34.0 (C-7), 33.8 (C-3), 13.3 (C-1), 9.0 (C-2).

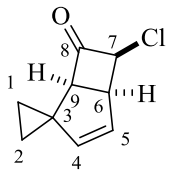
LRMS (+'ve EI): *m/z* 150 (M, 53%), 105 (91), 91 (90), 79 (100), 65 (24), 51 (27), 39 (54), 32 (39).

[IX] See appendix for crystal structure data.

IR ν_{max} (neat, cm^{-1}): 2983 (w), 2923 (w), 1765 (s), 1599 (w), 1419 (m), 1348 (m), 1306 (m), 1224 (m), 1152 (s), 1039 (m), 974 (m), 852 (m), 748 (s).

3.3 Synthesis of Lactone **238**

6-Chlorospiro[bicyclo[3.2.0]heptane-2,1'-cyclopropane]-3-en-7-one **234**



Following the modified procedure reported by Newton and colleagues[109]: To a stirred solution of zinc dust (17.38 g, 0.26 mol), and ammonium chloride (47.41 g, 0.88 mol) in methanol (380 mL) was added a solution of 6,6-dichlorospiro[bicyclo[3.2.0]heptane-2,1'-cyclopropane]-3-en-7-one **208** (18.00 g, 0.09 mol) in methanol (50 mL) in a dropwise manner, keeping the temperature below 40 ºC. The reaction mixture was stirred at 0 ºC for 8 hours, and was further left to stir at room temperature for 7 hours before being filtered. The filter cake was well washed with methanol, and the filtrate was concentrated under reduced pressure. The residue was partitioned between water (150 mL) and dichloromethane (125 mL), and the organic phase was separated. The aqueous component was extracted with dichloromethane (3 × 150 mL), and the combined organic extracts were dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. Purification by flash column chromatography, eluting with 5% diethyl ether/petroleum ether, afforded a white solid, which was recrystallised[X] from diethyl ether to give the title compound **234** as white monoclinic crystals (13.60 g, 82%).

M. P.: 59-61 ºC.

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 5.72 (1H, dd, *J* = 5.5, 2.3 Hz, H-5), 5.51 (1H, d, *J* = 5.5 Hz, H-4), 5.05 (1H, dd, *J* = 8.6, 2.8 Hz, H-7), 4.12 (1H, t, *J* = 7.9 Hz, H-6), 3.32 (1H, dd, *J* = 7.2, 2.8 Hz, H-9), 1.31-1.19 (1H, m, cyclopropyl), 0.94-0.84 (1H, m, cyclopropyl), 0.78-0.67 (2H, m, cyclopropyl).

[X] See appendix for crystal structure data.

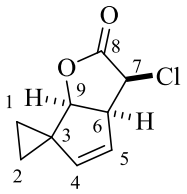
^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 203.7 (C-8), 142.7 (C-4), 125.6 (C-5), 65.7 (C-7), 64.7 (C-9), 46.5 (C-6), 32.8 (C-3), 13.2 (C-1), 8.7 (C-2).

HRMS (+'ve ESI): calculated for $C_9H_9ClONa^+$ 191.0234 $(M + Na)^+$, found 191.0230.

IR ν_{max} (neat, cm^{-1}): 2924 (w), 2854 (w), 1776 (s), 1600 (w), 1423 (w), 1293 (m), 1183 (m), 1017 (m), 952 (s), 751 (s), 728 (s), 550 (m).

3-Chloro-3a,6a-dihydrospiro[cyclopenta[*b*]furan-6,1'-cyclopropan]-2(3*H*)-one

238



Following the modified procedure reported by Marsh[2]: To a stirred solution of 6-chlorospiro[bicyclo[3.2.0]heptane-2,1'-cyclopropane]-3-en-7-one **234** (0.10 g, 0.59 mmol) in 90% aqueous acetic acid (4 mL) at 0 °C was added a mixture hydrogen peroxide (0.16 mL, 1.85 mmol, 35 wt.% solution in water) in 90% aqueous acetic acid (6 mL) in a dropwise manner. The reaction mixture was stirred at 0 °C for 16 hours before being added very slowly to a saturated aqueous solution of sodium hydrogen carbonate (50 mL). The product was extracted with diethyl ether (4 × 40 mL), and the combined organic extracts were washed successively with a 10 % aqueous sodium sulfite solution (50 mL), and a saturated aqueous sodium hydrogen carbonate solution (2 × 50 mL) before being dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. Purification by flash column chromatography, eluting with 30% diethyl ether/petroleum ether, afforded a white solid, which was recrystallised[XI] from diethyl ether to give the title compound **238** as white orthorhombic crystals (0.10 g, 99%).

M. P.: 65-67 ºC.

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 5.72 (1H, dd, *J* = 5.7, 1.6 Hz, H-5), 5.47 (1H, dd, *J* = 5.7, 2.2 Hz, H-4), 4.79 (1H, d, *J* = 8.9 Hz, H-9), 4.50 (1H, d, *J* = 5.4 Hz, H-7), 4.05-4.01 (1H, m, H-6), 1.26-1.13 (1H, m, cyclopropyl), 1.07-0.92 (2H, m, cyclopropyl), 0.89-0.76 (1H, m, cyclopropyl).

^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 171.5 (C-8), 138.5 (C-4), 124.6 (C-5), 87.4 (C-7), 55.2 (C-9), 50.8 (C-6), 34.5 (C-3), 13.0 (C-1), 8.8 (C-2).

HRMS (+'ve ESI): calculated for $C_9H_9ClO_2Na^+$ 207.0183 $(M + Na)^+$, found 207.0181.

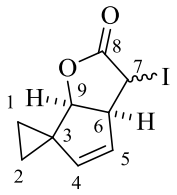
[XI] See appendix for crystal structure data.

IR ν_{max} (neat, cm^{-1}): 3082 (w), 2981 (m), 2844 (w), 1762 (s), 1700 (w), 1420 (w), 1333 (m), 1311 (m), 1222 (m), 1165 (s), 1033 (s), 978 (m), 846 (m), 763 (s), 603 (m).

3.4 Synthesis of Lactone **244**

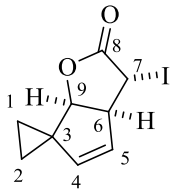
3-Iodo-3a,6a-dihydrospiro[cyclopenta[*b*]furan-6,1'-cyclopropan]-2(3*H*)-one

244



To a stirred solution of 3-chloro-3a,6a-dihydrospiro[cyclopenta[*b*]furan-6,1'-cyclopropan]-2(3*H*)-one **238** (6.90 g, 38.00 mmol) in acetone (200 mL) was added sodium iodide (85.53 g, 562.50 mmol) in small portions over 1 hour. The reaction mixture was heated to reflux for 48 hours. The flask was shielded from light throughout the reaction. After being allowed to cool to room temperature, the reaction mixture was diluted with diethyl ether (175 mL), and the extracts were filtered. The filter cake was washed with diethyl ether, and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography, eluting with 30% diethyl ether/hexane, afforded the title compound **244** as a colourless solid, and a separable mixture of diastereoisomers in a 24:1 ratio (7.30 g, 70%).

***Major* diastereoisomer:**



M. P.: 70-72 ºC. Recrystallised from diethyl ether.

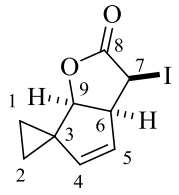
^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 5.57-5.52 (2H, m, H-5, H-4), 4.66 (1H, d, *J* = 7.6 Hz, H-9), 4.48 (1H, s, H-7), 4.06-3.84 (1H, m, H-6), 1.33-1.13 (1H, m, cyclopropyl), 1.13-0.91 (2H, m, cyclopropyl), 0.91-0.68 (1H, m, cyclopropyl).

^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 174.5 (C-8), 138.9 (C-4), 124.7 (C-5), 88.6 (C-9), 58.3 (C-6), 33.1 (C-3), 13.6 (C-7), 12.9 (C-1), 9.1 (C-2).

HRMS (+'ve ESI): calculated for $C_9H_9IO_2Na^+$ 298.9539 $(M + Na)^+$, found 298.9537.

IR ν_{max} (neat, cm^{-1}): 2955 (w), 1764 (s), 1598 (w), 1313 (m), 1225 (m), 1157 (s), 1033 (m), 1017 (m), 956 (m), 873 (m), 736 (s), 678 (m), 574 (s).

***Minor* diastereoisomer:**



M. P.: 76-78 ºC. Recrystallised from diethyl ether.

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 5.63 (1H, d, *J* = 5.6 Hz, H-5), 5.46 (1H, dd, *J* = 5.7, 1.8 Hz, H-4), 5.02 (1H, d, *J* = 9.1 Hz, H-7), 4.63 (1H, d, *J* = 5.8 Hz, H-9), 3.95-3.88 (1H, m, H-6), 1.21-1.09 (1H, m, cyclopropyl), 1.09-0.90 (2H, m, cyclopropyl), 0.90-0.77 (1H, m, cyclopropyl).

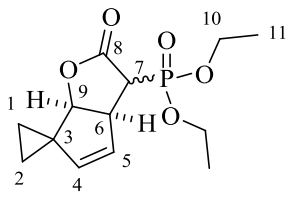
^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 173.2 (C-8), 138.3 (C-4), 130.8 (C-5), 88.6 (C-9), 50.3 (C-6), 34.4 (C-3), 18.7 (C-7), 13.1 (C-1), 9.7 (C-2).

HRMS (+'ve ESI): calculated for $C_9H_9IO_2Na^+$ 298.9539 $(M + Na)^+$, found 298.9537.

IR ν_{max} (neat, cm^{-1}): 2925 (w), 1753 (s), 1592 (w), 1427 (w), 1385 (w), 1308 (m), 1223 (s), 1161 (s), 1034 (m), 978 (s), 880 (m), 738 (s), 699 (s), 578 (s).

3.5 Synthesis of Phosphonated Lactones **226** and **245**

Diethyl (2-oxo-2,3,3a,6a-tetrahydrospiro[cyclopenta[*b*]furan-6,1'-cyclopropan]-3-yl)phosphonate **226**



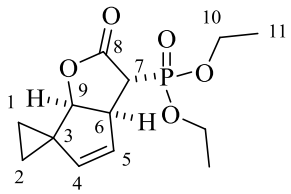
Method 1:

A solution of 3-iodo-3a,6a-dihydrospiro[cyclopenta[*b*]furan-6,1'-cyclopropan]-2(3*H*)-one **244** (2.00 g, 7.20 mmol), and triethyl phosphite (8.70 mL, 50.40 mmol) was treated with microwave irradiation (150 W, 125 °C) for 3 hours. The reaction mixture was cooled to ambient temperature, followed by the distillation of the triethyl phosphite excess using a Kugelrohr® short-path apparatus. Purification by flash column chromatography, eluting with 10% methanol/dichloromethane, followed by a second flash column chromatography, eluting with 50% ethyl acetate/hexane, afforded the title compound **226** as a pale yellow oil, and an inseparable mixture of diastereoisomers in a 5:1 ratio (1.25 g, 60%).

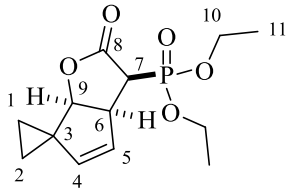
Method 2:

A solution of 3-iodo-3a,6a-dihydrospiro[cyclopenta[*b*]furan-6,1'-cyclopropan]-2(3*H*)-one **244** (300 mg, 1.08 mmol), and triethyl phosphite (0.23 mL, 1.29 mmol) was heated to reflux for 16 hours. The reaction mixture was cooled to ambient temperature, followed by the distillation of the triethyl phosphite excess using a Kugelrohr® short-path apparatus. Purification by flash column chromatography, eluting with 10% methanol/dichloromethane, followed by a second flash column chromatography, eluting with 50% ethyl acetate/hexane, afforded the title compound **226** as a pale yellow oil, and an inseparable mixture of diastereoisomers in a 5:1 ratio (64 mg, 20%).

***Major* diastereoisomer:**



***Minor* diastereoisomer:**



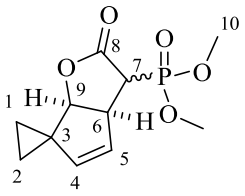
^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 5.89 (1H, dd, *J* = 5.7, 1.6 Hz, H-5$_{minor}$), 5.53 (1H, dd, *J* = 5.6, 1.5 Hz, H-5$_{major}$), 5.04-5.36 (2H, m, H-4$_{major\ and\ minor}$), 4.63 (1H, d, *J* = 6.1 Hz, H-9$_{major}$), 4.49 (1H, d, *J* = 5.8 Hz, H-9$_{minor}$), 4.28-4.17 (4H, m, H-10$_{major}$), 4.17-4.05 (4H, m, H-10$_{minor}$), 4.04-3.98 (1H, m, H-6$_{major}$), 3.98-3.93 (1H, m, H-6$_{minor}$), 3.40 (1H, dd, *J* = 25.4, 9.3 Hz, H-7$_{minor}$), 3.06 (1H, dd, *J* = 23.4, 2.1 Hz, H-7$_{major}$), 1.42-1.32 (12H, m, H-11$_{major\ and\ minor}$), 1.24-1.16 (2H, m, cyclopropyl$_{major\ and\ minor}$), 1.02-0.90 (4H, m, cyclopropyl$_{major\ and\ minor}$), 0.83-0.76 (2H, m, cyclopropyl$_{major\ and\ minor}$).

^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) *major*, 171.3 (C-8), 137.5 (C-4), 127.8 (C-5), 89.0 (C-9), 63.5 (C-10), 63.1 (C-10), 48.1 (C-6), 46.2 (C-7), 33.5 (C-3), 16.4 (C-11), 16.3 (C-11), 13.1 (cyclopropyl), 9.0 (cyclopropyl); *minor*, 171.3 (C-8), 137.5 (C-4), 127.8 (C-5), 88.9 (C-9), 63.5 (C-10), 63.1 (C-10), 48.0 (C-6), 45.1 (C-7), 33.5 (C-3), 16.4 (C-11), 16.3 (C-11), 13.1 (cyclopropyl), 9.0 (cyclopropyl).

HRMS (+'ve ESI): calculated for $C_{13}H_{19}PO_5Na^+$ 309.0856 $(M + Na)^+$, found 309.0865.

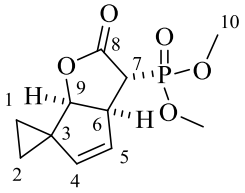
IR ν_{max} (neat, cm^{-1}): 3493 (w), 2982 (w), 2911 (w), 1764 (s), 1740 (w), 1635 (w), 1393 (w), 1248 (s), 1155 (s), 1014 (s), 960 (s), 733 (s), 640 (m).

Dimethyl (2-oxo-2,3,3a,6a-tetrahydrospiro[cyclopenta[*b*]furan-6,1'-cyclopropan]-3-yl)phosphonate **245**

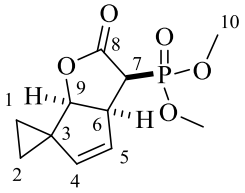


A solution of 3-iodo-3a,6a-dihydrospiro[cyclopenta[*b*]furan-6,1'-cyclopropan]-2(3*H*)-one **244** (0.10 g, 0.36 mmol), and trimethyl phosphite (0.30 mL, 2.50 mmol) was treated with microwave irradiation (150 W, 105 °C) for 3 hours. The reaction mixture was cooled to room temperature, followed by the distillation of the trimethyl phosphite excess using a Kugelrohr® short-path apparatus. Purification by flash column chromatography, eluting with 50% diethyl ether/hexane, followed by a second flash column chromatography, eluting with 5% methanol/dichloromethane, afforded the title compound **245** as a pale orange oil, and an inseparable mixture of diastereoisomers in a 3:1 ratio (0.01 g, 10%).

***Major* diastereoisomer:**



***Minor* diastereoisomer:**



^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 5.85 (1H, d, *J* = 5.3 Hz, H-5_{minor}), 5.53 (1H, d, *J* = 5.0 Hz, H-5_{major}), 5.41 (1H, dd, *J* = 5.7, 1.9 Hz, H-4_{minor}) 5.38 (1H, d, *J* = 4.7 Hz, H-4),

4.65 (1H, d, J = 6.1 Hz, H-9$_{major}$), 4.49 (1H, d, J = 5.8 Hz, H-9$_{minor}$), 4.05-3.97 (1H, m, H-6$_{major}$), 3.97-3.92 (1H, m, H-6$_{minor}$), 3.91-3.82 (6H, m, H-10$_{major}$), 3.82-3.71 (6H, m, H-10$_{minor}$), 3.44 (1H, dd, J = 25.5, 9.3 Hz, H-7$_{minor}$), 3.06 (1H, dd, J = 23.6, 1.9 Hz, H-7$_{major}$), 1.42-1.32 (12H, m, H-11$_{major\ and\ minor}$), 1.24-1.12 (2H, m, cyclopropyl$_{major\ and\ minor}$), 1.05-0.90 (4H, m, cyclopropyl$_{major\ and\ minor}$), 0.87-0.73 (2H, m, cyclopropyl$_{major\ and\ minor}$).

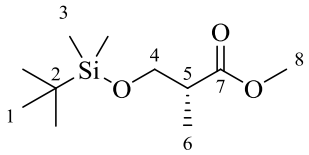
^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) *major*, 171.3 (C-8), 137.7 (C-4), 127.3 (C-5), 89.1 (C-9), 54.0 (C-10), 53.4 (C-10), 47.9 (C-6), 45.2 (C-7), 33.4 (C-3), 13.1 (cyclopropyl), 9.0 (cyclopropyl); *minor*, 171.3 (C-8), 137.7 (C-4), 126.7 (C-5), 88.9 (C-9), 54.0 (C-10), 53.4 (C-10), 47.9 (C-6), 43.6 (C-7), 33.4 (C-3), 13.1 (cyclopropyl), 9.0 (cyclopropyl).

HRMS (+'ve ESI): calculated for $C_{11}H_{15}PO_5Na^+$ 281.0549 $(M + Na)^+$, found 281.0548.

IR ν_{max} (neat, cm^{-1}): 3462 (w), 2960 (w), 2855 (w), 1760 (s), 1462 (w), 1311 (m), 1250 (s), 1157 (s), 1019 (s), 961 (m), 823 (m), 742 (m), 634 (m).

3.6 Synthesis of Aldehyde **217**

Methyl (2*R*)-3-{[*tert*-butyl(dimethyl)silyl]oxy}-2-methylpropanoate **248**



Following the modified procedure reported by Ansell[139]: To a stirred solution *tert*-butyldimethylsilyl chloride (35.45 g, 236.00 mmol) in dichloromethane (550 mL) at 0 °C was added imidazole (17.01 g, 253.00 mmol) as a single solid portion. The reaction mixture was stirred for 5 minutes, and a solution of methyl (2*R*)-(-)-(3)-hydroxy-2-methylpropionate **246** (19.95 g, 169.00 mol) in dichloromethane (115 mL) was added in a dropwise fashion, followed by the addition of *N*,*N*-dimethylaminopyridine (2.06 g, 17.00 mmol) as a single solid portion. The reaction mixture was allowed to slowly warm to room temperature and was left to stir for 16 hours. The reaction mixture was poured into water (800 mL), and the organic phase was separated. The aqueous component was extracted with dichloromethane (4 × 250 mL), and the combined organic extracts were dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. Purification by flash column chromatography, eluting with 3% diethyl ether/petroleum ether, afforded the title compound **248**[XII] as a colourless oil (37.40 g, 96%).

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 3.79-3.75 (1H, m, H-4$_{a\ or\ b}$), 3.69-3.62 (4H, m, H-4$_{a\ or\ b}$, H-8), 2.71-2.60 (1H, m, H-5), 1.14 (3H, d, *J* = 7.0 Hz, H-6), 0.88 (9H, s, H-1), 0.04 (3H, s, H-3).

^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 175.4 (C-7), 65.2 (C-4), 51.4 (C-8), 42.5 (C-5), 25.7 (C-1), 18.2 (C-2), 13.4 (C-6), -5.5 (C-3).

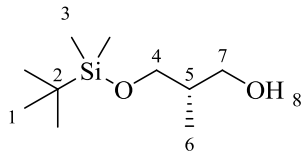
HRMS (+'ve ESI): calculated for $C_{11}H_{24}O_3SiNa^+$ 255.1386 $(M + Na)^+$, found 255.1391.

[XII] Spectral data concurrent with the literature: Ansell, G. K. University of Sussex **2001**.

IR ν_{max} (neat, cm^{-1}): 2931 (m), 2858 (m), 1741 (s), 1463 (m), 1435 (m), 1389 (m), 1362 (m), 1254 (s), 1197 (m), 1175 (m), 1092 (s), 1025 (m), 1006 (m), 939 (w), 840 (s), 774 (s), 665 (m).

$[\alpha]_D^{26}$ -18.7° (*c* 1.56 in $CHCl_3$).

(2*S*)-3-{[*tert*-Butyl(dimethyl)silyl]oxy}-2-methylpropan-1-ol **249**



Following the modified procedure reported by Ansell[139]: To a stirred solution of methyl (2*R*)-3-{[*tert*-butyl(dimethyl)silyl]oxy}-2-methylpropanoate **248** (6.00 g, 25.80 mmol) in dichloromethane (125 mL) at -78 °C was added diisobutylaluminium hydride (57.00 mL, 54.31 mmol, 1 M solution in dichloromethane) in a dropwise manner over 3 hours. The reaction mixture was allowed to slowly warm to ambient temperature and was stirred for 16 hours, before adding to an ice cooled solution of potassium sodium tartrate (37.00 g) in water (200 mL). The cloudy solution was stirred until clear, the layers were separate, and the aqueous phase was extracted with dichloromethane (4 × 100 mL). The combined organic extracts were dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. Purification by flash column chromatography, eluting with 10% diethyl ether/petroleum ether, afforded the title compound **249**[XIII] as a colourless oil (4.98 g, 94%).

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 3.74 (1H, dd, *J* = 9.8, 4.4 Hz, H-7$_{a\ or\ b}$), 3.68-3.52 (3H, m, H-4, H-7$_{a\ or\ b}$), 2.74 (1H, s, br, H-8), 2.01-1.88 (1H, m, H-5), 0.91 (9H, s, H-1), 0.85 (3H, d, *J* = 6.9 Hz, H-6), 0.08 (6H, s, H-3).

^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 68.7 (C-7), 68.2 (C-4), 37.0 (C-5), 25.8 (C-1), 18.2 (C-2), 13.5 (C-6), -5.5 and -5.6 (C-3).

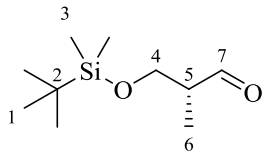
HRMS (+'ve ESI): calculated for $C_{10}H_{24}O_2SiNa^+$ 227.1437 $(M + Na)^+$, found 227.1437.

IR ν_{max} (neat, cm^{-1}): 3355 (br), 2954 (m), 2858 (m), 2959 (m), 1471 (m), 1389 (w), 1361 (w), 1251 (s), 1087 (s), 1033 (s), 1006 (m), 938 (m), 840 (s), 773 (s), 666 (m).

$[\alpha]_D^{24}$ -10.5° (*c* 1.12 in $CHCl_3$).

[XIII] Spectral data concurrent with the literature: Organ, M. G.; Wang, J. *J. Org. Chem.* **2003**, 68, 5568-5574.

(2*R*)-3-{[*tert*-Butyl(dimethyl)silyl]oxy}-2-methylpropanal **247**

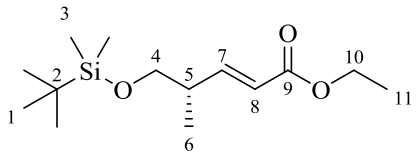


Following the modified procedure reported by Ansell[139]: To a stirred solution of (2*S*)-3-{[*tert*-butyl(dimethyl)silyl]oxy}-2-methylpropan-1-ol **249** (8.00 g, 39.20 mmol) in dichloromethane (160 mL) at 0 °C was added triethylamine (27.50 mL, 196.00 mmol), and a solution of sulfurtrioxide pyridinium complex (24.96 g, 156.80 mmol) in dimethylsulfoxide (32.00 mL) in a dropwise fashion over 3 hours. The reaction mixture was allowed to warm to room temperature was stirred for 16 hours, before adding to a saturated solution of aqueous ammonium chloride (150 mL). The layers were separated, and the aqueous phase was extracted using diethyl ether (7 × 150 mL). The combined organic extracts were washed with a saturated aqueous solution of sodium chloride (150 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. Purification by flash column chromatography, eluting with 10% diethyl ether/petroleum ether, afforded the title compound **247**[XIV] as a colourless oil (6.60 g, 84%).

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 9.74 (1H, s, H-7), 3.88-3.78 (2H, m, H-4), 2.58-2.48 (1H, m, H-5), 1.10 (3H, d, *J* = 7.0 Hz, H-6), 0.88 (9H, s, H-1), 0.06 (6H, s, H-3).
^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 204.5 (C-7), 63.4 (C-4), 48.7 (C-5), 25.7 (C-1), 18.2 (C-2), 10.2 (C-6), -5.5 and -5.6 (C-3).
HRMS (+'ve ESI): calculated for $C_{10}H_{22}O_2SiNa^+$ 225.1281 $(M + Na)^+$, found 225.1283.
IR ν_{max} (neat, cm^{-1}): 2931 (m), 2858 (m), 2720 (w), 1727 (m), 1472 (m), 1390 (w), 1361 (w), 1252 (s), 1095 (s), 1032 (s), 1006 (m), 938 (w), 842 (s), 774 (s), 668 (m).
$[\alpha]_D^{29}$ -25.6° (*c* 1.67 in $CHCl_3$).

[XIV] Spectral data concurrent with the literature: Ansell, G. K. University of Sussex **2001**.

Ethyl (2*E*,4*S*)-5-{[*tert*-butyl(dimethyl)silyl]oxy}-4-methylpent-2-enoate **250**



Following the procedure reported by Chandrasekhar[138]: To a stirred solution of (carbethoxymethylene)triphenylphosphorane (17.24 g, 49.50 mmol) in dichloromethane (180 mL) at room temperature was added a solution of (2*R*)-3-{[*tert*-butyl(dimethyl)silyl]oxy}-2-methylpropanal **247** (10.00 g, 49.50 mmol) in dichloromethane (80 mL). The reaction mixture was stirred for 16 hours. The resultant white precipitate was filtered, and concentrated under reduced pressure. The crude residue was triturated using petroleum ether (200 mL), and the remaining solvent was removed under reduced pressure. Purification by flash column chromatography, eluting with 3% diethyl ether/petroleum ether, afforded the title compound **250**[XV] as a colourless oil (13.50 g, 99%).

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 6.93 (1H, dd, *J* = 15.8, 7.2 Hz, H-7), 5.83 (1H, dd, *J* = 1.58, 0.9 Hz, H-8), 4.19 (2H, q, *J* = 7.1 Hz, H-10), 3.58-3.48 (2H, m, H-4), 2.53-2.45 (1H, m, H-5), 1.29 (3H, t, *J* = 7.1 Hz, H-11), 1.06 (3H, d, *J* = 6.8 Hz, H-6), 0.88 (9H, s, *J* = 6.1 Hz, H-1), 0.04 (6H, s, H-3).

^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 166.7 (C-9), 151.3 (C-7), 120.9 (C-8), 66.9 (C-4), 60.1 (C-10), 39.1 (C-5), 25.8 (C-1), 18.2 (C-2), 15.5 (C-6), 14.2 (C-11), -5.4 (C-3).

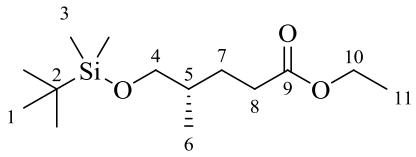
HRMS (+'ve ESI): calculated for $C_{14}H_{28}O_3SiNa^+$ 295.1705 $(M + Na)^+$, found 295.1701.

IR ν_{max} (neat, cm^{-1}): 2930 (m), 2858 (m), 1720 (s), 1654 (m), 1472 (m), 1388 (w), 1367 (m), 1252 (s), 1181 (m), 1149 (m), 1092 (s), 1033 (m), 983 (w), 840 (s), 774 (s), 719 (w), 666 (m).

$[\alpha]_D^{27}$ -14.5° (*c* 1.15 in $CHCl_3$).

[XV] Spectral data concurrent with the literature: Marshall, J. A.; Yanik, M. M. *J. Org. Chem.* **2001**, 66, 1373-1379.

Ethyl (4*S*)-5-{[*tert*-butyl(dimethyl)silyl]oxy}-4-methylpentanoate **251**

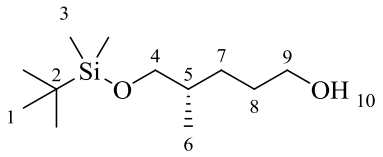


To a stirred solution of ethyl (2*E*,4*S*)-5-{[*tert*-butyl(dimethyl)silyl]oxy}-4-methylpent-2-enoate **250** (13.00 g, 47.70 mmol) in ethyl acetate (200 mL) at ambient temperature under hydrogen atmosphere was added platinum oxide (1.08 g, 4.70 mmol) as a single solid portion. The reaction mixture was vigorously stirred for 24 hours. The reaction mixture was filtered through Celite® pad, the residue was washed with ethyl acetate, and the solvent was concentrated under reduced pressure. Purification by flash column chromatography, eluting with 3% diethyl ether/petroleum ether, afforded the title compound **251**[XVI] as a colourless oil (12.70 g, 97%).

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 4.13 (2H, q, *J* = 7.1 Hz, H-10), 3.48-3.38 (2H, m, H-4), 2.40-2.25 (2H, m, H-8), 1.82-1.38 (3H, m, H-5, H-7), 1.25 (3H, t, *J* = 7.1 Hz, H-11), 0.91-0.87 (12H, m, H-1, H-6), 0.04 (6H, s, H-3).
^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 173.2 (C-9), 67.8 (C-4), 60.1 (C-10), 35.3 (C-5), 32.1 (C-8), 28.5 (C-7), 25.9 (C-1), 18.3 (C-2), 16.4 (C-6), 14.2 (C-11), -5.4 (C-3).
HRMS (+'ve ESI): calculated for $C_{14}H_{30}O_3SiNa^+$ 297.1861 $(M + Na)^+$, found 297.1856.
IR ν_{max} (neat, cm^{-1}): 2930 (m), 2858 (m), 1737 (s), 1463 (m), 1372 (w), 1251 (s), 1177 (s), 1088 (s), 1033 (m), 917 (w), 842 (s), 774 (s), 733 (s), 666 (m).
$[\alpha]_D^{26}$ -4.4° (*c* 1.86 in $CHCl_3$).

[XVI] Spectral data concurrent with the literature: Marshall, J. A.; Yanik, M. M. *J. Org. Chem.* **2001**, 66, 1373-1379.

(4*S*)-5-{[*tert*-Butyl(dimethyl)silyl]oxy}-4-methylpentan-1-ol **224**



To a stirred solution of ethyl (4*S*)-5-{[*tert*-butyl(dimethyl)silyl]oxy}-4-methylpentanoate **251** (11.50 g, 41.90 mmol) in tetrahydrofuran (150 mL) at 0 °C under was added lithium aluminium hydride (46.00 mL, 46.10 mmol, 1 M solution in tetrahydrofuran) in a dropwise fashion over 3 hours. The reaction mixture was allowed to warm to room temperature, before being slowly poured into water (80 mL). The aqueous layer was extracted with ether (4 × 150 mL). The combined organic extracts were dried over anhydrous magnesium sulfate, filtered, and the solvent was concentrated under reduced pressure. Purification by flash column chromatography, eluting with 3% diethyl ether/petroleum ether, afforded the title compound **224**[XVII] as a colourless oil (9.71 g, 99%).

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 3.64 (2H, t, *J* = 6.6 Hz, H-4), 3.49-3.37 (2H, m, H-9), 1.70-1.10 (6H, m, H-5, H-7, H-8, H-10), 0.91-0.87 (12 H, m, H-1, H-6), 0.04 (6H, s, H-3).

^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 68.2 (C-4), 63.3 (C-9), 35.5 (C-5), 30.1 (C-8), 29.2 (C-7), 25.8 (C-1) 18.3 (C-2), 16.7 (C-6), -5.4 (C-3).

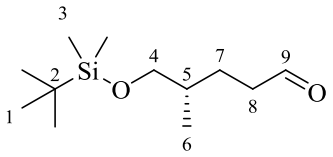
HRMS (+'ve ESI): calculated for $C_{14}H_{28}O_2SiNa^+$ 255.1756 $(M + Na)^+$, found 255.1750.

IR ν_{max} (neat, cm^{-1}): 3335 (b), 2939 (m), 2856 (m), 1471 (m), 1388 (w), 1251 (m), 1092 (s), 1059 (s), 1006 (m), 939 (w), 845 (s), 772 (s), 666 (m).

$[\alpha]_D^{26}$ -4.7° (*c* 1.17 in $CHCl_3$).

[XVII] Spectral data concurrent with the literature: Marshall, J. A.; Yanik, M. M. *J. Org. Chem.* **2001**, 66, 1373-1379.

(4*S*)-5-{[*tert*-Butyl(dimethyl)silyl]oxy}-4-methylpentanal **217**



To a stirred solution of (4*S*)-5-{[*tert*-butyl(dimethyl)silyl]oxy}-4-methylpentan-1-ol **224** (9.00 g, 38.70 mmol) in dichloromethane (180 mL) at 0 °C was added triethylamine (27.20 mL, 193.90 mmol), followed by the addition of a solution of sulfurtrioxide pyridinium complex (24.70 g, 155.10 mmol) in dimethylsulfoxide (32.00 mL) in a dropwise fashion over 3 hours. The reaction mixture was allowed to warm to ambient temperature and stirred for 16 hours, before pouring into a saturated solution of aqueous ammonium chloride (200 mL). The layers were separated, and the aqueous phase was extracted with diethyl ether (7 × 150 mL). The combined organic extracts were washed with a saturated aqueous solution of sodium chloride (200 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. Purification by flash column chromatography, eluting with 25% diethyl ether/petroleum ether, afforded the title compound **217**[XVIII] as a colourless oil (8.21 g, 92%).

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 9.77 (1H, t, *J* = 1.6 Hz, H-9), 3.74-3.40 (2H, m, H-4), 2.53-2.39 (2H, m, H-8), 1.82-1.74 (1H, m, H-5), 1.67-1.58 (1H, m, H-7$_{a\ or\ b}$), 1.50-1.40 (1H, m, H-7$_{a\ or\ b}$), 0.91-0.86 (12H, m, H-1, H-6), 0.04 (6H, s, H-3).

^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 202.5 (C-9), 67.8 (C-4), 41.6 (C-8), 35.2 (C-5), 25.8 (C-1), 25.5 (C-7), 18.3 (C-2), 16.4 (C-6), -5.4 (C-3).

HRMS (+'ve ESI): calculated for $C_{12}H_{26}O_2SiNa^+$ 253.1594 $(M + Na)^+$, found 253.1599.

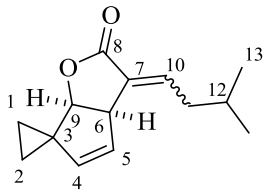
IR ν_{max} (neat, cm^{-1}): 2989 (m), 2857 (m), 1727 (s), 1471 (m), 1389 (w), 1251 (m), 1091 (s), 1006 (m), 938 (w), 834 (s), 774 (s), 665 (m).

$[\alpha]_D^{24}$ -4.5° (*c* 1.07 in $CHCl_3$).

[XVIII] Spectral data concurrent with the literature: Marsh, G. P. University of Sussex **2007**.

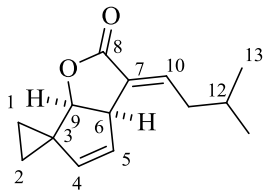
3.7 Horner-Wadswoth-Emmons Condensation: Model Study

3-(3-Methylbutylidene)-3a,6a-dihydrospiro[cyclopenta[*b*]furan-6,1'-cyclopropan]-2(3*H*)-one **262**

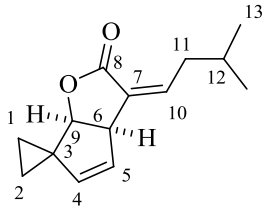


To a stirred solution of *tert*-butanol **261** (0.01 mL, 0.12 mmol) in tetrahydrofuran (0.25 mL) at -70 °C was added *n*-butyllithium (0.05 mL, 0.12 mmol, 2.5 M solution in tetrahydrofuran), and was left to stir for 10 minutes. To the reaction mixture was added a solution of diethyl (2-oxo-2,3,3a,6a-tetrahydrospiro[cyclopenta[*b*]furan-6,1'-cyclopropan]-3-yl)phosphonate **226** (0.03 g, 0.11 mmol) in tetrahydrofuran (0.25 mL) in a dropwise manner, and was allowed to warm to -50 °C for 15 minutes. The reaction mixture was cooled to -70 °C, and a solution of isovaleraldehyde (0.01 mL, 0.11 mmol) in tetrahydrofuran (0.25 mL) was added in a dropwise fashion over 2 hours. The reaction mixture was allowed to warm slowly to ambient temperature, and stirred for 16 hours, before pouring into a saturated aqueous solution of sodium hydrogen carbonate (10 mL). The layers were separated, and the aqueous phase was extracted with diethyl ether (3 × 15 mL). The combined organic extracts were washed with a saturated aqueous solution of sodium chloride (10 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. Purification by flash column chromatography, eluting with 10% methanol/dichloromethane, afforded the title compound **262** as colourless oil, and an inseparable mixture of *Z*/*E* diastereoisomers in a 1:1.1 ratio (0.01 g, 45%).

***Major* diastereoisomer:**



***Minor* diastereoisomer:**



^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 6.73 (1H, td, *J* = 7.8, 2.2 Hz, H-10$_{major}$), 6.28 (1H, td, *J* = 7.7, 1.6 Hz, H-10$_{minor}$), 5.55 (1H, dd, *J* = 5.6, 2.0 Hz, H-5$_{major}$), 5.48 (1H, dd, *J* = 5.5, 2.1 Hz, H-5$_{minor}$), 5.33-5.29 (2H, m, H-4$_{major\ and\ minor}$), 4.56 (1H, d, *J* = 6.6 Hz, H-9$_{major}$), 4.50 (1H, d, *J* = 6.5 Hz, H-9$_{minor}$), 4.24-4.20 (1H, m, H-6$_{major}$), 4.14-4.10 (1H, m, H-6$_{minor}$), 2.65 (2H, t, *J* = 7.2 Hz, H-11$_{minor}$), 2.21 (2H, t, *J* = 7.3 Hz, H-11$_{major}$), 1.89-1.71 (2H, m, H-12$_{major\ and\ minor}$), 1.33-1.20 (2H, m, cyclopropyl$_{major\ and\ minor}$), 1.04-0.79 (18H, m, H-13$_{major\ and\ minor}$, cyclopropyl$_{major\ and\ minor}$).

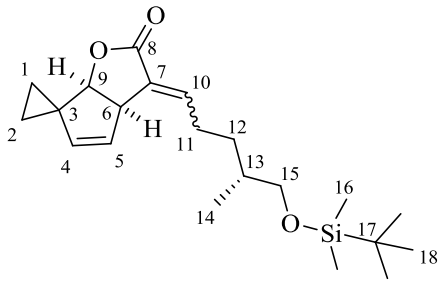
^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 177.5 (C-8$_{major\ or\ minor}$), 170.9 (C-8$_{major\ or\ minor}$), 143.3 (C-10$_{minor}$), 139.6 (C-10$_{major}$), 136.4 (C-4$_{major\ or\ minor}$), 136.3 (C-4$_{major\ or\ minor}$), 129.4 (C-7$_{major\ or\ minor}$), 129.0 (C-5$_{minor}$), 128.0 (C-7$_{major\ or\ minor}$), 126.6 (C-5$_{major}$), 86.3 (C-9$_{major}$), 85.7 (C-9$_{minor}$), 51.8 (C-6$_{minor}$), 48.5 (C-6$_{major}$), 38.9 (C-11$_{major}$), 36.1 (C-11$_{minor}$), 33.9 (C-3$_{major\ or\ minor}$), 33.8 (C-3$_{major\ or\ minor}$), 28.6 (C-12$_{major\ or\ minor}$), 28.2 (C-12$_{major\ or\ minor}$), 22.6 (C-13$_{major\ or\ minor}$), 22.4 (C-13$_{major\ or\ minor}$), 22.3 (C-13$_{major\ or\ minor}$), 22.2 (C-13$_{major\ or\ minor}$), 13.9 (C-1$_{major\ or\ minor}$), 13.7 (C-1$_{major\ or\ minor}$), 8.8 (C-2$_{major\ or\ minor}$), 8.7 (C-2$_{major\ or\ minor}$).

HRMS (+'ve ESI): calculated for $C_{14}H_{18}O_2Na^+$ 241.1199 $(M + Na)^+$, found 241.1197.

IR ν_{max} (neat, cm^{-1}): 2956 (m), 2930 (m), 2720 (w), 1770 (s), 1675 (m), 1465 (m), 1367 (w), 1221 (w), 1192 (s), 1136 (m), 1029 (s), 990 (m), 962 (m), 799 (m), 733 (m).

3.8 Synthesis of Nitroalkenes **215** and **269**

3-((4*R*)-5-{[*tert*-Butyl(dimethyl)silyl]oxy}-4-methylpentylidene)-3a,6a-dihydrospiro[cyclopenta[*b*]furan-6,1'-cyclopropan]-2(3*H*)-one **227**



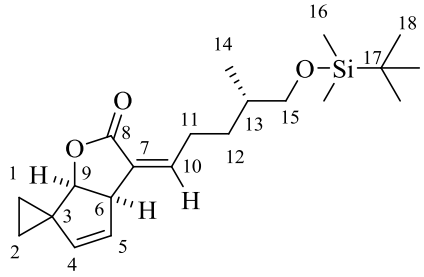
Method 1:

To a stirred solution of *tert*-butanol **261** (0.18 mL, 1.92 mmol) in tetrahydrofuran (5 mL) at -70 °C was added *n*-butyllithium (0.77 mL, 1.92 mmol, 2.5 M solution in tetrahydrofuran), and was left to stir for 10 minutes. To the reaction mixture was added a solution of diethyl (2-oxo-2,3,3a,6a-tetrahydrospiro[cyclopenta[*b*]furan-6,1'-cyclopropan]-3-yl)phosphonate **226** (0.50 g, 1.75 mmol) in tetrahydrofuran (5 mL) in a dropwise manner, and was allowed to warm to -50 °C for 15 minutes. The reaction mixture was cooled to -70 °C, and a solution of (4*S*)-5-{[*tert*-butyl(dimethyl)silyl]oxy}-4-methylpentanal **217** (0.44 g, 1.92 mmol) in tetrahydrofuran (4 mL) was added in a dropwise fashion over 2 hours. The reaction mixture was allowed to warm slowly to ambient temperature, and stirred for 16 hours, before pouring into a saturated aqueous solution of sodium hydrogen carbonate (25 mL). The layers were separated, and the aqueous phase was extracted with diethyl ether (3 × 30 mL). The combined organic extracts were washed with a saturated aqueous solution of sodium chloride (25 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. Purification by flash column chromatography, eluting with 5% diethyl ether/petroleum ether, afforded the title compound **227** as a colourless oil, and a separable mixture of *Z*/*E* diastereoisomers in a 1.1:1 ratio (0.42 g, 66%).

Method 2:

To a stirred solution of diethyl (2-oxo-2,3,3a,6a-tetrahydrospiro[cyclopenta[*b*]furan-6,1'-cyclopropan]-3-yl)phosphonate **226** (1.00 g, 3.49 mmol) in tetrahydrofuran (4 mL) at -10 ºC was added (4*S*)-5-{[*tert*-butyl(dimethyl)silyl]oxy}-4-methylpentanal **217** (0.80 g, 3.49 mmol), followed by a 8 M aqueous solution of potassium carbonate (42 mL, 336.00 mmol). The reaction mixture was allowed to warm slowly to ambient temperature, and was left to stir for 7 days. The layers were separated, and the aqueous phase was extracted with diethyl ether (5 × 40 mL). The combined organic extracts were washed with a saturated aqueous solution of sodium chloride (50 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. Purification by flash column chromatography, eluting with 3% diethyl ether/petroleum ether, afforded the title compound **227** as a colourless oil, and a separable mixture of *Z*/*E* diastereoisomers in a 1.2:1 ratio (1.01 g, 80%).

***Major* diastereoisomer:**



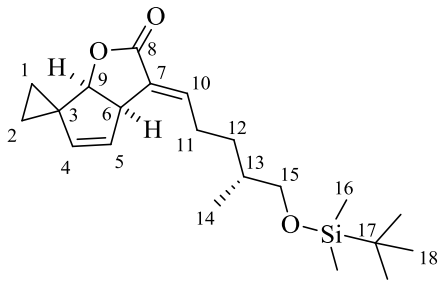
^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 6.23 (1H, t, *J* = 7.6 Hz, H-10), 5.46 (1H, dd, *J* = 5.5, 1.9 Hz, H-5), 5.28 (1H, dd, *J* = 5.5, 1.9 Hz, H-4), 4.48 (1H, d, *J* = 6.4 Hz, H-9), 4.10-4.06 (1H, m, H-6), 3.50-3.34 (2H, m, H-15), 2.87-2.61 (2H, m, H-11), 1.72-1.50 (2H, m, H-12$_{a\ or\ b}$, H-13), 1.30-1.15 (2H, m, H-12$_{a\ or\ b}$, cyclopropyl), 0.97-0.73 (15H, m, H-14, H-18, cyclopropyl), 0.03 (6H, s, H-16).

^{13}C NMR (125 MHz, $CDCl_3$): 169.6 (C-8), 144.5 (C-10), 136.3 (C-4), 128.9 (C-5), 127.4 (C-7), 85.7 (C-9), 67.9 (C-15), 51.6 (C-6), 35.4 (C-13), 33.9 (C-3), 32.5 (C-12), 25.8 (C-18), 25.1 (C-11), 18.3 (C-17), 16.5 (C-14), 13.7 (C-1), 8.7 (C-2), -5.4 (C-16).

HRMS (+'ve ESI): calculated for $C_{21}H_{34}O_3SiNa^+$ 385.2169 $(M + Na)^+$, found 385.2185.

IR ν_{max} (neat, cm^{-1}): 2953 (m), 2928 (m), 2856 (m), 1749 (s), 1668 (m), 1471 (m), 1366 (m), 1309 (w), 1250 (m), 1223 (w), 1181 (m), 1089 (s), 1032 (s), 990 (w), 960 (w), 897 (w), 833 (s), 773 (s), 666 (m).

***Minor* diastereoisomer:**



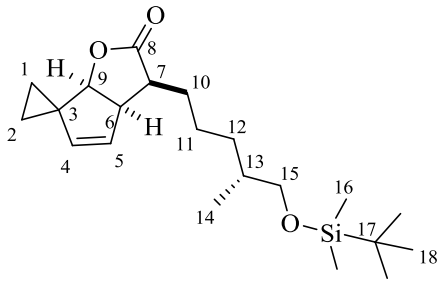
^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 6.75-6.72 (1H, m, H-10), 5.60-5.47 (1H, m, H-5), 5.30 (1H, dd, *J* = 5.4, 1.7 Hz, H-4), 4.54 (1H, d, *J* = 6.5 Hz, H-9), 4.25-4.19 (1H, m, H-6), 3.53-3.36 (2H, m, H-15), 2.43-2.20 (2H, m, H-11), 1.75-1.55 (2H, m, H-12$_{a\ or\ b}$, H-13), 1.39-1.21 (2H, m, H-12$_{a\ or\ b}$, cyclopropyl), 1.01-0.75 (15H, m, H-14, H-18, cyclopropyl), 0.03 (6H, s, H-16).

^{13}C NMR (125 MHz, $CDCl_3$): 170.7 (C-8), 140.7 (C-10), 136.8 (C-4), 128.7 (C-7), 126.6 (C-5), 86.3 (C-9), 67.8 (C-15), 48.5 (C-6), 35.4 (C-13), 33.7 (C-3), 32.0 (C-11), 27.5 (C-12), 25.9 (C-18), 18.3 (C-17), 16.5 (C-14), 13.9 (C-1), 8.8 (C-2), -5.4 (C-16).

HRMS (+'ve ESI): calculated for $C_{21}H_{34}O_3SiNa^+$ 385.2169 $(M + Na)^+$, found 385.2133.

IR ν_{max} (neat, cm^{-1}): 2952 (m), 2928 (m), 2857 (m), 1754 (s), 1677 (m), 1471 (m), 1387 (w), 1312 (w), 1249 (m), 1219 (w), 1184 (m), 1088 (m), 1032 (s), 1007 (w), 960 (w), 892 (w), 833 (s), 773 (s), 732 (m), 666 (m).

3-((4*R*)-5-{[*tert*-Butyl(dimethyl)silyl]oxy}-4-methylpentyl)-3a,6a-dihydrospiro[cyclopenta[*b*]furan-6,1'-cyclopropan]-2(3*H*)-one **263**

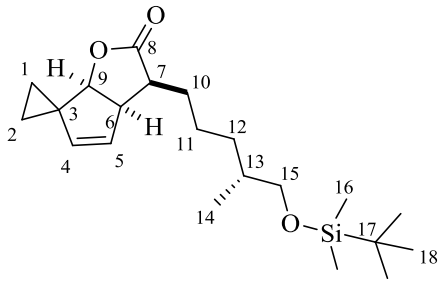


Method 1:

To a stirred solution of copper bromide (4.40 g, 30.93 mmol) in tetrahydrofuran (80 mL) at -5 ºC was added Red-Al® (9.30 mL, 30.93 mmol, 63 wt. % in toluene) in a dropwise manner, and was left to stir for 45 minutes. The reaction mixture was cooled to -70 ºC, and was added a solution of 3-((4*R*)-5-{[*tert*-butyl(dimethyl)silyl]oxy}-4-methylpentylidene)-3a,6a-dihydrospiro[cyclopenta[*b*]furan-6,1'-cyclopropan]-2(3*H*)-one **227** (2.80 g, 7.73 mmol) in tetrahydrofuran (60 mL) in a dropwise fashion, and stirred for 15 minutes. The reaction mixture was allowed to warm to – 10 ºC, and left to stir for 3 hours, before being warm to room temperature, and stirred for 16 hours. To the reaction mixture was added water (140 mL), followed by pouring a saturated aqueous solution of ammonium chloride (300 mL). The layers were separated, and the aqueous phase was extracted using diethyl ether (3 × 150 mL). The combined organic extracts were washed with a saturated aqueous solution of sodium hydrogen carbonate (150 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. Purification by flash column chromatography, eluting with 20% diethyl ether/petroleum ether, afforded the title compound **263** as colourless oil (0.77 g, 20%), and the corresponding diastereoisomer **264** (1.90 g, 50%).

Method 2:

To a stirred solution of 3-((4*R*)-5-{[*tert*-butyl(dimethyl)silyl]oxy}-4-methylpentylidene)-3a,6a-dihydrospiro[cyclopenta[*b*]furan-6,1'-cyclopropan]-2(3*H*)-one **227** (110 mg, 0.31 mmol) in methanol (3 mL) at ambient temperature was added magnesium turnings (70 mg, 3.09 mmol, predried in over at 120 ºC), and was left to stir for 16 hours. To the reaction mixture was added carefully a solution of hydrochloric acid (1 mL, 3.09 mmol of 3 M solution in water), and the mixture was extracted with diethyl ether (2 × 5 mL). The combined organic extracts were washed with a saturated aqueous solution of sodium chloride (10 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. Purification by flash column chromatography, eluting with 10% diethyl ether/petroleum ether, afforded the title compound **263** as a colourless oil (50 mg, 40%), and the corresponding diastereoisomer **264** (50 mg, 40%).



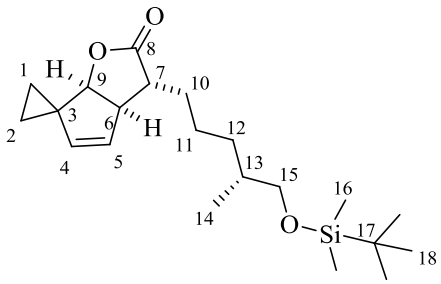
263

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 5.58 (1H, dd, *J* = 5.7, 1.7 Hz, H-5), 5.39 (1H, dd, *J* = 5.7, 1.9 Hz, H-4), 4.40 (1H, d, *J* = 5.6 Hz, H-9), 3.79-3.72 (1H, m, H-6), 3.47-3.35 (2H, m, H-15), 2.77-2.70 (1H, m, H-7), 1.96-1.84 (1H, m, H-10$_{a\ or\ b}$), 1.68-1.42 (5H, m, H-10$_{a\ or\ b}$, H-11, H-12$_{a\ or\ b}$, H-13), 1.23-1.07 (2H, m, H-12$_{a\ or\ b}$, cyclopropyl), 0.99-0.73 (15H, m, H-14, H-18, cyclopropyl), 0.04 (6H, s, H-16).

^{13}C NMR (125 MHz, $CDCl_3$): 178.1 (C-8), 137.9 (C-4), 125.1 (C-5), 87.4 (C-9), 68.2 (C-15), 49.1 (C-6), 43.9 (C-7), 35.5 (C-13), 34.0 (C-3), 32.9 (C-12), 27.8 (C-10), 25.8 (C-18), 25.3 (C-11), 18.3 (C-17), 16.6 (C-14), 12.9 (C-1), 8.6 (C-2), -5.3 (C-16).

HRMS (+'ve ESI): calculated for $C_{21}H_{36}O_3SiNa^+$ 387.2325 $(M + Na)^+$, found 387.2323.

IR ν_{max} (neat, cm^{-1}): 2929 (m), 2856 (m), 1766 (s), 1463 (m), 1388 (w), 1360 (w), 1311 (w), 1250 (m), 1226 (w), 1159 (s), 1090 (s), 1025 (w), 1005 (m), 981 (w), 947 (m), 833 (s), 773 (s), 666 (m).



264

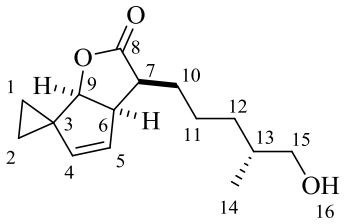
^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 5.55 (1H, dd, *J* = 5.7, 1.7 Hz, H-5), 5.32 (1H, dd, *J* = 5.7, 1.7 Hz, H-4), 4.54 (1H, d, *J* = 6.4 Hz, H-9), 3.47-3.35 (3H, m, H-6, H-15), 2.56-2.49 (1H, m, H-7), 1.84-1.72 (1H, m, H-10$_{a\ or\ b}$), 1.66-1.38 (5H, m, H-10$_{a\ or\ b}$, H-11, H-12$_{a\ or\ b}$, H-13), 1.21-1.08 (2H, m, H-12$_{a\ or\ b}$, cyclopropyl), 0.98-0.75 (15H, m, H-14, H-18, cyclopropyl), 0.03 (6H, s, H-16).

^{13}C NMR (125 MHz, $CDCl_3$): 179.4 (C-8), 136.6 (C-4), 129.0 (C-5), 87.8 (C-9), 68.2 (C-15), 51.5 (C-6), 46.1 (C-7), 35.5 (C-13), 32.4 (C-3), 33.6 (C-12), 32.9 (C-10), 25.9 (C-18), 24.5 (C-11), 18.3 (C-17), 16.6 (C-14), 13.2 (C-1), 9.1 (C-2), -5.2 (C-16).

HRMS (+'ve ESI): calculated for $C_{21}H_{36}O_3SiNa^+$ 387.2325 $(M + Na)^+$, found 387.2325.

IR ν_{max} (neat, cm^{-1}): 2928 (m), 2856 (m), 1767 (s), 1462 (m), 1387 (w), 1360 (w), 1250 (m), 1166 (s), 1089 (s), 1040 (w), 993 (w), 939 (w), 833 (s), 773 (s), 743 (m), 665 (m).

3-[(4*R*)-5-Hydroxy-4-methylpentyl]-3a,6a-dihydrospiro[cyclopenta[b]furan-6,1'-cyclopropan]-2(3*H*)-one **265**



To a stirred solution of 3-((4*R*)-5-{[*tert*-butyl(dimethyl)silyl]oxy}-4-methylpentyl)-3a,6a-dihydrospiro[cyclopenta[*b*]furan-6,1'-cyclopropan]-2(3*H*)-one **263** (1.78 g, 4.89 mmol) at 0 ºC was added hydrochloric acid (35.60 mL, 71.20 mmol, 2 M solution in ethanol) in a dropwise fashion for ten minutes, and was allow to warm to room temperature and left to stir for 4 hours, before pouring into water (40 mL). The product was extracted with diethyl ether (4 × 50 mL), and the combined organic extracts were washed successively with a saturated solution of sodium hydrogen carbonate (35 mL), and a saturated solution of sodium chloride (35 mL), before being dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. Purification by flash column chromatography, eluting with 50% diethyl ether/hexane, afforded the title compound **265** as a colourless oil (1.22 g, 99%).

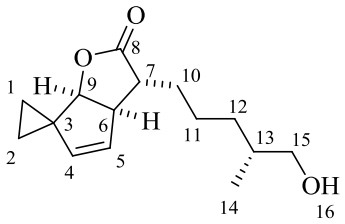
^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 5.58 (1H, dd, *J* = 5.8, 1.7 Hz, H-5), 5.39 (1H, dd, *J* = 5.8, 2.0 Hz, H-4), 4.41 (1H, d, *J* = 5.7 Hz, H-9), 3.79-3.72 (1H, m, H-6), 3.55-3.44 (2H, m, H-15), 2.78-2.72 (1H, m, H-7), 1.95-1.85 (1H, m, H-10$_{a\ or\ b}$), 1.71-1.16 (8H, m, H-10$_{a\ or\ b}$, H-11, H-12, H-13, H-16, cyclopropyl), 0.99-0.90 (5H, m, H-14, cyclopropyl), 0.80-0.73 (1H, m, cyclopropyl).

^{13}C NMR (125 MHz, $CDCl_3$): 177.8 (C-8), 138.0 (C-4), 125.0 (C-5), 87.4 (C-9), 68.2 (C-15), 49.2 (C-6), 43.4 (C-7), 35.5 (C-13), 34.0 (C-3), 32.9 (C-12), 27.8 (C-10), 25.3 (C-11), 16.6 (C-14), 12.9 (C-1), 8.7 (C-2).

HRMS (+'ve ESI): calculated for $C_{15}H_{22}O_3Na^+$ 273.1461 $(M + Na)^+$, found 273.1462.

IR ν_{max} (neat, cm^{-1}): 3473 (b), 2925 (m), 1747 (s), 1463 (w), 1312 (w), 1226 (w), 1161 (m), 1026 (w), 1003 (w), 980 (w), 908 (s), 802 (m), 770 (s), 646 (m).

3-[(4*R*)-5-Hydroxy-4-methylpentyl]-3a,6a-dihydrospiro[cyclopenta[*b*]furan-6,1'-cyclopropan]-2(3*H*)-one **266**



Method 1:

To a stirred solution of 3-((4*R*)-5-{[*tert*-butyl(dimethyl)silyl]oxy}-4-methylpentyl)-3a,6a-dihydrospiro[cyclopenta[*b*]furan-6,1'-cyclopropan]-2(3*H*)-one **264** (240 mg, 0.65 mmol) in tetrahydrofuran (30 mL) at 0 ºC was added terbutylammonium fluoride (0.92 mL, 0.91 mmol, 1 M solution in tetrahydrofuran) in a dropwise fashion, and the reaction mixture was stirred for 6 hours before pouring into water (25 mL). The product was extracted with diethyl ether (4 × 30 mL), and the combined organic extracts were washed successively with a saturated solution of sodium chloride (40 mL), before being dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. Purification by flash column chromatography, eluting with 30% diethyl ether/hexane, afforded the title compound **266** as a colourless oil (145 mg, 99%).

Method 2:

To a stirred solution of 3-((4*R*)-5-{[*tert*-butyl(dimethyl)silyl]oxy}-4-methylpentyl)-3a,6a-dihydrospiro[cyclopenta[*b*]furan-6,1'-cyclopropan]-2(3*H*)-one **264** (100 mg, 0.27 mmol) at 0 ºC was added hydrochloric acid (2.10 mL, 4.20 mmol, 2 M solution in ethanol) in a dropwise fashion, and was allow to warm to room temperature and left to stir for 4 hours, before pouring into water (5 mL). The product was extracted with diethyl ether (4 × 5 mL), and the combined organic extracts were washed successively with a saturated solution of sodium hydrogen carbonate (10 mL), and a saturated solution of sodium chloride (10 mL), before being dried over anhydrous magnesium sulfate, filtered, and concentrated under

reduced pressure. Purification by flash column chromatography, eluting with 50% diethyl ether/hexane, afforded the title compound **266** as a colourless oil (68 mg, 99%).

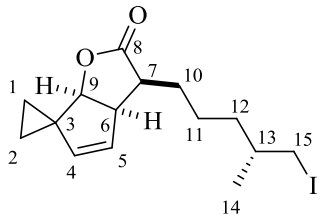
^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 5.54 (1H, dd, *J* = 5.7, 1.8 Hz, H-5), 5.32 (1H, dd, *J* = 5.7, 1.9 Hz, H-4), 4.54 (1H, d, *J* = 6.4 Hz, H-9), 3.52-3.42 (2H, m, H-15), 3.41-3.37 (1H, m, H-6), 2.57-2.53 (1H, m, H-7), 1.85-1.73 (1H, m, H-10$_{a\ or\ b}$), 1.70-1.14 (8H, m, H-10$_{a\ or\ b}$, H-11, H-12, H-13, H-16, cyclopropyl), 0.98-0.89 (5H, m, H-14, cyclopropyl), 0.82-0.75 (1H, m, cyclopropyl).

^{13}C NMR (125 MHz, $CDCl_3$): 179.4 (C-8), 136.6 (C-4), 128.9 (C-5), 87.9 (C-9), 68.0 (C-15), 51.6 (C-6), 46.0 (C-7), 35.5 (C-13), 33.6 (C-3), 32.7 (C-12), 32.3 (C-10), 24.4 (C-11), 16.5 (C-14), 13.2 (C-1), 9.0 (C-2).

HRMS (+'ve ESI): calculated for $C_{15}H_{22}O_3Na^+$ 273.1461 $(M + Na)^+$, found 273.1462.

IR ν_{max} (neat, cm^{-1}): 3473 (b), 2929 (m), 2962 (m), 1756 (s), 1462 (w), 1344 (w), 1313 (w), 1229 (w), 1168 (s), 1034 (s), 987 (s), 939 (m), 845 (w), 744 (s), 662 (m).

3-[(4*R*)-5-Iodo-4-methylpentyl]-3a,6a-dihydrospiro[cyclopenta[*b*]furan-6,1'-cyclopropan]-2(3*H*)-one **267**



To a stirred solution of triphenylphosphine (2.41 g, 9.20 mmol), and imidazole (0.62 g, 9.20 mmol) in dichloromethane (30 mL) at 0 ºC was added iodine (2.33 g, 9.20 mmol) in small solid portions. The reaction mixture was stirred for 20 minutes, before adding a solution of 3-[(4*R*)-5-hydroxy-4-methylpentyl]-3a,6a-dihydrospiro[cyclopenta[*b*]furan-6,1'-cyclopropan]-2(3*H*)-one **265** (1.15 g, 4.60 mmol) in dichloromethane (10 mL) in a dropwise manner. The reaction mixture was warm to room temperature, and was left to stir for 16 hours, before pouring into a saturated aqueous solution of sodium thiosulfate (80 mL). The aqueous component was extracted with dichloromethane (4 × 80 mL), and the combined organic extracts were washed with a saturated aqueous solution of sodium chloride (80 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. Purification by flash column chromatography, eluting with 5% diethyl ether/hexane, afforded the title compound **267** as a pale yellow solid (1.56 g, 95%).

M. P.: 62-64 ºC. Recrystallised from diethyl ether.

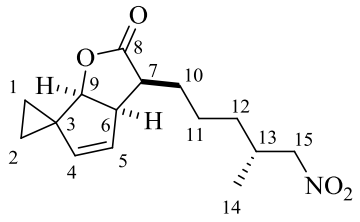
^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 5.63-5.56 (1H, m, H-5), 5.39 (1H, dd, *J* = 5.8, 1.8 Hz, H-4), 4.42 (1H, d, *J* = 5.6 Hz, H-9), 3.83-3.73 (1H, m, H-6), 3.26-3.16 (2H, m, H-15), 2.79-2.70 (1H, m, H-7), 1.96-1.86 (1H, m, H-10$_{a\ or\ b}$), 1.59-1.25 (6H, m, H-10$_{a\ or\ b}$, H-11, H-12, H-13), 1.29-1.17 (1H, m, cyclopropyl), 1.04-0.91 (5H, m, H-14, cyclopropyl), 0.81-0.74 (1H, m, cyclopropyl).

^{13}C NMR (125 MHz, $CDCl_3$): 178.0 (C-8), 138.1 (C-4), 124.9 (C-5), 87.4 (C-9), 49.2 (C-6), 43.3 (C-7), 36.2 (C-11 or C-12), 34.2 (C-13), 34.0 (C-3), 27.6 (C-10), 25.1 (C-11 or C-12), 20.5 (C-14), 17.4 (C-15), 12.9 (C-1), 8.6 (C-2).

HRMS (+'ve ESI): calculated for $C_{15}H_{21}IO_3Na^+$ 383.0478 $(M + Na)^+$, found 383.0473.

IR ν_{max} (neat, cm^{-1}): 2929 (m), 2865 (m), 1758 (s), 1459 (m), 1378 (w), 1311 (m), 1226 (m), 1194 (m), 1161 (s), 1025 (m), 999 (s), 979 (s), 946 (s), 887 (m), 803 (m), 753 (s), 732 (m), 579 (m).

3-[(4*R*)-4-Methyl-5-nitropentyl]-3a,6a-dihydrospiro[cyclopenta[*b*]furan-6,1'-cyclopropan]-2(3*H*)-one **215**



To a stirred solution of 3-[(4*R*)-5-iodo-4-methylpentyl]-3a,6a-dihydrospiro[cyclopenta [*b*]furan-6,1'-cyclopropan]-2(3*H*)-one **267** (1.30 g, 3.60 mmol), and Amberlite® IRA-900 nitrite (10.00 g, 40.00 mmol) in benzene (60 mL) was heated to reflux for 48 hours. The reaction mixture was cooled to ambient temperature, before the resin was filtered off, and washed with benzene. The filtrate was dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. Purification by flash column chromatography, eluting with 30% diethyl ether/hexane, afforded the title compound **215** as a pale yellow solid (0.81 g, 80%).

M. P.: 60-62 ºC. Recrystallised from diethyl ether.

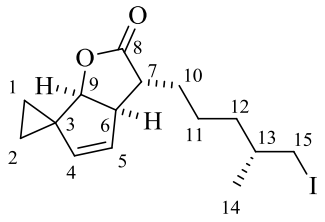
^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 5.57-5.54 (1H, m, H-5), 5.41 (1H, dd, *J* = 5.6, 2.3 Hz, H-4), 4.42 (1H, d, *J* = 5.6 Hz, H-9), 4.35-4.30 (1H, m, H-15$_{a\ or\ b}$), 4.26-4.20 (1H, m, H-15$_{a\ or\ b}$), 3.79-3.72 (1H, m, H-6), 2.72-2.69 (1H, m, H-7), 2.43-2.32 (1H, m, H-13), 1.95-1.19 (7H, m, H-10, H-11, H-12, cyclopropyl), 1.05 (3H, d, *J* = 6.8 Hz, H-14), 0.99-0.91 (2H, m, cyclopropyl), 0.81-0.79 (1H, m, cyclopropyl).

^{13}C NMR (125 MHz, $CDCl_3$): 177.5 (C-8), 138.1 (C-4), 124.6 (C-5), 87.7 (C-9), 81.1 (C-15), 49.2 (C-6), 43.3 (C-7), 34.0 (C-3), 33.5 (C-12), 32.5 (C-13), 27.6 (C-10), 24.8 (C-11), 17.2 (C-14), 12.9 (C-1), 8.7 (C-2).

HRMS (+'ve ESI): calculated for $C_{15}H_{21}NO_4Na^+$ 302.1363 $(M + Na)^+$, found 302.1365.

IR ν_{max} (neat, cm^{-1}): 2932 (m), 2870 (w), 1758 (s), 1544 (s), 1463 (w), 1383 (m), 1344 (w), 1312 (w), 1226 (m), 1158 (s), 1026 (w), 1002 (m), 980 (m), 946 (m), 897 (w), 803 (m), 756 (m), 732 (m), 624 (w).

3-[(4*R*)-5-Iodo-4-methylpentyl]-3a,6a-dihydrospiro[cyclopenta[*b*]furan-6,1'-cyclopropan]-2(3*H*)-one **268**



To a stirred solution of triphenylphosphine (0.28 g, 1.08 mmol), and imidazole (0.07 g, 1.08 mmol) in dichloromethane (10 mL) at 0 ºC was added iodine (270 mg, 1.08 mmol) in small solid portions. The reaction mixture was stirred for 20 minutes, before adding a solution of 3-[(4*R*)-5-hydroxy-4-methylpentyl]-3a,6a-dihydrospiro[cyclopenta[*b*]furan-6,1'-cyclopropan]-2(3*H*)-one **266** (0.14 g, 0.54 mmol) in dichloromethane (3 mL) in a dropwise manner. The reaction mixture was warm to room temperature, and was left to stir for 16 hours, before pouring into a saturated aqueous solution of sodium thiosulfate (10 mL). The aqueous component was extracted with dichloromethane (4 × 10 mL), and the combined organic extracts were washed with a saturated aqueous solution of sodium chloride (10 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. Purification by flash column chromatography, eluting with 5% diethyl ether/hexane, afforded the title compound **268** as a pale yellow oil (0.14 g, 74%).

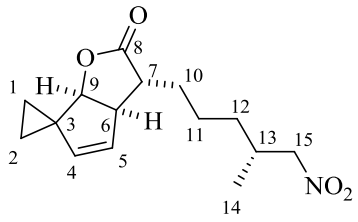
^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 5.57-5.53 (1H, m, H-5), 5.32 (1H, dd, *J* = 5.7, 1.9 Hz, H-4), 4.55 (1H, d, *J* = 6.1 Hz, H-9), 3.41-3.37 (1H, m, H-6), 3.23-3.15 (2H, m, H-15), 2.55-2.50 (1H, m, H-7), 1.82-1.73 (1H, m, H-10$_{a\ or\ b}$), 1.66-1.24 (6H, m, H-10$_{a\ or\ b}$, H-11, H-12, H-13), 1.20-1.14 (1H, m, cyclopropyl), 1.03-0.97 (5H, m, H-14, cyclopropyl), 0.96-0.76 (1H, m, cyclopropyl).

^{13}C NMR (125 MHz, $CDCl_3$): 179.2 (C-8), 136.7 (C-4), 128.8 (C-5), 87.8 (C-9), 51.5 (C-6), 45.9 (C-7), 36.1 (C-11 or C-12), 34.4 (C-13), 33.6 (C-3), 32.1 (C-10), 24.3 (C-11 or C-12), 20.5 (C-14), 17.3 (C-15), 13.2 (C-1), 9.0 (C-2).

HRMS (+'ve ESI): calculated for $C_{15}H_{21}IO_3Na^+$ 383.0478 $(M + Na)^+$, found 383.0477.

IR ν_{max} (neat, cm^{-1}): 2928 (m), 2860 (m), 1759 (s), 1458 (m), 1378 (w), 1312 (m), 1227 (m), 1169 (s), 1033 (m), 989 (s), 936 (m), 887 (w), 830 (w), 744 (s), 585 (m).

3-[(4*R*)-4-Methyl-5-nitropentyl]-3a,6a-dihydrospiro[cyclopenta[*b*]furan-6,1'-cyclopropan]-2(3*H*)-one **269**



To a stirred solution of 3-[(4*R*)-5-iodo-4-methylpentyl]-3a,6a-dihydrospiro[cyclopenta [*b*]furan-6,1'-cyclopropan]-2(3*H*)-one **268** (125 mg, 0.34 mmol), and Amberlite® IRA-900 nitrite (700 mg, 2.80 mmol) in benzene (7 mL) was heated to reflux for 48 hours. The reaction mixture was cooled to ambient temperature, before the resin was filtered off, and washed with benzene. The filtrate was dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. Purification by flash column chromatography, eluting with 30% diethyl ether/hexane, afforded the title compound **269** as a pale yellow oil (58 mg, 60%).

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 5.56-5.52 (1H, m, H-5), 5.32 (1H, dd, *J* = 5.5, 1.8 Hz, H-4), 4.55 (1H, d, *J* = 6.4 Hz, H-9), 4.33-4.28 (1H, m, H-15$_{a\ or\ b}$), 4.24-4.18 (1H, m, H-15$_{a\ or\ b}$), 3.39-3.35 (1H, m, H-6), 2.54-2.49 (1H, m, H-7), 2.39-2.29 (1H, m, H-13), 1.83-1.13 (7H, m, H-10, H-11, H-12, cyclopropyl), 1.03 (3H, d, *J* = 6.8 Hz, H-14), 0.96-0.86 (2H, m, cyclopropyl), 0.82-0.76 (1H, m, cyclopropyl).

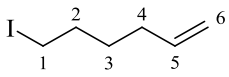
^{13}C NMR (125 MHz, $CDCl_3$): 178.6 (C-8), 136.8 (C-4), 128.6 (C-5), 87.8 (C-9), 81.4 (C-15), 51.6 (C-6), 45.8 (C-7), 33.6 (C-3), 33.3 (C-12), 32.5 (C-13), 32.0 (C-10), 24.0 (C-11), 17.1 (C-14), 13.2 (C-1), 9.0 (C-2).

HRMS (+'ve ESI): calculated for $C_{15}H_{21}NO_4Na^+$ 302.1363 $(M + Na)^+$, found 302.1361.

IR ν_{max} (neat, cm^{-1}): 2930 (m), 2868 (w), 1758 (s), 1545 (s), 1461 (m), 1382 (m), 1345 (w), 1310 (w), 1228 (m), 1167 (s), 1039 (m), 989 (s), 939 (m), 885 (w), 743 (s), 634 (w).

3.9 Intramolecular [3 + 2] Nitrile Oxide-Olefin Cycloaddition: Model Study

6-Iodohex-1-ene **276**



To a stirred solution of triphenylphosphine (3.66 g, 13.97 mmol), and imidazole (0.95 g, 13.97 mmol) in dichloromethane (30 mL) at 0 ºC was added iodine (3.55 g, 13.97 mmol) in small solid portions. The reaction mixture was stirred for 20 minutes, before adding a solution of hex-5-en-1-ol **275** (1.00 g, 9.90 mmol) in dichloromethane (10 mL) in a dropwise manner. The reaction mixture was warm to room temperature, and was left to stir for 16 hours, before pouring into a saturated aqueous solution of sodium thiosulfate (50 mL). The aqueous component was extracted with dichloromethane (4 × 50 mL), and the combined organic extracts were washed with a saturated aqueous solution of sodium chloride (50 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. Purification by flash column chromatography, eluting with hexane, afforded the title compound **276**[XIX] as a colourless oil (1.69 g, 80%).

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 5.80 (1H, ddt, *J* = 16.9, 2.6, 6.7 Hz, H-5), 5.08-4.91 (2H, m, H-6), 3.20 (2H, t, *J* = 7.0 Hz, H-1), 2.14-2.04 (2H, m, C-4), 1.90-1.80 (2H, m, C-2), 1.55-1.47 (2H, m, C-3).

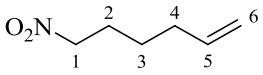
^{13}C NMR (125 MHz, $CDCl_3$): 138.0 (C-5), 114.9 (C-6), 32.8 (C-2), 32.5 (C-4), 29.6 (C-3), 6.7 (C-1).

LRMS (+'ve EI): *m/z* 210 (M, 100%), 205 (5), 183 (25), 167 (20), 155 (85), 141 (35), 137 (6), 133 (8), 127 (93), 111 (17), 105 (57).

IR ν_{max} (neat, cm^{-1}): 3030 (w), 2930 (m), 2860 (w), 1640 (m), 1435 (m), 1214 (s), 1173 (m), 989 (m), 910 (s), 741 (m), 634 (w), 584 (m).

[XIX] Spectral data concurrent with the literature: Samsel, E. G.; Kochi, J. K. *J. Am. Chem. Soc.* **1996**, 108, 4790-4804.

6-Nitrohex-1-ene **277**



To a stirred solution of sodium nitrite (0.18 g, 2.61 mmol) in *N*,*N*-dimethylformamide (10 mL) was added 6-iodohex-1-ene **276** (0.50 g, 2.38 mmol), and the reaction mixture was stirred at ambient temperature for 3 hours. The reaction mixture was then partitioned between ice-water (40 mL), and diethyl ether (12 mL), and the organic phase was separated. The aqueous component was extracted with diethyl ether (4 × 20 mL), and the combined organic extracts were subsequently washed with water (2 × 40 mL), dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. Purification by flash column chromatography, eluting with 10% diethyl ether/hexane, afforded the title compound **277**[XX] as a pale yellow oil (0.15 g, 49%).

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 5.77 (1H, ddt, *J* = 16.9, 2.6, 6.7 Hz, H-5), 5.09-4.97 (2H, m, H-6), 4.39 (2H, t, *J* = 7.0 Hz, H-1), 2.15-2.10 (2H, m, C-4), 2.07-1.96 (2H, m, C-2), 1.55-1.46 (2H, m, C-3).

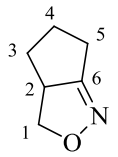
^{13}C NMR (125 MHz, $CDCl_3$): 137.3 (C-5), 115.5 (C-6), 75.5 (C-1), 32.7 (C-4), 26.7 (C-2), 25.3 (C-3).

LRMS (+'ve EI): *m/z* 129 (M, 13%), 125 (5), 113 (18), 97 (17), 83 (20), 71 (40), 57 (60), 43 (34), 32 (8), 28 (35).

IR ν_{max} (neat, cm^{-1}): 3040 (w), 2930 (m), 2870 (w), 1641 (w), 1560 (s), 1435 (m), 1381 (m), 994 (m), 913 (s), 751 (w), 615 (m).

[XX] Spectral data concurrent with the literature: Marsh, G. P.; Parsons, P. J.; McCarthy, C.; Corniquet, X. G. *Org. Lett.* **2007**, 9, 2613-2616.

3a,4,5,6-Tetrahydro-3*H*-cyclopenta[c]isoxazole **278**



To a stirred solution of 6-nitrohex-1-ene **277** (89 mg, 0.68 mmol), and *p*-toluenesulfonyl chloride (263 mg, 1.36 mmol) in dichloromethane (30 mL) at 0 ºC was added triethylamine (0.19 mL, 1.36 mmol) in a dropwise fashion. The reaction mixture was allowed to warm to room temperature, and stirred for 16 hours, before pouring into water (25 mL). The layers were separated, and the aqueous phase was extracted using dichloromethane (4 × 30 mL). The combined organic extracts were dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. Purification by flash column chromatography, eluting with 80% diethyl ether/petroleum ether, afforded the title compound **278** as a colourless oil (40 mg, 52%).

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 4.54-4.49 (1H, m, H-1$_{a\ or\ b}$), 3.80-3.69 (2H, m, H-1$_{a\ or\ b}$, H-2), 2.49-2.40 (2H, m, H-5), 2.31-2.22 (1H, m, C-4$_{a\ or\ b}$), 2.21-2.13 (1H, m, H-4$_{a\ or\ b}$), 2.10-2.03 (1H, m, H-3$_{a\ or\ b}$), 1.54-1.43 (1H, m, H-3$_{a\ or\ b}$).

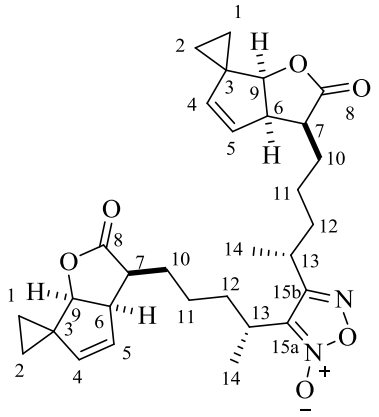
^{13}C NMR (125 MHz, $CDCl_3$): 172.4 (C-6), 74.5 (C-1), 28.4 (C-2), 28.4 (C-3 or C-4), 28.3 (C-3 or C-4), 20.9 (C-5).

HRMS (+'ve ESI): calculated for $C_6H_9ONNa^+$ 134.0576 $(M + Na)^+$, found 134.0577.

IR ν_{max} (neat, cm^{-1}): 2936 (m), 2870 (m), 1740 (w), 1610 (w), 1560 (w), 1450 (m), 1267 (m), 1162 (m), 1092 (w), 902 (s), 868 (m), 793 (s), 729 (s), 681 (w).

3.10 Synthesis of Furoxans **280** and **282**

3-((4*S*)-4-{4-[(1*R*)-1-Methyl-4-(2-oxo-3a,6a-dihydrospiro[cyclopenta[*b*]furan-6,1'-cyclopropan]-3(3*H*)-yl)butyl]-5-oxido-1,2,5-oxadiazol-3-yl}pentyl)-3a,6a-dihydrospiro[cyclopenta[*b*]furan-6,1'-cyclopropan]-2(3*H*)-one **280**



To a stirred solution of 3-[(4*R*)-4-methyl-5-nitropentyl]-3a,6a-dihydrospiro[cyclopenta [*b*]furan-6,1'-cyclopropan]-2(3*H*)-one **215** (40 mg, 0.13 mmol), and *p*-toluenesulfonyl chloride (53 mg, 0.26 mmol) in dichloromethane (10 mL) at 0 ºC was added triethylamine (38 μL, 0.26 mmol) in a dropwise fashion. The reaction mixture was allowed to warm to room temperature, and stirred for 16 hours, before pouring into water (10 mL). The layers were separated, and the aqueous phase was extracted using dichloromethane (4 × 15 mL). The combined organic extracts were dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. Purification by flash column chromatography, eluting with 90% diethyl ether/hexane, afforded the title compound **280** as a pale yellow oil (29 mg, 81%).

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 5.55-5.48 (2H, m, H-5), 5.42-5.36 (2H, m, H-4), 4.43-4.39 (2H, m, H-9), 3.76-3.69 (2H, m, H-6), 2.91-2.78 (2H, m, H-13), 2.77-2.63 (2H, m, H-7), 2.04-1.31 (18H, m, H-10, H-11, H-12, H-14), 1.22-1.15 (2H, m, cyclopropyl), 0.99-0.90 (4H, m, cyclopropyl), 0.80-0.73 (2H, m, cyclopropyl).

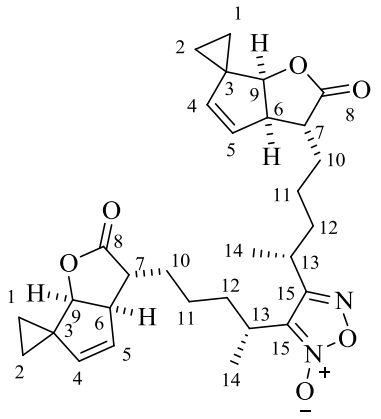
^{13}C NMR (125 MHz, $CDCl_3$): 177.9-177.8 (C-8), 161.4-161.3 (C-15_a), 138.4-138.3 (C-4), 124.7-124.6 (C-5), 117.8-117.7 (C-15_b), 87.5-87.4 (C-9), 49.2-49.1 (C-6), 43.2-42.9 (C-7), 34.8-34.6 (CH_2), 34.0-33.9 (C-3), 31.4 (C-13), 31.2 (CH_2), 29.1 (C-13), 27.6 (CH_2), 26.1-25.3 (CH_2), 19.1 (C-14), 15.7 (C-14), 12.9 (C-1), 12.8 (C-1), 8.6 (C-2), 8.5 (C-2).

HRMS (+'ve ESI): calculated for $C_{30}H_{38}N_2O_6Na^+$ 345.2622 $(M + Na)^+$, found 302.2622.

LRMS (+'ve EI): *m/z* 522 (M, 13%), 504 (17), 487 (10), 459 (11), 228 (4), 200 (16), 186 (6), 173 (18), 145 (36), 131 (30), 119 (35), 105 (67), 91 (100), 77 (44), 55 (42), 41 (38), 28 (12).

IR ν_{max} (neat, cm^{-1}): 2928 (m), 2865 (w), 1755 (s), 1588 (s), 1468 (m), 1382 (m), 1343 (w), 1312 (m), 1226 (m), 1156 (s), 1024 (w), 980 (s), 946 (m), 931 (m), 805 (w), 762 (m), 734 (m).

3-((4*S*)-4-{4-[(1*R*)-1-Methyl-4-(2-oxo-3a,6a-dihydrospiro[cyclopenta[*b*]furan-6,1'-cyclopropan]-3(3*H*)-yl)butyl]-5-oxido-1,2,5-oxadiazol-3-yl}pentyl)-3a,6a-dihydrospiro[cyclopenta[*b*]furan-6,1'-cyclopropan]-2(3*H*)-one **282**



To a stirred solution of 3-[(4*R*)-4-methyl-5-nitropentyl]-3a,6a-dihydrospiro[cyclopenta [*b*]furan-6,1'-cyclopropan]-2(3*H*)-one **269** (30 mg, 0.10 mmol), and *p*-toluenesulfonyl chloride (41 mg, 0.21 mmol) in dichloromethane (8 mL) at 0 ºC was added triethylamine (30 μL, 0.21 mmol) in a dropwise fashion. The reaction mixture was allowed to warm to room temperature, and stirred for 16 hours, before pouring into water (8 mL). The layers were separated, and the aqueous phase was extracted using dichloromethane (4 × 10 mL). The combined organic extracts were dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. Purification by flash column chromatography, eluting with 90% diethyl ether/hexane, afforded the title compound **282** as a pale yellow oil (18 mg, 64%).

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 5.56-5.50 (2H, m, H-5), 5.33-5.29 (2H, m, H-4), 4.57-4.49 (2H, m, H-9), 3.40-3.32 (2H, m, H-6), 2.87-2.73 (2H, m, H-13), 2.57-2.43 (2H, m, H-7), 1.97-1.25 (18H, m, H-10, H-11, H-12, H-14), 1.29-1.20 (2H, m, cyclopropyl), 0.98-0.84 (4H, m, cyclopropyl), 0.82-0.74 (2H, m, cyclopropyl).

^{13}C NMR (125 MHz, $CDCl_3$): 177.0-178.8 (C-8), 161.4-161.3 ($C\text{-}15_a$), 136.8-136.7 (C-4), 128.7-128.6 (C-5), 117.7-117.6 ($C\text{-}15_b$), 87.9-87.8 (C-9), 51.7-51.5 (C-6), 45.8-45.5 (C-7),

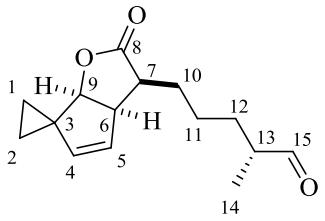
34.6-34.5 (CH_2), 33.6-33.5 (C-3), 31.9 (CH_2), 31.3 (C-13), 30.7 (CH_2), 28.9 (C-13), 25.3-24.5 (CH_2), 18.9 (C-14), 15.3 (C-14), 13.2 (C-1), 13.1 (C-1), 9.1 (C-2), 9.0 (C-2).

HRMS (+'ve ESI): calculated for $C_{30}H_{38}N_2O_6Na^+$ 345.2622 $(M + Na)^+$, found 302.2636.

IR ν_{max} (neat, cm^{-1}): 2923 (m), 2860 (w), 1759 (s), 1589 (s), 1433 (m), 1380 (w), 1345 (w), 1312 (m), 1226 (w), 1167 (s), 1090 (w), 1033 (m), 989 (s), 950 (w), 836 (w), 740 (s), 690 (m).

3.11 Synthesis of Aldehyde **291**

(2*R*)-2-Methyl-5-(2-oxo-2,3,3a,6a-tetrahydrospiro[cyclopenta[*b*]furan-6,1'-cyclopropan]-3-yl)pentanal **291**



To a stirred solution of 3-[(4*R*)-5-hydroxy-4-methylpentyl]-3a,6a-dihydrospiro[cyclopenta [b]furan-6,1'-cyclopropan]-2(3*H*)-one **265** (0.16 g, 0.64 mmol) in dichloromethane (15 mL) was added 4Å molecular sieves (0.18 g), and *N*-methylmorpholine-*N*-oxide (0.09 g, 0.76 mmol). The reaction mixture was stirred for 30 minutes, before adding tetrapropylammonium perruthenate (0.01 mg, 0.03 mmol) as a single solid portion, and left to stir for 2 hours. The reaction mixture was concentrated under reduced pressure. Purification by flash column chromatography, eluting with 50% diethyl ether/hexane, afforded the title compound **291** as a colourless oil (0.12 g, 75%).

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 9.63 (1H, dd, *J* = 5.5, 1.8 Hz, H-15), 5.56-5.53 (1H, m, H-5), 5.38 (1H, dd, *J* = 5.6, 1.7 Hz, H-4), 4.41 (1H, d, *J* = 5.7 Hz, H-9), 3.77-3.71 (1H, m, H-6), 2.76-2.69 (1H, m, H-7), 2.42-2.34 (1H, m, H-13), 1.92-1.14 (7H, m, H-10, H-11, H-12, cyclopropyl), 1.13 (3H, d, *J* = 7.0 Hz, C-14), 0.99-0.90 (5H, m, H-14, cyclopropyl), 0.98-0.89 (2H, m, cyclopropyl), 0.79-0.73 (1H, m, cyclopropyl).

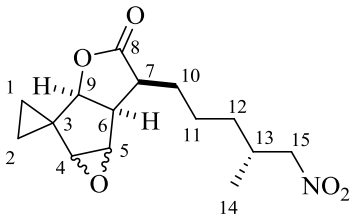
^{13}C NMR (125 MHz, $CDCl_3$): 204.6 (C-15), 177.8 (C-8), 138.2 (C-4), 124.9 (C-5), 87.5 (C-9), 49.1 (C-6), 45.9 (C-13), 43.2 (C-7), 34.0 (C-3), 30.2 (C-12), 27.6 (C-10), 25.2 (C-11), 13.4 (C-14), 12.9 (C-1), 8.6 (C-2).

HRMS (+'ve ESI): calculated for $C_{15}H_{20}O_3Na^+$ 271.1305 $(M + Na)^+$, found 271.1306.

IR ν_{max} (neat, cm^{-1}): 2934 (m), 2870 (w), 1759 (s), 1718 (s), 1460 (m), 1313 (m), 1226 (m), 1158 (s), 1025 (w), 1002 (m), 980 (m), 946 (m), 887 (m), 802 (m), 755 (m), 621 (w).

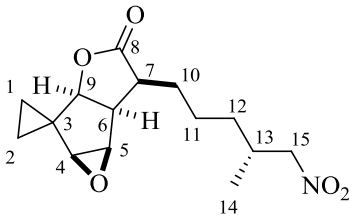
3.12 Synthesis of Nitroepoxide **298**

5'-[(4*R*)-4-Methyl-5-nitropentyl]tetrahydrospiro[cyclopropane-1,2'-oxireno[3,4]cyclopenta[1,2-b]furan]-4'(2a'*H*)-one **298**



To a stirred solution of sodium hydrogen carbonate (375 mg, 4.48 mmol), water (4 mL), acetone (519 mg, 8.96 mmol), and ethyl acetate (4 mL) at room temperature was added 3-[(4*R*)-4-methyl-5-nitropentyl]-3a,6a-dihydrospiro[cyclopenta[*b*]furan-6,1'-cyclopropan]-2(3*H*)-one **215** (50 mg, 0.18 mmol), and left to stir vigorously, before adding a solution of Oxone® monopersulfate (500 mg, 0.82 mmol) in water (4 mL) in a dropwise fashion over 1 hour. The reaction mixture was stirred for 16 hours. The product was extracted with diethyl ether (4 × 15 mL), before being washed with a saturated solution of sodium chloride (20 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. Purification by flash column chromatography, eluting with 50% diethyl ether/hexane, afforded the title compound **298** as a colourless oil, and white solid of a separable mixture of *endo*/*exo* diastereoisomers in a 1.7:1 ratio (51 mg, 99%).

***Major* diastereoisomer:**



^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 4.39-4.30 (2H, m, H-9, H-15$_{a\ or\ b}$), 4.27-4.20 (1H, m, H-15$_{a\ or\ b}$), 3.63 (1H, d, *J* = 2.3 Hz, H-5), 3.29-3.23 (1H, m, H-6), 3.12 (1H, d, *J* = 2.3

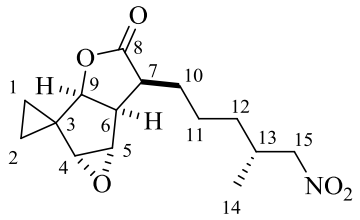
Hz H-4), 2.77-2.71 (1H, m, H-7), 2.41-2.33 (1H, m, H-13), 1.91-1.30 (6H, m, H-10, H-11, H-12), 1.10-1.00 (5H, m, H-14, cyclopropyl), 0.92-0.83 (2H, m, cyclopropyl).

^{13}C NMR (125 MHz, $CDCl_3$): 177.7 (C-8), 87.5 (C-9), 81.4 (C-15), 64.1 (C-4), 57.4 (C-5), 44.5 (C-6), 40.6 (C-7), 33.4 (C-12), 32.5 (C-13), 28.3 (C-3), 27.1 (C-10), 24.7 (C-11), 17.2 (C-14), 9.1 (C-1), 7.6 (C-2).

HRMS (+'ve ESI): calculated for $C_{15}H_{21}NO_5Na^+$ 318.1312 $(M + Na)^+$, found 318.1315.

IR ν_{max} (neat, cm^{-1}): 2937 (m), 2869 (w), 1763 (s), 1542 (s), 1463 (w), 1431 (w), 1382 (m), 1351 (w), 1303 (w), 1220 (w), 1163 (s), 1024 (m), 985 (m), 951 (m), 907 (m), 845 (m), 789 (w), 719 (m), 629 (w).

***Minor* diastereoisomer:**



M. P.: 107-109 ºC. Recrystallised from diethyl ether.

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 4.36-4.31 (1H, m, H-15$_{a\ or\ b}$), 4.28-4.21 (2H, m, H-9, H-15$_{a\ or\ b}$), 3.69-3.65 (1H, m, H-5), 3.19-3.14 (1H, m, H-6), 3.11-3.08 (1H, m, H-4), 2.72-2.66 (1H, m, H-7), 2.42-2.33 (1H, m, H-13), 2.10-2.00 (1H, m, H-10$_{a\ or\ b}$), 1.83-1.33 (5H, m, H-10$_{a\ or\ b}$, H-11, H-12), 1.21-1.15 (1H, m, cyclopropyl), 1.09-1.05 (4H, m, H-14, cyclopropyl), 0.87-0.81 (1H, m, cyclopropyl), 0.71-0.65 (1H, m, cyclopropyl).

^{13}C NMR (125 MHz, $CDCl_3$): 177.4 (C-8), 87.1 (C-9), 81.4 (C-15), 64.7 (C-4), 57.6 (C-5), 44.3 (C-6), 41.4 (C-7), 33.5 (C-12), 32.5 (C-13), 27.3 (C-3), 26.9 (C-10), 25.0 (C-11), 17.2 (C-14), 10.8 (C-1), 5.6 (C-2).

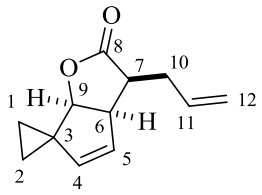
HRMS (+'ve ESI): calculated for $C_{15}H_{21}NO_5Na^+$ 318.1312 $(M + Na)^+$, found 318.1314.

IR ν_{max} (neat, cm^{-1}): 2941 (w), 2865 (w), 1748 (s), 1540 (s), 1465 (w), 1381 (m), 1344 (w), 1311 (w), 1228 (w), 1165 (s), 1037 (m), 1004 (m), 986 (s), 953 (m), 899 (m), 836 (m), 755 (m), 736 (m), 620 (m).

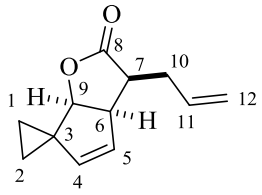
3.13 Synthesis of Epoxide **302**

3-Allyl-3a,6a-dihydrospiro[cyclopenta[*b*]furan-6,1'-cyclopropan]-2(3*H*)-one

204



Following the procedure reported by Marsh[2]: To a stirred solution of 3a,6a-dihydrospiro[cyclopenta[*b*]furan-6,1'-cyclopropan]-2(3*H*)-one **205** (3.60 g, 24.00 mmol) in tetrahydrofuran (70 mL) at -78 ºC was added lithium bis(trimethylsilyl)amide (26.40 mL, 26.40 mmol, 1 M solution in tetrahydrofuran) in a dropwise manner. The reaction mixture was stirred for 2 hours, before adding allyl bromide (4.20 mL, 48.00 mmol) in a dropwise fashion over 1 hour, keeping the temperature below -70 ºC. The reaction mixture was allowed to warm to room temperature, and left to stir for 16 hours, before being slowly poured into a saturated aqueous solution of ammonium chloride (50 mL). The aqueous layer was extracted with ether (4 × 50 mL). The combined organic extracts were dried over anhydrous magnesium sulfate, filtered, and the solvent was concentrated under reduced pressure. Purification by flash column chromatography, eluting with 5% diethyl ether/petroleum ether, afforded the title compound **204** as a pale yellow solid (1.69 g, 38%), and the corresponding diastereoisomer **210**[XXI] (1.67 g, 36%).



204

M. P.: 35-37 ºC. Recrystallised from diethyl ether.

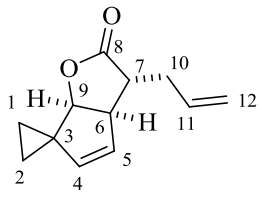
[XXI] Spectral datas concurrent with the literature: Marsh, G. P. University of Sussex **2007**.

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 5.98-5.88 (1H, m, H-11), 5.63 (1H, dd, *J* = 5.7, 1.4 Hz, H-5), 5.39 (1H, dd, *J* = 5.6, 1.9 Hz, H-4), 5.22-5.11 (2H, m, H-12), 4.44 (1H, d, *J* = 5.7 Hz, H-9), 3.82-3.77 (1H, m, H-6), 2.92-2.89 (1H, m, H-7), 2.76-2.70 (1H, m, H-10$_{a\ or\ b}$), 2.29-2.20 (1H, m, H-10$_{a\ or\ b}$), 1.22-1.18 (1H, m, cyclopropyl), 0.99-0.91 (2H, m, cyclopropyl), 0.81-0.79 (1H, m, cyclopropyl).

^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 177.5 (C-8), 138.0 (C-4), 135.4 (C-11), 125.1 (C-5), 116.6 (C-12), 87.5 (C-9), 49.0 (C-6), 43.0 (C-7), 34.0 (C-3), 31.8 (C-10), 13.0 (C-1), 8.7 (C-2).

HRMS (+'ve ESI): calculated for $C_{12}H_{14}O_2Na^+$ 213.0886 $(M + Na)^+$, found 213.0891.

IR ν_{max} (neat, cm^{-1}): 3078 (w), 2920 (w), 1755 (s), 1624 (m), 1602 (w), 1442 (w) 1346 (m), 1310 (m), 1225 (m), 1160 (s), 1000 (s), 914 (s), 808 (m), 748 (s).



210

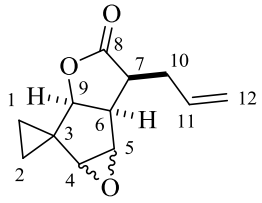
^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 5.83-5.79 (1H, m, H-11), 5.51 (1H, dd, *J* = 5.6, 1.8 Hz, H-5), 5.29 (1H, dd, *J* = 5.6, 2.0 Hz, H-4), 5.18-5.11 (2H, m, H-12), 4.49 (1H, d, *J* = 6.4 Hz, H-9), 3.44-3.39 (1H, m, H-6), 2.64-2.58 (1H, m, H-7), 2.56-2.48 (1H, m, H-10$_{a\ or\ b}$), 2.39-2.32 (1H, m, H-10$_{a\ or\ b}$), 1.16-1.10 (1H, m, cyclopropyl), 0.93-0.83 (2H, m, cyclopropyl), 0.79-0.73 (1H, m, cyclopropyl).

^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 178.8 (C-8), 136.6 (C-4), 133.9 (C-11), 128.7 (C-5), 118.3 (C-12), 88.0 (C-9), 50.6 (C-6), 45.7 (C-7), 36.0 (C-10), 33.6 (C-3), 13.2 (C-1), 9.0 (C-2).

HRMS (+'ve ESI): calculated for $C_{12}H_{14}O_2Na^+$ 213.0886 $(M + Na)^+$, found 213.0890.

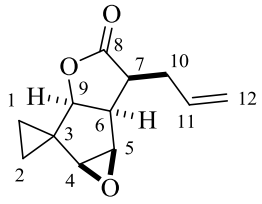
IR ν_{max} (neat, cm^{-1}): 3079 (w), 2918 (w), 1757 (s), 1641 (m), 1605 (w), 1440 (w) 1347 (m), 1318 (m), 1233 (m), 1167 (s), 1037 (s), 989 (s), 915 (s), 736 (s).

5'-Allyltetrahydrospiro[cyclopropane-1,2'-oxireno[3,4]cyclopenta[1,2-*b*]furan]-4'(2a'*H*)-one **302**



To a stirred solution of 3-allyl-3a,6a-dihydrospiro[cyclopenta[*b*]furan-6,1'-cyclopropan]-2(3*H*)-one **204** (0.53 g, 2.78 mmol) in dichloromethane (50 mL) was added a mixture of sodium hydrogen carbonate (0.26 g, 3.06 mmol), and *m*-chloroperoxybenzoic acid (0.53 mg, 3.06 mmol), in small solid portions at 0 ºC. The reaction mixture was warm to room temperature, and left to stir for 48 hours, before pouring into a 20% aqueous solution of sodium metabisulfite (40 mL). The reaction mixture was further stirred for 20 minutes. The layers were separated, and the aqueous phase was extracted using dichloromethane (4 × 50 mL). The combined organic extracts were washed with a 20% aqueous solution of sodium metabisulfite (50 mL), and water (50 mL), before being dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. Purification by flash column chromatography, eluting with 50% diethyl ether/hexane, afforded the title compound **302** as a white solid, and a separable mixture of *endo*/*exo* diastereoisomers in a 3.5:1 ratio (0.42 g, 73%).

***Major* diastereoisomer:**



M. P.: 72-74 ºC. Recrystallised from diethyl ether.

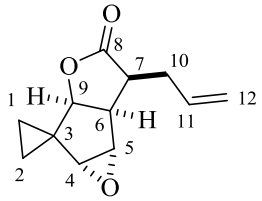
^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 6.02-5.93 (1H, m, H-11), 5.27-5.14 (2H, m, H-12), 4.25 (1H, d, *J* = 6.7 Hz, H-9), 3.74-3.72 (1H, m, H-5), 3.21-3.17 (1H, m, H-6), 3.10-3.09 (1H, m, H-4), 2.90-2.84 (2H, m, H-7, H-10$_{a\ or\ b}$), 2.59-2.48 (1H, m, H-10$_{a\ or\ b}$), 1.22-1.16 (1H, m, cyclopropyl), 1.10-1.06 (1H, m, cyclopropyl), 0.86-0.81 (1H, m, cyclopropyl), 0.71-0.66 (1H, m, cyclopropyl).

^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 177.5 (C-8), 135.6 (C-11), 116.6 (C-12), 87.2 (C-9), 64.4 (C-4), 57.6 (C-5), 44.1 (C-6), 41.2 (C-7), 31.3 (C-10), 27.3 (C-3), 10.9 (C-1), 5.5 (C-2).

HRMS (+'ve ESI): calculated for $C_{12}H_{14}O_3Na^+$ 229.0835 $(M + Na)^+$, found 229.0835.

IR ν_{max} (neat, cm^{-1}): 2920 (w), 2860 (w), 1747 (s), 1620 (m), 1340 (m), 1225 (m), 1170 (s), 1038 (m), 997 (s), 870 (s), 832 (s), 735 (m).

***Minor* diastereoisomer[XXII]:**



M. P.: 77-79 ºC. Recrystallised from diethyl ether.

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 6.00-5.92 (1H, m, H-11), 5.24-5.17 (2H, m, H-12), 4.37 (1H, d, *J* = 6.6 Hz, H-9), 3.75 (1H, dd, *J* = 2.6, 0.6 Hz, H-5), 3.35-3.30 (1H, m, H-6), 3.10 (1H, d, *J* = 2.6 Hz, H-4), 2.94-2.89 (1H, m, H-7), 2.75-2.64 (1H, m, H-10$_{a\ or\ b}$), 2.50-2.42 (1H, m, H-10$_{a\ or\ b}$), 1.07-1.00 (2H, m, cyclopropyl), 0.93-0.81 (2H, m, cyclopropyl).

^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 177.7 (C-8), 134.8 (C-11), 117.3 (C-12), 87.2 (C-9), 64.2 (C-4), 57.4 (C-5), 44.3 (C-6), 40.2 (C-7), 31.5 (C-10), 28.3 (C-3), 9.1 (C-1), 7.5 (C-2).

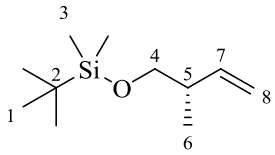
HRMS (+'ve ESI): calculated for $C_{12}H_{14}O_3Na^+$ 229.0835 $(M + Na)^+$, found 229.0835.

IR ν_{max} (neat, cm^{-1}): 2929 (w), 2854 (w), 1741 (s), 1622 (m), 1344 (m), 1210 (m), 1176 (s), 986 (m), 906 (s), 835 (s), 784 (m).

[XXII] See appendix for crystal structure data.

3.14 Synthesis of Nitroalkene **203**

tert-Butyl(dimethyl){[(2*S*)-2-methylbut-3-en-1-yl]oxy}silane **310**



Following the procedure reported by Marsh[2]: To a stirred solution of methyltriphenylphosphonium bromide (3.60 g, 9.89 mmol) in tetrahydrofuran (50 mL) at 0 ºC was added *n*-butyllithium (4.95 mL, 12.36 mmol, 2.5 M solution in tetrahydrofuran) in a dropwise fashion, and the reaction mixture was stirred for 20 minutes. A solution of (2*R*)-3-{[*tert*-butyl(dimethyl)silyl]oxy}-2-methylpropanal **247** (1.00 g, 4.94 mmol) in tetrahydrofuran (40 mL) was added in a dropwise manner, keeping the temperature below 5 ºC. The reaction mixture was allowed to warm slowly to ambient temperature, and was left to stir for 16 hours, before being poured into a saturated aqueous solution of ammonium chloride (150 mL). The organic phase was separated, and the aqueous component was extracted with diethyl ether (4 × 100 mL). The combined organic extracts were washed with a saturated aqueous solution of sodium chloride (150 mL), dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. Purification by flash column chromatography, eluting with pentane, afforded the title compound **310**[XXIII] as a colourless oil (0.80 g, 81%).

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 5.82-5.74 (1H, m, H-7), 5.07-4.97 (2H, m, H-8), 3.55-3.50 (1H, m, H-4$_{a\ or\ b}$), 3.44-3.39 (1H, m, H-4$_{a\ or\ b}$), 2.36-2.30 (1H, m, H-5), 1.00 (3H, d, J = 6.6 Hz, H-6), 0.89 (9H, s, H-1), 0.04 (6H, s, H-3).

^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 141.4 (C-7), 113.8 (C-6), 67.9 (C-4), 40.2 (C-5), 25.9 (C-1), 18.3 (C-2), 16.0 (C-6), -5.3 (C-3).

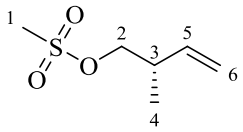
HRMS (+'ve ESI): calculated for $C_{11}H_{24}OSiNa^+$ 223.1489 $(M + Na)^+$, found 223.1493.

[XXIII] Spectral data concurrent with the literature: Marsh, G. P. University of Sussex **2007**.

IR ν_{max} (neat, cm^{-1}): 3040 (w), 2956 (m), 2930 (m), 2857 (m), 1620 (w), 1472 (m), 1385 (w), 1361 (w), 1253 (m), 1089 (s), 1006 (m), 912 (m), 833 (s), 773 (s), 667 (m).

$[\alpha]_D^{24}$ +0.68° (*c* 1.11 in $CHCl_3$).

(2*S*)-2-Methylbut-3-en-1-yl methanesulfonate **311**



To a stirred solution of *tert*-butyl(dimethyl){[(2*S*)-2-methylbut-3-en-1-yl]oxy}silane **310** (1.00 g, 4.90 mmol) in dichloromethane (250 mL) was added Dowex® 50W-X8 (30.00 g), and was left to stir for 48 hours. The reaction mixture was filtered, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. Following the procedure reported by Oishi *et al.*[198]: The crude product was poured into a flask with dichloromethane (50 mL), and was cooled to 0 ºC, before adding triethylamine (0.75 mL, 5.37 mmol), and methanesulfonyl chloride (0.42 mL, 5.37 mmol) in a dropwise manner, followed by adding 4-dimethylaminopyridine (0.06 g, 0.49 mmol) in a single solid portion. The reaction mixture was allowed to warm to room temperature, and stirred for 16 hours, before being poured into water (50 mL). The layers were separated, and the aqueous phase was extracted using dichloromethane (4 × 50 mL). The combined organic extracts were washed with a 10% aqueous solution of hydrochloric acid (100 mL), a saturated aqueous solution of sodium hydrogen carbonate (100 mL), and a saturated aqueous solution of sodium chloride (100 mL), before being dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. Purification by flash column chromatography, eluting with 20% diethyl ether/pentane, afforded the title compound **311** as a colourless oil (0.61 g, 75%).

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 5.78-5.70 (1H, m, H-5), 5.17-5.10 (2H, m, H-6), 4.14-4.10 (1H, m, H-2$_{a\ or\ b}$), 4.08-4.04 (1H, m, H-2$_{a\ or\ b}$), 3.00 (3H, s, H-1), 2.67-2.58 (1H, m, H-3), 1.11 (3H, d, *J* = 6.8 Hz, H-4).

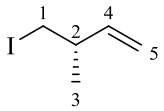
^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 138.4 (C-5), 116.1 (C-6), 73.3 (C-2), 37.4 (C-1), 37.2 (C-3), 16.0 (C-4).

HRMS (+'ve ESI): calculated for $C_6H_{12}O_3SNa^+$ 187.0399 $(M + Na)^+$, found 187.0400.

IR ν_{max} (neat, cm^{-1}): 3035 (w), 2975 (m), 2940 (w), 2860 (w), 1643 (w), 1460 (w), 1419 (w), 1349 (s), 1332 (s), 1170 (s), 955 (s), 915 (s), 842 (s), 811 (s), 748 (m), 673 (m).

$[\alpha]_D^{22}$ +1.38º (*c* 1.04 in $CHCl_3$).

(3*S*)-4-Iodo-3-methylbut-1-ene **312**



Following the procedure reported by Oishi *et al.*[198]: To a stirred solution of (2*S*)-2-methylbut-3-en-1-yl methanesulfonate **311** (1.10 g, 6.70 mmol) in acetone (150 mL) was added sodium iodide (10.00 g, 67.00 mmol) in small portions over 1 hour. The reaction mixture was heated to reflux for 16 hours. The flask was shielded from light throughout the reaction. After being allowed to cool to room temperature, the reaction mixture was diluted with diethyl ether (100 mL), and the extracts were filtered. The filter cake was washed with diethyl ether, and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography, eluting with 1% diethyl ether/pentane, afforded the title compound **312** as a pale yellow oil (0.93 g, 71%).

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 5.76-5.67 (1H, m, H-4), 5.10-5.05 (2H, m, H-5), 3.22-3.18 (1H, m, H-1$_{a\ or\ b}$), 3.16-3.11 (1H, m, H-1$_{a\ or\ b}$), 2.41-2.34 (1H, m, H-2), 1.13 (3H, d, *J* = 6.6 Hz, H-3).

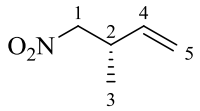
^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 141.4 (C-4), 114.8 (C-5), 39.4 (C-2), 20.2 (C-3), 14.5 (C-1).

LRMS (+'ve EI): *m/z* 196 (M, 18%), 181 (5), 141 (35), 128 (7), 127 (100), 70 (43), 68 (50), 67 (94), 65 (40), 63 (20), 62 (8), 57 (4).

IR ν_{max} (neat, cm^{-1}): 3030 (w), 2963 (m), 2926 (m), 2855 (w), 1640 (w), 1454 (w), 1415 (w), 1373 (w), 887 (s), 990 (s), 916 (s), 791 (w), 682 (m).

$[\alpha]_D^{22}$ -0.79° (*c* 1.04 in $CHCl_3$).

(3*S*)-3-Methyl-4-nitrobut-1-ene **203**



To a stirred solution of (3*S*)-4-iodo-3-methylbut-1-ene **312** (0.90 g, 4.50 mmol), and Amberlite® IRA-900 nitrite (5.10 g, 20.40 mmol) in benzene (50 mL) was heated to reflux for 48 hours. The reaction mixture was cooled to ambient temperature, before the resin was filtered off, and washed with benzene. The filtrate was dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. Purification by flash column chromatography, eluting with 10% diethyl ether/pentane, afforded the title compound **203** as a colourless oil (0.35 g, 67%).

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 5.77-5.69 (1H, m, H-4), 5.19-5.12 (2H, m, H-5), 4.36-4.25 (2H, m, H-1), 3.09-3.00 (1H, m, H-2), 1.13 (3H, d, *J* = 6.8 Hz, H-3).

^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 137.6 (C-4), 116.6 (C-5), 80.7 (C-1), 36.7 (C-2), 17.0 (C-3).

LRMS (+'ve EI): *m/z* 116 (M^+, 5%), 85 (7), 70 (90), 66 (76), 65 (63), 63 (19), 62 (20), 60 (8), 57 (18), 55 (60), 52 (70), 51 (100).

IR ν_{max} (neat, cm^{-1}): 3040 (w), 2967 (m), 2930 (m), 2850 (w), 1725 (m), 1640 (w), 1547 (s), 1459 (m), 1378 (w), 1275 (m), 1126 (m), 993 (m), 923 (s), 727 (m), 674 (m).

$[\alpha]_D^{22}$ -0.78° (*c* 1.06 in $CHCl_3$).

CHAPTER 4

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CHAPTER 5

APPENDICIES

5.1 Crystallography Data of Lactone **205**

3a,6a-Dihydrospiro[cyclopenta[*b*]furan-6,1'-cyclopropan]-2(3*H*)-one **205**

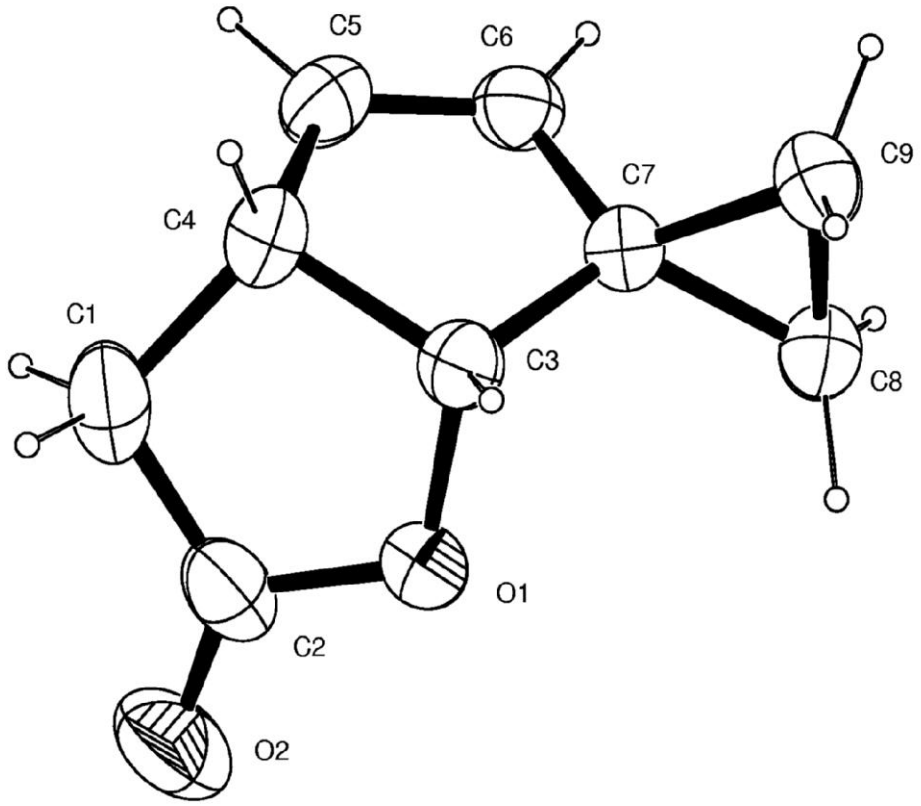

Table 1. Crystal data and structure refinement .

Identification code	nov1206	
Empirical formula	C9 H10 O2	
Formula weight	150.17	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1/n$ (No.14)	
Unit cell dimensions	a = 8.3287(12) Å	α= 90°.
	b = 9.1412(15) Å	β= 106.411(9)°.
	c = 10.3119(15) Å	γ = 90°.
Volume	753.1(2) $Å^3$	
Z	4	
Density (calculated)	1.32 Mg/m^3	
Absorption coefficient	0.09 mm^{-1}	
F(000)	320	
Crystal size	0.30 x 0.20 x 0.15 mm^3	
Theta range for data collection	3.57 to 26.14°.	
Index ranges	-10<=h<=10, -11<=k<=11, -12<=l<=12	
Reflections collected	9215	
Independent reflections	1479 [R(int) = 0.063]	
Reflections with I>2sigma(I)	1179	
Completeness to theta = 26.14°	98.5 %	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	1479 / 0 / 140	
Goodness-of-fit on F^2	1.064	
Final R indices [I>2sigma(I)]	R1 = 0.047, wR2 = 0.110	
R indices (all data)	R1 = 0.063, wR2 = 0.119	
Largest diff. peak and hole	0.15 and -0.16 $e.Å^{-3}$	

Data collection KappaCCD , Program package WinGX , Abs correction not applied ,

Refinement using SHELXL-97 , Drawing using ORTEP-3 for Windows

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for nov1206. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	1669(1)	3857(1)	770(1)	40(1)
O(2)	3594(2)	2801(2)	-28(1)	65(1)
C(1)	4444(2)	4441(2)	1914(2)	50(1)
C(2)	3271(2)	3596(2)	792(2)	45(1)
C(3)	1567(2)	4890(2)	1833(2)	35(1)
C(4)	3364(2)	4967(2)	2783(2)	39(1)
C(5)	3281(2)	3959(2)	3916(2)	40(1)
C(6)	1726(2)	3574(2)	3849(2)	38(1)
C(7)	516(2)	4242(2)	2661(2)	33(1)
C(8)	-1198(2)	3623(2)	1996(2)	41(1)
C(9)	-1039(2)	5016(2)	2782(2)	44(1)

Table 3. Bond lengths [Å] and angles [°] for nov1206.

O(1)-C(2)	1.349(2)
O(1)-C(3)	1.467(2)
O(2)-C(2)	1.201(2)
C(1)-C(2)	1.500(3)
C(1)-C(4)	1.517(3)
C(3)-C(7)	1.506(2)
C(3)-C(4)	1.542(2)
C(4)-C(5)	1.505(2)
C(5)-C(6)	1.324(2)
C(6)-C(7)	1.481(2)
C(7)-C(8)	1.508(2)
C(7)-C(9)	1.511(2)
C(8)-C(9)	1.495(3)
C(2)-O(1)-C(3)	111.49(13)
C(2)-C(1)-C(4)	104.70(14)
O(2)-C(2)-O(1)	120.78(17)
O(2)-C(2)-C(1)	128.86(17)
O(1)-C(2)-C(1)	110.35(15)
O(1)-C(3)-C(7)	109.63(12)
O(1)-C(3)-C(4)	104.72(12)
C(7)-C(3)-C(4)	105.84(13)
C(5)-C(4)-C(1)	115.45(15)
C(5)-C(4)-C(3)	102.47(13)
C(1)-C(4)-C(3)	103.92(14)
C(6)-C(5)-C(4)	112.40(14)
C(5)-C(6)-C(7)	111.13(16)
C(6)-C(7)-C(3)	105.21(13)
C(6)-C(7)-C(8)	123.84(15)
C(3)-C(7)-C(8)	121.10(14)
C(6)-C(7)-C(9)	121.56(14)
C(3)-C(7)-C(9)	120.81(15)
C(8)-C(7)-C(9)	59.37(11)
C(9)-C(8)-C(7)	60.41(11)

C(8)-C(9)-C(7)	60.22(11)

5.2 Crystallography Data of Precursor **234**

6-Chlorospiro[bicyclo[3.2.0]heptane-2,1'-cyclopropane]-3-en-7-one **234**

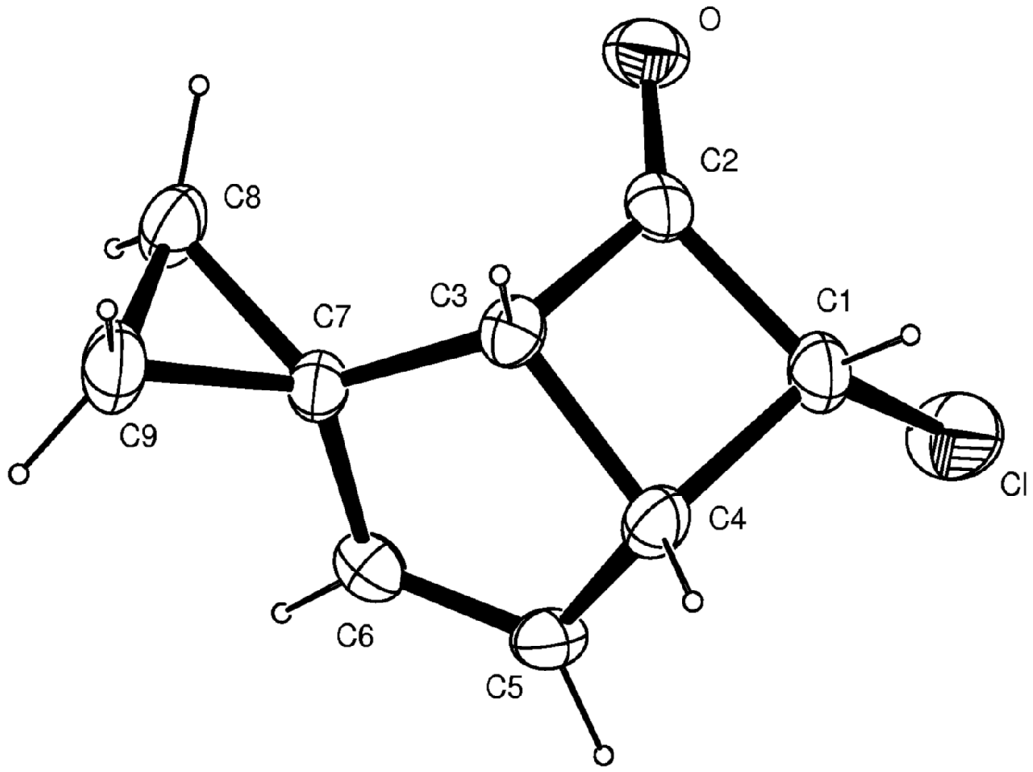

Table 1. Crystal data and structure refinement .

Identification code	oct1806	
Empirical formula	C9 H9 Cl O	
Formula weight	168.61	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1/n$ (No.14)	
Unit cell dimensions	a = 4.9201(2) Å	α= 90°.
	b = 12.4213(4) Å	β= 90.313(2)°.
	c = 13.3861(5) Å	γ = 90°.
Volume	818.07(5) $Å^3$	
Z	4	
Density (calculated)	1.37 Mg/m^3	
Absorption coefficient	0.40 mm^{-1}	
F(000)	352	
Crystal size	0.10 x 0.10 x 0.05 mm^3	
Theta range for data collection	3.46 to 26.70°.	
Index ranges	-6<=h<=6, -15<=k<=15, -16<=l<=16	
Reflections collected	12122	
Independent reflections	1714 [R(int) = 0.080]	
Reflections with I>2sigma(I)	1399	
Completeness to theta = 26.70°	99.1 %	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	1714 / 0 / 136	
Goodness-of-fit on F^2	1.060	
Final R indices [I>2sigma(I)]	R1 = 0.048, wR2 = 0.107	
R indices (all data)	R1 = 0.063, wR2 = 0.115	
Largest diff. peak and hole	0.35 and -0.43 e.$Å^{-3}$	

Data collection KappaCCD , Program package WinGX , Abs correction not applied ,

Refinement using SHELXL-97 , Drawing using ORTEP-3 for Windows

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for oct1806. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Cl	18(2)	9908(1)	6265(1)	47(1)
O	-2320(3)	10308(1)	8569(1)	31(1)
C(1)	1571(5)	9805(2)	7459(2)	26(1)
C(2)	-270(4)	9836(2)	8373(2)	22(1)
C(3)	1364(4)	8932(2)	8880(2)	20(1)
C(4)	2628(4)	8706(2)	7829(2)	23(1)
C(5)	1043(4)	7742(2)	7488(2)	27(1)
C(6)	-493(4)	7331(2)	8199(2)	26(1)
C(7)	-284(4)	7939(2)	9150(2)	21(1)
C(8)	-2561(4)	7962(2)	9895(2)	28(1)
C(9)	21(5)	7368(2)	10144(2)	31(1)

Table 3. Bond lengths [Å] and angles [°] for oct1806.

Cl-C(1)	1.773(2)
O-C(2)	1.197(3)
C(1)-C(2)	1.526(3)
C(1)-C(4)	1.542(3)
C(2)-C(3)	1.538(3)
C(3)-C(7)	1.521(3)
C(3)-C(4)	1.567(3)
C(4)-C(5)	1.498(3)
C(5)-C(6)	1.321(3)
C(6)-C(7)	1.483(3)
C(7)-C(8)	1.505(3)
C(7)-C(9)	1.515(3)
C(8)-C(9)	1.505(3)
C(2)-C(1)-C(4)	88.04(15)
C(2)-C(1)-Cl	117.78(16)
C(4)-C(1)-Cl	119.76(16)
O-C(2)-C(1)	133.82(19)
O-C(2)-C(3)	134.43(19)
C(1)-C(2)-C(3)	91.41(15)
C(7)-C(3)-C(2)	114.79(16)
C(7)-C(3)-C(4)	106.40(16)
C(2)-C(3)-C(4)	86.74(15)
C(5)-C(4)-C(1)	115.80(17)
C(5)-C(4)-C(3)	102.01(16)
C(1)-C(4)-C(3)	89.69(15)
C(6)-C(5)-C(4)	112.85(19)
C(5)-C(6)-C(7)	112.6(2)
C(6)-C(7)-C(8)	122.02(19)
C(6)-C(7)-C(9)	121.48(19)
C(8)-C(7)-C(9)	59.78(14)
C(6)-C(7)-C(3)	104.13(17)
C(8)-C(7)-C(3)	122.80(18)
C(9)-C(7)-C(3)	122.52(18)

C(7)-C(8)-C(9)	60.46(13)
C(8)-C(9)-C(7)	59.76(14)

5.3 Crystallography Data of Lactone **238**

3-Chloro-3a,6a-dihydrospiro[cyclopenta[*b*]furan-6,1'-cyclopropan]-2(3*H*)-one

238

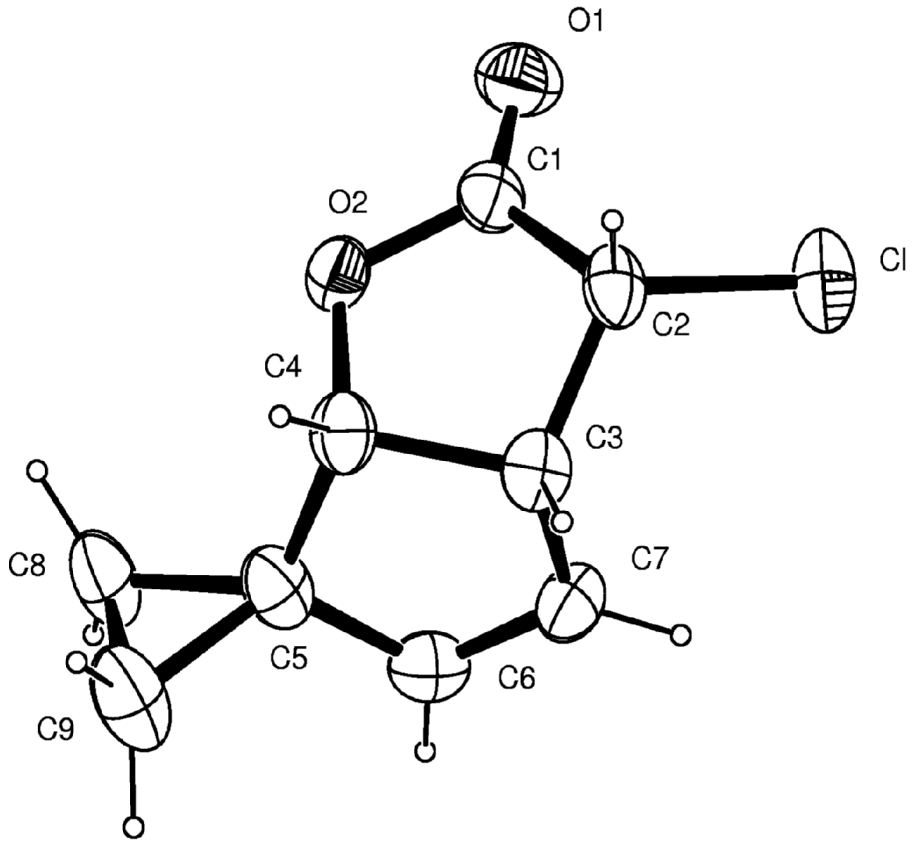

Table 1. Crystal data and structure refinement .

Identification code	apr707	
Empirical formula	C9 H9 Cl O2	
Formula weight	184.61	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	$Pca2_1$ (No.29)	
Unit cell dimensions	a = 24.0509(6) Å	α= 90°.
	b = 4.98650(10) Å	β= 90°.
	c = 28.5987(7) Å	γ = 90°.
Volume	3429.84(14) $Å^3$	
Z	16	
Density (calculated)	1.43 Mg/m^3	
Absorption coefficient	0.40 mm^{-1}	
F(000)	1536	
Crystal size	0.35 x 0.20 x 0.20 mm^3	
Theta range for data collection	3.46 to 26.02°.	
Index ranges	-29<=h<=29, -4<=k<=6, -35<=l<=34	
Reflections collected	18117	
Independent reflections	6268 [R(int) = 0.061]	
Reflections with I>2sigma(I)	4883	
Completeness to theta = 26.02°	98.9 %	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	6268 / 1 / 434	
Goodness-of-fit on F^2	1.006	
Final R indices [I>2sigma(I)]	R1 = 0.045, wR2 = 0.090	
R indices (all data)	R1 = 0.071, wR2 = 0.102	
Absolute structure parameter	0.54(5)	
Largest diff. peak and hole	0.22 and -0.26 e.$Å^{-3}$	

Four independent molecules .

Data collection KappaCCD , Program package WinGX , Abs correction not applied ,

Refinement using SHELXL-97 , Drawing using ORTEP-3 for Windows

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for apr707. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Cl	5565(1)	6375(2)	2020(1)	42(1)
O(1)	5973(1)	5187(6)	1031(1)	44(1)
O(2)	5403(1)	8280(5)	731(1)	35(1)
C(1)	5677(1)	7103(7)	1085(1)	31(1)
C(2)	5539(2)	8585(7)	1537(1)	32(1)
C(3)	4979(1)	9852(7)	1434(1)	31(1)
C(4)	5009(2)	10313(8)	900(1)	32(1)
C(5)	4439(2)	9646(8)	719(1)	36(1)
C(6)	4181(2)	7987(7)	1088(1)	36(1)
C(7)	4477(2)	8049(7)	1478(1)	35(1)
C(8)	4340(2)	9298(8)	200(1)	46(1)
C(9)	4119(2)	11724(8)	445(1)	52(1)
Cl(1B)	4391(1)	-617(3)	3529(1)	59(1)
O(1B)	4689(1)	2923(5)	2691(1)	45(1)
O(2B)	5587(1)	2159(5)	2833(1)	29(1)
C(1B)	5043(2)	1563(7)	2869(1)	32(1)
C(2B)	4970(2)	-971(7)	3149(1)	33(1)
C(3B)	5527(1)	-1384(7)	3391(1)	30(1)
C(4B)	5938(1)	194(7)	3081(1)	29(1)
C(5B)	6320(1)	1661(7)	3409(1)	27(1)
C(6B)	6033(2)	1565(8)	3867(1)	35(1)
C(7B)	5602(2)	-69(8)	3860(1)	36(1)
C(8B)	6947(1)	1384(7)	3374(1)	36(1)
C(9B)	6668(1)	3983(7)	3247(1)	34(1)
Cl(1C)	2152(1)	766(2)	1055(1)	46(1)
O(1C)	1695(1)	-426(5)	2033(1)	42(1)
O(2C)	2243(1)	2679(5)	2345(1)	33(1)
C(1C)	1989(1)	1528(8)	1980(1)	31(1)
C(2C)	2130(2)	3017(7)	1537(1)	34(1)
C(3C)	2669(1)	4422(8)	1656(1)	34(1)
C(4C)	2612(1)	4879(7)	2187(1)	33(1)

C(5C)	3182(2)	4414(7)	2387(1)	33(1)
C(6C)	3478(1)	2866(7)	2027(1)	35(1)
C(7C)	3201(2)	2806(8)	1630(1)	37(1)
C(8C)	3469(2)	6654(8)	2658(2)	49(1)
C(9C)	3265(2)	4190(8)	2908(1)	40(1)
Cl(1D)	1787(1)	-7212(2)	4527(1)	48(1)
O(1D)	2047(1)	-3187(5)	5330(1)	47(1)
O(2D)	2951(1)	-3878(5)	5207(1)	32(1)
C(1D)	2410(2)	-4558(7)	5170(1)	31(1)
C(2D)	2362(1)	-7194(7)	4913(1)	28(1)
C(3D)	2923(1)	-7583(7)	4680(1)	29(1)
C(4D)	3316(1)	-5879(7)	4988(1)	28(1)
C(5D)	3701(1)	-4497(7)	4646(1)	29(1)
C(6D)	3424(2)	-4710(9)	4190(1)	39(1)
C(7D)	2996(2)	-6384(8)	4205(1)	37(1)
C(8D)	4328(1)	-4793(8)	4691(1)	36(1)
C(9D)	4059(1)	-2157(7)	4795(1)	37(1)

Table 3. Bond lengths [Å] and angles [°] for apr707.

Cl-C(2)	1.768(3)
O(1)-C(1)	1.202(4)
O(2)-C(1)	1.344(4)
O(2)-C(4)	1.470(4)
C(1)-C(2)	1.525(5)
C(2)-C(3)	1.517(5)
C(3)-C(7)	1.511(5)
C(3)-C(4)	1.545(5)
C(4)-C(5)	1.503(5)
C(5)-C(6)	1.478(5)
C(5)-C(9)	1.512(5)
C(5)-C(8)	1.513(5)
C(6)-C(7)	1.325(5)
C(8)-C(9)	1.494(6)
Cl(1B)-C(2B)	1.776(4)
O(1B)-C(1B)	1.202(4)
O(2B)-C(1B)	1.345(4)
O(2B)-C(4B)	1.476(4)
C(1B)-C(2B)	1.506(5)
C(2B)-C(3B)	1.522(5)
C(3B)-C(7B)	1.506(5)
C(3B)-C(4B)	1.542(5)
C(4B)-C(5B)	1.502(5)
C(5B)-C(6B)	1.482(5)
C(5B)-C(9B)	1.502(5)
C(5B)-C(8B)	1.518(5)
C(6B)-C(7B)	1.319(5)
C(8B)-C(9B)	1.504(5)
Cl(1C)-C(2C)	1.779(4)
O(1C)-C(1C)	1.213(4)
O(2C)-C(1C)	1.338(4)
O(2C)-C(4C)	1.482(4)
C(1C)-C(2C)	1.508(5)
C(2C)-C(3C)	1.512(5)

C(3C)-C(7C)	1.514(5)
C(3C)-C(4C)	1.540(5)
C(4C)-C(5C)	1.502(5)
C(5C)-C(6C)	1.471(5)
C(5C)-C(9C)	1.508(5)
C(5C)-C(8C)	1.526(5)
C(6C)-C(7C)	1.317(5)
C(8C)-C(9C)	1.502(6)
Cl(1D)-C(2D)	1.769(3)
O(1D)-C(1D)	1.199(4)
O(2D)-C(1D)	1.351(4)
O(2D)-C(4D)	1.468(4)
C(1D)-C(2D)	1.509(5)
C(2D)-C(3D)	1.519(5)
C(3D)-C(7D)	1.495(5)
C(3D)-C(4D)	1.545(5)
C(4D)-C(5D)	1.513(5)
C(5D)-C(6D)	1.468(5)
C(5D)-C(9D)	1.512(5)
C(5D)-C(8D)	1.521(5)
C(6D)-C(7D)	1.325(5)
C(8D)-C(9D)	1.495(5)

C(1)-O(2)-C(4)	111.6(3)
O(1)-C(1)-O(2)	122.7(3)
O(1)-C(1)-C(2)	128.5(3)
O(2)-C(1)-C(2)	108.7(3)
C(3)-C(2)-C(1)	103.3(3)
C(3)-C(2)-Cl	116.2(3)
C(1)-C(2)-Cl	110.7(3)
C(7)-C(3)-C(2)	116.4(3)
C(7)-C(3)-C(4)	102.1(3)
C(2)-C(3)-C(4)	102.3(3)
O(2)-C(4)-C(5)	108.7(3)
O(2)-C(4)-C(3)	104.7(3)
C(5)-C(4)-C(3)	105.4(3)

C(6)-C(5)-C(4)	105.2(3)
C(6)-C(5)-C(9)	122.7(3)
C(4)-C(5)-C(9)	119.5(3)
C(6)-C(5)-C(8)	124.7(4)
C(4)-C(5)-C(8)	120.5(3)
C(9)-C(5)-C(8)	59.2(3)
C(7)-C(6)-C(5)	111.2(3)
C(6)-C(7)-C(3)	111.9(3)
C(9)-C(8)-C(5)	60.4(3)
C(8)-C(9)-C(5)	60.4(2)
C(1B)-O(2B)-C(4B)	112.0(2)
O(1B)-C(1B)-O(2B)	122.2(3)
O(1B)-C(1B)-C(2B)	128.0(3)
O(2B)-C(1B)-C(2B)	109.8(3)
C(1B)-C(2B)-C(3B)	104.6(3)
C(1B)-C(2B)-Cl(1B)	109.5(3)
C(3B)-C(2B)-Cl(1B)	115.1(2)
C(7B)-C(3B)-C(2B)	116.8(3)
C(7B)-C(3B)-C(4B)	102.3(3)
C(2B)-C(3B)-C(4B)	103.6(3)
O(2B)-C(4B)-C(5B)	109.1(3)
O(2B)-C(4B)-C(3B)	104.3(3)
C(5B)-C(4B)-C(3B)	106.4(3)
C(6B)-C(5B)-C(4B)	104.6(3)
C(6B)-C(5B)-C(9B)	123.9(3)
C(4B)-C(5B)-C(9B)	121.5(3)
C(6B)-C(5B)-C(8B)	121.2(3)
C(4B)-C(5B)-C(8B)	121.4(3)
C(9B)-C(5B)-C(8B)	59.7(2)
C(7B)-C(6B)-C(5B)	111.9(3)
C(6B)-C(7B)-C(3B)	112.1(3)
C(9B)-C(8B)-C(5B)	59.6(2)
C(5B)-C(9B)-C(8B)	60.6(2)
C(1C)-O(2C)-C(4C)	110.7(3)
O(1C)-C(1C)-O(2C)	120.9(3)
O(1C)-C(1C)-C(2C)	129.2(3)

O(2C)-C(1C)-C(2C)	109.9(3)
C(1C)-C(2C)-C(3C)	103.4(3)
C(1C)-C(2C)-Cl(1C)	110.3(3)
C(3C)-C(2C)-Cl(1C)	116.3(3)
C(2C)-C(3C)-C(7C)	117.8(3)
C(2C)-C(3C)-C(4C)	102.4(3)
C(7C)-C(3C)-C(4C)	101.7(3)
O(2C)-C(4C)-C(5C)	108.4(3)
O(2C)-C(4C)-C(3C)	104.1(3)
C(5C)-C(4C)-C(3C)	105.7(3)
C(6C)-C(5C)-C(4C)	104.9(3)
C(6C)-C(5C)-C(9C)	126.0(3)
C(4C)-C(5C)-C(9C)	120.6(3)
C(6C)-C(5C)-C(8C)	121.4(3)
C(4C)-C(5C)-C(8C)	119.5(3)
C(9C)-C(5C)-C(8C)	59.4(3)
C(7C)-C(6C)-C(5C)	111.7(3)
C(6C)-C(7C)-C(3C)	111.9(3)
C(9C)-C(8C)-C(5C)	59.7(2)
C(8C)-C(9C)-C(5C)	60.9(3)
C(1D)-O(2D)-C(4D)	111.9(3)
O(1D)-C(1D)-O(2D)	121.9(3)
O(1D)-C(1D)-C(2D)	128.8(3)
O(2D)-C(1D)-C(2D)	109.3(3)
C(1D)-C(2D)-C(3D)	104.9(3)
C(1D)-C(2D)-Cl(1D)	111.5(2)
C(3D)-C(2D)-Cl(1D)	114.8(2)
C(7D)-C(3D)-C(2D)	116.9(3)
C(7D)-C(3D)-C(4D)	103.1(3)
C(2D)-C(3D)-C(4D)	102.8(3)
O(2D)-C(4D)-C(5D)	109.4(3)
O(2D)-C(4D)-C(3D)	104.6(3)
C(5D)-C(4D)-C(3D)	104.8(3)
C(6D)-C(5D)-C(9D)	124.4(3)
C(6D)-C(5D)-C(4D)	105.3(3)
C(9D)-C(5D)-C(4D)	121.1(3)

C(6D)-C(5D)-C(8D)	121.2(3)
C(9D)-C(5D)-C(8D)	59.1(2)
C(4D)-C(5D)-C(8D)	120.5(3)
C(7D)-C(6D)-C(5D)	111.7(3)
C(6D)-C(7D)-C(3D)	111.9(3)
C(9D)-C(8D)-C(5D)	60.1(2)
C(8D)-C(9D)-C(5D)	60.8(2)

5.4 Crystallography Data of *Exo*-Epoxide **302**

5'-Allyltetrahydrospiro[cyclopropane-1,2'-oxireno[3,4]cyclopenta[1,2-*b*]furan]-4'(2a'*H*)-one **302**

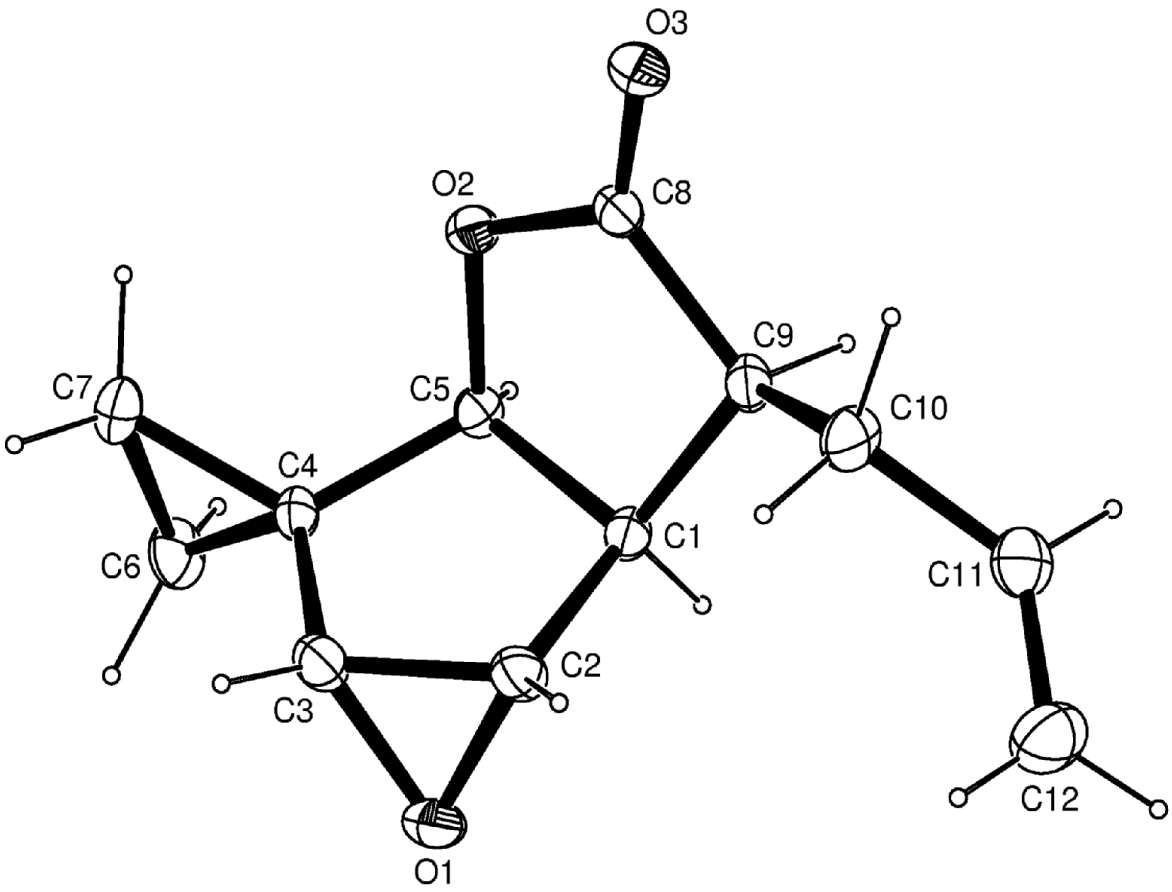

Table 1. Crystal data and structure refinement for $C_{12}H_{14}O_3$.

Identification code	apr310	
Empirical formula	C12 H14 O3	
Formula weight	206.23	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	*P* $2_1/c$ (No.14)	
Unit cell dimensions	a = 15.1394(4) Å	α= 90°.
	b = 7.2675(3) Å	β= 103.711(2)°.
	c = 9.7199(4) Å	γ = 90°.
Volume	1038.96(7) $Å^3$	
Z	4	
Density (calculated)	1.32 Mg/m^3	
Absorption coefficient	0.09 mm^{-1}	
F(000)	440	
Crystal size	0.21 x 0.17 x 0.15 mm^3	
Theta range for data collection	3.54 to 27.10°.	
Index ranges	-19<=h<=19, -9<=k<=9, -12<=l<=12	
Reflections collected	15615	
Independent reflections	2295 [R(int) = 0.058]	
Reflections with I>2sigma(I)	1899	
Completeness to theta = 27.10°	99.7 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2295 / 2 / 155	
Goodness-of-fit on F^2	1.001	
Final R indices [I>2sigma(I)]	R1 = 0.049, wR2 = 0.123	
R indices (all data)	R1 = 0.061, wR2 = 0.130	
Largest diff. peak and hole	0.32 and -0.20 e.$Å^{-3}$	

Data collection KappaCCD , Program package WinGX , Abs correction not applied

Refinement using SHELXL-97 , Drawing using ORTEP-3 for Windows

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for apr310. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	3010(1)	3524(2)	8606(2)	41(1)
O(2)	1271(1)	-413(2)	6402(1)	27(1)
O(3)	1787(1)	-2621(2)	5220(1)	33(1)
C(1)	2607(1)	270(2)	8196(2)	22(1)
C(2)	3051(1)	1938(2)	7711(2)	29(1)
C(3)	2371(1)	3378(2)	7228(2)	30(1)
C(4)	1463(1)	2690(2)	7343(2)	22(1)
C(5)	1575(1)	665(2)	7707(2)	22(1)
C(6)	840(1)	3916(3)	7930(2)	35(1)
C(7)	608(1)	3426(3)	6397(2)	35(1)
C(8)	1901(1)	-1625(2)	6233(2)	24(1)
C(9)	2717(1)	-1566(2)	7483(2)	24(1)
C(10)	3608(1)	-1972(3)	7074(2)	34(1)[a]
C(11)	4328(2)	-2508(6)	8381(4)	36(1)[a]
C(12)	5082(2)	-1648(5)	8793(4)	52(1)[a]
C(10A)	3608(1)	-1972(3)	7074(2)	34(1)[b]
C(11A)	4473(4)	-1659(10)	8241(8)	36(2)[b]
C(12A)	4816(4)	-3075(9)	9083(6)	39(1)[b]

a 66.1 %, 33.9 %

Table 3. Bond lengths [Å] and angles [°] for apr310.

O(1)-C(2)	1.455(2)
O(1)-C(3)	1.458(2)
O(2)-C(8)	1.3380(19)
O(2)-C(5)	1.4683(18)
O(3)-C(8)	1.2013(19)
C(1)-C(2)	1.515(2)
C(1)-C(9)	1.531(2)
C(1)-C(5)	1.548(2)
C(2)-C(3)	1.465(2)
C(3)-C(4)	1.492(2)
C(4)-C(7)	1.497(2)
C(4)-C(6)	1.504(2)
C(4)-C(5)	1.514(2)
C(6)-C(7)	1.491(2)
C(8)-C(9)	1.514(2)
C(9)-C(10)	1.523(2)
C(10)-C(11)	1.516(4)
C(11)-C(12)	1.280(5)
C(11A)-C(12A)	1.341(8)
C(2)-O(1)-C(3)	60.40(10)
C(8)-O(2)-C(5)	111.73(11)
C(2)-C(1)-C(9)	116.87(13)
C(2)-C(1)-C(5)	104.24(12)
C(9)-C(1)-C(5)	103.50(12)
O(1)-C(2)-C(3)	59.92(11)
O(1)-C(2)-C(1)	111.25(13)
C(3)-C(2)-C(1)	109.91(13)
O(1)-C(3)-C(2)	59.68(10)
O(1)-C(3)-C(4)	112.25(14)
C(2)-C(3)-C(4)	109.10(14)
C(3)-C(4)-C(7)	120.83(14)
C(3)-C(4)-C(6)	120.09(14)
C(7)-C(4)-C(6)	59.57(11)

C(3)-C(4)-C(5)	106.77(12)
C(7)-C(4)-C(5)	121.57(14)
C(6)-C(4)-C(5)	122.20(14)
O(2)-C(5)-C(4)	108.79(12)
O(2)-C(5)-C(1)	104.70(11)
C(4)-C(5)-C(1)	107.57(12)
C(7)-C(6)-C(4)	59.98(10)
C(6)-C(7)-C(4)	60.46(11)
O(3)-C(8)-O(2)	121.91(14)
O(3)-C(8)-C(9)	127.39(14)
O(2)-C(8)-C(9)	110.67(13)
C(8)-C(9)-C(10)	112.94(13)
C(8)-C(9)-C(1)	103.43(12)
C(10)-C(9)-C(1)	119.06(14)
C(11)-C(10)-C(9)	109.66(17)
C(12)-C(11)-C(10)	123.2(4)