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The total synthesis of neohalicholactone

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The Total Synthesis of Neohalicholactone.

Submitted by Douglas James Critcher

for the degree of PhD
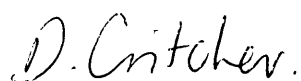
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Dedication.

This thesis is dedicated to my wonderful fiancé,

FIONA S. CUSDIN

My sincerest thanks go to Fiona for all the love, support, and fun

she has provided over the last three years.

Contents.

Acknowledgements.

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Glossary of Terms

Asymmetric	Non Symmetric

Chemoselective

When a functional group is selectively attacked in the presence of a different functional group, then the reaction is said to be *chemoselective*.

Chiral

An object which is not superimposable upon its mirror image.

Chirality

The general property of "Handedness".

R-clockwise   *S*-anticlockwise
Priority;- A>B>C>D. As defined by the Cahn-Ingold-Prelog rules.

Diastereomer

When two compounds are stereoisomers but are not enantiomers. The chemical properties of diastereomers are usually similar but not identical.

Diastereomeric excess

$$\frac{[A]-[B]}{[A]+[B]} \times 100 = \% \text{ d.e.}$$ where A and B are the amounts of individual diastereomers produced.

Diastereotopic

Replacement of an atom or group with a third group (unlike any existing group) gives rise diastereomers.

Enantiomer

When two molecules differ only in the left-and right handedness of their orientations. Enantiomers have identical physical and chemical properties except in two respects: (1) They rotate the plane of polarised light in opposite directions, though in equal amounts. (2) They react at different rates with other chiral compounds.

Enantiomeric excess	$\dfrac{[A]-[B]}{[A]+[B]} \times 100 = \%$ e.e. where A and B are the amounts of individual enantiomers produced.
Enantiotopic	Two atoms or groups that upon replacement with a third group (unlike any existing group) gives rise to an enantiomer.
Epimers	Two diastereomers that have a different configuration at only one chiral centre.
nuclear Overhauser effect	A technique used in ^{1}H-NMR to determine which protons in a molecule are spatially close to one another.
Prochiral	A compound or group that has two enantiotopic atoms or groups, e.g., CX_2WY.
Re-face	The face of a double bond in which the three groups, arranged by the priority rules have the order A>B>C, in a clockwise fashion.
Regioselective	When a reaction can potentially give rise to two or more structural isomers but actually produces only one, the reaction is said to be *regioselective*.
Si-face	The face of a double bond in which the three groups, arranged by the priority rules have the order A>B>C, in an anticlockwise fashion.
Stereoselective	Any reaction in which only one set of stereoisomers is formed exclusively or predominantly.

Abbreviations

Ac.......... acetyl (CH_3CO-)

AcO........ acetoxy (CH_3COO-)

BINAL-H. binaphthol-modified complex aluminium hydride

BMS....... borane-methyl sulfide complex

Bn......... benzyl ($C_6H_5CH_2$-)

B.pt........ boiling point

n-Bu....... normal-butyl ($CH_3[CH_2]_3$-)

t-Bu........ tert-butyl ($[CH_3]_3C$-)

br........... broad

CD......... circular dichroic

CI.......... chemical ionisation

CSA....... camphorsulfonic acid

d............. doublet

DBU....... 1,8-diazobicyclo[5.4.0]-undec-7-ene

DCC....... 1,3-dicyclohexylcarbodimide

DCM....... dichloromethane

DDQ....... 2,3-dichloro-5,6-dicyano-1,4-benzoquinone

d.e......... diastereomeric excess

DIPEA..... diisopropylamine

DIPT....... dissopropyltartrate

DIAB...... (-)-3-exo-(dimethylamino)-isoborneol

DHP   3,4-dihydro-2H-pyran

DMAP.... 4-dimethylaminopyridine

DME...... ethylene glycol dimethyl ether

DMF....... N,N-dimethylformamide

DMSO..... dimethyl sulfoxide

DMSY..... dimethylsulfoxonium methylide

DPMPM... diphenyl(1-methylpyrrolidine-2-yl)methanol

e.e.......... enantiomeric excess

EI.......... electron impact

Et........... ethyl (CH_3CH_2-)

eq.......... equivalents

FAB....... fast atom bombardment

HPLC..... high performance liquid chromatography

hr........... hour(s)

Hz.......... hertz

HMPA..... hexamethylphosphoramide

IR.......... infrared

J............. coupling constant

LDA....... lithium diisopropylamide

M^+........ molecular ion

Me......... methyl (CH_3-)

min......... minute(s)

m.pt........ melting point

MPM...... methylphenylmethyl

MTPA..... α-methoxy-α-(trifluoromethyl)-phenyl acetic acid

m/z........ mass-to-charge ratio

NMO...... N-methylmorpholine-N-oxide

NMR...... nuclear magnetic resonance

N.O.E..... nuclear Overhauser effect

Nu......... nucleophile

p............ *para*

PCC....... pyridinium chlorochromate

Ph.......... phenyl (C6H5-)

Pr.......... propyl (CH3[CH2]2-)

Pyr......... pyridine

q........... quartet

RT......... room temperature

s............ singlet

SN2........ bimolecular nucleophilic
substitution mechanism

t............ triplet

TBAF...... tetrabutylammonium fluoride

TBDPSCl. *tert*-butyldiphenylsilyl chloride

TBS........ *tert*-butyldimethylsilyl

TBHP..... *tert*-butyl hydroperoxide

TFA........ trifluoroacetic acid

TfOH...... trifluoromethanesulfonic acid

THF....... tetrahydrofuran

TLC....... thin layer chromatography

TMS....... trimethylsilyl

TPAP..... tetrapropylammonium
perruthenate

p-TsA...... *para*-toluenesulfonic acid mono-
hydrate (CH3C6H4SO3H.H2O)

Abstract

Both neohalicholactone **1** and halicholactone **2**, related marine metabolites of the sponge *Halichondria okadai* are structurally interesting, weakly active 5-lipoxygenase inhibitiors, and from a biosynthetic standpoint, most intriguing. This thesis describes the total synthesis of **1** and **2**, and the C_{15} epimer of **1, 277**.

The first section of the thesis provides a short review on the ever increasing class of marine natural products that possess both cyclopropane ring and lactone functionality. The possible biosynthetic pathways involved in the generation of compounds belonging to this intriguing structural class are also discussed.

In the second section our total enantioselective syntheses of 8*S*,9*R*,11*R*,12*R*,15*R*- **1** and **2**, and 8*S*,9*R*,11*R*,12*R*,15*S*-**277** are described. The convergent synthesis of **1**, **2**, and **277** involved the initial preparation of a common "right hand fragment," aldehyde **156**. Using chromium(II)/nickel(II) methodology developed independently by Kishi and Takai, we were able to achieve the desired coupling reactions using appropriate "left hand" fragments, *trans*-iodo alkenes. Other coupling procedures, most notably one that involved the use of an enantiomerically pure catalyst to direct the addition, were investigated, but proved to be unsuccessful.

We prepared a sample of C_{15}-epi-neohalicholactone **277** in the latter stages of the project since a disparity between our findings and Professor Gerwick's occurred. He believed that he had isolated a sample of neohalicholactone from a brown algal source (*Laminaria sinclairii*), indentical to that originally discovered from the marine sponge *Halichondria okadai*. Our synthetic work and subsequent extensive characterisation of both **1** and **277** led to the conclusion that Gerwick had most likely isolated C_{15}-epi-neohalicholactone (**277**) from *L. sinclairii*, and that sponge-derived neohalicholactone **1** does not possess antipodal 8*R*,9*S*,11*S*,12*S*,15*S* stereochemistry. The third section contains a formal account of experiments and procedures.

1. Introduction.

1. Introduction.

1.1 Neohalicholactone **1** and Halicholactone **2** from the Marine Sponge *Halichondria okadai* Kadota.

Examination of the constituents of the marine sponge *Halichondria okadai* Kadota, collected of the coast of Japan by the Yamada group, led to the isolation of the fatty acid metabolites neohalicholactone **1** and halicholactone **2**.[1(a)] The structural elucidation of these metabolites was achieved by evaluation of spectral data, coupled with chemical evidence. The absolute stereochemistry at carbon fifteen of halicholactone **2** was shown to be of *R* configuration by chemical degradation of its diacetate **3**. This gave the *R*-diacetate of 1,2-heptanediol **4** as one of the fragments, and the absolute stereochemistry of **4** was confirmed by comparison with authentic material (Scheme 1). In a more recent publication the relative stereochemistry of **1** was established by an X-ray crystallographic study.[1(b)] Since it is likely that a similar biosynthetic pathway yields both **1** and **2** then, in combining the aforementioned stereochemical knowledge, it seems reasonable to speculate that the absolute stereochemistry in both molecules should be 8*S*,9*R*,11*R*,12*R*,15*R* as shown below.

neohalicholactone **1** (R=H, X=*cis*-CH=CH)
halicholactone **2** (R=H, X=CH$_2$CH$_2$)
diacetate **3** (R=Ac, X=CH$_2$CH$_2$)
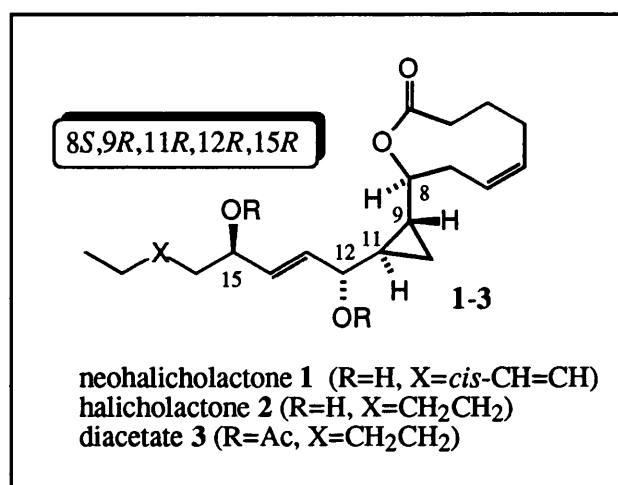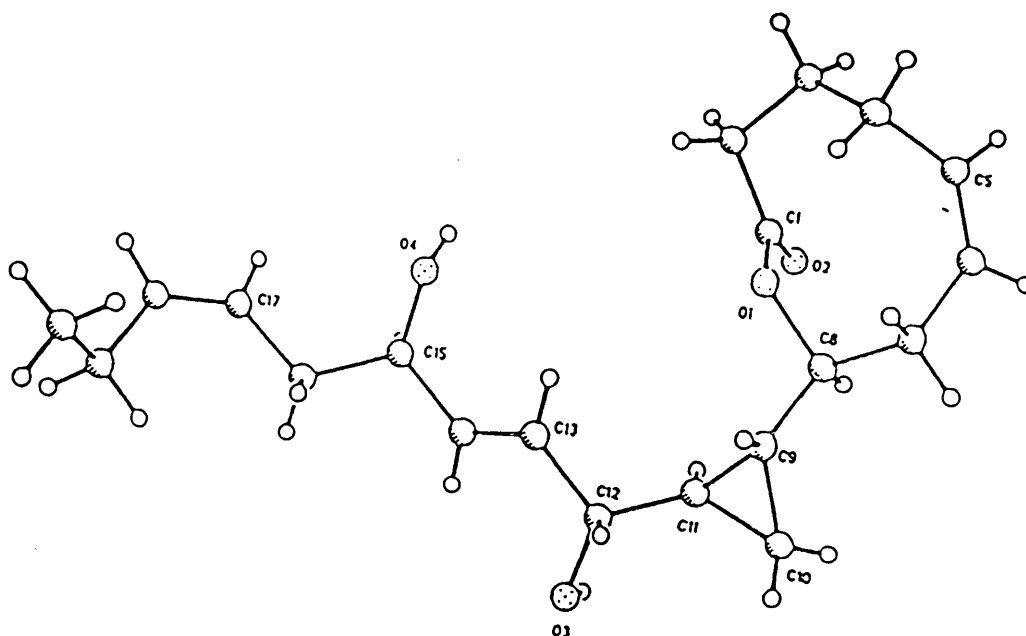
X-ray Crystal Structure of Neohalicholactone **1**

Scheme 1 Chemical Degradation of **3**

(*R*)- diacetate of 1, 2-heptanediol **4**

authentic material; $[\alpha]_D^{15}$ +4.1 (c 0.58, CHCl$_3$)

from chemical degradation; $[\alpha]_D^{17}$ +5.2 (c 0.23, CHCl$_3$)
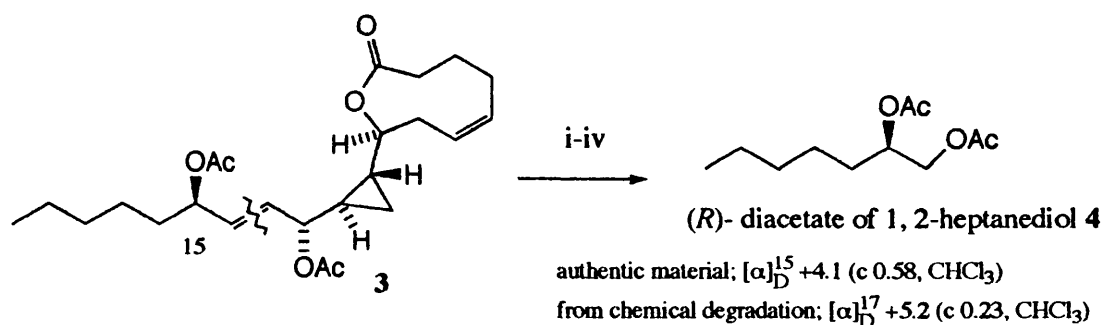
Reagents
i. OsO$_4$, pyridine, THF, ii. NaIO$_4$, EtOH, H$_2$O,
iii. NaBH$_4$, MeOH, iv. Ac$_2$O, pyridine.

As well as presenting a significant challenge to the synthetic chemist, compound **2** has been shown to exhibit inhibitory activity (IC$_{50}$=630μm, against 5-lipoxygenase of guinea pig polymorphonuclear leukocytes). These factors, as well as the necessity to unambiguously confirm the absolute stereochemistry of **1** and **2**, encouraged us to undertake an enantioselective total synthesis of these novel oxylipins. Before describing our results in this area, the target molecules **1** and **2** will be placed in context with similarly derived products of fatty acid metabolism.

1.2   The Discovery of the Marine Prostanoids and Their Biosynthesis.

A fascinating era in the field of marine natural product chemistry began in 1969 with the discovery that the Caribbean soft coral *Pleuxaura homomalla* was a rich source (2-3% net weight) of methyl (15*R*)-acetoxy prostaglandin A_2 5 (the C_{15} hydroxyl is epimeric to that found in mammalian systems).[2]
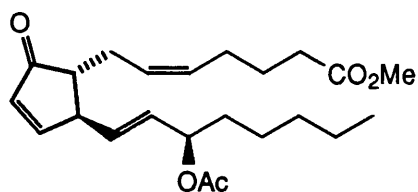
methyl (15*R*)-acetoxy-PGA$_2$ 5

Since this initial discovery prostaglandin $F_2\alpha$ 6 and prostaglandin E_2 7, with identical absolute stereochemistry to the mammalian prostaglandins, have been the most commonly encountered prostanoids from marine algae and invertebrates.[3] In fact as a result of intense investigations of the coral *P. homomalla*, methyl (15*S*)-acetoxy prostaglandin A_2 (identical absolute stereochemistry to that derived from mammalian sources) has also been isolated.[4] Interestingly the propensity of this coral to make 15*R* or 15*S* prostanoids appears to correlate with geographical region, 15*R* from Florida and 15*S* from the Cayman Islands.
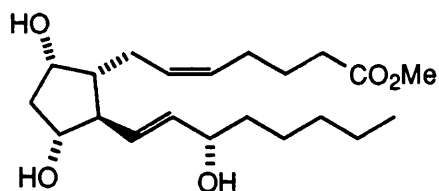
PGF$_2\alpha$ 6
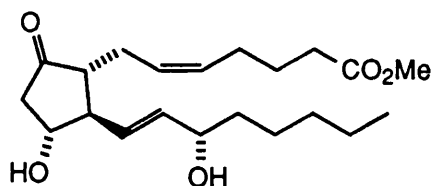
PGE$_2$ 7

All of these prostanoids can be found in mammalian systems where these arachidonic acid derived substances are of fundamental importance in maintaining normal physiological conditions (homeostasis). Clearly it is the relationship of the marine prostanoids to the mammalian substances that has generated such a huge research

interest in this area. In fact since the initial discovery a multitude of related compounds have been isolated from the full spectrum of marine life.[3] There exists an encompassing term for this structural type, (molecules derived from marine organisms as well as higher plants) which utilise 18-carbon fatty acids as well as 20-carbon fatty acids in their biosynthesis, and they are known as oxylipins. These oxidised compounds are formed from fatty acids *via* mechanisms involving at least one step of mono- or dioxygenase- dependant oxidation.[3]

Over the past twenty years numerous investigations into the biosynthesis of these coral prostanoids have been undertaken. This research effort has been led by the Corey group at Harvard and the Brash group at Vanderbilt. In 1975 Corey reported that the biosynthetic pathway to PGA_2 in the coral *P.homomalla* did not involve the endoperoxides PGH_2 **8** and PGG_2 **9**, and hence differed from the mammalian pathway.[5]

OR PGH_2 **8** R=H
      PGG_2 **9** R=OH
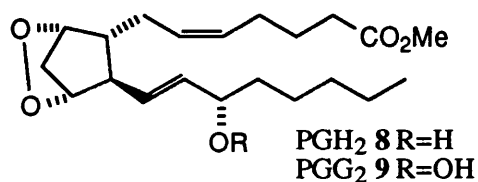
PGH_2 **8** and PGG_2 **9** had been shown to be intermediates in the biosynthesis of prostaglandins from arachidonic acid by the mammalian PGA_2 synthetase from sheep or bull seminal vesicles. However, using preparations of PGA_2 synthetase from the coral *P. homomalla*, no formation of PGA_2 was detected using carbon labelled samples of either **8** or **9** as the incubation substrates. Further, the coral and mammalian prostaglandin synthetases responded very differently to cofactors and inhibitors. For example, the biosynthesis of the prostaglandins in the coral was not markedly inhibited by the presence of either the potent mammalian prostaglandin synthetase inhibitors, indomethactin or aspirin. Corey and co-workers made progress in the field of marine prostanoid biosynthesis by examining the biosynthesis of a novel prostanoid family (exemplified by clavulone I **10**) produced by the Pacific coral *Clavularia virdis*.[6(a), (b)]

clavulone I 10
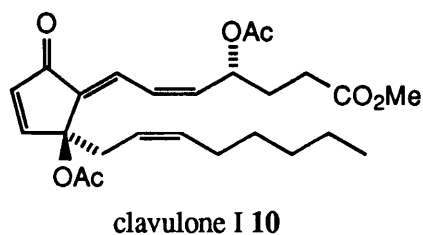
Incubation of arachidonic acid with an acetone powder from *C. virdis* provided a more polar compound, characterised as (8*R*)-hydroxyperoxy-5*Z*,11*Z*,14*Z*,9*E*-eicosatetraenoic acid {(8*R*)-HPETE} 11, in 19% yield. Whilst neither arachidonic acid or (8*R*)-HPETE 11 were converted to any of the clavulones (by an acetone powder or homogenate preparation), when radiolabelled (8*R*)-HPETE 11 was incubated with a *C. virdis* homogenate a new product was obtained in 13% radiochemical yield after diazomethane esterification and HPLC separation. This product was identified as racemic preclavulone A 12.[7(a)-(c)]

(8*R*)-HPETE 11

preclavulone A 12
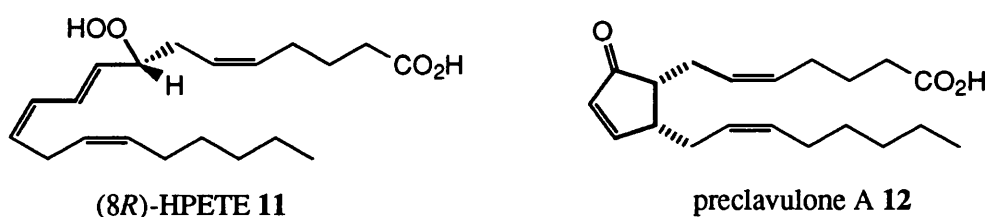
Corey and co-workers went on to demonstrate that homogenate or acetone powders of seven other coral species (*Pleuxaura homomalla*, *Plexaura nina*, *Pseudoplexaura porosa*, *Plexaura flexuosa*, *Pseudopterogorgia americana*, *Muriceopsis flavida* and *Eunicea asperula*) were all able to convert arachidonic acid to (8*R*)-HPETE 11 and preclavulone A 12. These results led Corey to propose the following biosynthesis for preclavulone A 12 (Scheme 2), and to speculate that 12 was a common intermediate in the synthesis of marine prostaglandins.[8(a), (b)] Arachidonic acid is first converted to 11 *via* an (8*R*)-lipoxygenase, which is in turn converted to an allene oxide 13. Pentadienyl cation 14 would then be the likely precursor to 12, formed via pericyclic ring closure. Further conversion to PGA$_2$ requires epimerisation and enzymatic oxidation steps.

Scheme 2

arachidonic acid

PGA$_2$

$(8R)$-HPETE **11**

preclavulone A **12**

Z allene oxide **13**

14
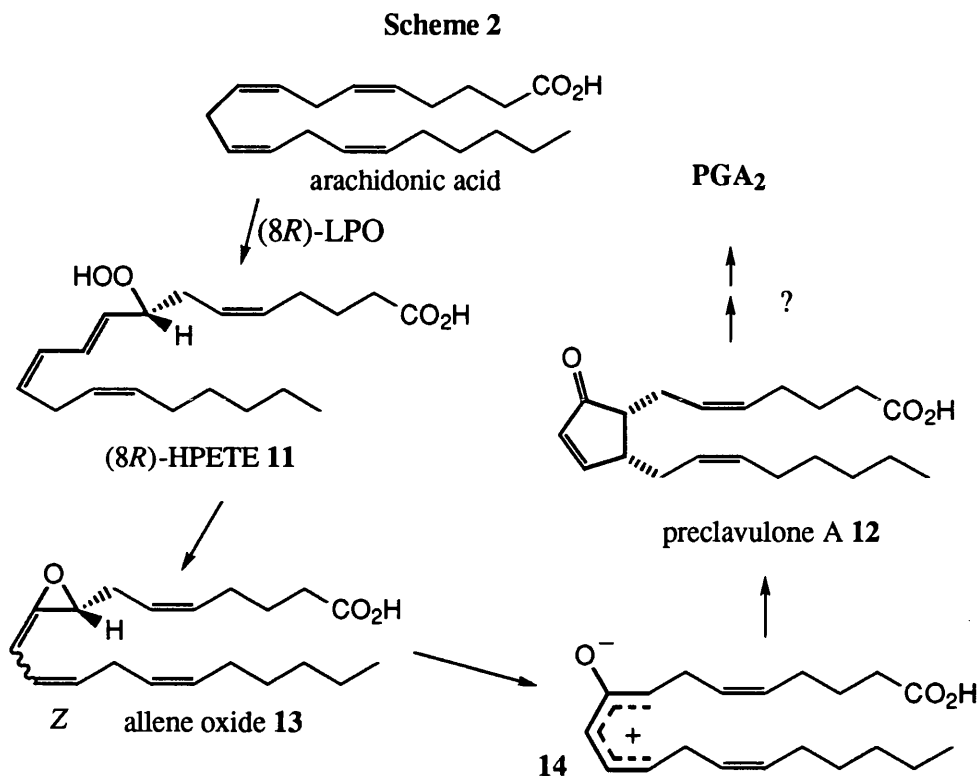
Evidence that supports this proposed biosynthesis are as follows;

(a) Brash and co-workers have isolated and characterised allene oxide **13**.[9] Conversion of $(8R)$-HPETE **11** to **13** was achieved by incubating **11** with an acetone powder of *P. homomalla* using specific conditions.

Scheme 3

preclavulone A **12**

a=cyclisation
b=hydrolysis

Z allene oxide **13**
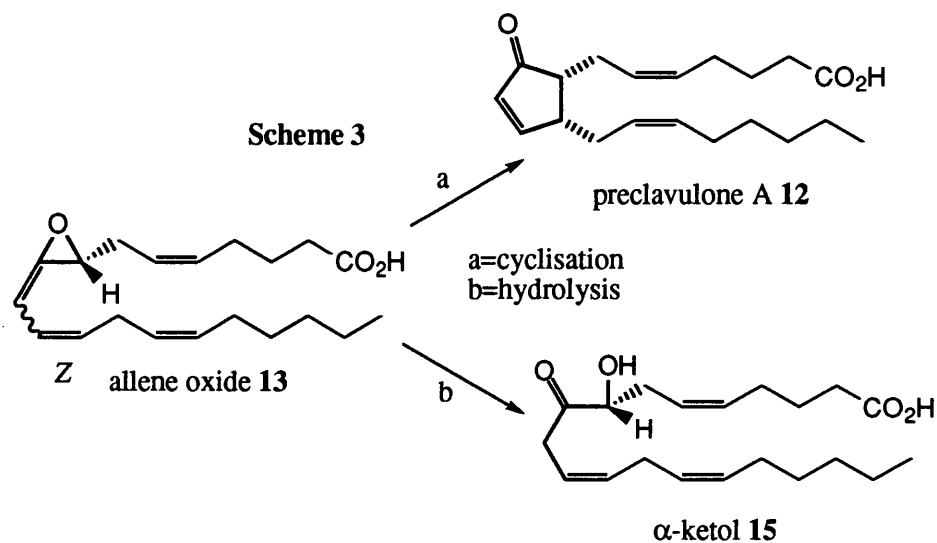
α-ketol **15**

Also, **13** was found to be rapidly cyclised to **12** and hydrolysed to the α-ketol **15** (Scheme 3).

(b)   Allene oxides are known to undergo a facile rearrangement to give cyclopentenones. Cha has shown that allene oxides with *cis*-olefin geometry (it is important to note that allene oxide **13** has, exclusively, a 11-*cis*-double bond) will cyclise to give a cyclopentenone with *cis*-geometry of the side chains. The annulation reaction involves the *in situ* epoxidation of vinyl allene **16** which in turn furnishes cyclopentenone **17** (Scheme 4).[10]

Scheme 4

40-70% yield

Reagent
i. ᵗBuOOH, VO(acac)₂, CH₂Cl₂
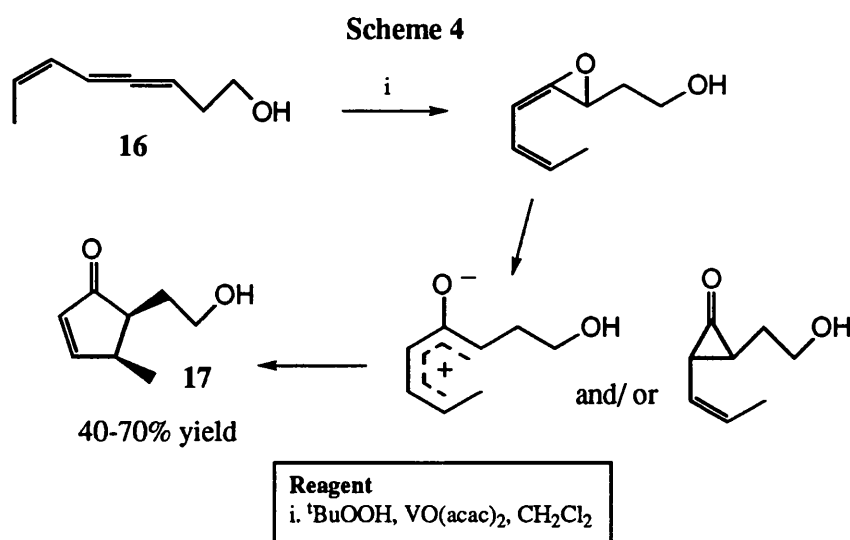
(c)   Preclavulone A **12** has the correct five membered ring and enone structural features.

Reasons to doubt the feasibility of the proposed biosynthesis are as follows;

(a)   The side chains found in preclavulone A **12** do not have the correct *trans*-geometry and the molecule is racemic. It has been suggested however that the enzyme contained in the homogenate could be unable to control the chirality in the oxopentadienyl cation **14** cyclisation due to subtle changes in the tertiary structure of the extracted enzyme to that which exists *in vivo*. [8(b)]

(b)   During the *in vitro* studies prostaglandin end products are not isolated, since all metabolites of these studies have lacked a C_{15} hydroxyl group. Brash and Song have studied the mechanism of introduction of the C_{15}-hydroxyl group in the prostaglandins produced by *P. homomalla*.[11] They have found no evidence of a 15-lipoxygenase in the coral and therefore the origin of the C_{15}-hydroxyl group is

unknown. However, they decided that in their studies they would not eliminate this type of activity (15-lipoxygenase) as a potential step in the biosynthetic pathway, and studied the metabolic fate of exogeneously added 15-hydroxy substrates (Scheme 5).

CO_2H

(15R)-OH **18** OH

Scheme 5

(8R)-LPO

OOH

CO_2H

OH

(8R)-OOH, (15R)-OH **19**

HO O

CO_2H

OH

20

O

CO_2H

OH **22**

O

CO_2H

OH **23**

allene oxide

O

CO_2H

OH

O OH

CO_2H

OH

21

plus 11E-isomer

oxygenation
(14-LPO)

reduction

O OH

CO_2H

major end
products

HO

HO
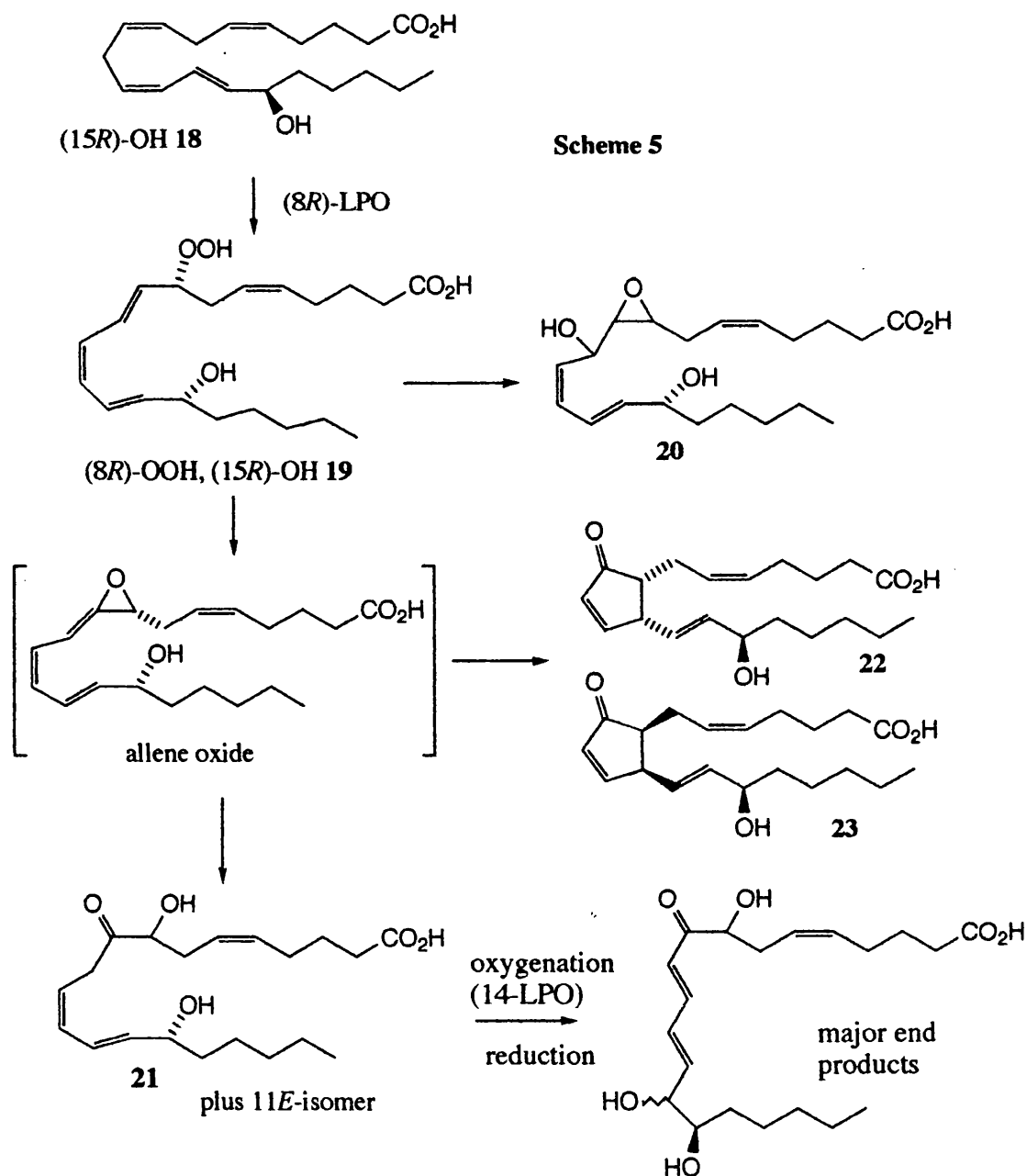
Firstly they found that a (15R)-hydroxy substrate **18** was preferentially metabolised by the coral (8R)-lipoxygenase to give an (8R)-hydroperoxy-15-hydroxy intermediate **19.**. Also they noted that **18** was a poor substrate for (8R)-lipoxygenase when compared to the rate of metabolism of arachidonic acid. Four products, characteristic of the metabolism of **19**, were analysed as epoxy alcohol **20**, hydrolysis product **21** and (15R)-PGA$_2$ isomers **22** and **23** with cis-arrangement of the side chains.

Whilst these results did show that **19** could be converted to a 15-hydroxy allene oxide by the *P. homomalla* allene oxide synthase, beyond this step the pathway led to hydrolysis and cyclisation products (with *cis* arrangements of side chains), **21, 22** and **23** respectively, which were most likely formed non-enzymatically. Therefore the biosynthesis of prostaglandins from corals has remained unresolved.

In fact, quite surprisingly, some recent intriguing results published by Samel and colleagues provided evidence that incubation of arachidonic acid with an acetone powder preparation of the soft coral *Gersemia fruticosa* gave a prostaglandin-endoperoxide which was identified as PGG$_2$ **9**.[12(a), (b)] Arctic soft coral *Gersemia fruticosa* was shown to be able to synthesise optically active PGD$_2$, PGE$_2$ **7**, PGF$_{2\alpha}$ **6** and 15-keto-PGF$_{2\alpha}$ as well as (8*R*)-HPETE **11** and (11*R*)-HPETE from tritiated arachidonic acid *in vitro*. This product pattern as well as the fact that the presence of SnCl$_2$ (as a mild reducing agent) led to the isolation of only PGF$_{2\alpha}$, encouraged this group to assume that a common prostaglandin-endoperoxide intermediate was present. Short incubation times led to the isolation of the PGG$_2$ **9** (identified by chemical and spectral studies). The similar product patterns obtained in the presence of active and heat denatured coral preparations used to convert PGG$_2$ **9** to prostaglandin end products gave evidence for the non-enzymatic character of these conversions. Only the purification of the coral enzyme will answer the question of whether a novel cyclooxygenase enzyme (since no inhibition by indomethacin was observed) is involved in the marine pathway or, alternatively, whether PGG$_2$ is formed *via* a lipoxygenase pathway. Importantly, Corey has recently shown that PGG$_2$ can be formed *via* a 15-peroxy-arachidonate during a successful biomimetic synthesis.[13] Another intriguing question is whether this observed PGG$_2$ intermediacy is in fact common to other corals including *P. homomalla* which produce prostaglandins.

1.3   Cyclopropyl-and Lactone-Containing Oxylipins from Marine Origin.

(a) Hybridalactone

The isolation of hybridalactone **24** from the marine red alga *Laurencia hybrida* (a species of Great Britain) represented the first example of a cyclopropyl and lactone containing oxylipin and was reported by Higgs in 1981.[14] The gross structure of **24** was assigned on the basis of spectroscopic data and the results of chemical degradation studies. In the original report partial assignment of stereochemistry was made based on coupling constants in the ^{1}H-NMR spectrum. These included; relative arrangement of the substituents on the five membered ring; the *cis* relationship of the protons on the cyclopropane ring; and the Z arrangement of the 5,6 and 8,9 double bonds. In a subsequent publication Corey proposed a stereoselective biosynthesis of **24** based on machine conformational analysis and ^{1}H-NMR data.[15] The first step of the biosynthesis of **24** was thought to involve a 12-lipoxygenase reaction with eicosapenteanoic acid to afford the (12S)-hydroperoxide **25**. Cationic oxirane formation and carbo-cyclisation then generates an allyl carbinyl cation **26**. After a 180° rotation (to relieve internal non-bonded repulsions), **26** would enter a cyclopropylcarbinyl to cyclobutyl to cyclopropylcarbinyl cation rearrangement to give **27**. Nucleophilic attack by the carboxylate neutralises the carbocation in **27** and hybridalactone **24** is formed (Scheme 6). Corey then produced two pieces of "hard evidence" to confirm the absolute stereochemistry of **24**, which were in full agreement with the biosynthetic analysis. Firstly a heavy atom labelled crystalline derivative of **24** was prepared. A C_{11}-hydroxy, C_{12}-bromide derivative of **24** was synthesised by firstly reacting **24** with dry hydrogen bromide. The bromohydrin intermediate was then hydrogenated to afford the saturated lactone bromohydrin **28**, and the X-ray crystallographic structure of **28** was determined (Scheme 7). Secondly an enantioselective synthesis of **24** was performed where natural and synthetically produced materials showed identical spectroscopic and chirotopical features (see section 1.4 for this synthesis).[16]

Scheme 6

Biosynthesis of Hybridalactone **24**

eicosapentaenoic acid

(12S)-LPO

25

26

180°

rotation

27

carbocation
rearrangements

lactonisation

24

X-ray Crystal Structure of **28**

Scheme 7

Reagents
i. HBr, CH$_2$Cl$_2$, 0°C
ii. H$_2$ (1 atm) Pd-C catalyst, EtOAc
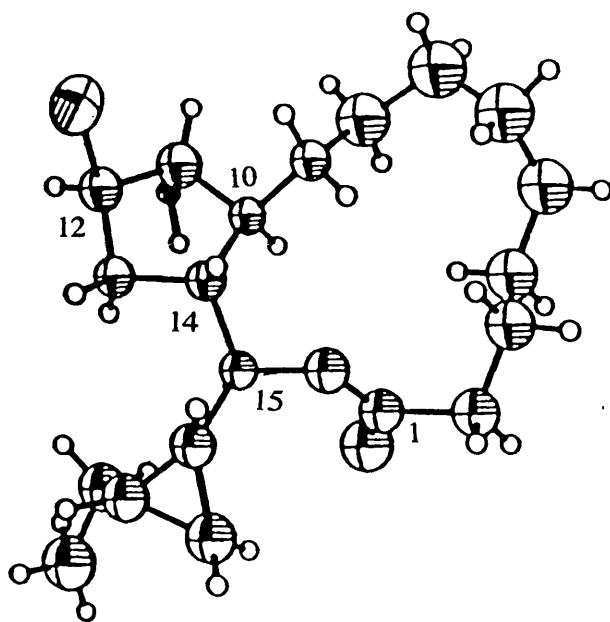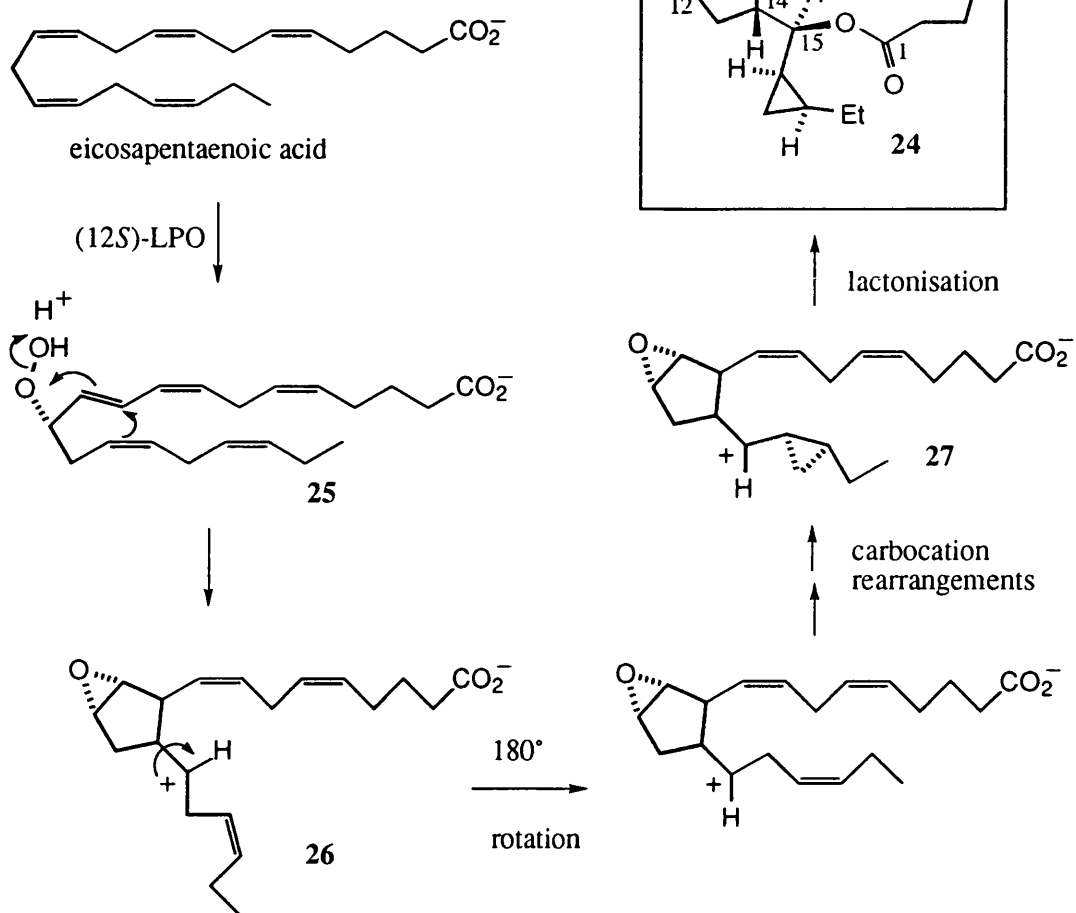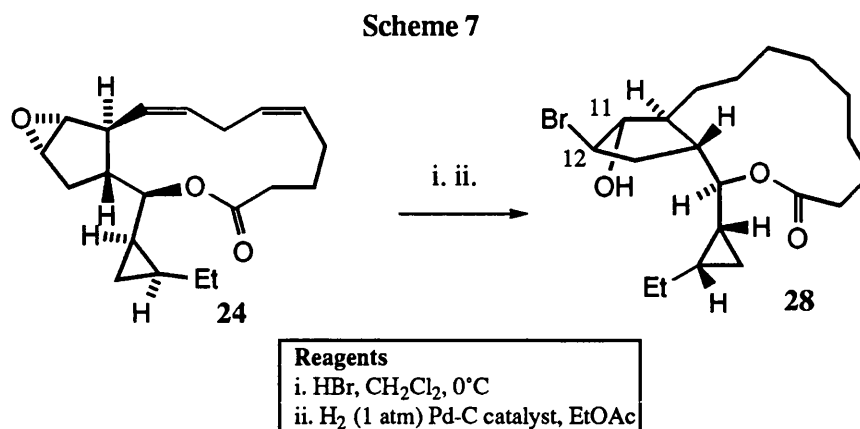
(b) Formation of a Cyclopropyl-Oxylipin from the Coral *Plexaura homomalla*.

The first monocarbocyclic cyclopropyl and lactone containing oxylipin was discovered as a result of studying the mechanism of prostaglandin biosynthesis by the soft coral *Plexaura homomalla*.[17] Brash and co-workers carefully examined the products of incubation of arachidonic acid incubation with an acetone powder of the coral. As well as observing well characterised compounds, such as (8R)-HPETE **11**, α-ketol **28**, preclavulone A **12** and γ-ketol **29**, a new unexpected compound **30** was isolated in low yield (Scheme 8). The structure of this new oxylipin (**30**) was assembled by spectroscopic analysis of **30** and the lactone **31**, and by chemical reactions. The geometry of the 10,11 and 14,15 double bonds were assigned E and Z respectively and cyclopropane ring substituents were *trans*. The circular dichroism spectrum was featureless suggesting that **30** was racemic. Interestingly it was shown that **30** was formed from allene oxide **13** and, whilst its production was non-enzymatic, a constituent of the coral was crucial for its formation (perhaps some inorganic material is critical).

Scheme 8

(8*R*)-HPETE **11**

allene oxide **13**

preclavulone A **12**

α-ketol **28**

new compound **30**

Lactonizes
on standing
in CDCl₃ or
mineral acid

γ-ketol **29**

5S*, 6R*, 8R*

* =relative stereochemistry

31
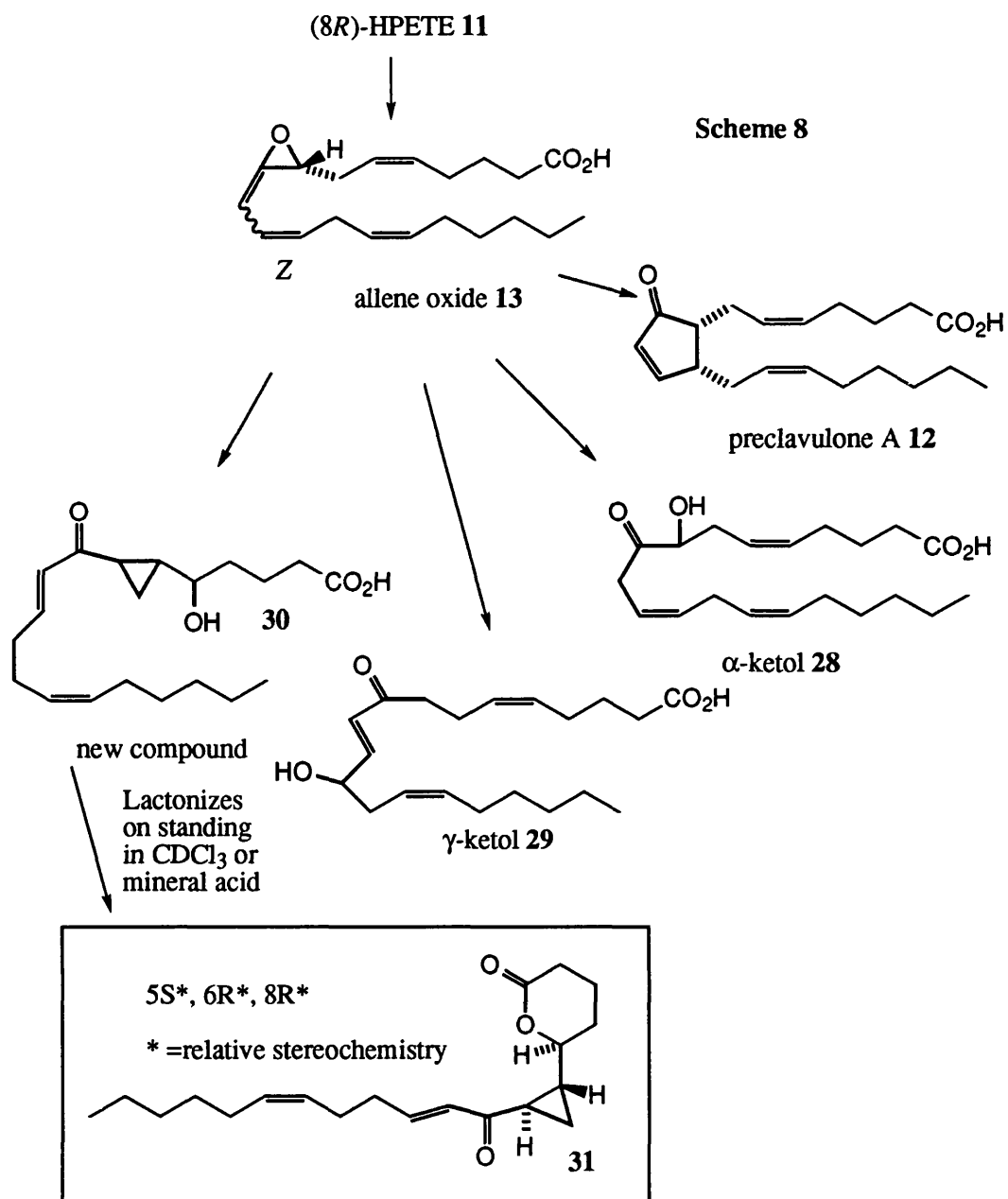
The further significance of this work was that it suggested a mechanism for the formation of 3-15% of the 5,6 *trans*-double bond isomer of PGA₂ from *P. homomalla*.

Arachidonic Acid ——??——▶
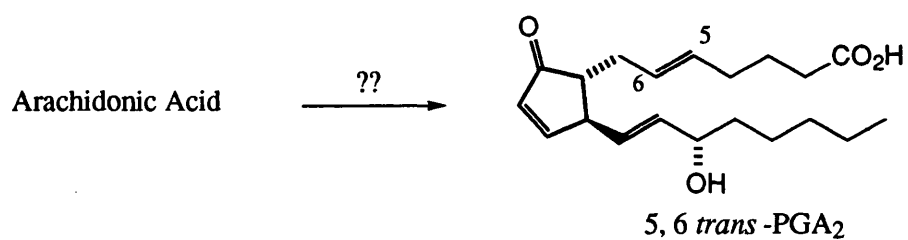
5, 6 *trans* -PGA₂

Since no 5,6 *trans*-arachidonic acid has been found in the coral, Brash proposed that 5,6 *cis*-arachidonic acid could give 5,6 *trans*-PGA$_2$ if the isomerisation sequence shown in Scheme 9 was to occur.

Scheme 9

allene oxide **13**

cyclisation
5, 6 *cis*-prostanoids

H$_2$O
30

cyclisation
5, 6 *trans*-prostanoids
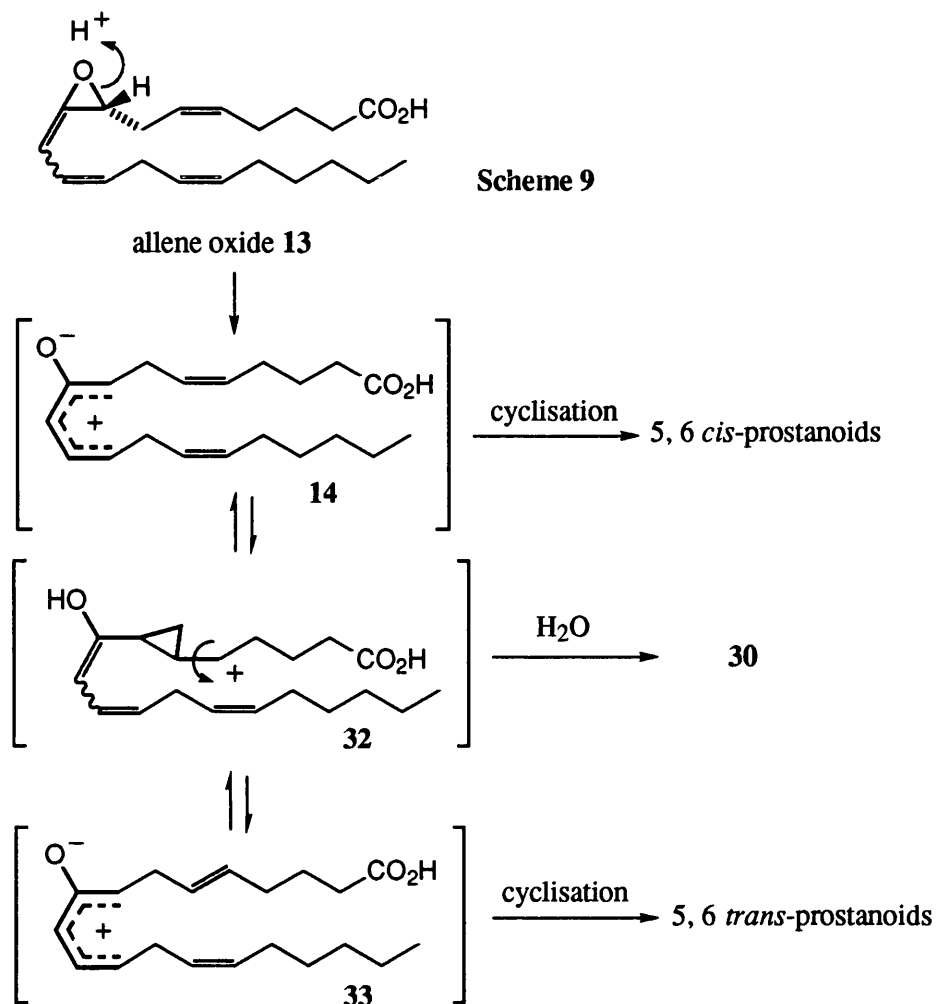
If the lifetime of the carbocation in **32** was sufficient then rotation about the 5,6 bond could occur and a 5,6-*trans* double bond **33** would arise by ring opening of the cyclopropane. Recently a biomimetic synthesis of **31** was achieved by White, and this confirmed the relative configuration to be as shown in Scheme 8 (see section 1.4 for the synthesis of **31**).[18(a)]

(c) Constanolactones.

Gerwick and Nagle reported the isolation of cyclopropyl- lactones constanolactone A **34** and constanolactone B **35** as major products (3-4% of extractable lipids) from the temperate red alga *Constantinea simplex* in 1990.[19(a)]
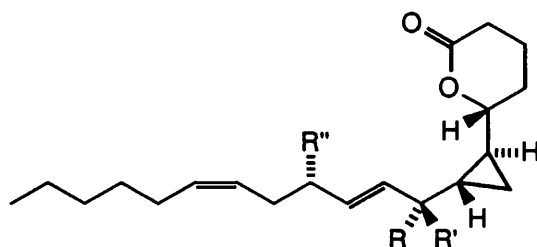
constanolactone A **34** (R=H, R'=R"=OH)
5*R*, 6*S*, 8*S*, 9*S*, 12*S*
constanolactone B **35** (R=R"=OH, R'=H)
5*R*, 6*S*, 8*S*, 9*R*, 12*S*

The original report describes the isolation of six oxylipin natural products from a crude lipid extract of *C. simplex*. One chromatographic fraction was derivatised with diazomethane and minor amounts of well characterised oxylipins, (12*S*)-HETE, (12*S*)-HEPE and 12-oxo-5*Z*,8*E*,10*E*, dodecatrienoic acid were all isolated as their methyl ester derivatives **36-38**.
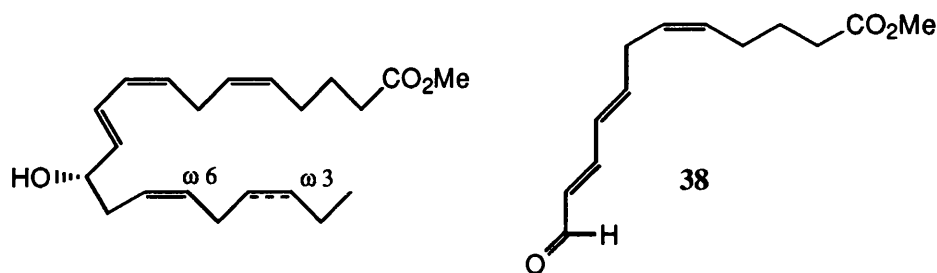
methyl ester of (12*S*)-HETE (ω 6) **36**
methyl ester of (12*S*)-HEPE (ω 3) **37**

Importantly, compounds **36-38** obviously provide strong evidence for an active (12*S*)-lipoxygenase system in this algae. In a different chromatography fraction which was treated with acetic anhydride and diazomethane three novel oxylipins were isolated: constanolactone A diacetate **39**, constanolactone B diacetate **40** and the hydrolysis product of **39** and **40**, **41** which is thought to be formed during the work-

up procedure of the acetylation reaction. These compounds (**39-41**) were characterised by spectroscopic information, principally proton and carbon magnetic resonance spectra, and the structures of the parent products **34** and **35** were then inferred.
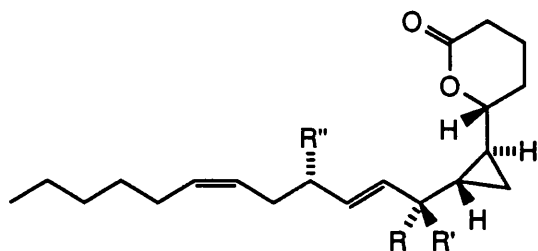
constanolactone A diacetate **39** (R=H, R'=R''=OAc)
constanolactone B diacetate **40** (R=R''=OAc, R=H)
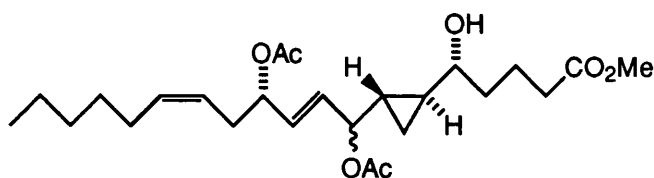
hydrolysis product **41**
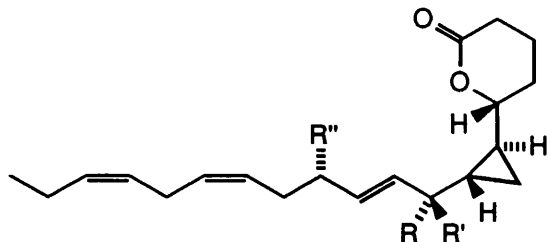
constanolactone C (ω3) **42** (R=H, R'=R''=OH)
5*R*, 6*S*, 8*S*, 9*S*, 12*S*
constanolactone D (ω3) **43** (R=R''=OH, R'=H)
5*R*, 6*S*, 8*S*, 9*R*, 12*S*
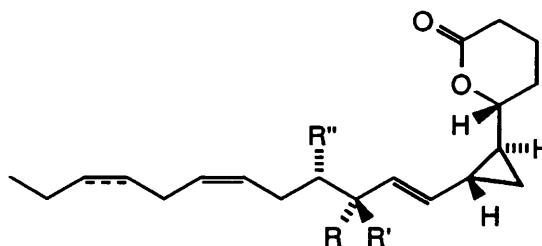
constanolactone E **44** (R=R''=OH, R'=H)
5*R**, 6*S**, 8*S**, 11*R*, 12*S*
constanolactone F **45** (R=H, R'=R''=OH)
5*R**, 6*S**, 8*S**, 11*S*, 12*S*
constanolactone G (ω3) **46** (R=H, R'=R''=OH)

* only relative stereochemistry known

In a more recent publication by Gerwick, the isolation of several more constanolactones **42-46** from *Constantinea simplex* was reported.[19(b)] Gerwick also reported the elucidation of the absolute stereochemistry of A-D (**34, 35, 42** and **43** respectively), as well as the C_{11} and C_{12} absolute stereochemistry of E and F (**44** and **45**) in this publication. Essentially three techniques were used to determine the absolute stereochemistry in the series. Degradative studies yielded enantiomerically

pure dimethyl (-)-menthoxy carbonyl malates, which were compared with the two dimethyl menthoxy carbonyl standards by proton magnetic resonance and gas chromatography techniques. This study clearly revealed the presence of C_{12}-(S) stereochemistry for constanolactones A-D (**34, 35, 42** and **43**). N.O.E profiles and coupling constants in the proton NMR spectra established the relative stereochemistry of C_5-C_9. Finally circular dichroic (CD) analysis of mono-or bis p-bromobenzoate derivatives of the constanolactones established the absolute configurations to be as shown. Also, the total asymmetric synthesis of constanolactones A and B (**34** and **35**) has recently been achieved (see section 1.4 (b)) and the absolute stereochemistry of these marine metabolites was in full agreement with Gerwick's analysis.[18(b)] A general biosynthetic pathway to all constanolactones A-G has been postulated. The first step involves the formation of (12S) HPETE (or (12S) HPEPE **25**). There is evidence that the next intermediate would be hepoxilin B$_3$ **47** (10-hydroxy-11,12 *trans*-epoxy-5Z,8Z,14Z-eicosatrienoic acid) which interestingly is a mammalian insulin release modulator. Hepoxilin B$_3$ **47** has been found in two plants, the tropical red marine algae *Platysiphonia miniata* and *Cottoniella filamentosa*.[19(c)] As well as the isolation of (12S)-HETE **48** as its synthetic derivative **49**, Hepoxilin B$_3$ **47** again as a synthetic derivative **50** was isolated.

(12S)-HETE **48** (R=R'=H)
49 (R'=COCH$_3$, R=CH$_3$)

hepoxilin **47** (R=R'=H)
50 (R'=COCH$_3$, R=CH$_3$)
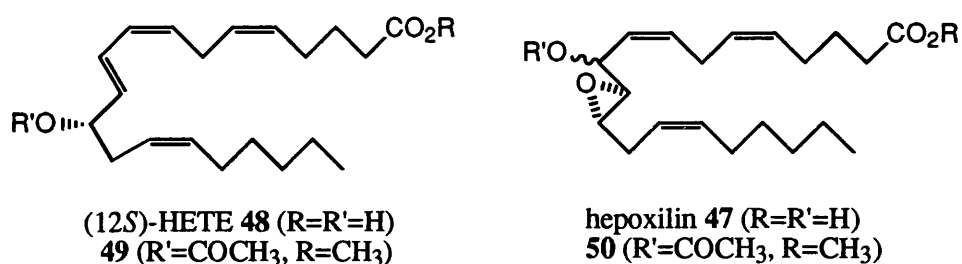
The generation of an epoxy cation **51** from **47** is thought to provide the driving force for the tandem, stereocontrolled, cyclisation to the α,β-unsaturated epoxide intermediate **52**. This is the likely end of the enzymatic pathway since constanolactones A and B (**34** and **35**) and C and D (**39** and **40**) were isolated as epimers at C-9, whilst constanolactones E **44** and F **45** are epimers at C-11. Therefore nonenzymatic 1,2 or 1,4 hydrolysis of α,β-unsaturated epoxide **52** yields the series of constanolactones A-G (**34, 35, 42, 43, 44, 45**, and **46**, (Scheme 10).

Scheme 10

arachidonic acid (ω6)
eicosapentaenoic acid (ω3)

(12S)-HPETE
(12S)-HPEPE 25

hepoxilin B₃ 47
hepoxilin B₄

-H₂O

51

cyclization

α,β-unsaturated epoxide 52

b
addition at C₁₁

H₂O   H₂O

a
addition at C₉

| constanolactones E-G 44, 45 and 46 | constanolactones A-D 34, 35, 42 and 43 |
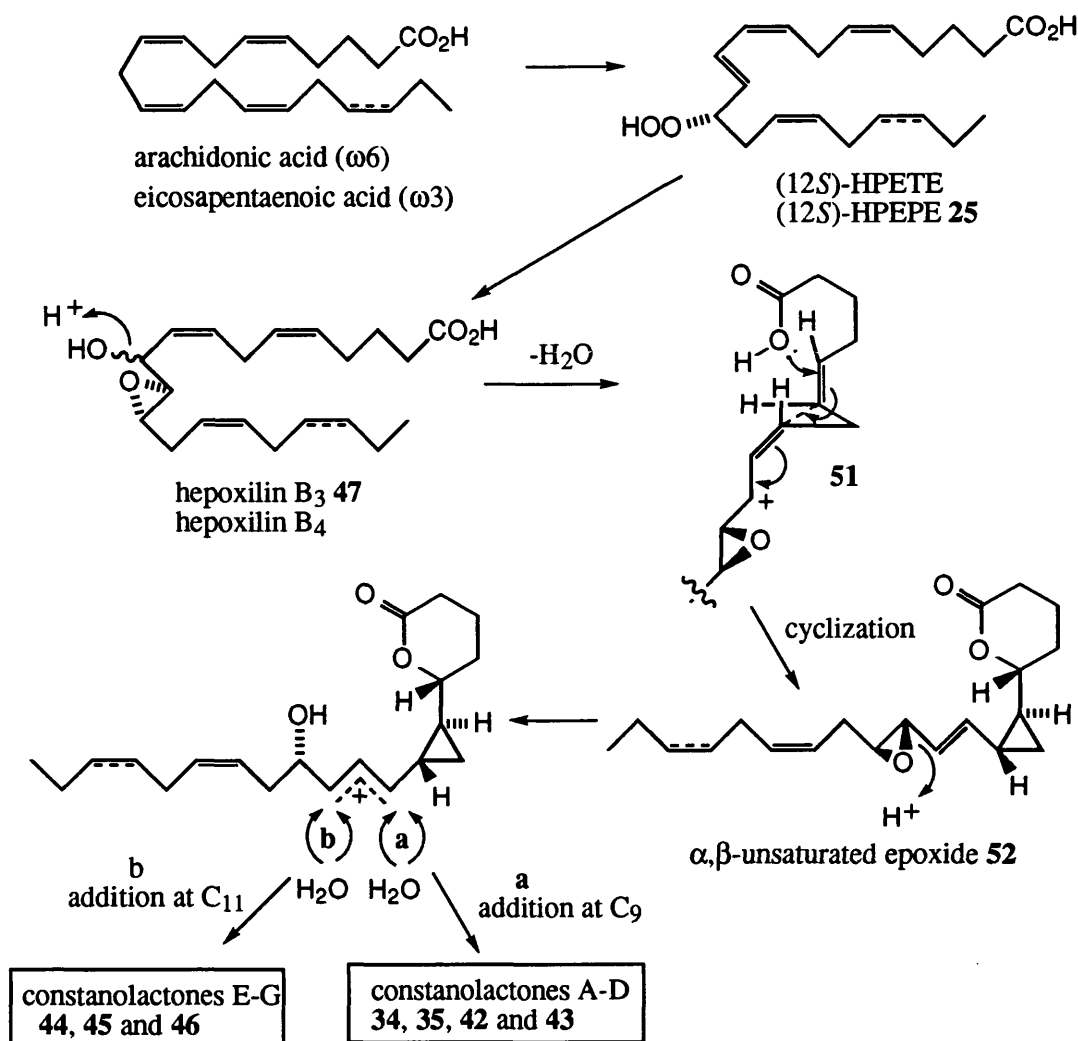
Finally it appears quite remarkable that the structurally related compounds, constanolactone A 34 and B 35 (from the red alga *Constantinea simplex*) and the cyclopropyl oxylipin 31 (from the coral *Plexaura homomalla*) are metabolites of arachidonic acid from varied marine life which have utilised completely different biosynthetic pathways.

(d) Aplydilactone from the Marine Mollusc *Aplysia Kurodai*.

Aplydilactone 53 is unique among the oxylipin natural products since it is dimeric. It was isolated by the Yamada group during their studies to find biologically significant marine natural products.[20] Aplydilactone 53 possesses weak phospholipase A2

activating activity (2-fold at 50mM). The structure was assigned from spectroscopic analysis of the full structure **53** and the partial structures **54-56** (Scheme 11).

Scheme 11

Reagents
i. H_2, PtO_2, ii. Ac_2O, pyr.
iii. OsO_4, pyr, THF, iv. $NaIO_4$,
EtOH, H_2O
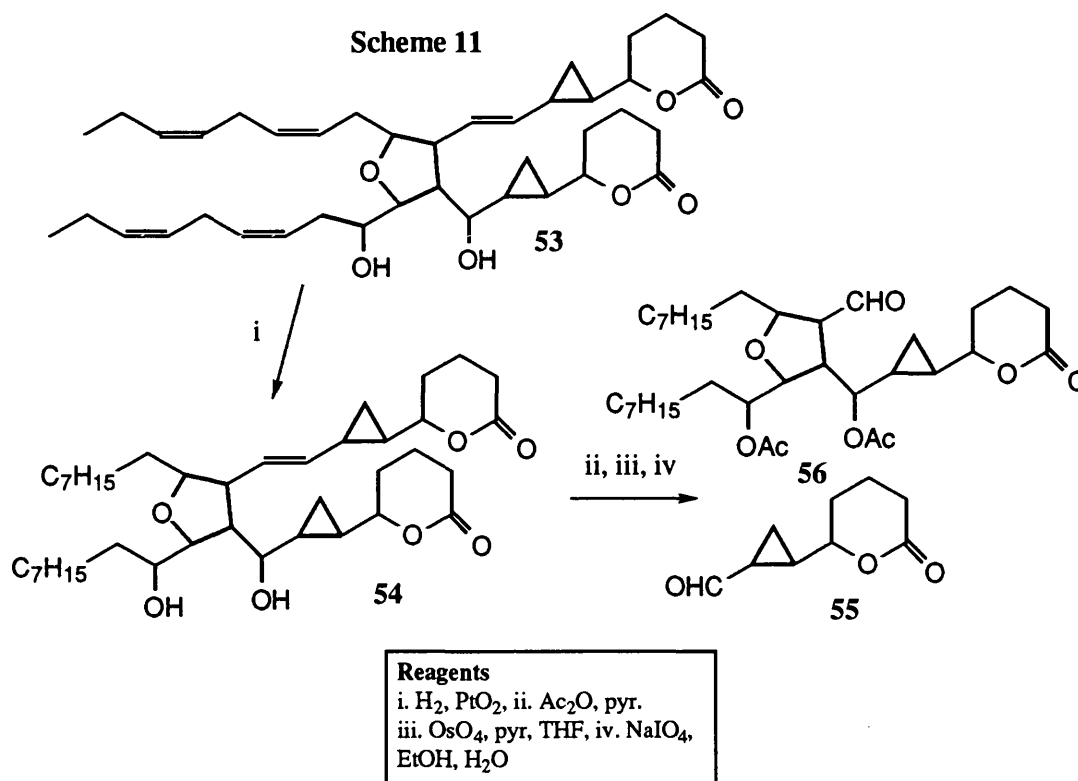
The biosynthesis of **53** is thought to occur by the dimerisation of two constanolactone C and/ or D monomeric units. The mechanism (shown in Scheme 12) involves an acid catalysed dehydration to give **53** as an unsymmetrical dimerisation product. The constanolactone C and/or D fragments probably originate from an algal source and since the sea hare *Aplysia kurodai* is known to assimilate and sequester the unique secondary metabolites of its algal diet (possibly as a way of enhancing their own defence against predation), **53** could conceivably be synthesised by a nonenzymatic process in the digestive gland of the sea hare.

Scheme 12

constanolactone C and/or D (**39** + **40**)
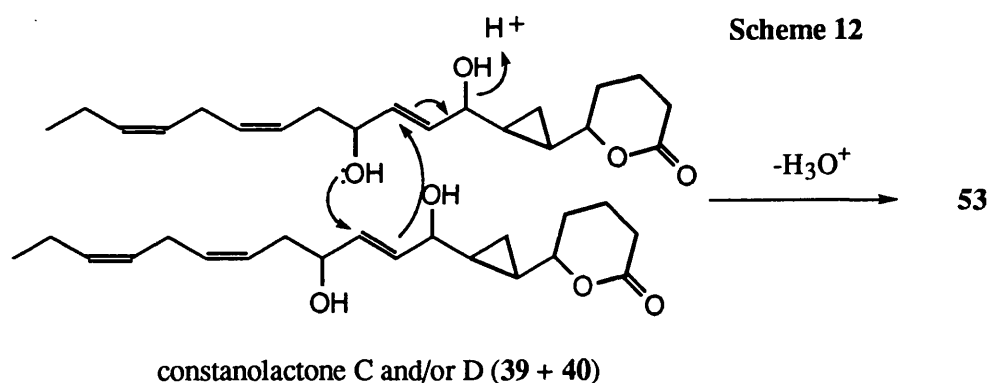
(e) A Proposed Biosynthesis for Neohalicholactone **1** and Halicholactone **2**.

The biosynthesis of **1** (from eicosapentaenoic acid) and **2** (from arachidonic acid) in the marine sponge *Halichondria okadai* is initiated by a (15*R*)-lipoxygenase (since the absolute stereochemistry at C_{15} in **2** was assigned as *R* and we are assuming that a common biosynthetic pathway is operating to give both **1** and **2**) to give (15*R*)-hydroperoxide **57**. In an analogous fashion to the proposed biosynthesis of the constanolactones, the next step involves rearrangement of **57** to give an epoxycation **58** which then cyclises with enzymatic control to the α,β-unsaturated epoxide **59**. 1,4 addition of water to **59** would then give the natural products **1** and **2** (Scheme 13).

Scheme 13
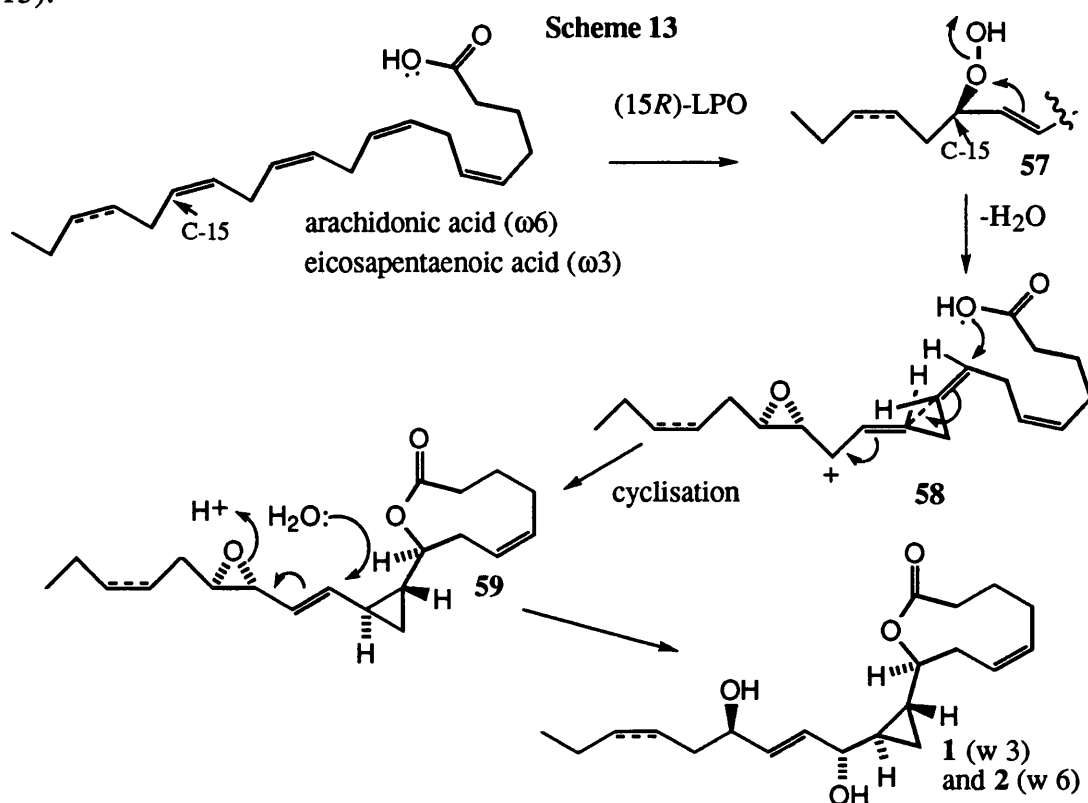
Whilst the relative stereochemistry at C_8, C_9, C_{11}, and C_{15} in **1** and **2** is the same as the corresponding C_5, C_6, C_8, and C_{12} chiral centres of the constanolactones, the absolute stereochemistry is in fact believed to be opposite. Also, no epimeric compounds at C_{12} of **1** or **2** have been reported from the *Halichondria okadai* source which is in contrast to the corresponding C_9 epimeric constanolactones where vicinal

diol functionality has also been reported in constanolactones E-G (**44-46**). This suggests that there are possibly more neohalicholactone **1** and halicholactone **2** derivatives to be isolated, or that the 1,4 addition of water to the α,β-unsaturated epoxide **59** is in fact a controlled enzymatic process.

The structural class of "cyclopropane-and-lactone containing oxylipins from marine origin", is a growing one. In fact it has been speculated that this new theme of oxylipin metabolism, with broad distribution, could mean that this structural class have important functions, and that in the future they may be isolated from more complex life forms.[19(b)]

1.4   Synthetic Approaches to Hybridalactone **24**, Monocarbocyclic Lactone and Cyclopropane Containing Oxylipin **31**, and Constanolactones A and B (**34** and **35**).

(a) Synthesis of Hybridalactone **24**.[16]

Corey and co-workers published their total synthesis of enantiomerically pure hybridalactone **24** in 1983. The synthesis was vital if their biosynthetic surmise (see 1.3 (a)) was to be fully substantiated. The two key starting materials, Z β-tosyloxy enone **60**, and (1R)-(tributylstannyl)-(2S)-ethylcyclopropane **61** were reacted to give **63** as a single product (Scheme 14).

<div align="center">Scheme 14</div>

Reagents
i. 2.0 eq. nBuLi, 0°C, THF, 3hr;
ii. Add^n of **62** to **60**, -78°C, 1 hr, 76%.

67

Scheme 15

OTs

Et

H OH H

63

i

H

O

64 Et

H

ii

H

OH

H

65 Et

H

iii

O

H

OTBDMS

H

66 Et

H

O

H

OTBDMS

O O

68

iv

O

H

OTBDMS

O O

69

v

vi

O

H

OH

Et

70

CO_2H

vii

O

H

O

O

Et **24**

Reagents

i. (a) (n-Bu)$_4$NF, THF/H$_2$O, (b) K$_2$CO$_3$, MeOH, 78%;
ii. L. selectride, THF, -78°C, 92%; iii. (a) VO(acac)$_2$,
t-BOOH, CH$_2$Cl$_2$, 87%, (b) TBDMSOTf, 2, 6-lutidine,
CH$_2$Cl$_2$, -40°C, 97%; iv. n-BuLi, THF, CuCN, THF/HMPA
then **67**, 86%, v. H$_2$, Pd-CaCO$_3$, Py, EtOAc, 92%;
vi. (a) (n-Bu)$_4$NF, THF, (b) PDC, 4Å mol. sieves, MgSO$_4$,
CH$_2$Cl$_2$, (c) L-selectride, THF, -45°C, 75% overall, (d)
NaHSO$_4$, DME, LiOH, H$_3$O$^+$, 96%, vii. bis(4-t-butyl-N-
isopropylimidazol-2-yl) disulfide-triphenylphosphine, toluene,
0°C then reflux, 83%.

Cyclopropyl carbinol **63** then underwent a fragmentation reaction using tetra-n-butylammonium fluoride to give acetylene **64**, after isomerisation to the more stable *trans* compound. The ketone functionality of **64** was reduced using L-selectride to give predominantly the wrong stereochemistry (R) at the carbinol centre. The mixture of diastereomers **65** were used in further steps without separation. Selective α-face

epoxidation was accomplished in high yield, followed by *tert*-butyldimethylsilyl protection of the hydroxyl group to give **66**. Terminal acetylene **66** was then lithiated, converted to the Gilman reagent and coupled to the allene oxabicyclo[2,2,2]octyl ortho ester **67** to produce **68** in excellent yield. Hydrogenation using Lindlar conditions converted the bis-acetylene compound **68** to the corresponding exclusively Z bis-alkene **69**. Inversion at C_{15} to give the required S configuration was achieved by deprotection, oxidation and then reduction steps. The ortho ester was then converted to the acid **70** using standard conditions. Lactonisation of hydroxy acid **70** by reaction with bis(4-*t*-butyl-N-isopropylimidazol-2-yl) disulfide and triphenylphosphine gave hybridalactone **24** which was indistinguishable from native **24** obtained by extraction of *L. hybrida* (Scheme 15).

(b)   A Biomimetic Approach to the Synthesis of the Monocarbocyclic Lactone and Cyclopropane Containing Oxylipin **31**, and Constanolactone A **34** and B **35**.

White and co-workers first employed their biomimetic strategy to the synthesis of **31**.[18(a)] This strategy was subsequently applied to the synthesis of constanolactones A and B (**34** and **35**).[18(b)] The biosynthesis of **31** is thought to involve epoxide ring opening of allene oxide **13** (of known 8(R) absolute stereochemistry[9]) which triggers carbocyclisation to a cyclopropyl carbinyl cation **32**. Trapping of the cation with the terminal carboxylic acid group would then yield **31** (see Scheme 8 and 9 in 1.3 (b)). The biomimetic strategy to **31** required the initial synthesis of the cyclisation precursors Z-alkene **71** and E-alkene **72**, whilst the respective antipodal alkenes **71'** and **72'** were required for the synthesis of **34** and **35**. These goals were achieved starting from methyl 5-hexynoate employing vinyl stannane and palladium-catalysed transformations, followed by Katsuki-Sharpless epoxidation (using (S)-(-)-diethyl tartrate for the epoxidation to give **71** and **72**, whilst (R)-(+)-diisopropyl tartrate gave **71'** and **72'**, see Scheme 16). The key cyclisation step was accomplished using a solution of stannic chloride in nitromethane (Scheme 17). Interestingly, both the Z-alkene **71** and E-alkene **72** gave identical results where the same 1.5:1 mixture of

isomers (73 and 74) were formed in each case in moderate yield. These isomers were then converted to their respective α-hydroxy ketones (73a and 74a) which were separable by radial chromatography. Analysis of these derivatives using both one and two-dimensional ^{1}H-NMR enabled the relative configuration, and hence absolute stereochemistry, since the C_8 configuration was known to be R (opening of the epoxides 71 and 72 was assumed to occur with inversion), to be assigned as $6R,8R,9S$. However, the configuration at C_5 of 73a and 74a could not be ascertained from the ^{1}H-NMR data and therefore X-ray crystal structures were required. Cyclopropane and lactone containing diols 73 and 74 were subjected to oxidative cleavage conditions and the resulting aldehydes were converted to crystalline (2,4-dinitrophenyl)hydrozones 75 and 76. Only 76 afforded crystals that were suitable for X-ray analysis, and the C_5 configuration of 76 was determined as R.

Scheme 16

Reagents
i. n-Bu$_3$SnH, AIBN, 65°C, 85%; ii. butadiene monoepoxide, PdCl$_2$(MeCN)$_2$, DMF-H$_2$O, 93%; iii. ^{t}BuOOH, Ti(O^{i}Pr)$_4$,(-)-diethyl tartrate (to give 71 and 72), or (+)-disopropyl tartrate (to give 71' and 72'), CH$_2$Cl$_2$, 91%, iv. LiOH-H$_2$O, 1.5 hr, 0°C, 99%.
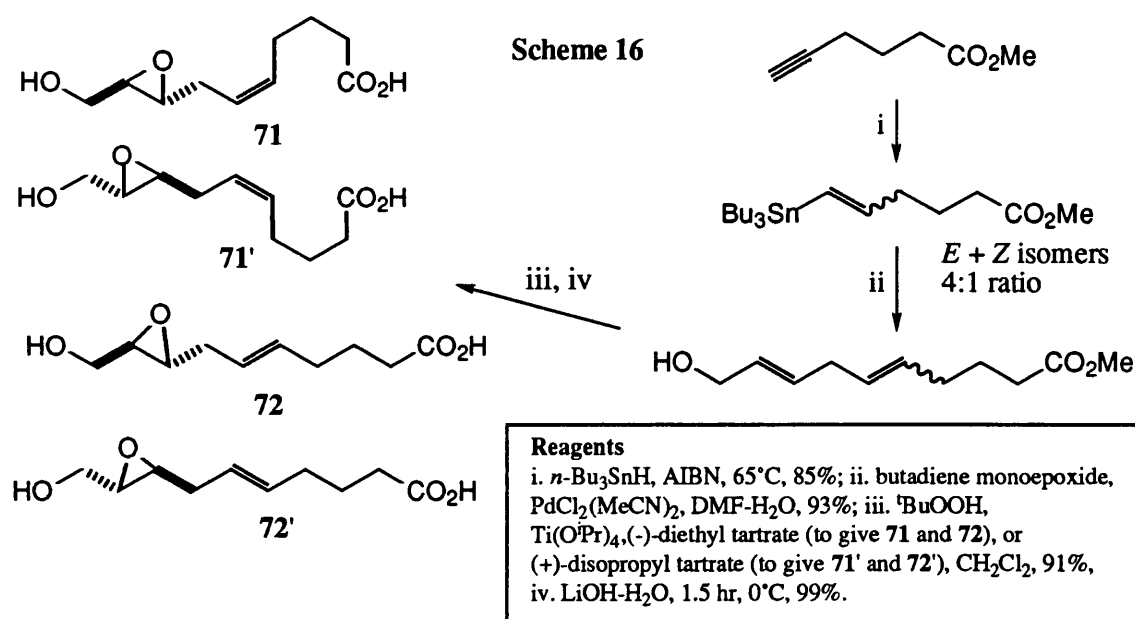
Ozonolysis of 75 returned pure aldehyde 77 whilst a series of reactions antipodal to those described to synthesise 77 gave 77' (required in the synthesis of 34 and 35). Aldehyde 77 was coupled with (1E,5Z)-1-iodo-undecene 79 (which was derived from Z-dec-4-enal 78), using the procedure reported by Takai and Kishi.[22] A 1:1 epimeric mixture of alcohols 80 resulted, which were oxidised to give 31 whose

spectral properties were identical to the authentic material, confirming the relative

stereochemistry as 5S,6R,8R (Scheme 18, part (a)).

Scheme 17

Ar= 2,4-dinitrophenyl

separated by medium-
pressure liquid chromatography

separated by radial chromatography

Also **71'** and **72'**

steps i-iii
then v
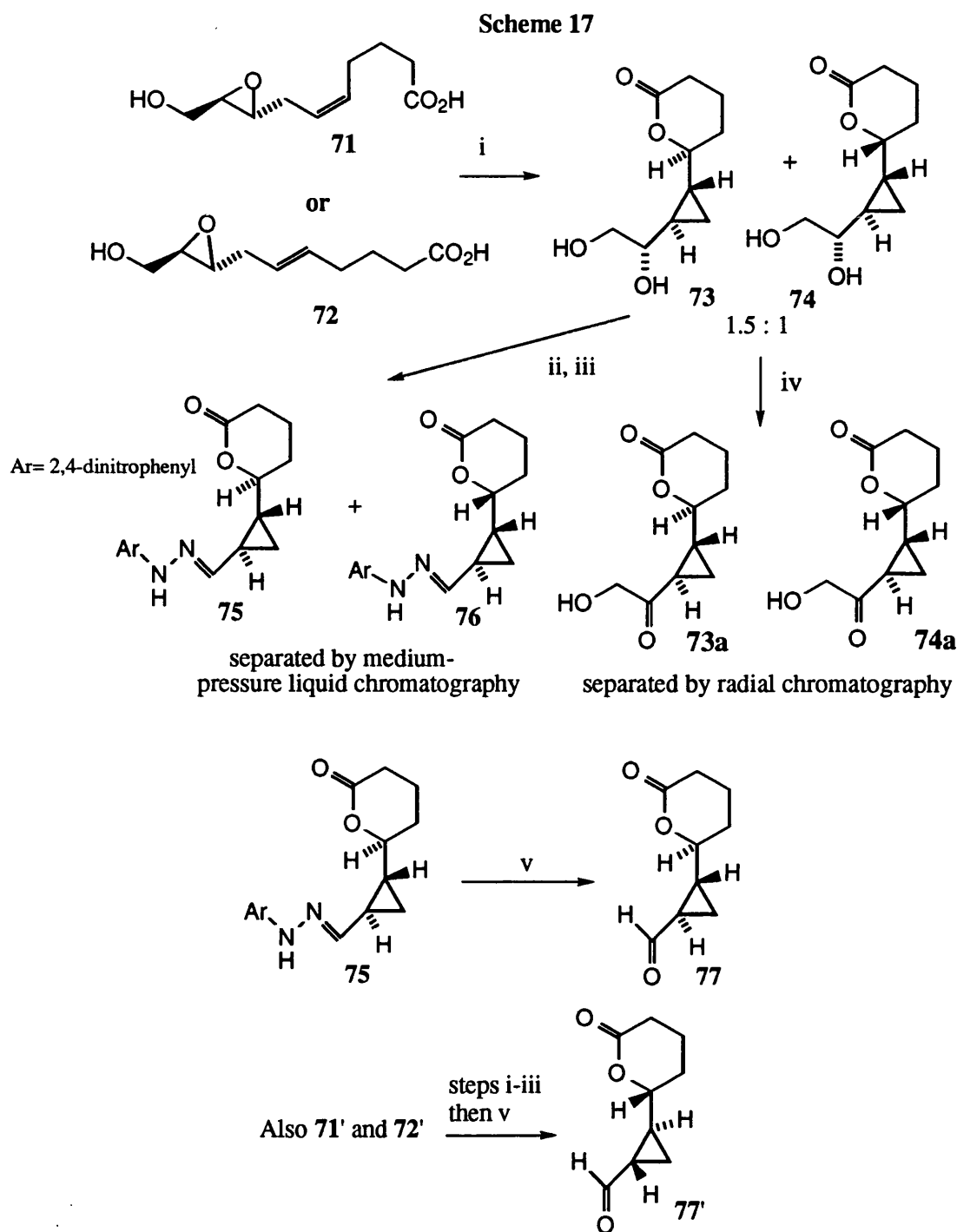
Reagents
i. SnCl₂, MeNO₂, 1.5hr, 0°C (54% from **71**, 44% from **72**); ii. NaIO₄, Et₂O-H₂O, 91%; iii. 2, 4- dinitro-
phenylhydrazine, EtOH, H₂O, 92%; iv. (n-Bu₃Sn)₂O, Br₂, CH₂Cl₂, 58-64%; v. O₃, EtOAc, then Me₂S, 61%.

The synthesis of constanolactone A **34** and constanolactone B **35** was completed

using antipodal aldehyde **77'**. Aldehyde **77'** was coupled with the appropriate vinyl

iodide **90** (prepared using a known procedure starting from D-rabinose, and discussed in section 2), using mild chromium conditions[22] to give **34** and **35** as a separable 1.4 to 1 mixture in 70% yield (Scheme 18, part (b)).

Scheme 18

(a) Preparation of **31**
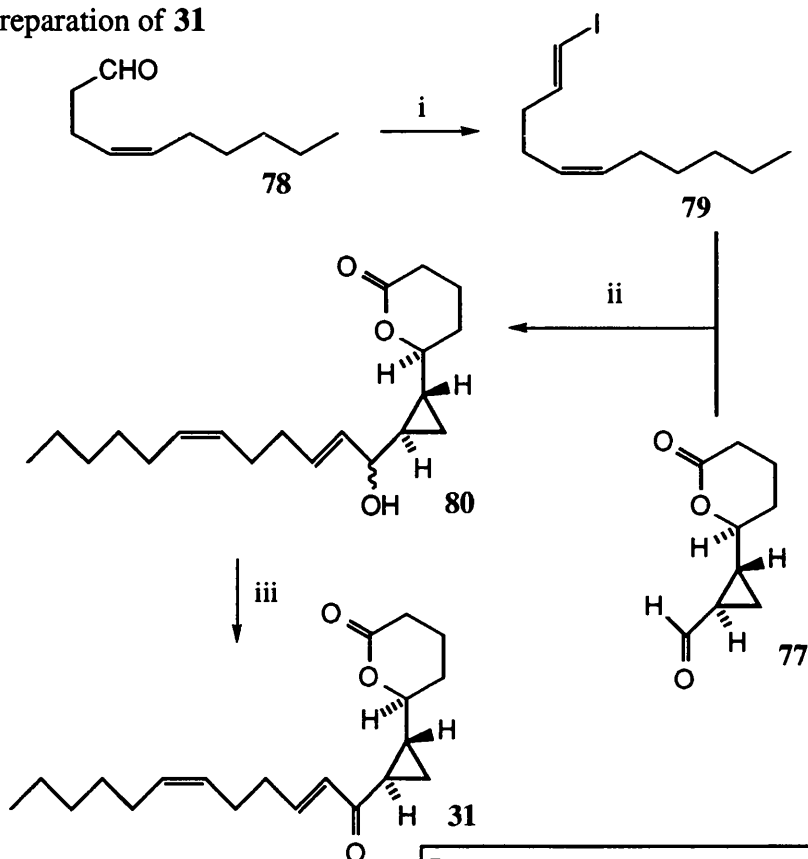
Reagents
i. CHI₃, CrCl₂, THF, 95%; ii. CrCl₂, NiCl₂ (cat),
DMF, 61%; iii. periodane, CH₂Cl₂, 84%; iv. CrCl₂,
NiCl₂(cat), DMSO, 70%.

(b) Preparation of **34** and **35**.

1.4:1 epimeric mixture

constanolactone A **34** R'=OH, R=H
constanolactone B **35** R'=H, R=OH
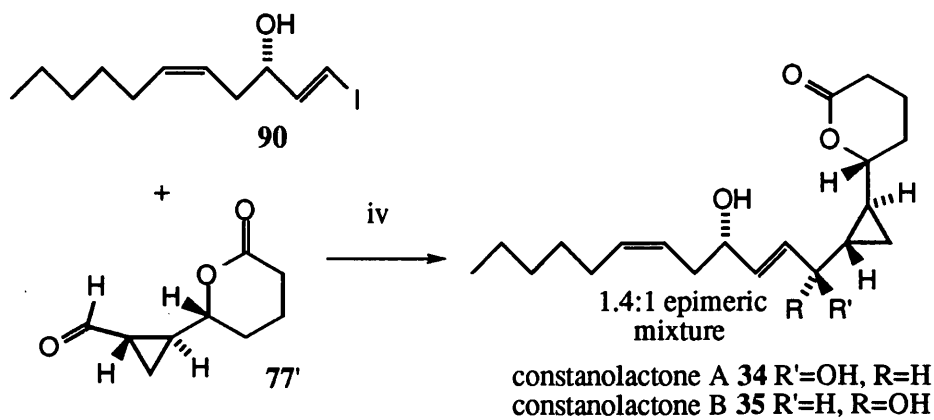
1.5   Retrosynthetic Analysis of Neohalicholactone 1 and Halicholactone 2.

Our retrosynthetic approach to **1** and **2** involved the key bond disconnection (as shown below in Scheme 19) to give the "right hand" fragment **81** and the "left hand" fragment **82**. The attraction to this approach is that methods exist which enable a vinylic anion to be added to an aldehyde with a high degree of selectivity.[21(a)-(f)] Also, high chemoselectivity has been achieved when a highly functionalised substrate is involved.[22]

Scheme 19

1 and 2
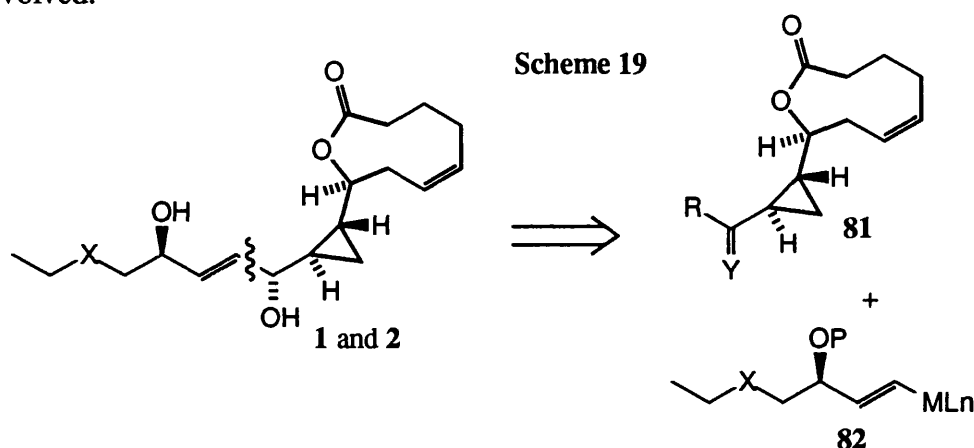
The further bond disconnections of right hand fragment (**81**) are now considered. The next disconnection is at the cyclopropane ring. The synthesis of cyclopropanes and in particular, their enantioselective synthesis, has been an intensive research area. We envisaged that the disconnections **a** and **b** would be the most logical (Scheme 20). Disconnection **a** would, in the forward direction, involve the formation of a carbene (derived from an alkyl diazoacetate) which must react exclusively with the *exo*-double bond in **83**. Also, there is the requirement to selectively synthesise only one of the four possible cyclopropane diastereomers. From literature precedent,[23] it is likely that both a regio- and stereoselective cyclopropanation of **83** using this approach (one where only the desired *trans*-cyclopropane is prepared with the correct relative stereochemistry), should be possible. In contrast to many other copper catalysts (such as copper(II) acetylacetonate), copper(I) triflate has been shown to promote cyclopropanation of the least alkylated olefin during both inter- and intramolecular competition studies.[23(a)] Therefore regioselective cyclopropanation at the *exo*-double bond of **83** should be possible. The use of a sterically demanding alkyl diazoacetate,

such as *t*-butyl-diazoacetate has, not unexpectedly, been shown to increase the observed *trans-cis* diastereoselectivity.[23(b)] Finally, asymmetric ligands based on bis(oxazoline), bipyridine, and semicorrin structures have been complexed to copper salts, thus generating highly effective catalysts for enantioselective cyclopropanation reactions (>95% e.e).[23(b)-(d)] However, these metal-catalysed asymmetric cyclopropanation reactions have been performed using a large excess (>5 equivalents) of very simple substrate alkene (e.g. styrene). A high concentration of alkene and slow addition of alkyl diazoacetate is imperative if the otherwise rapid dimerisation of the metal-carbene species and alkyl diazoacetate is to be suppressed.[23] Since it would be impractical to use a five fold excess of a valuable substrate during a total synthesis we did not favour the aforementioned disconnection **a** in our synthetic plan.

Alternatively, disconnection **b** yields an α,β-unsaturated synthon depicted as **84'** and **84"**. When **84'** is considered, the Simmons-Smith cyclopropanation reaction would participate in the forward direction, **84'** to **81**. This method of adding a "CH2" unit to a double bond has been widely exploited. Iodomethyl zinc reagents show generality to olefin structure, the reaction is stereospecific (strict retention of the olefin geometry is observed), and very importantly in the case of **84'**, substantial increases in the rate of reaction are observed for allylic alcohols (relative to isolated double bonds).[24(a)-(c)] Also, covalently bound chiral auxiliaries, and very recently, asymmetric ligands, have enabled efficient enantioselective versions of this reaction to be developed.[25] Synthon **84"** is now considered. The transformation **84"** to **81** could be achieved using a sulfur ylide, namely dimethylsulfoxonium methylide.[26] This method necessitates that **84"** has an electron poor double bond if high regioselectivity is to be achieved. Therefore we expected that **84"** would have either α,β-unsaturated ester or amide functionality.[27(a),(b)] Whilst methodologies (chiral auxiliaries[28] and chiral sulfur ylides[29]) do exist which might control the absolute stereochemistry of such a reaction, we believed this goal could be more simply achieved. The presence of α-alkoxy functionality at C(8) would be expected to promote preferential reagent attack to one face of the electron poor olefin, thus providing all the chemical information required for an enantioselective reaction. It

was this approach that we actually persued in the synthesis of **1** and **2**. Synthons **83**, **84'** and **84"** could all be synthesised from **85** which, after a multi-step sequence, could be prepared from (*S*)-malic acid **86**. The starting synthon **86**, is a versatile chiral building block from nature's 'chiral pool' (Scheme 20).

Scheme 20

81

(R=R'O, Y=O)   **83**   +   alkyl-diazoacetate

84' (R=H, Y=H, OH)
84" (R=O^{t}Bu, NMe(OMe), Y=O)

83 or 84' or 84"   **85**   **86**
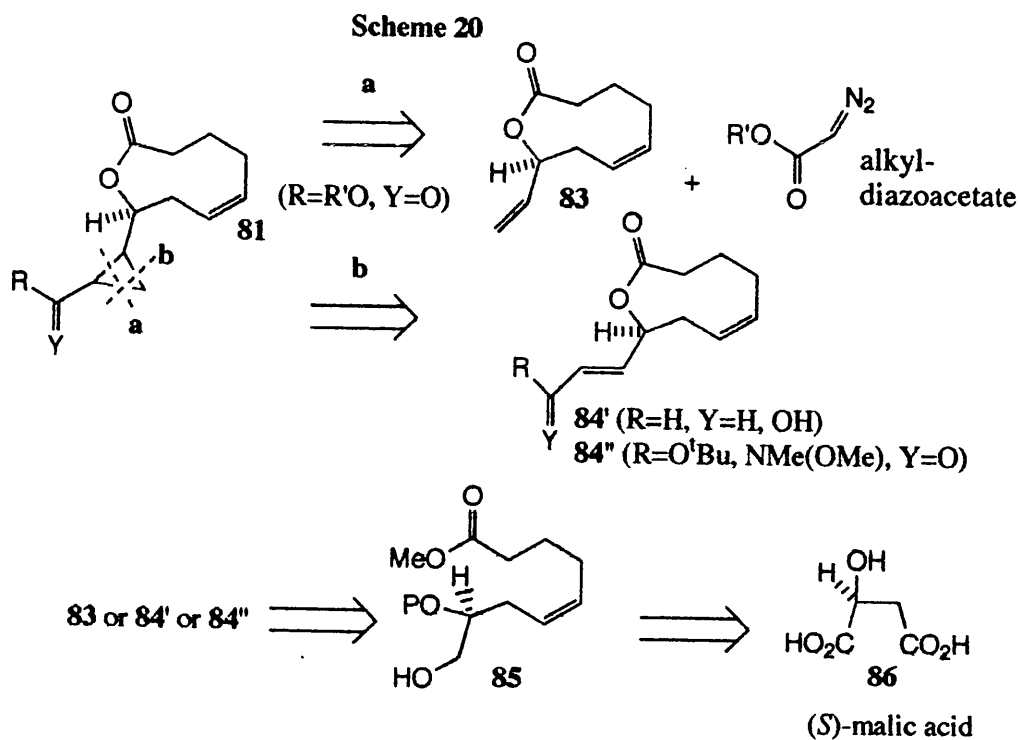
(*S*)-malic acid

One possible retrosynthetic approach to **82** where X=*cis*-CH=CH (ie. the left hand fragment of neohalicholactone **1**), gives **87** (an α-hydroxy aldehyde) which, *via* a multistep sequence, could be derived from (*R*)-malic acid **88**. In the case of **82** where X=CH$_2$CH$_2$ (ie. the left hand fragment of halicholactone **2**), then an obvious precursor is commercially available (*R*)-(+)-1-octyn-3-ol **89** (Scheme 21).

82   **87**

Scheme 21

89   **88**

(*R*)-malic acid
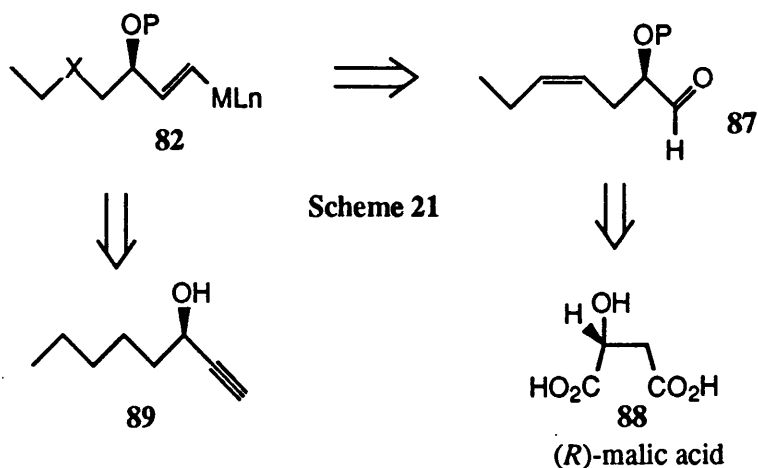
2. Results and Discussion.

2. Results and Discussion

2.1 Synthesis of The Right Hand Fragment of Neohalicholactone **1** and Halicholactone **2**.

We anticipated that a key intermediate in the synthesis of the right hand fragment of **1** and **2** would be a suitably C_8-protected derivative of methyl (S)-(8,9)-(Z)-dihydroxynon-5-enoate **85** (compound **85** is also shown in Scheme 20). The sequence of a methlyene unit, cis-double bond, three methylene units and a carboxylic acid terminus is found in arachidonic acid and eicosapentaenoic acid, and is unsurprisingly found in many of their derived natural products.[30]

arachidonic acid (ω6)
eicosapentaenoic acid (ω3)

R'= numerous metabolites
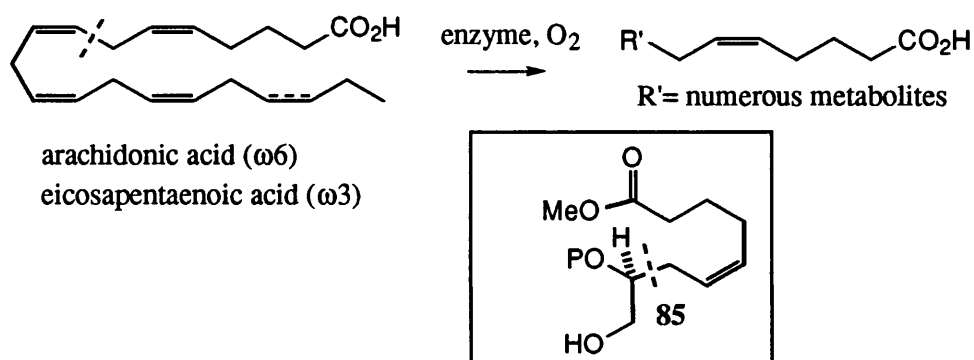
The introduction of this portion of a target molecule has been successfully achieved, in numerous cases, using a Wittig olefination reaction. The ylide derived from (4-carboxybutyl)triphenylphosphonium bromide **91** is condensed with an appropriate aldehyde.

(4-carboxybutyl)triphenyl phosphonium bromide **91**

2 equivalents of base

ylide

aldehyde

or

lactol
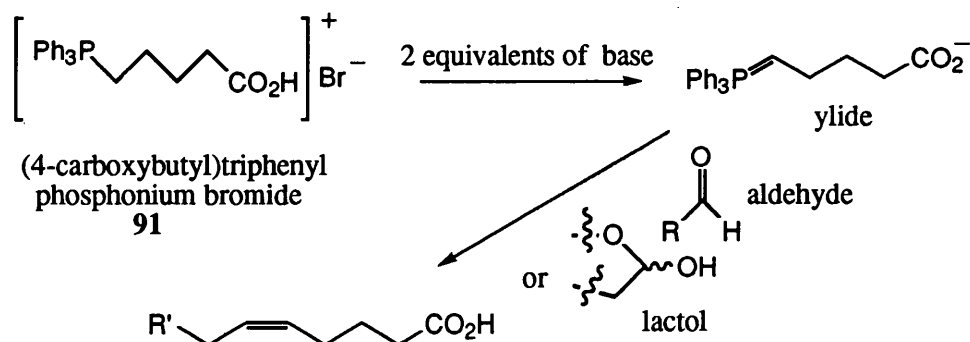
Corey and colleagues have used this approach in the synthesis of numerous naturally occurring prostaglandins and their derivatives. The penultimate step in the synthesis of dl-prostaglandin F$_{2\alpha}$ **92** is one of the earliest examples of such a strategy.[31] Reduction of lactone **93** with diisobutylaluminium hydride gave a lactol which was condensed with the ylide derived from phosphonium salt **91**, using dimsyl sodium (DMSO-Na) as base. Bis-tetrahydropyran-protected dl-prostaglandin F$_{2\alpha}$ **94** was isolated in excellent yield, 80% for the two steps. Acidic hydrolysis of the tetrahydropyran protecting groups gave **92** (Scheme 22).

Scheme 22
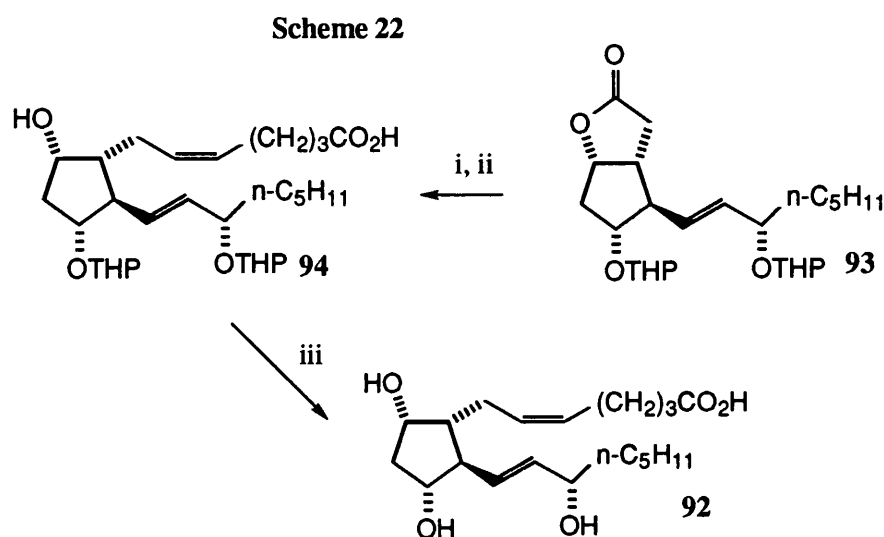
Reagents
i. 2.0 eq. DIBAL-H, toluene, -60°C, 30 min.; ii. 1.0eq. NaH, DMSO,
1.0 eq. phosphonium salt (91), RT, 80% overall; iii. 2:1 acetic acid-water,
37°C, 3 hr, 90%.

More recently, independent publications by Niwa and Holmes have described the application of the ylide derived from phosphonium salt **91** in their respective syntheses of (8S,9R)-neodidemnilactone **95**[32] and (8S,9R)-ascidiatrienolide A **96**.[33] Both are arachidonic acid metabolites. On completing the synthesis of their respective target molecules, both groups found that the related marine natural products **95** and **96** actually possessed 8R, 9S absolute stereochemistry. These structurally very similar compounds both contain identical ten-membered lactone rings, but they differ in the geometry of the three contiguous double bonds in the unsaturated side chains (10Z,12E,14E in **95** and 10E,12Z,14Z in **96**).

R= -(CH₂)₄CH₃
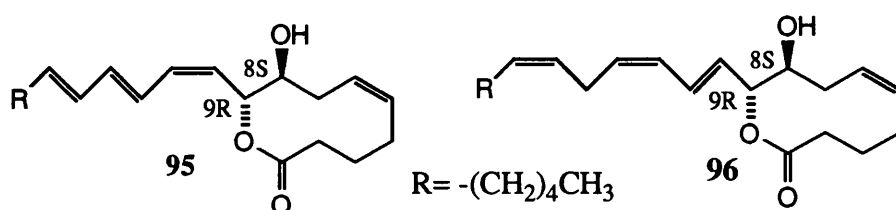
The synthesis of (8S,9R)-neodidemnilactone **95** involved the condensation of 3,4-O-isopropylidene-2-deoxy-D-ribose **97** with the ylide derived from phoshonium salt **91** using sodium bis(trimethylsilyl)amide as base. The reaction conditions employed in this transformation are typical of those often used to produce (Z)-olefinic linkages. Toluene is the solvent of choice since it enables so called "salt free conditions" to be reached (since the metal halide is insoluble). Low reaction temperatures are also important, and in the synthesis of **98**, lactol **97** was added to the ylide of **91** at -78°C and the mixture was then allowed to warm to -20°C before it was quenched. (Z)-olefinic acid **98** was isolated as its methyl ester in 58% yield for the two step transformation from **97** (Scheme 23).

Scheme 23
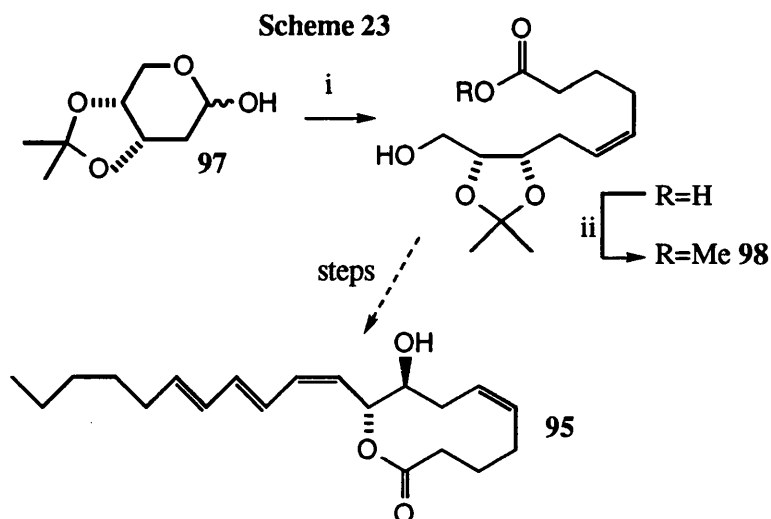
Reagents
i. excess of phosphonium salt **91**, NaN(SiMe₃)₂, toluene, then **97**, -78°C to -20°C; ii. CH₂N₂, 58%.

In the synthesis of (8S,9R)-ascidiatrienolide A **96** the ylide derived from **91** was again prepared using sodium bis(trimethylsilyl)amide as base with toluene as the solvent for the reaction. However, Holmes and colleagues prepared a more elaborate derivative of 2-deoxy-D-ribose as the other coupling component of the Wittig

reaction. Lactol **99** was prepared in three steps from 2-deoxy-D-ribose, and proved

to be an excellent substrate for the Wittig reaction, since (Z)-olefinic acid **100** was

isolated in 95% yield (Scheme 24).

The (Z)-olefinic products **98** and **100** both contain three hydroxyl components, but

the protecting group pattern in each is different. The completion of the synthesis of

(8S,9R)-neodidemnilactone **95** was most efficiently completed by building on the

14E,12E,10Z side chain from the unprotected C_{10} hydroxy group. The acetonide

protecting group was then cleaved and after basic hydrolysis of the ester group, the

resulting (8S,9R)-dihydroxy acid was preferentially cyclised to the ten-membered

lactone product **95** using the method described by Yamaguchi. Significantly, the

final cyclisation step had a choice of forming the ten-membered lactone product or its

nine-membered alternative; the formation of the latter is, however, not mentioned in

the publication. (Z)-olefinic acid **100**, a key intermediate in the synthesis of (8S,9R)

ascidiatrienolide A **96** was, in contrast, ideally suited to immediate cyclisation to a

ten-membered lactone, since both C_8 and C_{10} hydroxy groups were protected. The

lactone then remained intact for the remaining steps of the synthesis during which the

unsaturated C_9 side chain was constructed.

Scheme 24

Reagents
i. HCl, Et_2O, MeOH, 15 min.; ii. TBDPSCl, pyridine, RT, 30 min, 98%, iii. BCl_3.DMS,
Et_2O, RT, 10 min, aqueous Na_2CO_3, THF, (87-97%; iv. Phosphonium salt **91**, $NaN(SiMe_3)_2$,
toluene, THF, 0°C to -70°C then **99**, -70°C to 0°C, 95%.
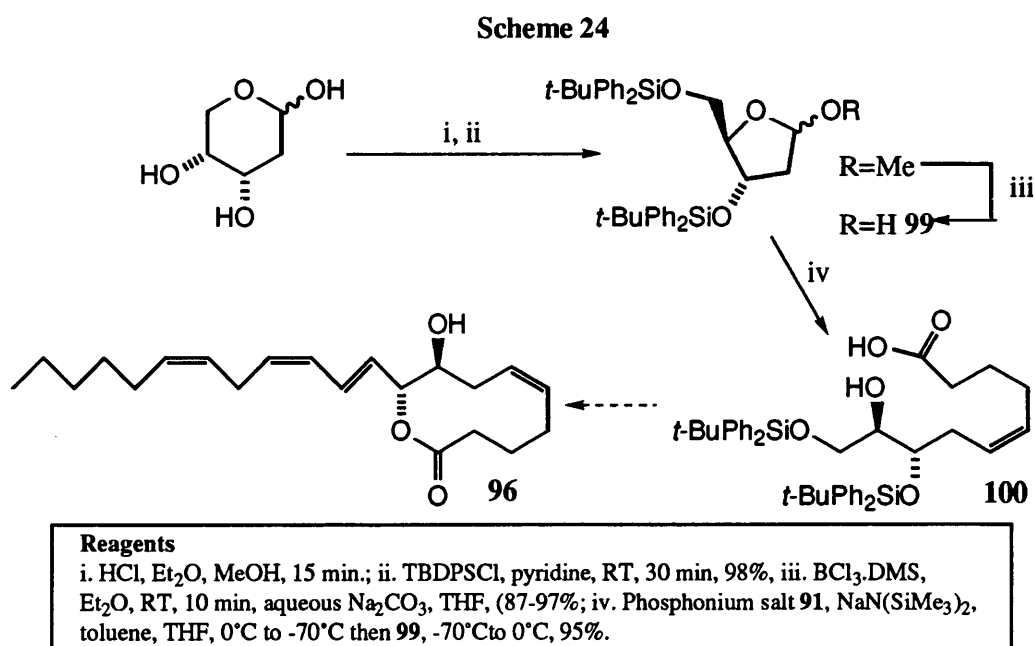
We hoped that suitably (8*S*)-protected-(*S*)-(8,9)-(*Z*)-dihydroxynon-5-enoate **85** could be converted to its cyclopropane derivative *via* manipulation of the unprotected C9 primary hydroxy group prior to a lactonisation step. We anticipated that direct lactonisation of a C9-hydroxy protected derivative of **85** to nine-membered lactone **101** would then be followed by a problematical C9-hydroxy deprotection step. It is reasonable to expect **101** to be converted to its more stable ten-membered lactone isomer **102** during C9-hydroxy deprotection *via* a facile translactonisation reaction.

Scheme 25

Holmes Precedent

Reagents
i. TBAF, THF, RT.

104
translactonisation
product

A favoured strategy

85

B disfavoured strategy

lactonise

101

deprotect

anticipated
translactonisation

102
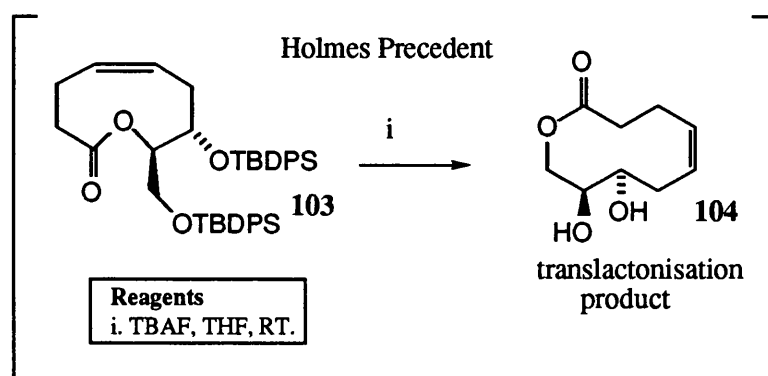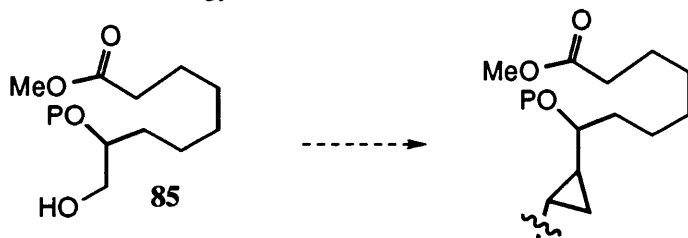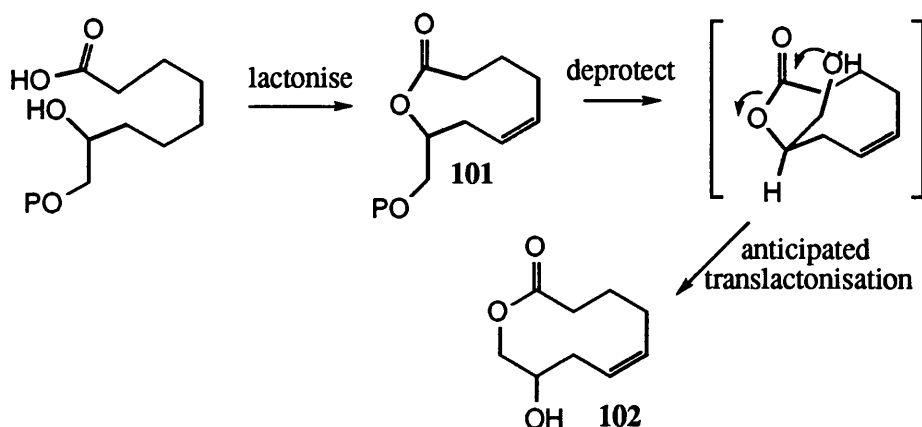
Evidence for such a transformation is provided by Holmes,[33] where deprotection of nine-membered lactone **103** with tetra-*n*-butylammonium fluoride (TBAF) resulted in translactonisation to its ten-membered lactone **104** (Scheme 25).

The synthesis of the acetonide of methyl 8,9-(Z)-dihydroxynon-5-enoate **105** has been achieved by Corey and co-workers. The ylide derived from 1-(triphenylphosphinio)butane-3,4-diol acetonide **106** was condensed with methyl 4-formyl-butyrate **107** in 70% yield (Scheme 26).[34(a),(b)] However, conversion of **105** to mono-(8*S*)-protected **85** would require inelegant deprotection, and reprotection steps. Further, the synthesis of phosphonium salt **106** involved five steps from malic acid whilst aldehyde **107** was prepared in two steps from monomethyl glutarate. Application of this approach would, therefore, require as many as twelve steps before target compound **85** was realised.

Scheme 26
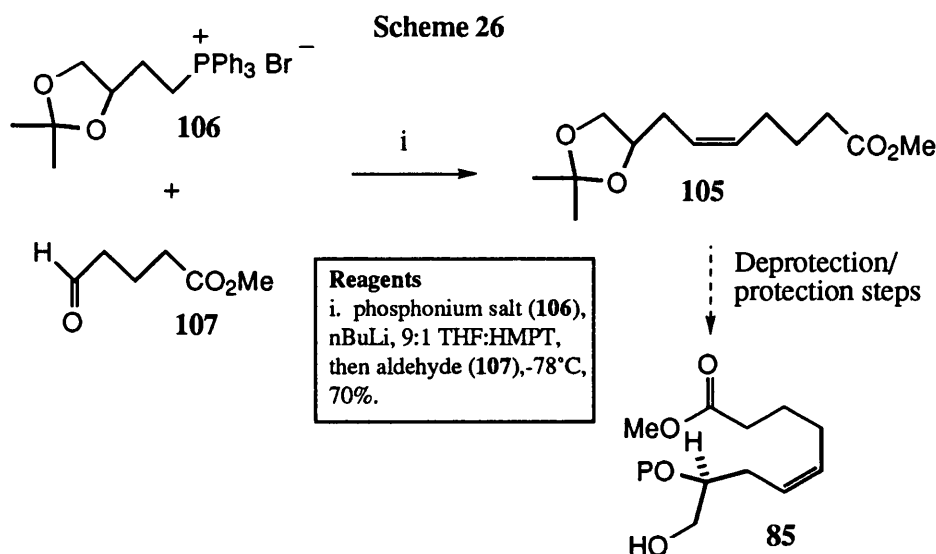
As a more efficient approach, we wished to prepare (3*S*)-3-O-((*p*-methoxyphenyl-methyl)oxy)-γ-butyrolactol **108** and condense this lactol with the ylide prepared from phoshonium salt **91**. The synthesis of **85** should then be possible in just seven steps.

108
MPM=CH₂C₆H₄OMe-*p*

109
Tr=CPh₃
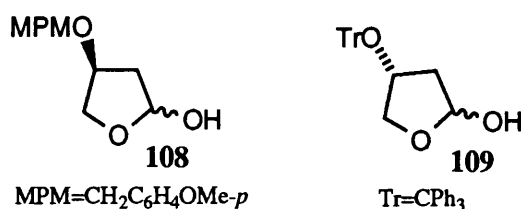
The antipodal trityl protected analogue of **108** has been reported, and has been employed in a Wittig olefination during the synthesis of the C_{11}-C_{20} segment of leukotriene B_4.[35] However, the preparation of **109** was achieved in **nine** steps from L-ascorbic acid using the procedure first described by Tanaka.[36] A key intermediate, the (3,4)-O-isopropyl derivative of methyl (3R)-3,4-dihydroxybutanoate **110** was the product of a six step synthesis. Acid promoted cyclisation of **110** to give (3R)-hydroxy-γ-butyrolactone **111** was followed by protection and reduction steps to furnish **109** (Scheme 27).

Scheme 27

L-ascorbic acid

six steps

110

leukotriene B_4

OSiPh₂ᵗBu

CHO

109

111

Reagents
i. 0.1N HCl, reflux, 95%; ii. (a) TrCl, pyridine, (b) DIBAL-H, -78°C, (yield not given).
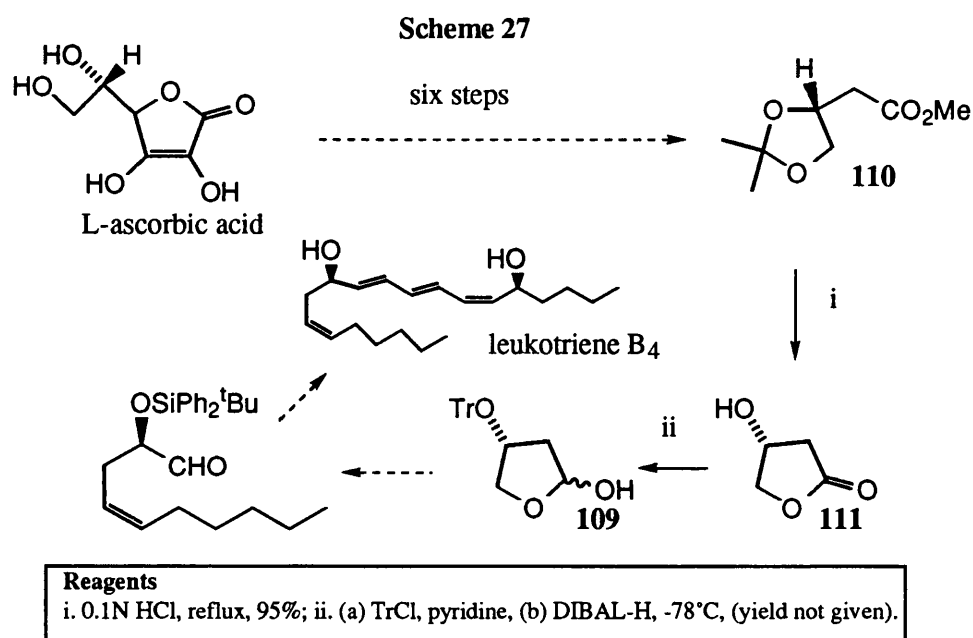
Shorter routes to (3R)-hydroxy-γ-butyrolactone **111** have been published. For example Seebach has reported its synthesis in four steps, where the (3R) absolute stereochemistry was introduced by reduction of ethyl t-butoxy-3-oxobutanoate with fermenting yeast in 97% enantiomeric excess.[37] Acid catalysed cyclisation of (3R)-ethyl 4-t-butoxy-3-hydroxy butanoate gave **111** in 28% yield overall. Also, it is possible to differentiate the two carboxylic acid groups in malic acid using a combination of borane-dimethyl sulfide complex in the presence of a catalytic amount of sodium borohydride. This discovery was reported in 1984, where dimethyl (S)-malate **112** was selectively reduced to methyl (S)-(3,4)-dihydroxybutanoate **113** using the aforementioned conditions in 88% yield.[38] The high selectivity observed in the reduction is probably the result of both electronic and entropic factors. The

lactonisation of **113** to (3*S*)-hydroxy-γ-butyrolactone **114** was then accomplished using standard acidic conditions in 90% yield. It was this short (only three steps), high yielding approach to the synthesis of hydroxy-lactone **114** that we wished to exploit.

(*S*)-Malic acid **86** was dissolved in a 3% anhydrous hydrochloric acid/ methanol solution to give dimethyl (*S*)-malate **112** in yields in excess of 80% after distillation.[39] In our hands the selective reduction of dimethyl (*S*)-malate **112** became extremely exothermic upon addition of a catalytic amount of sodium borohydride (NaBH₄). We therefore took the precaution of only performing this reaction on a moderate scale (between five and ten grams). If the reaction mixture was cooled to 0°C prior to the addition of NaBH₄ and subsequently allowed to warm slowly to room temperature, then the reaction was both more controllable and selective. It should be noted that whilst we were able to isolate methyl (*S*)-(3,4)-dihydroxybutanoate **113** in high yield (>90%), an inseparable impurity was always present (<6%). Methyl (*S*)-(2,4)-dihydroxy butanoate **115** was characterised as the unwanted contaminant by spectroscopic analysis of a pure derivative (**116**) generated during subsequent cyclisation and protection steps.

Cyclisation of methyl (*S*)-(3,4)-dihydroxybutanoate **113** to hydroxy-lactone **114** was achieved using an aqueous 18N H₂SO₄/ tetrahydrofuran solution in good yield (75% after chromatography).[40] Alternatively the cyclisation could also be mediated by heating **113** at reflux in dilute 0.1N HCl for several hours (72% yield, see Scheme 28).[36]

Scheme 28

Reagents
i. MeOH, 3%AcCl, 20 hr, RT, 81%; ii. BH₃.DMS, cat. NaBH₄, THF, RT, 1 hr, 92%; iii. 18N aqueous H₂SO₄, THF, RT, 3 days, 75% yield or 0.1N aqueous HCl, 60°C, 16 hr, 72%.
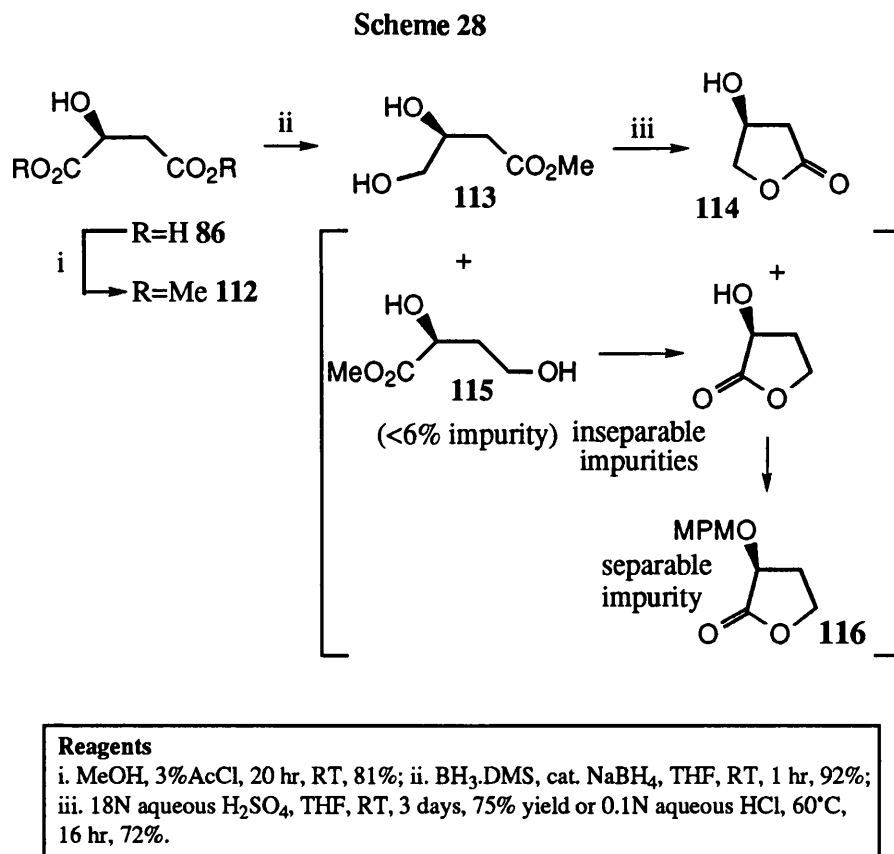
Since for benzylation of β-hydroxy esters, use of benzyl 2,2,2 trichloroacetimidate in the presence of a catalytic amount of trifluoromethane sulfonic acid (TfOH) is known to be the method of choice, we investigated the *p*-methoxyphenylmethyl (MPM) protection of hydroxy-lactone **114** using similar methodology. The preparation of optically pure benzylated β-hydroxy ester **117** and related structures is reported to be quite troublesome.[41] Benzylation under the normal basic conditions leads to the formation of retro-aldol and/or elimination reactions. However the acid catalysed procedure developed by Iversen and Bundle using benzyl 2,2,2 trichloroacetimidate, furnished **117** in 79% yield, and without racemisation at C-3 (Scheme 29).[42(a),(b)]

Scheme 29

Reagents
i. PhCH$_2$OC(NH)CCl$_3$, 10 mol% TfOH, cyclohexane/CH$_2$Cl$_2$, RT, 3 hr, 79%;
ii. benzyl halide, NaH, DMF, low yields + epimerization.
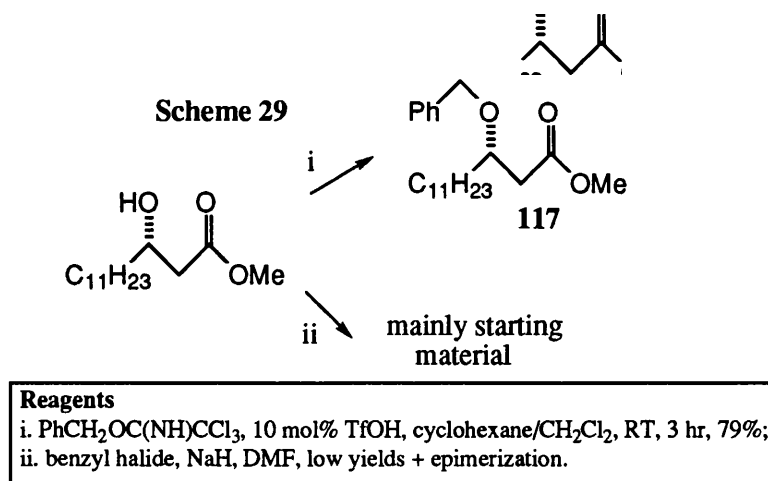
The p-methoxyphenylmethyl analogue of Bundle's reagent was reported by Yonemitsu in 1988.[43,44] p-Methoxyphenylmethyl trichloroacetimidate **118** is easily prepared from p-methoxybenzyl alcohol and trichloroacetonitrile in the presence of sodium hydride (10 mol%). p-Methoxyphenylmethyl trichloroacetimide **118** is more reactive than its benzyl analogue, and extremely sensitive to acids. It is best prepared immediately before use and the benzylation reaction requires only 0.3 mol% of TfOH. Addition of 10 mol% of TfOH causes the instant decomposition of **118**. The use of 10 mol% of a weaker acid, 10-camphor sulphonic acid (CSA), has also been reported as a suitable alternative to 0.3 mol% TfOH.[43] We found that the MPM-protection of hydroxy-lactone **114** proceeded in yields in excess of 70% using either 0.3 mol% TfOH or 5 mol% CSA to catalyse the reaction. The best recorded yield for this reaction was 92%. Since the addition of too much acid causes **118** to decompose very rapidly, we employed an excess of **118**, greater than 1.4 equivalents (Scheme 30).

Scheme 30

Reagents
i. 1.4 eq. p-MeOC$_6$H$_4$CH$_2$OC(NH)CCl$_3$ (**118**), 0.3 mol% F$_3$CSO$_3$H, CH$_2$Cl$_2$/cyclohexane (2:1), 3 hr, 75% or ii. 1.5eq.p-MeOC$_6$H$_4$CH$_2$OC(NH)CCl$_3$ (**118**), 5mol%, CSA, CH$_2$Cl$_2$, 16 hr, 73%.
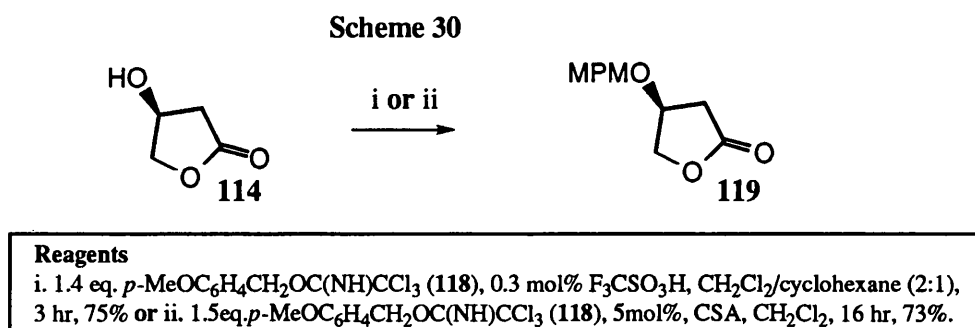
The product (3S)-3-O-((p-methoxyphenylmethyl)oxy)-γ-butyrolactone **119** was isolated free of impurities after flash chromatography. The great virtue of the p-methoxyphenylmethyl protecting group is that whilst it is resilient to many synthetic

reactions (although contact with mineral acid should be avoided), it can be removed under essentially neutral and very specific conditions. *p*-Methoxyphenylmethyl protecting groups have been removed by oxidative cleavage using 2,3-dichloro-5,6-dicyano benzoquinone (DDQ).[45] These conditions were not expected to have a detrimental effect on either double bond or ester functionality.

The reduction of lactone **119** was achieved using a slight excess of diisobutylaluminium hydride, in toluene, at low temperature (<-20°C). The target lactol **108** was either isolated in quantitative crude yield or could be chromatographed in which case the isolated yield was slightly lower (but still >80%). However, **108** was usually employed in the next Wittig olefination step without chromatographic purification being necessary. The key Wittig reaction was carried out using a slight modification to the conditions first described by Holmes and colleagues in the synthesis of (8*S*,9*R*) ascidiatrienolide A **96**, a step which has been described earlier in this section.[33] Using fresh sodium bis(trimethylsilyl)amide (1M solution in tetrahydrofuran from Aldrich) we prepared the ylide derived from phosphonium salt **91** in toluene. Before adding the deep red ylide (cooled to -78°C) to lactol **108** (cooled to -78°C), **108** was first deprotonated using one equivalent of sodium bis(trimethylsilyl)amide. This presumably produces the acyclic aldehyde derivative **120**, which was kept at low temperature (-78°C) with toluene as solvent. Since **120** was quite insoluble in toluene at low temperatures the volume of toluene was increased relative to the Holmes procedure. Also, the addition of the preformed ylide to the sodium alkoxide **120** was found to be more satisfactory than the inverse of this addition. Surprisingly, we found that **120** was prone to decomposition if sufficiently low temperatures were not maintained. On warming **120** from -78°C to room temperature, consumption of the stating material and its conversion to a less polar compound (which had identical Rf value to *p*-methoxybenzyl alcohol) could be monitored by thin layer chromatography. The crude (*Z*)-olefinic carboxylic acid **121** was then converted to its methyl ester **122** using a HCl/ methanol solution at pH 4-5, before being purified.

Scheme 31
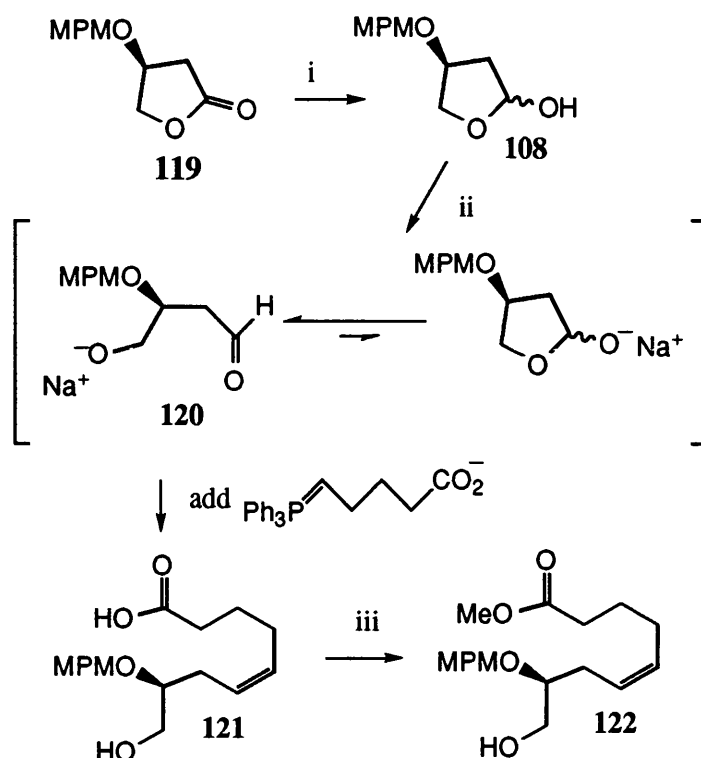
Reagents
i. 1.1 eq. DIBAL-H, toluene, -40°C to -20°C, 15 min; ii. (a) 1.1 eq. NaN(SiMe₃)₂, toluene, -78°C, (b) 1.2 eq. (4-carboxybutyl)triphenylphosphonium bromide 91, 2.3eq NaN(SiMe₃)₂, toluene, 0°C to RT, 20 min, then -78°C and add ylide *via* a cannula to sodium alkoxide 120; iii. MeOH, AcCl, 3.5 hr, RT, 69% overall.

An alternative procedure commonly used to generate methyl esters from carboxylic acids when acid labile functionality is present, such as a *p*-methoxyphenylmethyl ether or an acetonide, is the combination of sodium hydrogen carbonate and dimethyl sulfate. This procedure was not examined but may have proven to be beneficial. *p*-Methoxyphenylmethyl-deprotection was observed if the acidity of the HCl/ methanol solution was not carefully monitored and/or if reaction times were not kept at a minimum. However, by carefully employing the specific conditions described, methyl (8*S*,5*Z*)-8-*O*-((*p*-methoxyphenylmethyl)oxy)-8,9-dihydroxynon-5-enoate **122** was consistently isolated on a multi-gram scale in yields greater than 60% (and at best 69%) for the three step transformation from lactone **119** (Scheme 31). (*Z*)-olefin **122** was then smoothly converted to its (*E*)-γ-alkoxy-α,β-unsaturated-*t*-butylester **123**. This was achieved in two steps. Swern oxidation[46] of **122** gave the corresponding aldehyde **124** which was subsequently condensed with *t*-butyl diethyl phosphonoacetate using conditions described by Masamune and Roush in 1984,[47] to

furnish **123** in 75% yield for the two steps. The Masamune-Roush procedure provides a milder alternative to the conditions usually employed in the Horner-Wadsworth-Emmons reaction (NaH in DME or THF). It is therefore the method of choice when a base sensitive substrate or reagent is used. The milder conditions result from the use of lithium cations which increase the acidity of the phosphonate. This in turn enables the olefination reaction to proceed using weak bases, such as 1,8-diazobicyclo[5.4.0]undec-7-ene (DBU), diisopropylethylamine (DIPEA) and triethylamine. These bases are less likely to cause epimerisation of α-hydroxy-aldehyde precursors such as **124** (Scheme 32).

Scheme 32
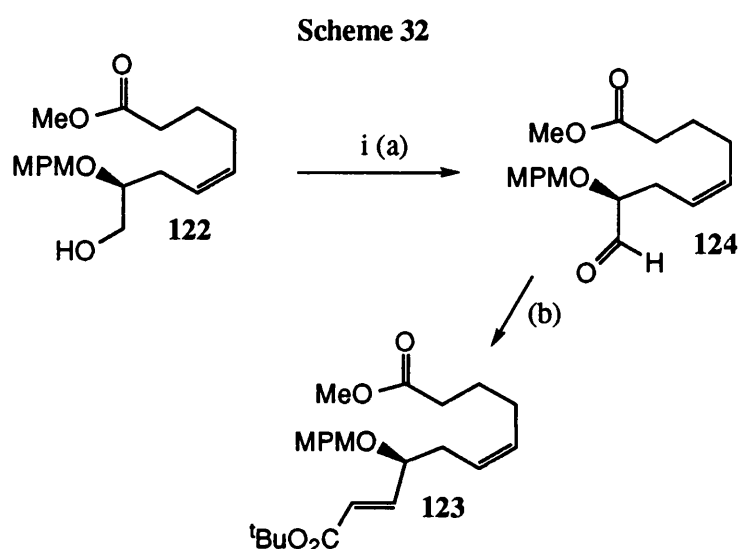
Reagents
i. (a) 1.2 eq. (COCl)$_2$, 2.4 eq. DMSO, 5.0 eq. Et$_3$N, CH$_2$Cl$_2$, -78°C to 0°C,
(b) 1.1 eq *t*-butyl diethylphosphonoacetate, 1.1eq. LiCl, 1.0 eq. DBU,
CH$_3$CN, RT, 5 hr, 75% overall.

The reaction of dimethylsulfoxonium methylide (DMSY) with (*E*)-γ-alkoxy-α,β-unsaturated-*t*-butyl ester **123** was then investigated as a means of introducing the cyclopropane ring. In 1962 Corey and Chaykovsky synthesised DMSY by the reaction of trimethylsulfoxonium iodide with sodium hydride in dimethyl sulfoxide (DMSO).[49] The application of the DMSY reagent in the synthesis of cyclopropanes from α,β-unsaturated ketones was reported in 1965, again by Corey and Chaykovsky.[26] They had earlier shown (1964) that isolated ethyl esters were inert to

DMSY, whilst α,β-unsaturated <u>ethyl</u> esters would undergo conjugative 1,4 addition but the major product of this reaction was <u>not</u> a cyclopropane ester.[50] Instead a more facile cyclisation to a β-ketosulfoxonium ylide resulted as exemplified by the reaction of ethyl cyclohexenyl carboxylate **125** with DMSY to give β-ketosulfoxonium ylide **126** (see Scheme 33).[51]
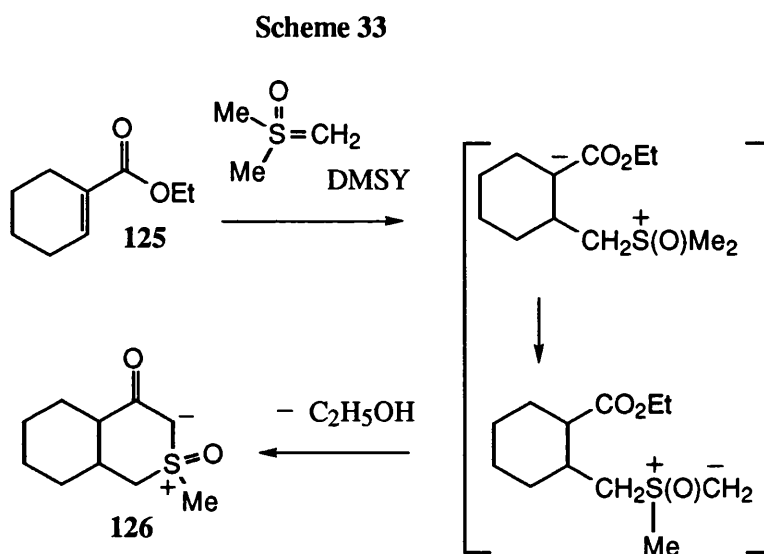
Scheme 33

However, C. Kaiser, B. Trost and colleagues reported in 1965 that *t*-butyl *trans*-cinnamate **127** could be exclusively converted to its *trans*-cyclopropane derivative **140** using 1.1 equivalents of DMSY in 69% yield (Scheme 34).[27(a)] Also, they found that whilst sterically small electron-withdrawing functionality such as the cyano group gave rise to considerable amounts of the *cis*-cyclopropane derivative, in contrast, a sterically demanding ester or amide group appeared to give entirely the *trans*-isomer. From this evidence they concluded that the stereochemical course of the reaction depended on the degree of interaction of the electron withdrawing substituent with the β-phenyl group in intermediates **128** leading to cyclopropane ring formation.

Scheme 34
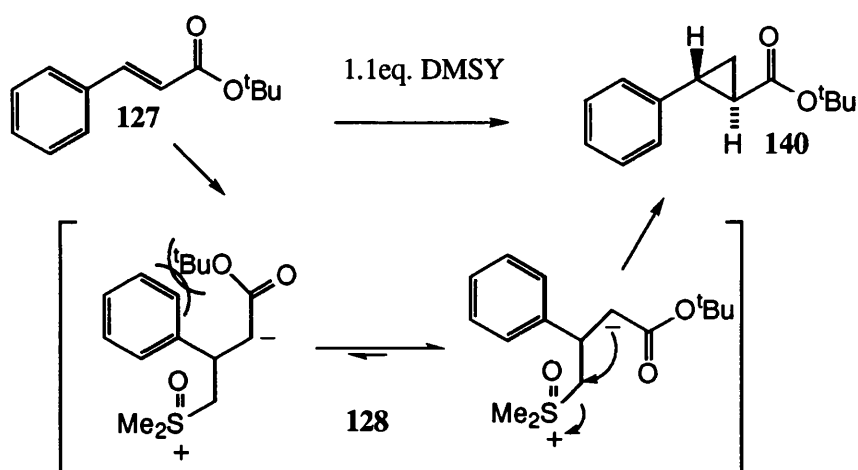
however with a small electron withdrawing group;

cis-cyclopropane product
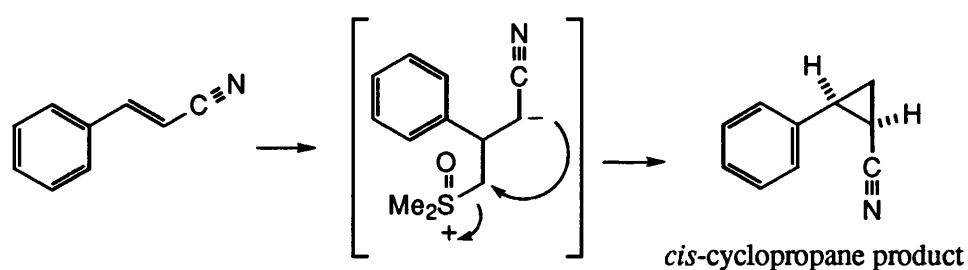
P. Magnus and colleagues have reported that the cyclopropanation of α,β-unsaturated *t*-butyl ester **129** can be achieved using DMSY to give cyclopropanated derivative **130**, a key intermediate in the synthesis of the antileukemic agent (±)-steganone **131** (see Scheme 35).[52] The cyclopropanation reaction was achieved in an excellent 82% yield where only one stereoisomer **130** was formed. A possible explanation for this stereoselectivity could again be that the sterically demanding *t*-butyl ester forces the formation of only one intermediate sulfoxonium ion (the result of initial 1,4 addition), i.e. formation of **132** rather than **133**, to be energetically favoured. A severe non-bonded interaction between the *t*-butoxide-group and the piperonyl ring would destabilise conformer **133**. The reaction therefore occurs *via* conformer **132** which gives the cyclopropane product **130** (Scheme 36).

Scheme 35
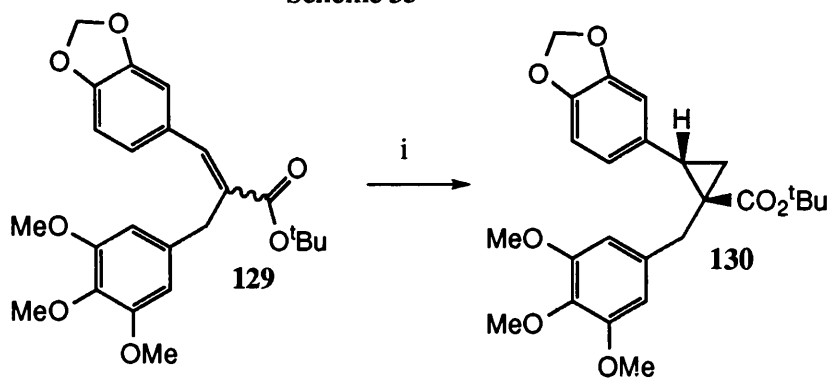
Reagent
i. 3.0 eq. DMSY (generated from trimethylsulfoxonium
iodide and NaH), DMSO, 20°C for 2 hr then 60°C for
15 hr, 82%.
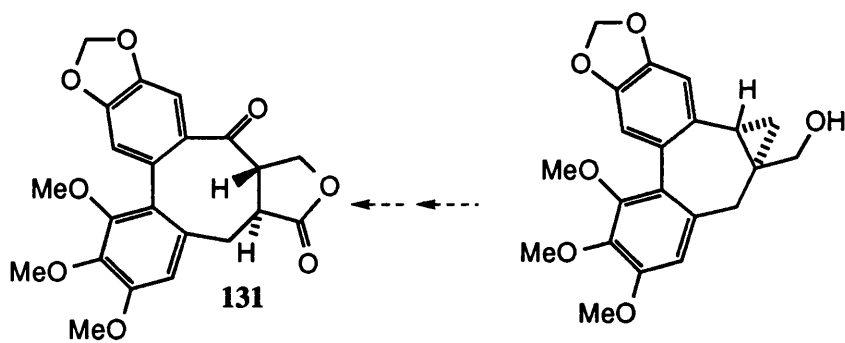
Scheme 36
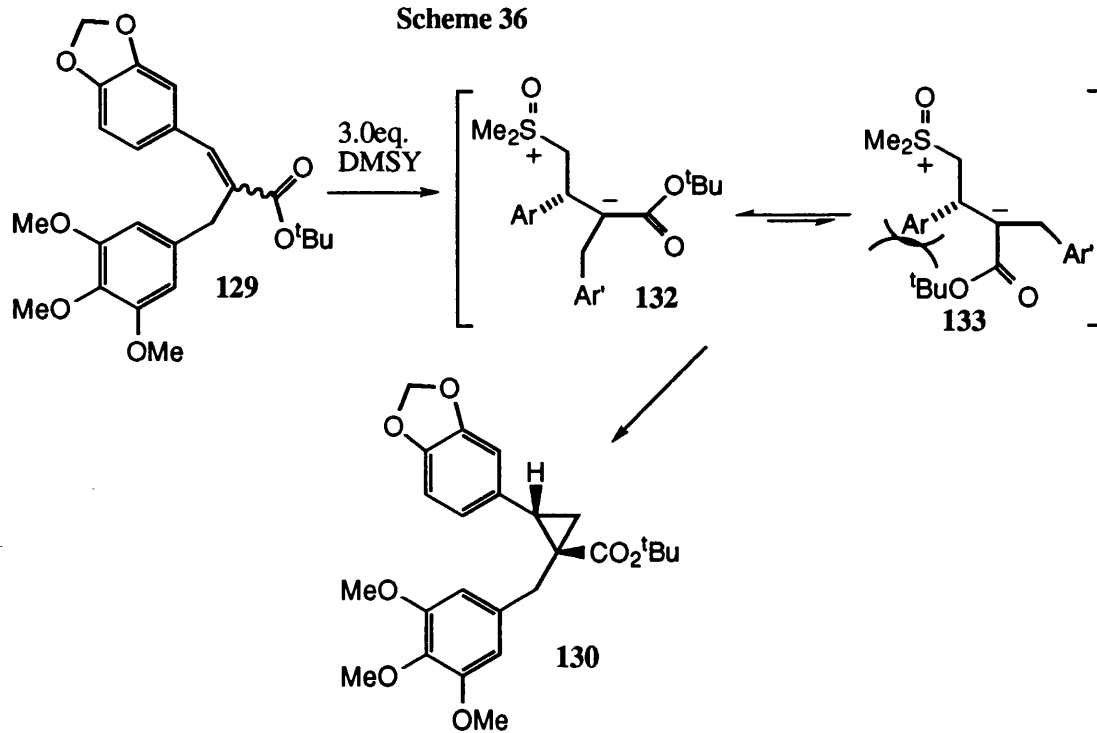
This literature precedent encouraged us to attempt to cyclopropanate (E)-γ-alkoxy-α,β-unsaturated t-butyl ester **123** using DMSY. In the event **123** was treated with two equivalents of DMSY (prepared from trimethylsulfoxonium iodide and NaH) in dimethyl sulfoxide and the solution was heated at 90°C for twenty hours. An inseparable 5:2 mixture of just two diastereomeric cyclopropanated compounds **134** were isolated in good yield (74%). Importantly no products corresponding to addition of DMSY to the exposed methyl ester in **123** were observed; in fact, the reaction appeared to be remarkably **chemoselective, regioselective** and modestly **stereoselective**. We found that more elevated temperatures were required in our reaction in comparison to the conditions described by Magnus. Cyclopropanation of **129** was reported to be achieved in high yield using 3.0 equivalents of DMSY and heating at 60°C over 16 hours. If we employed the aforementioned conditions, only unreacted starting material was returned from the reaction mixture.

Deprotection of the p-methoxybenzylmethyl group in **134** using DDQ[45] gave the two (8S)-hydroxy-cyclopropane diastereoisomers **135** and **136** in quantitative yield. Fortunately, these two compounds were now separable by flash chromatography and the major isomer **135** was isolated in 51% yield for the two step transformation from t-butyl ester **123** (Scheme 37). From literature precedent, the work of Magnus,[52] and Kaiser,[27(a)] we expected that the two diastereoisomers would both contain *trans*-cyclopropane rings. From the coupling constants of the terminal cyclopropane protons H_{10a} and H_{10b} in the ^{1}H-NMR spectrum of the major isomer **135** it was clear that a *trans*-cyclopropane ring was in place. Excellent agreement with coupling constants of the terminal cyclopropane protons H_{7a} and H_{7b} of *trans*-cyclopropane-and lactone-containing compound **137** were observed (see table 1). The ^{1}H-NMR data for **137** were published by J. White.[18(a),(b)] Compound **137** was an intermediate in the synthesis of **31**, a marine natural product isolated from the soft coral *Plexaura homomalla*, the synthesis of which is discussed in section 1.4b.

Scheme 37

MeO

MPMO

$^tBuO_2C$ **123**

i

MeO

MPMO

^tBuO

O H **134**

H

ii

MeO

HO

^tBuO

O H **135**

H

+

MeO

HO

^tBuO

O H **136**

H

5 : 2
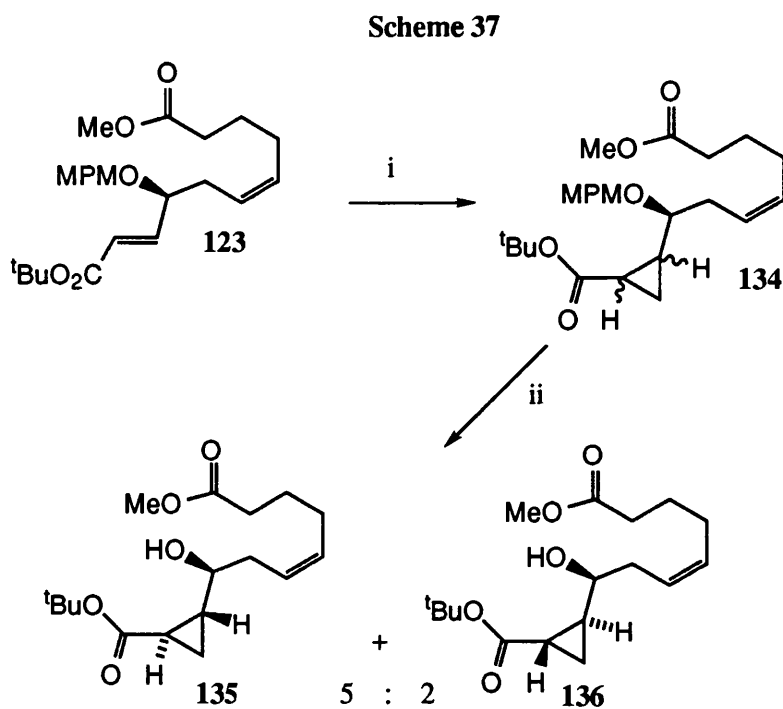
Reagents
i. 2.0 eq. $Me_2S^+(O)CH_3I^-$/NaH, DMSO, 90°C, 74%; ii. 1.1 eq. DDQ, CH_2Cl_2:H_2O
(18:1), RT, 100% mass recovery, 69% (**135**).

Table 1

Comparison of 1H-NMR Data of The Terminal Cyclopropane Protons in **135** and **137**

compound	proton	chemical shift (ppm)	coupling constant (Hz)
135	H_{10b}	0.79	$J H_{10a},H_{10b}$ 4.3 (gem) $J H_{10a},H_{11}$ 8.3 (cis) $J H_{10a}, H_9$ 6.2 (trans)
135	H_{10a}	1.10	$J H_{10a},H_{10b}$ 4.4 (gem) $J H_{10b},H_9$ 9.0 (cis) $J H_{10b},H_{11}$ 4.4 (trans)
137	H_{7a}	1.11	$J H_{7a},H_{7b}$ 4.3 (gem) $J H_{7a},H_8$ 9.2 (cis) $J H_{7a},H_6$ 4.6 (trans)
137	H_{7b}	1.41	$J H_{7a},H_{7b}$ 4.3 (gem) $J H_{7b},H_6$ 8.3 (cis) $J H_{7b},H_8$ 6.5 (trans)
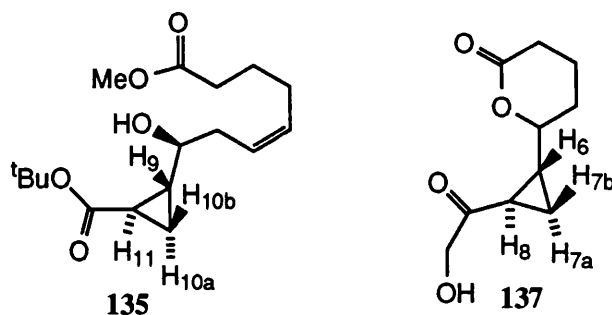
The cyclopropane protons gave unresolvable splitting patterns in the minor diastereomer **136**. However, subsequent manipulations of **136** gave derivatives whose coupling constants for H_{10a} and H_{10b} were in very good agreement with those described for **135**.

In fact an X-ray crystal structure of a derivative, whose synthesis has yet to be described, confirmed the *trans*-substitution pattern in **135**. The X-ray crystal structure also confirmed that **135**, the major diastereomer formed in the cyclopropanation reaction, had the correct relative stereochemistry ($8S,9R,11R$) to complete the synthesis of the right hand fragment of neohalicholactone **1** and halicholactone **2**. Therefore, to summarise, using the combination of (E)-γ-alkoxy-α,β-unsaturated-t-butyl ester **123** and Corey's DMSY reagent, a chemoselective (methyl ester unchanged), regioselective (observed exclusively 1,4 addition) and stereoselective reaction yielded a 5:2 mixture of two *trans*-cyclopropane diastereoisomers, where the major isomer possessed the desired $8S,9R,11R$ relative stereochemistry. The origin of the stereocontrol in the aforementioned reaction is worthy of discussion. There are two possible explanations for the exclusive formation of the two *trans*-cyclopropane products **134**. The first is that any *cis*-cyclopropane that forms is then equilibrated under the basic reaction conditions, *via* an enolate, to the thermodynamically favoured *trans*-cyclopropane product. However, the equilibration of *cis*-cyclopropanes bearing both electron withdrawing and hydroxymethylene groups has been studied.[53] Significantly, under the basic conditions of sodium hydride in dimethyl sulfoxide, no isomerisation of *cis*-cyclopropane **137** was observed. Dechoux and Doris found, quite interestingly, that by changing the solvent to hexamethylphosphoramide (HMPA) then the reaction did give the *trans*-isomer. They postulated that the isomerisation of the bis-anionic intermediate **138** occurred *via* a thermodynamically

controlled process that involved the formation of the enolate intermediate **139** (Scheme 38).

Scheme 38
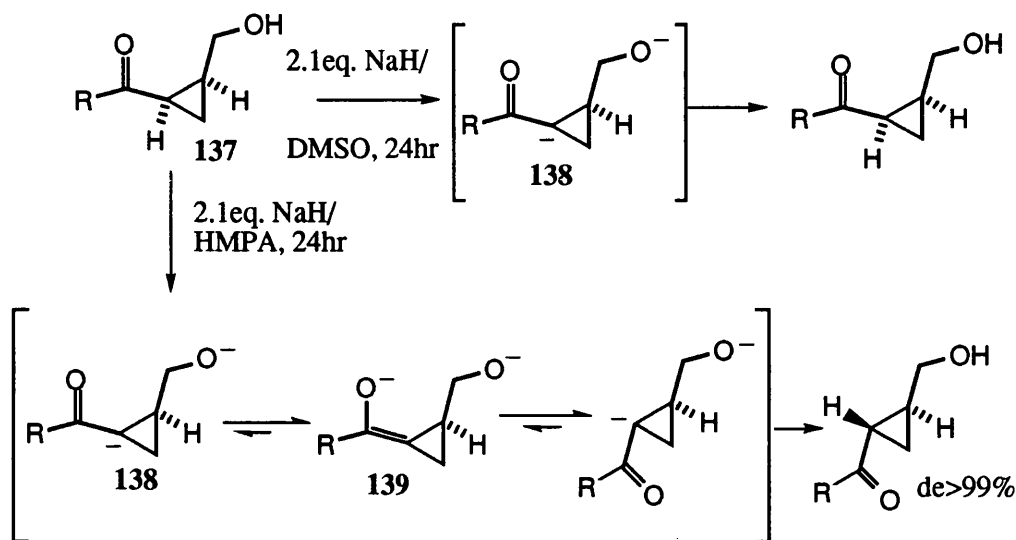
They reasoned that the cyclopropane ring provided an energy barrier to the inversion of bis-anionic species **138** and that the presence of HMPA offered a better driving force for the planarity of the carbanion. Therefore, in the latter case enolate **139** could be generated through which equilibration to the more stable *trans*-isomer then occurs. In view of these results and the fact that Kaiser and Trost isolated entirely *trans*-cyclopropanated *t*-butyl ester **140** using just 1.1 equivalents of DMSY (discussed earlier), an alternative, and more likely explanation for the exclusive formation of the *trans*-isomers **134** is as follows. Addition of DMSY to the β-carbon of unsaturated *t*-butyl ester **123** produces sulfoxonium ions **141a** and **141b**. The alternative conformations **142a** and **142b**, which would give a mixture of *cis*-cyclopropane products, are not as stable as **141a** and **141b** due to the steric demands of the *t*-butyl ester group. It is the energetically more stable conformations **141a** and **141b**, which are present in solution and they give the two *trans*-cyclopropane isomers **134** by S$_N$2 attack of the carbanion and loss of dimethylsulfoxide (Scheme 39).

Scheme 39

Nu = Me–S(=O)=CH₂ (Me)

Nu

a ⇓ R

H—⫽—H

b ⇑

ᵗBuO—C(=O)—O

Nu **123**

a: Me₂S⁺(=O) ... R, H—|—H, ᵗBuO—C(=O) **141a**

142a R, H ... H, ᵗBuO, Me₂(O)S⁺, O

b: **141b** H, R ... H, ᵗBuO, Me₂(O)S⁺, O

Me₂S⁺(=O) ... R, H ... H, ᵗBuO—C(=O), O **142b**

R, H—◁—H, ᵗBuO—C(=O)—O **134**

R, H—◁—H, ᵗBuO—C(=O)—O **5 : 2**

O, MeO—C(=O), MPMO
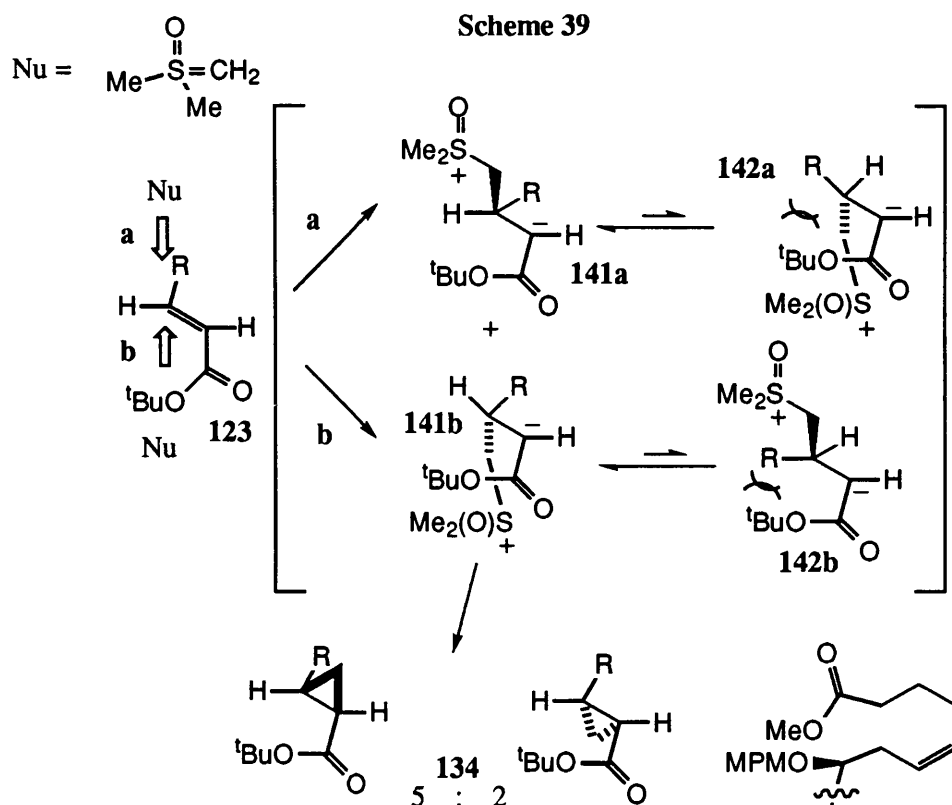
This proposal is consistent with arguments already described by Kaiser, Trost, and Magnus, used to explain the high selectivity observed in the cyclopropanation of α,β-unsaturated *t*-butyl esters.

Now the question of relative stereochemical control is discussed. Assuming that the addition of DMSY to **123** is irreversible then the following stereochemical arguments can be put forward. The reaction of γ-alkoxy-α,β-unsaturated esters with a variety of nucleophiles has been studied.[54-57] It appears that there are two distinct sets of experimental findings. There exists a set of reagents which lead to adducts whose stereochemistry at the β-carbon is exclusively related to that of the γ carbon on the γ-alkoxy-α,β-unsaturated ester. Therefore the double bond geometry of your substrate is not important to the stereochemical outcome in such reactions. Reagents that belong to this category include 1-acetoxy-2-(trimethylsilyl)methyl-2-propene, cyclopentadiene, isopropylidenediphenyl-sulfurane and amines. For either (*E*) or (*Z*) γ-alkoxy unsaturated esters the reactive conformation shown in **model B** explains the stereochemical outcome of reactions with these reagents. This model was rationalised by Trost, where the approach of the reagent takes place from the least hindered side of

the starting unsaturated ester adopting the conformation shown in **model B**, whatever the stereochemistry of its C-C bond.[56] In this model the large alkyl substituent is perpendicular to the conjugated double bond and the hydrogen atom is, for steric reasons, eclipsing the conjugated double bond. However, there is also a set of reagents which will react with (Z)-γ-alkoxy unsaturated esters to give products whose β-stereochemistry can also be rationalised using **Model B**, whilst the same nucleophiles will give the opposite β-stereochemistry if the (E)-double bond isomer is used. A different model is obviously required to explain the latter results, and the reactive conformation shown in **Model A** has been proposed by Stork[57] and supported by Krief[54] and Yamamoto.[55] The conformation shown in **Model A** is thought to result from a favourable interaction between the p-orbitals on the double bond and an unshaired pair of electrons of the γ-oxygen. Such an interaction is only active if an (E)-double bond is considered and could be due to the electron withdrawing ester functionality. Reagents that are consistent with these experimental findings are osmium tetroxide, organocopper-boron trifluoride complexes and isopropylidene-triphenyphosphorane.
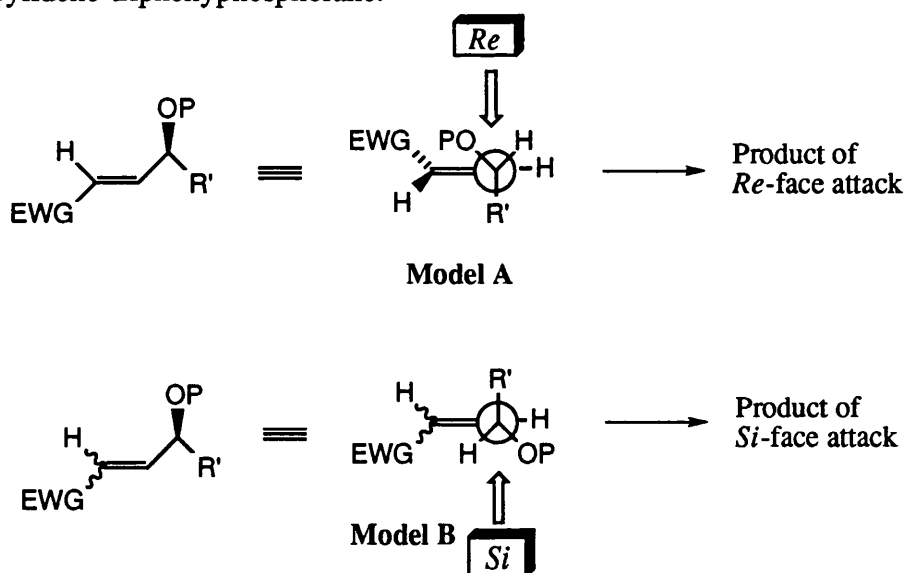
Model A

Model B

Therefore the 5:2 mixture of cyclopropane isomers was envisaged to be the result of (8S)-(E)-γ-alkoxy-α,β-unsaturated-t-butyl ester **123** preferentially adopting the conformation shown in **Model A**, since only this model predicts the generation of a 9R,11R cyclopropane product (Scheme 40).

Scheme 40

123   Model A

Model B

P=MPM=*p*-MeOC₆H₄CH₂-

134

5 : 2

8*S*,9*R*,11*R*

8*S*,9*S*,11*S*

R'=
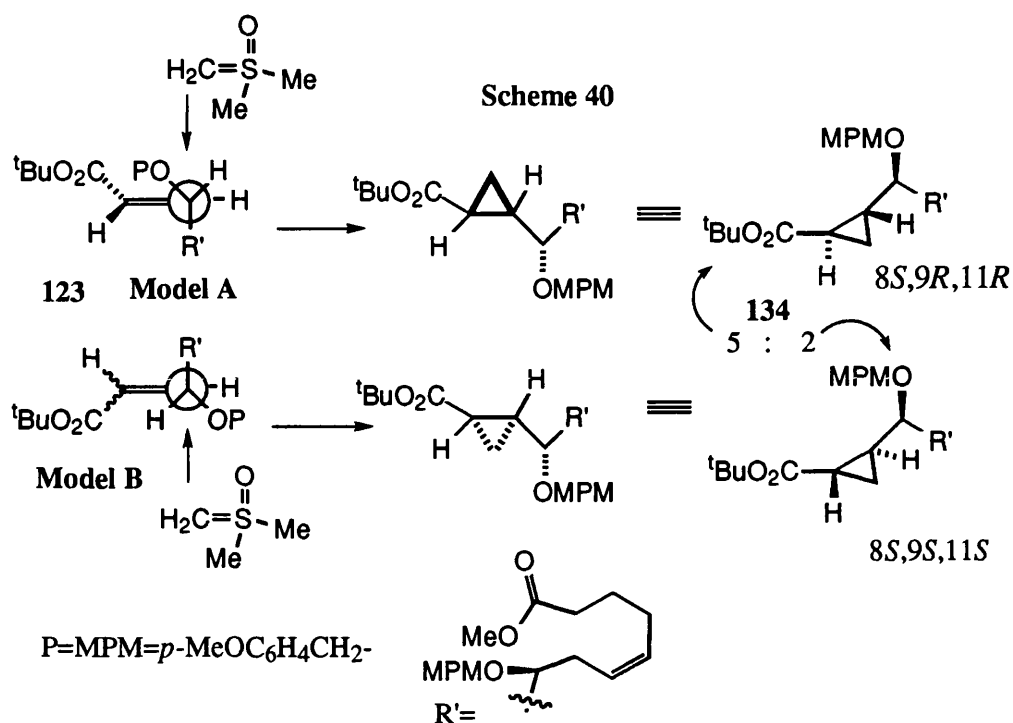
Since an understanding of a stereochemical outcome is best rationalised by considering the subtle energy differences between stereoisomeric transition states, the theoretical findings of Houk and colleagues are now discussed.[58] They have studied stereoselective additions to double bonds using *ab initio* quantum mechanics to predict transition state structures. By researching both nucleophilic and electrophilic additions to chiral allylic ethers the following generalisations have been made. For nucleophilic attack on π bonds, an electronegative allylic ether group (a=electron acceptor) would prefer to adopt an *anti* position so that the withdrawal of electrons from the π-system can be maximised. The most electropositive allylic substituent (d=electron donor) prefers the *outside* position in order to minimise the donation of electrons to the already electron rich π-system of the transition state, see **Model C**. Frontier molecular orbital theory has been used to qualitatively understand these preferences. When the σ*$_{C-A}$ orbital is aligned *anti* to the forming bond, its overlap with the HOMO of the transition state (which consists of the nucleophile HOMO and the alkene LUMO), is maximised, and the transition state is stabilised. An electropositive group prefers the *outside* position since the interaction of an occupied σ$_{C-D}$ orbital with the

transition state HOMO is destabilising. **Model C** and the accompanying frontier orbital diagram summarise this information.

Model C
D=electron donating
ie. alkyl chain
A=electron acceptor
ie. an alkyl ether

Important frontier orbital interactions

Transition State HOMO

Full arrow indicates a stabilising interaction
Dashed arrow indicates a destabilising interaction
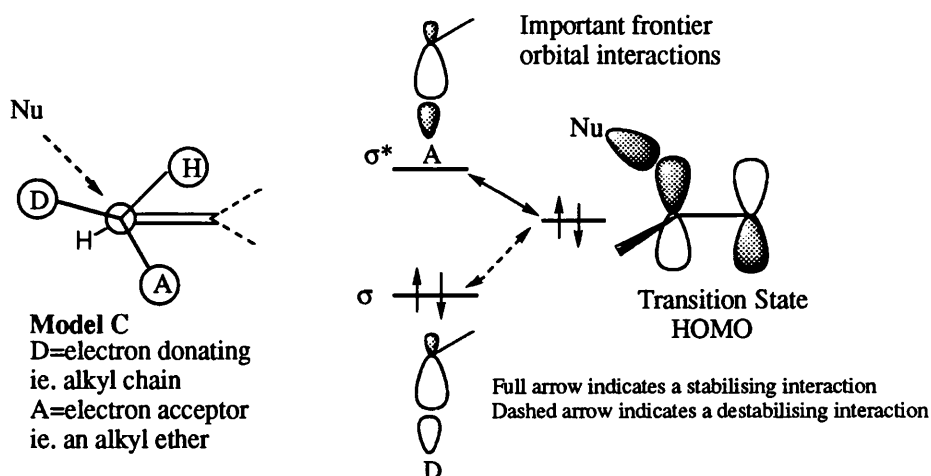
For electrophilic additions Houk has proposed that an allylic ether should adopt an inside position and that an alkyl substituent should prefer the sterically less crowded *anti* position in the transition state. In an electrophilic addition the olefin π-bond becomes electron deficient. Therefore only electron donating substituents on the alkene stabilise the transition state. With the alkyl substituent in the *anti* position its σ_{C-D} orbital can donate electron density to the LUMO transition state (which consists of the electrophile LUMO mixed the alkene HOMO. When the allylic ether is *anti*, the σ^*_{C-A} orbital will overlap with the alkene HOMO, which in turn has the undesired effect of decreasing the alkene HOMO interaction with the electrophile LUMO. Therefore, C-A favours the *inside* position to minimise electron withdrawal by σ^*_{C-A} from the already electron deficient transition state. Further, the allylic hydrogen atom is placed in the crowded *outside* position between the hydrogen atom on the double bond and approaching nucleophile. It is interesting that this information can be interpreted using the same **Model A** shown earlier, which was proposed by Stork to rationalise osmium tetroxide hydroxylations. Stork, however, established his model using very different arguments. The frontier orbital arguments of Houk are summarised below;

Important frontier
orbital interactions

Model A
D=electron donating
ie. alkyl chain
A=electron acceptor
ie. an alkyl ether

Full arrow indicates a stabilising interaction
Dashed arrow indicates a destabilising interaction

Transition state
LUMO
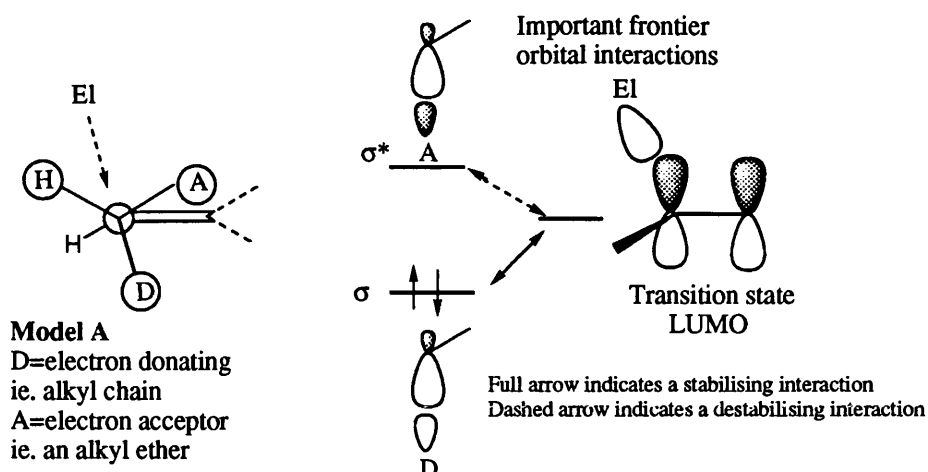
Strict application of the nucleophile addition **Model C** to our DMSY addition to α,β-unsaturated ester **123** does in fact predict the same stereochemical preference as we observed experimentally, *Re*-face attack. However, in **Model C** the large sterically demanding alkyl chain is positioned in the crowded *outside* region between the hydrogen atom on the double bond and the approaching nucleophile. It is possible that this factor accounts for the modest stereoselctivity we observed. The alkyl chain would prefer the less crowded *inside* position. Nucleophilic attack would occur, once again, *anti* to the electron withdrawing group as shown in **Model D** and *Si*-face attack is now predicted.
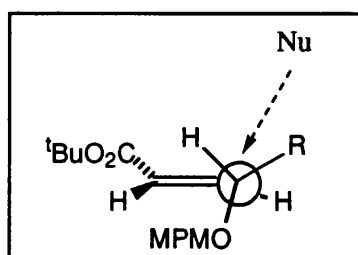
Application of **Model C**
to nucleophilic additions
to **123**. *Re*-face attack
is predicted.
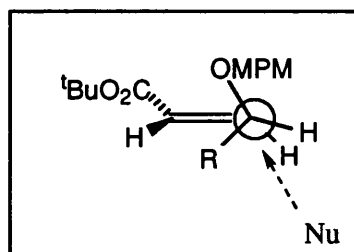
Application of **Model D**
to nucleophilic additions
to **123**. *Si*-face attack is
predicted.

In the knowledge that the $(8S,9R,11R)$-cyclopropane isomer **135** can be synthesised as the major component of the DMSY reaction with **123** (followed by deprotection), procedures to enhance the stereoselectivity could have been investigated. For example one might study different solvent, counter ion (i.e. could alternatively generate DMSY from trimethylsulfoxonium chloride), base, concentration and temperature effects. Changes in the protecting group could also have been looked at, where electronic and

steric factors could influence the stereoselectively dramatically. The conformations in **Model A** and **Model C** are both believed to exist due to dominating electronic factors. If such electronic interactions do exist then it would be interesting to probe this effect by making changes in the electron density at the γ-oxygen and the olefin. An enantiomerically pure sulfur-methylide, of matched selectivity to that which the reaction already possesses, would have enhanced its efficiency. For example Johnson in 1973 reported that (dimethylamino)phenyloxosulfonium methylide **144**, when resolved into enantiomerically pure form, could react with *trans*-methyl cinnamate **145** to give 76% of (+)-(1S,2S)-*trans*-methyl 2-phenylcyclopropanecarboxylate **146** in a modest 30% enantiomeric excess (Scheme 41).[29]

Scheme 41

Ylide precursor
(dimethylamino)methyl-*p*-
tolylsulfoxonium fluoroborate

enantiomerically pure sulfur ylide

30% e.e
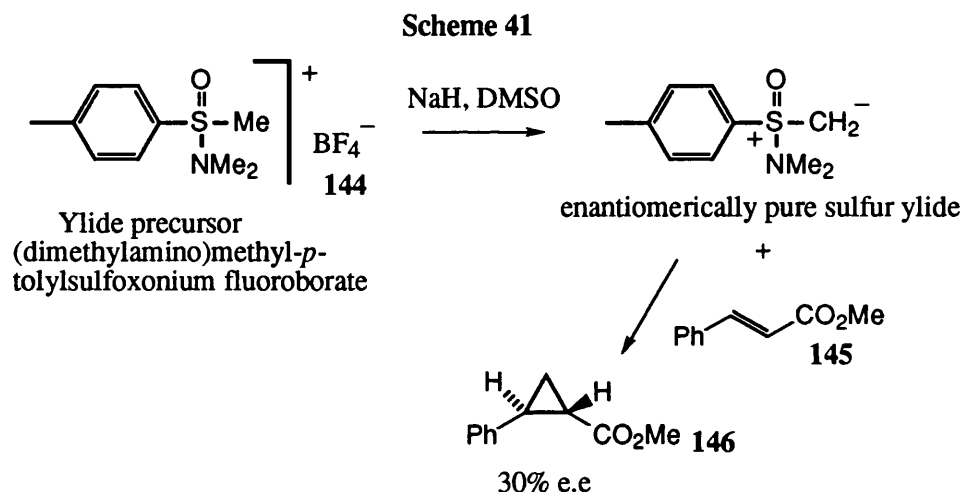
Optically active ylides derived from trialkyl-and diarylmethylsulfoxonium salts have been prepared but they racemise too quickly to be applicable to asymmetric synthesis.[29] The cyclopropanation of unsaturated N-methoxy-N-methyl amide compounds is known to proceed in higher yields and under milder conditions than is possible for the corresponding ketone analogues. Since the nitrogen atom of the hydroxamate is electron withdrawing it enhances the electrophilicity of the double bond thus making it more susceptible to Michael additions.[27(b)] Our application of an N-methoxy-N-methyl amide could, however, be problematical since its subsequent hydrolysis in the presence of lactone or ester functionality in order to expand the synthesis, might not have been possible.

In short, this interesting cyclopropanation reaction performed using the DMSY/ unsaturated ester combination, to give **134**, could have been thoroughly investigated, and thus optimised. However, we felt that due to time constraints the completion of the synthesis was our primary concern, and optimisation of this key step was not addressed.

We wished to continue the synthesis of the right fragment by converting both **135** and **136** to their respective nine-membered lactone derivatives. This was because we were only able to establish the relative stereochemistry of **135** once further synthetic manipulations had been performed. The cyclisation of hydroxy acids to furnish saturated nine-membered lactones is known to be problematical. Using any of the three standard macrolactonisation methods; the 2-thiopyridyl ester method of Corey,[59] the utilisation of 1-methyl-chloropyridium iodide-the method of Mukaiyama,[60] and the formation of a carboxylic 2,4,6-trichlorobenzoic anhydride, as described by Yamaguchi,[61] then at best saturated nine-membered lactones were isolated in 25%, 13% and 18% yields respectively. However, in 1982 Still reported[62] (with regard to his work on the C_{30}-C_{43} segment of Palytoxin **147**) that the presence of a (Z)-olefinic linkage provides "substantial enthalpic, as well as entropic benefit to the desired cyclisation." The enthalpic benefit is due to the elimination of important transannular repulsions in the product. Using molecular mechanics calculations, Still found that the most stable conformation of **148** was 6 kcal/mol more stable than saturated 8-methyl octanolide. In the event, the cyclisation of hydroxy acid **147** to **148** was achieved in 71% yield using the double-activation method of Corey which involves the formation of a 2-thiopyridyl ester (Scheme 42).

Scheme 42
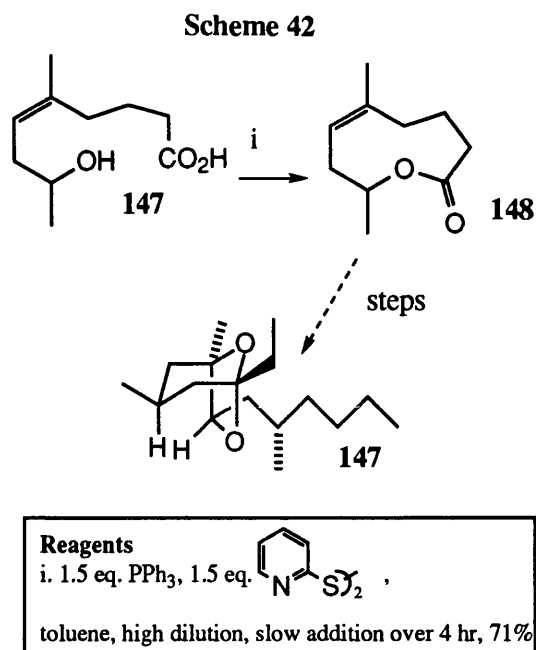
In common with the findings of Still, we were able to synthesise nine-membered lactones **149** and **150** in good yield by employing the lactonisation conditions first described by Yamaguchi.[61] Initially enantiomerically pure hydroxy *trans*-cyclopropane compounds **135** and **136** were smoothly converted to their nine-membered lactones by basic hydrolysis to give intermediate ω-hydroxy acids **135a** and **136a**. These were then lactonised to provide **149** and **150** in 75% and 76% yield respectively, over the two steps. The only observed side product was the dimeric species **151** which formed readily if high dilution and slow addition conditions were not employed. However, this unwanted eighteen-membered lactone **151** was usally formed in less than 5% yields and could be separated from the nine-membered lactone **149** by flash chromatography and then hydrolysed back to the hydroxy acid (**135a**) starting material (using lithium hydroxide) in excellent yield, >84% (Scheme 43).

Scheme 43

Reagents
i. 2.0 eq. LiOH, THF/H$_2$O/MeOH (4:1:1), RT, 16 hr, ii. 1.0eq. **135a** or **136a**, 1.5 eq. Et$_3$N, 1.1eq. 2,4,6-trichlorobenzoyl chloride, THF, RT, then 15 eq. DMAP, toluene, reflux, 75% yield (**149**) and 76% yield (**150**), iii. TFA, CH$_2$Cl$_2$, 2 hr, 100% yield (**152**) and 80% yield (**153**).
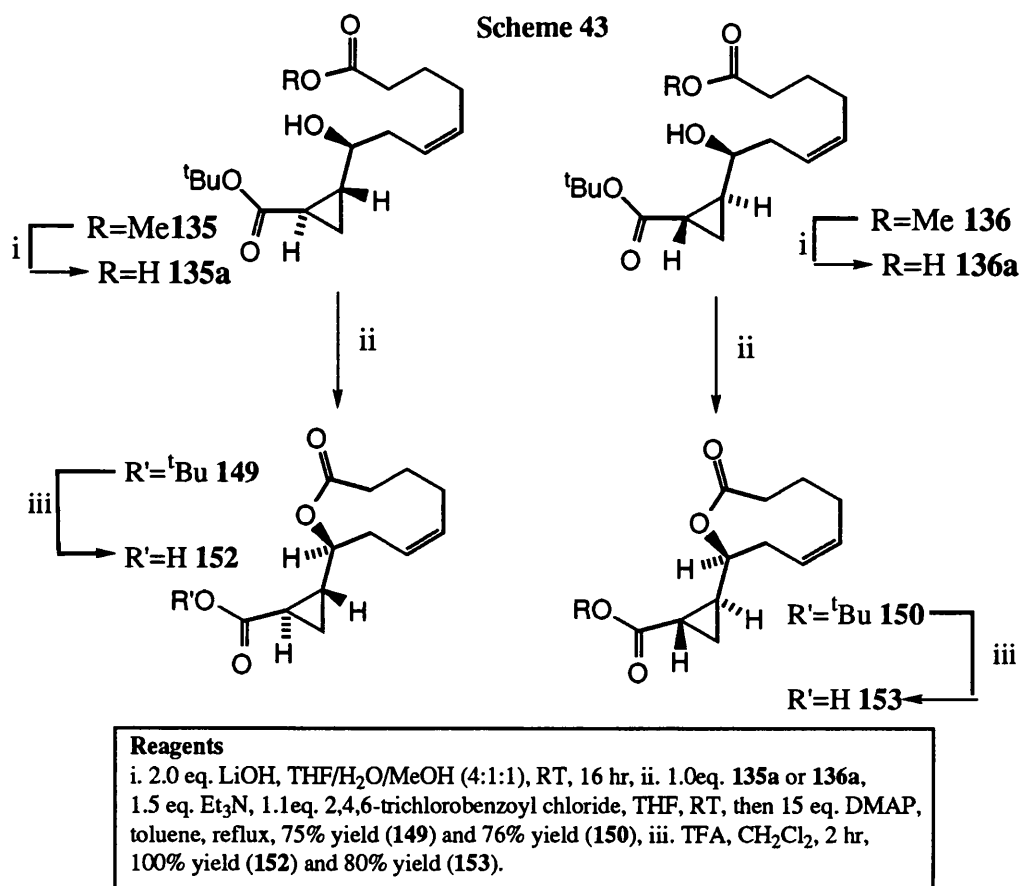
+ small amount of dimer, which is hydrolysed back to SM;
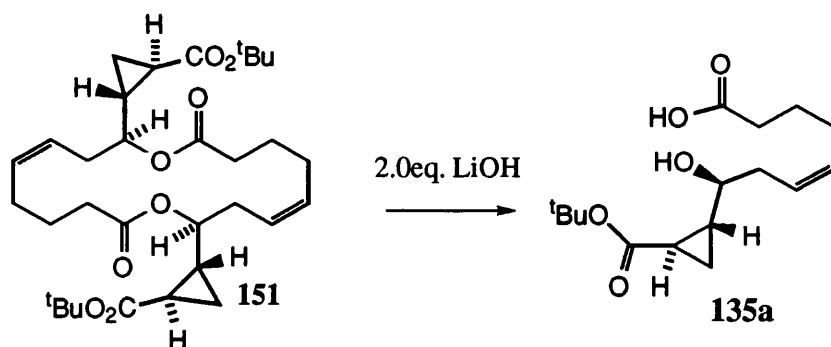
A detailed account of the lactonisation reaction(s) is as follows; First the carboxylic

2,4,6-trichlorobenzoic anhydride of **135a** (or **136a**) was prepared by mixing 1.1

equivalents of 2,4,6-trichlorobenzoyl chloride, 1.5 equivalents of triethylamine and

1.0 equivalent of hydroxy acid **135a** (or **136a**) in tetrahydrofuran at room

temperature over two hours. This solution, containing the mixed anhydride, was then

diluted with toluene and added very slowly to a dilute toluene solution containing

fifteen equivalents of 4-dimethylaminopyridine (DMAP) at reflux, using a syringe

pump (addition over six hours). Although DMAP is known to have remarkably high

catalytic activity in acyl transfer reactions, under these dilute lactonisation conditions a vast excess was required. It is thought that the hydroxyl group has an intramolecular interaction with the pyridinium ion, which due to entropic factors, facilitates the lactonisation (Scheme 44).

Scheme 44
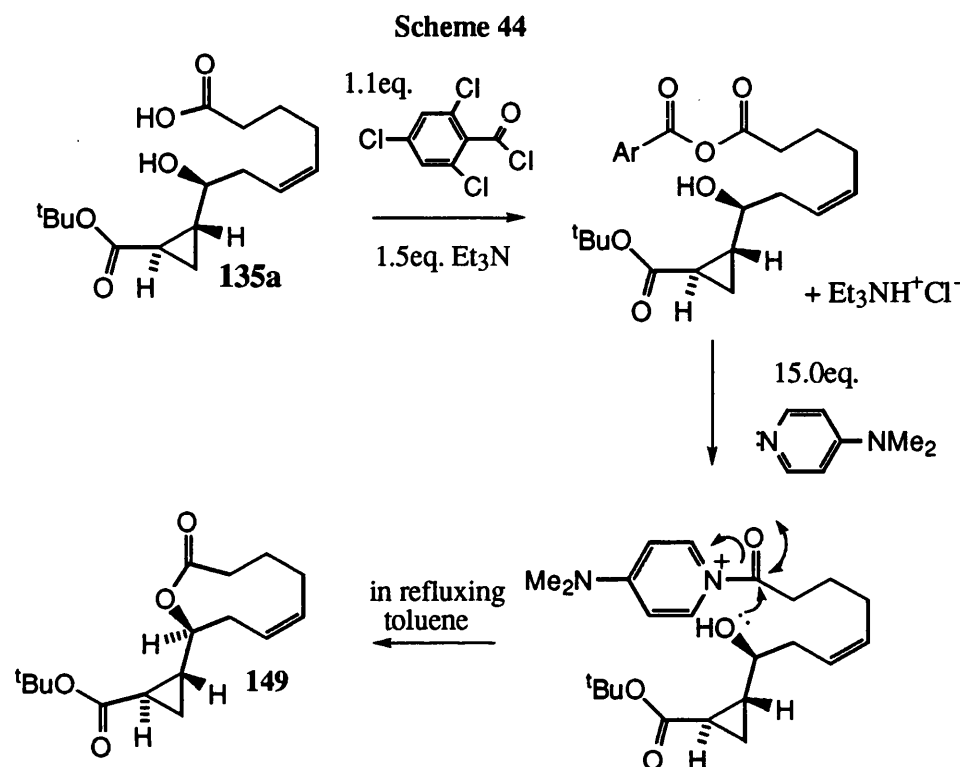
Conversion of **149** and **150** to their carboxylic acid derivatives **152** and **153** was achieved using trifluoroacetic acid in dichloromethane. Both carboxylic acid derivatives **152** and **153** were isolated in high yield using these conditions; 100% and 80% respectively. The acidic hydrolysis reaction to provide **152** and **153** was actually of some concern. In fact we found that extended reaction times did lead to the formation of a yet more polar by-product (observed by thin layer chromatography). This very polar compound was not characterised but could be the product of either slow acid hydrolysis of the lactone ring, or the reaction of trifluoroacetic acid with the cyclopropane ring. Since the reactions of cyclopropane rings are quite often analogous to those of double bonds, the electrophilic addition of trifluoroacetic acid to the cyclopropane ring would not be surprising. Suitable crystals for X-ray crystallographic analysis were grown from **152**, the major diastereomer, in a solution

of dichloromethane and cyclohexane over two weeks. The X-ray structure is shown below and reveals that isomer **152** contains the correct 8*S*,9*R*,11*R* relative stereochemistry for the completion of the synthesis of both neohalicholactone **1** and halicholactone **2**. It is interesting that **152** adopts a very similar conformation to the corresponding region of neohalicholactone itself (see Appendix 1).[63]

<u>Comparison of the X-Ray Crystal Structures of Neohalicholactone **1** and</u>

<u>8*S*,9*R*,11*R*-(-)-Carboxylic acid **152**.</u>

neohalicholactone **1**.

8*S*,9*R*,11*R*-(-)-**152**
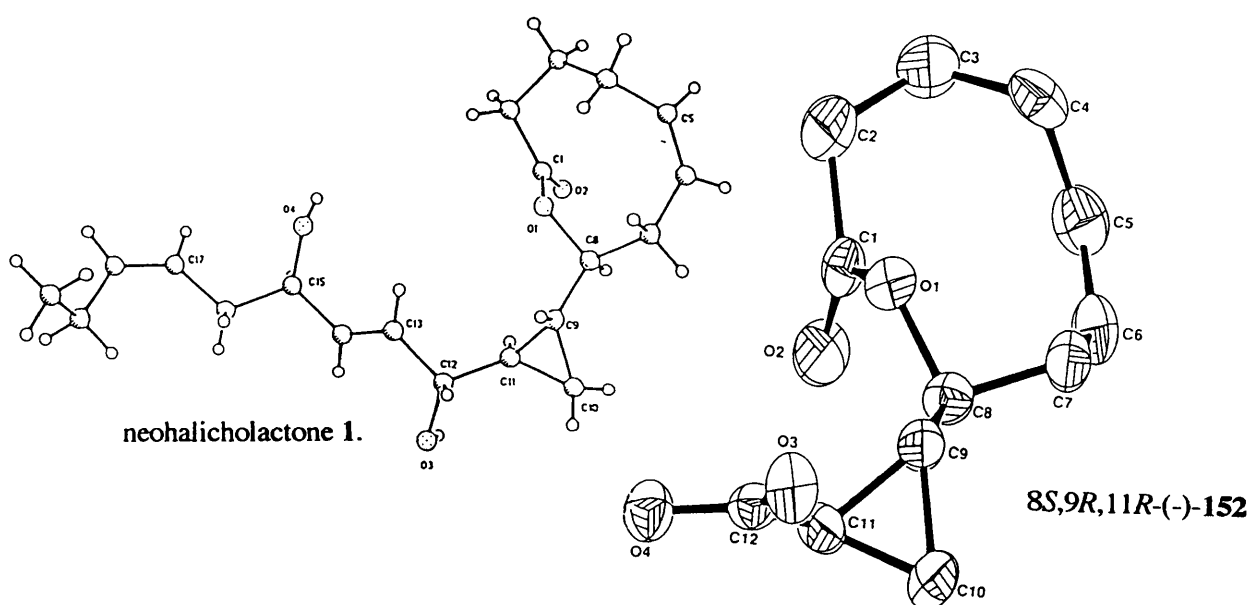
With 8*S*,9*R*,11*R*-carboxylic acid **152** in hand, its reduction to an aldehyde was then investigated. We anticipated that a two step procedure would be required, where reduction to an alcohol would be followed by oxidation to the desired aldehyde. One method of reducing carboxylic acids to alcohols in the presence of a wide range of functional groups is to use diborane.[64] For example diborane (B_2H_6) has been used to reduce selectively carboxylic acids in the presence of ketones, esters and electron deficient double bonds. In fact carboxylic acid **154** had been selectively reduced to its corresponding alcohol using borane-methyl sulfide complex (BMS). Importantly

BMS complex was not reported to react with either the double bond or ester functionality also found in **154** (Scheme 45).[65]

Scheme 45

The reduction step was one of four steps that yielded the azide in 31% overall.
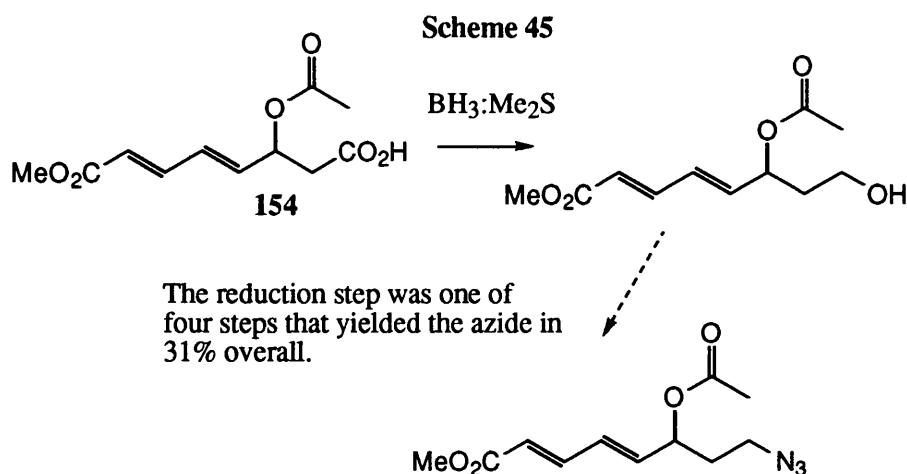
However our attempts to reduce carboxylic acid **152** with one equivalent of BMS complex in tetrahydrofuran at room temperature were unsuccessful. After the initial evolution of hydrogen as the carboxylic acid reacted with BMS complex, suddenly the reaction mixture solidified. After quenching the reaction, thin layer chromatography analysis indicated that the starting material had been consumed and that only base line material had formed. The ^{1}H-NMR of this crude polar material was extremely messy, but importantly no olefinic protons could be observed between 5-6 ppm. This indicated that the electron rich double bond in the lactone ring was undergoing hydroboration under these reaction conditions.

Instead we successfully employed methodology which involved the initial formation of a carbonic-carboxylic anhydride, which was then reduced using sodium borohydride (NaBH4).[66] Carboxylic acid **152** dissolved in tetrahydrofuran was treated with ethyl chloroformate in the presence of triethylamine to yield the corresponding mixed-anhydride. The deposited triethylamine hydrochloride was then filtered, and the purified mixed-anhydride reduced with NaBH4. Alcohol **155** was isolated in 77% yield, a yield indicative of a remarkably selective reduction. Finally **155** was oxidised to aldehyde **156** in almost quantitative yield using the catalytic, mild and convenient (5 mol% tetra-*n*-propylammonium perruthenate/1.5 equivalents N-morpholine N-oxide) procedure first described by Ley and colleagues in 1987 (Scheme 46).[67(a)-(c)]

Scheme 46

Reagents
i. (a) 1.0 eq. ethylchloroformate, 1.0 eq. Et$_3$N, THF, -5°C, 30 min,
(b) 2.5 eq. NaBH$_4$, H$_2$O, 77%; ii. 1.5eq. NMO/5mol% TPAP, CH$_2$Cl$_2$,
20 min, RT, 99%.
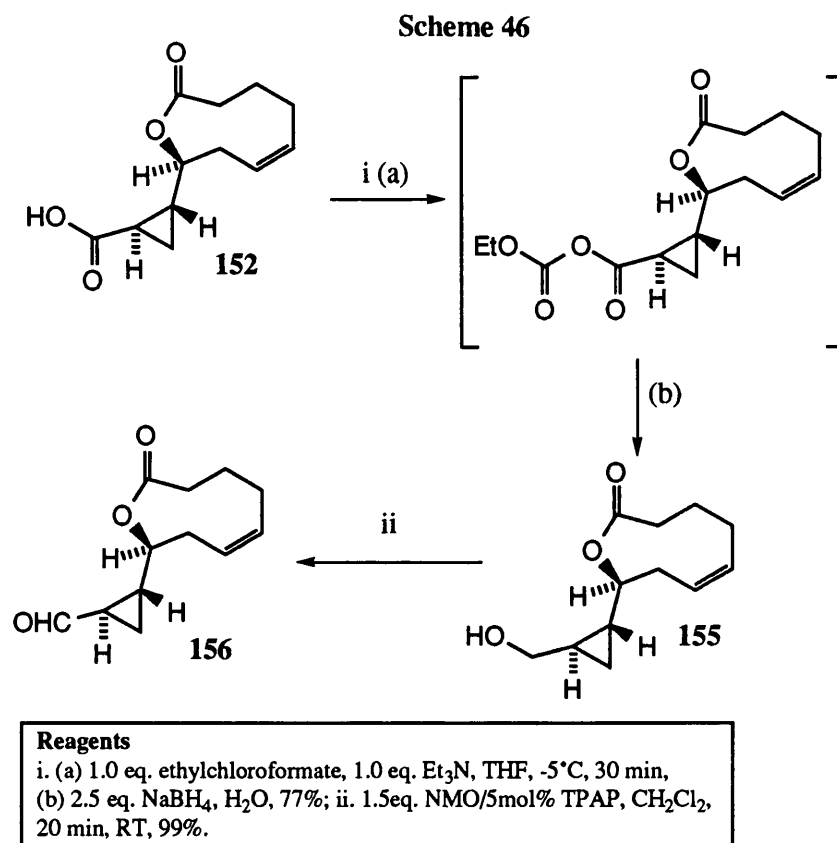
Therefore the synthesis of the right hand fragment was completed in sixteen steps from

(S)-malic acid **86**, in a satisfactory 7.5% overall yield. Using the reaction sequence

summarised below in Scheme 47, we were able to prepare several hundreds of

milligrams of enantiomerically pure 8S,9R,11R-aldehyde **156**.

Scheme 47

8S,9R,11R-(-)-135   5:2   8S,9S,11S-(+)-136

separate by
flash chromatography

MPM=p-methoxyphenylmethyl
-CH2C6H4OMe-p

8S,9R,11R-(+)-149   8S,9R,11R-(-)-156
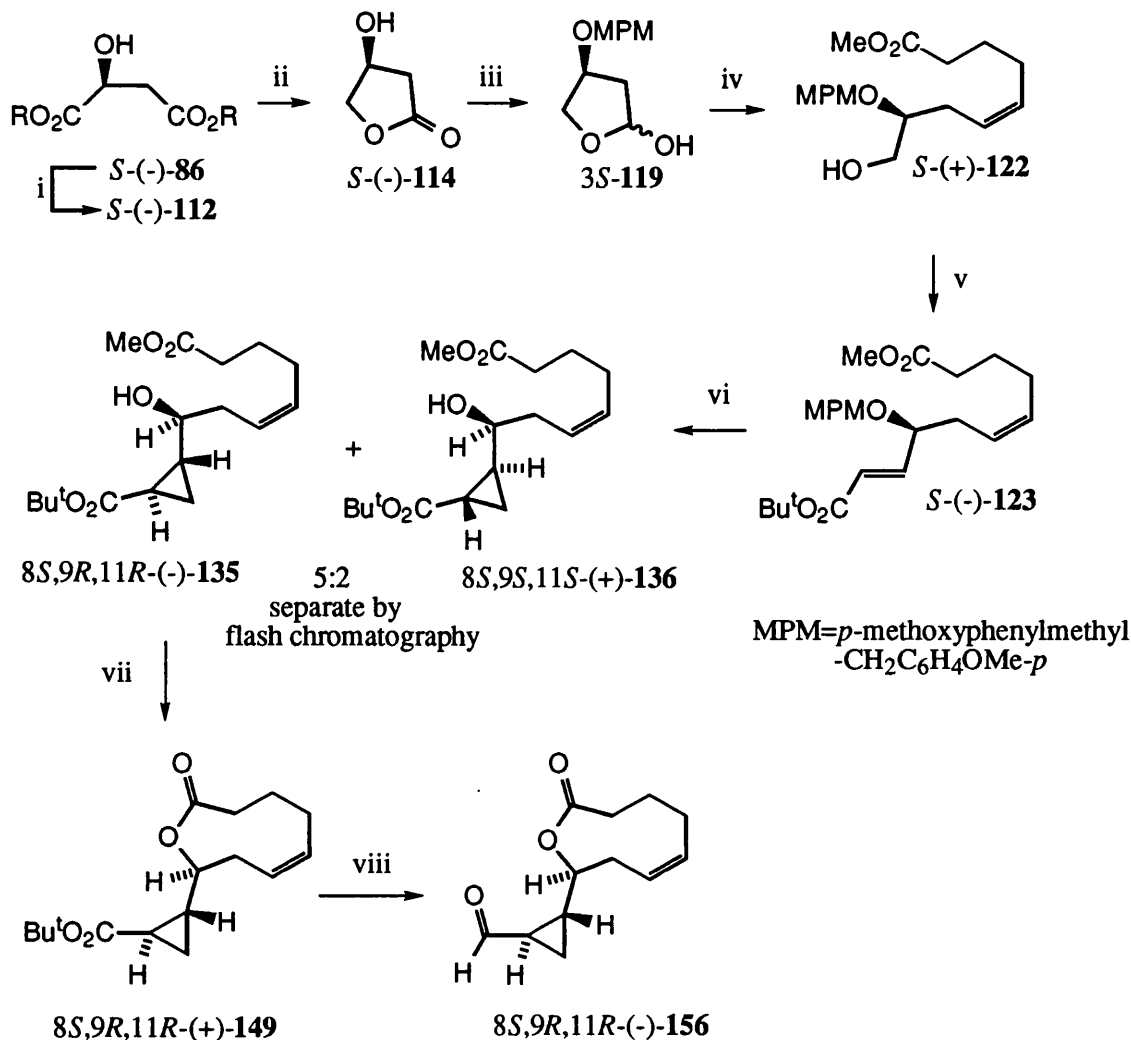
Reagents
i. MeOH, 3% AcCl, RT, 81%; ii. a) BH₃.SMe₂, cat. NaBH₄, THF, 92%; b) excess 0.1N HCl, 60°C, 72%; iii. a) 1.5 eq. MPM trichloroacetimidate, cat.F₃CSO₃H, 92%, b) 1.1 eq. DIBAL-H, toluene, -40°C to -20°C, 100%; iv. Wittig reaction (see Scheme 31), then esterification with MeOH/AcCl solution, 69%; v. a) 1.2 eq. (COCl)₂, 2.4 eq. DMSO, 5.0 eq. Et₃N, CH₂Cl₂, -78°C to 0°C, b) 1.1 eq. tert-butyl diethylphosphonoacetate, 1.1 eq. LiCl, 1.0 eq. DBU, CH₃CN, RT, 75% overall; vi. a) 2.0 eq. Me₂S⁺(O)CH₃I⁻/NaH, DMSO, 90°C, 74%, b) 1.1 eq. DDQ, CH₂Cl₂:H₂O (18:1), RT, 100% mass recovery, 69% desired isomer 135; vii. a) 2.0 eq. LiOH, THF:MeOH:H₂O (3:1:1), RT, 100%, b) 1.1 eq. 2,4,6,-trichlorobenzoyl chloride, 1.5 eq. Et₃N, THF, RT, then 15.0 eq. DMAP, toluene, reflux, 75%; viii. a) TFA, CH₂Cl₂, RT, 100%, b) 1.0 eq. ethylchloroformate, 1.0 eq. Et₃N, THF, -5°C, then 2.5 eq. NaBH₄, H₂O/THF, RT, 77%; c) 1.5 eq. NMO, 5 mol% TPAP, CH₂Cl₂, RT, 99%.

2.2 Synthesis of the Left Hand Fragments of Neohalicholactone **1** and Halicholactone **2**.

We wished to prepare both suitably protected vinyl-metal species **82a** and **82b**, the complementary fragments to the right hand fragment, aldehyde **156**, in the proposed synthesis of neohalicholactone **1** and halicholactone **2** respectively. We anticipated that vinyl metal species **82a** and **82b** could be prepared from either an alkyne or vinyl halide precursor *via* a hydrometallation or halogen metal exchange reaction, respectively.
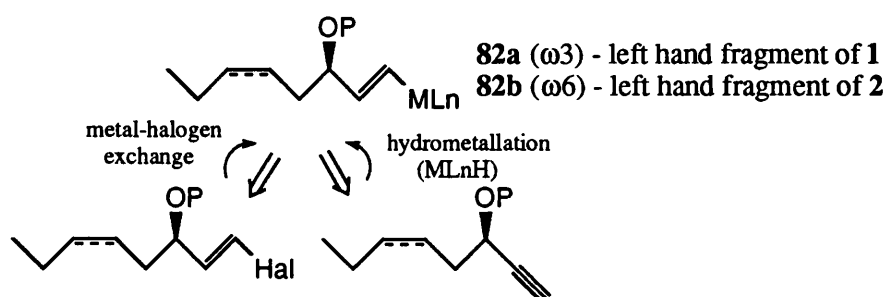
The (*E*)-1-octen-3-ol unit, in enantiomerically pure form, is present in numerous arachidonic acid metabolites. Therefore the synthesis of this structural unit has been studied extensively.[30] An efficient procedure used to obtain racemic (*E*)-1-iodo-1-octen-3-ol **157** was reported by Corey and Beams in 1972.[68(a)-(c)] The three step procedure (**A**), where **157** was isolated in 79% yield from hexanoyl chloride, is shown below in Scheme 48. Procedure (**B**) involves the reaction of lithiated (*E*)-1,2-bis(tributylstannyl)ethylene with hexanal at low temperature.[69,70] The vinyl tin intermediate **158** was then treated with iodine to give **157** in 83% yield (Scheme 48).

Scheme 48
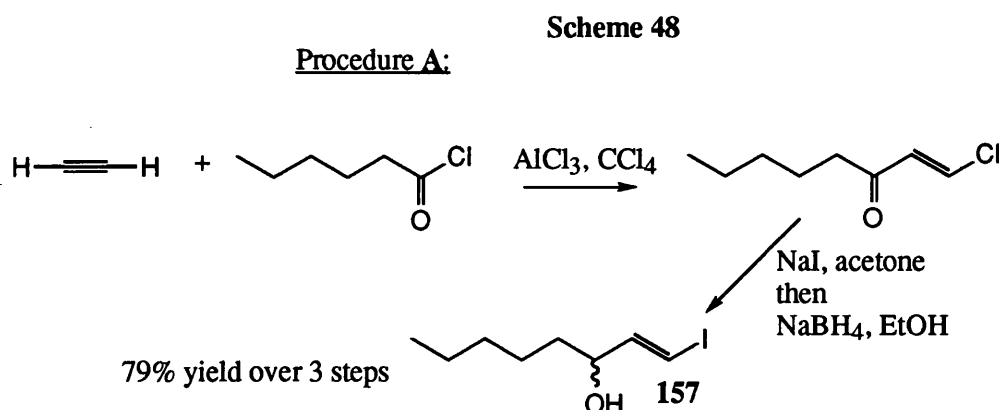
Procedure A:

Procedure B:
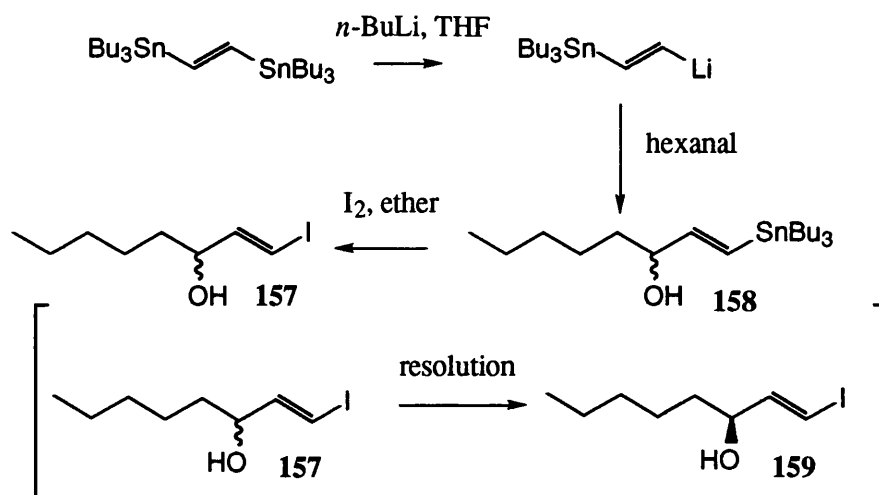
Resolution of racemic **157** to afford (3*S*,1*E*)-1-iodo-1-octen-3-ol **159** was achieved

through the crystalline (-)-α-methylbenzylamine salt of the hydrogen phthalate.[68(c)]

Subsequent hydrolysis returned **159** in enantiomerically pure form. However, **159**

was isolated in a poor yield, approximately 10%. Using the same resolution

procedure, (*S*)-1-octyn-3-ol **163** could also be prepared from racemic material.[71]

The acetylene to *trans*-iodo alkene transformation has been achieved by selective

hydroalumination,[72] hydroboration,[68(c)] hydrostannallation,[73(a)-(e)] and hydro-

zirconation reactions[74(a)-(d)] where the vinyl metal species that is generated *in situ* is

then treatedwith iodine. Such transformations are summarised below;

Metals = Sn, Al, B, Zr

Impotant fatures of the alkyne to *trans*-iodo
alkene transformation are; (1) the sterically
demanding metal regiospecifically adds to the
less hindered end of the acetylene and produces
an *E*-vinyl metal species.
(2) electrophilic carbon-metalbond cleavage
with retention

via front side attack
on the C-M bond

trans-iodo alkene
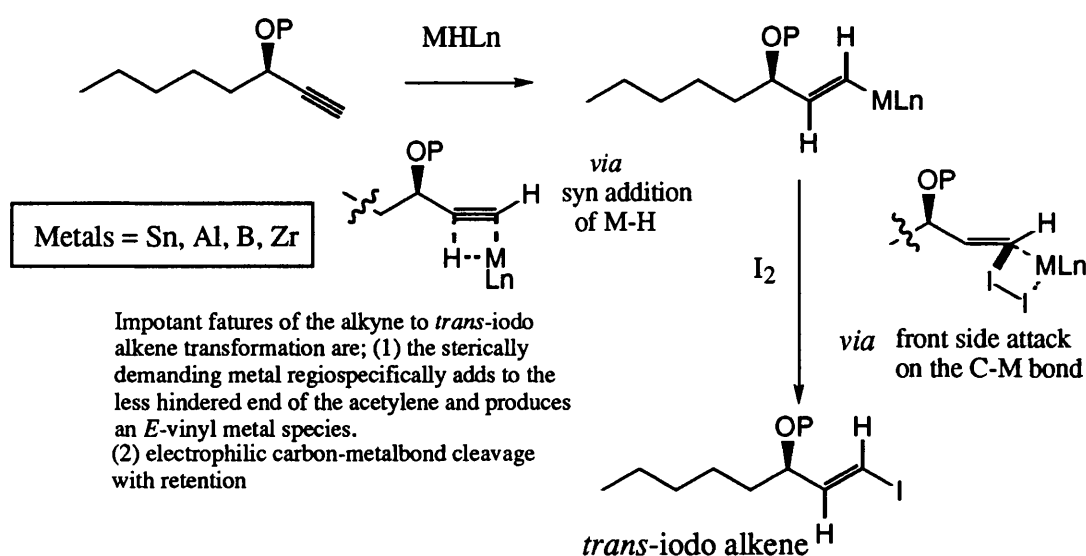
In 1975 Sih and colleagues reported that , whilst α,β-unsaturated ketones did not

yield allylic alcohols by enzymatic reduction (due to resonance stabilisation of the

ketone), (1E)-1-iodo-octen-3-one **160** could be reduced enzymatically.[75] An

electronegative substituent such as iodine interferes with the usual α,β-unsaturated

ketone resonance thus enabling the enzymatic reduction to be achieved. The reduction

of **160** using washed cells of *Penicillium decumbens* gave (3S)-alcohol **159** in 10%

yield and 80% enantiomeric purity. Some years later (in 1979) Noyori and coworkers

published their exciting experimental findings regarding the reduction of (1E)-1-iodo-

1-octene-3-one **160**.[76] Using a chiral binaphthol-modified aluminium hydride

reagent ((S)-BINAL-H **161**), *trans*-iodo ketone **160** was reduced to **159** in 95%

yield and in an impressive 97% enantiomeric excess. The asymmetric reduction of

acetylenic ketone **162** with (S)-BINAL-H **161** in tetrahydrofuran at low temperature

(-100°C) gave (S)-1-octyn-3-ol **163** in 84% enantiomeric excess and 87% yield

(Scheme 49).[77(a)-(b)]

Scheme 49

160 → a or b → **159**

(3S) stereochemistry
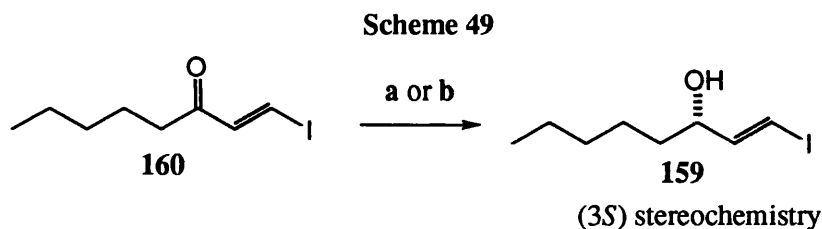
Method of reduction:
a. *Penicillium decumbens* (enzymatic reduction)-10% yield, 80% e.e
b. (S)-BINAL-H-95% yield, 97% e.e

162 → a or b → **163**
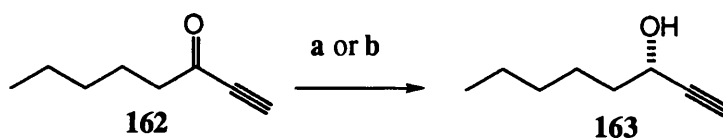
Method of reduction:
a. (S)-BINAL-H, 87% yield, 84% e.e; b. (S)-Alpine-borane, 65% yield, 92% e.e

161

(S)-BINAL-H

164

(S)-Alpine-borane
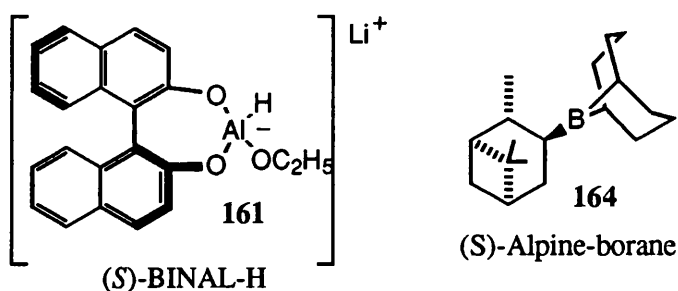
Alternatively, ketone **162** can be reduced using (S)-β-3-pinanyl-9-borabicyclo[3.3.1] nonane (Midland's reagent), in 92% enantiomeric excess and 65% yield (Scheme 49).[78] A more recent synthesis of *trans*-iodo alkene **159**, which employs the Sharpless asymmetric epoxidation reaction, has been reported by Sato. The Sharpless epoxidation of γ-tributylstannyl allylic alcohol **158** proceeded with a large rate difference for the two enantiomers, enabling a very efficient kinetic resolution.[79] In the event, (S)-**159** was isolated in 42% yield and >99% enantiomeric excess after quenching (S)-γ-tributylstannyl allylic alcohol **165** with iodine directly after the kinetic resolution. Fortunately, the epoxy alcohol **166** decomposed upon addition of iodine, thus (S)-**159** was readily isolated after chromatography. Similarly, kinetic resolution of racemic *trans*-iodo alkene **157** was achieved using D-(-)-diisopropyl tartrate as the chiral source.[70,80] By working up the reaction with aqueous sodium hydroxide, (S)-**159** was easily isolated in 45% yield and >99% enantiomeric excess (NaOH causes the decomposition of the epoxy alcohol by-product, see Scheme 50).

Scheme 50

Reagents
i. 1.0 eq. **158**, 1.5 eq. TBHP, 1.0 eq. Ti(i-OPr)$_4$
1.2 eq. D-(-)-DIPT, CH$_2$Cl$_2$, -20°C, 4.5 hr;
ii. I$_2$, ether.

159, 42% yield
> 99% e.e

R=C$_5$H$_{11}$

Decomposition

Also;

157

Reagents
i. 1.0 eq. **157**, 1.2 eq. D-(-)-DIPT, 1.0 eq. Ti(i-OPr)$_4$,
1.5 eq. TBHP, -20°C, CH$_2$Cl$_2$, 42 hr, followed by
aqueous sodium hydroxide work-up.

159, 45% yield,
>99% e.e

Decomposition
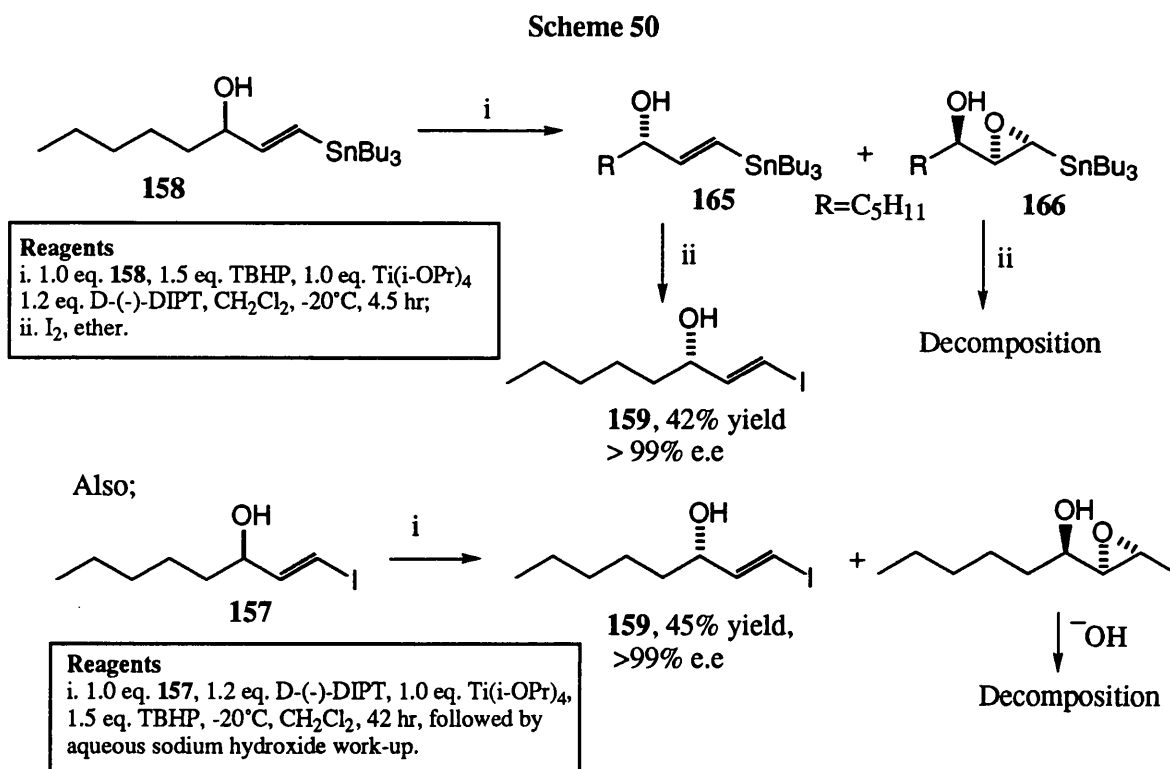
In 1988, Noyori and colleagues reported a convergent, one-pot construction of the prostaglandin framework.[81] For example, the synthesis of bis-silyl protected PGE2

methyl ester **167** was accomplished by the organocopper-mediated conjugate 1,4-addition of (3*S*)-*t*-butyldimethylsilyl-protected *trans*-iodo alkene **168** (prepared from (*E*)-1-iodo-1-octen-3-one **160** by asymmetric reduction using (*S*)-BINAL-H **161**, followed by silyl protection) to silyl-protected (*R*)-4-hydroxy-2-cyclopentenone **169** followed by trapping of the enolate intermediate by a side chain (*Z*)-allylic iodide **170**. Removal of the silyl groups and enzymatic ester hydrolysis furnished PGE₂ **171** in just three steps and in 61% overall yield from the three key building blocks **168-170** (Scheme 51). This work exemplifies the synthetic utility of *trans*-iodo alkene **168**.

Scheme 51

Reagents
i. organocopper reagent was prepared from 1.0 eq **168**, 2.0 eq *t*-BuLi in THF at -78°C for 2.5 hr, then add 1.0 eq. CuI in ether and 2.5 eq. Bu₃Ph. Then in THF add 1.0 eq. enone **169**, 11.0 eq. HMPA, 1.0 eq. Ph₃SnCl, at -78°C, and finally 5.0 eq. allylic iodide **170**, -30°C to -20°C, 78% yield; ii. 15% HF-Py mixture, 24°C, 4 hr, 98%; iii. enzymatic ester hydrolysis (porcine liver esterase), 86%.
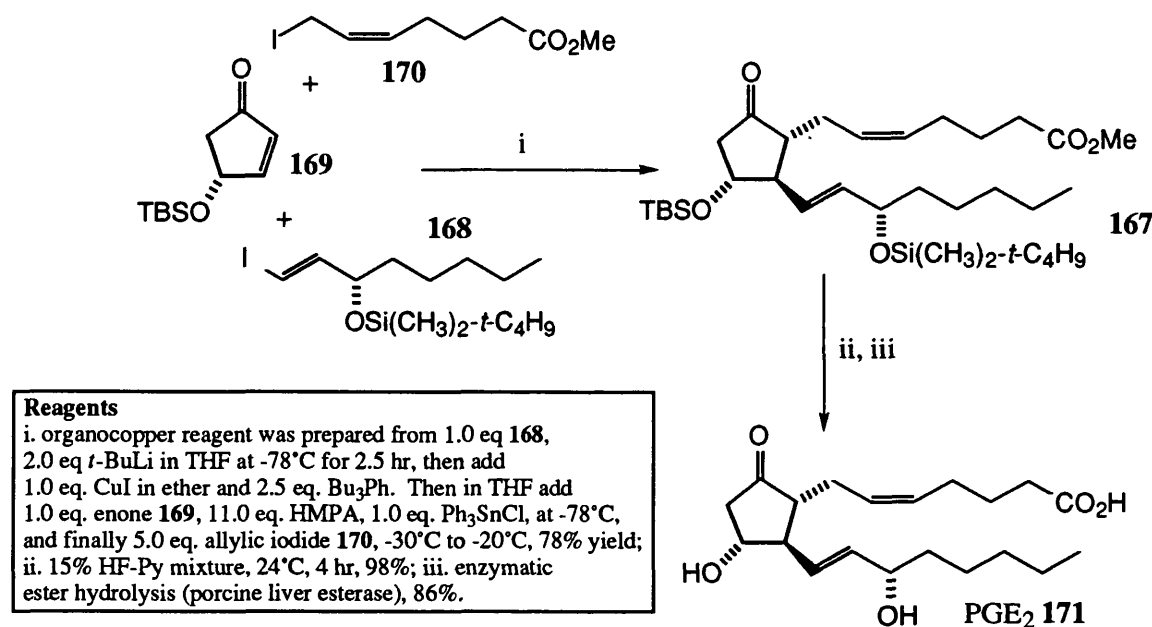
Recently, both (*S*)- and (*R*)-1-octyn-3-ol (**163 + 172**) have become commercially available. Therefore we could synthesise suitably protected 1-iodo-1-octene-3-ol derivatives **175** and **176** very simply from (*R*)-1-octyn-3-ol **172** in two steps and without the necessity for us to construct the C₃-*R* chirality (either using the asymmetric reduction methodology of Noyori (BINAL-H) or the kinetic resolution procedure reported by Sato). We synthesised both *t*-butyldiphenylsilyl and *p*-methoxyphenylmethyl protected derivatives of **172**, (**173** and **174** respectively).
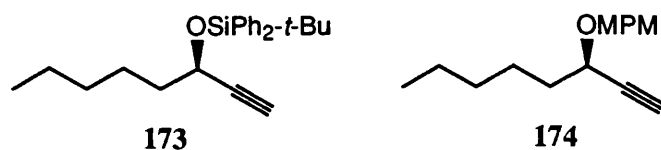
Differently protected intermediates **173** and **174** were prepared since we were not

sure which procedure would be most profitable in the coupling of the left and right

hand fragments. One coupling procedure, alkyne to vinyl borane and subsequent

transmetallation with diethyl zinc, (see section 2.3)[21(b)] that we wished to explore

would necessitate a protecting group stable to Lewis acidic conditions to be in place.

The t-butyldiphenylsilyl protecting group is stable to a vast range of reaction

conditions, including most importantly, Lewis acids such as boron-trifluoride etherate

and bromodimethylborane.[82] The p-methoxyphenylmethyl protecting group, whilst

unstable to Lewis acid conditions, would be compatible with the alternative mild

chromium(II) chloride/ catalytic nickel(II) chloride coupling procedure of Kishi and

Takai (see section 2.3).[22(a)-(b)] We felt that the p-methoxyphenylmethyl protecting

group would be advantageous, if the coupling conditions allowed, since it can be

deprotected using extremely mild and selective conditions.[45] Using the standard t-

butyldiphenylsilyl chloride/imidazole/N,N-dimethylformamide protocol, **173** was

isolated in 89% yield. The p-methoxyphenylmethyl derivative **174** was also

synthesised with ease using p-methoxybenzyl chloride/ sodium hydride/ catalytic

tetra-n-butylammonium iodide/ N,N-dimethylformamide in 56% yield. With

differently 3-oxy-protected alkynes **173** and **174** in hand, their conversion to the

respective *trans*-iodo alkenes **175** and **176** was then addressed. We, in common

with Larock[74(d)], achieved this goal using the hydrozirconation-iodination procedure

first reported by Schwartz.[74(a)] We employed bis(cylopentadienyl)zirconium

chloride hydride (Cp$_2$Zr(H)Cl), known as "Schwartz's reagent", purchased from the

Aldrich chemical company. The reagent was used within a few days of being

received since it is known to have a short shelf life. The hydro-metallated product

was then treated with iodide, providing (3R,1E)-3-((t-butyldiphenylsilyl)oxy)-1-iodo-

1-octene-3-ol **175** and (3R,1E)-3-((p-methoxyphenylmethyl)oxy)-1-iodo-1-octene-3-

ol **176** in 94% and 77% yields respectively (Scheme 52).

Scheme 52

OSiPh2-*t*-Bu

175

OH

172 (3R)
commercially available

i, ii

iii, iv

OMPM

176
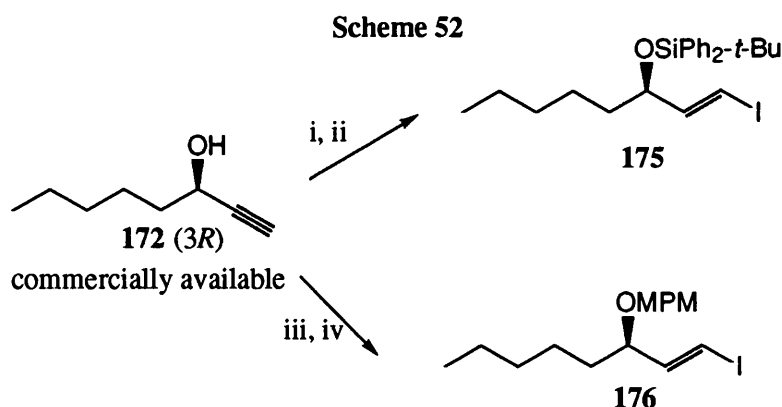
Reagents
i. 1.2 eq. TBDPSCl, 2.5 eq. imidazole, DMF, 89%; ii. 1.4 eq. Cp₂ZrHCl, 1.2 eq. I₂, THF, RT, 94%.
iii. 1.1 eq. *p*-methoxybenzyl chloride, 1.2 eq. NaH, 5 mol% Bu₄NI, DMF, 56%; iv. 1.4 eq.
Cp₂ZrHCl, 1.4 eq. I₂, THF, 0°C then further 0.8 eq. Cp₂ZrHCl, I₂, CH₂Cl₂, 77%.

We found the hydrozirconation reaction far more problematical with the *p*-
methoxyphenylmethyl protected substrate **174**. The reaction needed to be performed
at low temperature (0°C) and required 2.2 equivalents of bis(cylopentadienyl)
zirconium chloride hydride to achieve full conversion.

The synthesis of the more complex *t*-butyldiphenylsilyl protected-alkyne **178** and
trans-iodo alkene **179**, compounds possessing a 5*E* double bond, will now be
described. We wished to prepare (2*S*,4*Z*)-2-O-((*t*-butyldiphenylsilyl)oxy)-4-heptenal
180, a key intermediate in the synthesis of both alkyne **178** and *trans*-iodo alkene
179. We anticipated that from **180**, *trans*-iodo alkene **179** could be prepared in just
one step using the Takai olefination reaction,[83] whilst alkyne **178** could be
synthesised in one step using the anion of dimethyl (diazomethyl)phosphonate
(Gilbert reagent)[84] or in a two step sequence using Corey/Fuchs methodology-which
involves an intermediate dibromide **181** which is then treated with *n*-butyllithium
(Scheme 53).[85]

Scheme 53
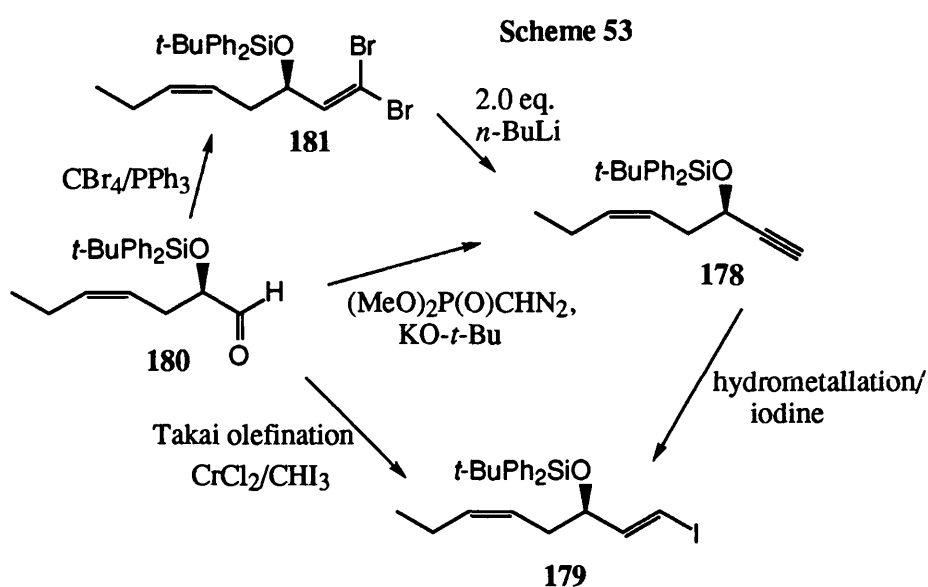
A literature search revealed that the Merck Frosst laboratories had reported the nine step synthesis of (2S,4Z)-2-O-((t-butyldiphenylsilyl)oxy)-4-decenal **182** (a two carbon homologue of aldehyde **180**) during the preparation of (12S)-HETE.[86] The synthesis of 2-deoxy-4,5-O-isopropylidene-D-erythro-pentose diethyl dithioacetal intermediate **183** was first described by Gray in 1978 (Scheme 54).[87] White and colleagues used identical chemistry to that described in Scheme 54 to prepare aldehyde **182**.[18(b)] They reacted **182** with iodoform and chromium(II) chloride (Takai reaction) to give (3S)-(1E,5Z)-3-O-((t-butyldiphenylsilyl)oxy)-1-iodo-1,5-undecadiene **184** in 54% yield. After deprotection, the free hydroxyl-*trans*-iodo alkene derivative **90** was coupled to the appropriate aldehyde fragment **77'** in the synthesis of constanolactones A **34** and B **35** using Kishi/Takai conditions[22] (see Scheme 18 in introduction and see Scheme 55).

Scheme 54
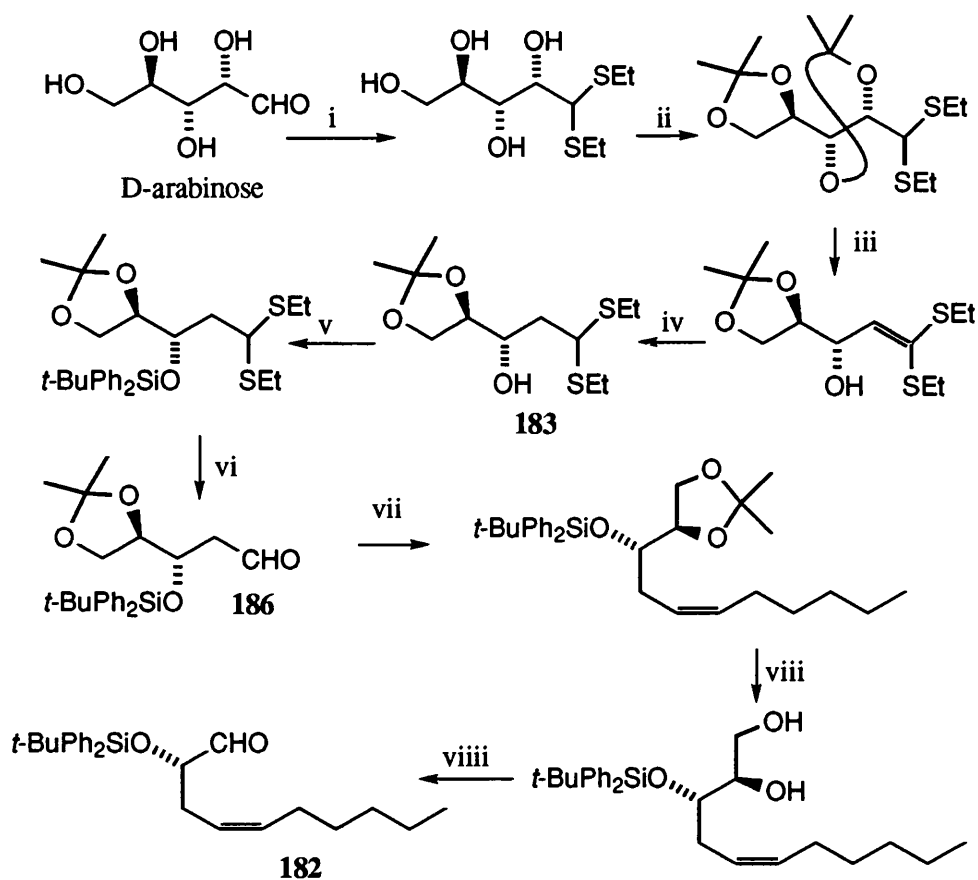
Reagents
i. EtSH, HCl; ii. Me₂CO, H₂SO₄, 80% two steps; iii. 1.5 eq. *t*-BuOK, Me₂SO-THF (1:3), 82% yield;
iv. 2.5 eq. LiAlH₄, THF, 80%; v. 1.1eq. NaN(SiMe₃)₂, 1.2 eq. *t*-BuPh₂SiCl, THF, -78°C, to RT, 92%;
vi. NCS/AgNO₃, CH₃CN/H₂O, 77%; vii. 3.0 eq. 1-hexylidenetriphenyl phosphorane, then at -78°C add
1.0 eq. aldehyde **186**, THF, -78°C, 10 mins then RT for 2 hr, 90%; viii. TFA, THF/H₂O (4:1),
16 hr, 83%; viiii. 3.2 eq. sodium carbonate, 1.5 eq. Pb(OAc)₄, CH₂Cl₂, -78°C, 15 min, 91%.

Scheme 55
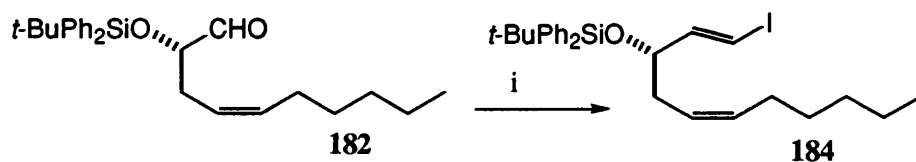
Reagents
i. 6.0eq. CrCl₂, 2.0eq CHI₃, THF,
18 hours, 0°C, 54%.

deprotection
then coupling
reaction

constanolactones A **34** and B **35**

Therefore by starting from L-arabinose (both L and D-arabinose are commercially available) aldehyde **185** antipodal to **186** should be easily prepared. The olefination reaction would be performed with 1-propylidene triphenylphosphorane (instead of 1-hexylidene triphenylphosphorane), and subsequent steps would be identical to those described in the synthesis of **182** (Scheme 56 and Scheme 54).

Scheme 56

L-arabinose

t-BuPh₂SiO **185**

t-BuPh₂SiO

180

t-BuPh₂SiO
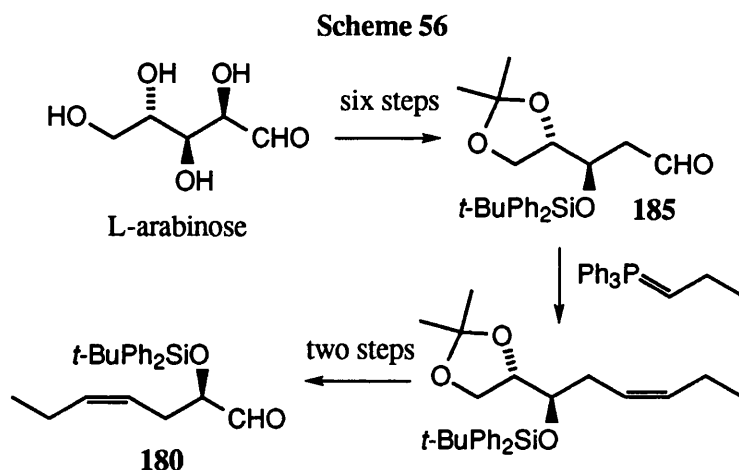
Aldehyde **180** would be prepared in nine steps using this methodology. We believed that a shorter synthesis of **180** (seven steps), as well as one which did not involve a degradation step, could be performed starting from (*R*)-malic acid **88**. Our approach to alkyne **178** and *trans*-iodo alkene **179** was as described in Scheme 57, which involved similar chemistry to that used in the synthesis of (*Z*)-olefin **122**, already described in section 2.1 and shown in Schemes 28, 30 and 31. During our preliminary experiments aimed at the synthesis of left hand fragments **178** and **179**, we used racemic malic acid to prepare racemic 3-hydroxy lactone **187**. The *t*-butyldiphenylsilyl protection of racemic-**187** followed by DIBAL-H reduction yielded **188** in 53% overall yield (Scheme 58).

Scheme 57

Proposed approach to alkyne **178** and vinyl iodide **179**;

HO

MeO₂C   CO₂Me   3 steps   2 steps

(*R*)-(+)-malic acid
88

t-BuPh₂SiO

CHO
180

oxidation   *t*-BuPh₂SiO   OH

Ph₃P

Takai
olefination

Gilbert's reagent
or Corey/Fuchs methodology

t-BuPh₂SiO   *t*-BuPh₂SiO

I
179   **178**

Therefore both alkyne **178**
and vinyl iodide **179** would be
synthesised in 8 steps from (*R*)-
malic acid.

Scheme 58

HO

i, ii   *t*-BuPh₂SiO

OH
187   **188**

Reagents
i. 1.1 eq. *t*-BuPh₂SiCl, 1.5 eq. imidazole, DMF, RT, 20 hr,
62%; ii. 1.1 eq. DIBAL-H, toluene, -20°C, 1 hr, 86%.

The Wittig reaction of lactol **188** using nine equivalents of 1-propylidene triphenylphosphorane (prepared from propyltriphenylphosphonium bromide and sodium bis(trimethylsilyl)amide) in toluene at -78°C with warming to -20°C over one hour, afforded two isomeric (*Z*)-olefinic compounds, **189** and **190**. They were isolated as an inseparable 4:1 mixture after chromatography in 72% yield. The minor component of this mixture was the desired compound, (4*Z*)-2-O-((*t*-butyldiphenylsilyl)-4-hepten-1,2-diol **190**. The major compound was isomeric to **190** being, (4*Z*)-1-O-((*t*-butyldiphenylsilyl)-4-hepten-1,2-diol **189**. The latter

isomer (**189**) must result from a facile migration (under the basic Wittig olefination reaction conditions) of the silyl protecting group from the secondary hydroxyl position to the sterically less demanding primary alternative in the product olefin (Scheme 59).

Scheme 59

Reagents
i. 10.0 eq. PrPPh₃Br, 9.0 eq. NaN(SiMe₃)₂, toluene, 0°C for 1 hr, then -78°C and add lactol **188** in toluene, -78°C to -20°C, 1 hr 72 %.
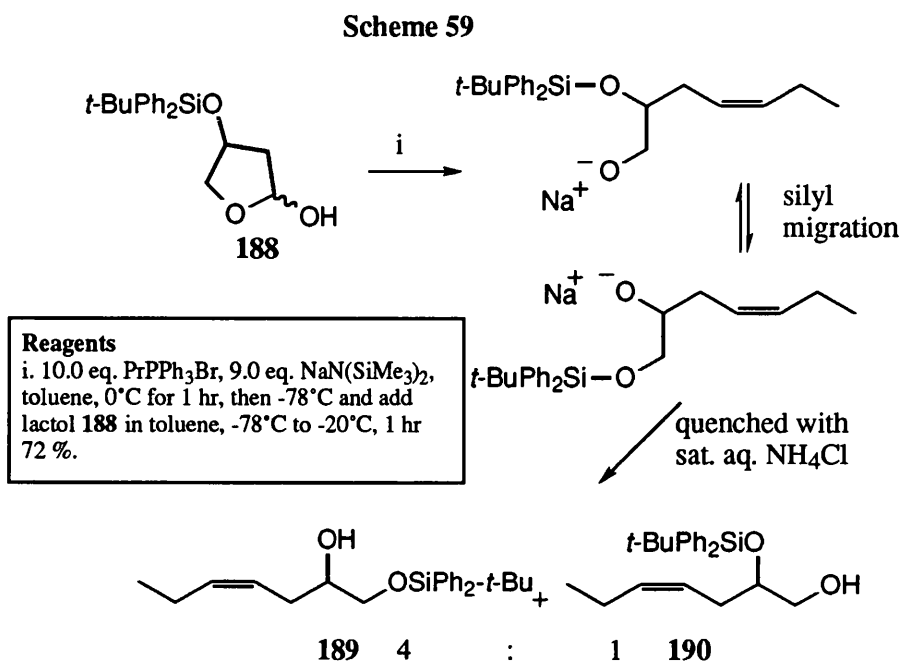
This same observation had been made in the Wittig reaction *t*-butyldiphenylsilyl-protected lactol **191** (where the (3*R*)-hydroxy-γ-butyrolactone **111** intermediate was prepared in seven steps as described in section 2.1, Scheme 27, using the procedure first reported by Tanaka), with 1-hexylidene triphenylphosphorane.[35,36] Wu, Shi and colleagues reported that **192**, the product formed by silyl migration, was isolated as the major product under their Wittig olefination conditions. This reaction formed part of the group's studies towards the synthesis of Leukotriene B₄ (Scheme 60).

Scheme 60
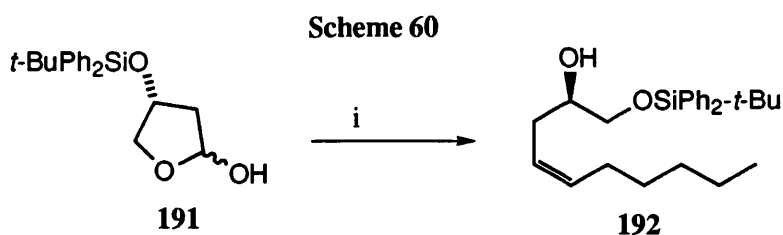
Reagents
i. hexyltriphenylphosphonium bromide, n-BuLi, THF/HMPA, yield not given.

Interestingly, we observed that oxidation of the 4:1 mixture of isomers **189** and **190** using 5 mol% tetrapropylammonium perruthenate/1.5 equivalents of 4-methylmorpholine N-oxide[67] for one hour at room temperature, returned the major isomer **189** unchanged. However, **190** appeared to have been completely oxidised to aldehyde **180**, which implies that a substantial rate difference exists (under the described reaction conditions) for the respective oxidations at the secondary and primary hydroxyl positions (Scheme 61). Ley and co-workers have noted that primary alcohols react more rapidly than secondary alcohols which suggests that the reagent is sterically demanding.[67(c)]

Scheme 61
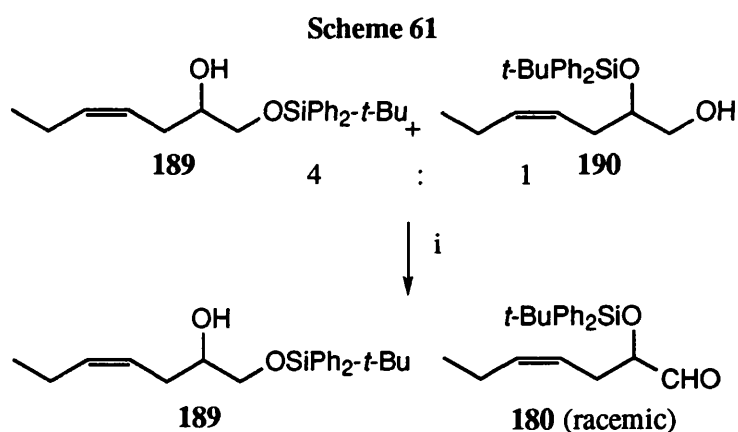
Reagents
i. 5 mol% TPAP, 1.5 eq. NMO, CH_2Cl_2, powdered molecular sieves, 1 hr, RT, 59%.

This new mixture of compounds **189** and **180** were purified by flash chromatography, and isolated together in 59% yield (not an optimised yield). By proton NMR analysis it was clear that aldehyde **180** had formed; new signals at δ 9.57 (1H, d, J 1.8 Hz, CHO) and δ 1.11 (9H, s, ^{t}Bu), and that alcohol **190** had been completely and selectively consumed; disappearance of olefinic signals at δ

5.21-5.15 (1H, m) and the *t*-butyl silyl signal at 1.08 (9H, s). Alcohol **189** was not oxidised (at least not by a detectable amount) since its ^{1}H-NMR features remained unchanged from that of the original starting mixture.

Due to the facile migration of the silyl protecting group we sought a more appropriate alternative. In the synthesis of the right hand fragment of **1** and **2**, we employed the *p*-methoxyphenylmethyl protecting group. Starting from (*R*)-malic acid **88** we were able to synthesise (3*R*)-3-O-((*p*-methoxyphenylmethyl)oxy)-γ-butyrolactol **193** using the same procedure already described in section 2.1 for the preparation the antipodal lactol **108**. The reaction of **193** with 1-propylidene triphenylphosphorane **194**, under the conditions previously found essential for the Wittig olefination of antipodal lactol **108** with the ylide derived from 4-(carboxybutyl)triphenylphosphonium bromide **91**, was disappointing in this case. Lactol **193** dissolved in toluene was cooled to -78°C and its sodium alkoxide **195** formed by the addition of 1.0 equivalent of sodium bis(trimethylsilyl)amide. A slight excess (1.1 equivalents) of the pre-formed orange-red ylide **194** in toluene (formed using one equivalent of sodium bis(trimethylsilyl)amide at room temperature over thirty minutes) was cooled to -78°C and added *via* cannula to the sodium alkoxide of lactol **193**. At best (2*R*,4*Z*)-2-O-((*p*-methoxyphenylmethyl)-4-heptene-1,2-diol **196** was synthesised in a poor 30% yield. By thin layer chromatography analysis the reaction appeared to produce a multi-component mixture. One of the side products was assigned as the β-elimination product (2*E*,4*Z*)-hepta-2,4-diene-1-ol **197** based on ^{1}H-NMR analysis. Therefore it appeared that, under these conditions, either excess base or the warming of the sodium alkoxide **195** prior to the Wittig reaction, led to a quite facile β-elimination of *p*-methoxybenzyl alcohol (Scheme 62).

Scheme 62
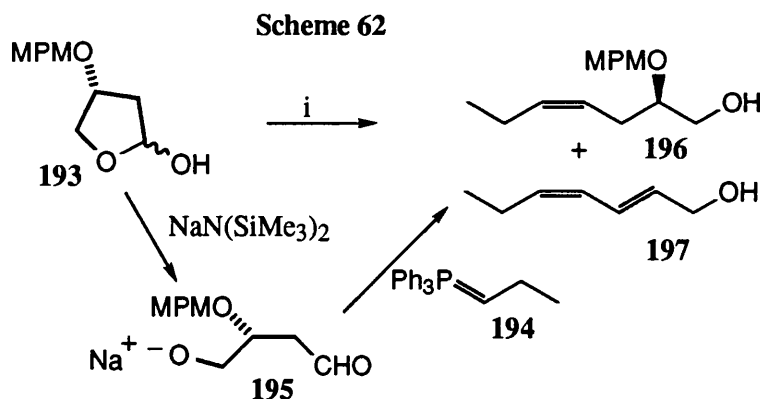
Reagents
i. 1.2 eq. propyltriphenylphosphonium bromide, 1.1 eq. NaN(SiMe₃)₂, toluene, 0°C, 5 min, then RT for 30 min, 1.0 eq. lactol **193**, 1.1 eq. NaN(SiMe₃)₂, toluene, -78°C, then *via* cannula add the ylide **194** at -78°C to the sodium alkoxide **195**, -78°C, 10min, then warm to 0°C over 30 min, 30%.

Next we performed the Wittig reaction without the prior formation of the sodium alkoxide **195**. Now, 2.1 equivalents of ylide **194** were prepared as before, and **194** at -78°C was added to lactol **193**, also at -78°C, *via* cannula. The first equivalent of the ylide is quenched by the released hydroxyl functionality in **193** and presumably **195** is formed again. The resulting reaction mixture was maintained at low temperature for a short period (five minutes), and then warmed to 0°C, stirring at this temperature for thirty minutes. The reaction was then quenched using a saturated aqueous ammonium chloride solution. After chromatography, the desired (Z)-olefin **196** was now isolated in a much improved 76% yield. The only detected side product was the non-polar trimethylsilyl-primary hydroxyl protected compound **198**, a derivative of **196**, in 11% yield (Scheme 63). The partial trimethylsilyl protection of the desired compound **196** was a result of the protonation of hexamethyldisilazide during work-up, which then provided a good source of a trimethylsilyl group (Scheme 64).

Scheme 63

196 R=H 76% yield

198 R=SiMe₃ 11% yield
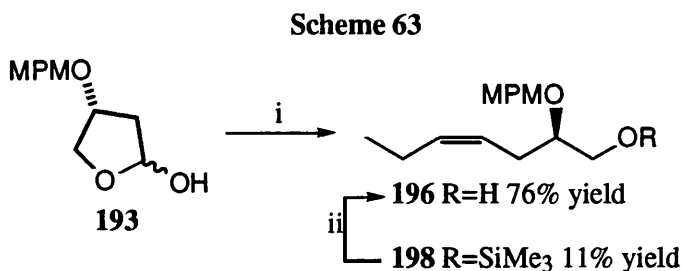
Reagents
i. 2.05 eq. propyltriphenylphosphonium bromide, 2.0 eq. NaN(SiMe₃)₂,
toluene, 0°C, 5 min, then RT for 30 min, and add ylide **194** (cooled to -78°C)
to the lactol **193**, -78°C, 5 min, then warm to 0°C over 30 min, 76% **196**
+ 11% **198**; ii. dilute HCl/THF solution, RT, 10 min, quantitative.

Scheme 64
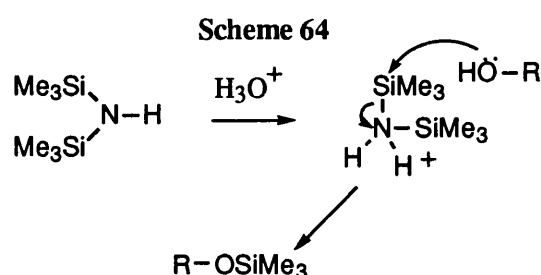
The trimethylsilyl protecting group is very labile to hydrolysis[82] and we were

therefore able to cleave it in quantitative yield under mildly acidic conditions (dilute

hydrochloric acid/tetrahydrofuran solution) which left the p-methoxyphenylmethyl

group still intact. This implies that the total yield for the olefination reaction was in

fact at least 87%. The oxidation of the key alcohol **196** to give (2R,4Z)-2-O-((p-

methoxyphenylmethyl)oxy)-4-heptenal **199** was achieved cleanly and quantitatively

using the Swern oxidation conditions.[46] Aldehyde **196** could also be isolated in

yields in excess of 96% after chromatography. Interestingly we found that the

catalytic oxidation conditions (5 mol% tetrapropylammonium perruthenate/ 1.5

equivalents of 4-methylmorpholine N-oxide) described by Ley, Griffith and

colleagues were not satisfactory for the formation of aldehyde **199** in high yield.[67]

After one hour, the described catalytic oxidation conditions produced a complex

mixture of products, as revealed by thin layer chromatography. The three major

components of the reaction mixture were isolated separately after chromatography.

The major fraction was in fact the desired aldehyde **199** which had formed in a

disappointing 39% yield. The next most abundant compound was easily identified

since it was recovered starting material **196** (19%). However, we also observed the

competitive formation of a diastereomeric mixture of tetrahydrofuran containing

compounds **200a** and **200b** in approximately a 1:1 ratio and 13% yield. We have

tentatively assigned the structures **200a** and **200b** based on spectroscopic analysis

(1H NMR, IR, and mass spectrum (CI)) and some related literature observations

(Scheme 65).

Scheme 65

Reagents
i. Swern oxidation conditions
(as in text), quantitative crude yield.
ii. 5 mol% TPAP, 1.5 eq. NMO,
powdered molecular sieves, CH₂Cl₂,
RT, 1 hr, mixture of products.
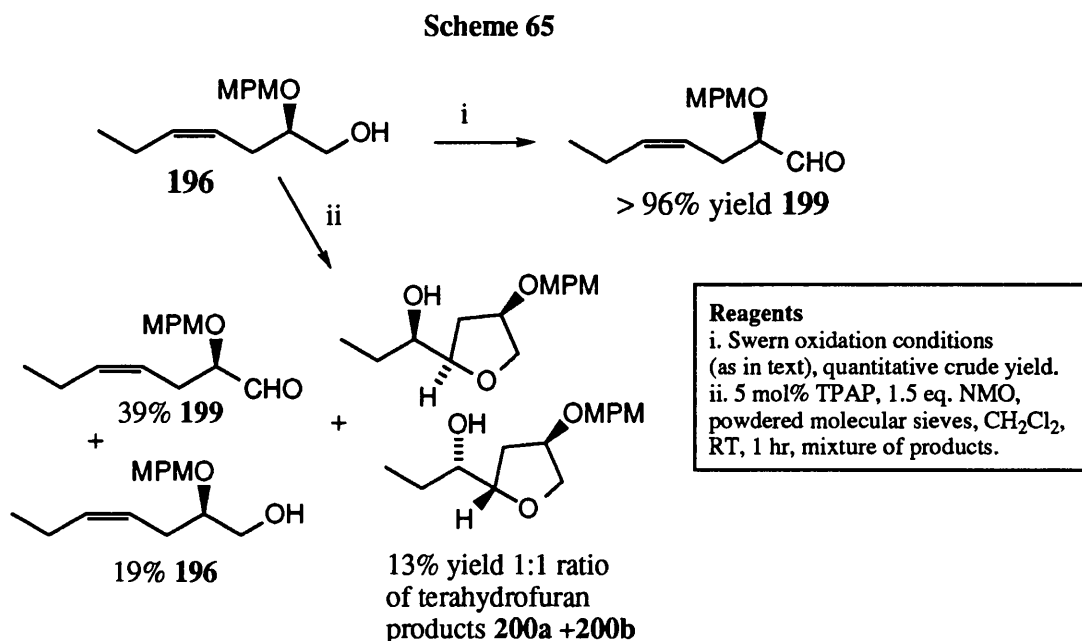
Proposed mechanism for the formation of the tetrahydrofuran side products.
Non-selective *syn*-oxidative cyclisation *via* either a [2 + 2] or [3 + 2] mechanism;
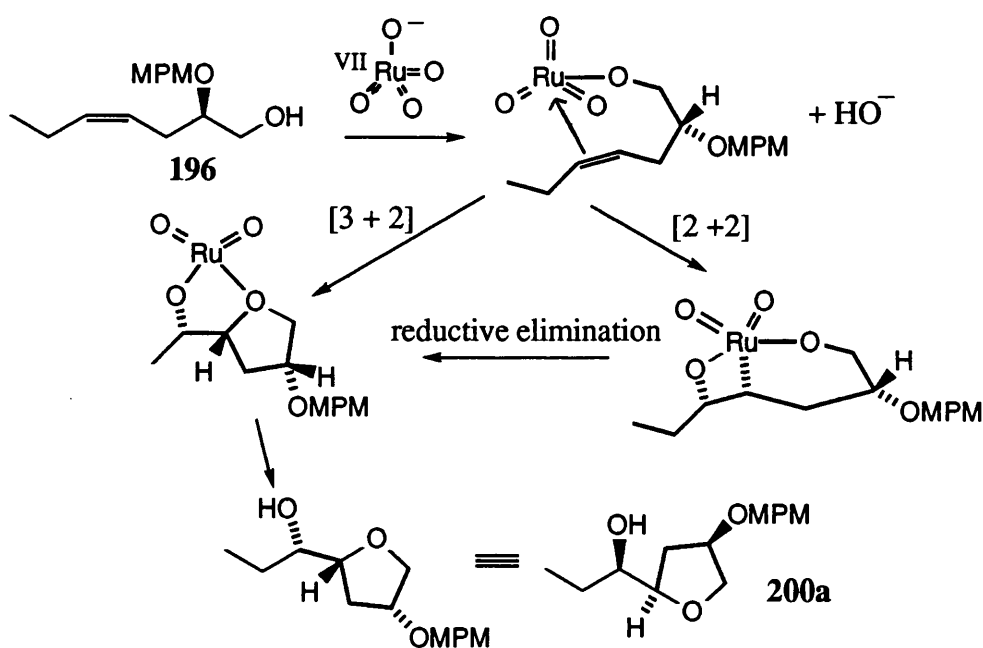
Also; Reduced Ru species $\xrightarrow{\text{NMO}}$ Ru(VII) ie.catalytic species is regenerated

Two possible mechanisms for the formation of **200a** and **200b** are shown in Scheme 65. The work of McDonald[88] and coworker, which is targeted towards producing a reagent(s) to facilitate the biomimetic, tandem *syn*-oxidative cyclisations of acid sensitive hydroxydiene substrates and thus generate chain polyethers, provides good precedent for the formation of compounds **200a** and **200b**. They have shown that acyclic compounds possessing 1-hydroxy-4-alkene functionality **201** (as also found in **196**) could be oxidatively cyclised using (trifluoroacetyl)perrhenate **202** to give *trans*-tetrahydrofuran alcohols **203** in good yield and with excellent stereoselectivity. A [3+2] mechanism was proposed by McDonald to account for the excellent *trans*-selectivity observed in the aforementioned transformations (Scheme 66a).

Scheme 66a

Yields: 65-90%
trans-tetrahydrofuran alcohol
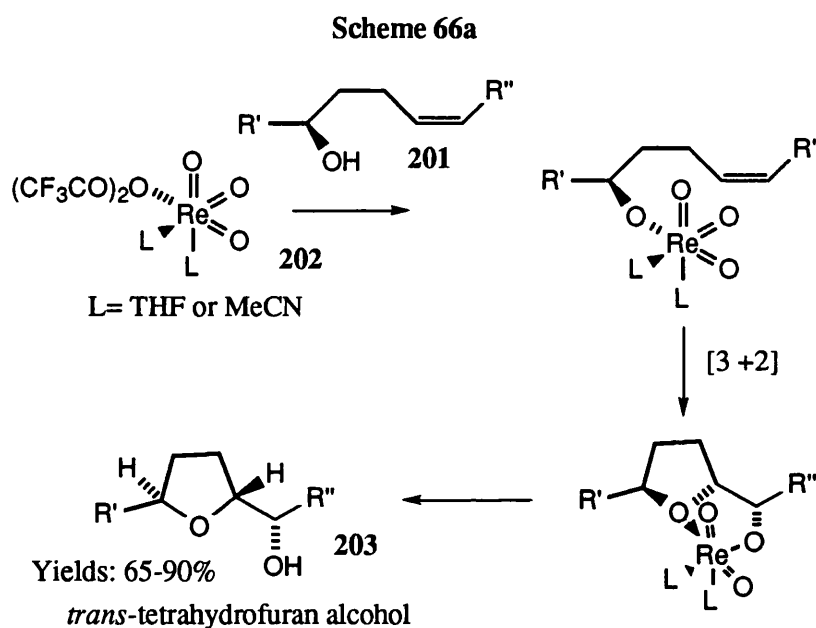
In a different study, Sharpless found that the oxidation of geranyl acetate using a catalytic amount of ruthenium trichloride hydrate (0.022 mol. equivalents) and excess sodium periodate (4.1 mol. equivalents) in a mixture of tetrachloromethane: acetonitrile:water (2:2:3), only gave products which possessed a tetrahydrofuran ring (A-C) (Scheme 66b).[89(a)] It was in fact anticipated that carboxylic acid products, the result of oxidative cleavage of a double bond(s) of geranyl acetate, would be isolated. The synthesis of these tetrahydrofuran products is thought to be the result

of an analogous mechanism to that found in permaganate promoted stereospecific oxidative cyclisation of 1,5-dienes, being operative.[89(b)-(d)]

Scheme 66b

geranyl acetate

A 39% yield   B 12% yield   C 12% yield

tetrahydrofuran products

Reagents
i. cat. RuCl₃.(H₂O)n, 4.1 eq. NaIO₄, CCl₄:CH₃CN:H₂O (2:2:3).
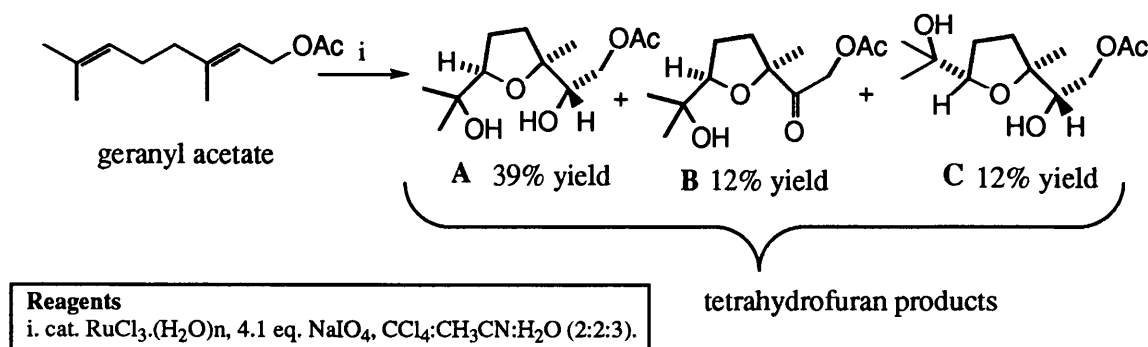
A possible mechanism for the formation of "*cis*-diol" tetrahydrofuran A is shown below;

Ru(VIII)

Ru(VIII)   OAc

Ru(VI)

a. [2+2] insertions of the olefinic
π-bonds into the metal oxo bonds
of the ruthenium.
b. alkyl migration with retention.
c. reductive elimination with
retention.

H₂O

A

O Ru(IV)
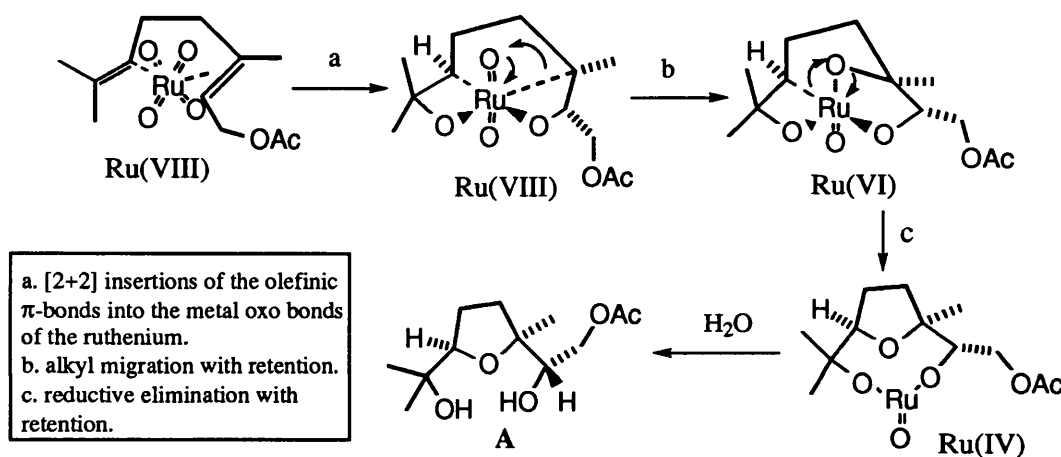
With aldehyde **199** in hand we then examined the potential of exploiting the Takai olefination reaction[83] in the formation of (3*R*)-(1*E*,5*Z*)-3-O-((*p*-methoxyphenyl-methyl)oxy)-1-iodo-1,5-octadiene **204** directly in one synthetic step. However, the reaction of **199** with 6.0 equivalents of chromium chloride and 2.0 equivalents of iodoform in tetrahydrofuran for sixteen hours at room temperature resulted in only a 11% yield of pure *trans* iodo alkene **204** being isolated. The reaction in fact gave rise to a multi-component mixture. Further, compound **204** appeared to be prone to decomposition on silica during attempted purification which also contributed to the low yield of this reaction (Scheme 67).

Scheme 67
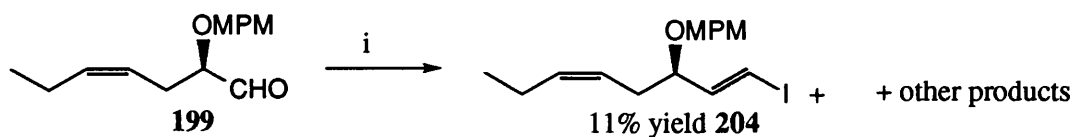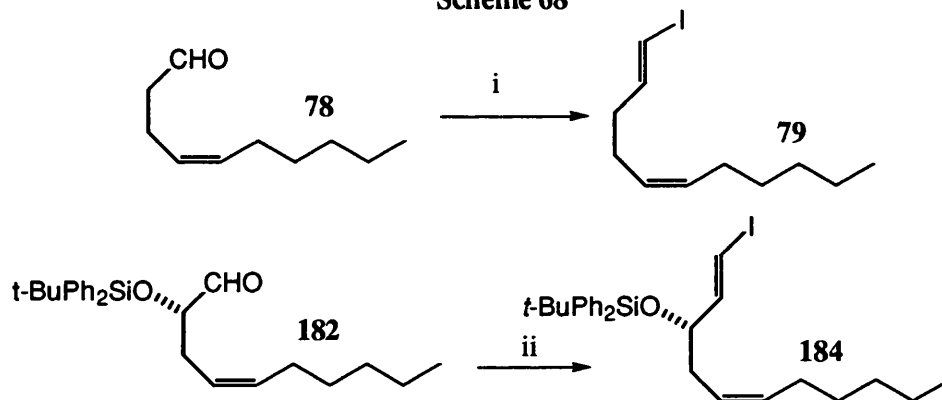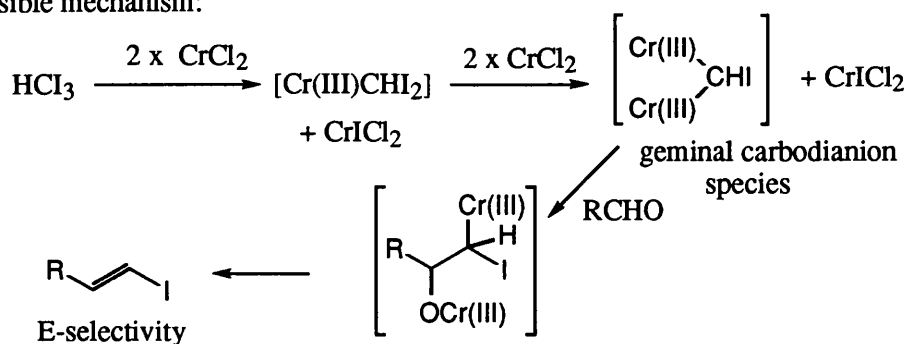
OMPM
~~~~CHO
199

i →

OMPM
~~~~~~I + + other products
11% yield **204**

Reagents
i. 6.0 eq. CrCl$_2$, 2.0 eq. CHI$_3$, THF, 0°C, 1 hr, then RT for 16 hr, 11%.

No optimisation of this reaction was attempted. White has reported the Takai olefination of both (Z)-4-decenal **78** and (2S,4Z)-2-O-((t-butyldiphenylsilyl)oxy)-4-decenal **182** where the respective trans-iodo alkenes **79** and **184** were synthesised in 95% yield (after just 3 hours at 0°C) and a more modest 54% yield (after 18 hours at 0°C), see Scheme 68.[18(b)] Therefore it appears that oxygen functionality in the substrate severely retards the desired reaction (presumably via complexation to chromium) which in our case appeared to permit alternative reaction pathways to become competitive. A further limitation to the Takai procedure is the requirement to use six equivalents of expensive chromium(II) chloride.

Scheme 68

CHO
78

i →

I
79

t-BuPh$_2$SiO,,,CHO
182

ii →

t-BuPh$_2$SiO,,,
I
184

Reagents
i. 6.0 eq. CrCl$_2$, 2.0 eq. CHI$_3$, THF, 0°C, 3 hr, 95%.
ii. 6.0 eq. CrCl$_2$, 2.0 eq. CHI$_3$, THF, 0°C, 18 hr, 54%.

Possible mechanism:

$$HCI_3 \xrightarrow{2 \times CrCl_2} [Cr(III)CHI_2] + CrICl_2 \xrightarrow{2 \times CrCl_2} \left[\begin{array}{c} Cr(III) \\ \diagdown CHI \\ Cr(III) \diagup \end{array} \right] + CrICl_2$$

geminal carbodianion species

RCHO

$$\left[\begin{array}{c} Cr(III) \\ R \diagdown \diagup \diagdown_{I}^{H} \\ | \\ OCr(III) \end{array} \right]$$

R ⟵⟶ I

E-selectivity

We then considered an alternative approach to a suitably protected *trans* -iodo alkene which would involve the intermediacy of alkyne **205**.

199 **205**

The synthesis of alkynes directly from aldehydes has been described, where the anion of dimethyl (diazomethyl)phosphonate (Gilbert's reagent) is generated using potassium *t*-butoxide at low temperature (-78°C) in tetrahydrofuran.[84] By maintaining temperatures at -78°C for extended reaction times (12-24 hours), Gilbert has reported the successful synthesis of aldehydes or ketones containing enolisable protons (problems such as aldol condensations are avoided). Further, Schreiber and colleagues have employed Gilbert's reagent in the preparation of enantiomerically pure **206** used in the synthesis of an advanced intermediate **207** of the immunosuppresive reagent FK-506, and shown that no epimerisation at the enolisable carbon occurred (see Scheme 69).[90] However, the use of dimethyl (diazomethyl)phosphonate has its shortcomings. The reaction must be carried out at low temperature, -78°C, over a long period, where an excess of both Gilbert's reagent and potassium *t*-butoxide (2-3 equivalents) must be used due to the low nucleophilicity of the corresponding anion. In addition dimethyl (diazomethyl)-phosphonate is not commercially available and its preparation involves a multi-step sequence.[91]

Scheme 69

Reagents
i. (MeO)₂P(O)CHN₂, KO-t-Bu, 95%;
ii. n-BuLi, MeI, 96%, iii. Cp₂ZrHCl,
NBS, 86%.

Alternatively the generation of acetylenes from aryl ketones and aldehydes has been reported by Colvin and Ohira respectively using lithiotrimethylsilyldiazomethane.[92,93] Trimethylsilyldiazomethane is commercially available, and can be purchased from Aldrich as a 2.0M solution in hexanes. However, Ohira has reported that even a very simple aliphatic aldehyde ($C_9H_{19}CHO$), was transformed into its acetylenic product ($C_9H_{19}CH{\equiv}CH$) in only modest yield (61%) using this alternative approach. Therefore we decided to synthesise the desired alkyne **205** via a two step process involving an intermediate dibromide **208**. Using a modification of the Corey-Fuchs procedure[85] (2.0 equivalents of carbon tetrabromide, 4.0 equivalents of triphenylphosphine and 8.0 equivalents of triethylamine in dichloromethane at low temperature (-78°C)), (3R,5Z)-3-O-((p-methoxyphenylmethyl)oxy)-1,1-dibromo-1,5-octadiene **208** was synthesised in good yield (73%). The mixture of triphenylphosphine, carbon tetrabromide and

triethylamine produces a deep burgundy coloured solution, the result of dibromomethylene triphenylphosphorane **209** being generated *in situ* (Scheme 70).

Scheme 70

2.0 equivalents CBr_4 + 4.0 equivalents Ph_3P

$$Ph_3P\!=\!\!\!\!\begin{array}{c}Br\\ \\Br\end{array}\quad + \quad Ph_3PBr_2 \rightleftharpoons \overset{+}{Ph_3}PBr\ \ \overset{-}{Br}$$

209
2.0 equivalents

210 reactive by-product
2.0 equivalents

excess
Et_3N

$Et_3N\overset{+}{Br}\ \overset{-}{Br} + Ph_3P$

199

i

MPMO

- Ph_3P=O

208

Reagents
i. 2.0 eq. CBr_4, 4.0 eq. Ph_3P, 8 eq. Et_3N, CH_2Cl_2, RT, 15 min, then 1.0 eq aldehyde **199**, -78°C to 0°C over 2 hr then RT for 16 hr, 73%.

The modification to the procedure is the addition of triethylamine to the reaction. When the dibromo ylide **209** is generated it is always accompanied by the formation of triphenylphosphine dibromide **210**. Compound **210** is known to open epoxides to form halohydrins,[94] can induce cyclisation of acetals to generate tetrahydropyrans,[95] as well as being able to brominate various tetrahydropyran protected alcohols (by S_N2 displacement),[96] and hindered trialkylesters and trialkyl ethers to give either the corresponding alkyl bromide or carboxylic acid bromide.[97] It is the dual electrophilic (at the phosphorous atom) and nucleophilic (halide ion) nature of this reagent that allows it to react with a range of functionality, and it is therefore the probable source of side reactions in the Corey-Fuchs procedure. The addition of triethylamine

suppresses side reactions by reacting with triphenylphosphine dibromide **210** (Scheme 70), forming triethylamine dibromide, which liberates an equivalent of triphenylphosphine. The reaction conditions we employed were analogous to those reported by Marshall and Anderson in 1993.[98] We generated two equivalents of both the dibromo ylide **209** and the corresponding triphenylphoshine dibromide **210**, the latter being neutralised with four equivalents of triethylamine. Alternatively McIntosh and Weinreb reported, in 1993, the use of two equivalents of dibromo ylide and one equivalent of triethylamine in the synthesis of a key intermediate **211** which was used in the preparation of a protected version of (+)-lycoricidine **212** (Scheme 71).[99] Also, Pale and colleagues have used similar conditions (2.0 equivalents of carbon tetrabromide, 2.0 equivalents of triphenylphosphine and 1.0 equivalent of triethylamine) whilst developing an improved general procedure towards this olefination reaction .[100]

Scheme 71

protected version of
(+)-lycoricidine

Reagents
i. 4.0 eq. Ph$_3$P, 2.0 eq. CBr$_4$, 1.0 eq. Et$_3$N, CH$_2$Cl$_2$, 0°C, 5 min,. then added aldehyde at -78°C,2min, sat. NaHCO$_3$, 75%; ii. 2.05 eq., n-BuLi, THF, TMEDA,-78°C, TMSCl, 81%.

The reaction of dibromide **208** with two equivalents of n-butyllithium was expected to be non-problematical, affording the desired alkyne, (3R,5Z)-3-O-((p-methoxy-phenylmethyl)oxy)-5-octene-1-yne **205** in high yield. However, the reaction of **208** with two equivalents of n-butyllithium in tetrahydrofuran at low temperature in fact gave a mixture of compounds where at best alkyne **205** was isolated in 70%

yield (one yield however was as poor as 46%). The major impurity formed in this reaction (10% yield) was assigned as the 2,5-disubstituted-3,4-dihydrofuran derivative **213** based on the ^{1}H-NMR and mass spectrum data. Intriguingly **213** appeared to be diastereomerically pure since we did not observe any doubling of peaks in its ^{1}H-NMR spectrum (Scheme 72).

Scheme 72

MPMO **Br**

208

i

MPMO

205 71% yield

+

213 10% yield

Reagents
i. 2.05 eq. *n*-BuLi, THF, -78°C, 30min, then warm to 0°C, sat. NH₄Cl, (yields as above).

The formation of the side product **213** is quite illuminating with regard to the mechanism for the transformation of a dibromide to an acetylene using two equivalents of *n*-butyllithium. This transformation probably does <u>not</u> involve β-elimination followed by metal-halogen exchange.[100] Instead there is substantial evidence, which in common with our own experimental finding (the isolation of **213**), suggests that the mechanism involves initial metal-halogen exchange to give an α-halo-metallic compound. In fact dibromoalkenes have been reacted with alkyllithiums and then quenched at low temperature to produce mono-bromoalkenes.[101] Therefore it appears that metal-halogen exchange occurs more rapidly than the alternative β-elimination process, when an alkyllithium is used as base. By allowing the α-halo-metallic compound to warm then α-elimination of lithium bromide takes place and an alkylidene carbene is produced (Scheme 73).[102] Such species are known to undergo very rapid 1,2-hydrogen shift to produce an alkyne.[103,104(a)] However, alkylidene carbenes are also known to undergo intramolecular 1,5-insertion[104] as well as intermolecular insertion reactions.[105] It is the former intramolecular process that we believe results in the formation of the 3,4-dihydrofuran derivative **213**. For example Baird and colleagues have generated

alkylidene carbenes from 1,1-dibromo-2-methyl alkenes.[102] Their results clearly provide evidence for the well known 1,2-migration step to give alkynes, as well as the intramolecular insertion of a carbenoid into a C(5)-H bond to yield 3,4-dihydofuran ring systems. The reaction of 3,3-dibromo-2-methyl prop-2-enyl-isopropylether **214** with 2.2 equivalents of methyllithium produced a 3:1 ratio of 2,2,4-trimethyl-3,4-dihydrofuran **215** and but-2-ynyl isopropyl ether **216** in a 70% combined yield (Scheme 73).

Scheme 73

Me—⟨ ⟩—O—⟨⟩   —i→   Me—⟨ ⟩—O   +   ⟨⟩—O—≡—Me
Br   Br   **214**   Me Me
                            215 3 : 1 **216**

Reagents
2.2 eq. MeLi, ether, RT, 3 min, H_2O, 70%.

Mechanism;

Me—⟨ ⟩—O—⟨⟩   **MeLi**   Me—⟨ ⟩—O—⟨⟩   α-elimination
Br   Br   metal-halogen   Br   Li   of LiBr
      214   exchange

Me—⟨ ⟩   1,5 C-H   Me—⟨ ⟩—O—⟨⟩
215   insertion   H
Me Me   1,2-alkyl
                    migration
70% combined   O—⟨⟩
yield   **216**   ≡—Me

Note that 1,2 alkyl migration is slower than the corresponding 1,2 hydrogen shift that generates terminal alkynes. (Hence a methyl substituent in the 2-position retards alkyne formation, and 1,5 C-H insertion is therefore the major reaction pathway in the example shown above).

The C(5)-H insertion process is known to be favoured in the presence of alkoxy and phenyl groups.[102] The example just reviewed, as well as the work of Taber and colleagues, highlights the facile nature of the C(5)-H insertion of an alkylidene carbene when an adjacent alkoxy group is present.[104(h)] In the diastereoselective synthesis of a Taxol A ring synthon **217** the group of Taber reacted ketone **218** with

the anion of (trimethylsilyl)diazomethane to give **219** in 72% yield. Thermal α-elimination of nitrogen (but well below ambient temperature) generates the alkylidene carbene species which inserts into the most activated C(5)-H bond. In this case it is the methine (rather than methyl) C(5)-H bond which is activated by α-alkoxy substitution that selectively undergoes the insertion reaction (Scheme 74).

Scheme 74

Kim and Cho have shown that the thermal reaction of α,β-epoxy-N-aziridinylimine **220** produces an alkylidene carbene **221**.[104(e)] The C(5)-H insertion of this transient inermediate **(221)** is activated by the α-phenyl substituent, and consequently 2-methyl-4-phenyl-2-cyclopenten-1-ol **222** was isolated in good yield (73%) and as a 6:4 mixture of the *syn-* and the *anti-*isomers (Scheme 75).

Scheme 75

It therefore appears that the unexpected C(5)-H insertion process (as a minor reaction pathway) observed in the reaction of dibromide **208** with n-butyllithium is an artefact of the double activation of the C(5)-methylene hydrogens by both the p-methoxy-phenyl and α-alkoxy substituents. This ensures that the rapid 1,2-hydrogen shift to form an acetylene is not the only reaction pathway. Fascinatingly, diastereomerically pure 2,5 disubstituted dihydrofuran **213** appeared to be formed. Rhodium-mediated intramolecular C(5)-H insertions have been reported to proceed with substantial diastereoselectivity.[106(a)-(c)] Further, Taber and Meagley have recently (1994) published results concerning the diastereoselectivity in an uncatalysed intramolecular C(5)-H insertion by an alkylidene carbene. They found that by using the anion of trimethylsilyldiazomethane to generate a transient alkylidene carbene derived from ketone **223**, that cyclopentenes **224a** and **224b** formed in a 4.4:1 ratio and 57% yield (Scheme 76). A competing side reaction was the 1,2-hydrogen migration to give alkyne **225**. A "chair-like" transition state was used to predict the stereochemical outcome of the rhodium-mediated C(5)-H insertion reaction. Insertion into one of the two diastereotopic methylene protons (Ha) is preferred since this enables the methyl substituent to adopt an equatorial position. Although Taber has not gone on to infer that the same "chair-like" transition state is operating in the non-catalysed reaction, such a model does fit the latter experimental results as well.

Scheme 76

Reagents
i. Me₃SiCHN₂, MeLi, DME, -60°C, 2 hr, 57%.

We have therefore tentatively assigned the 2,5 disubstituted 3,4-dihydrofuran **213**

that we formed as the 2*R*,5*R*-*syn* isomer based on the above transition state model

(Scheme 77).

Scheme 77

insertion into 1,5 C-Ha bond
via a chair-like transition state

syn-2,5 disubstituted
isomer

We wished to have a left hand fragment of neohalicholactone **1** protected as a *t*-

butyldiphenylsilyl ether. As mentioned earlier in this section, we felt that the *p*-

methoxyphenylmethyl protecting group would be cleaved in the coupling of aldehyde

156 (right hand fragment) and terminal alkyne **205**, using the procedure described

by Oppolzer which involves Lewis acidic conditions.[21(b)] Therefore we were now

faced with an inelegant protecting group change to perform. As expected,

conventional *p*-methoxybenzyl deprotection was smoothly achieved using DDQ,[45] to

provide a crude sample of propargylic alcohol intermediate which was then silylated

under standard conditions to give the *t*-butyldiphenylsilyl derivative **178** in high yield (93%) (Scheme 78).

Scheme 78

Reagents
i.(a) 1.1 eq. DDQ, CH_2Cl_2:H_2O (18:1), RT, 1.5 hr, (b) 1.2 eq. TBDPSCl, 2.5 eq. imidazole, DMF, 93%.

However, in view of the fact that the 70% yield for the transformation of *p*-methoxyphenylmethyl-protected dibromide **208** was not reproducible we felt that the earlier introduction of the *t*-butyldiphenylsilyl protecting group (before the alkyne was produced), would improve the overall efficiency of the synthesis of the desired left fragment. Therefore dibromide **208** was now deprotected (DDQ) and then reprotected using *t*-butyldiphenylsilyl chloride in 92% overall yield (Scheme 79).

Scheme 79

Reagents
i.(a) 1.1 eq. DDQ, CH_2Cl_2:H_2O (18:1), RT, 30min, (b) 1.2 eq. TBDPSCl, 2.4 eq. imidazole, DMF, 16 hr, 92%.

We now anticipated that the reaction of *t*-butyldiphenylsilyl protected dibromide **181** with two equivalents of *n*-butyllithium would afford the desired alkyne **178** cleanly in high yield. However, **178** was isolated in a modest yield, 67%. A substantial amount of non-polar materials (at least four different compounds were present in these fractions since four *t*-butyl signals were observed in the ^{1}H-NMR spectrum) were also isolated after chromatography. From 559 milligrams of starting material we isolated 260 milligrams (67% yield) of the desired alkyne **178** and 67 milligrams of a mixture of side products. Therefore we examined the possibility of affecting a complete change in the mechanism of the dibromide to acetylene transformation. By

adding at least one equivalent of lithium diisopropylamide to the dibromide **181**,

literature precedent suggested that the corresponding bromo-alkyne should form *via*

an *anti*-dehydrobromination reaction.[107] *In situ* metal-halogen exchange using an

alkyllithium would then be expected to produce a terminal acetylene.

The addition of 1.5 equivalents of lithium diisopropylamide to **181** at -78°C in

tetrahydrofuran followed by 2.2 equivalents of *n*-butyllithium (one equivalent of *n*-

butyllithium is required to neutralise the proton of diisopropylamine) afforded the

desired alkyne **178** in a much improved 92% yield (Scheme 80).

Scheme 80

Reagents
i. 1.5 eq. LDA, THF, -78°C to 0°C, 30min, then 2.2 eq. *n*-BuLi, -78°C, 5 min, sat. NH₄Cl, 92%.

Whilst we did not apply this procedure to the *p*-methoxyphenylmethyl-protected

dibromide **208**, there is no apparent reason why this modification should not also

prove fruitful in this case. Recently (1994), a similar approach was developed by

Pale and colleagues in an attempt to improve the overall efficiency of the

transformation of a dibromide into an acetylene. They found that the addition of

sodium bis(trimethylsilyl)amide at very low temperature (-100°C) provided a range of

bromoalkynes in quantitative yield.[100] Then in a separate step the bromine atom was

exchanged for hydrogen using with one equivalent of *n*-butyllithium followed by an

aqueous quench. With the suitably protected alkyne **178** in hand it was finally

converted to (3*R*)-(1*E*,5*Z*)-3-O-((*t*-butyldiphenylsilyl)oxy)-1-iodo-1,5-octadiene **179**

using Schwartz's reagent (Cp₂ZrHCl) in tetrahydrofuran or dichloromethane, and the

resultant vinyl metal species was then treated with iodine.[74(a)] After

chromatography **179** was isolated in high yield (92%), but this material was contaminated with < 9% of unreacted starting material (Scheme 81).

Scheme 81

Reagents
i. 1.2 eq. Cp$_2$ZrHCl, (follow consumption of alkyne by thin layer chromatography), RT, then 1.2 eq. I$_2$, THF, RT, 45min, 92% (crude).

Trans-iodo alkene **179** was used directly without further purification due to the sensitivity of *iodo* alkenes to sunlight and acids.

We have assumed that **179** is enantiomerically pure. However, there is literature precedent to suggest that no epimerisation should occur in the subsequent steps used to convert aldehyde **199** to *trans*-iodo alkene **179**.[108] In summary, we were able to prepare both the *t*-butyldiphenylsilyl protected alkyne **178** and *trans*-iodo alkene **179** in 11 steps (27% yield) and 12 steps (24% yield) respectively starting from (*R*)-malic acid **88**. Whilst a fairly long linear reaction sequence has been described in our final preparation of **178** and **179**, all of the steps were achieved in good to excellent yields, without the need for extensive optimisation studies (Scheme 82).

With the 12 step to **179** in mind, an alternative, much shorter approach could have been investigated. Following the precedent set by Sato,[79] Taylor and Borer have reported an extremely direct approach to (3*S*)-(1*E*,5*Z*)-3-O-((*t*-butyldimethylsilyl)-oxy)-1-iodo-1,5-undecadiene **184** starting from readily available 3(*Z*)-nonenal. Treatment of this aldehyde with lithiated vinyl stannane **226** gave racemic allylic alcohol **227** in 70% yield. Kinetic resolution of **227** was then achieved using a modification of the Sato procedure (cumene hydroperoxide, titanium(IV) isopropoxide, L-(+)-diisopropyltartrate (DIPT), followed by treatment of the crude reaction mixture with iodide). Homochiral **184** was isolated after silylation in 43% overall yield (and >98% enantiomeric excess) for the three steps (Scheme 83).[109]

Scheme 82

Reagents

i. 2.05 eq. PrPPh$_3$ Br, 2.0eq. NaN(SiMe$_3$)$_2$, toluene, RT, then add ylide to lactol 193, toluene, -78°C to 0°C, 30 min, 87% ; ii. (a) Swern oxidation, 100% crude, (b) 2.0 eq. CBr$_4$, 4.0 eq. PPh$_3$, 8.0 eq. Et$_3$N, CH$_2$Cl$_2$, RT, then 1.0 eq. aldehyde 199, 0°C, CH$_2$Cl$_2$, 73%; iii. (a)1.1 eq. DDQ, CH$_2$Cl$_2$:H$_2$O (18:1), (b) 1.2 eq. t-BuPh$_2$SiCl, 2.4 eq. imidazole, DMF, 92%; iv. 1.5 eq. LDA, -78°C to 0°C, then 2.2 eq. n-BuLi, -78°C, 5 min, 92%, v. 1.2 eq. Cp$_2$ZrHCl, 1.2 eq. I$_2$, RT, 92%.

Therefore in an analogous manner, starting from (3Z)-hexenal ((3Z)-hexen-1-ol is commercially available) we should in principle be able to synthesise our desired vinyl iodide **179** in just five steps. The alternative alkyne **178** being available in six steps by simple base induced dehydroiodination of **179** (Scheme 84). We did not examine the use of this methodology at the start of the project since we felt that the kinetic resolution procedure would be substrate dependent and would therefore most likely involve carefully performed optimisation studies. Also, in a kinetic resolution step the maximum yield is of course 50%, which is usually regarded as unsatisfactory. However, in light of the fact that if this procedure did work well it would halve the number of steps necessary to synthesise vinyl iodide **179**, then the feasibility of the reaction sequence shown in scheme 84 would have been assessed if more time had been available.

Scheme 83

3(Z)-nonenal

227

(R)-184

Reagents
i. (E)-Bu₃SnCH=CHSnBu₃ **226**, n-BuLi, THF, -78°C, 70%; ii. L-(+)-DIPT,
Ti(i-OPr)₄, cumene-OOH; iii. I₂, Et₂O, 46%; iv. t-BuMe₂SiCl, imidazole, 94%.

Scheme 84

cis-3-hexen-1-ol
commercially available

oxidise

226

kinetic
resolution

silylation

179

hydrometallation/
iodine

base

178

2.3   The Coupling of the Left and Right Hand Fragments.

Before discussing the work that led to the completion of the total synthesis of both neohalicholactone **1** and halicholactone **2**, some unsuccessful approaches to this goal will be described.

Our initial strategy involved the combination of advanced synthons, 8*S*,9*R*,11*R*-carboxylic acid **152** and aldehyde **199** in the synthesis of **1**. In similar fashion, the synthesis of **2** would involve MPM-protected-α-hydroxy aldehyde **228** and carboxylic acid **152**. We intended to prepare the β-keto phosphonate derivative **229** of **152**, and then couple this intermediate with either aldehyde **199** or **228** under Horner-Wadsworth-Emmons type conditions.[47,48] β-Keto phosphonates are usually prepared either *via* the Arbuzov reaction[110] (coupling of an α-halo ketone and trialkylphosphite) or alternatively by the reaction of a methyl ester with the lithium anion of dialkyl methylphosphonate.[111] It was the latter process that we wished to exploit. However, rather than using the highly reactive lithium anion **230** of diethyl methylphosphonate in conjunction with a methyl ester, we sought milder and more selective conditions. We hoped that by converting carboxylic acid **152** to the corresponding acid chloride **231**, and by modifying the reactivity of the methylphosphonate anion, that addition to **231** would occur selectively to give **229**. A paper published in 1978 by Mathey and Savignac described the use of copper(I) iodide as a means of transforming the very reactive organolithium reagent **230**, into a much milder and potentially very selective reagent **232**.[112] Further they had developed conditions that were shown to work well when an acid chloride was used as the substrate for the milder organocopper reagent **232**. Our strategy for the synthesis of the advanced enone synthons **233** and **234** is shown in Scheme 85.

Scheme 85

<u>step 1</u>   acid chloride synthesis

(COCl)₂, cat DMF
────────────→
CH₂Cl₂

152   **231**

<u>step 2</u>   conversion of **231** to β-ketophosphonate **229**

diethyl methyl-
phosphonate

230

232

add **231**

selective addition
to acid chloride

229

<u>step 3</u>   Horner-Wadsworth-Emmons condensations

MPMO   ω3 **199**
          and 228
              CHO

229

ω3 **233** and ω7 **234**

<u>step 4</u>   final transformations to give **1** and **2**

reduction and
deprotection
────────────→

ω3 **233** and ω7 **234**

ω3-neohalicholactone **1**
and ω7-halicholactone **2**

In separate reactions, **233** and **234** would then be reduced using either non-chiral or more likely asymmetric reducing agents, depending on the inherent diastereoselectivity invoked by these molecules. There is literature precedent to suggest that the reduction of a carbonyl adjacent to a *trans*-cyclopropane ring will result in a 1:1 mixture of epimeric alcohols being formed.[113] Finally a deprotection step would then give **1** or **2** from their respective diastereomerically pure allylic alcohol precursors. In order to evaluate the feasibility of this strategy we first performed a model study. We were able to react the non-enolisable acid chloride, trimethylacetyl chloride with the organocopper derivative **232** to give the β-keto phosphonate product **235** in good yield, 79%. In order to obtain this yield it was essential that the previously described experimental procedure was followed exactly. Having gained experience with regards to this delicate transformation, we then turned to a more suitable model substrate, one which contained both ester and acid chloride functionality. The reaction of adipic acid chloride monomethyl ester **236** (either purchased from Lancaster or prepared from adipic acid monomethyl ester using oxalyl chloride) under essentially the same conditions as previously used, provided the desired β-keto phosphonate **237** in poor yields, at best 38%. We also recovered unreacted methyl diethylphosphonate and a dimeric compound **238** from the reaction mixture. The isolation of these materials suggests that as **237** was formed, excess anionic methyl phosphonate (either the lithium or copper anionic species) was being consumed by deprotonating **237**. This is quite likely since **237** contains more acidic α-hydrogens than the starting material **236**. Such a process would return the starting methyl diethylphoshonate whilst the reaction of the newly formed anionic species **239** with acid chloride **236** would explain the isolation of the dimeric species **238**. It should be noted that non-polar impurities were also observed by thin layer chromatography, but these compounds were not characterised (Scheme 86).

Scheme 86

O
‖
CI

trimethylacetyl
chloride

i →

O   O
‖   ‖
P–OEt
|
OEt

235   79% yield

O
‖
CI   OMe
‖
O   **236**

ii →

EtO
\
EtO–P   OMe
‖   ‖
O   O   **237**   38% yield

excess of the anion of
methyl phosphonante

via

Li
O   O   **239**
‖
P
EtO
EtO

CI

O   **237**

O
‖
OMe
O
EtO
‖
EtO–P   OMe
‖   ‖
O   O

dimeric species **238**

+ methyl diethylphosphonate
+ unidentified by-products.

Reagents
i. 1.1 eq. *n*-BuLi, THF (degassed), -60°C, add 1.0 eq. methyl diethylphosphonate in THF, -60°C,add 1.1 eq. CuI,
-60°C to -30°C, then -30°C for 1 hr, add 1.1 eq. trimethylacetyl chloride, ether, -35°C, 45 min, then warm to RT and
stir for 16hr, 79%. ii. 1.0 eq. methyl diethylphosphonate in THF (degassed), 1.1 eq. *n*-BuLi, THF (degassed),
-70°C, add 1.1 eq. CuI, -70°C to -35°C, then -35°C for 40 min, add 1.1 eq. **236**, THF, -40°C then warm to RT and
stir for 16hr, 38%

The reaction of β-ketophosphonate **237** with a crude sample of aldehyde **199** using
the Masamune-Roush olefination conditions provided enone **240** in 48% yield.[47]
This reaction was only performed once and appeared to appeared to be very clean.
Therefore we anticipate that this yield could in fact be much higher if optimised
(Scheme 87).

Scheme 87

Reagents
i. Swern oxidation, quantitative crude yield; ii. 1.2eq. LiCl, 1.2eq. β-keto phosphonate **237**, 1.0eq. DBU, acetonitrile, then 1.0 eq. **199**, RT, 12 hr, 48% yield.

We were concerned by the amount of effort required to generate our target model structures using the β-ketophosphonate approach. For this reason we did not examine methods for the 1,2 reduction of **240** to produce the desired relative stereochemistry in the allylic alcohol product. Furthermore we now felt that this strategy (involving an intermediate β-ketophosphonate) would not prove fruitful in the preparation of the relevant enones **233** and **234**, and therefore this line of research was discontinued.

A procedure that had excellent precedent for its efficient application to the coupling reactions of both *trans*-iodo alkenes **179** and **175** with aldehyde **156** was the chromium(II) chloride (containing a trace amount of nickel(II) chloride) method developed by Kishi[22a] and Takai.[22b] However, an efficient asymmetric version of this reaction does not exist, although Kishi has reported that the stereochemical outcome of such a reaction should be able to be controlled using a suitable chiral ligand. His attempts along this line have only met with limited success so far.[115(c),(d)] We believed that if high diastereoselectivity was to be observed in the coupling reaction then the use of asymmetric catalysis would be essential. This was because the presence of the adjacent *trans*-1,2-disubstituted cyclopropane moiety in aldehyde **156** would prevent any inherent control in the coupling reaction being possible, since the bulky lactone-containing substituent would be oriented away from the aldehyde functionality.

In 1992 Oppolzer and Radinov reported the preparation of enantiomerically enriched secondary (*E*)-allylic alcohols from the coupling of aldehydes and acetylenes *via* (*E*-1-alkenyl)ethylzinc intermediates using homochiral amino alcohols.[21(b)] A non-functionalised alkyne, for example oct-1-yne, was hydroborated using freshly prepared dicyclohexylborane to give selectively an (*E*-1-alkenyl)dicyclohexylborane **242**. Transmetallation of the borane intermediate was achieved using either diethyl- or dimethyl zinc. The addition of simple aldehydes (e.g. benzaldehyde or valeraldehyde) to the zinc reagent **243** in the presence of a catalytic amount of (-)-3-*exo*-(dimethylamino)isoborneol (DIAB) **244**, gave the (*E*)-allylic alcohol product **241** in good yields and respectable enantiomeric excesses (Scheme 88). The catalyst-directed π-selective 1-alkenyl/ aldehyde addition is believed to occur *via* a transition state # consistent with that shown below.

Scheme 88

R—≡≡

R=-(CH2)₅CH₃
octyn-1-ol

hexane, 0°C,
RT

R⌒⌒B(c-hexyl)₂
242

Et₂Zn, hexane, -78°C

R⌒⌒Zn-Et
243

R'CHO
1 mol%
(-)-DIAB **244**

#

C=O
Si- face attack
aq. NH₄Cl

R⌒⌒R'
241   OH
R'=Ph, 72% yield, 92% e.e
R'=Bu, 86% yield, 85% e.e

Oppolzer and colleagues have also shown that this methodology can be applied to macrolactonisation reactions, and both (*R*)-(-)-muscone[21(e)] and (+)-aspicilin[21(f)] have been prepared using this approach (Scheme 89).

Scheme 89

A.

1. HB(C6H11)2

hexane, 0°C

2.add to Et2Zn,
1% (+)-DIAB
3. aq. NH4Cl

75% yield
92% e.e

(R)-muscone

B.

steps

1. HB(C6H11)2

hexane, 0°C

2.add to Et2Zn,
1% (-)-DIAB
244
3. aq. NH4Cl

60% yield
91% d.e

steps

(+)-Aspicilin

We believed that this would be an excellent method for the controlled addition of both acetylenes **178** and **173** to the aldehyde portion **156** in the synthesis of neohalicholactone **1** and halicholactone **2** respectively. One problem with this procedure is that (-)-DIAB **244** and its enantiomer are not commercially available. We would in fact require (+)-DIAB in the synthesis of **1** and **2**. The preparation of these catalysts involves a three step synthesis from either (1R,E)-(+)-camphorquinone-3-oxime or its S-antipode.

(1R,E)-(+)-camphor-
quinone-3-oxime

(-)-DIAB **244**

Therefore we felt that it would be beneficial to use (R)-diphenyl(1-methylpyrrolidine-2-yl)methanol ((R)-DPMPM) since this material could synthesised in one step from commercially available starting material. Oppolzer has reported that the (S)-DPMPM **245** ligand directed the (1-alkenyl)zinc/ aldehyde addition with the same π-face selectivity as (-)-DIAB **244**. Further, competitive yields and enantiomeric excesses were reported for the reactions performed using **245**. In our model studies we prepared (S)-DPMPM **245** since its commercially available precursor, (S)-(-)-α,α-diphenyl-2-pyrollidine methanol **246**, was much less expensive than the unnatural (R)-enantiomer. The methylation of **246** was achieved in 69% yield after recrystalisation using the formaldehyde/formic acid procedure.[137] We were able to show that we could successfully repeat the work of Oppolzer and Radinov[21(b)] using **245** as the asymmetric catalyst. By closely following the reported reaction conditions we were able to synthesise allylic alcohol **247** in 79% yield from the coupling of oct-1-yne and heptaldehyde using 1 mol% of **245**. The enantiomeric purity of this product **247** was not ascertained (Scheme 90). We then introduced oxygen functionality into our model substrate by preparing t-butyldiphenylsilyl-protected propargyl alcohol **248**. Oxygen functionality in substrates as well as oxygen containing solvents can interfere with the desired asymmetric alkenyl transfer reaction. Bulky silyl ethers such as t-butyl-diphenylsilyl- or triisopropylsilyl ethers have been shown to diminish the chelating ability of the oxygen functionality in the presence of certain organometallic reagents.[114] By in effect "hiding" the oxygen functionality in our model substrate **248** with the bulky t-butyldiphenylsilyl protecting group we expected the reaction to proceed smoothly.

Scheme 90

Reagents
i. 2.0 eq. cyclohexane, 1.0 eq. BH$_3$.DMS, 0°C, degassed hexane, 3 hr, 1.0 eq. oct-1-yne, RT, 1 hr, then at -78°C add 1.0 eq. ZnEt$_2$ in hexane and 0.01eq. 245, 0°C, 1.0 eq. heptaldehyde, 0°C to RT, 12 hr, 79% yield.

Unfortunately, however, we were not unable to isolate any of the desired allylic alcohol **249** from the coupling of **248** with hexanal using the same reaction conditions that had been successful in the synthesis of **247** (Scheme 91).

Scheme 91

From the crude ^{1}H-NMR it appeared that the likely fate of the aldehyde was simply self-aldolisation giving polymeric products. The remaining material appeared to consist wholly of silicon residues. We therefore concluded that the application of this methodology to the synthesis of **1** or **2** was not realistic. In 1994 Wipf and Xu reported that allylic alcohols could be prepared via a hydrozirconation reaction (using Schwartz's reagent) of an alkyne (rather than hydroboration) followed by transmetallation with dimethyl- or diethyl zinc and subsequent addition of the (1-alkenyl)ethyl zinc species to an aldehyde.[21(c)] Whilst a catalyst was not essential for this transformation they were able to show that a modest enantiomeric excess could be achieved in the coupling of hex-1-yne with benzaldehyde in the presence of 8 mol% of

the proline derived ligand **245** using the aforementioned reaction conditions. Also they found that the reaction was tolerant towards *t*-butyldiphenylsilyl ethers and ester functionality (Scheme 92).

Scheme 92

1. Cp_2ZrHCl, CH_2Cl_2 ,RT
2. Me_2Zn, -65°C
3. 8 mol% (S)-DPMPM **245**

4. PhCHO, -20°C

92% yield, 38% e.e

1. 1.0 eq. Cp_2ZrHCl, CH_2Cl_2 ,RT
2. 1.0 eq. Me_2Zn, -65°C

3. 1.0 eq. hexaldehyde

t-BuPh$_2$SiO

0.8 eq.

t-BuPh$_2$SiO — n-C$_5$H$_{11}$

OH

83% yield

We were pleased to find that application of this methodology, in the absence of directing ligand **245**, enabled us to react the oxygen containing model substrate **248** with hexanal to produce racemic allylic alcohol **249** in 50% yield (Scheme 93).

Scheme 93

t-BuPh$_2$SiO

H

248

i

t-BuPh$_2$SiO

OH

249

Reagents
i. 0.95 eq. **248**, 1.0 eq. Cp_2ZrHCl, CH_2Cl_2, RT, then cool to -78°C,1.0 eq. $ZnEt_2$ (1.1M in toluene), warm to 0°C, then at RT add 1.0 eq. hexanal in CH_2Cl_2, 1.5 hr, 50% yield.

Whilst we felt convinced that this yield could be greatly improved by optimisation studies and the use of the asymmetric catalyst **245** then assessed, we decided that it would be more beneficial to work on the real system, the reaction of either alkyne **178** or **173** with aldehyde **156**. The reaction of **178** with **156** afforded none of the desired allylic alcohol product under the reaction conditions used to synthesise **249**. The crude ^{1}H-NMR spectrum indicated that the hydrozirconation reaction had proceeded smoothly since almost all of the alkyne **178** had been consumed, but it had

simply been converted to its alkene derivative **250**. Also, a great deal of the aldehyde

starting material **156** had also been consumed, but the product of its consumption was

not the desired allylic achohol **252**. Instead, it appeared that a problem with the

zirconium-zinc metal exchange existed and that the aldehyde **156** was simply reacting

with excess diethylzinc to give the alcohol product **251** (Scheme 94).

Scheme 94

desired product not isolated

Reagents
i. 1.0 eq. Cp₂ZrHCl, CH₂Cl₂, RT, 20 min, 1.0 eq. Et₂Zn -55°C, add 156 at 0°C, 1 hr, 0°C, sat. aq. NH₄Cl.

We therefore left this line of research despite the earlier encouraging result in preparing

allylic alcohol **249**.

Organochromium mediated transformations were now investigated.[115] In 1983 Takai

and colleagues described the addition of alkenyl halides to aldehydes mediated by

chromium(II) chloride.[116] The coupling of 2 equivalents of 2-iodopropene **253** with

1 equivalent of benzaldehyde in DMF in the presence of 4 equivalents of chromium(II)

chloride led to the quantitative isolation of 2-methyl-1-phenyl-2-propen-1-ol **254** after

just fifteen minutes at room temperature (Scheme 95).

Scheme 95

$$\text{253} + \text{Ph-CHO} \xrightarrow[\text{15 min, 100\% yield.}]{\text{CrCl}_2, \text{DMF, 25°C,}} \text{254}$$

Interestingly whilst a quantitative yield of **254** was obtained using purchased anhydrous chromium(II) chloride, the chromium reagent prepared from $\text{CrCl}_3\text{-LiAlH}_4$ was less effective for the reaction shown in scheme 95 and **254** was isolated in just 8% yield. In 1986 both Takai[22(b)] and Kishi[22(a)] reported the importance of a catalytic amount of nickel(II) chloride to be present in the chromium(II) chloride if the coupling reaction was to be successful. The chromium(II) chloride/ nickel(II) chloride procedure was thoroughly investigated by Kishi's group during their synthetic studies on the marine natural product palytoxin.[22(a)] They wished to couple aldehyde **255** and *trans*-iodo alkene **256**. By much trial and error experimentation they accomplished the desired coupling reaction by adding six equivalents of chromium(II) chloride, containing 0.1% nickel(II) chloride, to aldehyde **255** and 3 equivalents of *trans*-iodo alkene **256** in dimethylsulfoxide. The allylic alcohol product **257** was isolated in 71% yield as a 1.3 to 1 mixture of isomers (see Scheme 96)

Scheme 96

1.0 eq. **255**

+

3.0 eq. **256**

6.0 eq. CrCl_2, 0.1% NiCl_2, DMSO, RT, 20 hr, 71% yield.

257

16α:16β=1.3:1

Kishi's group went on to demonstrate that a number of highly oxygenated molecules, which importantly included α-oxygenated iodo olefins, were compatible with the

reaction conditions that they had developed.[22(a)] Functional groups that were tested included esters, amides, nitriles, ketones, acyls (acetate, benzoate), acetals, ketals, ethers (benzyl, *p*-methoxyphenylmethyl), silyl ethers (*t*-BuMe$_2$Si and *t*-BuPh$_2$Si), alcohols and olefins. They also established that the stereochemistry of a disubstituted *trans*-iodo olefin was retained in the coupled product and demonstrated that dimethyl sulfoxide as solvent was critical, at least for the synthesis of **257**. A substantial amount of an α,β-unsaturated aldehyde, a derivative of **255**, was isolated if DMF or mixtures of DMF and DMSO were used. However it was noted that reactions were generally quicker in DMF or DMF/DMSO mixtures whilst the use of DMSO alone resulted in cleaner reactions which occurred more slowly. Finally they found that if substantially more than the 0.1% of nickel(II) chloride was present, for example greater than 2%, then a significant amount of 1,3 diene was formed from the coupling of two molecules of iodo alkene **256**.[117]

High selectivity is a hallmark of most organochromium-mediated transformations since organochromium compounds possess mild nucleophilic properties when compared with other organometalic reagents. An example of the of the excellent chemoselectivity observed in vinyl-chromium additions is found in the approach of Parsons and co-workers to the histrionicotoxin framework (Scheme 97).[118] The vinyl-chromium species adds selectively to the aldehyde leaving both the ketone and ester functionality untouched. Unsurprisingly this chromium mediated reaction has been widely employed *en route* to the synthesis of many natural products. Kishi in particular, has employed this reaction to great effect in the syntheses of the left half of palytoxin[22(a),115(c)], the right hand fragment of the halichondrins[115(c),119] (in which five of the key C-C bonds were constructed using this chemistry), and more recently towards the taxane class of natural products using an intramolecular version.[120]

Scheme 97

Before discussing our own experimental findings using this powerful chromium reaction, a possible mechanism for this is presented first. Chromium(II) salts are single electron reducing agents where the metal is oxidised to the +3 oxidation state at the end of the reaction. Therefore in order to form an organochromium species a minimum of two equivalents of chromium(II) chloride are required per halide atom removed from the halo-olefin. The mechanistic cycle that has been postulated by Takai is shown in Scheme 98.

Scheme 98

The synthesis of natural product **31** (which is related to constanolactones A and B), is described in Scheme 18. One of the key steps in the synthesis is the Takai-Kishi

coupling of *trans*-iodo alkene **79** with aldehyde **77**. Importantly aldehyde **77** contains an α-*trans* 1,2 disubstituted cyclopropane ring and a 1:1 mixture of allylic alcohols resulted from the coupling reaction. This result confirmed our suspicions that the *trans* cyclopropane ring prevents any inherent stereocontrol in the coupling reaction. We therefore expected that any diastereocontrol in the coupling of *trans*-iodo alkenes **179** and **175** with aldehyde **156** would have to come from the enantiomerically pure vinylic anion species (derived from **179** or **175**). This is obviously disfavoured due to the remote location of the chiral centre in the *trans*-iodo olefin. In order to determine to what extent the (3*R*)-ether centre of the *trans*-vinylic chromium species could control the addition, we reacted both *p*-methoxyphenylmethyl and *t*-butyldiphenylsilyl protected *trans*-iodo alkenes **175** and **176** with a prochiral aldehyde, 2-methylpropanal. We isolated the *p*-methoxyphenylmethyl-protected allylic alcohol **259** as a 1:1 mixture of diastereomers, whilst the coupling of **175** with **156** did proceed with moderate selectivity. A 2.1:1 mixture of allylic alcohol diastereomers **258** was isolated in the latter case. Further, the differently protected allylic alcohols **258** and **259** were both isolated in quantitative yield by closely following the experimental conditions reported by Kishi in his original report (Scheme 99).[22(a)]

Scheme 99

258 2.1:1 epimeric mixture

259 1:1 epimeric mixture

Reagents
i. 3.0 eq. **175**, 1.0 eq. 2-methyl propanal, 6.0 eq. CrCl$_2$ (containing 0.5 wt% NiCl$_2$), 2:1 dimethylsulfoxide: N,N-dimethylformamide, 1 hr, quantitative yield.
ii. 1.6 eq. **176**, 1.0 eq. 2-methyl propanal, 3.3 eq.CrCl$_2$ (containing 0.5 wt% NiCl$_2$),dimethylsulfoxide, 2 hr, quantitative yield.

Although we did not determine the relative stereochemistry in the major diastereomer of
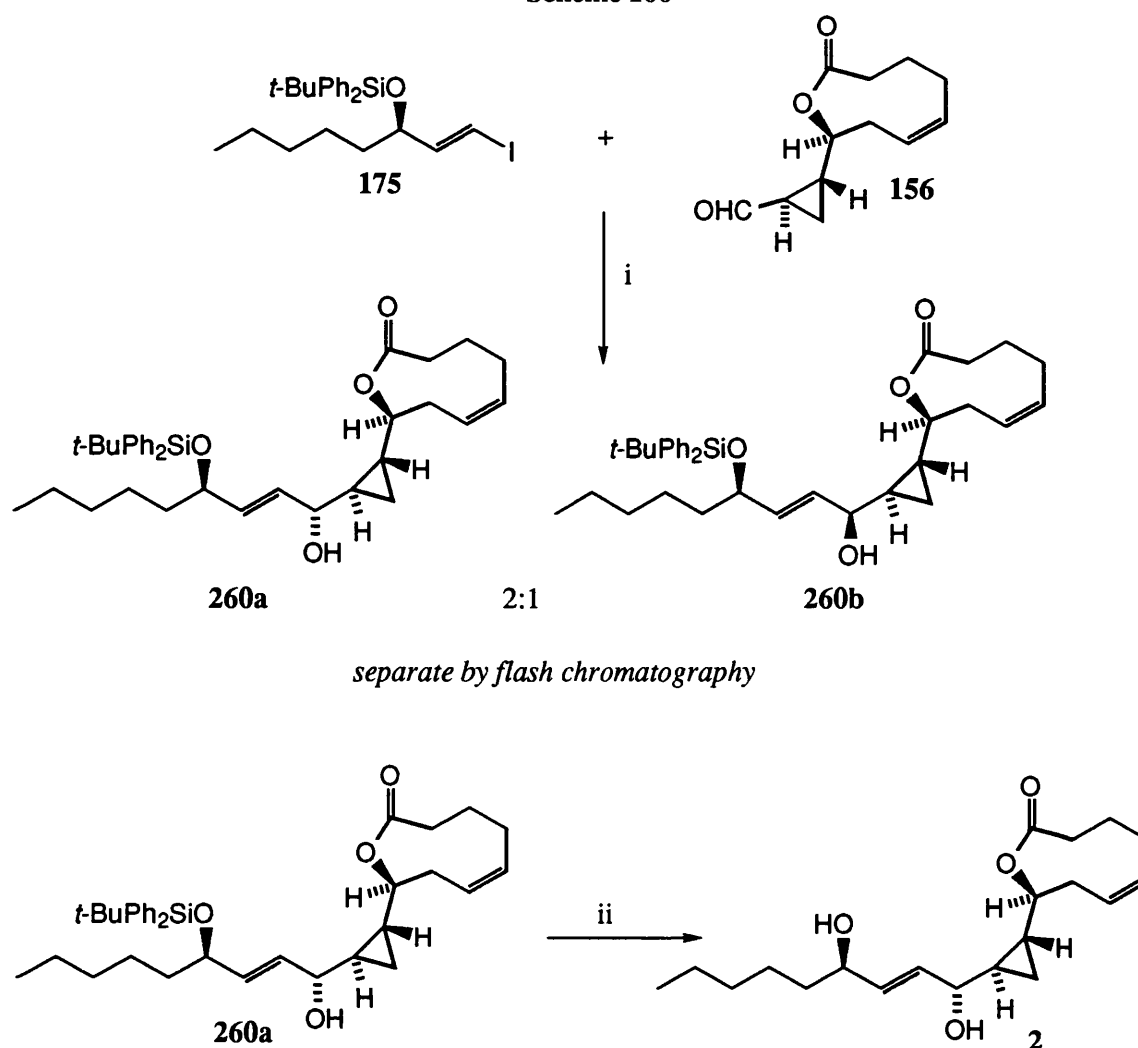
258 we were hopeful that it would be the desired *anti*-3S,6R product.

We then applied this methodology to the synthesis of halicholactone **2**. The reaction of

1.0 equivalent of aldehyde **156** with 1.7 equivalents of *trans*-iodo alkene **175** in the

presence of 3.3 equivalents of chromium(II) chloride (containing 0.5wt.% $NiCl_2$)

provided the desired allylic alcohol **260** as a 2:1 mixture of diastereomers in good yield

73% (Scheme 100). This yield was not optimised and presumably would have

approached being quantitative given further experimentation since the reaction was very

clean by thin layer chromatography analysis. It should also be noted that the quoted

yield, 73%, is representative of the amount of material we isolated after repeated

purification processes. The two diastereomers **260a**-(major) and **260b**-(minor) were

partially separated by three repeated chromatography runs such that a 43% yield of the

major isomer **260a** was isolated pure. All remaining **260a** had not been separated

from **260b**. With pure **260a** in hand we then attempted the final deprotection step

which would give, if this diastereomer possessed the correct relative stereochemistry at

C_{12}, enantiomerically pure halicholactone **2**. The reaction of **260a** with 3.0

equivalents of tetrabutylammonium fluoride in tetrahydrofuran at room temperature for

2 days did not give any of the desired desilylated product. Instead we recovered 62%

of the starting material **260a** and a decomposition product(s) which was not

characterised. The reaction of **260a** with excess hydrogen fluoride-pyridine solution

in tetrahydrofuran was also unsuccessful and only starting material was observed by

thin layer chromatography after leaving the reaction at room temperature for 16 hours.

However to our releif, the reaction of **260a** with 2.5 equivalents of

tetrabutylammonium fluoride in tetrahydrofuran at reflux for 3 hours did give the

desilylated product in almost quantitative yield (99%). The 400MHz ^{1}H-NMR (in

C_6D_6) and 125MHz ^{13}C-NMR (in $CDCl_3$) spectra for this compound exactly matched

the data reported for halicholactone **2**. Also the optical rotation of our product, $[\alpha]_D^{18} =$

-91.7 (c 0.29 in chloroform), corresponded well with the literature value, $[\alpha]_D^{23} = $ -85.4

(c 1.16 in chloroform).

Scheme 100

separate by flash chromatography

Reagents
i. 1.0 eq. **156**. 1.7 eq. **175**, 3.3 eq. CrCl$_2$ (containg 0.5 wt% NiCl$_2$), DMSO, 3 hr, 73% (43% yield of pure **260a**); ii. 2.5 eq. TBAF (1M in THF), reflux, RT, 3hr, 99% yield.

Further, we were able to unequivocally confirm that we had synthesised halicholactone **2** and not the C$_{12}$-epimer by performing the following enlightening transformations. The reaction of 1.2 equivalents of **175** with 2.13 equivalents of *t*-butyllitium generated 0.93 equivalents of the corresponding *trans*-lithio alkene species. The reaction of the lithium anion of **175** with **156** provided the coupled product **260** in disappointing yield, 28%, but with improved diastereoselectivity; **260a:260b** 3.2:1. We also isolated 50% yield of aldehyde **156** and a 57% yield of alkene **261**. The isolation of **261** implies that there was not a problem with the metal-halogen exchange reaction since **261** presumably results from either the quenching of the lithium anion of **175**

during the reaction or by the addition of water at the end of the reaction. We felt that it was most likely that the lithium anion of **175** was too basic and was being quenched by abstraction of an α-hydrogen from aldehyde **156** at a competitive rate to which it was adding to the aldehyde centre. Whilst we were able to separate the diastereomers **260a** and **260b** by flash chromatography and hence determine the 3.2:1 diastereomeric ratio, both of these compounds were contaminated by unreacted aldehyde **156** (Scheme 101). Therefore we decided to recombine the two mixtures of compounds and subject **260a**, **260b** and **156** to pyridinium chlorochromate oxidation conditions.[39] In doing so we hoped to be able to recover the precious aldehyde **156** pure, whilst **260a** and **260b** would be converted to a single compound, enone **262**. In the event we were able to recover 87% of **156** and isolated enone **262** in 54% yield from the oxidation reaction after chromatography (Scheme 102).

Scheme 101

Reagents
i. 1.2 eq. **175**, 2.13 eq. *t*-BuLi, THF, -78°C, 30 min, 1.0 eq. **156**, -78°C to 0°C, 1 hr.

Scheme 102

156 + t-BuPh₂SiO

inseparable mixture

3.2:1 260a:260b

i

156
87% yield

+ t-BuPh₂SiO

262
54% yield

separated after flash chromatography

Reagents
i. 3.0 eq. P.C.C, CH₂Cl₂, powdered mol.sieves, RT, 30 mins.

The reaction of enone **262** with 3.0 equivalents of tetrabutylammonium fluoride in tetrahydrofuran at room temperature gave the desired product **263** in 81% yield after just 1 hour (a small amount of starting material **262** was also isolated). This is a more typical rate for a desilylation reaction under these conditions. We therefore believe that the desilylation of **260a** was extremely slow due to a retardation effect caused by the presence of the proximal C_{12} hydroxyl group. Finally we reduced **263** by employing Luche conditions[121] (selective 1,2-reduction of conjugated enones using 1.0 equivalent of cerium trichloride heptahydrate and 1.0 equivalent of sodium borohydride) and isolated halicholactone **2** and its C_{12} epimer **264** as a 1:1 mixture of diastereomers in a modest 40% yield. Some unreacted starting material **263** was also observed by thin layer chromatography which explains why the yield of this reaction was so poor. The reaction confirmed our suspicions that carbonyl reduction adjacent to the *trans*-cyclopropane ring would not be a diastereoselective process, and this was in keeping with other literature reports on related systems.[113] Importantly, the 400MHz ^{1}H-NMR spectrum of the 1:1 mixture of diastereomers (**2** and **264**) provided conclusive evidence that the isomerically pure compound we had earlier isolated by direct desilylation of **260a** was in fact halicholactone **2** (Scheme 103). The signals

which belonged to **264** in the 400MHz ^{1}H-NMR of the 1:1 mixture could be determined by subtraction of the signals that we new belonged to **2** since we had earlier obtained a pure spectrum of this material. The ^{1}H-NMR features of the C$_{12}$-epimer **264** were not in such good agreement with the published data for halicholactone **2**. Therefore, we could now be certain that the major isomer **260a** of the chromium mediated coupling, possessed the correct relative stereochemistry for the synthesis of halicholactone **2**.

We have therefore completed a convergent 20 step synthesis of halicholactone **2** in 3.1% overall yield starting from commercially available materials.

Scheme 103

1:1 mixture **264** : **2**

Reagents
i. 3.0 eq. TBAF (1M in THF), RT, 1 hr, 81%; ii. 1.0 eq. NaBH$_4$, 1,0 eq. CeCl$_3$.7H$_2$O, MeOH, 5 min, 40%.

The synthesis of neohalicholactone **1** now became relatively straightforward since we could draw on the knowledge we had earlier gained in the synthesis of **2**. The coupling of 1.0 equivalent of aldehyde **156** with 2.0 equivalents of *trans* iodo alkene **179** mediated by 6.0 equivalents of chromium(II) chloride (containing 0.5wt% NiCl$_2$) gave as before a 2:1 mixture of diastereomers **252a** and **252b** which were isolated together in 61% yield. Due to solubility problems this reaction was carried out in a 1:1 mixture of DMSO and DMF, and the full consumption of aldehyde **156** was observed

after just 3 hours at room temperature. The moderate yield of this reaction could certainly be improved since again the reaction appeared to be free of by-products by thin layer chromatography analysis. We only performed this reaction once (Scheme 104).

Scheme 104

Reagents
i. 1.0 eq. **156**, 2.0 eq. **179**, 6.0 eq. CrCl$_2$ (containing 0.5 wt% NiCl$_2$), 1:1 DMSO:DMF, 3 hr, RT, 60% yield (40% yield major isomer **252a**); ii. 3.0 eq. TBAF (1m in THF), THF, reflux, 2 hr, 90% yield.

A small amount (22mg) of the mixture of the 2:1 mixture of diastereomers **252a** and **252b** was desilylated under the forcing conditions we had found necessary to synthesise **2**. The reaction of **252a** and **252b** with 3.0 equivalents of tetra-butylammonium fluoride in tetrahydrofuran at reflux for 2 hours provided a mixture of

neohalicholactone **1** and the C_{12}-epimer of neohalicholactone **265** in 90% yield after chromatography. From the 400MHz ^{1}H-NMR spectrum (in C_6D_6) of this diastereomeric mixture it was clear that the major compound, a result of the mildly selective coupling reaction, was most likely to be **1**. The distinguishing features of the ^{1}H-NMR spectrum were the signals that belonged to the C_{10} cyclopropane protons, and the C_{12} proton. In the original 500MHz ^{1}H-NMR data of the authentic sponge derived **1**, these signals were found at 0.27 (H_{10a}, ddd, J 8.5, 5.0, 5.0), 0.45 (H_{10b}, ddd, J 8.5 ,5.0, 5.0) and 3.52 (H_{12}, m) respectively. Our 400MHz ^{1}H-NMR spectrum clearly showed that it was the major isomer **1** that was in excellent agreement with this published data; 0.31 (H_{10a}, ddd, J 8.6, 5.2, 5.2), 0.51 (H_{10b}, ddd, J 8.9, 5.2, 5.2), and 3.58 (H_{12}, dd, J 6.7, 3.4). The agreement for the minor isomer **265** was less consistent with the published data for neohalicholactone; 0.31 (H_{10a}, m), 0.42 (H_{10b}, ddd, J 8.6, 4.9, 4.9), and 3.50 (H_{12}, dd, J 6.7, 3.4). Therefore we returned to our diastereomeric mixture of **252a** and **252b** and separated them during one very careful flash chromatography run. The major compound **252a** was then desilylated as before to provide a pure sample of neohalicholactone **1**. From our pure sample of **1** we obtained an identical 500MHz ^{1}H-NMR (in D_6-benzene) spectrum and 125MHz ^{13}C-NMR (in $CDCl_3$) spectrum to those generously supplied by Professor K.Yamada for the sponge derived sample of **1**. The optical rotation we obtained, $[\alpha]_D^{18} = -54.6$ (c 0.76 in chloroform), was also in excellent agreement with the literature value, $[\alpha]_D^{16} = -54.2$ (c 0.73 in chloroform). Finally in an attempt to convert the otherwise wasted C_{12}-epimer **252b** into **252a** we performed the following reactions. The minor isomer **252b** (containing a small amount of **252a**) was oxidised to **266** using 5 mol% TPAP/1.5 equivalents of NMO conditions in 91% yield. However, the reduction of the carbonyl group in **266** under Luche conditions[121] returned a 3:1 mixture of **252b:252a**. The undesired isomer, **252b**, was unfortunately the diastereomer which formed in excess (Scheme 105).

Scheme 105

Reagents
i. 1.5 eq. NMO, 5 mol% TPAP, powdered mol. sieves, CH_2Cl_2, RT, 30 mins, 91%; ii. 1.0 eq. $NaBH_4$, 1.0 eq. $CeCl_3.7H_2O$, MeOH, 5 min, 65% (based on recovered starting material).

Both more bulky and homochiral reducing agents could have been examined and shown to be more beneficial for the selective reduction of **266** to **252a**. These experiments have to date not been performed.

Therefore in summary, we have completed the first total synthesis of an enantiomerically pure sample of **1**. The convergent synthesis was achieved in 30 steps and 0.65% overall yield starting from commercially available materials, (R)- and (S)-malic acid. The total synthesis of **1** and **2** unambiguously confirms that the relative stereochemistry of both these substrates is 8S,9R,11R,12R,15R, as we had suspected at the outset of this project.[122]

After we had completed our synthesis of **1** and **2**, White and Jenson published the synthesis of the related compounds, constanolactones A and B (**34** and **35**).[18(b)] They wished to synthesise **34** and **35** by coupling *trans* iodo alkene **184** with aldehyde **77'** by again using the excellent chromium mediated approach. The coupling reaction did in fact proceed smoothly and interestingly a 2:1 mixture of diastereomers

267a and **267b** were isolated where the major isomer **267a** contained the same relative stereochemistry as that we had observed in our coupling reactions (Scheme 106).

Scheme 106

separated by HPLC

Various desilylation conditions

DECOMPOSITION PRODUCTS

However, the final seemingly trivial task of removing the silyl protecting group from **267a** and **267b** could not be achieved. All the conventional reagents for this purpose were reported to result in decomposition products. It is interesting to note that this problem was solved by performing the chromium mediated coupling reaction using the desilylated derivative of **184** as shown in Scheme 18. The problematical final desilyation step reported by White is in keeping with our own findings. In our attempted desilylation of **260a** using tetrabutylammonium fluoride only decomposition product(s) were observed after the reaction had been left at room temperature for 2 days. This decomposition serves to show how sensitive cyclopropane-containing structures of this type are. It is worthy of note that we observed (by thin layer chromatography) a significant amount of degradation products from a sample of **1** which had been stored between 0-5 °C temperatures for several weeks.

2.4 The Absolute Stereochemistry of "Neohalicholactone" from the Brown Alga *Laminaria sinclairii*.

In 1993 Gerwick and Proteau reported that the brown alga, *Laminaria sinclairii*, produced a variety of interesting oxylipins including several hydroxy-containing compounds such as methyl (15S)-hydroxy-5(Z),8(Z),11(Z),13(E),17(Z)-eicosa-pentaenoate **268** and methyl (15S)-hydroxy-5(Z),8(Z),11(Z),13(E)-eicosatetraenoate **269**.[123]

methyl (15S)-HEPE **268**

methyl (15S)-HETE **269**

The isolation of **268** and **269** suggests that *L.sinclairii* possesses an active lipoxygenase with positional specificity for C_{15} in C-20 substrates, and significantly that the C_{15} hydroxy centre that is formed is of S stereochemistry. In December 1994, just as we completing the synthesis of neohalicholactone **1**, Gerwick and co-workers reported the isolation of "neohalicholactone" from *L. sinclairii*.[124] This had been achieved by careful scrutiny of several minor fractions obtained during the isolation of more major metabolites such as **268** and **269**. From spectroscopic analysis, Gerwick reported that his isolate of "neohalicholactone" was identical in every way, overall structure, relative and absolute stereochemistry, to neohalicholactone **1** isolated from the marine sponge *Halichondria okadai*. The maximal difference in the ^{13}C-NMR was 0.1 ppm and in the ^{1}H-NMR it was 0.05 ppm. Further the optical rotation value they had obtained for *L.sinclairii* derived "neohalicholactone" was $[\alpha]_D^{27} = -77$ (c 0.14 in chloroform). The corresponding value for the *H.okadai* derived material was $[\alpha]_D^{16} = -54.2°$ (c 0.73 in chloroform). Therefore, Gerwick and colleagues believed that since

the optical rotation value of the *L.sinclairii* derived material was not substantially different from the original value and of the same sign (negative rotation), that they had isolated an identical sample of neohalicholactone **1**. Since the absolute stereochemistry of **1** had not been reported at this time Gerwick's group went on to perform a degradative study which established the absolute stereochemistry at C_{15} of *L.sinclairii* derived "neohalicholactone". They converted their sample of "neohalicholactone" to its corresponding (-)-menthoxycarbonyl derivative, performed oxidative ozonolysis to release the C_{14}-C_{17} fragment, and this fragment was then esterified using diazomethane to give bis-methyl ester **270** (Scheme 107).

Scheme 107

"neohalicholactone" from *L. sinclairii*

1) (-)-menthyl chloroformate, pyridine, toluene.
2) O_3, CH_2Cl_2, -10°C. 10 min, then HCOOH, 50°C, 16 hr.

3) CH_2N_2

270 100%S

Authentic standards of (-)-menthoxy carbonyl derivatised *R* and *S* malates were then synthesised. Using gas chromatography-electron impact mass spectroscopy apparatus, the *R* and *S* malate standards gave base-line separation. Under the same conditions their "neohalicholactone" derived malate fragment **270** analysed as essentially 100% S. This result was in keeping with other C_{15} hydroxyl metabolites from the same source (for example **268** and **269**). They concluded that in both the algae and sponge derived neohalicholactone samples, the absolute stereochemistry was in fact 8*R*,9*S*,11*S*,12*S*,15*S* and therefore opposite to that originally proposed. This publication obviously had substantial implications with regard to our synthetically produced sample of **1**. It appeared that if Gerwick was correct then we would in fact be synthesising the opposite enantiomer to that found in the marine life. However as already described in section 2.3 the 8*S*,9*R*,11*R*,12*R*,15*R* sample of neohalicholactone **1** we had synthesised matched exactly every piece of spectroscopic data published for

the original sponge derived material, including most significantly the sign and magnitude of the optical rotation value.[1(a),122] Therefore a curious disparity existed between our findings and those reported by Gerwick.[124] Either something was subtly wrong in our synthesis of **1** such that we had in fact synthesised the opposite enantiomer to that we thought we would produce, or Gerwick had actually isolated a C_{15} epimer of neohalicholactone which possessed very similar spectroscopic properties to those of *H.okadai* derived neohalicholactone. The former hypothesis was addressed first. In order for us to have synthesised the enantiomeric form of **1** this would by definition involve the inversion of all five chiral centres. Such an occurrence would be most likely if the inversion took place early in the synthesis whilst a synthetic intermediate only contained one chiral centre. Therefore the question of relative stereochemistry is not an issue. Our preparation of the left and right hand fragments **179** and **156** relied on the intermediacy of (3*R*)-hydroxy lactone **111** and 3S-hydroxy lactone **114** respectively. These lactone intermediates **111** and **114** were synthesised by acid cyclisation of either methyl (*R*) or (*S*)-3,4-dihydroxybutanoate (**113**). If the mechanism for this cyclisation reaction was such that inversion of stereochemistry transpired then this would subsequently mean that no change in the overall relative stereochemistry of our product would occur. However we would in fact synthesise the opposite enantiomer, which was implied by Gerwick's results. The acid promoted cyclisation transformation (to give **111** or **114**) was the only step in our synthesis that we could provide any semi-rational mechanism (mechanism A) that could lead to an early inversion of stereochemistry of a simple intermediate and would ultimately account for the complete inversion of stereochemistry in our final product **1** (Scheme 108).

Scheme 108

inversion mechanism A

HO:—O
HO ⟶ OMe
113 H⁺

-MeOH ⟶ H⁺ O O HO: **271**

H⁺ | inversion

H⁺ O H HO O

HO O O **111**

mechanism B

HO H⁺ OMe HO: O **113**

-MeOH ⟶ HO O O **114**

Mechanism **B** appears to be far more probable since cyclisation to a give a five-membered lactone is known to be favoured when compared with the energetically less attractive four-membered lactone ring formation to give **271**. However if under these conditions the 2-oxetanone intermediate **271** was formed then the subsequent steps shown in mechanism **A** appear to be quite reasonable. There is literature precedent for the β-cleavage step shown in mechanism **A** which would account for the inversion of stereochemistry (see Scheme 108).[125] Intramolecular ring opening of 2-oxetanones under Lewis acidic conditions has been demonstrated. For example 2-oxetanone **272** was cyclised to tetrahydrofuran product **273** in 75% yield using 1.1 equivalents of titanium tetrachloride where the initial step in the formation of **273** was believed to involve the Lewis acid promoted β-cleavage of **272** (see Scheme 109).

Scheme 109

1.1 eq. TiCl4, -78°C,
CH2Cl2, 30 min.

272

273
75% yield

We were able to test the feasibility of mechanism **A** very simply. Most likely (3*S*)-hydroxy lactone product **114**, formed *via* the acid mediated cyclisation of **113**, was converted to (*S*)-(-)-1,2,4-butanetriol **274**. The synthesis of (*R*)-(+)-1,2,4-butanetriol **276** had previously been described by a procedure which did not involve any steps where inversion of stereochemistry could conceivably occur.[39] Dimethyl (*R*)-(-)- malate **275** was converted to (*R*)-triol **276** during a three step procedure and an optical rotation value of +22.5° (*c* 2.3 in ethanol) recorded. We converted **114** to (*S*)-triol **274** also in three steps by a similar protection, reduction, deprotection sequence in 90% (Scheme 110).

Scheme 110

1) DHP, cat. pTsA
ether, 20 hr, RT, 92%
2) 2.3 eq. DIBAL-H,
-50°C to RT, 2 hr,
100% crude

3) MeOH, cat pTsA
RT, 3 hr, 98%.

113

114

274

$[\alpha]_D^{18} = -23.5$ (*c* 1.9 in ethanol)

literature work

1) DHP, cat. pTsA
2) excess LiAlH4

3) MeOH, cat. pTsA

275

276

$[\alpha]_D^{20} = +22.5$ (*c* 2.3 in ethanol)

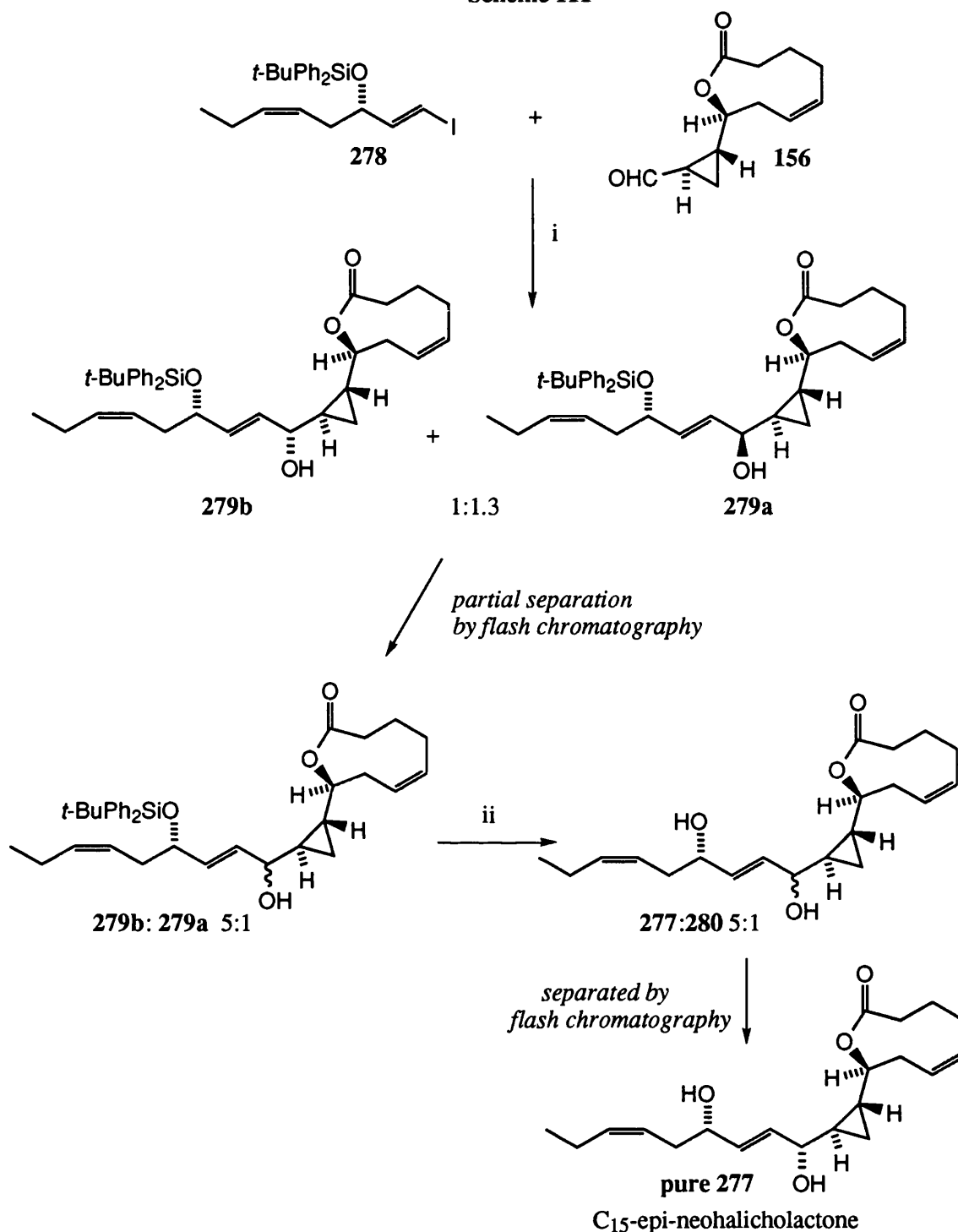If inversion had occurred in the acid promoted cyclisation of **113** then the triol product that we isolated would have had the same positive optical rotation value as that published for (R)-$(+)$-triol **276**. Instead, as expected, the product we isolated had a negative rotation thus proving that $(3S)$-**113** was converted to $(3S)$-**114** without inversion. In our opinion this result unequivocally proved that we had synthesised $8S,9R,11R,12R,15R$ neohalicholactone **1** and that the sponge-derived material also contained this absolute stereochemistry. Therefore the most likely explanation for the apparent disparity between our and Gerwick's findings was that he had, quite fascinatingly, isolated C_{15}-epi-neohalicholactone **277** from *L.sinclairii*. It was our belief that the C_{13}-C_{14} *trans* olefin would form a natural break in the stereochemical information of the molecule such that inversion of stereochemistry at C_{15} would not significantly manifest itself in the ^{1}H or ^{13}C-NMR spectra. Further Gerwick had obtained his 1H-NMR at 300MHz and ^{13}C-NMR at 75MHz, whilst we, in common with Yamada, performed our corresponding analyses at 500MHz and 125MHz respectively. We believed that if Gerwick had isolated C_{15}-epi-neohalicholactone **277** then it would only be in the higher field ^{1}H-NMR spectrum that any differences between **277** and **1** would reveal themselves. We therefore prepared a sample of **277** in order to test these ideas. $(3S)$-$(1E,5Z)$-3-O-$((t$-butyldiphenylsilyl$))$oxy-1-iodo-1,5-octadiene **278** was prepared as previously described for the synthesis of **179** by now starting from (S)-malic acid **86**. The coupling of 2.0 equivalents of *trans*-iodo alkene **278** and 1.0 equivalent of aldehyde **156** was performed using 4.4 equivalents of chromium(II) chloride (containing 0.5 wt% $NiCl_2$) in DMSO at room temperature over 16 hours. A 1:1.3 mixture of isomers **279b** and **279a** resulted, and after careful separation of these isomers during five chromatography runs the minor isomer **279b** was isolated in 24% yield and unfortunately this material was still contaminated with 17% of **279a**. However, the major isomer **279a** was isolated pure in 30% yield, whilst a further 16% yield of a 1:1 mixture of **279a:279b** was isolated. This implies that the overall yield for the coupling reaction was at least 70% (Scheme 111).

Scheme 111

Reagents
i. 1.0 eq. **156**, 2.0 eq. **278**, 4.4 eq. $CrCl_2$ (containing 0.5 wt% $NiCl_2$), DMSO, 16 hr, RT, 70% yield (30% yield minor isomer **279b**); ii. 2.5 eq. TBAF (1m in THF), THF, reflux, 5 hr, 84% yield.

Encouragingly the ^{1}H-NMR and ^{13}C-NMR of **279b**, the minor isomer of the coupling reaction, were in excellent agreement with those we had previously obtained for **252a** which had then been converted to **1**. Further, the data we obtained from **279a** were

quite different from both **252a** and **279b**. Therefore we presumed that **279b** possessed the correct relative stereochemistry for the synthesis of C_{15}-epi-neohalicholactone **277**. The minor isomer of the coupling reaction **279b** (contaminated with 17% of **279a**) was then desilylated using tetrabutylammonium fluoride and **277** (contaminated with 17% of C_{15},C_{12}-epi-neohalicholactone **280**) was isolated in 84% yield. We obtained 400MHz and 270MHz ^{1}H-NMR spectra of this 5:1 mixture of isomers (**277:280**), as well as a 67.8MHz ^{13}C-NMR spectrum. From our proton NMR comparisons with the data Gerwick had compiled from a 300MHz spectrum of *L.sinclairii* derived "neohalicholactone", it became apparent that the latter material could indeed be C_{15}-epi-neohalicholactone **277**. Remarkably the ^{1}H-NMR and ^{13}C-NMR spectra of **277** and **1** were indistinguishable at the quoted field strengths. Also, due to the 17% of **280** (of $8S,9R,11R,12S,15S$ absolute stereochemistry) being present in the ^{1}H-NMR spectra we obtained for **277**, it was clear that this isomer (**280**) did not closely match Yamada's and our own data for **1**. In order to obtain an accurate optical rotation value for our sample of **277** the small amount of **280** contaminant was removed by very careful column chromatography purification. Our purified sample of **277** had an optical rotation value of -84.9° (c 0.43 in chloroform). This value was of the same sign and similar magnitude to that reported for *L.sinclairii* derived "neohalicholactone", -77.0° (c 0.1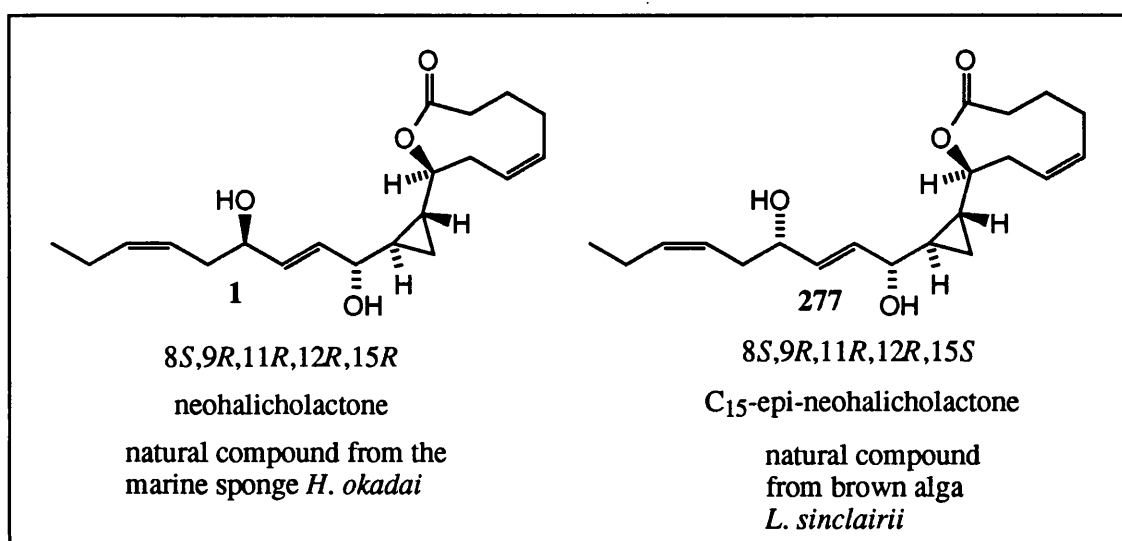4 in chloroform). Finally we obtained a 500MHz ^{1}H-NMR spectrum of **277** in D_6-benzene. Comparison of this spectrum with our 500MHz spectrum of **1**, and that provided by Yamada for the sponge derived **1** was quite illuminating. Every signal appeared to be identical in every respect (shape, size, position, and coupling constants) throughout the spectra of **277** and **1** except for the signals resulting from the C_{16} protons. The splitting pattern for the C_{16} protons in **277** was significantly more dispersed than that found in **1** (see the comparison of authentic *Halichondria okadai* derived neohalicholactone spectrum (A), our 500MHz spectrum of **1** (B), and our 500MHz spectrum of **277** (C), shown on the next page).

A

(500MHz, C6D6)
Spectrum provided by
Professor Yamada

Neohalicholactone Derived
From *Halichondria okadai*.
8S,9R,11R,12R,15R

B

Our Synthetic
Neohalicholactone 1
8S,9R,11R,12R,15R

(500MHz, C6D6)

C

(500MHz, C6D6)

Our Synthetic
C15-epi-Neohalicolactone 277
8S,9R,11R,12R,15S

5.5   5.0   4.5   4.0   3.5   3.0   2.5   2.0   1.5   1.0   0.5

Therefore we found that 500MHz ^{1}H-NMR was able to distinguish between **277** and **1**. However to date only a 300MHz ^{1}H-NMR of *L.sinclairii* derived "neohalicholactone" exists. A 500MHz ^{1}H-NMR of this material is subject to it being reisolated from more collections of *L.sinclairii* in the future. Therefore until this final ^{1}H-NMR experiment is performed we are only able to conclude that *L.sinclairii* derived "neohalicholactone" is <u>most likely</u> to be a C_{15}-epimer (**277**) of the sponge derived material **1** that we originally synthesised.

8*S*,9*R*,11*R*,12*R*,15*R*

neohalicholactone

natural compound from the
marine sponge *H. okadai*

8*S*,9*R*,11*R*,12*R*,15*S*

C_{15}-epi-neohalicholactone

natural compound
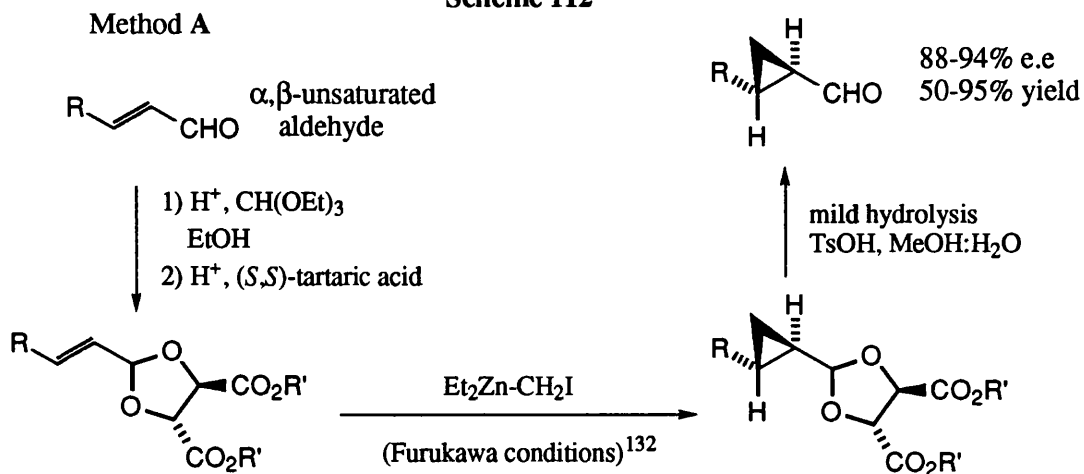from brown alga
L. sinclairii

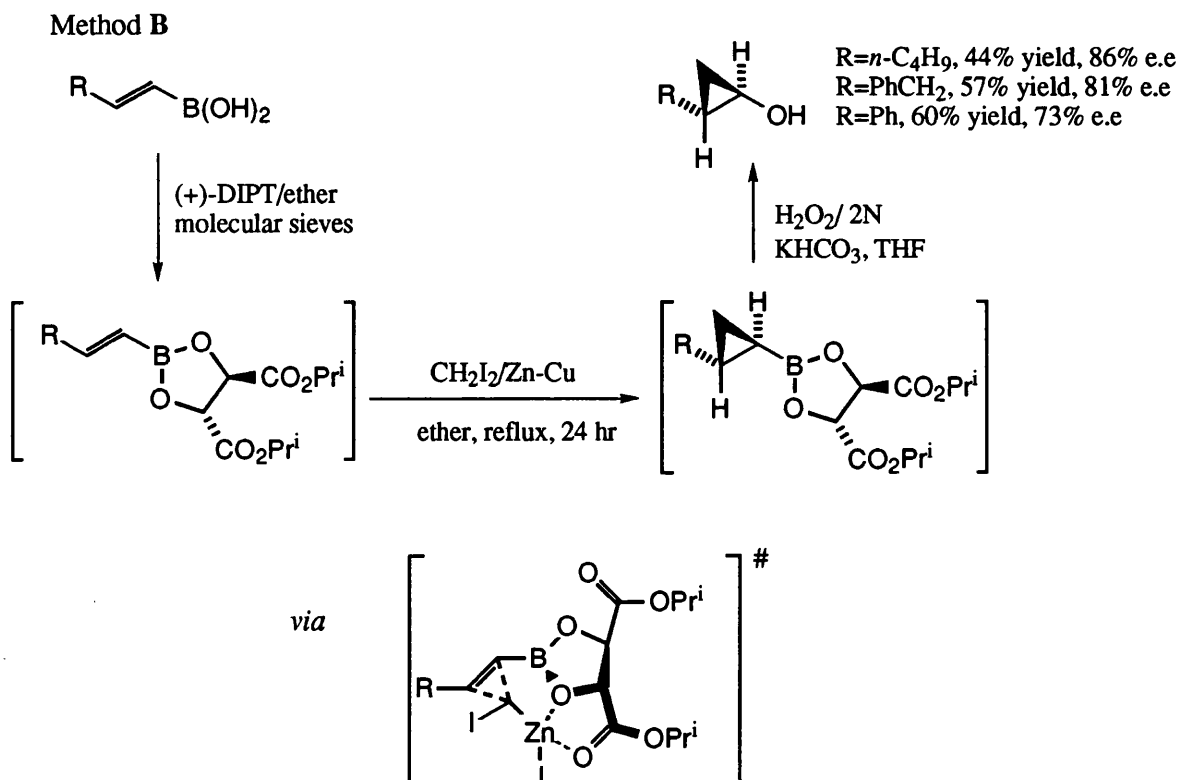## 2.5   The Enantioselective Simmons-Smith Cyclopropanation Reaction.

In 1958 Simmons and Smith discovered that treatment of an ethereal suspension of a zinc/copper couple with diiodomethane generated an organometallic reagent which transformed olefins into cyclopropanes.[126,23] The Simmons-Smith reaction is now accepted as a primary method for the preparation of cyclopropane rings. Extensive research has been devoted to both understanding the mechanism and improving the experimental procedure of this very important reaction. The synthetic utility of the Simmons-Smith cyclopropanation reaction derives from the following characteristics; (1) strict retention of olefin geometry, (2) generality with regard to the olefin structure, and (3) the *syn*-directing effect of hydroxyl and ether functions.[24(a),(b)] The cyclopropyl subunit, in enantiomerically pure form, is quite commonly found in natural products (recent examples include the oxylipins described in the introduction, section 1) and is also present in various drugs of potential therapeutic use.[127] It is therefore unsurprising that over the last decade attention has been focused on modifying the Simmons-Smith reaction in order to produce enantiomerically pure cyclopropane rings. Until very recently this has been achieved most efficiently by employing covalently bound chiral auxiliaries. The most effective of these methods include the use of chiral acetals derived from the reaction of dialkyl tartrate (or (2*R*,4*R*)-2,4-pentanediol) with an aldehyde (method A developed by Yamamoto)[128], 1-alkenylboronic esters derivatised with dialkyl tartrates (method B developed by Imai)[129], and the coupling of allylic alcohols to a suitably protected carbohydrate (method C developed by Charette)[130], (Scheme 112). However very recently Charette and Jeuteau have published a more elegant approach to an asymmetric version of the Simmons-Smith reaction using a homochiral dioxaboralane ligand (281).[25] The advantage of using amphoteric bifunctional ligand 281 is that it avoids the introduction and subsequent removal of covalently bound chiral auxiliaries whilst providing cyclopropanated products in high yields ($\geq$ 80%) and enantiomeric excesses ($\geq$ 90%). It is worthy of note that the use of homochiral ligands in the Simmons-Smith cyclopropanation reaction has been studied by other groups.[131(a)-(c)] In fact Kobayashi has developed

a catalytic asymmetric cyclopropanation reaction using a C-2-symmetric disulfonamide as a chiral ligand.[131(d)] However, to date the dioxaborolane ligand developed by Charette is the most efficient.

Scheme 112

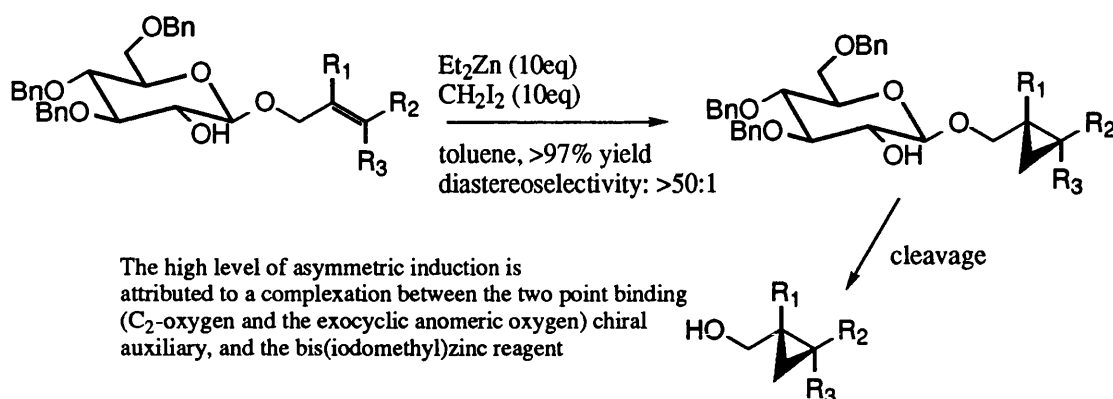Method A

The observed selectivity is ascribed to the high affinity of the zinc reagent for ethereal oxygen. The complexed organozinc reagent then stereoselectivity delivers a methylene unit to the nearest face of a neighbouring double bond.

Method B

Method C

Et$_2$Zn (10eq)
CH$_2$I$_2$ (10eq)

toluene, >97% yield
diastereoselectivity: >50:1

The high level of asymmetric induction is
attributed to a complexation between the two point binding
(C$_2$-oxygen and the exocyclic anomeric oxygen) chiral
auxiliary, and the bis(iodomethyl)zinc reagent

cleavage

The design of Charette's ligand (281) is such that it contains coordination sites that allow the simultaneous chelation of the acidic zinc reagent (complexes to carbonyl functionality) and the basic allylic alcohol (complexes to boron). The transition state # shown in Scheme 113 has been postulated by Charette to explain the highly selective *pseudo* intramolecular delivery of a methylene unit to a double bond using the homochiral dioxaborolane ligand 281.[25] Several types of substituted allylic alcohols including, *trans*-substituted, *cis*-substituted, and trisubstituted olefins, were shown to be suitable substrates for the Charette procedure. Further the synthetic utility of this excellent new method has already been shown in its application to the synthesis of natural products. For example the cyclopropyl fragment 282 of Curacin A (potent *anti* mitotic activity) was prepared using this methodology.[133] Cyclopropanation of *cis*-crotyl alcohol 283 in the presence of (*S,S*)-dioxaborolane 281 (derived from (*S,S*)-(-)-N,N,N',N'-tetramethyltartaric acid diamide and 1-butaneboronic acid) gave the desired 19*R*,21*S* cyclopropane fragment 282 of Curacin A in 70% yield and greater than 95% e.e (Scheme 114).

Scheme 113

Bifuntional ligand capable
of simultaneous chelation of
the zinc reagent and basic
allylic alcohol

Yields: >80%
91-94% e.e

Scheme 114

282   70% yield
       > 95%e.e

Curacin A

Barrett and co-workers have reported the employment of the Charette protocol in the
preparation of key tetracyclopropane fragments **285** and **286** of the antifungal agent
FR-900848.[134] These fragments are relevant to the complete structural assignment
and total synthesis of FR-900848. Starting from muconaldehyde, diol **284** was
synthesised in 5 steps and 32% overall yield as shown in Scheme 115. The reaction of
diol **234** premixed with (*S,S*)-dioxaborolane **281** and treated with bis(iodomethyl)zinc
reagent gave diastereomerically pure tetracyclopropane **285** in 94% yield. Only an

insignificant amount of minor isomer was observed by ^{13}C-NMR. Likewise the use of (R,R)-dioxaborolane **281** provided the other diastereomerically pure tetracyclopropane isomer **286** in 100% yield (Scheme 115).

Scheme 115

Antifungal Agent FR-900848

muconaldehyde

i, ii

ii, iv

3.7 + 1

v

vi

vii

284

285

286

Reagents
i. Noryori acetalation, 73%; ii. Et$_2$Zn, CH$_2$I$_2$, ClCH$_2$CH$_2$Cl, -20°C, -78%; iii. TsOH, THF/H$_2$O, 55°C; iv. Ph$_3$P=CHCO$_2$Et, CH$_2$Cl$_2$, 61%; v. DIBAL-H, CH$_2$Cl$_2$, -78°C, 91%; vi. (S,S)-**281**, Zn(CH$_2$I)$_2$, CH$_2$Cl$_2$, 0-25°C, 94%; vii. (R,R)-**281**, Zn(CH$_2$I)$_2$, CH$_2$Cl$_2$, 0-25°C, 100%.

We felt that these two studies[133,134] provided excellent precedent for the application of the Charette protocol to the synthesis of neohalicholactone **1** and halicholactone **2**. During the synthesis of the common "right hand" fragment used in the preparation of

both **1** and **2** (described in section 2.1), we employed the sulfur ylide methodology of Corey[26] to generate a 5:2 mixture of *trans*-cyclopropane products **134**. After deprotection and subsequent separation of the two isomers, the desired 8*S*,9*R*,11*R*-isomer **135** was isolated in 51% yield (see Scheme 37, page 47). This modest yield would obviously be improved if the cyclopropanation reaction was more diastereoselective. In order to incorporate the Charette modification of the Simmons-Smith reaction into our synthesis, a key allylic alcohol substrate would first need to be prepared. We have described a synthesis of (*E*)-γ-alkoxy-α-β-unsaturated *t*-butyl ester **123** (see section 2.1). This compound (**123**) should be easily converted to allylic alcohol **287** *via* deprotection/reprotection steps (to put an acid stable silyl protecting group in place) followed by acidic hydrolysis of the *t*-butyl ester and reduction of the intermediate carboxylic acid as shown in Sch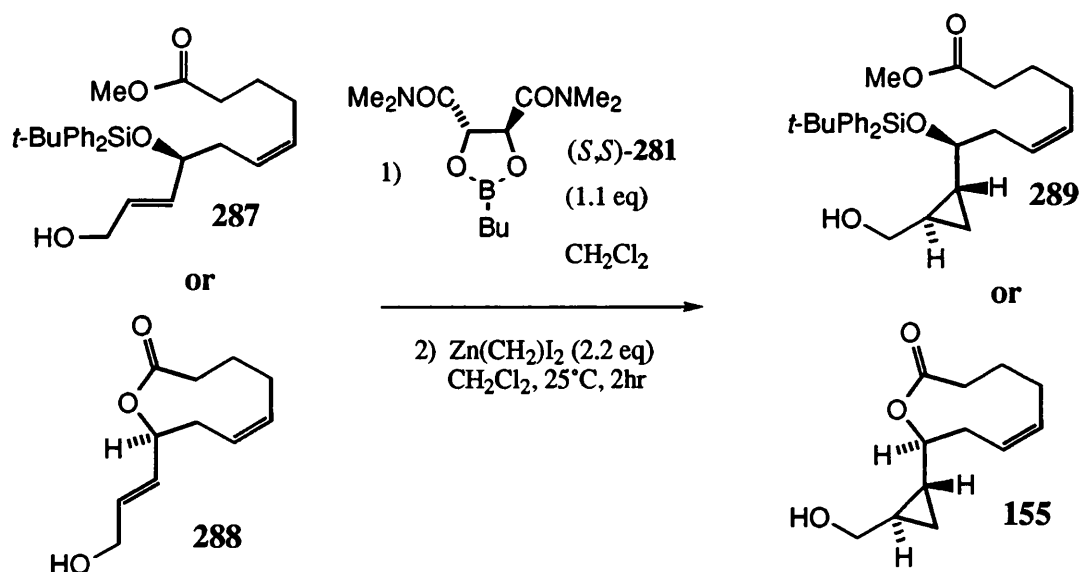eme 116. Perhaps a more attractive alternative strategy would be to prepare the 9-membered lactone and allylic alcohol containing substrate **288** from **123**. The synthesis of **288** would avoid the inelegant deprotection/protection steps that would be anticipated in the synthesis of an acyclic allylic alcohol, **287**, from **123** (Scheme 116). From analogy with the absolute stereochemistry of cyclopropanations observed by Charette it transpires that we would require (*S*,*S*)-dioxaborolane **281** to direct the cyclopropanation reactions of **287** and/or **288** and thus generate the desired 8*S*,9*R*,11*R* relative stereochemistry in the products **289** and **155** respectively.

It is known that prior coordination of the bis(iodomethyl)zinc reagent to the hydroxyl group of an allylic alcohol both directs the addition of methylene to the neighbouring alkene and substantially enhances the rate of this reaction.[24] We were therefore quite hopeful that insignificant competing cyclopropanation of the exposed 5,6-double bond in both **287** and **288** would occur using the Charette method.

Scheme 116

1) DDQ
2) t-BuPh₂SiCl
   Imidazole, DMF

3) TFA, CH₂Cl₂
4) EtOC(O)Cl, Et₃N
   NaBH₄

allylic alcohol **287**

1) DDQ
2) LiOH
3) Yamaguchi
   cyclisation

4) TFA, CH₂Cl₂
5) EtOC(O)Cl, Et₃N
   NaBH₄

allylic alcohol **288**

then Asymmetric Simmons-Smith Cyclopropanation reaction using Charette Protocol

1) (S,S)-**281**
    (1.1 eq)
    CH₂Cl₂

2) Zn(CH₂)I₂ (2.2 eq)
   CH₂Cl₂, 25°C, 2hr

Unfortunately we had completely used up our supply of **123** in previous synthetic work. The preparation of **123** from (S)-malic acid **86** would necessitate considerable synthetic effort, and we did not feel that adequate time remained to synthesise **123**, convert it to either allylic alcohol **287** or **288**, and then most interestingly evaluate the efficiency of the Charette protocol when applied to these substrates. Therefore, we wished to both familiarised ourselves with the important experimental features of the
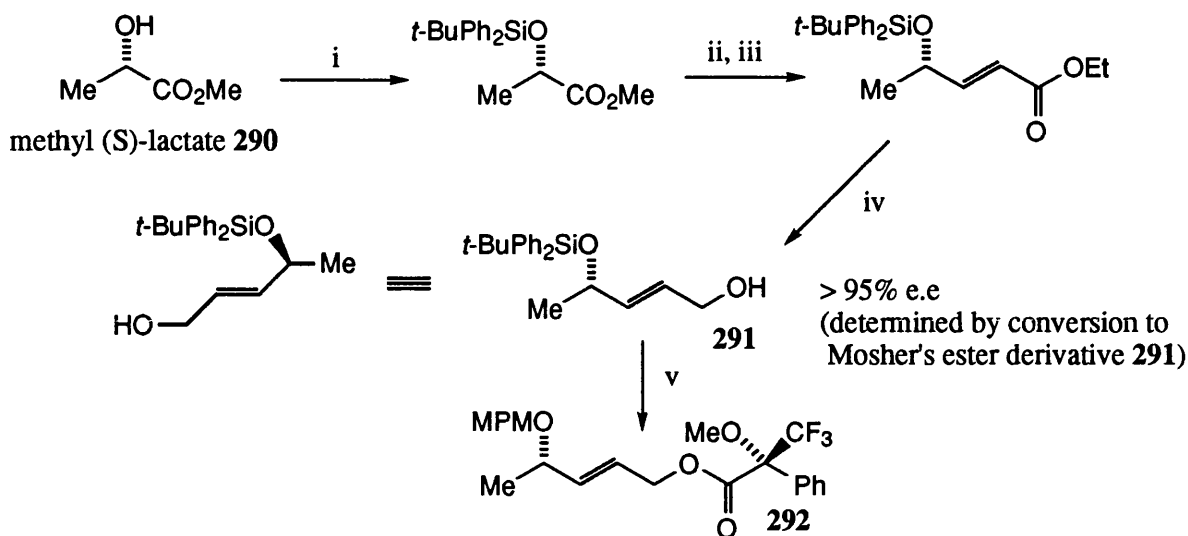
Charette protocol, and make some important observations by employing a model 2-pentene-1,4-diol synthon (291) (which importantly contained the same features as found in one of our actual substrates 287). It is possible that the existing *t*-butyldiphenylsilyl ether chiral centre in 287 could influence the stereochemical outcome of the cyclopropanation reaction.[131(d),(e)] Therefore by using 291 we wished to perform experiments both with and without the (*S,S*)-dioxaborolane ligand (281) being present in order to establish whether a mismatching of the ligands stereochemical influence and the inherent stereochemical course would exist. We were hopeful however, that in having the alkoxyl position protected with a sterically demanding group then competitive zinc complexation at this centre would be suppressed.

Starting from commercially available methyl (*S*)-lactate 290 we prepared (4*S*,2*E*)-4-*O*-(*t*-butyldiphenylsilyl)-pent-2-en-1,4-diol 291 in four steps and 35% overall yield (Scheme 117). It was important to prove that this product was enantiomerically pure if it was going to be used in the Charette version of the Simmons-Smith asymmetric cyclopropanation reaction. For example if 10% of a minor enantiomer was present in this starting material (291), then the dioxoborolane ligand 281 could be 100% efficient but 10% of a minor cyclopropane diastereomer would be observed in the ^{1}H-NMR and ^{13}C-NMR spectra of the product. We were able to show that 291 was enantiomerically pure (>95% e.e) by converting it to the Mosher's ester[135] of a *p*-methoxyphenylmethyl protected derivative 292 (Scheme 117).

In an attempt to synthesise an enantiomerically pure sample of *p*-methoxyphenyl-methyl-protected allylic alcohol 293 we actually prepared racemic material. The synthesis was completed in five steps and 32% overall yield starting from methyl (*S*)-lactate 290. Although we did not monitor the enantiomeric purity of our product after each transformation we expect that the protection, Swern oxidation,[46] and Wadsworth-Emmons olefination[48] reactions could all have contributed to the eventual isolation of racemic 293.

Scheme 117

methyl (S)-lactate **290**

> 95% e.e
(determined by conversion to
Mosher's ester derivative **291**)

Reagents
i. 1.2 eq. *t*-BuPh$_2$SiCl, 2.5 eq. imidazole, DMF, 25°C, 16 hr, 75%; ii. 1.1 eq. DIBAL-H, toluene, -78°C to -20°C, 40 min; iii. 1.1 eq. LiCl, 1.0 eq. triethyl phosphonoacetate, 1.0 eq. DBU, acetonitrile, 25°C, 2 hr, 48% (two steps); iv. 1.2 eq. DIBAL-H, toluene, -20°C to 0°C, 1 hr, 96%; v. a) 1.5 eq DCC, 1.5 eq. (R)-(+)-MTPA, 0.1 eq. DMAP, CH$_2$Cl$_2$, 25°C, 30 min, 89% yield, b) 1.5 eq TBAF, THF, 25°C, 2 hr, 100% yield, c) 1.5 eq.*p*-MeOC$_6$H$_4$CH$_2$OC(NH)CCl$_3$, 5 mol% CSA, CH$_2$Cl$_2$, 25°C, 16 hr.

Preparation of the racemic Mosher's ester comparison (±)-**292**.

methyl (S)-lactate **290**

the (R,S) and (R,R)-diastereomers
were distinguishable by ^{1}H-NMR

Reagents
i. 1.2 eq. 4-methoxybenzyl chloride, 1.3 eq. NaH, 5 mol% Bu$_4$NI, DMF, DMF, 61%; ii. 2.2 eq DIBAL-H, toluene, -40C to 25°C, 1 hr; iii. 1.2 eq. oxalyl chloride, 2.4 eq. DMSO, 3 eq. Et$_3$N, CH$_2$Cl$_2$, -78°C to 0°C; iv. 1.0 eq. NaH, 1.0eq. triethyl phosphonoacetate, DME, 25°C, 1 hr, 74% (3 steps); v. 2.2 eq. DIBAL-H, toluene, -40°C to 25°C, 30 min, 70%; vi. 1.5 eq. DCC, 1.5 eq. (R)-(+)-MTPA, 0.1 eq. DMAP, CHCl$_3$, 5 min, 100%.

The Mosher's ester, (±)-**292**, of racemic **293** was prepared in quantitative yield *via*

the standard 1,3-dicyclohexylcarbodiimide/ catalytic 4-dimethylaminopyridine coupling

conditions (see Scheme 117). The diastereomeric mixture of Mosher's esters ((±)-
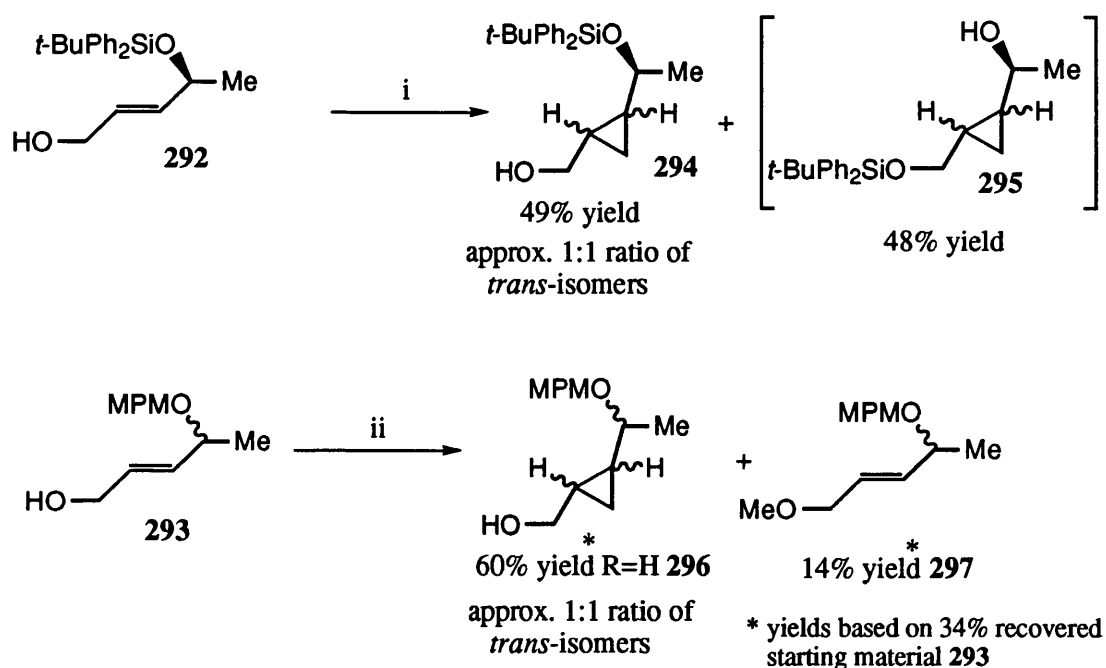
292) gave base line separation in certain regions of the ^{1}H-NMR spectrum and therefore by comparison with the spectrum derived from **291** we were able to assess the enantiomeric purity of the latter material.

First we examined the reaction of enantiomerically pure allylic alcohol **291** without homochiral ligand **281** being present. We prepared a solution of $Zn(CH_2I)_2.DME$ complex in dichloromethane as described by Charette.[136] The use of this reagent was found to be much safer than the analogous potentially explosive reagent-$Zn(CH_2I)_2$ (prepared using 2 equivalents of diiodomethane and 1 equivalent of diethylzinc in a non-coordinating solvent as first described by Furukawa[132]) whilst being just as effective in the asymmetric reaction. We wished to make the reaction conditions even safer by either using diethylzinc as a 1.1 molar solution in toluene or a 1.0 molar solution in hexanes. Commercially available neat diethylzinc is a highly pyrophoric material and we wished to avoid its use. Charette had previously shown that asymmetric cyclopropanation reactions using **281** could be carried out in toluene where compatible yields and enantiomeric excesses to those obtained in dichloromethane were observed,[25] whilst Kobayashi performed his cyclopropanation reactions using diethyl zinc as a 1.0M solution in hexane.[131(d)] Therefore we did not expect toluene or hexane to have a detrimental effect on our reactions. The reaction of **291** with 3 equivalents of freshly prepared $Zn(CH_2I)_2.DME$ complex (prepared from 1 equivalent of diethylzinc (1.0M in hexane from Aldrich chemical company), 1 equivalent of ethylene glygol dimethyl ether (DME), and 2 equivalents of diiodomethane in dichloromethane) resulted in its complete consumption over a 12 hour period. The desired *trans*-cyclopropane product **294** was isolated as approximately a 1:1 ratio of isomers. Therefore it appears that the existing chiral centre in **291** exhibits no influence over the stereochemical outcome of the reaction. This was an encouraging result since it implied that a problem with mismatched chiral induction between the chiral ligand and substrate would not manifest itself. The yield of this reaction was, however, disappointing (49%). The reason for this modest yield was that another less polar cyclopropanated product **295** was also isolated which accounted for almost all the remaining material balance of the reaction, 48%. Although

the unwanted product **295** was not fully characterised, its mass spectrum and ^{1}H-NMR provided strong evidence to suggest that it was the product of silyl migration to the less hindered primary alcohol position (Scheme 118).

Since we also had a sample of p-methoxyphenylmethyl protected racemic allylic alcohol **293** in hand we examined its reaction under the same cyclpropanation conditions.

Scheme 118

49% yield

approx. 1:1 ratio of
trans-isomers

48% yield

60% yield R=H **296**

approx. 1:1 ratio of
trans-isomers

14% yield **297**

* yields based on 34% recovered
starting material **293**

Reagents
i. 3.0 eq. Et$_2$Zn (1.0M in hexane), CH$_2$Cl$_2$, 3.0 eq. DME, -15°C, add 6.0 eq. CH$_2$I$_2$ over 15 min, then added this mixture *via* cannula to 1.0 eq. **292** in CH$_2$Cl$_2$ at -15°C over 30 mins, RT, 16 hr, 49% **294**; ii. 5.0 eq. Et$_2$Zn (1.0M in hexane), CH$_2$Cl$_2$, 5.0 eq. DME, -15°C, add 10.0 eq. CH$_2$I$_2$ over 20 min, then added this mixture *via* cannula to 1.0 eq. **293** in CH$_2$Cl$_2$ at 0°C over 20 mins, RT for 2.5 hr, aq. NH$_4$Cl.

The reaction of **293** with 5 equivalents of Zn(CH$_2$I)$_2$.DME complex at room temperature for 2.5 hours led to incomplete consumption of the starting material. A 1:1 mixture of cyclopropane isomers **296** were isolated in 60% yield (based on recovered starting material). The only other product we isolated from this reaction was the methylated derivative of **293** in 14% yield (based on recovered starting material). The presence of this methylated side product (**297**) presumably results from the *in situ* formation of methyl iodide when allylic alcohol **293** was mixed with Zn(CH$_2$I)$_2$.DME. Charette has observed the formation of methyl iodide by 400MHz ^{1}H-NMR when an alcohol is mixed with Zn(CH$_2$I)$_2$. The cyclopropanation reaction

using **293** was not unoptimised but adequately shows that the existing chiral centre in **293**, in common with **291**, does not influence the stereochemical outcome of the reaction, and that the *p*-methoxyphenylmethyl-protecting group is stable to the Lewis acidic cyclopropanation conditions (Scheme 118).

Next we prepared the desired (*S*,*S*)-dioxaborolane ligand **281** from the condensation of commercially available (*S*,*S*)-N,N,N',N'-tetramethyltartaric acid diamide **298** and 1-butaneboronic acid **299**. Charette has described the preparation of **281** by heating **298** and **299** in anhydrous toluene under reflux for 15 hours using Dean-Stark apparatus to remove the water produced in the reaction.[136] We found these harsh reaction conditions unnecessary. Ligand **281** was prepared by gently heating **298** and **299** in toluene until all **299** had dissolved (approx. 10 minutes). We tested the efficiency of the dioxaborolane ligand **281** prepared using these conditions by examining the cyclopropanation of cinnamyl alcohol **300**. Charette has studied the cyclopropanation of cinnamyl alcohol **300** quite intensively and found that under optimised conditions the cyclopropanated product could be synthesised in quantitative yield and 93% enantiomeric purity (determined by gas chromatography analysis of the trifluoroacetate derivative of the cyclopropane product).[25,136] We found that we could prepare (*2R*,*3R*)-*trans*-(3-phenylcyclopropyl)methanol **301** in 76% yield and 89% enantiomeric excess (determined by chiral HPLC analysis) using our slightly modified conditions (Scheme 119). Charette has reported that slightly lower enantiomeric excesses can be expected if the commercially available 1-butaneboronic acid is not purified before use.[136] Also, he has found the optimum rate of addition of the Zn(CH$_2$I)$_2$.DME complex to vary depending on the scale of the reaction. Therefore, considering that we only attempted the cyclopropanation once and used unpurified 1-boraneboronic acid to prepare **281**, we found our result very gratifying. We now attempted the asymmetric cyclopropanation of enantiomerically pure **291**. First we prepared 5 equivalents of the Zn(CH$_2$I)$_2$.DME complex. This zinc reagent was added slowly over a 45 minute period to 1.0 equivalent of **291** and 1.1 equivalents of ligand **281** in dichloromethane (containing powdered 4Å molecular sieves) at -10°C. The reaction was then stirred at -10°C for 2 hours and then allowed
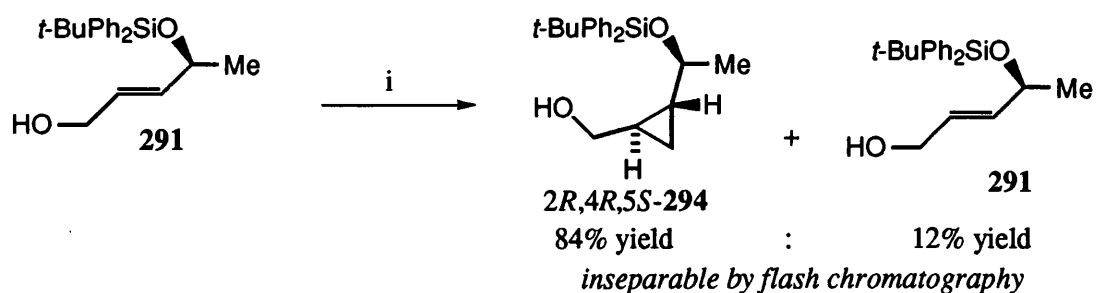
to warm to room temperature over the next 3 hours, at which time the reaction was quenched. After flash chromatography the desired cyclopropanated product **294** was isolated in excellent yield, 84%, and as one pure 2*R*,4*R*,5*S*-diastereomer (>95%, determined by ^{1}H-NMR and ^{13}C-NMR). The product was however contaminated with 12% yield of unreacted and inseparable starting material **291** (Scheme 120).

Scheme 119

HO\ /OH
B
1.0 eq. |
Bu
299

1-butaneborinic acid

Me₂NOC,,, CONMe₂

HO OH 1.05 eq.
298

(*S*,*S*)-(-)-N,N,N',N'-tetramethyl-tartaric acid diamide

i

Me₂NOC,,, CONMe₂

O\ /O
B
|
Bu (*S*,*S*)-**281**

Ph OH
300

ii

Ph OH **301**

$[\alpha]_D^{20}$ = -69.6°(*c* 1.24 in chloroform)
89% e.e by chiral HPLC

Reagents
i. Toluene, gentle heating for 10 min, quantitative crude yield; ii. 5.0 eq. Et₂Zn (1.1M in toluene), CH₂Cl₂, 5.0 eq. DME, -15°C, add 10.0 eq. CH₂I₂ over 15 min, then added this mixture *via* cannula to 1.0 eq. cinnamyl alcohol **300** and 1.1 eq. (*S*,*S*)-**281** in CH₂Cl₂ containing some powdered 4Å molecular sieves at -15°C over 45 mins, then -10°C for 1.45 hr, and 25°C for 20 min, 76%.

Scheme 120

t-BuPh₂SiO
Me

HO **291**

i

t-BuPh₂SiO
Me
HO H

H
2*R*,4*R*,5*S*-**294**
84% yield

+

t-BuPh₂SiO
Me

HO **291**
12% yield

:

inseparable by flash chromatography

Reagents
i. 5.0 eq. Et₂Zn (1.1M in toluene), CH₂Cl₂, 5.0 eq. DME, -15°C, add 10.0 eq. CH₂I₂ over 15 min, then added this mixture *via* cannula to 1.0 eq. **291** and 1.2 eq. (*S*,*S*)-**281** in CH₂Cl₂ containing some powdered 4Å molecular sieves at -15°C over 45 mins, then -10°C to 0°C over 2 hr, and 25°C for 3 hr, 84%.

From this model study we learnt that the dioxaborolane ligand **281** could be prepared more simply than the described Charette procedure,[136] and that diethylzinc could be used as a 1.1M solution in toluene, thus making the procedure safer. Finally and most importantly, by extrapolation of the fact the Charette procedure worked so impressively in our model system, it seems most likely that it would also be applicable to the synthesis of **1** and **2** *via* allylic alcohols **287** and/ or **288** (Scheme 116).

3. Conclusions.

3.   Conclusions.

We have completed efficient enantioselective syntheses of the related marine natural products neohalicholactone **1** (in 30 steps, 0.65% overall yield) and halicholactone **2** (in 20 steps, 3.1% overall yield). The sign and magnitude of the optical rotation values we obtained for **1** and **2** confirmed for the first time the absolute configuration of *Halichondria okadai* derived neohalicholactone and halicholactone.[1(a)] The most significant challenges in the synthesis of **1** and **2** were the diastereoselective introduction of the cyclopropane ring moiety and the penultimate coupling reaction of the advanced left and right-hand fragments in each case.

Using methodology developed by Corey,[26] we were able to achieve a regioselective, chemoselective and modestly diastereoselective addition of dimethylsulfoxonium methylide to (E)-γ-alkoxy-α,β-unsaturated t-butyl ester **123**, whereby the *trans*-cyclopropane ring with desired relative stereochemistry was produced as the major product. The stereochemical outcome of the cyclopropanation reaction was subsequently determined by X-ray crystallographic analysis of a carboxylic acid derivative, $8S,9R,11R$-**152** (see appendix 1).[63] By employing the mild chromium coupling conditions first described by Takai[22(b)] and Kishi[22(a)] we were able to synthesise both advanced allylic alcohols, **252a** and **260a** in good yield. These coupling reactions were achieved with moderate stereoselectivity owing to a long-distance protecting group mediated, stereocontrolled addition.[122] Other points of interest were; (1) an unexpected retardation effect in the final desilylation step to give either **1** or **2**, and (2) during a model study we were able to show that the right hand fragment **156** could potentially be made more efficiently (>95% diastereoselectivity in the cyclopropanation step) using the asymmetric cyclopropanation conditions described by Charette.[25]

Finally we were able to prepare a sample of C_{15}-epi-neohalicholactone **277** and thus show that the spectroscopic properties of **277** were in excellent agreement with those published by Gerwick for a *Laminaria sinclairii* derived sample of "neohalicholactone". We have therefore adjudged the isolation of **277** and not **1** from

L. sinclairii as the most likely reason for the apparent disparity between our synthetic

results and the paper that was published by Gerwick.[124]

4. Experimental.

4. Experimental.

4.1 General Details

Tetrahydrofuran and ether were freshly distilled from sodium using benzophenone as an indicator. Toluene was freshly distilled from sodium; dichloromethane from phosphorous pentoxide; acetonitrile, dimethylsulfoxide and hexane from calcium hydride. N,N-dimethylformamide was fractional distilled at water pump pressure. All the aforementioned solvents were distilled under an inert atmosphere of either argon or nitrogen. Reagents were either used as received, from commercial sources or purified by recognised methods.[138] Petroleum ether refers to that fraction which boils in the range 60-80°C, and it was distilled prior to use as was ethyl acetate.

All reactions were carried out in vacuum-flame-dried Schlenk tubes under an argon atmosphere, unless otherwise stated.

Flash chromatography[139] was performed using Matrex normal phase silica, pore size 60Å. All reactions were monitored by thin layer chromatography using aluminium sheets pre-coated with 250 μm silica gel, and were visualised by UV light and then by potassium permanganate solution, phosphomolybdic acid solution, ninhydrin solution or anisaldehyde solution.

^{1}H-NMR were recorded at the University of Bath using Joel GX270 FT and Joel EX400 instruments operating at 270.2 MHz and 399.8 MHz respectively. ^{1}H-NMR were recorded at Fisons plc, (Pharmaceutical Division) using either a Bruker 360 or Bruker AMX500 instrument operating at 360.1 MHz and 500.1 MHz respectively. The observed spectra were for solutions in deuteriochloroform unless otherwise stated. The chemical shifts (δ) were recorded relative to tetramethylsilane as an internal standard; all coupling constants, J, are reported in Hz. ^{13}C-NMR spectra were recorded using the same Joel GX270 FT, Joel EX400, Bruker 360 and Bruker 500 instruments, now operating at 67.8 MHz, 100.4 MHz, 90.6 MHz, and 125.8 MHz respectively. The spectra were recorded in deuteriochloroform unless otherwise stated using the resonances of $CDCl_3$ (δ_C=77.0ppm, t) as internal reference. The multiplicities were obtained by using 135° and 90° "Distortionless Enhancement by

Polarisation Transfer" (DEPT) or Off-Resonance Decoupling experiments to aid in assignments (q, methyl; t, methylene; d, methine; s, quaternary). Homonuclear J-Correlated Spectroscopy (^{1}H-^{1}H-COSY) and Heteronuclear J-Correlated Spectroscopy (^{1}H-^{13}C-COSY) were conducted on a Bruker 500 instrument to aid assignments if required.

Infra red spectra were recorded on both Perkin-Elmer 1600 FT-IR and Perkin-Elmer 1720X FT-IR spectrometers, either as liquid films, evaporated films from chloroform solutions, or as nujol mulls, between sodium chloride plates (bs=broad signal, s=strong signal, vs=very strong signal, m=medium signal, w=weak signal). Mass spectra were recorded at the EPSRC Mass Spectrometry Service in Swansea or at the University of Bath on a VG analytical 7070E instrument with VG2000 data system using either an ionising potential of 70 eV (EI), or by chemical ionisation (isobutane) (CI), or fast atom bombardment (FAB) in 3NBA matrix, unless otherwise stated. The one melting point was recorded on a Gallenkamp melting point apparatus. Optical rotations were recorded on an Optical Activity AA1000 Polarimeter or a Perkin-Elmer 141 Polarimeter at ambient temperature. $[\alpha]_D$ values are recorded in units of 10^{-1} deg cm^2 g^{-1}. Microanalytic data were obtained on a Carlo Erba 1106 Elemental Analyser.
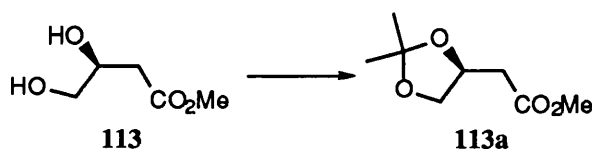
4.2 Experimental For Section 2.1;

Preparation of Dimethyl (S)-(-)-Malate 112.

To an anhydrous hydrochloric acid/methanol solution, prepared by adding acetyl chloride (6.8ml) cautiously to methanol (134ml) at room temperature under an atmosphere of argon, was added (S)-(+)-malic acid **86** (20.00g, 0.15mol). The mixture was stirred at room temperature for 16 hours and then the solvent was removed under reduced pressure. The residue was then dissolved in ethyl acetate (50ml) and solid sodium hydrogen carbonate added until neutral pH was obtained. The solid was then removed by suction filtration washing with ethyl acetate and the crude product was isolated by removal of the solvent at reduced pressure. The colourless oil was distilled to yield **112** (19.68g, 81%). Rf 0.6 (1:1, ethyl acetate/petroleum ether); b.pt. 63°C/0.1mmHg; $[\alpha]_D^{20}$ -6.2 (neat), {Lit; $[\alpha]_D^{20}$-6.5

(neat), *Aldrich Catalogue* }; ν_{max}(neat)/ cm^{-1} 3482 br (OH), 1741 s (CO); δ_H

(360MHz;CDCl$_3$) 2.80 (1H, dd, J 6.2, 16.4, MeCO$_2$CHH), 2.88 (1H, dd, J 4.4,

16.4, MeCO$_2$CHH), 3.40 (1H, bs, OH), 3.72 (3H, s, CH_3), 3.81 (3H, s, CH$_3$),

4.51 (1H, t, J 5.3, CHOH). Our data was consistent with that reported.[39]

Preparation of Methyl (S)-(3,4)-dihydroxybutanoate 113.

To a solution of dimethyl (S)-(-)-malate **112** (1.00g, 6.17mmol) in tetrahydrofuran

(13ml) at room temperature under a nitrogen atmosphere was added boron-

methylsulfide complex (0.62ml, 6.17mmol, 10.0M solution from Aldrich) and the

mixture was stirred at room temperature for 0.5 hours. Then a catalytic amount of

NaBH$_4$ (12mg, 0.31mmol) was added, and after approximatly 5 minutes and an

exothermic reaction took place with rapid evolution of hydrogen gas (on larger scale

preparations (*ca.* 10g) a reflux condenser needed to be fitted and the solution was

cooled to 0°C for the addition of the NaBH$_4$). This vigorous reaction was complete

after a few minutes and the mixture was then allowed to cool to room temperature with

stirring for an additional 0.5 hours. The reaction was quenched by the addition of dry

methanol (4ml), stirring being continued for 0.5 hours. The solvent was removed

under reduced pressure and the residue purified by column chromatography on silica

eluting with ethyl acetate (neat). Methyl (S)-3,4-dihydroxybutanoate **113** (762mg,

92%) was obtained as a colourless oil which often contained an inseparable impurity.

Rf 0.3(10:3 ethyl acetate/petroleum ether); δ_H (270MHz;CDCl$_3$) 2.47-2.60 (2H, m,

MeCO$_2$CH_2), 2.95 (2H, bs, 2 x OH), 3.53 (1H, dd, J 6.1, 11.3, -CHHOH), 3.67

(1H, dd, J 3.4, 11.3, -CHHOH), 3.72 (3H, s, -CO$_2$CH_3), 4.11-4.16 (1H, m,

CHOH). Further structural determination was performed by converting a sample of

113 to its 3,4-O-isopropylidene derivative **113a** (excess acetone and 0.3mol% pTsA,

room temperature, 16 hours, 53% yield after distillation {B.pt. 60°C/0.1mmHg}).

HO
HO —/ \—CO$_2$Me → —/\O / \—CO$_2$Me
   113   **113a**

Data for **113a**; δ_H (270MHz;CDCl₃) 1.36 (3H, s, CH₃), 1.42 (3H, s, CH₃). 2.53 (1H, dd, J 7.0, 15.9, CHHCO₂Me), 2.72 (1H, dd, J 6.4, 15.8, CHHCO₂Me), 3.65 (1H, dd, J 6.4, 8.4, CHHO-), 3.71 (3H, s, -CO₂Me), 4.16 (1H, dd, J 8.4 and 6.0, CHHO-), 4.53-4.43 (1H, m, CHO-). Our data was consistent with that reported .[38]

Methyl (S)-(3,4)-dihydroxybutanoate **113** was used in the next step without any further purification.

Preparation of (3S)-Hydroxy-γ-Butyrolactone 114.

To methyl (S)-3,4-dihydroxybutanoate **113** (6.84g, 51.0mmol) in tetrahydrofuran (80ml) was added 18.0M H₂SO₄ (3.9ml) and the reaction mixture was left stirring for three days at room temperature. Solid sodium hydrogen carbonate was then added to the solution portion wise until neutral pH was obtained. The mixture was suction filtrated, washing the filter cake with ethyl acetate (100ml). The organic washings were evaporated under reduced pressure and the residue purified by column chromatography on silica eluting with ethyl acetate-hexane (10:3). The product **114** (4.33g, 75%) was isolated as a colourless oil; Rf 0.35 (10:3, ethyl acetate/petroleum ether); ν_{max}(neat)/cm⁻¹ 3432 br (OH), 1770 s (CO); δ_H (270MHz;CDCl₃) 2.53 (1H, dm, J 18.0, -COCHH), 2.76 (1H, dd, J 6.1, 18.0, -COCHH), 4.31 (1H, dm, J 10.2, -OCHH), 4.42 (1H, dd, J 4.5, 10.2, -OCHH), 4.66-4.70 (1H, m, -CHOH). Our data was consistent with that reported.[40] This material was used without any further purification in the next step although a small amount of inseparable impurity was again present.

An alternative procedure was also used to yield **114**:

The reduction of dimethyl (S)-(-)-malate **112** (7.90g, 48.8mmol) was carried out as described above. After quenching this reaction and subsequent removal of the solvent the crude mixture was used in the next step. 0.1N HCl (15ml) was poured into the crude residue and the mixture was then stirred at 60°C for 16 hours. The solution was then cooled and poured slowly on to excess solid sodium hydrogen carbonate. Once neutral pH had been reached the solid material was removed by suction filtration, washing the solid with ethyl acetate. The solvent was removed under reduced pressure

and the crude residue was purified by column chromatography on silica eluting with neat ethyl acetate. The product **114** (2.35g, 47% for the two steps) was isolated as an almost pure colourless oil.

*Preparation of (3S)-3-O-((p-methoxyphenylmethyl)oxy)-γ-butyrolactone **119** .*

To (3S)-hydroxy-γ-butyrolactone **114** (5.41g, 53.0mmol) in dry dichloromethane (120ml) and cyclohexane (50ml) at room temperature under a nitrogen atmosphere, *p*-methoxyphenylmethyl trichloroacetimidate **118** (13.2ml, 63.6mmol) was added. After 5 minutes a catalytic amount of trifluoromethanesulphonic acid (14.0μl, 0.16mmol) was injected into the reaction mixture and within a few minutes trichloroacetamide could be seen precipitating out of solution as the reaction progressed. After 2 hours there was still starting material visible by thin layer chromatography and therefore a further 2.0ml (9.6mmol) of *p*-methoxyphenylmethyl trichloroacetimidate **118** was required to achieve full consumption of starting material. The reaction was quenched after a total reaction time of 3 hours by adding solid sodium hydrogen carbonate until neutral pH was obtained. The mixture was then diluted with a solution of CH_2Cl_2 (100ml) : cyclohexane (50ml) followed by suction filtration. The filter cake was washed with a 2:1 mixture of CH_2Cl_2 and cyclohexane (150ml), and the solvent removed from the organic washings under reduced pressure. The residue was purified by column chromatography on silica eluting with ethyl acetate/ hexane (1:2), to afford **119** (8.9g, 75%) as a colourless oil. Rf 0.5 (2:1, hexane/ethyl acetate); $[\alpha]_D^{22}$ -18.1 (*c* 0.18 in $CHCl_3$); v_{max}(neat)/cm^{-1} 1780 s (CO), 1615, 1580, 1520, 1460; δ_H (360MHz;$CDCl_3$) 2.60 (1H, dd, *J* 2.7, 18.0,-COC*HH*), 2.68 (1H, dd, *J* 5.4, 18.0,-COCH*H*), 3.81 (3H, s, O*CH₃*), 4.34-4.40 (3H, m, -C*H*OH and -OC*H₂*), 4.44 (1H, d, *J* AB 11.4, benzylic C*H*H), 4.48 (1H, d, *J* AB 11.4, benzylic CH*H*), 6.89 (2H, d, *J* 8.6, aryl), 7.25 (2H, d, *J* 8.6, aryl); δ_C (90.6MHz;$CDCl_3$) 34.9 (t), 55.2 (q), 70.9 (t), 72.5 (t), 73.5 (d), 113.8 (d, 2 x aryl C), 128.7 (s, aryl C), 129.4 (d, aryl C), 159.5 (s, aryl C), 175.4 (s, C=O); *m/z* (G.C/E.I) 222 (M$^+$, 15%), 121 (100); (Found: M$^+$ 222.0903. $C_{12}H_{14}O_4$ requires M, 222.0892).

A side product was identified as $(2S)$-2-O-$((p$-methoxyphenylmethyl)oxy)-γ-butyrolactone **116** (Scheme 28); v_{max}(neat)/cm^{-1} 1780s (CO), 1615m, 1580m, 1520m; δ_H (360MHz;CDCl$_3$) 2.17-2.31 (1H, m, -CHH), 2.39-2.47 (1H, m, -CHH), 3.81 (3H, s, OCH_3), 4.15 (1H, t, J 7.7, -CHOCH$_2$Ar), 4.20-4.24 (1H, m, -OCHH), 4.36-4.44 (1H, m, -OCHH), 4.67 (1H, d, J_{AB} 11.4, -CHHAr), 4.86 (1H, d, J_{AB} 11.4, -CHHAr), 6.89 (2H, d, J 8.5, aryl), 7.31 (2H, d, J 8.5, aryl); m/z (GC/ EI) 222 (M$^+$, 5%), 137 (82), 121 (100).

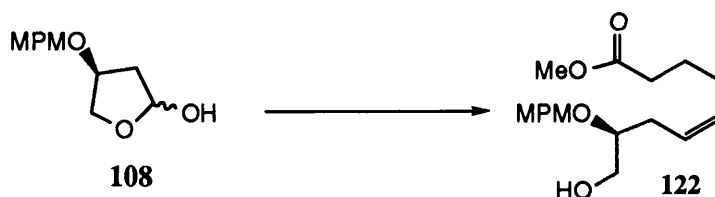An alternative procedure used to obtain **119** was as follows;

To $(3S)$-hydroxy-γ-butyrolactone **114** (3.70g, 36.3mmol) in dichloromethane (40ml) under at argon atmosphere at room temperature added p-methoxyphenylmethyl trichloroacetimidate **118** (11.3ml, 54.4mmol) followed by solid ($\pm$) camphor sulfonic acid (422mg, 1.82mmol). The reaction was stirred at room temperature for 16 hours, then diluted with petroleum ether (100ml), and the precipitate was removed by filtration. The filtrate was then washed saturated aqueous sodium hydrogen carbonate (40ml) and the organic layer dried over anhydrous magnesium sulphate. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica, eluting with ethyl acetate/hexane (1:2). The product **119** (5.87g, 73%) was isolated as a colourless oil.

Preparation of (3S)-3-O-((p-methoxyphenylmethyl)oxy)-γ-butyrolactol 108.

To lactone **119** (2.00g, 9.00mmol) in dry toluene (60ml) at -20°C under a nitrogen atmosphere DIBAL-H (1.5M, 6.6ml, 9.9mmol) was added slowly over a five minute period (making sure that the internal temperature did not rise above -20°C). After a few minutes the reaction was complete (by TLC analysis) and was quenched with H$_2$O (6.6ml), and the solution was then warmed to room temperature. Solid sodium hydrogen carbonate and ethyl acetate (50ml) were added sequentially and the mixture stirred vigorously for approximately 0.5 hours. After this time the mixture was suction filtrated and the filter cake was washed with ethyl acetate (75ml). The organic washings were evaporated under reduced pressure to give the crude lactol **108** (2.02g, 100%), as a mixture of epimers (3:2) and as a colourless crystalline solid. Rf 0.3 (2:1,

hexane/ethyl acetate); (Found: C, 64.1; H, 7.16. $C_{12}H_{16}O_4$ requires C, 64.3, H, 7.14 %); ν_{max}(Nujol)/cm^{-1} 3419 br (OH), 1780s (C=O, open chain form); δ_H (360MHz;CDCl₃) 1.84-2.20 (2H, m, -CH_2), 2.64 (0.4H, d, J 2.8, -CHOH), 3.68 (0.6H, d, J 11.2, CHOH) 3.80 (1.2H, s, OCH_3), 3.81 (1.8H, s, OCH_3), 3.80-4.55 (5H, m), 5.42 (0.6H, dd, J 5.0, 11.1 -CHOH), 5.68 (0.4H, dd, J 2.7, 5.2, -CHOH), 6.87-6.90 (2H, m, aryl), 7.24-7.27 (2H, m, aryl); m/z (FAB) 247 ([M+Na]$^+$, 11%), 224 (M+,8%), 223 ([M-1]$^+$, 8%), 121 (100); (Found: M$^+$ 224.1046. $C_{12}H_{16}O_4$ requires M, 224.1049).

Preparation of methyl (8S,5Z)-8-O-((p-methoxyphenylmethyl)oxy)-8,9-dihydroxynon-5-enoate 122.

To a suspension of (4-carboxybutyl)triphenylphoshonium bromide **91** (5.15g, 11.62mmol) in dry toluene (50ml) at room temperature under an argon atmosphere was added sodium bis(trimethylsilyl)amide (20.3ml, 20.3mmol, from a new bottle bought as a 1.0M solution in tetrahydrofuran) slowly over 5 minutes at 0°C. The solution was then stirred at room temperature for 0.5 hours and a red colour developed, at which time the mixture was cooled to -78°C. Then in a different reaction vessel; to a solution of lactol **108** (2.17g, 6.89mmol) in dry toluene (100ml) at -78°C under an argon atmosphere was added sodium bis(trimethylsilyl)amide (10.17ml, 10.17mmol, a new bottle as a 1.0M solution in tetrahydrofuran) quite rapidly (*ca.*5 minutes). The solution now containing the sodium alkoxide of **108** was stirred for 15 minutes at -78°C. The phosphonium ylide was then transferred *via* cannula into the sodium alkoxide solution of **108** over a 20 minute period whilst both mixtures were kept at -78°C. After the addition the resultant red solution was left at -78°C for 5 minutes, and allowed to warm 0°C over 45 minutes. At this time the solution was a pale yellow colour, and TLC analysis indicated that full consumption of starting material had
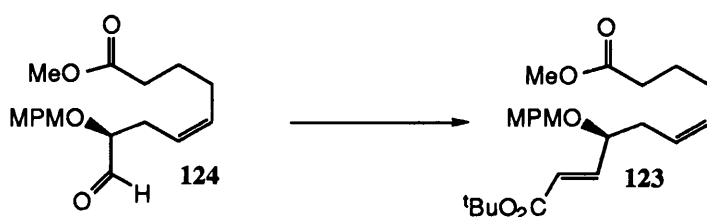
occurred. The reaction mixture was therefore quenched by adding MeOH (20ml) and 5% HCl (10ml) at -60°C. After warming to room temperature, CH_2Cl_2 (150ml) and more 5% HCl (added enough to make the solution acidic pH 2-3) were added and the two layers were then separated. The aqueous solution was further extracted with CH_2Cl_2 (2 x 50ml) and the combined organic layers were dried over anhydrous sodium sulphate. After the solvent had been evaporated at reduced pressure the residue was dissolved in MeOH (20ml) and a MeOH/AcCl (30ml: 0.5ml) mixture was then added until the reaction mixture was at pH 4 and slow conversion to the methyl ester could be monitored by TLC. After 3.5 hours the solvent was removed under reduced pressure and the residue purified by column chromatography on silica eluting with ethyl acetate:petroleum ether (1:1). The product **122** (2.15g, 69%) was a colourless oil. Rf 0.5 (2:1, hexane/ethyl acetate); (Found: C, 67.0; H, 8.07. $C_{18}H_{26}O_5$ requires C, 67.1; H, 8.15%), $[\alpha]_D^{22}$ +23.3 (c 0.24 in $CHCl_3$); ν_{max}(neat)/cm^{-1} 3440 br (OH), 1740 s (CO), 1610 m, 1580 m, 1510 s; δ_H (360MHz;$CDCl_3$) 1.69 (2H, pentet, J 7.5, CH_2) 2.05-2.11 (2H, m, CH_2) 2.29-2.35 (4H, m, 2 x CH_2), 3.48-3.52 (2H, m), 3.60-3.65 (1H, m) 3.66 (3H, s, -OCH_3), 3.80 (3H, s, OCH_3), 4.47 (1H, d J_{AB} 11.2, -$CHHAr$), 4.60 (1H, d, J_{AB} 11.2 -$CHHAr$), 5.40-5.50 (2H, m, 2 x olefinic CH), 6.88 (2H, d, J 8.5, aryl), 7.27 (2H, d, J 8.5, aryl); δ_C (90.6MHz;$CDCl_3$) 24.7 (t), 26.6 (t), 28.7(t), 33.4 (t), 51.5 (q, OCH_3), 55.2 (q, OCH_3), 64.0 (t), 71.2 (t), 79.1 (d), 113.9 (d, 2 x arylCH), 125.7 (d, olefinic CH), 130.1 (d, 2 x arylCH), 130.4 (s), 131.1 (d, olefinic CH), 159.3 (s), 174.0 (s, C=O); m/z (FAB) 407/409 ([M+Rb]$^+$, 5%), 323 ([M+H]$^+$, 6%), 250 (5), 241 (11), 185 (4), 154 (10), 137 (15), 121 (100), 93 (14).

Oxidation to give aldehyde 124.

A solution of oxalyl chloride (0.65ml, 7.45mmol) in dichloromethane (20 ml) was cooled to -78°C under an argon atmosphere and a solution of dimethylsulfoxide (1.06ml, 14.9mmol) in dichloromethane (15ml) was added over a five minute period *via* a dropping funnel. Stirring was continued at -78°C for 10 minutes followed by addition of **122** (2.0g, 6.21mmol) over *ca.* 5 minutes. The reaction mixture was

stirred for 15 minutes and triethylamine (4.3ml, 31.1mmol) was added with stirring at -78°C. The cooling bath was then removed and water (20ml) was added at room temperature. Stirring was continued for 10 minutes and the two layers were then separated. The aqueous phase was extracted with dichloromethane (3 x 30ml) and the organic layers were combined, dried over anhydrous magnesium sulphate and the solvent evaporated to give crude aldehyde **124** (1.99g, quantitative yield) as a pale yellow coloured oil which was used directly in the next step.
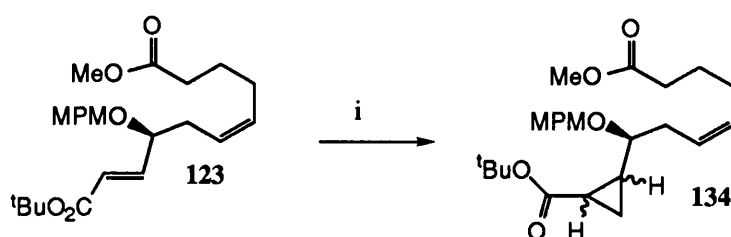
Olefination of 124 Using the Masamune and Roush Modification of the Horner-Wadsworth-Emmons Reaction to Give (E)-γ-Alkoxy-α,β-unsaturated-t-Butyl Ester 123

To a stirred suspension of LiCl (316mg, 7.45mmol) in acetonitrile (40ml) at room temperature under an argon atmosphere was added *t*-butyl diethylphosphonoacetate (2.33ml, 9.94mmol), DBU (0.93ml, 6.21mmol), and finally a solution of aldehyde **124** (1.99g, 6.21mmol) in dry acetonitrile (40ml). The reaction mixture was stirred at room temperature for 5 hours at which time it was quenched by adding H_2O (30ml). The aqueous layer was then extracted with ethyl acetate (3 x 50ml) and the combined organic layers were dried over anhydrous magnesium sulphate. After the solvent had been evaporated at reduced pressure the residue was purified by column chromatography on silica eluting with hexane-ethyl acetate (6:1). The product **123** (1.95g, 75% for the two steps from **122**) was a colourless oil. Rf 0.6 (5:1, hexane/ethyl acetate); $[\alpha]_D^{21}$-35.2 (*c* 0.05 in $CHCl_3$); v_{max} (neat)/cm^{-1} 1740 s (CO), 1720 s (CO), 1660 m, 1610 m, 1590 w, 1520 s; δ_H (360MHz; $CDCl_3$) 1.50 (9H, s, -CO$_2$*^{t}Bu*), 1.65 (2H, pentet, *J* 7.4, C*H$_2$*), 2.01-2.07 (2H, m, C*H$_2$*), 2.28 (2H, t, *J* 7.5, C*H$_2$*), 2.32-2.41 (2H, m, C*H$_2$*), 3.66 (3H, s, CO$_2$C*H$_3$*), 3.81 (3H, s, OC*H$_3$*), 3.92 (1H, q, *J* 6.5, -C*H*O-), 4.32 (1H, d, *J$_{AB}$* 11.5, OC*H*HAr), 4.52 (1H, d, *J$_{AB}$*

11.5, OCH*H*Ar), 5.40-5.47 (2H, m, 2 x olefinic C*H*), 5.92 (1H, d, *J* 15.7, α-C*H*),

6.73 (1H, dd, *J* 6.6, 15.6, β-C*H*), 6.87 (2H, d, *J* 8.5, aryl), 7.25 (2H, d, *J* 8.5,

aryl); δ$_C$ (90.6MHz;CDCl$_3$) 24.7 (t), 26.8 (t), 28.1 (q, 3 x C*H*$_3$), 32.9 (t), 33.5 (t),

51.5 (q, CO$_2$C*H*$_3$), 55.3 (q, OC*H*$_3$), 70.7 (t, benzylic C*H*$_2$), 77.6 (d), 80.5 (s,

CO$_2$^{t}Bu), 113.8 (d, 2 x arylC*H*), 124.1 (d, olefinic C*H*), 125.3 (d, olefinic C*H*),

129.3 (d, 2 x aryl C*H*), 130.2 (s), 131.2 (d, olefinic C*H*), 146.6 (d, olefinic C*H*),

159.2 (s), 165.5 (s, CO), 174.0 (s, CO); *m/z* FAB 505/503 ([M+Rb]$^+$, 5%), 419

([M+H]$^+$, 2%), 363 (3), 241 (6), 207 (4), 154 (4), 137 (7), 121 (100);

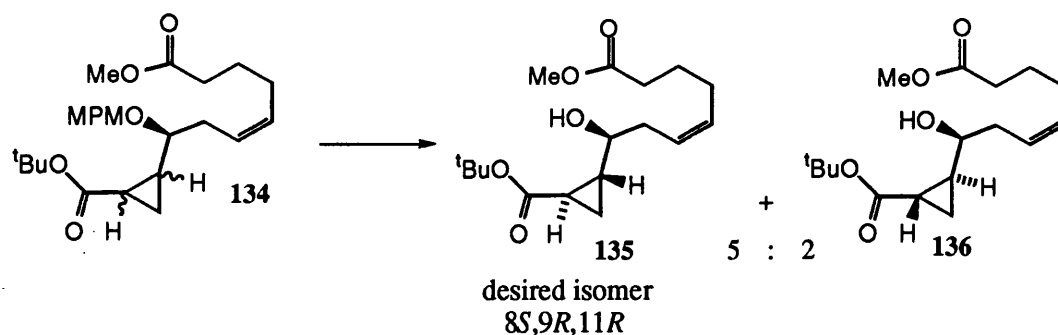(Found:[M+H]$^+$ 419.2423. C$_{24}$H$_{34}$O$_6$ requires, 419.2434).

*Cyclopropanation Reaction to Give **134** as a Mixture of Trans -Diastereomers.*

Dimethylsulfoxonium methylide {2.2 equivalents generated from trimethylsulfoxonium

iodide (757mg, 3.44mmol) and sodium hydride (138mg, 5.73mmol, 60% dispersion

in mineral oil} in dry dimethylsulfoxide (6ml) at room temperature was treated with

tert-butyl ester **123** (720mg, 1.72mmol) in dimethylsulfoxide (6ml). The mixture was

stirred for 0.5 hours at room temperature and then 20 hours at 90°C. The reaction was

then quenched at room temperature by adding saturated aqueous NH$_4$Cl (10ml). The

product was extracted with ethyl acetate (3 x 15ml) and the combined organic extracts

were dried with anhydrous sodium sulphate and the solvent evaporated at reduced

pressure. The crude residue was then purified by column chromatography on silica

eluting with ethyl acetate/hexane (1:6) which gave **134** (550mg, 74%) as a colourless

oil. The product was a 5:2 mixture of inseparable but exclusively *trans*-diastereomers

where the major diastereomer contained the desired relative stereochemistry

(8*S*,9*R*,11*R*). Rf 0.5 (6:1, hexane/ethyl acetate); (Found: C, 68.9; H, 8.54.

C$_{25}$H$_{36}$O$_6$ requires C, 69.4; H, 8.33%); reverse phase HPLC (75% to 95% MeOH/

25% to 5% H$_2$O+0.1% trifluoroacetic acid) retention time 5.4mins, 95% pure;

v_{max}(neat)/cm^{-1} 1740 s (CO), 1720 s (CO), 1610 m, 1580 m, 1510 s; δ_H

(360MHz;CDCl$_3$) major isomer, 0.62-1.55 (4H, m, cyclopropane), 1.45 (9H, s,

CO$_2{}^t$Bu), 1.69 (2H, pentet, J 7.4, CH$_2$), 2.05-2.11 (2H, m, CH$_2$), 2.30 (2H, t, J

7.4, CH$_2$), 2.35-2.42 (2H, m, CH$_2$), 2.91 (1H, q, J 6.5, -CHO-), 3.66 (3H, s,

CO$_2$CH$_3$), 3.80 (3H, s, OCH$_3$), 4.45-4.58 (2H, m, benzylic CH$_2$), 5.40-5.60 (2H,

m, 2 x olefinic CH), 6.86-6.88 (2H, m, aryl), 7.23-7.26 (2H, m, aryl), minor

isomer (360MHz;CDCl$_3$) 1.43 (9H, s, CO$_2{}^t$Bu), 3.00 (1H, q, J 6.5, -CHO-) all other

peaks were coincidental with the major isomer; δ_C (67.8MHz;CDCl$_3$) major isomer,

10.8 (t), 20.2 (d), 24.7 (t), 25.4 (d), 26.6 (t), 28.1 (q,3 xCH$_3$), 32.8 (t), 33.4 (t),

51.4 (q, OCH$_3$), 55.2 (q, OCH$_3$), 70.6 (t), 79.2 (d), 80.1 (s), 113.7 (d, 2 x aryl

CH), 126.3 (d, olefinic CH), 129.0 (d, 2 x aryl CH), 130.5 (d, olefinic CH), 130.6

(s), 159.1 (s), 172.9 (s), 173.9 (s), minor isomer, 13.1 (t), 18.3 (d), 24.7 (t), 25.1

(d), 26.6 (t), 28.1 (q,3 xCH$_3$), 32.7 (t), 33.4 (t), 51.4 (q, OCH$_3$), 55.2 (q, OCH$_3$),

70.3 (t), 79.3 (d), 80.1 (s), 113.7 (d, 2 x aryl CH), 126.2 (d, olefinic CH), 129.0 (d,

2 x aryl CH), 130.5 (d, olefinic CH), 130.6 (s), 159.1 (s), 172.9 (s), 173.0 (s); m/z

FAB 433 ([M+H]$^+$, 2%), 377 ([M-^{t}Bu]$^+$, 3%), 239 (6), 189 (5), 137 (6), 121 (100),

57 (8).

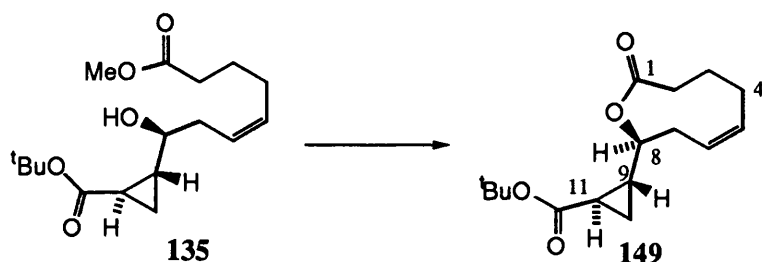*DDQ Deprotection of 134 and Subsequent Separation of Isomers 135 and 136.*

To 134 (2.13g, 4.93mmol) in a dichloromethane/water mixture (30ml:1.6ml) was

added solid DDQ (1.23g, 5.42mmol) at room temperature. After one hour the reaction

was complete and the solvent was evaporated. Complete separation of the two

hydroxy isomers 135 and 136 required repeated column chromatography eluting with

hexane/ethyl acetate (4:1). The products (combined yield of 1.54g, 100%) were both oils where the major isomer **135** was isolated pure (1.06g, 69%). Rf$_{major}$ 0.5 (5:1, hexane/ethyl acetate) and Rf$_{minor}$ 0.47 (5:1, hexane/ethyl acetate) ; major isomer **135**; $[\alpha]_D^{21}$ -114.1 (c 0.7 in CHCl$_3$); υ_{max}(neat)/cm^{-1} 3500 br (OH), 1740 vs (CO), 1720 vs (CO), 1360 m, 1150 m; δ_H (360MHz;CDCl$_3$) 0.79 (1H, ddd, J 4.3, 6.2, 8.3, cyclopropane CHH), 1.08-1.13 (1H, m, cyclopropane CHH), 1.43 (9H, s, ^{t}Bu), 1.47-1.57 (2H, m, 2 x cyclopropane CH), 1.70 (2H, pentet, J 7.4, -CH$_2$-), 1.86 (1H, bs, OH), 2.10 (2H, q, J 7.2, -CH$_2$-), 2.30-2.34 (4H, m, 2 x-CH$_2$-), 3.14 (1H, q, J 6.6, -CHOH-), 3.66 (3H, s, -CO$_2$CH$_3$), 5.45-5.56 (2H, m, -CH=CH-); δ_C (90.6MHz;CDCl$_3$) 12.2 (t), 18.9 (d), 24.7 (t), 26.6 (t), 27.6 (d), 28.1 (q, 3 xCH$_3$), 33.3 (t), 34.9 (t), 51.5 (q, OCH$_3$), 73.2 (d), 80.3 (s), 125.8 (d, olefinic CH), 131.8 (d, olefinic CH), 173.0 (s, C=O), 174.1 (s, C=O); m/z (FAB) 313 ([M+H]$^+$, 47%), 257 (65), 239 (97), 221 (57), 189 (85), 57 (100); (Found: [M+H]$^+$ 313.2012. C$_{17}$H$_{29}$O$_5$ requires, 313.2015). minor isomer **136**; $[\alpha]_D^{21}$ +30.4 (c 0.09 in CHCl$_3$); δ_H (360MHz;CDCl$_3$) 0.89-0.94 (1H, m, cyclopropane CHH), 1.06-1.11 (1H, m, cyclopropane CHH), 1.44 (9H, s, ^{t}Bu), 1.48-1.57 (2H, m, 2 x cyclopropane CH), 1.70 (2H, pentet, J 7.3, -CH$_2$-), 2.11 (2H, q, J 7.2, -CH$_2$-), 2.31-2.40 (4H, m, 2 x -CH$_2$-), 3.28 (1H, m, -CHOH-), 3.67 (3H, s, -CO$_2$CH$_3$), 5.45-5.58 (2H, m, -CH=CH); δ_C (90.6MHz;CDCl$_3$) 11.7 (t), 18.9 (d), 24.7 (t), 26.6 (t), 27.0 (d), 28.1 (q, 3 xCH$_3$), 33.3 (t), 35.2 (t), 51.5 (q, OCH$_3$), 72.3 (d), 80.3 (s), 125.8 (d, olefinic CH), 132.0 (d, olefinic CH), 173.0 (s, C=O), 174.1 (s, C=O); m/z (FAB) 313 ([M+H]$^+$, 44%), 257 (47), 239 (100), 221 (54), 207 (16), 189 (75), 57 (97); (Found: [M+H]$^+$ 313.2009. C$_{17}$H$_{29}$O$_5$ requires, 313.2015).

The following experiments were performed using the major 8S,9R,11R cyclopropane diastereomer 135:

Ester Hydrolysis to Give an Hydroxy Acid Intermediate 135a which was

Subsequently Lactonised to 149.

To 8S,9R,11R-135 (250mg, 0.80mmol), in a tetrahydrofuran/H_2O/MeOH (4ml:1ml:1ml) solution was added solid lithium hydroxide (67.0mg, 1.60mmol) at room temperature. After stirring for 16 hours the mixture was quenched with 5% HCl (2ml). The aqueous layer was then extracted with ethyl acetate (5 x 5ml). The combined organic layers were dried over anhydrous magnesium sulphate and then the solvent was removed under reduced pressure. The crude oil 135a (0.24g, 100%) was used directly in the next step; v_{max}(neat)/cm^{-1} 3500-2800 br (CO_2H), 1712 vs (CO), δ_H (360MHz;CDCl$_3$) 0.80 (1H, ddd, J 4.4, 6.3, 8.3, cyclopropane -C*H*H-), 1.10-1.15 (1H, m, cyclopropane -CH*H*-), 1.44 (9H, s, ^{t}Bu), 1.49-1.60 (2H, m, 2 x cyclopropane C*H*), 1.72 (2H, pentet, J 7.3, CH$_2$), 2.10-2.17 (2H, m, -C*H*$_2$-), 2.35-2.43 (4H, m, 2 x -C*H*$_2$-), 3.15 (1H, q, J 6.5, -C*H*OH-), 5.47-5.57 (2H, m, -C*H*=C*H*-), 5.50-6.00 (2H, bs, O*H*+COO*H*).

To a solution of crude 8S,9R,11R-hydroxy-acid 135a (650mg, 2.18mmol) in tetrahydrofuran (6ml) under an argon atmosphere was added triethylamine (0.49ml, 3.49mmol) at room temperature with stirring for 10 minutes. Then at room temperature, 2,4,6-trichlorobenzoyl chloride (0.37, 2.40mmol) was added slowly with stirring for 2 hours. After dilution with toluene (60ml) this solution was added (using a syringe pump) to excess 4-dimethylaminopyridine (4.00g, 32.7mmol) in toluene (100ml) at reflux over 6 hours. After the addition had been completed the reaction mixture was allowed to cool to room temperature and the solvent was then
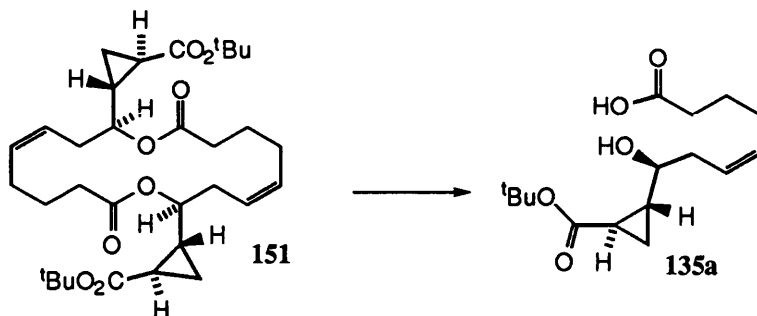
evaporated. The residue was purified by column chromatography on silica eluting with petroleum ether/ethyl acetate (10:1 to 5:1). The product **149** (460mg, 75%) was isolated as a colourless oil. Rf 0.6 (10:1, petroleum ether/ethyl acetate). The only observed side product was the dimeric species **151** (16.6mg, 2.7%). Rf 0.4 (10:1, petroleum ether/ethyl acetate) . The dimer was formed in much larger quantities if the addition was too rapid or the mixture was too concentrated. (In the event of significant amounts of dimer being formed it was hydrolysed back to the starting hydroxy-acid **135a**).

Monomer **149**: (Found: C, 68.5; H, 8.75. $C_{16}H_{24}O_4$ requires C, 68.6; H, 8.57%) $[\alpha]_D^{21}$ -81.5 (c 0.01, CHCl3); ν_{max}(neat)/cm^{-1} 1740 vs (CO), 1720 vs (CO), 1460 m, 1360 m; the assignment of all the proton and carbon signals was achieved using phase-sensitive ^{1}H-^{1}H COSY, normal ^{1}H-^{13}C correlation and long-range ^{1}H-^{13}C correlation; δ_H (500MHz;CDCl3) 0.80-0.86 (1H, m, cyclopropane -CHH- (10)), 1.13-1.18 (1H, m, cyclopropane -CHH- (10')), 1.45 (9H, s, ^{t}Bu (14)), 1.60-1.68 (2H, m, 2 x cyclopropane -CH (9+11)), 1.77 (1H, dddd, J 6.5, 11.9, 11.9, 11.9, -CHH- (3)), 2.04-2.09 (2H, m, -CHH- and -CHH- (4) and (3')), 2.13-2.18 (1H, m, -CHH- (7)), 2.22-2.26 (1H, m, -CHH-(2)), 2.29-2.36 (1H, m, -CHH-(2')), 2.45-2.56 (2H, m, 2 x -CHH- (7') and (4')), 4.27 (1H, ddd, J 1.5, 7.5, 10.9, -CHOCO-), 5.45-5.49 (2H, m, -CH=CH-); δ_C (125.8MHz;CDCl3) 12.5 (t, (10)), 19.6 (d, (9 or 11), 24.6 (d, (9 or 11)), 25.3 (t, (4)), 26.4 (t, (3)), 28.1 (q, (14)), 33.6 (t, (2)), 33.7 (t, (7), 74.6 (d, (8)), 80.5 (s, (13)), 124.4 (d, (6)), 134.9 (d, (5)), 172.7 (s, (12)), 174.0 (s, (1)); m/z (GC/EIMS) 224 (3), 207 (7), 110 (100), 82 (92), m/z (FAB) 281 ([M+H]$^+$, 32%), 225 (100), 207 ([M-^{t}BuO$^-$]$^+$, 83%), 189 (43); (Found: [M+H]$^+$, 281.1749. $C_{16}H_{25}O_4$ requires, 281.1753).

DIMER **151**: ν_{max}(neat)/cm^{-1} 1723 vs (C=O), 1600m, 1456m; δ_H (270MHz;CDCl3) 0.77-0.88 (2H, m, 2 x cyclopropane CH), 1.12-1.18 (2H, m, 2 x cyclopropane -CH-), 1.44 (18H, s, 2 x ^{t}Bu), 1.55-1.73 (8H, m), 2.05-2.35 (10H, m), 2.50-2.59 (2H, m), 4.45-4.56 (2H, m), 5.30-5.50 (4H, m, 4 x olefinic CH); δ_C (67.8MHz;CDCl3) 12.4 (t), 19.6 (d), 24.4 (d), 25.2 (t), 26.3 (t), 28.1 (q 6 x CH3), 32.5 (t), 33.5 (t), 74.6 (d), 80.4 (s), 125.6 (d), 131.6 (d), 172.6 (s, 2 x C=O), 173.1

(s, 2 x C=O); m/z FAB 583 ([M+Na]$^+$, 16%), 561 ([M+H]$^+$, 11%), 449 (35), 225 (100), 207 (82); (Found: [M-1]$^+$ 559.3285. $C_{32}H_{47}O_8$ requires, 559.3271).

Hydrolysis of the Dimeric Species 151.

To the dimer **151** (56.0mg, 0.10mmol) in a 3:1:1 tetrahydrofuran (1.0ml), H_2O (0.3ml) and MeOH (0.3ml) mixture, solid lithium hydroxide (17.0mg, 0.4mmol) was added in one portion. The resultant homogeneous solution was stirred at room temperature for 16 hours. The reaction was quenched by adding 2N HCl until pH 1-2 was obtained. The aqueous phase was extracted with ethyl acetate (3x 4ml). The solvent was then removed from the combined organic extracts under reduced pressure to give the crude product **135a** (50.3mg, 84%).

Acid Hydrolysis of t-Butyl Ester 149.

To the lactone **149** (160mg, 0.57mmol) in dichloromethane (6ml) at room temperature under an argon atmosphere was added trifluoroacetic acid (1.5ml) dropwise. The reaction was complete after 2 hours and the solvent was then removed under reduced pressure. To ensure all the trifluoroacetic acid had been removed, toluene (4ml) was added to the crude residue and the solvent was again removed under reduced pressure. This process was then repeated several times to give a crude solid which was then crystallised from dichloromethane and cyclohexane to give 8S,9R,11R-**152** (103mg, 80%) as a colourless crystalline solid. {Some less pure material (22.2mg, 17%) was also obtained by removal of the solvent under reduced pressure of the mother-liquor}; (Found: C, 64.3; H, 7.44. $C_{12}H_{16}O_4$ requires C, 64.3; H, 7.14%); $[\alpha]_D^{21}$ -238.0 (c 0.06, CHCl$_3$); v_{max}(neat)/cm^{-1} 3300-2400 br (COOH), 1740 vs (CO), 1700 vs (CO);

δ_H (270MHz;CDCl₃) 1.01 (1H, ddd, *J* 4.6, 6.6, 8.1, cyclopropane -C*H*H-), 1.33

(1H, ddd, *J* 4.8, 4.8, 9.0, cyclopropane -CH*H*-), 1.71-1.79 (3H, m, 2 x

cyclopropane C*H* + lactone -C*H*H-), 2.00-2.10 (2H, m, 2 x lactone -C*H*H-), 2.11-

2.21 (1H, m, lactone -C*H*H-), 2.23-2.37 (2H, m, 2 x lactone -C*H*H-), 2.41-2.60

(2H, m, 2 x lactone -C*H*H-), 4.31 (1H, ddd, *J* 1.5, 7.5, 11.0, -C*H*OCO-), 5.42-5.55

(2H, m, 2 x olefinic C*H*); δ_C (90.6MHz;CDCl₃) 13.5 (t), 18.2 (d), 25.3 (t), 26.0 (d),

26.3 (t), 33.4 (t), 33.7 (t), 74.2 (d), 124.1 (d, olefinic *C*H), 135.0 (d, olefinic *C*H),

173.9 (s), 179.4 (s); *m/z* (ESI-LOOP, ammonium acetate) 447 ([2M-H]⁺, 99%), 283

([M+OAc]⁺, 100%), 223 ([M-H]⁺, 59%. An X-ray crystal structure of **152** was

obtained which confirmed the absolute stereochemistry. Suitable crystals for X-ray

analysis were grown from a solution of hexane/ethyl acetate (10:1) over a two week

period (see Apendix 1).

The following set of experimental data was compiled from the minor 8S,9S,11S

cyclopropane diastereomer **136**:

Yamguchi Lactoisation: to Give 150.

A similar procedure to that already described in the preparation of **149** was used; A

crude sample of 8S,9S,11S hydroxy-acid **136a** was prepared by basic hydrolysis of

136 (2.0 equivalents of LiOH, tetrahydrofuran:H₂O:MeOH (4:1:1), room

temperature, 16 hours, quantitative crude yield). Then to the crude sample of

8S,9S,11S hydroxy-acid **136a** (461mg, 1.55mmol) in tetrahydrofuran (10ml), under

an argon atmosphere was added, triethylamine (0.34ml, 2.48mmol) and 2,4,6

trichlorobenzoyl chloride (0.27ml, 1.70mmol) at room temperature and the resulting

mixture was stirred for 2.5 hours. The precipitate was then removed by filtration and
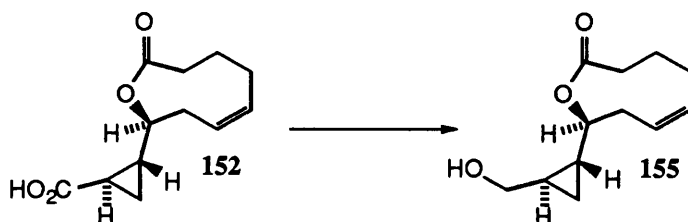
the filtrate was diluted with toluene (50ml). This dilute solution was added (using a syringe pump) to excess 4-dimethylaminopyridine (2.83g, 23.2mmol) in toluene (100ml) at reflux over 3 hours. After the addition the reaction mixture was allowed to cool to room temperature and the solvent was then removed under reduced pressure. The residue was purified by column chromatography on silica eluting with petroleum ether/ethyl acetate (7:1). The product **150** (329mg, 76%) was isolated as a colourless crystalline solid. Rf 0.6 (7:1, petroleum ether/ethyl acetate). $[\alpha]_D^{20}$ -2.1 (c 1.55, CHCl$_3$); δ_H (400MHz;CDCl$_3$) 0.94 (1H, ddd, J 4.3, 6.4, 8.5, cyclopropane -CHH), 1.12 (1H, ddd, J 4.6, 4.6, 8.9, cyclopropane-CHH-), 1.45 (9H, s, ^{t}Bu), 1.53 (1H, ddd, J 4.6, 4.6, 8.5, cyclopropane -CH-), 1.58-1.65 (1H, m, cyclopropane -CHH-), 1.77 (1H, dddd, J 6.7, 11.9, 11.9, 11.9, -CHH-), 2.02-2.34 (5H, m), 2.44-2.54 (2H, m), 4.38 (1H, ddd, J 1.2, 7.3, 10.7, -CHO-), 5.44-5.49 (2H, m, 2 x olefinic CH); δ_C (67.8MHz;CDCl$_3$) 12.5 (t), 19.2 (d), 24.4 (d), 25.3 (t), 26.4 (t), 28.1 (q, 3x CH$_3$), 33.5 (t), 33.8 (t), 74.1 (d), 80.6 (s), 124.4 (d, olefinic CH), 134.8 (d, olefinic CH), 173.0 (s), 179.0 (s); m/z (FAB) 281 ([M+H]$^+$, 33%), 225 (100), 207 (85), 189 (45).

Acidic Hydrolysis of the t-Butyl ester in 150.

To **150** (300mg, 1.07mmol) in dichloromethane (5ml) at room temperature under an argon atmosphere was added freshly distilled trifluoroacetic acid (1.5ml) in dichloromethane (5ml) dropwise. The reaction was complete after 2 hours and the solvent was then removed under reduced pressure. To ensure all the trifluoroacetic acid had been removed, toluene (15ml) was added to the crude residue and the solvent was again removed under reduced pressure. This process was then repeated several times to give a crude residue which was purified by column chromatography on silica eluting with ethyl acetate/petroleum ether (1:1). The product **153** (191mg, 80%) was isolated as a colourless oil. $[\alpha]_D^{21}$ -17.0 (c 0.5, CHCl$_3$); (Found: C, 64.3; H, 7.25. C$_{12}$H$_{16}$O$_4$ requires C, 64.3; H, 7.14%); v_{max}(neat)/cm^{-1} 3300-2400 br (COOH), 1736 vs (CO), 1699 vs (CO); δ_H (270MHz;CDCl$_3$) 1.07-1.14 (1H, m, cyclopropane -CHH-), 1.28 (1H, ddd, J 4.8, 4.8, 8.8, cyclopropane -CHH-), 1.63 (1H, ddd, J

4.4, 4.4, 8.4 -C*H*-), 1.69-1.87 (2H, m, lactone -C*H*- + cyclopropane C*H*), 2.00-2.37

(5H, m, 5 x lactone C*H*) 2.44-2.56 (2H, m, 2 x lactone C*H*), 4.40 (1H, ddd, *J* 1.5,

7.3, 11.0, -C*H*OCO-), 5.40-5.54 (2H, m, olefinic C*H*) 9.93 (1H, bs, -COO*H*); δ_C

(67.8MHz;CDCl$_3$) 13.6 (t), 18.0 (d), 25.2 (t), 25.7 (d), 26.3 (t), 33.6 (t), 33.7 (t),

73.8 (d), 124.1 (d, olefinic *C*H), 134.9 (d, olefinic *C*H), 173.9 (s), 179.6 (s); *m/z*

(CI-isobutane) 225 ([M+H]$^+$, 15%), 207 ([M-OH]$^+$, 100%), 189 (60), 179 (5), 110
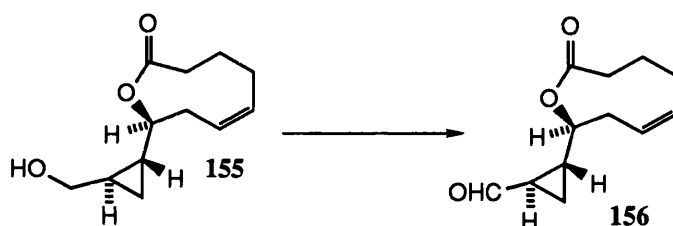
(32).

Selective reduction of the Carboxylic Acid Functionality in the

8S,9R,11R isomer 152.

To 8*S*,9*R*,11*R*-carboxcylic acid **152** (67.3mg, 0.30mmol) in tetrahydrofuran (1ml)

under an argon atmosphere at room temperature was added triethylamine (30.3mg,

0.3mmol) and the mixture was stirred for 5 minutes. After cooling the mixture to

-5°C, ethylchloroformate (32.4mg, 0.3mmol) in tetrahydrofuran (0.5ml) was added

dropwise. Stirring was continued at -5°C for 0.5 hours and then the precipitated

triethylamine hydrogen chloride was filtered and washed with tetrahydrofuran (2ml).

The mixed anhydride was then slowly added to a solution of sodium borohydride in

H$_2$O (0.3ml) at 0°C. The resultant mixture was stirred at 0°C for 0.5 hours and

subsequently at room temperature until effervescence ceased (*ca* 0.5 hours). Addition

of 2N HCl (1ml) followed, and the aqueous layer was repeatedly extracted with ethyl

acetate (3 x 4ml). The combined organic extracts were dried over anhydrous

magnesium sulphate and the solvent was removed under reduced pressure. The

residue was purified by column chromatography on silica eluting with ethyl

acetate/petroleum ether (1:2). The product **155** (48.5mg, 77%) was isolated as a

colourless oil. Rf 0.4 (2:1, hexane/ethyl acetate); $[\alpha]_D^{20}$ -86.2 (*c* 1.75, CHCl$_3$) v_{max}

(neat) / cm^{-1} 3444 br (OH), 1734 vs (CO); δ_H (270MHz;CDCl$_3$) 0.55-0.64 (2H, m, cyclopropane -CH_2-), 0.94-1.04 (1H, m, cyclopropane -CH-), 1.14-1.25 (1H, m, cyclopropane -CH-), 1.75 (1H, bs, OH), 1.70-1.85 (1H, m, -CHH-), 2.03-2.60 (7H, m), 3.45 (1H, dd, J 7.2, 11.4, -CHHOH), 3.52 (1H, dd, J 6.6, 11.4, -CHHOH), 4.19 (1H, ddd, J 1.5, 8.4, 10.4, -CHOCO-), 5.41-5.53 (2H, m, 2 x olefinic CH); δ_C (67.8MHz;CDCl$_3$) 8.3 (t), 19.8 (d), 20.5 (d), 25.3 (t), 26.5 (t), 33.7 (t), 33.8 (t), 66.0 (t), 76.4 (d), 124.7 (d, olefinic CH), 134.6 (d, olefinic CH), 174.1 (s); m/z (GC/EIMS) 282 ([M-H+TMS]$^+$, 1%), 182 ([M-H$_2$O]$^+$, 5%), 110 (100), 82 (85), and m/z (FAB) 233 ([M+Na]$^+$, 100%), 211 ([M+H]$^+$, 71%), 193 ([M+H-H$_2$O]$^+$, 85%). (Attempt to obtain an accurate mass [M+H] peak failed).

Oxidation to Give Aldehyde 156.

To 8S,9R,11R alcohol **155** (60.0mg, 0.29mmol) in dichloromethane (3ml, containing powdered molecular sieves) under an argon atmosphere at room temperature was added N-methyl morpholine N-oxide (50.2mg, 0.43mmol) followed by tetrapropylammonium perruthenate (5.0mg, 0.014mmol). The mixture was stired at room temperature for 20 minutes and then filtered directly down a silica column eluting with petroleum ether/ethyl acetate (2:1). The product **156** (59mg, quantitative yield) was isolated as a colourless oil. Rf 0.7 (10:3, petroleum ether/ethyl acetate); v_{max} (neat)/cm^{-1} 1730 vs (CO + CHO), 1449 m, 1355 m, 1258 m, 1216 m, 1168; δH (270MHz;CDCl$_3$) 1.12 (1H, ddd, J 4.9, 6.4, 8.4, cyclopropane CHH), 1.36-1.43 (1H, m, cyclopropane -CHH), 1.69-1.85 (2H, m, 2 x cyclopropane CH), 1.98-2.58 (8H, m), 4.35 (1H, ddd, J 1.7, 7.9, 11.0, -CHOCO), 5.41-5.54 (2H, m, 2 x olefinic CH), 9.24 (1H, d, J 4.6, aldehyde C(O)H). Aldehyde **156** was used directly in the next step.

4.3 Experimental For Section 2.2:

Towards the Left Hand Fragment of Halicholactone 2:

Preparation of (R)-3-O-((t-butyldiphenylsilyl)oxy)-1-octyn-3-ol 173.

To (R)-(+)-octyn-3-ol **172** (0.58ml, 3.96mmol) in N,N-dimethylformamide (10ml) under an argon atmosphere at room temperature was added imidazole (0.67g, 9.90mmol). Once the imidazole had dissolved *t*-butyldiphenylsilyl chloride (1.24ml, 4.75mmol) was added slowly over a 5 minute period. The reaction mixture was then stirred at room temperature for 3 hours and then quenched with ice. The two layers were separated and the aqueous layer was extracted with diethyl ether (3 x 15ml). The combined organic layers were dried over anhydrous magnesium sulphate and the solvent evaporated. The residue was purified by column chromatography on silica eluting with ethyl acetate/petroleum ether (1:10). The product **173** (1.29g, 89%) was a colourless oil. Rf 0.6 (neat petroleum ether). (Found C, 78.9; H, 9.00. $C_{24}H_{32}OSi$ requires C, 79.1; H, 8.80%); $[\alpha]_D^{20}$ +39.2 (c 0.66 in $CHCl_3$); ν_{max}(neat)/cm^{-1} 3304 m (C≡C-H), 3060 m, 2933 s, 2860 s, 2361 m (C≡C), 1651 w, 1558 w, 1465 m, 1428 m; δ_H (270MHz;CDCl$_3$) 0.85 (3H, t, J 6.6, -CH$_2$CH_3), 1.09 (9H, s, ^{t}Bu), 1.17-1.70 (8H, m), 2.31 (1H, d, J 2.01, C≡CH), 4.32 (1H, dt, J 2.2, 6.2, -CHOSi-), 7.35-7.47 (6H, m, aryl), 7.68-7.77 (4H, m, aryl) *m/z* (FAB) 365 ([M+H]$^+$, 13%), 319 (15), 308 ([M+H-^{t}Bu]$^+$, 85%), 237 (41), 207 (100), 199 (92).

Preparation of (R,E)-((t-butyldiphenylsilyl)oxy)-1-iodo-octene-3-ol 175.

To **173** (255mg, 0.70mmol) in degassed tetrahydrofuran (5ml) at room temperature under an argon atmosphere was added bis(cylopentadienyl)zirconium chloride hydride (266mg, 0.91mmol) rapidly. Once a homogeneous solution had formed we analysed the reaction by TLC which indicated that all the starting material (**173**) had been consumed. Therefore iodine (212mg, 0.84mmol) was added and the solution was stirred at room temperature for 30 minutes. Then an equal volume of saturated aqueous NH$_4$Cl and diethyl ether were added, the two layers were separated, and the aqueous phase was extracted with diethyl ether (2 x 10ml). The combined organic

extracts were dried over anhydrous magnesium sulphate and the solvent was removed at reduced pressure. The residue was then purified by column chromatography on silica, eluting with neat petroleum ether. The product **175** (322mg, 94%) was a colourless oil. Rf 0.8 (neat petroleum ether); (Found C, 58.4; H, 6.9. $C_{24}H_{33}OSiI$ requires C, 58.5; H, 6.70%); $[\alpha]_D^{20}$ +79.8 (c 0.48 in CHCl$_3$); v_{max} (neat)/cm^{-1} 3069 m, 2931 m, 2859 s, 1607 m, 1465, m, 1428, m; δ_H (270MHz;CDCl$_3$) 0.83 (3H, t, J 6.6, -CH$_2$CH_3), 1.06 (9H, s, ^{t}Bu), 1.03-1.47 (8H, m), 4.06 (1H, qm, J 6.6, -CHOSi-), 5.90 (1H, dd, J 1.0, 14.5, trans-β –CHI-), 6.45 (1H, dd, J 6.8, 14.5, α -CH-), 7.34-7.46 (6H, m, aryl), 7.60-7.67 (4H, m, aryl) m/z (FAB) 492 ([M]$^+$, 0.5%), 491 ([M-H]$^+$, 2.5%), 435 (26), 415 (16), 365 ([M-I]$^+$, 8%), 309 (40), 199 ([Ph$_2$SiOH]$^+$,100%).

Preparation of (3R)-3-O-((p-mthoxyphenylmethyl)oxy)-1-octyn-3-ol **173**.

Sodium hydride (190mg, 4.75mmol, 60% dispersion in mineral oil) was washed twice with petroleum ether in order to remove the mineral oil. The remaining neat sodium hydride was then dried at reduced pressure prior to the reaction. To the solid sodium hydride was added N,N-dimethylformamide (8ml) followed by the slow addition of (R)-(+)-1-octyn-3-ol **172** (0.58ml, 3.96mmol) at 0°C under an argon atmosphere. The reaction was left at 0°C until the effervescence had ceased (ca. 30 minutes) and then tetrabutylammonium iodide (73.0mg, 0.20mmol) and 4-methoxybenzyl chloride (0.59ml, 4.36mmol, freshly distilled) were added sequentially at room temperature. The resultant mixture was left at room temperature for 2 hours and then quenched using saturated aqueous NH$_4$Cl. The aqueous layer was repeatedly extracted with diethyl ether (3 x 15ml), and the combined organic layers were dried over magnesium sulphate. Evaporation of the solvent under reduced pressure gave a crude residue which was purified by column chromatography on silica eluting with petroleum ether/ ethyl acetate (10:1). The product **174** (543mg, 56%) was obtained as a colourless oil. Rf 0.8 (10:1 petroleum ether/ethyl acetate); $[\alpha]_D^{18}$ +102.4 (c 1.27 in CHCl$_3$); δ_H (270MHz;CDCl$_3$) 0.83 (3H, t, J 7.0, CH_3), 1.18-1.30 (4H, m), 1.37-1.42 (2H, m, -CH_2-), 1.64-1.74 (2H, m, -CH_2-), 2.41 (1H, d, J 2.0, -C≡C-H), 3.76 (3H, s,
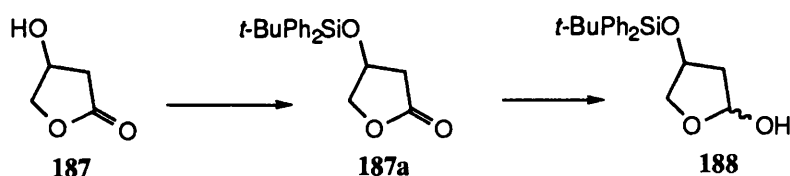
OCH_3), 3.99 (1H, dt, J 2.0, 6.6, -CHO-), 4.39 (1H, d, J_{AB} 11.4, -CHHAr), 4.69

(1H, d, J_{AB} 11.4, -CHHAr), 6.83 (2H, d, J 8.8, aryl), 7.52 (2H, d, J 8.8, aryl); m/z

(GC/EI) 246 ([M]$^+$, 8%), 121 ([CH$_3$OC$_6$H$_4$CH$_2$]$^+$, 100%), and 93% pure by gas

chromatography. A small amount of unreacted 4-methoxybenzyl chloride contaminant

was observed in the ^{1}H-NMR spectrum of **174**.

*Preparation of (R,E)-((p-methoxyphenylmethyl)oxy)-1-iodo-octene-3-ol **176**.*

To **174** (161mg, 0.58mmol) in tetrahydrofuran (5ml) at 0°C under an argon

atmosphere was added bis(cylopentadienyl)zirconium chloride hydride (0.24mg,

0.81mmol) rapidly. Once a homogeneous solution had formed iodine (177mg,

0.70mmol) was added and the solution was stirred at room temperature for 35 minutes.

Then an equal volume of saturated aqueous NH$_4$Cl and diethyl ether were added. The

two layers were separated and the aqueous phase was extracted with diethyl ether (2 x

10ml). The combined organic extracts were then washed with aqueous Na$_2$S$_2$O$_3$ and

dried over anhydrous magnesium sulphate. Removal of the solvent under reduced

pressure gave a residue which was purified by column chromatography on silica

eluting with neat petroleum ether. ^{1}H-NMR analysis of the purified material revealed

that we had isolated a 1:1 mixture of starting material **174** and product **176**. Therefore

this 1:1 mixture of compounds were redissolved in dichloromethane (4ml) and treated

sequentially with bis(cylopentadienyl)zirconium chloride hydride (123mg, 0.42mmol)

, with stirring at room temperature for 45 minutes, followed by the addition of iodide

(107mg, 0.42mmol). After 30 minutes the reaction was worked up as previously

described and the product **176** (181mg, 77%) isolated pure as a colourless oil. δ_H

(270MHz;CDCl$_3$) 0.87 (3H, t, J 6.8, CH_3), 1.21-1.48 (8H, m), 3.70 (1H, q, J 7.3,

-CHO-), 3.80 (3H, s, OCH_3), 4.28 (1H, d, J_{AB} 11.4, -CHHAr), 4.52 (1H, d, J_{AB}

11.4, -CHHAr), 6.26 (1H, d, J 14.5, *trans*-β -CHI-), 6.46 (1H, dd, J 7.7, 14.5,

trans-α -CH-), 6.87 (2H, d, J 8.8, aryl), 7.52 (2H, d, J 8.8, aryl). This compound

was used directly after its preparation and was therefore not fully characterised.

Towards the Left Hand Fragment of Neohalicholactone 1;

Preparation of Racemic 3-O-((t-butyldiphenylsilyl)oxy)-γ-Butyrolactone 187a and
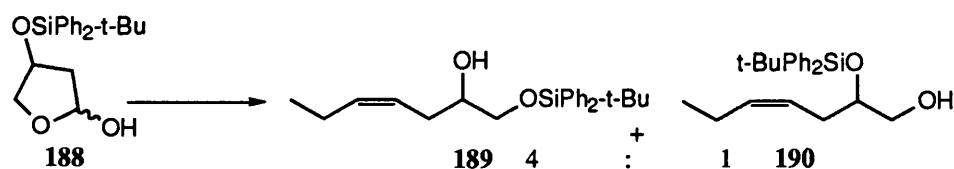
Subsequent Reduction to Lactol 188.

To a stirred solution of (±)-187 (0.50g, 4.90mmol) and imidazole (0.50 g, 7.40mmol) in DMF (10ml), *t*-butyldiphenylsilyl chloride (1.48g, 1.40 ml, 5.40 mmol) was added slowly. After stirring at room temperature for 20 hours the reaction was quenched with NH_4Cl (5 ml). The two layers were separated and the aqueous phase was extracted with ethyl acetate (3 x 5ml). The combined organic layers were dried over anhydrous sodium sulphate and the solvent evaporated. The residue was purified by flash chromatography on silica eluting with ethyl acetate/petroleum ether (1:5), followed by recrystallisation from petroleum ether. The product 187a (1.04g, 62%) was isolated as a colourless crystalline solid; Rf 0.5 (1:5, ethyl acetate/petroleum ether); (Found: C, 70.7; H, 7.22. $C_{20}H_{24}O_3Si$ requires C, 70.6; H, 7.06 %); v_{max} (nujol)/cm^{-1} 1779 s (C=O); δ_H (270MHz;CDCl3) 1.06 (9H, s, ^tBu), 2.49-2.51(2H, m, CH2), 4.15 (1H, dd, *J* 4.6, 9.9, -OCH*H*-), 4.20 (1H, dd, *J* 2.8, 9.9, -OC*H*H), 4.52-4.59 (1H, m, -C*H*OH-), 7.37-7.64 (10H, m, aryl); δ_C (67.8MHz;CDCl3) 18.9 (s), 26.7 (q), 37.8 (t), 69.0 (d), 75.6 (t), 128.0 (d), 130.2 (d), 132.8 (s-ipso), 135.5 (d), 175.5 (s, C=O); *m/z* (CI) 341 [(M+H), 48%], 283 ([M-^tBu]$^+$, 100%), 263 (98), 241 (38), 221 (45).

Reduction of 187a

To a solution of 187a (0.5g, 1.47mmol) in toluene (5ml) under an argon atmosphere, DIBAL-H (1.10 ml, 1.62mmol, 1.5M solution in toluene from Aldrich) was added dropwise at -20°C. After 1 hour at -20°C the reaction was quenched with H_2O (1.3 ml) and allowed to warm to room temperature. Then solid $NaHCO_3$ and ethyl acetate (10ml) were added. The mixture was stirred for 0.5 hours before being filtered, and

the filter cake was washed thoroughly with ethyl acetate. The solvent was then removed under reduced pressure and the residue was purified by column chromatography eluting with ethyl acetate/petroleum ether (1:5). Rf 0.3 (1:5, ethyl acetate/petroleum ether) . The product **188** (431 mg, 86%) was isolated as a 1:1 diastereomeric mixture of epimers (this ratio was variable); (Found: C, 69.9; H, 7.33, $C_{20}H_{26}O_3Si$ requires C, 70.2; H, 7.60%); ν_{max}(nujol)/cm^{-1} 3412 br (OH), 1739 (C=O of open chain form), 1472 m, 1428 m; first epimer, δ_H (400MHz; CDCl$_3$) 1.05 (9H, s, ^{t}Bu), 1.87 (1H, td, J 4.9, 13.7, -CHH), 2.11 (1H, d, J 13.4, -CHH), 3.67-3.71 (1H, dd, J 4.0, 9.8, -OCHH-), 3.96 (1H, d, J 11.6, -OH), 4.06-4.09 (1H, d, J 9.8, -OCHH-), 4.44-4.46 (1H, m, -CHOSi), 5.40-5.44 (1H, dd, J 4.9, 11.3, -CHOH), 7.36-7.66 (10H, m, aryl); δ_C (67.8MHz;CDCl$_3$) 18.8 (s), 26.8 (q), 42.3 (t), 73.2 (d), 75.5 (t), 99.2 (d), 127.9 (d), 130.1 (d), 132.7 (s-ipso), 135.6 (d); second epimer, δ_H (400MHz;CDCl$_3$) 1.08 (9H, s, ^{t}Bu), 1.95 (1H, ddd, J 2.7, 6.4, 13.7, -CHH), 2.10-2.15 (1H, m), 2.56 (1H, d, J 3.1, -OH), 3.76 (1H, dd, J 2.4, 9.2, -OCHH-), 3.91 (1H, dd, J 4.9, 9.2, -OCHH-) 4.55-4.60 (1H, m, -CHOSi), 5.66 (1H, ddd, J 3.4, 3.4, 5.6, -CHOH), 7.36-7.66 (10H, m, aryl); δ_C (67.8MHz;CDCl$_3$) 18.9 (s), 26.7 (q), 42.4 (t), 72.8 (d), 74.1 (t), 98.8 (d), 127.7 (d), 129.7 (d), 132.7 (s-ipso), 135.6 (d); m/z (CI) 341([M-H]$^+$, 4%), 325 ([MH-H$_2$O]$^+$, 10%), 221 (100), 207 (9), 187 (11), 161 (12).

Silyl Migration in the Wittig Olefination Reaction of 188.

Propyltriphenylphosphonium bromide (1.69g, 4.39mmol) in dry toluene (5ml) was treated with sodium bis(trimethylsilyl)amide (3.95ml, 3.95 mmol, 1M solution in tetrahydrofuran from Aldrich) at 0°C under an argon atmosphere. After 1 hour the red-orange mixture was cooled to -78°C and **188** (150mg, 0.44mmol) dissolved in toluene (1ml) was added dropwise. After warming to -20°C over 1 hour the reaction

mixture was quenched with saturated aqueous NH4Cl (5ml). The two layers were separated and the aqueous phase was extracted with ethyl acetate (3 x 5ml). The organic layers were dried over anhydrous sodium sulphate and the solvent evaporated. The residue was purified by column chromatography on silica eluting with ethyl acetate/petroleum ether (1:5). The isomeric products **189** and **190** (117mg, 72%) were isolated together in a ratio of 4 to 1, where **189** was the major product; Rf 0.8 (1:5, ethyl acetate/petroleum ether); ν_{max}(neat)/cm^{-1} 3423 br (OH), 1590 m, 1463 s, 1428 s; __major isomer__ **189**; δ_H (270MHz;CDCl3) 0.83 (3H, t, J 7.5, CH3), 1.07 (9H, s, ^{t}Bu), 2.00 (2H, pentet, J 7.1, -CH2), 2.15-2.26 (2H, m), 2.45 (1H, d, J 3.9, -OH), 3.53 (1H, dd, J 6.9, 10.0, -OCHH-), 3.67 (1H, dd, J 3.7, 10.1, -OCHH-), 3.73-3.80 (1H, m, -CHOH), 5.26-5.38 (1H, m, cis-CH), 5.43-5.55 (1H, m, cis-CH), 7.37-7.44 (6H, m, aryl), 7.65-7.69 (4H, m, aryl); δ_C (67.8MHz;CDCl3) 14.1 (q), 19.2 (s), 20.6 (t), 26.9 (q), 30.9 (t), 67.5 (t), 71.9 (d), 124.0 (d), 127.8 (d), 139.8 (d), 132.2 (s-ipso), 134.4 (d), 135.6 (d); __minor isomer__ **190**; δ_H (270MHz;CDCl3) 0.83 (3H, t, J 7.5, CH3), 1.08 (9H, s, ^{t}Bu), 1.43 (1H, d, J 2.4, -OH), 1.78-1.87 (2H, m), 2.15-2.26 (2H, m), 3.90-3.40 (3H, m), 5.15-5.21 (1H, m, cis-CH), 5.26-5.38 (1H, m, cis-CH), 7.37-7.44 (6H, m, aryl), 7.65-7.69 (4H, m, aryl); δ_C (67.8MHz;CDCl3) 14.1 (q), 19.3 (s), 20.5 (t), 27.0 (q), 31.5 (t), 65.6 (t), 73.9 (d), 123.6 (d), 127.7 (d), 129.8 (d), 133.2 (s-ipso), 134.8 (d), 135.7 (d); m/z (EI, 70eV) 311 ([M-^{t}Bu]$^+$, 4%), 199 (100), 95 (15).
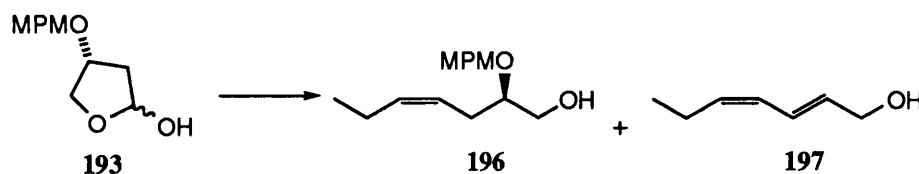
Selective Oxidation of 190 in the Presence of 189.

To a mixture of **189** and **190** (4:1) (100mg, 0.27mmol), N-methyl morpholine N-oxide (48mg, 0.41mmol), and powdered 4Åmolecular seives (100mg) in dry CH2Cl2

(4ml), solid TPAP (4.7mg, 13.5μmol) was added in one portion. The resultant solution was stirred at room temperature for 1 hour and then passed through a short silica column, which was eluted with ethyl acetate (15 ml). The organic washings were dried (Na_2SO_4) and the solvent evaporated. The residue was purified by column chromatography, eluting with ethyl acetate/petroleum ether (1:10). The products, alcohol **190** and aldehyde **180**, (59mg, 59%) were isolated together in a ratio of 4 to 1, where **190** was the major product; **190** - see data given in the previous experiment; Aldehyde **180**; δ_H (270MHz;CDCl$_3$) 0.86 (3H, t, J 7.5, -CH_3), 1.11 (9H, s, ^{t}Bu), 1.92 (2H, pentet, J 7.5, CH_2), 2.18-2.35 (2H, m, CH_2), 4.04 (1H, dt, J 1.8, 6.0, -CHOSi-), 5.26-5.52 (2H, m, 2 x cis-CH), 9.57 (1H, d, J 1.8, -CH=O). This data is in very good agreement with the published data for the homologous aldehyde **182**.[86,18(b)]

Preparation of (2R,4Z)-2-O-((p-methoxyphenylmethyl)-

4-heptene-1,2-diol 196.

The first unsatisfactory procedure we used for the preparation of **196** was as follows;

To propyltriphenylphosphonium bromide (2.80g, 7.28mmol) in toluene (10ml) at room temperature under an argon atmosphere was added sodium bis(trimethylsilyl)amide (6.7ml, 6.7mmol, new bottle, 1.0M in tetrahydrofuran). This solution was left at room temperature for 30 minutes at which time an orange/ red colour had developed. In a different reaction vessel, (3R)-lactol **193** (1.36g, 6.07mmol) was dissolved in toluene (30ml) and the solution was then cooled to -78°C. At this temperature sodium bis(trimethylsilyl)amide (6.07ml, 6.07mmol) was added quite rapidly and the sodium alkoxide of **193** left to form over a 10 minute period. The pre-formed ylide **194** was then cooled to -78°C and added via cannula to the reaction vessel containing the sodium alkoxide of **193** which was also at -78°C. This

addition was completed over a 20 minute period and the mixture was then left at -78°C

for 10 minutes followed by warming to 0°C and stirring at this temperature for 1 hour.

The reaction mixture was now a light brown colour and it was quenched at -60°C by

the addition of methanol (15ml) and saturated aqueous NH4Cl (20ml). After adding

CH2Cl2 (100ml) to the solution at room temperature the two layers were separated and

the aqueous layer was extracted with CH2Cl2 (3 x 50ml) after it had been acidified to

pH 4 using 2N HCl. The combined organic layers were dried over anhydrous

magnesium sulphate and the solvent evaporated. The residue was purified by column

chromatography on silica eluting with ethyl acetate/petroleum ether (1:3). Two

products 196 (451mg, 30%) and 197 (65mg, 10%) were isolated as a colourless oils;

Data for 196; Rf 0.5 (4:1, petroleum ether/ethyl acetate); $[\alpha]_D^{24}$ -23.3 (c 0.22,

CHCl3); v_{max}(neat)/cm^{-1} 3439 br (OH), 1612 s, 1514 s, 1464 m; δ_H (270MHz;

CDCl3) 0.96 (3H, t, J 7.5, CH3), 2.02-2.12 (2H, m), 2.20-2.45 (2H, m), 3.49-3.67

(3H, m), 3.80 (3H, s, OCH3), 4.46 (1H, d, J_{AB} 11.2,-CHHAr), 4.62 (1H, d, J_{AB},

11.2, -CHHAr), 5.29-5.53 (2H, m, 2 x cis-CH), 6.88 (2H, d, J 8.6, aryl), 7.28

(2H, d, J 8.6, aryl); δ_C (67.8MHz;CDCl3) 14.1 (q), 20.6 (t), 28.6 (t), 55.3 (q,

OCH3), 64.2 (t), 71.2 (t), 79.3 (d), 113.9 (d, 2 x aryl), 123.7 (d), 129.4 (d, 2 x

aryl), 130.4 (s-ipso), 134.2 (d), 159.3 (s-ipso); m/z (CI, NH3) 268 ([M+NH4]$^+$,

6%), 138 (22), 121 (100). (Found: [M+NH4]$^+$ 268.1913. C15H26O3N requires,

268.1913).

Data for 197; δ_H (270MHz;CDCl3) 1.00 (3H, t, J 7.5, CH3), 2.20 (2H, pentet d, J

7.5 and 1.5, CH2), 4.19 (2H, d, J 5.3, -CH2OH), 5.40-5.52 (1H, m, cis -CH), 5.80

(1H, td, J 5.7, 15.2 trans-CH), 5.96 (1H, broad t, J 11.0, cis-CH), 6.48-6.58 (1H,

ddm, J 11.2, 15.2, trans-CH).

A much improved procedure for the synthesis of 196 was as follows;

Propyltriphenylphosphonium bromide (2.82g, 7.32mmol) in toluene (10ml) was

treated with sodium bis(trimethylsilyl)amide (7.14ml, 7.14mmol, 1M solution in

tetrahydrofuran) at 0°C under an argon atmosphere. After 10 minutes at 0°C and then

30 minutes at room temperature the red-orange mixture was cooled to -78°C and 193

(800mg, 3.57mmol) dissolved in toluene (5ml) was added slowly via cannula. After

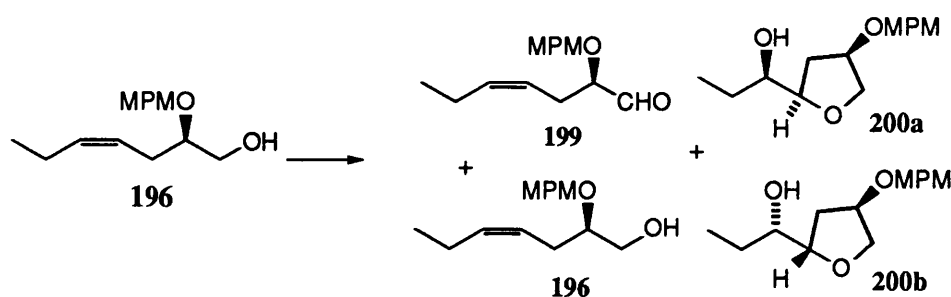stirring at -78°C for 5 minutes and 0°C for 30 minutes the reaction mixture was quenched with saturated aqueous NH_4Cl. The two layers were separated and the aqueous phase was extracted with ethyl acetate (3 x 15ml). The organic layers were dried over anhydrous magnesium sulphate and the solvent evaporated. The residue was purified by column chromatography on silica, eluting with ethyl acetate/petroleum ether (1:4). The desired product **196** (676mg, 76%) and trimethylsilyl protected derivative **198** (126mg, 11%) were both isolated as colourless oils. Data for **196** as above. Data for **198**; δ_H (270MHz;$CDCl_3$) 0.11 (9H, s, -Si(CH_3)$_3$), 0.95 (3H, t, J 7.5, CH_3), 2.04 (2H, pentet, J 7.3, -CH_2CH_3), 2.20-2.40 (2H, m), 3.40-3.50 (1H, m, -CHOCH$_2$Ar), 3.55-3.63 (2H, m, -CH_2OSi(CH_3)$_3$), 4.53 (1H, d, J_{AB} 11.2,-CHHAr), 4.58 (1H, d, J_{AB} 11.2, -CHHAr), 5.32-5.52 (2H, m, 2 x cis-CH), 6.86 (2H, d, J 8.8, aryl), 7.27 (2H, d, J 8.8, aryl). [Note that by stirring **198** in a mixture of tetrahydrofuran and dilute mineral acid it could be quantitatively converted to **196**].

*Preparation of (2R,4Z)-2-O-((p-methoxyphenylmethyl)oxy)-4-heptenal **199**.*

A solution of oxalyl chloride (62.8µl, 0.72mmol) in dichloromethane (1.5ml) was cooled to -78°C under an argon atmosphere and a solution of dimethylsulfoxide (0.1ml, 1.44mmol) in dichloromethane (2ml) was added over a five minute period *via* syringe. Stirring was continued at -78°C for 10 minutes followed by addition of **196** (150mg, 0.60mmol) in dichloromethane (2ml) over *ca.* 10 minutes. The reaction mixture was stirred for 20 minutes and triethylamine (0.42ml, 3.0mmol) was added slowly with stirring at -78°C. The cooling bath was removed and at room temperature water (4ml) was added. Stirring was continued for 5 minutes and then the layers were separated. The aqueous phase was extracted with dichloromethane (3 x 5ml) and the combined organic layers were dried over anhydrous magnesium sulphate and the solvent evaporated to give crude aldehyde **199** (188mg, greater than quantitative yield) as a pale yellow oil. Crude aldehyde **199** was either used directly or was purified by column chromatography eluting with petroleum ether/ethyl acetate (5:1). Aldehyde **199** (144mg, 96%) was now isolated as a colourless oil; Rf 0.6 (5:1, petroleum ether/ethyl acetate); v_{max}(neat)/cm^{-1} 1727 s (CH=O), 1612 s, 1513 s, 1463 m; δ_H

(270MHz;CDCl3) 0.95 (3H, t, *J* 7.5, C*H*3), 2.00-2.20 (2H, m, -C*H*2CH3), 2.42-

2.50 (2H, m), 3.75 (1H, dt, *J* 2.2, 6.6, -C*H*OCH2Ar), 3.81 (3H, s, OC*H*3), 4.53 (

1H, d, *J*AB 11.5,-CH*H*Ar), 4.59 (1H, d, *J*AB 11.5, -C*H*HAr), 5.31-5.41 (1H,

m,*cis*-C*H*), 5.48-5.57 (1H, m,*cis*-C*H*), 6.88 (2H, d, *J* 8.6, aryl), 7.27 (2H, d, *J* 8.6,

aryl), 9.61 (1H, d, *J* 2.2, -C*H*=O). No further data was obtained since the aldehyde

appeared to be quite unstable and was therefore used directly in subsequent steps.

Unsatisfactory Oxidation of 196 Using Catalytic TPAP Conditions

To **196** (356mg, 1.42mmol), N-methyl morpholine N-oxide (250mg, 2.14mmol), and

powdered 4Å molecular seives in dry dichloromethane (10ml), solid TPAP (25mg,

71.2μmol) was added in one portion. The solution was stirred at room temperature for

45 minutes at which time TLC analysis indicated that in addition to the desired

aldehyde an unexpected product was also forming. Therefore the reaction was worked

up at this time. The reaction mixture was passed through a short silica column eluting

with ethyl acetate. The organic washings were dried over anhydrous magnesium

sulphate and the solvent evaporated. The residue was purified by column

chromatography, eluting with ethyl acetate/petroleum ether (1:5 to 1:2). The products,

alcohol **196** (69mg, 19%), aldehyde **199** (137mg, 39%) and **200a** + **200b** (47mg,

13%), were all isolated as colourless oils. Data for **196** and **199** as already described.

Data for **200a:200b** (1:1 mixture of isomers); Rf 0.2 (5:1, petroleum ether/ethyl

acetate) ; νmax (neat)/cm⁻¹ 3455 br (OH), 2935 s, 2876 s, 1613 s, 1514 s, 1464 m,

1302 m; δH (270MHz;CDCl3) 0.99 (3H, t, *J* 7.5, C*H*3), 1.38-1.52 (2H, m,

-C*H*2CH3), 1.91-2.15 (2H, m), 2.68 (0.5H, d, *J* 2.0 , -O*H*), 3.61 (0.5H, dd, *J* 4.2,

9.9 -OC*H*H-), 3.789 (1.5H, s, OC*H*3), 3.794 (1.5H, s, OC*H*3), 3.85-4.19 (4.5H,

m), 4.37-4.49 (2H, m, -OCH_2Ar), 6.86 (1H, d, J 8.6, aryl), 6.87 (1H, d, J 8.6,

aryl), 7.22-7.30 (2H, m, aryl); m/z (CI) 266 ([M]$^+$, 13%), 207 ([M-

CH$_3$CH$_2$CH(OH)]$^+$, 12%), 177 (14), 137 (38), 121 ([CH$_3$OC$_6$H$_4$CH$_2$]$^+$, 100%).

(Found: [M]$^+$, 266.1510. C$_{15}$H$_{22}$O$_4$ requires, 266.1518).

Preparation of (3R)-(1E,5Z)-3-O-((p-methoxyphenylmethyl) oxy)-1-iodo-1,5-

octadiene 204

To a stirred suspension of chromium(II) chloride (357mg, 2.90mmol) in

tetrahydrofuran (4ml) under an argon atmosphere was added dropwise a solution of

pure **199** (120mg, 0.48mmol) and iodoform in tetrahydrofuran (3ml). The mixture

was stirred for 1 hour at 0°C and then left at room temperature for 16 hours. Water

(4ml) was then added followed by ethyl acetate (10ml). The two layers were separated

and the aqueous layer was extracted with ethyl acetate (3 x 10ml). The combined

organic extracts were dried over anhydrous magnesium sulphate and the solvent was

evaporated. The residue was purified by column chromatography on silica eluting with

petroleum ether/ ethyl acetate (2:1). The product **204** (20mg, 11%) was isolated as a

colourless oil. Rf 0.5 (10:1, petroleum ether/ethyl acetate); δ_H (270MHz:CDCl$_3$) 0.95

(3H, t, J 7.5, CH_3), 2.02 (2H, pentet, J 7.1, CH_2CH$_3$), 2.23-2.40 (2H, m, -CH_2),

3.73 (1H, q, J 7.0, -CHO-), 3.80 (3H, s, OCH_3), 4.31(1H, d, J_{AB} 11.4,

-OCHHAr), 4.52 (1H, d, J_{AB} 11.4, -OCHHAr), 5.35-5.25 (1H, m, cis-CH), 5.52-

5.41 (1H, m, cis-CH), 6.29 (1H, d, J 14.7, trans -CHI), 6.48 (1H, dd, J 7.5, 14.7,

trans α-CH), 6.88 (2H, d, J 8.8, aryl), 7.24 (2H, d, J 8.8, aryl).
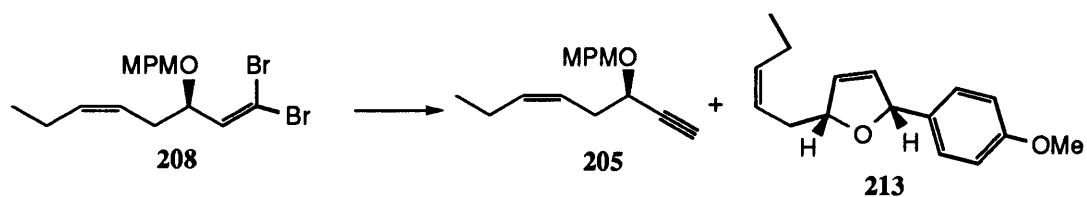
Preparation of (3R,5Z)-3-O-((p-methoxyphenylmethyl)oxy)-1,1-dibromo-1,5-

octadiene 208.

To a solution of triphenylphosphine (2.31g, 8.8mmol) in dichloromethane (10ml)

under an argon atmosphere at room temperature was added carbon tetrabromide

(1.46g, 4.4mmol) followed by triethylamine (2.47ml, 17.6mmol). After 15 minutes at room temperature a deep burgundy coloured solution had developed and the mixture was cooled to -78°C. Crude aldehyde **199** (546mg, 2.20mmol) dissolved in dichloromethane (10ml) was then added slowly *via* cannula. The temperature was allowed to warm to 0°C slowly over a 2 hour period and was then left at room temperature for 16 hours. The burgundy coloured solution was poured into 100ml of stirring petroleum ether, and the precipitated solids were removed by suction filtration. The filtrate was concentrated by evaporation of the solvent and the residue was purified by column chromatography on silica eluting with petroleum ether/ethyl acetate (15:1 to 10:1). The product **208** (650mg, 73% from **196**) was isolated as a colourless oil. Rf 0.6 (15:1, petroleum ether/ethyl acetate); $[\alpha]_D^{22}$ +20.8 (*c* 0.98, CHCl3); ν_{max}(neat)/cm^{-1} 1614 m, 1514 s, 1457 m, 1302 w, 1248 s; δ_H (270MHz;CDCl3) 0.95 (3H, t, *J* 7.5, C*H*3), 2.00-2.10 (2H, m), 2.25-2.45 (2H, m), 3.79 (3H, s, OC*H*3), 4.04-4.12 (1H, m, -C*H*O-), 4.35 (1H, d, J_{AB} 11.4,-CH*H*Ar), 4.53 (1H, d, J_{AB}, 11.4, -C*H*HAr), 5.29-5.55 (2H, m, 2 x *cis*-C*H*), 6.41 (1H, d, *J* 8.6, -C*H*=Br2), 6.87 (2H, d, *J* 8.6, aryl), 7.28 (2H, d, *J* 8.6, aryl); δ_C (67.8MHz; CDCl3) 14.1 (q), 20.7 (t), 32.1 (t), 55.2 (q, OC*H*3), 70.6 (t), 78.7 (d), 91.1 (s), 113.7 (d, 2 x aryl), 122.8 (d), 129.4 (d, 2 x aryl), 130.1 (s), 134.6 (d), 139.7 (d), 159.2 (s-ipso); *m/z* (FAB) 406 ([M]$^+$, 0.7%), 404 ([M]$^+$, 1.5%), 402 ([M]$^+$, 0.7%), 121 (100). (Found: [M]$^+$, 401.9816. $C_{16}H_{20}O_2Br_2$ requires, 401.9830; also Found [M-1]$^+$, 400.9750. $C_{16}H_{19}O_2Br_2$ requires, 400.9752.

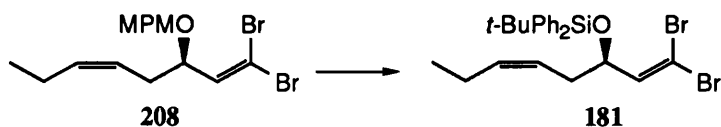*Preparation of (3R,5Z)-3-O-((p-methoxyphenylmethyl)oxy)-5-octene-1-yne* **205** *(and Side Product* **213***).*

To a solution of dibromide **208** (123mg, 0.30mmol) in tetrahydrofuran (1ml) at -78°C under an argon atmosphere was added *n*-BuLi (0.40ml, 0.61mmol, 1.5M in hexanes)

dropwise. The reaction was stirred at -78°C for 30 minutes and then allowed to warm to 0°C for 5 minutes. Then saturated aqueous NH_4Cl (1.5ml) and ethyl acetate (3ml) were added and the two layers separated. The aqueous layer was extracted with ethyl acetate (2 x 5ml) and the combined organic layers were dried over anhydrous magnesium sulphate. The solvent was evaporated and the residue purified by column chromatography on silica eluting with petroleum ether/ ethyl acetate (10:1). The reaction produced several products and we isolated the most abundant compounds, the desired product **205** (53mg, 71%) and the side product **213** (7.7mg, 10%). Data for **205**; Rf 0.6 (10:1, petroleum ether/ethyl acetate); $[\alpha]_D^{18}$ +87.3 (c 0.63 in $CHCl_3$); v_{max}(neat)/cm^{-1} 3292 m ($-C{\equiv}C\text{-}H$), 1613 m, 1514 s, 1464 m; δ_H (270MHz;$CDCl_3$) 0.95 (3H, t, J 7.5, CH$_3$), 2.06 (2H, pentet, J 7.5, -CH$_2$CH$_3$), 2.47 (1H, d, J 2.0, -C≡CH), 2.47-2.53 (2H, m), 3.79 (3H, s, OCH$_3$), 4.05 (1H, dt, J 2.0, 6.8, -CHO-), 4.45 (1H, d, J$_{AB}$ 11.5,-CHHAr), 4.53 (1H, d, J$_{AB}$, 11.5, -CHHAr), 5.37-5.58 (2H, m, 2 x cis-CH), 6.87 (2H, d, J 8.6, aryl), 7.28 (2H, d, J 8.6, aryl); δ_C (67.8MHz;$CDCl_3$) 14.1 (q), 20.7 (t), 33.5 (t), 55.2 (q, OCH$_3$), 67.9 (d, -C≡CH), 70.1 (t), 73.8 (s, -C≡CH), 82.7 (d), 113.7 (d, 2 x aryl), 123.2 (d, CH olefinic), 129.6 (d, 2 x aryl), 129.8 (s-ipso), 134.5 (d, CH olefinic), 159.2 (s-ipso); m/z (FAB) 267 ([M+Na]$^+$, 1.5%), 244 ([M]$^+$, 3%), 243 ([M]$^+$, 4%), 121 (100). (Found: [M-H]$^+$, 243.1387. $C_{16}H_{19}O_2$ requires, 243.1385. Data for 2,5-disubstituted-3,4-dihydrofuran derivative **213**; Rf 0.5 (15:1, petroleum ether/ethyl acetate); δ_H (270MHz;$CDCl_3$) 0.93 (3H, t, J 7.5, CH3), 2.03 (2H, pentet, J 7.5, -CH$_2$CH3), 2.30-2.52 (2H, m), 3.79 (3H, s, -OCH$_3$), 4.81-4.90 (1H, m, -CHO-), 5.35-5.55 (2H, m, 2 x cis-CH of chain), 5.69-5.72 (1H, m, -OCHAr), 5.83 (1H, ddd, J 2.2, 2.2, 6.1*, olefinic CH in ring), 5.93 (1H, ddd, J 1.3, 2.4, 6.1*, olefinic-CH in ring), 6.86 (2H, d, J 8.8, aryl), 7.24 (2H, d, J 8.8, aryl); m/z (EI) 244 ([M]$^+$, 3%), 175 ([M-C$_5$H$_9$]$^+$, 90%), 121 ([MeOC$_6$H$_4$CH$_2$]$^+$, 100%). * A typical cis coupling constant between the olefinic protons in a 5-membered cyclic alkene is J 5.1-7.0 Hz.[140]

Preparation of (3R,5Z)-3-O-((t-butyldiphenylsilyl)oxy)-1,1

-dibromo-1,5-octadiene 181.

To a solution of **208** (309mg, 0.77mmol) in dichloromethane (6ml) and water (0.3ml) was added DDQ (191mg, 0.84mmol) in one portion. The reaction was stirred at room temperature for 30 minutes and then the volume of solvent was reduced by evaporation under reduced pressure. The concentrated mixture was placed directly onto a column containing a plug of silica eluting with petroleum ether/ ethyl acetate (5:1). The desired hydroxyl intermediate (assumed quantitative yield, 7.65mmol) was isolated contaminated with 4-methoxybenzaldehyde. The crude hydroxyl intermediate was then reprotected; To the aforementioned material dissolved in DMF (4ml) was added imidazole (125mg, 1.84mmol) followed by *t*-butyldiphenylsilyl chloride (0.24ml, 0.92mmol) at room temperature under an argon atmosphere. After stirring at room temperature for 16 hours water (5ml) was added. The aqueous phase was extracted with diethyl ether (3 x 10ml) and the combined organic layers dried over anhydrous magnesium sulphate. The solvent was removed by evaporation under reduced pressure and the residue purified by column chromatography eluting with neat petroleum ether. The product **181** (368mg, 92%) was isolated as a colourless oil. Rf 0.7 (neat petroleum ether); (Found: C, 55.5; H, 5.86. $C_{24}H_{30}OBr_2Si$ requires C, 55.2; H, 5.75%); $[\alpha]_{365}^{18}$ +10.5 (c 0.73 in $CHCl_3$) v_{max} (neat)/ cm^{-1} 3014 w, 2961 s, 2931 s, 2893 m, 2857 s, 1620 w, 1590 w, 1472 m, 1462 m, 1427 s, 1390 w, 1362 w; δ_H (270MHz;CDCl3) 0.90 (3H, t, *J* 7.5, C*H*3), 1.06 (9H, s, ^tBu), 1.92 (2H, pentet, *J* 7.3, -C*H*2CH3), 2.18-2.40 (2H, m), 4.32-4.39 (1H, m, -C*H*O-), 5.29-5.43 (2H, m, 2 x*cis*-C*H*), 6.40 (1H, d, *J* 8.2, −C*H*=Br2), 7.35-7.43 (6H, m, aryl), 7.63-7.69 (4H, m, aryl); δ_C (67.8MHz;CDCl3) 14.1 (q), 19.2 (s), 20.6 (t), 26.9 (q, ^tBu), 34.5 (t), 73.9 (d), 89.0 (s), 122.7 (d), 127.6 (d, aryl), 129.7 (d, aryl), 133.5 (s-ipso), 133.6 (s-ipso), 134.7 (d), 135.9 (d, aryl), 141.0 (d); *m/z* (FAB) 521 ([M-1]$^+$, 1%), 465 ([M-^tBu]$^+$, 13%), 359 (10), 239 (16), 199 (73), 135 (100).
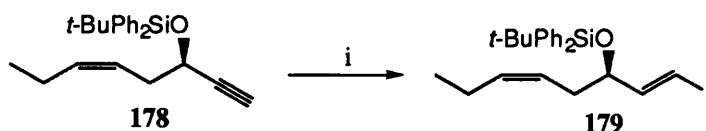
Preparation of (3R,5Z)-3-O-((t-butyldiphenylsilyl)oxy)-5-octene-1-yne 178.

To a solution of dibromide **181** (120mg, 0.23mmol) in tetrahydrofuran (1ml) at -78°C under an argon atmosphere was added LDA (0.35mmol) {prepared by adding *n*-BuLi (0.14ml, 0.35mmol, 2.5M solution in hexanes) to diisopropylamine (48µl, 0.35mmol) in tetrahydrofuran (2ml) at 0°C and then warming to room temperature after 15 minutes} *via* cannula. The reaction was stirred at -78°C for 30 minutes and then allowed to warm to 0°C for 20 minutes. After cooling to -78°C, *n*-BuLi (0.20ml, 0.51mmol) was added slowly and the mixture was allowed to warm to room temperature. The reaction was quenched with saturated aqueous NH_4Cl (2ml) and ethyl acetate (5ml) was added. The two layers were separated and the aqueous layer was extracted with ethyl acetate (2 x 5ml). The combined organic layers were dried over anhydrous magnesium sulphate and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography on silica eluting with neat petroleum ether. The product **178** (76mg, 92%) was isolated as a colourless oil. Rf 0.5 (petroleum ether/ethyl acetate); $[\alpha]_D^{20}$ +14.5 (*c* 1.47 in $CHCl_3$); v_{max}(neat)/cm^{-1} 3302 m (-C≡*C-H*), 2361 (-*C*≡*C*-H), 1651m, 1462 m; δ_H (270MHz;CDCl$_3$) 0.88 (3H, t, *J* 7.5, C*H*$_3$), 1.09 (9H, s, ^{t}Bu), 1.83-2.00 (2H, m, -C*H*$_2$CH$_3$), 2.34 (1H, d, *J* 2.0, -C≡C*H*), 2.39-2.43 (2H, m), 4.32 (1H, dt, *J* 2.0, 6.4, -C*H*O-), 5.38-5.50 (2H, m, 2 x*cis*-C*H*), 7.35-7.44 (6H, m, aryl), 7.69-7.78 (4H, m, aryl); δ_C (67.8MHz;CDCl$_3$) 14.2 (q), 19.3 (s), 20.7 (t), 26.9 (q, ^{t}Bu), 36.2 (t), 63.6 (d, -C≡*C*H), 72.6 (s, -*C*≡CH), 84.8 (d), 123.2 (d), 127.4 (d, *C*H aryl), 127.6 (d, *C*H aryl), 129.7 (d, *C*H aryl), 129.8 (d, *C*H aryl), 133.4 (s-ipso), 133.6 (s-ipso), 134.6 (d), 135.9 (d, *C*H aryl), 136.0 (d, *C*H aryl); *m/z* (FAB) 363 ([M+H]$^+$, 9%), 319 (15), 305 ([M-^{t}Bu]$^+$, 34%), 227 (29), 207 (31), 199 (100). (Found: [M+H]$^+$, 363.2155. $C_{24}H_{30}OSi$ requires, 363.2144).

We also prepared **178** from **181** using an alternative and less efficient procedure; To a solution of dibromide **181** (559mg, 1.07mmol) in tetrahydrofuran (6ml) at -78°C under an argon atmosphere was added *n*-BuLi (0.94ml, 2.36mmol, 2.5M in hexanes) dropwise. The reaction was stirred at -78°C for 15 minutes and then allowed to warm to 0°C for 15 minutes. Then water (5ml) and diethyl ether (10ml) were added and the

two layers separated. The aqueous layer was acidified using 2N HCl and extracted with diethyl ether (3 x 15ml) and the combined organic layers were dried over anhydrous magnesium sulphate. The solvent was evaporated under reduced pressure and the residue purified by column chromatography on silica eluting with neat petroleum ether. The product **178** (260mg, 67%) and a mixture of by-products (67mg) were isolated.

Preparation of (3R)-(1E,5Z)-3-O-((t-butyldiphenylsilyl)oxy)-1-iodo-1,5-octadiene 179

To **178** (322mg, 0.89mmol) in tetrahydrofuran (10ml) at room temperature under an argon atmosphere was added bis(cylopentadienyl)zirconium chloride hydride (312mg, 1.07mmol) rapidly. Once an homogeneous solution had formed we analysed the reaction by TLC and all the starting material (**178**) had been consumed. Therefore iodine (271mg, 1.07mmol) was added and the solution was stirred at room temperature for 45 minutes. Then an equal volume of saturated aqueous NH$_4$Cl and diethyl ether were added. The two layers were separated and the aqueous phase was extracted with diethyl ether (3 x 10ml). The combined organic extracts were dried over anhydrous magnesium sulphate followed by evaporation of the solvent under reduced pressure. The residue was then purified by column chromatography on silica eluting with neat petroleum ether. The product **179** (404mg, 92%) was a colourless oil which still contained *ca.* 9% starting material **178**. Rf (neat petroleum ether) 0.8; δ_H (270MHz;CDCl$_3$) 0.86 (3H, t, *J* 7.5, -CH$_2$C*H*$_3$), 1.06 (9H, s, ^{t}Bu), 1.83 (2H, pentet, *J* 7.3, -CH$_2$CH$_3$), 2.10-2.25 (2H, m), 4.06 (1H, q, *J* 6.6, -C*H*OSi-), 5.16-5.24 (1H, m, *cis*-C*H*), 5.31-5.42 (1H, m, *cis*-C*H*), 5.97 (1H, dd, *J* 1.0, 14.5, *trans*-β =C*H*I-), 6.48 (1H, dd, *J* 6.4, 14.5, *trans*-α -C*H*=), 7.34-7.46 (6H, m, aryl), 7.61-7.77 (4H, m, aryl). No further purification was attempted and this material was used directly without storage.

4.4. Experimental for Section 2.3;

Preparation of Methyl (2-oxoheptan-7-oate)Phosphonic Acid Diethyl Ester 237.

+

dimeric species **238**

+ methyl diethylphosphonate
+ unidentified by-products.

To diethyl methylphosphonate (192μl, 1.31mmol) in degassed tetrahydrofuran (1ml) at -78°C under and argon atmosphere was added *n*-BuLi (0.96ml, 1.44mmol, 1.5M in hexanes) dropwise. The mixture was stirred at -70°C for 15 minutes at which time a cloudy suspension had developed and finely ground copper(I) iodide (274mg, 1.44mmol) was then added. After stirring at -70°C for 15 minutes and warming to -35°C for 40 minutes the solution became a very dark green colour. Then at -40°C adipic acid chloride monomethyl ester (**236**) (234mg, 1.31mmol) dissolved in tetrahydrofuran (1ml) was added slowly *via* cannula. The reaction mixture was allowed to slowly warm to room temperature and stirred for 16 hours. Water (2ml) was added and the mixture was suction filtrated through a plug of celite washing with copious amounts of dichloromethane. The filtrate was dried over anhydrous magnesium sulphate and the solvent evaporated under reduced pressure. The residue was purified by column chromatography eluting with ethyl acetate/petroleum ether (10:3). The product **237** (146mg, 38%) was isolated as a colourless oil. Rf 0.2 (neat ethyl acetate); v_{max}(neat)/cm^{-1} 1735 vs (CO), 1720 vs (CO), 1438 m, 1369 m, 1253 s; δ_H (360MHz;CDCl$_3$) 1.34 (6H, t, *J* 7.0, 2xCH_3), 1.61-1.64 (4H, m, 2 x CH_2), 2.30-2.35 (2H, m, -CH_2-), 2.64-2.67 (2H, m, -CH_2-), 3.07 (2H, d, *J* 22.8, -P-CH_2-C(O)-), 3.67 (3H, s, OCH_3), 4.03-4.19 (4H, m, 2 x CH$_3$CH_2O-P); *m/z* (GC:EI) 294 ([M]$^+$, 3%), 245 (18), 221 (30), 207 (58), 194 (82), 179 (100), 151 (79), and 95% pure by G.C; *m/z* (FAB) 317 ([M+Na]$^+$, 32%), 295 ([M+H]$^+$, 100%),

245 (11), 217 (23), 189 (19); (Found: [M+H]$^+$, 295.1290. $C_{12}H_{24}O_6P$ requires, 295.1311).

We also isolated dimeric side product **238** (approx. 9%); δ_H (360MHz;CDCl$_3$) 1.30 (6H, t, J 7.1, 2 x CH_2CH$_3$), 1.51-1.80 (8H, m), 2.25-2.55 (8H, m), 3.67 (6H, s, 2 x OCH_3), 3.98-4.10 (4H, m), 5.30 (1H, m, -C(O)CHP(O)C(O)-); m/z (ESI) 437 ([M+H]$^+$, 100%), 311 (10), 295 (22).

Olefination Reaction Using β-Ketophoshonate 237.

To lithium(I) chloride (10.0mg, 0.24mmol) in acetonitrile (0.4ml) at room temperature under an argon atmosphere was added **237** (70mg, 0.24mmol) dissolved in acetonitrile (0.3ml), DBU (30mg, 0.20mmol) dissolved in acetonitrile (0.3ml), followed by crude aldehyde **199** (49mg, 0.20mmol, prepared from Swern oxidation of alcohol **196**) dissolved in acetonitrile (0.5ml). The mixture was stirred for 16 hours at room temperature and then water (3ml) and ethyl acetate (4ml) were added. The two layers were separated and the aqueous phase extracted with ethyl acetate (3 x 10ml). The combined organic layers were dried over anhydrous magnesium sulphate and the solvent evaporated under reduced pressure. The residue was purified by column chromatography eluting with petroleum ether/ethyl acetate (3:1), and the product **240** (37mg, 48%) was isolated as a colourless oil. Rf 0.4 (10:3, petroleum ether/ ethyl acetate); $[\alpha]_D^{19}$ +16.5 (c 0.85 in CHCl$_3$); ν_{max}(neat)/cm^{-1} 1736 vs (CO), 1697 m, 1676 m, 1630 w, 1613 m, 1514 s; δ_H (270MHz;CDCl$_3$) 0.93 (3H, t, J 7.5, -CH$_2$CH_3), 1.64-1.68 (4H, m, 2 x CH_2), 1.98-2.04 (2H, m, -CH_2CH$_3$), 2.34-2.39 (4H, m, 2 x -CH_2-), 2.55-2.60 (2H, m), 3.67 (3H, s, -OCH_3), 3.80 (3H, s, -CO$_2$CH_3), 3.94-4.00 (1H, m, -CHO-), 4.37 (1H, d, J_{AB} 11.5, -OCHHAr), 4.51

(1H, d, J_{AB} 11.5, -OCHHAr), 5.28-5.52 (2H, m, 2 xcis-CH), 6.23 (1H, dd, J 1.1 and 15.9, $trans$ CH), 6.69 (1H, dd, J 6.2, 15.9, $trans$-CH), 6.87 (2H, d, J_{AB} 8.8, aryl), 7.25 (2H, d, J_{AB} 8.8, aryl); δ_C (67.8MHz; CDCl$_3$) 14.0 (q), 20.7 (t), 23.4 (t), 24.5 (t), 32.7 (t), 33.8 (t), 39.8 (t), 51.4 (q), 55.2 (q), 70.8 (t), 77.9 (d), 113.8 (d, 2 x aryl), 123.1 (d, CH olefinic), 129.3 (d, 2 x aryl), 130.1 (d + s, CH olefinic + ipso), 134.5 (d, CH olefinic), 145.9 (d, CH olefinic), 159.3 (s, ipso), 173.8 (s, -C=O), 199.7 (s, -C=O); m/z (FAB) 411 ([M+Na]$^+$, 3%), 389 ([M+H]$^+$, 2%), 252 (4), 241 (9), 121 (100); (Found: [M+H]$^+$, 389.2321. C$_{23}$H$_{33}$O$_5$ requires, 389.2328).

*Enantioselective Addition of Oct-1yne to Heptanal Using (S)-diphenyl(1-methylpyrrolidine-2-yl)methanol **245** as Catalyst.*

To borane dimethylsulfoxide complex (100μl, 1.00mmol, 10M solution) in degassed hexane (1ml) was added cyclohexene (203μl, 2.00mmol) dropwise at 0°C with stirring at this temperature for 1 hour. Then oct-1-yne (147μl, 1.00mmol) was added at 0°C with stirring for 30 minutes followed by warming to room temperature for 30 minutes. At -78°C diethylzinc (1.0ml, 1.00mmol, 1.0M solution in hexane) was added slowly, followed by (S)-diphenyl(1-methylpyrrolidine-2-yl)methanol **245** (2.7mg, 0.01mmol) and the solution was warmed to -20°C for 10 minutes. Then at -20°C, heptaldehyde (139μl, 1.00mmol) in hexane (4ml) was added slowly. After 5 minutes the solution was warmed to 0°C and left at this temperature for 2 hours followed by stirring at room temperature overnight. Saturated aqueous NH$_4$Cl (4ml) and ethyl acetate (7ml) were added and the two layers separated. The aqueous layer was extracted with ethyl acetate (3 x 10ml) and the combined organic layers dried over anhydrous magnesium sulphate. The solvent was evaporated at reduced pressure and the residue purified by column chromatography eluting with petroleum ether/ethyl

acetate (5:1). The product **247** (179mg, 79%) was isolated as a colourless oil. Rf 0.6

(10:1, petroleum ether/ethyl acetate); $[\alpha]_D^{18}$ +4.3 (c 0.35 in CHCl$_3$); v$_{max}$(neat)/cm^{-1}

3348 br (OH), 2927 s, 2856 s, 1670 m, 1466 m, 1378 m; δ_H (270MHz;CDCl$_3$) 0.90

(6H, m, 2 x -CH$_2$CH_3), 1.25-1.45 (16H, m, 8 x -CH_2-), 1.45-1.60 (2H, m), 1.98-

2.06 (2H, m), 4.03 (1H, q, J 6.8, -CHOH-), 5.43 (1H, dd, J 7.2, 15.4, α-trans-

CH), 5.62 (1H, td, J 6.6, 15.4, β-trans-CH); m/z (CI) 225 ([M-1]$^+$, 30%), 209 ([M-

OH]$^+$, 100%), 141 (72)

Preparation of Racemic (2E)-1-O-((t-butyldiphenylsilyl)oxy)-oct-2-ene-1,4-diol **249**.

To alkyne **248** (64mg, 0.22mmol) in dichloromethane (1ml) at room temperature

under an argon atmosphere was added bis(cylopentadienyl)zirconium chloride hydride

(67mg, 0.23mmol). Once a homogeneous solution had formed the mixture was cooled

to -78°C and diethylzinc (0.20ml, 0.23mmol, 1.1M in toluene) was added over 5

minutes. After warming the solution to 0°C and stirring for 10 minutes, hexanal

(23mg, 0.23mmol) in dichloromethane (2.5ml) was added dropwise via syringe. The

mixture was stirred at 0°C for 1.5 hours and then saturated aqueous NH$_4$Cl (3ml) was

added. The two layers were separated and the aqueous layer was extracted with diethyl

ether (2 x 10ml) . The combined organic layers were washed with saturated aqueous

NaHCO$_3$ and dried over anhydrous magnesium sulphate. The solvent was evaporated

at reduced pressure and the residue was purified by column chromatography on silica

gel eluting with hexane/ethyl acetate (3:1). The product **249** (43mg, 51%) was

isolated as a colourless oil; Rf 0.5 (4:1, petroleum ether/ethyl acetate); v$_{max}$(neat)/

cm^{-1} 3381 br (OH), 1590 m, 1464 s, 1480 m, 1378 m, 1258 m; δ_H (400MHz;

CDCl$_3$); 0.82 (3H, t, J 6.7, -CH$_2$CH_3), 0.99 (9H, s, ^{t}Bu), 1.22-1.47 (8H, m), 1.35

(1H, d, J 4.0, -OH), 4.10-4.29 (1H, m, -CHOH-), 4.44-4.48 (2H, m,

-CH_2OSiPh$_2$^{t}Bu), 5.61-5.70 (2H, m, 2 xtrans-CH), 7.28-7.37 (6H, m, aryl), 7.59-

7.79 (4H, m, aryl); m/z 379 ([M-OH]⁺, 35%), 339 ([M-ᵗBu]⁺, 10%), 267 (6), 239

(19), 221 (20), 207 (16), 199 (100).

Preparation of (6R,4E)-6-O-((t-Butyldiphenylsilyl)-2-Methyl-4-Undecene-3,6-Diol

258 as a 2.1:1 Mixture of Diastereomers at C-3.

To a mixture of *trans*-iodo alkene **175** (450mg, 0.92mmol) and 2-methylpropanal

(28μl, 0.31mmol) in a mixture of dimethylsulfoxide and N,N-dimethylformamide

(5ml:3ml) at room temperature under an argon atmosphere was added chromium(II)

chloride (225mg, 1.83mmol) containing a catalytic amount of nickel(II) chloride

(0.5wt%, 1.0mg, 7.71 μmol) in one portion. The dark green solution was stirred at

room temperature for 1 hour and then quenched by adding saturated aqueous NH₄Cl

(5ml) and chloroform (6ml). The mixture was extracted with ethyl acetate (3 x 5ml)

and the combined organic layers were dried over anhydrous magnesium sulphate. The

solvent was evaporated at reduced pressure to give a crude residue which was purified

by column chromatography eluting with petroleum ether/ethyl acetate (10:1). The

product **258** (136mg, 100%) was isolated as a 2.1:1 mixture of diastereomers. Rf 0.3

(10:1, petroleum ether/ethyl acetate) ; vₘₐₓ(neat)/cm⁻¹ 3420 br (OH), 3069 m, 2931 s,

2860 s, 1651 w, 1464 m, 1428 w, 1367 w; major isomer, δH (270MHz; CDCl₃)

0.73-0.88 (9H, m, -CH₂CH₃ + -CHC(CH₃)₂), 1.06 (9H, s, ᵗBu), 1.08-1.30 (6H,

m), 1.38-1.64 (3H, m), 3.66-3.73 (1H, m, -CHOH-), 4.15-4.24 (1H, m,

-CHOSiPh₂ᵗBu), 5.37 (1H, ddd, J 1.5, 6.5, 15.2, trans-CH), 5.54 (1H, ddd, J 1.5,

6.8, 15.2, trans-CH), 7.30-7.44 (6H, m, aryl), 7.64-7.76 (4H, m, aryl). minor

isomer, δH (270MHz; CDCl₃) 0.73-0.88 (9H, m, -CH₂CH₃ + -CHC(CH₃)₂), 1.05

(9H, s, ᵗBu), 1.08-1.30 (6H, m), 1.38-1.64 (3H, m), 3.52-3.58 (1H, m, -CHOH-),

4.10-4.18 (1H, m, -CHOSiPh₂ᵗBu), 5.37 (1H, ddd, J 1.0, 7.5, 15.8, trans-CH),

5.54 (1H, ddd, J 1.0, 8.3, 15.8, trans-CH), 7.30-7.44 (6H, m, aryl), 7.64-7.76 (4H,

m, aryl); major isomer, m/z (GC:EI CF₃C[=NSi(CH₃)₃]OSiMe₃. CH₃CN) 495 ([M-

H+Si(Me3)3-CH3]$^+$, 1%), 467 ([M-H+Si(Me3)3-(CH3)2CH]$^+$, 11%), 453 (M-H+Si(Me3)3-^{t}Bu]$^+$, 31%), 439 (4), 381 (7), 271 (100), 211 (18), 199 (95), minor isomer, m/z (GC:EI CF3C[= NSi(CH3)3]OSiMe3. CH3CN) 467 ([M-H+Si(Me3)3-(CH3)2CH]$^+$, 12%), 453 (M-H+Si(Me3)3-^{t}Bu]$^+$, 35%), 439 (5), 381 (7), 271 (100), 211 (17), 199 (95), and 95% pure by gas chromatography; m/z (FAB) 437 ([M-H]$^+$, 1%), 421 ([M-OH]$^+$, 28%), 339 (6), 239 (10), 199 (56), 135 (100). (Found: [M-OH]$^+$, 421.2918. C28H41OSi requires, 421.2927).

Preparation of (6R,4E)-6-O-((p-Methoxyphenylmethyl)-2-Methyl-4-Undecene-3,6-Diol 259 as a 1:1 Mixture of Diastereomers at C-3.

To a mixture of *trans*-iodo alkene **176** (181mg, 0.45mmol) and 2-methylpropanal (24.3μl, 0.27mmol) in dimethylsulfoxide (2ml) at room temperature under an argon atmosphere was added chromium(II) chloride (110mg, 0.89mmol), containing a catalytic amount of nickel(II) chloride (0.5wt%, 0.5mg, 3.86 μmol) in one portion. The dark green solution was stirred at room temperature for 2 hours and quenched by adding saturated aqueous NH4Cl (3ml) and chloroform (5ml). The mixture was then extracted with ethyl acetate (3 x 5ml) and the combined organic layers were dried over anhydrous magnesium sulphate. The solvent evaporated at reduced pressure to give a crude residue which was purified by column chromatography eluting with petroleum ether/ethyl acetate (3:1). The product **259** (86.4mg, 100%) was isolated as a 1:1 mixture of diastereomers. Rf 0.4 (10:3, petroleum ether/ethyl acetate); (Found: C, 74.9; H, 10.1. C20H32O3 requires C, 75.0; H, 10.0 %); v_{max} (neat)/cm^{-1} 3443 br (OH), 3069 m, 2931 s, 2863 s, 1612 m, 1512 m, 1462 m, 1376 w, 1248 m; δ_H (270MHz; CDCl3) 0.83-0.97 (9H, m, -CH2CH3 + -CHC(CH3)2), 1.26-1.80 (9H, m), 3.73 (1H, q,J 6.0, -CHOH-), 3.80 (3H, s, -OCH3), 3.85-3.95 (1H, m, -CHOSiPh2^{t}Bu-), 4.27 (0.5H, d, J_{AB} 11.5, OCHHAr), 4.30 (0.5H, d, J_{AB} 11.5, OCHHAr), 4.51 (0.5H, d, J_{AB} 11.5, OCHHAr), 4.52 (0.5H, d, J_{AB} 11.5,

OCH*H*Ar), 5.54 (0.5H, dd, *J* 7.3, 15.8, *trans-CH*), 5.55 (0.5H, dd, *J* 7.3, 15.8, *trans-CH*), 5.65 (0.5H, dd, *J* 6.1, 15.6, *trans-CH*), 5.67 (0.5H, dd, *J* 6.1, 15.8, *trans-CH*), 6.87 (2H, d, *J* 8.8, aryl), 7.22-7.38 (2H, m, aryl); *m/z* (GC:EI, CF3C[=NSi(CH3)]OSiMe3. CH3CN) 349 ([M-H+Si(Me3)3-(CH3)2CH]+, 2%), 319 (M-H+Si(Me3)3-(CH3)2CH -2 x CH3]+, 1%), 259 (3), 241 (2), 137 (8), 121 (100) and *m/z* (FAB) 320 ([M]+, 0.2%), 303 ([M-OH]+, 0.4%), 289 (1), 242 (1.6), 137 (7), 121 (100).

*Preparation of 15-O-(t-butyldiphenylsilyl)-Halicholactone **260a** and 12-epi-15-O-(t-butyldipenylsilyl)-Halicholactone **260b** As A 2.1 Mixture of Isomers At C-12.*

To a mixture of *trans*-iodo alkene **175** (155mg, 0.32mmol) and 8*S*,9*R*,11*R*-aldehyde **156** (39.4mg, 0.19mmol) in dimethylsulfoxide (3ml) at room temperature under an argon atmosphere was added chromium(II) chloride (77.4mg, 0.63mmol) containing a catalytic amount of nickel(II) chloride (approx. 0.5wt%, 0.5mg, 3.87 μmol) in one portion. The dark green solution was stirred at room temperature for 3 hours and then quenched by adding saturated aqueous NH4Cl (3ml) and chloroform (5ml). The mixture was then extracted with ethyl acetate (3 x 5ml) and the combined organic layers were dried over anhydrous magnesium sulphate. After the solvent had been evaporated under reduced pressure the crude residue was purified by column chromatography on silica eluting with petroleum ether/ethyl acetate (7:1 to 5:1). By repeating the column chromatography process a total of three times the two

diastereomers were sufficiently separated such that the major isomer **260a** (47.0mg, 44%) was isolated approx. 95% pure as a colourless oil. The minor isomer **260b** was still contaminated with **260a** (32.0mg, 30%, **260b**:**260a** 4:1). Data for **260a**; Rf 0.3 (5:1, petroleum ether/ethyl acetate); $[\alpha]_D^{15}$ -43.7 (c 0.59 in CHCl$_3$); ν_{max}(neat)/cm^{-1} 3744 m, 3430 (OH), 2929 s, 2859 s, 1738 s (CO), 1720 s, 1650 m, 1496 m, 1455 m; δ_H (500MHz;CDCl$_3$) 0.48 (1H, ddd, J 5.0, 5.0, 8.5, cyclopropane C*H*), 0.58 (1H, ddd, J 5.0, 5.0, 8.5, cyclopropane C*H*), 0.84 (3H, t, J 8.0, C*H*$_3$CH$_2$-), 0.88-0.98 (2H, m, 2 x cyclopropane C*H*), 1.05 (9H, s, ^{t}Bu), 1.12-1.32 (6H, m, 3 x C*H*$_2$ of alkyl chain), 1.40-1.55 (2H, m, C*H*$_2$ of alkyl chain), 1.72-1.80 (1H, m, -C*H*H- of lactone), 2.00-2.12 (3H, m, 3 x C*H* of lactone), 2.16-2.28 (2H, m, 2 x C*H* of lactone), 2.38-2.52 (2H, m, 2 x C*H* of lactone), 3.53-3.58 (1H, m, -C(12)*H*OH-), 4.15-4.25 (2H, m, -C(8)*H*OC(O)- and -C(15)*H*OH-), 5.39 (1H, dd, J 5.0, 15.6, *trans*-C*H*), 5.43-5.48 (2H, m, lactone olefinics), 5.64 (1H, dd, J 7.5, 15.6, *trans*-C*H*), 7.32-7.42 (6H, m, aryl), 7.65-7.69 (4H, m, aryl); δ_C (125.8MHz;CDCl$_3$) 7.7, 14.0, 19.1, 19.3 (s, ^{t}Bu), 22.5, 22.6, 24.3, 25.3, 26.5, 27.0 (q, ^{t}Bu), 31.7, 33.6, 33.9, 37.9, 73.4, 73.8, 76.0, 124.8, 127.4, 127.5, 129.5, 129.6, 131.1, 134.0, 134.4, 134.6, 134.7, 135.9, 136.0, 174.0 (s, C$_1$); m/z (FAB) 597 ([M+Na]$^+$, 12%), 557 ([M-OH]$^+$, 14%), 301 ([M-OH-^{t}BuPh$_2$SiOH]$^+$, 199 (100); (Found: [M-OH]$^+$ 557.3425. C$_{36}$H$_{49}$O$_3$Si requires, 557.3451). Data for **260b**; Rf 0.4 (5:1, petroleum ether/ethyl acetate); δ_H (270MHz;CDCl$_3$) 0.43-0.48 (2H, m, 2 x cyclopropane C*H*), 0.84 (3H, t, J 6.6, C*H*$_3$CH$_2$-), 0.84-0.95 (1H, m, cyclopropane C*H*), 0.97-1.06 (1H, m, cyclopropane C*H*), 1.05 (9H, s, ^{t}Bu), 1.12-1.60 (8H, m, 4 x C*H*$_2$ of alkyl chain), 1.72-2.60 (8H, m, 4 x C*H*$_2$of lactone), 3.36-3.42 (1H, m, -C(12)*H*OH-), 4.05-4.15 (2H, m, -C(8)*H*OC(O)- and -C(15)*H*OH-), 5.39 (1H, dd, J 6.2, 15.6, *trans*-C*H*), 5.43-5.48 (2H, m, 2 *cis*-C*H*), 5.51 (1H, dd, J 7.0, 15.6, *trans*-C*H*), 7.32-7.43 (6H, m, aryl), 7.64-7.69 (4H, m, aryl).

Preparation of Halicholactone 2.

To a solution of **260a** (34.0mg, 59.4μmol) in tetrahydrofuran (2ml) was added

tetrabutylammonium fluoride (150μl, 0.15mmol, 1.0M in tetrahydrofuran) and the

solution was then heated at reflux for 3 hours. The volume of solvent was then

reduced and the solution directly chromatographed on silica eluting with ethyl

acetate/petroleum ether (10:3). The product **2** (19.6mg, 99%) was isolated as a

colourless oil. Rf 0.4 (10:3, ethyl acetate/petroleum ether); $[\alpha]_D^{15}$ -91.7 (c 0.29 in

CHCl$_3$); v$_{max}$(neat)/cm^{-1} 3408 br (OH), 2930 s, 2858 m, 1738 s (CO), 1716 s, 1652

m, 1448 m, 1354 m, 1332 w, 1263 m, 1224 m, 1208 m, 1137 s; δH (400MHz;C$_6$D$_6$)

0.34 (1H, ddd, J 5.2, 5.2, 8.9, cyclopropane CH), 0.53 (1H, ddd, J 5.0, 5.0, 8.9,

cyclopropane CH), 0.93 (3H, t, J 7.0, CH_3CH$_2$-), 0.89-0.96 (1H, m, cyclopropane

CH), 1.08-1.15 (1H, m, cyclopropane CH), 1.30-1.69 (12H, m, 4 x CH_2 of alkyl

chain, CH_2 of lactone, 2 x OH), 1.76-1.84 (1H, m, -CHH- of lactone), 1.94 (1H,

ddd, J 1.2, 6.1, 12.2, -CH- of lactone), 2.12-2.19 (2H, m, 2 x CH of lactone), 2.36-

2.48 (2H, m, 2 x CH of lactone), 3.60 (1H, dd, J 3.5, 7.0, -C(12)HOH-), 3.98-4.04

(1H, m, -C(15)HOH-), 4.35-4.40 (1H, ddd, J 1.2, 8.0, 12.0, -C(8)HOC(O)-), 5.38-

5.48 (2H, m, lactone olefinics), 5.71-5.81 (2H, m, 2 x$trans$-CH); also

(500MHz;CDCl$_3$); 0.60 (1H, ddd, J 5.1, 5.1, 8.5, cyclopropane CH), 0.71 (1H, ddd,

J 5.2, 5.2, 8.8, cyclopropane CH), 0.89 (3H, t, J 6.9, CH_3CH$_2$-), 1.00-1.06 (1H,

m, cyclopropane CH), 1.08-1.13 (1H, m, cyclopropane CH), 1.30-1.45 (6H, m, 3 x

CH_2 of alkyl chain), 1.47-1.65 (4H, m, CH_2 of alkyl chain + 2 x OH), 1.94 (1H,

dddd, J 5.9, 12.5, 12.5, 12.5, -CH- of lactone), 2.03-2.10 (2H, m, 2 x CH of

lactone), 2.13-2.16 (1H, m, -CHH- of lactone), 2.22-2.32 (2H, m, 2 x CH of

lactone), 2.43-2.52 (2H, m, 2 x -CHH- of lactone), 3.70 (1H, dd, J 4.2, 7.4,

-C(12)HOH-), 4.11 (1H, q, J 6.2, -C(15)HOH-), 4.22 (1H, ddd, J 1.5, 8.3, 10.6,

-C(8)HOC(O)-), 5.45-5.50 (2H, m, 2 xcis-CH), 5.72-5.80 (2H, m, 2 x$trans$-CH); δ_C (125.8MHz;CDCl$_3$) 8.2, 14.0, 19.5, 22.6, 23.4, 25.0, 25.3, 26.5, 31.7, 33.6, 33.8, 37.2, 72.2, 74.1, 76.1, 124.7, 131.7, 134.0, 134.6, 174.0; m/z (FAB) 359 ([M+Na]$^+$, 33%), 337 ([M+H]$^+$, 3%) 319 ([M-OH]$^+$, 100%), 301 ([M-(OH+H$_2$O)]$^+$, 15%), 149 (28); (Found: [M-OH]$^+$ 319.2276. $C_{20}H_{31}O_3$ requires, 319.2273). Our data was consistent with that reported.[1(a)]

Alternative Approach to The Preparation of 15-O-(t-butyldiphenylsilyl)-halicholactone-260a and its C$_{12}$ isomer 260b. The Vinyl Lithium Derivative of 175 was Added to Aldehyde 156.

To *trans*-iodo alkene 175 (90.2mg, 183μmol) in tetrahydrofuran (2ml) at -78°C under an argon atmosphere was added t-BuLi (204μl, 326μmol, 1.6M in pentanes) dropwise. The solution was stirred at -78°C for 30 minutes and then aldehyde 156 (31.8mg, 153μmol) in tetrahydrofuran (3ml) was added *via* cannula over a 10 minute period. After stirring at -78°C for 30 minutes the solution was warmed to 0°C for 5 minutes. Saturated aqueous ammonium chloride (3ml) and ethyl acetate (5ml) were then added and the two layers separated. The aqueous layer was extracted with ethyl acetate (3 x 5ml) and the combined organic layers were dried over magnesium sulphate. The solvent was evaporated at reduced pressure and the residue purified by column chromatography eluting with petroleum ether/ethyl acetate (5:1). The two isomers 260a and 260b were separated from each other but not from unreacted aldehyde 156. The major isomer 260a and 156 (23.3mg in total; 18.2mg 260a and 5.1mg 156) were isolated together, whilst the minor isomer 260b and 156 (16.4mg

in total; 5.7mg **260b** and 10.7mg **156**) were also isolated together. In addition alkene **261** (38.0mg, 57%) was recovered. Therefore the addition was diastereoselective, providing a 3:1 ratio of **260a:260b** (23.9mg, 28%) which were contaminated with **156** (15.8mg, 50%). Data for **260a, 260b** and **156** has already been given. Data for alkene **261**; Rf 0.9 (10:1, petroleum ether/ethyl acetate); δH (270MHz;CDCl3) 0.82 (3H, t, C*H*3CH2-), 1.07 (9H, s, ᵗBu), 1.07-1.30 (6H, m, 3 x C*H*2), 1.36-1.55 (2H, m, -C*H*2-), 4.13 (1H, q, *J* 6.4, -C*H*OSiPh2ᵗBu-), 4.93-5.02 (2H, m, 2 x terminal olefinic C*H*), 5.79 (1H, ddd, *J* 6.4, 10.4, 17.0, olefinic C*H*), 7.31-7.44 (6H, m, aryl), 7.64-7.07 (4H, m, aryl).

Oxidation of Allylic Alcohols 260a and 260b in the Presence of Aldehyde 156. The Recovery of Precious 156.

To a mixture of **260a, 260b** and **156** (**260a** + **260b**; 23.9mg, 41.6μmol and **156**; 15.8mg, 75.9μmol) in dichloromethane (2ml) containing powdered 4Å molecular sieves at room temperature was added solid pyridinium chlorochromate (28mg, 128μmol) in one portion. The dark green solution was stirred at room temperature for 30 minutes and then the volume of solvent reduced before the mixture was placed directly on a silica column, eluting with petroleum ether/ethyl acetate (5:1). The product **262** (12.8mg, 54%) and aldehyde **156** (13.7mg, 87%) were isolated separately. Data for **262**; Rf 0.8 (5:1, petroleum ether/ethyl acetate); δH (270MHz;CDCl3) 0.81 (3H, t, *J* 6.8, C*H*3CH2-), 0.93 (1H, ddd, *J* 4.2, 6.4, 8.4,

cyclopropane -CHH-), 1.08 (9H, s, ^{t}Bu), 1.10-1.34 (7H, m), 1.42-1.51 (3H, m), 1.71-1.86 (2H, m), 2.06-2.34 (5H, m), 2.47-2.50 (2H, m), 4.27 (1H, ddd, J 1.3, 8.0, 10.7, -CHO-CO-), 4. 35 (1H, q, J 5.3, -CHOSiPh$_2$^{t}Bu), 5.46-5.50 (2H, m, lactone olefinics), 6.16 (1H, dd, J 1.3, 15.9, *trans* CH), 6.73 (1H, dd, J 5.5, 15.8, *trans* CH), 7.30-7.46 (6H, m, aryl), 7.56-7.68 (4H, m, aryl).

Desilylation of Enone 262.

To a solution of **262** (12.8mg, 22.4μmol) in tetrahydrofuran (0.5ml) was added tetrabutylammonium fluoride (69μml, 69mmol, 1.0M solution in tetrahydrofuran) at room temperature. After 1 hour the solution was concentrated and then placed directly onto a silica column eluting with petroleum ether/ethyl acetate (3:1). The product **263** (6.2mg, 81%) was isolated as a colourless oil. Rf 0.4 (3:1, petroleum ether/ethyl acetate) ; δ$_H$ (270MHz;CDCl$_3$) 0.81 (3H, t, J 6.8, CH_3CH$_2$-), 0.93 (1H, ddd, J 4.2, 6.3, 8.3, cyclopropane -CHH-), 1.15-1.80 (12H, m), 1.97-2.30 (6H, m, 5 x CH of lactone + OH), 2.37-2.50 (2H, m), 4.20 (1H, ddd, J 1.3, 7.7, 10.7, -CHO-CO-), 4.22-4.35 (1H, m, -CHOSiPh$_2$^{t}Bu), 5.38-5.42 (2H, m, lactone olefinics), 6.36 (1H, dd, J 1.5, 15.8, *trans* CH), 6.79 (1H, dd, J 5.0, 15.8, *trans* CH).

Leuche Reduction of Enone 263.

263   1:1 mixture 264 : 2

To enone **263** (6.2mg, 18.6μmol) and cerium(III) chloride heptahydrate (7.0mg, 18.6μmol) in methanol (1ml) at room temperature was added NaBH$_4$ (0.7mg, 18.6μmol) in one portion. After 5 minutes saturated aqueous ammonium chloride (1ml) was added and the solution was acidified with 2N HCl. The aqueous layer was extracted with diethyl ether (3 x 2ml) and the combined organic layers were dried over

anhydrous magnesium sulphate. The solvent was evaporated at reduced pressure and the residue purified by column chromatography on silica eluting with ethyl acetate/petroleum ether (10:3). Compounds **264** and **2** (2.5mg, 40%) were isolated together as a 1:1 diastereomeric mixture. (We also observed some unreacted starting material by thin layer chromography which accounts for the low yield in this reaction). The two products (**2** and **264**) had identical Rf values. By subtracting the signals we had observed in the pure spectrum of **2** from the spectrum we now had for the 1:1 mixture of **2** and **264**, then the unique and distinguishing signals belonging to **264** could be determined and were as follows; δ_H(400MHz;C_6D_6) 0.30 (1H, m, cyclopropane C(10)H*H*), 0.40 (1H, ddd, *J* 4.7, 4.7, 8.6, cyclopropane C(10)*H*H) and 3.47 (1H, dd, *J* 2.0, 7.0, -C(12)*H*OH-). The corresponding values for **2** in the mixed spectrum were; 0.31 (1H, ddd, *J* 5.2, 5.2, 8.9, cyclopropane C*H*), 0.49 (1H, ddd, *J* 5.0, 5.0, 8.9, cyclopropane C*H*) and 3.57 (1H, dd, *J* 3.5, 7.0, -C(12)*H*OH-). The latter values are in better agreement with the published data for *Halichondria okadai* derived halicholactone; 0.29 (1H, ddd, *J* 5.0, 5.0, 8.0, cyclopropane C*H*), 0.47 (1H, ddd, *J* 5.0, 5.0, 8.0, cyclopropane C*H*) and 3.53 (1H, dd, *J* 4.0, 7.0, -C(12)*H*OH-).

Preparation of 15-O-(t-butyldiphenylsilyl)-Neohalicholactone 252a and C$_{12}$-epi-15-O-(t-butyldipenylsilyl)-Neohalicholactone 252b As A 2.1 Mixture of Isomers At C-12.

To a mixture of *trans*-iodo alkene **179** (274mg, 0.56mmol) and 8*S*,9*R*,11*R*-aldehyde **156** (58.0mg, 279μmol) in dimethylsulfoxide (2.5ml) and N,N-dimethylformamide (2.5ml) at room temperature under an argon atmosphere was added chromium(II) chloride (205mg, 1.67mmol) containing a catalytic amount of nickel(II) chloride (approx. 0.5wt%, 1.0mg, 7.74 μmol) in one portion. The dark green solution was

stirred at room temperature for 3 hours and then quenched by adding saturated aqueous

NH_4Cl (5ml) and chloroform (8ml). The mixture was extracted with ethyl acetate (3 x

10ml) and the combined organic layers were dried over anhydrous magnesium

sulphate. After the solvent had been evaporated under reduced pressure the crude

residue was purified on silica eluting with petroleum ether/ethyl acetate (5:1). The

products **252a** and **252b** (97mg, 61%) were isolated together as a 2:1 mixture. Then

75mg (of the total 97mg) of the product mixture was rechromatographed eluting with

petroleum ether/ ethyl acetate (5:1) in an effort to separate the two diastereomers. The

two diastereomers were sufficiently separated such that the major isomer **252a**

(44.3mg) was isolated pure as a colourless oil. The minor isomer **252b** (30.0mg) was

still contaminated with **252a**. Data for **252a**; Rf 0.5 (5:1, petroleum ether/ethyl

acetate); $[\alpha]_D^{15}$ -44.6 (c 0.50 in $CHCl_3$); ν_{max}(neat)/cm^{-1} 3650 m, 3430 br (OH),

2925 s, 2845 s, 1736 s (CO), 1650 m, 1558 w, 1453 m, 1356 m, 1262 m, 1213 m;

δ_H (500MHz;$CDCl_3$) 0.51 (1H, ddd, J 5.1, 5.1, 8.5, cyclopropane CH), 0.59 (1H,

ddd, J 5.2, 5.2, 8.7, cyclopropane CH), 0.84 (3H, t, J 7.0, CH_3CH$_2$-), 0.90-0.98

(2H, m, 2 x cyclopropane CH), 1.05 (9H, s, ^{t}Bu), 1.76 (1H, dddd, J 6.4, 12.1,

12.1, 12.1, -CHH- of lactone), 1.87 (2H, pentet, J 7.2, CH_2 of alkyl chain), 2.01-

2.12 (3H, m, 3 x -CHH- of lactone), 2.18-2.32 (4H, m), 2.39-2.48 (2H, m, 2 x

-CHH- of lactone), 3.54-3.59 (1H, m, -C(12)HOH-), 4.19-4.24 (2H, m,

-C(8)HOC(O)- and -C(15)HOH-), 5.26-5.30 (1H, m, cis-CH), 5.36-5.41 (1H, m,

cis-CH), 5.44-5.48 (3H, m, lactone olefinics+$trans$-CH), 5.68 (1H, ddd, J 1.3, 6.4,

15.6,$trans$-CH), 7.32-7.42 (6H, m, aryl), 7.65-7.69 (4H, m, aryl); δ_C

(125.8MHz;$CDCl_3$) 7.8, 14.2, 19.1, 19.3 (s, ^{t}Bu), 20.6, 22.6, 25.3, 26.5, 27.0 (q,

^{t}Bu), 33.6, 33.9, 35.9, 73.5 (x2), 76.0, 124.1, 124.8, 127.4, 127.5, 129.5, 129.6,

131.2, 133.5, 133.6, 134.2, 134.4, 134.6, 135.9, 136.0, 174.0 (s, C$_1$); m/z (FAB)

595 ([M+Na]$^+$, 40%), 555 ([M-OH]$^+$, 27%), 457 (5), 239 (10), 199 (100); (Found:

[M-OH]$^+$ 555.3262. $C_{36}H_{47}O_3Si$ requires, 555.3294). Data for **252b**; Rf 0.55

(5:1, petroleum ether/ ethyl acetate); The ^{1}H-NMR spectrum of **252a**:**252b** (2:1)

revealed that only two signals from **252b** were not coincident with the corresponding

signals for **252a**; δ_H (270MHz;$CDCl_3$) 3.39-3.43 (1H, m, -C(12)HOH-) and 5.58

(1H, ddd, *J* 0.9, 6.7, 15.8, *trans*-C*H*) for **252b**, *versus* 3.52-3.60 (1H, m,

-C(12)*H*OH) and 5.67 (1H, ddd, *J* 1.3, 6.7, 15.2, *trans*-C*H*) for **252a**. A pure ^{1}H-

NMR spectrum of **252b** was not obtained at this time.

Preparation of Neohalicholactone 1.

To a solution of pure **252a** (34.0mg, 61.4μmol) in tetrahydrofuran (2ml) was added

tetrabutylammonium fluoride (123μl, 123μmol, 1.0M in tetrahydrofuran) and the

solution was then heated at reflux for 3.5 hours. After this time a small amount of

starting material **252a** was still visible by TLC. However the reaction was worked-up

since we did not wish to decompose any product **1**. The volume of solvent was

reduced and the solution was directly chromatographed on silica eluting with ethyl

acetate/petroleum ether (10:3). The product **1** (15.2mg, 74%) was isolated as a

colourless oil, which later solidified on leaving at 0°C for several hours. A small

amount of the product was recrystallised from an ethyl acetate/hexane mixture (1:5)

over 3 days; Rf 0.4 (10:3, ethyl acetate/petroleum ether); $[\alpha]_D^{18}$ -54.6 (*c* 0.76 in

CHCl3); M.pt. 72°C (literature value[1(a)] 69-70°C); By performing a ^{1}H-^{1}H-COSY

experiment the assignment of all proton signals was possible, δH (500MHz;C6D6)

0.31 (1H, ddd, *J* 5.0, 5.0, 8.6, cyclopropane C(10)*H*), 0.50 (1H, ddd, *J* 5.1, 5.1,

8.7, cyclopropane C(10)*H*), 0.89-0.92 (1H, m, cyclopropane C(11)*H*), 0.94 (3H, t, *J*

7.5, C(20)*H*3CH2-), 1.02 (1H, d, *J* 4.4, -C(12)O*H*), 1.06-1.09 (1H, m,

cyclopropane C(11)*H*), 1.22 (1H, d, *J* 4.2, C(15)O*H*), 1.55-1.64 (2H, m, C(3)*H*2),

1.76-1.84 (1H, m, -C(4)*H*H-), 1.95 (1H, ddd, *J* 1.5, 7.2, 13.3, -C(7)H*H*- of

lactone), 2.02 (2H, dpentet, *J* 1.3, 7.4, -C(19)*H*2-), 2.11-2.15 (2H, m, -C(2)C*H*2-),

2.18-2.29 (2H, m, -C(16)*H*2-), 2.37-2.43 (2H, m, -C(4)H*H*- + -C(7)*H*H-), 3.55-

3.59 (1H, m, -C(12)*H*OH-), 3.99-4.04 (1H, m, -C(15)*H*OH-), 4.38 (1H, ddd, *J* 1.5,

8.3 and 11.0, -C(8)*H*OC(O)-), 5.41-5.48 (3H, m, lactone olefinics (C5 +C6) and *cis*-C(17)*H*), 5.52-5.55 (1H, m, *cis*-C(18)*H*), 5.71-5.79 (2H, m, 2 x*trans*-C(13 + 14)*H*); also (500MHz;CDCl₃); 0.60 (1H, ddd, *J* 5.1, 5.1, 8.4, cyclopropane C*H*), 0.71 (1H, ddd, *J* 5.2, 5.2, 8.8, cyclopropane C*H*), 0.97 (3H, t, *J* 7.5, C*H*₃CH₂-), 1.00-1.11 (2H, m, 2 x cyclopropane C*H*), 1.60-1.70 (2H, bs, 2 x O*H*), 1.94 (1H, dddd, *J* 6.4, 11.9, 11.9, 11.9, -C*H*- of lactone), 2.03-2.10 (4H, m), 2.13-2.17 (1H, m, -C*H*H- of lactone), 2.24-2.33 (4H, m), 2.45-2.52 (2H, m), 3.70 (1H, dd, *J* 3.8, 7.4, -C(12)*H*OH-), 4.16-4.19 (1H, m, -C(15)*H*OH-), 4.23 (1H, ddd, *J* 1.4, 8.3, 10.6, -C(8)*H*OC(O)-), 5.34-5.36 (1H, m, *cis*-C*H*), 5.45-5.50 (2H, m, 2 x*cis*-C*H*), 5.56-5.59 (1H, m, *cis*-C*H*), 5.75-5.80 (2H, m, 2 x*trans*-C*H*); By performing a ^{1}H-^{13}C-COSY experiment most of the carbon signals were assigned, δ_C (125.8MHz;CDCl₃) 8.2 (C10), 14.2 (C20), 19.5 (C9), 20.7 (C19), 23.4 (C11), 25.3 (C4), 26.4 (C3), 33.6 (C2), 33.8 (C7), 35.2 (C16), 71.5 (C15), 74.2 (C12), 76.1 (C8), 123.7 (C17), 124.7 (C6), 131.8 (C14 or 13), 133.2 (C13 or 14), 134.7 (C18 or C5), 135.3 (C5 or C18), 174.1 (C1); *m/z* (FAB) 357 ([M+Na]⁺, 40%), 317 ([M-OH]⁺, 100%), 299 ([M-(OH+H₂O)]⁺, 13%), 149 (41), 119 (52), 105 (63); (Found: [M-OH]⁺ 317.2096. C₂₀H₂₉O₃ requires, 317.2117). Our data was consistent with that reported.[1(a)]

Preparation of Neohalicolactone 1 and C₁₂-epi-Neohalichilactone 265 from the 2:1 Mixture of 252a and 252b.

To a solution of **252a** and **252b** (2:1 mixture, 21.9mg, 39.5μmol) in tetrahydrofuran (2ml) was added tetrabutylammonium fluoride (120μl, 120μmol, 1.0M in tetrahydrofuran) and the solution was then heated at reflux for 2 hours. The volume of solvent was then reduced and the solution directly chromatographed on silica eluting with petroleum ether/ ethyl acetate (10:3). The products **1** and **265** (11.9mg, 90%) were isolated together in the 2:1 ratio. Rf 0.4 (10:3, ethyl acetate/petroleum ether). By subtracting the signals we had observed in the pure spectrum of **1**, from the spectrum we then acquired from the 2:1 mixture of **1** and **265**, then the unique and distinguishing signals belonging to **265** were as follows; δ_H(400MHz;C₆D₆) 0.31

(1H, m, cyclopropane C(10)H*H*), 0.42 (1H, ddd, *J* 4.9, 4.9, 8.6, cyclopropane C(10)*H*H) and 3.50 (1H, dd, *J* 4.9, 7.0, -C(12)*H*OH-). The corresponding values for 1 in the mixed spectrum were; 0.31 (1H, ddd, *J* 5.2, 5.2, 8.6, cyclopropane C*H*), 0.51 (1H, ddd, *J* 5.2, 5.2, 8.9, cyclopropane C*H*) and 3.57 (1H, dd, *J* 3.5, 7.0, -C(12)*H*OH-). The latter values are in better agreement with the published data for *Halichondria okadai* derived neohalicholactone; 0.27 (1H, ddd, *J* 5.0, 5.0, 8.5, cyclopropane C*H*), 0.45 (1H, ddd, *J* 5.0, 5.0, 8.5, cyclopropane C*H*) and 3.52 (1H, m, -C(12)*H*OH-).

Oxidation of Undesired Isomer 252b to Enone 266.

To the C$_{12}$-isomer **252b** (30.0mg, 52.4μmol, containing a small amount of **252a**) and 4-methyl morpholine N-oxide (9.5mg, 81.2μmol) in dichloromethane (1ml) containing powdered 4Å molecular sieves was added tetrapropylammonium perruthenate (1.0mg, 2.7μmol) at room temperature. After 30 minutes the mixture was added directly to the top of a silica column eluting with petroleum ether/ethyl acetate (5:1). The product **266** (27.3mg, 91%) was isolated as a colourless oil. Rf (5:1, petroleum ether 60:80/ ethyl acetate) 0.8; δ$_H$ (270MHz;CDCl$_3$) 0.83 (3H, t, *J* 7.3, C*H*$_3$CH$_2$-), 0.84-0.96 (2H, m), 1.09 (9H, s, ^{t}Bu), 1.25-1.33 (2H, m), 1.62-2.38 (10H, m), 2.40-2.60 (2H, m), 4.26 (1H, ddd, *J* 1.3, 8.0, 11.3, -C*H*O-CO-), 4. 32-4.42 (1H, m, C*H*OSiPh$_2$^{t}Bu), 5.16-5.32 (1H, m, *cis*-C*H*), 5.35-5.50 (3H, m, lactone olefinics + 1 x *cis* C*H*), 6.20 (1H, dd, *J* 1.3,15.9, *trans* C*H*), 6.75 (1H, dd, *J* 5.3, 15.9, *trans* C*H*), 7.31-7.47 (6H, m, aryl), 7.60-7.70 (4H, m, aryl).

Leuche Reduction of Enone 266.

To enone **266** (27.3mg, 47.9μmol) and cerium(III) chloride heptahydrate (17.8mg, 47.9μmol) in methanol (2ml) at room temperature was added NaBH₄ (1.8mg, 47.9μmol) in one portion. After 5 minutes saturated aqueous ammonium chloride (2ml) was added and the solution was acidified with 2N HCl. The aqueous layer was extracted with ethyl acetate (3 x 5ml) and the combined organic layers were dried over anhydrous magnesium sulphate. The solvent was evaporated under reduced pressure and the residue purified by column chromatography on silica eluting with petroleum ether/ethyl acetate (10:3). Compounds **252a** and **252b** (15.7mg, 58%) were isolated together as a 1:3 diastereomeric mixture, where the major isomer (**252b**) possessed the undesired 8*S*,9*R*,11*R*,12*S*,15*R* relative stereochemistry. We also recovered some unreacted starting material **266** (3.3mg, 12%). Data for **252b**; δH (270MHz;CDCl₃) 0.44-0.49 (2H, m, 2 x cyclopropane C*H*), 0.88 (3H, t, *J* 7.5, C*H*₃CH₂-), 0.96-1.06 (2H, m, 2 x cyclopropane C*H*), 1.06 (9H, s, ᵗBu), 1.77-1.90 (3H, m), 2.00-2.28 (7H, m), 2.40-2.48 (2H, m), 3.41 (1H, t, *J* 6.6, -C(12)*H*OH), 4.10-4.23 (2H, m), 5.22-5.45 (5H, m), 5.58 (1H, ddd, *J* 0.9, 6.7, 15.8, *trans*-C*H*), 7.34-7.48 (6H, m, aryl), 7.64-7.70 (4H, m, aryl); *m/z* (FAB) 595 ([M+Na]⁺, 7%), 555 ([M-OH]+, 30%), 457 (6), 299 (5), 253 (5), 239 (11), 199 (100); (Found: [M-OH]⁺ 555.3282. C₃₆H₄₇O₃Si requires, 555.3294). The non-superimpossible signals belonging to **252a** were; δH (270MHz;CDCl₃) 0.51-0.59 (2H, m, 2 x cyclopropane C*H*), 3.54-3.59 (1H, m, -C(12)*H*OH-) and 5.64 (1H, ddd, *J* 1.3, 6.4, 15.6, *trans*-C*H*).

4.5. Experimental For Section 2.4.

Reactions Towards Proving That No Inversion of Stereochemistry Occured In The

Acid Promoted Cyclisation of Methyl (3S)-3,4-Dihydroxybutanoate 113 (to Give

(3S)-Hydroxy-γ-butyrolactone 114).

Step 1: Tetrahydropyran Protection of 114.

To hydroxy-lactone **114** (0.5g, 4.90mmol, prepared by acid promoted cyclisation of

(3*S*)-**113** as described in "Experimental For Section 2.1") in a mixture of

tetrahydrofuran (5ml) and diethyl ether (20ml) was added dihydropyran (0.63ml,

6.86mmol) followed by *p*-toluenesulfonic acid monohydrate (93.2mg, 0.49mmol) at

room temperature. After stirring the mixture at room temperature for 20 hours the

reaction was quenched by adding saturated aqueous sodium hydrogen carbonate

(10ml). The two layers were separated and the aqueous phase was extracted with

diethyl ether (3 x 15ml). The combined organic layers were dried over anhydrous

magnesium sulphate and the solvent was evaporated at reduced pressure. The residue

was purified by column chromatography eluting with petroleum ether/ethyl acetate

(2:1). The product **114a** (838mg, 92%) was isolated as a colourless oil and a 1:1

mixture of diastereomers. Rf 0.6 (2:1, petroleum ether/ethyl acetate); v_{max}(neat)/cm^{-1}

2945 s, 2870 s, 1770 vs (C=O), 1453 m, 1442 m, 1407 m, 1372 m, 1337 m; δ_H

(270MHz;CDCl$_3$) 1.54-1.85 (6H, m, 3 x CH_2 of THP group), 2.56 (0.5H, dd, *J* 3.0,

18.0), 2.70 (0.5H, dd, *J* 6.2, 18.0), 2.68 (0.5H, dd, *J* 3.0, 18.0), 2.77 (0.5H, dd, *J*

6.0, 18.0), 3.51-3.55 (1H, m), 3.78-3.84 (1H, m), 4.34-4.37 (1H, m), 4.43-4.45

(1H, m), 4.55-4.63 (1H, m), 4.64-4.67 (0.5H, m), 4.70-4.73 (0.5H, m); δ_C

(67.8MHz;CDCl$_3$) 19.1 (t), 19.3 (t), 25.2 (t x 2), 30.5 (t), 30.6 (t), 34.8 (t), 35.9 (t),

62.6 (t), 62.9 (t), 71.4 (d), 71.9 (d), 72.9 (t), 74.3 (t), 97.7 (d), 98.3 (d); *m/z* (CI)

187 ([M+H]$^+$, 40%), 103 (18), 85 (100).

Step 2: Dibal Reduction To Give Tetrahydropyran Protected-114b.

114a → **114b**

To THP-protected **114a** (0.76g, 4.08mmol) in toluene (15ml) at -50°C under an argon atmosphere was added DIBAL-H (6.26ml, 9.40mmol, 1.5M solution in toluene) slowly over 10 minutes. The solution was then allowed to slowly warm to room temperature over 30 minutes and then stirred at room temperature for 2 hours. The reaction was quenched by the addition of water (7ml), ethyl acetate (20ml) and solid sodium hydrogen carbonate. This mixture was stirred vigorously for 45 minutes and the solid removed by suction filtration, washing with ethyl acetate. The filtrate was evaporated to give the desired diol **114b** (800mg, quantitative crude yield) as an oil. v_{max} (neat)/ cm^{-1} 3406 br (OH), 1135 s, 1072 s, 1024 s; δ_H (270MHz;CDCl$_3$) 1.50-1.56 (4H, m), 1.69-1.96 (4H, m). 2.36 (1H, bs, O*H*), 3.40-3.58 (3H, m), 3.62-3.92 (3H, m), 3,97-4.10 (2H, m), 4.55-4.57 (0.5H, m), 4.64-4.66 (0.5H, m). Our data was consistent with that reported.[39]

Step 3; Deprotection of 114b to Give (3S)-1,2,4-Butane triol 274.

114b → **274**

To **114b** (770mg, 4.05mmol) in methanol (16ml) at room temperature was added *p*-toluenesulfonic acid monohydrate (15mg, 78.9μmol) and the mixture was stirred for 3 hours. The reaction was quenched by the addition of excess solid sodium hydrogen carbonate. After stirring for 10 minutes the solid was removed by suction filtration washing with ethyl acetate. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography on silica eluting with ethyl acetate/

methanol (10:1). The product **274** (423mg, 98%) was isolated as a colourless oil. Rf

0.5 (10:1, ethyl acetate/methanol); $[\alpha]_D^{18}$ -23.5 (c 1.9 in ethanol); ν_{max}(neat)/cm^{-1}

3352 br (OH), 1062 s; δ_H (270MHz;CD$_3$OD) 1.50-1.80 (2H, m), 3.40-3.54 (2H,

m), 3.70 (2H, t, J 6.4), 3.72-3.80 (1H, m), and δ_H (270MHz;(CD$_3$)$_2$SO) 1.30-1.42

(1H, m), 1.50-1.65 (1H, m), 3.20-3.30 (2H, m), 3.43-3.55 (3H, m), 4.34-4.40 (2H,

m, 2 x OH), 4.49 (1H, t, J 5.5, -OH). Our data was consistent with that reported.[39]

The sign and magnitude of the rotation confirmed that no inversion was occurring in

the cyclisation of (S)-**113** to hydroxy-lactone **114**.

*Preparation of C$_{15}$-epi-15-O-(t-butyldiphenylsilyl)-Neohalicholactone **279b** and*

*C$_{12}$,C$_{15}$-epi-15-O-(t-butyldipenylsilyl)-neohalicholactone **279b** As A 1:1.3 Mixture*

of Isomers At C-12.

To a mixture of *trans*-iodo alkene **278** (169mg, 0.35mmol) and 8S,9R,11R-aldehyde

156 (36.0mg, 173μmol) in dimethylsulfoxide (2.0ml) at room temperature under an

argon atmosphere was added chromium(II) chloride (93mg, 0.76mmol), containing a

catalytic amount of nickel(II) chloride (approx. 0.5wt%, 0.5mg, 3.87μmol) in one

portion. The dark green solution was stirred at room temperature for 16 hours and

then quenched by adding saturated aqueous NH$_4$Cl (3ml) and chloroform (4ml). The

mixture was extracted with ethyl acetate (3 x 5ml) and the combined organic layers

were dried over anhydrous magnesium sulphate. After the solvent had been

evaporated under reduced pressure the crude residue was purified on silica eluting with

petroleum ether/ethyl acetate (5:1). The products **279a** and **279b** (69.3mg, 70%) were

isolated together as a 1.3:1 mixture. This mixture was rechromatographed a further

four times, eluting with petroleum ether/ethyl acetate (5:1) in an effort to separate the

two diastereomers. The two diastereomers were sufficiently separated such that the

major isomer **279a** (27.7mg) was isolated pure as a colourless oil. The minor isomer

279b (23.5mg) was still contaminated with 17% of **279a**. Also a 1:1 mixture of

279a:279b (15.7mg) was isolated. Data for **279a**; Rf 0.6 (5:1, petroleum ether/

ethyl acetate) ; $[\alpha]_D^{19}$ -50.3 (c 0.94 in CHCl$_3$); v_{max}(neat)/cm^{-1} 3454 br (OH), 3009

w, 2931 s, 2858 s, 1737 vs (C=O), 1428 m, 1355 m, 1261m, 1215m; δH

(400MHz;CDCl$_3$) 0.45-0.48 (2H, m, 2 x cyclopropane CH), 0.87 (3H, t, J 7.3,

CH3), 0.91-1.06 (2H, m, 2 x cyclopropane CH), 1.06 (9H, s, ^{t}Bu), 1.77 (1H, dddd,

J 6.4, 12.5, 12.5, 12.5, lactone -CHH-), 1.87 (2H, pentet, J 7.3, CH$_3$CH_2-), 2.07-

2.35 (7H, m), 2.43-2.51 (2H, m, 2 x lactone -CHH-), 3.44 (1H, t, J 6.4,

C$_{(12)}$$H$OH), 4.13-4.21 (2H, m, C$_{(15)}$$H$OH + C$_{(8)}$$H$O-), 5.26-5.48 (5H, m), 5.63

(1H, ddd, J 1.2, 6.4, 15.6, $trans$-CH), 7.33-7.44 (6H, m, aryl), 7.65-7.69 (4H, m,

aryl); δC (100.4MHz;CDCl$_3$) 7.5, 14.2, 19.3, 20.3, 20.6, 23.2, 25.2, 26.5, 27.0 (q,

tBu), 33.6, 33.8, 35.8, 73.5, 74.5, 76.3, 124.0, 124.7, 127.4, 129.5, 129.6, 131.2,

133.6, 134.2, 134.3, 134.6, 135.9, 136.0, 174.2 (s, C=O); m/z (FAB) 595

([M+Na]$^+$, 16%), ([M-1]$^+$, 3%), 555 ([M-OH]$^+$, 57%), 503 (8), 457 (8), 317 (7),

299 (8), 239 (10), 199 (100); (Found: [M-OH]$^+$ 555.3313. C$_{36}$H$_{47}$O$_3$Si requires,

555.3294); Data for **279b** (contaminated with **279b**); δH (500MHz;CDCl$_3$) 0.52

(1H, ddd, J 5.2, 5.2 and 8.2, cyclopropane CH), 0.60 (1H, ddd, J 5.0, 5.0, 8.5,

cyclopropane CH), 0.88 (3H, t, J 7.3, CH_3CH$_2$-), 0.90-0.98 (2H, m, 2 x

cyclopropane CH), 1.06 (9H, s, ^{t}Bu), 1.72-1.80 (1H, m, -CHH- of lactone), 1.87

(2H, pentet, J 7.3, CH$_2$ of alkyl chain), 2.01-2.12 (3H, m, 3 x -CHH- of lactone),

2.18-2.35 (4H, m), 2.43-2.50 (2H, m, 2 x -CHH- of lactone), 3.45-3.41 (1H, m,

-C(12)HOH-), 4.10-4.21 (2H, m, -C(8)HOC(O)- and -C(15)HOH-), 5.26-5.41 (2H,

m, 2 x cis-CH), 5.43-5.48 (3H, m, 2 x cis-CH +$trans$-CH), 5.64 (1H, ddd, J 1.2,

6.4, 15.6, $trans$-CH), 7.33-7.44 (6H, m, aryl), 7.65-7.69 (4H, m, aryl); δC

(125.8MHz;CDCl$_3$) 7.9, 14.2, 19.1, 19.3 (s, ^{t}Bu), 20.6, 22.7, 25.2, 26.5, 27.0 (q,

^{t}Bu), 33.5, 33.9, 35.9, 73.8, 74.1, 76.0, 124.1, 124.7, 127.4, 127.5, 129.5, 129.6,

131.4, 133.4, 133.8, 134.1, 134.3, 134.6, 135.9, 136.0, 174.0 (s, C$_1$); m/z (FAB)

595 ([M+Na]$^+$, 29%), 555 ([M-OH]$^+$, 89%), 503 (13), 497 (6), 457 (11), 317 (11),

299 (11), 239 (11), 199 (100). (Found: [M-OH]$^+$ 555.3301. C$_{36}$H$_{47}$O$_3$Si requires,

555.3294).

Preparation of C$_{15}$-epi-neohalicholactone 277.

To a 5:1 mixture of **279b:279a** (23.5mg, 41.1μmol) in tetrahydrofuran (2ml) was

added tetrabutylammonium fluoride (103μl, 103μmol, 1.0M in tetrahydrofuran) and

the solution was then heated at reflux for 5 hours. After this time a small amount of

starting material was still visible by TLC. However the reaction was worked-up after

this time since we did not wish to decompose any product **277**. The volume of

solvent was reduced and the solution was directly chromatographed on silica eluting

with ethyl acetate/petroleum ether (10:3). The product **277** (11.5mg, 84%) was

isolated as a colourless oil which still contained 17% of the C$_{12}$-isomer **280**. The

mixture of **277** (major) and **280** were rechromatographed eluting with petroleum

ether/ethyl acetate (1:1). We now isolated some fractions that contained pure **277**

(4.3mg) whilst many of the fractions were still mixtures of **277** and **280** (6.0mg).

Data for pure **277**; Rf 0.5 (10:3, ethyl acetate/petroleum ether); $[\alpha]_D^{20}$ -84.9 (c 0.43 in

CHCl$_3$); ν$_{max}$(neat)/cm^{-1} 3387 br (OH), 3009 m, 2957 m, 2869 m, 1738 vs (CO),

1716 vs, 1447 m, 1353 m, 1262 m, 1224 m, 1207 m, 1136 s, 1089 m; By

performing a ^{1}H-^{1}H-COSY experiment the assignment of all proton signals was

possible, δ$_H$ (500MHz;C$_6$D$_6$) 0.27 (1H, ddd, J 4.9, 4.9, 8.6, cyclopropane C(10)H),

0.47 (1H, ddd, J 5.1, 5.1, 8.8, cyclopropane C(10)H), 0.82-0.89 (1H, m,

cyclopropane C(11)H), 0.89 (3H, t, J 7.4, C(20)H_3CH$_2$-), 1.01-1.07 (1H, m,

cyclopropane C(11)H), 1.51-1.58 (2H, m, C(3)H_2), 1.73-1.78 (1H, m, -C(4)HH-),

1.90 (1H, ddd, J 1.4, 7.3, 13.5, -C(7)HH- of lactone), 1.97 (2H, dpentet, J 1.2 and

7.4, -C(19)H_2-), 2.06-2.13 (2H, m, -C(2)CH_2-), 2.18-2.32 (2H, m, -C(16)H_2-),

2.31-2.40 (2H, m, -C(4)HH- + -C(7)HH-), 3.54 (1H, dd, J 2.6, 6.8, -C(12)HOH-),

3.97-4.00 (1H, m, -C(15)HOH-), 4.34 (1H, ddd, J 1.5, 8.3, 12.2, -C(8)HOC(O)-),

5.35-5.44 (3H, m, cis-C(5)H, cis-C(6)H and cis-C(17)H), 5.49-5.54 (1H, m, cis-

C(18)H), 5.68-5.71 (2H, m, 2 x trans-C(13 + 14)H); δ_C (67.8MHz;CDCl$_3$) 8.2,

14.2, 19.5, 20.7, 23.3, 25.3, 26.5, 33.6, 33.8, 35.2, 71.6, 74.2, 76.1, 123.6,

124.7, 131.9, 133.3, 134.7, 135.4, 174.1 (C$_1$), and δ_C (125.8MHz;C$_6$D$_6$) 7.7,

14.4, 19.5, 21.0, 23.8, 25.6, 26.6, 33.7, 34.1, 35.8, 71.7, 73.5, 76.0, 124.7,

125.1, 132.3, 133.4, 134.6, 134.7, 172.9 (C$_1$); m/z (FAB) 357 ([M+Na]$^+$, 100%),

317 ([M-OH]$^+$, 93%), 299 ([M-(OH+H$_2$O)]$^+$, 12%), 259 (18), 165 (42), 149 (70),

123 (71), 109 (74), 105 (94); (Found: [M-OH]$^+$ 317.2129. C$_{20}$H$_{29}$O$_3$ requires,

317.2117). The peaks that distinguished **280** from **277** in the ^{1}H-NMR spectrum at

270MHz were; 0.49-0.53 (1H, m), 0.59-0.65 (1H, m), 3.47 (1H, dd, J 3.7, 6.3,

C$_{(12)}$$H$OH). Our data was consistent with that reported for *L.sinclairii* derived

"neohalicholactone." [124]

4.6. Experimental for Section 2.5.

*Four Step Synthesis of (2E,4S)-4-O-(t-butyldiphenylsilyl)-pent-2-en-1,4-diol **290***

*Starting from Methyl (S)-Lactate **290**.*

Step 1:

To **290** (2.00g, 19.2mmol) in N,N-dimethylformamide (20ml) at room temperature under an argon atmosphere was added imidazole (3.27g, 48.0mmol) followed by *t*-butyldiphenylsilyl chloride (5.41ml, 23.1mmol). After stirring at room temperature for 16 hours the mixture was quenched by adding saturated aqueous ammonium chloride (10ml) and diethyl ether (20ml). The two layers were separated and the aqueous layer was extracted with diethyl ether (3 x 10ml). The combined organic layers were washed with water (20ml) and then dried over anhydrous magnesium sulphate. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography eluting with petroleum ether/ ethyl acetate (10:1). The product **290a** (4.92g, 75%) was isolated as a colourless oil. Rf 0.8 (10:1, petroleum ether/ethyl acetate); $[\alpha]_D^{20}$ -43.1 (*c* 1.05 in $CHCl_3$); v_{max}(neat)/cm^{-1} 3049 m, 2953 s, 2893 m, 2858 m, 1750 vs (CO), 1590 m, 1472 m, 1428 s, 1372 m, 1279 m, 1205 m; δ_H (270MHz;$CDCl_3$) 1.10 (9H, s, tBu), 1.37 (3H, d, *J* 6.8, CH_3CH-), 3.56 (3H, s, OCH_3), 4.28 (1H, q, *J* 6.8, -CHOSiPh$_2$^{t}Bu), 7.34-7.44 (6H, m, aryl), 7.65-7.70 (4H, m, aryl); δ_C (67.8MHz;$CDCl_3$) 19.2 (s, tBu), 21.2 (q, CH_3), 26.8 (q, ^{t}Bu), 51.5 (q), 68.9 (d), 127.5 (d x 2), 129.7 (d x 2), 133.2 (s-ipso), 135.8 (d x 2), 174.1 (s, C=O).

Steps 2 and 3:

To **290a** (3.90g, 11.4mmol) in toluene (100ml) at -78°C under an argon atmosphere was added DIBAL-H (7.6ml, 11.4mmol, 1.5M in toluene) over 10 minutes. The solution was allowed to warm to -60°C stirring at this temperature for 1.5 hours. After warming to -20°C the reaction was quenched by adding water (7.6ml) followed by ethyl acetate (50ml) and excess solid sodium hydrogen carbonate. This mixture was stirred vigorously for 30 minutes and then the solid was removed by suction filtration washing with ethyl acetate. The filtrate was then dried over anhydrous magnesium sulphate and the solvent evaporated under reduced pressure to provide the crude aldehyde (3.60g, quantitative crude yield); v_{max}(neat)/cm^{-1} 3049 m, 2958 s, 2893 m, 2858 m, 1739 vs (CO), 1567 m, 1472 m, 1428 s, 1374 m; δ_H (270MHz;$CDCl_3$) 1.11 (9H, s, ^{t}Bu), 1.22 (3H, d, *J* 7.0, CH_3CH-), 4.00 (1H, dq, *J* 1.1, 7.0,

-CHOSiPh$_2$^{t}Bu), 7.33-7.45 (6H, m, aryl), 7.61-7.69 (4H, m, aryl) 9.57 (1H, d, J

1.1, CHO). The aldehyde was used directly in the next step without purification.

To a stirred suspension of LiCl (581mg, 13.7mmol) in acetonitrile (50ml) at room

temperature under an argon atmosphere was added t-butyl diethylphosphonoacetate

(4.28ml, 18.2mmol), DBU (1.70ml, 11.4mmol), and finally a solution of crude

aldehyde (3.60g, 11.4mmol) in dry acetonitrile (40ml). The reaction mixture was then

stirred at room temperature for 1 hour at which time it was quenched by adding water

(30ml). The aqueous layer was then extracted with ethyl acetate (3 x 50ml). The

combined organic layers were dried over anhydrous magnesium sulphate and then

evaporated under reduced pressure. The residue was purified by column

chromatography on silica eluting with petroleum ether/ethyl acetate (20:1) and the

product **290b** (2.09g, 48% for the two steps from **290a**) isolated as a colourless oil.

Rf 0.5 (20:1, petroleum ether/ethyl acetate); $[\alpha]_D^{20}$ -44.6 (c 1.4 in CHCl$_3$); v_{max}

(neat)/cm^{-1} 3049 m, 2931 s, 2894 m, 2858 m, 1720 vs (CO), 1660 m, 1472 m, 1428

s, 1368 m, 1293 s, 1272 m; δ_H (270MHz;CDCl$_3$) 1.08 (9H, s, ^{t}Bu), 1.12 (3H, d, J

6.8, CH_3CH-), 1.30 (3H, t, J 7.2, -OCH$_2$CH_3), 4.20 (2H, dq, J 1.3, 7.0,

-OCH_2CH$_3$), 4.42-4.50 (1H, m, -CHOSiPh$_2$^{t}Bu), 6.01 (1H, dd, J 1.7, 15.4, $trans$-

CH), 6.90 (1H, dd, J 4.4, 15.4, $trans$-CH), 7.33-7.47 (6H, m, aryl), 7.61-7.70 (4H,

m, aryl); δ_C (100.4MHz;CDCl$_3$) 14.3 (q), 19.2 (s, ^{t}Bu), 23.3 (q), 26.9 (q, ^{t}Bu),

60.3(t), 68.9 (d), 119.1 (d), 127.6 (d x 2), 129.7 (d x 2), 134.0 (s-ipso), 135.8 (d x

2), 151.5 (d), 166.8 (s, C=O). m/z (EI) 325 ([M-^{t}Bu]$^+$, 15%), 285 (26), 257 (10),

227 (19), 213 (100), 199 (26), 183 (40) and m/z (FAB) 405 ([M+Na]$^+$, 8%), 383

([M+H]$^+$, 15%), 381 ([M-H]$^+$, 15%), 325 ([M-^{t}Bu]$^+$, 65%), 305 (50), 285 (44), 27

(40), 213 (24), 199 (100). (Found: [M+H]$^+$ 383.2030. C$_{23}$H$_{31}$O$_3$Si requires,

383.2043).

Step 4.

To **290b** (1.20g, 3.14mmol) in toluene (50ml) at -20°C under an argon atmosphere

was added DIBAL-H (5.0ml, 7.50mmol, 1.5M in toluene) over 10 minutes. The

solution was allowed to warm to room temperature stirring at this temperature for 1

hour. The reaction was quenched by adding water (5.0ml) followed by ethyl acetate

(30ml) and excess solid sodium hydrogen carbonate. This mixture was stirred

vigorously for 30 minutes and then the solid was removed by suction filtration

washing with ethyl acetate. The filtrate was dried over anhydrous magnesium sulphate

and the solvent evaporated under reduced pressure. The residue was purified by

column chromatography eluting with petroleum ether/ethyl acetate (5:1 to 5:2). The

product **291** (1.02g, 96%) was isolated as a colourless oil. Rf 0.3 (5:1, petroleum

ether/ethyl acetate); $[\alpha]_D^{20}$ -34.0 (c 1.0 in CHCl3); δ_H (400MHz;CDCl3) 1.06 (9H, s,

^tBu), 1.17 (3H, d, J 6.3, CH_3CH-), 3.95-4.00 (2H, m, $-CH_2OH$), 4.34 (1H, pentet,

J 6.3, $-CHOSiPh_2{}^tBu$), 5.52-5.68 (2H, m, 2 x trans -CH), 7.33-7.47 (6H, m, aryl),

7.61-7.70 (4H, m, aryl); δ_C (67.8MHz;CDCl3) 19.2 (s, ^tBu), 24.2 (q), 27.0 (q,

^tBu), 63.1 (t), 69.7 (d), 127.4 (d), 127.5 (d), 127.7 (d), 129.5 (d), 129.6 (d), 134.4

(s-ipso), 135.9 (d), 136.0 (d x 2). m/z (EI) 283 ([M-^tBu]$^+$, 11%), 239 (9), 199 (100),

181 (7); and m/z (FAB) 363 ([M+Na]$^+$, 8%), 339 ([M-H]$^+$, 3%), 323 ([M-OH]$^+$,

16%), 283 ([M-^tBu]$^+$, 11%), 239 (19), 199 (100). (Found: [M-OH]$^+$ 323.1822.

$C_{21}H_{27}OSi$ requires, 323.1831).

*Conversion of Allylic Alcohol **291** to Mosher's Ester Derivative **292***

for Enantiomeric Purity Determination.

Step 1:

To **291** (25.0mg, 74.0μmol) and 1,3-dicyclohexylcarbodiimide (23.0mg, 111.5μmol)

in dichloromethane (1.0ml) at room temperature under an argon atmosphere was added

(R)-(+)-α-methoxy-α-(trifluoromethyl)phenyl acetic acid (26.0mg, 111.5μmol)

followed by 4-dimethylaminopyridine (0.90mg, 7.4μmol). The reaction was stirred at

room temperature for 1 hour and the precipitate was removed by filtration washing with dichloromethane (2ml). The filtrate was then evaporated under reduced pressure and the residue was purified by column chromatography on silica eluting with petroleum ether/ethyl acetate (10:1). The product **291a** (36.4mg, 89%) was isolated as a colourless oil. δ_H (270MHz;CDCl$_3$) 1.05 (9H, s, ^{t}Bu), 1.10 (3H, d, J 6.4, CH_3CH-), 3.53 (3H, d, J 1.1, -OCH_3), 4.30 (1H, pentet, J 6.2, -CHOSiPh$_2{}^t$Bu), 4.73 (2H, d, J 6.1, -CH_2O-), 5.65 (1H, td, J 6.0, 15.4, trans-CH), 5.81 (1H, dd, J 6.1, 15.4, trans-CH), 7.29-7.68 (15H, m, aryl).

Step 2:

To **291a** (36.4mg, 65.7μmol) in tetrahydrofuran (1.0ml) was added tetrabutylammonium fluoride (98.6μl, 98.6μmol, 1.0M in tetrahydrofuran) at room temperature and the solution was stirred for 2 hours. The volume of solvent was then reduced and the mixture placed directly onto a silica column eluting with petroleum ether/ ethyl acetate (5:1 to 5:2). The product **291b** (21.0mg, quantitative yield) was isolated as a colourless oil. δ_H (270MHz;CDCl$_3$) 1.26 (3H, d, J 6.4, CH_3CH-), 3.56 (3H, d, J 1.1, -OCH_3), 4.30 (1H, pentet, J 6.4, -CHOSiPh$_2{}^t$Bu), 4.80 (2H, d, J 5.5, -CH_2O-), 5.66-5.83 (1H, m, trans-CH), 5.88 (1H, dd, J 6.0, 15.6, trans-CH), 7.38-7.53 (5H, m, aryl).

Step 3:

To **291b** (21.0mg, 66.0μmol) in dichloromethane (1.0ml) under a nitrogen atmosphere at room temperature was added p-methoxyphenylmethyl trichloro-acetimidate (28.0mg, 99.1μmol) and ($\pm$)-10-camphorsulfonic acid (0.8mg, 3.30μmol). The mixture was stirred at room temperature for 16 hours and then placed directly on a silica column eluting with petroleum ether/ethyl acetate (10:1). The product **292** (44mg) was isolated as a colourless oil which was contaminated with an inseparable by-product. δ_H (270MHz;CDCl$_3$) 1.24 (3H, d, J 6.4, CH_3CH-), 3.56 (3H, d, J 1.1, -OCH_3), 3.78 (3H, s, -C$_6$H$_4$OCH_3), 3.88-3.98 (1H, m, -CHO-), 4.28 (1H, d, J 11.5, -CHHAr), 4.43 (1H, d, J 11.5, -CHHAr), 4.82-4.88 (2H, m, -CH_2O-), 5.76-5.79 (2H, m, 2 x trans CH), 6.86 (2H, d, J 8.4, aryl), 7.22 (2H, d, J 8.5, aryl), 7.36-7.58 (5H, m, aryl).

Preparation of Racemic Mosher's Ester Comparison (±)-292.

Step 1

First sodium hydride (250mg, 6.25mmol, 60% dispersion in mineral oil) was washed several times with petroleum ether to remove the mineral oil. Then to the neat and dried solid sodium hydride was added N,N-dimethylformamide (8ml), methyl (S)-lactate **290** (0.50g, 4.81mmol), 4-methoxy benzyl chloride (0.78ml, 5.77mmol) and tetrabutylammonium iodide (87.9mg, 0.24mmol) at room temperature under an argon atmosphere. After stirring the reaction at room temperature for 1 hour the reaction was quenched with saturated aqueous ammonium chloride (8ml) and the aqueous layer was extracted with diethyl ether (3 x 10ml). The combined organic layers were dried over anhydrous magnesium sulphate and the solvent removed at reduced pressure. The residue was purified by column chromatography on silica eluting with petroleum ether/ethyl acetate (6:1). The product **293a** (0.66g, 61%) was isolated as a colourless oil. δ_H (270MHz;CDCl$_3$) 1.41 (3H, d, J 7.0, CH$_3$CH-), 3.75 (3H, s, -OCH$_3$), 3.79 (3H, s, -OCH$_3$), 4.02 (1H, q, J 7.0, -CHOCH$_2$Ar), 4.38 (1H, d, J 11.4, -OCHHAr), 4.61 (1H, d, J 11.4, -OCHHAr), 6.87 (2H, d, J 8.6, aryl), 7.28 (2H, d, J 8.6, aryl).

Steps 2-4:

To **293a** (1.38g, 6.16mmol) in toluene (20ml) at -40°C under an argon atmosphere was added DIBAL-H (9.00ml, 13.6mmol, 1.5M solution in toluene) over a five minute period. The solution was allowed to warm to room temperature with stirring for 1 hour and then quenched by adding water (9.0ml). Ethyl acetate (40ml) and excess sodium hydrogen carbonate were also added and the resultant mixture was vigorously stirred for 30 minutes. The solid was removed by suction filtration

washing with ethyl acetate. The filtrate was dried over anhydrous magnesium sulphate and the solvent removed evaporated under reduced pressure to give a crude alcohol (assumed quantitative yield; 6.16mmol) which was used directly in the next step.

To oxalyl chloride (0.64ml, 7.39mmol) in dichloromethane (20ml) at -78°C was added dimethylsulfoxide (1.05ml, 14.8mmol) in dichloromethane (20ml) slowly over a 10 minute period. After stirring for 10 minutes at -78°C the crude alcohol (1.20g, 6.16mmol) in dichloromethane (20ml) was added slowly *via* cannula and stirring continued at -78°C for 20 minutes. Then triethylamine (2.59ml, 18.5mmol) was injected and the solution was allowed to warm to room temperature over 30 minutes. The reaction was quenched by adding water (20ml) and the aqueous phase was extracted with dichloromethane (2 x 20ml). The combined organic layers were dried over anhydrous magnesium sulphate and the solvent evaporated at reduced pressure to give the crude aldehyde (assumed quantitative yield, 6.16mmol).

To sodium hydride (271mg, 6.16mmol, 60% dispersion in mineral oil) in ethylene glycol dimethyl ether (20ml) was added triethylphosphonoacetate (1.22ml, 6.16mmol) and the solution was stirred at room temperature under an argon atmosphere until the evolution of hydrogen had ceased (approx. 1 hour). Then the crude aldehyde (assumed 6.16mmol) in ethylene glycol dimethyl ether (5ml) was added *via* syringe over 5 minutes and the resultant solution was stirred at room temperature for 1 hour. The reaction was quenched by the addition of saturated aqueous ammonium chloride (15ml) and the aqueous phase was extracted with ethyl acetate (3 x 20ml). The combined organic layers were dried over anhydrous magnesium sulphate and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography on silica eluting with petroleum ether/ethyl acetate (10:1). The product **293b** (1.20g, 74% from **293a**) was isolated as a colourless oil. δ_H (270MHz;CDCl$_3$) 1.31 (3H, t, *J* 7.1, -OCH$_2$C*H*$_3$), 1.31 (3H, d, *J* 6.6, C*H*$_3$CH), 4.09 (1H, dpentet, *J* 1.1, 6.4, -C*H*OCH$_2$Ar), 4.21 (2H, q, *J* 7.1, -OC*H*$_2$CH$_3$), 4.36 (1H, d, *J* 11.5, -OC*H*HAr), 4.50 (1H, d, *J* 11.4, -OCH*H*Ar), 5.98 (1H, dd, *J* 1.3, 15.8, *trans*-C*H*), 6.84-6.93 (3H, m, aryl + *trans*-C*H*), 7.26 (2H, d, *J* 8.8, Ar); δ_C

(100.4MHz;CDCl₃) 14.8 (q), 21.2 (q), 55.8 (q), 61.0 (t), 70.9 (t), 74.0 (d), 114.4 (d), 121.8 (d), 130.7 (s), 149.9 (d), 159.8 (s-ipso), 166.9 (s, C=O).

Step 5:

To **293b** (1.20g, 4.55mmol) in toluene (20ml) at -40°C under an argon atmosphere was added DIBAL-H (6.7ml, 10.00mmol, 1.5M in toluene) over 10 minutes. The solution was allowed to warm to room temperature stirring at this temperature for 30 minutes. The reaction was quenched by adding water (6.7ml) followed by ethyl acetate (20ml) and excess solid sodium hydrogen carbonate. This mixture was stirred vigorously for 30 minutes and then the solid was removed by suction filtration washing with ethyl acetate. The filtrate was then dried over anhydrous magnesium sulphate and the solvent evaporated under reduced pressure. The residue was purified by column chromatography eluting with petroleum ether/ethyl acetate (5:1 to 5:2). The product **293** (704mg, 70%) was isolated as a colourless oil. Rf 0.5 (5:2, petroleum ether/ethyl acetate). $[\alpha]_D^{20}$ +0.89 (c 1.23 in chloroform); δ_H (270MHz;CDCl₃) 1.27 (3H, d, J 6.2, CH₃CH-), 3.80 (3H, s, -OCH₃), 3.95 (1H, pentet, J 6.6, -CHOCH₂Ar), 4.15-4.17 (2H, m, -CH₂OH), 4.33 (1H, d, J 11.4, -OCHHAr), 4.49 (1H, d, J 11.4, -OCHHAr), 5.67 (1H, ddd, J 1.3, 5.9, 15.6, trans-CH), 5.81 (1H, td, J 5.3, 15.9, trans-CH), 6.87 (2H, d, J 8.6, aryl), 7.25 (2H, d, J 8.6, aryl). m/z (FAB) 245 ([M+Na]⁺, 33%), 222 ([M]⁺, 52%), 121(100). (Found: [M]⁺ 222.1265. C₁₃H₁₈O₃ requires, 222.1256).

Step 6:

To **293** (24.0mg, 108μmol) and 1,3-dicyclohexylcarbodiimide (33.0mg, 162μmol) in chloroform (1.0ml) at room temperature under an argon atmosphere was added (R)-(+)-α-methoxy-α-(trifluoromethyl)phenyl acetic acid (38.0mg, 162μmol) followed by 4-dimethylaminopyridine (1.3mg, 10.6μmol). The reaction was stirred at room temperature for 5 minutes and the precipitate was removed by filtration washing with dichloromethane (2ml). The filtrate was then evaporated under reduced pressure and the residue was purified by column chromatography on silica eluting with petroleum ether/ethyl acetate (10:1 to 5:1). The product (±)-**292** (47.3mg, 100%) was isolated as a colourless oil. δ_H (270MHz;CDCl₃) 1.24 (3H, m, CH₃CH-), 3.56 (3H, d, J 1.1,

-OCH_3), 3.79 (3H, s, -C$_6$H$_4$OCH_3), 3.91-3.96 (1H, m, -CHO-), 4.28 (1H, d, J

11.4, -CHHAr), 4.43 (0.5H, d, J 11.4, -CHHAr), 4.45 (0.5H, d, J 11.4, -CHHAr),

4.82-4.88 (2H, m, -CH_2O-), 5.76-5.79 (2H, m, 2 x trans CH), 6.86 (2H, d, J 8.4,

aryl), 7.22 (2H, d, J 8.4, aryl), 7.36-7.58 (5H, m, aryl).

Simmons-Smith Cyclopropanation of Allylic Alcohol 291

(in the absence of a chiral ligand).

To a solution of Et$_2$Zn (575μl, 575μmol, 1.0M in hexane) and freshly distilled

ethylene glycol dimethyl ether (51.8mg, 575μmol) in dichloromethane (1.0ml) at

-15°C was added CH$_2$I$_2$ (92.6μl, 1.15mmol) over a 15 minute period. Then this

colourless solution was added *via* cannula to **292** (65.2mg, 192μmol) in

dichloromethane (1.0ml) at -15°C over a 30 minute period. The solution was then

allowed to warm to room temperature and stirred for 16 hours. The reaction was

quenched with saturated ammonium chloride (1.0ml) and the aqueous phase was

extracted with diethyl ether (3 x 2ml). The combined organic layers were dried over

anhydrous magnesium sulphate and the solvent was evaporated at reduced pressure.

The residue was purified by column chromatography on silica eluting with petroleum

ether/ethyl acetate (5:1). The desired product **294** (33.6mg, 49%) was isolated as

approximately a 1:1 mixture of *trans*-cyclopropane isomers. We also isolated the silyl

migration product **295** (32.8mg, 48%) as a mixture of *trans*-cyclopropane isomers.

Data for **294**; Rf 0.4 (5:1, petroleum ether/ethyl acetate); v_{max}(neat)/cm^{-1} 3362 br

(OH), 3049 m, 2961 s, 2929 s, 2857 s, 1472 m, 1428 m, 1372 w, 1111 s; δ_H

(400MHz;CDCl$_3$) 0.25-0.33 (2H, m, 2 x cyclopropane CH), 0.78-0.88 (2H, m, 2 x

cyclopropane CH), 1.039 (4.5H, s, ^{t}Bu), 1.043 (4.5H, s, ^{t}Bu), 1.16 (1.5H, d, J 6.4,

CH_3CH), 1.17 (1.5H, d, J 5.9, CH_3CH), 3.18-3.40 (3H, m), 7.34-7.43 (6H, m,

aryl), 7.64-7.72 (4H, m, aryl); δ_C (100.4MHz;CDCl3) 7.3 (t), 8.7 (t), 18.4 (d), 19.2 (s, ^tBu), 19.3 (s, ^tBu), 19.8 (d), 23.4 (d), 23.6 (d), 25.2 (q), 27.0 (q, ^tBu), 66.5 (t), 71.7 (d), 72.3 (d), 127.4-127.7 (d x 4), 129.4-129.6 (d x 3), 134.4-134.5 (s-ipso x 3), 135.6-135.9 (d x 4); m/z (FAB) 355 ($[M+H]^+$, 2%), 353 ($[M-H]^+$, 3%), 337 ($[M-OH]^+$, 16%), 297 ($[M-^tBu]^+$, 12%), 239 (14%), 199 (100). (Found: $[M-OH]^+$ 337.2008. $C_{22}H_{29}OSi$ requires, 337.1988). Data for **295**; Rf 0.7 (5:1, petroleum ether/ ethyl acetate); ν_{max}(neat)/cm^{-1} 3370 br (OH, quite weak), 3049 m, 2961 s, 2929 s, 2857 s, 1472 m, 1428 m, 1372 w, 1111 s; δ_H (400MHz;CDCl3) 0.25-0.37 (2H, 2 x cyclopropane CH), 0.80-0.94 (2H, m, 2 x cyclopropane CH), 1.04 (9H, s, ^tBu), 1.16 (3H, d, J 6.3, CH_3CH), 3.27-3.29 (2H, m, -CH_2OSiPh$_2$$^tBu$), 3.30-3.40 (1H, m, C$H$OH), 7.33-7.43 (6H, m, aryl), 7.64-7.71 (4H, m, aryl); m/z (CI) 337 ($[M-OH]+$, 11%), 311 (33), 297 ($[M-^tBu]^+$, 5%), 257 (18), 227 (55), 213 (100), 199 (48).

Simmons-Smith Cyclopropanation of Allylic Alcohol (±)-293

(in the absence of a chiral ligand).

To a solution of Et$_2$Zn (4.50ml, 4.50mmol, 1.0M in hexane) and freshly distilled ethylene glycol dimethyl ether (0.36ml, 4.50mmol) in dichloromethane (5.0ml) at -20°C was added CH$_2$I$_2$ (0.72ml, 9.00mmol) over a 15 minute period. Then this colourless solution was added *via* cannula to **293** (0.20g, 0.90mmol) in dichloromethane (5.0ml) at 0°C over a 20 minute period. The solution was then allowed to warm to room temperature and stirred for 2.5 hours. The reaction was quenched with saturated ammonium chloride (5.0ml) and the aqueous phase was extracted with diethyl ether (3 x 8ml). The combined organic layers were dried over anhydrous magnesium sulphate and the solvent was evaporated at reduced pressure. The residue was purified by column chromatography on silica eluting with petroleum

ether/ ethyl acetate (5:1 to 5:2). The desired product **296** (84.7mg, 60% based on recovered **293**) was isolated as approximately a 1:1 mixture of *trans*-cyclopropane isomers. We also isolated the methyl ether product **297** (19.4mg, 14% based on recovered **293**), and recovered **293** (67.8mg, 34%). Data for **296**; Rf 0.4 (5:2, petroleum ether/ethyl acetate); δ_H (270MHz;CDCl$_3$) 0.30-0.41 (1H, m, cyclopropane C*H*), 0.45-0.65 (1H, m, cyclopropane C*H*), 0.70-0.90 (1.5H, m, cyclopropane C*H*), 1.05-1.15 (0.5H, m, cyclopropane C*H*), 1.25 (1.5H, d, *J* 6.2, C*H*$_3$CH-), 1.26 (1.5H, d, *J* 6.2, C*H*$_3$CH-), 2.60 (1H, bs, O*H*), 2.82-2.92 (0.5H, m, C*H*OCH$_2$Ar), 2.93-3.03 (0.5H, m, C*H*OCH$_2$Ar), 3.31 (0.5H, dd, *J* 7.5, 11.2, -C*H*HOH), 3.38-3.41 (1H, m, -C*H*$_2$OH), 3.50 (0.5H, dd, *J* 6.4, 11.4, -CH*H*OH), 3.78 (3H, s, -OC*H*$_3$), 4.44-4.56 (2H, m, -OC*H*$_2$Ar), 6.85-6.89 (2H, m, aryl), 7.24-7.28 (2H, m, aryl); *m/z* (FAB) 259 ([M+Na]$^+$, 21%), 237 ([M+H]$^+$, 4%), 236 ([M]$^+$, 20%), 121 (100). (Found: [M+H]$^+$ 237.1489. C$_{14}$H$_{21}$O$_3$ requires, 237.1491, and found: [M]$^+$ 236.1411. C$_{14}$H$_{20}$O$_3$ requires 236.1412). Data for **297**: Rf 0.8 (5:2, petroleum ether/ethyl acetate); δ_H (270MHz;CDCl$_3$) 1.27 (3H, d, *J* 6.4, C*H*$_3$CH-), 3.36 (3H, s, OC*H*$_3$), 3.80 (3H, s, OC*H*$_3$), 3.92-3.96 (3H, m, -C*H*$_2$OCH$_3$ + -C*H*O-), 4.31 (1H, d, *J* 11.5, -OC*H*HAr), 4.50 (1H, d, *J* 11.5, -OCH*H*Ar), 5.60-5.80 (2H, m, 2 x *trans* C*H*), 6.86 (2H, d, *J* 8.6, aryl), 7.25 (2H, d, *J* 8.4, aryl).

Preparation of Dioxaborolane Ligand (S,S)-281

To a solution of **298** (1.00g, 4.90mmol) in toluene (10ml) at room temperature under an argon atmosphere was added **299** (473mg, 4.66mmol) in one portion. The mixture was then heated until all **299** had dissolved (approximatly 10 minutes). The solvent was removed at reduced pressure and the crude product (*S,S*)-**281** (1.28g, quantitative yield) was used without further purification. ν_{max}(neat)/cm^{-1} 2930 s, 2872 s, 1652 vs, 1501 m, 1465w; δ_H (270MHz;CDCl$_3$) 0.80-0.90 (5H,m), 1.20-1.40 (4H, m),

3.00 (6H, s), 3.20 (6H, s), 5.53 (2H, s). Our data was consistent with that reported.[136]

Preparation of (2R,3S)-trans-(3-Phenyl-cyclopropyl)methanol 301.

To a solution of Et_2Zn (2.70ml, 3.02mmol, 1.1M in toluene) and freshly distilled ethylene glycol dimethyl ether (0.31ml, 3.02mmol) in dichloromethane (5.0ml) at -15°C was added CH_2I_2 (0.49ml, 6.04mmol) over a 15 minute period. Then this colourless solution was added *via* cannula to **300** (81.0mg, 0.60mmol), (*S,S*)-**281** (180mg, 0.67mmol) and 4Å molecular sieves (25mg) in dichloromethane (5.0ml) at -15°C over a 45 minute period. The solution was then stirred at -20°C to -10°C over 1.45 hours and then warmed to room temperature for 20 minutes. The reaction was quenched with saturated ammonium chloride (5.0ml) and the aqueous phase was extracted with diethyl ether (3 x 10ml). The combined organic layers were dried over anhydrous magnesium sulphate and the solvent was evaporated at reduced pressure. The residue was purified by column chromatography on silica eluting with petroleum ether/ ethyl acetate (5:1). The product **301** (67.5mg, 76%) was isolated as a colourless oil. $[\alpha]_D^{20}$ -69.6 (*c* 1.24 in $CHCl_3$); Enantiomeric excess was determined by chiral HPLC (hexane:IPA (97:3), 0.9ml/ min) 89% e.e; δ_H (270MHz;$CDCl_3$) 0.88-0.99 (2H, m, 2 x cyclopropane C*H*), 1.38-1.50 (1H, m, cyclopropane CH), 1.71 (1H, bs, OH), 1.81 (1H, ddd, *J* 5.0, 5.0, 9.7, cyclopropane CH), 3.57-3.62 (2H, m, -C*H*₂OH), 7.05-7.29 (5H, m, aryl).

Diastereoselective Cyclopropanation of 291.

To a solution of Et_2Zn (3.10ml, 3.24mmol, 1.1M in toluene) and freshly distilled ethylene glycol dimethyl ether (0.36ml, 3.24mmol) in dichloromethane (5.0ml) at

-15°C was added CH_2I_2 (0.55ml, 6.48mmol) over a 15 minute period. Then this colourless solution was added *via* cannula to **291** (231mg, 0.68mmol), (S,S)-**281** (221mg, 0.82mmol) and 4Å molecular sieves (40mg) in dichloromethane (4.0ml) at -15°C over a 45 minute period. The solution was then stirred at -10°C to 0°C over 2 hours and then warmed to room temperature for 3 hours. The reaction was quenched with saturated ammonium chloride (5.0ml) and the aqueous phase was extracted with diethyl ether (3 x 15ml). The combined organic layers were dried over anhydrous magnesium sulphate and the solvent was evaporated at reduced pressure. The residue was purified by column chromatography on silica eluting with petroleum ether/ethyl acetate (5:1). The product 2*R*,4*R*,5*S*-**294** (238mg, 98%, >95% d.e) was isolated as a colourless oil which was contaminated with 12% of **291**. $[\alpha]_D^{20}$ -24.0 (*c* 0.25 in $CHCl_3$); δ_H (400MHz;$CDCl_3$) 0.26-0.33 (2H, m, 2 x cyclopropane C*H*), 0.73-0.89 (2H, m, 2 x cyclopropane C*H*), 1.047 (9H, s, ^tBu), 1.16 (3H, d, *J* 6.1, C*H*$_3$CH), 3.21 (1H, dd, *J* 7.3, 11.3, -CH*H*OH), 3.30 (1H, pentet, *J* 7.0, C*H*OSiPh$_2$$^tBu$), 3.36 (1H, dd, *J* 6.7, 11.3, -C*H*HOH), 7.32-7.43 (6H, m, aryl), 7.66-7.72 (4H, m, aryl); δ_C (100.4MHz;$CDCl_3$) 7.3 (t), 19.2 (s, ^tBu), 19.6 (d), 23.6 (d), 25.0 (q), 26.9 (q, ^tBu), 66.3 (t), 72.3 (d), 127.4 (d), 127.5 (d), 129.5(d x 2), 134.3 (s-ipso), 134.4 (s-ipso), 135.8 (d), 135.9 (d). Note that in the ^{13}C-NMR spectrum the signals belonging to the 2*S*,4*S*,5*S*-*trans* cyclopropane isomer of **294** were just visible.

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increasing temperature

(A)
Nucleophilic carbenoid

(B)
Electrophilic carbenoid

(C)
Carbene

The reaction of a gem-dihalide with an alkyllithium at -100°C is believed to produce a nucleophilic carbenoid (A) which will react with a variety of electrophiles. On warming to -80°C the process of "metal assisted ionisation" (MAI) takes place, the carbon-halogen bond is weakened and the carbenoid in turn becomes electrophilic in nature (B). It has been indicated that it is this species (B) that is responsible for observed electrophilic properties and not the carbene intermediate (C). A carbene (C) would be generated from (B) once the elimination of the metal-halide has occurred, see M. Topolski, *J. Org. Chem.*, 1995, **60**, 5588-5594 and references cited within.

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6. Appendix

Appendix

Single Crystal X-ray Study of 8S,9R,11R-(-)-Carboxylic Acid **152**.

A crystal of approximate dimensions 0.3 x 0.3 x 0.5 mm was used for data collection.

Crystal data: $C_{12}H_{16}O_4$, M = 224.2 monoclinic, a = 26.362(6), b = 6.890(3), c = 13.422(4)Å, β = 96.98(2)°, U = 2419.8 Å^3, space group $C2$, Z = 8, D_c = 1.23 gcm^{-3}, m(Mo-K_α) = 0.90 cm^{-1}, F(000) = 960. Data were measured at room temperature on a CAD4 automatic four-circle diffractometer in the range $2 \le \theta \le 22°$. 1676 reflections were collected of which 1106 were unique with $I \ge 2\sigma(I)$. Data were corrected for Lorentz and polarization but not for absorption. The structure was solved by Direct methods and refined using the SHELX† suite of programs.

The asymmetric unit consisted of 2 molecules (hydrogen bonded via the carboxylic groups as illustrated in the ORTEP plot) which were seen to be identical within the bounds of experimental error. In the final least squares cycles all atoms were allowed to vibrate anisotropically. Hydrogen atoms were included at calculated positions except for the acidic and olefinic protons. H1 and H2, attached to O4 and O8 respectively, were located in the latter stages of convergence and refined at a fixed distance of 0.98 Å from the relevant parent atoms. H51, H61, H171 and H181, attached to C5, C6, C17 and C18 respectively, were similarly located, and refined fixed distance of 0.98 Å from the relevant parent atoms.

Final residuals after 12 cycles of least squares were R = 0.0423, R_W = 0.0437, for a weighting scheme of w = 1.2570/[σ^2(F) + 0.000618(F)^2]. Max. final shift/esd was 0.000. The max. and min. residual densities were 0.07 and -0.06 eÅ^{-3} respectively. Final fractional atomic coordinates and isotropic thermal parameters, bond distances and angles are given in Tables A1.1, A1.2 and A1.3 respectively. Tables of anisotropic temperature factors, hydrogen fractional atomic coordinates and selected non-bonded distances are available as supplementary data. The asymmetric unit is shown in Fig. A1.1, along with the labelling scheme used.

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† G. M. Sheldrick, SHELX86, a computer for crystal stucture determination, University of Gottingen, 1986; G. M. Sheldrick, SHELX76, a computer programme for crystal structure determination, University of Gottingen.

Figure A1.1

8S,9R,11R-**152**

Table A1.1

Fractional atomic co-ordinates (x10^4) and equivalent isotropic temperature factors (Å^2 x10^3) for 8S,9R,11R-(-)-**152**.

	x	y	z	U
O(1)	475 (2)	1919	7142 (3)	64 (2)
O(2)	-268 (2)	768 (11)	6386 (4)	93 (2)
O(3)	2061 (2)	173 (10)	6008 (4)	81 (2)
O(4)	1528 (2)	-2336 (11)	5667 (3)	76 (2)
C(1)	6 (3)	1094 (12)	7131 (6)	64 (3)
C(2)	-102 (3)	755 (15)	8179 (6)	85 (3)
C(3)	-357 (3)	2510 (16)	8592 (6)	97 (4)
C(4)	-120 (3)	4500 (16)	8418 (6)	97 (4)
C(5)	-285 (3)	5336 (16)	7424 (7)	95 (4)
C(6)	-35 (3)	5644 (14)	6647 (7)	83 (4)
C(7)	513 (3)	5164 (13)	6558 (5)	77 (3)
C(8)	582 (2)	3018 (13)	6283 (5)	65 (3)
C(9)	1118 (2)	2528 (14)	6074 (4)	64 (3)
C(10)	1266 (3)	2812 (15)	5068 (5)	76 (3)
C(11)	1185 (2)	782 (13)	5442 (4)	66 (3)
C(12)	1630 (3)	-475 (15)	5736 (4)	64 (3)
O(5)	3257 (2)	-6153 (10)	9311 (3)	72 (2)
O(6)	4086 (2)	-5929 (14)	9887 (4)	121 (3)
O(7)	2318 (2)	-4532 (11)	6246 (4)	82 (2)
O(8)	2849 (2)	-2067 (11)	6613 (4)	76 (2)
C(13)	3650 (4)	-5731 (14)	10011 (6)	83 (3)
C(14)	3455 (4)	-4994 (16)	10938 (5)	97 (4)
C(15)	3324 (4)	-6614 (18)	11611 (6)	114 (5)
C(16)	3077 (4)	-8414 (18)	11145 (7)	122 (5)
C(17)	3434 (5)	-9692 (18)	10755 (7)	111 (4)

C(18)	3496 (4)	-10190 (17)	9817 (7)	116 (5)
C(19)	3190 (3)	-9500 (14)	8899 (5)	99 (4)
C(20)	3346 (3)	-7488 (14)	8529 (4)	72 (3)
C(21)	3011 (2)	-6898 (13)	7597 (4)	64 (3)
C(22)	3164 (3)	-7250 (15)	6602 (5)	74 (3)
C(23)	3162 (2)	-5202 (13)	7004 (5)	65 (3)
C(24)	2746 (3)	-3925 (16)	6585 (5)	66 (3)

Table A1.2.

Bond lengths (Å) for $8S,9R,11R$-(-)-**152**.

C (1)-O (1)	1.358 (9)	C (8)-O (1)	1.435 (8)
C (1)-O (2)	1.182 (8)	C (12)-O (3)	1.235 (9)
C (12)-O (4)	1.311 (10)	C (2)-C (1)	1.487 (11)
C (3)-C (2)	1.519 (13)	C (4)-C (3)	1.537 (15)
C (5)-C (4)	1.470 (13)	C (6)-C (5)	1.316 (12)
C (7)-C (6)	1.500 (12)	C (8)-C (7)	1.540 (12)
C (9)-C (8)	1.512 (10)	C (10)-C (9)	1.464 (9)
C (11)-C (9)	1.495 (11)	C (11)-C (10)	1.510 (13)
C (12)-C (11)	1.473 (10)	C (13)-O (5)	1.344 (10)
C (20)-O (5)	1.436 (9)	C (13)-O (6)	1.187 (10)
C (24)-O (7)	1.237 (9)	C (24)-O (8)	1.308 (10)
C (14)-C (13)	1.492 (11)	C (15)-C (14)	1.503 (15)
C (16)-C (15)	1.501 (15)	C (17)-C (16)	1.435 (15)
C (18)-C (17)	1.334 (13)	C (19)-C (18)	1.467 (12)
C (20)-C (19)	1.545 (13)	C (21)-C (20)	1.497 (9)
C (22)-C (21)	1.463 (9)	C (23)-C (21)	1.495 (10)
C (23)-C (22)	1.512 (13)	C (24)-C (23)	1.463 (10)
H (1)-O (4)	0.980 (2)	H (21)-C (2)	0.960
H (22)-C (2)	0.960	H (31)-C (3)	0.960

H (32)-C (3)	0.960	H (41)-C (4)	0.960
H (42)-C (4)	0.960	H (51)-C (5)	0.960 (2)
H (61)-C (6)	0.960 (2)	H (71)-C (7)	0.960
H (72)-C (7)	0.960	H (81)-C (8)	0.960
H (91)-C (9)	0.960	H (101)-C (10)	0.960
H (102)-C (10)	0.960	H (111)-C (11)	0.960
H (2)-O (8)	0.980 (2)	H (141)-C (14)	0.960
H (142)-C (14)	0.960	H (151)-C (15)	0.960
H (152)-C (15)	0.960	H (161)-C (16)	0.960
H (162)-C (16)	0.960	H (171)-C (17)	0.960 (2)
H (181)-C (18)	0.960 (2)	H (191)-C (19)	0.960
H (192)-C (19)	0.960	H (201)-C (20)	0.960
H (211)-C (21)	0.960	H (221)-C (22)	0.960
H (222)-C (22)	0.960	H (231)-C (23)	0.960

Table A1.3.

Bond angles (deg.) for $8S,9R,11R$-(-)-**152**.

C (8)-O (1)-C (1)	118.7 (6)	O (2)-C (1)-O (1)	123.3 (7)
C (2)-C (1)-O (1)	109.6 (7)	C (2)-C (1)-O (2)	127.1 (8)
C (3)-C (2)-C (1)	111.3 (7)	C (4)-C (3)-C (2)	116.7 (7)
C (5)-C (4)-C (3)	114.0 (8)	C (6)-C (5)-C (4)	131.3 (8)
C (7)-C (6)-C (5)	127.3 (9)	C (8)-C (7)-C (6)	111.9 (7)
C (7)-C (8)-O (1)	105.9 (6)	C (9)-C (8)-O (1)	108.0 (6)
C (9)-C (8)-C (7)	113.5 (7)	C (10)-C (9)-C (8)	120.1 (7)
C (11)-C (9)-C (8)	117.5 (7)	C (11)-C (9)-C (10)	61.4 (6)
C (11)-C (10)-C (9)	60.3 (5)	C (10)-C (11)-C (9)	58.3 (6)
C (12)-C (11)-C (9)	117.8 (6)	C (12)-C (11)-C (10)	119.6 (7)
O (4)-C (12)-O (3)	123.2 (8)	C (11)-C (12)-O (3)	122.8 (9)
C (11)-C (12)-O (4)	114.0 (8)	C (20)-O (5)-C (13)	117.9 (7)

O (6)-C (13)-O (5)	123.7 (8)	C (14)-C (13)-O (5)	109.9 (8)
C (14)-C (13)-O (6)	126.4 (9)	C (15)-C (14)-C (13)	112.1 (9)
C (16)-C (15)-C (14)	118.9 (8)	C (17)-C (16)-C (15)	112.8 (10)
C (18)-C (17)-C (16)	131.5 (9)	C (19)-C (18)-C (17)	126.3 (11)
C (20)-C (19)-C (18)	114.9 (8)	C (19)-C (20)-O (5)	105.4 (6)
C (21)-C (20)-O (5)	107.7 (7)	C (21)-C (20)-C (19)	111.1 (7)
C (22)-C (21)-C (20)	121.2 (7)	C (23)-C (21)-C (20)	119.3 (7)
C (23)-C (21)-C (22)	61.5 (5)	C (23)-C (22)-C (21)	60.3 (6)
C (22)-C (23)-C (21)	58.2 (5)	C (24)-C (23)-C (21)	116.0 (7)
C (24)-C (23)-C (22)	117.3 (8)	O (8)-C (24)-O (7)	121.1 (8)
C (23)-C (24)-O (7)	123.1 (9)	C (23)-C (24)-O (8)	115.8 (8)
C (12)-O (4)-H (1)	114.2 (46)	H (21)-C (2)-C (1)	109.0 (5)
H (22)-C (2)-C (1)	109.0 (5)	H (22)-C (2)-H (21)	109.5
C (3)-C (2)-H (21)	109.0 (5)	C (3)-C (2)-H (22)	109.0 (5)
H (31)-C (3)-C (2)	107.7 (5)	H (32)-C (3)-C (2)	107.6 (5)
H (32)-C (3)-H (31)	109.5	C (4)-C (3)-H (31)	107.7 (6)
C (4)-C (3)-H (32)	107.6 (5)	H (41)-C (4)-C (3)	108.3 (6)
H (42)-C (4)-C (3)	108.4 (5)	H (42)-C (4)-H (41)	109.5
C (5)-C (4)-H (41)	108.3 (6)	C (5)-C (4)-H (42)	108.4 (6)
H (51)-C (5)-C (4)	110.5 (43)	C (6)-C (5)-H (51)	118.1 (44)
H (61)-C (6)-C (5)	121.0 (47)	C (7)-C (6)-H (61)	111.7 (47)
H (71)-C (7)-C (6)	108.8 (5)	H (72)-C (7)-C (6)	108.9 (5)
H (72)-C (7)-H (71)	109.5	C (8)-C (7)-H (71)	108.9 (5)
C (8)-C (7)-H (72)	108.9 (5)	H (81)-C (8)-O (1)	114.2 (4)
H (81)-C (8)-C (7)	108.8 (5)	C (9)-C (8)-H (81)	106.6 (4)
H (91)-C (9)-C (8)	91.5 (4)	C (10)-C (9)-H (91)	133.4 (4)
C (11)-C (9)-H (91)	135.5 (3)	H (101)-C (10)-C (9)	119.9 (5)
H (102)-C (10)-C (9)	119.9 (5)	H (102)-C (10)-H (101)	109.5
C (11)-C (10)-H (101)	119.9 (5)	C (11)-C (10)-H (102)	120.0 (5)

H (111)-C (11)-C (9)	136.5 (3)	H (111)-C (11)-C (10)	135.0 (4)
C (12)-C (11)-H (111)	91.6 (6)	C (24)-O (8)-H (2)	115.8 (47)
H (141)-C (14)-C (13)	108.8 (6)	H (142)-C (14)-C (13)	108.8 (6)
H (142)-C (14)-H (141)	109.5	C (15)-C (14)-H (141)	108.8 (6)
C (15)-C (14)-H (142)	108.8 (6)	H (151)-C (15)-C (14)	107.1 (6)
H (152)-C (15)-H (14)	107.0 (6)	H (152)-C (15)-H (151)	109.5
C (16)-C (15)-H (151)	107.1 (7)	C (16)-C (15)-H (152)	107.1 (7)
H (161)-C 16)-C (15)	108.6 (6)	H (162)-C (16)-C (15)	108.7 (6)
H (162)-C (16)-H (161)	109.5	C (17)-C (16)-H (161)	108.6 (7)
C (17)-C (16)-H (162)	108.7 (7)	H (171)-C (17)-C (16)	102.8 (51)
C (18)-C (17)-H (171)	123.8 (50)	H (181)-C (18)-C (17)	128.9 (48)
C (19)-C (18)-H (181)	101.4 (47)	H (191)-C (19)-C (18)	108.0 (6)
H (192)-C (19)-C (18)	108.2 (7)	H (192)-C (19)-H (191)	109.5
C (20)-C (19)-H (191)	108.0 (5)	C (20)-C (19)-H (192)	108.2 (5)
H (201)-C (20)-O (5)	113.6 (5)	H (201)-C (20)-C (19)	110.6 (5)
C (21)-C (20)-H (201)	108.4 (4)	H (211)-C (21)-C (20)	89.7 (5)
C (22)-C (21)-H (211)	133.5 (4)	C (23)-C (21)-H (211)	135.2 (4)
H (221)-C (22)-C (21)	119.9 (5)	H (222)-C (22)-C (21)	120.0 (5)
H (222)-C (22)-H (221)	109.5	C (23)-C (22)-H (221)	119.9 (5)
C (23)-C (22)-H (222)	120.0 (5)	H (231)-C (23)-C (21)	136.4 (3)
H (231)-C (23)-C (22)	135.3 (4)	C (24)-C (23)-H (231)	93.9 (6)