New Methods for Carbohydrate Annulation

Thesis submitted for the degree of
Doctor of Philosophy
at the University of Leicester

by

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University of Leicester

October 1996

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STATEMENT

The accompanying thesis submitted for the degree of Ph.D. entitled "New Methods for Carbohydrate Annulation" is based on work conducted by the author in the Department of Chemistry at the University of Leicester between the period October 1993 to September 1996.

All the work recorded in this thesis is original unless otherwise acknowledged in the text or by references. None of the work has been submitted for another degree in this or any other university.

Signed: .... Date: 22nd October 1996

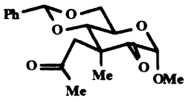
Parts of this work have been published as a communication.
The Synthesis and X-Ray Crystal Structure of a Cyclopentaannulated Sugar; The First Example of an Intramolecular Aldol Cyclopentaannulation in Carbohydrate Chemistry, A. J. Wood, P. R. Jenkins, J. Fawcett, D. R. Russell, *J. Chem. Soc., Chem. Commun.*, 1995, 1567.

New Methods for Carbohydrate Annulation

by Andrew Joseph Wood

ABSTRACT

Chapter 1 describes the synthesis of a 1,4-dicarbonyl compound **1** which was constructed by a sequence involving opening of a protected glucose epoxide with allyl magnesium chloride, alkylation and Wacker oxidation; the 1,4-dicarbonyl compound **1** readily underwent cyclisation under basic conditions to produce the cyclopentaannulated sugar derivative **2**. Treatment of the cyclopentaannulated sugar derivative with N-bromosuccinimide and subsequent treatment with activated zinc completed the fragmentation of **2** to furnish the cyclopentanes **3**.



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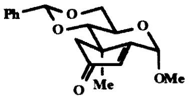

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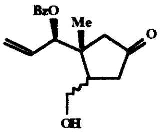

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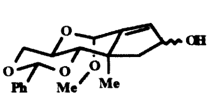
Chapter 2 describes the reduction of **2** which furnished a mixture of allylic alcohols **4** in a ratio of 8:1 in favour of either isomer depending on the conditions and reagents employed. The application of a Stork silyl methylene radical cyclisation of the α-cyclopentaannulated derivative led to a 2:1 mixture of *trans* and *cis* fused tricyclic ring systems. Treatment of the β-allylic cyclopentaannulated derivative, however, led to a single *cis*-fused product **5**. This is in contrast to previous examples which show a mixture of *cis* and *trans*-fused 6,5-ring systems.



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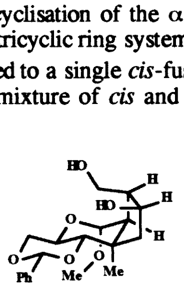

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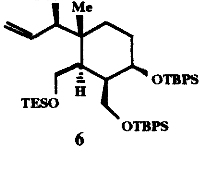
Chapter 3 describes the continuation of work in the Jenkins group directed towards the synthesis of taxanes from glucose. A model study was undertaken to show the viability of a stepwise diene synthesis utilising selenium chemistry. This succesful model study showed that an enone to diene conversion was possible. The application of this methodology to the C-ring synthon **6** produced **7**, the most advanced intermediate to date, as a single isomer.



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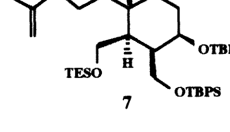

7

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Lastly, I would like to thank my wife, Sally, for all her love, help and encouragement, especially over the final three months; to her I dedicate this thesis.

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ABBREVIATIONS

10-DAB III	10-deacetyl baccatin III
Ac	acetate
AIBN	α,α'-azoisobutyronitrile
BOM	benzyloxymethyl
CI	chemical ionisation
DBN	1,5-diazabicyclo[4.3.0]non-5-ene
DBU	1,8-diazabicylo(5.4.0.)undec-7-ene
DMAP	4-dimethylaminopyridine
DMF	*N,N*-dimethylformide
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
EI	electrical ionisation
ESR	electron spin resonance
FAB	fast atom bombardment
KHMDS	potassium hexamthyldisilazide
LDA	lithium diisopropylamide
LTMP	lithium 2,2,6,6-tetramethylpiperidide
mCPBA	*meta*-chloroperbenzoic acid
NBS	*N*-bromosuccinimide
^{n}BuLi	normal-butyllithium
NMR	nuclear magnetic resonance
n.O.e.	nuclear Overhauser effect
PCC	pyridinium chlorochromate
PPTS	pyridinium *para*-toluene-sulphonate
^{s}BuLi	secondary-butyllithium
Si^{t}BuMe$_2$	tertiary butyldimethylsilyl
TASF	tris(diethylamino)sulphonium difluorotrimethyl silicate
TBPS	tertiary butyldiphenylsilyl

^{t}BuLi	tertiary buyllithium
TES	triethylsilyl
TF	trifluoromethane sulphonyl
THF	tetrahydrofuran
TMSCl	trimethylsilyl chloride
TPAP	tetrapropylammonium peruthenate

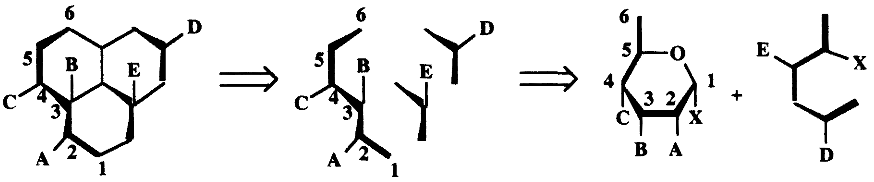
Chapter 1

THE CONVERSION OF CARBOHYDRATE DERIVATIVES INTO FUNCTIONALISED CYCLOPENTANES

CARBOCYCLES FROM CARBOHYDRATES

Carbocyclic molecules are widespread in nature and as a consequence methods for the preparation of rings are the cornerstones of the organic synthesis of natural products. In recent years the specific synthesis of single enantiomers of target molecules has become the standard by which all syntheses are judged. The synthesis of chiral molecules can be achieved in principle by modifying a chiral starting material or using a chiral reagent. Carbohydrates seem an obvious choice as they are a cheap and readily available replenishable source of chiral carbon compounds. They are also available in a variety of forms: cyclic, acyclic, varying chain lengths and oxidation states; they contain a plethora of functional, stereochemical and conformational features which render themselves susceptible to chemical exploitation. The synthesis of natural products from carbohydrates has become much more prevalent in recent years including their use in the synthesis of taxane natural products [1] (See Chapter 3).

The key to the use of carbohydrates in synthesis is to discover a fragment of the target molecule which can be prepared from a carbohydrate. This fragment has been termed a chiron by Hanessian.[2] Scheme 1 illustrates the concept, the target molecule **1** may be broken down into chirons **S**, **R** and **Q**. The chiron **S** has 6 carbon atoms with substituents A, B and C, these 6 carbon atoms could be derived from a sugar **2** where A, B and C are usually oxygen substituents. The sugar **2** is termed a chiral template and much of the chirality of the target molecule is gained from this compound.



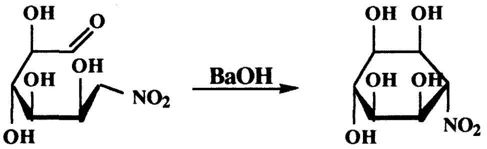
1
Target

Chirons: S R Q

2
Chiral Templates

Scheme 1

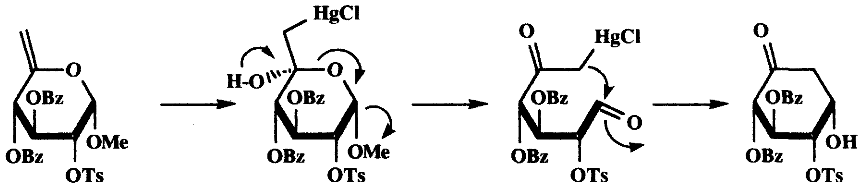
The first rational conversion of a carbohydrate to carbocycle was carried out by Fischer in 1948.[3] The carbohydrate derivative **3** was converted into the cyclohexane analogue **4** *via* a base catalysed intramolecular aldol-like cyclisation (Scheme 2).



3 **4**

Scheme 2

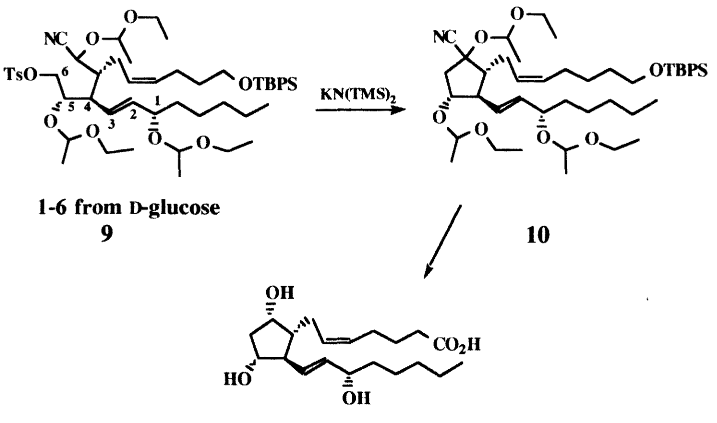
Ferrier was also instrumental in the conversion of carbohydrates to carbocycles when in 1979 he published a convenient procedure for converting carbohydrate derivatives into cyclohexanone analogues.[4] The key step was an hydroxymercuration of the alkene **5** by treatment with mercury(II) chloride in refluxing aqueous acetone. The unstable hemiacetal **6** loses methanol to afford the dicarbonyl compound **7** which then undergoes an aldol-like cyclisation to give the cyclohexanone **8** (Scheme 3).



5 **6** **7** **8**

Scheme 3

A landmark in the use of carbohydrates in the synthesis of non-carbohydrate natural products was shown by Stork in his synthesis of prostaglandin $F_{2\alpha}$ **11** by chiral transfer from D-glucose (Scheme 4).[5] The key step in the synthesis is an S_N2-like displacement of the tosylate by the nitrile stabilised anion of **9** to give the chiral cyclopentane **10**.



1-6 from D-glucose
9

10

Prostaglandin $F_{2\alpha}$
11

Scheme 4

In the example by Ferrier, Scheme 3, all 6 carbon atoms of the sugar are incorporated into the cyclohexanone ring whereas in the example by Stork, Scheme 4, all 6 carbon atoms from D-glucose are incorporated into the molecule but only 3 are contained in the carbocycle. This emphasises the two discrete methods of carbohydrate to carbocycle conversion. In the following literature review those reactions in which all the sugar atoms of the carbocycle are derived from the sugar will be classified as F-type reactions. Those reactions in which some of the carbons making up the carbocycle are derived from a sugar will be classified as S-type reactions.

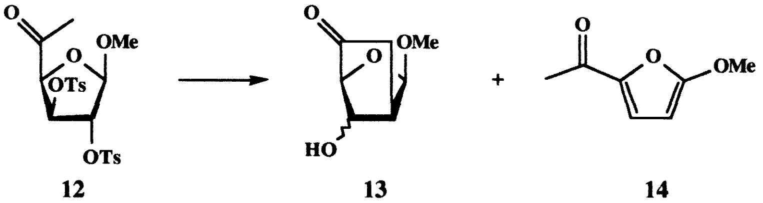
THE CONVERSION OF CARBOHYDRATE DERIVATIVES INTO FUNCTIONALISED CYCLOPENTANES

Carbanion Cyclisations

In the conversion of carbohydrates to carbocycles the use of intramolecular nucleophilic displacement by carbanions or carbanion equivalents is the most popular pathway taken by synthetic chemists. The carbanions are generated most commonly by proton abstraction α to a number of different groups e.g. carbonyl groups (enolate formation), phosphonate groups and nitro groups.

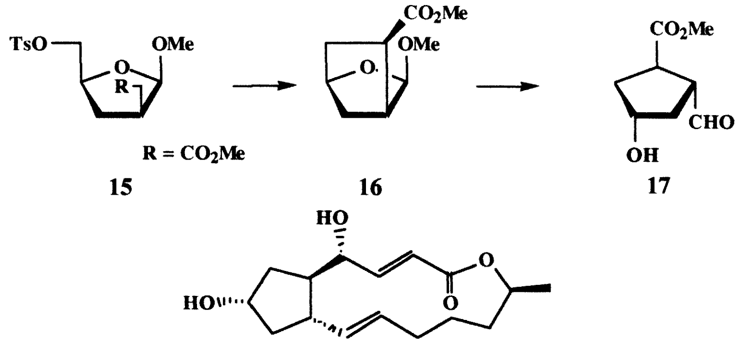
Enolate Carbanions: S-type Conversions

Early attempts to obtain cyclopentane derivatives from carbohydrate derived precursors using an enolate and intramolecular S_N2 displacement met with limited success. The D-glucofuranose derivative **12** afforded the bicyclic ketone **13** (or its isomer) on treatment with DBU in only 34% yield, the major product was the furan **14** in 65% yield [6] (Scheme 5).



Scheme 5

Ohrui and Kuzuhara,[7] as part of their synthesis of (+)-brefeldin A **18**, the biologically active macrocyclic lactone, treated tosylate **15** with lithium hexamethyldisilazide to give the bicyclic product **16** which was then hydrolysed to the cyclopentane **17**, the functionality and stereochemistry of which is congruous with that of (+)-brefeldin A **18** (Scheme 6).



R = CO_2Me

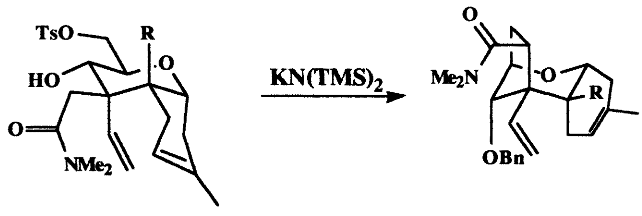
15 16 17

Brefeldin A

18

Scheme 6

In the stereocontrolled synthesis of polycyclic ring systems developed by Fraser-Reid,[8] the *cis*-fused oxadecalin derivative **19** was treated with potassium hexamethyldisilazide to effect the conversion to the tricyclic trichothecene derivative **20** which was isolated as a single diastereoisomer (Scheme 7). The *cis*-fused system is conformationally mobile and thus facilitates the cyclopentane ring formation by an intramolecular nucleophilic displacement of the tosylate anion.

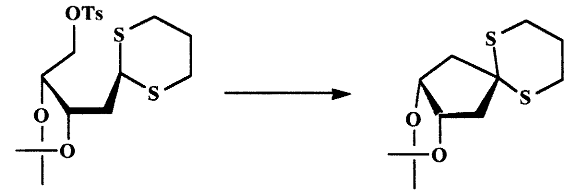


19 R = CO_2Me 20

Scheme 7

Acylanion Equivalent: F-type Conversion

Carbanions derived from dithianes can also be used in the synthesis of cyclopentane rings.[9] On treatment with *n*-butyllithium compound **21** was converted into the cyclopentane **22** (Scheme 8).

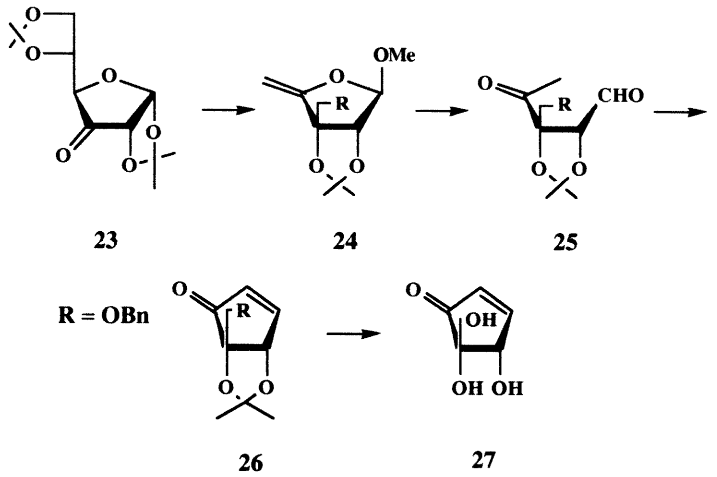


21 **22**

Scheme 8

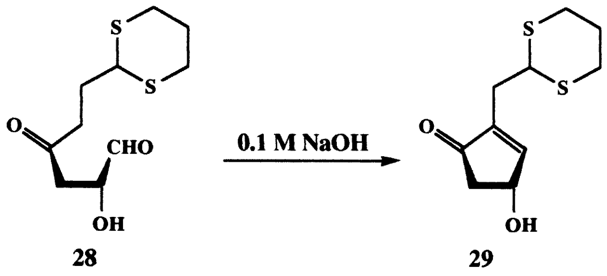
Aldol and Aldol-like Reactions: F-type Conversions

This class of reactions concerns the formation of cyclopentane derivatives from intramolecular nucleophilic attack by enolate, or their equivalents, at aldehyde, ketone, or ester carbonyl groups. The required enolates are most commonly generated by deprotonation of the appropriate dicarbonyl compound. The ring forming step is a 5-*exo*-trig type process[10] and in most cases the resulting β-hydroxy ketones undergo dehydration to the more thermodynamically favoured enones. Moffatt published the first synthesis of a cyclopentane from a carbohydrate derivative some 30 years after the first cyclohexane counterpart.[11] He successfully converted the α-D-ribo-hexofuranos-3-ulose derivative **23** into the unsaturated glycoside **24** which was then hydrolysed into the 1,4-dicarbonyl derivative **25**. The enone **26** was obtained on treatment of **25** with neutral alumina at 100 - 120 °C. This was then transformed into the antibiotic pentomycin I **27** (Scheme 9).


OMe
CHO
R
R = OBn
OH
OH OH
23
24
25
26
27

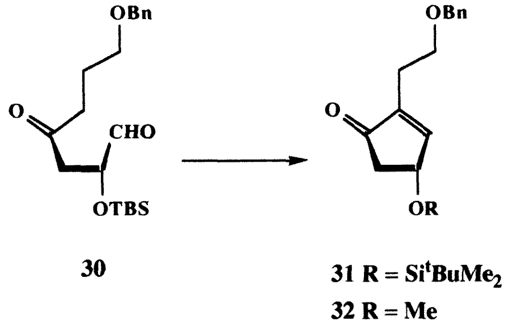
Scheme 9

Achab and Das[12a-c] obtained the potential prostaglandin E_2 precursor **29** by cyclisation of the keto-aldehyde **28** (Scheme 10).


S
S
CHO
OH
0.1 M NaOH
OH
28
29

Scheme 10

Umani-Ronchi experienced difficulty in effecting aldol cyclisation of his keto-aldehyde **30** derived from diacetone glucose, but found that barium hydroxide in methanol effected cyclisation to give the enone **31** together with appreciable amounts of the corresponding methoxy enone **32** and its enantiomer[13] (Scheme 11).



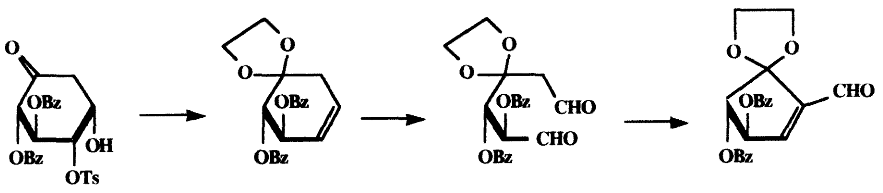
30

31 R = Si^{t}BuMe$_2$

32 R = Me

Scheme 11

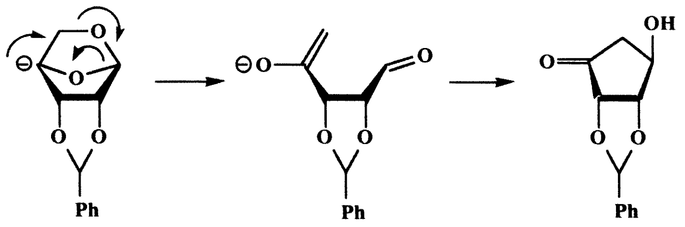
The only known example of a 1,6-dicarbonyl cyclisation from a carbohydrate derived compound came from Ferrier.[14] A cyclohexanone derivative **33** obtained from α-D-glucopyranoside was the source of the cyclohexene **34** and hence the dicarbonyl compound **35**. Aldol cyclisation of this dialdehyde using pyrrolidinium acetate in benzene then gave the unsaturated aldehyde **36** (Scheme 12).



33 **34** **35** **36**

Scheme 12

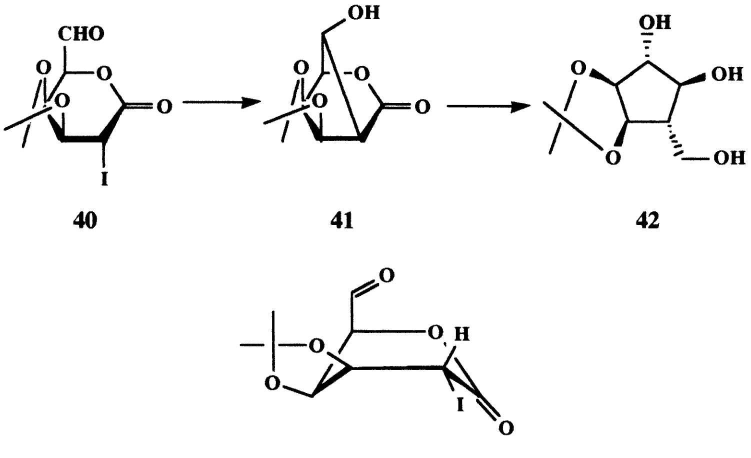
Klemer and Kohla[15] treated 1,5-anhydro-2,3-*O*-benzylidene-β-D-ribofuranose with LDA presumably forming the carbanion **37** enolate **38** and eventually β-hydroxyketone **39** (Scheme 13).


O
O
O O
Ph
O
O O
Ph
OH
O
O O
Ph

37 **38** **39**

Scheme 13

A novel kind of cyclisation occurred when the α-iodolactone **40** was treated with lithium iodide, the resulting enolate attacking the aldehyde to give the cyclopentane **41**, reduction of which produced the triol **42** (Scheme 14).[16] This cyclisation is thought to occur *via* the proposed conformation **43**.


CHO
O
O
O
O
I
OH
O
O
O
O
OH
OH
O
O
OH
O
O
O
H
I
O

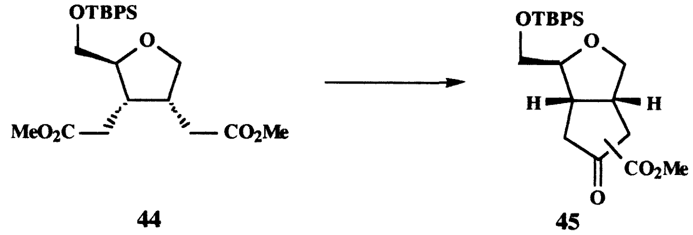
40 **41** **42**

43

Scheme 14

Aldol and Aldol-like Reactions: S-type Conversions

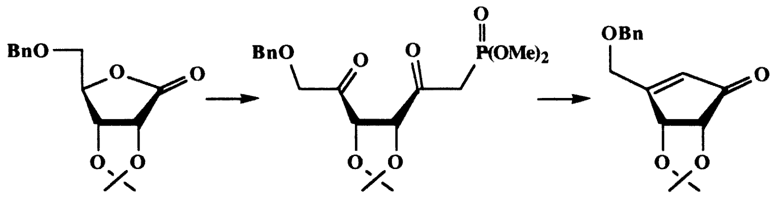
There are few examples of the S-type conversions of carbohydrates into functionalised cyclopentanes. Mann, however, successfully completed the Dieckmann cyclisation of the diester **44** into the keto-esters **45** (Scheme 15).[17] This method was later used in the synthesis of prostacyclin and carbocyclin analogues.[18]



Scheme 15

Phosphonate Stabilised Species: F-Type Conversions

Reactions involving aldol-like cyclisation of carbanions which are stabilised both by neighbouring phosphonate and carbonyl groups have been used in the enantioselective synthesis of cyclopentane derivatives from carbohydrates. Lim and Marquez[19] used the lactone **46** which was treated with lithium dimethylphosphonate and then sodium methoxide in methanol to give the ring opened alcohol which was then oxidised using the Collins' reagent to the dicarbonyl **47**. Cyclisation was effected by heating with potassium carbonate and 18-crown-6 in toluene to give the cyclopentanone **48** (Scheme 16).



46

47

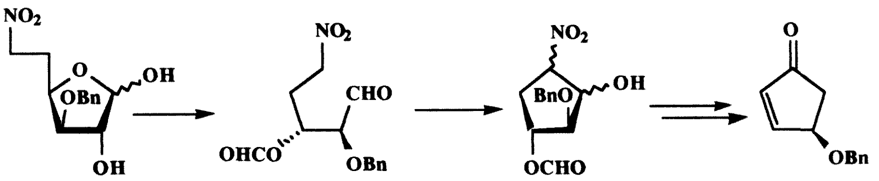
48

Scheme 16

Similar syntheses have been undertaken by other groups where the intermediate compounds to be cyclised have all been of the same structural type.[20]

Nitrogen Stabilised Species: S-type Conversion

Torii started with nitrofuranose **49** which was treated with sodium periodate. The resultant open chain aldehyde **50** cyclised upon treatment with triethylamine to give a mixture of nitrocyclopentanols **51**, which were then converted into the enone prostaglandin synthon **52** (Scheme 17).[21]



49

50

51

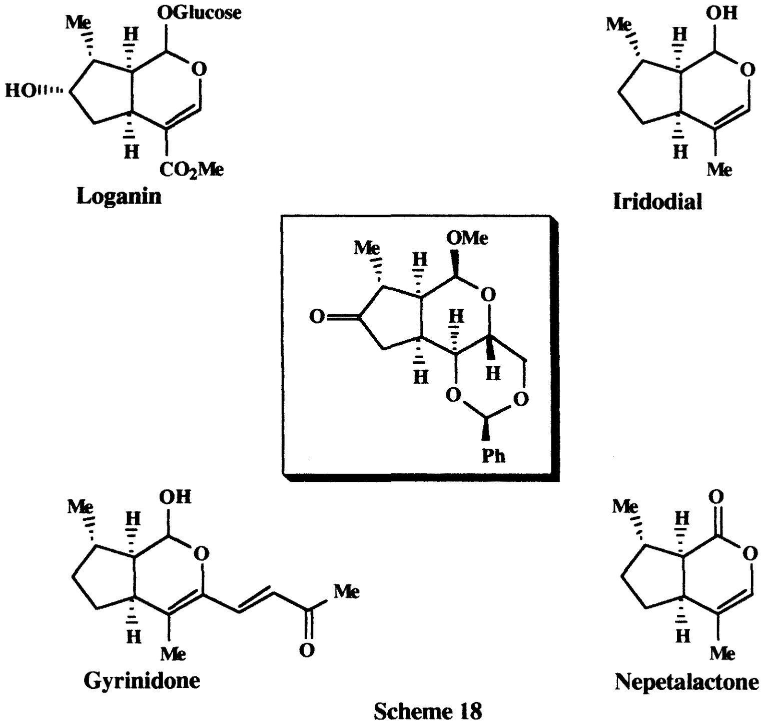
52

Scheme 17

NEW S-TYPE SUGAR ANNULATIONS

The iridoid natural products are a huge class of structures consisting mostly of cyclopentaannulated sugars.[22] Concise, simple methods for the cyclopentaannulation of sugar derivatives would consequently have great potential in the synthesis of iridoids and other targets. Scheme 18 shows a general structure for a cyclopentaannulated sugar in the highlighted box and its relationship to 4 iridoidal structures. Two of the sugar carbons are contained in the five-membered ring and the five-six-ring junction is almost always *cis*. Clearly an S-type synthesis is required where only two of the sugar carbons end up in the five-membered ring and both the sugar and the cyclopentane are in the iridoid target. In fact a definite class of S-type reactions is required here in which the sugar is cyclopentaannulated.

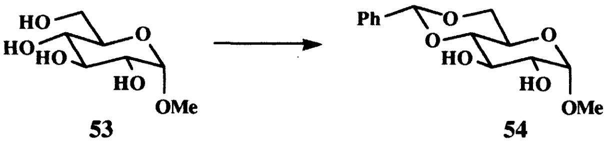
To date the synthesis of cyclopentaannulated sugars has been achieved most commonly by using radical reactions which will be covered in Chapter 2. Our aim was to develop a simple method for the cyclopentaannulation of a glucose derivative and to fragment the sugar to leave a chiral cyclopentane.


Me
H
OGlucose
O
HO
H
CO2Me
Loganin
Me
H
OH
O
H
Me
Iridodial
Me
H
OMe
O
O
H
H
H
O
O
Ph
Me
H
OH
O
H
Me
Me
O
Gyrinidone
Me
H
O
O
H
Me
Nepetalactone

Scheme 18

Work Carried Out at Leicester

The starting point for our work was the protection of methyl-α-D-glucopyranoside **53** by reaction with benzaldehyde dimethylacetal to afford the diol **54** [23] (Scheme 19).

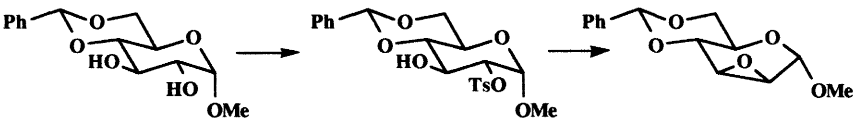


53 **54**

Scheme 19

Synthesis of Sugar Epoxides

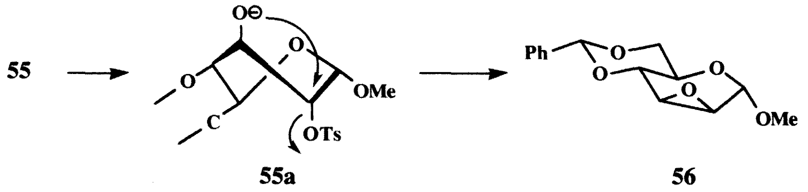
The next step was the preparation of the glucose-2,3 epoxides. Treatment of the diol **54** with *p*-toluenesulphonyl chloride and triethylamine gave the selectively tosylated product **55**.[24] This was then treated with sodium hydride to yield the epoxide **56** [25] (Scheme 20).



54 **55** **56**

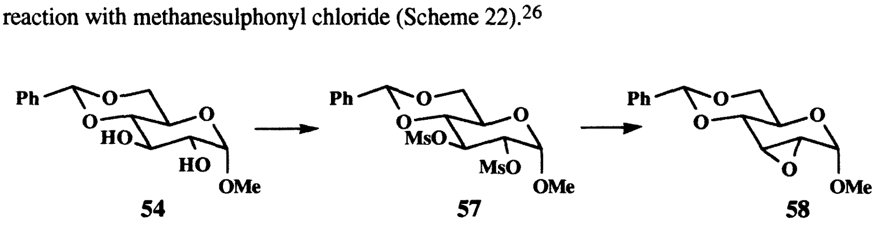
Scheme 20

The intramolecular epoxidation involves an S_N2-like reaction where the tosylate group and the alkoxide anion must be anti-periplanar leading to inversion of configuration at C-2. In structure **55** the tosylate and alkoxide anion are diequatorial and the *trans*-ring junction prevents ring flipping to the alternative chair conformation. The *trans*-diaxial arrangement of the tosylate and alkoxide anion is achieved through the adoption of a twist boat conformation **55a** (Scheme 21).


55
55a
56
O⊖
O
OTs
OMe
C
Ph
O
O
O
O
OMe

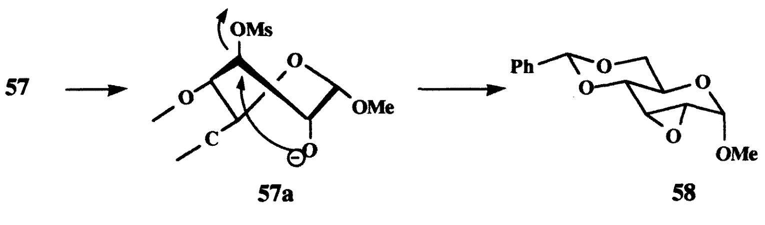
Scheme 21

The isomeric epoxide **58** was prepared by converting the diol **54** into the dimesylate **57**, by reaction with methanesulphonyl chloride (Scheme 22).[26]


Ph
O
O
HO
HO
O
OMe
54
Ph
O
O
MsO
MsO
O
OMe
57
Ph
O
O
O
O
OMe
58

Scheme 22

Treatment of the dimesylate **57** with sodium methoxide selectively deprotected the C-2 position leaving the mesylate and alkoxide anion diequatorially arranged. The twist boat confirmation **57a** was adopted to give the transdiaxial arrangement required for the S_N2-like displacement, yielding the epoxide **58** [26] (Scheme 23).


57
OMs
O
O
C
OMe
⊖O
57a
Ph
O
O
O
O
OMe
58

Scheme 23

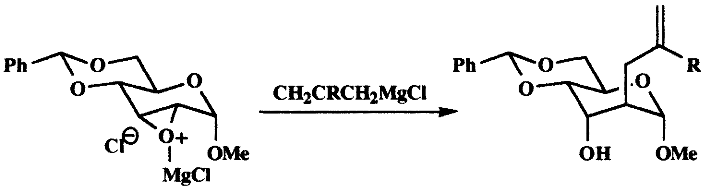
The Reaction of Grignard Reagents with Epoxy Sugars

The next step in the synthesis required the selective opening of the epoxide with Grignard reagents. In order to understand the reaction of a Grignard reagent with an epoxide we first need to consider the Schlenk equilibrium[27] (Scheme 24). The Grignard reagent, allylmagnesium chloride, is in equilibrium with diallylmagnesium and magnesium chloride.

$$2CH_2CHCH_2MgCl \rightleftharpoons (CH_2CHCH_2)_2Mg + MgCl_2$$

Scheme 24

Co-ordination of the Lewis acid $MgCl_2$ to the epoxide **58a** followed by an S_N2 displacement at C-2 by allylmagnesium chloride or diallylmagnesium gives the *trans*-diaxial opened alcohol **59a**.[28] The analogous alcohol **59b**[28] was obtained using 2-methyl-2-propenylmagnesium chloride; the chloride ion is not a strong enough nucleophile to cleave the epoxide (Scheme 25).

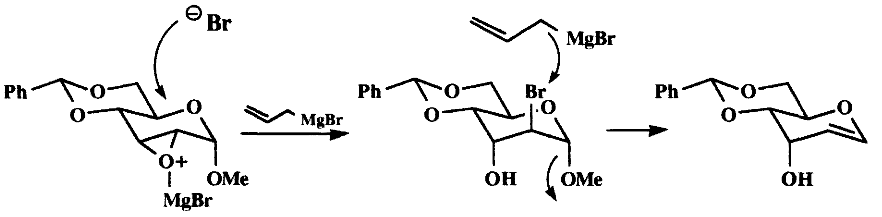


58a

59a R = H
59b R = Me

Scheme 25

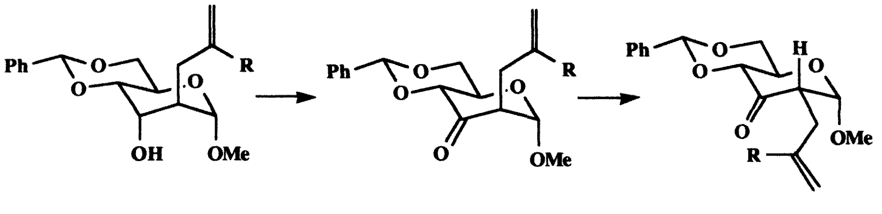
The use of bromo-Grignard reagents results in a different product.[29] The $MgBr_2$ again co-ordinates to the epoxide **58b** but the bromide ion is a strong enough nucleophile to open the epoxide ring resulting in the bromohydrin **60**. This is attacked further by the allylmagnesium bromide resulting in the elimination product **61** (Scheme 26).



58b **60** **61**

Scheme 26

The alcohols **59a** and **59b** were then oxidised using the Swern procedure[30] to the ketones **62a** and **62b**. The next step was the epimerisation of the allylic group at C-2. Ferrier had previously reported that epimerisation of **62a** could not be effected.[31] However, treatment of ketone **62a** with triethylamine in DMF for 36 hours was found to epimerise the C-2 centre to give the ketone **63a**, ketone **62b** required a stir period of 3 days to completely epimerise the C-2 centre (Scheme 27).



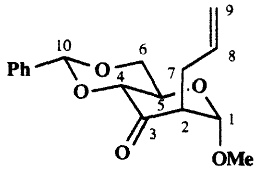
59a R = H
59b R = Me

62a R = H
62b R = Me

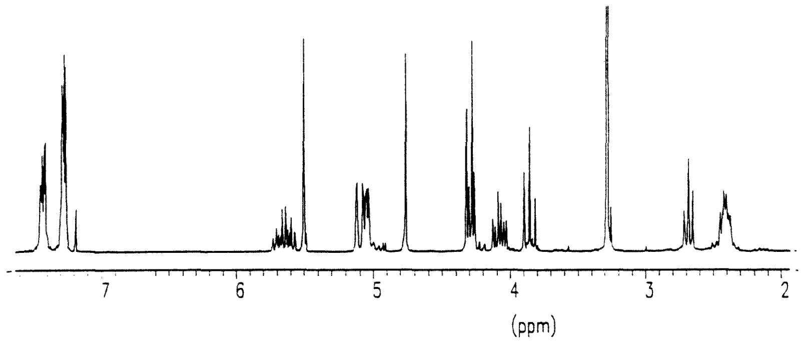
63a R = H
63b R = Me

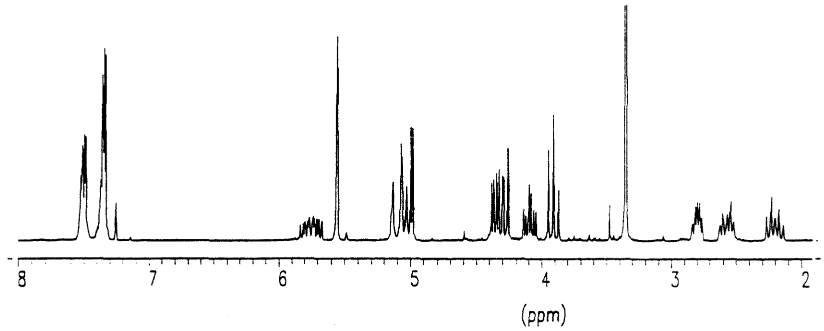
Scheme 27

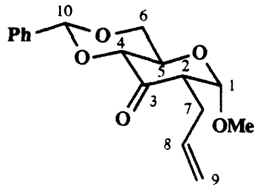
Comparison of the ^1H NMR data for the epimerised ketone **63a** and the parent ketone **62a** shows that H-2 **62a** shows a triplet J 8.2 Hz, and the methylene hydrogens show a multiplet, where H-2 **63a** shows a multiplet and the methylene protons are now two discrete signals. Ferrier reported that J_{1-2} was 0 Hz for the ketone **62a**, where the epimerised ketone **63a** shows J_{1-2} 4.1 Hz (Scheme 28).[31] Similar changes in the NMR data are seen for the ketone **63b**.


9
10
6
8
Ph
O
O
4
7
O
5
O
3
2
1
OMe

62a



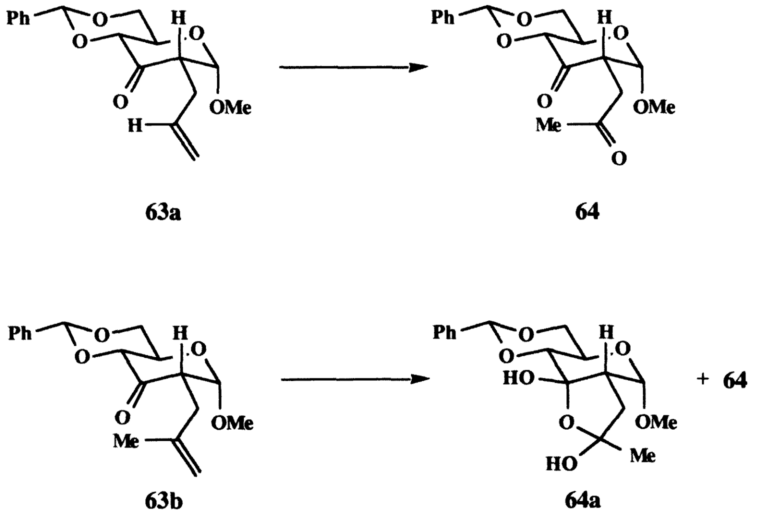



10
6
Ph
O
O
4
O
5
2
1
3
7
O
OMe
8
9

63a

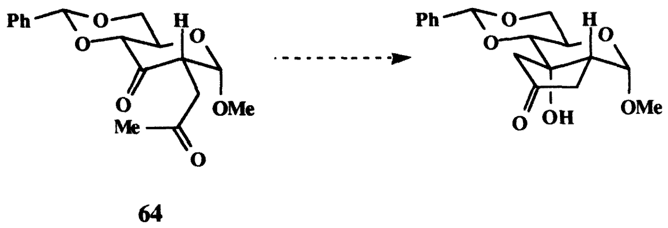
Scheme 28

After epimerisation, oxidation of the olefin **63a** to the 1,4-dicarbonyl compound **64** was achieved by reaction with palladium chloride, water and copper(II) chloride in a Wacker oxidation.[32] The ketone **63b** was also converted to the diketone **64** by ozonolysis but the reaction proved to be very problematic and low yielding with the acetal **64a** being isolated from the reaction mixture as the major product (Scheme 29).



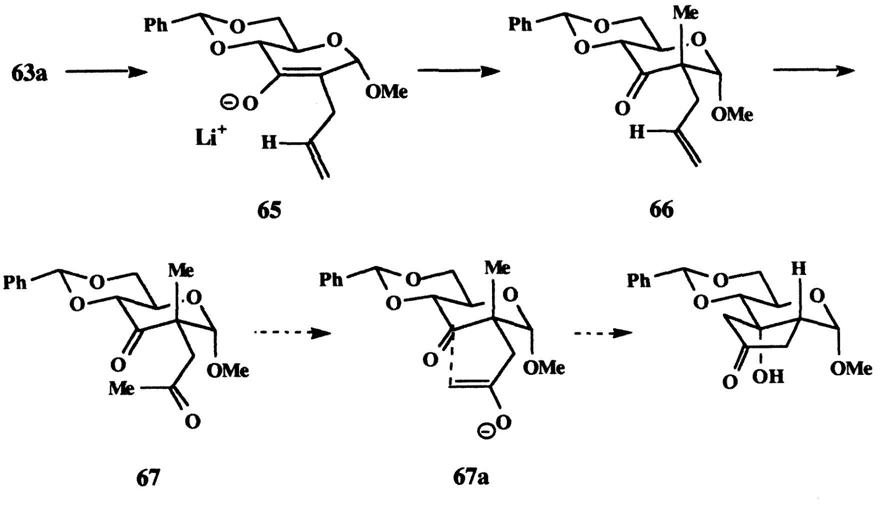
Scheme 29

We were now in a position to attempt cyclisation of the dicarbonyl compound **64** *via* an intramolecular aldol reaction. Treatment of the diketone **64** with sodium hydroxide in refluxing methanol failed to give any of the cyclised product. Decomposition was observed when the diketone **64** was treated with lithium hexamethyldisilazide (Scheme 30).[33]



Scheme 30

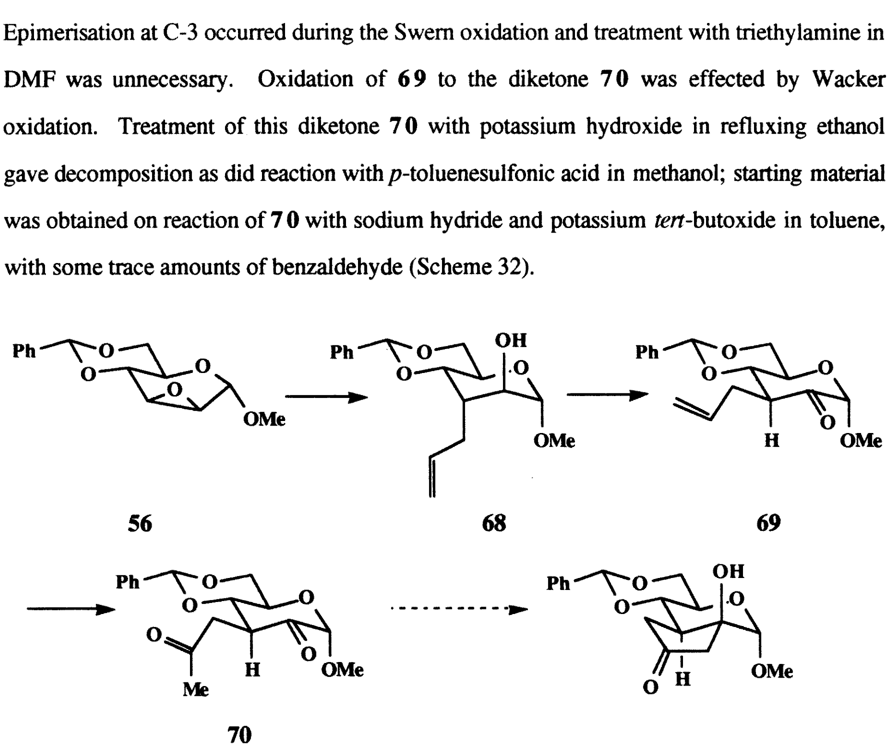
The problem was thought to be due to deprotonation at C-2 rather than the end of the sidechain required for cyclisation. To overcome this problem treatment of the diketone **63a** with LTMP, to generate the enolate **65**, and reaction with methyl iodide, to form a quaternary centre at C-2, produced compound **66**, albeit in a poor yield. The observed product results from alkylation on the less hindered β-face of the enolate **65** as previously observed by Chapleur.[34] Clearly an alternative site for deprotonation exists at C-4 and alkylation has been observed at this site as the minor product when attempting alkylation at C-2.[34] The ketone **66** was converted to a diketone **67** *via* a Wacker oxidation. Cyclisation of this diketone **67** was attempted with potassium *tert*-butoxide in toluene, sodium carbonate in methanol and sodium methoxide in methanol, in all cases starting material was obtained with trace amounts of benzaldehyde (Scheme 31). Clearly the conformation of the enolate **67a** in which the enolate carbon and the carbonyl group are close enough to form a bond is sterically unfavoured.



Scheme 31

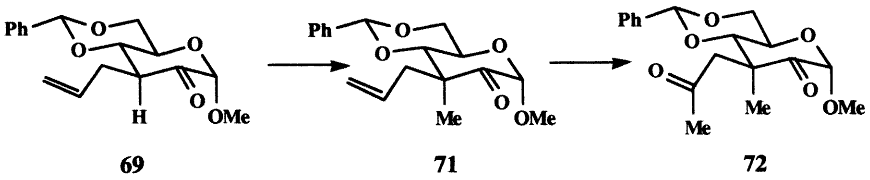
Attention was then switched to the alternative epoxide **56**. In the same way as the epoxide **58** the epoxide **56** was opened with allymagnesium chloride[28] to furnish the alcohol **68**, which was subsequently oxidised to the ketone **69** using the Swern procedure.

Epimerisation at C-3 occurred during the Swern oxidation and treatment with triethylamine in DMF was unnecessary. Oxidation of **69** to the diketone **70** was effected by Wacker oxidation. Treatment of this diketone **70** with potassium hydroxide in refluxing ethanol gave decomposition as did reaction with *p*-toluenesulfonic acid in methanol; starting material was obtained on reaction of **70** with sodium hydride and potassium *tert*-butoxide in toluene, with some trace amounts of benzaldehyde (Scheme 32).



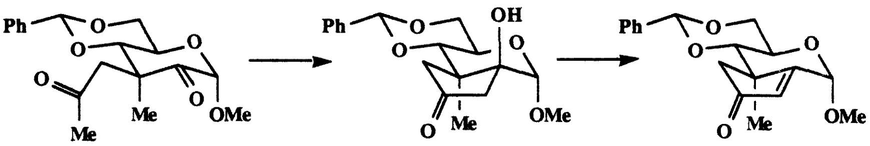
Scheme32

The problem again appeared to be deprotonation α to the ketone at C-2 of **70** rather than at the end of the sidechain. The ketone **69** was treated with sodium hexamethyldisilazide and methyl iodide to give the ketone **71** which now contains a quaternary centre at C-3. This was then oxidised to the diketone **72** by a Wacker oxidation (Scheme 33).



Scheme 33

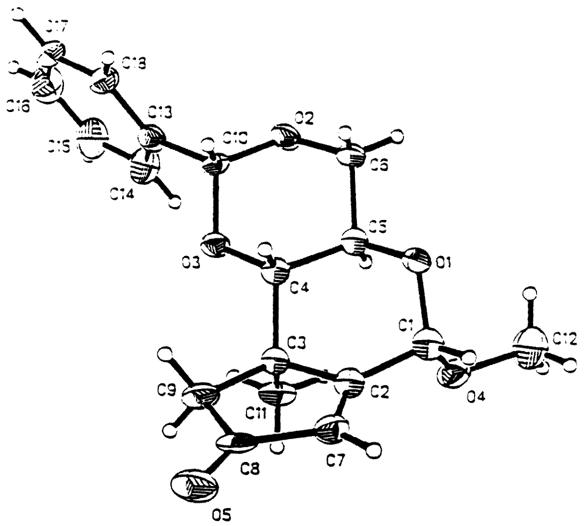
Cyclisation of the diketone **72** was achieved at the first attempt with potassium *tert*-butoxide in toluene to produce the alcohol **73** and enone **74** in excellent yield.[33] The alcohol **73** was difficult to isolate as elimination of water occurred during purification to give the thermodynamically more stable enone **74** (Scheme 34).


Ph
O
O
O
Me
O
Me
OMe
Ph
O
OH
O
O
O
Me
OMe
Ph
O
O
O
O
Me
OMe

72 **73** **74**

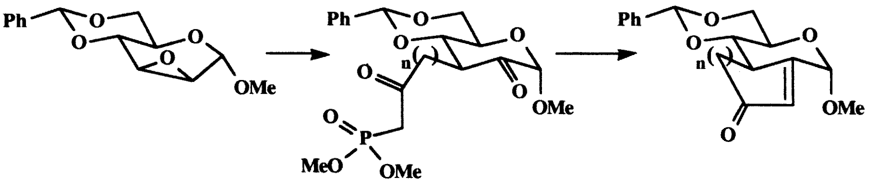
Scheme 34

The absolute configuration of the enone **74** was proven by X-ray crystallography (Scheme 35).


C17
C18
C16
C13
C10
O2
C6
C15
C14
C5
O3
O1
C4
C1
C12
C3
C9
C2
O4
C11
C8
C7
O5

Scheme 35

A recent publication by Ermolenko[35] demonstrated the use of phosphonate stabilised anions in S-type conversions of carbohydrate derivatives into annulated derivatives. The key step in the conversions is an intramolecular Horner-Wadsworth-Emmons olefination of vicinal β-ketophosphonates of pyranosulosides (Scheme 36). The starting material was the epoxide **56** which was converted into the compounds **75** and **76** in 7 and 9 steps respectively. Cyclisation was affected by treatment with potassium carbonate and 18-crown-6 to afford the cyclopentanone **77** and cyclohexanone **78**.



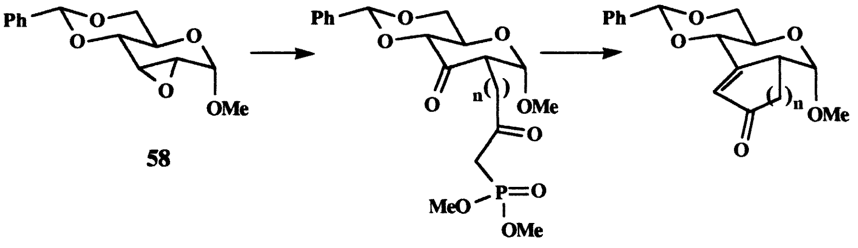
56

75 n = 1
76 n = 2

77 n = 1
78 n = 2

Scheme 36

Using the same methodology the epoxide **58** was converted to the cyclopentanone **81** and cyclohexanone **82** in 8 and 9 steps respectively *via* the corresponding β-ketophosphonates **79** and **80** (Scheme 37).[35]



58

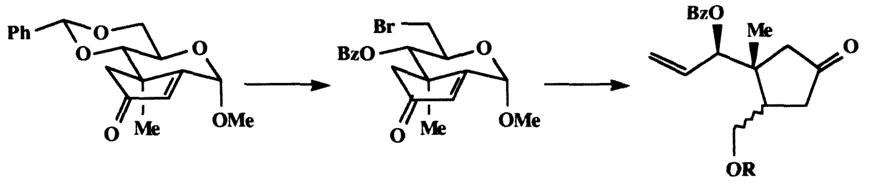
79 n = 1
80 n = 2

81 n = 1
82 n = 2

Scheme 37

Carbohydrate to Chiral Cyclopentane

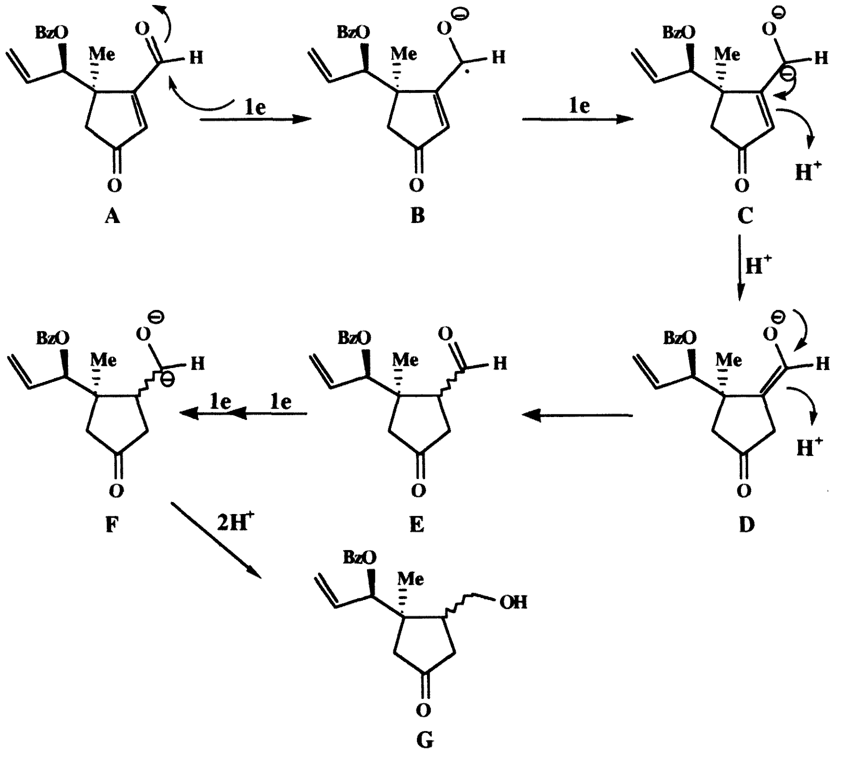
The fragmentation of the benzylidene group of the enone **74** was achieved upon treatment with NBS following the method of Hanessian.[36] The resulting bromo-ester **83** was treated with activated zinc according to the method of Vasella[37] to produce a mixture of the alcohols **84** in good yield. The fragmentation reactions were carried out by Erasmus student, Maria Dominguez. The diastereoisomers were then separated by conversion to the *p*-nitrobenzoate derivatives **85a** and **85b** (Scheme 38).



74 **83** **84 R = H**
85a,b R = *p*-nitrobenzoate

Scheme 38

The initial product from the treatment of the bromo-ester **83** is the keto-aldehyde **A** which contains the enedione functionality. There are several examples of the reduction of the olefin in this grouping using zinc.[38] A proposed mechanism for the reduction of this compound is shown in Scheme 39. The first step is sequential electron transfer on to **A** giving radical anion **B** and then dianion **C**. Protonation produces the enolate **D** which is protonated to give the dicarbonyl **E**. Electron transfer again gives the dianion **F** which is then protonated to give the observed product **G**.

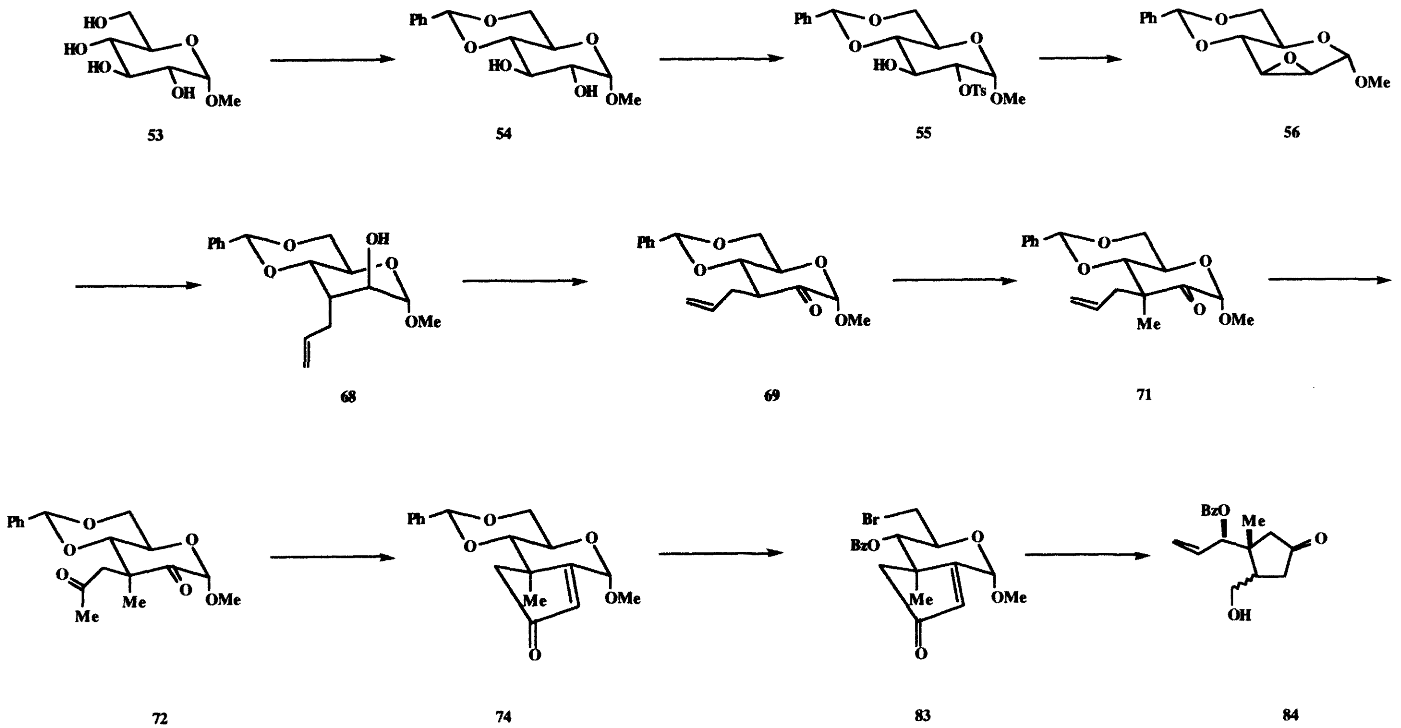


Scheme 39

The overall conversion is illustrated in Scheme 40, which shows the conversion of α-D-glucopyranoside **53** into functionalised cyclopentanes **84** which were esterified and separated by column chromatography.

Summary

In conclusion we have developed a route for the cyclopentaannulation of a glucose derivative which may prove useful in the synthesis of iridoids, and produces chiral cyclopentanes containing a quaternary centre upon fragmentation of the sugar rings.


53
54
55
56
68
69
71
72
74
83
84
HO
OH
OMe
Ph
O
OTs
Me
Br
BzO

Scheme 40

Chapter 2

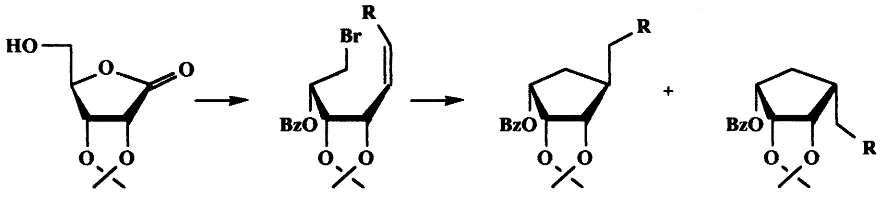
RADICAL REACTIONS OF CARBOHYDRATE DERIVATIVES

RADICAL REACTIONS OF CARBOHYDRATE DERIVATIVES

Annulation of carbohydrate derivatives using radical reactions has been studied extensively over the last 10 years.[39] There are many examples of radical reactions of sidechains appended to carbohydrates which may be classed as S-type reactions as only two of the carbohydrate carbons usually end up in the carbocycle. The sugar ring can be removed at a later stage to yield highly functionalised carbocycles. There are also examples of the F-type reactions involving radical cyclisation.

F-type Cyclisations

Wilcox used D-ribono-γ-lactone **86** as starting material and converted it into the acyclic bromoester **87**. Treatment of the bromoester **87** with tributyltin hydride gave the functionalised cyclopentanes **88** and **89** in a ratio of 10:1 (Scheme 41).[40] The predominant cyclopentane derivative obtained was **88** which has the sidechain with the ester group in an *exo* orientation that is expected if the 5-*exo*-trig radical cyclisation proceeds through the chair-like transition state suggested by Beckwith.[41]

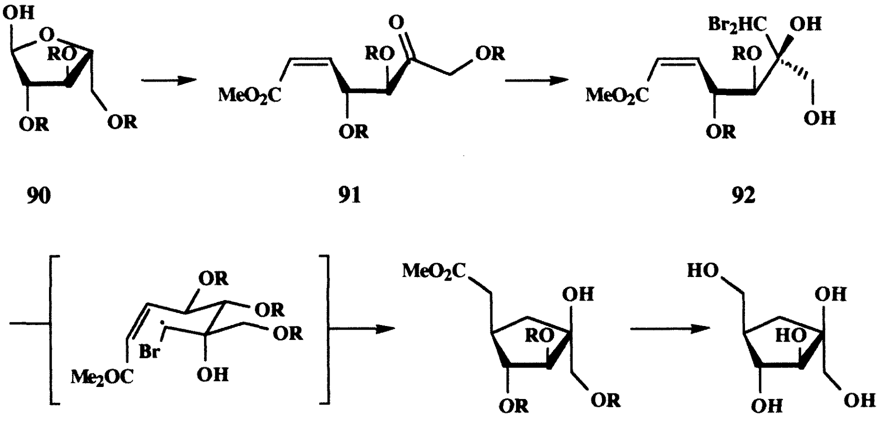


86 **87** **88** **89**

$R = CO_2Et$

Scheme 41

In similar work the D-arabinose derivative was converted into the acyclic ketone **91** *via* a Wittig reaction and Swern oxidation of the resultant alcohol.[42] Nucleophilic addition of (dibromomethyl)lithium gave the radical precursor **92**. Cyclisation was achieved on treatment with tributyltin hydride which furnished the functionalised cyclopentane **93** *via* a chair transition state **92a.** This was later converted into the carbocyclic analogue of an enzyme regulator[43] (Scheme 42).



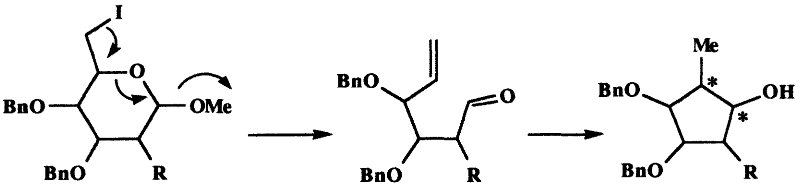
90 **91** **92**

92a **93**

Enzyme regulator analogue

Scheme 42

Recently a procedure for converting carbohydrate derivatives into cyclopentanols was reported.[44] The conversion involved a Grob-fragmentation of the iodoglycoside **94** upon treatment with activated zinc which afforded the aldehyde **95** which then cyclised to give the cyclopentanol **96** upon treatment with samarium iodide (Scheme 43).

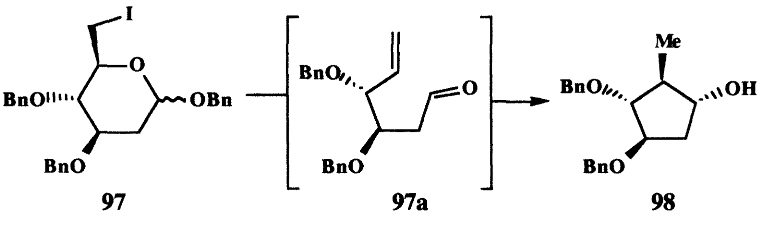


94 **95** **96**

R = H, OBn

Scheme 43

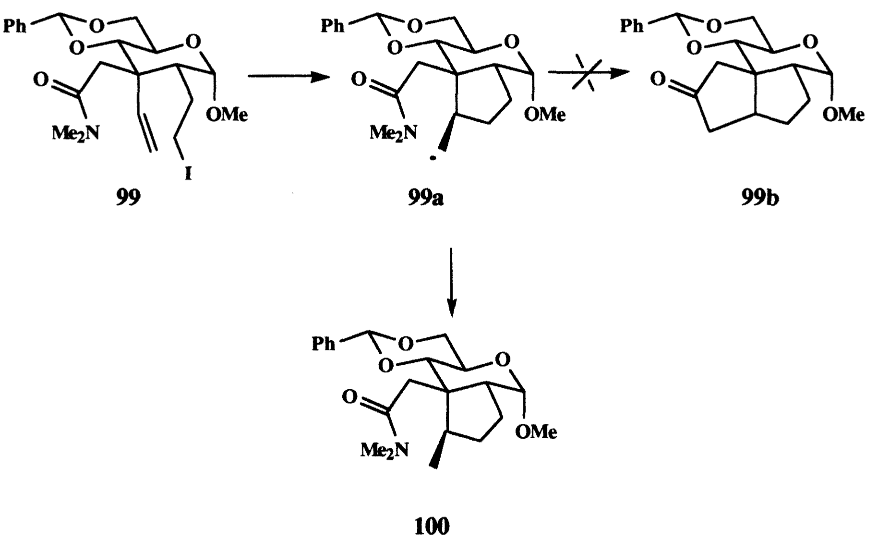
A one-pot synthesis using samarium iodide to initiate the Grob-fragmentation instead of activated zinc met with limited success using methyl glycosides; the major reaction was reductive de-iodination. A better leaving group at the anomeric centre as in **97** was found to enhance the fragmentation (Scheme 44).[45] The reaction presumably proceeds through the aldehyde **97a** which cyclises to the cyclopentanol **98**.



Scheme 44

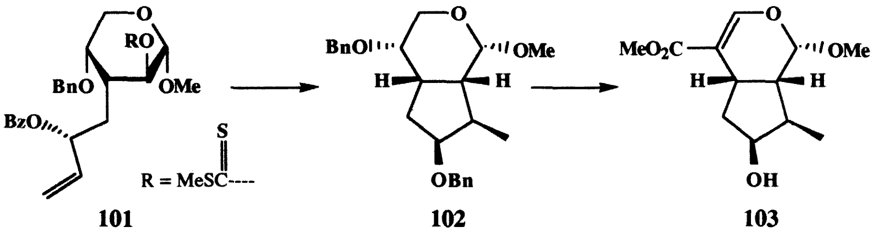
S-type Cyclisations

A great deal of the work in this area has been championed by Fraser-Reid.[46] The unsaturated iodide **99** was converted to the cyclopentane derivative **100** on treatment with tributyltin hydride. The intermediate radical **99a** is presumably quenched by tributyltin hydride faster than intramolecular trapping by the amide group which would have yielded **99b** (Scheme 45).[47]


Ph
O
O
O
O
Me2N
OMe
I
99
99a
99b
100

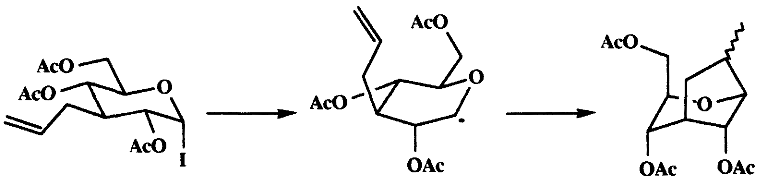
Scheme 45

The dithiocarbonate **101** was treated with tributyltin hydride to give the *cis*-fused cyclopentanopyranoside **102**. The cyclopentaannulated sugar **102** was then converted to the iridoid 1-α-*O*-methylloganin **103** (Scheme 46).[48]


O
RO
BnO
OMe
BzO
S
R = MeSC----
101
BnO
OMe
H
H
OBn
102
MeO2C
OMe
H
H
OH
103

Scheme 46

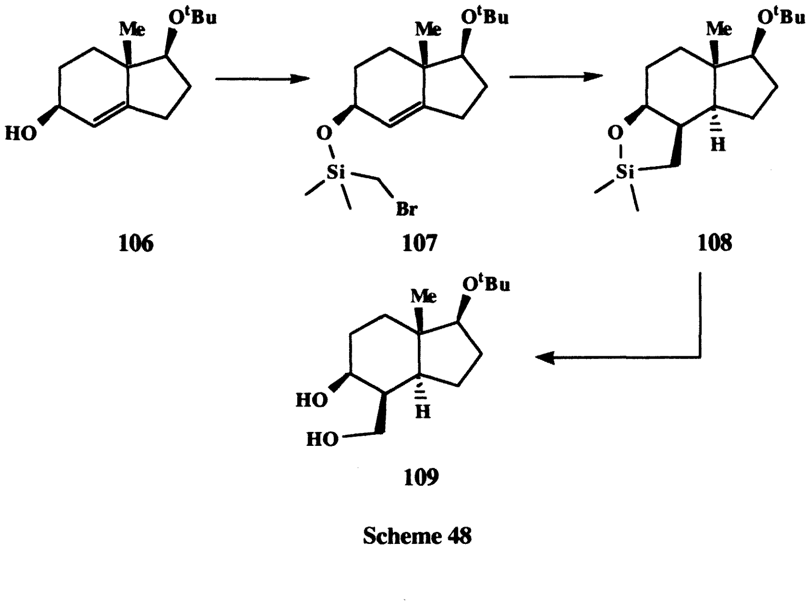
Giese has developed a route to 2-oxabicyclo [3.2.1] octanes such as **105** by treatment of 3-C-allyl-α-D-glucopyranosyl iodide **104** with tributyltin hydride to give the products **105**. ESR studies suggest that the intermediate radical **104a** is in a boat conformation where the allylic group at C-3 is pseudo-axially disposed.[49]


104 **104a** **105**

Scheme 47

Stork Silyl Methylene Radical Cyclisation

This attractive protocol involves the intramolecular reaction of an alkene with a radical species temporarily tethered to the molecule and was investigated independently by Stork[50] and Nishiyama.[51] The allylic alcohol **106** was reacted with (bromomethyl)chlorodimethyl silane to produce the silyl ether **107**. Reaction of **107** with tributyltin hydride gave a 5-*exo* type cyclisation to furnish the five-membered siloxane **108**, subsequent Tamao-Kumada[52] oxidation yielded the diol **109** (Scheme 48).

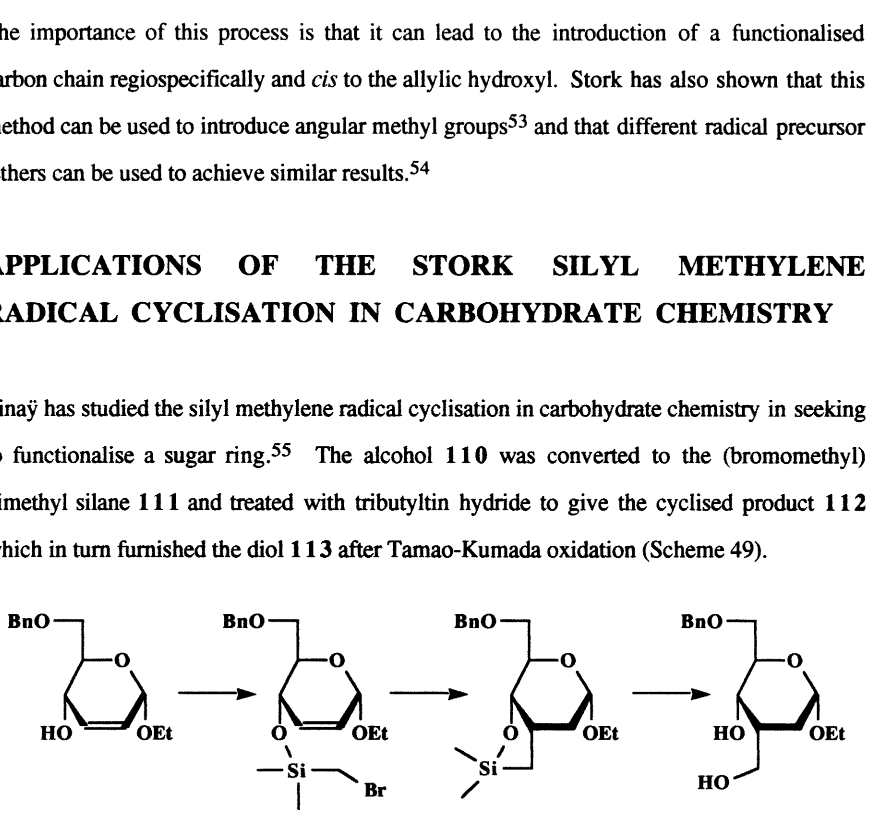

106 **107** **108** **109**

Scheme 48

The importance of this process is that it can lead to the introduction of a functionalised carbon chain regiospecifically and *cis* to the allylic hydroxyl. Stork has also shown that this method can be used to introduce angular methyl groups[53] and that different radical precursor tethers can be used to achieve similar results.[54]

APPLICATIONS OF THE STORK SILYL METHYLENE RADICAL CYCLISATION IN CARBOHYDRATE CHEMISTRY

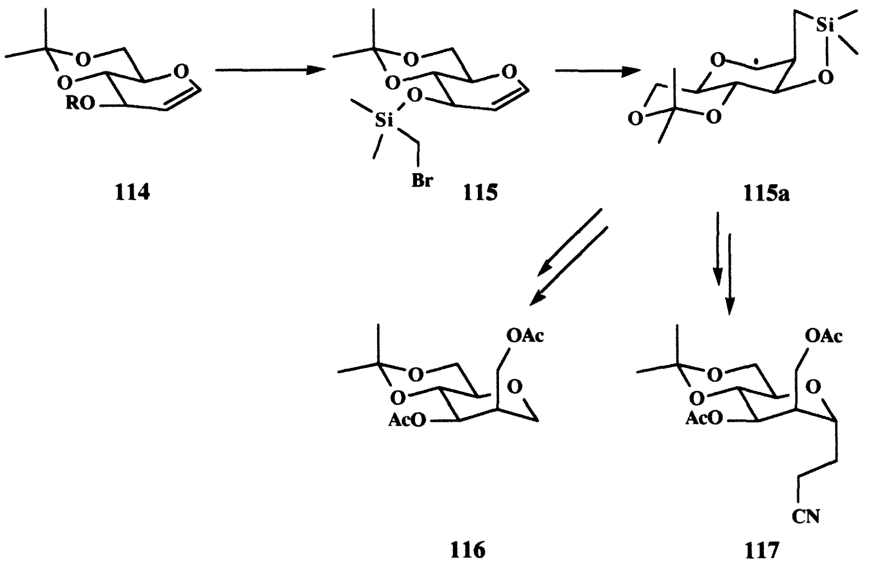
Sinaÿ has studied the silyl methylene radical cyclisation in carbohydrate chemistry in seeking to functionalise a sugar ring.[55] The alcohol **110** was converted to the (bromomethyl) dimethyl silane **111** and treated with tributyltin hydride to give the cyclised product **112** which in turn furnished the diol **113** after Tamao-Kumada oxidation (Scheme 49).



110 **111** **112** **113**

Scheme 49

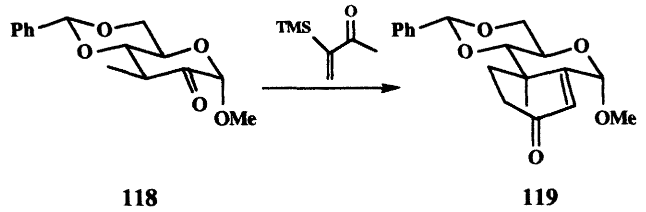
Fraser-Reid has also studied the application of the silymethylene radical cyclisations of carbohydrate derivatives and found the conversion of the alcohol **114** into the diacetate **116** proceeded in good yield.[46f] The alcohol **114** was first converted into the silyl ether **115** which was then treated under the catalytic tributyltin hydride conditions recommended by Stork (Bu_3SnCl, $NaCNBH_3$, tBuOH)[56] to furnish a tricyclic radical intermediate **115a** which abstracts a hydrogen from tributyltin hydride and furnishes the diacetate **116** after oxidation and acetylation. He also found that he could alkylate at the anomeric position by including a large excess of a radical trap in the reaction mixture such as acrylonitrile to produce the now more functionalised diacetate analogue **117** (Scheme 50).



Scheme 50

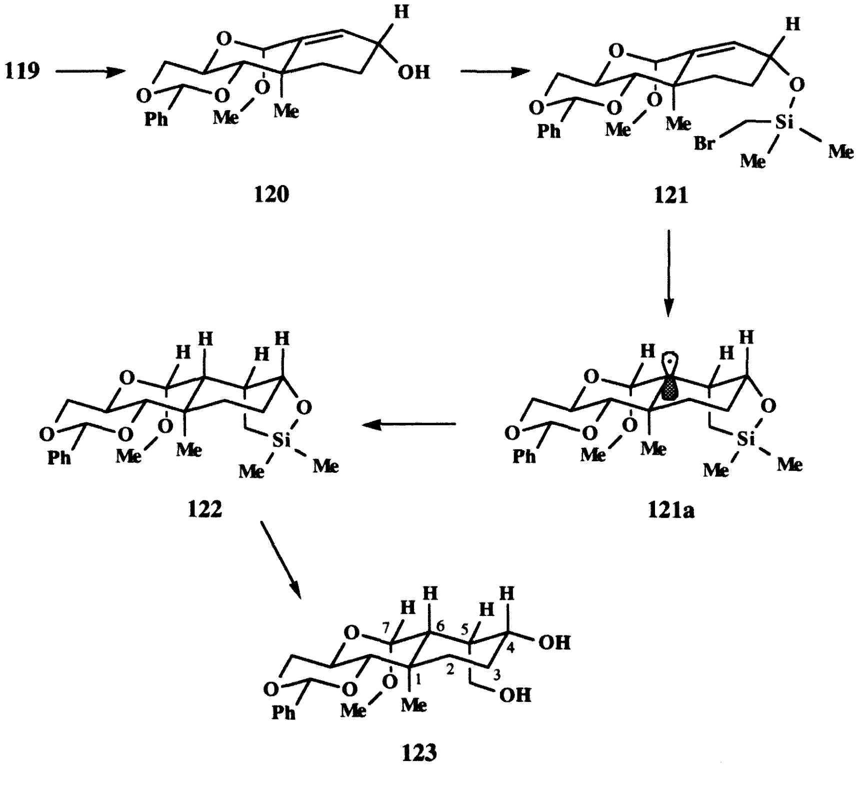
Previous Work at Leicester

Previous work at Leicester by R. Bonnert has shown that an S-type process of a carbohydrate derivative using a Robinson annulation is possible (Scheme 51).[1a,b]



Scheme 51

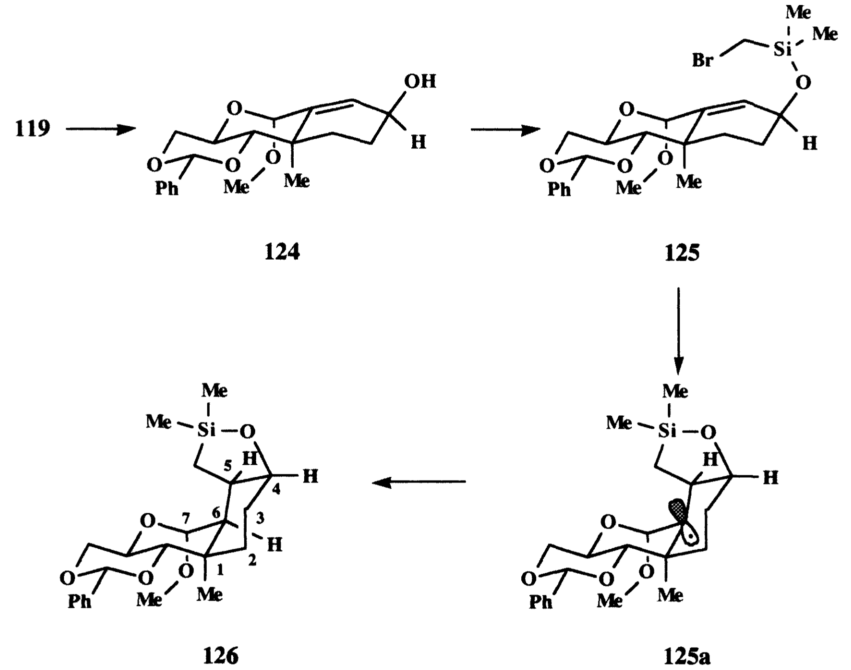
The sugar derivative **118**[25] was treated with lithium tetramethylpiperidide and the resulting enolate reacted with 2-trimethylsilyl-1-buten-3-one to furnish the cyclohexaannulated enone **119**. Reduction of **119** yielded the allylic alcohol **120** which was subjected to the Stork radical cyclisation conditions by J. Howarth (Scheme 52).[57]



Scheme 52

Silylation of the alcohol **120** proceeded smoothly to furnish the silyl ether **121** which was subsequently treated with tributyltin hydride to give the tetracyclic siloxane **122**. Tamao-Kumada oxidation of **122** produced the diol **123** which is an intermediate in our taxane synthesis (see Chapter 3). The *trans* C-1, C-6 ring junction of compound **123** would be expected from steric arguments, since approach of a hydrogen species to the intermediate radical **121a** will be blocked by the C-7 methoxy, C-1 methyl, and C-5 alcohol groups on the α face of the molecule.

In similar fashion the epimeric alcohol **124** was silylated to give the silyl ether **125** and subjected to the radical cyclisation conditions yielding a single product **126** (Scheme 53).[57]

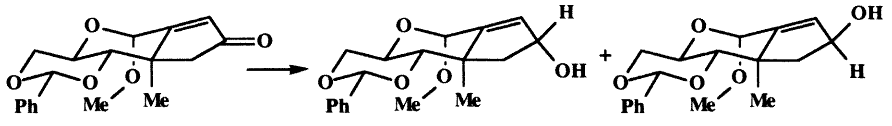


Scheme 53

Approach of the hydrogen species to the radical **125a** this time involves a play off between the steric effects of the methoxy and methyl groups and the silylmethyl groups. As the single product **126** has the C-1, C-6 ring junction *cis*, the steric effect of the silylmethyl groups appears to exceed that of the methoxy and methyl groups and the least crowded face of the molecule is the lower α face.

Radical Cyclisations of a Cyclopentaannulated Derivative

In seeking to further functionalise our cyclopentaannulated derivative **74** we decided to carry out the reductive hydroxymethylation as previously seen in the cyclohexannulated derivatives **120** and **124**. The enone **74** was reduced to the allylic alcohols **127** and **128** using various reagents with a ratio up to 8:1 in favour of either epimer possible (Scheme 54).



74

127
α-allylic alcohol

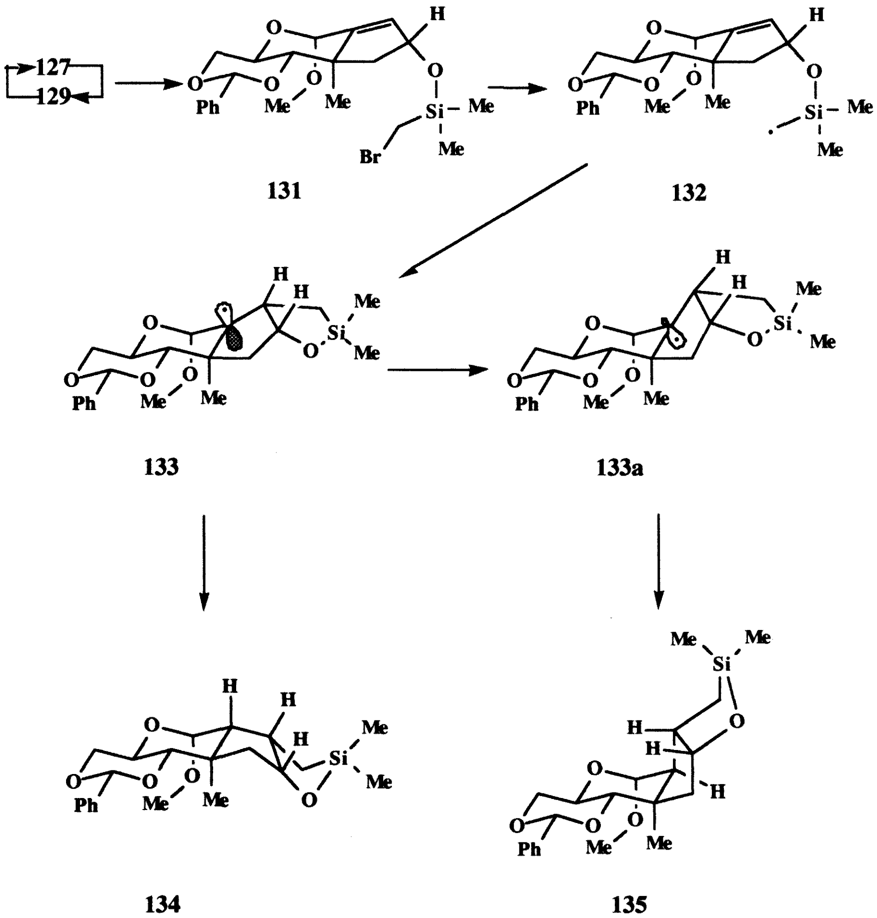
128
β-allylic alcohol

REDUCING AGENT	RATIO 127 : 128
LS-Selectride®	8.0 : 1.0
Thexyliminoyl Borohydride	2.9 : 1.0
DIBAL-H®	1.0 : 1.6
RED-AL®	1.0 : 2.5
$NaBH_4.CeCl_3$	1.0 : 8.0

Scheme 54

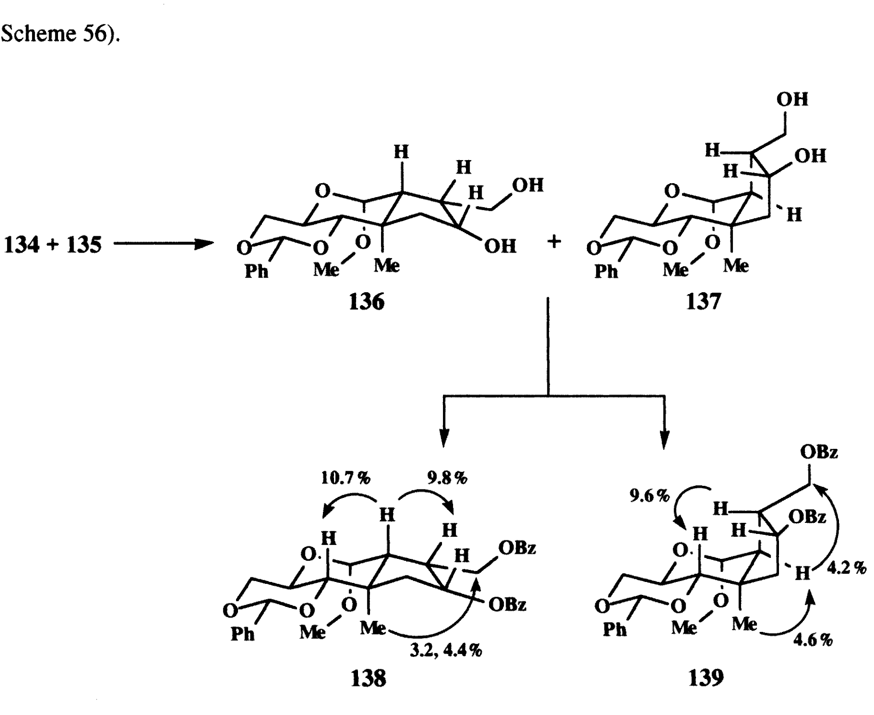
The explanation of these results may be that in the case of LS-Selectride® approach of the bulky reducing agent is more favourable from the β-face of the molecule leading to the allylic alcohol **127**, whereas the less hindered sodium borohydride cerium chloride[58] favours the delivery of the hydride from the α-face of the molecule leading to the allylic alcohol **128** as the major product. This can be explained by the cerium chloride co-ordinating to the carbonyl group and steric hindrance to the β-face of the molecule leading to reduction from the apparently more hindered α face of the carbonyl group.

The epimeric allylic alcohols **127** and **128** were converted to their benzoate esters **129** and **130** and separated by flash column chromatography; hydrolysis of the esters furnished the desired pure allylic alcohol. We were now in a position to prepare the substrates for the Stork-Nishiyama radical cyclisation reaction. The α-allylic alcohol **127** was treated with (bromomethyl) chlorodimethyl silane to furnish the silane **131**. Reduction with tributyltin hydride of **131** gave the radical **132**. The next step was the abstraction of an hydrogen atom from tributyltin hydride on either face of the molecule. It would appear that the easiest approach of the tributyltin hydride to the radical **133** is from the β-face of the molecule leading to the siloxane **134**. Approach from the α-face of the molecule is hindered by the methyl and methoxy groups and the siloxane ring. The siloxane **135** is, however, a product of the reaction where the ratio of **134** to **135** is 2:1 (Scheme 55).



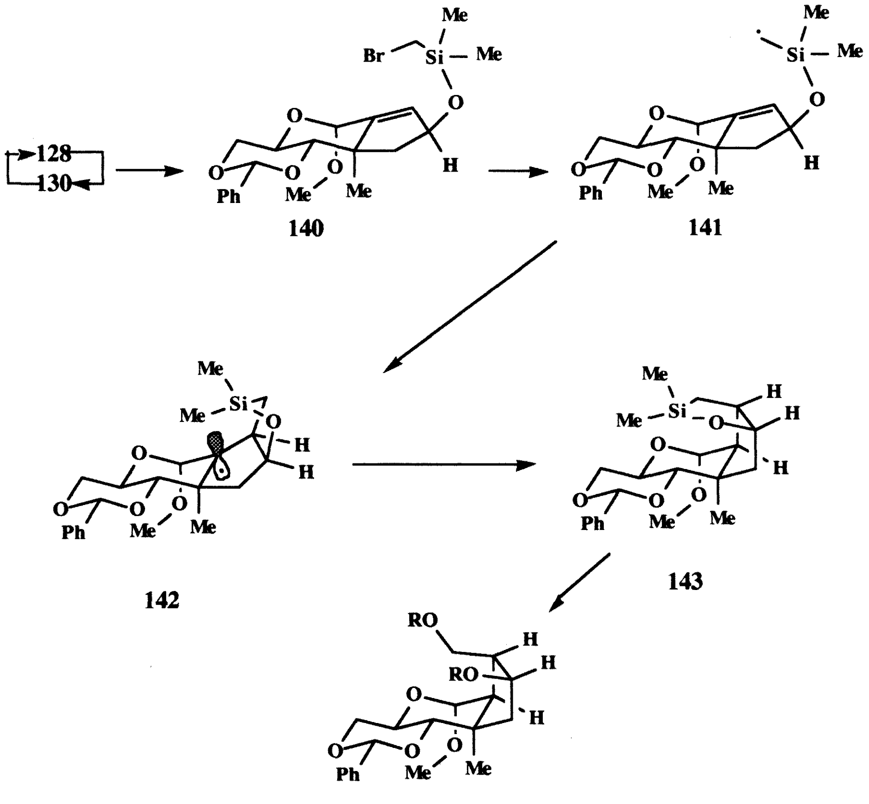
Scheme 55

The most likely explanation for the formation of **135** is that the sp^2-radical **133** re-hybridises to an sp^3 radical **133a** on the α-face of the molecule reducing the unfavourable interaction between the methyl and methoxy groups with an incoming hydrogen donor, delivery from the (lower) α-face then results in the siloxane **135** which has a *cis*-ring fusion of the 5,6-ring system. The fact that we see any of this product may be explained by the propensity for a 5,6-ring system to be *cis*-fused. The siloxanes were not separable and under the Tamao-Kumada oxidation, conditions were converted to the diols **136** and **137**, which were separated by flash column chromatography of their dibenzoate esters **138** and **139**. The structures were confirmed by n.O.e study on the dibenzoates **138** and **139** (Scheme 56).



Scheme 56

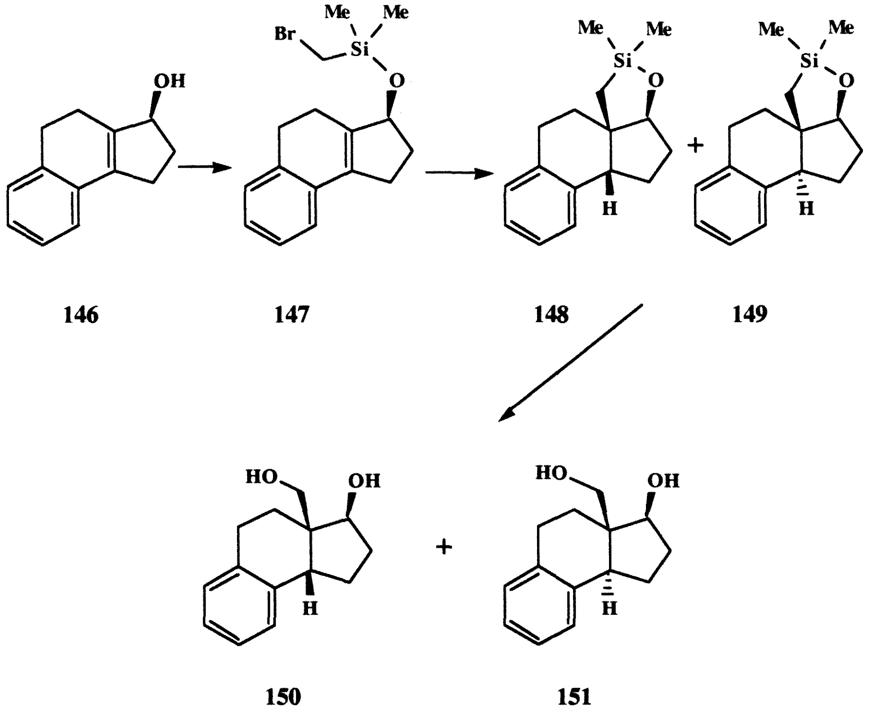
In contrast to these results the allylic alcohol **128** was converted to the silane **140** which was treated with tributyltin hydride to give the radical **141**, which adds across the olefin to furnish the radical **142**. In this case the siloxane ring hinders the β-face of the molecule such that the hydrogen is delivered on the α-face of the molecule to produce the 5,6-*cis*-fused ring system **143**. Attack from the least hindered face of the molecule and the formation of the more thermodynamically favoured 5,6-*cis*-fused ring system combine to give the single product **143**, which was subjected to the Tamao-Kumada oxidation to give the diol **144** which in turn afforded the protected compound **145** on treatment with t-butyldiphenylsilyl chloride (Scheme 57).



144 R = H
145 R = ^{t}Bu(Ph)$_2$Si

Scheme 57

The nearest literature example of this type of cyclisation is the Stork radical cyclisation of 5,6-fused ring systems.[53] The tricyclic allylic alcohol **146** was converted to the silyl ether **147** and treated with tributyltin hydride to give the siloxanes **148** and **149**. Tamao-Kumada oxidation gave the diols **150** and **151** in a ratio of 3.7:1 in favour of the *cis*-fused ring system (Scheme 58).

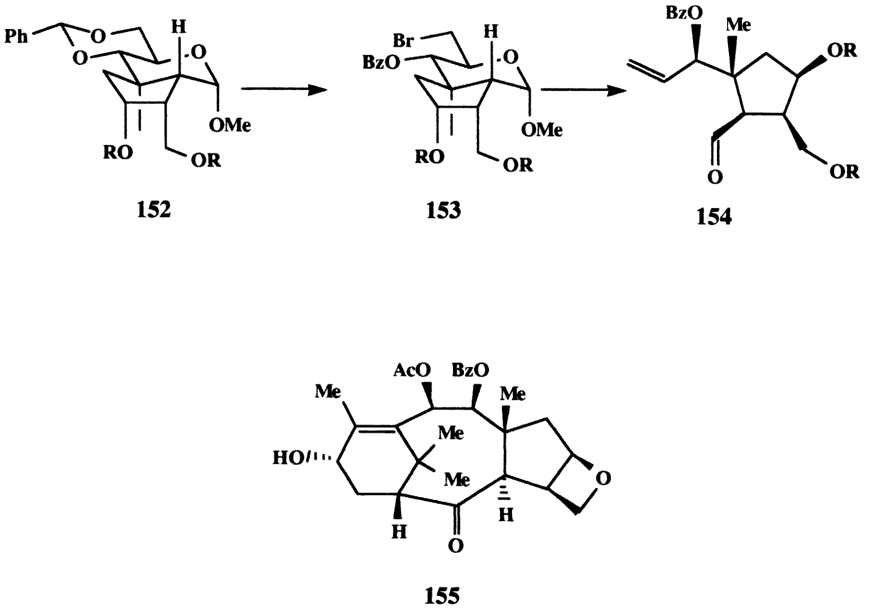


Scheme 58

We found that the preference for *trans* addition across the olefin is counterbalanced by a contrary preference for the formation of the *cis* fused 6,5-ring system.

Future Work

Fragmentation of the functionalised carbohydrate derivatives such as **152** should produce highly functionalised chiral cyclopentanes. Treatment of the carbohydrate derivative **152** with NBS may produce the bromide **153** which could be further treated with activated zinc in a Grob-type fragmentation to give the chiral cyclopentane **154**. This highly functionalised cyclopentane **154** could represent a C-ring synthon for the novel taxol-like structure **155** (Scheme 59).



Scheme 59

A recent publication reported a similar structure to that of **155** resulting from the contraction of the C-ring of Taxol.[59] The reported compound showed less activity than Taxol itself but also lacked the oxetane ring which is known to be essential for activity.[60] The oxetane ring could be constructed from the protected diol part of the molecule.

Summary

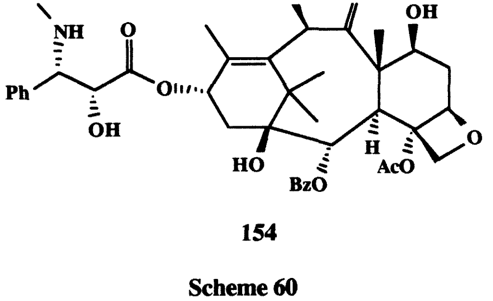
In conclusion it has been shown that the silyl methylene radical cyclisation of the allylic alcohol **128** leads to a single *cis* product **143** where delivery of the hydride from the least hindered face of the intermediate radical **142** leads to the preferred *cis*-fused 5,6-ring system, whereas the corresponding cyclisation on the allylic alcohol **127** leads to a mixture of products as previously observed,[53] but with the predominant isomer being the *trans*-fused 5,6-ring system.

Chapter 3

PROGRESS TOWARDS THE SYNTHESIS OF TAXOL FROM AN ANNULATED CARBOHYDRATE

TAXOL - INTRODUCTION

The leaves of the yew tree were known to be poisonous to animals and man for centuries. Yew wood was used to make long bows and so a substantial supply of the material was required. To avoid poisoning cattle yew trees were planted in churchyards. The religious connotation of the yew tree arises from the fact that the tree is very slow growing and has a sombre appearance. The Pacific Yew tree, *Taxus brevifolia*, is native to western North America; an NCI initiative to screen plants and trees for anti-cancer activity led Wani and Wall[61] to discover Taxol, a compound found in the bark of this tree. They were able to isolate Taxol **154** (Scheme 60) by a number of purification steps, each time collecting the fractions which showed cytotoxic activity. The structure of Taxol was determined in 1971 some nine years after the collection of *Taxus brevifolia* in the Gifford Pinchot National Forest in the state of Washington by a USDA botanist. Interest in Taxol increased considerably when Susan Horwitz[62] showed that the cellular target for Taxol was tubulin and that the mode of action was unique.

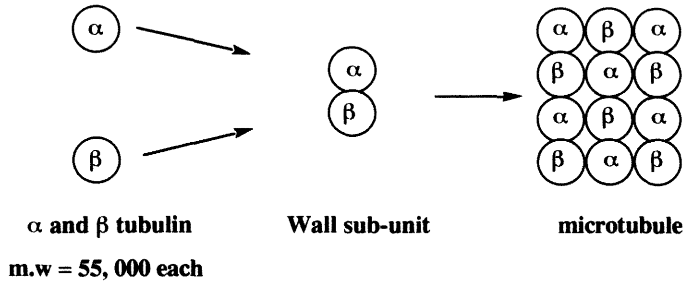


154

Scheme 60

Anti-Cancer Activity of Taxol

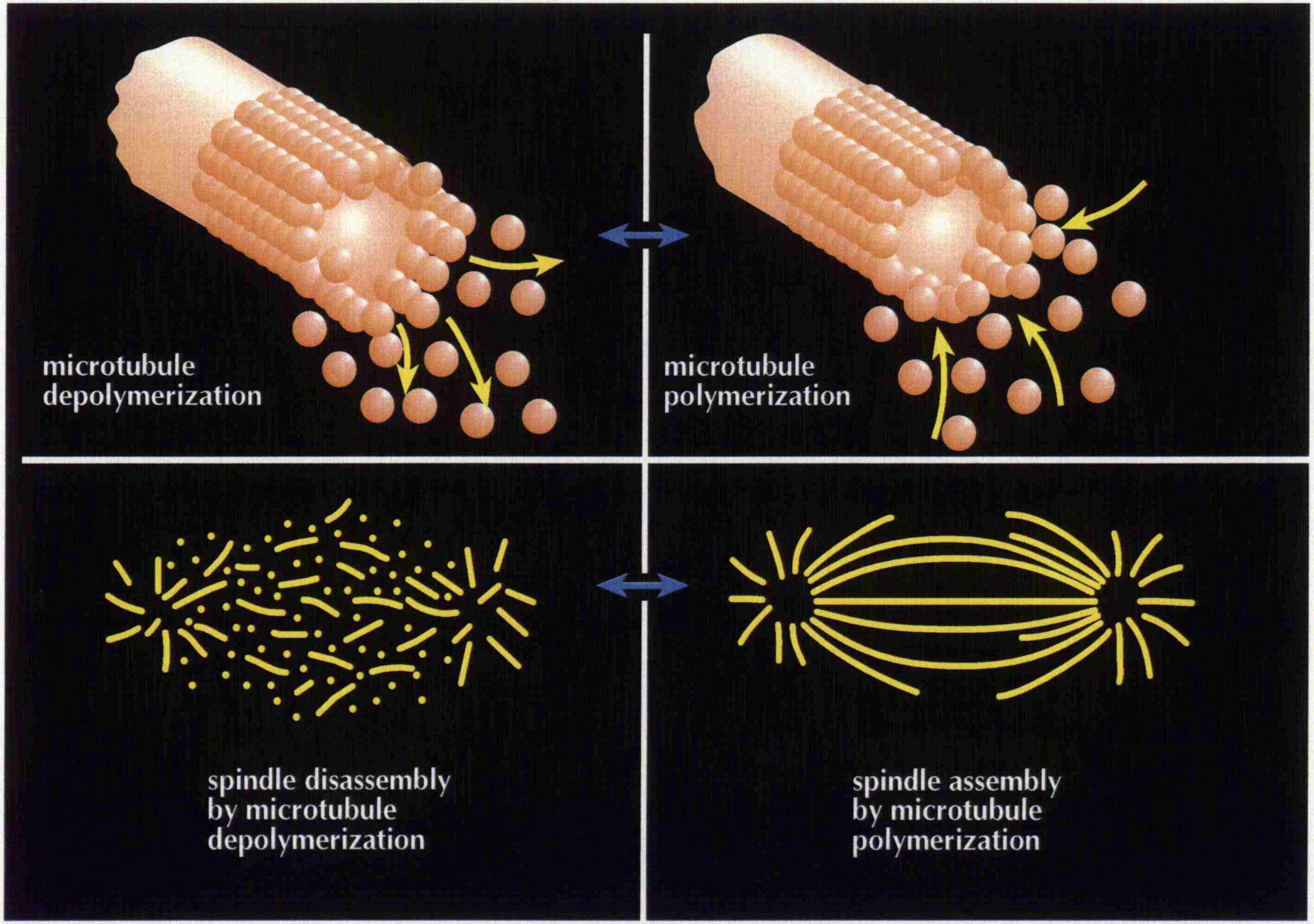
Tubulin is a protein in eucaryotic cells and consists of two forms, α and β. These combine to form a wall sub-unit which then polymerises further to produce a microtubule (Scheme 61).



Scheme 61

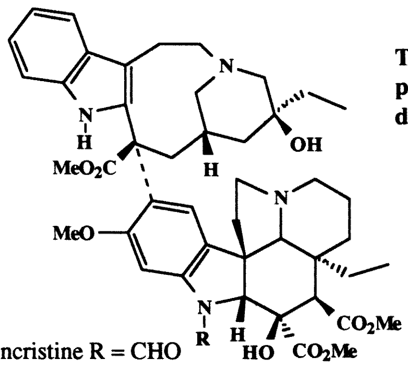
Microtubules normally provide a skeleton for the cell or for organs of movement. However, before cell division takes place depolymerisation of microtubules occurs to give tubulin monomer and re-polymerisation occurs to form the spindle of cell division. The purpose of the microtubules that make up the spindle is to lengthen by the process of tubulin polymerisation and push the daughter cells apart, also the microtubules move the chromosomes from the original nucleus into the daughter nuclei. It is thought that a long microtubule originating from the daughter nucleus attaches itself to a chromosome in the original nucleus and then depolymerises and shortens, thereby dragging the chromosome to the nucleus of the daughter cell. Consequently the process of polymerisation and depolymerisation of tubulin is a crucial factor in the process of cell division. Any interference with this process stops normal cell division taking place.

There is a group of compounds known as spindle poisons, vincristine, vinblastine, podophilotoxin and colchicine (Scheme 62). These prevent the formation of the spindle stopping normal cell division taking place. In contrast to the spindle poisons, Taxol stimulates the formation of microtubules and prevents their breakdown. The action of Taxol is therefore an interference in the free polymerisation of tubulin which prevents normal cell division from taking place. Because of this unique mode of action and encouraging results from clinical trials Taxol has received enormous media attention. The discovery and progress of Taxol over the last 34 years is detailed in Scheme 63.


microtubule depolymerization
microtubule polymerization
spindle disassembly by microtubule depolymerization
spindle assembly by microtubule polymerization

Spindle Poisons

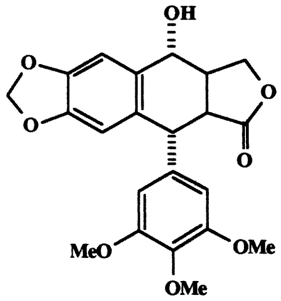
1) Vincristine and Vinblastine


N
N
H
OH
MeO2C
H
N
MeO
N
R
H
HO
CO2Me
CO2Me

Vincristine R = CHO
Vinblastine R = Me

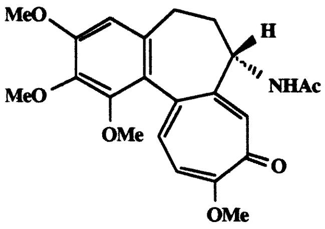
The Vinca alkaloids cause mitotic poisoning linked to spindle destruction

2) Podophilotoxin


OH
O
O
O
O
MeO
OMe
OMe

Prevents the formation of microtubules and is used in chemotherapy.

3) Colchicine


MeO
MeO
OMe
H
NHAc
O
OMe

Binds specifically to tubulin and prevents the formation of microtubules

Scheme 62

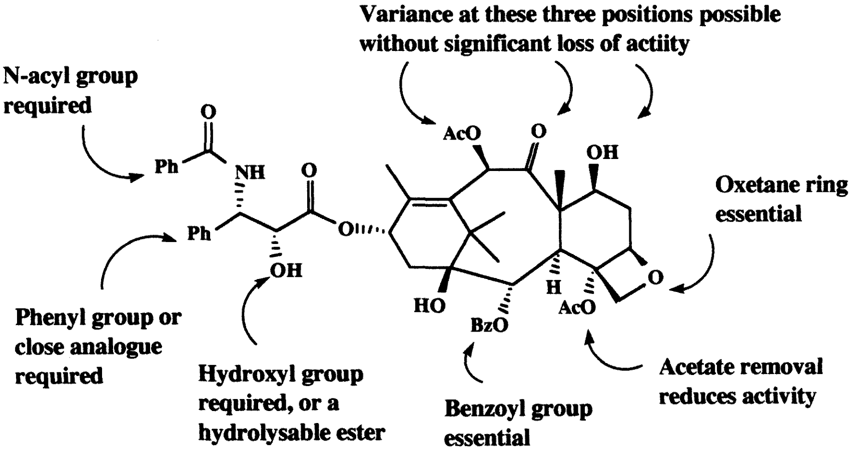
THE DEVELOPMENT OF TAXOL AS AN ANTI-CANCER DRUG

1962-66	Collection of *Taxus brevifolia.* as part of an NCI programme of natural products screening for cytotoxicity and anti-leukaemic activity
1969	Pure Taxol is isolated.
1971	Wani and Wall report anti-leukaemic properties of Taxol in the Journal of the American Chemical Society.
1979	Susan Horwitz reports that Taxol stimulates microtubule assembly.
1980	10-Deacetyl baccatin III is isolated from *Taxus baccata* (European Yew tree) and identified as a suitable starting material for the semi-synthesis of Taxol by the group of Potier.
1984-85	Phase I and Phase II clinical trials for all types of cancer. Most favourable results obtained for breast and ovarian cancer.
1986-88	Semi-synthesis of Taxol - Potier and Greene (1986), later improved (1988).
1989	Semi-synthesis of Taxol - Holton.
1991-94	Further extensive hospital trials and application for Federal Drug Administration approval; approved for ovarian cancer treatment 1992, Taxol® marketed by Bristol-Myers Squibb Co. 1993, approved for breast cancer treatment 1994.
1994	The first total syntheses of Taxol - Nicolaou, Holton.
1995	Taxol total synthesis - Danishefsky.

Scheme 63

The Semi-Synthesis of Taxol

Taxol is extracted from the stem bark of several species of yew, namely the Pacific Yew tree, *Taxus brevifolia*, which results in the destruction of the tree. Typically, the bark from two one century old trees is needed to treat one patient; this has obvious ecological consequences. The demand for yew tree bark in the U.S. was so high that the Yew Act was drafted in 1992 which provided for the efficient collection and utilisation of the pacific yew and also ensured its long term conservation. Such an act was needed as the supply of yew bark had escalated from 60,000 lbs of dry bark in 1989 to 850,000 lbs in 1991. With a projected demand of 750,000 lbs of bark until other sources of Taxol could be found, the issue of semi-synthesis became extremely important. Scheme 64 shows which parts of Taxol give rise to activity and what changes can be made to the structure without reducing its potency.



Variance at these three positions possible without significant loss of actiity

N-acyl group required

Oxetane ring essential

Phenyl group or close analogue required

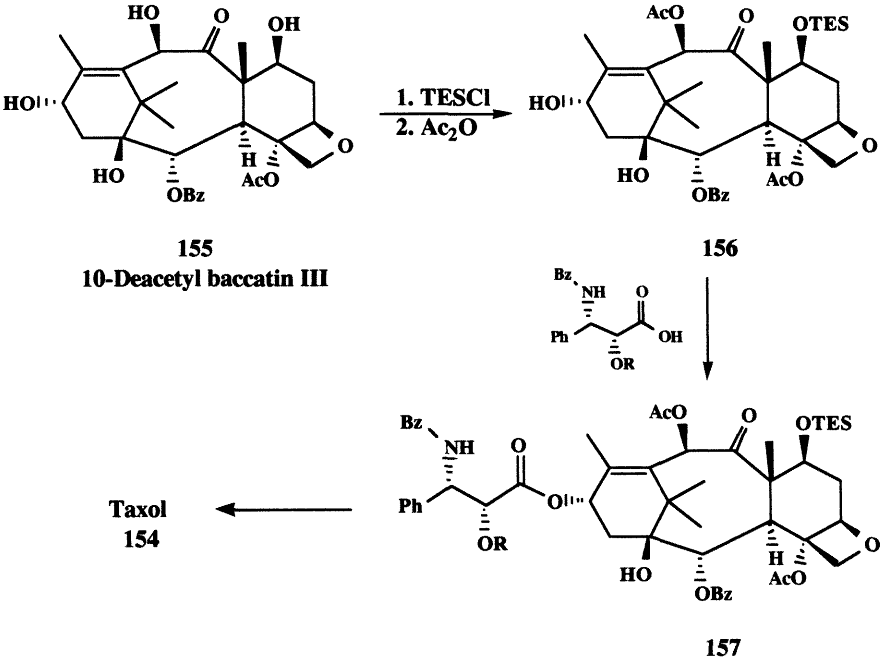
Hydroxyl group required, or a hydrolysable ester

Benzoyl group essential

Acetate removal reduces activity

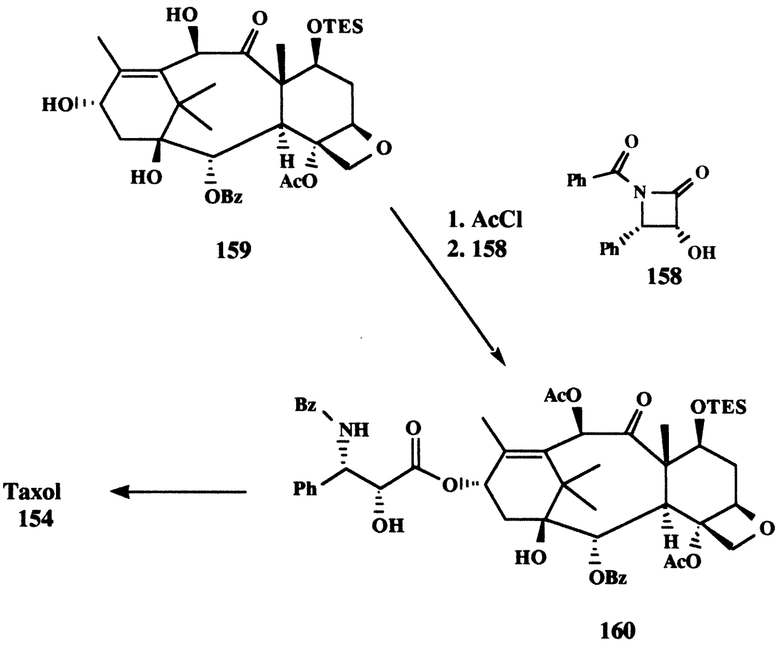
Scheme 64

The semi-synthesis to date has been the most successful way of making Taxol and biologically active analogues. Potential starting materials for semi-synthesis must be easy to obtain, renewable and require as little elaboration as possible. 10-Deacetylbaccatin III **155** (10-DAB III) was described as a degradation product of Taxol,[61] and can also be isolated from the needles of the European Yew, *Taxus baccata*. Because the leaves are renewable and 1 g of 10-DAB III can be extracted from 1 kg of dry leaves, a semi-synthetic route to Taxol from **155** is attractive. Synthetic routes from **155** have been developed which make use of the differing reactivity of the free hydroxyl groups; 7-OH > 10-OH >> 13-OH. Potier[63] utilised 10-DAB III and selectively protected the C-7 position followed by acetylation at C-10 to give **156**. Finally, forced acylation of the secondary hydroxyl at C-13 by the suitably protected N-benzoyl-phenyl-isoserine side chain and deprotection of C-7 and C-2' positions gave Taxol **154** in 36% yield (Scheme 65).


HO
O
OH
HO
HO
OBz
H
AcO
O
155
10-Deacetyl baccatin III
1. TESCl
2. Ac_2O
AcO
O
OTES
HO
HO
OBz
H
AcO
O
156
Bz
NH
O
Ph
OH
OR
Taxol
154
Bz
NH
O
Ph
O
OR
AcO
O
OTES
HO
OBz
H
AcO
O
157

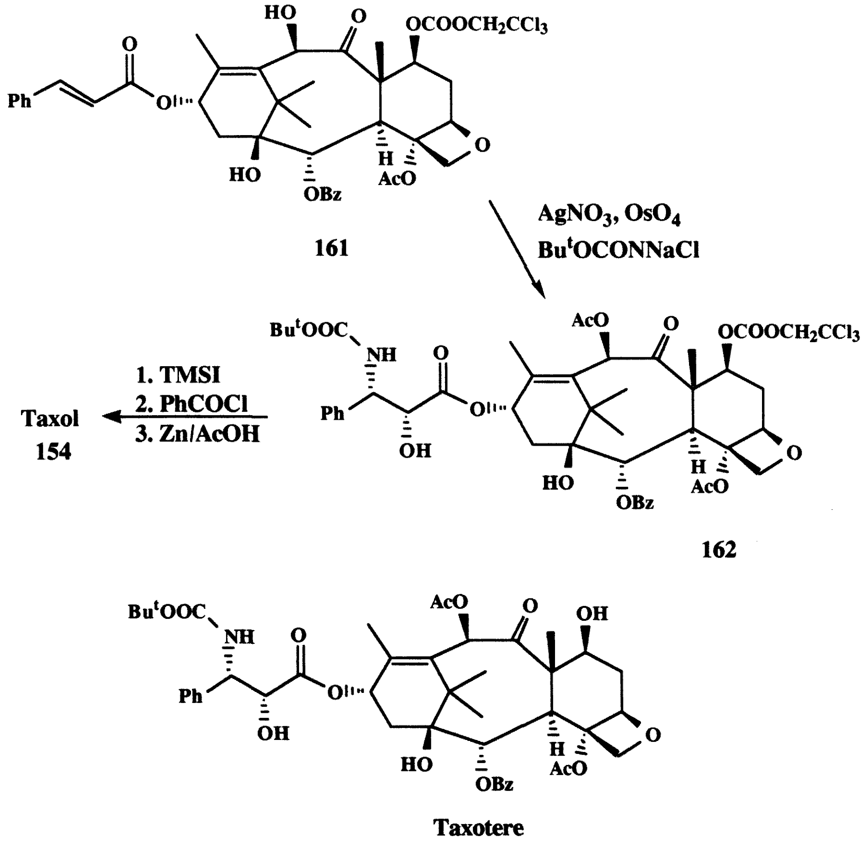
Scheme 65

Other methods of attaching the sidechain have been used in attempts to overcome the problems of low reactivity at C-13 OH. Ojima[64] and Holton[65] have independently used the β-lactam derivative **158** to directly couple with 7-TES-10-DAB III **159** to give **160** which affords Taxol **154** after removal of the TES group (Scheme 66). Ojima has further reported an improvement to this method achieving a near quantitative coupling of the β-lactam using sodium hexamethyldisilazide.[66]


HO
O
OTES
HO
HO
OBz
H
AcO
O
159
1. AcCl
2. 158
O
Ph
N
O
Ph
OH
158
Bz
NH
O
Ph
OH
O
AcO
O
OTES
HO
OBz
H
AcO
O
160
Taxol
154

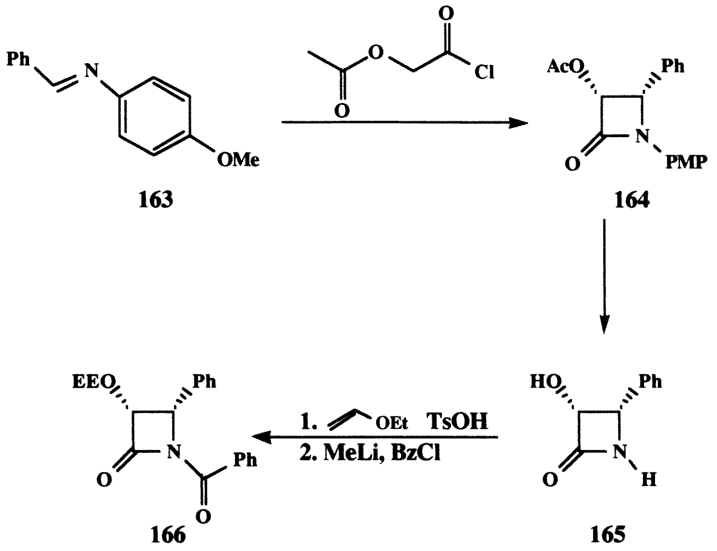
Scheme 66

In another approach, Poitier[67] used the Sharpless oxyamination of **161** - obtained by sequential protection of 10-DAB III and formation of the C-13 cinnamate - to give a mixture of regio- and stereoisomers. Although this route was later improved[68] by the use of chiral reagents during the oxyamination reaction, regiocontrol was still poor, but the major product was **162**. This isomer was then converted to Taxol by removal of the BOC (t-butyl amido) group, followed by benzoylation and removal of the trichloroethoxycarbonyl group. The approach is impractical due to the poor control of the oxyamination reaction but has led to numerous analogues,[69] one of which is Taxotere®,[70] which has similar pharmacological activity to Taxol (Scheme 67).


161
AgNO3, OsO4
ButOCONNaCl
162
1. TMSI
2. PhCOCl
3. Zn/AcOH
Taxol
154
Taxotere
HO
O
OCOOCH2CCl3
Ph
OBz
AcO
H
ButOOC
NH
OH

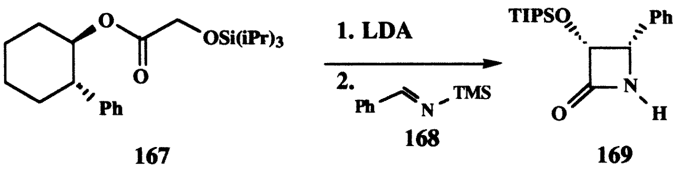
Scheme 67

Holton[65] used the β-lactam **166** to make Taxol from 7-TES-10-DAB III **159**. The lactam was made using the Staudinger reaction[71] between α-acyloxy acetyl chloride and the imine **163** as the key step to give the lactam **164** which was subsequently converted into **166** by deprotection and benzoylation of the nitrogen, and protection of the hydroxyl. Resolution of the alcohol **165** was needed to gain the required enantiomer (Scheme 68).


Ph
N
OMe
163
O
O
Cl
O
AcO
Ph
N
O
PMP
164
HO
Ph
N
O
H
165
1. OEt TsOH
2. MeLi, BzCl
EEO
Ph
N
O
Ph
O
166

Scheme 68

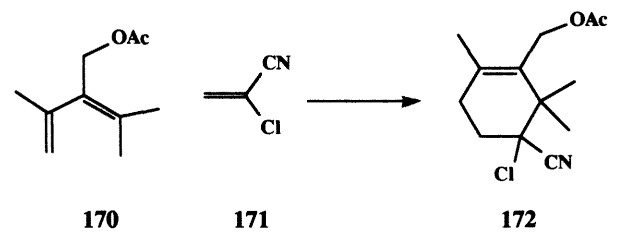
Ojima[72] also used the β-lactam **169** which he synthesised using a highly selective ester enolate-imine condensation. Deprotection of the protected ester **167** with LDA followed by condensation with the imine **168** gave the *cis* β-lactam **169** (Scheme 69).


O
OSi(iPr)3
O
Ph
167
1. LDA
2.
Ph
N
TMS
168
TIPSO
Ph
N
O
H
169

Scheme 69

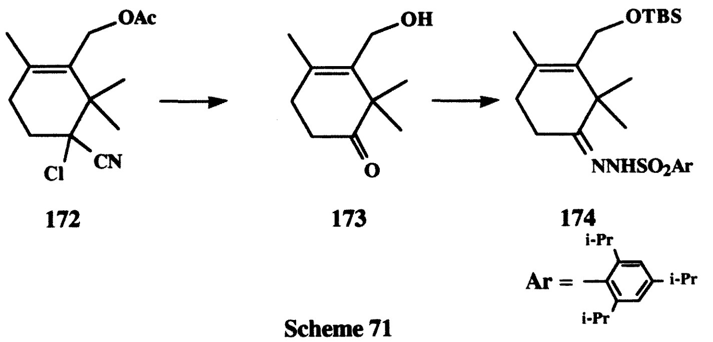
THE TOTAL SYNTHESIS OF TAXOL - NICOLAOU

The first published total syntheses of Taxol came from the groups of Nicolaou [73] and Holton.[81] The synthesis is convergent where the A-ring and C-ring are synthesised separately and subsequently coupled together. The Diels-Alder reaction was used to construct both the A and C-rings of Taxol. Scheme 70 shows the reaction of the diene **170** and dienophile **171** to produce the A-ring intermediate **172** as a single regioisomer.



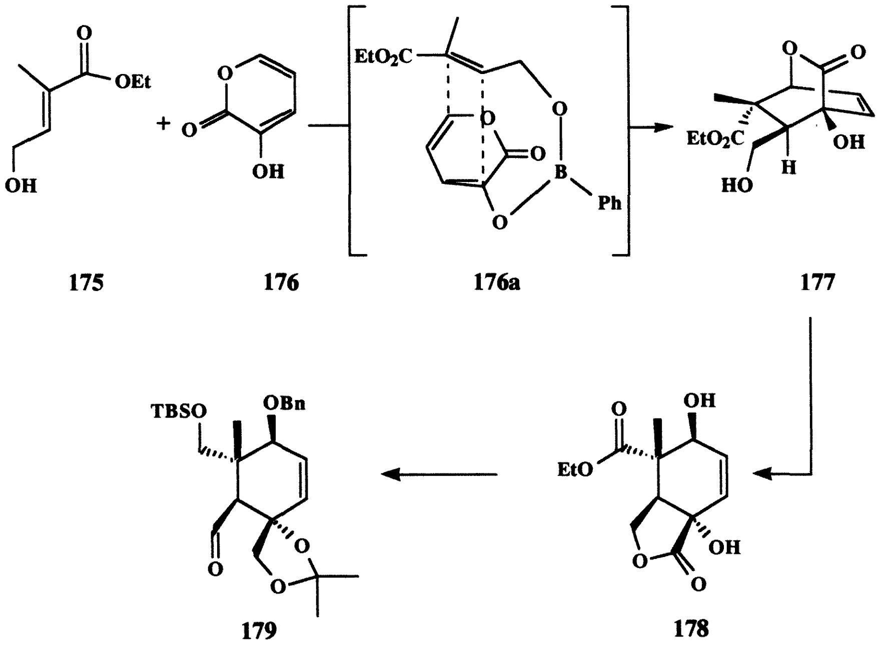
Scheme 70

Intermediate **172** was converted to the hydroxyketone **173** by reaction with potassium hydroxide in t-butanol at reflux. Attempts to react **174** with nucleophilic species failed so the hydrazone **174** was prepared and provided a method of turning the A-ring into the nucleophile *via* a Shapiro reaction and thus couple with a C-ring synthon (Scheme 71).



Scheme 71

The C-ring synthon was constructed using the Diels-Alder reaction of **175** and **176** in the presence of phenyl boronic acid following the method of Narasaka.[74] It is envisaged that the two components are temporarily tethered together in an intermediate **176a** before cyclisation to furnish the cycloadduct **178** (Scheme 72).

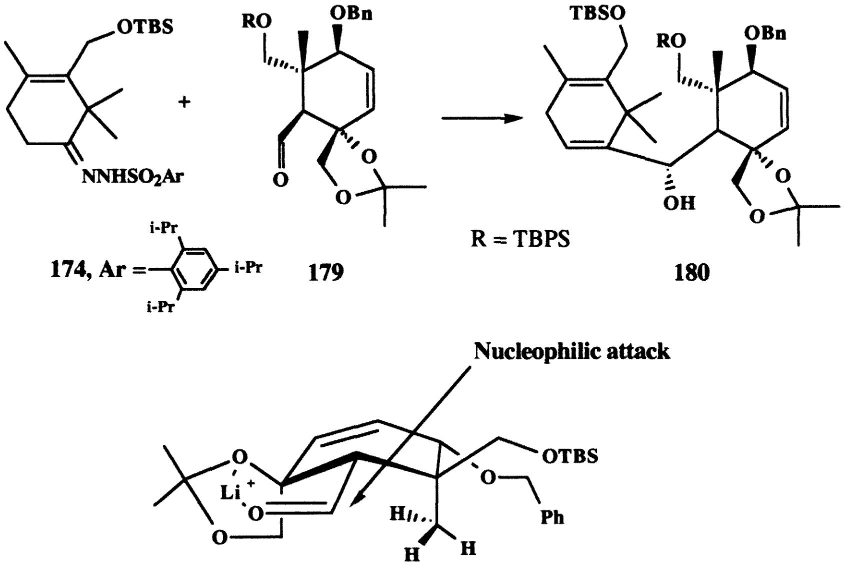

O
OEt
OH
+
O
O
OH
EtO2C
O
O
O
B
Ph
O
O
O
EtO2C
OH
H
HO
175
176
176a
177
TBSO
OBn
O
O
O
179
O
OH
EtO
OH
O
O
178

Scheme 72

It would appear that the initially formed product **177** re-arranges under the reaction conditions such that acyl transfer from the secondary to the primary hydroxyl group has occurred, further elaboration of this C-ring intermediate **178** led to the more advanced C-ring synthon **179**.[75]

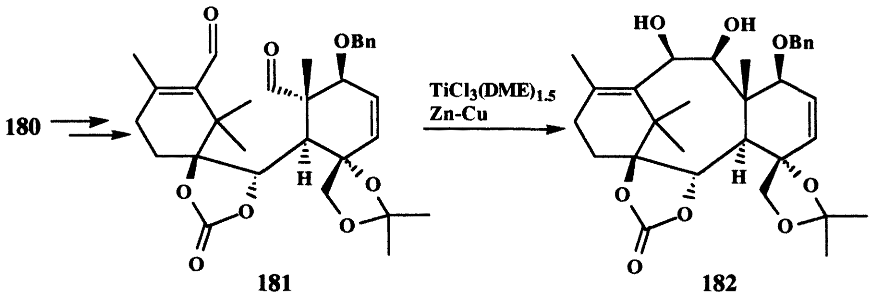
Construction of the ABC Ring Skeleton of Taxol

The next stage in the synthesis required the coupling of the A and C-rings. A Shapiro reaction was employed to form the C-1,C-2 bond to give the alcohol **180** as a single diastereoisomer on reaction of **174** with **179**. The stereoselectivity of this reaction was explained by the lithium chelate **179a** where the aldehyde is fixed by the lithium co-ordination to the acetonide facilitating nucleophilic attack from only one face of the molecule (Scheme 73).


OTBS
NNHSO$_2$Ar
174, Ar =
i-Pr
i-Pr
i-Pr
RO
OBn
O
O
O
179
R = TBPS
TBSO
RO
OBn
OH
O
O
180
Nucleophilic attack
O
Li$^+$
O
O
OTBS
O
Ph
H
H
H
179a

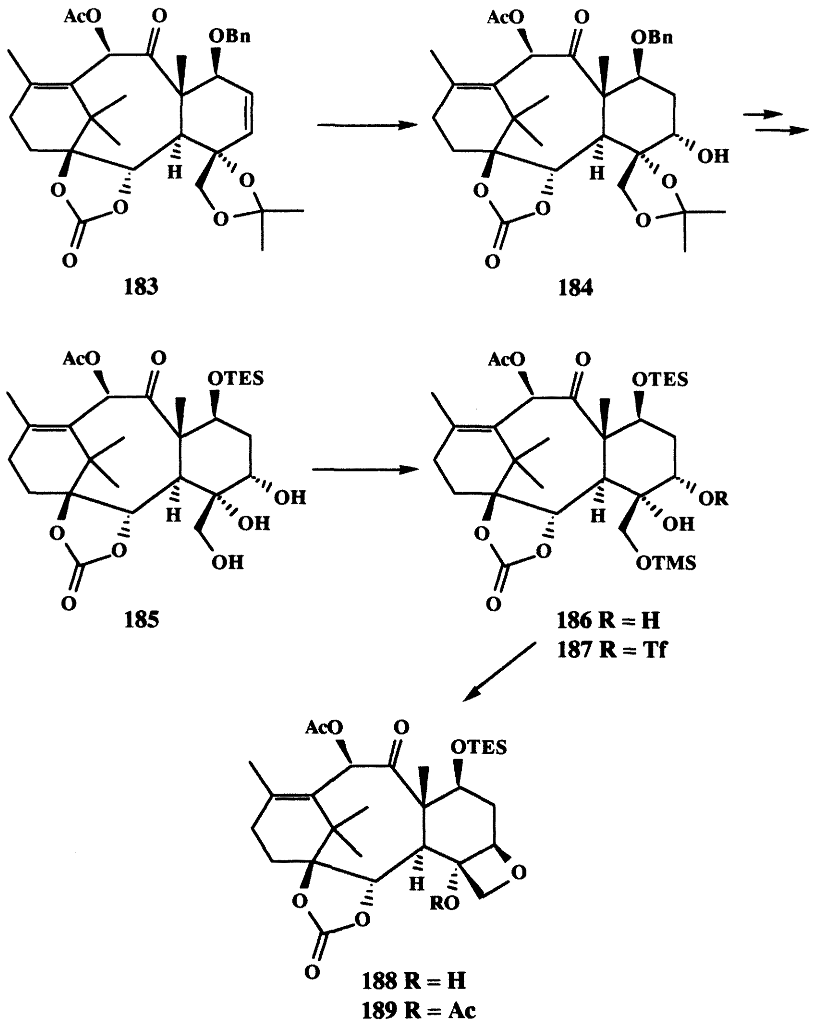
Scheme 73

To complete the formation of the B-ring, a McMurry pinacol reaction was used to join C-9 and C-10 and therefore this required a dialdehyde at these centres. The C-1, C-14 olefin of **180** was first selectively epoxidised and reduced to put in place the C-1 hydroxyl group, deprotection of C-9 and C-10 followed by oxidation furnished the desired di-aldehyde **181**[76] (Scheme 74).



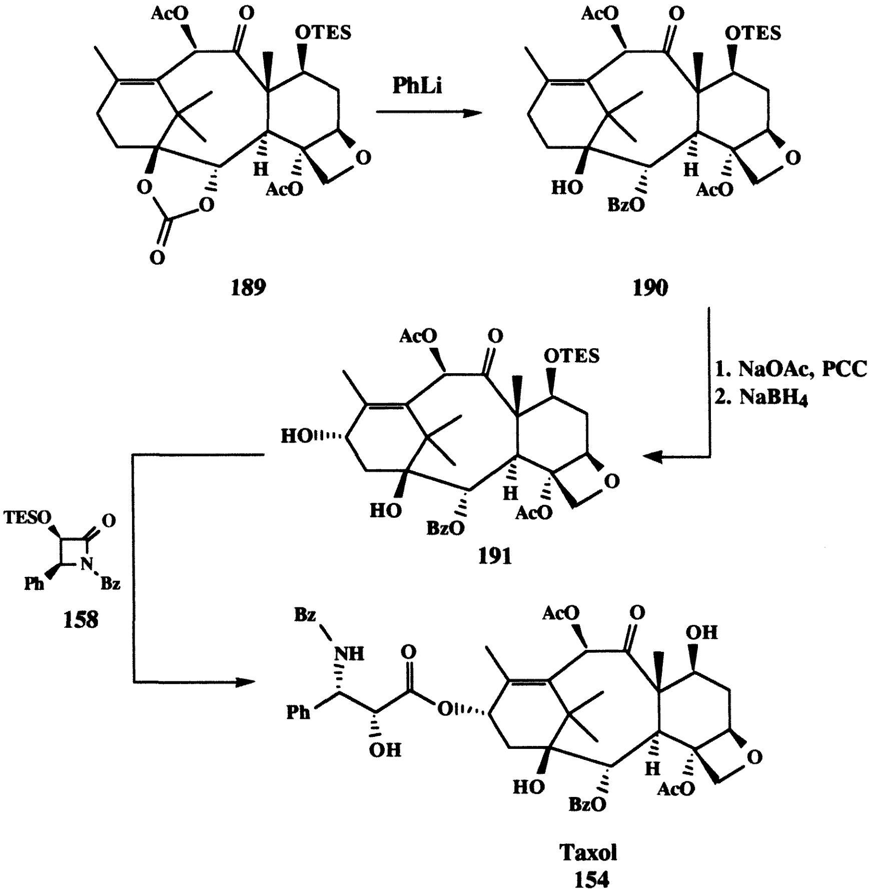
Scheme 74

Although the McMurry pinacol reaction did give the desired product **182** the optimised yield was only 28% with several other products being obtained. At this point in the synthesis a resolution of the racemic diol was needed to obtain an enantiomerically pure intermediate for the final stages of the synthesis. The tricyclic ring system now required the formation of the D-ring and the introduction of some oxygen functionality at C-13 (Scheme 75). The key step in the synthesis of the oxetane ring was the introduction of an hydroxyl group at C-5. This was achieved by hydroboration of **183** and oxidation of the resulting organoborane to yield a 3:1 mixture of C-5 : C-6 isomers with alcohol **184** being the major product. The acetonide was then removed by treatment with acid and after some further protecting group interconversions furnished the diol **185.** The construction of the oxetane ring was achieved using the methods of Danishefsky[77], and Potier[78]; the approach modelled on Danishefsky's work is shown. The primary alcohol of **185** was selectively silylated with TMSCl in the presence of base and exposed to triflic anhydride and base to afford the triflate silyl ether **187** *via* **186**. The oxetane ring was formed on treatment with silica gel in dichloromethane through sequential desilylation of the C-20 hydroxyl group followed by intramolecular displacement of the triflate to give **188** which was then acetylated to give **189**.


AcO
O
OBn
O
O
O
H
O
O
183
184
OH
OTES
OH
OH
OH
185
OR
OTMS
186 R = H
187 R = Tf
RO
188 R = H
189 R = Ac

Scheme 75

The remaining steps required the oxidation and reduction sequence at C-13 followed by attachment of the side chain which had already been performed from degradation and re-constitution studies.[79] The tetracyclic compound **189** was treated with phenyllithium to open the cyclic carbonate to give **190** which has the same southern hemisphere make-up as Taxol. The introduction of the C-13 hydroxyl was achieved by an allylic oxidation and then stereoselective reduction of the enone, as described by Potier,[80] with $NaBH_4$ to furnish the alcohol **191**. The sidechain was introduced to **191** using the Ojima[64]-Holton[65] β-lactam **158** and NaN(TMS)$_2$ to produce Taxol **154** after de-silylation (Scheme 76).

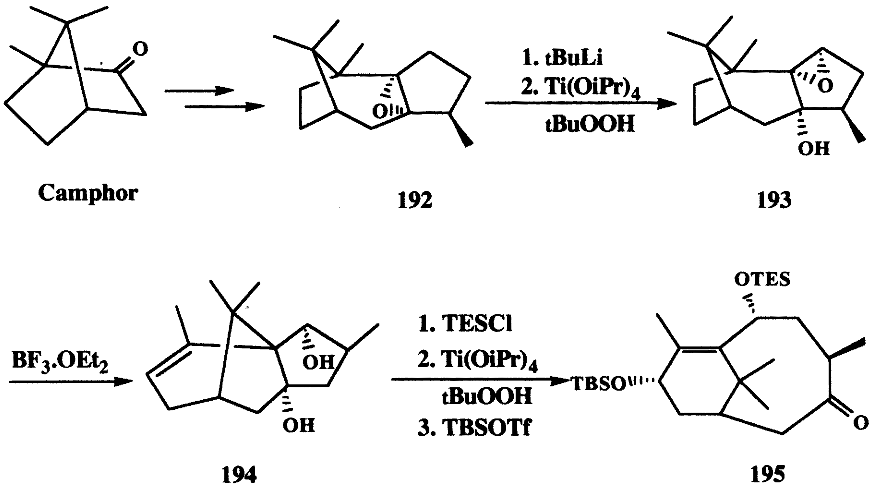

AcO
O
OTES
O
O
O
O
H
AcO
189
PhLi
AcO
O
OTES
HO
BzO
H
AcO
O
190
1. NaOAc, PCC
2. NaBH$_4$
AcO
O
OTES
HO
HO
BzO
H
AcO
O
191
TESO
O
N
Ph
Bz
158
Bz
NH
O
Ph
OH
O
AcO
O
OH
HO
BzO
H
AcO
O
Taxol
154

Scheme 76

Due to the large number of steps, some very low yielding, this synthesis can not constitute a plausible alternative to the semi-synthesis of Taxol from baccatin III; also the need to rely on resolutions and synthetic relays make it less attractive than later published total syntheses.

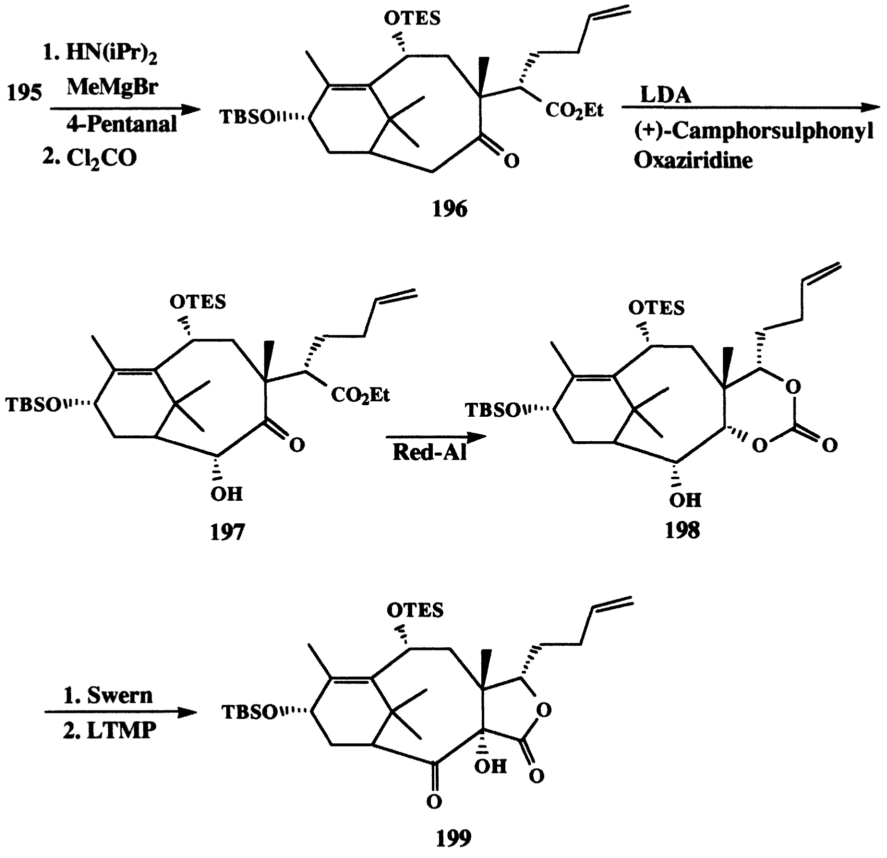
THE TOTAL SYNTHESIS OF TAXOL - HOLTON

The Holton synthesis of Taxol involves an elegant route from camphor; he was also able to synthesise the enantiomer of Taxol using the same methodology.[81] The approach was a linear synthesis which would result in a C-7, C-13-protected baccatin III species, the synthesis of Taxol from such compounds being well documented.[63-65] The commercially available epoxide **192** (derived from camphor) was converted to the hydroxy epoxide **193** which then rearranged to the diol **194**. Protection of the C-19 hydroxyl followed by epoxy alcohol fragmentation[82] and protection of C-13 gave the ketone **195** representing the A, B-ring system of Taxol (Scheme 77).



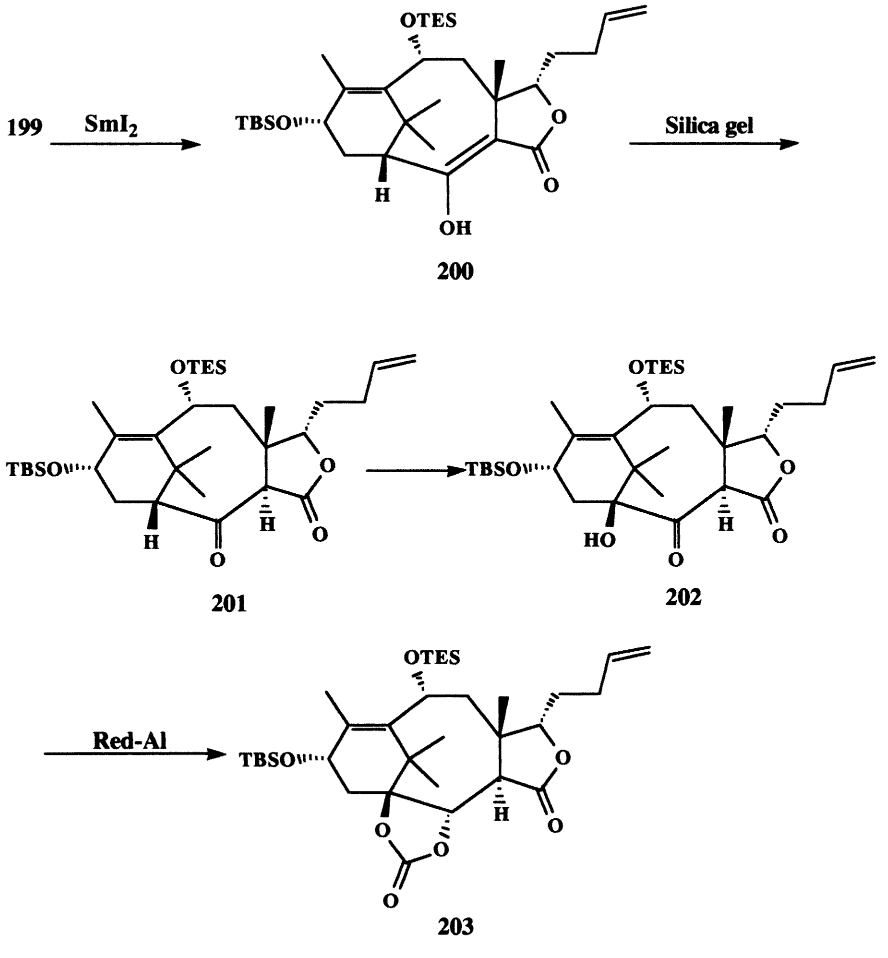
Scheme 77

Holton then set about the construction of the C-ring by alkylation of the B-ring; thus the magnesium enolate of the ketone **195** underwent aldol condensation with 4-pentenal and after protection with phosgene gave the ethyl carbonate **196**. Further elaboration of this functionalised A, B-ring system put in place an hydroxyl group at C-2 to give the α-hydroxy ketone **197**. Reduction of **197** gave a triol which was directly reacted with phosgene to give the carbonate **198**. Oxidation of **198** and subsequent treatment with base gave the hydroxy lactone **199** (Scheme 78).


195
1. HN(iPr)2
MeMgBr
4-Pentanal
2. Cl2CO
OTES
TBSO
CO2Et
O
196
LDA
(+)-Camphorsulphonyl
Oxaziridine
OH
197
Red-Al
198
1. Swern
2. LTMP
199

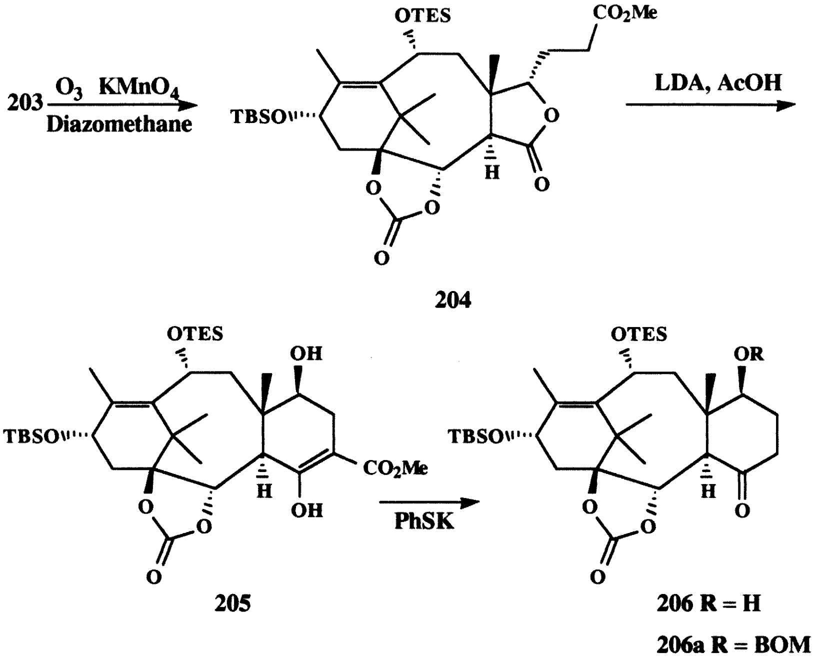
Scheme 78

The lactone **199** was then treated with samarium(II) iodide to produce the enol **200** which gave a 6:1 mixture of *cis* and *trans*-fused lactones when treated with silica gel. The required lactone **201** was crystallised out of solution and the undesired lactone recycled by treatment with KO^{t}Bu and then acetic acid to give the enol **200**. Hydroxylation of **201** at C-2 was achieved in a similar fashion to the hydroxylation at C-5 to afford **202**. Reduction of **202** followed by a basic work-up gave the lactone carbonate **203** in fifteen steps and 36% overall yield (Scheme 79).


199
SmI2
TBSO
OTES
OH
O
O
H
200
Silica gel
201
202
HO
Red-Al
203

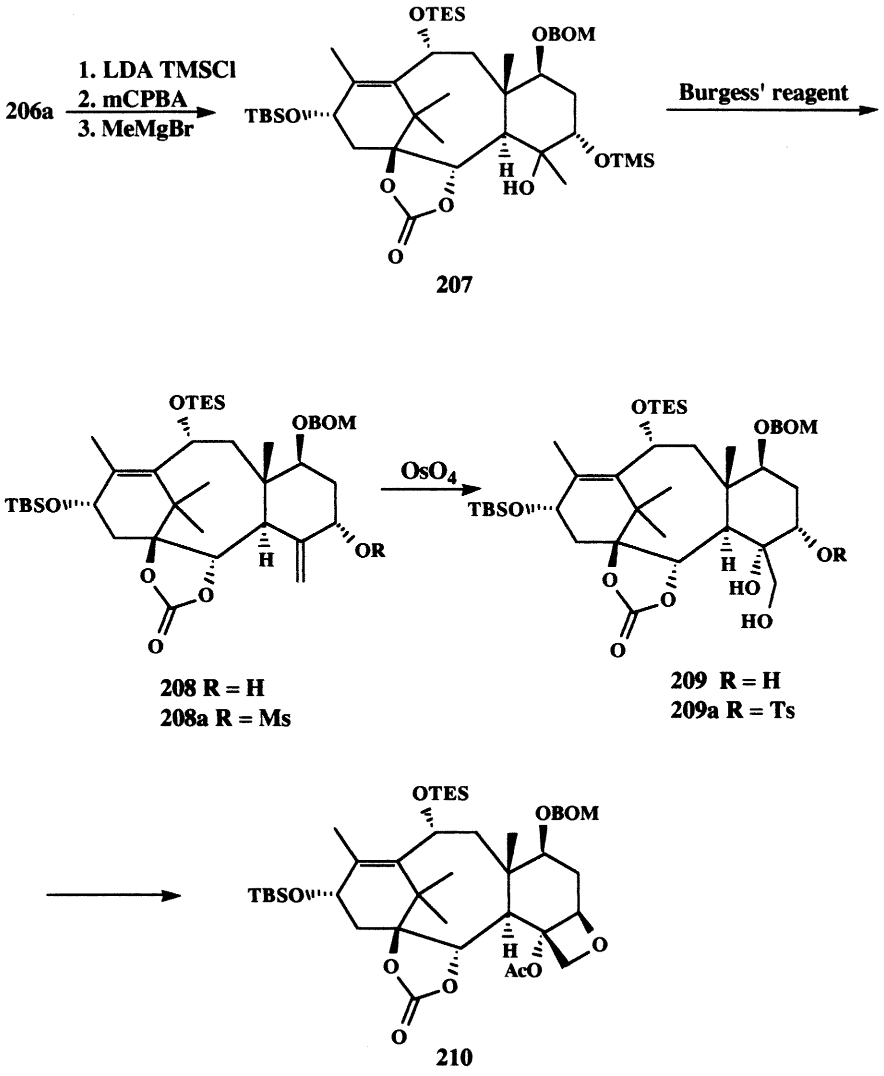
Scheme 79

Oxidative cleavage of the terminal olefin of **203** by ozonolysis and oxidation to the acid and esterification gave the ester **204**. Dieckmann cyclisation of **204** furnished the enol ester **205** and after temporary protection of C-7 and decarbomethoxylation, gave the hydroxy ketone **206** which was then protected to give the BOM ether **206a** (Scheme 80).


203
O3 KMnO4
Diazomethane
OTES
CO2Me
TBSO
O
H
O
O
O
O
204
LDA, AcOH
OTES
OH
TBSO
CO2Me
H
OH
O
O
O
205
PhSK
OTES
OR
TBSO
H
O
O
O
O
206 R = H
206a R = BOM

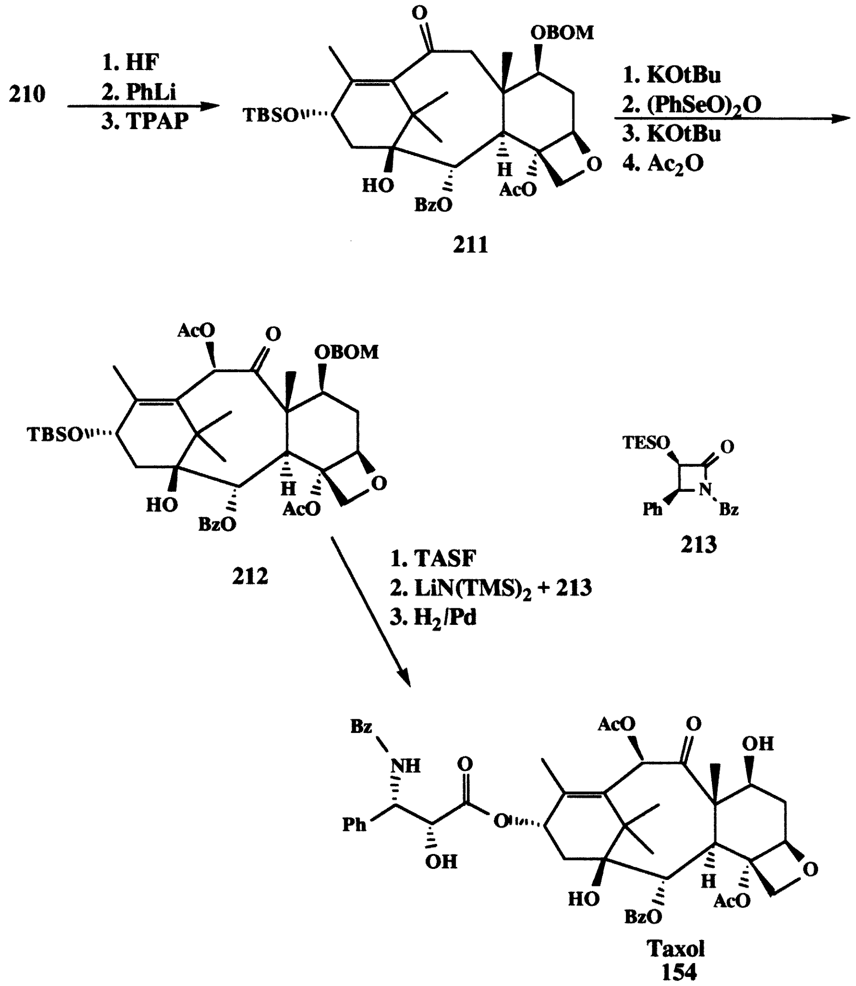
Scheme 80

Now that the C-ring was in place Holton needed to construct the oxetane ring. This proved to be the most problematic part of the synthesis. The C-7 protected compound **206a** was converted to the TMS enol ether and underwent oxidation to stereoselectively provide the C-5 hydroxy ketone and then addition of methyl magnesium bromide furnished the tertiary alcohol **207**; elimination using the Burgess reagent and acidic work-up provided the allylic alcohol **208** which was then converted to the mesylate **208a**. Osmylation of **208a** gave **209** which was converted to the tosylate **209a** through temporary protection of the C-20 hydroxyl as a TMS ether. Treatment of **209a** with DBU furnished the much sought after oxetane ring; acetylation of the C-4 hydroxyl gave **210** (Scheme 81).


206a
1. LDA TMSCl
2. mCPBA
3. MeMgBr
OTES
OBOM
TBSO
OTMS
H
HO
O
207
Burgess' reagent
208 R = H
208a R = Ms
OR
OsO4
209 R = H
209a R = Ts
AcO
210

Scheme 81

The final stages of the synthesis concerned chemistry already known to the group from studies on baccatin III analogues. Desilylation removed the TES group from the C-10 position of **210** and treatment with phenyllithium provided the C-2 benzoate followed by oxidation which yielded the ketone **211**. The enolate of **211** was treated with benzeneseleninic anhydride and the product treated directly with KOtBu; acetylation of this product provided 7-BOM-13-TBS baccatin III **212**. Desilylation at C-13 and attachment of the side chain *via* the β-lactam **213** and deprotection at C-7 afforded Taxol (Scheme 82).

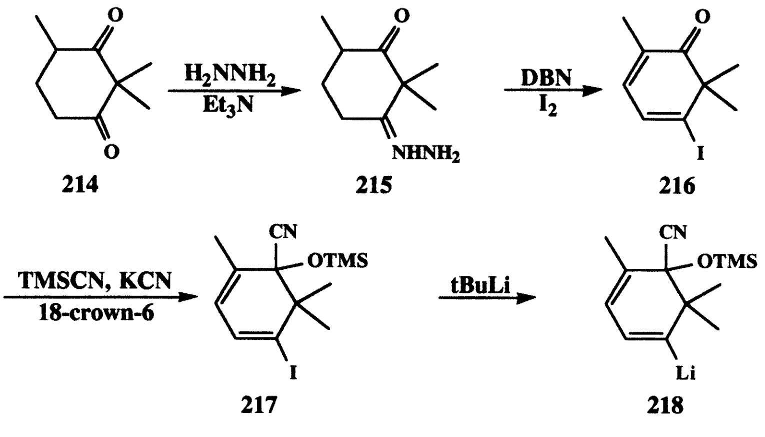

210
1. HF
2. PhLi
3. TPAP
TBSO
O
OBOM
HO
BzO
H
AcO
O
211
1. KOtBu
2. (PhSeO)$_2$O
3. KOtBu
4. Ac$_2$O
AcO
O
OBOM
TBSO
HO
BzO
H
AcO
O
212
TESO
O
N
Ph
Bz
213
1. TASF
2. LiN(TMS)$_2$ + 213
3. H$_2$/Pd
Bz
NH
O
Ph
OH
O
AcO
O
OH
HO
BzO
H
AcO
O
Taxol
154

Scheme 82

Holton not only describes the total synthesis of Taxol but also of its enantiomer and reportedly risked the glory of publishing first by waiting to complete both syntheses.

THE TOTAL SYNTHESIS OF TAXOL - DANISHEFSKY

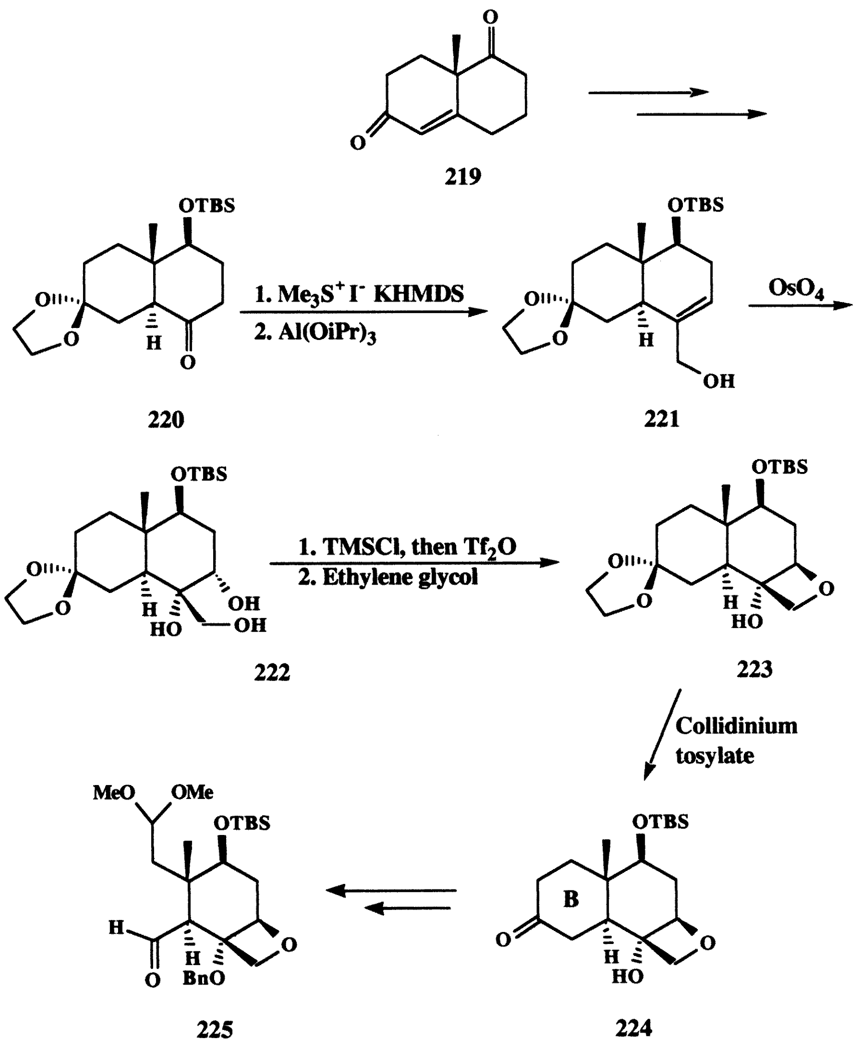
The Danishefsky synthesis of Taxol is the most recent route to be published.[83] The synthesis is similar in many respects to that of Nicolaou, but has the advantage of not relying on resolutions or synthetic relays. The strategy of joining suitably functionalised A and C fragments to build 1, 2 constrained *seco*-B structures *en route* to closure of the B-ring was, however, evident in earlier publications.[84] The synthesis of the A-ring started with the diketone **214** (Scheme 83). Reaction of the hydrazone **215** with DBN and iodine gave **216**, which furnished the TMS-ether **217**. Treatment of **217** with tBuLi gave the lithiated A-ring **218** which would eventually couple to the C-ring.[85]



Scheme 83

The synthesis of the C-ring started with the (S)-Wieland Miescher ketone **219**, from which all asymmetric induction ultimately accrues (Scheme 84). The protected C-7 alcohol **220** was prepared by the method of Heathcock[86] in high yielding steps. The conversion of **220** to the alcohol **221** was an improved transformation to that previously published by the group.[87] Dihydroxylation of **221** using osmium tetroxide furnished the triol **222** which was converted in one pot to oxetane **223** by selective silylation of the primary alcohol, conversion of the secondary alcohol to the triflate followed by alcohol induced desilylation. The acetal of **223** was cleaved under mildly acidic conditions to give the ketone **224**. The

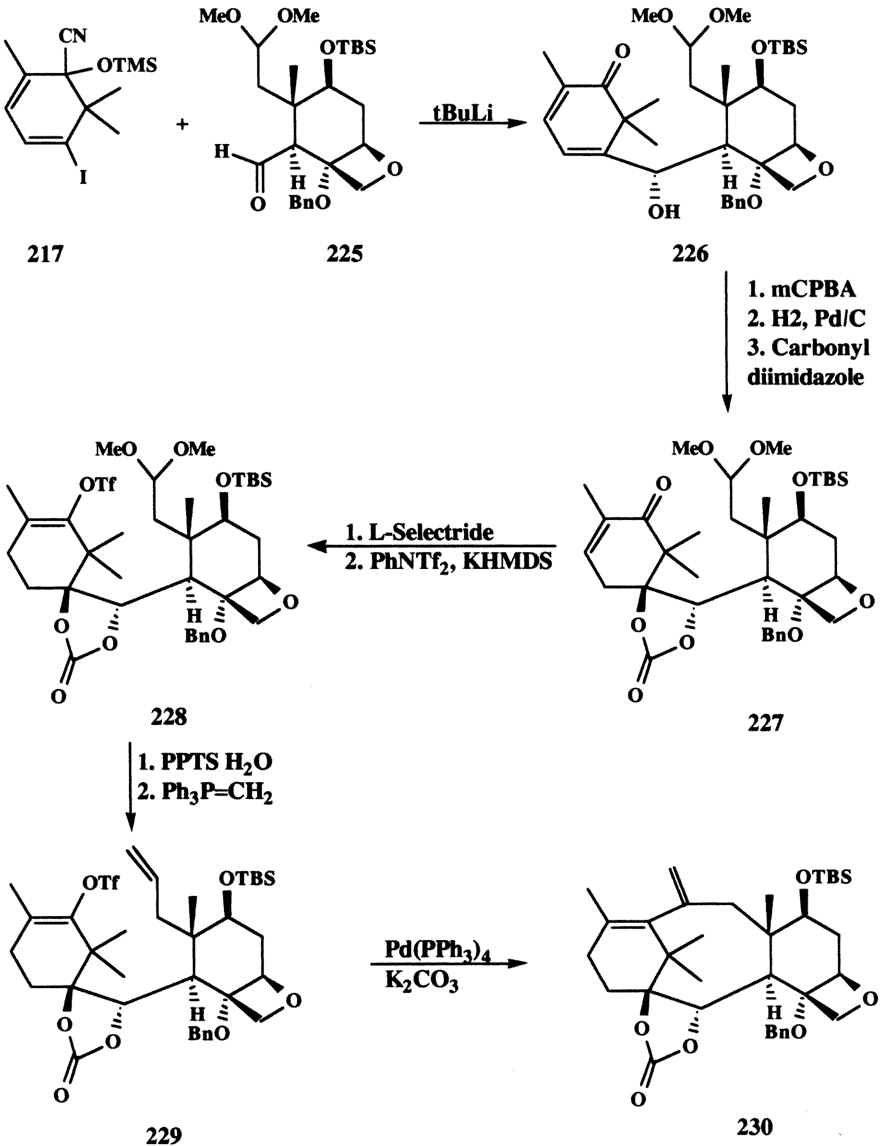
B-ring of **224** was cleaved in an easily conducted and high yielding sequence to produce the aldehyde **225**.[88]


219
OTBS
1. $Me_3S^+ I^-$ KHMDS
2. $Al(OiPr)_3$
220
221
OsO_4
OH
222
1. TMSCl, then Tf_2O
2. Ethylene glycol
223
Collidinium tosylate
B
224
MeO
OMe
H
BnO
HO
225

Scheme 84

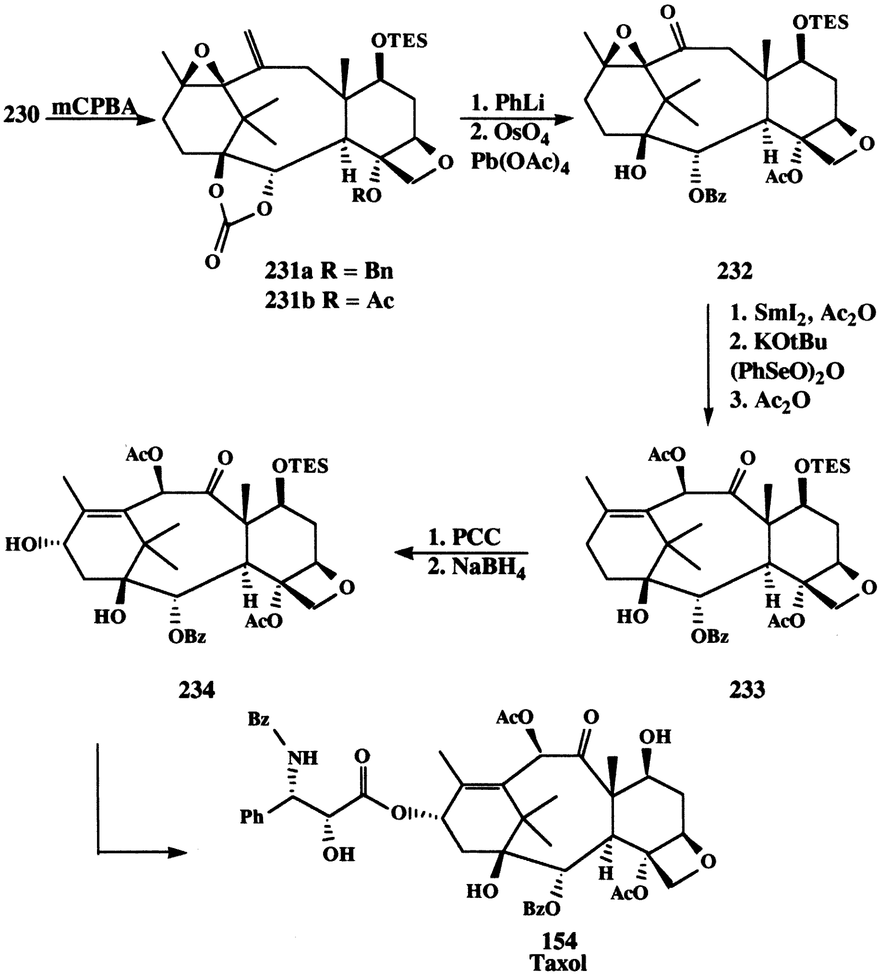
After some initial problems with the lability of the oxetane ring the A and C-Rings were coupled together to give **226** (Scheme 85). Epoxidation across the C-1, C-14 bond and subsequent reduction put in the required C-1 hydroxyl which was joined together with the C-

2 hydroxyl as the carbonate to give **227**. The C-12, C-13 double bond was reduced and treatment with base and trapping of the enol as the triflate furnished the vinyl triflate **228**. Cleavage of the dimethyl acetal of **228** and chain elongation afforded **229**, which was ring closed *via* a Heck reaction to give the tetracyclic intermediate **230**.


CN
OTMS
I
217
+
MeO
OMe
OTBS
H
O
H
BnO
O
225
tBuLi
MeO
OMe
O
OTBS
OH
H
BnO
O
226
1. mCPBA
2. H2, Pd/C
3. Carbonyl diimidazole
MeO
OMe
O
OTBS
O
O
O
H
BnO
O
227
1. L-Selectride
2. PhNTf$_2$, KHMDS
MeO
OMe
OTf
OTBS
O
O
O
H
BnO
O
228
1. PPTS H$_2$O
2. Ph$_3$P=CH$_2$
OTf
OTBS
O
O
O
H
BnO
O
229
Pd(PPh$_3$)$_4$
K$_2$CO$_3$
OTBS
O
O
O
H
BnO
O
230

Scheme 85

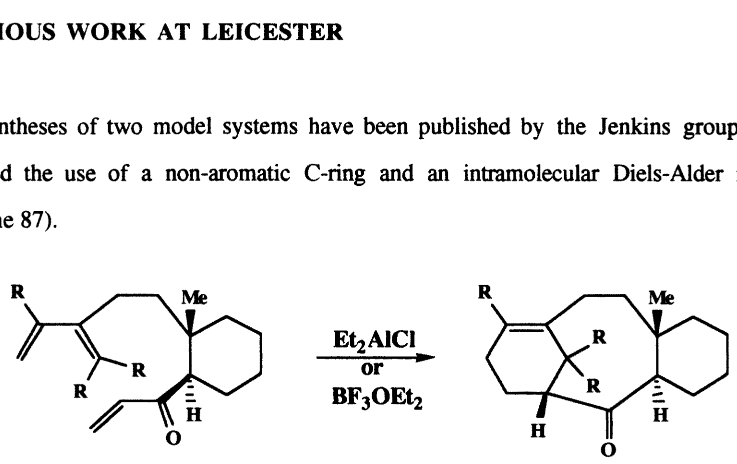
As in previous syntheses, protecting group interconversion was necessary, and the TBS group of **230** was changed to a TES group reducing the need for the vigorous conditions required for its removal. Epoxidation of **230** afforded the epoxide **231a** which was subsequently converted to the acetate **231b**. Opening of the carbonate with phenyllithium gave the C-1 hydroxyl and C-2 benzoate, and treatment with osmium tetroxide and lead tetracetate afforded the ketone **232**. Deoxygenation of the epoxide with samarium(II) iodide, oxidation at C-9 followed by an α-ketol interchange and acetylation provided **233**. Allylic oxidation and reduction furnished 7-triethylsilyl baccatin III **234** which after deprotection and introduction of the side-chain by the method Ojima[66] gave Taxol (Scheme 86).


230
mCPBA
OTES
O
O
O
O
H
RO
O
231a R = Bn
231b R = Ac
1. PhLi
2. OsO4
Pb(OAc)4
O
OTES
HO
OBz
H
AcO
O
232
1. SmI2, Ac2O
2. KOtBu
(PhSeO)2O
3. Ac2O
AcO
O
OTES
HO
OBz
H
AcO
O
233
1. PCC
2. NaBH4
AcO
O
OTES
HO
HO
OBz
H
AcO
O
234
Bz
NH
O
Ph
OH
O
AcO
O
OH
HO
BzO
H
AcO
O
154
Taxol

Scheme 86

PREVIOUS WORK AT LEICESTER

The syntheses of two model systems have been published by the Jenkins group,[89] and involved the use of a non-aromatic C-ring and an intramolecular Diels-Alder reaction (Scheme 87).

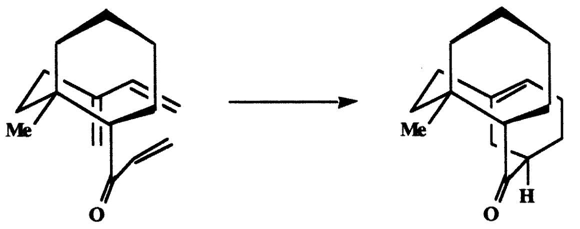


235 R = H
237 R = Me

236 R = H
238 R = Me

Scheme 87

The first model study produced a crystalline taxoid ring system **236**, the X-ray crystal structure of which showed the eight-membered B-ring to be in a boat-chair conformation; this suggests that the Diels-Alder reaction proceeds *via* the transition state **236a** (Scheme 88). The boat-chair conformation is the conformation of the eight-membered ring in all the X-ray crystal structures of yew tree natural products.[90]

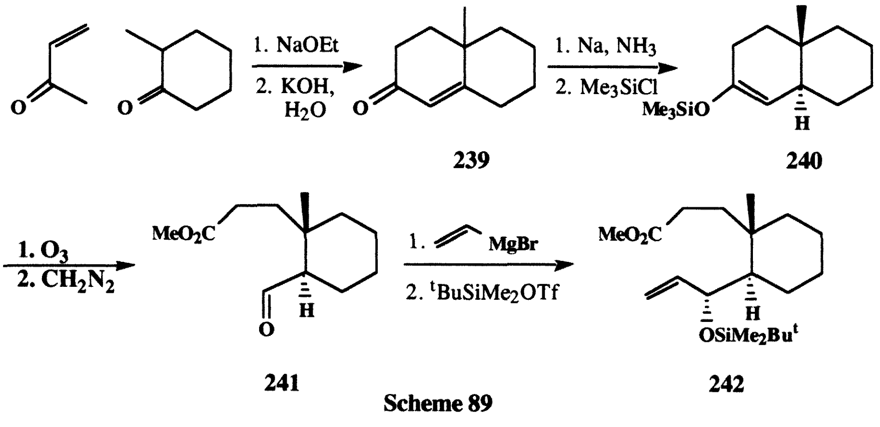


236a

236

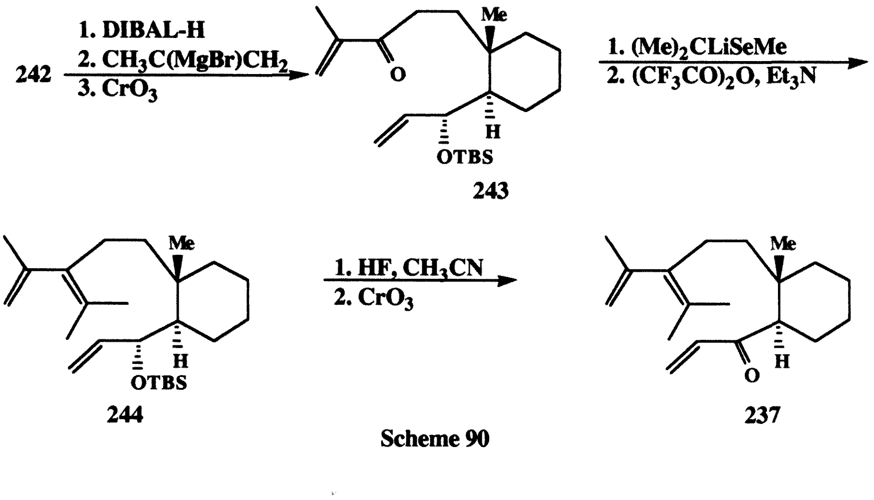
Scheme 88

The second model study required the intoduction of three methyl groups in the A-ring of the taxoid structure. Robinson annulation of 2-methyl cyclohexanone and methyl vinyl ketone gave the known decalin **239**.[91] Lithium in ammonia reduction and trapping of the enolate gave the trimethyl silyl ether **240** following the method of Stork.[92] Ozonolysis and methylation produced the ester aldehyde **241** which was further treated with vinyl magnesium bromide and protected as the dimethyl tertiary butyl silyl ether **242** (Scheme 89).


1. NaOEt
2. KOH, H2O
239
1. Na, NH3
2. Me3SiCl
Me3SiO
H
240
1. O3
2. CH2N2
MeO2C
O
H
241
1. MgBr
2. tBuSiMe2OTf
MeO2C
H
OSiMe2Bu^t
242

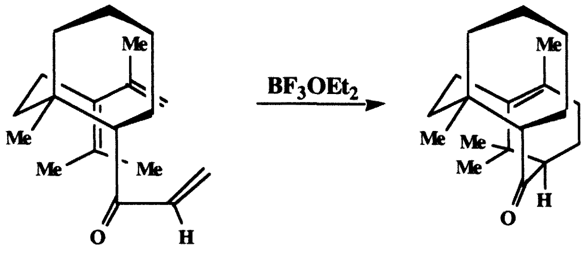
Scheme 89

The intermediate **242** was reduced to an aldehyde which was further reacted with propenyl magnesium chloride and the resulting allylic alcohol oxidised to the enone **243**. The synthesis of the diene was achieved by the introduction of the anion $Me_2CLiSePh$, developed by the work of Krief[93] and Reich[94], and subsequent elimination to give the triene **244**. Deprotection and oxidation furnished the trienone **237** (Scheme 90).


242
1. DIBAL-H
2. CH3C(MgBr)CH2
3. CrO3
Me
O
H
OTBS
243
1. (Me)2CLiSeMe
2. (CF3CO)2O, Et3N
Me
H
OTBS
244
1. HF, CH3CN
2. CrO3
Me
O
H
237

Scheme 90

The trienone **237** was again thought to adopt a boat-chair conformation **237a** in an intramolecular Diels-Alder reaction to give the alkylated taxane model **238** (Scheme 91). Unfortunately the product was not a solid but NMR analysis showed that the B-ring in **238** was indeed in a boat-chair conformation.



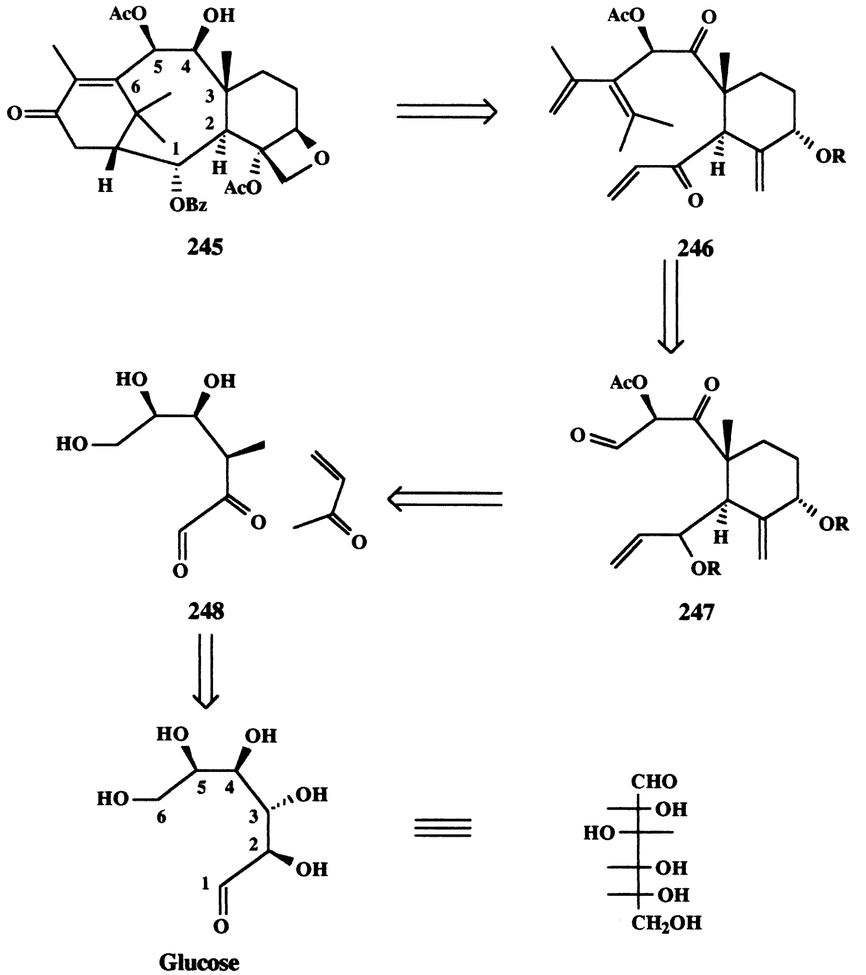
237a

238

Scheme 91

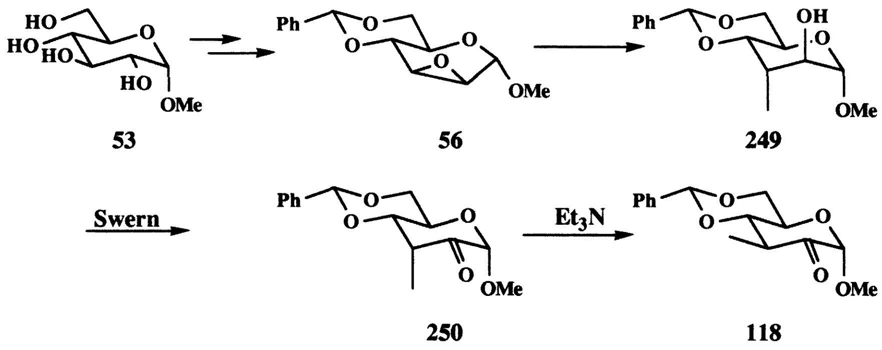
Chiral Taxoids from Glucose

The next stage in the project was to devise a route that would incorporate as much of the functionality found in natural taxanes as possible. The retrosynthetic plan for taxoid structure **245** is shown in Scheme 92. It is assumed at this stage that oxidation at C-13 and introduction of the side chain will be carried out using known procedures. The hydroxyl groups at C-7 and C-1 are also missing but it is envisaged that modification of the route may be possible once its viability has been proven.



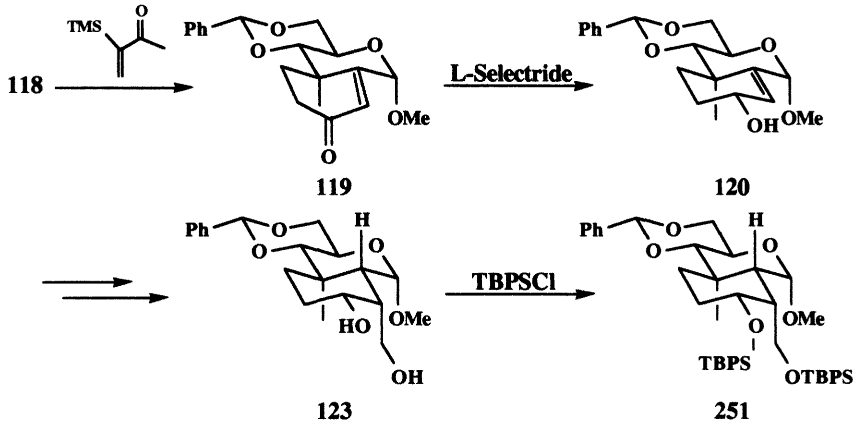
Scheme 92

The C-7 hydroxyl has in fact been shown not to be needed for biological activity.[95] Working backwards from the tricyclic compound **245** we obtain the triene **246**, which in turn arises from the aldehyde **247**. Then Robinson annulation of a protected form of the sugar methyl ketone **248** should give the C-ring synthon **247**. The starting point was glucose for which there was a literature preparation of a protected methyl ketone **118** from the work of Sinaÿ[25] (Scheme 93).



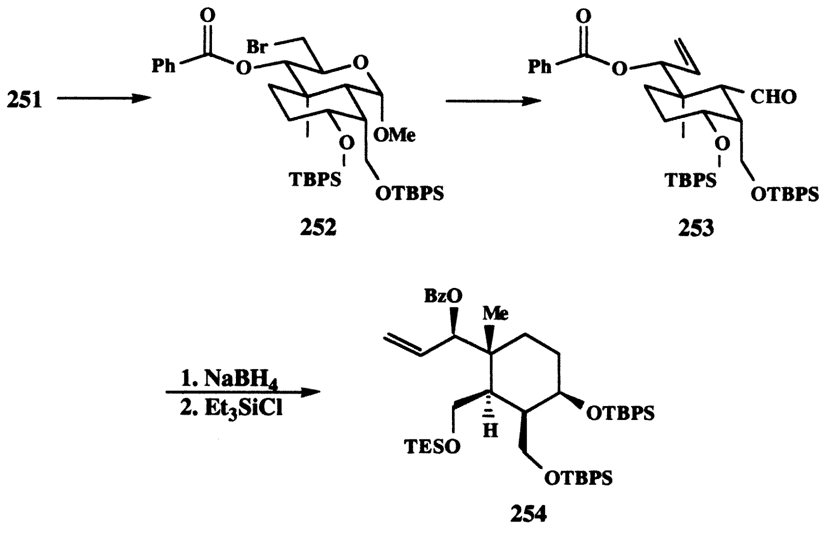
Scheme 93

The conversion of **53** into the epoxide **56** has already been described in Chapter 1. The epoxide **56** was then selectively opened with methyl magnesium chloride to give the alcohol **249** which furnished the ketone **250** after Swern oxidation. Epimerisation of the ketone **250** to **118**[25] was achieved by treatment with triethylamine in DMF for 36 hours at room temperature. The first reaction of the methyl ketone **118** is the formation of the enolate with Li(TMS)$_2$ followed by the first known example of a Robinson annulation on a sugar derivative.[1a] Reduction of the enone **119** with L-Selectride® furnished the allylic alcohol **120**. The conversion of allylic alcohol **120** to the diol **123** has been described in Chapter 2.[57] Protection of the diol **123** led to the *bis* silyl ether **251** (Scheme 94).



Scheme 94

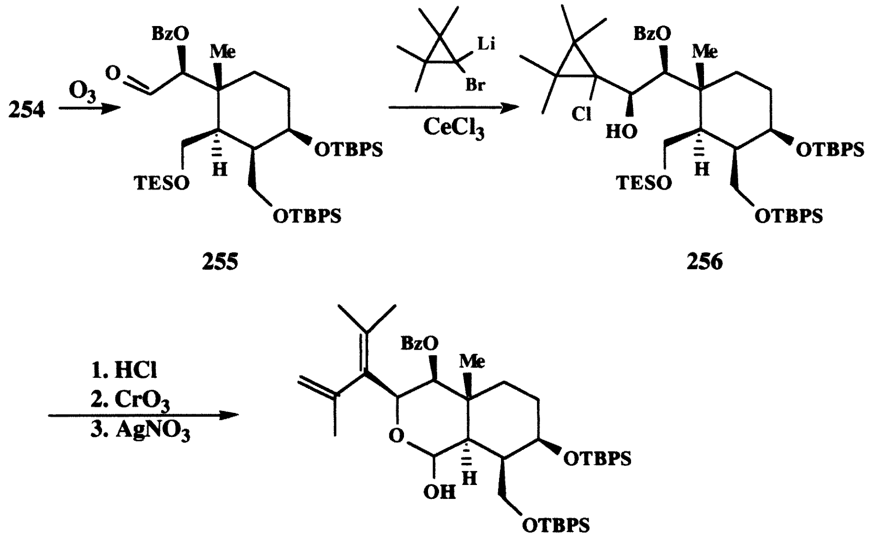
Having used the protected carbohydrate ring as a chiral template it was then necessary to fragment the sugar ring leaving a chiral functionalised cyclohexane C-ring synthon. The first step was reaction with NBS following the work of Hanessian^{36} to produce the bromo ester **252**. Treatment of **252** with activated zinc then produced aldehyde **253** in a Vasella elimination reaction.^{37} Reduction and protection of the aldehyde gave the required chiral C-ring synthon **254**^{1b} (Scheme 95).



Scheme 95

Construction of the Diene

The first attempt at constructing the diene focused on adding all the required carbons as a single unit. Ozonolysis of the C-ring synthon **254** gave the aldehyde **255**,^{1b} addition of the known tetramethylcyclopropyl reagent^{96} and catalysis with CeCl$_3$ furnished the cyclopropane **256**. Rearrangement of **256** was achieved on a small scale to give the diene **257**^{97} but the reaction was,very difficult to repeat (Scheme 96).


254
O₃
BzO
Me
O
TESO
H
OTBPS
OTBPS
Li
Br
CeCl₃
Cl
HO
1. HCl
2. CrO₃
3. AgNO₃
O
OH

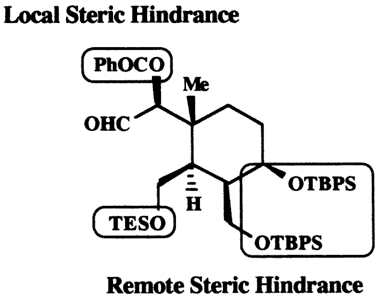
255

256

257

Scheme 96

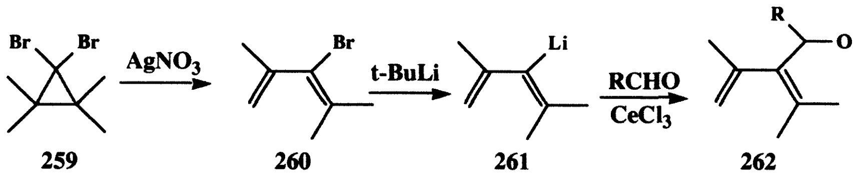
The reasons for the low reactivity were thought to be due to two types of steric hindrance. The first is local steric hindrance by the benzoate ester and the second is remote steric hindrance from the three bulky silyl protecting groups, this is shown by **258** (Scheme 97).


Local Steric Hindrance
PhOCO
Me
OHC
TESO
H
OTBPS
OTBPS
Remote Steric Hindrance

258

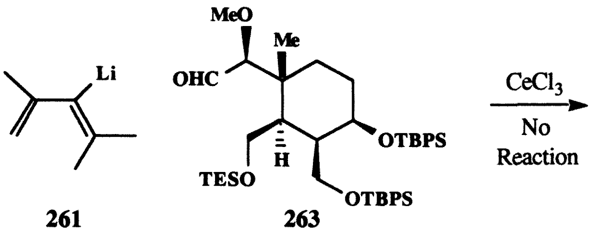
Scheme 97

In order to probe this hypothesis systematic changes to the local and remote steric hindrance were needed. It was also decided that the size of the incoming nucleophile should be as small as possible and that rearrangement of the cyclopropane **259** to the diene **260** prior to the reaction may increase the chances of addition to the hindered aldehyde. Shea published[98] the formation of the lithiated diene **261** and the addition of this anion to aldehydes catalysed by $CeCl_3$ to furnish the diene **262** in good yields (Scheme 98).



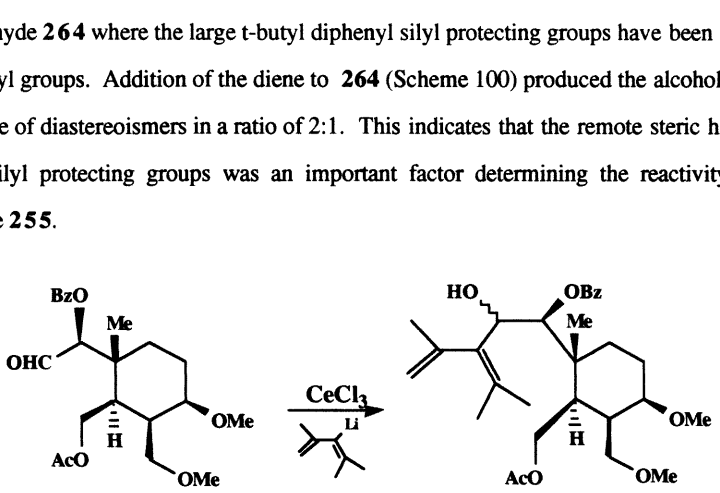
Scheme 98

To test the importance of the local steric hindrance the benzoate group of **254** was removed by DIBAL-H reduction and the corresponding alcohol converted into the methyl ether, subsequent ozonolysis produced the aldehyde **263**. No reaction took place when the lithiated diene **261** was added to the aldehyde **263** in the presence of $CeCl_3$,[99] which indicated that the local steric hindrance of the benzoate ester was not important to the reactivity of the aldehyde group in **255** (Scheme 99).



Scheme 99

The importance of the remote steric hindrance was probed by changing the silyl ethers of **251** for several different groups.[100] It was found however that the only group to survive the NBS reaction was the methyl ether. Methylation of the diol **123** (Scheme 94) gave the dimethyl ether corresponding to **251**. The same reaction sequence as for **251** then produced the aldehyde **264** where the large t-butyl diphenyl silyl protecting groups have been replaced by methyl groups. Addition of the diene to **264** (Scheme 100) produced the alcohol **265** as a mixture of diastereoismers in a ratio of 2:1. This indicates that the remote steric hindrance of the silyl protecting groups was an important factor determining the reactivity of the aldehyde **255**.



264 **265**

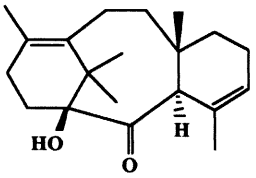
Scheme 100

Clearly the methyl groups in **265** are not ideal protecting groups and their removal to construct the oxetane ring would be very difficult.

RECENT APPROACHES TOWARDS THE DIENE CONSTRUCTION

On starting the taxane project two things became very clear, firstly that any progress through the route relied upon a constant supply of starting materials and secondly that team work would be essential as the route from glucose comprised 21 steps, not including the synthesis of any additional reagents. We decided that a stock pile of starting material should be synthesised before embarking on any new chemistry. The previous end game strategy of adding the diene as a single unit was contrary to the diene synthesis in the alkylated model (Scheme 90) where the use of selenium chemistry helped to build the diene in a stepwise fashion. Previous attempts to use selenium chemistry in the chiral route have proved fruitless due to the failure of the reagent $Me_2CLiSePh$ to add effectively and then eliminate to form a diene. During the initial synthesis of starting materials a publication by Professor R.

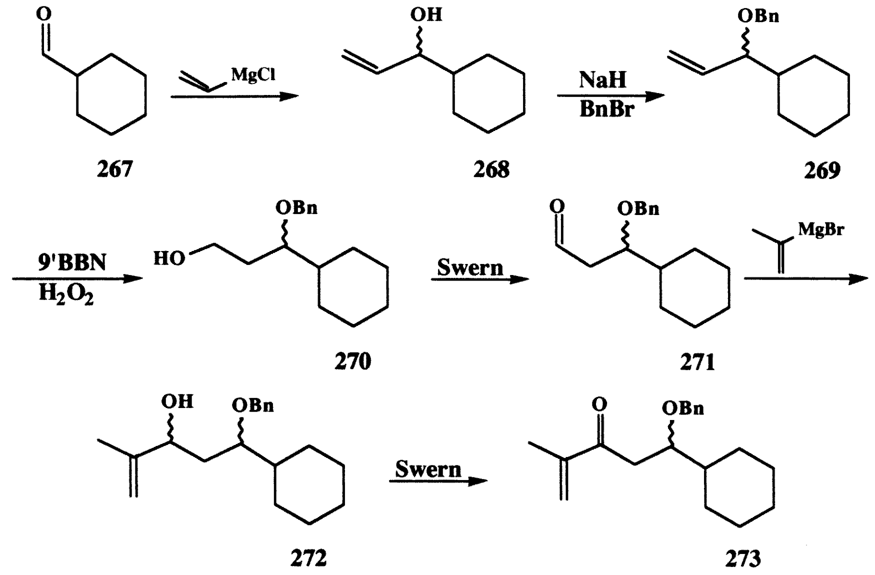
M. Williams appeared.[101] This used an adaptation of the synthesis described in Scheme 90 to give the first synthesis of taxadiene, **266**, the proposed first fully cyclised intermediate in the biosynthesis of Taxol (Scheme 101).



266

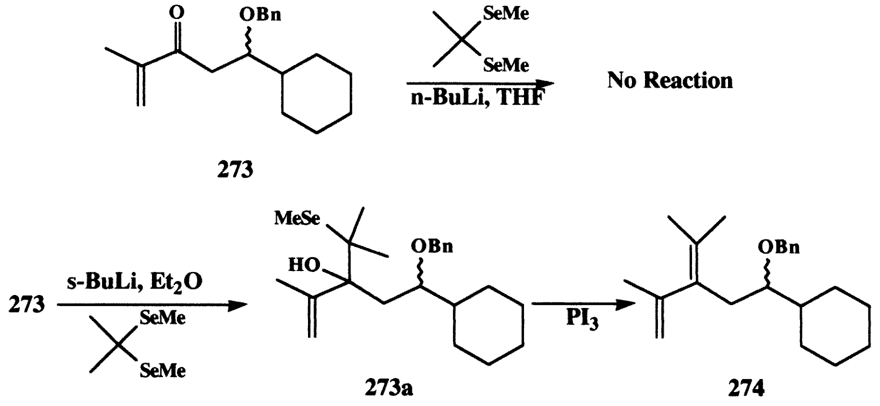
Scheme 101

The authors had also found difficulties with the stepwise diene synthesis, but had overcome these problems by carrying out the reaction with $Me_2CLiSeMe$. We were progressing well with the synthesis of the starting material and decided to carry out a model study and construct a diene using the new reagent $Me_2CLiSeMe$. The starting point was cyclohexane carboxaldehyde **267** which was reacted with vinyl magnesium chloride to furnish the alcohol **268**. This was subsequently treated with triethylamine and benzyl bromide to give **269**. Treatment of the olefin **269** with 9'BBN and oxidation of the resulting organoborane with hydrogen peroxide furnished the alcohol **270** which was oxidised using the Swern procedure to the aldehyde **271**. The aldehyde **271** was then treated with propenyl magnesium chloride to furnish a 2:1 mixture of diastereoismers which were then oxidised to the enone *via* the Swern procedure (Scheme 102).


MgCl
NaH
BnBr
9'BBN
H_2O_2
Swern
MgBr
Swern
OH
OBn
HO
O
267
268
269
270
271
272
273

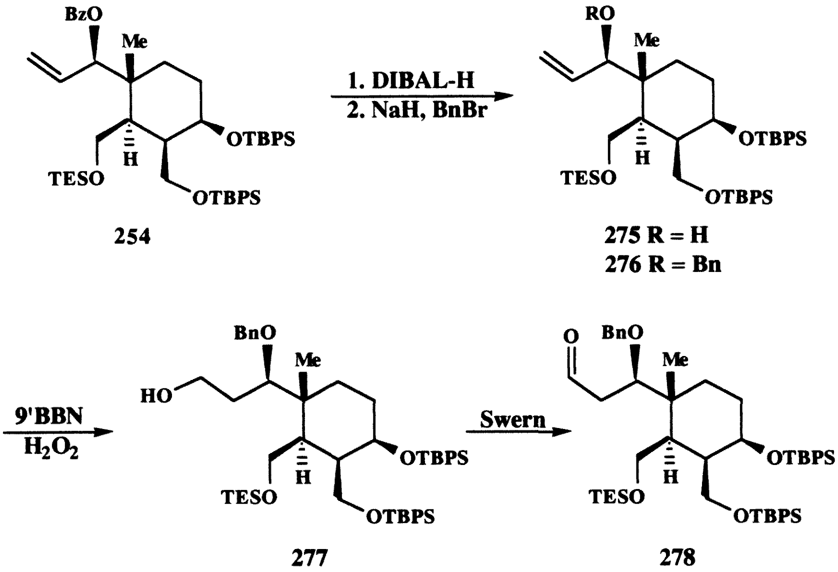
Scheme 102

Having achieved the synthesis of the enone **273** in good yield we needed to add the lithiated seleno-acetal $Me_2CLiSeMe$ following the work of Professor Krief.[93] Numerous attempts to follow the literature procedure for cleavage of the selenium acetal (n-butyllithium in THF) failed we therefore decided to contact Professor Krief for help. After visiting Namur, Belgium, with the model compound and a similar model synthesised by the postdoctoral worker Gary Tustin, the correct conditions for the acetal cleavage were set and successful addition to the enone **274** was achieved (Scheme 103).



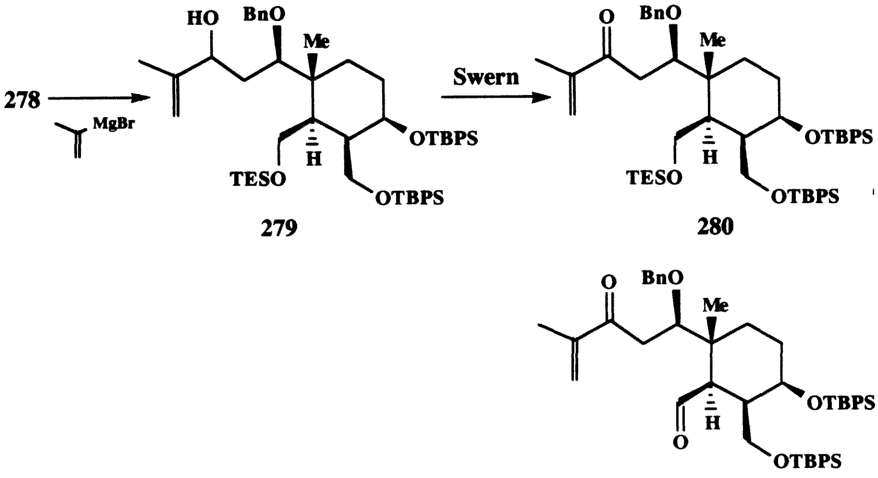
Scheme 103

On returning to Leicester filled with confidence from our trip we treated the compound **273a** with PI$_3$ to furnish the diene **274** completing the much sought after enone to diene conversion. Unfortunately all attempts to repeat the acetal lithiation and addition to the enone **273** failed at Leicester. Having taken great lengths to ensure the purity of the reagents that we were using and following exactly the procedure set out on our visit we were at a loss as to the nature of our failures. We again decided to contact Professor Krief who made several suggestions during a telephone conversation and just before ringing off said "by the way don't use your NMR sample in the reaction." Armed with this information we duly repeated the reaction on our model compounds and found them to proceed smoothly! Once the model study was working well we set about the conversion of the chiral C-ring synthon **254** (Scheme 104). The first step was reduction of the benzoyl group by reaction with DIBAL-H to furnish the alcohol **275** followed by reaction with sodium hydride and benzyl bromide to give **276**. This conversion from a benzoyl to benzyl group was shown to be necessary in the model study where hydroboration of an allylic benzoate led to destruction of the starting material. Hydroboration of the olefin **276** and oxidation led to the primary alcohol **277**, which afforded the aldehyde **278** after Swern oxidation (Scheme 104).


BzO
Me
OTBPS
H
TESO
OTBPS
254
1. DIBAL-H
2. NaH, BnBr
RO
Me
OTBPS
H
TESO
OTBPS
275 R = H
276 R = Bn
9'BBN
H_2O_2
BnO
HO
Me
OTBPS
H
TESO
OTBPS
277
Swern
O
BnO
Me
OTBPS
H
TESO
OTBPS
278

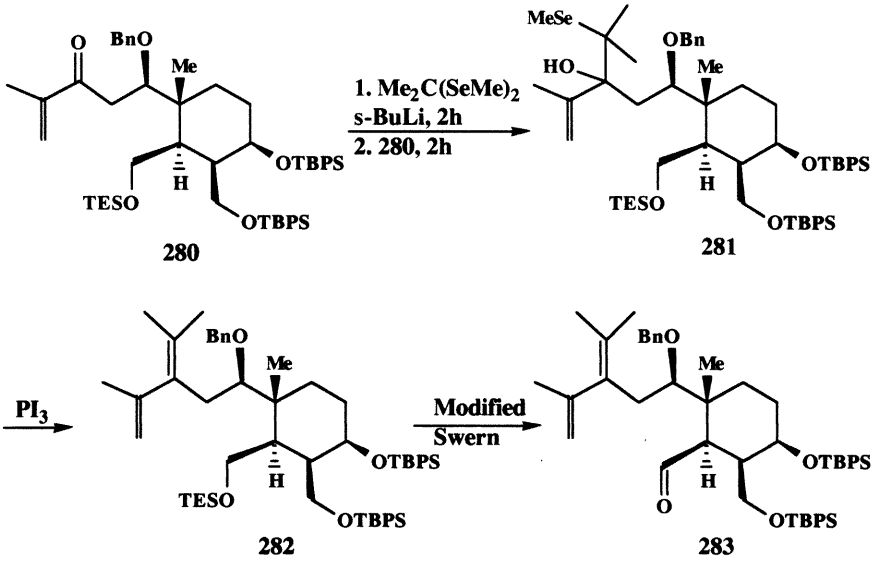
Scheme 104

In a similar fashion to the model study propenyl magnesium bromide was added to the aldehyde **278** to furnish the allylic alcohol **279** as a 2:1 mixture of diastereoisomers, again Swern oxidation of both isomers yielded the enone **280** (Scheme 105).


278
MgBr
HO
BnO
Me
OTBPS
H
TESO
OTBPS
279
Swern
O
BnO
Me
OTBPS
H
TESO
OTBPS
280
O
BnO
Me
OTBPS
O
H
OTBPS
280a

Scheme 105

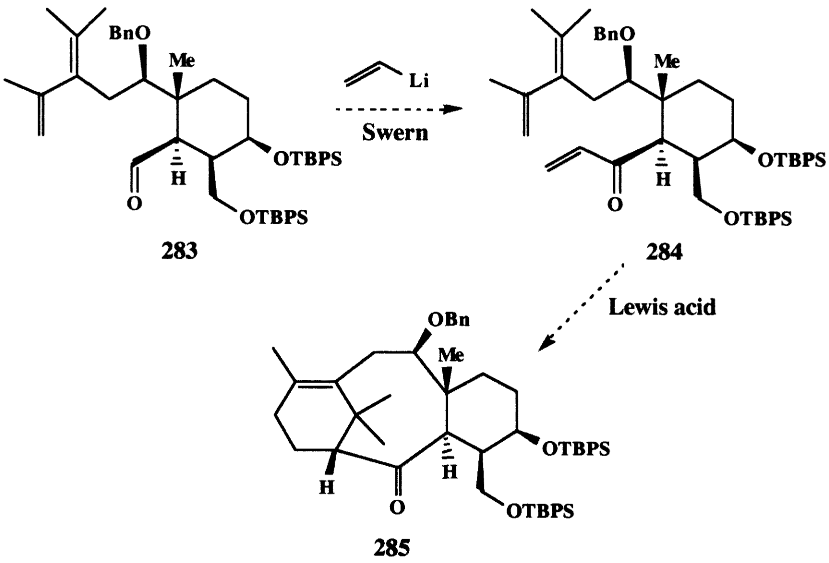
On one occasion, however, the temperature of the reaction mixture was accidentally allowed to rise to -40 °C during the Swern oxidation of **279** to **280**, this resulted in a second product being isolated which was thought to be the enone aldehyde **280a**. The higher temperature had enabled the removal of the triethyl silyl group, and subsequent oxidation furnished the aldehyde. This interesting observation proved very useful later in the route. Initial attempts to add the lithiated acetal to the enone **280** again met with failure. After several attempts it became obvious that the lithiation of the acetal was still causing problems. The eventual conditions for success are shown in Scheme 106. The condition of the s-BuLi seems to be a crucial factor and reaction times approaching 3 hours are needed to ensure complete lithiation of the acetal as opposed to the 20 minutes quoted in the literature.[93] The fickleness of the reaction is greatly exaggerated by the small scale, typically 0.1 mmol, where reactions in the model study often had starting material remaining but were carried out on a 1 mmol scale. The diene synthesis has, however, been achieved since the start of this thesis. Scheme 106 shows that the lithiation of the acetal took 2 hours and the addition of the lithiated acetal to the enone **280** took a further 2 hours, subsequent elimination of the intermediate **281** to the diene was achieved with PI_3. Conversion of **281** to the aldehyde was completed in a one pot procedure utilising the earlier observation that a temperature of -40 °C during a Swern oxidation was sufficient to cleave the triethylsilyl ether and allow oxidation to the aldehyde **283** to take place (Scheme 106).


O
BnO
Me
OTBPS
TESO
H
OTBPS
280
1. Me2C(SeMe)2
s-BuLi, 2h
2. 280, 2h
MeSe
HO
OBn
Me
OTBPS
TESO
H
OTBPS
281
PI3
BnO
Me
OTBPS
TESO
H
OTBPS
282
Modified
Swern
BnO
Me
OTBPS
O
H
OTBPS
283

Scheme 106

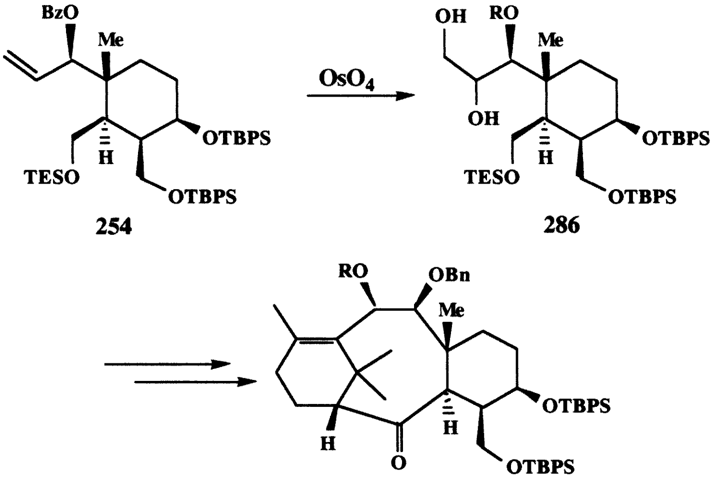
Future Work

The advanced intermediate **283** is now only 2 steps from the final Diels-Alder reaction which will test whether or not a highly functionalised chiral intermediate such as **284** can undergo the required intermolecular Diels-Alder reaction to furnish a chiral taxoid structure such as **285** (Scheme 107).


BnO
Me
OTBPS
H
O
OTBPS
283
Li
Swern
BnO
Me
OTBPS
H
O
OTBPS
284
Lewis acid
OBn
Me
OTBPS
H
H
O
OTBPS
285

Scheme 107

If the viability of the route can be proven, the next stages in the synthesis require the construction of the oxetane ring and oxidation at C-7, C-10 and C-13. It may be possible to modify the route to introduce the C-10 hydroxyl at an earlier stage (Scheme 108). Instead of hydroboration of the olefin **254** with 9’BBN treatment with OsO_4 would furnish the diol **286**. Elaboration of the diol **286** would require some protecting group interconversion but the opportunity to introduce the C-10 hydroxyl at this stage should be possible.


BzO
Me
OTBPS
H
TESO
OTBPS
OsO_4
OH
RO
Me
OH
OTBPS
H
TESO
OTBPS
RO
OBn
Me
OTBPS
H
H
O
OTBPS

254

286

287

Scheme 108

Summary

The advanced C-ring synthon **254** had resisted all previous attempts at conversion to a diene.[97,99,100] A return to the application of selenium chemistry eventually yielded the desired result and also holds with it the opportunity for further elaboration and construction of more advanced taxoid structures such as **287**.

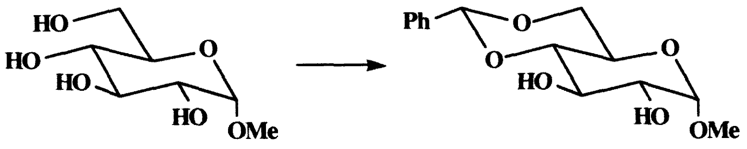
Chapter 4

EXPERIMENTAL

GENERAL EXPERIMENTAL

The synthesis of some compounds on a large scale proved to be not trivial and therefore experimental procedures for compounds prepared previously have been included where modifications to the published procedure have been employed, or little or no data for compounds was available. All reactions were performed under an atmosphere of nitrogen (unless otherwise stated in the text) and solvent extractions dried with $MgSO_4$. Tetrahydrofuran was freshly distilled from sodium benzophenone ketyl. Carbon tetrachloride was distilled from phosphorus pentoxide and stored under nitrogen. Diethyl ether was distilled from lithium aluminium hydride or in the case of the diene synthesis diethyl ether was distilled from sodium benzophenone ketyl. Dichloromethane was distilled from calcium hydride. Petroleum ether refers to the 40-60 °C boiling fraction. The concentrations of n-BuLi and s-BuLi were determined by titration against diphenylacetic acid.[102] Flash column chromatography was performed on Sorbsil C-60 silica gel (Crosfield Chemicals) 40-60 M. Mps were obtained on a Kofler hotstage and are uncorrected. Elemental analyses were performed by Butterworth Laboratories, Teddington, Middlesex. IR spectra were obtained on a Perkin Elmer PE 298 spectrophotometer. NMR spectra were recorded in $CDCl_3$ with Me_4Si as the internal standard at room temperature on a Varian EM-390 (90 MHz ^1H), Bruker ARX 250 (250 MHz ^1H, 62.9 MHz ^{13}C) and Bruker AM 300 (300 MHz ^1H, 75 MHz ^{13}C) spectrometers at Leicester University, n.O.e experiments were recorded on a Bruker WH 400 (400 MHz ^1H) spectrometer at Warwick University. All chemical shifts were taken directly from the spectra and *J* values are given in Hz. Optical rotations were recorded on a Perkin Elmer 341 Polarimeter. Mass spectra were recorded on a Kratos Concept at Leicester University.

Methyl 4,6-*O*-benzylidene-α-*D*-glucopyranoside

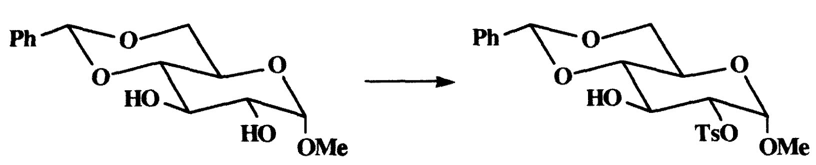


53 **54**

Methyl α-D-glucopyranoside **53** (50.0 g, 0.26 mol), benzaldehyde dimethyl acetal (38.65 cm^3, 0.26 mol), dry DMF (300 cm^3), and *para*-toluenesulphonic acid monohydrate (147 mg, 0.77 mmol), were placed in a flask fitted with a water condenser attached to a water pump. The solution was then heated to reflux (65 °C), for 3h. The DMF was then removed under reduced pressure and the resulting white solid dispersed in sodium hydrogen carbonate (560 cm^3 water, 11 g carbonate), on a water bath. After cooling the product was filtered, washed with water (400 cm^3), and dried *in vacuo* overnight over phosphorus pentoxide. The white solid was then recrystallised from isopropanol (180 cm^3) and pyridine (3.0 cm^3) to give **54** (24.03 g, 58%), mp 166 - 167 °C, (lit.,[23] 166 - 167 °C); δ_H (250 MHz; CDCl$_3$) 3.41 (3H, s, OMe), 3.44 (1H, obscured t, *J* 9.2, 4-H), 3.57 (1H, dd, *J* 8.9, 3.9, 2-H), 3.73 (2H, dt, t, *J* 8.5, 4.3, *J* 10.3, 5-H, 6ax-H), 3.89 (1H, t, *J* 9.1, 3-H), 4.26 (1H, dd, *J* 9.1, 3.9, 6eq-H), 4.72 (1H, d, *J* 3.8, 1-H), 5.49 (1H, s, 7-H), 7.35 (3H, m, Ph), 7.48 (2H, m, *o*-Ph); δ_C (62.9 MHz; CDCl$_3$) 55.8 (CH$_3$, OMe), 62.8 (CH, C5), 69.3 (CH$_2$, C6), 71.5 (CH, C3), 73.1 (CH, C2), 81.4 (CH, C4), 100.4 (CH, C1), 102.3 (CH, C7), 126.8 (CH, Ph), 128.8 (CH, Ph), 129.0 (CH, Ph), 137.6 (C, Ph).

This is a literature compound and method.[23]

Methyl 4,6-*O*-benzylidene-2-*O*-p-toluenesulphonyl-α-*D*-glucopyranoside

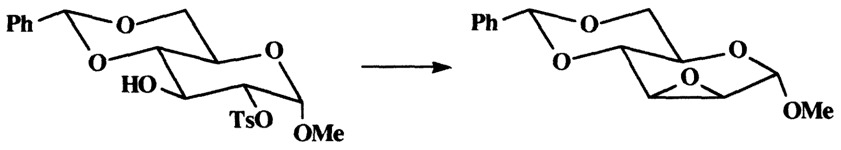


54 55

Methyl 4, 6-*O* -benzylidene-α-D-glucopyranoside **54** (55.54 g, 0.20 mol), was dissolved in dry dichloromethane (780 cm^3). To this solution was added *N,N*-dimethyl-4-aminopyridene (4.33 g, 0.03 mol), and triethylamine (82.26 cm^3, 0.59 mol). This solution was cooled to 0 °C and *para*-toluenesulphonyl chloride (41.26 g, 0.22 mol), added in portions. The reaction was left to stir for 0.15h at this temperature and then at room temperature for 2h. The reaction was quenched by the addition of water (470 cm^3), extracted into dichloromethane (2x400 cm^3), dried and evaporated to dryness. The resultant yellow syrup was dissolved in isopropanol (75 cm^3), and concentrated. This addition and concentration was repeated until a white foam was obtained. The product was then precipitated by the addition of hot isopropanol, the white solid was then filtered, washed with isopropanol and dried *in vacuo* to give a white crystalline solid **55** (64.18 g, 75%), mp 150 - 152 °C (lit.,[24] 153 - 155 °C); R_f: 0.65, diethyl ether; δ_H (250 MHz; $CDCl_3$) 2.43 (3H, s, Ts-Me), 3.34 (3H, s, OMe), 3.46 (1H, t, *J* 9.3, 4-H), 3.70 (1H, t, *J* 10.2, 6ax-H), 3.89 (1H, dt, *J* 10.0, 4.4, 5-H), 4.26 (1H, t, *J* 9.3, 3-H), 4.3 (1H, dd, *J* 9.8, 4.5, 6eq-H), 4.42 (1H, dd, *J* 9.3, 3.8, 2-H), 4.87 (1H, d, *J* 3.7, 1-H), 5.53 (1H, s, 7-H), 7.35 (5H, m, Ph), 7.48 (2H, m, *o*-Ph), 7.84 (2H, m, *o*-Ts); δ_C (62.9 MHz; $CDCl_3$) 22.1 (CH_3, Ts), 56.3 (CH_3, OMe), 62.8 (CH, C5), 68.8 (CH, C3), 69.1 (CH_2, C6), 80.1 (CH, C2), 81.3 (CH, C4), 98.8 (CH, C1), 102.2 (CH, C7), 126.7 (CH, Ph), 128.4 (CH, Ts), 128.9 (CH, Ph), 129.6 (CH, Ph), 130.2 (CH, Ts), 133.6 (C, Ts), 137.4 (C, Ph).

This is a literature compound and method.[24]

Methyl 2,3-anhydro-4,6-*O*-benzylidene-α-*D*-mannopyranoside

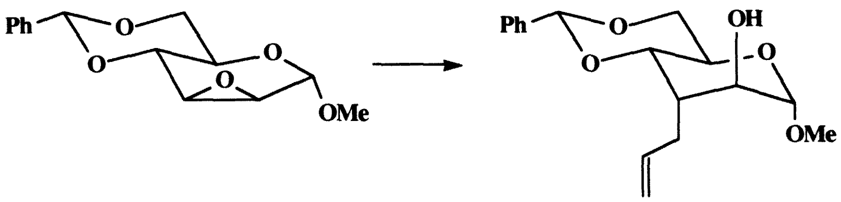


55 **56**

The tosylate **55** (64.18 g, 0.15 mol), was dissolved in dry DMF (500 cm^3), and cooled to 0 °C in an ice bath. Portions of sodium hydride (4.86 g, 0.16 mol) were added and the reaction allowed to stir at room temperature for 2h. Ethanol (50.0 cm^3) was then added with cooling and the resulting solution poured into ice/water (250 cm^3). The resulting white precipitate was filtered and dried under suction for 1h. The solid was recrystallised from isopropanol (200 cm^3) to give a white crystalline solid **56** (26.2 g, 67%) mp 144 - 145 °C, (lit.,[25] 145 - 147 °C); δ_H (250 MHz; CDCl$_3$) 3.00 (1H, d, *J* 3.78, 2-H), 3.30 (3H, s, OMe), 3.37 (1H, obscured, 4-H), 3.54 (3H, m, 3-H, 5-H, 6ax-H), 4.15 (1H, m, 6eq-H), 4.74 (1H, s, 1-H), 5.40 (1H, s, 7-H), 7.21 (3H, m, Ph), 7.34 (2H, m, *o*-Ph); δ_C (62.9 MHz; CDCl$_3$) 51.0 (CH, C3), 54.2 (CH, C2), 56.2 (CH$_3$, OMe), 62.1 (CH, C5), 69.8 (CH$_2$, C6), 75.3 (CH, C4), 97.3 (CH, C1), 102.8 (CH, C7), 126.6 (CH, Ph), 128.9 (CH, Ph), 129.7 (CH, Ph), 137.5 (C, Ph).

This is a literature compound and method.[25]

Methyl 4,6-*O*-benzylidene-3-deoxy-3-*C*-propenyl-α-*D*-glucopyranoside

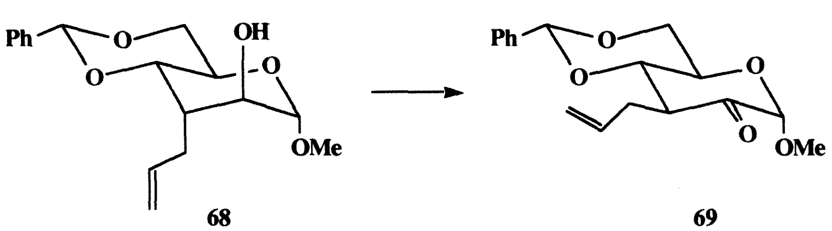


56 **68**

To a suspension of the epoxide **56** (17.62 g, 66.60 mmol) in dry THF (100 cm^3) was added allylmagnesium chloride (100 cm^3, 2M solution in THF, 0.20 mol) dropwise whilst cooling the flask in an ice bath. The reaction was then heated to reflux for 2h. The reaction was then quenched by the dropwise addition of water (50 cm^3). The product was extracted into diethyl ether (2x200 cm^3) and the combined organic layers washed with brine (2x75 cm^3) and the solution dried and evaporated to dryness. Chromatography on silica gel with petroleum ether : diethyl ether (3:1 to 1:1) as the eluent yielded **68** as a clear sticky oil (18.95 g, 86%); R_f. 0.22, 1:1 petroleum ether : diethyl ether; (Found : C, 65.5; H, 7.2. $C_{17}H_{22}O_5$ requires C, 66.7; H, 7.4%); δ_H(250 MHz; $CDCl_3$) 2.25 (1H, m, 2-H), 2.53 (3H, m, 7-H), 3.37 (3H, s, OMe), 3.78 (1H, t, *J* 10.0, 6ax-H), 3.9 (1H, bs, OH), 3.97 (1H, m, 5-H), 4.11 (1H, dd, *J* 9.7, 5.3, 4-H), 4.28 (1H, dd, *J* 10.1, 4.8, 6eq-H), 4.55 (1H, s, 1-H), 5.08 (2H, m, 9-H), 5.59 (1H, s, 10-H), 5.84 (1H, m, 8-H), 7.4 (3H, m, Ph), 7.5 (2H, m, *o*-Ph); δ_C (62.9 MHz, $CDCl_3$) 29.2 (CH_2, C7), 42.7 (CH, C3), 55.7 (CH_3, OMe), 55.9 (CH, C5), 69.6 (CH, C2), 70.0 (CH_2, C6), 76.4 (CH, C4), 102.5 (CH, C1), 102.8 (CH, C10), 117.2 (CH_2, C9), 126.7 (CH, Ph), 128.8 (CH, Ph), 129.6 (CH, Ph), 137.6 (CH, C8), 138.1 (C, Ph); *m/z* (EI) 306 (M^+, 1.9%) 305 $[M-H]^+$ (3.6), 274 (2.9), 256 (3.3), 105 ($PhCO^+$) (100) (Found: M^+, 306.14665, $C_{17}H_{22}O_5$ requires 306.1467).

This is a literature compound and method.[28]

Methyl 4,6-*O*-benzylidene-3-deoxy-3-*C*-propenyl-α-*D*-*arabino*-hexopyranoside-2-ulose

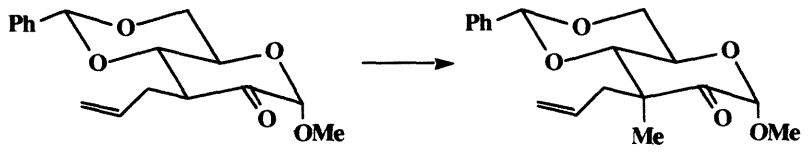


68 69

Trifluoroacetic anhydride (12.67 cm^3, 89.73 mmol) in dry dichloromethane (40 cm^3) was added dropwise to a cooled solution (-65 °C) of dimethyl sulphoxide (8.36 ml, 0.12 mol) in dry dichloromethane (130 cm^3), under an atmosphere of nitrogen. Once addition was complete the mixture was stirred for 0.3h at -65 °C, then a solution of **68** (18.95 g, 61.90 mmol) in dry dichloromethane (20 cm^3), was added slowly dropwise keeping the internal temperature at -65 °C. Once addition was complete the reaction was stirred for a further 1.5h at this temperature. Triethylamine (48.64 cm^3, 0.35 mol) was then added dropwise and the solution allowed to warm to room temperature. The reaction was diluted with dichloromethane (200 cm^3) and this solution washed with 1M hydrochloric acid, until the aqueous layer remained and then washed with enough sodium hydrogen carbonate to neutralise the acid, followed by saturated sodium chloride solution (200 cm^3). The dichloromethane layer was then dried and evaporated to dryness. Chromatography on silica gel with petroleum ether : diethyl ether (3:1) as the eluent yielded **69** as a white solid (16.18 g, 86%), mp 99 - 101 °C (from petroleum ether) (lit.,[31] 100 - 102 °C); (Found : C, 66.83; H, 6.58. $C_{17}H_{20}O_5$ requires C, 67.14; H, 6.62%); R_f 0.72, 1:1 petroleum ether : diethyl ether; υ_{max} (CH_2Cl_2)/cm^{-1} 2920 s, 1740 s (CO), 1640 m; δ_H (250 MHz; $CDCl_3$) 2.45 (2H, m, 7-H), 3.03 (1H, m, 3-H), 3.46 (3H, s, OMe), 3.53 (1H, dd, *J* 10.3, 9.4, 4-H), 3.67 (1H, t, *J* 10.3, 6ax-H), 4.14 (1H, ddd, *J* 4.9, 9.7, 10.3, 5-H), 4.31 (1H, dd, *J* 4.9, 10.3, 6eq-H), 4.53 (1H, s, 1-H), 5.01 (2H, m, 9-H), 5.41 (1H, s, 10-H), 5.77 (1H, m, 8-H), 7.33-7.44 (5H, m, Ph); (62.9 MHz, $CDCl_3$) δ_C 28.0 (CH_2, C7), 51.1 (CH, C3), 56.1 (CH_3, OMe), 64.6 (CH, C5), 69.5 (CH_2, C6), 80.4 (CH, C4), 101.3 (CH, C1), 101.6

(CH, C10), 117.8 (CH_2, C9), 126.5 (CH, Ph), 128.7 (CH, Ph), 129.6 (CH, Ph), 135.2 (CH, C8), 137.5 (C, Ph), 200.1 (C, CO); *m/z* (EI) 304 (M^+, 2.4%), 276 (M^+ - C_2H_4) (5.2), 105 ($PhCO^+$) (100); (Found M^+, 304.1311. $C_{17}H_{20}O_5$ requires M^+, 304.1311). This is a literature compound[31] but not a literature method.

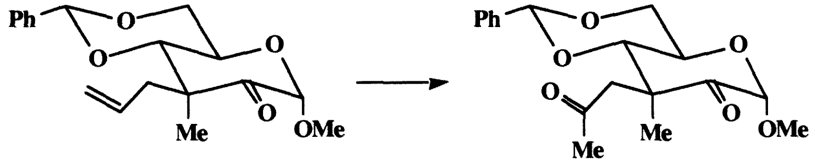
Methyl 4,6-*O*-benzylidene-3-deoxy-3-*C*-methyl-3-*C*-propenyl, methyl-α-*D*-*erythro*-hexopyranoside



69 71

Lithium hexamethydisilazide (18.08 cm^3, 18.08 mmol, 1M solution in THF) was cooled to 0 °C and a solution of **69** (5.0 g, 16.44 mmol) was added dropwise in THF (15 cm^3) maintaining the temperature at 0 °C. The solution was allowed to stir for 1h at 0 °C, then methyl iodide (7.8 cm^3, 98.64 mmol) was added followed by DMPU (1.0 cm^3, 8.22 mmol). The solution was allowed to warm to room temperature and left to stir overnight. The product was extracted into diethyl ether (2x200 cm^3), the combined organic layers washed with brine (2x25 cm^3), dried and evaporated to dryness. Chromatography on silica gel with petroleum ether : diethyl ether (10:1) as the eluent yielded **71** as a clear oil (4.19 g, 80%); (Found : C, 67.83; H, 7.21. $C_{18}H_{22}O_5$ requires C, 67.96; H 6.97%); R_f: 0.75, 1:1 petroleum ether : diethyl ether (1:1); $[\alpha]_D^{20}$ - 3.3° (*c* 2.07, $CHCl_3$); δ_H(250 MHz; $CDCl_3$) 1.26 (3H, s, C3-Me), 2.21 (1H, dd, *J* 13.8, 9.15, 7a-H), 2.59 (1H, dd, *J* 13.8, 5.5, 7b-H), 3.37 (3H, s, OMe), 3.64 (1H, t, *J* 10.1, 6ax-H), 3.73 (1H, d, *J* 10.0, 4-H), 4.23 (1H, dt, *J* 10.0, 5.16, 5-H), 4.33 (1H, dd, *J* 10.1, 5.2, 6eq-H), 4.48 (1H, s, 1-H), 5.0 (2H, m, 9-H), 5.4 (1H, s, 10-H), 5.65 (1H, m, 8-H), 7.3 (3H, m, Ph), 7.42 (2H, m, *o*-Ph); δ_C (62.9 MHz; $CDCl_3$) 19.3 (CH_3, C3-CH_3), 38.5 (CH_2, C7), 51.8 (C, C3), 55.6 (CH_3, OMe), 60.0 (CH, C5), 69.8 (CH_2, C6), 77.5 (CH, C4), 101.5 (CH, C1), 101.7 (CH, C10), 119.21 (CH_2, C9), 126.5 (CH, Ph), 128.7 (CH, Ph), 129.5 (CH, Ph), 134.5 (CH, C8), 137.9 (C, Ph), 203.7 (C, C2); *m/z* (EI) 318 (M^+, 0.9%) 290 (M^+,-CH_2CH_2) (1.3), 174 (100) (Found M^+, 318.1467. $C_{18}H_{22}O_5$ requires 318.1467).

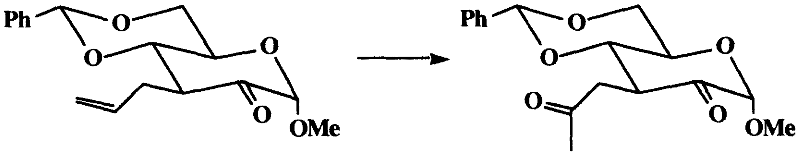
Methyl 4,6-*O*-benzylidene-3-deoxy-3-*C*-methyl-3-*C*-propenone-α-*D*-*erythro*-hexopyranosid-2-ulose



71 72

To a stirred solution of **71** (4.17 g, 13.16 mmol) in DMF and water (80 cm^3, 1:1) was added palladium(II) chloride (233 mg, 1.32 mmol) and copper(II) chloride (2.24 g, 13.16 mmol). The reaction was allowed to stir at room temperature whilst oxygen was bubbled into the solution for 5h. The product was extracted into dichloromethane (2x75 cm^3), the combined organic layers washed with brine (2x25 cm^3), dried and evaporated to dryness. Chromatography on silica gel with petroleum ether : diethyl ether (10:1) as the eluent yielded **72** as a white solid (2.48 g, 56%); m.p 112 - 114 °C (Found : C, 64.83; H, 6.59. $C_{18}H_{22}O_6$ requires C, 64.70; H, 6.63%); R_f: 0.75, petroleum ether : diethyl ether (1:1); $[\alpha]_D^{20}$ - 78° (*c* 1.0, $CHCl_3$); υ_{max} ($CHCl_3$)/cm^{-1} 3940 w, 1760 m, 1730 m ; δ_H (250 MHz; $CDCl_3$) 1.19 (3H, s, C3-Me), 2.01 (3H, s, 9-H), 2.77 (1H, d, *J* 18.6, 7a-H), 2.98 (1H, d, *J* 18.6, 7b-H), 3.36 (3H, s, OMe), 3.70 (1H, t, *J* 10.0, 6ax-H), 4.06 (1H, d, *J* 10.1, 4-H), 4.18 (1H, dt, *J* 10.1, 4.97, 5-H), 4.31 (1H, dd, *J* 10.1, 4.97, 6eq-H), 4.63 (1H, s, 1-H), 5.40 (1H, s, 10-H), 7.33 (5H, m, Ph); δ_C (62.9 MHz; $CDCl_3$) 19.2 (CH_3, C3-CH_3), 30.4 (CH_3, C9), 48.1 (CH_2, C7), 49.0 (C, C3), 56.6 (CH_3, OMe), 60.1 (CH, C5), 69.7 (CH_2, C6), 79.5 (CH, C4), 100.7 (CH, C1), 101.7 (CH, C10), 126.7 (CH, Ph), 128.7 (CH, Ph), 129.6 (CH, Ph), 137.9 (C, Ph), 204.4 (C, C2), 206.8 (C, C8); *m/z* (EI) 334 (M^+, 4.8%) 228 (M^+,- PhCHO) (5.8) 188 (88.7) 159 (100) (Found M^+, 334.1416. $C_{18}H_{22}O_6$ requires 334.1416).

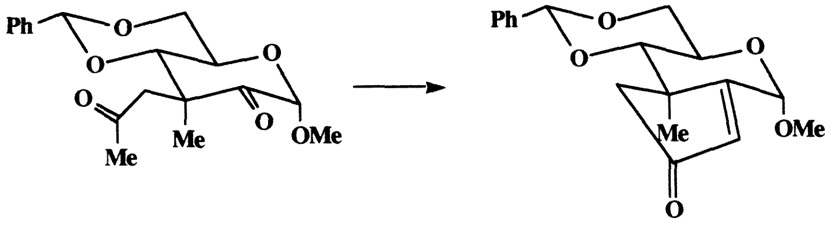
Methyl 4,6-*O*-benzylidene-3-deoxy-3-*C*-propenone-α-*D*-*arabino*-hexopyranosid-2-ulose



69 70

To a stirred solution of **69** (657 mg, 2.10 mmol) in DMF and water (25 cm^3, 1:1) was added palladium(II) chloride (40 mg, 0.21 mmol) and copper(II) chloride (106 mg, 2.1 mmol). The reaction was allowed to stir at room temperature whilst oxygen was bubbled into the solution for 0.5h. The product was extracted into dichloromethane (2x25 cm^3) and the combined organic layers washed with brine (2x15 cm^3) and the solution dried and evaporated to dryness. Chromatography on silica gel with petroleum ether : diethyl ether (2:1) as the eluent yielded **70** as a clear oil (429 mg, 62%); R_f: 0.50, petroleum ether : diethyl ether (2:1); υ_{max} ($CHCl_3$)/cm^{-1} 3940 w, 1760 m, 1730 m; δ_H (250 MHz; $CDCl_3$) 2.20 (3H, s, 9-H), 2.75 (1H, dd, *J* 3.9, 17.7, 7a-H), 2.87 (1H, dd, *J* 6.9, 17.6, 7b-H), 3.50 (3H, s, OMe, and obscured, 1H, m, *J* 3.9, 6.9, 3-H), 3.67 (1H, dd, *J* 9.4, 11.6, 4-H), 3.78 (1H, t, *J* 10.0, 6_{ax}-H), 4.23 (1H, ddd, *J* 5.0, 9.4, 10.0, 5-H), 4.39 (1H, dd, *J* 5.0, 10.0, 6eq-H), 4.65 (1H, s, 1-H), 5.49 (1H, s, 10-H), 7.37-7.48 (5H, m, Ph); δ_C (62.9 MHz; $CDCl_3$) 30.2 (CH_3, C9), 37.3 (CH_2, C7), 47.6 (CH, C3), 55.7 (CH_3, OMe), 64.4 (CH, C5), 69.0 (CH_2, C6), 79.9 (CH, C4), 100.6 (CH, C1), 101.5 (CH, C10), 126.2 (CH, Ph), 128.4 (CH, Ph), 129.3 (CH, Ph), 136.9 (C, Ph), 199.2 (C, C2), 205.8 (C, C8); *m/z* (EI) 320 (M^+, 2.1%), 292 (15.5) 174 (30.8) 145 (100) (Found M^+, 320.1260. $C_{17}H_{20}O_6$ requires 320.1260).

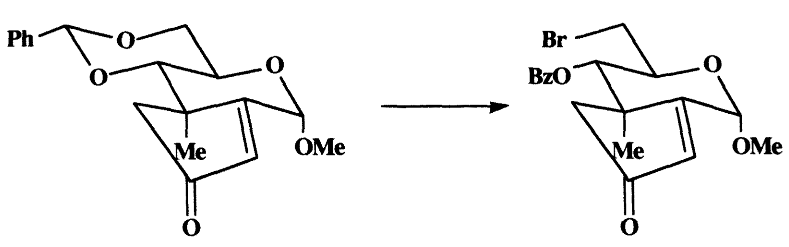
Methyl 4,6-*O*-benzylidene-2,3-dideoxy-3-*C*-methyl-3,2-*C*-(2'-oxapropan-1'-yl-3'-ylidene)-α-*D*-*arabino*-hexopyranoside



72 74

To a solution of **72** (239 mg, 0.79 mmol) in dry toluene (5.0 cm^3) was added potassium tertiary butoxide (91 mg, 0.86 mmol). The solution was allowed to stir at room temperature, under an atmosphere of nitrogen for 0.5h. The product was extracted into dichloromethane (2x200 cm^3), the combined organic layers washed with brine (2x25 cm^3), dried and evaporated to dryness. Chromatography on silica gel with petroleum ether : diethyl ether (2 : 1) as the eluent yielded **74** as a white solid (2.48 g, 56%); m.p 134 - 136 °C (petroleum ether) (Found : C, 68.14; H, 6.24. $C_{18}H_{20}O_5$ requires C, 68.39; H, 6.37%); R$_f$: 0.75, petroleum ether : diethyl ether (1:2); $[\alpha]_D^{23}$ + 25.5° (*c* 1.73, $CHCl_3$); υ_{max} ($CHCl_3$)/cm^{-1} 3000 w, 1720 s, 1090 s; δ_H(250 MHz; $CDCl_3$) 1.42 (3H, s, C3-Me), 2.28 (1H, d, *J* 18.8, 9a-H), 2.47 (1H, d, *J* 18.8, 9b-H), 3.41 (1H, d, *J* 9.4, 4-H), 3.42 (3H, s, OMe), 3.65 (1H, t, *J* 10.2, 6ax-H), 4.12 (1H, ddd, *J* 10.0, 9.37, 5.08, 5-H), 4.27 (1H, dd, *J* 10.1, 5.06, 6eq-H), 5.29 (1H, s, 1-H), 5.48 (1H, s, 10-H), 5.96 (1H, s, 7-H), 7.33 (5H, m, Ph); δ_C (62.9 MHz; $CDCl_3$) 20.5 (CH_3, C3-CH_3), 46.2 (C, C3), 50.5 (CH_2, C9), 55.9 (CH_3, OMe), 61.2 (CH, C5), 69.6 (CH_2, C6), 86.3 (CH, C4), 98.1 (CH, C1), 102.3 (CH, C10), 126.6 (CH, Ph), 128.7 (CH, Ph), 129.7 (CH, Ph), 130.2 (CH, C7), 137.7 (C, Ph), 174.0 (C, C2), 207.4 (C, C8); *m/z* (EI) 316 (M$^+$, 6.5%) 273 (9.2) 167 (73.8) 138 (100) (Found M$^+$, 334.1416. $C_{18}H_{20}O_5$ requires 334.1416).

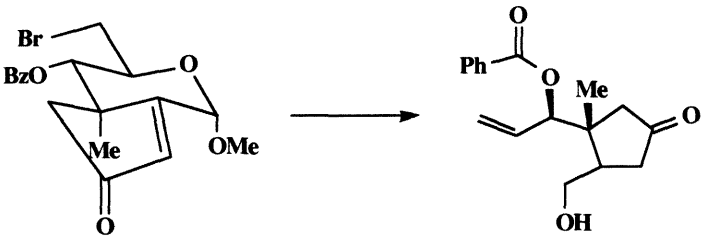
4-Benzoyloxy-5-bromomethyl-2,3-*C*-(2-propen-2'one)-3-deoxy-3-*C*-methyl-α-*D*-*arabino*-hexopyranosid-2-ulose



74 **83**

To a solution of **74** (708 mg, 2.31 mmol) in dry carbon tetrachloride (73.0 cm^3) was added barium carbonate (2.6 g, 13.0 mmol) followed by N-bromosuccinimide (507 mg, 1.28 mmol). This solution was stirred under an atmosphere of nitrogen at reflux for 3h. The barium carbonate was removed by filtration, washed with diethyl ether (75 cm^3), the combined organic layers washed with water (2x75 cm^3), dried and evaporated to dryness. Chromatography on silica gel with petroleum ether : diethyl ether (3:1) as the eluent yielded **83** as a white solid (654 mg, 72%); m.p 131-132 °C (petroleum ether 40-60); R_f: 0.50, petroleum ether : ethyl acetate (1:1); $[\alpha]_D^{22}$ + 128.2° (*c* 2.0, $CHCl_3$); υ_{max} (CH_2Cl_2)/cm^{-1} 2960 m, 1730 s, 1710 s, 1640 w, 1600 w, 1450 m, 1260 s, 1180 m, 1110 s; δ_H(250 MHz; $CDCl_3$) 1.47 (3H, s, C3-Me), 2.18 (1H, d, *J* 18.7, 9a-H), 2.66 (1H, d, *J* 18.6, 9b-H), 3.37 (1H, dd, *J* 11.0, 7.6, 6a-H), 3.46 (1H, obscured dd, *J* 11.0, 2.5, 6b-H), 3.77 (3H, s, OMe), 4.36 (1H, dt, *J* 9.8, 7.4, 2.5, 5-H), 5.06 (1H, d, *J* 9.8, 4-H), 5.40 (1H, s, 1-H), 6.00 (1H, s, 7-H), 7.43 (1H, m, *m* -Ph), 7.57 (2H, m, *p* -Ph), 7.99 (2H, m, *o* -Ph); δ_C (62.9 MHz; $CDCl_3$) 20.1 (CH_3, C3-CH_3), 31.0 (CH_2, C6), 45.7 (C, C3), 49.6 (CH_2, C9), 54.6 (CH_3, OMe), 66.8 (CH, C5), 76.1 (CH, C4), 96.1 (CH, C1), 127.7 (2CH, *m* -Ph), 127.0 (CH, C7), 128.5 (CH, *p* -Ph), 128.8 (CH, *o* -Ph), 132.9 (C, Ph), 164.2 (CO, OBz), 205.0 (C, C8); *m/z* (EI) 394/396 (M^+, 3%) 365, 353, 315 (M^+ - Br), 105 ($PhCO^+$) (100) (Found M^+, 394.0518. $C_{18}H_{19}O_5Br$ requires 394.0518).

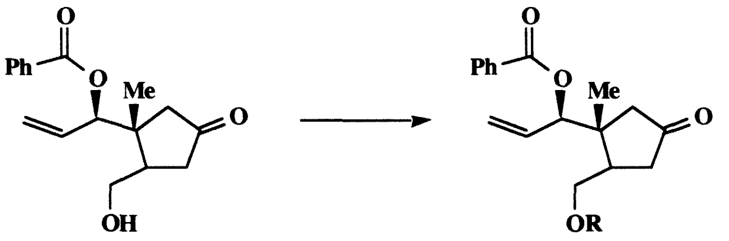
(3*R*,1'*R*,2'*R*)-2'-Hydroxymethyl-1'-methyl-3-cyclopentan-4'-one-2-propenyl-3-benzoate and (3*R*,1'*R*,2'*S*)-2'-Hydroxymethyl-1'-methyl-3-cyclopentan-4'-one-2-propenyl-3-benzoate



83 84

Zinc was activated by washing with 2M hydrochloric acid (2x50 cm^3), water (50 cm^3), isopropanol (75 cm^3) and ether (2x100 cm^3). This was left to stand open to the air for up to 1 month. The bromo compound **83** (200 mg, 0.51 mmol) was heated to reflux with the activated zinc in isopropanol (28.0 cm^3) for 3h. The zinc was removed by filtration, washed with diethyl ether (3x25 cm^3), the combined organic layers washed with brine (2x25 cm^3), dried and evaporated to dryness. Chromatography on silica gel with petroleum ether : diethyl ether (4:6) as the eluent yielded **84** as a mixture of diastereoisomers (105 mg, 72%); R_f: 0.26, diethyl ether : petroleum ether (7:3); υ_{max} (Et_2O)/cm^{-1} 3440 s, 2920 w, 2890 w, 1745 s, 1720 s, 1605 w, 1270 s, 1100 w, 1110 s; δ_H(250 MHz; $CDCl_3$) 1.10 (3H, s, C1'-Me minor), 1.21 (3H, s, C1'-Me major), 1.72 (1H, br s, OH minor), 1.86 (1H, br s, OH major), 1.97-2.72 (10H, m, minor and major), 3.72 (4H, m, CH_2OH major and minor), 5.6 (2H, d, *J* 6.3, 3-H major, minor obscured), 5.81 (2H, m, 2-H major and minor), 7.36-7.48 (6H, m, Ph major and minor), 7.90 (4H, m, Ph major and minor); major compound only δ_C (62.9 MHz; $CDCl_3$) 24.0 (CH_3, C1' Me), 40.8 (CH_2, C3'), 43.3 (C, C1'), 47.1 (CH, C2'), 47.8 (CH_2, C5'), 61.3 (CH_2, CH_2OH), 77.2 (CH, C3), 118.2 (CH_2, C1), 127.6 (2CH, Ph), 128.6 (CH, C2), 128.6 (CH, Ph), 131.6 (CH, Ph), 132.4 (C, Ph), 164.2 (CO, OBz), 217.0 (C, C4'); *m/z* (EI) 288.1365 (M^+, 12%) 257 (M^+,-CH_2OH) (4) 183 (M^+,-PhCO+) (18) 166 (M^+,- $PhCO_2H$) (65) 105 ($PhCO^+$) (100) (Found M^+, 288.1365. $C_{17}H_{20}O_4$ requires 288.1365).

(3*R*,1’*R*,2’*R*)-1’-Methyl-2’-p-nitrobenzoyloxymethyl-cyclopentan-4’-one-2-propenyl-3-benzoate and (3*R*,1’*R*,2’*S*)-3-1’-Methyl-2’-p-nitrobenzoate-methyl-cyclopentan-4’-one-2-propenyl-3-benzoate



84

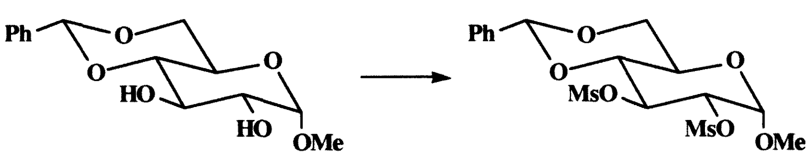
85a,b

R = *p*-nitrobenzoate

The mixture of alcohols **84** (57 mg, 0.20 mmol) in dry toluene (2.0 cm^3) was stirred magnetically at 0°C with trietylamine (0.07 cm, 0.49 mmol) *para*-nitro-benzyl chloride was added and the solution left to stir until no starting material remained. The product was extracted into diethyl ether (2x10 cm^3), washed with brine (2x5 cm^3) and evaporated to dryness. Chromatography on silica gel with petroleum ether : diethyl ether (2 : 1) as the eluent yielded **85a, 85b** (5:1) (72 mg, 96%); **85a** R_f: 0.75, petroleum ether : ethyl acetate (4:1); $[\alpha]_D^{22}$ + 20.4° (*c* 3.3, $CHCl_3$); υ_{max} (CH_2Cl_2)/cm^{-1} 2960 m, 1730 s, 1710 s, 1640 w, 1600 w, 1450 m, 1260 s, 1180 m, 1110 s; δ_H(250 MHz; $CDCl_3$) 1.30 (3H, s, C1’-Me), 2.15 (1H, d, *J* 18.3, 5’a-H), 2.22 (1H, ddd, *J* 1.6, 9.8, 18.9, 3’a-H), 2.54 (1H, dd, *J* 9.44, 18.9, 3’b-H), 2.65 (1H, m, 2-H), 2.78 (1H, d, *J* 18.3, 5’b-H), 4.42 (1H, dd, *J* 11.3, 7.2, C*H*HO), 4.52 (1H, dd, *J* 11.3, 6.3, CH*H*O), 5.28 (1H, d, *J* 4.4, 1a-H), 5.33 (1H, d, *J* 11.3, 1b-H), 5.62 (1H, d, *J* 6.3, 3-H), 5.85 (1H, ddd overlapping, *J* 4.4, 6.0, 10.7, 2-H), 7.35-7.55 (3H, m, Ph), 7.86 (2H, m, Ph), 8.06 (1H, dd, *J* 6.9, 1.9, Ph), 8.18 (1H, dd, *J* 6.92, 1.89, Ph); δ_C (62.9 MHz; $CDCl_3$) 25.5 (CH_3, C1’-Me), 42.1 (CH_2, C3’), 44.9 (C, C1’), 45.9 (CH, C2’), 48.9 (CH_2, C5’), 65.6 (CH_2, CH_2O), 78.4 (CH, C3), 120.4 (CH_2, C1), 124.0 (CH, Ph), 129.1 (CH, Ph), 129.8 (C, Ph), 130.1 (CH, Ph), 131.1 (CH, Ph), 132.6 (CH, Ph), 134.0 (CH, Ph), 135.5 (C, Ph), 151.0 (C, *p*-NO_2Ph), 164.8 (C, OBz), 165.3 (C, OBz), 214.4 (C, C4’).

85b R_f 0.35 petroleum ether : ethyl acetate (4:1); $[\alpha]_D^{22}$ - 31.3° (*c* 0.8, CHCl$_3$); δ_H(250 MHz; CDCl$_3$) 1.48 (3H, s, C1'-Me), 2.17 (2H, m, 5'a-H, 3'a-H), 2.54 (1H, dd, *J* 8.8, 18.9, 3'b-H), 2.74 (1H, d, *J* 18.3, 5'b-H), 2.86 (1H, m, 2'-H), 4.38 (1H, dd, *J* 11.3, 6.92, C*H*HO), 4.52 (1H, dd, *J* 11.3, 6.6, CH*H*O), 5.33 (2H, m, 1-H), 5.59 (1H, d, *J* 7.2, 3-H), 5.80 (1H, m, 2-H), 7.36-7.57 (3H, m, Ph), 7.94-8.25 (7H, m, Ph).

Methyl 4,6-*O*-benzylidene-2,3-di-*O*-methylsulphonyl-α-*D*-glucopyranoside

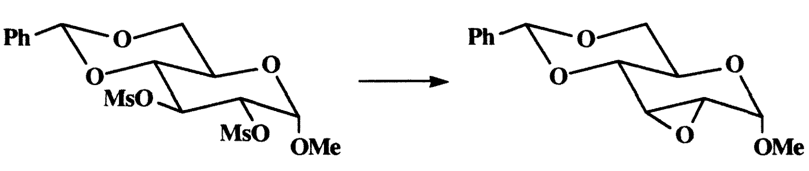


54 **57**

Methyl 4, 6-*O*-benzylidene-α-D-glucopyranoside **54** (20.0 g, 71.00 mol), was dissolved in dry dichloromethane (100 cm^3) and triethylamine (25.0 cm^3, 177.00 mmol) and cooled in an ice bath. To this solution was added methanesulphonyl chloride (11.5 cm^3, 148.00 mmol) dropwise. This solution was then allowed to warm to room temperature and left to stir for 18h. The reaction was quenched by the addition of water (400 cm^3), extracted into dichloromethane (2x400 cm^3), dried and evaporated to dryness. The resultant yellow solid **57** (29.0 g, 93%) was used without any further purification. A small sample was purified by re-crystallisation from CHCl$_3$ mp 156-160 °C (lit.,[26] 163-165 °C); δ_H (300 MHz; CDCl$_3$) 2.97 (3H, s, Ms-Me), 3.17 (3H, s, Ms-Me), 3.49 (3H, s, OMe), 3.77 (1H, m, 6ax-H), 3.94 (1H, dt, *J* 4.7, 10.0, 5-H), 4.34 (1H, dd, *J* 4.7, 4.8, 6eq-H), 4.63 (1H, dd, *J* 9.6, 3.7, 2-H), 5.02 (1H, d, *J* 3.7, 1-H), 5.08 (1H, t, *J* 9.6, 3-H), 5.55 (1H, s, 7-H), 7.36-7.53 (5H, m, Ph).

This is a literature compound and method.[26]

2,3-Anhydro-4,6-*O*-benzylidene-α-methyl-*D*-alloside

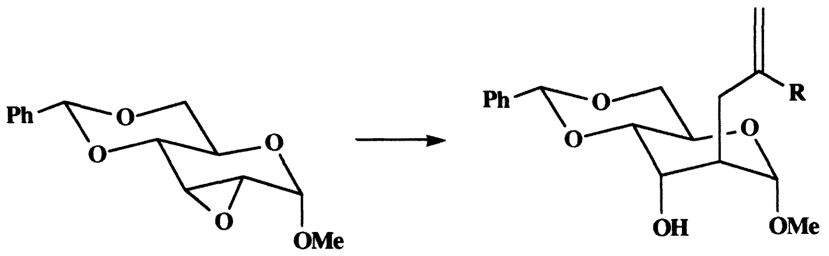


57 **58**

Sodium metal (7.6 g, 9.90 mmol) was added cautiously to methanol with cooling. This was added to a cooled solution of the dimesylate **57** (28.8 g, 0.66 mol) and allowed to stand in the refrigerator with occasional stirring for 3 days. The resulting solution was poured into water (100 cm^3) to which saturated potassium carbonate (150 cm^3) was added. The product was extracted into dichloromethane (2x125 cm^3), dried and evaporated to dryness. The solid was re-dissolved in dichloromethane and isopropanol added to give a white crystalline solid **58** (10.4 g, 60%) mp 199 - 200 °C, (lit.,[26],199 - 200 °C); δ_H (300 MHz; $CDCl_3$) 3.46 (3H, s, OMe), 3.45-3.51 (2H, m, 4-H, 2-H obscured), 3.69 (1H, t, J 10.2, 3-H), 3.94 (1H, dd, J 1.5, 9.1, 6_{ax}-H), 4.10 (1H, dt, *J* 5.0, 9.3, 5-H), 4.20 (1H, dd, *J* 5.6, 9.1, 6_{eq}-H), 4.87 (1H, d, *J* 2.6, 1-H), 5.60 (1H, s, 7-H), 7.30-7.53 (5H, m, Ph).

This is a literature compound and method.[26]

Methyl 4,6-*O*-benzylidene-2-deoxy-2-*C*-propenyl-α-*D*-altropyranoside and Methyl 4,6-*O*-benzylidene-2-deoxy-2-*C*-(2-methyl-2-propenyl)-α-*D*-altropyranoside



58

59a R = H
59b R = Me

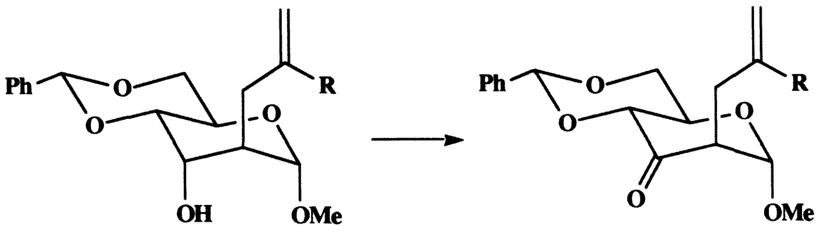
To a suspension of the epoxide **58** (4.75 g, 18.00 mmol) in dry THF (65.0 cm^3) was added allylmagnesium chloride (27.0 cm^3, 2M solution in THF) dropwise whilst cooling the flask in an ice bath. The reaction was then heated to reflux for 2h. The reaction was quenched by the dropwise addition of water (30 cm^3). The product was extracted into diethyl ether (2x75 cm^3), the combined organic layers washed with brine (2x50 cm^3), dried and evaporated to dryness. Chromatography on silica gel with petroleum ether : diethyl ether (5:1 to 1:1) as the eluent yielded **59a** as a white solid (4.98 g, 86%); $[\alpha]_D^{20}$ 59° (*c* 1.0, $CHCl_3$); R_f 0.45, 2:1 petroleum ether : ethyl acetate; υ_{max} (CH_2Cl_2)/cm^{-1} 3575 brs, 1650 s, 1380 s; δ_H(300 MHz; $CDCl_3$) 2.17 (2H, m, 7-H), 3.13 (1H, d, *J* 6.9, 2-H), 3.39 (3H, s, OMe), 3.42 (1H, t, obscured, 4-H), 3.67 (1H, dd, *J* 2.9, 9.8, 3-H), 3.79 (1H, t, *J* 10.0, 6ax-H), 4.2 (1H, m, 5-H), 4.31 (1H, dd, *J* 5.0, 9.9, 6eq-H), 4.55 (1H, s, 1-H), 5.12 (2H, m, 9-H), 5.61 (1H, s, 10-H), 5.78 (1H, m, 8-H), 7.4 (5H, m, Ph); δ_C (75 MHz, $CDCl_3$) 34.1 (CH_2, C7), 44.6 (CH, C2), 55.4 (CH_3, OMe), 58.3 (CH, C5), 68.3 (CH, C3), 69.2 (CH_2, C6), 76.7 (CH, C4), 101.2 (CH, C1), 102.1 (CH, C10), 117.3 (CH_2, C9), 126.5 (CH, Ph), 128.1 (CH, Ph), 128.9 (CH, Ph), 135.3 (CH, C8), 137.2 (C, Ph); *m/z* (EI) 306 (M^+, 1.9%) 306 (M^+, 2.9%) 274 (15.8), 179 (25.9), 105 ($PhCO^+$) (100) (Found: M^+, 306.14665, $C_{17}H_{22}O_5$ requires 306.1467).

This is a literature compound and method.[28]

In the same way the epoxide **58** (497 mg, 1.88 mmol) was treated with 2-methyl-2-propenylmagnesium chloride to yield **59b** as a white solid (576 mg, 92%); mp 97-99 °C (lit.,[28] 98-100°c); R_f: 0.45, 2:1 petroleum ether : ethyl acetate; R_f: 0.45, 2:1 petroleum ether : ethyl acetate; υ_{max} (CH_2Cl_2)/cm^{-1} 3510 brw, 2940 s, 1690 w; δ_H(300 MHz; $CDCl_3$) 1.7 (3H, s, 11-H), 2.2 (2H, m, 7-H), 2.43 (1H, m, 2-H), 3.43 (3H, s, OMe), 3.72 (1H, dd, *J* 3.0, 9.7, 3-H), 3.83 (1H, t, *J* 9.9, 6ax-H), 3.99 (1H, br s, 4-H), 4.27 (1H, m, 5-H), 4.35 (1H, dd, *J* 4.9, 9.9, 6eq-H), 4.57 (1H, s, 1-H), 4.81 (1H, s, 9-H), 4.88(1H, s, 9-H), 5.65 (1H, s, 10-H), 7.37-7.39 (5H, m, Ph); δ_C (75 MHz, $CDCl_3$) 21.8 (CH_3, C11), 38.1 (CH_2, C7), 42.5 (CH, C3), 55.4 (CH_3, OMe), 58.3 (CH, C2), 68.7 (CH, C5), 69.3 (CH_2, C6), 76.7 (CH, C4), 101.5 (CH, C1), 102.1 (CH, C10), 113.0 (CH_2, C9), 126.1 (CH, Ph), 128.1 (CH, Ph), 128.9 (CH,Ph), 137.2 (C, Ph), 142.0 (CH, C8); *m/z* (EI) 306 (M^+, 1.9%) 320 (M^+, 29.6%) 288 (110.5) 264 (14.5) 179 (29.4) 105 ($PhCO^+$) (100) (Found: M^+, 320.1625, $C_{18}H_{24}O_5$ requires 320.1625).

This is a literature compound and method.[28]

Methyl 4,6-*O*-benzylidene-2-deoxy-2-*C*-propenyl-α-*D*-*arabino*-hexo-pyranoside-3-ulose and Methyl 4,6-*O*-benzylidene-2-deoxy-2-*C*-(2-methyl-2-propenyl)-α-*D*-*arabino*-hexo-pyranoside-3-ulose



59a R = H
59b R = Me

62a R = H
62b R = Me

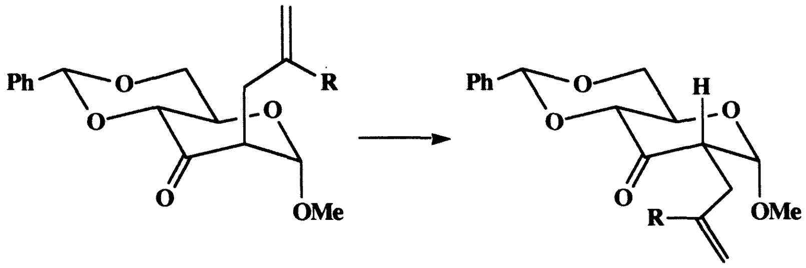
Trifluoroacetic anhydride (0.96 cm^3, 6.80 mmol) in dry dichloromethane (1.0 cm^3) was added dropwise to a cooled solution (-65 °C) of dimethyl sulphoxide (0.63 cm^3, 6.78 mmol) in dry dichloromethane (4.0 cm^3), under an atmosphere of nitrogen. Once addition was complete the mixture was stirred for 0.3h at -65 ^{o}C, then a solution of **59a** (1.5 g, 4.90 mmol) in dry dichloromethane (6.0 cm^3), was added slowly dropwise keeping the temperature at -65 ^{o}C. Once addition was complete the reaction was stirred for a further 1.5h at this temperature. Triethylamine (3.67 cm^3, 26.30 mmol) was then added dropwise and the solution allowed to warm to room temperature. The reaction was diluted with dichloromethane (30 cm^3), washed with 1M hydrochloric acid until the aqueous layer was just acidic and then washed with sodium hydrogen carbonate followed by saturated sodium chloride solution (20 cm^3). The dichloromethane layer was then dried and evaporated to dryness. Chromatography on silica gel with petroleum ether : ethyl acetate (5:1) as the eluent yielded **62a** as a white solid (1.27 g, 85%), R_f: 0.8, 2:1 petroleum ether : ethyl acetate; $[\alpha]_D^{23}$ + 23.9^o (*c* 1.89, $CHCl_3$); δ_H (250 MHz; $CDCl_3$) 2.40 (2H, m, 7-H), 2.69 (1H, t, *J* 7.9, 2-H), 3.31 (3H, s, OMe), 3.86 (1H, t, *J* 10.1, 6ax-H), 4.10 (1H, ddd, *J* 4.4, 10.1, 5-H), 4.30 (2H, overlapping d and dd, *J* 9.8, 4-H, *J* 4.4, 10.1, 6eq-H), 4.77 (1H, s, 1-H), 5.05 (2H, m, 9-H), 5.51 (1H, s, 10-H), 5.63 (1H, m, 8-H), 7.36-7.55 (5H, m, Ph); δ_C (62.9 MHz, $CDCl_3$) 34.0 (CH_2, C7), 54.0 (CH_3, OMe), 55.3 (CH, C2), 65.0 (CH, C5), 68.5 (CH_2, C6), 79.9 (CH, C4), 101.3 (CH, C1), 102.1 (CH, C10), 117.4 (CH_2, C9), 127.3 (CH, Ph), 128.3 (CH, Ph), 129.2 (CH, Ph), 133.9 (CH, C8), 135.6 (C, Ph), 199.5 (C, C3); *m/z* (EI) 304 (M^+, 4.7%), 273 (8.9) 263 (6.1) 149 (40.2) 105 ($COPh^+$) (100) (Found M^+, 304.1311. $C_{17}H_{20}O_5$ requires 304.1311);

This is a literature compound[31] but not a literature method.

In the same way the alcohol **59b** (1.5 g, 4.68 mmol) was oxidised to the the ketone and the crude material purified by chromatography on silica gel with petroleum ether : ethyl acetate (5:1) as the eluent to yield **62b** as a white solid (1.05 g, 71%), mp 115-117°C; R_f: 0.8, 2:1 petroleum ether : ethyl acetate; $[\alpha]_D^{23}$ + 12.2^o (*c* 1.26, $CHCl_3$); υ_{max} (CH_2Cl_2)/cm^{-1} 2915 s, 1735 s (CO), 1650 m 1400 s; δ_H (300 MHz; $CDCl_3$) 1.77 (3H, s, 11-H), 2.40 (1H, dd, *J* 7.2, 14,1, 7a-H), 2.52 (1H, dd, *J* 9.2, 14.0, 7b-H), 2.93 (1H, m, 2-H), 3.38 (3H, s, OMe), 3.96 (1H, t, *J* 10.2, 6ax-H), 4.17 (1H, dt, *J* 4.8, 10.0, 5-H), 4.39 (1H, dd, *J* 4.8, 10.1, 6eq-H), 4.45 (1H, obscured d, *J* 9.9, 4-H), 4.85 (1H, s, 1-H), 4.87 (2H, m, 9-H), 5.61 (1H, s, 10-H), 7.33-7.55 (5H, m, Ph); δ_C (75MHz, $CDCl_3$) 21.6 (CH_3, C11), 39.0

(CH_2, C7), 54.6 (CH_3, OMe), 54.9 (CH, C2), 65.1 (CH, C5), 69.4 (CH_2, C6), 80.6 (CH, C4), 102.2 (CH, C1), 103.4 (CH, C10), 113.9 (CH_2, C9), 126.3 (CH, Ph), 128.1 (CH, Ph), 129.2 (CH, Ph), 136.5 (C, Ph), 140.8 (CH, C8), 200.5 (C, C3); *m/z* (EI) 318 (M^+, 46.6%), 287 (15.5) 183(17.4) 149 (57.3) 105 ($COPh^+$) (100); (Found M^+, 318.1467. $C_{18}H_{22}O_5$ requires M^+, 318.1467).

Methyl 4,6-*O*-benzylidene-2-deoxy-2-*C*-propenyl-α-*D*-*erythro*-hexopyranoside-3-ulose and Methyl 4,6-*O*-benzylidene-2-deoxy-2-*C*-(2-methyl-2-propenyl)-α-*D*-*erythro*-hexopyranoside-3-ulose



62a R = H
62b R = Me

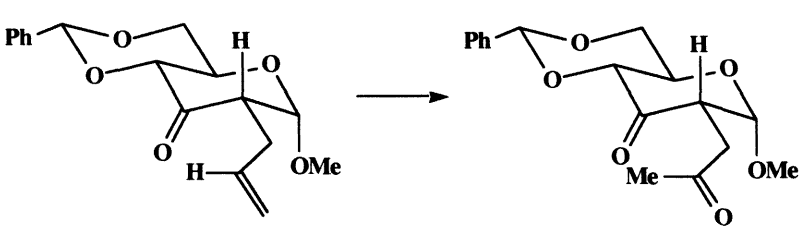
63a R = H
63b R = Me

Ketone **62a** (131 mg, 4.30 mmol) was dissolved in DMF : triethylamine (50.0 cm^3, 1:1) left to stir for 48h. The reaction was diluted with dichloromethane (75 cm^3) and this solution washed with sodium chloride solution (3x25 cm^3). The dichloromethane layer was then dried and evaporated to dryness. Chromatography on silica gel with petroleum ether : ethyl acetate (5:1) as the eluent yielded **63a** as a white solid (0.73 g, 56%); mp 148-152 °C ; R_f: 0.6, 2:1 petroleum ether : ethyl acetate; $[\alpha]_D^{21}$ + 75.3° (*c* 0.96, $CHCl_3$); υ_{max} (CH_2Cl_2)/cm^{-1} 2920 s, 1745 s, 1595 m 1400 m; δ_H (250 MHz; $CDCl_3$) 2.21 (1H, m, 7a-H), 2.60 (1H, m, 7b-H), 2.78 (1H, m, 2-H), 3.35 (3H, s, OMe), 3.91 (1H, t, *J* 10.1, 6ax-H), 4.08 (1H, ddd, *J* 4.4, 9.8, 10.1, 5-H), 4.28 (1H, dd, *J* 1.3, 9.8, 4-H), 4.37 (1H, dd, *J* 4.4, 10.1, 6eq-H), 4.99 (1H, d, *J* 4.1, 1-H), 5.13 (2H, m, 9-H), 5.54 (1H, s, 10-H), 5.73 (1H, m, 8-H), 7.35-7.52 (5H, m, Ph); (62.9 MHz, $CDCl_3$) δ_C 27.6 (CH_2, C7), 53.5 (CH, C2), 55.3 (CH_3, OMe), 66.0 (CH, C5), 69.6 (CH_2, C6), 83.1 (CH, C4), 102.0 (CH, C1), 103.2

(CH, C10), 117.3 (CH_2, C9), 126.1 (CH, Ph), 128.3 (CH, Ph), 129.3 (CH, Ph), 134.9 (CH, C8), 136.7 (C, Ph), 198.4 (C, C3); *m/z* (EI) 304 (M^+, 26.2%), 263 (11.6) 169 (19.7) 149 (64.7) 98 (100) (Found $M^{+\cdot}$ 304.1310. $C_{17}H_{20}O_5$ requires 304.1310);

In the same way the ketone **62b** (1.27 g, 4.00 mmol) was dissolved in DMF : triethylamine (100 cm^3, 1:1) and left to stir for 7 days. The reulting solution was reduced *in vacuo* and then diluted with dichloromethane (30 cm^3) and this solution washed with saturated sodium chloride solution (2x20 cm^3). The dichloromethane layer was then dried and evaporated to dryness. Chromatography on silica gel with petroleum ether : ethyl acetate (5:1) as the eluent yielded **63b** as a white solid (1.1 g, 84%); mp 135-137 °C (from petroleum ether); (Found : C, 67.83, H, 6.77. $C_{18}H_{22}O_5$ requires C, 67.91, H, 6.96%; R_f: 0.8, 2:1 petroleum ether : ethyl acetate; $[\alpha]_D^{17}$ + 103.1° (*c* 0.99, $CHCl_3$); υ_{max} (CH_2Cl_2)/cm^{-1} 2940 s, 1780 s, 1650 m, 1450 m, 1410 m, 1280 m, 1210 m; δ_H (250 MHz; $CDCl_3$) 1.74 (3H, s, C8-Me), 2.26 (1H, dd, *J* 9.4, 14.8, 7a-H), 2.50 (1H, dd, *J* 5.0, 14.8, 7b-H), 2.96 (1H, m, 2-H), 3.35 (3H, s, OMe), 3.93 (1H, t, *J* 10.1, 6ax-H), 4.11 (1H, ddd, *J* 4.4, 9.8, 10.1, 5-H), 4.31 (1H, overlapping dd, *J* 1.3, 9.8, 4-H), 4.37 (1H, overlapping dd, *J* 4.4, 9.8, 6eq-H), 4.75 (1H, br s, 9a-H), 4.83 (1H, br s, 9b-H), 4.97 (1H, d, *J* 4.1, 1-H), 5.57 (1H, s, 10-H), 7.33-7.54 (5H, m, Ph); δ_C (62.9 MHz, $CDCl_3$) 22.9 (CH_3, C11), 31.9 (CH_2, C7), 52.2 (CH, C2), 55.7 (CH_3, OMe), 66.5 (CH, C5), 70.0 (CH_2, C6), 83.6 (CH, C4), 102.4 (CH, C1), 103.6 (CH, C10), 112.9 (CH_2, C9), 126.8 (CH, Ph), 128.7 (CH, Ph), 129.6 (CH, Ph), 137.1 (C, Ph), 142.3 (C, C8), 198.9 (C, C3); *m/z* (EI) 318 (M^+, 9.8%), 256 (6.1) 167 (5.4) 149 (52.8) 145 (20.2) 105 (100) (Found : 318.1467 $C_{18}H_{22}O_5$ requires 318.1467).

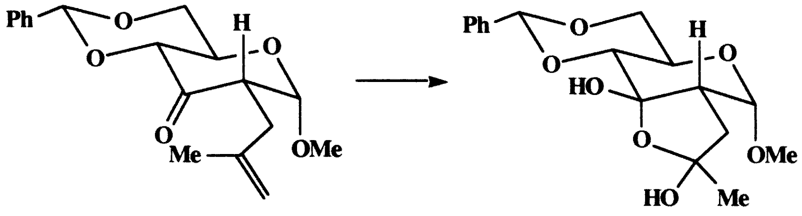
Methyl 4,6-*O*-benzylidene-2-deoxy-2-*C*-(propen-2-one)-α-D-*ribo*-hexopyranosid-3-ulose



63a **64**

To a solution of **63a** (398 mg, 1.31 mmol) in DMF and water (42.0 cm^3, 1:1) was added palladium(II) chloride (23.0 mg, 0.13 mmol) and copper(II) chloride (130 mg, 1.31 mmol). The reaction was allowed to stir at room temperature whilst oxygen was bubbled into the solution for 5h. The product was extracted into dichloromethane (2x20 cm^3), the combined organic layers washed with brine (2x25 cm^3), dried and evaporated to dryness. Chromatography on silica gel with petroleum ether : ethyl acetate (5:1) as the eluent yielded **64** as a white solid (388 mg, 92%); m.p 180-182 °C; R_f: 0.75, petroleum ether : ethyl acetate (2:1); $[\alpha]_D^{19}$ + 136.8° (*c* 2.0, $CHCl_3$); υ_{max} ($CHCl_3$)/cm^{-1} 3000 w, 1745 s, 1710 w, 1410 w, 1145 m, 1050 s; δ_H (300 MHz; $CDCl_3$) 2.24 (3H, s, 9-H), 2.45 (1H, dd, *J* 5.8, 18.5, 7a-H), 3.13 (1H, dd, *J* 7.1, 18.4, 7b-H), 3.36 (3H, s, OMe), 3.44 (1H, m, 2-H), 3.96 (1H, t, *J* 10.1, 6ax-H), 4.10 (1H, dt, *J* 4.5, 10.0, 5-H), 4.39 (2H, m, 4-H, 6eq-H), 5.09 (1H, d, *J* 4.3, 1-H), 5.60 (1H, s, 10-H), 7.35-7.54 (5H, m, Ph); δ_C (75 MHz; $CDCl_3$) 30.1 (CH_3, C9), 37.4 (CH_2, C7), 49.3 (C, C2), 55.1 (CH_3, OMe), 65.6 (CH, C5), 69.3 (CH_2, C6), 82.6 (CH, C4), 101.8 (CH, C1), 102.9 (CH, C10), 126.2 (CH, Ph), 128.1 (CH, Ph), 129.1 (CH, Ph), 136.4 (C, Ph), 197.8 (C, C3), 206.1 (C, C8); *m/z* (EI) 319 (M^+, 3.0%) 279 (18.1) 263 (12) 171 (12.6) 149 (100) (Found $[M-H]^+$, 319.1182. $C_{17}H_{19}O_6$ requires $[M-H]^+$319.1182.

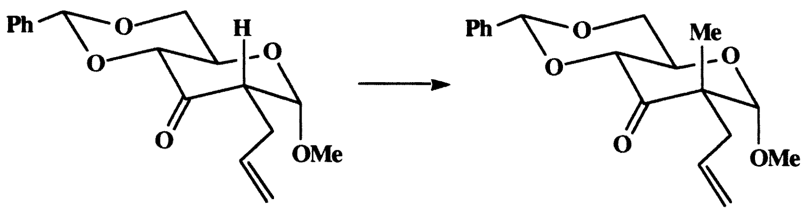
Ozonolysis of Methyl 4, 6-*O*-benzylidene-2-deoxy-2-*C*-(2-methyl-2-propenyl)-α-*D*-*ribo*-hexopyranosid-3-ulose



63b **64a**

Olefin **63b** (0.20 g, 0.63 mmol) was dissolved in dichloromethane (25 cm^3) and ozone was bubbled through the solution for 0.5h. The flask was then flushed with nitrogen for 0.3h and thiourea added (48.0 mg, 0.63 mmol) and the solution stirred for 3h. The product was extracted into dichloromethane (2x30 cm^3), washed with brine (2x30 cm^3), dried and evaporated to dryness. Chromatography on silica gel with petroleum ether : ethyl acetate (5:1) as the eluent yielded **64a** as a white solid (77 mg, 36%); δ_H (300 MHz; $CDCl_3$) 1.76 (3H, s, 9-H), 2.10 (1H, m, 7-H), 2.95 (1H, m, 2-H), 3.48 (3H, s, OMe), 3.89 (1H, t, *J* 10.0, 6_{ax}-H), 3.92 (1H, d, *J* 9.4, 4-H), 4.14 (1H, ddd, *J* 4.4, 9.63, 5-H), 4.42 (1H, dd, *J* 4.4, 10.1, 6eq-H), 5.00 (1H, d, *J* 8.3, 1-H), 5.64 (1H, s, 10-H), 7.35-7.54 (5H, m, Ph); δ_C (62.9 MHz; $CDCl_3$) 15.1 (CH_3, C9), 34.5 (CH_2, C7), 47.5 (CH, C2), 55.6 (CH_3, OMe), 65.4 (CH, C5), 70.1 (CH_2, C6), 76.2 (CH, C4), 102.2 (CH, C1), 103.4 (CH, C10), 106.94 (C, C8), 115 3 (C, C3), 126.3 (CH, Ph), 128.2 (CH, Ph), 129.2 (CH, Ph), 136.4 (C, Ph); *m/z* 338 (M^+, 7.2%), 289 (56.8) 52 (100).

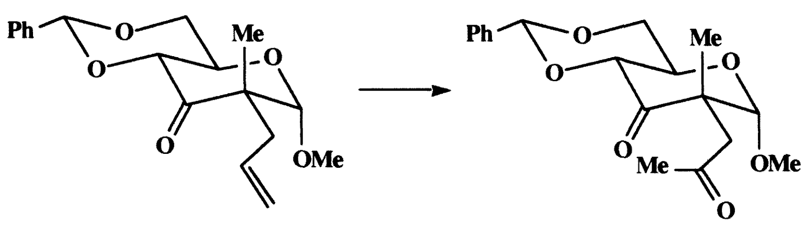
Methyl 4,6-*O*-benzylidene-2-deoxy-2-*C*-methyl-2-*C*-propenyl-α-*D*-*erythro*-hexopyranosid-3-ulose



63a **66**

Sodium hexamethyl-trisilazane (0.4 cm^3, 0.40 mmol, 1M solution in THF) was cooled to 0 °C and a solution of **63a** (136 mg, 0.40 mmol) was added dropwise in THF (15.0 cm^3) maintaining the temperature at 0 °C. The solution was allowed to stir for 1h at 0 °C, then methyl iodide (0.2 cm^3, 3.20 mmol) was added followed by DMPU (0.04 cm^3, 0.04 mmol). The solution was allowed to warm to room temperature and left to stir overnight. The product was extracted into diethyl ether (2x10 cm^3), the combined organic layers washed with brine (2x10 cm^3), dried and evaporated to dryness. Chromatography on silica gel with petroleum ether : ethyl acatate (5:1) as the eluent yielded **66** as a clear oil (but also containing an unidentified compound) (59 mg, 42%); δ_H(250 MHz; CDCl$_3$) 1.38 (3H, s, C2-Me), 2.33 (1H, dd, *J* 7.9, 13.5, 7a-H), 2.46 (1H, dd, *J*, 7.5, 13.8, 7b-H), 3.35 (3H, s, OMe), 3.94 (1H, t, *J* 10.1, 6ax-H), 4.12 (1H, ddd, *J* 4.4, 9.8, 10.1, 5-H), 4.36 (1H, dd, *J* 4.4, 10.1, 6eq-H), 4.55 (1H, s, 1-H), 4.59 (1H, d, *J* 9.8, 4-H), 5.10 (2H, m, 9-H), 5.57 (1H, s, 10-H), 5.72 (1H, m, 8-H), 7.33-7.54 (5H, m, Ph); δ_C (62.9 MHz; CDCl$_3$) 21.5 (CH$_3$, C2-Me), 36.4 (CH$_2$, C7), 53.5 (C, C2), 55.2 (CH$_3$, OMe), 65.8 (CH, C5), 69.6 (CH$_2$, C6), 80.0 (CH, C4), 102.2 (CH, C1), 107.0 (CH, C10), 119.3 (CH$_2$, C9), 126.5 (CH, Ph), 128.3 (CH, Ph), 129.3 (CH, Ph), 133.0 (CH, C8), 136.7 (C, Ph), 202.6 (C, C3); *m/z* (EI) 318 (M$^+$, 2.8%) 277 (6.1) 191 (8.9) 149 (26.6) 121 (16.4) 113 (10.6) 112 (100) (Found : M$^+$ 318.1467. $C_{18}H_{22}O_5$ requires 318.1467).

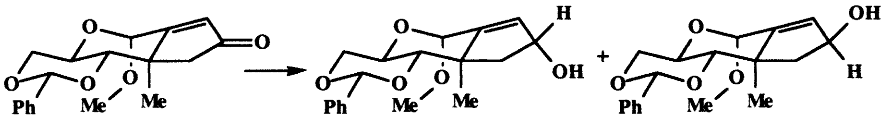
Methyl 4,6-*O*-benzylidene-2-deoxy-2-*C*-methyl-2-*C*-propenone-α-*D*-*erythro*-hexopyranosid-3-ulose



66 **67**

To a solution of **66** (173 mg, 0.54 mmol) in DMF and water (20.0 cm^3, 1:1) was added palladium (II) chloride (10.0 mg, 0.05 mmol) and copper (II) chloride (73 mg, 0.54 mmol). The reaction was allowed to stir at room temperature whilst oxygen was bubbled into the solution for 5h. The product was extracted into dichloromethane (2x20 cm^3), the combined organic layers washed with brine (2x25 cm^3), dried and evaporated to dryness. Chromatography on silica gel with petroleum ether : diethyl ether (10:1) as the eluent yielded **66** as a white solid (90 g, 45%); R_f: 0.5, petroleum ether : diethyl ether (1:2); $[\alpha]_D^{20}$ + 50.9 (c 0.95, $CHCl_3$); υ_{max} ($CHCl_3$)/cm^{-1} 3045 m, 1765 s, 1755 s; δ_H (250 MHz; $CDCl_3$) 1.53 (3H, s, C2-Me), 2.14 (3H, s, 9-H), 2.74 (1H, d, *J* 18.3, 7a-H), 2.99 (1H, d, *J* 18.2, 7b-H), 3.29 (3H, s, OMe), 3.93 (1H, t, *J* 10.1, 6ax-H), 4.08 (1H, dt, *J* 4.4, 10.1, 5-H), 4.36 (1H, dd, *J* 4.4, 10.1, 6eq-H), 4.56 (1H, d, *J* 10.1, 4-H), 5.19 (1H, s, 1-H), 5.58 (1H, s, 10-H), 7.34-7.52 (5H, m, Ph); δ_C (62.9 MHz; $CDCl_3$) 22.4 (CH_3, C2), 31.7 (CH_3, C9), 44.8 (CH_2, C7), 53.6 (C, C2), 55.8 (CH_3, OMe), 65.6 (CH, C5), 69.9 (CH_2, C6), 79.9 (CH, C4), 102.6 (CH, C1), 106.3 (CH, C10), 126.8 (CH, Ph), 128.7 (CH, Ph), 129.7 (CH, Ph), 137.0 (C, Ph), 202.7 (C, C3), 207.4 (C, C8); *m/z* (EI) 334 (M^+, 0.9%) 276 (10.6) 149 (45.9) 129 (10.5) 128 (66.5) 121 (15.2) 105 (36.2) 97 (15.4) 91 (34.1) 85 (100) (Found : M^+, 334.1416. $C_{18}H_{22}O_6$ requires 334.1416).

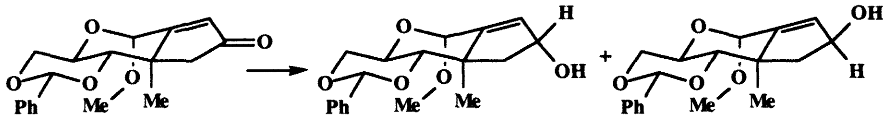
(1*R*,2*S*,4*R*,7*R*,9*S*,12*R*)-12-Hydroxy-9-methoxy-1-methyl-4-phenyl-3,5,8-trioxatricyclo[8.3.0.0^{2,7}]tridec-10-ene and (1*R*,2*S*,4*R*,7*R*,9*S*,12*S*)-12-hydroxy-9-methoxy-1-methyl-4-phenyl-3,5,8-trioxatricyclo[8.3.0.0^{2,7}]tridec-10-ene



74 **127** **128**

DIBAL-H (0.2 cm^3, 0.32 mmol) was added to a cooled solution (-78 ^{o}C) of the enone **74** (100 mg, 0.32 mmol) in toluene (5.0 cm^3). After 15h the reaction was quenched by the addition of saturated aqueous ammonium chloride (2 cm^3), the product was extracted into diethyl ether (2x15 cm^3), the combined organic layers washed with brine (2x10 cm^3), dried and evaporated to dryness. Chromatography on silica gel with petroleum ether : diethyl ether (1:1) as the eluent yielded **127** and **128** as an oil (1.0:1.6) (88 mg, 80%); R$_f$: 0.3, petroleum ether : diethyl ether (1:1); δ_H(250 MHz; CDCl$_3$) 1.25 (3H, s, C1-Me, **128**), 1.49 (3H, s, C1-Me, **127**),1.64 (1H, dd, *J* 13.2, 6.8, 13a-H, **128**), 1.88 (1H, d, *J* 14.5, 13a-H, **127**), 2.21 (1H, dd, *J* 7.6, 14.5, 13b-H, **127**), 2.33 (1H, dd, *J* 7.1, 13.2, 13b-H, **128**), 3.26 (1H, d, *J* 9.4, 2-H, **127**), 3.32 (3H, s, OMe, **128**), 3.42 (3H, s, OMe, **127**), 3.43 (1H, d, *J* 9.4, 2-H, **128**), 3.62 (2H, m, 6ax-H, **127** and **128**), 4.00 (2H, m, 7-H, **127** and **128**), 4.22 (2H, m, 6eq-H, **127** and **128**), 4.71 (1H, dd, *J* 6.6, 2.5, 12-H, **127**), 4.96 (1H, dt, *J* 7.1, 6.9, 1.31, 12-H, **128**), 5.05 (1H, s, 9-H,**128**), 5.16 (1H, s, 9-H, **127**), 5.54 (1H, s, 4-H, **127**), 5.47 (1H, s, 4-H, **128**), 5.65 (1H, d, *J* 1.5, 11-H, **128**), 5.85 (1H, d, *J* 2.8, 11-H, **127**), 7.35-7.54 (10H, m, Ph, **127** and **128**).

(1*R*,2*S*,4*R*,7*R*,9*S*,12*R*)-12-Hydroxy-9-methoxy-1-methyl-4-phenyl-3,5,8-trioxatricyclo[8.3.0.0^{2,7}]tridec-10-ene and (1*R*,2*S*,4*R*,7*R*,9*S*,12*S*)-12-hydroxy-9-methoxy-1-methyl-4-phenyl-3,5,8-trioxatricyclo[8.3.0.0^{2,7}]tridec-10-ene

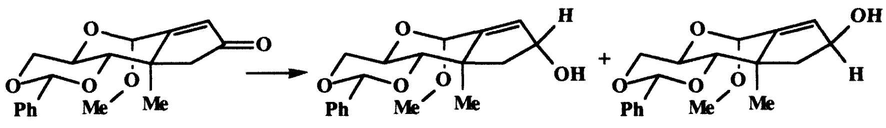


74 **127** **128**

The enone **74** (54 mg, 0.18 mmol) was dissolved in ethanol (5.0 cm^3) and sodium borohydride (29 mg, 0.73 mmol) was added with stirring for 3h. The reaction was quenched by the addition of ammonium chloride (5 cm^3), the product was extracted into diethyl ether (2x15 cm^3), the combined organic layers washed with brine (2x10 cm^3), and evaporated to dryness. Chromatography on silica gel with petroleum ether : diethyl ether (1:1) as the eluent yielded **127** and **128** as an oil (1.0:2.1) (46 mg, 75%); R$_f$: 0.3, petroleum ether : diethyl ether (1:1);

The data from the highfield ^{1}H NMR was identical to that obtained in the previous reaction using DIBAL-H with only the ratio **127** : **128** varying.

(1*R*, 2*S*, 4*R*, 7*R*, 9*S*, 12*R*)-12-Hydroxy-9-methoxy-1-methyl-4-phenyl-3,5,8-trioxatricyclo[8.3.0.0^{2,7}]tridec-10-ene and (1*R*, 2*S*, 4*R*, 7*R*, 9*S*, 12*S*)-12-hydroxy-9-methoxy-1-methyl-4-phenyl-3,5,8-trioxatricyclo[8.3.0.0^{2,7}]tridec-10-ene

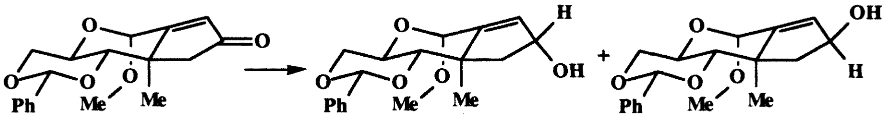


74 **127** **128**

The enone **74** (50 mg, 0.15 mmol) in THF (1.0 cm^3) was stirred at room temperature with lithium borohydride (14 mg, 0.63 mmol) for 1h. The reaction was quenched by the addition of ammonium chloride (5 cm^3), the product extracted into diethyl ether (2x15 cm^3), the combined organic layers washed with brine (2x10 cm^3), dried and evaporated to dryness. Chromatography on silica gel with petroleum ether : diethyl ether (1:1) as the eluent yielded **127** and **128** as an oil (1.0:2.5) (49 mg, 95%); R$_f$: 0.3, petroleum ether : diethyl ether (1:1).

The data from the highfield ^{1}H NMR was identical to that obtained in the reaction using DIBAL-H with only the ratio **127** : **128** varying.

(1*R*,2*S*,4*R*,7*R*,9*S*,12*R*)-12-Hydroxy-9-methoxy-1-methyl-4-phenyl-3,5,8-trioxatricyclo[8.3.0.$0^{2,7}$]tridec-10-ene and (1*R*,2*S*,4*R*,7*R*,9*S*,12*S*)-12-hydroxy-9-methoxy-1-methyl-4-phenyl-3,5,8-trioxatricyclo[8.3.0.$0^{2,7}$]tridec-10-ene

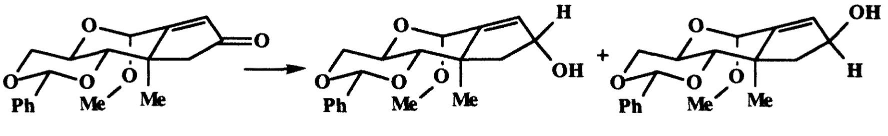


74 **127** **128**

The enone **74** (50 mg, 0.15 mmol) in THF (1.0 cm^3) was added to a solution of lithium aluminium hydride (12 mg, 0.32 mmol, 2.0 cm^3 THF). The reaction was quenched by the addition of water (0.36 cm^3). The precipitate was filtered and the product extracted into diethyl ether (2x15 cm^3), the combined organic layers washed with brine (2x10 cm^3) , dried and evaporated to dryness. Chromatography on silica gel with petroleum ether : diethyl ether (1:1) as the eluent yielded **127** and **128** as an oil (1.0:2.0) (35 mg, 65%); *R*f: 0.3, petroleum ether : diethyl ether (1:1).

The data from the highfield ^{1}H NMR was identical to that obtained in the reaction using DIBAL-H with only the ratio **127** : **128** varying.

(1*R*,2*S*,4*R*,7*R*,9*S*,12*R*)-12-Hydroxy-9-methoxy-1-methyl-4-phenyl-3,5,8-trioxatricyclo[8.3.0.$0^{2,7}$]tridec-10-ene and (1*R*,2*S*,4*R*,7*R*,9*S*,12*S*)-12-hydroxy-9-methoxy-1-methyl-4-phenyl-3,5,8-trioxatricyclo[8.3.0.$0^{2,7}$]tridec-10-ene

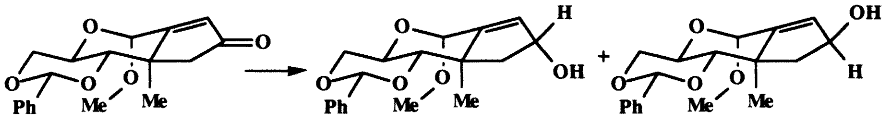


74 **127** **128**

The enone **74** (500 mg, 1.58 mmol) in THF (20.0 cm^3) was cooled to -78°C with stirring. To this stirred solution was added LS-Selectride® (1.58 cm^3, 1.58 mmol) dropwise. The reaction was allowed to stir for 1.5h and then quenched by the addition of water (5 cm^3). The product was extracted into diethyl ether (2x25 cm^3), the combined organic layers washed with brine (2x20 cm^3), dried and evaporated to dryness. Chromatography on silica gel with petroleum ether : diethyl ether (1:1) as the eluent yielded **127** and **128** as an oil (7.2:1.0) (497 mg, 91%); R$_f$ 0.3, petroleum ether : diethyl ether (1:1). The reaction was repeated using L-Selectride® under the same conditions with only the ratio **127** : **128** (5.2:1) differing.

The data from the highfield ^{1}H NMR was identical to that obtained in the reaction using DIBAL-H with only the ratio **127** : **128** varying.

(1*R*,2*S*,4*R*,7*R*,9*S*,12*R*)-12-Hydroxy-9-methoxy-1-methyl-4-phenyl-3,5,8-trioxatricyclo[8.3.0.$0^{2,7}$]tridec-10-ene and (1*R*,2*S*,4*R*,7*R*,9*S*,12*S*)-12-hydroxy-9-methoxy-1-methyl-4-phenyl-3,5,8-trioxatricyclo[8.3.0.$0^{2,7}$]tridec-10-ene

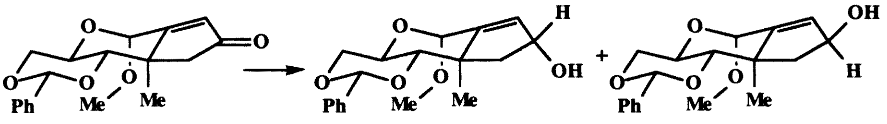


74 **127** **128**

The enone **74** (50 mg, 0.15 mmol) in THF (1.0 cm^3) was cooled to -78°C with stirring. To this stirred solution was added lithium thexyliminoyl borohydride (0.30 cm^3, 0.30 mmol) dropwise. The reaction was quenched by the addition of water (0.5 cm^3). The product extracted into diethyl ether (2x5 cm^3), the combined organic layers washed with brine (2x5 cm^3), dried and evaporated to dryness. Chromatography on silica gel with petroleum ether : diethyl ether (1:1) as the eluent yielded **127** and **128** as an oil (2.9:1.0) (30 mg, 60%); *R*f: 0.3, petroleum ether : diethyl ether (1:1).

The data from the highfield ^{1}H NMR was identical to that obtained in the reaction using DIBAL-H with only the ratio **127** : **128** varying.

(1*R*,2*S*,4*R*,7*R*,9*S*,12*R*)-12-Hydroxy-9-methoxy-1-methyl-4-phenyl-3,5,8-trioxatricyclo[8.3.0.$0^{2,7}$]tridec-10-ene and (1*R*,2*S*,4*R*,7*R*,9*S*,12*S*)-12-hydroxy-9-methoxy-1-methyl-4-phenyl-3,5,8-trioxatricyclo[8.3.0.$0^{2,7}$]tridec-10-ene

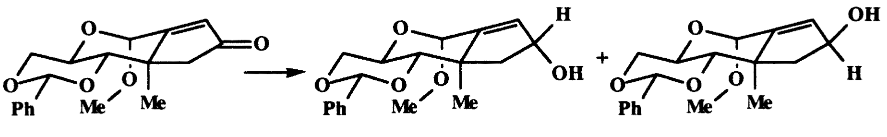


74 **127** **128**

The enone **74** (100 mg, 0.32 mmol) in toluene (2.0 cm^3) was cooled to -78°C with stirring. To this stirred solution was added RED-AL® (0.30 cm^3, 0.96 mmol) dropwise. The reaction was quenched by the addition of water (1.5 cm^3) with cooling and the fitrate removed by filtration The product was extracted into diethyl ether (2x5 cm^3), the combined organic layers washed with brine (2x5 cm^3), dried and evaporated to dryness. Chromatography on silica gel with petroleum ether : diethyl ether (1:1) as the eluent yielded **127** and **128** as an oil (1.0:2.5) (60 mg, 60%); Rf: 0.3, petroleum ether : diethyl ether (1:1).

The data from the highfield ^{1}H NMR was identical to that obtained in the reaction using DIBAL-H with only the ratio **127** : **128** varying.

(1*R*, 2*S*, 4*R*, 7*R*, 9*S*, 12*R*)-12-Hydroxy-9-methoxy-1-methyl-4-phenyl-3,5,8-trioxatricyclo[8.3.0.0^{2,7}]tridec-10-ene and (1*R*, 2*S*, 4*R*, 7*R*, 9*S*, 12*S*)-12-hydroxy-9-methoxy-1-methyl-4-phenyl-3,5,8-trioxatricyclo[8.3.0.0^{2,7}]tridec-10-ene

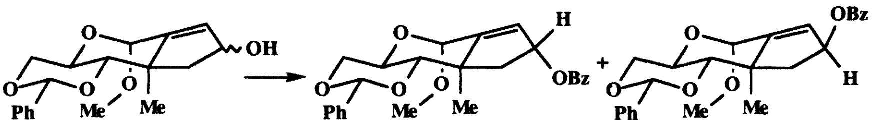


74 **127** **128**

The enone **74** (50 mg, 0.15 mmol) in THF (1.0 cm^3) was cooled to 0°C with stirring. To this stirred solution was added 9'BBN (0.35 cm^3, 0.18 mmol) dropwise. The reaction was quenched by the addition of methanol (0.5 cm^3) and allowed to stir for 1h. The product was extracted into diethyl ether (2x5 cm^3), the combined organic layers washed with brine (2x5 cm^3), dried and evaporated to dryness. Chromatography on silica gel with petroleum ether : diethyl ether (1:1) as the eluent yielded **127** and **128** as an oil (1.0:1.3) (26 mg, 52%); *R*f: 0.3, petroleum ether : diethyl ether (1:1).

The data from the highfield ^{1}H NMR was identical to that obtained in the reaction using DIBAL-H with only the ratio **127** : **128** varying.

(1*R*, 2*S*, 4*R*, 7*R*, 9*S*, 12*R*)-12-Benzoyloxy-9-methoxy-1-methyl-4-phenyl-3,5,8-trioxatricyclo[8.3.0.0^{2,7}]tridec-10-ene and (1*R*, 2*S*, 4*R*, 7*R*, 9*S*, 12*S*)-12-Benzoyloxy-9-methoxy-1-methyl-4-phenyl-3,5,8-trioxatricyclo[8.3.0.0^{2,7}]tridec-10-ene



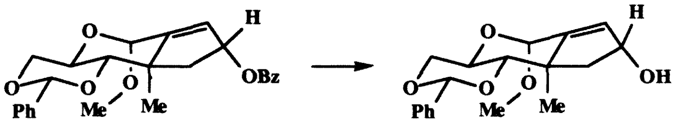
127 + 128 **129** **130**

To a mixture of alcohols **127** and **128** (581 mg, 1.83 mmol) in dichloromethane (5.0 cm^3) was added DMAP (2.6 g, 21.00 mmol) and benzoic anhydride (2.1 g, 9.13 mmol) and the reaction left to stir for 5 minutes. Triethylamine (1.02 cm^3, 7.30 mmol) was then added and the reaction allowed to stir for 2h. The reaction was quenched by the addition of aqueous ammonium chloride solution (5 cm^3), the product extracted into diethyl ether (2x15 cm^3), the combined organic layers washed with brine (2x10 cm^3), dried and evaporated to dryness. Chromatography on silica gel with petroleum ether : diethyl ether (10:1) as the eluent yielded **129** and **130** (513 mg, 66%); R_f 0.75, 0.85, petroleum ether : diethyl ether (1:1);

129 $[\alpha]_D^{20}$ + 108.3° (*c* 1.9, $CHCl_3$); υ_{max} ($CHCl_3$)/cm^{-1} 3005 w, 1690 s, 1450 w, 1150 m, 1105 w; δ_H(250 MHz; $CDCl_3$) 1.53 (3H, s, C1-Me), 2.13 (1H, d, *J* 14.8, 13a-H), 2.34 (1H, dd, *J* 7.3, 14.8, 13b-H), 3.35 (1H, d, *J* 9.5, 2-H), 3.43 (3H, s, OMe), 3.70 (1H, t, *J* 10.1, 6ax-H), 4.07 (1H, dt, *J* 9.8, 5.0, 7-H), 4.34 (1H, dd, *J* 10.1, 5.0, 6eq-H), 5.19 (1H, s, 9-H), 5.56 (1H, s, 4-H), 5.80 (1H, dd, *J* 7.2, 2.8, 12-H), 6.01 (1H, d, *J* 2.5, 11-H), 7.36-7.57 (8H, m, Ph), 8.01 (2H, m, *o*-Ph); δ_C (62.9 MHz; $CDCl_3$) 21.4 (CH_3, C1-Me), 46.1 (CH_2, C13), 48.7 (C, C1), 55.5 (CH_3, OMe), 60.5 (CH, C7), 69.9 (CH_2, C6), 78.2 (CH, C12), 87.8 (CH, C2), 98.5 (CH, C9), 102.1 (CH, C4), 126.4-130.7 (6xCH, Ph), 130.7 (C, Ph), 133.4 (C, C11), 138.1 (C, Ph), 150.7 (C, C10), 166.6 (C, O*C*OPh); *m/z* (EI) 422 (M^+) 422, 273, 149, 122 (100) (Found : M^+, 422.1729. $C_{25}H_{26}O_6$ requires 422.1729).

130 $[\alpha]_D^{22}$ - 169.3° (*c* 1.54, $CHCl_3$); υ_{max} ($CHCl_3$)/cm^{-1} 2920 m, 1720 s, 1450 w; δ_H(250 MHz; $CDCl_3$) 1.42 (3H, s, C1-Me), 2.06 (1H, dd, *J* 13.5, 7.5, 13a-H), 2.58 (1H, dd, *J* 13.8, 7.2, 13b-H), 3.42 (3H, s, OMe), 3.56 (1H, d, *J* 9.4, 2-H), 3.72 (1H, t, *J* 10.1, 6ax-H), 4.10 (1H, dt, *J* 9.8, 5.0, 7-H), 4.32 (1H, dd, *J* 10.1, 5.0, 6eq-H), 5.17 (1H, s, 9-H), 5.56 (1H, s, 4-H), 5.86 (1H, d, *J* 1.3, 11-H), 6.09 (1H, br t, *J* 6.3, 12-H), 7.35-7.56 (8H, m, Ph), 8.03 (2H, m, *o*-Ph); δ_C (62.9 MHz; $CDCl_3$) 20.6 (CH_3, C1-Me), 46.8 (CH_2, C13), 48.8 (C, C1), 55.5 (CH_3, OMe), 60.8 (CH, C7), 69.9 (CH_2, C6), 79.5 (CH, C12), 87.3 (CH, C2), 98.4 (CH, C9), 102.1 (CH, C4), 126.7-130.0 (6xCH, Ph), 130.6 (C, Ph), 133.4 (C, C11), 138.1 (C, Ph), 148.0 (C, C10), 166.8 (C, OCOPh); *m/z* (EI) 422 (M^+, 0.9%) 273 (7.8) 166 (8.4) 149 (7.0) 127 (9.0) 123 (15.5) 122 (38.2) 105 (100) (Found : M^+, 422.1730. $C_{25}H_{26}O_6$ requires 422.1730).

(1*R*,2*S*,4*R*,7*R*,9*S*,12*R*)-12-Hydroxy-9-methoxy-1-methyl-4-phenyl-3,5,8-trioxatricyclo[8.3.0.$0^{2,7}$]tridec-10-ene

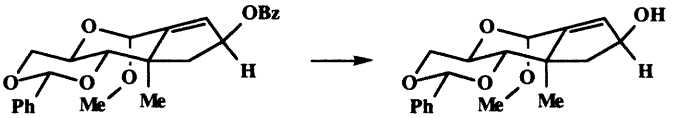


129 **127**

The allylic benzoate **129** (447 mg, 1.06 mmol) was dissolved in methanol (5.0 cm^3) and potassium carbonate added (161 mg, 1.16 mmol) and the solution stirred for 8h. The methanol was removed, the solid dissolved in diethyl ether (2x15 cm^3), washed with brine (2x10 cm^3), dried and evaporated to dryness. Chromatography on silica gel with petroleum ether : diethyl ether (1:1) as the eluent yielded **127** as an oil (314 mg, 86%); R_f 0.3, petroleum ether : diethyl ether (1:1); $[\alpha]_D^{21}$ +64.3° (*c* 0.7, $CHCl_3$); υ_{max} ($CHCl_3$)/cm^{-1} 3420 s, 2940 s, 1450 m, 1400 m, 1350 m, 1100 s; δ_H(250 MHz; $CDCl_3$) 1.49 (3H, s, C1-Me), 1.88 (1H, d, *J* 14.5, 13a-H), 2.21 (1H, dd, *J* 7.6, 14.5, 13b-H), 3.26 (1H, d, *J* 9.4, 2-H), 3.44 (3H, s, OMe), 3.68 (1H, t, *J* 10.4, 6ax-H), 4.05 (1H, dt, *J* 9.8, 5.0, 7-H), 4.33 (1H, dd, *J* 10.4, 5.0, 6eq-H), 4.71 (1H, dd, *J* 6.6, 2.5, 12-H), 5.16 (1H, s, 9-H), 5.54

(1H, s, 4-H), 5.85 (1H, d, *J* 2.8, 11-H), 7.37-7.54 (5H, m, Ph); δ_C (62.9 MHz; $CDCl_3$) 22.3 (CH_3, C1-Me), 48.4 (C, C1), 48.9 (CH_2, C13), 55.4 (CH_3, OMe), 60.6 (CH, C7), 69.9 (CH_2, C6), 75.1 (CH, C12), 88.0 (CH, C2), 98.8 (CH, C9), 102.1 (CH, C4), 126.7 (CH, Ph), 128.7 (CH, Ph), 129.5 (CH, Ph), 129.9 (CH, C11), 138.1 (C, Ph), 147.9 (C, C10); *m/z* (EI) 318 (M^+, 1.2%) 287 (5.5) 169 (54.7) 149 (27) 141 (11) 140 (100) (Found : M^+, 318.1467. $C_{18}H_{22}O_5$ requires 318.1467).

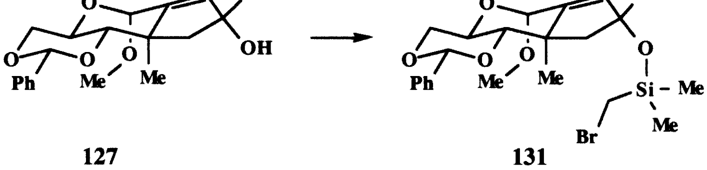
(1*R*, 2*S*, 4*R*, 7*R*, 9*S*, 12*S*)-12-Hydroxy-9-methoxy-1-methyl-4-phenyl-3,5,8-trioxatricyclo[8.3.0.0^{2,7}]tridec-10-ene



130 **128**

The allylic benzoate **130** (599 mg, 1.42 mmol) was dissolved in methanol (5.0 cm^3) and potassium carbonate added (216 mg, 1.56 mmol) and the solution stirred for 8h. The methanol was removed, the solid extracted with diethyl ether (2x15 cm^3), the organic layers washed with brine (2x10 cm^3), dried and evaporated to dryness. Chromatography on silica gel with petroleum ether : diethyl ether (4:1) as the eluent yielded **128** as an oil (328 mg, 67%); *Rf*: 0.35, petroleum ether : diethyl ether (1:1); $[\alpha]_D^{21}$ - 19.9° (*c* 0.94, $CHCl_3$); υ_{max} ($CHCl_3$)/cm^{-1} 3440 brs, 2940 s, 1450 s, 1100 s; δ_H(250 MHz; $CDCl_3$) 1.25 (3H, s, C1-Me), 1.64 (1H, dd, *J* 13.2, 6.8, 13a-H), 1.87 (1H, s, OH), 2.33 (1H, dd, *J* 13.2, 7.1, 13b-H), 3.32 (3H, s, OMe), 3.43 (1H, d, *J* 9.4, 2-H), 3.62 (1H, t, *J* 10.2, 6ax-H), 3.98 (1H, dt, *J* 9.8, 9.74, 5.0, 7-H), 4.21 (1H, dd, *J* 10.3, 5.1, 6eq-H), 4.96 (1H, dt, *J* 7.1, 6.9, 1.3, 12-H), 5.05 (1H, s, 9-H), 5.47 (1H, s, 4-H), 5.65 (1H, d, *J* 1.5, 11-H), 7.35-7.54 (5H, m, Ph); δ_C (62.9 MHz; $CDCl_3$) 20.3 (CH_3, C1-Me), 48.8 (C, C1), 50.5 (CH_2, C13), 55.5 (CH_3, OMe), 60.7 (CH, C7), 69.9 (CH_2, C6), 76.2 (CH, C12), 87.4 (CH, C2), 98.5 (CH, C9), 102.1 (CH, C4), 126.7 (CH, Ph), 128.7 (CH, Ph), 129.5 (CH, Ph), 129.9 (CH, C11), 138.1 (C, Ph), 145.9 (C, C10); *m/z* (EI) 318 (M^+, 1.1%) 287 (8.6) 169 (45) 167 (26)149 (19) 140 (100) (Found : M^+, 318.1467. $C_{18}H_{22}O_5$ requires 318.1467).

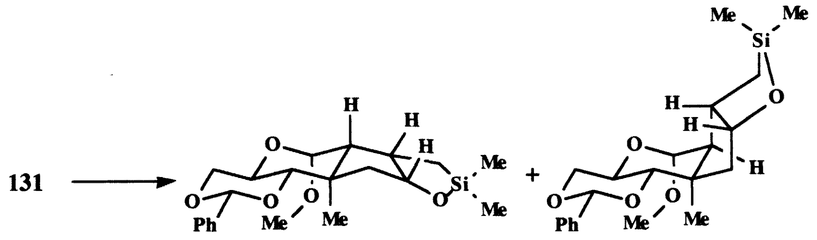
(1*R*,2*S*,4*R*,7*R*,9*S*,12*R*)-12[(Bromomethyl)dimethylsiloxy]9-methoxy-1-methyl-4-phenyl-3,5,8-trioxatricyclo[8.3.0.$0^{2,7}$]tridec-10-ene



127 **131**

To the alcohol **127** (314 mg, 0.99 mmol) in dichloromethane (1.0 cm^3) and triethylamine (0.25 cm^3, 1.78 mmol) was added bromomethyl chlorodimethylsilane (204 mg, 1.10 mmol) dropwise. This solution was allowed to stir overnight, when it became a yellow viscous liquid. The reaction was quenched by the addition of water (2 cm^3), the product was extracted into diethyl ether (2x15 cm^3), the combined organic layers washed with brine (2x10 cm^3), dried and evaporated to dryness. Chromatography on silica gel with diethyl ether (and 0.1% triethylamine) as the eluent yielded **131** as a pale yellow oil (412 mg, 89%); R_f: 0.75, petroleum ether : diethyl ether (1:1); $[\alpha]_D^{20}$ 64.06° (*c* 1.92, $CHCl_3$); υ_{max} ($CHCl_3$)/cm^{-1} 2930 m, 1725 s, 1450 m, 1280 s, 1110 s, 950 s, 825 m; δ_H(250 MHz; $CDCl_3$) 0.30 (6H, s, Me_2Si), 1.50 (3H, s, C1-Me), 1.89 (1H, d, *J* 14.2, 13a-H), 2.18 (1H, dd, *J* 6.9, 14.2, 13b-H), 2.50 (2H, s, $C\mathit{H}_2Br$), 3.26 (1H, d, *J* 9.4, 2-H), 3.44 (3H, s, OMe), 3.69 (1H, t, *J* 10.1, 6ax-H), 4.07 (1H, dt, *J* 9.8, 5.1, 7-H), 4.34 (1H, dd, *J* 10.1, 5.0, 6eq-H), 4.83 (1H, dd, *J* 6.9, 3.1, 12-H), 5.16 (1H, s, 9-H), 5.55 (1H, s, 4-H), 5.81 (1H, d, *J* 2.5, 11-H), 7.38-7.54 (5H, m, Ph); δ_C (62.9 MHz; $CDCl_3$) -0.1 (2xCH_3, $\mathit{C}H_3CH_3Si$), 0.1 (CH_3, $CH_3\mathit{C}H_3Si$), 18.8 (CH_2, $\mathit{C}H_2Br$), 23.6 (CH_3, C1-Me), 50.5 (C, C1), 51.1 (CH_2, C13), 57.4 (CH_3, OMe), 62.5 (CH, C7), 71.9 (CH_2, C6), 77.7 (CH, C2), 90.0 (CH, C12), 100.8 (CH, C9), 104.0 (CH, C4), 128.7 (CH, Ph), 130.7 (CH, Ph), 131.4 (CH, Ph), 131.6 (CH, C11), 140.2 (C, Ph), 149.4 (C, C10); *m/z* (EI) 468 (M^+, 2.2%) 470 (M$^+$, 2.3%) 437 (7.4) 322 (10.2) 321 (56.2) 320 (11.0) 319 (55.5) 293 (17.8) 292 (99.4) 290 (100) (Found : M$^+$, 468.0968. $C_{21}H_{29}O_5BrSi$ requires 468.0968).

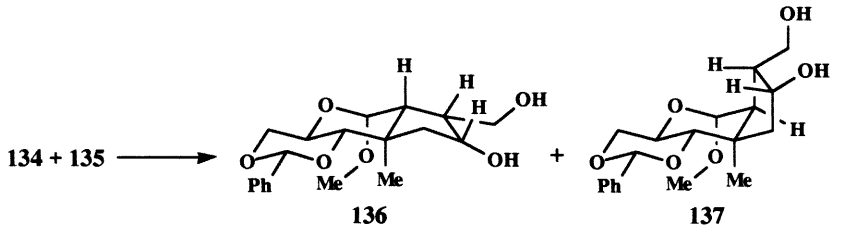
(1*R*, 2*S*, 4*R*, 7*R*, 9*S*, 10*R*, 11*S*, 15*R*)-9-Methoxy-1,13,13-trimethyl-4-phenyl-3,5,8,14-tetraoxa-13-silatetracyclo[8.6.0.0^{2,7}0^{11,15}]hexadecane and (1*R*, 2*S*, 4*R*, 7*R*, 9*S*, 10*S*, 11*S*, 15*R*)-9-Methoxy-1,13,13-trimethyl-4-phenyl-3,5,8,14-tetraoxa-13-silatetracyclo[8.6.0.0^{2,7}0^{11,15}]hexadecane



134 **135**

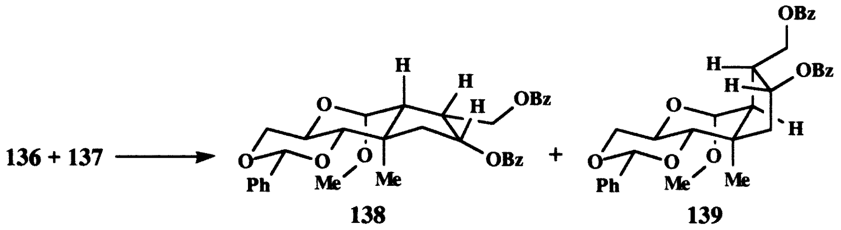
To the silane **131** (412 mg, 0.88 mmol) in t-butanol (10.0 cm^3) was added sodium cyanoborohydride (138 mg, 22 mmol), tributyltin hydride (29 mg, 0.09 mmol) and finally AIBN (14 mg, 0.09 mmol). The solution was refluxed for 16h, the t-butanol was removed *in vacuo*, the solid dissolved in diethyl ether (10 cm^3) and water (10 cm^3), extracted with diethyl ether (2x15 cm^3), the combined organic layers washed with brine (2x10 cm^3), dried and evaporated to dryness. The products **133** and **135** were not stable to column chromatography and were therefore used crude in the next step.

(1*R*,2*S*,4*R*,7*R*,9*S*,10*S*,11*R*,12*R*)-11-Hydroxymethyl-9-methoxy-1-methyl-4-phenyl-3,5,8-trioxatricyclo[8.3.0.$0^{2,7}$]tridecan-12-ol and (1*R*,2*S*,4*R*,7*R*,9*S*,10*R*,11*R*,12*R*)-11-Hydroxymethyl-9-methoxy-1-methyl-4-phenyl-3,5,8-trioxatricyclo[8.3.0.$0^{2,7}$]tridecan-12-ol



The crude cyclic silyl ethers **134** and **135** (447 mg, 1.14 mmol) were dissolved in THF and methanol (10.0 cm^3, 1:1) and sodium carbonate (145 mg, 1.37 mmol) was added. Hydrogen peroxide (0.65 cm^3, 5.71 mmol) as a 30% w/v solution in water was added dropwise. The solution was then refluxed for 20h. The product was extracted into ethyl acetate (2x15 cm^3), the combined organic layers washed with brine (2x10 cm^3), dried and evaporated to dryness. Chromatography on silica gel with diethyl ether increasing in 50% steps to ethyl acetate as the eluent yielded **136** and **137** as an oil (1.0:1.6) (234 mg, 83%). The yield is based on recovered starting material and is over two steps; R_f: 0.3, diethyl ether; δ_H(250 MHz; $CDCl_3$) 1.32 (3H, s, C1-Me, **136**), 1.37 (1H, m, 10-H, **136** or **137**), 1.50 (3H, s, C1-Me, **137**), 1.59 (1H, dd, *J* 7.6, 13.5, 13a-H, **137**), 1.80 (1H, m, 10-H, **136** or **137**), 1.89 (1h, br d, *J* 13.5, 13b-H, **137**), 2.13 (1H, br d, *J* 12.0, 13a-H, **136**), 2.28 (1H, m, 11-H, **136**), 2.5 (1H, dd, *J* 6.9, 13.8, 13b-H, **136**), 2.68 (1H, m, 11-H, **137**), 3.25-3.34 (2H, m, 2-H, **136** and **137**), 3.34 (3H, s, OMe, **136**), 3.38 (3H, s, OMe, **137**), 3.64 (1H, overlapping t, *J* 10.1, 6ax-H, **136**), 3.65 (1H, obscured t, 6ax-H, **137**), 3.72-4.00 (6H, m, 2x5-H, 2xCH_2OH, **136** and **137**), 4.25 (2H, overlapping dd, *J* 5.1, 10.1, 6eq-H, **136**, *J* 10.1, 5.4, 6eq-H, **137**), 4.54 (2H, m, 12-H, **136**), 4.55 (1H, s, 9-H, **136**), 4.62 (1H, t, *J* 7.9, 12-H, **137**), 4.80 (1H, d, *J* 2.8, 9-H, **137**), 5.51 (1H, s, 4-H, **136**), 5.54 (1H, s, 4-H, **137**), 7.36 (10H, m, Ph, **136** and **137**); *m/z* (EI) 350 (M^+, 5.3%) 335 (10.8) 201 (75.2) 183 (23.0) 169 (54.6) 149 (41.8) 123 (38.5) 107 (47.2) 105 (100).

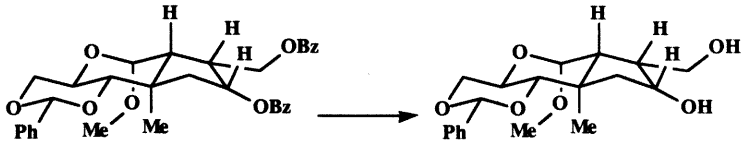
(1*R*,2*S*,4*R*,7*R*,9*S*,10*S*,11*R*,12*R*)-12-Benzoyloxy-11-benzoyloxymethyl-9-methoxy-1-methyl-4-phenyl-3,5,8-trioxatricyclo[8.3.0.0^{2,7}]tridecane and (1*R*,2*S*,4*R*,7*R*,9*S*,10*R*,11*R*,12*R*)-12-Benzoyloxy-11-benzoyloxymethyl-9-methoxy-1-methyl-4-phenyl-3,5,8-trioxatricyclo[8.3.0.0^{2,7}]tridecane



The mixture of diols **136** and **137** (203 mg, 0.58 mmol) were dissolved in dichloromethane (11.0 cm^3) and DMAP (814 mg, 6.67 mmol), and benzoic anhydride (1.31g, 5.80 mmol) were added. Triethylamine (0.65 cm^3, 4.64 mmol) was added to the stirred solution dropwise and allowed to stir overnight. The reaction was quenched by the addition of saturated sodium chloride solution (10 cm^3), the product extracted into diethyl ether (2x30 cm^3), the combined organic layers washed with brine (2x10 cm^3), dried and evaporated to dryness. Chromatography on silica gel with petroleum ether : diethyl ether (2:1) as the eluent yielded **138** and **139** as an oil (1.0:1.6) (152 mg, 47%); R$_f$ 0.78, 0.75, petroleum ether : diethyl ether (1:1); **138** $[\alpha]_D^{20}$ 26.7^o (*c* 1.0, CHCl$_3$); υ_{max} (CHCl$_3$)/cm^{-1} 2920 w, 1740 s, 1450 m, 1280 s; δ_H(250 MHz; CDCl$_3$) 1.61 (3H, s, C1-Me), 1.85 (1H, dd, *J* 7.6, 14.2, 13a-H), 2.05 (1H, dd, *J* 9.8, 2.9, 10-H), 2.13 (2H, d, *J* 14.2, 13b-H), 3.20 (1H, br q, *J* 9.1, 11-H), 3.30 (3H, s, OMe), 3.41 (1H, d, *J* 9.1, 2-H), 3.77 (1H, t, *J* 10.1, 6ax-H), 4.02 (1H, dt, *J* 4.7, 10.0, 7-H), 4.31 (1H, dd, *J* 4.7, 10.1, 6eq-H), 4.53 (1H, dd, *J* 7.9, 11.3, C*H*HBz), 4.82 (1H, dd, *J* 7.6, 11.3, CH*H*Bz), 4.99 (1H, d, *J* 2.5, 9-H), 5.60 (1H, s, 4-H), 5.96 (1H, t, *J* 8.2, 12-H), 7.35-7.58 (10H, m, Ph), 7.85-8.13 (5H, m, Ph); δ_C (62.9 MHz; CDCl$_3$) 17.4 (CH$_3$, C1-Me), 43.5 (C, C1), 48.1 (CH$_2$, C13), 51.5 (CH, C11), 55.8 (CH_3, OMe), 61.4 (CH, C7), 64.3 (CH_2, *C*H_2OBz), 70.1 (CH_2, C6), 74.5 (CH, C2), 88.4 (CH, C12), 100.9 (CH, C9), 101.9 (CH, C4), 126.6-133.5 (9xCH, 3C, Ph), 138.1 (C, Ph), 167.8 (C, CO), 168.5 (C, CO); *m/z* (FAB) 559 (MH^+, 24%) 527 (100) 405 (52) 299 (18.6) 206 (98) (Found : MH^+ 559.2332. $C_{33}H_{35}O_8$ requires 559.2332).

139 $[\alpha]_D^{20}$ - 47.2° (*c* 2.81, $CHCl_3$); υ_{max} ($CHCl_3$)/cm^{-1} 2930 w, 1740 s, 1450 m; 1280 m, 1110 m; δ_H(250 MHz; $CDCl_3$) 1.45 (3H, s, C1-Me), 1.72 (1H, dd, *J* 5.4, 14.8, 13a-H), 2.28 (1H, d, *J* 12.0, 10-H), 2.75 (1H, dd, *J* 6.9, 14.8, 13b-H), 2.94 (1H, dt, *J* 6.6, 12.0, 11-H), 3.41 (3H, s, OMe), 3.55 (1H, d, *J* 9.9, 2-H), 3.76 (1H, t, *J* 10.1, 6ax-H), 4.03 (1H, dt, *J* 5.0, 9.9, 7-H), 4.35 (1H, dd, *J* 5.0, 10.0, 6eq-H), 4.55 (2H, apparent d, *J* 6.9, C*H*$_2$OBz), 5.55 (1H, s, 9-H), 5.62 (1H, s, 4-H), 5.86 (1H, br q, *J* 6.9, 12-H), 7.35-7.55 (10H, m, Ph) 7.96-8.12 (5H, m, Ph); δ_C (62.9 MHz; $CDCl_3$) 21.9 (CH_3, C1-Me), 42.1 (C, C1), 43.9 (CH, C10), 45.3 (CH_2, C13), 53.1 (CH, C11), 55.6 (CH_3, OMe), 59.5 (CH, C7), 63.9 (CH_2, *C*H_2OBz), 69.9 (CH_2, C6), 74.5 (CH, C2), 81.8 (CH, C12), 100.1 (CH, C9), 102.5 (CH, C4), 126.6-134.1 (9xCH, 2C, Ph), 138.2 (C, Ph), 166.3 (C, CO ester), 166.8 (C, CO ester); *m/z* (FAB) 559 (MH^+, 10%) 557 (12) 405 (36) 307 (12) 154 (100) (Found : MH^+ 559.2331. $C_{33}H_{35}O_8$ requires 559.2331).

(1*R*,2*S*,4*R*,7*R*,9*S*,10*S*,11*R*,12*R*)-11-Hydroxymethyl-9-methoxy-1-methyl-4-phenyl-3,5,8-trioxatricyclo[8.3.0.0^{2,7}]tridecan-12-ol

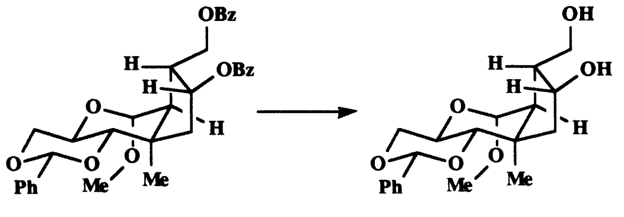


138 **136**

The dibenzoate **138** (66 mg, 0.12 mmol) was dissolved in dichloromethane (2.0 cm^3) and cooled to -78°C before DIBAL-H (2.2 cm^3, 1.10 mmol) was added dropwise. After stirring for 1h the reaction was quenched by the addition of isopropanol (3 cm^3) and a saturated aqueous solution of sodium sulphate (3 cm^3) and left to warm to room temperature. The solid was removed by filtration through celite, the product was extracted into diethyl ether

(2x10 cm^3), the organic layers washed with brine (2x5 cm^3), dried and evaporated to dryness. Chromatography on silica gel with diethyl ether increasing to ethyl acetate as the eluent yielded **136** as an oil (22 mg, 52%); R_f: 0.75, diethyl ether; $[\alpha]_D^{19}$ 25.5° (*c* 1.24, $CHCl_3$); υ_{max} ($CHCl_3$)/cm^{-1} 3620 w, 3500 brw, 2920 s, 1460 m, 1360 m; δ_H(250 MHz; $CDCl_3$) 1.51 (3H, s, C1-Me), 1.62 (1H, dd, *J* 7.6, 13.9, 13a-H), 1.87 (1H, overlapping dd, *J* 9.4, 3.2, 10-H) overlapping 1.92 (1H, d, *J* 13.5, 13b-H), 2.70 (1H, m, 11-H), 3.29 (1H, d, *J* 9.2, 2-H), 3.41 (3H, s, OMe), 3.72 (1H, t, *J* 10.1, 6ax-H), 3.88 (1H, m, C*H*HOBz), 3.94 (1H, ddd, *J* 5.0, 9.8, 10.1, 7-H) overlapping 4.08 (1H, apparent t, *J* 10.7, CH*H*OBz-H), 4.28 (1H, dd, *J* 5., 10.0, 6eq-H), 4.67 (1H, br t, *J* 7.6, 12-H), 4.84 (1H, d, *J* 2.8, 9-H), 5.56 (1H, s, 4-H), 7.36-7.53 (5H, m, Ph); δ_C (62.9 MHz; $CDCl_3$) 17.7 (CH_3, C1-Me), 43.3 (C, C1), 45.6 (CH, C10), 50.3 (CH_2, C13), 51.9 (CH, C11), 55.7 (CH_3, OMe), 61.5 (CH, C7), 62.6 (CH_2, *C*H_2OBz), 70.1 (CH_2, C6), 74.2 (CH, C2), 88.8 (CH, C12), 101.1 (CH, C9), 101.9 (CH, C4), 126.7 (CH, Ph), 128.6 (CH, Ph), 129.4 (CH, Ph), 138.3 (C, Ph).

(1*R*,2*S*,4*R*,7*R*,9*S*,10*R*,11*R*,12*R*)-11-Hydroxymethyl-9-methoxy-1-methyl-4-phenyl-3,5,8-trioxatricyclo[8.3.0.$0^{2,7}$]tridecan-12-ol

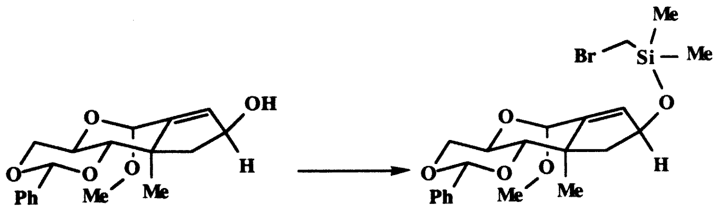


139 **137**

The dibenzoate **139** (141 mg, 0.25 mmol) was dissolved in dichloromethane (2.0 cm^3) and cooled to -78°C before DIBAL-H (3.0 cm^3, 1.51 mmol) was added dropwise. After stirring for 1h the reaction was quenched by the addition of isopropanol (3.0 cm^3) and a saturated aqueous solution of sodium sulphate (3.0 cm^3) and left to warm to room temperature. The solid was removed by filtration through celite, the product was extracted with diethyl ether

(2x10 cm^3), the organic layers washed with brine (2x5 cm^3), dried and evaporated to dryness. Chromatography on silica gel with diethyl ether increasing to ethyl acetate as the eluent yielded **137** as an oil (44 mg, 50%); R_f 0.75, diethyl ether; $[\alpha]_D^{19}$ -14.7° (*c* 0.88, $CHCl_3$); υ_{max} ($CHCl_3$)/cm^{-1} 3420 s, 2930 m, 1450 w, 1370 m, 1230 m, 1090 s; δ_H(250 MHz; $CDCl_3$) 1.48 (3H, s, C1-Me), 1.50 (1H, dd, *J* 5.7, 13.83, 13a-H), 2.28 (1H, d, *J* 12.0, 10-H), 2.44 (1H, m, 11-H), 2.65 (1H, dd, *J* 6.9, 14.16, 13b-H), 3.14 (2H, brs, 2xOH), 3.47 (1H, d, *J* 9.4, 2-H), 3.52 (3H, s, OMe), 3.80 (1H, t, *J* 10.4, 6ax-H), 3.90 (1H, m, C*H*HOH), 3.99 (1H, m, CH*H*OH) overlapping 4.07 (1H, overlapping dt, *J* 5.0, 10.4, 7-H), 4.41 (1H, dd, *J* 5.0, 10.4, 6eq-H), 4.66 (1H, t, *J* 6.6, 12-H), 4.80 (1H, s, 9-H), 5.66 (1H, s, 4-H), 7.35-7.51 (5H, m, Ph); δ_C (62.9 MHz; $CDCl_3$) 21.6 (CH_3, C1-Me), 41.9 (C, C1), 46.8 (CH, C10), 48.2 (CH_2, C13), 50.2 (CH, C11), 55.5 (CH_3, OMe), 59.5 (CH, C7), 61.9 (CH_2, CH_2OH), 69.9 (CH_2, C6), 73.5 (CH, C2), 81.8 (CH, C12), 100.4 (CH, C9), 102.5 (CH, C4), 126.6 (CH, Ph), 128.7 (CH, Ph), 129.4 (CH, Ph), 138.2 (C, Ph); *m/z* (EI) 350 (M^+, 6.5%) 318 (12.9) 270 (15.9) 201 (100) (Found : M^+, 350.1729. $C_{19}H_{26}O_6$ requires 350.1729).

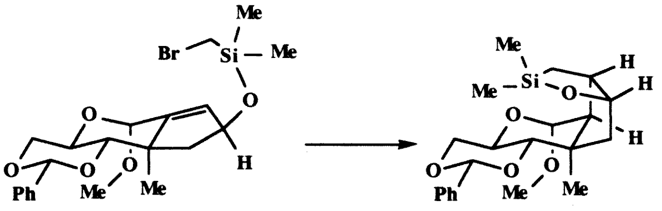
(1*R*, 2*S*, 4*R*, 7*R*, 9*S*, 12*S*)-12[(Bromomethyl)dimethylsiloxy]9-methoxy-1-methyl-4-phenyl-3,5,8-trioxatricyclo[8.3.0.0^{2,7}]tridec-10-ene



128 **140**

To the alcohol **128** (314 mg, 0.99 mmol) in dichloromethane (1.0 cm^3) and triethylamine (0.25 cm^3, 1.78 mmol) was added bromomethyl chlorodimethylsilane (204 mg, 1.10 mmol) dropwise. This solution was allowed to stir overnight, when it became a yellow viscous liquid. The reaction was quenched by the addition of water (2 cm^3), the product was extracted into diethyl ether (2x15 cm^3), the combined organic layers washed with brine (2x10 cm^3), dried and evaporated to dryness. Chromatography on silica gel with diethyl ether (and 0.1% triethylamine) as the eluent yielded **140** as a pale yellow oil (412 mg, 89%); R_f: 0.75, petroleum ether : diethyl ether (1:1); υ_{max} ($CHCl_3$)/cm^{-1} 2930 w, 1450 w, 1315 m, 1260 m, 1110 s, 1080 s; δ_H(250 MHz; $CDCl_3$) 0.26 (3H, s, C*H*$_3$Si), 0.30 (3H, s, C*H*$_3$Si), 1.35 (3H, s, C1-Me), 1.80 (1H, dd, *J* 6.9, 12.6, 13a-H), 2.37 (1H, dd, *J* 6.9, 12.9, 13b-H), 2.47 (2H, d, *J* 8.8, C*H*$_2$Br), 3.41 (3H, s, OMe), 3.56 (1H, d, *J* 9.8, 2-H), 3.71 (1H, t, *J* 10.1, 6ax-H), 4.06 (1H, ddd, *J* 5.0, 9.8, 10.0, 7-H), 4.30 (1H, dd, *J* 10.1, 5.03, 6eq-H), 5.13 (2H, m, 1-H, 12-H), 5.55 (1H, s, 4-H), 5.71 (1H, s, 11-H), 7.37-7.52 (5H, m, Ph); δ_C (62.9 MHz; $CDCl_3$) -1.7 (CH_3, MeSi), 0.0 (CH_3, MeSi), 16.8 (CH_2, *C*H$_2$Br), 20.7 (CH_3, C1-Me), 49.0 (C, C1), 51.2 (CH_2, C13), 55.9 (CH_3, OMe), 61.1 (CH, C7), 70.4 (CH_2, C6), 77.5 (CH, C2), 87.7 (CH, C12), 98.9 (CH, C9), 102.5 (CH, C4), 127.2 (CH, Ph), 129.2 (CH, Ph), 129.9 (CH, Ph), 132.2 (CH, C11), 138.7 (C, Ph), 145.9 (C, C10); *m/z* (EI) 468 (M^+, 1.3%) 470 (M^+, 1.3%) 439 (10.4) 321 (47.8) 319 (47.0) 293 (19.8) 292 (98.7) 290 (100) (Found : M^+, 468.0968. $C_{21}H_{29}O_5BrSi$ requires 468.0968).

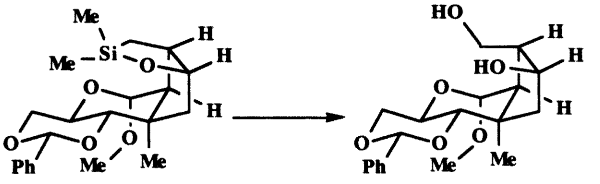
(1*R*, 2*S*, 4*R*, 7*R*, 9*S*, 10*R*, 11*S*, 15*R*)-9-Methoxy-1,13,13-trimethyl-4-phenyl-3,5,8,14-tetraoxa-13-silatetracyclo[8.6.0.$0^{2,7}0^{11,15}$]hexadecane



140 **143**

To the silane **140** (412 mg, 0.88 mmol) in t-butanol (10.0 cm^3) was added sodium cyanoborohydride (138 mg, 2_2 mmol), tributyltin hydride (29 mg, 0.09 mmol) and finally AIBN (14 mg, 0.09 mmol). The solution was refluxed for 16h, the t-butanol was removed *in vacuo*, the solid dissolved in diethyl ether (10cm^3) and water (10 cm^3), extracted with diethyl ether (2x15 cm^3), the combined organic layers washed with brine (2x10 cm^3), dried and evaporated to dryness. The product **143** was not stable to column chromatography and was therefore used crude in the next step.

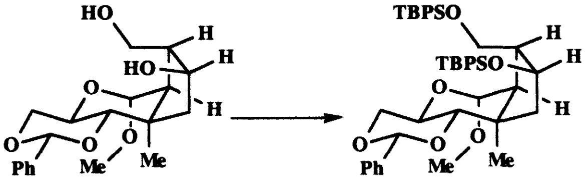
(1*R*, 2*S*, 4*R*, 7*R*, 9*S*, 10*S*, 11*S*, 12*S*)-11-Hydroxymethyl-9-methoxy-1-methyl-4-phenyl-3,5,8-trioxatricyclo[8.3.0.$0^{2,7}$]tridecan-12-ol



143 **144**

The crude cyclic silyl ether **143** (447 mg, 1.14 mmol) was dissolved in THF and methanol (10.0 cm^3, 1:1) and sodium carbonate (145 mg, 1.37 mmol) was added. Hydrogen peroxide (0.65 cm^3, 5.71 mmol) as a 30% w/v solution in water was added dropwise. The solution was then refluxed for 20h. The product was extracted into ethyl acetate (2x15 cm^3), the combined organic layers washed with brine (2x10 cm^3), dried and evaporated to dryness. Chromatography on silica gel with diethyl ether increasing in 50% steps to ethyl acetate as the eluent yielded **144** as an oil (234 mg, 83%). The yield is based on recovered starting material and is over two steps; R$_f$: 0.3, diethyl ether; δ_H(250 MHz; CDCl$_3$) 1.26 (3H, s, C1-Me), 1.71 (1H, dd, *J* 7.2, 14.15, 13a-H), 2.03 (2H, obscured dd, d, *J* 4.7, 14.15, 13b-H, *J* 8.8, 10-H), 2.52 (1H, m, 11-H), 3.33 (2H, br s, OH), 3.34 (3H, s, OMe), 3.70 (2H, m, C*H*HOH, 7-H), 3.87 (1H, t, *J* 8.2, 6ax-H) overlapping 3.87 (1H, m, 2-H), 4.04 (1H, t, *J* 10.7, CH*H*OH), 4.26 (1H, m, *J* 4.06, 8.2, 6eq-H), 4.44 (1H, m, 12-H), 4.76 (1H, s, 9-H), 5.57 (1H, s, 4-H), 7.36-7.52 (5H, m, Ph); δ_C (62.9 MHz; CDCl$_3$) 22.9 (CH$_3$, C1-Me), 42.2 (C, C1), 46.8 (CH$_2$, C13), 47.8 (CH, C11), 52.0 (CH, C10), 55.4 (CH$_3$, OMe), 59.7 (CH, C7), 62.0 (CH$_2$, CH$_2$OH), 70.1 (CH$_2$, C6), 74.7 (CH, C12), 83.1 (CH, C2), 99.4 (CH, C9), 102.3 (CH, C4), 126.6 (CH, Ph), 128.6 (CH, Ph), 129.4 (CH, Ph), 138.3 (C, Ph).

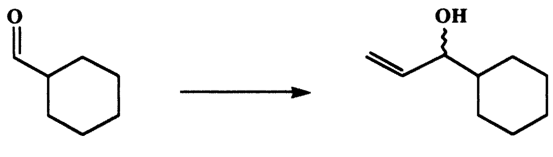
(1*R*,2*S*,4*R*,7*R*,9*S*,10*S*,11*S*,12*S*)-12-*tert*-Butyldiphenylsiloxy-11-*tert*-butyldiphenylsiloxymethyl-9-methoxy-1-methyl-4-phenyl-3,5,8-trioxatricyclo[8.3.0.0^{2,7}]tridecane



144 145

The diol **144** (120 mg, 0.34 mmol) was dissolved in dichloromethane (2.0 cm^3) tand cooled to 0°C. To this was added imidazole (93 mg, 1.37 mmol) and DMAP (2 mg, 0.02 mmol) and the solution allowed to stir for 10 min. t-Butyldiphenylsilylchloride (283 mg, 1.00 mmol) was then added dropwise and the solution left to stir for 3 days. The reaction was quenched by the addition of methanol (2 cm^3) and water (2 cm^3), the product extracted into dichloromethane (2x4 cm^3), washed with brine (2x4 cm^3) dried and evaporated to dryness. Chromatography on silica gel with petroleum ether : diethyl ether (2:1) as the eluent yielded **145** as an oil (188 mg, 94%); R_f: 0.75, petroleum ether : diethyl ether (1:1); $[\alpha]_D^{20}$ 19.0° (*c* 1.4, $CHCl_3$); υ_{max} ($CHCl_3$)/cm^{-1} 3070 w, 2930 s, 1595 s, 1110 s, 840 m; δ_H(250 MHz; $CDCl_3$) 0.89 (9H, s, ^{t}Bu), 1.06 (9H, s, ^{t}Bu), 1.18 (3H, s, C1-Me), 1.35 (1H, dd, *J* 7.3, 14.15, 13a-H), 1.40 (1H, dd, *J* 4.1, 14.15, 13b-H), 1.99 (1H, d, *J* 9.8, 10-H), 2.49 (1H, m, 11-H), 3.34 (3H, s, OMe), 3.70 (1H, t, *J* 10.1, 6ax-H), 3.94 (1H, ddd, *J* 5.1, 9.8, 10.1, 7-H), 4.18 (3H, m, 4-H, C*H*$_2$OSi), 4.29 (1H, m, 12-H), 4.36 (1H, dd, *J* 5.0, 10.1, 6eq-H), 5.58 (1H, s, 9-H), 5.53 (1H, s, 4-H), 7.34-7.92 (25H, m, Ph); δ_C (62.9 MHz; $CDCl_3$) 19.6 (2xC, ^{t}Bu), 22.8 (CH_3, C1-Me), 27.4 (CH_3, ^{t}Bu), 27.5 (CH_3, ^{t}Bu), 41.8 (C, C1), 46.9 (CH_2, C13), 49.5 (CH, C11), 52.8 (CH, C10), 55.2 (CH_3, OMe), 59.0 (CH, C7), 63.6 (CH_2, CCH_2OSi), 70.5 (CH_2, C6), 75.3 (CH, C2), 82.8 (CH, C12), 98.9 (CH, C9), 102.3 (CH, C4), 126.8-130.0 (8xCH, Ph), 133.6 (C, Ph), 134.1 (C, Ph), 134.1 (C, Ph), 134.2 (C, Ph), 136.0 (CH, Ph), 136.1 (CH, Ph), 136.3 (CH, Ph), 138.6 (C, Ph); *m/z* (FAB) 825 (M^+-H, 0.1%) 319 (7.4) 257 (9.3) 197 (68.5) 135 (100) (Found : $[M^-H]^+$, 825.4005. $C_{51}H_{61}O_6Si_2$ requires 825.4007).

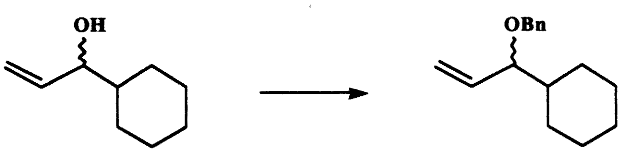
1-Benzoyloxy-1-cyclohexyl-1-hydroxy-prop-2-ene



267 **268**

Cyclohexane carboxaldehyde **267** (5.0 g, 45.00 mol) was dissolved in THF (20.0 cm^3) and stirred at 0 °C. Vinyl magnesium chloride (3.91 g, 45.00 mol) was added dropwise as a 25% w/v solution in THF and the solution allowed to warm to room temperature. The reaction was diluted with diethyl ether (100 cm^3) and quenched by the addition of water (25 cm^3). The organic layer was separated, washed with dilute HCl (25 cm^3) and brine (25 cm^3), dried and evaporated to dryness. Chromatography on silica gel with petroleum ether : ethyl acetate (9:1) as the eluent yielded the alcohol **268** (5.59 g, 89%) as a colourless oil; υ_{max} (film)/cm^{-1} 3360 br m (OH), 2920 s, 2850 s, 1450 m; δ_H(250 MHz; CDCl$_3$) 0.98 (5H, m, 2'-6'$_{ax}$-H), 1.37 (1H, m, 1'-H), 1.68 (5H, m, 2'-6'$_{eq}$-H), 2.05 (1H, d, *J* 3.5, OH), 3.8 (1H, br m, 1-H), 5.12 (2H, 2dd overlapping, *J* 10.4, 1.3, 3_{cis}-H, *J* 17.3, 1.3, 3_{trans}-H), 5.82 (1H, ddd overlapping, *J* 6.6, 10.4, 17.3, 2-H); δ_C (62.9 MHz; CDCl$_3$), 26.2- 30.0 (5CH$_2$, C2'-6'), 43.8 (CH, C1'), 78.1 (CH, C1), 115.7 (CH$_2$, C3), 140.2 (CH, C2).

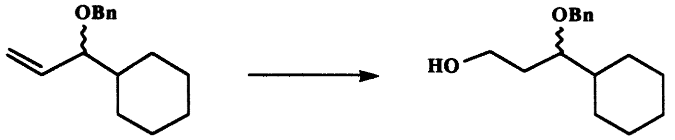
1-Benzyloxy-1-cyclohexyl-prop-2-ene



268 **269**

A solution of the alcohol **268** (635 mg, 4.53 mmol) in THF (20.0 cm^3) was cooled to 0 °C with stirring. Sodium hydride (149 mg, 80% dispersion in mineral oil, 4.98 mmol) was added in portions, and the solution allowed to stir for 1h. Benzyl bromide (1.16 g, 6.80 mmol) was then added dropwise and the solution allowed to stir for a further 2h at room temperature. The solution was then cooled in ice and ethanol (5 cm^3) added, to destroy the excess sodium hydride, and then poured into iced water. The aqueous layer was extracted with diethyl ether (2x50 cm^3), the combined organic layers washed with brine (2x25 cm^3), dried and evaporated to dryness. Chromatography on silica gel with petroleum ether : ethyl acetate (9.5:1) as the eluent yielded **269** as a colourless oil (853 mg, 81%); R_f: 0.7 (Petroleum ether : ethyl acetate 9.5:1); υ_{max} (film)/cm^{-1} 2920s, 1500 w, 1450 m; δ_H (250 MHz; $CDCl_3$) 0.83-0.26 (5H, m, 2'-6'$_{ax}$-H), 1.37-1.48 (1H, m, 1'-H), 1.51-1.69 (5H, m, 2'-6'$_{eq}$-H), 3.37 (1H, t, *J* 7.6, 1-H), 4.25 (1H, d, *J* 12.0, OC*H*HPh), 4.53 (1H, d, *J* 12.0, OC*H*HPh), 5.10 (2H, dd overlapping, *J* 1.9, 17.2, 2a-H), 5.21 (1H, dd, *J* 1.9, 10.4, 2b-H), 7.22-7.28 (5H, m, Ph); δ_C (62.9 MHz; $CDCl_3$) 26.5 -29.7 (5CH_2, C2'-6'), 42.8 (CH, C1'), 70.5 (CH_2, $COCH_2$), 85.8 (CH, C1), 118.4 (CH_2, C3), 127.7-128.1 (3CH, Ph), 138.2 (CH, C8), 139.4 (C, Ph); *m/z* (EI) 230 (M^+, 0.9%), 147 (M^+,-C_6H_{11}) (13.6), 139 (M^+,- OBn) (3.3), 91 (C_7H_7) (100) (Found : M^+, 230.1671. $C_{16}H_{22}0$ requires 230.1671).

1-Benzyloxy-1-cyclohexyl-propan-3-ol

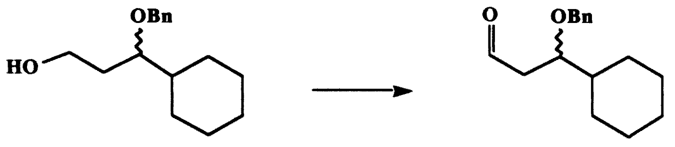


269 **270**

To a solution of **269** (70 mg, 0.30 mmol) in THF (1.0 cm^3) was added 9'BBN (1.5 cm^3, 1.50 mmol) dropwise with cooling. The resulting solution was warmed to 40 °C and held at this temperature for 2h with stirring. The reaction was quenched by the addition of sodium acetate (2 cm^3, 1M solution) and oxidised by the addition of sodium hydroxide (3 cm^3, 6N solution) and hydrogen peroxide (3 cm^3, 20% w/v solution in water) and allowed to stir overnight. The resulting solution was diluted with diethyl ether (50 cm^3), washed with brine (2x20 cm^3), the combined organic layers were dried and evaporated to dryness.

Chromatography on silica gel with petroleum ether : ethyl acetate (9:1) as eluent yielded the primary alcohol **270** (56 mg, 75%) as a colourless oil; υ_{max} (film)/cm^{-1} 3320 br m (OH), 2920 s, 1500 w, 1450 m; δ_H (250 MHz; $CDCl_3$) 0.80-1.20 (5H, m, 2'-6'$_{ax}$-H), 1.30-1.70 (6H, m, 2-H, 2'-6'$_{eq}$-H), 3.28 (1H, br dd, *J* 12.0, 5.35, 1-H), 3.62 (2H, m, 3-H), 4.36 (1H, d, *J* 11.3, OC*H*HPh), 4.46 (1H, d, *J* 11.3, OCH*H*Ph), 7.22 (5H, m, Ph); δ_C (69.2 MHz; $CDCl_3$) 23.1 (CH_2, C2), 26.1-35.1 (CH_2, C2'-6'), 41.0 (CH, C1'), 61.3 (CH_2, C3), 72.2 (CH_2, OCH_2Ph), 83.3 (CH, C1), 128.1 (CH, Ph), 128.3 (CH, Ph), 128.9 (CH, Ph), 138.9 (C, Ph); *m/z* (EI) 248 (M^+, 1.1%), 230 (M^+,- H_2O) (5), 203 (M^+,-C_2H_5O) (1), 165 (M^+,-C_6H_{11}) (6.1), 91 (C_7H_7) (100) (Found : M^+, 248.1776. $C_{16}H_{24}O_2$ requires 248.1776).

1-Benzyloxy-1-cyclohexyl-propan-3-al

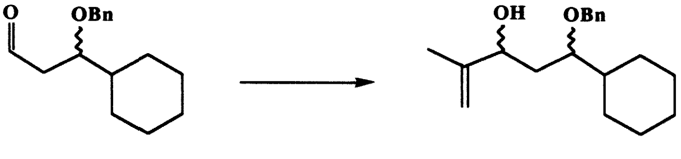


270 **271**

To a stirred solution of oxalyl chloride (3.62 cm^3, 28.50 mmol) in dichloromethane (10.0 cm^3) at -78 °C was added dimethyl sulphoxide (4.46 cm^3, 28.50 mmol) in dichloromethane (10.0 cm^3) dropwise under an atmosphere of nitrogen. After allowing the solution to stir for 0.25h a solution of the alcohol **270** (2.36 g, 9.50 mmol) in dichloromethane (10 cm^3) was added dropwise and the solution allowed to stir for 1h. Triethylamine (15.9 cm^3, 0.11 mol) was then added and the solution allowed to warm to room temperature. The reaction was diluted with diethyl ether (50 cm^3), the combined organic layers washed with brine (2x75 cm^3) and water (75 cm^3), dried and evaporated to dryness. Chromatography on silica gel with petroleum ether : ethyl acetate (95:5) as eluent yielded the aldehyde **271** as a colourless oil (1.06 g, 67%); Rf:0.65 (petrol-ethyl acetate 9:1); υ_{max} (film)/cm^{-1} 2920s, 1750m (CO), 1500w, 1450m; δ_H (250 MHz; $CDCl_3$) 0.70-1.30 (5H, m, 2'-6'ax-H), 1.10-1.70 (5H, m, 2'-6'eq-H), 2.35 (1H, ddd, *J* 16.4, 4.4, 1.9, 2a-H), 2.48 (1H, ddd, *J*16.4, 7.55, 2.36, 2b-

H), 3.58 (1H, overlapping dt, *J* 7.6, 4.7, 1-H), 4.32 (1H, apparent d, *J* 11.6, OC*H*HPh), 4.39 (1H, apparent d, *J* 11.3, OCH*H*Ph), 7.1-7.15 (5H, br m, Ph), 9.62 (1H, brt, *J* 2.2, 3-H); δ_C (62.9 MHz; $CDCl_3$), 26.1 (CH_2, C2'-C6'), 41.9 (CH, C1'), 46.0 (CH_2, C2), 72.3 (CH_2, OCH_2Ph), 79.1 (CH, C1), 128.1 (2CH, CHPh), 138.8 (C, Ph), 202.5 (CH, C3); *m/z* (EI) 246 (M^+, 0.2%), 217 (M^+,- CHO) (0.2), 91 (C_7H_7) (100), (Found : M^+, 246.1620. $C_{16}H_{22}O_2$ requires 246.1620).

1-Benzyloxy-1-cyclohexyl-3-hydroxy-4-methyl-pent-4-ene

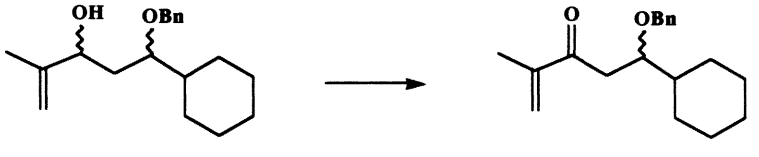


271 **272**

2-bromopropene (450 mg, 3.72 mmol) in dry THF (1.0 cm^3) was added dropwise to magnesium turnings (95 mg, 3.91 mmol) in dry THF (1.0 cm^3). When the initiation of the reaction was complete a gentle reflux was maintained by the addition of the bromide. The solution was then heated to reflux for 1h. The freshly prepared Grignard reagent was then added dropwise at 0 °C to the aldehyde **271** (643 mg, 2.23 mmol). The reaction was quenched by the addition of water (5.0 cm^3), diluted with diethyl ether (50 cm^3), the combined organic layers washed with brine (2x15 cm^3) and water (25 cm^3), dried and evaporated to dryness. Chromatography on silica gel with petroleum ether : ethyl acetate (80:20) as eluent yielded the allylic alcohol **272** as a colourless oil (643 mg, 60%) as a ratio of 2 : 1; Rf: 0.65, 0.70 (petroleum : ethyl acetate 4:1); **272** (minor isomer) υ_{max} (film)/cm^{-1} 3460 br m (OH), 2920 s, 1500 w, 1450 m, 1140 br m; δ_H (250 MHz; $CDCl_3$) 0.60-1.20 (5H, m, 2'ax-H, 6'ax-H), 1.30-1.70 (11H, m, 1'-H, 2'-6'eq-H, 2a-H, 8b-H,C*H*$_3$CH-H), 2.72 (1H, br s, OH), 3.31 (1H, m, 1-H), 4.09 (1H, br m, 3-H), 4.33 (1H, d, *J* 11.0, OC*H*HPh), 4.40 (1H, d, *J* 11.0, OCH*H*Ph), 4.67 (1H, s, 5a-H), 4.85 (1H, s, 5b-H), 7.1-7.2 (5H, m, Ph); δ_C (62.9 MHz; $CDCl_3$), 19.1 (CH_3, CH_3CH), 26.7 - 29.9 ($5CH_2$, C2'-C6'), 35.3 (CH_2, C6), 41.0 (CH, C1'), 72.4 (CH_2, OCH_2Ph), 73.0 (CH, C6), 81.9 (CH, C1), 110.4 (CH_2, C5), 128.1 (CH, Ph), 128.3 (CH, Ph), 128.8 (CH, Ph), 138.9 (C, Ph), 148.1 (C, C4); *m/z* (EI) 288 (M^+, 0.1%), 270 (M^+,- H_2O) (0.3), 108 (BnOH) (0.5), 91 (C_7H_7) (100), (Found : M^+, 288.2089. $C_{19}H_{28}O_2$ requires 288.2089);

272 (major isomer) υ_{max} (film)/cm^{-1} 3460 br m (OH), 2920 s, 1500 w, 1450 m, 1140 m; δ_H (250 MHz; $CDCl_3$) 0.80-1.35 (5H, m, 2'-6'ax-H), 1.5-1.83 (11H, m, 1'-H, 2'-6'eq-H, 2a-H, 2b-H, C*H*$_3$CH), 3.48 (2H, m, 1-H, OH), 4.18 (1H, m, 3-H), 4.40 (1H, d, *J* 11.00, OC*H*HPh), 4.61 (1H, d, *J* 11.00, OCH*H*Ph), 4.76 (1H, s, 5a-H), 4.91 (1H, s, 5b-H), 7.28- 7.3 (5H, m, Ph); δ_C (62.9 MHz; $CDCl_3$), 18.2 (CH_3, *C*H$_3$CH), 26.8-29.6 (5CH_2, C2'-C6'), 36.3 (CH_2, C2), 40.8 (CH, C1'), 71.8 (CH_2, O*C*H$_2$Ph), 76.1 (CH, C1), 84.7 (CH, C3), 111.2 (CH_2, C5), 128.2 (CH, Ph), 128.3 (CH, Ph), 128.9 (CH, Ph), 138.6 (C, Ph), 147.7 (C, C10); *m/z* (EI) 288 (M^+, 0.1%), 270 (M^+,- H_2O) (0.3), 108 (BnOH) (2.8), 91 (C_7H_7) (100), (Found : M^+, 288.2089. $C_{19}H_{28}O_2$ requires 288.2089).

1-Benzyloxy-1-cyclohexyl-4-methyl-pent-4-en-3-one

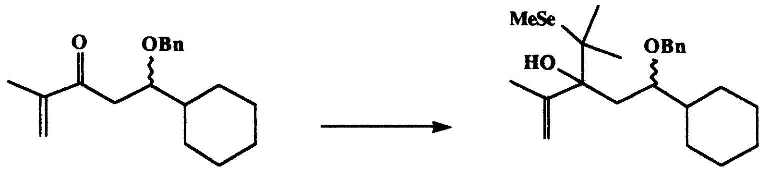


272 **273**

To a stirred solution of oxalyl chloride (0.9 cm^3, 1.04 mmol) in dichloromethane (3.0 cm^3) at -78 °C was added dimethyl sulphoxide (0.15 cm^3, 2.08 mmol) in dichloromethane (3.0 cm^3) dropwise under an atmosphere of nitrogen. After allowing the solution to stir for 0.25h a solution of the alcohol **272** (100 mg, 0.35 mmol) in dichloromethane (2.0 cm^3) was added dropwise and the solution allowed to stir for 1h. Triethylamine (0.6 cm^3, 4.20 mmol) was then added and the solution allowed to warm to room temperature. The reaction was diluted with diethyl ether (15 cm^3), the combined organic layers washed with brine (2x15 cm^3) and water (15 cm^3), dried and evaporated to dryness. Chromatography on silica gel with petroleum ether : ethyl acetate (98:2) as eluent yielded the enone **273** as a colourless oil (63 mg, 63%); R_f:0.65 (petroleum : ethyl acetate 9.5:1); υ_{max} (film)/cm^{-1} 2920s, 1750s

(CO), 1500 w, 1450 m, 1140 br m; δ_H (250 MHz; $CDCl_3$) 0.80-1.20 (5H, m, 2'-6'ax-H), 1.35-1.70 (5H, m, 1'-H, 2'-6'eq-H), 1.75 (3H, s, CH_3CH), 2.58 (1H, dd, *J* 16.1, 4.1, 2a-H), 2.90 (1H, dd, *J* 16.0, 7.9, 2b-H), 3.72 (1H,overlapping dt, *J* 7.9, 4.1, 1-H), 4.36 (2H, s, OCH_2Ph), 5.64 (1H, s, 5a-H), 5.83 (1H, s, 5b-H), 7.12 (5H, m, Ph); δ_C (62.9 MHz; $CDCl_3$), 18.1 (CH_3, CH_3CH), 26.8 - 29.2 (4CH_2, C2'-C6'), 40.4 (CH_2, C2), 42.7 (CH, C1'), 73.0 (CH_2, OCH_2Ph), 80.8 (CH, C1), 125.4 (CH_2, C5), 127.8 (CH, Ph), 128.1 (CH, Ph), 128.6 (CH, Ph), 139.3 (C, Ph), 145.4 (C, C4), 201.5 (CO, C3); *m/z* (EI) 287 (MH^+), 180 (MH^+,- OBn) 91 (C_7H_7) (100), (Found :: M^+, 286.1933. $C_{19}H_{26}O_2$ requires 286.1933).

1-Benzyloxy-1-cyclohexyl-3-hydroxy-4-methyl-3-(1'-methyl-1'-methylselenoethyl)-pent-4-ene

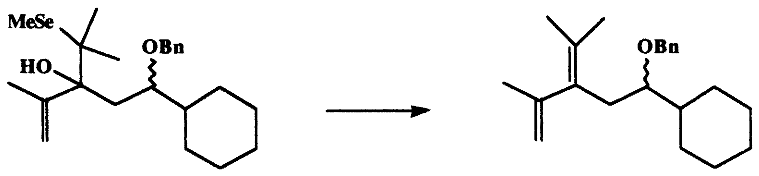


273 **273a**

A solution of the acetal 2-(*bis*-methyl seleno) propane (230 mg, 1.00 mmol) in ether (1.0 cm^3) was stirred at -78 °C under an atmosphere of argon. s-BuLi (0.77 cm^3, 1.00 mmol) in ether (1.0 cm^3) was added dropwise and allowed to stir for 1h. The enone **273** (288 mg, 1.00 mmol) in ether (1.0 cm^3) was then added and the solution allowed to stir for 0.5h. The reaction was quenched by the addition of water (5.0 cm^3), diluted with diethyl ether (15 cm^3) and the combined organic layers washed with brine (2x10 cm^3) and water (15 cm^3), dried and evaporated to dryness. Chromatography on silica gel with petroleum ether : ethyl acetate (80:20) as eluent yielded the alcohols **273a** as a colourless oil (382 mg, 90%) in a ratio of 2 : 1; Rf:0.65, (petroleum : ethyl acetate 4:1); (mixture of isomers) υ_{max} (film)/cm^{-1} 3450 br m (OH), 2920 s, 1450 m, 1140 br m, 900 w; δ_H (250 MHz; $CDCl_3$) 0.90-1.30 (10H, m, 2'-6'ax-H), 1.39-1.5 (12H, 4s, $MeSeC(CH_3)_2$, major and minor), 1.60-1.90

(12H, m, 1-H, 2'-6'eq-H, major and minor), 1.84 (3H, s, *C*H$_3$CH, major), 1.85 (3H, s, CH$_3$CH, minor), 1.94 (3H, s, Se-Me major), 1.99 (3H, s, Se-Me minor), 2.06 (4H, m, 2a and 2b-H, major and minor), 2.95 (1H, s, OH), 3.5 (1H, m, 1'-H minor), 3.51 (1H, m, 1'-H major), 4.30 (1H, d, *J* 10.7, OC*H*HPh major) 4.41 (2H, br s, OC*H*$_2$Ph minor), 4.56 (1H, d, *J* 10.7, OCH*H*Ph major), 4.80 (1H, s, 5a-H major), 5.01 (1H, brs, 5b-H minor), 5.12 (2H, brs, 5b-H minor and major), 7.3 (10H, m, Ph, major and minor); δ_C (62.9 MHz; CDCl$_3$), 3.7 (CH$_3$, CH*C*H$_3$ major), 4.5 (CH$_3$, CH*C*H$_3$ minor), 23.3 (CH$_3$, C(*Me*)SeMe, minor), 23.5 (CH$_3$, C(*Me*)SeMe, major), 26.0 (CH$_3$, C(Me)*Me*, minor), 26.2 (CH$_3$, C(Me)*Me*, major), 26.4-30.0 (10CH$_2$, C2'-C6', major and minor), 37.8 (CH$_2$, C2), 40.7 (CH, C1', major), 42.3 (CH$_3$, C1', minor), 51.6 (C, C(Me)$_2$, minor), 55.9 (C, C(Me)$_2$, major), 71.3 (CH$_2$, O*C*H$_2$Ph, major), 72.1 (CH$_2$, O*C*H$_2$Ph, minor), 81.0 (C, C3, major), 81.4 (C, C3, minor), 83.2 (CH, C1, major), 82.6 (CH, C1, minor), 114.6 (CH$_2$, C5, major), 115.3 (CH$_2$, C5, minor), 127.6-128.9 (6CH, Ph, major and minor), 138.1(C, Ph, major), 139.6 (C, CPh, minor), 146.5 (C, C4, major), 147.9 (C, C4, minor); *m/z* (EI) 424 (M$^+$, 1.3%), 287 (M$^+$- C$_6$H$_{10}$Se) (40.3), 91 (C$_7$H$_7$) (100), (Found :: M$^+$, 424.1881. C$_{23}$H$_{36}$O$_2$Se requires 424.1881).

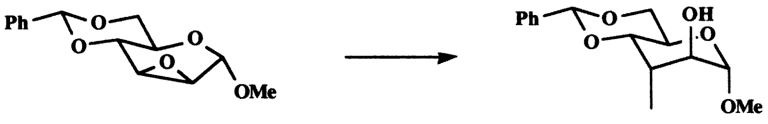
1-Cyclohexyl-4-methyl-1-3-(2-propylidene)-pent-3-ene



273a **274**

To a stirred solution of phosphorus (III) iodide (430 mg, 1.04 mmol) in dichloromethane (3.0 cm^3) at 0 ^{o}C was added a solution of the alcohol **273a** (380 mg, 0.90 mmol) in dichloromethane (3 cm^3) and triethylamine (0.25 cm^3, 2.47 mmol) dropwise under an atmosphere of nitrogen. The reaction was diluted with diethyl ether (15 cm^3) and the combined organic layers washed with brine (2x15 cm^3) and water (15.cm^3), dried and evaporated to dryness. Chromatography on silica gel with petroleum ether : ethyl acetate (98:2) as eluent yielded the diene **274** as a colourless oil (341 mg, 90%); R_f:0.65 (petroleum : ethyl acetate 4:1); υ_{max} (film)/cm^{-1} 2920 m, 1450 w, 1100 w; δ_H (250 MHz; $CDCl_3$) 1.10-1.30 (5H, m, 2'-6'ax-H), 1.40-1.55 (1H, m, 1'-H), 1.60-1.80 (5H, m, 2'-6'eq-H), 1.70 (3H, s, $CC\mathit{H}_3CH_3$), 1.71 (3H, s, $CCH_3C\mathit{H}_3$), 1.75 (3H, s, $C\mathit{H}_3C$-H), 2.24 (1H, dd, *J* 5.0, 14.16, 2a-H), 2.44 (1H, dd, *J* 7.6, 14.2, 2b-H), 3.27 (1H, dt, J 4.7, 7.6, 1-H), 4.43 (2H, apparent d, *J* 11.3, $OC\mathit{H}HPh$), 4.51 (1H, apparent d, *J* 11.7, $OCH\mathit{H}Ph$), 4.55 (1H, s, 5a-H with some fine splitting), 4.97 (1H, s, 5b-H with some fine splitting), 7.32 (5H, m, Ph); δ_C (62.9 MHz; $CDCl_3$), 21.3 (CH_3, $\mathit{C}H_3C$), 23.1 (CH_3, $C\mathit{C}H_3CH_3$), 23.8 (CH_3, $CCH_3\mathit{C}H_3$), 27.6-30.7 ($5CH_2$, C2', C6'), 33.9 (CH_2, C2), 42.7 (CH, C1'), 73.4 (CH_2, $O\mathit{C}H_2Ph$), 83.7 (CH, C1), 115.0 (CH_2, C5), 128.1-129.1 (3CH, Ph), 135.2 (C, C4), 140 .6 (C, C3), 147.3 (C, Ph); *m/z* (EI) 312 ($M^{+\cdot}$ 0.1%) 205 (20.0) 123 (7.0) 108 (22.0) 91 (100) (Found :: M^+, 312.2453. $C_{22}H_{32}O$ requires 312.2453).

Methyl 4,6-*O*-benzylidene-3-deoxy-3-*C*-methyl-α-D-altropyranoside

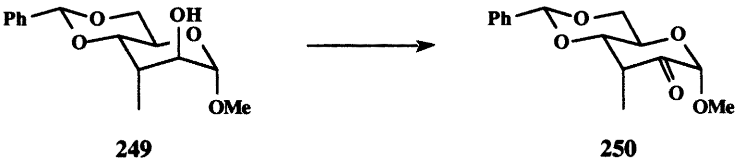


56 **249**

To a suspension of the epoxide **56** (50.0 g, 0.19 mol) in dry THF (200 cm^3) was added methylmagnesium chloride (3M solution in THF, 315.3 cm^3, 0.95 mol) dropwise while cooling the reaction flask in ice. The reaction mixture was then heated under gentle reflux, under an atmosphere of nitrogen for 5h, then stirred at room temperature overnight. The reaction was quenched by the addition of water (150 cm^3) dropwise, cautiously, while cooling the flask in ice. The reaction was diluted with diethyl ether (350 cm^3), the combined organic layers washed with brine (2x150 cm^3) and water (150 cm^3), dried and evaporated to dryness to give a thick oil. The oil was then redissolved in ether and petroleum ether added until the solution became cloudy and this solution was concentrated under reduced pressure to give a white solid. This solid was dissolved in diethyl ether and petroleum ether again added until the solution became cloudy, the solution was concentrated under reduced pressure to approximately half volume and the product precipitated out of solution to give **249** as a white crystalline solid (38.13 g, 72%) m.p. 114 - 116°C (lit.,[25] 115°C); δ_H(90 MHz; $CDCl_3$) 1.23 (3H, d, *J* 7.5, C3-Me), 2.10 (1H, br s, OH), 2.35 (1H, br m, 3-H), 3.38 (3H, s, OMe), 3.65-4.40 (5H, m, 2-H, 4-H, 5-H, 6ax-H, 6eq-H), 4.57 (1H, s, 1-H), 5.60 (1H, s, 10-H), 7.27-7.57 (5H, m, Ph).

This is a literature compound and method.[25]

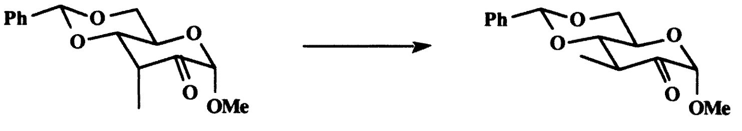
Methyl 4,6-*O*-benzylidne-3-deoxy-3-*C*-methyl-α-D-ribo-hexopyranosid-2-ulose



Trifluoroactetic anhydride (15.1 cm^3,0.11 mol) in dry dichloromethane (40.0 cm^3) was added dropwise to a cooled solution of dimethylsulphoxide (10.1 cm^3, 0.43 mol) in dry dichloromethane (144 cm^3), under an atmosphere of nitrogen. Once addition was complete this mixture was stirred for 20 minutes at -65 °C, then a solution of **249** (20.0 g, 71.35 mmol) in dry dichloromethane (20.0 cm^3) was added slowly dropwise, keeping the mixture at -65 °C. Once the addition was complete the reaction was stirred for a further 1.5h at -65 °C under nitrogen. Triethylamine (28.8 cm^3, 0.21 mol) was then added dropwise and the solution allowed to warm to room temperature. The reaction was diluted with dichloromethane (400 cm^3) and this solution washed with 1M aqueous hydrochloric acid (2x200 cm^3) followed by saturated aqueous sodium hydrogen carbonate (2x200 cm^3) and the saturated aqueous sodium chloride (200 cm^3). The dichloromethane layer was dried and evaporated to dryness to give a yellow oil (20.2 g, >100%) which was used without any further purification in the next step.

This is a literature compound and method.[25]

Methyl 4,6-*O*-benzylidne-3-deoxy-3-*C*-methyl-α-D-*arabino*hexopyranosid-2-ulose

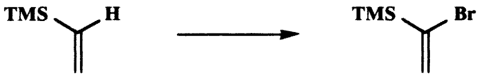


249 **118**

To a solution **249** (19.86 g, 71.35 mmol) in dry *N,N*-dimehtylformamide (62.0 cm^3) was added triethylamine (31.0 cm^3, 0.22 mol) and the reaction was stirred at room temperature for 3 days. The reaction was diluted with dichloromethane (200 cm^3) and this solution washed with 1M aqueous hydrochloric acid (2x100cm^3), saturated aqueous sodium hydrogen carbonate (2x200cm^3) and finally saturated aqueous sodium chloride (200 cm^3). The dichloromehtane layer was dried and evaporated to dryness to give a brown solid. Chromatography on silica gel with petroleum : ethyl acetate (80:20) as eluent yielded **118** as a white crystalline solid (12.22 g, 61%); m.p. 124 - 125°C (lit.,[25] 125.5 - 126°C); δ_H(300 MHz; CDCl$_3$) 1.25 (3H, d, *J* 6.4, C3-Me), 3.09 (1H, t, *J* 12.8, 3-H), 3.46 (1H, dd, *J* 9.2, 11.4, 4-H), 3.52 (3H, s, OMe), 3.79 (1H, t, *J* 10.3, 6ax-H), 4.25 (1H, dt, *J* 5.0, 9.7, 5-H), 4.41 (1H, dd, *J* 5.0, 10.4, 6eq-H), 4.66 (1H, s, 1-H), 5.55 (1H, s, 10-H), 7.41-7.54 (5H, m, Ph); δ_C (75 MHz, CDCl$_3$) 8.79 (CH$_3$, C3-Me), 46.2 (CH, C3), 55.6 (CH$_3$, OMe), 64.2 (CH, C5), 69.0 (CH$_2$, C6), 82.53 (CH, C4), 100.7 (CH, C1), 101.3 (CH, C10), 126.1 (CH, Ph), 128.3 (CH, Ph), 129.1 (CH, Ph), 138.0 (C, Ph), 200.8 (C, C2).

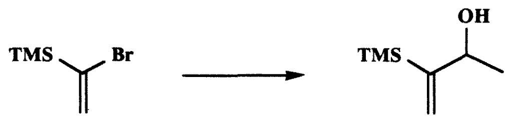
This is a literature compound and method.[25]

1-(Bromovinyl)trimethylsilane



Trimethylsilane (50.0 g, 0.50 mol) was cooled to -70 °C (dry ice acetone bath) and bromine (28.4 cm^3, 0.55 mol) added dropwise over 1.5h. The mixture was then allowed to slowly warm to room temperature and the pale yellow solution cooled in ice. To this solution was added diethylamine (300 cm^3, 2.90 mol) dropwise. Once the addition was complete the pale yellow suspension was heated under gentle reflux (60 °C) overnight. The thick suspension was cooled to room temperature and the precipitate of diethylamine hydrobromide removed by filtration and the solid washed with diethyl ether (3x100 cm^3). The ether filtrate was washed with 100 cm^3 portions of 10% aqueous hydrochloric acid until the aqueous layer remained acidic. When the wash was complete and the aqueous layer remained acidic, the yellow/orange colour of the organic phase transferred to the aqueous phase. The ether layer was then washed with water (100 cm^3) followed by saturated aqueous sodium chloride (200 cm^3). The ether layer was dried and the ether then removed from the solution by distillation at atmospheric pressure. The remaining pale yellow solution containing the product was distilled under reduced pressure. The bromide was obtained as a clear colourless liquid which was light sensitive (68.37 g, 77%), bp.: 48-50 °C at 50 mbar; δ_H(90 MHz; $CDCl_3$) 0.15 (9H, s, $Si(CH_3)_3$), 6.6 (1H, d, *J*, 1.5-2.0, vinyl H) 6.70 (1H, d, *J* 1.5-2.0, vinyl H). This is a literature compound and method.[103]

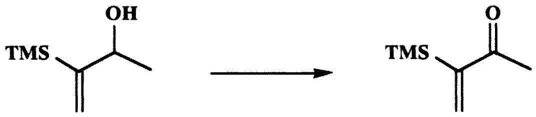
2-Trimethylsilyl-3-buten-2-ol



To a suspension of magnesium turnings (6.48 g, 0.28 mol) in dry THF (35.0 cm^3) under an atmosphere of nitrogen, was added a few drops of iodomethane and approximately 2.0 - 3.0 cm^3 of a solution of the bromide (36.0 g, 0.20 mol) in dry THF (51.5 cm^3). Once the reaction was initiated, the remainder of the bromide solution was added dropwise while maintaining a gentle reflux. When addition was complete the reaction was heated under reflux for a further hour. The reaction was then cooled in an ice bath and a solution of acetaldehyde (23.1 cm^3, 0.41 mol) in dry THF (18.0 cm^3) added dropwise with stirring. The reaction was then heated under reflux at 70 °C for 1h then the THF removed by distillation at atmospheric pressure. The reaction was cooled in ice and diluted with diethyl ether (100 cm^3). This mixture was quenched by adding saturated aqueous ammonium chloride (50 cm^3) dropwise while cooling the flask in ice. The ethereal solution was decanted from the resulting white solid, then the solid washed with ether (100 cm^3). The ether solution and wash were combined, washed with saturated aqueous sodium chloride (100 cm^3), dried and the ether (and some THF) removed by distillation at atmospheric pressure, leaving the crude product as a yellow liquid (Yield: >100%).

This is a literature compound and method.[103]

3-Trimetylsilyl-3-buten-2-one

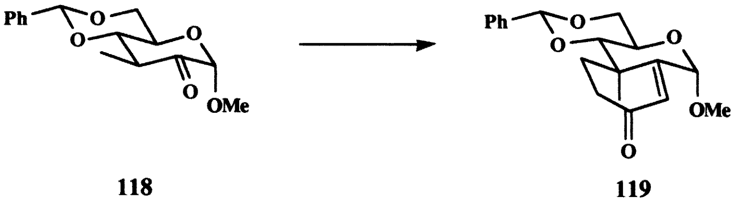


To a cooled (0 °C, ice bath) solution of the allylic alcohol in acetone (345 cm^3) was added Jones' reagent (45.0 cm^3). The solution changed from yellow to green and finaly red/brown at the end point. After addition was complete the reaction was stirred at 0 °C for 0.5h then saturated aqueous sodium metabisulphite (50.0 cm^3) added to destroy any excess chromic acid. Water (150 cm^3) and diethyl ether (300 cm^3) were added and the reaction stirred until the Cr^{3+} salts dissolved. The aqueous and ether layers were separated and the aqueous layer washed with ether (2x150 cm^3). The ether layer and washes were combined, washed with water (3x150 cm^3), then 10% aqueous potassium carbonate (4x150 cm^3) and finally saturated aqueous sodium chloride (2x150 cm^3). The ether layer was dried and the ether removed on a rotary evaporator at atmospheric pressure, water bath temperature 40 °C. The last traces of ether were removed by distillation under reduced pressure. The remaining yellow liquid was distilled using Kugelrohr apparatus to give a pale yellow liquid.

δ_H(90 MHz; $CDCl_3$) 0.00 (9H, s, $SiMe_3$), 2.20 (3H, s, CH_3), 6.03 (1H, s, $SiMe_3$-C=CH_aH_b), 6.37 (1H, s, $SiMe_3$-C=CH_aH_b).

This is a literature compound.[103]

(1*R*, 2*S*, 4*R*, 7*R*, 9*S*,)-9-methoxy-1-methyl-4-phenyl-3,5,8-trioxatricyclo[8.4.0.0^{2,7}]tetradec-10-en-12-one



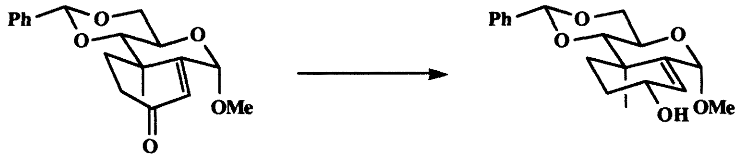
118 **119**

To a cooled solution of the ketone **118** (2.9 cm^3, 17.27 mmol) in dry THF (20.0 cm^3) was added sodium hexamethyl disilazide (17.27 cm^3, 17.27 mmol) dropwise and the reaction stirred at 0 °C under nitrogen for 1h. 3-trimethylsilyl-3-buten-2-one (3.44 g, 24.18 mmol) was then added dropwise and the solution allowed to warm to room temperature and stirred for a further 1h under nitrogen. The mixture was poured into water (250 cm^3) and extracted into ether (3x200 cm^3). Each ether extract was washed with saturated aqueous sodium chloride (75.0 cm^3), then the ether extracts combined, dried and evaporated to dryness to give a deep yellow oil (5.8 g), which was used without any further purification in the next step.

A solution of the intermediate in methanol (96 cm^3) containing 4% solution potassium hydroxide (11.5 cm^3, 8.12 mmol) was heated at 80 °C for 2h. The methanol was removed under reduced pressure, the residue dissolved in ether (200 cm^3),.washed with saturated aqueous sodium chloride (2x100 cm^3), dried and evaporated to dryness. Chromatography on silica gel with petroleum ether : ethyl acetate (4:1) as eluent yielded the enone **119** as an off-white foam (3.86 g, 68%); δ_H(300 MHz; CDCl$_3$) 1.49 (3H, s, C1-CH$_3$), 1.88 (1H, br dt, *J* 5.0, 14.1, 14a-H), 2.26 (1H, ddd, *J*, 2.6, 5.0, 13.5, 14b-H), 2.45 (1H, dddd, *J* 0.7, 2.5, 5.0, 17.6, 13a-H), 2.56 (1H, ddd, *J* 5.0, 14.6, 17.6, 13b-H), 3.38-3.41 (1H, obscured d, 2-H, 3H, s, OCH$_3$), 3.72 (1H, t, *J* 10.2, 6a-H), 4.20 (1H, dt, *J* 5.2, 9.7, 7-H), 4.35 (1H, dd, *J* 5.2, 10.2, 6b-H), 4.89 (1H, s, 9-H), 5.55 (1H, s, 4-H), 5.87 (1H, s, 11-H), 7.33-7.49 (5H, m, Ph); δ_C (75 MHz; CDCl$_3$) 16.6 (CH$_3$, C1-Me), 33.5 (CH$_2$, C14), 34.6 (CH$_2$, 13), 37.8 (C, C-1), 55.2 (CH$_3$, OCH$_3$), 59.7 (CH, C7), 69.1 (CH$_2$, C6), 85.3 (CH, C2), 10.4 (CH, C4 and C9), 126.0 (CH, Ph), 127.2 (CH, Ph), 128.0 (CH, Ph), 128.9 (CH, C11), 137.3 (C, Ph), 158.0 (C, C10), 198.6 (C, C12).

This is a literature compound.[1a]

(1*R*,2*S*,4*R*,7*R*,9*S*,12*R*)-12-hydroxy-9-methoxy-1-methyl-4-phenyl-3,5,8-trioxatricyclo[8.4.0.0^{2,7}]tetradec-10-ene

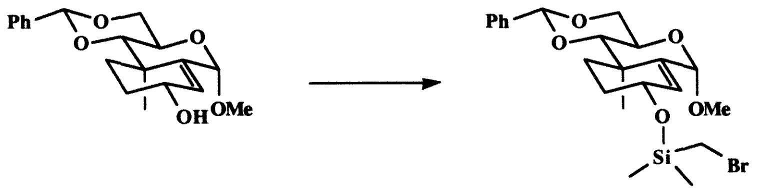


119 **120**

A solution of **119** (3.94 g, 11.92 mmol) in dry THF (58.0 cm^3) was cooled to -78 °C under nitrogen. To this solution was added L-Selectride® (1 M in THF, 11.92 cm^3, 11.92 mmol) and the reaction was then stirred at -78 °C for 1.5h. The reaction was allowed to warm to room temperature, then water (70.0 cm^3) was added and the reaction stirred at room temperature for 1h. The reaction was extracted with diethyl ether (2x200 cm^3) and each extract washed with saturated aqueous soldium chloride (100 cm^3). The combined ether extracts were dried and concentrated under reduced pressure to give a yellow oil. Chromatography on silica gel with petroleum ether : ethyl acetate (60:40) as eluent yielded the diene **120** as a white foam (2.96 g, 75%); δ_H(300 MHz; CDCl$_3$) 1.40 (3H, s, C1-CH$_3$) overlapping with 1.43-1.52 (1H, m) overlapping with 1.56 (1H, tdd, *J* 14.3, 9.5, 2.5), 1.73 (1H, br s, OH), 1.89-1.97 (1H, m), 2.01-2.09 (1H, m), 3.27 (1H, d, *J* 9.5, 2-H), 3.38 (3H, s, OCH$_3$), 3.68 (1H, t, *J* 10.2, 6ax-H), 4.12 (1H, dt, *J* 5.0, 9.7, 7-H), 4.23 (1H, br t, *J* 5.0, 12-H), 4.30 (1H, dd, *J* 5.0, 10.2, 6eq-H), 4.78 (1H, s, 9-H), 5.51 (1H, s, 4-H), 5.72 (1H, s, 11-H), 7.31-7.49 (5H, m, Ph); δ_C (75 MHz; CDCl$_3$) 18.9 (CH$_3$, C1-Me), 28.2 (CH$_2$, C14), 34.4 (CH$_2$, C13), 37.3 (C, C1), 54.9 (CH$_3$, OCH$_3$), 60.4 (CH, C7), 67.4 (CH, C2), 69.6 (CH$_2$, C6), 86.7 (CH, C12), 101.5 (CH, C9), 103.3 (CH, C4), 126.1 (CH, Ph), 128.1 (CH, Ph), 128.9 (CH, Ph), 131.7 (CH), 137.8 (C), 139.3 (C).

This is a literature compound and method.[1a]

(1*R*,2*S*,4*R*,7*R*,9*S*,12*R*)-12[(Bromomethyl)dimethylsiloxy]9-methoxy-1-methyl-4-phenyl-3,5,8-trioxatricyclo[8.4.0.0^{2,7}]tetradec-10-ene

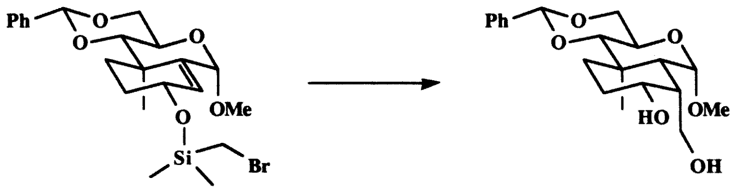


120 **121**

To a solution of **120** (5.37 g, 16.14 mmol) in dry dichloromethane (67.0 cm^3) and triethylamine (4.1 cm^3, 29.04 mmol) was added (bromomethyl)chlorodimethylsilane (2.4 cm^3, 17.76 mmol) over 5 minutes dropwise. The reaction was stirred under nitrogen at room temperature for 2.5h. The reaction was poured into water (150 cm^3) and extracted with dichloromethane (2x75.0 cm^3) the combined organic layers were washed with saturated aqueous sodium chloride solution, dried and evaporated to dryness. Chromatography on silica gel with petroleum ether : ethyl acetate (60:40) as eluent yielded the silyl bromide **121** as a pale yellow oil (7.91 g, 100%); δ_H(300 MHz; $CDCl_3$) 0.35 (6H, $SiMe_2$), 1.46 (3H, s, C1-CH_3) overlapping with 1.48 (1H, br m, 13a-H), 1.74 (1H, br m, 13b-H), 1.97 (2H, br m, 14-H), 2.47 (2H, s, CH_2Br), 3.30 (1H, d, *J* 10.00, 2-H), 3.45 (3H, s, OCH_3), 3.72 (1H, t, *J* 10.1, 6ax-H), 4.15 (1H, dt, *J* 5.1, 10.1, 7-H), 4.35 (1H, dd, *J* 5.1, 10.1, 6eq-H) overlapping with 4.45 (1H, ddd, *J* 3.5, 8.1, 9.3, 12-H), 4.80 (1H, s, 9-H), 5.57 (1H, s, 4-H), 5.69 (1H, br s, 11-H), 7.40-7.60 (5H, m, Ph); δ_C (75 MHz; $CDCl_3$) -2.42 (CH3, $SiMe_2$), 16.2 (CH_3, C1-Me), 18.9 (CH_2, CH_2Br), 28.13 (CH_2, C14), 34.4 (CH_2, C13), 37.2 (C, C1), 54.9 (CH_3, OCH_3), 60.3 (CH, C7), 68.6 (CH, C2), 69.6 (CH_2, C6), 86.3 (CH, C12), 101.5 (CH, C9), 103.3 (CH, C4), 126.1 (CH, Ph), 128.1 (CH, Ph), 128.8 (CH, Ph), 131.9 (CH), 137.8 (C), 138.8 (C).

This is a literature compound and method.[57]

(1*R*,2*S*,4*R*,7*R*,9*S*,10*R*,11*R*,12*R*)-11-Hydroxymethyl-9-methoxy-1-methyl-4-phenyl-3,5,8-trioxatricyclo[8.4.0.$0^{2,7}$]tetradecan-12-ol



121 **123**

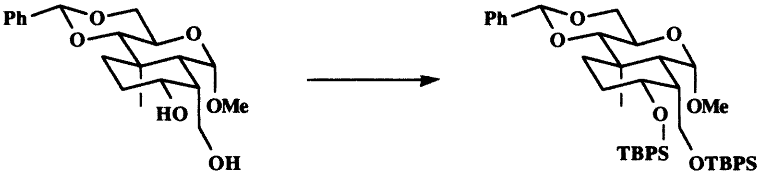
To a solution of **121** (4.33 g, 8.95 mmol) in dry ^{t}butanol (120 cm^3) was added sodium cyanoborohydride (1.41 g, 22.37 mmol) then tribuyltin chloride (0.24 cm^3, 0 09 mmol) and finally AIBN (0.15 g, 0.90 mmol). The reaction mixture was then heated under reflux (90 °C) for 4h. The reaction was cooled to room temperature and poured into water (200 cm^3), the product extracted into diethyl ether (2x300 cm^3), the combined ether layers were washed with water (2x100 cm^3), dried and evaporated to dryness. The resulting white solid was used directly in the next step without further purification.

To a solution of the intermediate white solid (3.45 g, 8.53 mmol) in THF/methanol was added sodium carbonate (1.08 g, 10.23 mmol) followed by the dropwise addition of hydrogen peroxide (30%, w/v. 4.8 cm^3, 42.64 mmol). The reaction was heated under reflux for 4h then cooled to room temperature and concentrated under reducted pressure. The resulting residue was poured into saturated aqueous sodium chloride (250 cm^3) and the product extracted with ethyl acetate (3x75.0 cm^3). The ethyl acetate layer was dried and evaporated to dryness to give a white solid. Chromatography on silica gel with ethyl acetate as the eluent yielded the diol **123** as a waxy solid (2.26 g, 69% over two steps); δ_H(300 MHz; CDCl$_3$) 1.50 (1H, br t, *J* 10.1, 5.1, 14a-H) overlapping with 1.20 (3H, s, C1-CH$_3$), 1.69 (3H, br m, 13a,b-H and 10-H), 1.87 (1H, dt, *J* 6.7, 13.3, 14b-H), 2.31 (1H, br m, 11-H), 3.15 (1H, d, *J* 9.5, 2-H), 3.35 (3H, s, OCH$_3$), 3.49 (1H, br s, OH), 3.65 (1H, t, *J* 10.0, 6ax-H), 3.85 (1H, br m, 12-H), 3.95 (1H, dt, *J* 5.2, 10.0, 7-H), 4.02 (1H, br t, *J* 9.8, C*H*HOH), 4.20 (1H, dd, *J* 5.2, 10.0, 6eq-H) overlapping with 4.19 (1H, br m, CH*H*OH), 4.60 (1H, d, *J* 4.5, 9-H), 5.50 (1H, s, 4-H), 7.30-7.50 (5H, m, Ph); δ_C (75

MHz; $CDCl_3$) 15.6 (CH_3, C1-Me), 26.7 (CH_2, C14), 35.7 (C, C1), 36.8 (CH_2, C13), 44.9 (CH, C11), 47.75 (CH, 10), 55.1 (CH_3, OCH_3), 60.2 (CH_2, CH_2OH), 60.3, (CH, C7), 69.5 (CH_2, C6), 74.57 (CH, C2), 87.7 (CH, C12), 101.3 (CH, C9), 102.6 (CH, C4), 126.1 (CH, Ph), 128.1 (CH, Ph), 128.8 (CH, Ph), 137.8 (C), 138.8 (C).

This is a literature compound and method.[57]

(1*R*,2*S*,4*R*,7*R*,9*S*,10*R*,11*R*,12*R*)-12-*tert*-Butyldiphenylsiloxy-11-*tert*-butyldiphenylsiloxymethyl-9-methoxy-1-methyl-4-phenyl-3,5,8-trioxatricyclo[8.4.0.0^{2,7}]tetradecane

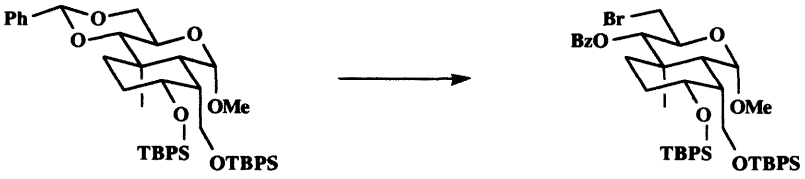


123 251

Diol **123** (2.02 g, 5.54 mmol), imidazole (1.51 g, 22.15 mmol) and 4-(dimethylamino) pyridine (33.80 mg, 0.28 mmol) were dissolved in dry dichloromethane (13.0 cm^3). This solution was cooled in an icebath and *ter*-butylchlorodiphenylsilane (4.3 cm^3, 16.62 mmol) added dropwise. The reaction was then stirred at room temperature under nitrogen for 3 days. A small amount of imidazole was added to ensure the reaction was basic then the reaction was quenched by the addition of methanol (10.0 cm^3), diluted with dichloromethane (400 cm^3) and this solution washed with water (200 cm^3), dried and concentrated under reduced pressure to give a yellow oil. Chromatography on silica gel with petroleum ether : ethyl acetate (95:5) as eluent yielded the protected diol **251** as a white foam (1.06 g, 67%); δ_H(250 MHz; $CDCl_3$) 0.97 (1H, m, 14-H), 1.12 (3H, s, C1-CH_3), 1.21 (9H, s, tBu), 1.23 (9H, s, tBu), 1.39-1.44 (1H, m), 1.58-1.69 (3H, m), 2.59 (1H, br m, 11-H), 2.89 (3H, s, OMe), 3.09 (1H, d, *J* 9.4, 2-H), 3.66 (1H, t, *J* 10.0, 6ax-H), 3.75 (1H, m, 12-H), 3.88 (1H, dt, *J* 5.0, 9.8, 12-H), 4.25 (1H, dd, *J* 5.0, 10.1, C*H*HOSi), 4.34 (1H, dd, *J* 3.8, 9.8, CH*H*OSi), 4.58 (2H, m, 6eqH overlapping 9-H), 5.49 (1H, s, 4-H), 7.38-7.52 (17H, m,

Ph), 7.84-7.93 (8H, m, Ph); δ_C (62.9 MHz; $CDCl_3$) 15.8 (CH_3, C1-Me), 19.7 (C, ^{t}Bu), 19.8 (C, ^{t}Bu), 27.7 (CH_3, CH_3-^{t}Bu), 27.8 (CH_3, CH_3-^{t}Bu), 28.2 (CH_2, C14), 36.4 (C, C1), 37.4 (CH_2, C13), 48.0-48.3 (2xCH, C10 and C11), 54.9 (CH_3, OCH_3), 60.5, (CH, C7), 61.0 (CH_2, CH_2OSi), 70.1 (CH_2, C6), 75.6 (CH, C2), 88.3 (CH, C12), 101.8 (CH, C9), 103.0 (CH, C4), 126.6-136.6 (14xCH, Ph), 138.5 (C).
This is a literature compound.[1b]

(1*R*, 2*S*, 3*R*, 5*S*, 6*S*)-2-Benzoyloxy-3-bromomethyl-8-*tert*butyldiphenylsiloxy-7-*tert*-butyldiphenylsiloxymethyl-5-methoxy-1-methyl-4-oxabicyclo[4.4.0]decane



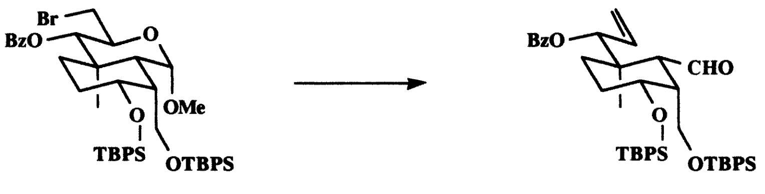
251 **252**

To a solution of **251** (1.02 g, 1.21 mmol) in dry carbon tetrachloride (35.0 cm^3) was added barium carbonate (1.32 g, 6.67 mmol) followed by *n*-bromosuccinimide (0.26 g, 1.45 mmol). The reaction was then heated at 80 °C for 3h. The reaction was cooled to room temperature and the barium carbonate removed by filtration, the residue was washed with dichloromethane (200 cm^3), then the organic filtrate washed with water (2x100 cm^3), dried and evaporated to dryness. Chromatography on silica gel with petroleum ether : ethyl acetate (20:1) as eluent yielded the bromo ester **252** as a white foam (0.85 g, 76%); δ_H(250 MHz; $CDCl_3$) 0.72-0.91 (2H, m), 0.94 (3H, s, C1-CH_3), 0.96 (9H, s, tBu), 0.97 (9H, s, tBu), 1.21-1.33 (1H, m), 1.33-1.42 (1H, m), 1.50 (1H, m, 6-H), 2.37 (1H, m, 7-H), 2.70 (3H, s, OMe), 3.18 (2H, m, C*H*$_2$Br), 3.53 (1H, m, 8-H), 3.89 (1H, dd, *J* 2.5, 7.6, 10.1, 3-H), 4.08 (1H, dd, *J* 3.8, 9.4, C*H*HOSi), 4.34 (1H, dd, *J* 1.9, 9.5, CH*H*OSi), 4.42 (1H, d, *J* 2.8, 5-H), 4.52 (1H, d, *J* 10.1, 2-H), 7.17-7.49 (15H, m), 7.57-7.66 (8H, m), 7.81-7.84 (2H, m); δ_C (62.9 MHz; $CDCl_3$) 16.1 (CH_3, C1-Me), 19.6 (C, ^{t}Bu), 19.8 (C, ^{t}Bu), 27.5

(CH_3, CH_3-^{t}Bu), 27.7 (CH_3, CH_3-^{t}Bu), 28.0 (CH_2, C10), 33.6 (CH_2, CH_2Br), 37.9 (CH_2, C9), 38.0 (C, C1), 47.4-47.7 (2xCH, C6 and C7), 55.0 (CH_3, OCH_3), 60.9 (CH_2, CH_2OSi), 67.8 (CH, C3), 74.9 (CH, C8), 79.5 (CH, C2), 102.4 (CH, C5), 127.8-133.9 (7xCH, Ph), 134.7-135.1 (4xC, Ph), 136.4 (3xCH, Ph), 166.0 (C, CO).

This is a literature compound.[1b]

(1*R*,1'*R*,2'*R*,3'*R*,4'*R*)-1'-Methyl-2'-formyl-3'-*tert*-butyldiphenylsiloxymethyl-4'-*tert*-butyldiphenylsiloxy-1-cyclohexyl-2-propenyl-1-benzoate

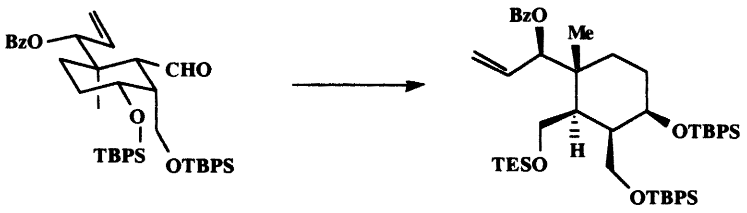


252 253

Zinc (14.44 g, 0.22 mmol) was activated by washing with 2M aqueous hydrochloric acid ($2x50\ cm^3$), water ($150\ cm^3$), isopropanol ($75.0\ cm^3$) and finally ether ($2x100\ cm^3$). To a solution of **252** (1.56 g, 1.70 mmol) in isopropanol water (78 : 8.5 cm^3) was added the activated zinc. The reaction was heated under reflux for 3h then cooled to room temperature, the zinc removed by flitration and washed with ether ($2x100\ cm^3$). The ether filtrate was concentrated under reduced pressure, the resulting residue dissolved in ether ($250\ cm^3$), washed with water ($2x75\ cm^3$), dried and evaporated to dryness. Chromatography on silica gel with petroleum ether : dichloromethane (1:1) as eluent yielded the aldehyde **253** as a white foam (0.866 g, 63%); δ_H(250 MHz; $CDCl_3$) 0.87 (9H, s, tBu), 0.89 (9H, s, tBu), 1.42-1.53 (3H, m), 1.89 (2H, m), 2.34 (1H, t, *J* 4.4, 2'-H), 3.46 (2H, apparent d, *J* 6.9, C*H*$_2$OSi), 4.02 (1H, br s, 4'-H), 5.08 (2H, m, 3_{cis}, 3_{trans}-H), 5.42-5.67 (2H, m, 1-H, 2-H), 7.05-7.51 (23H, m, Ph), 7.89 (2H, m, Ph), 10.05 (1H, d, *J* 5.03, C*HO*); δ_C (62.9 MHz; $CDCl_3$) 19.6 (C, ^{t}Bu), 19.7 (C, ^{t}Bu), 21.0 (CH_3, C1-Me), 26.4 (CH_2, C6'), 27.3 (CH_3, CH_3-^{t}Bu), 27.5 (CH_3, CH_3-^{t}Bu), 28.7 (CH_2, C5'), 38.5 (C, C1'), 44.6 (CH, C3'), 53.2 (CH, C2'), 64.2 (CH_2, CH_2OSi), 68.5 (CH, C4'), 75.2 (CH, C1), 120.9 (CH, C3), 127.9-130.1 (7xCH, Ph), 130.5 (C, Ph), 132.4 (CH, Ph), 133.2 (CH, Ph), 133.6-134.3 (4xC, Ph), 136.0-136.5 (4xCH, Ph), 165.9 (C, CO), 205.0 (CH, CHO).

This is a literature compound.[1b]

(1*R*,1'*R*,2'*R*,3'*R*,4'*R*)-1'-Methyl-2'-triethylsiloxy-3'-*tert*-butyldiphenylsiloxymethyl-4'-*tert*-butyldiphenylsiloxy-1-cyclohexyl-2-propenyl-1-benzoate



253 **254**

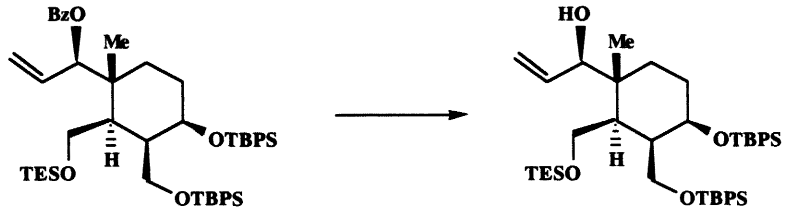
To a solution of aldehyde **253** (310 mg, 0.38 mmol) in isopropanol/methanol (5.5:2.2 cm^3) was added sodium borohydride (58 mg, 1.53 mmol). The reaction was then stirred at room temperature overnight. The solvent was removed under reduced pressure, the residue dissolved in dichloromethane (100 cm^3), washed with water (50 cm^3), dried and concentrated under reduced pressure to give a white solid which was used directly in the next reaction.

To a solution of the crude alcohol (91 mg, 0.11 mmol) in dry dichloromethane (1.1 cm^3) was added imidazole (1.91 mg, 0.28 mmol) followed by chlorotriethylsilane (0.04 cm^3 0.23 mmol). The reaction was then stirred overnight at room temperature under nitrogen. A small amount of imidazole was added to make sure the reaction was basic, then diluted with dichloromethane (100 cm^3). This solution was washed with water (50 cm^3), dried and concentrated under reduced pressure to give an oil. Chromatography on silica gel with petroleum ether : diethyl ether (30:1) as eluent yielded **254** as a foam (85 mg, 82%); δ_H(250 MHz; $CDCl_3$) 0.45 (6H, q, *J* 8.0, CH_3CH_2Si), 0.83 (9H, t, *J* 8.1, CH_3CH_2Si), 0.92 (9H, s, ^tBu), 0.96 (10H, s, ^tBu and 6'-H), 1.09 (3H, s, C1'-CH_3), 1.31-1.36 (1H, br.m), 1.42-1.51 (1H, br.m), 1.69-1.71 (1H, br m), 1.84 (1H, br s), 1.92 (1H, br s), 3.60 (1H, dd, *J*

5.5, 10.0), 3.68-3.90 (3H, br m), 4.04 (1H, br s, 4'-H), 5.15 (2H, m, 1-H and 3-H), 5.77-5.93 (2H, m, 2-H and 3-H), 7.25-7.50 (15H, m, Ph), 7.58-7.67 (8H, m, Ph), 7.94 (2H, d with fine splitting, *J* 7.1, Ph); δ_C (62.9 MHz; $CDCl_3$) 4.2 (CH_2, CH_2Si), 7.0 (CH_3, CH_3CH_2Si), 19.1 (C, ^{t}Bu), 19.3 (C, ^{t}Bu), 20.7 (CH_3, C1-Me), 25.0 (CH_2, C6'), 26.8 (CH_3, CH_3-^{t}Bu), 27.0 (CH_3, CH_3-^{t}Bu), 28.3 (CH_2, C5'), 39.1 (C, C1'), 42.4 (CH, C3' or C2'), 43.8 (CH, C2' or C3'), 61.0 (CH_2, C2'-CH_2OSi), 64.3 (CH_2, C3'-CH_2OSi), 67.7 (CH, C4'), 76.1 (CH, C1), 119.7 (CH_2, C3), 127.3-129.5 (6xCH, Ph), 130.1 (C, Ph), 132.7 (CH, Ph or C2), 133.0 (CH, Ph or C2), 133.2-134.1 (3xC, Ph), 135.4-135.9 (3xCH, Ph), 165.6 (C, CO).

This is a literature compound.[1b]

(3*R*,1'*R*,2'*R*,3'*R*,4'*R*)-4'-*tert*-Butyldiphenylsiloxy-3'-*tert*-butyldiphenylsiloxymethyl-3-hydroxy-1'-methyl-2'-triethylsiloxymethyl-3-cyclohexylpropene

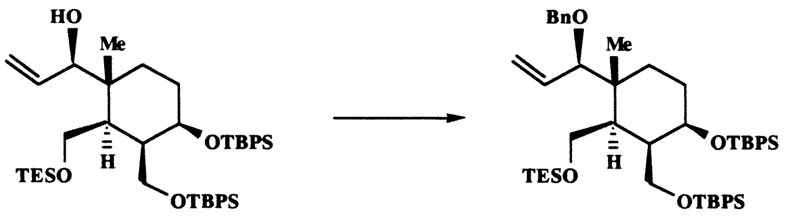


254 **275**

To a cooled (-78 °C, dry ice/acetone) solution of **254** (260 mg, 0.28 mmol) in dry dichloromethane (15.0 cm^3) was added DIBAL-H (1.5 M solution in toluene, 0.56 cm^3, 0.84 mmol). This reaction was stirred under nitrogen at -78 °C for 1h. The reaction was quenched with isopropanol (5.0 cm^3) and a saturated sodium sulphate solution (5 cm^3) and the reaction solution allowed to warm to room temperature. The gelatinous solid was filtered through celite, washed with dichloromethane (2x25 cm^3), the combined organic layers washed with water (2x25 cm^3), dried and evaporated to dryness. Chromatography on silica gel with petroleum ether : diethyl ether (97.5:2.5) as eluent yielded the alcohol **275** as a

foam (141 mg, 61%); R_f: 0.33, petroleum ether : diethyl ether (4:1); $[\alpha]_D^{30}$ 8.8° (*c* 2.82, CHCl$_3$); υ_{max} (film)/cm^{-1} 3430 br m, 2940 s, 1470 m, 1430 s, 1100 s, 840 m; δ_H(250 MHz; CDCl$_3$) 0.45 (6H, q, *J* 7.6, CH$_3$C*H*$_2$Si), 0.80 (3H, s, C1'-CH$_3$), 0.81 (9H, t overlapping, *J* 7.9, C*H*$_3$CH$_2$Si), 0.86 (9H, s, ^{t}Bu), 1.00 (9H, s, ^{t}Bu), 1.15-1.40 (4H, br m), 1.72 (1H, m, 3'-H), 2.09 (1H, br s, OH), 3.67 (1H, apparent d, *J* 11.3, 3-H), 3.83 (4H, m, 2xC*H*$_2$OSi), 4.06 (1H, m, 4'-H), 5.01 (1H, d, *J* 10.1, 1-H) overlapping 5.05 (1H, d, *J* 17.4, 1_{trans}-H), 5.71 (1H, ddd, *J* 6.8, 10.3, 17.3, 2-H), 7.18-7.56 (20H, m, Ph); δ_C (62.9 MHz; CDCl$_3$) 3.6 (CH$_2$, CH$_3$*C*H$_2$Si), 5.7 (CH$_3$, *C*H$_3$CH$_2$Si), 17.2 (CH$_3$, C1'-Me), 18.1 (2xC, ^{t}Bu), 26.0 (CH$_2$ and 2xCH$_3$, ^{t}Bu and C6' or C5'), 28.7 (CH$_2$, C6' or C5'), 38.9 (C, C1'), 44.3 (CH, C3' or C2'), 62.0 (CH$_2$, *C*H$_2$OSi), 64.1 (CH$_2$, *C*H$_2$OSi), 76.2 (CH, C4', or C3), 115.6 (CH$_2$, C1), 126.4 (CH, Ph), 126.5 (CH, Ph), 126.5 (CH, Ph), 128.5 (CH, Ph), 128.6 (CH, Ph), 132.6 (C, Ph), 133.0 (C, Ph), 133.3 (C, Ph), 134.6 (CH, Ph), 134.7 (CH, Ph), 135.9 (C, Ph); m/z (EI) 763 (M$^+$-^{t}Bu, 1.1%) 319 (3) 199 (100) (Found : M$^+$-^{t}Bu, 763.4028 C$_{47}$H$_{67}$O$_3$Si$_3$ requires 763.4399).

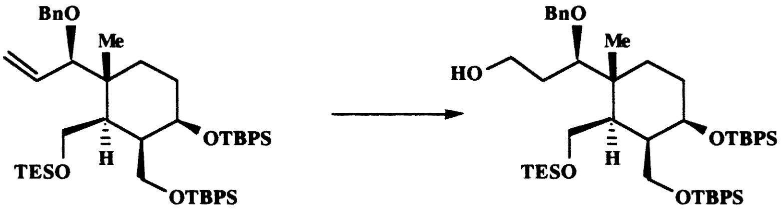
(3*R*,1'*R*,2'*R*,3'*R*,4'*R*)-4'-*tert*-Butyldiphenylsiloxy-3'-*tert*-butyldiphenylsiloxymethyl-1'-methyl-3-benzyloxy-2'-triethylsiloxymethyl-3-cyclohexylpropene



275 **276**

A solution of the alcohol **275** (141 mg, 0.17 mmol) in THF (5.0 cm^3) was cooled to 0 °C with stirring. Sodium hydride (5.0 mg, 80% dispersion in mineral oil, 0.12 mmol) was added in portions, and the solution allowed to stir for 1h. Benzyl bromide (44 mg, 0.30 mmol) was then added dropwise and the solution allowed to stir at 40 °C overnight. The solution was then cooled in ice and ethanol (5 cm^3) added, to destroy the excess sodium hydride, and then poured into iced water. The aqueous layer was extracted with diethyl ether (2x10 cm^3) and the combined organic layers washed with brine (2x10 cm^3) dried and evaporated to dryness. Chromatography on silica gel with petroleum ether : diethyl ether (98:2) as the eluent yielded **276** as a colourless oil (131 mg, 85%); R_f: 0.25, petroleum ether : diethyl ether (98:2); $[\alpha]_D^{20}$ -20.6° (*c* 2.0, $CHCl_3$); υ_{max} (film)/cm^{-1} 2920 s, 1590 w, 1450 w, 1425 m, 1100 s, 840 m; δ_H(250 MHz; $CDCl_3$) 0.42 (6H, q, *J* 8.2, $CH_3C\mathit{H}_2Si$), 0.80 (9H, t, *J* 8.2, $C\mathit{H}_3CH_2Si$), 0.90 (9H, s, ^{t}Bu), 0.93 (3H, s, C1'-CH_3), 0.96 (9H, s, ^{t}Bu), 1.05-1.30 (4H, m), 1.40-1.70 (2H, m), 3.55 (1H, dd, *J* 4.1, 9.43, C*H*HOSi), 3.72 (1H, dd obscured, *J* 4.1, CH*H*OSi) overlaping 3.72 (2H, m, $C\mathit{H}_2OSi$), 3.88 (1H, br t, *J* 7.6, 4'-H), 4.00 (1H, br s, 3-H), 4.08 (1H, d, *J* 11.8, C*H*HPh), 4.43 (1H, d, *J* 11.8, CH*H*Ph), 4.88 (1H, dd, *J* 1.6, 17.3, 1-H_{trans}), 5.13 (1H, dd, *J* 1.6, 10.1, 1_{cis}-H), 5.62 (1H, ddd, *J* 1.3, 10.1, 17.3, 2-H), 7.14-7.99 (25H, m, Ph); δ_C (62.9 MHz; $CDCl_3$) 5.0 (CH_2, $CH_3\mathit{C}H_2Si$), 7.4 (CH_3, $\mathit{C}H_3CH_2Si$), 19.7 (C, ^{t}Bu), 19.8 (C, ^{t}Bu), 20.8 (CH_3, C1'-Me), 25.5 (CH_2, C6' or C5'), 27.4 (CH_3, ^{t}Bu), 27.6 (CH_3, ^{t}Bu), 29.0 (CH_2, C6' or C5'), 40.6 (C, C1'), 43.4 (CH, C2'), 44.9 (CH, C3'), 61.9 (CH_2, $\mathit{C}H_2OSi$), 65.3 (CH_2, $\mathit{C}H_2OSi$), 68.9 (CH, C4'), 82.3 (CH, C3), 119.6 (CH_2, C1), 127.6-128.6 (7xCH, Ph), 129.9 (CH, Ph or C2), 129.9 (CH, Ph or C2), 134.2-135.0 (4xC, Ph), 135.9-136.6 (5xCH, Ph), 139.7 (C, Ph).

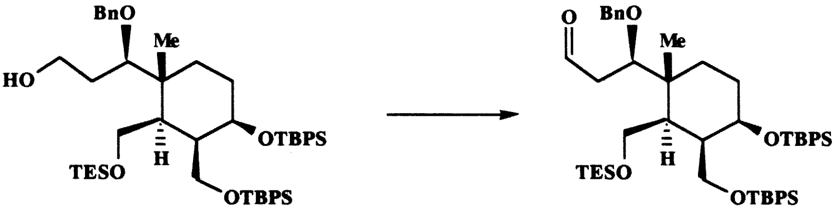
(3*R*,1'*R*,2'*R*,3'*R*,4'*R*)-4'-*tert*-Butyldiphenylsiloxy-3'-*tert*-butyldiphenylsiloxymethyl-1'-methyl-3-benzyloxy-2'-triethylsiloxymethyl-3-cyclohexylpropan-1-ol



276 **277**

To a solution of **276** (131 mg, 0.14 mmol) in THF (1.0 cm^3) was added 9'BBN (1.44 cm^3, 0.72 mmol) dropwise with cooling. The resulting solution was warmed to 40 °C and held at this temperature for 2h with stirring. The reaction was quenched (care) by the addition of sodium hydroxide (3.0 cm^3, 6N solution) followed by hydrogen peroxide (3.0 cm^3, 20% w/v solution in water) and allowed to stir overnight. The resulting solution was diluted with diethyl ether (15 cm^3), washed with brine (2x10 cm^3), the combined organic layers were dried and evaporated to dryness. Chromatography on silica gel with petroleum ether : ethyl acetate (95:5) as the eluent yielded **277** as a colourless oil (80 mg, 60%); Rf: 0.30, petroleum ether : ethyl acetate (95:5); $[\alpha]_D^{20}$ -15.5° (*c* 2.08, $CHCl_3$); υ_{max} (film)/cm^{-1} 2940 m, 1460 w, 1425 m, 1110 m, 850 w; δ_H(250 MHz; $CDCl_3$) 0.43 (6H, q, *J* 8.1, CH_3CH_2Si), 0.79 (9H, t, *J* 8.0, CH_3CH_2Si), 0.89 (9H, s, ^tBu) overlapping 0.89 (3H, s, C1'-CH_3), 0.94 (9H, s, ^tBu), 1.22-1.35 (2H, m), 1.40-1.62 (6H, m), 3.59 (4H, m, 2xCH_2OSi), 3.78 (3H, m, 4'H, CH_2OH), 3.97 (1H, br s, 3-H), 4.37 (1H, d, *J* 11.3, *C*HHPh), 4.46 (1H, d, *J* 11.3, CH*H*Ph), 7.10-7.54 (25H, m, Ph); δ_C (62.9 MHz; $CDCl_3$) 5.0 (CH_2, CH_3CH_2Si), 7.4 (CH_3, CH_3CH_2Si), 19.7 (C, ^tBu), 19.8 (C, ^tBu), 20.6 (CH_3, C1'-Me), 26.1 (CH_2, C6' or C5'), 27.4 (CH_3, ^tBu), 27.6 (CH_3, ^tBu), 29.5 (CH_2, C6' or C5'), 33.3 (CH_2, C-2), 41.7 (C, C1'), 43.5 (CH, C2' or C3'), 45.0 (CH, C2' or C3'), 61.5 (CH_2, CH_2OSi), 61.8 (CH_2, CH_2OSi), 65.3 (CH, C1), 69.4 (CH, C4'), 75.0 (CH_2, CH_2Ph), 78.8 (CH, C3), 127.6-130.0 (8xCH, Ph), 134.0-134.8 (4xC, Ph), 136.0-136.6 (4xCH, Ph), 139.3 (C, Ph).

(3*R*,1'*R*,2'*R*,3'*R*,4'*R*)-4'-*tert*-Butyldiphenylsiloxy-3'-*tert*-butyldiphenylsiloxymethyl-1'-methyl-3-benzyloxy-2'-triethylsiloxymethyl-3-cyclohexylpropanal

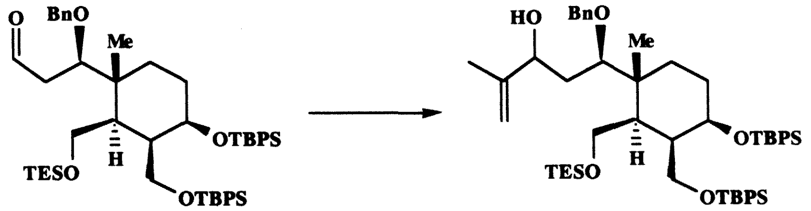


277 **278**

To a stirred solution of oxalyl chloride (0.26 cm^3, 3.00 mmol) in dichloromethane (5.0 cm^3) at -78 °C was added dimethyl sulphoxide (0.43 cm^3, 6.00 mmol) in dichloromethane (1.0 cm^3) dropwise under an atmosphere of nitrogen. After allowing the solution to stir for 0.25h a solution of the alcohol **277** (2.48 g, 2.00 mmol) in dichloromethane (5.0 cm^3) was added dropwise and the solution allowed to stir for 1h. Triethylamine (0.84 cm^3, 6.00 mmol) was then added and the solution allowed to warm to room temperature. The reaction was diluted with diethyl ether (50 cm^3) and the combined organic layers washed with brine (2x50 cm^3) and water (50 cm^3), dried and evaporated to dryness. Chromatography on silica gel with petroleum ether : ethyl acetate (97.5:2.5) as the eluent yielded **278** as a colourless oil (1.85 g, 75%); R_f 0.30, petroleum ether : ethyl acetate (97.5:2.5); $[\alpha]_D^{25}$ -17.6° (*c* 1.12, $CHCl_3$); ν_{max} (film)/cm^{-1} 3075 m, 2940 ms, 1725 s, 1590 w, 1470 s, 1100 s, 820 m; δ_H(250 MHz; $CDCl_3$) 0.56 (6H, q, *J* 8.2, CH_3CH_2Si), 0.93 (9H, t, *J* 8.2, CH_3CH_2Si), 1.01 (9H, s, ^tBu), 1.03 (3H, s, C1'-CH_3), 1.06 (9H, s, ^tBu), 1.30-1.45 (2H, m), 1.55-

1.80 (4H, m), 2.62 (2H, m, C2-HH), 3.71 (1H, m, 4'H), 3.81-4.01 (4H, m, 2xC*H*$_2$OSi), 4.20 (1H, m, 3-H), 4.38 (1H, d, *J* 11.33, C*H*HPh), 4.51 (1H, d, *J* 11.33, CH*H*Ph), 7.21-7.66 (25H, m, Ph), 9.80 (1H, s, 1-H); δ_C (62.9 MHz; CDCl$_3$) 5.0 (CH$_2$, CH$_3$*C*H$_2$Si), 7.5 (CH$_3$, *C*H$_3$CH$_2$Si), 15.8 (CH$_3$, C1'-Me), 19.7 (C, ^{t}Bu), 19.8 (C, ^{t}Bu), 26.0 (CH$_2$, C6' or C5'), 27.4 (CH$_3$, ^{t}Bu), 27.7 (CH$_3$, ^{t}Bu), 29.4 (CH$_2$, C6' or C5'), 41.5 (C, C1'), 43.5 (CH, C2' or C3'), 45.1 (CH, C2' or C3'), 46.3 (CH, C2), 65.1 (CH$_2$, *C*H$_2$OSi), 66.3 (CH$_2$, *C*H$_2$OSi), 69.1 (CH, C4'), 73.9 (CH$_2$, *C*H$_2$Ph), 75.2 (CH, C3), 127.7-130.1 (9xCH, Ph), 134.0-134.8 (4xC, Ph), 136.0-136.6 (4xCH, Ph), 139.2 (C, Ph), 201.9 (CH, C1).

(3*R*,5*R*,1'*R*,2'*R*,3'*R*,4'*R*)-4'-*tert*-Butyldiphenylsiloxy-3'-*tert*-butyldiphenylsiloxymethyl-3-hydroxy-2,1'-dimethyl-5-benzyloxy-2'-triethylsiloxymethyl-5-cyclohexyl-pent-1-ene and (3*S*,5*R*,1'*R*,2'*R*,3'*R*,4'*R*)-4'-*tert*-Butyldiphenylsiloxy-3'-*tert*-butyldiphenylsiloxymethyl-3-hydroxy-2,1'-dimethyl-5-benzyloxy-2'-triethylsiloxymethyl-5-cyclohexyl-pent-1-ene

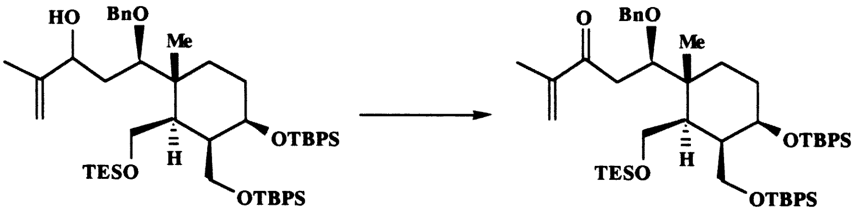


278 279

2-bromopropene (242 mg, 2.00 mmol) in dry THF (5.0 cm^3) was added dropwise to magnesium turnings (53 mg, 2.20 mmol) in dry THF (1.0 cm^3). When the initiation of the reaction was complete a gentle reflux was maintained by the addition of the bromide. The solution was then heated to reflux for 1h. The freshly prepared Grignard reagent was then added dropwise at 0 °C to the aldehyde **278** (1.94 g, 2.00 mmol). The reaction was quenched by the addition of water (5 cm^3), diluted with diethyl ether (50 cm^3), the combined organic layers washed with brine (2x15 cm^3), water (25 cm^3), dried and evaporated to dryness. Chromatography on silica gel with petroleum ether : ethyl acetate (90:10) as the eluent yielded 279 as a colourless oil (1.26 g, 65%); R_f: 0.40, petroleum ether : ethyl acetate (90:10); $[\alpha]_D^{21}$ -10.63^o (*c* 3.87, $CHCl_3$); υ_{max} (film)/cm^{-1} 3430 br w, 2940 s, 1520 w, 1430 s, 1110 s, 840 m; δ_H(250 MHz; $CDCl_3$) 0.69 (6H, q, *J* 8.2, $CH_3C\mathit{H}_2Si$), 1.06 (9H, t, *J* 8.2, $C\mathit{H}_3CH_2Si$), 1.15 (9H, s, ^{t}Bu), 1.17 (12H, s, ^{t}Bu and s, C1'-CH_3), 1.60-2.00 (8H, m) overlapping 1.78 (3H, s, C2-CH_3), 3.92-4.20 (6H, m), 4.20-4.37 (1H, m), 4.69 (1H, d, *J* 11.3, C*H*HPh), 4.84 (1H, d, *J* 11.3, CH*H*Ph), 4.89 (1H, br s, 1a-H), 5.03 (1H, br s, 1b-H), 7.32-7.78 (25H, m, Ph); δ_C (62.9 MHz; $CDCl_3$) 7.0 (CH_2, $CH_3\mathit{C}H_2Si$), 9.5 (CH_3, $\mathit{C}H_3CH_2Si$), 21.1 (CH_3, C1'-Me), 21.7 (C, ^{t}Bu), 21.8 (C, ^{t}Bu), 22.9 (CH_3, C2-Me), 28.4 (CH_2, C6' or C5'), 29.5 (CH_3, ^{t}Bu), 29.6 (CH_3, ^{t}Bu), 31.7 (CH_2, C6' or C5'), 38.7 (CH_2, C4), 43.7 (CH, C2' or C3'), 45.3 (CH, C2' or C3'), 46.8 (C, C1'), 63.8 (CH_2, $\mathit{C}H_2OSi$), 67.4 (CH_2, $\mathit{C}H_2OSi$), 71.4 (CH, C4' or C3), 75.3 (CH, C4' or C3), 77.1 (CH_2, $\mathit{C}H_2Ph$), 79.7 (CH, C5), 112.2 (CH_2, C1), 129.5-132.0 (9xCH, Ph), 136.1-136.9 (3xC, Ph), 138.1-138.6 (4xCH, Ph), 141.9 (C, Ph), 151.1 (C, C2),

Minor isomer; R_f: 0.35, petroleum ether : ethyl acetate (90:10); $[\alpha]_D^{19}$ -23.53^o (*c* 3.45, $CHCl_3$); υ_{max} (film)/cm^{-1} 3460 br s, 2910 m, 1425 m, 1110 w, 840 w; δ_H(250 MHz; $CDCl_3$) 0.66 (6H, q, *J* 7.9, $CH_3C\mathit{H}_2Si$), 1.04 (9H, t, *J* 7.9, $C\mathit{H}_3CH_2Si$), 1.10 (9H, s, ^{t}Bu), 1.14 (9H, s, ^{t}Bu), 1.17 (3H, s, C1'-CH_3), 1.50-2.00 (8H, m) overlapping 1.74 (3H, s, C2-CH_3), 3.80-4.28 (7H, m), 4.61 (1H, d, *J* 11.0, C*H*HPh), 4.75 (1H, d, *J* 11.0, CH*H*Ph), 4.86 (1H, br s, 1a-H), 5.02 (1H, br s, 1b-H), 7.38-7.69 (25H, m, Ph); δ_C (62.9 MHz; $CDCl_3$) 6.7 (CH_2, $CH_3\mathit{C}H_2Si$), 9.1 (CH_3, $\mathit{C}H_3CH_2Si$), 19.9 (CH_3, C1'-Me), 21.4 (C, ^{t}Bu), 21.5 (C, ^{t}Bu), 22.3 (CH_3, C2-Me), 27.8 (CH_2, C6' or C5'), 29.2 (CH_3, ^{t}Bu), 29.3 (CH_3, ^{t}Bu), 31.3 (CH_2, C6' or C5'), 38.3 (CH_2, C4), 44.0 (CH, C2' or C3'), 45.3 (CH, C2' or C3'), 46.4 (C, C1'), 63.4 (CH_2, $\mathit{C}H_2OSi$), 67.0 (CH_2, $\mathit{C}H_2OSi$), 71.0 (CH, C4' or C3), 76.5 (CH, C4' or C3), 77.1 (CH_2, $\mathit{C}H_2Ph$), 82.2 (CH, C5), 113.1 (CH_2, C1), 129.1-131.7 (7xCH, Ph), 135.6-136.5 (4xC, Ph), 137.7-138.2 (4xCH, Ph), 140.6 (C, Ph), 149.5 (C, C2),

(5*R*,1'*R*,2'*R*,3'*R*,4'*R*)-4'-*tert*-Butyldiphenylsiloxy-3'-*tert*-butyldiphenylsiloxymethyl-3-hydroxy-2,1'-dimethyl-5-benzyloxy-2'-triethylsiloxymethyl-5-cyclohexyl-pent-1-en-2-one



279 **280**

To a stirred solution of oxalyl chloride (0.08 cm^3, 0.90 mmol) in dichloromethane (5.0 cm^3) at -78 ^{o}C was added dimethyl sulphoxide (0.13 cm^3, 1.79 mmol) in dichloromethane (5.0 cm^3) dropwise under an atmosphere of nitrogen. After allowing the solution to stir for 0.25h a solution of the alcohol **279** (577 mg, 0.60 mmol) in dichloromethane (2.0 cm^3) was added dropwise and the solution allowed to stir for 1h. Triethylamine (0.50 cm^3, 3.58 mmol) was then added and the solution allowed to warm to room temperature. The reaction was diluted with diethyl ether (15 cm^3), the combined organic layers washed with brine (2x15 cm^3), water (15 cm^3), dried and evaporated to dryness. Chromatography on silica gel with petroleum ether : ethyl acetate (95:5) as the eluent yielded **280** as a colourless oil (520 mg, 90%); R_f: 0.75, petroleum ether : ethyl acetate (90:10); υ_{max} (film)/cm^{-1} 2920 s, 1680 m, 1470 w, 1430 s, 1110 s, 825 w; δ_H(250 MHz; CDCl$_3$) 0.47 (6H, q, *J* 7.9, CH$_3$C*H*$_2$Si), 0.81 (9H, t, *J* 7.8, C*H*$_3$CH$_2$Si), 0.90 (9H, s, ^{t}Bu), 0.95 (9H, s, ^{t}Bu), 0.98 (3H, s, C1'-CH$_3$), 1.17-1.90 (6H, m) overlapping 1.77 (3H, s, C2-CH$_3$), 2.62 (1H, br d, *J* 16.8, 4a-H), 3.03 (1H, dd, *J* 8.5, 16.8, 4b-H), 3.65 (2H, m), 3.84-3.91 (5H, m), 4.29 (1H, d, *J* 11.3, C*H*HPh), 4.34 (1H, m), 4.39 (1H, d, *J* 11.3, CH*H*Ph), 5.62 (1H, br s, 1a-H), 5.87 (1H, br s, 1b-H), 7.10-7.58 (25H, m, Ph); δ_C (62.9 MHz; CDCl$_3$) 3.5 (CH$_2$, CH$_3$*C*H$_2$Si), 5.9 (CH$_3$, *C*H$_3$CH$_2$Si), 17.7 (CH$_3$, C1'-Me or C2-CH$_3$), 18.1 (C, ^{t}Bu), 18.3 (C, ^{t}Bu), 19.4 (CH$_3$, C2-CH$_3$ or C1'-CH$_3$), 26.6 (CH$_2$, C6' or C5'), 27.9 (CH$_3$, ^{t}Bu), 28.0 (CH$_3$, ^{t}Bu), 28.7 (C, C1'), 31.0 (CH$_2$, C6' or C5'), 38.1 (CH$_2$, C4), 41.8 (CH, C2' or C3'), 43.4 (CH, C2' or C3'), 60.2 (CH$_2$, *C*H$_2$OSi), 63.6 (CH$_2$, *C*H$_2$OSi), 67.9 (CH, C4'), 72.5

(CH_2, *C*H_2Ph), 75.2 (CH, C5), 123.9 (CH_2, C1), 126.0-128.5 (9xCH, Ph), 132.5-133.3 (4xC, Ph), 134.5-135.0 (4xCH, Ph), 138.3 (C, Ph), 143.8 (C, C2), 200.0 (C, C3).

Appendix

X-RAY CHRYSTALLOGRAPHY DATA

Table 1. Crystal data and structure refinement for C18H20O5

Identification code	1
Empirical formula	$C_{18}H_{20}O_5$
Formula weight	316.34
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Unit cell dimensions	a = 8.3430(10) Å α = 90°
	b = 8.9150(10) Å β = 90°
	c = 22.506(3) Å γ = 90°
Volume	1673.9(4) $Å^3$
Z	4
Density (calculated)	1.255 Mg/m^3
Absorption coefficient	0.091 mm^{-1}
F(000)	672
Crystal size	0.53 x 0.24 x 0.12 mm
θ range for data collection	2.60 to 21.98°
Index ranges	$-1 \le h \le 8$, $-1 \le k \le 9$, $-1 \le \ell \le 23$
Reflections collected	1695
Independent reflections	1535 (R_{int} = 0.0337)
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1535 / 0 / 171
Goodness-of-fit on F^2	1.072
Final R indices [$I>2\sigma(I)$]	R1 = 0.0596, wR2 = 0.1240
R indices (all data)	R1 = 0.0986, wR2 = 0.1469
Absolute structure parameter	4(4)
Largest diff. peak and hole	0.173 and -0.262 $eÅ^{-3}$

Table 2. Atomic coordinates [x 10^4] and equivalent isotropic displacement parameters [$Å^2$ x 10^3] for C18H20O5 U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U(eq)
O(1)	2587(5)	12032(5)	9257(2)	49(1)
O(2)	-317(5)	9289(5)	8736(2)	48(1)
O(3)	2204(5)	8172(5)	8728(2)	44(1)
O(4)	4475(5)	12960(5)	8579(2)	58(1)
O(5)	7767(6)	8591(6)	9970(2)	68(2)
C(1)	4233(9)	12370(9)	9146(3)	53(2)
C(2)	5188(8)	10971(8)	9219(3)	43(2)
C(3)	4699(8)	9554(8)	8904(3)	40(2)
C(4)	2894(8)	9398(7)	9040(3)	39(2)
C(5)	2010(8)	10832(7)	8891(3)	42(2)
C(6)	241(8)	10607(8)	9037(3)	52(2)
C(7)	6324(8)	10747(8)	9621(3)	49(2)
C(8)	6769(8)	9150(10)	9639(3)	49(2)
C(9)	5703(8)	8335(8)	9206(3)	53(2)
C(10)	568(8)	8036(7)	8912(3)	41(2)
C(11)	5033(9)	9583(9)	8231(3)	59(2)
C(12)	3741(11)	14402(8)	8500(4)	90(3)
C(13)	-151(5)	6663(5)	8647(2)	43(2)
C(14)	-29(7)	6359(6)	8040(2)	67(2)
C(15)	-792(8)	5104(7)	7801(2)	78(3)
C(16)	-1678(7)	4154(5)	8169(3)	78(3)
C(17)	-1800(6)	4458(5)	8775(3)	72(3)
C(18)	-1036(6)	5712(6)	9014(2)	55(2)

Table 3. Bond lengths [Å] and angles [°] for C18H20O5

O(1)-C(1)	1.428(8)	O(1)-C(5)	1.435(7)
O(2)-C(10)	1.396(7)	O(2)-C(6)	1.433(8)
O(3)-C(4)	1.421(7)	O(3)-C(10)	1.432(7)
O(4)-C(1)	1.394(8)	O(4)-C(12)	1.436(8)
O(5)-C(8)	1.222(8)	C(1)-C(2)	1.490(9)
C(2)-C(7)	1.326(9)	C(2)-C(3)	1.505(9)
C(3)-C(9)	1.531(9)	C(3)-C(11)	1.541(8)
C(3)-C(4)	1.543(9)	C(4)-C(5)	1.513(8)
C(5)-C(6)	1.526(9)	C(7)-C(8)	1.472(10)
C(8)-C(9)	1.507(9)	C(10)-C(13)	1.489(7)
C(13)-C(18)	1.39	C(13)-C(14)	1.40
C(14)-C(15)	1.40	C(15)-C(16)	1.39
C(16)-C(17)	1.39	C(17)-C(18)	1.39
C(1)-O(1)-C(5)	112.2(5)	C(10)-O(2)-C(6)	110.5(5)
C(4)-O(3)-C(10)	108.0(5)	C(1)-O(4)-C(12)	112.9(6)
O(4)-C(1)-O(1)	112.3(6)	O(4)-C(1)-C(2)	109.8(6)
O(1)-C(1)-C(2)	108.6(6)	C(7)-C(2)-C(1)	125.8(7)
C(7)-C(2)-C(3)	112.9(6)	C(1)-C(2)-C(3)	120.4(6)
C(2)-C(3)-C(9)	103.8(5)	C(2)-C(3)-C(11)	113.6(6)
C(9)-C(3)-C(11)	110.4(6)	C(2)-C(3)-C(4)	104.3(5)
C(9)-C(3)-C(4)	112.4(6)	C(11)-C(3)-C(4)	111.9(6)
O(3)-C(4)-C(5)	110.0(5)	O(3)-C(4)-C(3)	111.5(5)
C(5)-C(4)-C(3)	110.8(5)	O(1)-C(5)-C(4)	109.8(5)
O(1)-C(5)-C(6)	107.3(6)	C(4)-C(5)-C(6)	108.2(6)
O(2)-C(6)-C(5)	108.7(6)	C(2)-C(7)-C(8)	110.2(7)
O(5)-C(8)-C(7)	125.6(7)	O(5)-C(8)-C(9)	126.9(7)
C(7)-C(8)-C(9)	107.4(6)	C(8)-C(9)-C(3)	105.6(6)
O(2)-C(10)-O(3)	110.8(5)	O(2)-C(10)-C(13)	109.3(5)
O(3)-C(10)-C(13)	109.7(5)	C(18)-C(13)-C(14)	120.0
C(18)-C(13)-C(10)	118.4(4)	C(14)-C(13)-C(10)	121.5(4)
C(15)-C(14)-C(13)	120.0	C(16)-C(15)-C(14)	120.0
C(17)-C(16)-C(15)	120.0	C(16)-C(17)-C(18)	120.0
C(17)-C(18)-C(13)	120.0		

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters [$Å^2 \times 10^3$] for C18H20O5

The anisotropic displacement factor exponent takes the form:

$-2\pi^2 [(ha^*)^2 U_{11} + \ldots + 2hka^*b^*U_{12}]$

	U11	U22	U33	U23	U13	U12
O(1)	33(3)	46(3)	67(3)	-16(3)	6(3)	0(3)
O(2)	27(3)	46(3)	71(3)	-4(3)	-8(2)	4(3)
O(3)	31(3)	47(3)	54(3)	-11(3)	1(2)	-5(3)
O(4)	47(3)	53(3)	73(3)	14(3)	3(3)	-3(3)
O(5)	40(3)	97(4)	65(3)	17(3)	-9(3)	6(3)
C(6)	27(4)	45(5)	84(5)	-6(5)	2(4)	-2(4)
C(7)	33(4)	55(5)	59(5)	-5(4)	-2(4)	-5(5)
C(8)	19(4)	77(6)	51(5)	5(5)	14(4)	-5(5)
C(9)	31(4)	63(5)	67(5)	-5(5)	-4(4)	-4(4)
C(10)	32(4)	39(4)	54(4)	7(4)	1(4)	-11(4)
C(11)	33(4)	77(6)	65(5)	-16(5)	7(4)	-5(5)
C(12)	91(7)	60(6)	120(7)	30(6)	12(7)	9(6)
C(13)	35(4)	39(4)	56(5)	-1(4)	-10(4)	2(4)
C(14)	86(6)	60(5)	56(5)	-5(4)	-12(5)	-5(6)
C(15)	99(8)	71(6)	65(6)	-19(5)	-20(6)	-7(6)
C(16)	64(6)	60(6)	111(8)	-15(6)	-18(6)	-14(6)
C(17)	57(6)	54(6)	106(7)	2(6)	19(6)	-12(5)
C(18)	48(5)	45(4)	72(5)	-5(5)	10(4)	-4(5)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^2 x 10^3) for $C_{18}H_{20}O_5$

	x	y	z	U(eq)
H(1)	4599(9)	13092(9)	9432(3)	80
H(4)	2752(8)	9237(7)	9458(3)	80
H(5)	2139(8)	11076(7)	8478(3)	80
H(6A)	143(8)	10476(8)	9459(3)	80
H(6B)	-374(8)	11467(8)	8919(3)	80
H(7)	6773(8)	11515(8)	9870(3)	80
H(9A)	6331(8)	7779(8)	8924(3)	80
H(9B)	5018(8)	7657(8)	9418(3)	80
H(10)	526(8)	7956(7)	9337(3)	80
H(11A)	6160(9)	9683(9)	8154(3)	80
H(11B)	4643(9)	8679(9)	8050(3)	80
H(11C)	4475(9)	10430(9)	8067(3)	80
H(12A)	3915(11)	14760(8)	8102(4)	80
H(12B)	2610(11)	14322(8)	8573(4)	80
H(12C)	4206(11)	15093(8)	8778(4)	80
H(14)	580(9)	7012(8)	7788(3)	80
H(15)	-708(11)	4894(10)	7384(2)	80
H(16)	-2203(9)	3290(6)	8004(4)	80
H(17)	-2409(8)	3804(7)	9027(4)	80
H(18)	-1120(9)	5922(9)	9431(2)	80

Table 6. Observed and calculated structure factors for $C_{18}H_{20}O_5$

h	k	l	10Fo	10Fc	10s
2	0	0	709	699	2
4	0	0	373	332	4
6	0	0	53	28	17
8	0	0	0	14	1
1	1	0	464	486	3
2	1	0	484	493	9
3	1	0	230	225	3
4	1	0	198	177	3
5	1	0	117	102	5
6	1	0	87	98	7
7	1	0	0	11	1
8	1	0	70	68	12
0	2	0	577	623	2
1	2	0	535	557	3
2	2	0	199	208	4
3	2	0	304	319	4
4	2	0	155	170	5
5	2	0	46	45	19
6	2	0	372	353	6
7	2	0	11	49	10
8	2	0	35	44	35
1	3	0	7	27	6
2	3	0	485	481	4
3	3	0	276	280	4
4	3	0	400	406	5
5	3	0	0	24	1
6	3	0	320	308	6
7	3	0	62	74	20
8	3	0	0	26	1
0	4	0	197	192	4
1	4	0	0	10	1
2	4	0	154	166	6
3	4	0	295	274	4
4	4	0	113	107	7
5	4	0	142	126	8
6	4	0	125	134	10
7	4	0	131	151	12
1	5	0	196	197	4
2	5	0	55	48	14
3	5	0	93	86	8
4	5	0	146	130	7
5	5	0	158	156	8
6	5	0	99	96	13
7	5	0	0	5	1
0	6	0	250	239	6
1	6	0	129	142	6
2	6	0	35	5	35
3	6	0	84	87	12
4	6	0	122	113	9
5	6	0	0	15	1
6	6	0	141	130	9
1	7	0	196	184	5
2	7	0	70	55	15
3	7	0	165	163	9
4	7	0	49	23	26
5	7	0	68	61	16
0	8	0	413	399	7
1	8	0	154	174	6
2	8	0	37	3	37
3	8	0	158	147	9
4	8	0	110	87	10
1	9	0	32	30	31
2	9	0	0	9	1
1	0	1	259	254	1
2	0	1	248	234	7
3	0	1	110	91	4
4	0	1	139	129	4
5	0	1	215	209	4
6	0	1	96	99	7
7	0	1	19	21	19
8	0	1	50	56	17
-8	1	1	64	58	11
-7	1	1	102	98	7
-6	1	1	14	21	13
-5	1	1	140	140	4
-4	1	1	149	134	4
-3	1	1	373	368	2
-2	1	1	161	166	3
-1	1	1	457	455	6
1	1	1	458	455	7
2	1	1	762	766	21
3	1	1	368	368	6
4	1	1	138	134	4
5	1	1	140	140	4
6	1	1	40	21	23
7	1	1	94	98	3
8	1	1	56	57	29
-8	2	1	85	104	16
-7	2	1	89	92	11
-6	2	1	38	35	37
-5	2	1	129	125	7
-4	2	1	41	41	23
-3	2	1	372	363	4
-2	2	1	230	224	4
-1	2	1	292	300	2
0	2	1	380	410	3
1	2	1	290	300	2
2	2	1	223	224	4
3	2	1	364	363	4
4	2	1	51	41	15
5	2	1	116	125	8
6	2	1	35	35	35
7	2	1	84	92	13
8	2	1	110	104	11
-8	3	1	46	44	45
-7	3	1	107	102	12
-6	3	1	196	204	8
-5	3	1	78	98	13
-4	3	1	156	163	6
-3	3	1	188	196	5
-2	3	1	0	35	1
-1	3	1	61	48	6
0	3	1	217	221	3
1	3	1	53	48	13
2	3	1	0	35	1
3	3	1	185	196	5
4	3	1	158	163	6
5	3	1	99	98	8
6	3	1	207	204	7
7	3	1	108	101	11
8	3	1	56	44	20
-7	4	1	221	238	8
-6	4	1	173	166	8
-5	4	1	114	113	8
-4	4	1	98	103	9
-3	4	1	92	83	9
-2	4	1	154	143	6
-1	4	1	229	234	3
0	4	1	130	132	4
1	4	1	220	234	3
2	4	1	150	143	6
3	4	1	76	83	10
4	4	1	101	103	9
5	4	1	94	113	11
6	4	1	168	166	8
7	4	1	221	238	8
-7	5	1	12	29	11
-6	5	1	78	104	17
-5	5	1	0	52	1
-4	5	1	186	177	6
-3	5	1	103	106	8
-2	5	1	55	84	21
-1	5	1	151	154	9
0	5	1	262	267	5
1	5	1	149	154	5
2	5	1	34	84	10
3	5	1	108	106	8
4	5	1	175	177	7
5	5	1	47	52	46
6	5	1	111	104	10
7	5	1	0	29	1
-6	6	1	74	59	16
-5	6	1	0	28	1
-4	6	1	129	128	8
-3	6	1	61	69	15
-2	6	1	153	150	7
-1	6	1	83	84	7
0	6	1	302	294	5
1	6	1	96	84	6
2	6	1	148	150	7
3	6	1	68	68	14
4	6	1	114	128	9
5	6	1	0	28	1
6	6	1	66	59	20
-5	7	1	0	14	1
-4	7	1	96	31	12
-3	7	1	192	195	8
-2	7	1	129	128	8
-1	7	1	132	133	10
0	7	1	169	170	5
1	7	1	58	73	12
2	7	1	126	128	9
3	7	1	108	95	8
4	7	1	41	31	15
5	7	1	40	14	30
-4	8	1	40	20	39
-3	8	1	55	54	26
-2	8	1	24	56	24
-1	8	1	[illegible]	49	24
0	8	1	0	17	1
1	8	1	52	49	15
2	8	1	32	56	32
3	8	1	48	64	37
4	8	1	0	20	1
-2	9	1	28	28	28
-1	9	1	0	16	1
0	9	1	76	42	11
1	9	1	44	16	43
2	9	1	47	28	33
1	0	2	577	581	1
2	0	2	592	590	3
3	0	2	417	368	3
4	0	2	125	126	6
5	0	2	442	426	5
6	0	2	107	108	9
7	0	2	62	78	20
8	0	2	19	14	18
-8	1	2	0	4	1
-7	1	2	86	88	11
-6	1	2	77	89	12
-5	1	2	59	62	15
-4	1	2	644	609	4
-3	1	2	373	358	3
-2	1	2	334	331	3
-1	1	2	880	891	16
0	1	2	788	834	14
1	1	2	890	892	7
2	1	2	322	331	3
3	1	2	354	358	4
4	1	2	626	609	4
5	1	2	78	62	9
6	1	2	89	89	11
7	1	2	96	88	10
8	1	2	12	4	11
-1	2	2	498	502	3
0	2	2	301	309	3
1	2	2	497	502	3
2	2	2	214	219	4
3	2	2	196	200	4
4	2	2	106	91	7
5	2	2	195	198	6
6	2	2	169	160	7
7	2	2	31	30	31
8	2	2	118	127	12
-1	3	2	226	232	4
0	3	2	158	164	4
1	3	2	225	232	4
2	3	2	639	634	3
3	3	2	191	198	5
4	3	2	142	133	6
5	3	2	255	260	6
6	3	2	226	236	7
7	3	2	170	161	9
8	3	2	91	67	12
-1	4	2	169	176	5
0	4	2	226	225	4
1	4	2	175	176	5
2	4	2	456	451	4
3	4	2	254	240	4
4	4	2	76	74	11
5	4	2	197	191	6
6	4	2	337	319	6
7	4	2	83	82	16
-1	5	2	165	167	6
0	5	2	8	21	8
1	5	2	171	167	6
2	5	2	275	279	5
3	5	2	75	67	11
4	5	2	62	74	18
5	5	2	324	333	6
6	5	2	114	141	12
7	5	2	48	38	27
-1	6	2	67	60	12
0	6	2	165	152	8
1	6	2	52	60	18
2	6	2	130	110	8
3	6	2	59	27	14
4	6	2	54	29	18
5	6	2	64	66	19
6	6	2	49	75	35
-1	7	2	113	92	9
0	7	2	226	238	7
1	7	2	114	93	9
2	7	2	44	51	38
3	7	2	89	83	16
4	7	2	198	210	8
5	7	2	114	117	11
-1	8	2	95	94	12
0	8	2	65	87	22
1	8	2	113	94	9
2	8	2	0	32	1
3	8	2	33	34	15
4	8	2	0	9	1
-1	9	2	91	97	12
0	9	2	32	39	32
1	9	2	100	97	11
2	9	2	39	46	38
1	0	3	379	388	3
2	0	3	788	771	3
3	0	3	57	47	11
4	0	3	299	278	4
5	0	3	130	142	7
6	0	3	0	38	1
7	0	3	0	31	1
8	0	3	203	208	8
-8	1	3	100	96	12
-7	1	3	77	34	12
-6	1	3	67	50	13
-5	1	3	203	204	5
-4	1	3	175	165	5
-3	1	3	277	268	3
-2	1	3	553	540	3
-1	1	3	356	362	8
0	1	3	40	34	8
1	1	3	365	361	4
2	1	3	565	540	3
3	1	3	267	268	4
4	1	3	152	165	6
5	1	3	202	204	5
6	1	3	54	50	18
7	1	3	18	34	17
8	1	3	91	96	12
-1	2	3	298	304	3
0	2	3	152	165	4
1	2	3	304	304	3
2	2	3	411	399	3
3	2	3	170	167	5
4	2	3	152	145	6
5	2	3	196	195	6
6	2	3	49	45	23
7	2	3	65	44	14
8	2	3	155	155	10
-1	3	3	138	133	5
0	3	3	63	77	10
1	3	3	138	133	5
2	3	3	722	714	4
3	3	3	94	92	7
4	3	3	238	241	5
5	3	3	51	61	16
6	3	3	162	171	8
7	3	3	78	113	19
8	3	3	105	132	10
-1	4	3	335	336	4
0	4	3	156	157	5
1	4	3	327	336	4
2	4	3	235	259	6
3	4	3	0	20	1
4	4	3	126	113	8
5	4	3	189	196	7
6	4	3	34	77	33
7	4	3	103	107	12
-1	5	3	38	18	32
0	5	3	70	55	10
1	5	3	23	18	23
2	5	3	59	75	18
3	5	3	62	53	13
4	5	3	98	91	9
5	5	3	36	32	19
6	5	3	39	30	38
7	5	3	46	82	45
-1	6	3	20	50	20
0	6	3	129	133	8
1	6	3	51	50	18
2	6	3	165	167	7
3	6	3	92	87	10
4	6	3	90	92	12
5	6	3	31	35	13
6	6	3	38	33	37
-1	7	3	217	207	7
0	7	3	142	140	9
1	7	3	192	201	3
2	7	3	[illegible]	[illegible]	9
3	7	3	60	66	21
4	7	3	[illegible]	89	27
5	7	3	[illegible]	58	22
-1	8	3	135	128	9
0	8	3	133	128	9
1	8	3	[illegible]	[illegible]	9
2	8	3	33	31	14
3	8	3	50	59	22
4	8	3	0	22	1
-1	9	3	67	45	15
0	9	3	0	16	1
1	9	3	35	45	34
2	9	3	102	59	9
0	0	4	2052	2168	2
1	0	4	221	201	2
2	0	4	672	654	3
3	0	4	343	369	4
4	0	4	466	455	4
5	0	4	230	219	5
6	0	4	25	22	24
7	0	4	48	10	21
8	0	4	59	51	25
-8	1	4	118	121	10
-7	1	4	74	39	13
-6	1	4	120	120	8
-5	1	4	69	68	12
-4	1	4	98	68	7
-3	1	4	440	454	3
-2	1	4	378	367	3
-1	1	4	754	764	13
0	1	4	1198	1236	23
1	1	4	771	764	4
2	1	4	383	367	3
3	1	4	446	454	4
4	1	4	83	68	9
5	1	4	67	68	12
6	1	4	113	121	9
7	1	4	63	39	16
8	1	4	117	121	11
-1	2	4	309	314	3
0	2	4	0	18	1
1	2	4	313	314	3
2	2	4	224	231	4
3	2	4	45	66	15
4	2	4	44	67	19
5	2	4	0	22	1
6	2	4	178	174	7
7	2	4	95	100	12
8	2	4	0	52	1
-1	3	4	330	342	4
0	3	4	443	467	3
1	3	4	324	341	4
2	3	4	330	315	4
3	3	4	209	203	4
4	3	4	294	294	5
5	3	4	152	145	7
6	3	4	276	279	7
7	3	4	127	123	9
8	3	4	16	47	16
-1	4	4	183	169	5
0	4	4	120	118	6
1	4	4	162	168	6
2	4	4	159	156	6
3	4	4	226	212	5
4	4	4	166	162	6
5	4	4	84	92	13
6	4	4	149	143	9
7	4	4	51	67	35
-1	5	4	134	129	7
0	5	4	44	33	16
1	5	4	138	129	6
2	5	4	42	62	27
3	5	4	32	92	10
4	5	4	13	35	13
5	5	4	123	122	9
6	5	4	265	266	7
7	5	4	0	17	1
-1	6	4	89	86	10
0	6	4	165	169	7
1	6	4	64	36	14
2	6	4	58	45	18
3	6	4	102	98	7
4	6	4	0	48	1
5	6	4	24	46	24
6	6	4	0	6	1
-1	7	4	140	159	9
0	7	4	198	195	7
1	7	4	144	159	9
2	7	4	132	126	9
3	7	4	21	35	21
4	7	4	50	37	29
5	7	4	47	37	27
-1	8	4	87	34	13
0	8	4	347	335	7
1	8	4	93	[illegible]	11
2	8	4	48	64	28
3	8	4	124	133	11
4	8	4	116	118	11

Table 6. Observed and calculated structure factors for $C_{18}H_{20}O_5$

h	k	l	10Fo	10Fc	10s
-1	9	4	37	70	36
0	9	4	28	6	28
1	9	4	77	70	14
2	9	4	0	17	1
1	0	5	319	300	2
2	0	5	0	27	1
3	0	5	278	268	4
4	0	5	110	102	7
5	0	5	318	310	5
6	0	5	96	110	11
7	0	5	29	23	29
8	0	5	0	56	1
-8	1	5	101	106	13
-7	1	5	109	120	10
-6	1	5	0	17	1
-5	1	5	72	93	11
-4	1	5	319	302	4
-3	1	5	378	388	4
-2	1	5	133	132	5
-1	1	5	463	468	9
0	1	5	172	170	3
1	1	5	469	468	2
2	1	5	132	131	5
3	1	5	378	388	4
4	1	5	311	302	4
5	1	5	87	93	9
6	1	5	0	17	1
7	1	5	114	120	10
8	1	5	110	106	10
-1	2	5	298	315	3
0	2	5	585	623	3
1	2	5	300	315	3
2	2	5	160	154	5
3	2	5	153	150	5
4	2	5	92	91	7
5	2	5	71	62	12
6	2	5	36	75	36
7	2	5	48	33	26
8	2	5	81	69	14
-1	3	5	179	174	5
0	3	5	41	20	15
1	3	5	169	174	5
2	3	5	141	129	5
3	3	5	41	36	19
4	3	5	173	180	6
5	3	5	109	104	8
6	3	5	193	190	8
7	3	5	80	84	16
8	3	5	37	17	36
-1	4	5	313	305	4
0	4	5	180	181	5
1	4	5	315	305	4
2	4	5	407	400	4
3	4	5	80	69	10
4	4	5	80	35	11
5	4	5	113	100	8
6	4	5	182	182	8
7	4	5	56	97	24
-1	5	5	98	95	3
0	5	5	46	52	16
1	5	5	74	95	11
2	5	5	103	130	9
3	5	5	53	40	15
4	5	5	73	60	13
5	5	5	62	52	17
6	5	5	85	102	16
7	5	5	58	50	22
-1	6	5	82	90	12
0	6	5	362	352	5
1	6	5	79	90	12
2	6	5	158	146	7
3	6	5	112	83	9
4	6	5	125	109	9
5	6	5	0	21	1
6	6	5	0	39	1
-1	7	5	77	72	16
0	7	5	157	163	3
1	7	5	58	73	20
[illegible]	[illegible]	5	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	5	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	5	88	[illegible]	[illegible]
[illegible]	[illegible]	5	85	[illegible]	[illegible]
[illegible]	8	5	[illegible]	[illegible]	22
[illegible]	8	5	93	[illegible]	6
[illegible]	8	5	[illegible]	[illegible]	[illegible]
[illegible]	8	5	[illegible]	[illegible]	3
[illegible]	8	5	88	[illegible]	[illegible]
[illegible]	8	5	40	[illegible]	40
[illegible]	8	5	91	31	14

h	k	l	10Fo	10Fc	10s
1	9	5	51	19	16
0	0	6	483	554	3
1	0	6	[illegible]	764	7
2	0	6	257	256	3
3	0	6	53	48	12
4	0	6	55	64	15
5	0	6	0	28	1
6	0	6	207	203	6
7	0	6	49	55	25
8	0	6	54	54	25
-8	1	6	94	85	12
-7	1	6	84	76	12
-6	1	6	41	58	40
-5	1	6	136	131	6
-4	1	6	325	300	4
-3	1	6	129	118	5
-2	1	6	236	234	4
-1	1	6	645	669	13
0	1	6	133	138	5
1	1	6	654	669	3
2	1	6	241	234	4
3	1	6	120	118	6
4	1	6	322	300	4
5	1	6	138	131	6
6	1	6	44	58	29
7	1	6	55	76	26
8	1	6	109	85	11
-1	2	6	79	74	8
0	2	6	101	97	6
1	2	6	85	74	7
2	2	6	117	118	6
3	2	6	326	303	4
4	2	6	69	52	9
5	2	6	142	140	7
6	2	6	152	149	7
7	2	6	122	124	10
8	2	6	77	66	14
-1	3	6	184	177	5
0	3	6	0	5	1
1	3	6	177	177	5
2	3	6	476	455	4
3	3	6	271	258	4
4	3	6	79	62	9
5	3	6	77	36	13
6	3	6	102	95	11
7	3	6	81	88	15
8	3	6	0	4	1
-1	4	6	211	199	5
0	4	6	219	222	5
1	4	6	212	199	5
2	4	6	264	252	5
3	4	6	160	164	6
4	4	6	93	88	10
5	4	6	107	118	10
6	4	6	273	267	6
7	4	6	73	61	15
-1	5	6	65	61	11
0	5	6	56	3	11
1	5	6	59	60	12
2	5	6	234	227	6
3	5	6	73	31	12
4	5	6	136	123	7
5	5	6	135	131	8
6	5	6	155	124	9
7	5	6	0	33	1
-1	6	6	0	27	1
0	6	6	110	127	11
1	6	6	53	27	15
2	6	6	71	74	14
3	6	6	65	63	14
4	6	6	95	100	12
5	6	6	104	106	10
6	6	6	38	60	38
-1	7	6	151	151	9
0	7	6	0	0	1
1	7	6	139	151	9
2	7	6	132	129	32
3	7	6	[illegible]	75	12
[illegible]	7	6	105	[illegible]	12
[illegible]	[illegible]	6	[illegible]	87	14
[illegible]	8	6	[illegible]	99	12
[illegible]	8	6	104	86	11
[illegible]	8	6	104	99	11
[illegible]	8	6	[illegible]	47	[illegible]
[illegible]	8	6	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	6	89	65	14
[illegible]	[illegible]	6	[illegible]	86	22
[illegible]	[illegible]	6	[illegible]	0	20
[illegible]	[illegible]	6	[illegible]	36	47
[illegible]	0	7	583	583	6

h	k	l	10Fo	10Fc	10s
2	0	7	181	168	4
3	0	7	108	100	5
4	0	7	279	271	5
5	0	7	95	107	9
6	0	7	130	137	3
7	0	7	33	37	33
8	0	7	181	169	9
-8	1	7	140	144	10
-7	1	7	115	98	9
-6	1	7	52	44	18
-5	1	7	63	61	13
-4	1	7	363	351	4
-3	1	7	146	156	5
-2	1	7	403	391	3
-1	1	7	567	583	7
0	1	7	354	358	8
1	1	7	575	583	2
2	1	7	406	391	3
3	1	7	162	156	5
4	1	7	358	351	4
5	1	7	39	61	38
6	1	7	45	44	22
7	1	7	95	98	13
8	1	7	141	144	10
-1	2	7	269	282	4
0	2	7	37	8	18
1	2	7	278	282	4
2	2	7	94	87	7
3	2	7	108	100	6
4	2	7	135	136	6
5	2	7	63	58	14
6	2	7	96	93	9
7	2	7	100	91	10
8	2	7	56	8	18
-1	3	7	143	153	6
0	3	7	64	41	8
1	3	7	156	153	5
2	3	7	408	397	4
3	3	7	145	132	6
4	3	7	147	135	6
5	3	7	121	103	8
6	3	7	166	160	8
7	3	7	151	145	8
-1	4	7	345	346	5
0	4	7	208	206	5
1	4	7	342	346	5
2	4	7	108	110	8
3	4	7	107	85	7
4	4	7	88	63	9
5	4	7	251	247	6
6	4	7	21	60	21
7	4	7	59	48	22
-1	5	7	54	47	15
0	5	7	53	80	21
1	5	7	73	47	10
2	5	7	289	282	5
3	5	7	78	72	12
4	5	7	17	15	17
5	5	7	73	69	16
6	5	7	60	50	18
-1	6	7	163	174	3
0	6	7	77	92	12
1	6	7	179	174	7
2	6	7	73	61	12
3	6	7	0	52	1
4	6	7	0	29	1
5	6	7	120	113	9
6	6	7	0	17	1
-1	7	7	137	144	9
0	7	7	0	24	1
1	7	7	155	144	8
2	7	7	105	83	9
3	7	7	37	27	37
4	7	7	79	87	16
5	7	7	43	38	43
-1	8	7	133	140	10
0	8	7	65	87	20
1	8	7	130	140	[illegible]
2	8	7	93	73	12
3	8	7	66	36	[illegible]
[illegible]	0	8	418	436	[illegible]
[illegible]	0	8	320	318	[illegible]
2	0	8	164	163	5
3	0	8	265	263	5
[illegible]	0	8	186	195	[illegible]
[illegible]	0	8	0	33	[illegible]
[illegible]	0	8	31	36	31
[illegible]	0	8	115	120	[illegible]
[illegible]	0	8	84	88	15
-8	1	8	26	28	25

h	k	l	10Fo	10Fc	10s
-7	1	8	43	46	42
-6	1	8	22	26	22
-5	1	8	57	72	16
-4	1	8	266	253	5
-3	1	8	46	41	17
-2	1	8	129	118	5
-1	1	8	28	70	8
0	1	8	164	170	7
1	1	8	127	70	28
2	1	8	120	118	6
3	1	8	71	41	8
4	1	8	262	253	5
5	1	8	79	71	10
6	1	8	0	26	1
7	1	8	72	46	15
8	1	8	50	28	24
-1	2	8	76	38	3
0	2	8	22	36	21
1	2	8	82	88	7
2	2	8	157	166	5
3	2	8	90	75	7
4	2	8	168	171	6
5	2	8	93	88	9
6	2	8	128	143	9
7	2	8	155	153	8
8	2	8	35	56	35
-1	3	8	132	138	6
0	3	8	265	267	4
1	3	8	130	138	6
2	3	8	264	261	5
3	3	8	126	123	6
4	3	8	0	33	1
5	3	8	38	13	38
6	3	8	170	165	8
7	3	8	50	50	31
-1	4	8	63	36	11
0	4	8	30	35	29
1	4	8	41	36	22
2	4	8	185	187	6
3	4	8	188	170	6
4	4	8	83	90	10
5	4	8	87	81	11
6	4	8	252	252	7
7	4	8	111	95	10
-1	5	8	35	20	35
0	5	8	151	147	6
1	5	8	42	20	19
2	5	8	52	44	16
3	5	8	0	25	1
4	5	8	56	66	20
5	5	8	98	86	11
6	5	8	73	77	17
-1	6	8	122	123	10
0	6	8	62	61	16
1	6	8	103	123	11
2	6	8	100	90	9
3	6	8	20	3	20
4	6	8	82	83	12
5	6	8	71	20	13
6	6	8	53	31	21
-1	7	8	132	114	8
0	7	8	167	170	8
1	7	8	91	114	14
2	7	8	60	50	18
3	7	8	47	45	24
4	7	8	139	134	9
5	7	8	44	63	43
-1	8	8	33	54	33
0	8	8	158	151	9
1	8	8	75	54	14
2	8	8	79	90	15
3	8	8	68	64	18
[illegible]	0	9	122	122	4
2	0	9	184	177	5
3	0	9	203	205	5
[illegible]	0	9	90	35	9
[illegible]	0	9	220	208	6
[illegible]	[illegible]	9	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	9	[illegible]	[illegible]	10
[illegible]	[illegible]	9	[illegible]	[illegible]	20
[illegible]	[illegible]	9	[illegible]	[illegible]	26
[illegible]	[illegible]	9	[illegible]	163	[illegible]
[illegible]	[illegible]	9	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	9	186	188	[illegible]
[illegible]	[illegible]	9	282	273	5
[illegible]	[illegible]	9	125	128	6
[illegible]	[illegible]	9	134	131	6
[illegible]	[illegible]	9	204	199	3
[illegible]	[illegible]	9	521	525	[illegible]
[illegible]	[illegible]	9	204	199	5

h	k	l	10Fo	10Fc	10s
2	1	9	138	130	6
3	1	9	129	128	6
4	1	9	274	273	5
5	1	9	195	188	6
6	1	9	35	111	13
7	1	9	153	163	9
8	1	9	31	57	31
-1	2	9	67	63	10
0	2	9	391	394	4
1	2	9	50	62	15
2	2	9	275	269	4
3	2	9	220	215	5
4	2	9	218	222	5
5	2	9	77	83	13
6	2	9	104	97	10
7	2	9	45	27	29
-1	3	9	280	275	5
0	3	9	32	31	8
1	3	9	265	275	5
2	3	9	112	108	7
3	3	9	154	167	6
4	3	9	63	60	13
5	3	9	93	90	10
6	3	9	80	75	13
7	3	9	134	133	10
-1	4	9	141	142	6
0	4	9	22	31	21
1	4	9	138	142	6
2	4	9	307	307	5
3	4	9	75	83	11
4	4	9	43	41	29
5	4	9	82	75	11
6	4	9	111	109	11
7	4	9	0	38	1
-1	5	9	84	90	10
0	5	9	0	8	1
1	5	9	95	91	9
2	5	9	114	125	10
3	5	9	43	56	24
4	5	9	119	123	9
5	5	9	28	51	28
6	5	9	104	104	11
-1	6	9	103	106	11
0	6	9	143	142	8
1	6	9	103	106	10
2	6	9	47	42	25
3	6	9	105	110	10
4	6	9	30	26	30
5	6	9	113	105	10
-1	7	9	83	80	14
0	7	9	105	98	11
1	7	9	85	79	14
2	7	9	89	73	12
3	7	9	86	74	11
4	7	9	71	64	15
-1	8	9	44	20	43
0	8	9	104	122	14
1	8	9	63	20	15
2	8	9	73	32	15
3	8	9	56	39	18
0	0	10	570	575	4
1	0	10	137	130	4
2	0	10	0	3	[illegible]
3	0	10	48	22	15
4	0	10	188	190	6
5	0	10	36	48	36
6	0	10	66	67	16
7	0	10	22	14	21
-7	1	10	100	38	[illegible]
-6	1	10	98	107	[illegible]
-5	1	10	39	49	38
-4	1	10	130	115	7
-3	1	10	235	[illegible]	[illegible]
-2	1	10	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	10	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	10	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	10	377	[illegible]	[illegible]
[illegible]	[illegible]	10	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	10	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	10	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	10	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	10	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	10	209	[illegible]	[illegible]
[illegible]	[illegible]	10	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	10	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	10	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	10	[illegible]	[illegible]	33

Table 6. Observed and calculated structure factors for C18H20O5

h	k	l	10Fo	10Fc	10s
6	2	10	60	44	17
7	2	10	77	66	14
-1	3	10	182	180	6
0	3	10	46	0	14
1	3	10	183	180	5
2	3	10	261	235	5
3	3	10	112	119	3
4	3	10	0	45	1
5	3	10	45	72	39
6	3	10	110	119	11
7	3	10	41	40	40
-1	4	10	284	283	5
0	4	10	50	57	16
1	4	10	284	283	5
2	4	10	39	39	38
3	4	10	110	108	3
4	4	10	86	76	11
5	4	10	85	83	12
6	4	10	40	48	39
7	4	10	71	55	16
-1	5	10	71	79	12
0	5	10	239	232	6
1	5	10	45	79	25
2	5	10	76	69	12
3	5	10	118	101	8
4	5	10	37	52	37
5	5	10	121	110	9
6	5	10	51	58	27
-1	6	10	101	75	9
0	6	10	43	63	43
1	6	10	71	75	15
2	6	10	61	51	16
3	6	10	91	65	10
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3	7	10	71	78	16
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2	0	11	82	100	8
3	0	11	103	89	8
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6	0	11	31	67	31
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2	0	12	81	81	9
3	0	12	46	60	20
4	0	12	49	60	24
5	0	12	106	116	10
6	0	12	147	155	9
7	0	12	136	103	8
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-3	1	13	156	173	7
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1	1	14	135	132	5
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3	1	14	67	76	14
4	1	14	87	84	11
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4	2	14	146	147	9
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1	4	14	263	261	6
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3	4	14	158	174	8
4	4	14	99	100	12
5	4	14	115	113	10
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1	5	14	118	116	9
2	5	14	67	75	17
3	5	14	107	109	11
4	5	14	69	48	15
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2	0	15	95	115	11
3	0	15	42	49	42
4	0	15	0	5	1
5	0	15	0	38	1
6	0	15	79	68	16
-6	1	15	0	36	1
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-4	1	15	205	213	7
-3	1	15	123	123	9
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0	5	15	162	166	9
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2	5	15	57	47	22
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4	5	15	75	76	16
-1	6	15	75	86	17
0	6	15	124	108	10
1	6	15	70	86	17
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0	7	15	54	42	24
1	7	15	78	91	17
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1	0	16	43	60	42
2	0	16	43	49	26
3	0	16	52	20	20
4	0	16	211	213	7
5	0	16	61	75	21
6	0	16	19	30	19
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0	1	16	153	151	8
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3	1	16	56	69	19
4	1	16	106	83	11
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3	4	16	21	24	21
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2	5	16	136	157	10
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3	6	16	53	68	28
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2	0	17	0	10	[illegible]
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4	0	17	0	34	[illegible]
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-2	1	17	97	81	10
-1	1	17	37	[illegible]	23
0	1	17	165	162	[illegible]
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2	1	17	92	[illegible]	15
3	1	17	82	[illegible]	[illegible]
4	1	17	38	[illegible]	13
5	1	17	98	[illegible]	[illegible]
6	1	17	83	38	[illegible]
-1	2	17	60	[illegible]	37
0	2	17	28	48	[illegible]
1	2	17	104	[illegible]	10
2	2	17	93	103	12

Table 5. Observed and calculated structure factors for C18H20O5

h	k	l	10Fo	10Fc	10s	h	k	l	10Fo	10Fc	10s	h	k	l	10Fo	10Fc	10s	h	k	l	10Fo	10Fc	10s	h	k	l	10Fo	10Fc	10s
3	2	17	31	34	31	1	1	18	68	63	10	-5	1	19	77	66	15	-4	1	20	92	90	13	0	2	21	47	34	25
4	2	17	113	109	10	2	1	18	105	116	11	-4	1	19	55	44	21	-3	1	20	90	76	13	1	2	21	62	56	17
5	2	17	37	3	37	3	1	18	104	93	10	-3	1	19	64	78	18	-2	1	20	64	43	17	2	2	21	54	67	27
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1	3	17	117	116	9	-1	2	18	86	79	11	0	1	19	61	48	11	1	1	20	53	70	14	0	3	21	49	75	42
2	3	17	96	117	13	0	2	18	133	136	8	1	1	19	58	40	18	2	1	20	44	44	37	1	3	21	39	49	39
3	3	17	15	50	14	1	2	18	33	79	13	2	1	19	35	40	34	3	1	20	94	76	13	2	3	21	55	25	17
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1	4	17	113	118	10	-1	3	18	75	77	15	0	2	19	29	55	29	2	2	20	122	102	9	1	0	22	34	41	33
2	4	17	116	87	9	0	3	18	106	94	10	1	2	19	50	38	22	3	2	20	0	18	1	2	0	22	0	12	1
3	4	17	61	8	19	1	3	18	82	77	12	2	2	19	118	124	9	4	2	20	38	39	38	3	0	22	120	98	11
4	4	17	61	33	16	2	3	18	125	116	9	3	2	19	112	116	11	-1	3	20	103	85	11	-3	1	22	12	11	11
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0	1	18	49	27	17	5	0	19	0	3	1	4	0	20	46	56	45	-1	2	21	58	56	21	1	2	23	0	24	1

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