Novel Methods for the Conversion of Carbohydrates to Carbocycles

University of Leicester

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by

David John Holt
Department of Chemistry
University of Leicester

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ProQuest LLC
789 East Eisenhower Parkway
P.O. Box 1346
Ann Arbor, MI 48106-1346

STATEMENT

The accompanying thesis submitted for the degree of Ph.D. entitled "Novel Methods for the Conversion of Carbohydrates to Carbocycles" is based on work conducted by the author in the Department of Chemistry at the University of Leicester between the period October 1996 to September 1999.

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: David Holt ..... Date: 27/01/00 .....

Parts of this work have been published:

The Stereoselective Preparation of an Enantiomerically Pure Cyclopentane Using Intramolecular Aldol Cyclopentaannulation of a Glucose Derivative; Andrew J. Wood, David J. Holt, Maria-Consuelo Dominguez, and Paul R. Jenkins *J. Org. Chem.* **1998**, *63*, 8522.

Ring-Closing Metathesis in Carbohydrate Annulation; David J. Holt, William D. Barker, Paul R. Jenkins, David L. Davies, Shaun Garratt, John Fawcett, David R. Russell, and Subrata Ghosh *Angew. Chem. Int. Ed.* **1998**, *37*, 3298.

The Copper(I) Catalysed [2+2] Intramolecular Photoannulation of Carbohydrate Derivatives; David J. Holt, William D. Barker, Paul R. Jenkins, Subrata Ghosh, David R. Russell and John Fawcett, *Synlett*, **1999**, S1, 1003-1005.

Stereoselective Preparation of Enantiomerically Pure Annulated Carbohydrates Using Ring-Closing Metathesis; David J. Holt, William D. Barker, Paul R. Jenkins, Jagannath Panda, and Subrata Ghosh *J. Org. Chem.* **2000**, *65*, 482.

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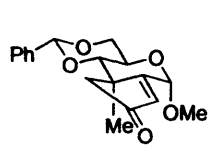
Novel Methods for the Conversion of Carbohydrates to Carbocycles

by David John Holt

ABSTRACT

The 'chiron' approach to the synthesis of chiral target molecules from carbohydrates is now a well established component in the armoury of organic chemistry. A key element of this strategy is the range of methods available for the synthesis of cyclic compounds, which can include *some* or *all* of the carbons of the original carbohydrate (Chapter 1).

The cyclopentaannulated sugar derivative **1**, a product of intramolecular aldol condensation, was treated with *N*-bromosuccinimide (NBS), followed by activated zinc shot, to furnish a *ca.* 4:1 mixture of cyclopentane derivatives **2** and **3** (Chapter 2).



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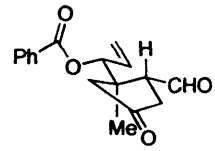

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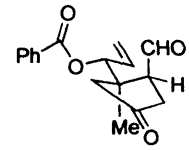

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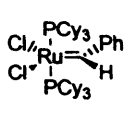
Ring-closing metathesis has been applied to a series of substituted glucose derivatives, employing the Grubbs catalyst **4**, to produce fused enantiomerically pure annulated sugars **5**, containing five- to eight-membered carbocyclic rings (Chapter 3). Copper(I) triflate catalyzed intramolecular [2+2] photocyclization has also been studied as a method for carbohydrate annulation (Chapter 4). Photoannulation of 1,6-diene glucose derivatives leads efficiently to fused tetracyclic enantiomerically pure products, e.g. **6**. Investigations into the fragmentation of these annulated sugars, utilizing NBS and zinc methodology, in an attempt to synthesize enantiomerically pure carbocycles, are also described.



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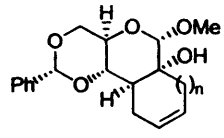
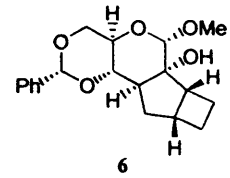


5 (n = 0-3)



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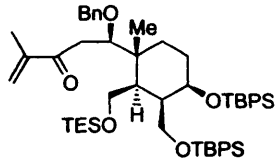
As a continuation of work in the Jenkins group, directed towards the synthesis of a chiral taxoid from glucose, model studies were undertaken to test the viability of an enone to diene conversion, utilizing selenium chemistry (Chapter 5). Even though model studies showed this conversion to be successful, the enone **7** produced the diene **8** in a very poor yield (12%). Alternative methods for diene construction were investigated, including Wittig and Stille chemistry, with a limited amount of success.



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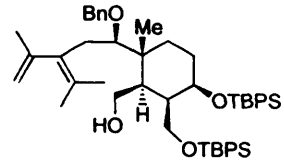

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CHAPTER 1 INTRODUCTION

CHAPTER 5 PROGRESS TOWARDS THE SYNTHESIS OF A CHIRAL TAXOID FROM GLUCOSE

ABBREVIATIONS

10-DAB III	10-deacetyl baccatin III
Ac	acetyl
AIBN	azobisisobutyrylnitrile
BOM	benzyloxymethyl
CI	chemical ionization
DABCO	1,4-diazabicyclo[2.2.2]octane
DBN	1,5-diazabicyclo[3.4.0]non-5-ene
DBU	1,8-diazabicyclo[5.4.0.]undec-7-ene
DIBAH	diisobutylaluminium hydride
DMAP	4-dimethylaminopyridine
DMF	*N,N*-dimethylformamide
DMPU	1,3-dimethyltetrahydro-2(1*H*)-pyrimidone
ee	enantiomeric excess
EE	ethoxyethyl
EI	electron impact
ESR	electron spin resonance
FAB	fast atom bombardment
HPLC	high-pressure liquid chromatography
J	coupling constant
KHMDS	potassium hexamethyldisilazide
LDA	lithium diisopropylamide
LTMP	lithium 2,2,6,6-tetramethylpiperidide
m-CPBA	*meta*-chloroperbenzoic acid
NBS	*N*-bromosuccinimide
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
NOESY	nuclear Overhauser effect spectroscopy
PCC	pyridinium chlorochromate
PPTS	pyridinium *para*-toluene-sulphonate
RCM	ring-closing metathesis
TASF	tris(diethylamino)sulphonium difluorotrimethylsilicate

TBAF	tetrabutylammonium fluoride
TBPS	tertiary butyldiphenylsilyl
TBS	tertiary butyldimethylsilyl
TES	triethylsilyl
Tf	trifluoromethanesulphonyl
THF	tetrahydrofuran
TMSCl	trimethylsilyl chloride
TPAP	tetrapropylammonium perruthenate
TrocCl	2,2,2-trichloroethyl chloroformate
UV	ultraviolet

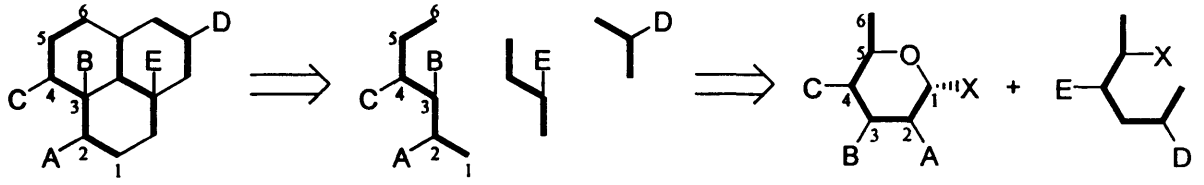
CHAPTER 1

INTRODUCTION

1.1 The Conversion of Carbohydrates to Carbocycles - The 'Chiron' Approach

The practice of natural product synthesis challenges the organic chemist to conquer the formation of enantiomerically pure target molecules. In principle, chiral molecules can be synthesized by using a chiral reagent or by modifying a chiral starting material. Carbohydrates are a cheap, replenishable source of chiral carbon compounds, available in a variety of cyclic and acyclic forms, chain lengths and oxidation states. They contain an abundance of functional, stereochemical and conformational features which lend themselves to chemical manipulation. Therefore, carbohydrates can be utilized as starting materials in the synthesis of natural products, and other target molecules, which contain predisposed centres of asymmetry.

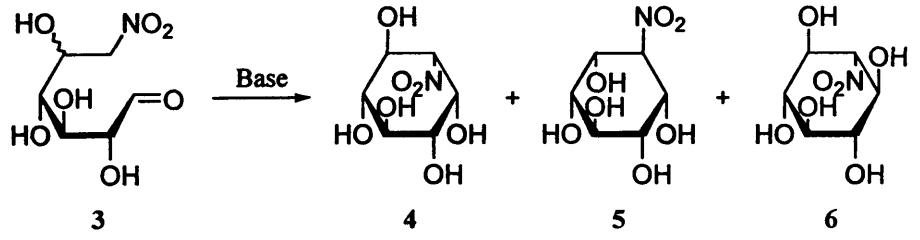
The concept of "chiral templates" and 'chirons' was introduced by Hanessian.[1] A carbohydrate can be visualized as a "chiral template" in the sense that it contains inherent natural chirality which can be related to the stereochemical code of the target molecule, and that the carbon framework is a replica of a segment of the target molecule. A 'chiron' simply represents an enantiomerically pure synthon. Scheme 1 illustrates the synthetic design of a target molecule **1**. The 'chirons' **I**, **II** and **III** are derived from the target molecule by retrosynthetic analysis. The 'chiron' **I** contains the basic acyclic carbohydrate backbone and is produced from a cyclic sugar **2**, via synthetic operations.



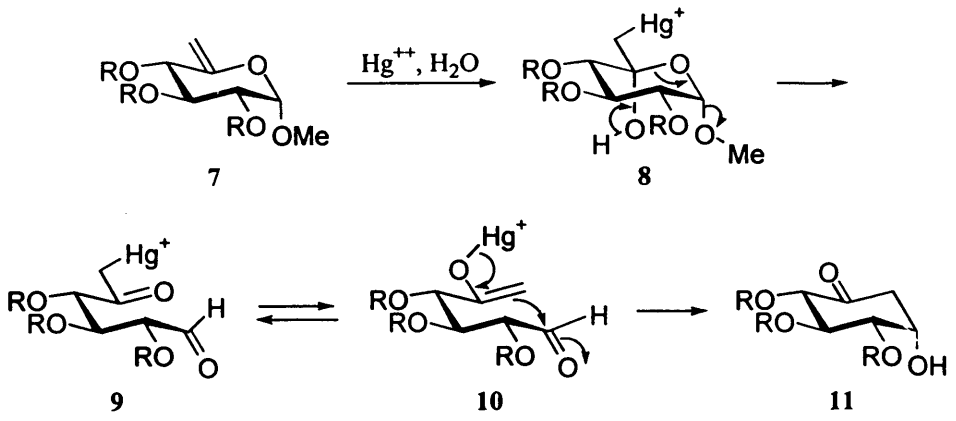
Scheme 1

1.2 Classification of Carbohydrate Annulation

A key element of the 'chiron' approach from carbohydrates is the range of methods available for the synthesis of cyclic compounds. Strategies for the conversion of carbohydrates to carbocycles are of two types; the first involves the cyclization of an open chain sugar derivative so that most, if not *all* the carbons of the sugar are incorporated into the carbocyclic ring. The second type usually involves formation of the carbocycle onto the sugar ring which is then modified or removed, leaving only *some* of the carbons of the sugar in the new carbocyclic ring. The first chemical conversion of a carbohydrate to a carbocycle was carried out by Fischer and co-workers in 1948.[2] Base catalyzed intramolecular aldol-like cyclization of nitro sugar **3** furnished cyclohexane derivatives **4-6**.

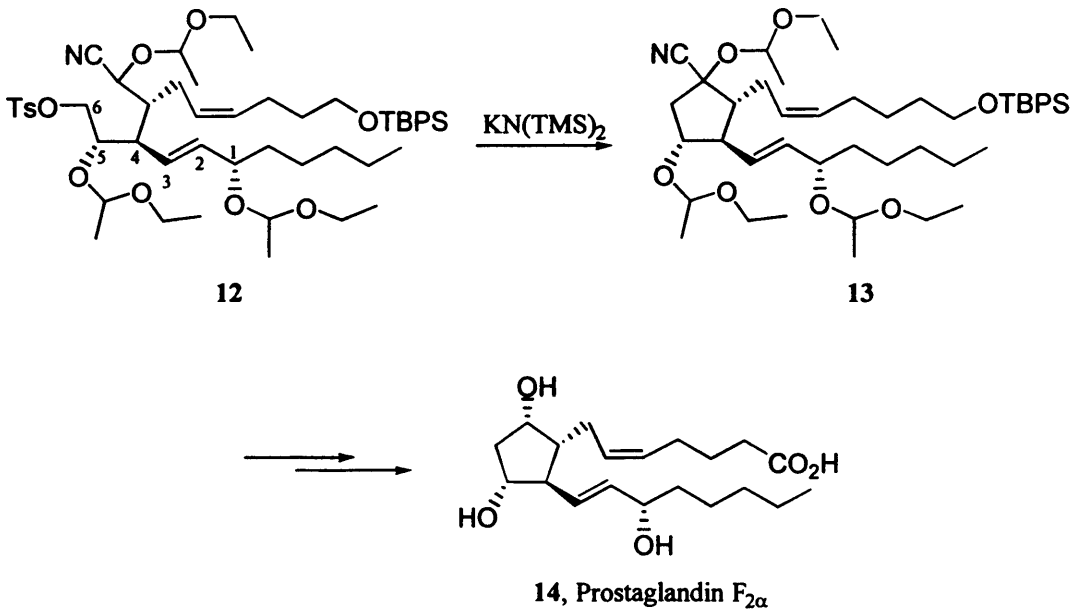


In the last 30 years, pioneering studies on the syntheses of carbasugars, starting from true sugars have been carried out.[3] The work of Ferrier has been instrumental in this field. In 1979, he presented a convenient method for converting carbohydrate derivatives into cyclohexanone analogues (Scheme 2).[4] Upon treatment with mercury(II) chloride in the presence of water, the double bond of unsaturated derivative **7** is hydroxymercuriated to afford the hemiacetal **8**, which spontaneously opens to the keto aldehyde **9**, mercuriated at the carbon α to the carbonyl group. This intermediate gives the product **11**, via aldol-like condensation, probably through the enolic form **10**. We find it convenient to classify this type of reaction as an **'F-type' annulation**, after Ferrier, where *all* the carbons of the sugar are incorporated into the carbocyclic ring, leading to a "carbohydrate-like" product.



Scheme 2

A milestone in the use of carbohydrates in the synthesis of non-carbohydrate natural products was emphatically shown by Stork and co-workers in the synthesis of prostaglandin $F_{2\alpha}$ (**14**), by chiral transfer from D-glucose.[5] Intramolecular displacement of the tosyloxy group by the nitrile-stabilized carbanion of **12** furnished the chiral cyclopentane derivative **13** in good yield (Scheme 3). We can classify this type of reaction as an **'S-type' annulation**, after Stork, where only *some* of the carbons of the sugar are incorporated into the carbocyclic ring, leading to a "carbohydrate-unlike" product.



14, Prostaglandin $F_{2\alpha}$

Scheme 3

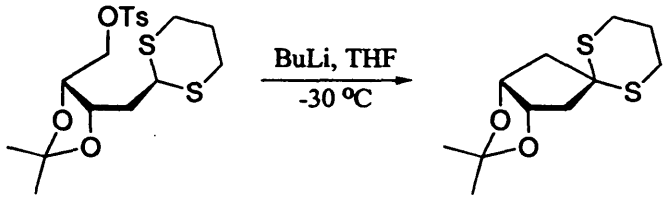
1.3 Syntheses of Functionalized Cyclopentanes from Carbohydrates

A. Carbanion Cyclizations

In the majority of cases, the conversion of carbohydrates into cyclopentane and cyclohexane derivatives involves intramolecular nucleophilic displacement by carbanions or carbanion equivalents. These carbanions are usually generated by proton abstraction α to a stabilizing group, e.g. carbonyl, phosphonate and nitro groups.

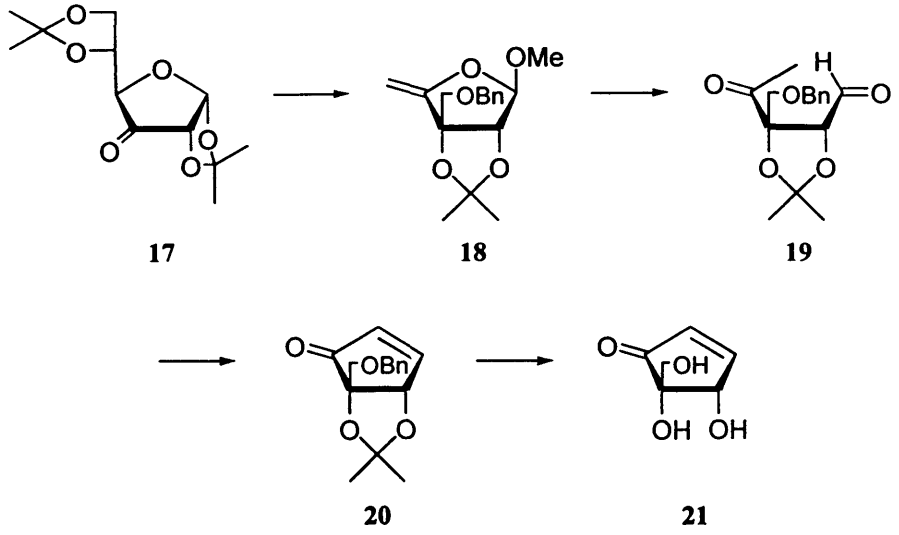
(i) 'F-Type' Reactions

Carbanions derivable from 1,3-dithianes can be used to form cyclopentane rings. This was illustrated in the case of 2-deoxy-D-ribose dithioacetal **15**, from which, with *n*-butyllithium, a sulphur-stabilized carbanion was produced to displace the tosyloxy group and furnish the cyclopentane **16** in a 71% yield.[6]



15 **16**, 71%

The formation of cyclopentane derivatives from carbohydrate-derived 1,4-dicarbonyl compounds is well documented. The cyclization step is a 5-*exo-trig* process,[7] and in most cases the resulting β-ketols undergo dehydration to give thermodynamically stable conjugated enones. This type of reaction was first published by the Moffatt group as a key step in the synthesis of the antibiotic pentenomycin I (**21**) (Scheme 4).[8] The α-D-*ribo*-hexofuranos-3-ulose derivative **17** was converted into the unsaturated glycoside **18**. Subsequent selective hydrolysis of **18** afforded the keto aldehyde **19**, which underwent aldol cyclization on treatment with neutral alumina at 100-120 °C to furnish the enone **20**. Deprotection of enone **20** ultimately gave the antibiotic pentenomycin I (**21**).

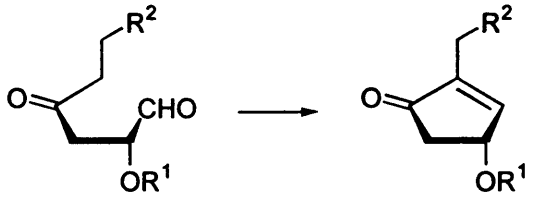


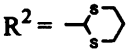
17 18 19

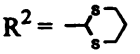
20 21

Scheme 4

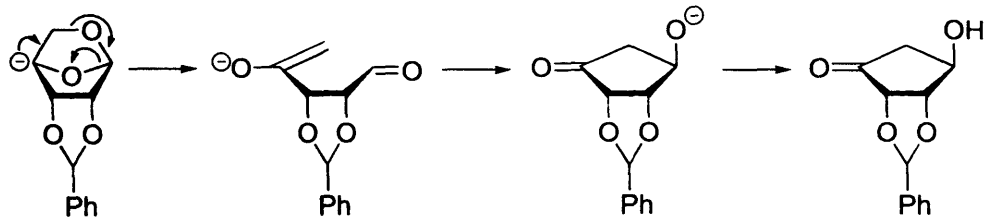
Achab and Das cyclized the 1,4-dicarbonyl **22**, a derivative of diacetone glucose, by treatment with 0.1M sodium hydroxide, affording the potential prostaglandin E_2 precursor **24** in a 35% yield.[9] Similarly, Umani-Ronchi and co-workers found that, on treatment with barium hydroxide in methanol at room temperature, keto aldehyde **23** furnished silyloxy enone **25** in a 33% yield, together with appreciable amounts of the methoxy enone **26** and its enantiomer.[10]



22, R^1 = H
R^2 = 
23, R^1 = TBS
$R^2 = (CH_2)_2OBn$

24, R^1 = H
R^2 = 
25, R^1 = TBS
$R^2 = (CH_2)_2OBn$
26, R^1 = Me
$R^2 = (CH_2)_2OBn$

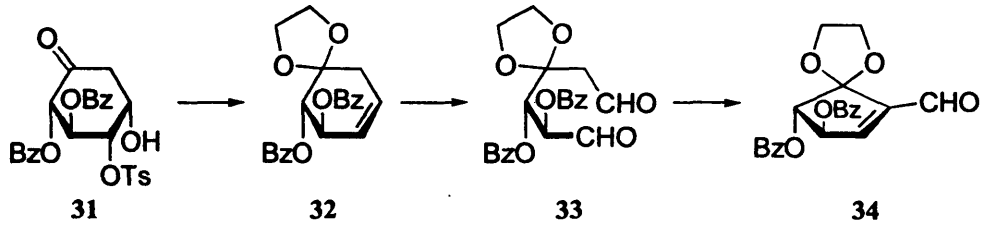
A novel method for generating the enolate of a carbohydrate-derived 1,4-dicarbonyl compound, and ultimately a cyclopentane derivative was proposed by Klemer and Kohla.[11] Treatment of 1,5-anhydro-2,3-*O*-benzylidene-β-D-ribofuranose with LDA generated carbanion **27**, enolate **28**, cycloalkoxide **29** and finally the β-ketol **30** (Scheme 5).



27 **28** **29** **30**

Scheme 5

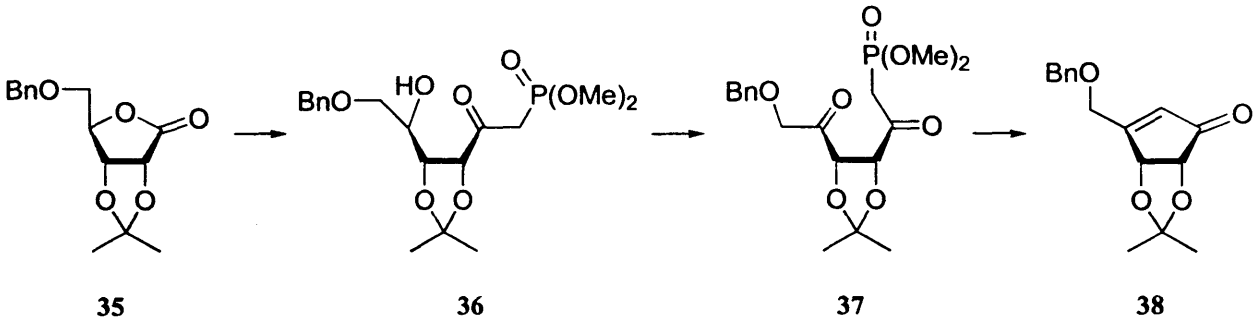
Ferrier and co-workers provided the only recorded instance of cyclopentane ring formation from a carbohydrate-derived 1,6-dicarbonyl compound.[12] Cyclohexanone **31**, a derivative of methyl-α-D-glucopyranoside, was easily converted to the 1,6-dialdehyde **33**, via cyclohexene **32**. Kinetically favoured aldol cyclization of dialdehyde **33**, using pyrrolidinium acetate in benzene, furnished the cyclopentene derivative **34** (Scheme 6).



31 **32** **33** **34**

Scheme 6

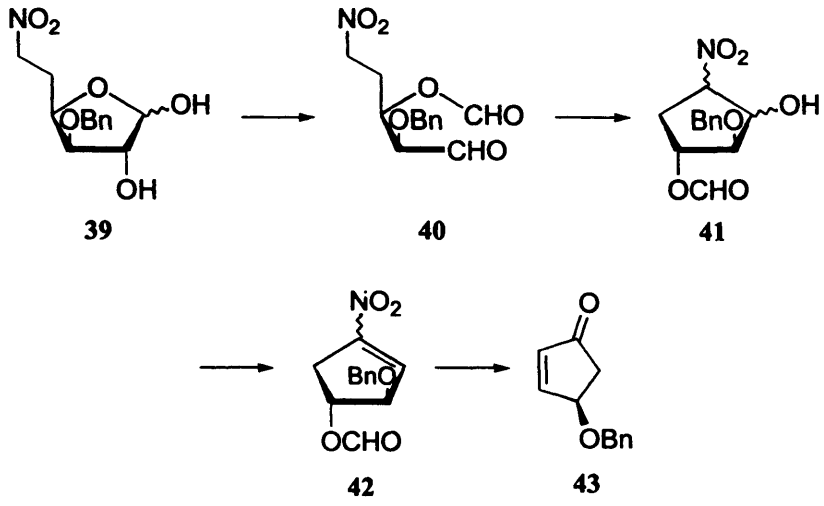
Reactions involving aldol-like cyclization of carbanions, which are stabilized by neighbouring phosphonate and carbonyl groups, have been utilized in the enantioselective synthesis of cyclopentane derivatives from carbohydrates. Lim and Marquez[13] treated the lactone **35** with lithium dimethyl methyl phosphonate, followed by sodium methoxide in methanol, furnishing the ring-opened alcohol **36**. Oxidation to the 1,4-dicarbonyl **37**, followed by subsequent heating with potassium carbonate and 18-crown-6 in a hydrocarbon solvent, effected cyclization to the cyclopentenone **38** (Scheme 7). A very similar approach has been used by other research groups, where the cyclization precursors are of the same structural type as **37**.[14]



35 36 37 38

Scheme 7

Torii *et al.* have reported the synthesis of a cyclopentane derivative by cyclization of a nitro sugar.[15] Nitrofuranose **39**, a derivative of diacetone glucose, was treated with periodate, affording the open-chain aldehyde **40**. On reaction with triethylamine, **40** cyclized to give a mixture of stereoisomeric nitrocyclopentanols **41**. The chiral prostaglandin synthon **43** was readily synthesized from **41**, via nitroalkene **42** (Scheme 8).

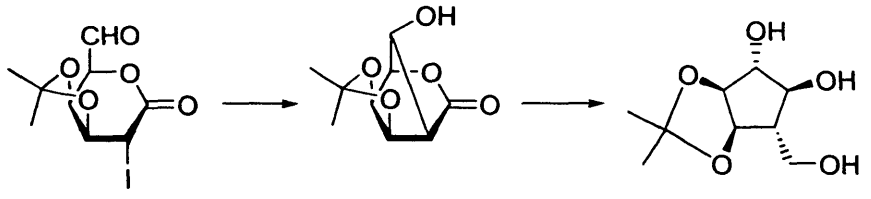


39 40 41 42 43

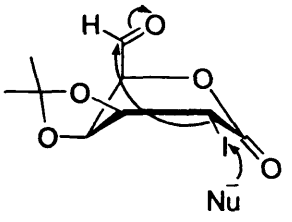
Scheme 8

(ii) 'S-Type' Reactions

Fleet and co-workers have developed an original cyclization, involving treatment of α-iodolactone **44** with lithium iodide in tetrahydrofuran.[16] The derived enolate attacks the aldehyde intramolecularly to give the cyclopentane **45**, from which the triol **46** was obtained by reduction (Scheme 9). The reaction is thought to proceed via the proposed boat-like conformation **47**.



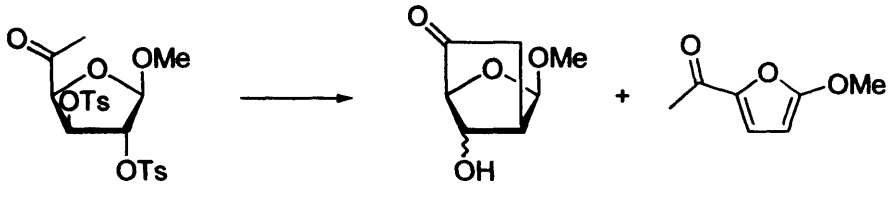
44 **45** **46**



47

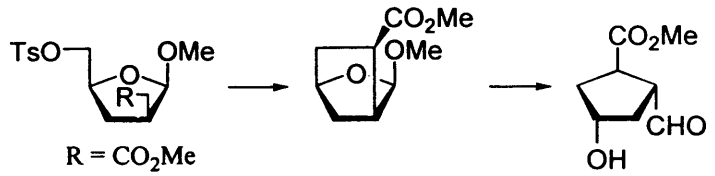
Scheme 9

Early attempts by Ferrier and co-workers to obtain cyclopentane derivatives from carbohydrates, using intramolecular nucleophilic displacement by carbanions, met with limited success.[17] The ditosylate **48**, a D-glucofuranose derivative, furnished bicyclic ketone **49** (or its isomer) in a 34% isolated yield on treatment with DBU at 5 °C. The major product from this reaction was furan **50**, obtained in a 65% isolated yield.

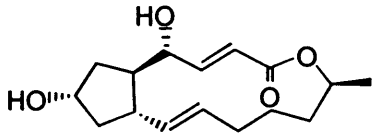


48 **49** **50**

Ohrui and Kuzuhara have used carbohydrate-derived precursors in an approach to (+)-brefeldin A (**54**), a biologically active macrocyclic lactone.[18] The tosylate **51** was treated with lithium hexamethyldisilazide, affording the bicyclic product **52** in a 90% yield. Subsequent hydrolysis of **52** gave the cyclopentane derivative **53**, which contains the functionality and stereochemistry required for its conversion into (+)-brefeldin A (**54**, Scheme 10).



51 **52** **53**



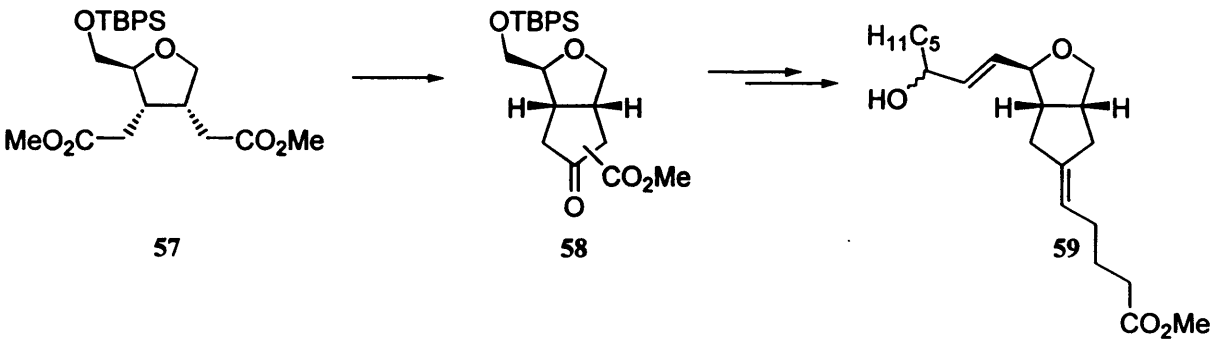
54, (+)-Brefeldin A

Scheme 10

Elegant stereocontrolled syntheses of polycyclic ring systems have been developed by the Fraser-Reid group.[19] For example, the conformationally mobile *cis*-fused oxadecalin derivative **55** was treated with potassium hexamethyldisilazide, to effect conversion to the tricyclic derivative **56**, which was isolated as a single diastereoisomer.

55 R = CO_2Me **56**

Mann and co-workers have successfully formed cyclopentane derivatives **58**, through Dieckmann cyclization of the diester **57**.[20] The keto-esters **58** were subsequently transformed into a mixture of epimers **59**, whose structures are analogous to those of prostacyclin and carbacyclin (Scheme 11).[21]



57 **58** **59**

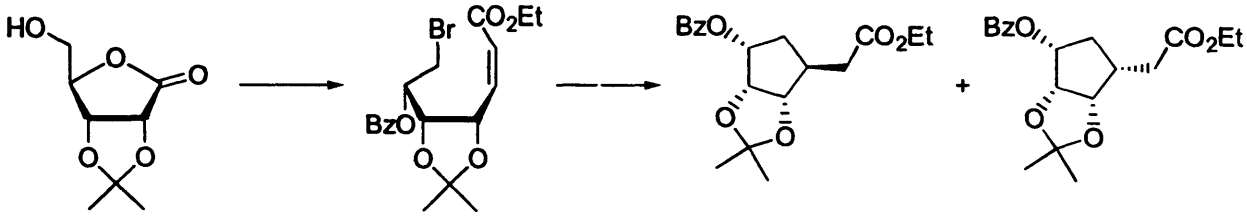
Scheme 11

B. Free-Radical Cyclizations

Over the last 15 years several research groups have shown that radical reactions are highly suited to the formation of cyclopentane derivatives from carbohydrates. In most reactions of this type, the annulation precursor contains a radical source and a radical-acceptor group.

(i) 'F-Type' Reactions

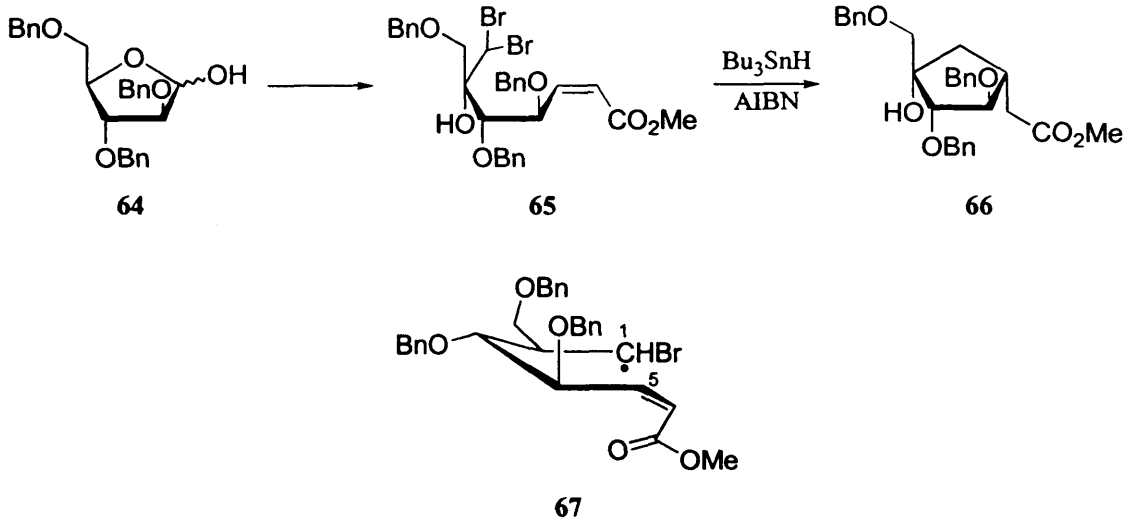
Using the D-ribono-γ-lactone acetal **60** as starting material, Wilcox and Thomasco synthesized the unsaturated bromo ester **61**. On treatment with tributyltin hydride, bromo ester **61** furnished cyclopentane derivatives **62** and **63** (10:1) in an 89% yield (Scheme 12).[22] The predominant diastereoisomer **62**, with the side chain ester group in the *exo* orientation, is expected if 5-*exo-trig* radical cyclization proceeds via a "chairlike" transition state proposed by Beckwith and co-workers,[23] with the substituents at C-2 and C-4 (with respect to the radical centre) preferentially occupying pseudoequatorial positions.



60 **61** **62** **63**

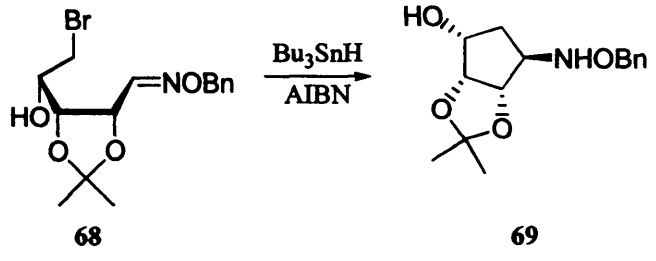
Scheme 12

In subsequent investigations, Wilcox and Gaudino cyclized the unsaturated *gem*-dibromo ester **65**, a derivative of D-arabino-furanose triether **64**.[24] On treatment with AIBN/tributyltin hydride, exclusive formation of cyclopentane derivative **66** was observed. The ring closure is thought to proceed via the radical intermediate in the "chairlike" conformation **67**, which allows for ready overlap between C-1 and C-5, while minimizing steric interactions involving the terminal ester group (Scheme 13).

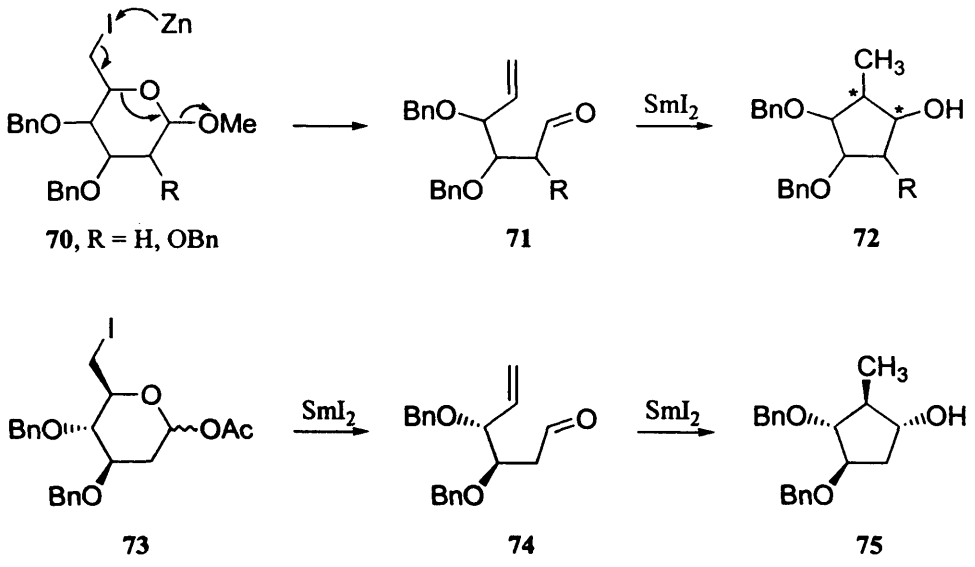


Scheme 13

Marco-Contelles and co-workers have successfully cyclized a series of oxime-ethers readily prepared from 5-bromo-5-deoxy-2,3-*O*-isopropylidene-α-D-ribofuranose.[25] For example, oxime-ether **68** (*syn*/*anti* = 70/30) was treated with AIBN/tributyltin hydride, affording exclusively the *exo* cyclopentane derivative **69** in a 75% yield.



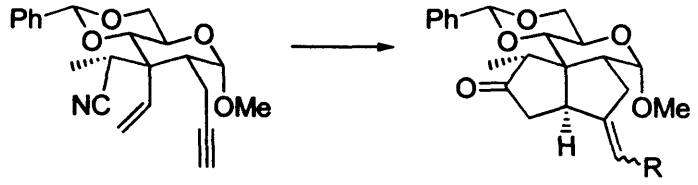
Carbohydrate derivatives were employed as precursors in the synthesis of stereodefined cyclopentanols by the Holzapfel group.[26a] Zinc-assisted Grob-fragmentation of methyl 6-deoxy-6-iodoglycosides **70**, furnished the corresponding 5-hexenals **71**. These compounds were sequentially cyclized to stereodefined cyclopentanols **72**, under the action of samarium(II) iodide (Scheme 14). One-pot SmI_2-promoted transformation of carbohydrate derivatives into cyclopentanols has also been achieved.[26b] For example, upon treatment with excess SmI_2-THF/HMPA, iodoglucoside **73** afforded cyclopentanol **75** in a 76% yield, presumably via 5-hexenal **74**.

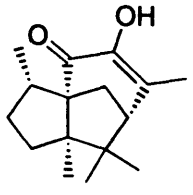


Scheme 14

(ii) 'S-Type' Reactions

A vast amount of work involving radical cyclization within branched sugar chains was pioneered by Fraser-Reid and co-workers.[27] In an example utilizing tributyltin hydride-induced serial radical cyclization, enyne **76** gave the alkenylstannane **77** which, on stirring with silica gel afforded diquinane **78** (65% from **76**). This methodology was used in the synthesis of (–)-α-pipitzol **79**.[27c]

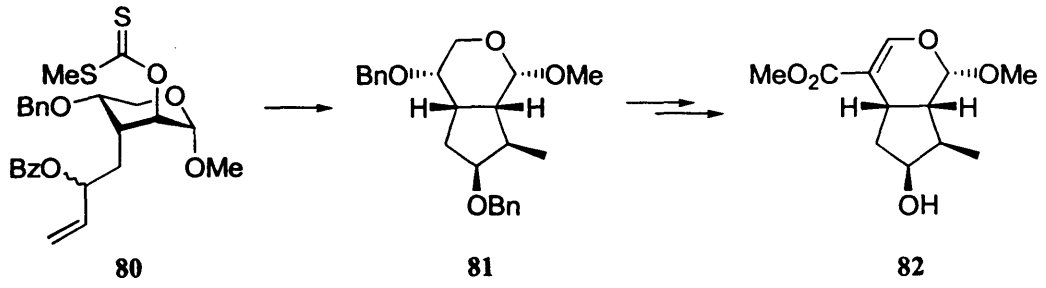




79

In a simpler example, the unsaturated dithiocarbonate **80**, a derivative of methyl 2,3-anhydro-α-D-lyxopyranoside, was treated with AIBN/tributyltin hydride to give the *cis*-

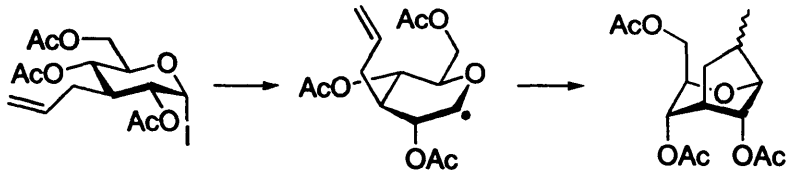
fused cyclopentanopyranoside **81**. The annulated sugar **81** was then converted into the iridoid, 1-α-*O*-methylloganin **82** (Scheme 15).[28]



80 **81** **82**

Scheme 15

Giese and co-workers have applied radical cyclization in an alternative route to 2-oxabicyclo[3.2.1] octanes, such as **85**.[29] Treatment of 3-*C*-allyl-α-D-glucopyranosyl iodide **83** with AIBN/tributyltin hydride furnished cyclopentane derivative **85** in a 59% yield. ESR studies suggest that the reacting conformation of the radical intermediate is the boat **84**, in which the allyl group at C-3 is in a pseudoaxial position (Scheme 16).



83 **84** **85**

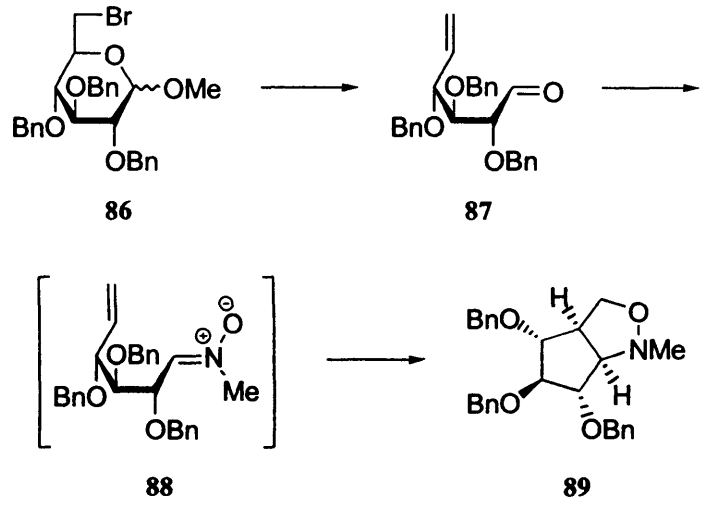
Scheme 16

C. Cycloaddition Reactions

(i) 'F-Type' Reactions

Intramolecular 1,3-dipolar cycloadditions have been found to be useful for the synthesis of five-membered carbocycles from carbohydrates. For example, Bernet and Vasella have utilized nitrones as key intermediates in the synthesis of 2-aza-3-oxabicyclo[3.3.0]-octane derivatives.[30] On treatment with zinc in ethanol, 6-bromo-6-deoxyglucopyranosides **86** undergo reductive ring opening to the corresponding acyclic 5,6-dideoxyhex-5-enose **87**. Reaction of **87** with *N*-methylhydroxylamine readily furnishes the unsaturated nitrone **88**, which undergoes spontaneous cyclization to the 2-aza-3-

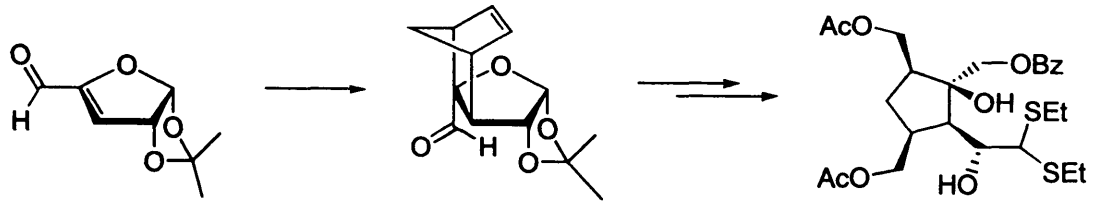
oxabicyclo[3.3.0]octane derivative **89**, in an 80% yield (Scheme 17).[30a] The same procedure has been used to synthesize cyclopentane derivatives from mannose and galactose derivatives.[30b,c]



Scheme 17

(ii) 'S-Type' Reactions

Diels-Alder reactions of carbohydrate dienophiles with cyclopentadiene incorporate new five-membered carbocyclic rings into the adduct formed (the adduct also contains a new six-membered carbocyclic unit). The reaction of aldehyde **90** with cyclopentadiene afforded the *exo* adduct **91** (90%) as a single diastereoisomer, with addition occurring exclusively on the more accessible face of the dienophile. Adduct **91** was subsequently transformed into the highly functionalized cyclopentane derivative **92** (Scheme 18).[31]



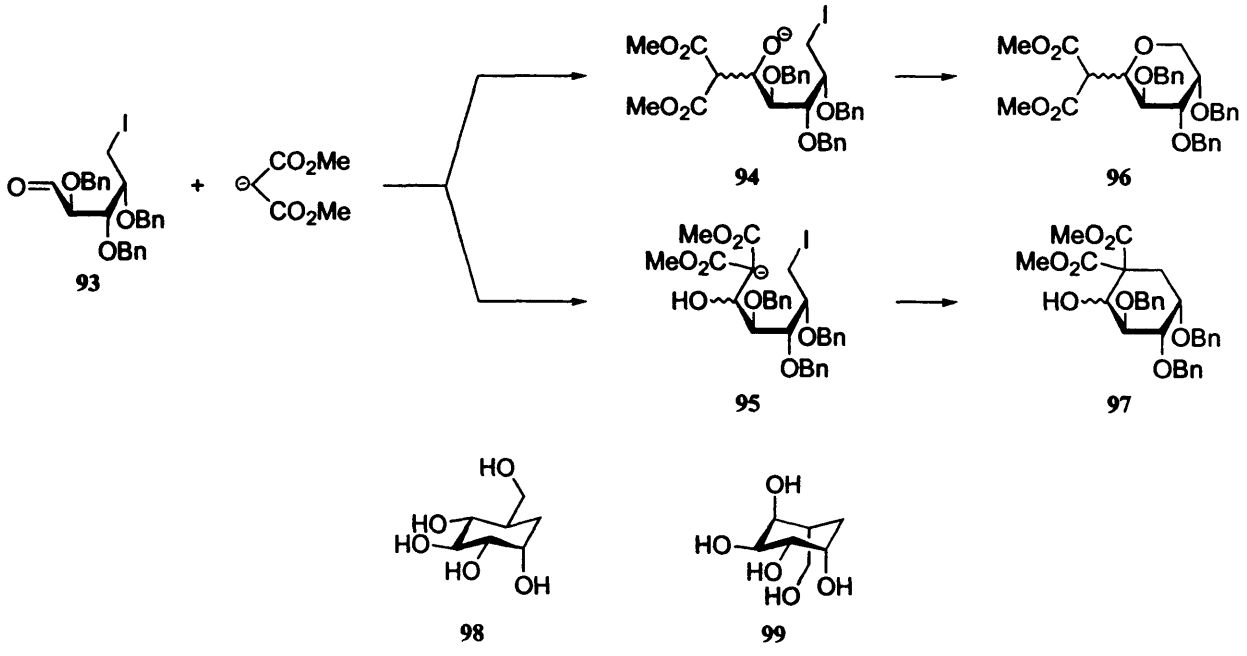
Scheme 18

1.4 Syntheses of Functionalized Cyclohexanes from Carbohydrates

A. Carbanion Cyclizations

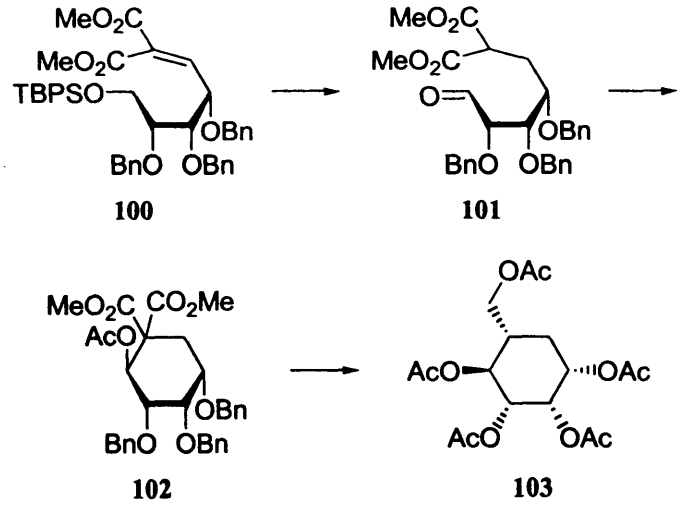
(i) 'F-Type' Reactions

Intramolecular nucleophilic displacement reactions of carbohydrates derivatives which result in cyclohexane products, are facilitated by two-carbon chain-extension of *aldehydo*-pentose compounds bearing leaving groups at C-5. For example, reaction of the anion of dimethyl malonate with the 5-deoxy-5-iodo-L-arabinose derivative **93** furnished intermediates **94** and **95**, from which the tetrahydropyrans **96** (43%) and cyclohexanes **97** (33%, isolated as the acetates) were obtained (Scheme 19).[32] Compounds **97** allowed access to carba-α-D-glucopyranose **98** and, via an alkene, the β-L-altrose isomer **99**.



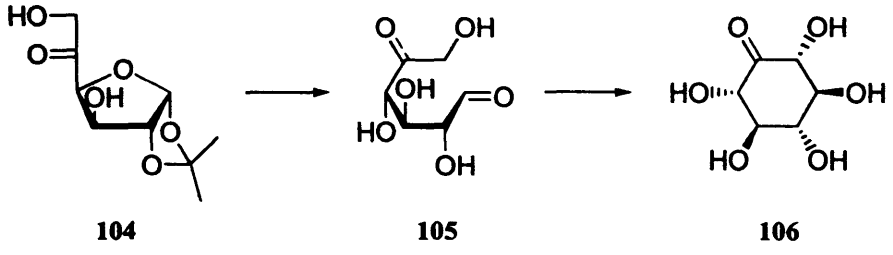
Scheme 19

As a way of avoiding the competitive formation of tetrahydropyrans (e.g. **96**), the stepwise procedure illustrated in Scheme 20 was adopted.[33] Condensation of dimethyl malonate with 2,3,4-tri-*O*-benzyl-5-*O*-(*tert*-butyldiphenylsilyl)-D-ribose furnished the alkene **100**. Hydrogenation and deprotection of **100**, followed by oxidation of the resulting alcohol, gave the aldehyde **101**. The acetate **102**, and hence carba-β-L-mannopyranose peracetate **103**, were obtained following aldol cyclization of **101**.



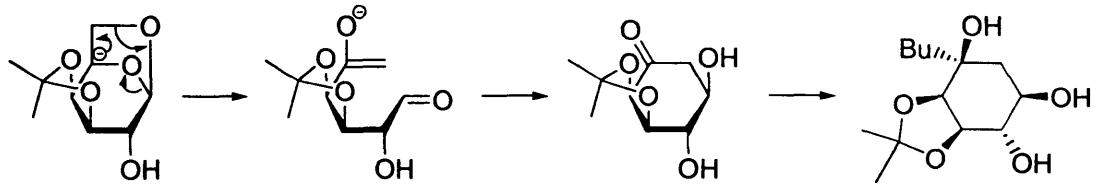
Scheme 20

Kiely and Fletcher were the first to show that aldol cyclization of 1,5-dicarbonyl carbohydrates afforded cyclohexanone derivatives.[34] On treatment with alkali, D-xylo-hexos-5-ulose **105**, prepared from the acetal **104**, was converted into the inososе **106** (Scheme 21).



Scheme 21

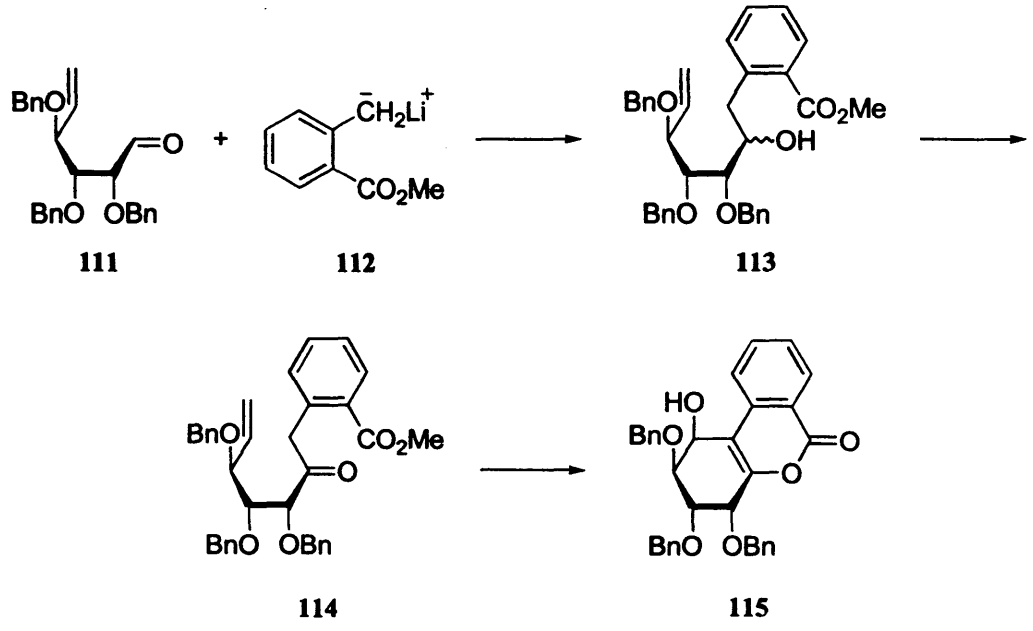
Klemer and Kohla found that on treatment with *n*-butyllithium, 1,6-anhydro-3,4-*O*-isopropylidene-β-D-galactose furnished the *C*-butylinositol derivative **110** in an 85% yield.[35] This can be envisaged by proton abstraction at C-5, generating carbanion **107**, which upon rearrangement gave enolate **108**. Aldol cyclization afforded the cyclohexanone **109**, with which the nucleophilic reagent gave the tertiary alcohol **110** (Scheme 22).



107 **108** **109** **110**

Scheme 22

In their pursuit of phenanthridone alkaloids, Thompson and Kallmerten have applied aldol cyclization of a 1,5-dicarbonyl carbohydrate derivative.[36] The enal **111**, derived from L-arabinose, was treated with the lithium reagent **112** to give alcohols **113**, and hence the enone **114** (Scheme 23). Ozonolysis of **114** gave a 1,5-dicarbonyl product that underwent base-catalyzed aldol cyclization and lactonization to the isocoumarin **115**, from which alkaloid precursors were obtained.



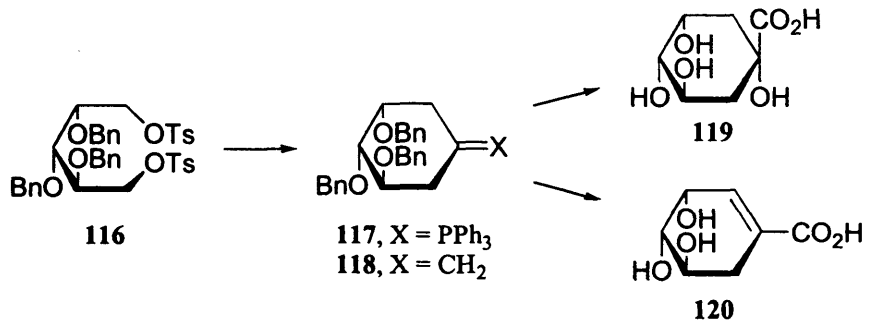
111 **112** **113**

114 **115**

Scheme 23

Short alkanes having halogen or sulfonyloxy substituents at the α- and ω-positions react with methylenetriphenylphosphorane to give carbocyclic products.[37] Bestmann and Heid have applied this knowledge to the synthesis of quinic acid (**119**) and (–)-shikimic acid (**120**).[38] The D-arabinitol derivative **116** was reacted with methylenetriphenylphosphorane to give the cyclohexylidene ylide **117**. This new Wittig reagent, on reaction with formaldehyde, gave the cyclohexane **118** with an *exo*-methylene

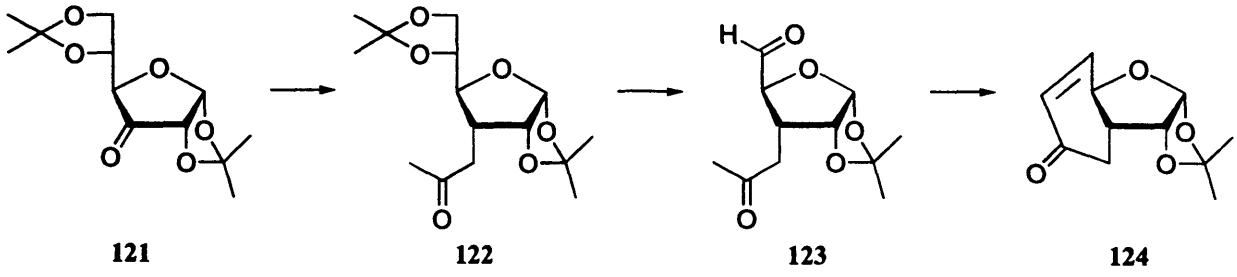
group, from which quinic acid (**119**) and (–)-shikimic acid (**120**) were derived (Scheme 24).



Scheme 24

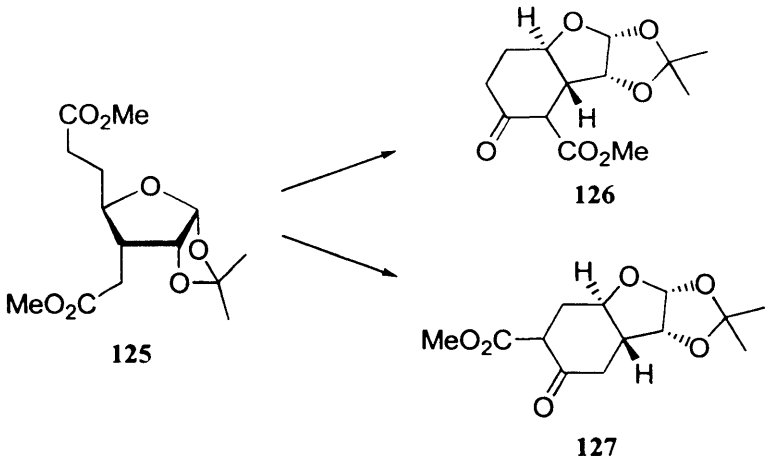
(ii) 'S-Type' Reactions

The use of 1,5-dicarbonyl sugar derivatives, having one of the carbonyl groups in a branched chain, has been significant. For example, through the use of Wittig methodology, the D-glucose derived ketone **121** was converted into the branched ketone **122**. Partial deprotection, followed by periodate oxidation of the exposed diol, afforded the 1,5-dicarbonyl compound **123**. Cyclization to give the cyclohexenone **124** was achieved in a 45% yield, by the use of DBU followed by acetic anhydride and pyridine (Scheme 25).[39]



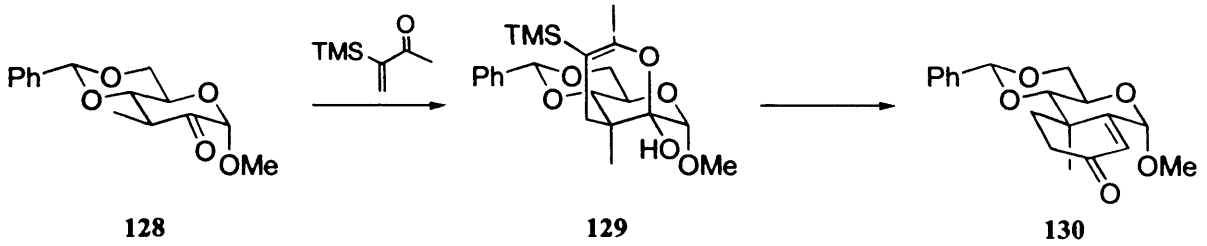
Scheme 25

Fraser-Reid and co-workers have prepared cyclohexane derivatives, via Dieckmann cyclization of the branched-chain uronic acid derivative **125**.[40] Treatment with potassium *tert*-butoxide alone gave keto ester **126**, through the carbanion in the C-3 branched chain. The product **127** of the other possible ring closure was achieved when 18-crown-6 was used in conjunction with potassium *tert*-butoxide (Scheme 26).



Scheme 26

Previous work in Leicester by Jenkins and co-workers provided the first example of a Robinson annulation on a carbohydrate derivative.[41] The ketone **128** was treated with lithium 2,2,6,6-tetramethylpiperidide, and the resulting enolate reacted cleanly with 3-trimethylsilyl-3-buten-2-one to afford the alcohol **129**, which gave the cyclohexenone **130** upon treatment with 4% methanolic potassium hydroxide, in a 58% yield (Scheme 27). The Robinson product **130** provides a C-ring synthon in the synthesis of a chiral taxoid (see Chapter 5).



128 **129** **130**

Scheme 27

B. Free-Radical Cyclizations

The number of reported syntheses of cyclohexanes by carbohydrate radical cyclization is far less than in analogous cyclopentanes. This is because common carbohydrates offer fewer opportunities to produce 6-heptenyl radicals **131** than 5-hexenyl species **132**, both of which normally cyclize by *exo* processes (Scheme 28).[42]

131 132

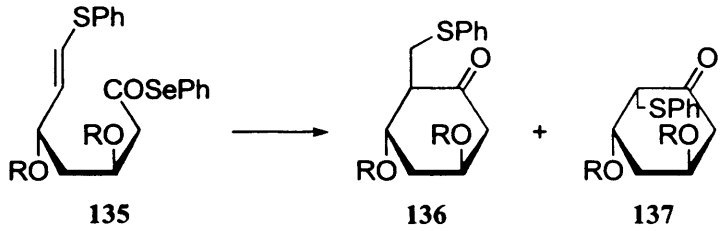
Scheme 28

(i) 'F-Type' Reactions

Redlich and co-workers have reported ring closures involving 6-heptenyl radicals of several 1,2-dideoxyhept-1-enitol derivatives.[43] For example, the radical **133**, derived from the corresponding D-*allo*-iodide, by treatment with tributyltin hydride, furnished the cyclohexane **134** in an 87% yield.

133 134

Acyl radicals may also be utilized to facilitate cyclohexane ring formation. The radical derived from the hept-6-enonic selenoester **135** cyclized to give a 1:1 mixture of the cyclohexanones **136** and **137** in a 90% yield.[44]



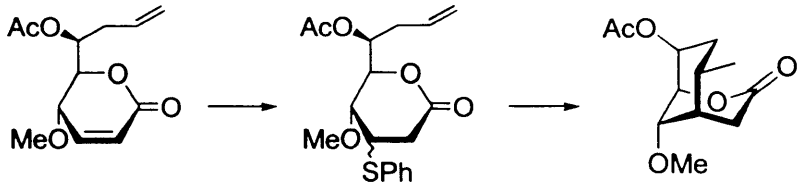
135 136 137

(R = $SiMe_2{}^tBu$)

(ii) 'S-Type' Reactions

Gómez and López have utilized a one-pot procedure, based on the selective addition of benzenethiol to the conjugated double bond of non-2,8-dienonic acid lactones, in the synthesis of cyclohexane derivatives.[45] For example, the enone **138**, on reaction with benzenethiol in the presence of triethylamine, furnished the epimeric adducts **139**, which

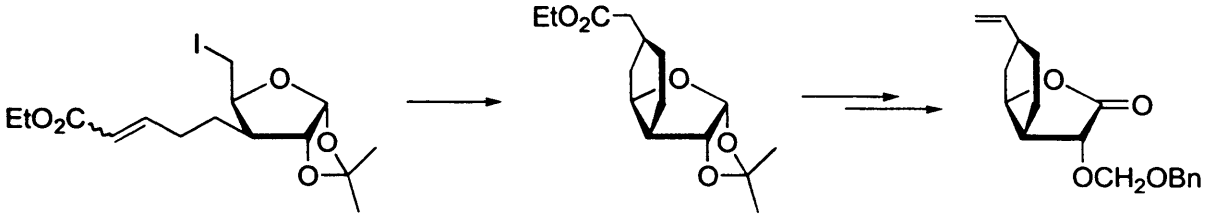
without isolation, were treated with AIBN/tributyltin hydride to give the cyclohexane **140** in a 77% yield (Scheme 29).



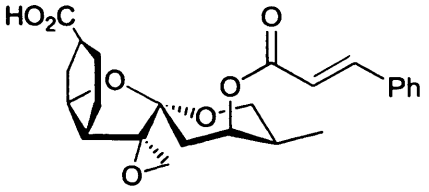
138 **139** **140**

Scheme 29

Fraser-Reid *et al.* have carried out similar work in the furanoid series with compounds having radical traps in branched chains.[46] The 5-iodopentose derivatives **141** gave the cyclohexane **142** and its epimer in 74 and 85% combined yields from the (*E*)- and (*Z*)-alkenes respectively, the epimeric ratio being 2:1 and 9:1 in favour of **142** in each case (Scheme 30). Compound **142** was converted to the annulated sugar **143**, which is a key intermediate in a synthesis of (+)-phyllanthocin **144**, an anti-leukemia plant product.



141 **142** **143**



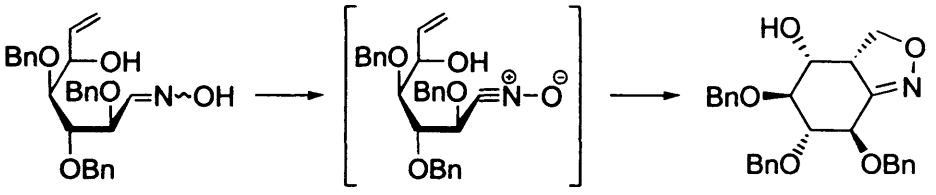
144, (+)-Phyllanthocin

Scheme 30

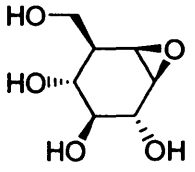
C. Cycloaddition Reactions

(i) 'F-Type' Reactions

The use of intramolecular 1,3-dipolar cycloaddition reactions of sugar derivatives, to produce carbocycles, has been less frequent for cyclohexanes than for cyclopentanes. However, some syntheses have appeared in the literature. For example, oxidation of the oxime of a hept-6-enose derivative **145** with hypochlorite furnished the nitrile oxide **146**, which cyclized to give the cyclohexane **147** in a 70% yield. (+)-Cyclophellitol (**148**), a β-glucosidase inhibitor, was derived from compound **147** (Scheme 31).[47]



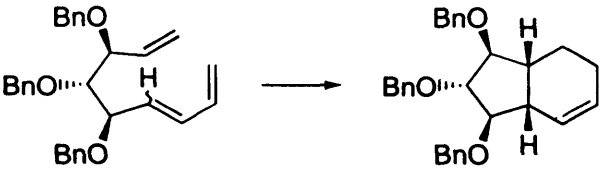
145 **146** **147**



148, (+)-Cyclophellitol

Scheme 31

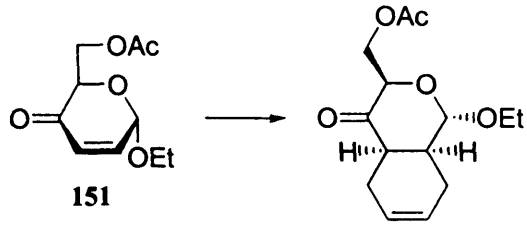
Intramolecular Diels-Alder reactions of acyclic carbohydrate derivatives, that contain both a diene and a suitably situated dienophile, are well documented. For example, the mixed isomers **149**, derived from 2,3,4-tri-*O*-benzyl-D-xylose using Wittig methodology, gave the cyclohexene **150** in an 83% yield on heating in toluene at 160 °C. This suggests thermal interconversion of isomers either before or after cyclization.[48]



149 **150**

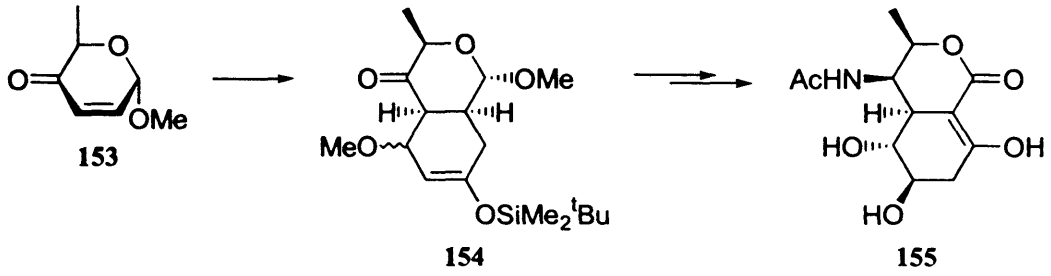
(ii) **'S-Type' Reactions**

A major thrust of research in the area of [4+2] cycloaddition reactions of carbohydrate derivatives was provided by Fraser-Reid and co-workers, who found that Diels-Alder addition of 1,3-butadiene to the enone **151**, at -60 °C in dichloromethane in the presence of an excess of aluminium chloride, selectively gave the cyclohexene **152** (81%).[49]



151 **152**

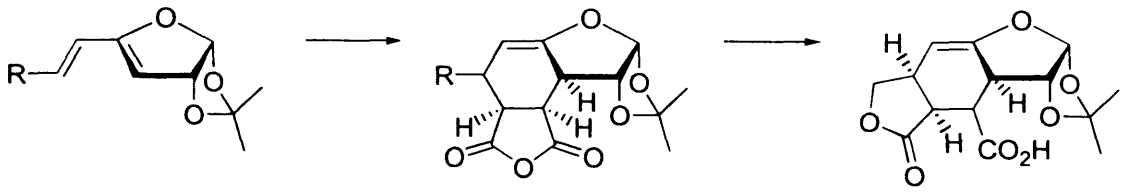
With this knowledge in hand, Fraser-Reid *et al.* synthesized the *N*-acetyl derivative **155**, which forms a major part of the antibiotic actinobolin. Reaction of the 6-deoxy-D-hexose-based enone **153** with the appropriate Danishefsky diene, afforded the key intermediate **154** (Scheme 32).[50]



153 **154** **155**

Scheme 32

Conjugated dienes can be produced within carbohydrate derivatives for use in intermolecular Diels-Alder reactions. Again Fraser-Reid led the way by showing the efficient addition of maleic anhydride to the hexofuranose derivative **156** to give **158**.[40] Subsequently, on repetition of the reaction with the heptose analogue **157**, the product **159** underwent spontaneous rearrangement to the lactone **160** (Scheme 33).[51]



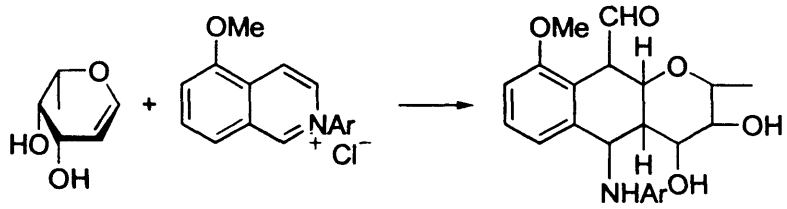
156, R = H
157, R = CH_2OH

158, R = H
159, R = CH_2OH

160

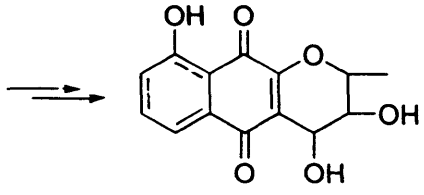
Scheme 33

Franck and co-workers have applied carbohydrate annulation, via a Diels-Alder reaction, to the synthesis of (–)-cryptosporin (**164**).[52] Reaction of L-fucal **161** with the isoquinolinium salt **162** at 55-60 °C in methanol, followed by acid-catalyzed hydrolysis gave the aldehyde **163** (95%), which was converted into **164** in eight steps (Scheme 34).



161 **162** **163**

(Ar = 2,4-dinitrobenzene)



164

Scheme 34

1.5 Summary

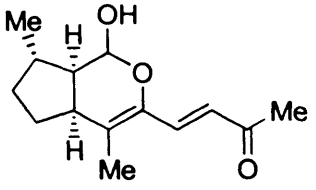
The progress made in recent years, using carbohydrates as synthetic precursors of many functionalized carbocyclic compounds, represents only a small part of the new age of carbohydrate chemistry. In the coming chapters, many more examples of carbohydrate annulation are discussed, with our new chemistry focusing on 'S-type' reactions, where only *some* of the carbons of the sugar are incorporated into the new ring.

CHAPTER 2

THE STEREOSELECTIVE PREPARATION OF AN ENANTIOMERICALLY PURE CYCLOPENTANE

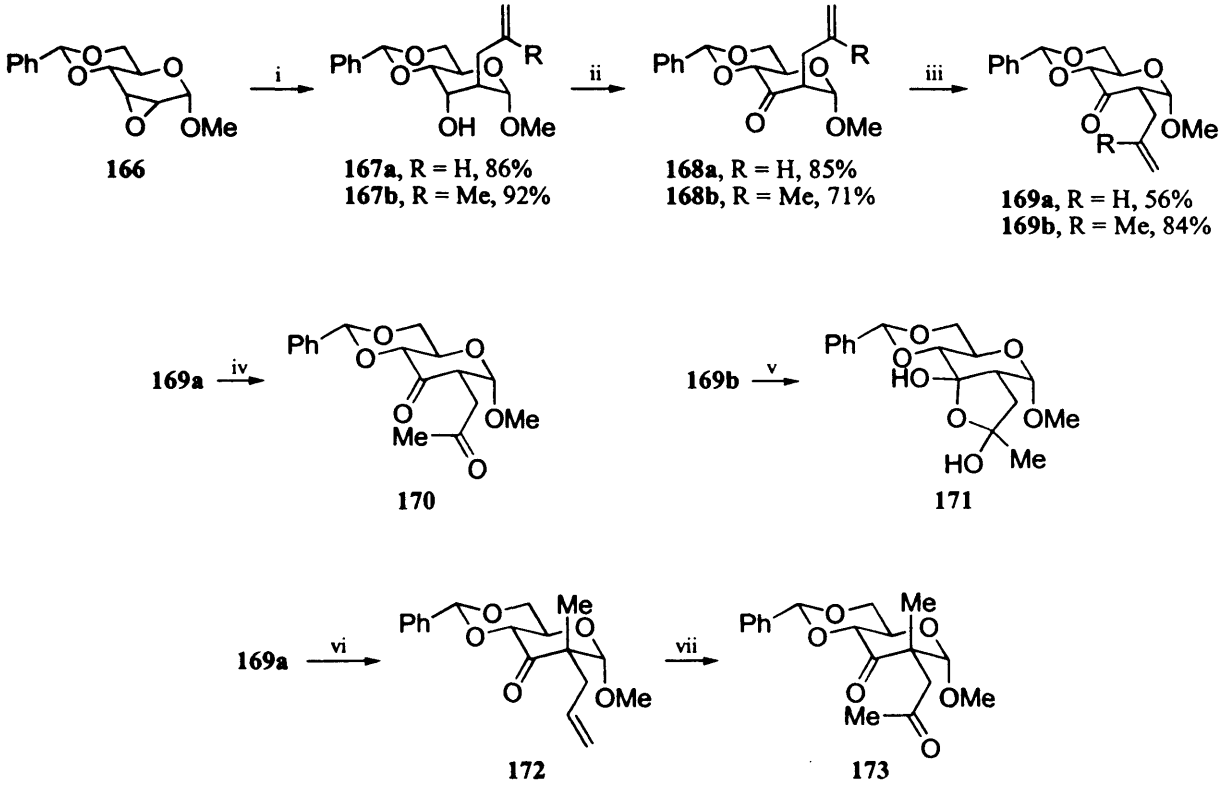
2.1 Cyclopentaannulation of Glucose Derivatives

The iridoids are a vast class of natural products consisting mostly of cyclopentaannulated sugars, e.g. gyrinidone (**165**).[53] Therefore, methods for the cyclopentaannulation of sugar derivatives would have great potential in the synthesis of iridoids and other targets.



Gyrinidone (**165**)

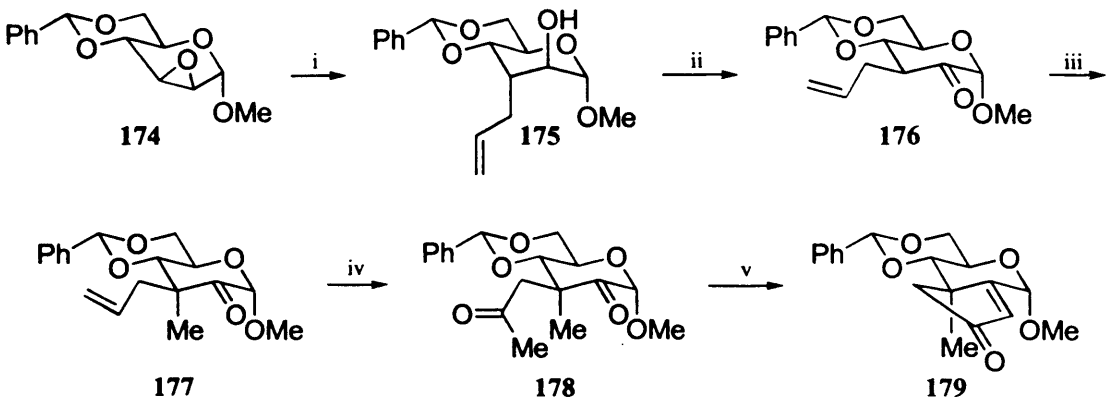
As a member of the Jenkins group, Dr. Andrew Wood carried out studies on cyclopentaannulation of glucose derivatives based on the intramolecular aldol reaction,[54a] and the subsequent removal of the sugar component to produce stereoselectively a chiral cyclopentane derivative.[54b] The initial studies on this topic are summarized in Scheme 35.



Scheme 35, Reagents and conditions: i, CH_2=$CRCH_2MgCl$, THF, 2 h reflux; ii, DMSO, $(CF_3CO)_2O$, DCM, 1.5 h, -78 °C, Et_3N; iii, Et_3N, DMF; 48 h for **168a**, 7 days for **168b**; iv, $PdCl_2$, $CuCl_2$, O_2, DMF-H_2O (1:1), 5 h, 92%; v, O_3, DCM, 0.5 h; H_2NCSNH_2, 3 h, 36%; vi, $NaN(SiMe_3)_2$, THF, 0 °C, 1 h, then MeI, DMPU, 24 h, 42%; vii, $PdCl_2$, $CuCl_2$, O_2, DMF-H_2O (1:1), 5 h, 45%.

Epoxide **166** is a known compound[55] and this was reacted separately with allylmagnesium chloride[56] and methallylmagnesium chloride to give the alcohols **167a** and **167b**. Oxidation to the ketones **168a** and **168b** using the Swern procedure[57] was followed by epimerization to produce the ketones **169a** and **169b** with the equatorial allyl groups, despite a previous report by Ferrier that the latter reaction was not possible.[58] Ketone **169a** was oxidized by the Wacker reaction[59] with oxygen in the presence of palladium(II) chloride and copper(II) chloride to produce the diketone **170**, the first substrate for cyclization. Ozonolysis of **169b** gave a poor yield of the hemiacetal **171**. Treatment of diketone **170** with sodium hydroxide in refluxing methanol gave no cyclization. To remove one position of enolization, the ketone **169a** was converted into the methylated ketone **173**, which was subjected to three different conditions of cyclization: potassium *tert*-butoxide in toluene, sodium carbonate in methanol and sodium methoxide in methanol. In each case the starting material was isolated with a trace of benzaldehyde; no evidence in favour of cyclization was observed.

The search for a viable cyclopentaannulation method was continued using the reaction sequence described in Scheme 36. The known β-epoxide **174**[60] was reacted with allylmagnesium chloride to produce the alcohol **175**[56] which was oxidised[57] and epimerized[58] to give the ketone **176**. Deprotonation and methylation of **176** furnished the ketone **177**, which was subsequently oxidized by the Wacker procedure[59] to furnish the diketone **178**. Successful cyclization, followed by the elimination of water, was achieved using potassium *tert*-butoxide in toluene to give the cyclopentenone **179** in excellent yield. The structure of **179** was confirmed by an X-ray crystal structure (Figure 1).



Scheme 36, Reagents and conditions: i, CH_2=$CHCH_2MgCl$, THF, 2 h reflux, 86%; ii, DMSO, $(CF_3CO)_2O$, DCM, 1.5 h, -78 °C, then Et_3N, 24 h, 86%; iii, $LiN(SiMe_3)_2$, THF, 0 °C, 1 h, then MeI, DMPU, 24 h, 80%; iv, $PdCl_2$, $CuCl_2$, O_2, DMF-H_2O (1:1), 5 h, 56%; v, Bu^tOK, toluene, 0.5 h, 90%.

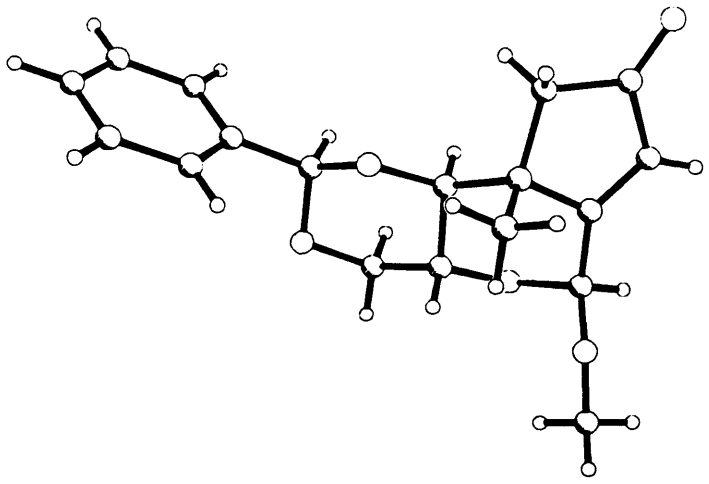
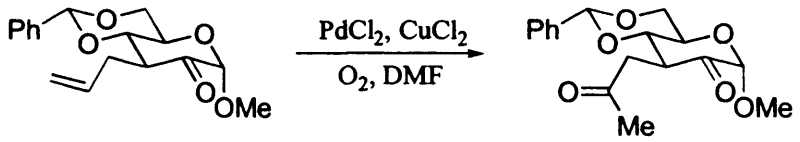


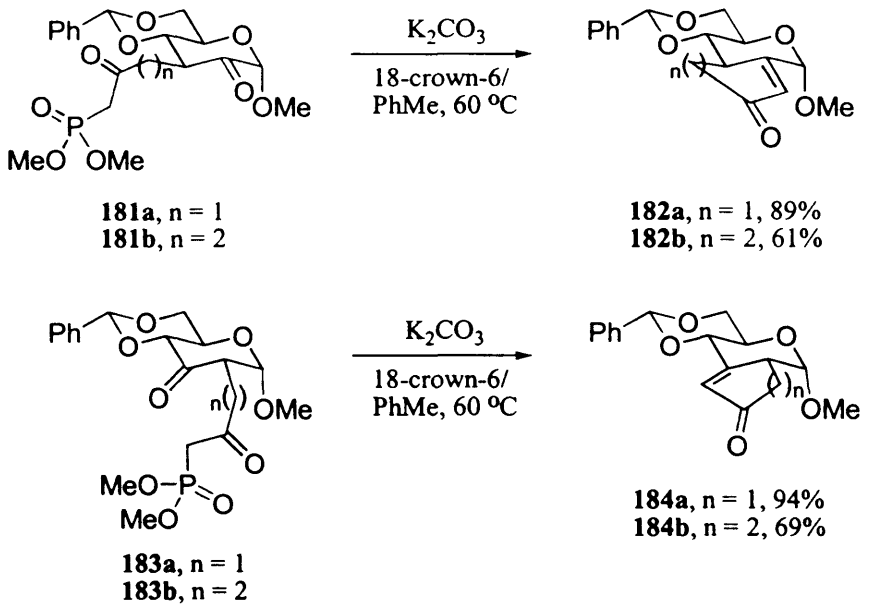
Figure 1. X-ray crystal structure of cyclopentenone **179**

The structural requirements for facile cyclopentaannulation are very stringent, the only substrate to cyclize was **178**. An especially important feature seems to be the quaternary centre α to the carbonyl group. Wacker oxidation of **176** was used to produce the diketone **180** without the quaternary centre. However, all attempts to cyclize this material failed. One possible explanation of this phenomenon is that a Thorpe-Ingold Effect[61] may be restricting the number of degrees of conformational freedom of the side-chain in ketone **178**, so that cyclization is favoured.



176 **180**

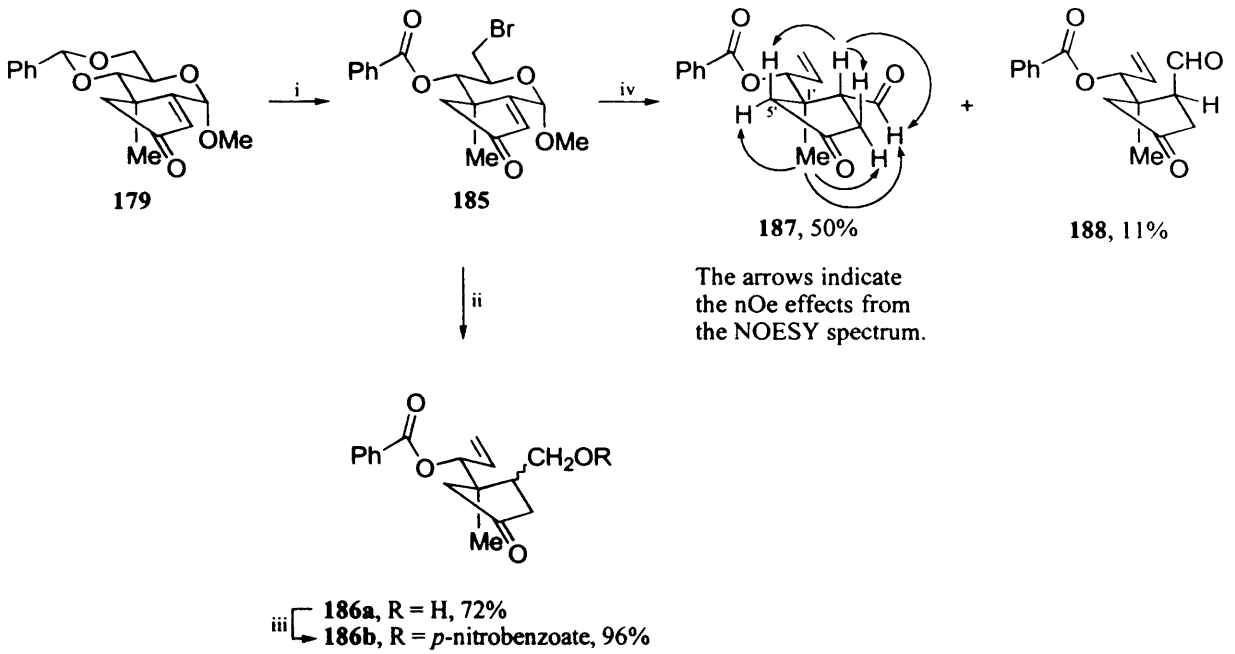
Shortly after this work was communicated,[54a] a report on the synthesis of cyclopenta- and cyclohexaannulated sugars using phosphonate stabilized anions was published by Ermolenko and co-workers.[62] The key step in these annulations is an intramolecular Horner-Wadsworth-Emmons olefination of vicinal β-ketophosphonates of pyranosulosides (Scheme 37). Diketones **181a** and **181b**, derived from β-epoxide **174**, cyclized smoothly upon treatment with potassium carbonate and 18-crown-6 in toluene at 60 °C, to furnish cyclopentenone **182a** and cyclohexenone **182b** in good yield. Similarly, diketones **183a** and **183b**, derived from α-epoxide **166**, were converted to cyclopentenone **184a** and cyclohexenone **184b** in good yield.



Scheme 37

2.2 **Preparation of an Enantiomerically Pure Cyclopentane**

Having successfully synthesized the cyclopentaannulated sugar **179**, attention was switched to the conversion of this annulated sugar into an enantiomerically pure cyclopentane. The fragmentation of the benzylidene group of **179** was achieved upon treatment with NBS, following the method of Hanessian,[63] furnishing the expected product **185** (Scheme 38). The nature of the zinc used in the Vasella reduction[30a] of bromo ester **185** has an important effect on the products obtained. Dr. Andrew Wood found that when activated *powdered* zinc was used in the reduction of **185**, the alcohols **186a** were obtained as a mixture of diastereoisomers (*ca.* 5:1), in good yield. These alcohols were isolated and characterized as their *p*-nitrobenzoate esters **186b**. However, we found that treatment of bromo ester **185** with zinc *shot* gave the two aldehydes **187** and **188**, in 50 and 11% yield respectively. This form of zinc is different to the activated *powdered* zinc described by Vasella.[30a] We believe the explanation for obtaining different products with the two different types of zinc is that *powdered* zinc prepared by the Vasella method is a more reactive reducing agent, due to its greater active surface area, than the equivalent material prepared from zinc *shot*.



Scheme 38, Reagents and conditions: i, NBS, $BaCO_3$, CCl_4, overnight reflux, 72%; ii, Zinc powder, IPA, reflux, 3 h; iii, Et_3N, *p*-nitrobenzoyl chloride, toluene; iv, Zinc shot, IPA:H_2O (10:1), reflux, 22 h.

The configurational assignment of the major aldehyde product **187** was determined with the aid of a NOESY spectrum (Figure 2). Firstly, we are sure of the configuration of the C-1' centre in **187** from the X-ray crystal structure of **179**. The assignment of the signals of the CH_2 protons at carbons 3' and 5', in the ^1H NMR spectrum of **187**, are clear from the chemical shift expected of protons adjacent to a carbonyl group. From the NOESY spectrum we see a strong nOe between the methyl group at the quaternary centre and one of the protons of each methylene group at C-3' and C-5'. Consequently, we can assign the signals at δ 2.20 and δ 2.84 to the two α-hydrogens H-5' and H-3'; and the signals at δ 2.37 and δ 2.70 to the β-hydrogens H-3' and H-5'. Turning now to the hydrogen on C-2', we see a strong nOe to the β-hydrogens confirming that the C-2' proton is on the β-face of the molecule. This assignment is confirmed by the nOe between the aldehyde proton and the methyl group.

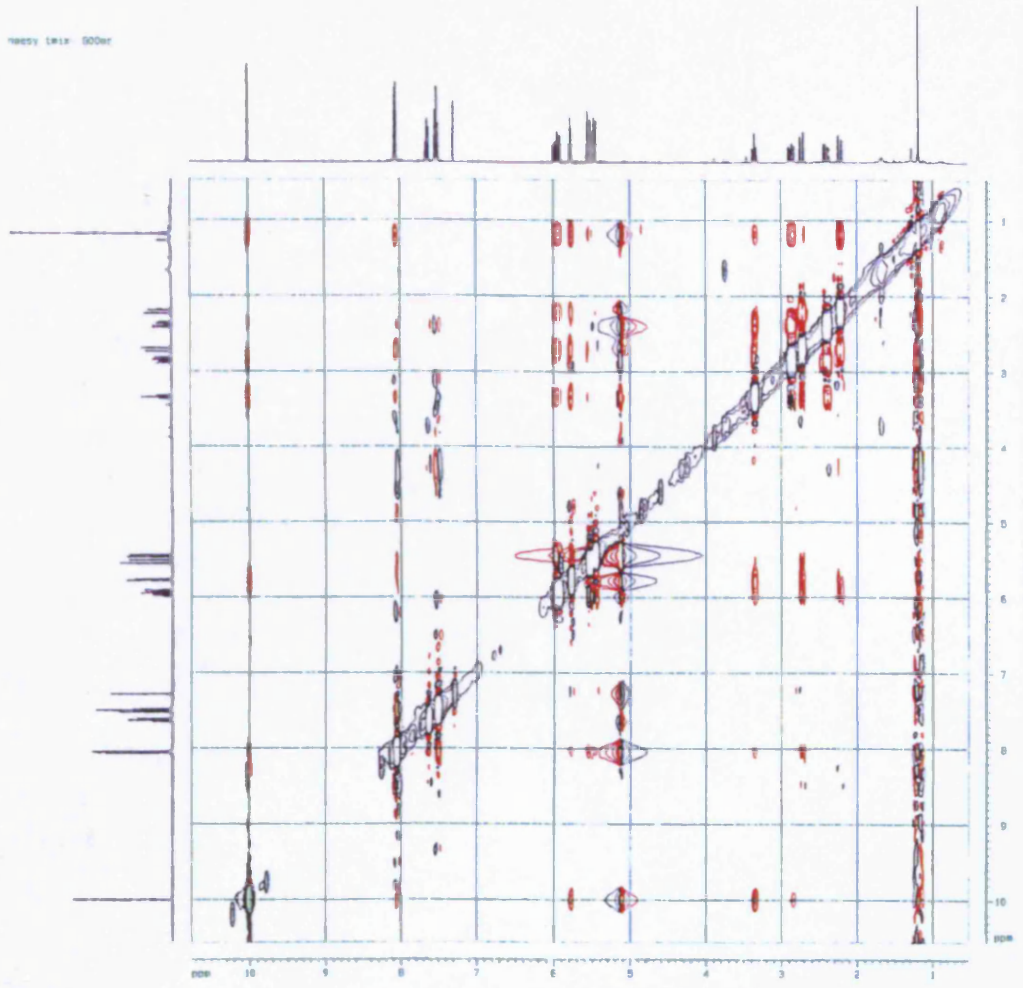
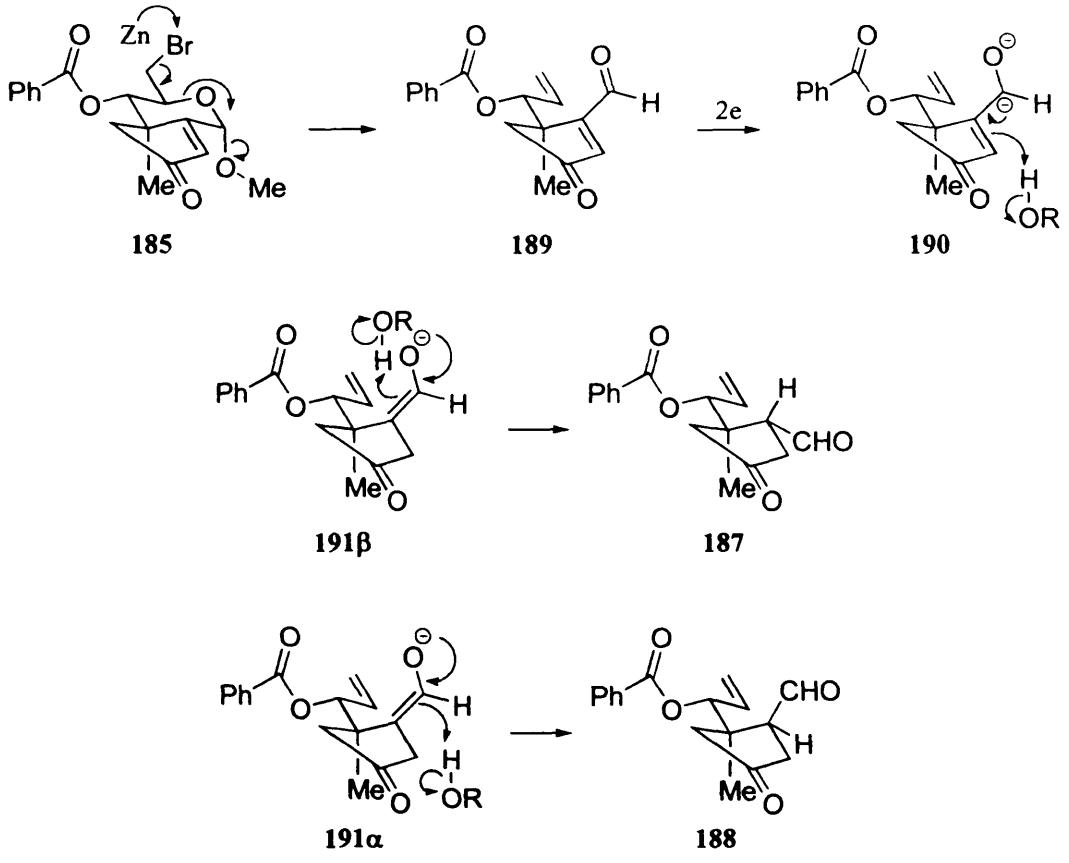


Figure 2. The NOESY spectrum of aldehyde **187**

A possible mechanism for the zinc reduction is shown in Scheme 39. The Vasella reaction normally occurs by attack of the zinc on the bromo substituent to give the aldehyde **189**, which can be regarded as an enedione. The electron transfer reduction of enediones using zinc is known,[64] and this mechanism can be adapted to explain the formation of **187** and **188**. Transfer of two electrons from the zinc may be expected to produce the dianion **190**, which protonates on carbon to give the enolate **191**. Protonation of the enolate from the β-face as shown in **191β** would furnish the aldehyde **187**. Protonation from the α-face is shown in **191α** yielding the aldehyde **188**.



185 189 190

191β 187

191α 188

Scheme 39

2.3 **Summary**

A procedure for the cyclopentaannulation of a glucose derivative has been developed. An enantiomerically pure cyclopentane **187**, with a quaternary stereogenic centre, has been produced using reaction with *N*-bromosuccinimide, followed by reductive elimination using activated zinc shot. The cyclopentane **187** could be a useful as a building block in the synthesis of steroids and Vitamin D derivatives.

CHAPTER 3

RING-CLOSING METATHESIS IN CARBOHYDRATE ANNULATION

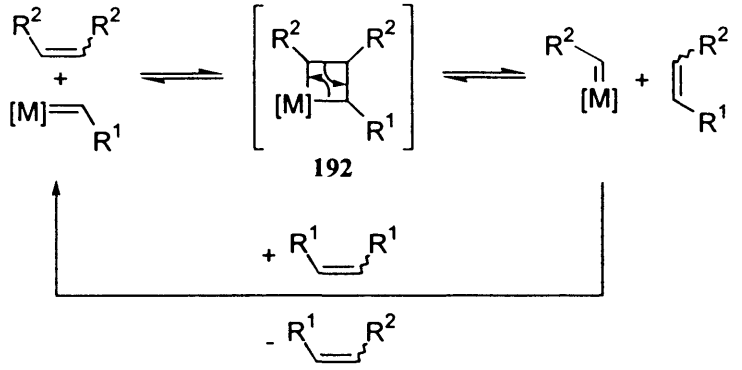
3.1 Introduction

Transition metal catalyzed carbon-carbon bond formations are among the most important reactions in organic chemistry. Olefin metathesis utilizes transition metal catalysis in order to bring about a unique carbon skeleton redistribution, whereby unsaturated carbon-carbon bonds are rearranged in the presence of metal carbene complexes. The potential of olefin metathesis as an invaluable tool in the armory of organic synthesis was not realized for many years. The reasoning behind this comes from the incompatibility of early metathesis catalysts with polar functional groups, and the concept of substrate-catalyst interaction being poorly understood.

The arrival of metal alkylidene chemistry completely changed the situation. Various novel complexes of this type were found to be well-defined catalysts, tolerant to a wide range of functionality, with an ability to produce high yields under mild conditions. These discoveries have allowed metathesis to provide new routes to low molecular weight compounds and a growing number of natural products, via the highly developed method of ring-closing metathesis (RCM).

3.2 History of Metathesis[65]

Olefin metathesis has its roots in polymer chemistry, where ring-opening metathesis polymerization (ROMP) was applied. In 1955 Anderson and Merckling described the catalytic polymerization of norbornene by Ti(II) compounds formed *in situ*. In 1964 Banks and Bailey found that olefins disproportionate at high temperatures in the presence of heterogeneous catalysts. At a similar time, Natta and co-workers reported ROMP of cyclic olefins by homogeneous catalysis. Calderon *et al.* and Mol *et al.* brought about advances in the fundamental understanding of metathesis reactions. They demonstrated that an exchange of alkylidene groups occurred during the metathesis of labelled olefins. Initially it was assumed that the alkylidene rearrangement proceeds via a bis(alkylidene)metal intermediate in which both olefin ligands are coordinated to the metal atom. Chauvin and co-workers were the first to cogitate that the reaction proceeds through a metallacyclobutane **192** (Scheme 40).



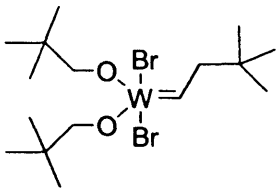
Scheme 40

According to this hypothesis, olefin metathesis advances via a [2+2] cycloaddition between a carbon-carbon double bond and a metal-carbene complex, to give an unstable intermediate metallacyclobutane ring **192**, which subsequently undergoes cycloreversion. All possible reactions of this general type are reversible and in competition with each other. The overall outcome depends heavily on relative rates, and in the case of formation of volatile or insoluble products, displacement of equilibria as those products form.

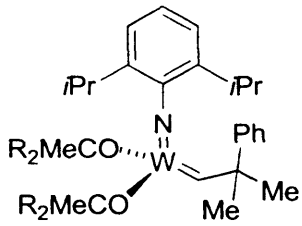
Olefin metathesis also has several industrial applications. One classical example is the Phillips triolefin process, in which propene is converted into a mixture of ethene and 2-butene.

3.3 Well-Defined Catalyst Systems[65, 66]

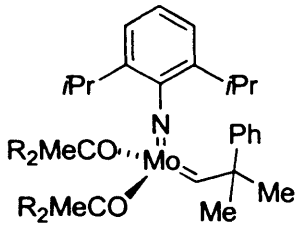
There are a vast number of both heterogeneous and homogeneous catalyst systems that initiate olefin metathesis. Many of the initial studies in olefin metathesis used ill-defined multicomponent catalytic systems. Only in recent years have well-defined single component metal carbene complexes been prepared and put to use in olefin metathesis. Osborn (**193**) and Schrock (**194** and **195**) obtained the first catalysts of this type by some variant of the α hydrogen abstraction reaction. In the early 1990s Grubbs and co-workers reported that ruthenium-carbene complexes of the general type **196** are highly active single component catalysts for any kind of olefin metathesis reaction.



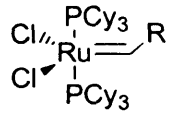
193



194a, R = Me
194b, R = CF_3

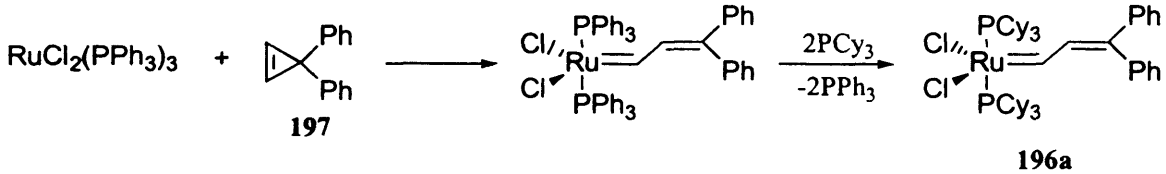


195a, R = Me
195b, R = CF_3

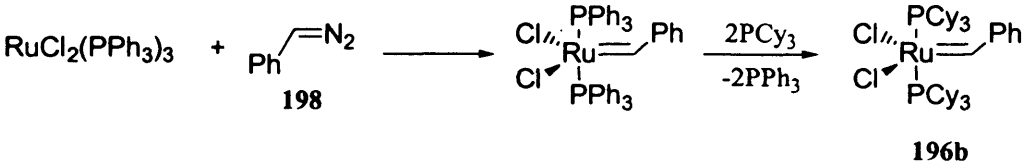


196a, R = $CH{=}CPh_2$
196b, R = Ph

These stabilized alkylidene-transition metal complexes are correctly referred to as *initiators*, as they must first be converted into the catalytically active metal-carbene complexes via alkylidene exchange with a double bond. The Grubbs ruthenium-alkylidene complexes **196** are neutral, 16-electron, Ru(II) fragments that tolerate a large number of polar functional groups and are not particularly sensitive to humidity and oxygen, unlike the Schrock catalysts. Thus, they meet crucial criteria for application in organic synthesis, and belong to the most popular group of catalysts that set the standard in this field. The ruthenium vinylidene complex **196a** can be easily prepared by reaction of $RuCl_2(PPh)_3$ with 3,3-diphenylcyclopropene **197** followed by ligand exchange with PCy_3 (Scheme 41).[67] Another closely related ruthenium-benzylidene complex **196b** was prepared using phenyldiazomethane **198** instead of the cyclopropene.[68]



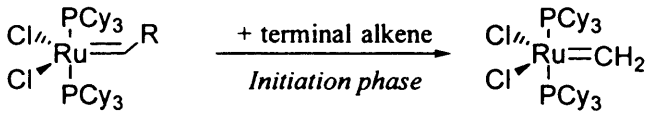
197 **196a**



198 **196b**

Scheme 41

In a formal sense, complexes **196a** and **196b** represent pre-catalysts that convert in the first turn of the catalytic cycle into the ruthenium methylidene species **199**, which is believed to be the propagating species in solution.



196a, R = $CH{=}CPh_2$
196b, R = Ph

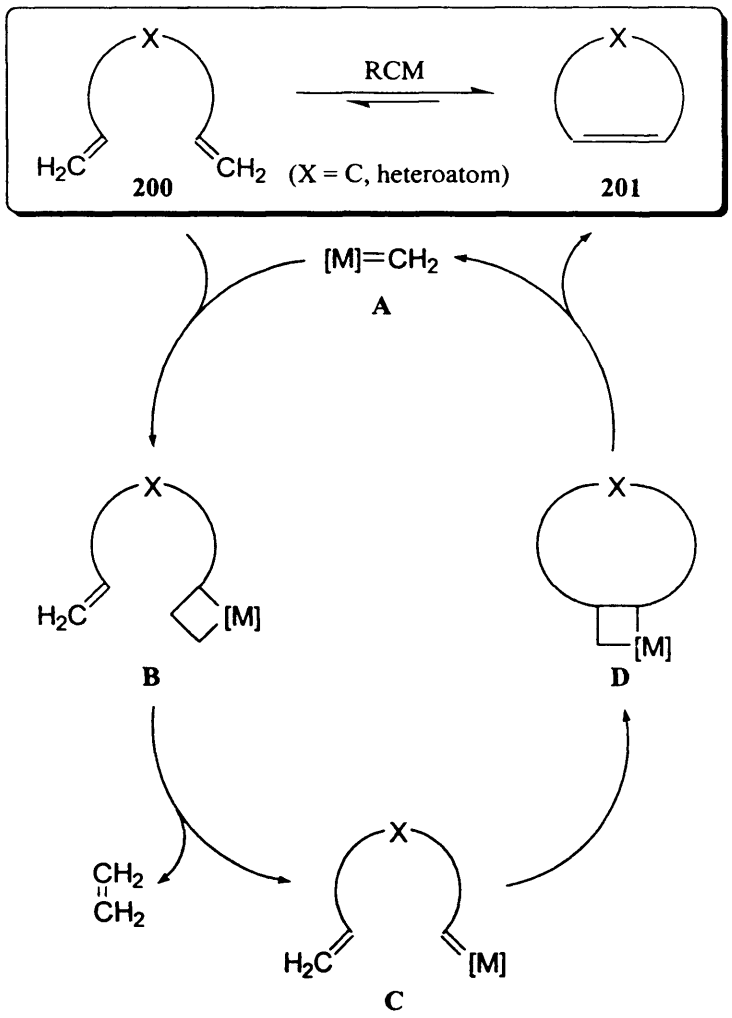
199

Since the groundbreaking development of alkylidene-metal complexes, the truly remarkable scope of olefin metathesis has been demonstrated, with many elegant applications to the synthesis of complex target molecules and structurally diverse natural products.

3.4 RCM Reactions in Organic Synthesis

Although the first example of catalytic RCM was reported in 1980 by Tsuji,[69] it is only recently that it has become established as an effective strategy in organic synthesis. The overall mechanism of RCM (**200** → **201**) is generally believed to proceed via an alternating series of formal [2+2] cycloaddition/cycloreversion steps (Scheme 42):

- Diene **200** undergoes [2+2] cycloaddition with metal-carbene catalyst **A** to produce metallacyclobutane **B**.
- Cycloreversion yields ethylene and metal-carbene complex **C**, which undergoes intramolecular [2+2] cycloaddition to furnish bicyclic metal complex **D**.
- Finally, intramolecular cycloreversion affords the cycloalkene product **201** and regenerates metal-carbene catalyst **A**.



Scheme 42

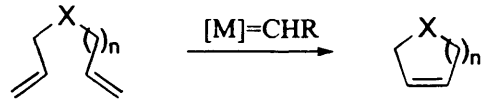
Although the catalytic cycle is - in principle - reversible, RCM is useful in preparative terms mainly due to the following features:

- The equilibrium is constantly shifted towards the cycloalkene if ethylene or another volatile olefin is formed as the by-product.
- The forward reaction is entropically driven, since RCM ultimately cuts one molecule into two.
- Polymerization via acyclic diene metathesis (ADMET) can compete with RCM for a given diene substrate. RCM can be favoured by moving to high dilution conditions.
- Most catalysts are sensitive to the substitution pattern of olefins. If the product has a more highly substituted double bond than the substrate, the retro-reaction is kinetically impeded.

- The tendency of a given diene to undergo RCM depends on the ring size formed, the presence of functional groups, the conformational constraints of the substrate, and on the interactions with the specific catalyst used.

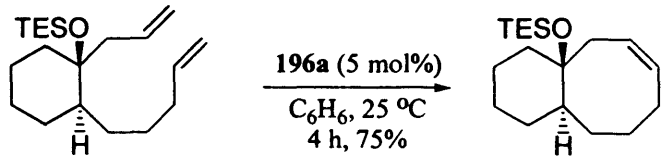
3.4.1 Syntheses of Five- to Nine-Membered Rings

Modern day use of olefin metathesis can be traced to the series of papers by Grubbs and co-workers[70] that illustrate high yielding RCM of dienes **202** to furnish five-, six- and seven-membered rings **203** with divergent functionality and double bond substitution.

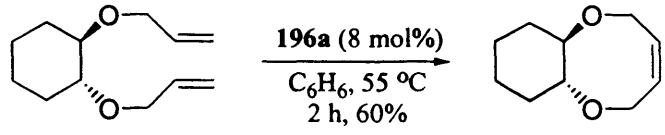


202 X = O, NR, CHR n = 1, 2, 3 **203**

The synthesis of eight-membered rings, common structural elements in numerous natural products, has proven to be a challenging extension of RCM methodology. Grubbs *et al.* have reported RCM of diene substrates **204** and **205**, affording eight-membered carbocyclic and heterocyclic rings **206** and **207**, respectively.[71]



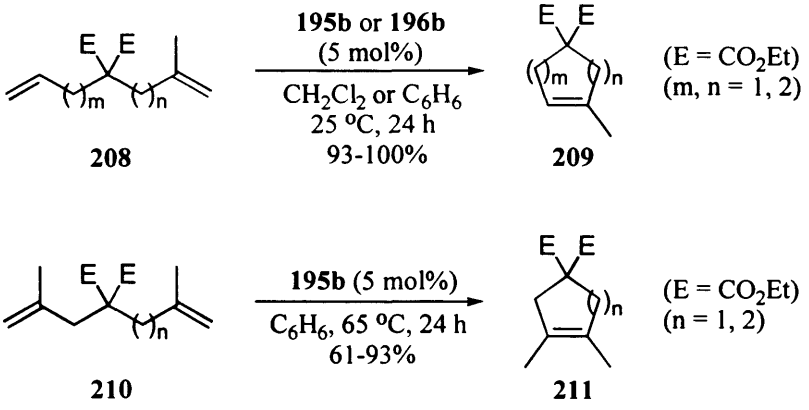
204 **206**



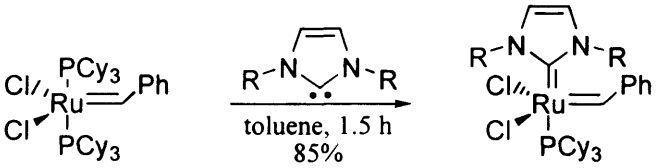
205 **207**

Studies on the RCM of dienes containing *gem*-disubstituted olefins to yield tri- and tetrasubstituted cyclic olefins have recently appeared,[72a] which distinguish the efficacy of molybdenum alkylidene **195b** and ruthenium alkylidene **196b**. Cyclization of mono *gem*-substituted dienes **208** gave trisubstituted cyclic olefins **209** in excellent yield with both

catalysts. Dienes **210** gave the corresponding tetrasubstituted cyclic olefins **211**, only with alkylidene **195b**.

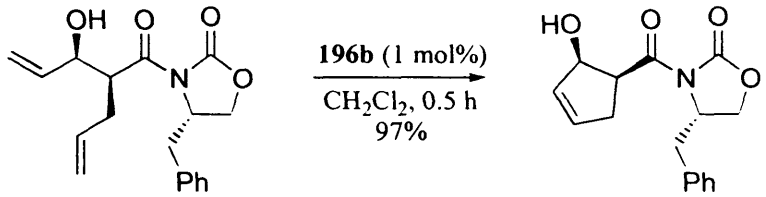


Clearly, ruthenium alkylidene **196b** shows a distinctly lower metathesis activity than the molybdenum alkylidene **195b**. However, the ruthenium compound compensates for this lower intrinsic reactivity by an increased tolerance towards functional groups and a somewhat higher selectivity. A very recent publication[72b] has reported that the imidazolinylidene-substituted ruthenium-based complex **212**, derived from the parent complex **196b**, shows a comparable RCM activity to that of the molybdenum complex **195b**. The imidazolinylidene ligand exchange reaction in toluene is rapid at room temperature, furnishing **212** in 85% yield after recrystallization. Even the tetrasubstituted cyclic olefins **211** are easily prepared with this novel air and water stable complex.



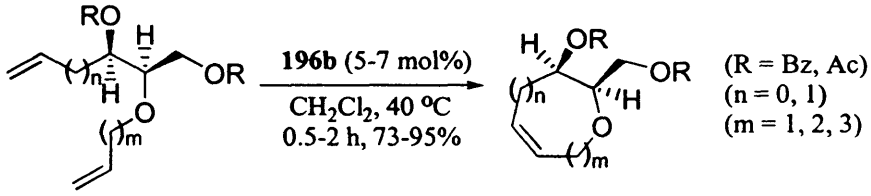
(R = C_6H_2-2,4,6-$(CH_3)_3$)

Due to its high tolerance towards substituents, catalyst **196b** can be utilized in the crucial RCM step, for the highly convergent synthesis of carbocyclic nucleosides.[73] Diene **213**, obtained by aldol addition, was cyclized in 97% yield to furnish cyclopentenol derivative **214**.

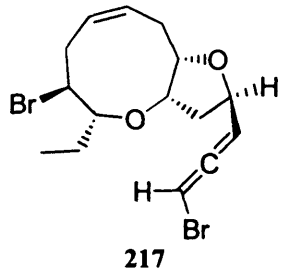


213 **214**

An extension of this aldol-metathesis strategy led efficiently to the asymmetric synthesis of six- to nine-membered cyclic ethers **216**, from the corresponding dienes **215**.[74] Eight- and nine-membered cyclic ethers are of particular interest, since they are metabolites abundant in marine algae, e.g. isolaurallene **217**.

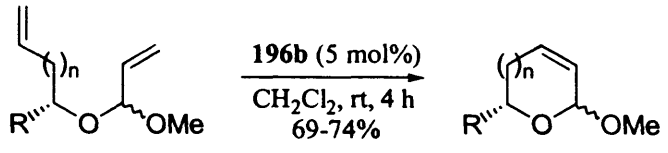


215 **216**



217

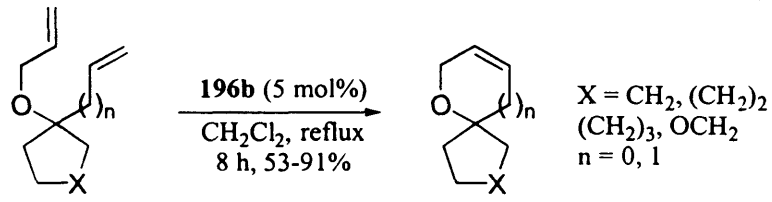
An efficient route for the synthesis of α,α'-disubstituted oxygen heterocycles has been developed by Rutjes and co-workers involving ruthenium catalyzed RCM.[75] Dienes **218** were converted to the corresponding heterocyclic products **219** in good yield. These compounds could serve as useful building blocks for the synthesis of a wide range of natural products.



218 **219**

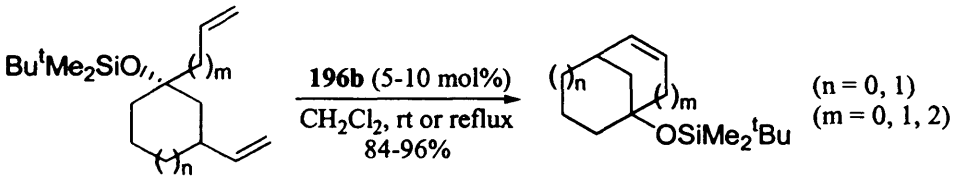
(R = CO_2Me, CH_2OBn)
(n = 1, 2)

Spiro compounds are encountered less frequently in natural products as opposed to annulated or bridged ring systems, yet they are of some importance in spiroacetals. Maier and co-workers have reported RCM of 1-allyl- and 1-vinyl-1-(allyloxy)cycles **220**, furnishing 1-oxaspiro compounds **221**.[76]



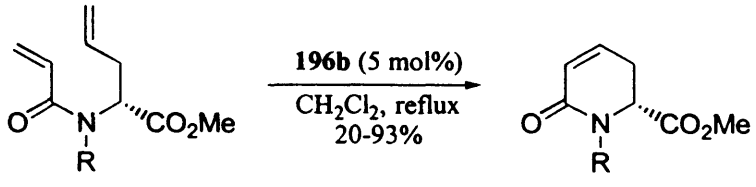
220 **221**

Grubbs *et al.* have applied RCM to the synthesis of a series of small ring bridged bicycloalkanes **223** from monocyclic diene precursors **222**.[77] The application of RCM in ring closures of this type broadens the usefulness of this method, since small ring bridged bicycloalkanes and heterocycles are universal in natural products.



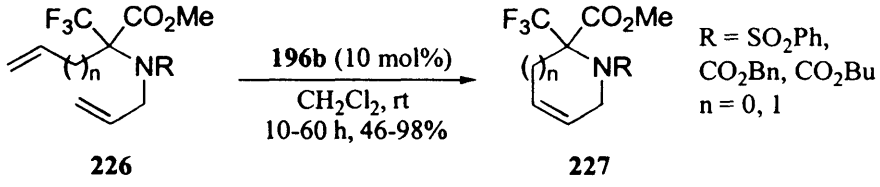
222 **223**

Various studies in recent years have demonstrated the usefulness of RCM for constructing nitrogen heterocycles. Due to the fact that many biologically active substances are nitrogen-containing compounds, the method enhances synthetic chemistry. For example, Rutjes *et al.* have utilized RCM of enantiopure amino acid-derived dienes **224** in the synthesis of highly functionalized α,β-unsaturated amides **225**.[78]



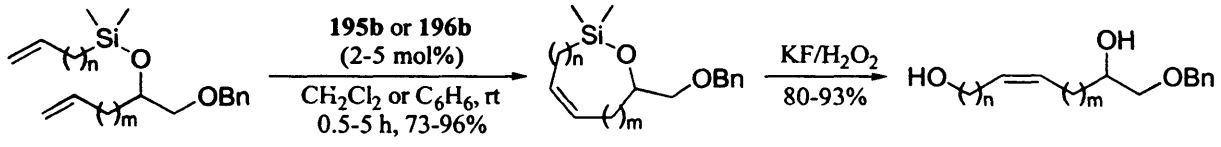
224 R = H, *p*-MeO-$C_6H_4CH_2$, CH_2Ferrocenyl **225**

Furthermore, Osipov and Dixneuf have reported the synthesis of α-CF_3 cyclic amino acid derivatives via RCM.[79] Dienes **226** have been converted to the corresponding α-CF_3 dehydropipecolinate and prolinate derivatives **227** in good yield. Compounds of this type have potential application in the modification of peptide drugs, making them less susceptible to protease degradation.



226 **227**

RCM of temporarily connected dienes and ensuing removal of the tether can furnish acyclic alkenes with various functionality. Grubbs *et al.* have reported one example in which silicon is the connecting atom between two olefins (Scheme 43).[80] Dienes **228** were successfully converted to the cyclic silyloxyalkenes **229**. Subsequent oxidative cleavage gave the *cis*-olefinic dihydroxy compounds **230** in high yield.

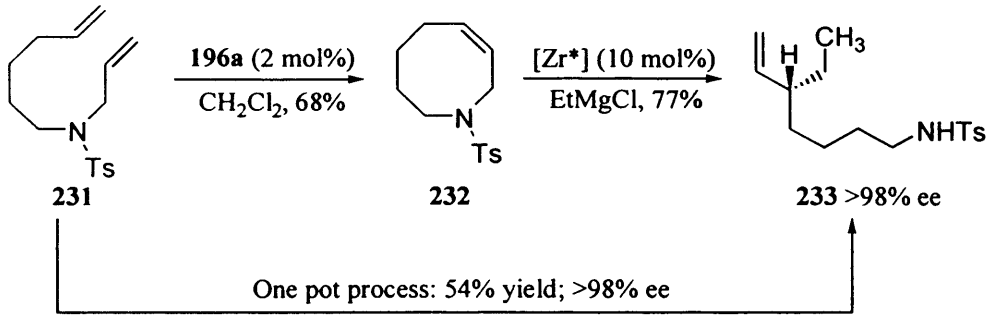


228 **229** **230**

(n = 0-2, m = 1-3)

Scheme 43

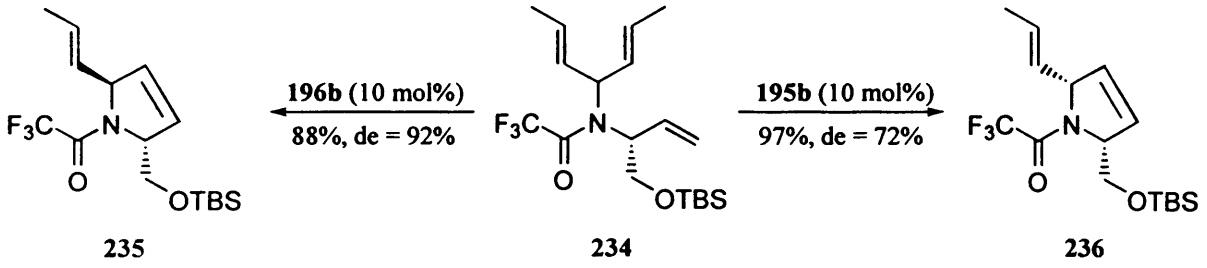
In another example of this type, the Hoveyda group have illustrated that when RCM is applied in combination with asymmetric carbomagnesation, an efficient route to unsaturated alcohols and amides is provided (Scheme 44).[81] Tosylamide diene **231** underwent facile RCM to give the eight-membered heterocycle **232** in reasonable yield. Subsequent treatment of **232** under catalytic ethylmagnesation conditions furnished the unsaturated amide **233** in >98% ee. Metathesis and carbomagnesation of diene **231** can also be carried out in the same reaction vessel.



Scheme 44

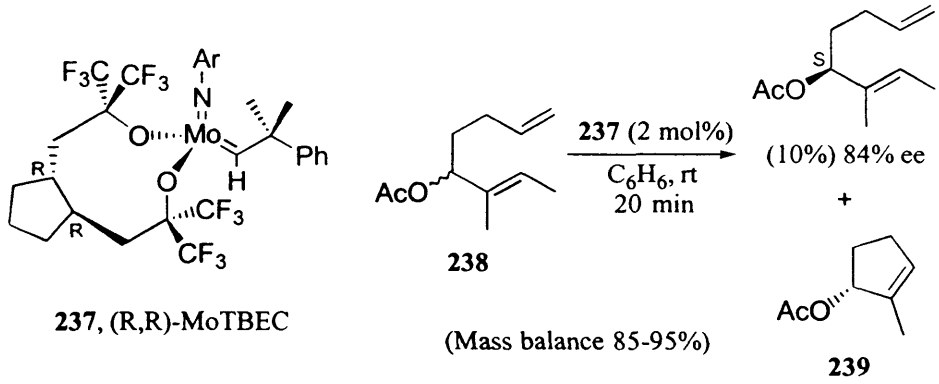
3.4.2 Stereoselective RCM

Due to the large synthetic potential of RCM, asymmetric variants are particularly important. Blechert and co-workers have recently described diastereoselective RCM reactions in which an existing chiral centre controls the direction of cyclization of prochiral dienes (Scheme 45).[82] The reaction in all probability starts at the terminal olefin site in enantiopure **234**, independent of whether **195b** or **196b** is used as the catalyst. Ruthenium and molybdenum have different coordination geometries, thus the developing carbene reacts with either diastereotopic olefin attached to the nitrogen substituent, leading to the selective formation of **235** and **236**, respectively.



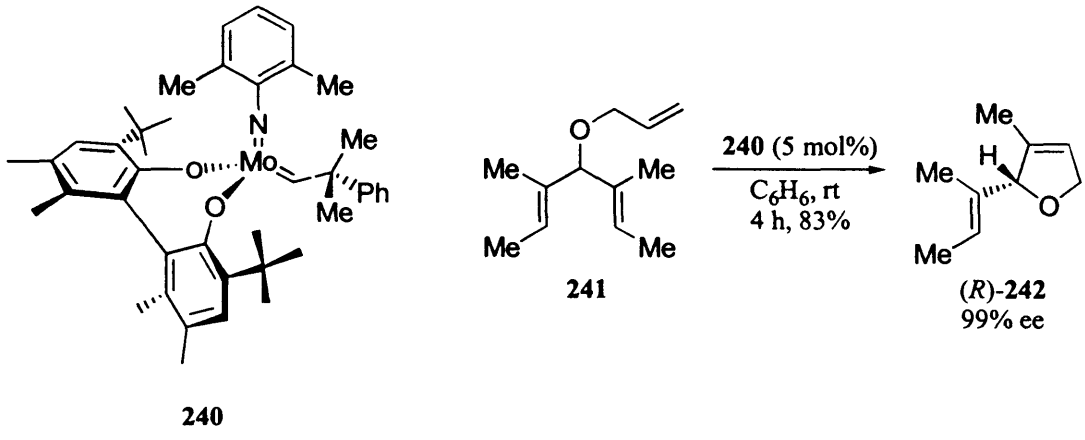
Scheme 45

Kinetic resolution was observed in RCM of racemic dienes catalyzed by the newly developed chiral molybdenum alkylidene complex **237**, by the Grubbs group.[83] When racemic diene **238** was treated with 2 mol% of **237** at 25 °C in benzene, RCM was observed and gave cyclic product **239**. The reaction was quenched after 20 minutes, at which time 90% of **238** had been consumed. The unreacted **238** (10%) was determined to have an 84% enantiomer excess of the *S* isomer.



Ar = 2,6-*i*-$Pr_2C_6H_3$
TBEC = 2',2',2",2"-tetrakis(trifluoromethyl)-1,2-bis(2'-hydroxyethyl)cyclopentane

An attractive extension to the strategy of asymmetric RCM was proposed by Hoveyda and Schrock, in which catalytic enantioselective desymmetrization delivered heterocycles with high optical purity in good yield.[84] For instance, in the presence of chiral catalyst **240**, triene **241** is converted to the dihydrofuran (*R*)-**242** in 99% ee and 83% isolated yield.

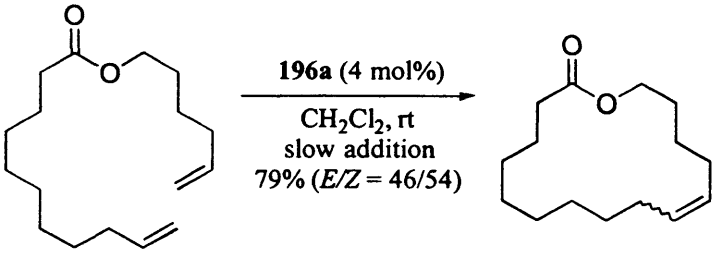


3.4.3 Syntheses of Macrocycles and Natural Products

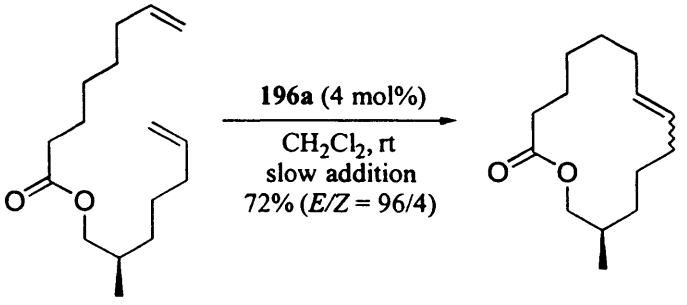
The efficiency of a cyclization reaction often becomes apparent in the synthesis of highly flexible large (≥9) ring systems. One major consideration for macrocyclization using RCM is the conformational predisposition of starting material for favourable intramolecular reaction. Nevertheless, it has been ascertained that macrocyclic RCM is highly efficient, not only with substrates having suitable constraints, but also with substrates lacking rigorous conformational restrictions by modification of reaction conditions. Hence, RCM is seen as one of the most favourable synthetic methods for the

formation of large ring systems. The reaction conditions that usually favour ring closure over competing oligomerization are low concentration of the diene, or slow addition of the substrate. High temperatures also assist ring closure, which means a high catalyst loading is required because of catalyst decomposition.

Fürstner and co-workers have reported macrocyclization of acyclic dienes using RCM.[85] The highly flexible α,ω-diene **243** undergoes RCM, upon slow addition to a solution of the catalyst **196a** in dichloromethane, generating the 16-membered lactone **244** in good yield. Notably, RCM of diene **245** provides the 14-membered lactone **246** with an extremely high stereoselectivity. This implies that the methyl group remote to the terminal olefin is influencing the kinetics of the reaction, and hence the stereochemistry.

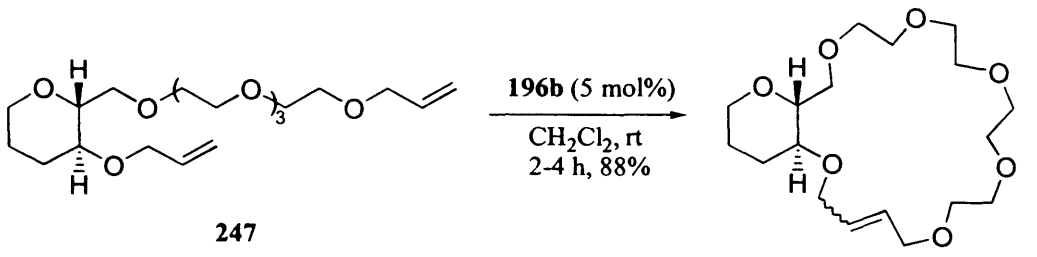


243 **244**



245 **246**

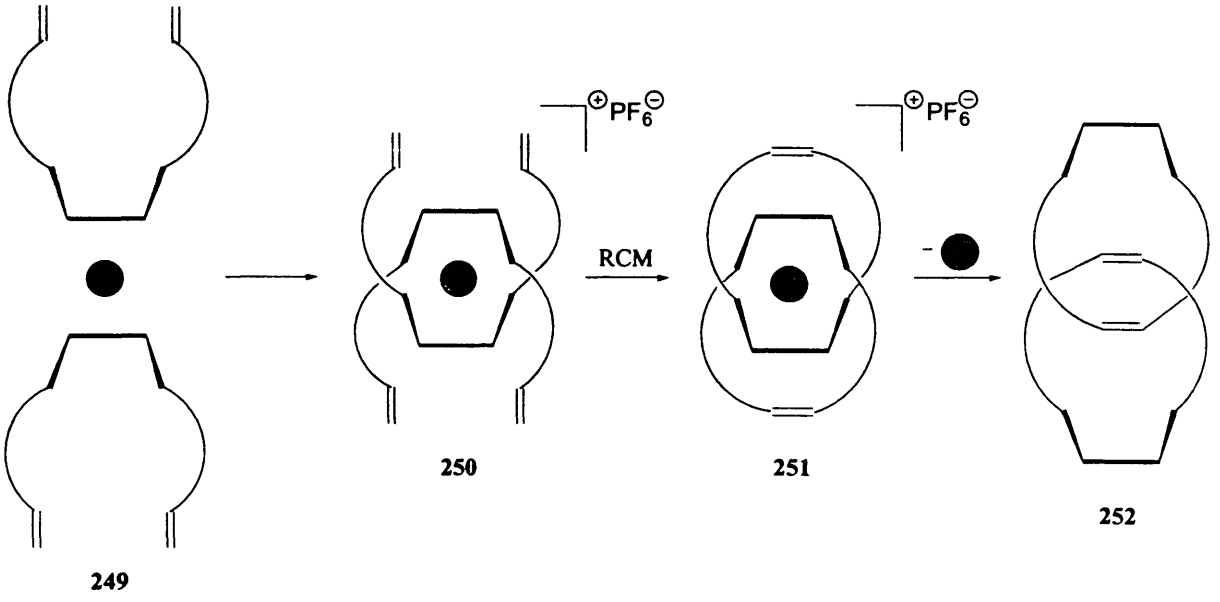
Martín *et al.* have applied RCM to the synthesis of mono- and polyoxygenated macrocycles, with rings ranging in size from 10 to 21 members, in *trans*-fused polyether systems which resemble natural marine toxins such as breve- and ciguatoxins.[86] For example, diene **247**, under typical RCM conditions, furnished the 21-membered crown ether **248** in excellent yield.



247

248 (*E*:*Z* = 13:1)

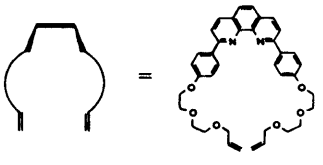
A recent communication by Grubbs and co-workers has shown that RCM is a highly efficient protocol for the synthesis of [2]catenanes by intramolecular cyclization.[87] A transition metal based template strategy is used in conjunction with RCM (Scheme 46). Complexation of two equivalents of the bidentate diene **249** with a copper complex gave the intertwined complex **250** in quantitative yield. Twofold RCM led exclusively to the 32-membered catenate complex **251** in remarkably high yield, with the energetically favoured *trans* double bond configuration predominant. Subsequent demetallation gave the catenane **252** in almost quantitative yield.



249 **250** **251** **252**

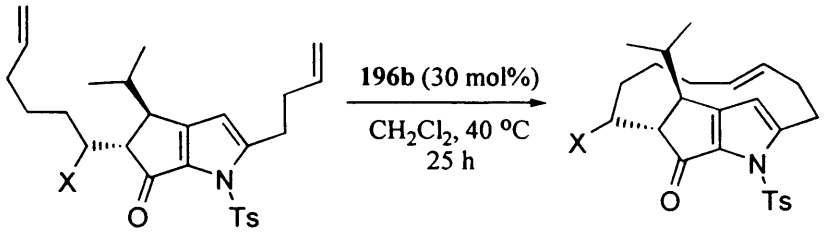
RCM - **196b** (5 mol%), CH_2Cl_2, rt, 6 h, 92% (trans:cis = 98:2)

● = Cu^+



Scheme 46

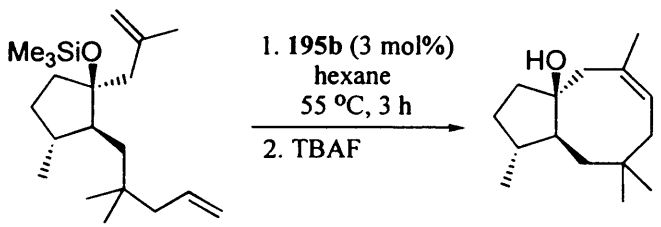
A good example of how the ability of RCM to build up strain in a molecule is limited was illustrated in a recent report on the synthesis of the macrotricyclic core of roseophilin.[88] Only after a conformational control element X had been introduced to help bring the terminal olefins of **253** closer together (therefore lowering the enthalpy barrier during ring formation), was RCM able to form the rather strained ansa chain of the target molecule **254**.



253 **254**

X = H, 0%, only dimer
X = OTIPS, 60%

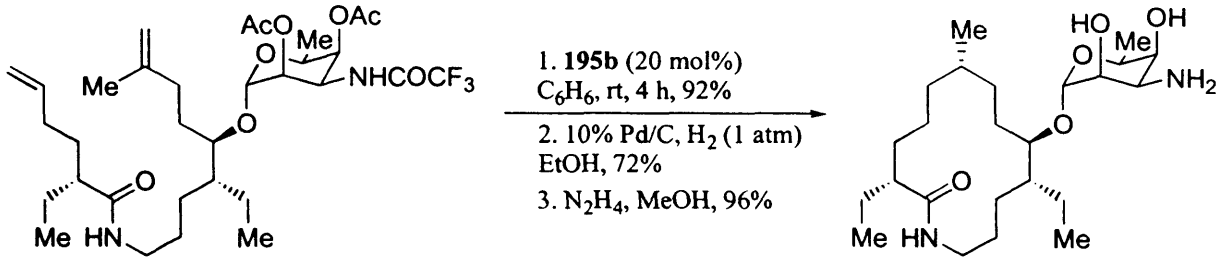
The experimental ease with which the reactions can be performed, along with the possibility of manipulating the olefinic functionality formed by the process, has made RCM one of the most powerful tools in modern organic synthesis. RCM has become increasingly utilized in the area of natural-product synthesis as a direct result of the pronounced tolerance of ruthenium-alkylidene complexes to a variety of functional groups. Fürstner and Langemann recently reported a straightforward synthesis of dactylol **256**, an cyclooctanoid terpene isolated from maritime organisms, via RCM.[89] The diene **255**, prepared in five steps from cyclopentenone, was efficiently cyclized and desilylated to furnish dactylol **256** in an 85% yield, and 17% overall yield in six synthetic operations.



255 **256**, 85%

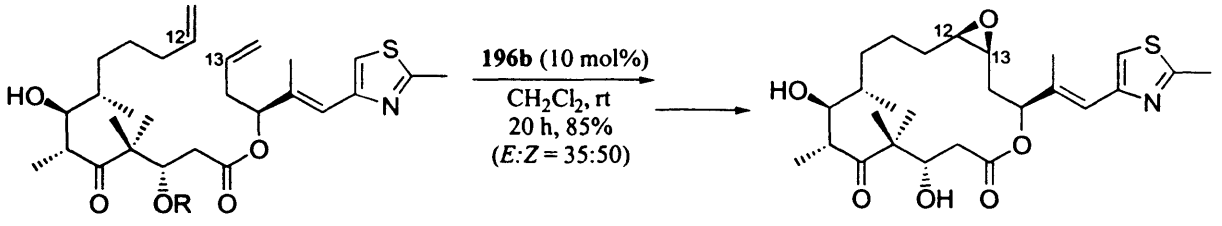
Hoveyda and co-workers have reported the synthesis of the 14-membered lactam Sch 38516 (fluvirucin B_1) **258**, an antifungal agent.[90] The Mo-catalyzed RCM of diene

257 gave the cyclized product in excellent yield, with almost exclusive formation of the (*Z*)-isomer. Stereocontrolled hydrogenation, followed removal of the acetate and trifluoroacetate groups with hydrazine in methanol, delivered **258** to complete the total synthesis.



257 **258**

Nicolaou *et al.* were the first to report a RCM based approach to the macrocyclic skeleton of the epothilones, a class of naturally occurring antitumor agents.[91] Like Taxol®, the epothilones promote the combination of α- and β-tubulin subunits and stabilize the resulting microtubule structures. This mode of action inhibits the cell division process and is, therefore, an attractive strategy for cancer chemotherapy. The metathesis of highly functionalized acyclic diene **259** proceeds smoothly to furnish the 16-membered macrocyclic *Z*-olefin in 50% yield together with its separable *E*-isomer (35%). Deprotection and epoxidation of the *Z*-isomer achieved the total synthesis of epothilone A (**260**) (Scheme 47). Using a similar C12,C13 disconnection approach, Schinzer *et al.* reported the total synthesis of epothilone A.[92] Danishefsky *et al.* also applied a C12,C13 disconnection strategy to prepare a range of epothilone A intermediates.[93]

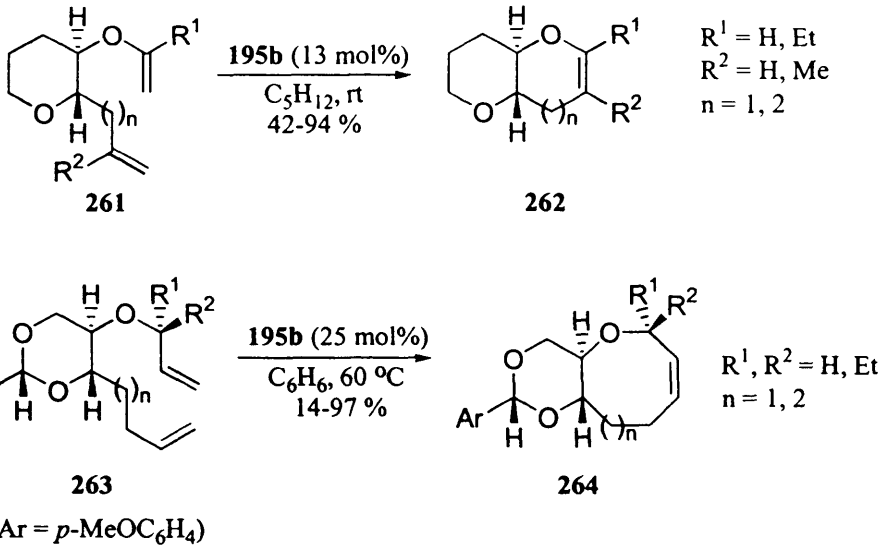


259 (R = TBS) **260**

Scheme 47

Cyclic ether components are abundant in natural products and strategies for their synthesis, corresponding to sub-units of brevetoxins, have been developed utilizing RCM.[94] Dienes **261** were successfully cyclized with Mo-catalyst **195b** to give bicyclic

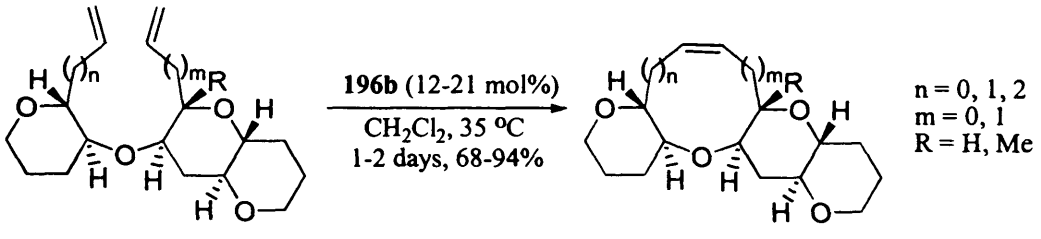
products **262** in good yield. Eight- and nine-membered cyclic ethers such as **264** were also obtained by RCM of the diolefins **263** with catalyst **195b** under high dilution conditions.



261 **262**

263 (Ar = *p*-MeOC$_6$H$_4$) **264**

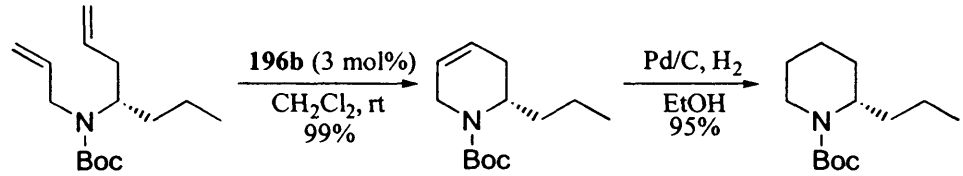
In the course of their synthetic study of ciguatoxin, Hirama and co-workers have developed a convergent route to *trans*-fused 6-*n*-6-6 (*n* = 7-10) tetracyclic polyether systems **266**, the final step of which is RCM.[95] Dienes **265** were reacted with the Grubbs catalyst **196b** to provide medium ring systems in good yield. This technique could serve as a versatile tool for the synthesis of polyether marine toxins.



265 **266**

Piperidine alkaloids are prevalent in various natural products, therefore strategies for the construction of these physiologically important compounds are of interest to the synthetic chemist. Chang *et al.* have reported the synthesis of optically active (*S*)-(+)-coniine (as the *N*-Boc protected form), the poisonous hemlock alkaloid, starting from the amino acid L-norvaline.[96] The key step involved RCM of the diolefin **267** to give the corresponding cyclic olefin **268** in excellent yield. Subsequent hydrogenation of alkene **268** furnished (*S*)-(+)-*N*-Boc-coniine **269** in seven steps with a 35% overall yield (Scheme

48). This approach should be applicable to the synthesis of a wide range of optically active piperidine moieties by choosing suitable amino acids as the starting point.

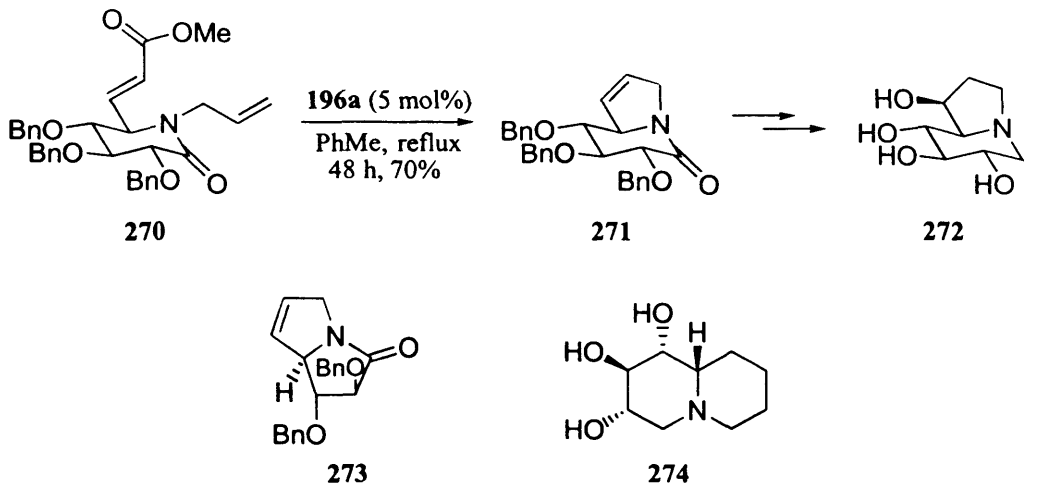


267 **268** **269**, 98% ee

Scheme 48

3.4.4 RCM Reactions of Carbohydrate Derivatives

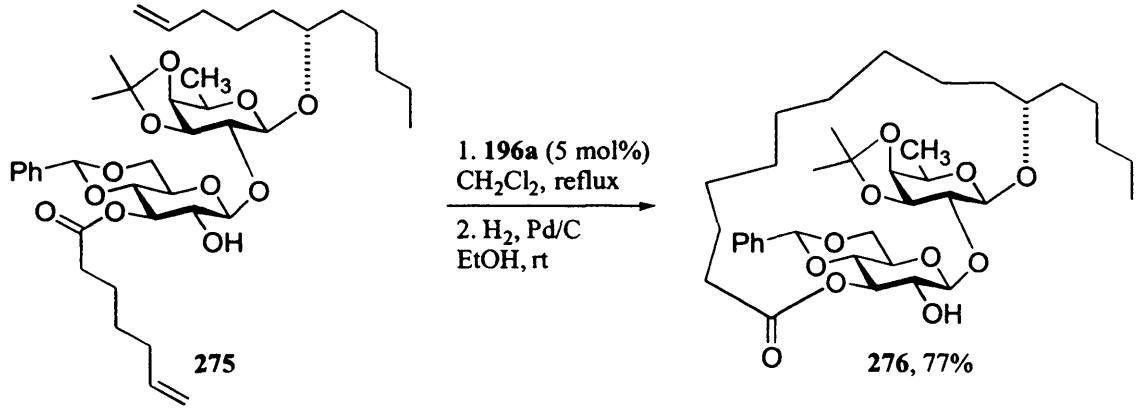
As a distinct chemical group, the carbohydrates, comprising mono-, oligo-, and polysaccharides and their derivatives, are the most abundant group of natural products. They play a number of key roles in living systems and are involved in a wide range of cellular processes, such as cell-cell recognition. This fresh understanding of carbohydrates has forced their study to the forefront of modern chemical research. Ring-closing metathesis provides no exception, with many literature examples involving carbohydrate derivatives emerging. Overkleeft and Pandit employed RCM as a key step in the synthesis of the azasugar castanospermine (**272**), a glycosidase inhibitor.[97] Cyclization of diene **270** proceeded smoothly to give the bicyclic lactam **271** in good yield, yet required relatively drastic reaction conditions. This is because one of the olefinic groups is an acrylic ester, rather than a terminal olefin, thus the by-product of the ring closure is methyl acrylate instead of the more volatile ethylene (Scheme 49). Novel pyrrolizidine (**273**) and quinolizidine (**274**) azasugars have been synthesized utilizing a similar strategy.[98]



270 271 272 273 274

Scheme 49

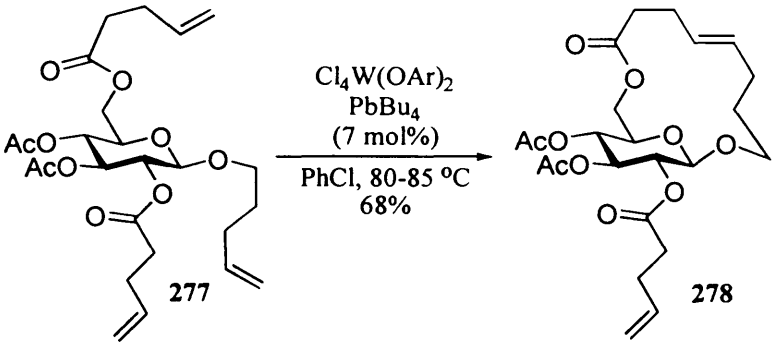
Fürstner and co-workers have synthesized the disaccharide subunit **276** of tricolorin A, a cytotoxic resin glycoside isolated from *Ipomoea tricolor*, using a RCM-mediated macrocyclization reaction rather than the more conventional macrolactonization strategy.[99] Diene **275** cleanly cyclized to the desired 19-membered ring, as a mixture of (*E*)- and (*Z*)-isomers, on reaction with **196a** in refluxing dichloromethane. Subsequent hydrogenation furnished the disaccharide **276** in 77% yield over both steps. This confirms that RCM is a very effective method for macrocyclization, provided that the site of ring closure is chosen carefully. The presence of a polar functional group in the substrate and low steric hindrance close to the double bonds favour RCM.



275 276, 77%

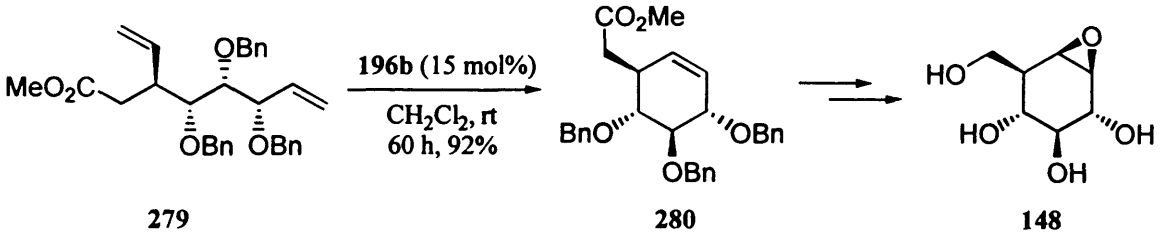
Descotes *et al.* have demonstrated that tungsten aryloxo complexes catalyze the RCM reactions of di- and tri- substituted ω-unsaturated glucose and glucosamine derivatives, yielding bicyclic carbohydrate-based compounds containing 12- and 14-

membered rings.[100] For example, triene **277** successfully undergoes RCM to afford the bridged bicyclic system **278** in reasonable yield.



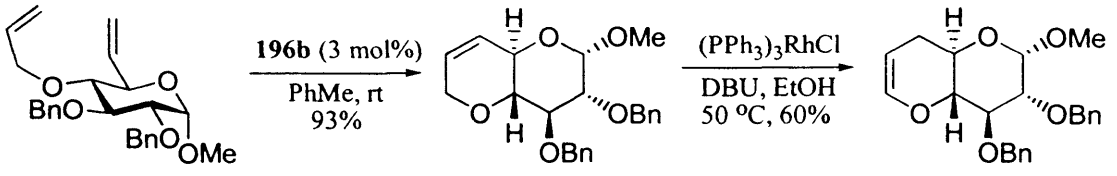
Ar = 2,6-diphenylphenyl

(+)-Cyclophellitol (**148**), a β-glucosidase inhibitor, has potential inhibitor activity against human immunodeficiency virus (HIV), and is therefore a popular target for synthetic chemists (see Scheme 31). A key step in the synthesis of **148** from D-xylose, by the Ziegler group, is RCM.[101] Diene **279** was converted to the cyclohexene derivative **280** in excellent yield. Further chemical modification of **280** gave enantiomerically pure (+)-cyclophellitol (**148**, Scheme 50).



Scheme 50

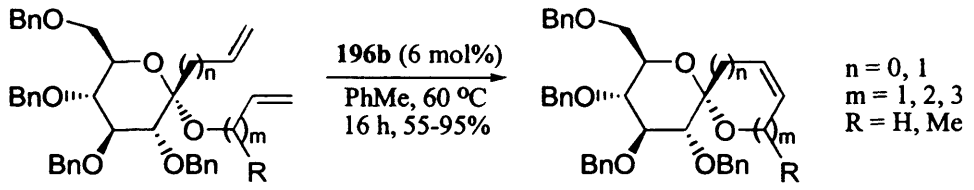
The van Boom group have made several contributions to the synthesis of carbohydrate derivatives via RCM. A novel synthesis of both *cis*- and *trans*-fused pyranopyran systems, based on RCM of glycal derived dienes, has been reported.[102] For example diene **281**, obtained in five steps from methyl 2,3-di-*O*-benzyl-α-D-glucopyranose, was efficiently converted to the *trans*-fused allylic bicyclic ether **282** by RCM reaction. Isomerisation of the double bond in **282** afforded the *trans*-fused vinylic bicyclic ether **283** in 60% yield as a single isomer (Scheme 51). It is well recognized that *trans*-fused polytetrahydropyrans are essential structural elements of several marine toxins, including brevetoxins and ciguatoxins.



281 **282** **283**

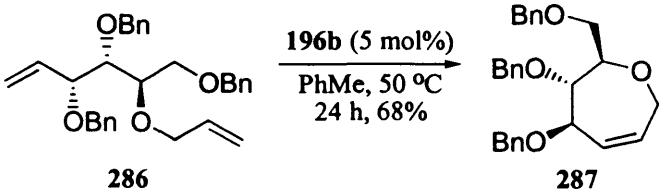
Scheme 51

The semi-rigid dioxa-spiroacetal function is a characteristic element of several biologically important natural products, for example the antiparasitic agent milbemycin. A very recent three-step approach to chiral pyranose [5,4] to [5,7] unsaturated spiroacetal derivatives from perbenzylated glucopyranolactone has been presented, in which the key step is RCM.[103] Diolefins **284** were successfully cyclized to the pyranose spiroacetal derivatives **285**, in the presence of catalyst **196b**, in good to excellent yield.



284 **285**

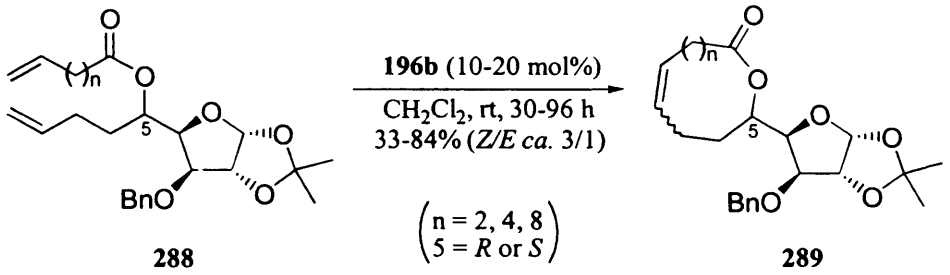
Seven-membered oxacyclic rings are common structural elements of many natural products, e.g. zoapatanol. A concise route to the synthesis of highly functionalized chiral oxepines from monosaccharides has been described, applying RCM.[104] For example vinyl-*O*-allyl adduct **286**, derived from 2,3,5-tri-*O*-benzyl-D-arabinofuranose, when treated with catalyst **196b** in toluene for 24 hours at 50 °C, resulted in the isolation oxepine **287** in good yield.



286 **287**

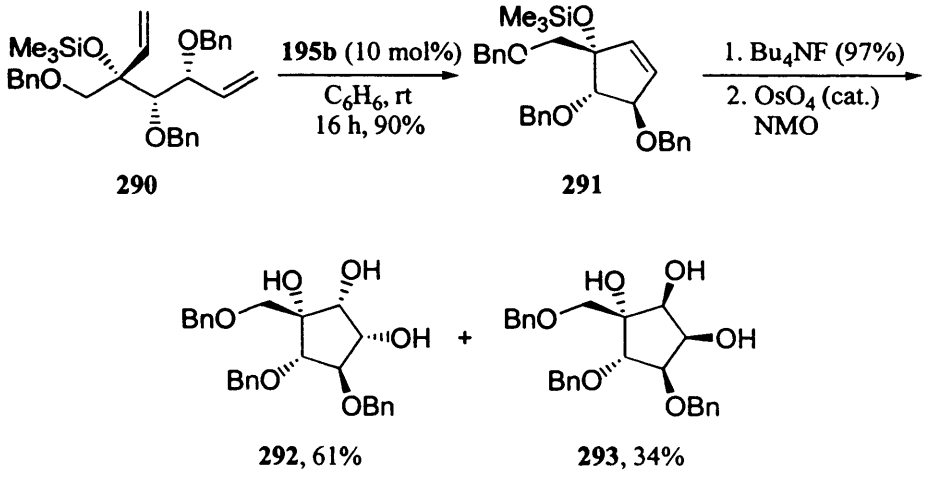
In connection with the synthesis of annonaceous acetogenins and analogues, RCM of unsaturated esters, prepared from diacetone-D-glucose, has been studied by Gesson and

co-workers.[105] Dienes **288** were successfully cyclized under standard Ru-catalyzed RCM conditions to give nine- to fifteen-membered lactones **289** in moderate to good yield.



288 **289**

Eustache *et al.* have reported RCM of a sterically hindered 1,6-diene **290**, obtained in four steps from commercially available 2,3,5-tri-*O*-benzyl-D-arabinofuranose.[106] The product, cyclopentene derivative **291**, was subsequently converted into new five-membered cyclitols **292** and **293**, and is a potential precursor of other biologically relevant aminocyclitols (Scheme 52).

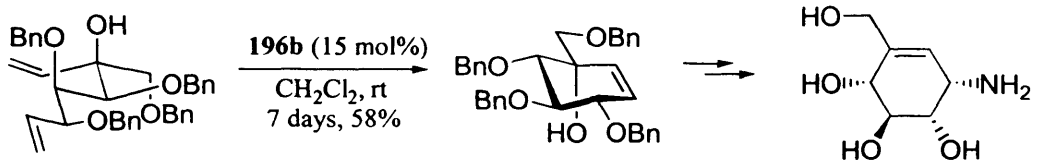


290 **291**

292, 61% **293**, 34%

Scheme 52

In their pursuit of carbosaccharides as potential glycosidase inhibitors, Vasella and co-worker have incorporated RCM into the synthesis of (+)-valienamine (**296**) from D-glucose.[107] Diene **294**, derived from 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose, undergoes RCM on treatment with catalyst **196b** to furnish cyclohexene **295** in 58% yield. Subsequent chemical transformation of **295** gave (+)-valienamine (**296**) in three steps and in 47% yield (Scheme 53).

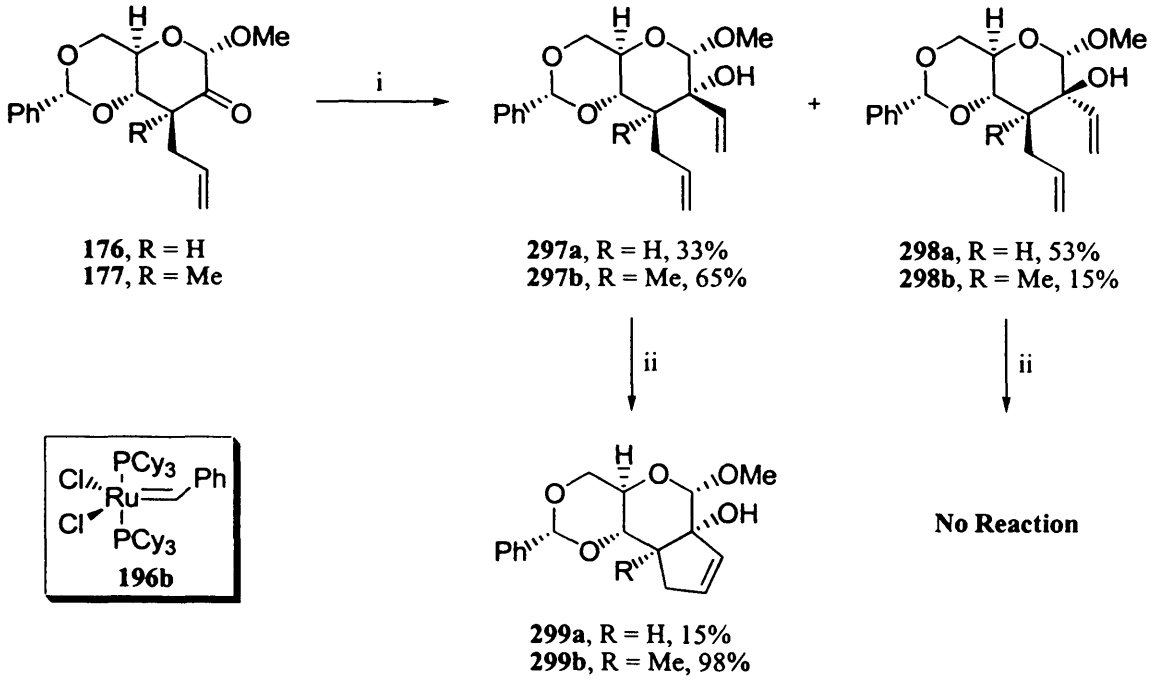


294 295 296

Scheme 53

3.5 **Results and Discussion**[108]

As part of our continuing interest in carbohydrate annulation, initial studies into the potential use of RCM are summarized in Scheme 54.[108a] The starting material was the ketone **176**, a derivative of methyl-α-D-glucopyranoside.[58] Reaction with vinylmagnesium chloride furnished allylic alcohols **297a** and **298a** in 33 and 53% yield respectively. The *cis* isomer **297a** was converted into the cyclopentene **299a** via RCM in a modest 15% yield, with 75% starting material recovered. An X-ray crystal structure of cyclopentene **299a** was obtained (Figure 3). Reaction of ketone **177** with vinylmagnesium chloride gave allylic alcohols **297b** and **298b** in 65 and 15% yield respectively. RCM of the *cis* isomer **297b** afforded cyclopentene **299b** in a vastly improved yield of 98%.



176, R = H
177, R = Me

297a, R = H, 33%
297b, R = Me, 65%

298a, R = H, 53%
298b, R = Me, 15%

299a, R = H, 15%
299b, R = Me, 98%

Scheme 54, Reagents and conditions: i, H_2C=CHMgCl, THF, reflux, 2 h; ii, **196b** (3 mol%), benzene, 60 °C, 48 h for **297a** and 17 h for **297b**.

This kind of phenomenon has been observed in previous work from the Jenkins group on intramolecular aldol condensation in carbohydrate chemistry, where cyclizaton was only possible when the side-chain was attached to the sugar at a quaternary centre (see Chapter 2).[54] These RCM results may also be explained by a Thorpe-Ingold type of effect, in which the quaternary centre restricts the number of degrees of freedom of the allyl side-chain, thus providing some conformational predisposition favouring ring closure in the diene substrate **297b**.[61] The assignment of cyclopentene structure **299b** was confirmed by X-ray crystallography (Figure 4). Dienes **298** did not undergo RCM probably because of the steric strain that would be associated with the *trans*-fused 5-6 ring systems in the products.

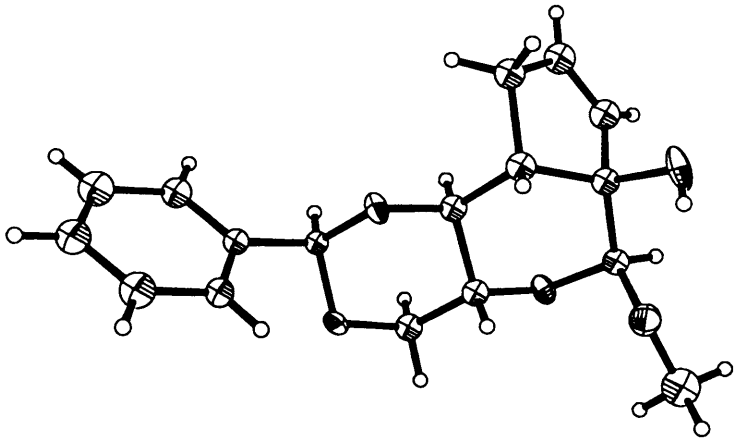


Figure 3. X-ray crystal structure of cyclopentene **299a**

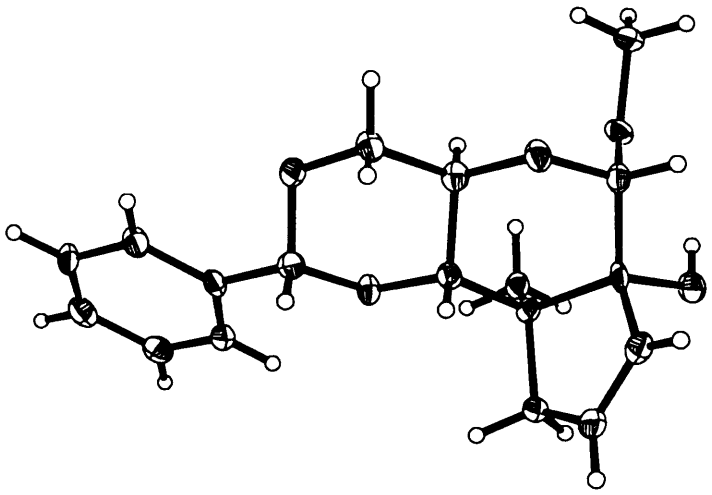
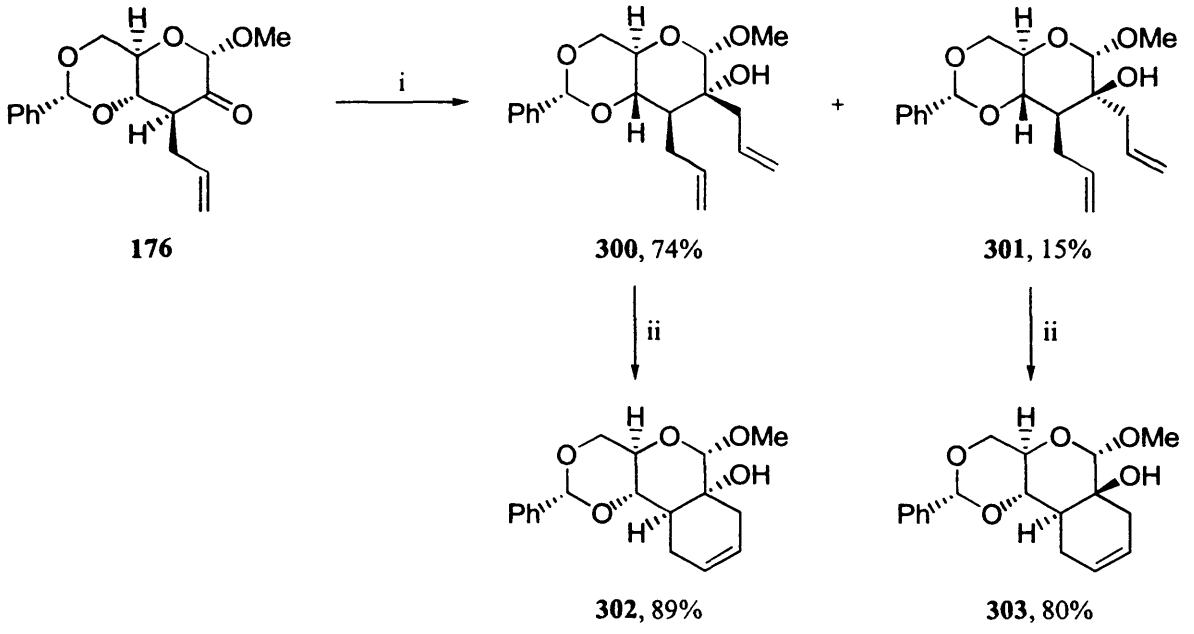


Figure 4. X-ray crystal structure of cyclopentene **299b**

The major product in the addition of allyl Grignard to ketone **176** is the *cis* diene **300** as opposed to the *trans* diene **298a**, the major product with vinyl Grignard (Scheme 55). This may be tentatively explained by coordination of the magnesium to the ketone and reaction via allylic rearrangement in the case of allyl Grignard, which is not possible with the equivalent vinyl reagent. We believe allylic rearrangement is best accommodated by axial attack of allylmagnesium chloride. Both diene isomers **300** and **301** underwent RCM to produce cyclohexene derivatives **302** and **303** in 89 and 80% yield respectively. The assignment of the *cis* product **302** was confirmed by an X-ray crystal structure (Figure 5). Clearly there is no steric impediment to the formation of the *cis* and *trans* 6-6 ring systems in **302** and **303**, respectively.



176 **300**, 74% **301**, 15%

302, 89% **303**, 80%

Scheme 55, Reagents and conditions: i, $H_2C{=}CHCH_2MgCl$, THF, reflux, 2 h; ii, **196b** (3 mol%), benzene, 60 °C, 17 h.

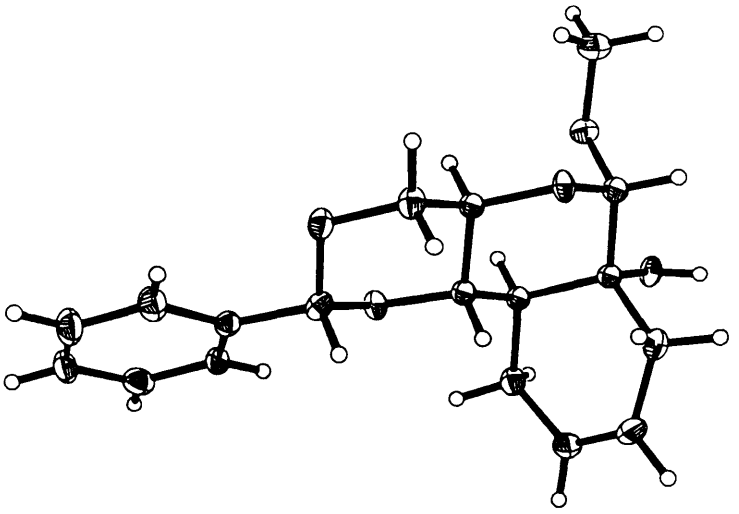
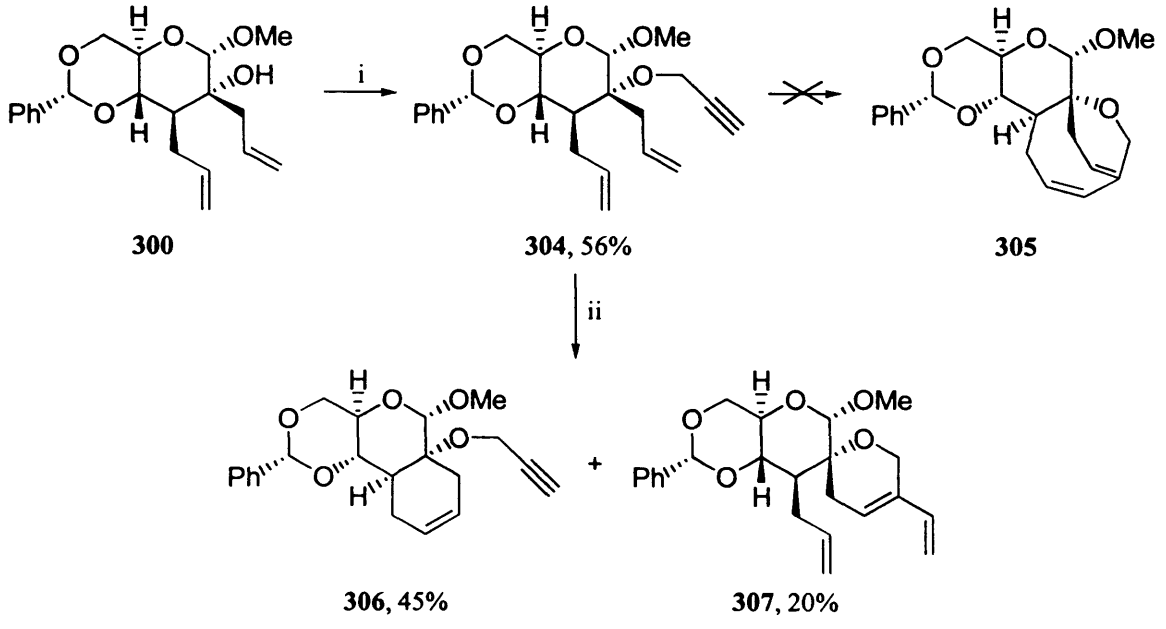


Figure 5. X-ray crystal structure of cyclohexene **302**

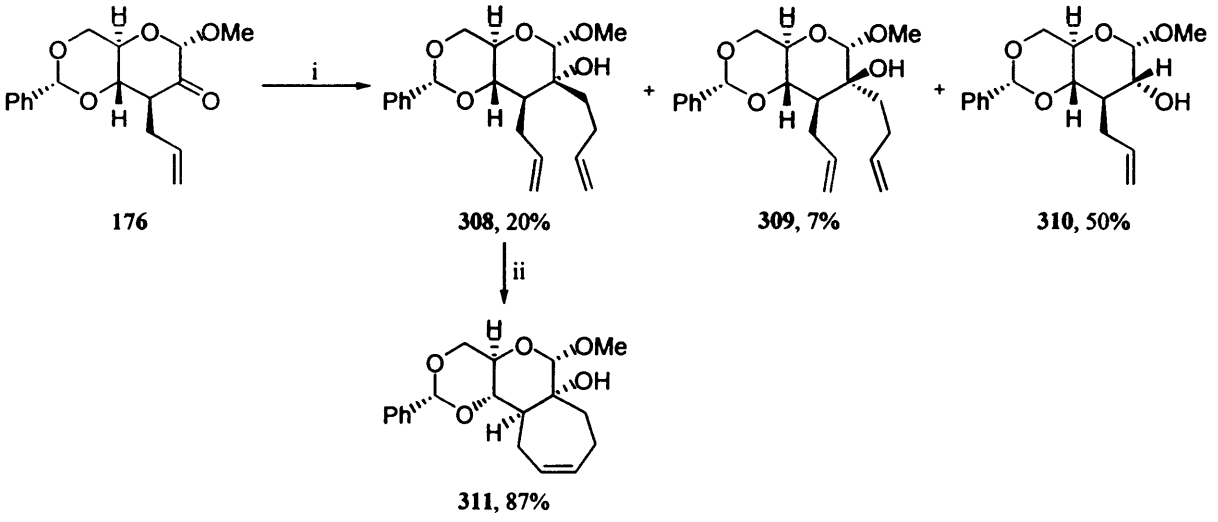
A tandem or domino RCM reaction was carried out in an attempt to form the [4.2.2] bicyclic annulated sugar **305** in one step (Scheme 56). Deprotonation of diene **300** with sodium hydride, followed by reaction with propargyl bromide furnished dieneyne **304** in 56% yield. Under standard RCM conditions **304** did not produce the desired bicyclic system **305**. Two products were isolated from the reaction mixture, cyclohexene derivative **306** (45%) and spiro dihydropyran **307** (20%).



Scheme 56, Reagents and conditions: i, NaH, $HC{\equiv}CCH_2Br$, KI, DMPU, THF; ii, **196b** (6 mol%), benzene, 60 °C, 6.5 h.

On reflection, the absence of tandem RCM is probably due to the 'olefinic arms' in **307** being too far apart for reaction to occur. This reaction would probably be more successful if in the substrate, the acetylene was positioned between the two olefins so as to act as an olefin metathesis relay, and if one of the 'olefinic arms' had a longer carbon chain, to accommodate the formation of a bridge head double bond.

The addition of alkyl Grignard reagents to ketones is significantly enhanced by anhydrous cerium(III) chloride, with notable suppression of β-hydrogen elimination which leads to unwanted reduction products.[109] Reaction of butenylmagnesium bromide with ketone **176** in the presence of anhydrous cerium(III) chloride gave a 20% yield of alcohol **308** along with 7% of its isomer **309**. However, the major product from this reaction, alcohol **310** (50%), arises from the Grignard reagent delivering hydride as a nucleophile. Cycloheptaannulation of **308** by RCM occurred readily to furnish the *cis*-fused alcohol **311** in 87% yield (Scheme 57). The assignment of the cycloheptene **311** was confirmed by an X-ray crystal structure (Figure 6).



Scheme 57, Reagents and conditions: i, $H_2C{=}CH(CH_2)_2MgBr.CeCl_3$, diethyl ether, -40 °C, 1.5 h; ii, **196b** (3 mol%), benzene, 60 °C, 17 h.

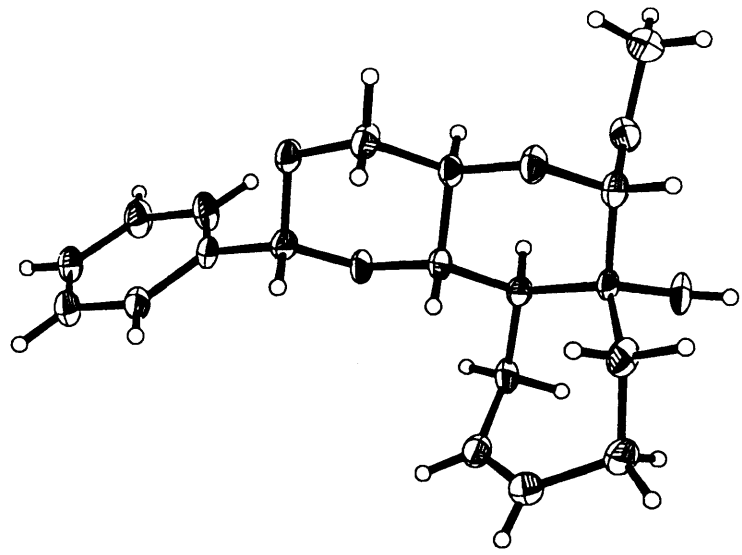
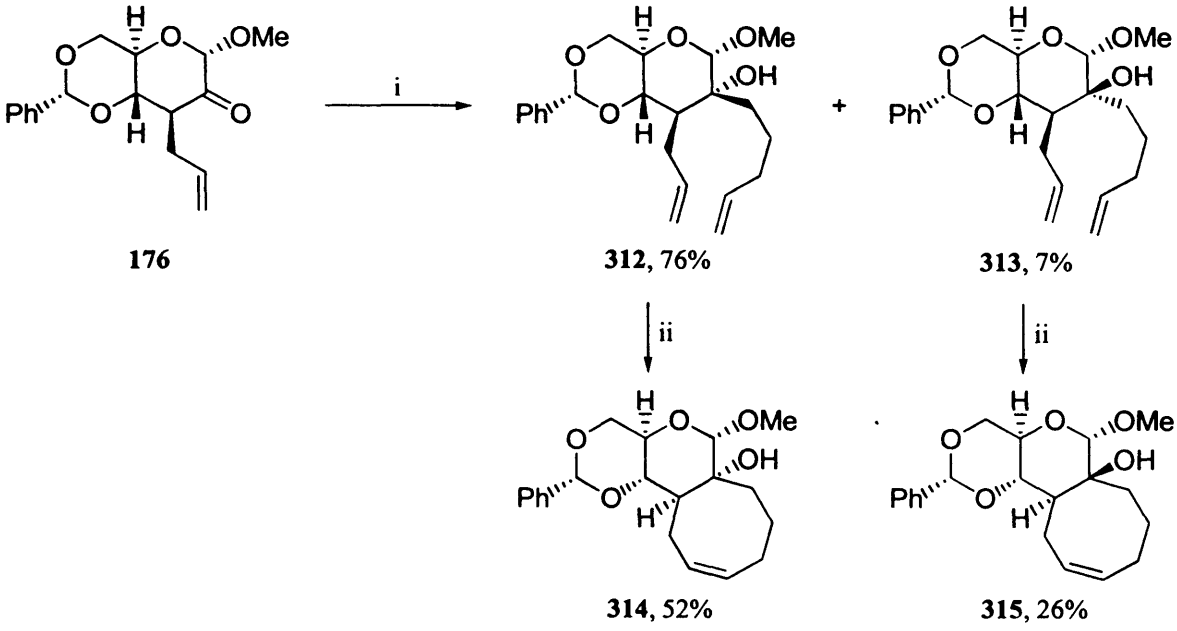


Figure 6. X-ray crystal structure of cycloheptene **311**

Reaction of the pentenyl Grignard reagent with ketone **176** gave dienes **312** and **313** in poor yields of 13 and 7%, respectively, along with 37% of alcohol **310** and 37% recovered starting material. However, an efficient reaction occurred in the addition of 4-pentenylmagnesium bromide to ketone **176**, in the presence of anhydrous cerium(III) chloride, producing the diene **312** in 76% yield (Scheme 58).



Scheme 58, Reagents and conditions: i, $H_2C{=}CH(CH_2)_3MgBr.CeCl_3$, diethyl ether, -40 °C, 2 h; ii, **196b** (6-9 mol%), benzene, 60-80 °C, 41-65 h.

RCM of **312** furnished the *cis*-fused cyclooctenyl alcohol **314** in 52% yield, along with 30% recovered starting material. Diene **313** afforded the *trans*-fused cyclooctenyl alcohol **315** in 26% yield, along with 48% recovered starting material. The assignment of the cyclooctene **314** was confirmed by X-ray crystal structure analysis (Figure 7). The crystals were all weak diffractors, but the assignment of structure **314** was unambiguous.

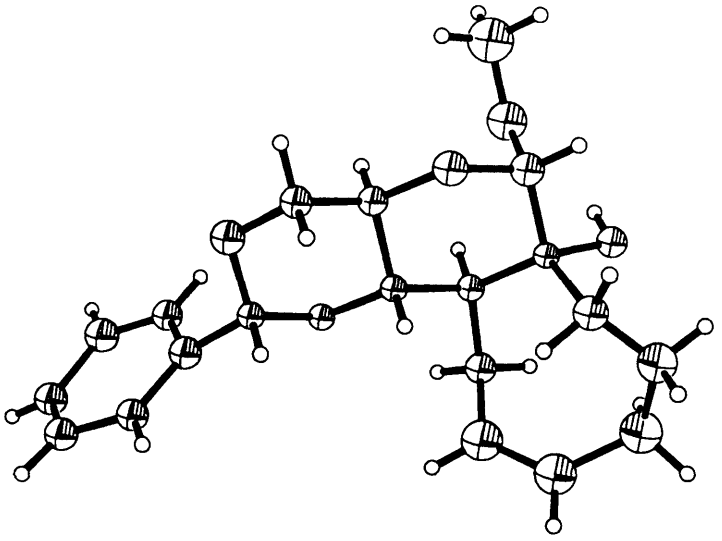
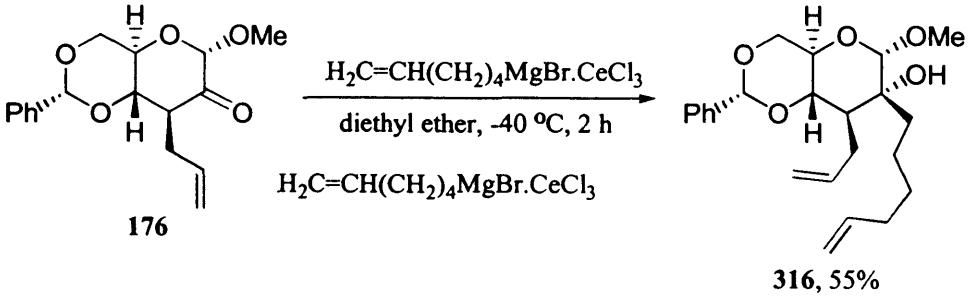
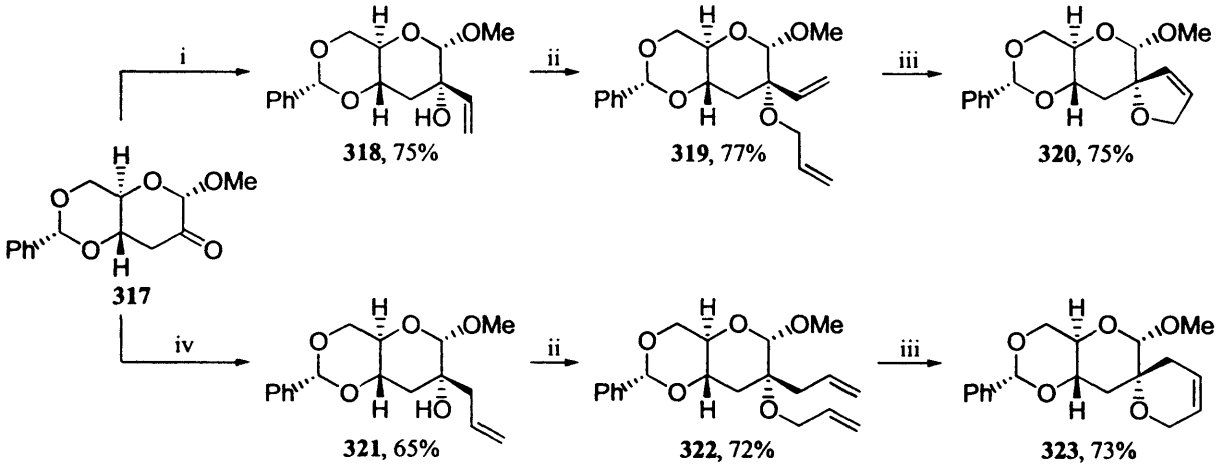


Figure 7. X-ray crystal structure of cyclooctene **314**

Addition of 5-hexenylmagnesium bromide to ketone **176** in the presence of anhydrous cerium(III) chloride gave alcohol **316** in 55% yield. When this compound was subjected to the standard RCM conditions no evidence of ring closure was obtained. However, a peak consistent with an intermolecular metathesis product was observed in the mass spectrum. When the reaction was carried out under more dilute conditions with a larger amount of catalyst, only starting material was recovered. Therefore, it seems that the formation of carbocyclic annulated sugars is limited to five- to eight-membered rings, with acyclic diene metathesis competing favourably with RCM in the case of the nine-membered ring diene substrate **316**.

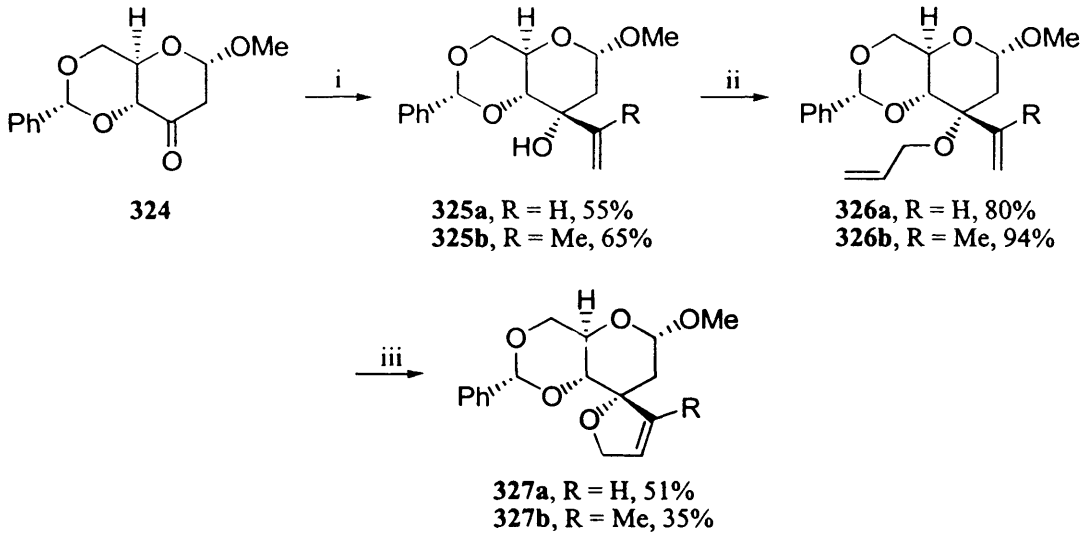


RCM has also been utilized in the formation of spiro annulated sugars within the Jenkins group by Mr. Will Barker. Ketone **317**[110], again a derivative of methyl-α-D-glucopyranoside, was reacted with vinylmagnesium chloride to provide the alcohol **318** in 75% yield (Scheme 59). Deprotonation with sodium hydride and reaction with allyl bromide produced the ether **319** in 77% yield, which was readily cyclized to the spiro product **320** in 75% yield, via RCM. A similar sequence involving addition of allylmagnesium chloride gave alcohol **321** in 65% yield, the ether **322** was obtained in 72% yield and the RCM reaction gave the spiro dihydropyran **323** in 73% yield.



Scheme 59, Reagents and conditions: i, H_2C=CHMgCl, THF, reflux, 2 h; ii, NaH, H_2C=$CHCH_2Br$, THF; iii, **196b** (2 mol%), benzene, 60 °C, 36 h; iv, H_2C=$CHCH_2MgCl$, THF, reflux, 2 h.

This sequence seems to have general applicability as shown by the results described in Scheme 60. Addition of vinylmagnesium chloride to ketone **324** gave a 55% yield of alcohol **325a**, which was converted into the diene **326a** in an 80% yield. RCM of diene **326a** produced the spiro dihydrofuran **327a** in 51% yield. The same sequence was carried out using isopropenyl Grignard to give alcohol **325b** (65%), ether **326b** (94%) and the spiro compound **327b** in 35% yield.



324

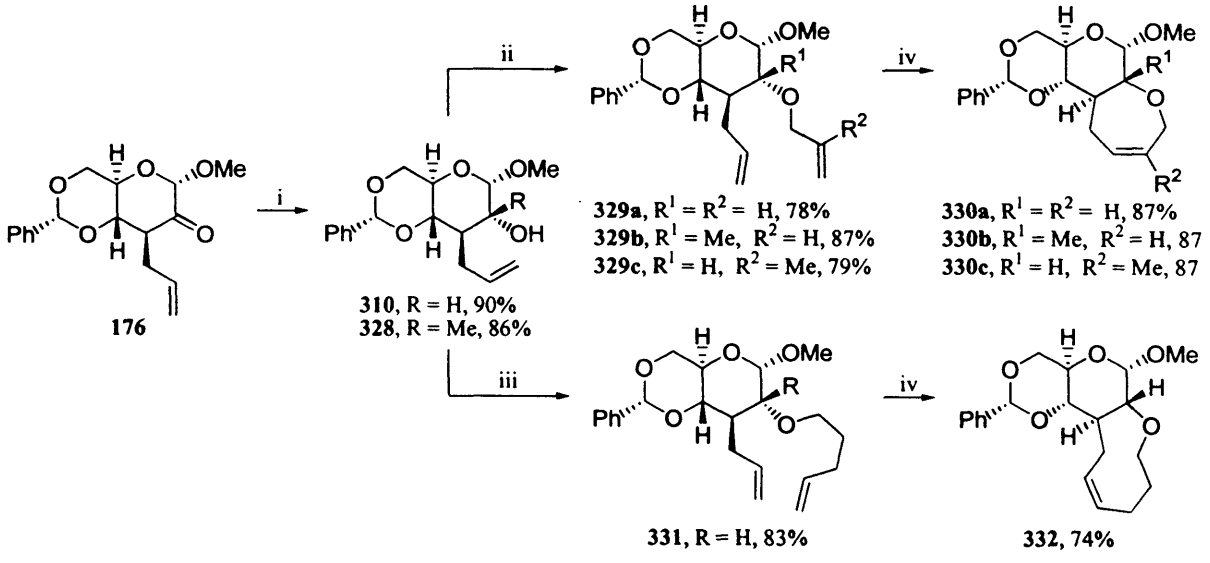
325a, R = H, 55%
325b, R = Me, 65%

326a, R = H, 80%
326b, R = Me, 94%

327a, R = H, 51%
327b, R = Me, 35%

Scheme 60, Reagents and conditions: i, H_2C=CRMgCl, THF, reflux, 2 h; ii, NaH, H_2C=$CHCH_2Br$, DMPU, THF; iii, **196b** (4 mol%), benzene, 60 °C, 36 h.

Studies on the synthesis of medium ring oxygen-containing heterocyclic annulated sugars, via RCM, was carried out within the research group of our Indian collaborator, Professor Subrata Ghosh, by Jagannath Panda. The addition of $LiAlH_4$ or MeLi to ketone **176** produced alcohols **310** and **328** in 90 and 86% yield, respectively (Scheme 61). Conversion to the ethers **329a-c** was achieved in 78-87% yield and the three RCM reactions occurred in 87% yield coincidentally, affording oxepine derivatives **330a-c**. Alcohol **310** was converted into the ether **331** in 83% yield, which gave the oxo-cyclononene **332** in 74% yield, as a product of RCM.



176

310, R = H, 90%
328, R = Me, 86%

329a, $R^1 = R^2 =$ H, 78%
329b, R^1 = Me, R^2 = H, 87%
329c, R^1 = H, R^2 = Me, 79%

330a, $R^1 = R^2 =$ H, 87%
330b, R^1 = Me, R^2 = H, 87
330c, R^1 = H, R^2 = Me, 87

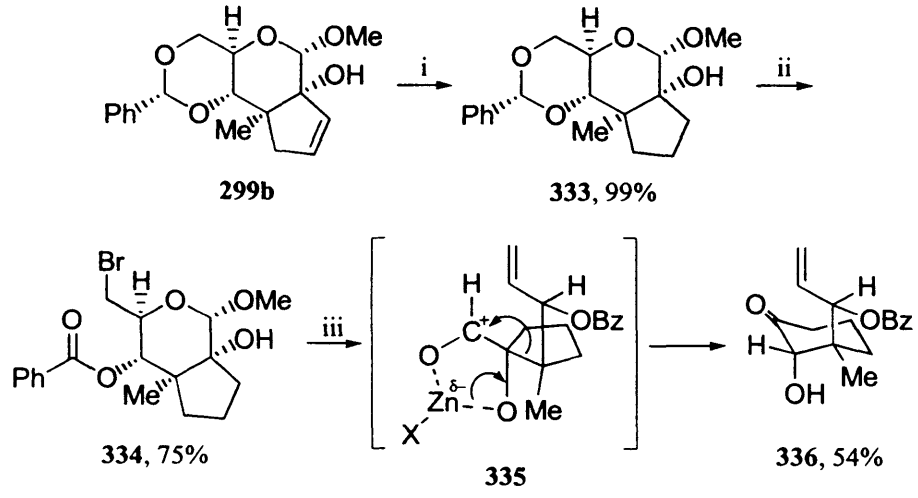
331, R = H, 83%

332, 74%

Scheme 61, Reagents and conditions: i, **310** - $LiAlH_4$, THF, 0 °C, then 3 h reflux; **328** - MeLi, THF, 0 °C, then 6 h rt; ii, NaH, THF, HMPA, H_2C=CR^2CH_2Br, 2 h reflux; iii, NaH, THF, HMPA, H_2C=$CH(CH_2)_3Br$, 2 h reflux; iv, **196b** (4 mol%), benzene, 60 °C, 6-14 h.

The successful formation of the nine-membered heterocyclic ring **332** is in stark contrast to the failure of RCM in the case of the carbon containing analogue, **316**. One difference between the two substrates is that in **316** the chains are *cis* and in **331** they are *trans*. Another reason for the difference in reactivity could be due to the oxygen, although a convincing explanation does not seem possible on the basis of the available data.

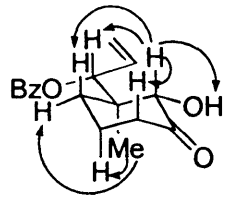
Having demonstrated that RCM is an effective tool for carbohydrate annulation, we turned our attention to the conversion of these annulated sugars into enantiomerically pure carbocyclic and heterocyclic rings.[108b] The cyclopentaannulated sugar **299b** was reduced to the saturated derivative **333** in 99% yield (Scheme 62). Reaction with *N*-bromosuccinimide according to the procedure of Hanessian[63] gave the bromo ester **334** in good yield. Treatment of **334** with activated zinc in a Vasella elimination[30a] did not produce the expected cyclopentane product. Instead ring-expansion occurred, via the α-ketol rearrangement, to produce the cyclohexanone derivative **336** as a single diastereoisomer in 54% yield. The configuration of the new stereogenic centre in **336** is in accord with literature precedent[111] where rearrangement occurs via the chelated transition state **335**. Zinc bromide is formed as a by-product in the Vasella reaction and is the Lewis acid for the rearrangement.



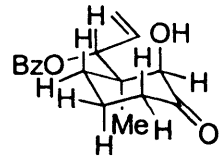
Scheme 62, Reagents and conditions: i, H_2, EtOH, 5% Pd/C; ii, NBS, $BaCO_3$, $CHCl_3$, reflux; iii, Activated Zn, IPA:H_2O (10:1), reflux.

We believe the most stable ring conformation of the product **336** is as indicated by structure **337**. From the NOESY spectrum of alcohol **336**, it can be seen that the major nOe effects of the methyl group are across the α-face of the ring to the adjacent equatorial

proton, and the axial proton. The nOe effects of the proton on the carbon bearing the hydroxyl are to the two axial protons on the β-face of the molecule, to the side chain C*H* and to the O*H*. On the assumption that the conformation of the cyclohexane ring is controlled by the largest substituent being equatorial, the other possible rearrangement product (instead of **336**) is shown by structure **338**. Here we would not expect to see an nOe between the equatorial proton on the carbon bearing the hydroxyl and the CH_2 protons in the ring.

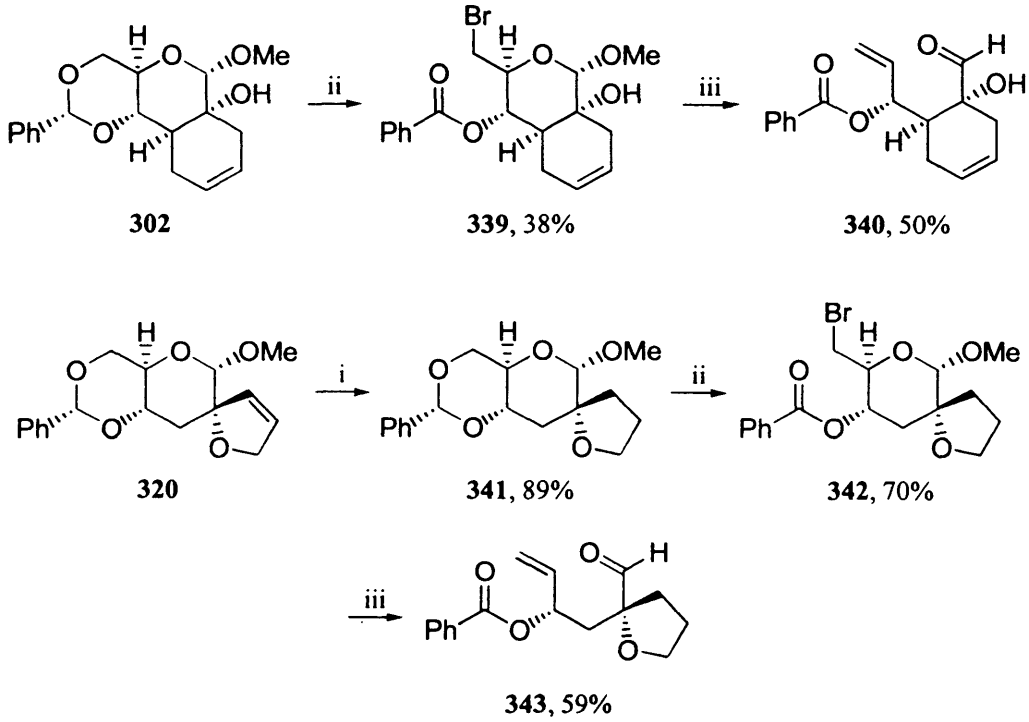


337



338

In the case of the cyclohexene derivative **302**, direct bromination was possible, furnishing the bromo ester **339** in 38% yield (Scheme 63). Treatment of **339** with activated zinc gave the aldehyde **340** in 50% yield; no ring-expansion was observed. The driving force for expanding a five-membered ring in **335** to a six-membered ring in **336** is clearly greater than for a six-membered ring in **340**, to what would be a seven-membered ring.



302 **339**, 38% **340**, 50%

320 **341**, 89% **342**, 70%

343, 59%

Scheme 63, Reagents and conditions: i, H_2, MeOH, 5% Pd/C; ii, NBS, $BaCO_3$, $CHCl_3$, reflux; iii, Activated Zn, IPA:H_2O (10:1), reflux.

Mr. Will Barker showed that the spiro compound **320** could be reduced to the saturated analogue **341** in 89% yield. Subsequent reaction with *N*-bromosuccinimide gave the bromo ester **342** in good yield, which was subjected to Vasella elimination, yielding the aldehyde **343** in 59% yield.

3.6 **Summary**

Clearly from the examples discussed, olefin metathesis has emerged as a very powerful strategy for carbon-carbon bond formation. RCM catalysts show the tolerance and activity required for use in synthetic approaches to complex molecules. Our contribution to this area of chemistry has demonstrated that RCM can be applied to carbohydrate substrates for the formation of five to nine-membered rings, and that the products can be converted into highly substituted enantiomerically pure alicyclic compounds.

CHAPTER 4

COPPER(I) CATALYZED [2+2] INTRAMOLECULAR PHOTOANNULATION OF CARBOHYDRATE DERIVATIVES

4.1 Introduction

Most reactions in organic chemistry occur between molecules in their ground electronic states. However, in a *photochemical reaction*, a reacting molecule has been previously promoted to an electronically excited state by absorption of light. Homogeneous transition metal catalysis of organic photochemical reactions provides a multitude of synthetically useful transformations not readily achievable via ground state processes. Many of these reactions involve olefinic substrates which undergo various types of transformation, including geometric isomerization, allylic [1.3] hydrogen shift, hydrogenation, addition, oxidation and [2+2] cycloaddition. According to Frontier-Orbital theory, a concerted [2+2] cyclization of two monoolefins is *not* allowed because it would require that a positive lobe overlap with a negative lobe (Figure 8). When considering a *photochemically induced* [2+2] cyclization, an electron is promoted to a vacant orbital (usually a triplet excited state) and this reacts with a ground-state molecule (Figure 9). Obviously, the [2+2] reaction is now allowed, and is likely to proceed via a diradical (**344**) mechanism.

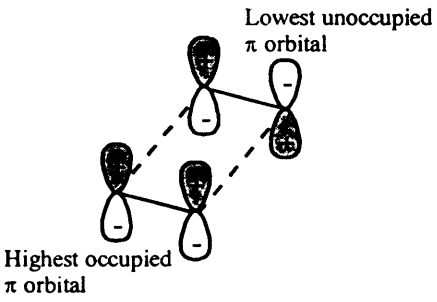


Figure 8. Thermal [2+2] cycloaddition

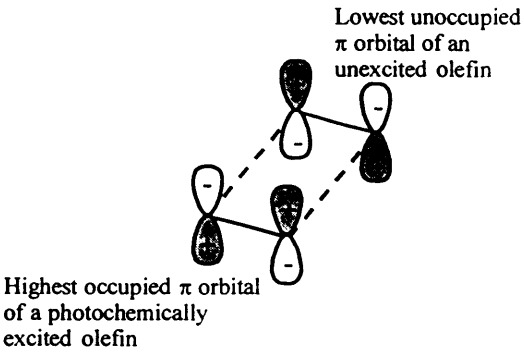


Figure 9. Photochemical [2+2] cycloaddition

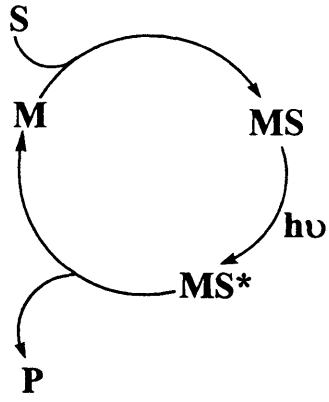
344

Mechanism

4.2 Mechanism of Catalyzed [2+2] Cycloaddition[112]

The mechanism of homogeneous transition metal catalyzed [2+2] cycloaddition can be termed *catalyzed photolysis*. The mechanistic process involves several steps (Scheme 64):

- coordination of a transition metal catalyst **M** to an olefinic substrate **S**, promotes photoexcitation to an excited state **MS***.
- excited state **MS*** allows inter- or intramolecular [2+2] cycloaddition to occur, leading to product **P**.
- product **P** can no longer coordinate to the transition metal catalyst **M**, and hence is released to complete the catalytic cycle.



Scheme 64

Since the photochemical step does not generate the catalyst, yet is an essential component of the catalytic cycle, the catalyzed photolysis stops immediately when irradiation ceases (Figure 10). While the catalyzed photolysis is catalytic with respect to the metal, it is *not catalytic* in photons.

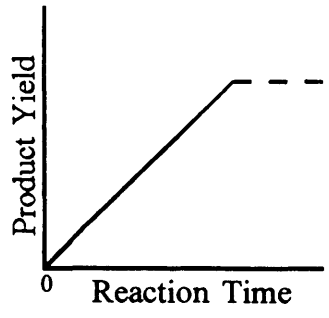


Figure 10. Catalyzed photolysis during (—) and after (---) irradiation

4.3 Copper(I) Catalyzed [2+2] Cycloaddition Reactions

Copper(I) salts are known to catalytically promote various photochemical reactions of olefins, including [2+2] cycloaddition reactions. The UV spectrum of a coordination complex between copper(I) bromide and bicyclo[2.2.1]hept-2-ene (BH) was reported by Trecker, Henry and McKeon in 1965 (Figure 11).[113]

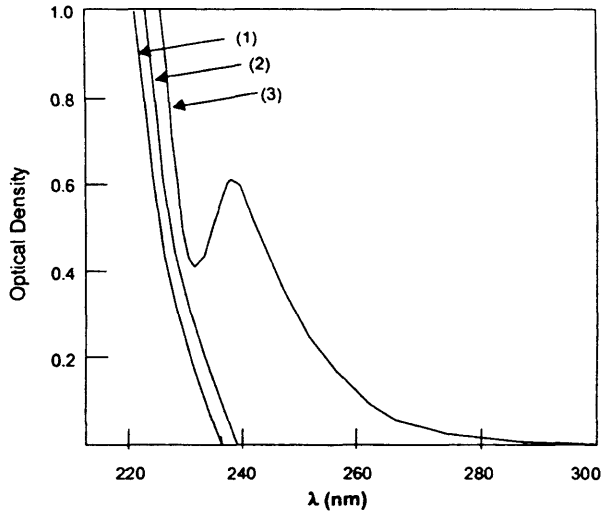
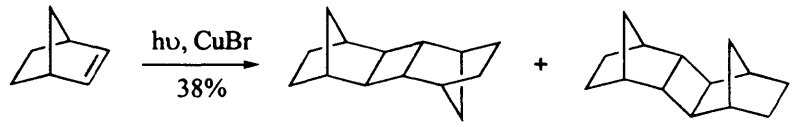


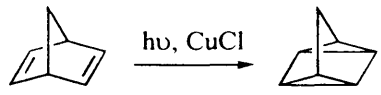
Figure 11. Ultraviolet spectra of (1) CuBr in ether, (2) BH in ether and (3) BH and CuBr in ether

The copper-alkene complex is indicated by an intense UV absorption band at 239 nm in a solution containing both BH and CuBr. No significant absorption was seen for solutions of BH or CuBr separately. Irradiation of excess BH in the presence of CuBr furnished dimers **345** and **346** (97:3) in 38% isolated yield.



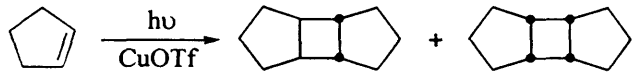
BH **345** (97:3) **346**

The UV spectrum of a coordination complex between copper(I) chloride and bicyclo[2.2.1]hepta-2,5-diene (BHD) was recorded by Schwendiman and Kutal in 1977.[114] In contrast to other transition metal catalysts, copper(I) selectively promotes *intra*molecular [2+2] photocycloaddition to give quadricyclane (Q).[115]



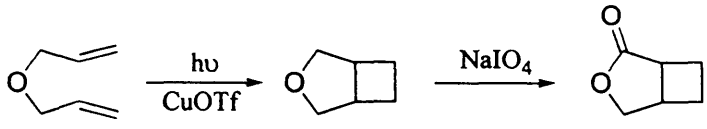
BHD Q

Copper(I) triflate catalyzed photoreactions involve light absorption by preformed alkene-copper(I) complexes, which exchange rapidly with free alkene. These copper(I) triflate-alkene complexes generally show two strong UV absorption bands at 230-241 nm and 260-288 nm,[116] while the free non-conjugated alkenes are nearly transparent in this region. Unlike CuBr and CuCl, copper(I) triflate promotes dimerization of cyclopentene to give **347** and **348** in 30 and 2% yield respectively.[117] The reasoning behind this is that halide ions compete with alkene for coordination with copper(I), whereas trifluoromethanesulfonate is a much weaker coordinating anion and therefore does not compete.

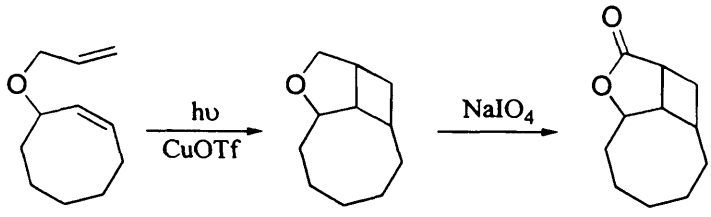


347, 30% **348**, 2%

Photobicyclization of acyclic and monocyclic diallyl ethers (**349** and **350**) can also be achieved with copper(I) triflate as the catalyst (Scheme 65).[118] The bicyclic and tricyclic products **351** and **352** can be readily oxidized to furnish bicyclic and tricyclic lactones **353** and **354** in good yield.



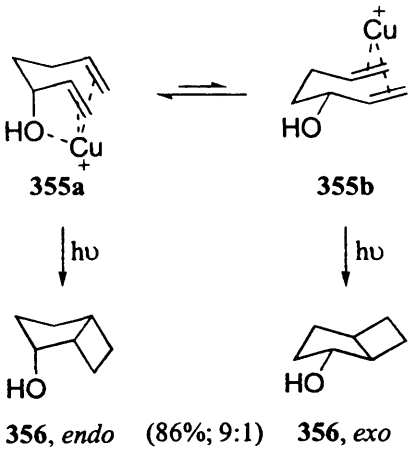
349 **351**, 52% **353**, 91%



350 **352**, 56% **354**, 56%

Scheme 65

Copper(I) catalyzed intramolecular photocycloaddition provides an effective stereoselective route to bicyclo[3.2.0]heptan-2-ols.[119] For example, the photobicyclization of 1,6-heptadiene-3-ol **355** shows a 9:1 preference for the thermodynamically less stable *endo*-2-hydroxy epimer **356** (Scheme 66). This selectivity is expected because **355** acts preferentially as a tridentate ligand (**355a**) rather than a bidentate ligand (**355b**).

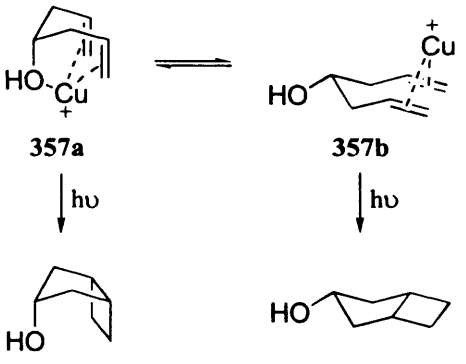


355a **355b**

356, *endo* (86%; 9:1) **356**, *exo*

Scheme 66

Evers and Mackor showed that photobicyclization of 1,6-heptadiene-4-ol **357** with CuOTf catalyst is non-stereoselective (Scheme 67).[120] To achieve tridentate coordination of **357** to copper(I), a boat-like conformation must be adopted (**357a**). Apparently there is no preference for **357a** over the alternative bidentate coordination, as in the chair-like arrangement **357b**. Therefore, there is no *endo*/*exo* preference in the bicyclic product **358**.



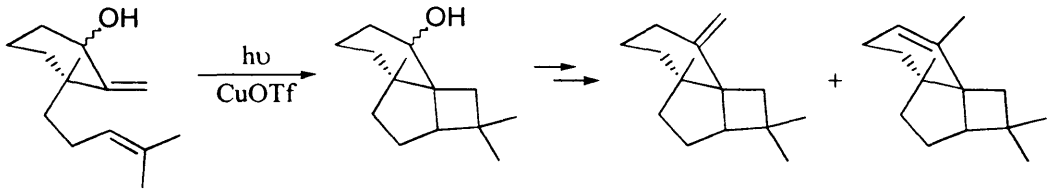
357a **357b**

358, *endo* (1:1) **358**, *exo*

Scheme 67

Photochemical [2+2] cycloaddition can also be applied to natural product synthesis. A key step in a total synthesis of α-panasinsene (**361**) and β-panasinsene (**362**),

sequiterpenes obtained from ginsing, is the CuOTf catalyzed photobicyclization of monocyclic allylic alcohol **359**, furnishing tricyclic ring system **360** (Scheme 68).[121]

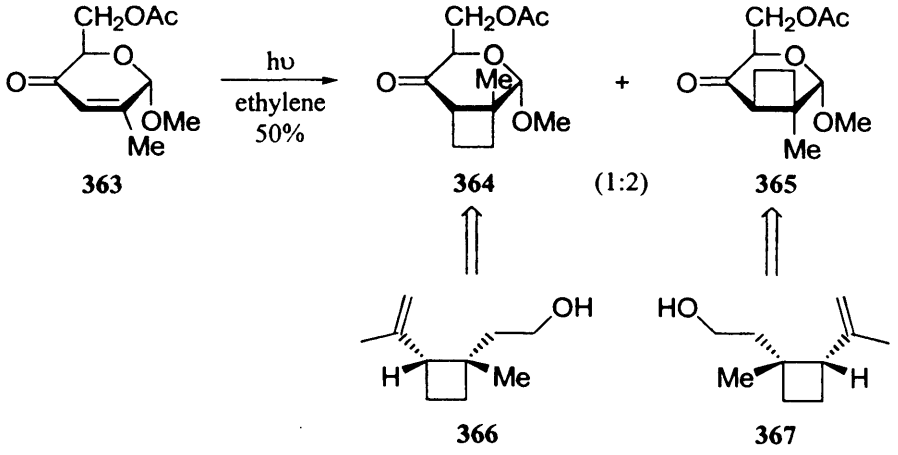


359 **360** **361** **362**

Scheme 68

4.4 [2+2] Cycloaddition Reactions of Carbohydrate Derivatives

The formation of cyclobutanes via intramolecular nucleophilic displacement reactions is uncommon within the field of carbohydrate annulation. However, there are several examples of [2+2] cycloaddition reactions in the preparation of cyclobutane carbohydrate derivatives. Fraser-Reid and co-workers have prepared cyclobutanopyranosides **364** and **365**, by intermolecular [2+2] photocycloaddition of ethylene to methyl 6-*O*-acetyl-2,3-dideoxy-2-*C*-methyl-α-D-*glycero*-hex-2-enopyranosid-4-ulose (**363**), in an approach to the boll-weevil pheromone (–)-grandisol **366**, and its enantiomer **367** (Scheme 69).[122] In this type of reaction, an enone-olefin photocycloaddition, the *enone* can be photoexcited, therefore the reaction does not require a catalyst.

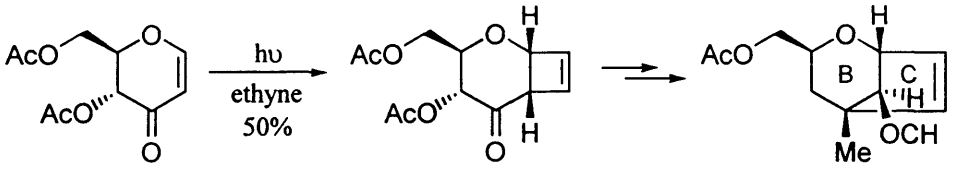


363 **364** (1:2) **365**

366 **367**

Scheme 69

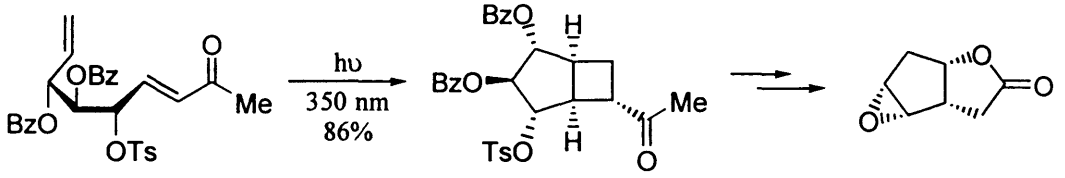
Fetizon and co-workers have described a chiral synthesis of the B-C ring system of trichothecenes, a diverse family of mycotoxins that exhibit a broad range of biological activities, including anticancer activity.[123] Application of intermolecular [2+2] photocycloaddition of ethyne to the enone **368**, a derivative of tri-*O*-acetyl-D-glucal, gave cyclobutene derivative **369** in 50% yield (Scheme 70). Deacetoxylation of **369** at C-4, methyllithium addition at the carbonyl centre, followed by formic acid catalyzed rearrangement afforded the 2-oxabicyclo[3.2.1]octane system **370** in 14% yield over three steps.



368 **369** **370**

Scheme 70

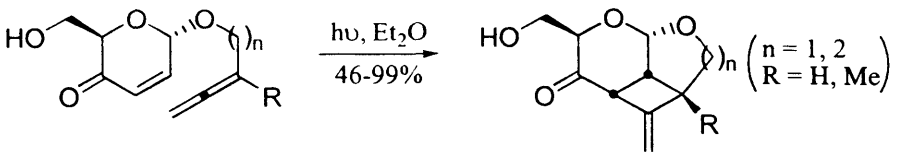
Ferrier *et al.* have reported the intramolecular [2+2] photocycloaddition of the nona-3,8-dienulose derivative **371**, furnishing the bicyclo[3.2.0]heptyl methyl ketone **372**, which itself is an intermediate in the preparation of the epoxy lactone **373**, a synthetic precursor of the prostaglandins (Scheme 71).[124]



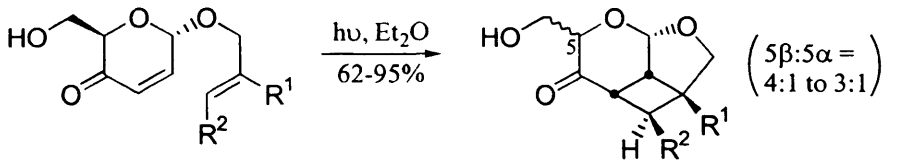
371 **372** **373**

Scheme 71

Tenaglia and co-workers have described efficient intramolecular [2+2] photocycloaddition of alkyl hex-2-enopyranosid-4-uloses, allowing the construction of two new cyclic systems annulated to the sugar moiety with stereocontrol of 3 or 4 carbogenic centres.[125] On irradiation, uloses **374** and **376** were converted into tricyclic derivatives **375** and **377** in fair to excellent yield. In the case of compounds **377**, some epimerization at C-5 was observed.



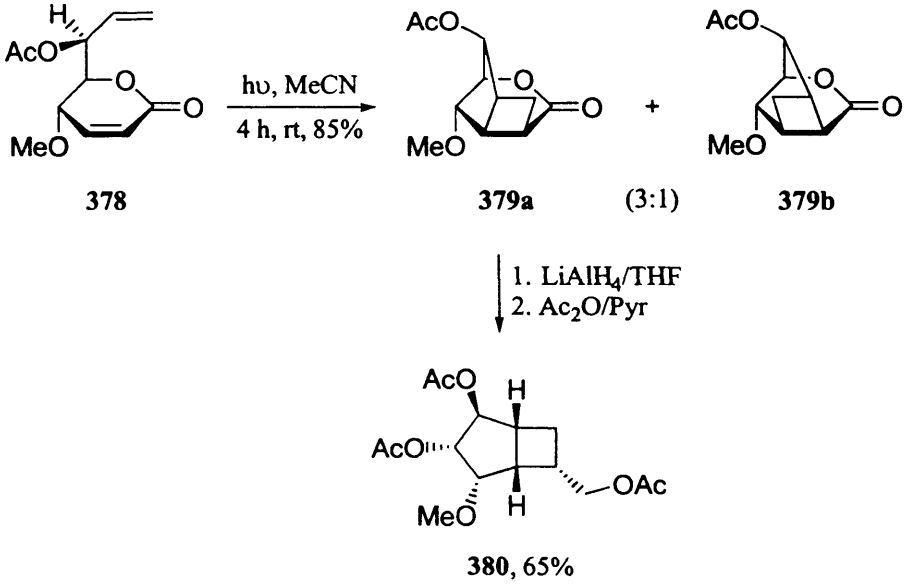
374 375



376a, $R^1 = R^2 = H$
376b, R^1 = Me, $R^2 = H$
376c, R^1-$R^2 = (CH_2)_3$
376d, R^1-$R^2 = (CH_2)_4$

377a-d

In a similar fashion, Gómez and López have generated densely functionalized, fused carbocyclic systems, via intramolecular [2+2] photocycloaddition of carbohydrate derived dienic 2-enono-δ-lactones.[126] For example, irradiation of dienic lactone **378** in acetonitrile furnished *head to head* photoadduct **379a** and *tail to head* photoadduct **379b** in a 3:1 ratio and an 85% yield (Scheme 72). Reductive ring opening of tricyclic compound **379a**, followed by hydroxyl group protection afforded the synthetically useful bicyclo[3.2.0]heptane **380** in good yield.



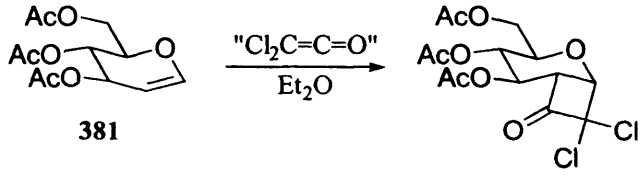
378 **379a** (3:1) **379b**

380, 65%

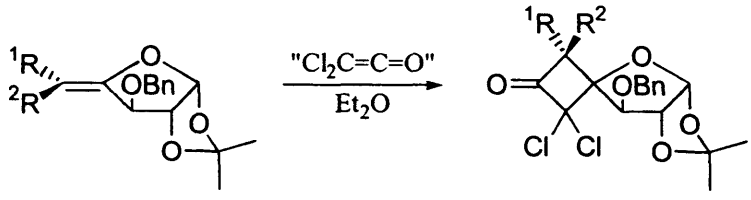
Scheme 72

Two research groups have explored the use of ketenes in *thermal* [2+2] cycloaddition reactions of carbohydrate derivatives, whereby the manner of bond formation

is *antarafacial*. The preparation of chiral cyclobutanones by [2+2] cycloaddition of dichloroketene to carbohydrate enol ethers has been reported extensively by Redlich and co-workers.[127] Reaction of 3,4,6-tri-*O*-acetyl-D-glucal **381** with dichloroketene (generated *in situ* from trichloroacetyl chloride and Zn/Cu couple) gave the expected α-oriented cyclobutanone **382** in excellent yield. The stereochemical course of the reaction is as a result of the regiochemistry established by enol ether **381**, and by the attack of dichloroketene from the less hindered α-face. Similarly, with glucofuranose derivatives **383a** and **383b**, dichloroketene added exclusively from the α-face to furnish spiro annulated sugars **384a** and **384b** in good yield.



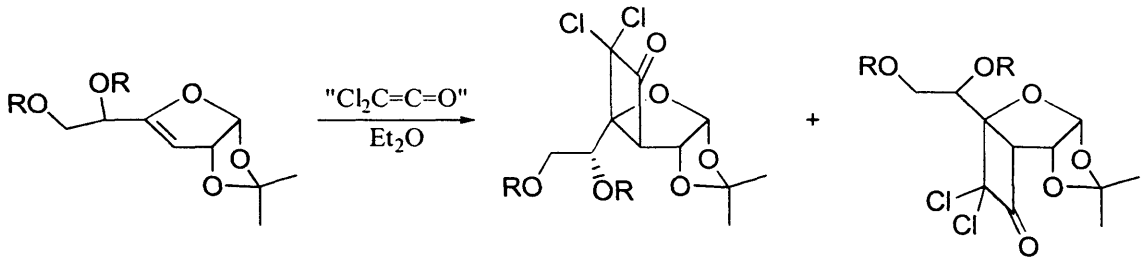
381 **382**, 89%



383a, R^1 = Me, R^2 = H
383b, R^1 = H, R^2 = Me

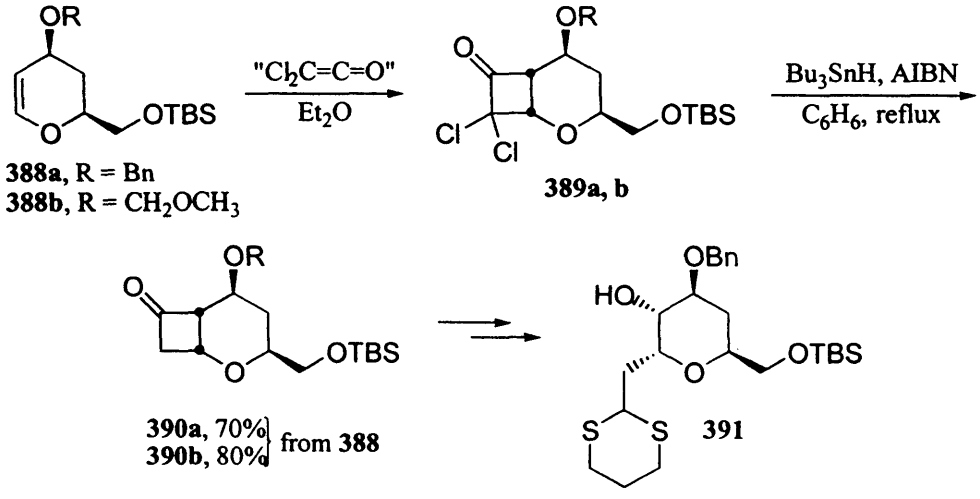
384a, 83%
384b, 86%

Extensive data from carbohydrate chemistry demonstrates that sp^2-hybridized carbon atoms at positions 3 and 4 of 1,2;5,6-di-*O*-isopropylidene-α-D-glucofuranose derivatives are almost always attacked from the β-face. However, in the case of **385a**, attack from the α-face (**387a**) is favoured slightly. A change of hydroxyl protecting group at positions 5 and 6 (**385b**) facilitated the formation of expected product **386b** in a fourfold excess over **387b**.



385a, R, R = $\rangle$CMe$_2$ **386a** (1:1.2, 93%) **387a**
385b, R = CH_2Ph **386b** (4:1, 42%) **387b**

Hanna *et al.* have prepared chiral cyclobutanone-annulated tetrahydropyrans by [2+2] cycloaddition of dichloroketene and glycals, followed by dehalogenation.[128] Protected glycals **388** were readily converted to dichlorobicyclobutanones **389**, which upon tributyltin hydride dehalogenation afforded the expected α-oriented cyclobutanones **390** in excellent yield (Scheme 73). The cyclobutanone rings of **390** can be regioselectively cleaved in new approaches to enantiomerically pure mono and bifunctionalized glycals **(e.g. 390a → 391)**.



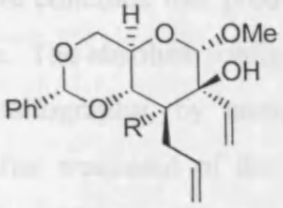
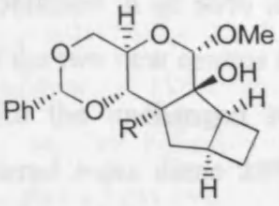
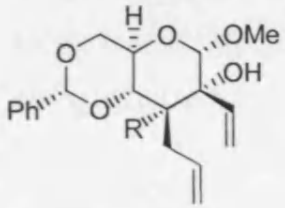
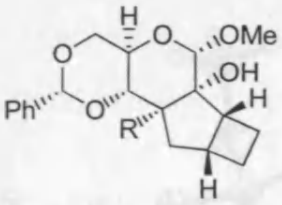
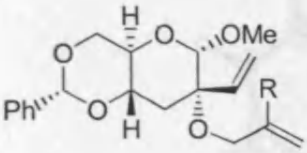
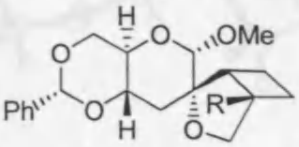
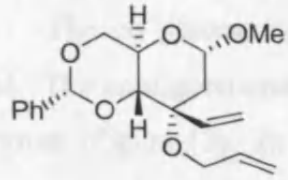
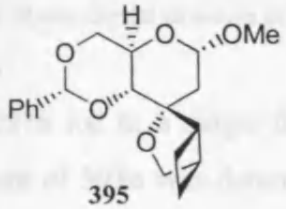
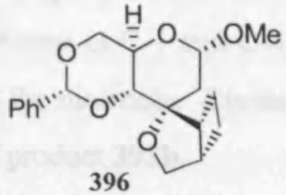
Scheme 73

4.5 Results and Discussion[129]

Our investigations centered on the application of the copper(I) triflate catalyzed [2+2] photocycloaddition as a method of carbohydrate annulation. We were particularly interested to see if the promising results of Salomon and Ghosh,[119] on the stereocontrol of these reactions, could be applied in carbohydrate examples to produce single enantiomerically pure diastereoisomers. The diene substrates for this work were prepared

by the methods described in Chapter 3. The results of our photoannulation reactions are summarized in Table 1.

Table 1. Summary of the results of photoannulation reactions carried out on 1,6-diene carbohydrate derivatives.

Substrate	Product	Isolated Yield (%)
 **298a**, R = H **298b**, R = Me	 **392a**, R = H **392b**, R = Me	**392a** = 86 **392b** = 18
 **297a**, R = H **297b**, R = Me	 **393a**, R = H **393b**, R = Me	**393a** = 86 **393b** = 89
 **319**, R = H **319a**, R = Me	 **394a**, R = H **394b**, R = Me	**394a** = 72 **394b** = 61
 **326a**	 **395** +  **396**	**395** = 30 **396** = 33

The first photoannulation substrate was the *trans* glucose derivative **298a**, which was irradiated at 254 nm in benzene, using a Rayonet photochemical reactor, with 5 mol% of copper(I) triflate benzene complex. Two diastereoisomeric products are possible in this reaction, arising from the facial selectivity of the [2+2] cycloaddition. The ^{13}C NMR spectrum of the crude product showed that only one diastereoisomer was formed, and only a single peak was observed by HPLC. The six stereogenic centres in the enantiomerically pure starting material **298a** would not reasonably be expected to change on irradiation, and so we conclude that product **392a**, obtained in an 86% isolated yield, is enantiomerically pure. The absolute configurations of the two new centres in **392a** were confirmed by X-ray crystallography, by comparison with the unchanged stereogenic centres (Figure 12). Similar treatment of the more hindered *trans* diene **298b** gave a modest 18% yield of product **392b**.

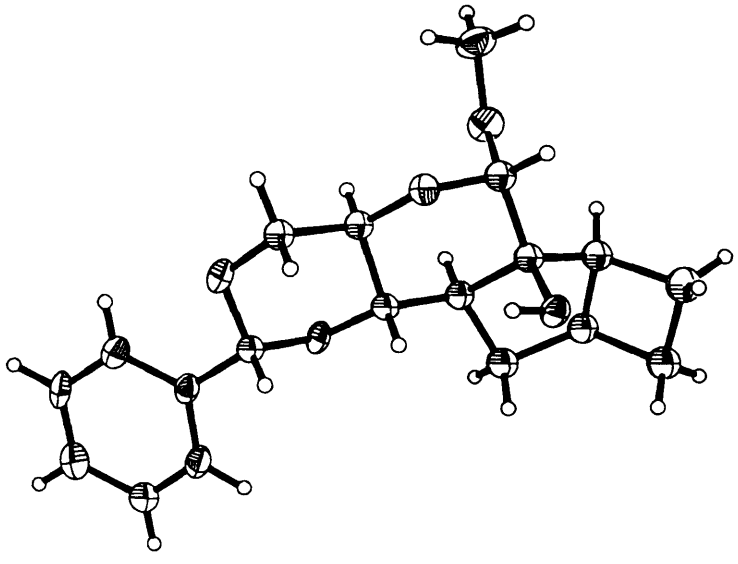


Figure 12. X-ray crystal structure of **392a**

The *cis* glucose derivative **297a** led to a single diastereoisomer **393a** in an 86% yield. The configurational assignment of **393a** was determined with the aid of a NOESY spectrum (Figure 13). In the NOESY spectrum we can clearly see a strong nOe between the proton at C-7 and each of the protons at C-1 and C-4, leading us to conclude that the cyclobutane ring is on the α-face of the molecule. Similarly, the more hindered *cis* diene **297b** gave an excellent 89% yield of product **393b**.

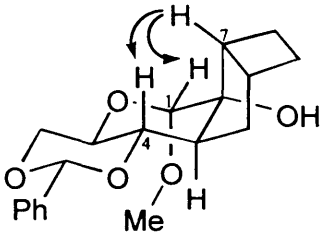
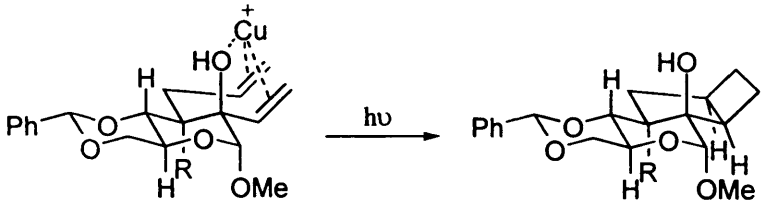


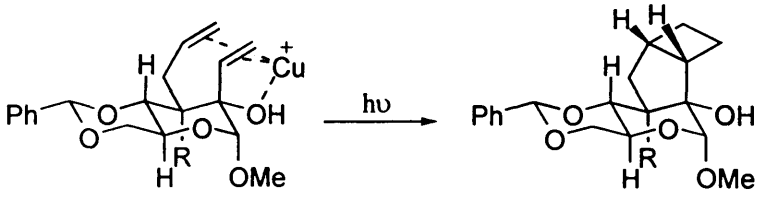
Figure 13. The nOe effects seen in compound **393a**

In order to explain the stereochemistry of these reactions we returned to the work of Salomon and Ghosh,[119] in which there is a preference for the formation of the *endo* product in the photobicyclization of 1,6-heptadiene-3-ol (Scheme 66). Applying these arguments to the photoannulation of our diene glucose derivatives, we arrive at the hypotheses illustrated below. Tridentate coordination of the two olefins and the hydroxyl oxygen to copper(I), as shown in structures **397a** and **397b**, means that in the products **392a** and **392b** the cyclobutane ring and the hydroxyl group are on the β-face of the molecule. In the same way the chelated structures **398a** and **398b** lead to the products **393a** and **393b**, in which the cyclobutane ring and the hydroxyl group are on the α-face of the molecule.



397a, R = H
397b, R = Me

392a, R = H
392b, R = Me

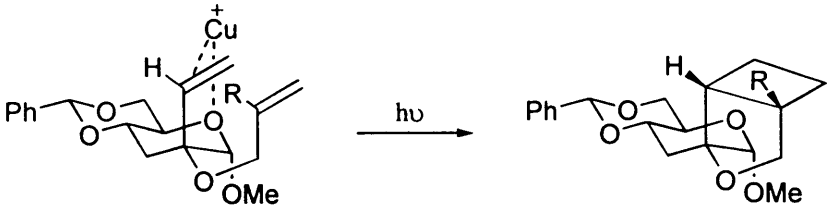


398a, R = H
398b, R = Me

393a, R = H
393b, R = Me

Mr. Will Barker extended the range of this work by investigating spiro [2+2] photoannulation of carbohydrate derivatives. Irradiation of substrates **319** and **319a** (Table 1) under the usual conditions furnished the products **394a** and **394b** as single diastereoisomers in moderate yield, whose structures were confirmed by X-ray crystallography. In contrast, diene **326a** gave an approximate 1:1 mixture of the two possible products **395** and **396** in a 63% yield. Chelated structures **399a** and **399b** explain

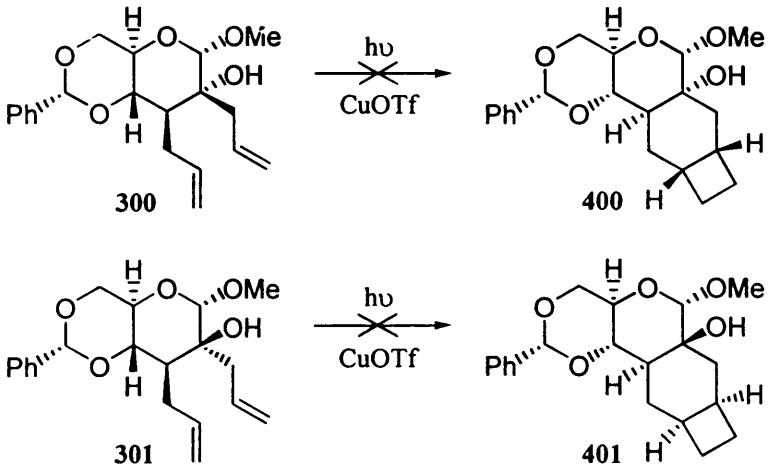
the stereochemistry of the products **394a** and **394b**. Bidentate coordination of one of the olefins and the sugar ring oxygen to the copper(I) leads to the observed products **394a** and **394b** on irradiation. Clearly, in compound **326a**, the anomeric oxygen is too far away to coordinate to the copper(I)-diene chelate, hence the formation of both possible products is observed.



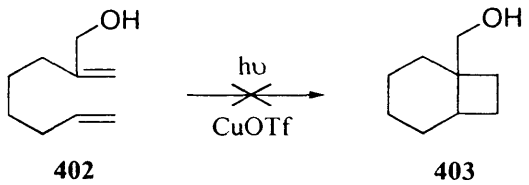
399a, R = H
399b, R = Me

394a, R = H
394b, R = Me

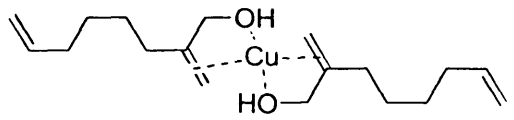
Attempts to carry out [2+2] photoannulation reactions on 1,7-diene carbohydrate derivatives **300** and **301** met with failure. Evidence for the formation of desired products **400** and **401** was not detected; only starting material was isolated from each reaction mixture.



These results are analogous with the lack of intramolecular photocycloaddition product (**403**) observed on irradiation of β-hexenylallyl alcohol **402**.[119] This may be due to **402** preferring to form a 2:1 intermolecular complex (**404**) with copper(I).

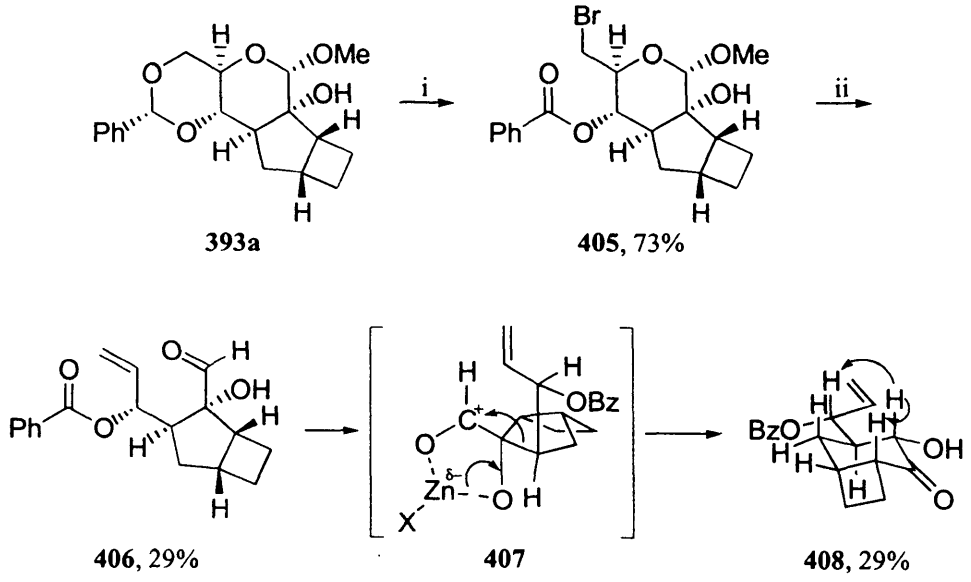


402 403



404

Having explored copper(I) catalyzed [2+2] cycloaddition as a method for carbohydrate annulation, we turned our attention to the conversion of these annulated sugars into enantiomerically pure carbocyclic compounds. Tetracycle **393a** was reacted with *N*-bromosuccinimide[63] to give the bromo ester **405** in a 73% yield (Scheme 74). Treatment of **405** with activated zinc, in a Vasella elimination,[30a] furnished aldehyde **406** (29%) and the ring-expanded cyclohexanone derivative **408** (29%). The configuration of the new stereogenic centre in **408** is again in accord with literature precedent,[111] where rearrangement occurs via the chelated transition state **407**. We believe the most stable ring conformation of the ring-expanded product to be structure **408**. In the NOESY spectrum of **408**, we observe a strong nOe between the proton on the carbon bearing the hydroxyl, and both the axial bridge head proton on the β-face of the molecule, and the side chain C*H*.



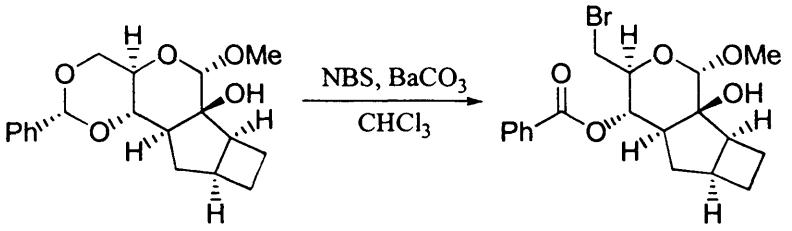
393a 405, 73%

406, 29% 407 408, 29%

Scheme 74, Reagents and conditions: i, NBS, $BaCO_3$, $CHCl_3$, reflux; ii, Activated Zn, IPA:H_2O (10:1), reflux.

In chapter three, we observed a similar ring-expansion, to give the cyclohexanone **336** as the *only* product. The lack of complete ring-expansion in *this* case may be due to the migrating centre being tertiary, rather than quaternary (**336**), therefore lowering the migratory aptitude.

Having successfully fragmented the sugar moiety of compound **393a**, tetracycle **392a** was reacted with *N*-bromosuccinimide to give the bromo ester **409** in a 72% yield. Unusually, several attempts to fragment **409** with activated zinc met with failure.



392a **409**, 72%

4.6 Summary

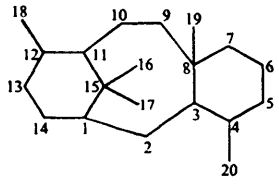
Copper(I) triflate catalysis has been utilized to provide stereocontrol in the [2+2] photoannulation of unactivated 1,6-diene carbohydrate derivatives. Fragmentation of the sugar moiety in tetracycle **393a** furnished the highly substituted enantiomerically pure carbocyclic compounds **406** and **408**.

CHAPTER 5

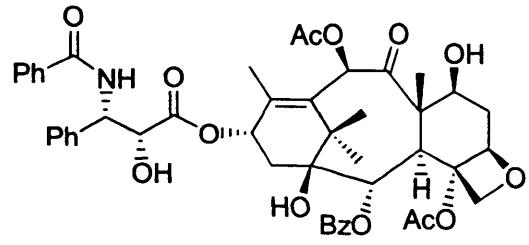
PROGRESS TOWARDS THE SYNTHESIS OF A CHIRAL TAXOID FROM GLUCOSE

5.1 Introduction

The yew tree, as well as providing food or habitat for many forest species, has been utilized by man for centuries. Native Americans used the extremely hard and decay-resistant wood for tools, weapons, and decorative items. Foliage, fruits and bark were used medicinally. In 1960 the National Cancer Institute (NCI), in collaboration with the United States Department of Agriculture (USDA), initiated a screening programme for antitumour agents in the plant kingdom. In 1962, USDA botanist Arthur Barclay collected bark, twigs, leaves and fruit from the Pacific yew, *Taxus brevifolia*, in Washington state. This slow growing yew, native to western North America, ranges from southeast Alaska to northern California, and from the Pacific coast to the interior states of Idaho and Montana. In 1964, bark extracts were found to be cytotoxic towards KB cells (human carcinoma of the nasopharynx); by 1966, the pure active substance had been isolated by Wani and Wall, who determined the structure of this active substance by X-ray crystallography in 1971.[130] It was shown to contain the unusual taxane diterpenoid skeleton **410**, attached to a β-amino acid side-chain, and was named Taxol® (**411**).



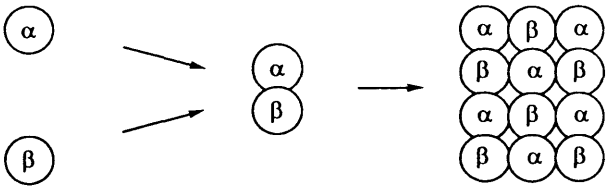
410



411

5.2 Mechanism of Action of Taxol

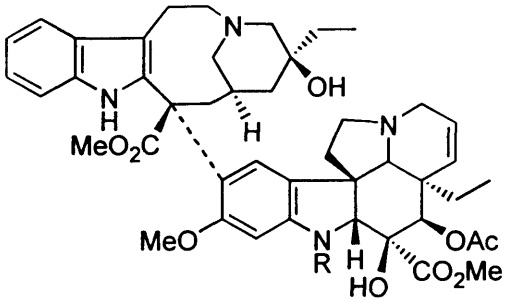
Interest in Taxol increased considerably when, in 1979, Horwitz and co-workers reported that Taxol has a unique mechanism for antitumour activity involving cell microtubules.[131] Microtubules are built up from two subunits: α- and β-tubulin. These combine to form a wall sub-unit, which then polymerizes further to produce a microtubule (Scheme 75).



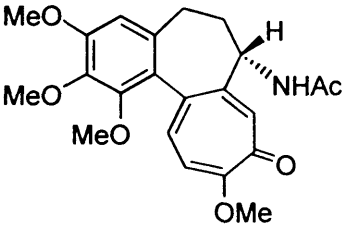
Scheme 75

Microtubules play an important role in cellular activity, for example, in the formation of the cytoskeleton and in the communication of cellular signals. However, during cell division, depolymerization of microtubules occurs to give tubulin monomer. Subsequent repolymerization forms the mitotic spindle of cell division. The purpose of the microtubules that make up the mitotic spindle is to lengthen, by the process of tubulin polymerization, 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 depolymerizes, thereby shortening and dragging the chromosome to the nucleus of the daughter cell. Consequently, the tubulin/microtubule equilibrium is critical to cell division; any interference with this equilibrium stops normal cell division taking place, and therefore uncontrolled cell proliferation (cancer) can be targeted.

Taxol belongs to a class of cancer therapeutics that are *spindle poisons*, in that they either prevent, or promote, the formation of the mitotic spindle during cell division. Drugs such as vinblastine (**412**), vincristine (**413**) and colchicine (**414**) are *spindle destroyers* which bind to tubulin, preventing the formation of microtubules.



412 , R = Me
413 , R = CHO



414

In contrast, Taxol *stimulates* the formation of stable microtubules and prevents their breakdown. This disruption of the tubulin/microtubule equilibrium makes Taxol a potent

inhibitor of eukaryotic cell replication. Taxol is thus a prototype for a new class of antitumour drugs and has focused attention on microtubules as a worthy target for cancer chemotherapeutic drugs. The importance of the functional groups within Taxol, and their effect on biological activity are summarized in Figure 14.[132]

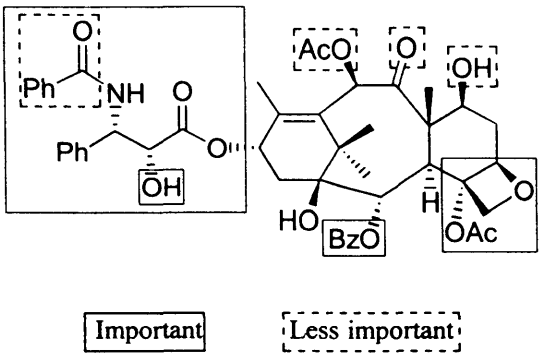
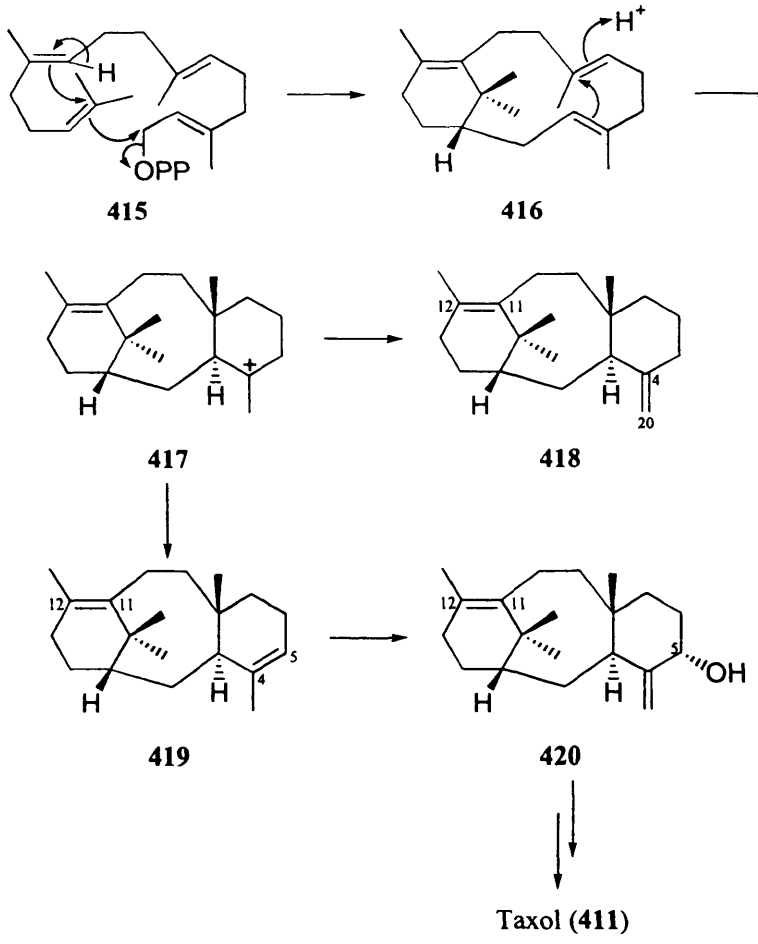


Figure 14. Structure-activity relationships of Taxol

5.3 Biosynthesis of Taxol

Lythgoe and co-workers proposed a logical biosynthetic pathway to Taxol, involving cyclization of geranylgeranyl diphosphate **415** to taxa-4(20),11(12)-diene **418** (Scheme 76).[133] Since taxoids bearing a 4(20)- and 11(12)-double bond pair are very common, this intermediate was assumed for many years. However, recently, Croteau *et al.* used tritium-labelled **415** to show that cyclization actually furnishes taxa-4(5),11(12)-diene **419** (via verticellene **416**), and not **418**.[134] Extensive, largely oxidative, modification of **419**, followed by side-chain attachment, would produce Taxol (**411**). Cytochrome P450 hydroxylase catalyzes the first hydroxylation of **419**, at position 5, to furnish taxa-4(20), 11(12)-dien-5-ol **420**.[135]



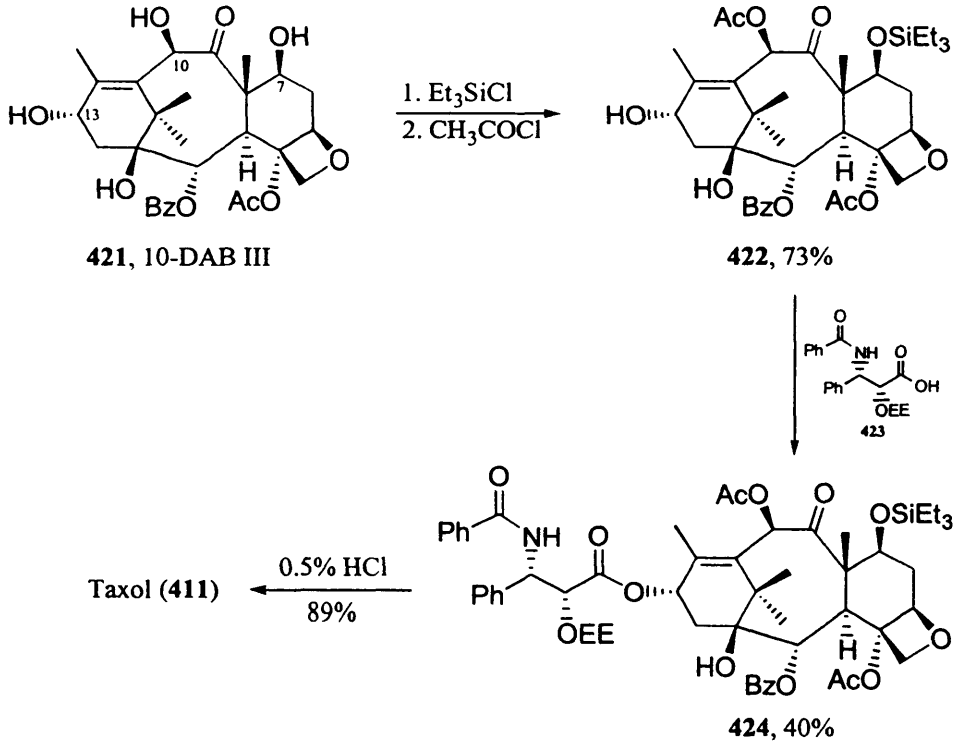
Scheme 76

5.4 Semi-Syntheses of Taxol and Analogues

The potential for Taxol to be a major force in the treatment of cancer created a dilemma: how to ensure an adequate supply. Taxol is isolated primarily from the inner bark of the relatively rare, slow growing Pacific yew, *Taxus brevifolia*, in extremely small yields (0.1 g/kg).[130] A mature Pacific yew (100 years old) yields approximately 10 lb of dry bark. With current isolation methodologies, 1 kg of Taxol is isolated from 25,000 lb of dried bark, or the bark of 2500 yew trees. A single course of clinical treatment is 125-300 mg of Taxol, and typical treatments may extend for 10 or more courses.[136] This means that, on average, the bark from *five* yew trees would be needed to treat a single patient: this has obvious ecological consequences. In 1992, the Yew Act was drafted in response to public concern about the need for Taxol and the long-term conservation of the Pacific yew.

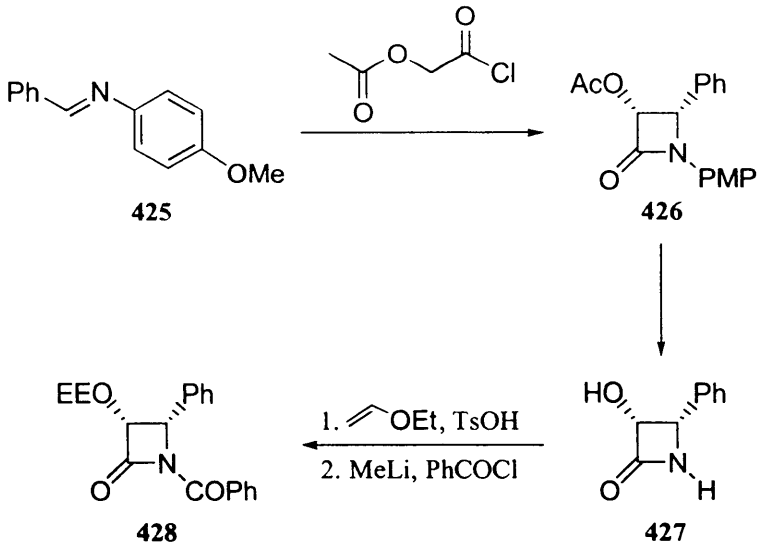
Several research groups have laboured to alleviate the supply problem using semi-synthetic methods. The discovery by the Potier group that 10-deacetylbaccatin III **421** (10-DAB III) can be isolated in significant quantities from a regenerable source, the needles of the European yew tree *Taxus baccata* L., was the most significant finding in the attempt to

secure the long-term supply of Taxol through semi-synthesis.[137] Extraction of the fresh needles yields 10-DAB III in amounts of up to 1 g/kg, which is about ten times the amount of Taxol isolated from the bark. Harvesting the needles of the yew tree does not threaten the survival of the yew species. Potier utilized the differing reactivity of the free hydroxyl groups of **421** (7-OH > 10-OH >> 13-OH) in the semi-synthesis of Taxol (Scheme 77).[137] Selective protection of the C-7 hydroxyl of **421**, followed by acetylation of the C-10 hydroxyl, furnished **422** in good yield. Treatment of this protected baccatin derivative with the protected side-chain **423** afforded the coupled product **424** in a 40% yield. Removal of the protecting groups gave Taxol (**411**) in an overall yield of 26%.



Scheme 77

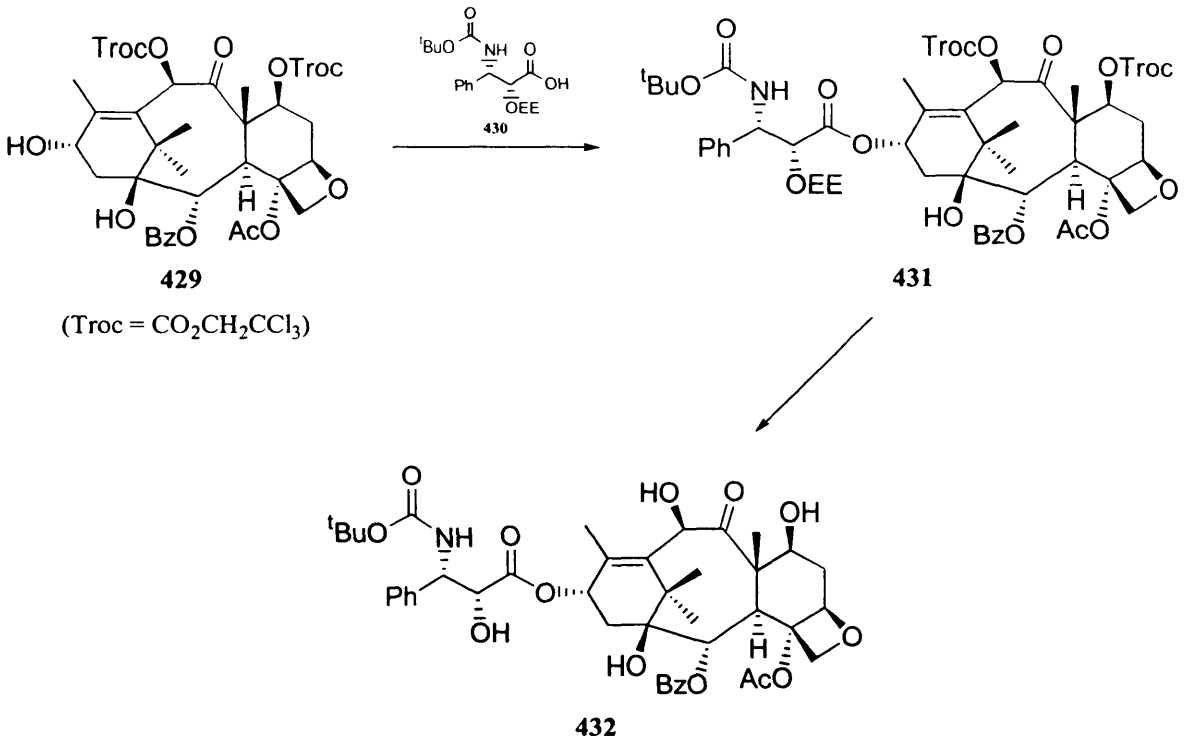
In addition to the acylation of baccatin III with a protected *N*-benzoyl-3-phenylisoserine such as **423**, acylation has also been achieved with *N*-benzoyl β-lactam **428** by Holton[138] and Ojima[139] independently. For example, Holton used the Staudinger reaction between α-acyloxy acetyl chloride and the imine **425** to give the β-lactam **426** (Scheme 78). Subsequent deprotection, protection of the hydroxyl, and benzoylation of the nitrogen furnished **428**. The required enantiomer of alcohol **427** was obtained by resolution.



Scheme 78

Reaction of 7-(triethylsilyl) baccatin III **422** with excess **428**, followed by removal of both protecting groups, afforded Taxol in an 83% yield.[138] Ojima has reported an improvement to this method, achieving a near quantitative coupling of the β-lactam **428** using sodium hexamethyldisilazide.[140]

During the course of their semi-synthetic work, Potier and co-workers discovered the biologically potent taxoid Taxotere® (**432**).[141] The structural differences between Taxol® and Taxotere® are a *tert*-butoxycarbonyl group instead of a benzoyl group on the nitrogen atom at C-3' on the side-chain, and a hydroxyl function instead of an acetate at C-10 in the diterpene moiety. Potier and co-workers coupled the O-protected 10-DAB III derivative **429** with the modified protected side-chain **430** to give **431**. Subsequent deprotection of **431** furnished Taxotere® (**432**, Scheme 79).



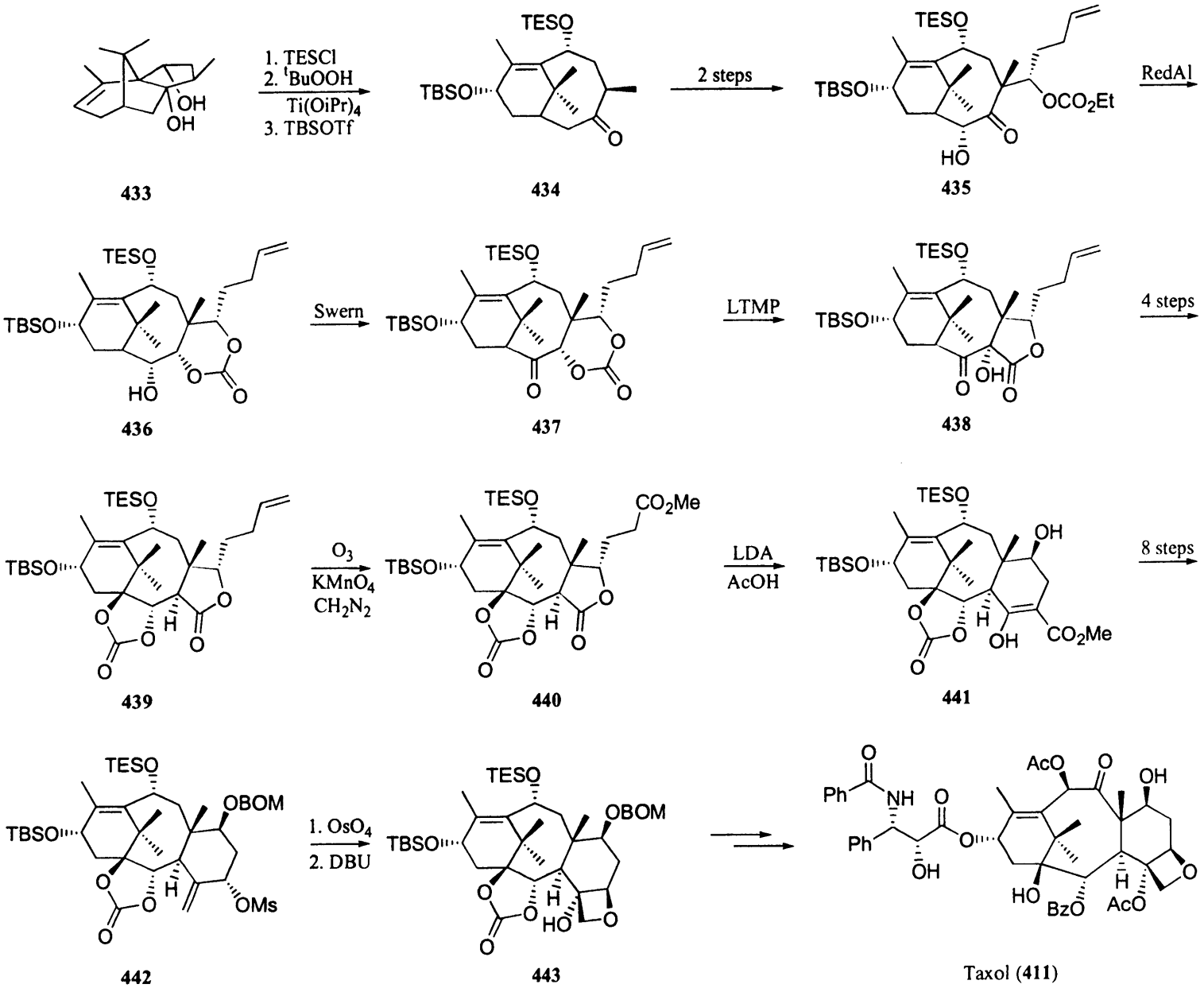
Scheme 79

5.5 Total Syntheses of Taxol

The total synthesis of Taxol has been a challenging goal to organic chemists since the publication of its structure in 1971.[130] To date, five research groups have successfully completed the total synthesis of Taxol. The complexity of the Taxol structure makes it unlikely that these syntheses will provide a commercially viable supply source, although the availability of synthetic methodology may lead to important new information. In this section these synthetic routes will be summarized, giving a general overview of the reactions involved in the construction of the complex diterpenoid skeleton.

5.5.1 Holton[142]

Holton and co-workers completed the total synthesis of Taxol in 1993. The synthesis proceeds from commercially available camphor, and builds the Taxol molecule in a linear fashion. An overview of the synthetic route is summarized in Scheme 80.



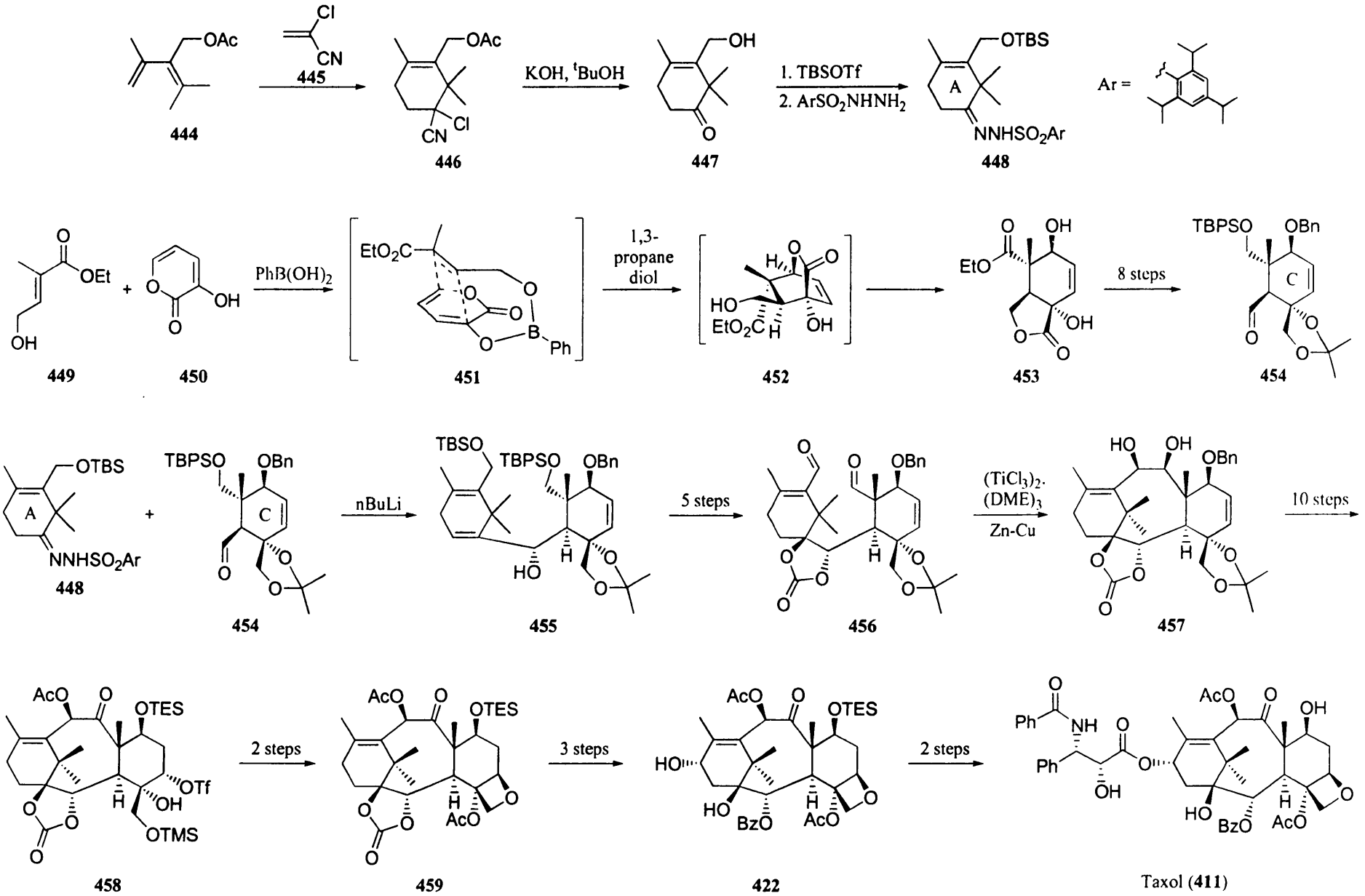
433 **434** **435** **436** **437** **438** **439** **440** **441** **442** **443** Taxol (**411**)

Scheme 80

Silylation of diol **433**, readily available from camphor, followed by epoxy alcohol fragmentation[143] and protection at C-13 gave the ketone **434**, and therefore the required AB-ring system of Taxol. The magnesium enolate of ketone **434** underwent aldol condensation with 4-pentenal. Protection of the crude aldol product with phosgene, followed by hydroxylation at C-2 gave the hydroxy carbonate **435**. Reduction of **435** with RedAl gave a triol which, without isolation, was reacted with phosgene to give carbonate **436**. Swern oxidation furnished the C-2 ketone **437** which, on treatment with LTMP, underwent rearrangement to the hydroxy lactone **438**. Reductive removal of the C-3 hydroxyl, hydroxylation at C-1, followed by C-2 reduction and reaction with phosgene, gave the lactone carbonate **439** in 12 steps and 40% overall yield from **433**. Oxidative cleavage of the terminal olefin of **439** by ozonolysis to the aldehyde, followed by oxidation to the acid and esterification with diazomethane, afforded the methyl ester **440**. Dieckmann cyclization of **440**, gave the enol ester **441**, with the desired ABC-ring system of Taxol. Several reactions were then required to construct the protected allylic alcohol **442**. Osmylation of **442** gave a diol which, on treatment with DBU, underwent cyclization to the oxetanol **443**. The final stages of the synthesis primarily involved oxidation at C-9 and side-chain attachment, to give Taxol (**411**) in an overall yield of *ca.* 4-5% from diol **433**.

5.5.2 **Nicolaou**[144]

At almost the same time as Holton *et al.*, Nicolaou and co-workers completed their total synthesis of Taxol. The synthesis is convergent in that the ABC-ring system of Taxol is constructed through coupling versatile A- and C-ring synthons. The Diels-Alder reaction was used to construct both the A- and C-ring. The overall synthetic route is summarized in Scheme 81. Diene **444** and 1-chloroacrylonitrile (**445**) provided, through a Diels-Alder reaction, the A-ring cycloadduct **446** as a single regioisomer. Reaction with potassium hydroxide in *tert*-butanol furnished the hydroxy ketone **447**. Treatment with *tert*-butyldimethylsilyl triflate reprotected the alcohol as the silyl ether. Finally, conversion of the ketone into its arylsulfonylhydrazone **448** produced the A-ring as a suitable substrate for Shapiro reaction.


OAc
Cl
CN
445
444
446
KOH, tBuOH
OH
447
1. TBSOTf
2. ArSO2NHNH2
OTBS
A
NNHSO2Ar
448
Ar =
OEt
OH
449
450
PhB(OH)2
EtO2C
O
B
Ph
451
1,3-
propane
diol
HO
EtO2C
H
452
EtO
453
8 steps
TBPSO
OBn
C
454
OTBS
A
NNHSO2Ar
448
TBPSO
OBn
C
454
nBuLi
TBSO
TBPSO
OBn
HO
455
5 steps
456
(TiCl3)2.
(DME)3
Zn-Cu
HO
OH
OBn
457
10 steps
AcO
OTES
OTf
OH
OTMS
458
2 steps
AcO
OTES
AcO
459
3 steps
HO
BzO
AcO
422
2 steps
Ph
NH
OH
Taxol (411)

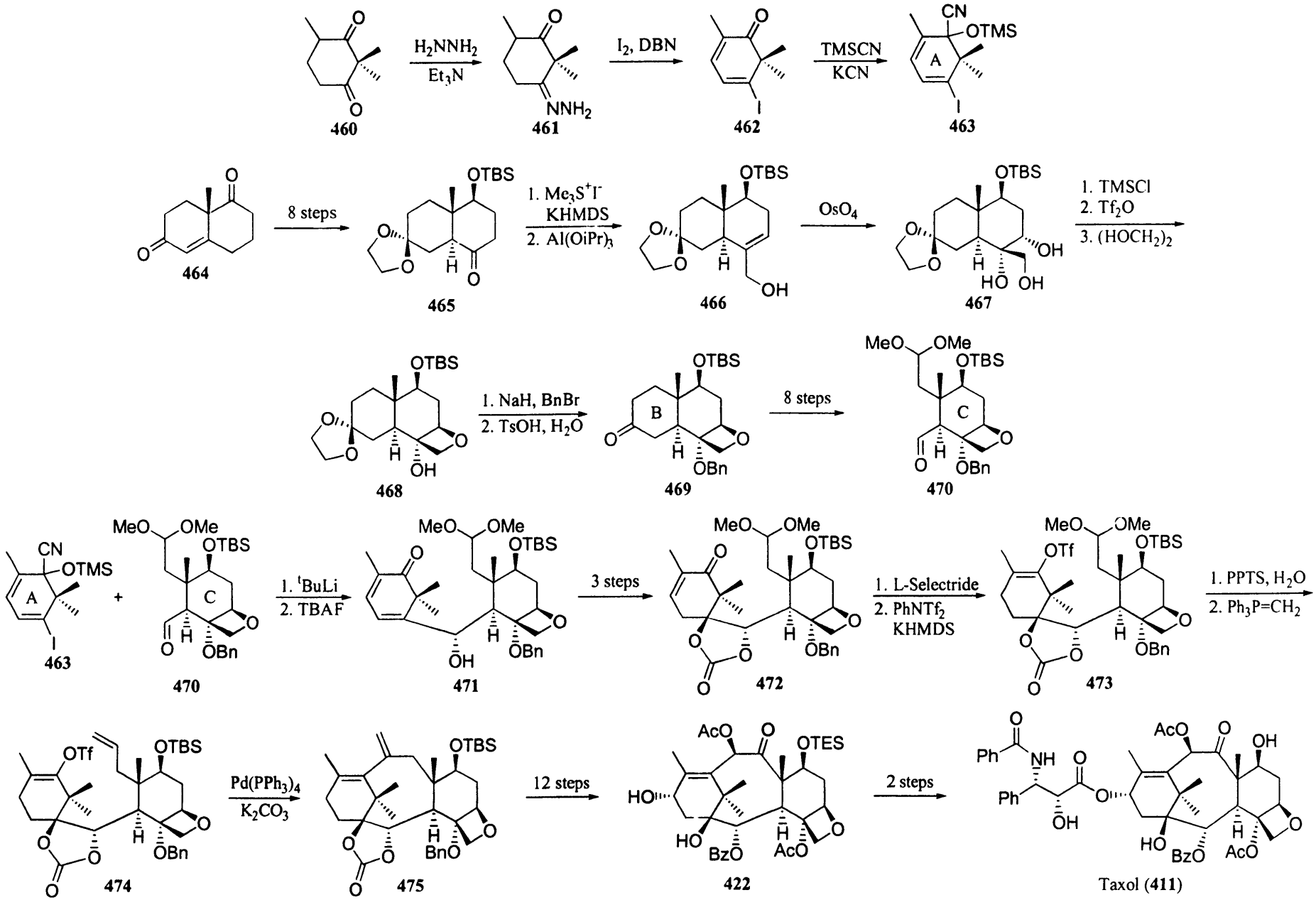
Scheme 81

The C-ring was constructed by Diels-Alder reaction of dienophile **449** and diene **450**, in the presence of phenylboric acid, following the method of Narasaka.[145] Formation of a temporary tether (**451**) leads to the selective synthesis of the desired product. Decomplexation with 1,3-propane diol gave the [2.2.2] cycloaddition product **452**, that rearranged, by transesterification under the acidic conditions, to the less strained fused [3.4.0] system **453**. The conversion of C-ring intermediate **453** into the more advanced C-ring aldehyde **454** was achieved in a number of steps, including, ester reduction, reductive ring-opening of the lactone, protection and oxidation.

The next stage in the synthesis was to couple the A- and C-ring intermediates. A Shapiro reaction between the vinyl anion of **448** and the aldehyde **454** gave one diastereoisomer of the allylic alcohol **455**. The facial selectivity of the incoming nucleophile is controlled by a chelate formed between the oxygens of the acetonide, the aldehyde, and the lithium cation. Epoxidation of the C1, C14 olefin of **455**, followed by reduction, introduced the C-1 hydroxyl group. Diol protection, deprotection of the C-9 and C-10 hydroxyl groups, and subsequent oxidation, afforded the dialdehyde **456**, a suitable precursor for a McMurry reaction. Indeed, exposure of this substrate to the titanium(0) reagent, generated by the reduction of titanium (III) with zinc-copper couple, gave the desired racemic diol **457**, in a modest 23% yield. Resolution of this diol proceeded smoothly, providing an enantiomerically pure ABC-ring system for the final stages of the synthesis. Chemical modification of **457**, including oxidation at C-5 and C-9, and protecting group manipulation, furnished the triflate **458**. The desired oxetane **459** was obtained on treatment with acid, followed by acetylation. Opening of the cyclic carbonate with phenyllithium, and introduction of the C-13 hydroxyl through allylic oxidation and reduction, gave 7-(triethylsilyl) baccatin III **422**. Attachment of the side-chain by the method of Holton[138] and Ojima,[139] followed by desilylation, gave Taxol (**411**).

5.5.3 **Danishefsky**[146]

In 1995, Danishefsky and co-workers completed a third successful total synthesis of Taxol. Again, the synthesis is convergent with the ABC-ring system of Taxol being constructed through coupling versatile A- and C-ring synthons. The synthetic route is summarized in Scheme 82.


H2NNH2
Et3N
I2, DBN
TMSCN
KCN
460
461
462
463
8 steps
1. Me3S+I-
KHMDS
2. Al(OiPr)3
OsO4
1. TMSCl
2. Tf2O
3. (HOCH2)2
464
465
466
467
1. NaH, BnBr
2. TsOH, H2O
8 steps
468
469
470
1. tBuLi
2. TBAF
3 steps
1. L-Selectride
2. PhNTf2
KHMDS
1. PPTS, H2O
2. Ph3P=CH2
471
472
473
Pd(PPh3)4
K2CO3
12 steps
2 steps
474
475
422
Taxol (411)

Scheme 82

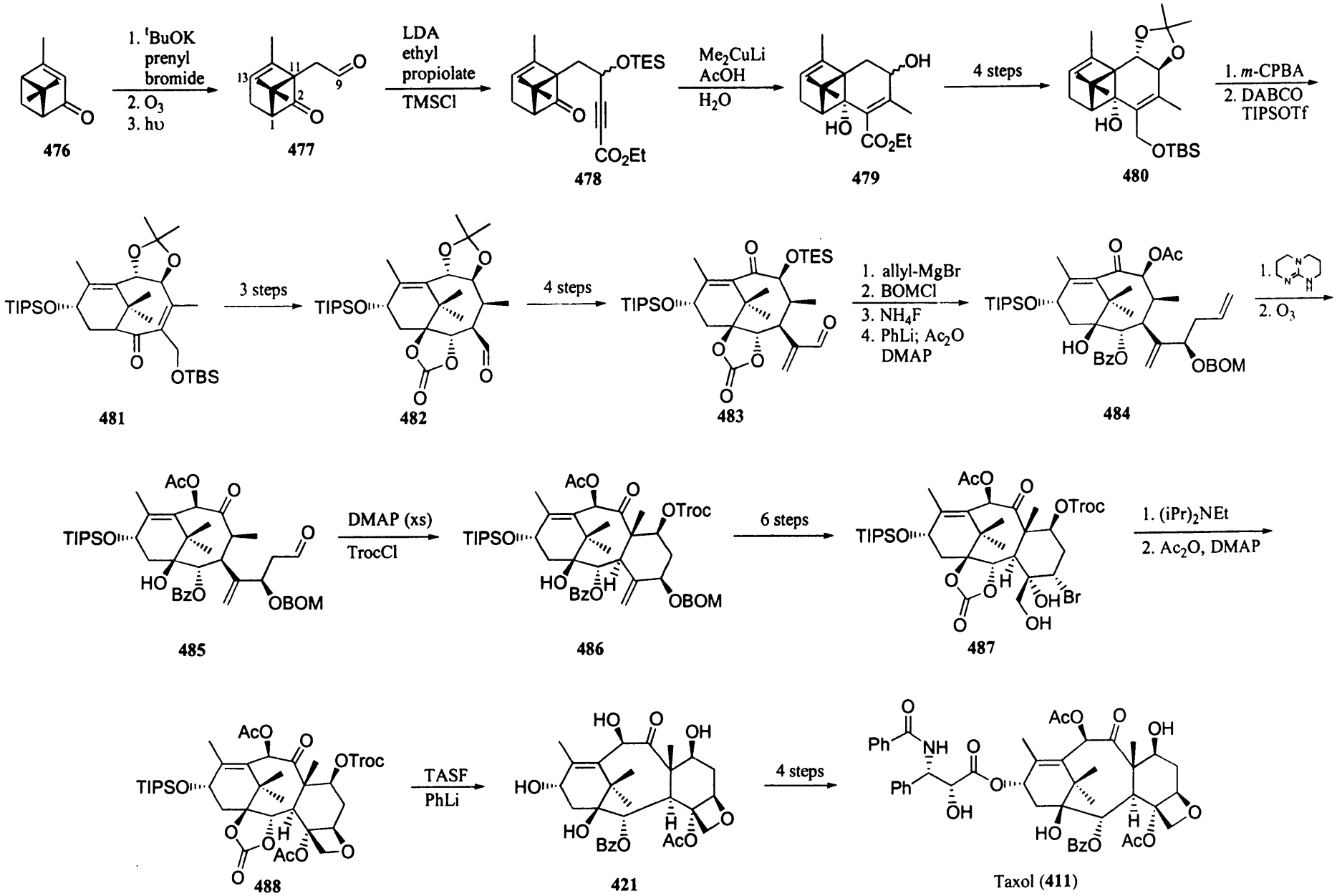
The synthesis of the A-ring started with dione **460**, which was converted to its monohydrazone **461**. On treatment with iodine and DBN, **461** gave rise to the iododienone **462**. The latter was converted to the cyanohydrin **463** in racemic form, providing a suitable A-ring intermediate.

The starting point for construction of the C-ring was the (*S*)-Wieland-Miescher ketone **464**, from which all asymmetric induction ultimately accrues. The *trans*-fused ketone **465** was prepared by classical, high-yielding steps.[147] The almost quantitative conversion of **465** to allylic alcohol **466**, via a spiroepoxide, was a significant improvement on that previously described in the literature.[148] Treatment of allylic alcohol **466** with osmium tetroxide gave rise to the triol **467** in good yield. The primary alcohol of **467** was selectively silylated with TMS chloride, the secondary alcohol was activated by triflation, and the oxetane **468** was produced on subsequent treatment with ethylene glycol. Benzylation of alcohol **468**, followed by cleavage of the ketal linkage under mildly acidic conditions, furnished the ketone **469**. The B-ring of **469** was cleaved in a high-yielding sequence to produce aldehyde acetal **470**.[149]

The next stage in the synthesis was to connect the suitably functionalized A and C fragments. Treatment of **463** with *tert*-butyllithium, followed by addition of **470**, gave rise to a single carbinol **471** after deprotection of the C-11 ketone. Epoxidation of the C1, C14 olefin of **471**, followed by hydrogenation, introduced the C-1 hydroxyl group. The C-1 and C-2 hydroxyl groups were protected as a cyclic carbonate, affording the enone **472**. Conjugate reduction of enone **472** gave a ketone, which was successfully converted to the vinyl triflate **473**. Cleavage of the dimethylacetal linkage of **473**, followed by Wittig olefination provided the highly functionalized substrate **474**. The critical intramolecular Heck reaction proceeded smoothly to give the tetracyclic intermediate **475** (49%). Chemical modification of this taxoid, including protecting group manipulation and the introduction of oxygen functionality at C-9, C-10, and C-13, gave 7-(triethylsilyl) baccatin III **422**. Attachment of the side-chain by the method of Ojima,[140] followed by desilylation, completed a total synthesis of Taxol (**411**).

5.5.4 Wender[150]

In 1996, Wender and co-workers completed their total synthesis of Taxol. The synthetic strategy was based on their recognition that pinene, an abundant component of pine trees, could supply 10 of the 20 carbons and the chirality of the taxane core. The overall synthetic route is summarized in Scheme 83. The starting point for this synthesis was verbenone (**476**), the air oxidation product of pinene. Treatment with ^{t}BuOK, followed by addition of prenyl bromide, gave a C-11 alkylated product. Selective ozonolysis of the terminal double bond gave an aldehyde. The A-ring skeleton was then established by photorearrangement, furnishing the chrysanthenone derivative **477**. Construction of the taxane B-ring involved the introduction of a two-carbon linker between the C-2 and C-9 carbonyls of **477**. The lithium salt of ethyl propiolate was added selectively to the aldehyde and the resultant alkoxide was trapped *in situ* with TMSCl to produce **478** as a mixture of diastereoisomers. Conjugate addition of Me_2CuLi to **478**, served additionally to effect intramolecular C2-C3 bond formation, furnishing the tricycle **479**. The conformational rigidity and stereochemical bias of **479** were utilized in a series of oxidation/reduction reactions, to selectively introduce the C9-C10 acetonide of **480**. Reaction of tricycle **480** with *m*-CPBA resulted in chemoselective epoxidation of the trisubstituted alkene from its α-face. DABCO induced fragmentation of this hydroxy-epoxide, followed by *in situ* protection of the C-13 alcohol, furnished the taxane AB-ring system **481**. The acetonide of **481** was then enlisted to control C-1 oxidation and stereogenesis at C-2, C-3, and C-8, affording the aldehyde **482** in 14 steps from verbenone (**476**). The elaboration of general taxane precursor **482** began with chain extension to the enal **483**. The remaining carbons of the skeleton were introduced through allyl Grignard addition to enal **483**, which after BOM protection gave a single diastereomer of an ether. Further protecting group manipulation furnished the acetate **484**. Transposition of the acetoxyketone in **484** with guanidinium base, followed by ozonolysis of the terminal alkene, afforded the aldehyde **485** in good yield. The key aldol cyclization reaction was addressed at this point. Exposure of **485** to excess DMAP, followed by protection of the C-7 hydroxyl with TrocCl, gave the desired taxane ABC-tricyclic core **486**. Introduction of the oxetane, via the intermediate diol **487**, proceeded smoothly with Hünig's base. Subsequent acetylation of the C-4 hydroxyl gave **488**. Protecting group manipulation produced 10-DAB III (**421**), which was converted to Taxol (**411**) by the known four-step sequence.[139]

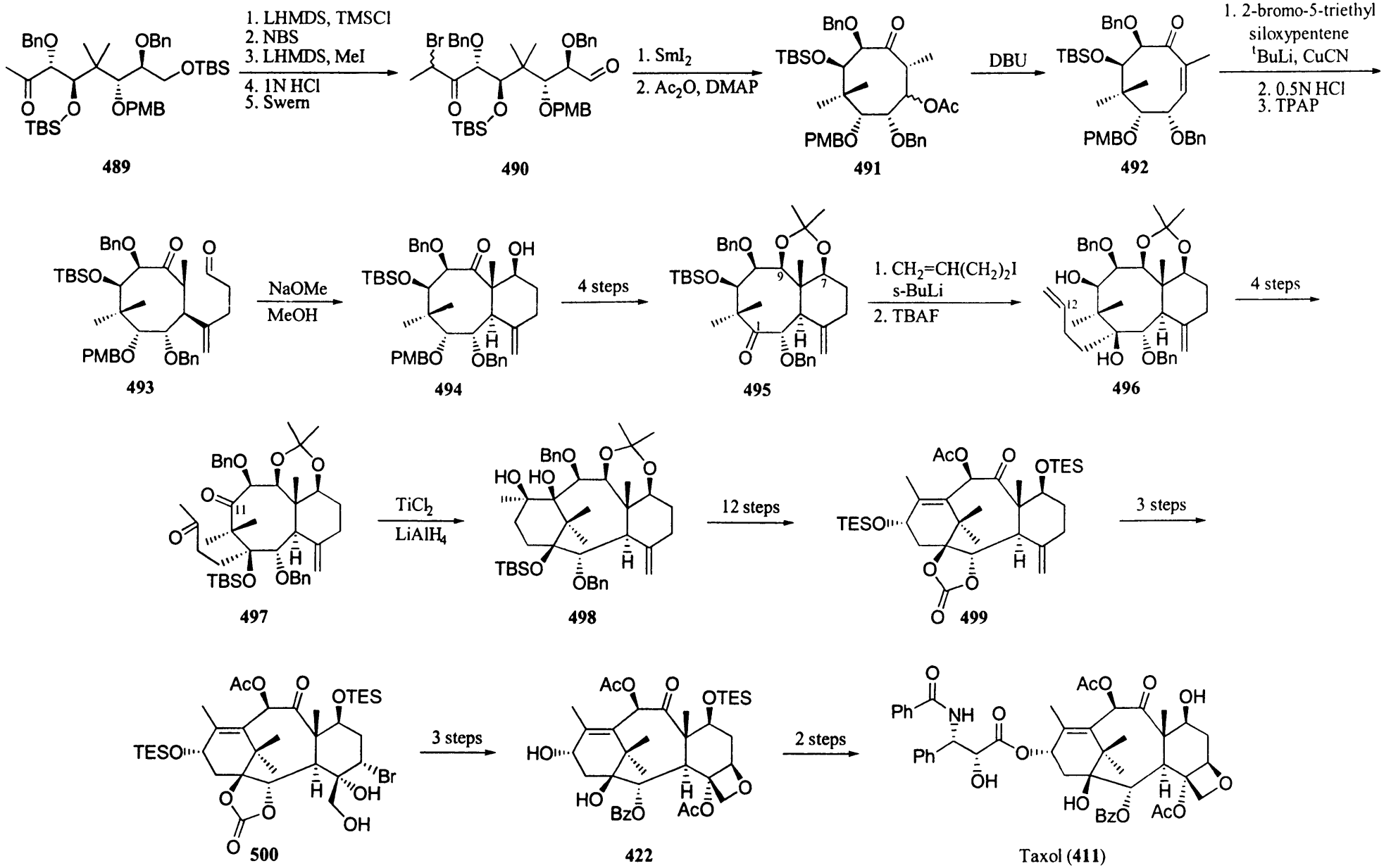

1. tBuOK
prenyl
bromide
2. O3
3. hυ
LDA
ethyl
propiolate
TMSCl
Me2CuLi
AcOH
H2O
4 steps
1. m-CPBA
2. DABCO
TIPSOTf
3 steps
4 steps
1. allyl-MgBr
2. BOMCl
3. NH4F
4. PhLi; Ac2O
DMAP
1.
2. O3
DMAP (xs)
TrocCl
6 steps
1. (iPr)2NEt
2. Ac2O, DMAP
TASF
PhLi
4 steps
476
477
478
479
480
481
482
483
484
485
486
487
488
421
Taxol (411)

Scheme 83

5.5.5 **Mukaiyama**[151]

Mukaiyama and co-workers completed the most recent total synthesis of Taxol in 1997. The strategy was to construct A- and C-ring systems onto a B-ring framework, prepared from the optically active polyoxy-unit **489**. The overall synthetic route is summarized in Scheme 84. Bromination of methyl ketone **489** with NBS, followed by methylation of the α-position, deprotection of the *tert*-butyldimethylsilyl group, and Swern oxidation gave the desired α-bromoketoaldehyde **490**. In the presence of excess SmI_2, the intramolecular aldol cyclization reaction of **490** proceeded smoothly to give a mixture of β-hydroxycyclooctanones. Acetylation of this mixture gave compounds **491**, which on treatment with DBU gave the desired 8-membered ring enone **492** in good yield. Michael addition of a cuprate reagent (generated *in situ*) to the enone **492**, followed by deprotection and oxidation gave the ketone **493**, having a C-3,8 *cis* configuration, in high yield with high diastereoselectivity. Intramolecular aldol reaction of **493** afforded the BC-ring compound **494** in high yield with good diastereoselectivity.

Transformation of **494** to the C-1 ketone **495** was achieved via a series of reactions including reduction at C-9, diol protection and C-1 oxidation. Alkylation of the C-1 position of **495** with the homoallyllithium reagent, followed by deprotection of the TBS group gave the desired *cis*-diol **496**. Diketone **497** was obtained via a series of reactions including protection, oxidation and Wacker oxidation. Intramolecular pinacol coupling reaction of the diketone **497**, using low-valent titanium, gave the desired ABC-ring system **498**. Transformation of **498** to taxoid **499** was achieved in a number of steps including protecting group modification, oxidation at C-9 and C-13, and C-11, C-12 olefination. Allylic bromination of **499**, followed by selective dihydroxylation with OsO_4, furnished the dihydroxy bromide **500**. Oxetane formation, acetylation, treatment with phenyllithium, and deprotection at C-13 gave 7-(triethylsilyl) baccatin III **422**. Attachment of the side-chain, followed by desilylation, completed a total synthesis of Taxol (**411**).


1. LHMDS, TMSCl
2. NBS
3. LHMDS, MeI
4. 1N HCl
5. Swern
1. SmI_2
2. Ac_2O, DMAP
DBU
1. 2-bromo-5-triethyl siloxypentene
^{t}BuLi, CuCN
2. 0.5N HCl
3. TPAP
NaOMe
MeOH
4 steps
1. $CH_2=CH(CH_2)_2I$
s-BuLi
2. TBAF
4 steps
$TiCl_3$
$LiAlH_4$
12 steps
3 steps
3 steps
2 steps
489
490
491
492
493
494
495
496
497
498
499
500
422
Taxol (411)

Scheme 84

5.6 Summary of Taxol Development

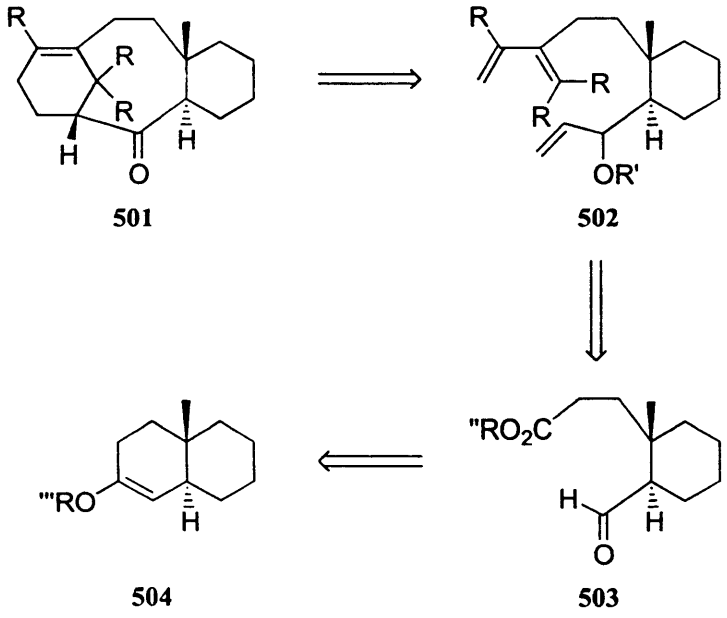
Since the initial discovery of Taxol there has been rapid progress both in clinical developments and chemical syntheses. It has now reached a stage where Taxol is available in adequate quantity for therapeutic use. The chronology of Taxol development, from discovery to clinic, is detailed in Table 2.

Table 2. Chronology of Taxol Development

• Collection of *Taxus brevifolia* as part of an NCI programme, screening for cytotoxic natural products.	1962
• Bark extracts of *Taxus brevifolia* were found to be cytotoxic towards KB cells.	1964
• Pure Taxol was isolated.	1966
• Wani and Wall determined the structure of Taxol by X-ray crystallography.	1971
• Susan Horwitz reported that Taxol stimulates microtubule assembly.	1979
• 10-Deacetylbaccatin III was isolated from *Taxus baccata* (European Yew tree) and identified as a suitable starting material for the semi-synthesis of Taxol by the Potier group.	1980
• Phase I and Phase II clinical trials for all types of cancer. Most favourable results obtained for breast and ovarian cancer.	1983-1986
• Semi-synthesis of Taxol - Potier and Greene (1986), later improved (1988). Semi-synthesis of Taxol - Holton (1989).	1986-1989
• Further extensive hospital trials and application for Food and Drug Administration (FDA) approval. Approved for ovarian cancer treatment (1992). Taxol® marketed by Bristol-Myers Squibb Co. (1993); approved for breast cancer treatment (1994).	1991-1994
• The first total syntheses of Taxol - Holton, Nicolaou.	1994
• Taxol total synthesis - Danishefsky.	1995
• Taxol total synthesis - Wender.	1996
• Taxol total synthesis - Mukaiyama.	1997

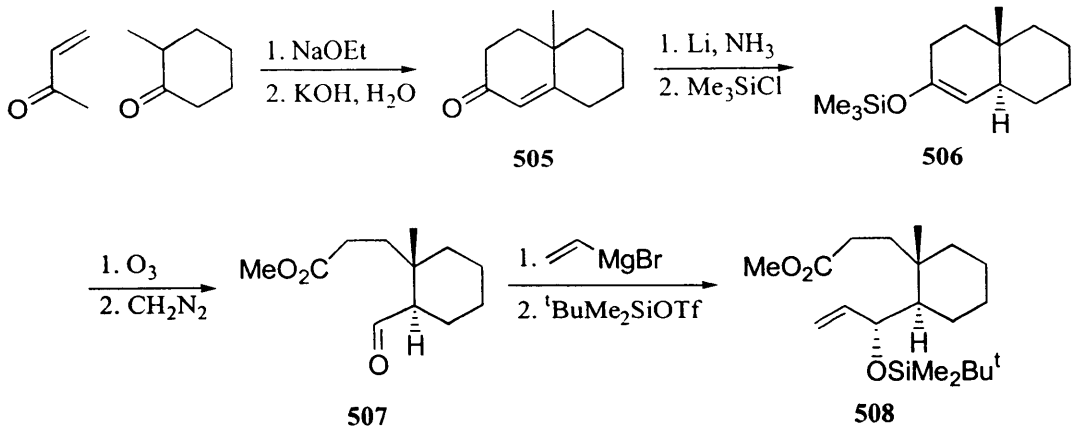
5.7 Previous Work at Leicester

The syntheses of two model taxane ring systems have been published by the Jenkins group.[152] Retrosynthetically, the key stage in each synthesis is the intramolecular Diels-Alder reaction to construct both the A- and B-rings in model system **501**, which leads back to the triene precursor **502** (Scheme 85). Suitable methods for diene and olefin construction will then be required, a convenient substrate being **503** where the two carbonyl groups are distinguishable and can react separately. The 1,6-dicarbonyl reconnection leads to the decalin **504** which could be readily cleaved by ozonolysis.



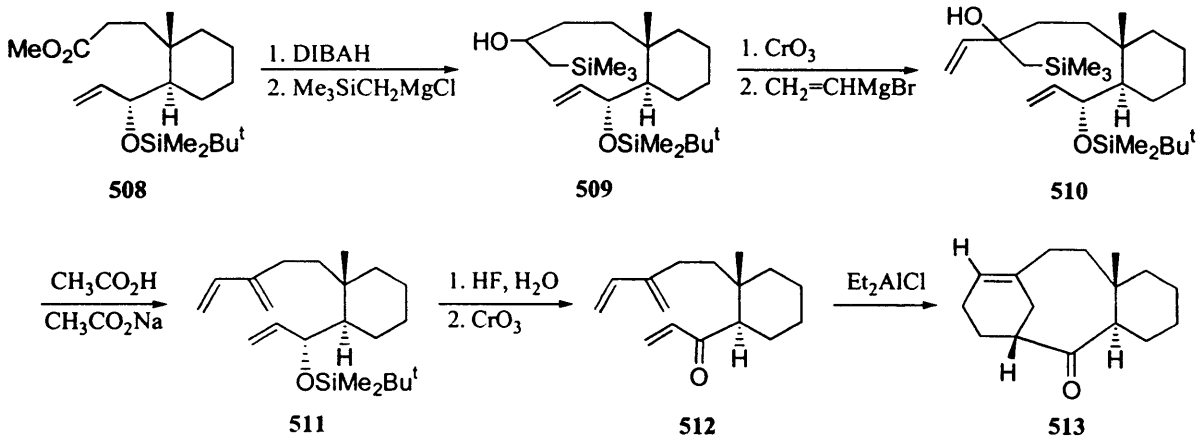
Scheme 85

The starting point for each synthesis was the Robinson annulation reaction between 2-methylcyclohexanone and methyl vinyl ketone to give the known decalin **505**.[153] Lithium in ammonia reduction followed by enolate trapping gave the silyl enol ether **506** with the *trans* decalin stereochemistry.[154] Ozonolysis led to cleavage of the double bond and treatment with diazomethane furnished the ester-aldehyde **507**, which was further treated with vinylmagnesium bromide and protected as the silyl ether **508** (Scheme 86).



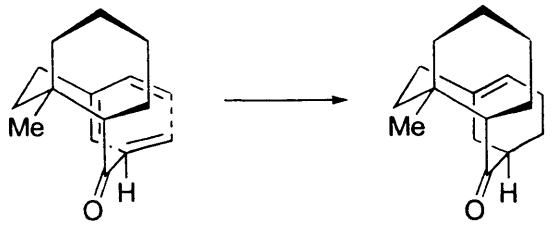
Scheme 86

In the first model study[152a] the ester **508** was converted into a diene using silicon as a control element (Scheme 87). Diisobutylaluminium hydride (DIBAH) reduction of ester **508** gave an aldehyde, which on treatment with trimethylsilylmethyl magnesium chloride gave the β-hydroxy silane **509**. Oxidation followed by reaction with vinylmagnesium bromide provided the crude product **510**, which was treated with acetic acid and sodium acetate[155] to effect controlled elimination, yielding the triene **511**. Deprotection was followed by oxidation to give trienone **512**, which underwent Diels-Alder cyclization in the presence of a catalytic amount of diethylaluminium chloride to give ketone **513** as a white crystalline single isomer.



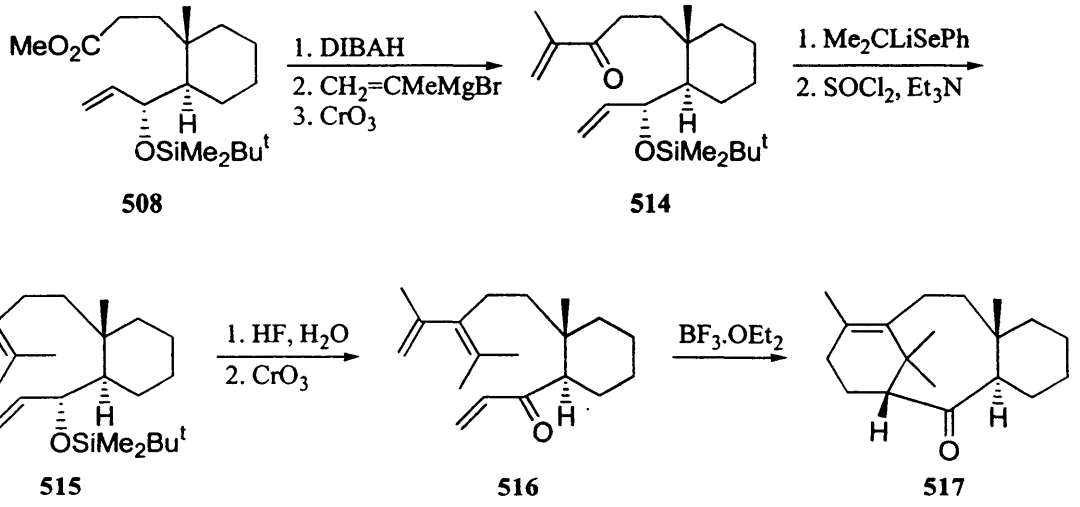
Scheme 87

The X-ray crystal structure of **513** showed the eight-membered B-ring to be in a boat-chair conformation. A reasonable prediction would be that the Diels-Alder reaction proceeds via the transition state **512a**, with the eight-membered ring in a boat-chair conformation.



512a **513**

The second model study required the introduction of three methyl groups in the A-ring of the taxoid structure.[152b] The intermediate **508** was reduced to an aldehyde, which was reacted with isopropenylmagnesium bromide, and the resulting allylic alcohol oxidized to the enone **514**. The synthesis of the diene was achieved by the introduction of the anion $Me_2CLiSePh$, developed by the work of Krief[156] and Reich,[157] and subsequent elimination to give the triene **515**. Deprotection and oxidation furnished the trienone **516**, which underwent Diels-Alder cyclization on treatment with $BF_3.OEt_2$ to give ketone **517** in good yield (Scheme 88).

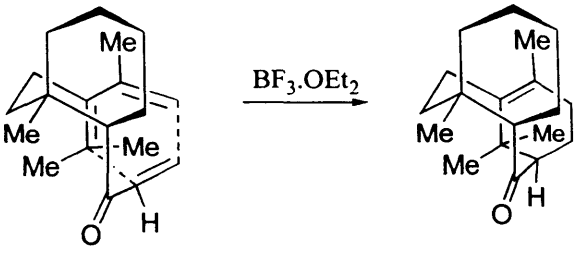


508 **514**

515 **516** **517**

Scheme 88

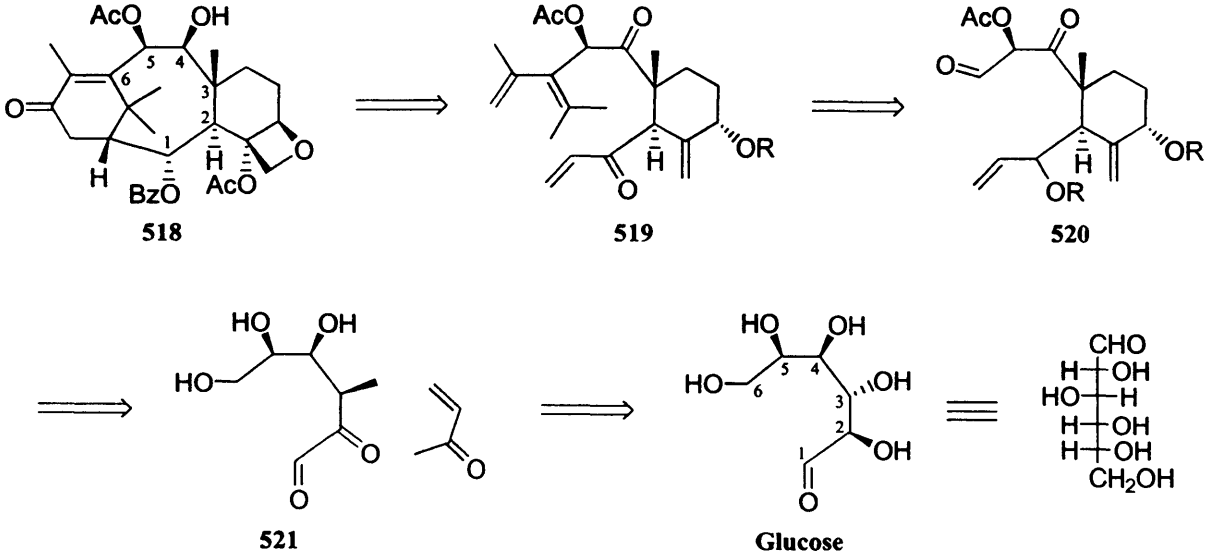
The trienone **516** was again thought to adopt a boat-chair conformation **516a** in the intramolecular Diels-Alder reaction, to give the alkylated taxane model **517**. Unfortunately the product was not a solid, but NMR analysis (nOe) showed that the B-ring in **517** was indeed in a boat-chair conformation.



516a **517**

5.8 Synthesis of a Chiral Taxoid from Glucose

The next stage in the project was to devise a synthetic route that would incorporate as much of the functionality and chirality found in natural taxanes as possible. The retrosynthetic plan for taxoid structure **518** is shown in Scheme 89. 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. Working backwards from the tricyclic compound **518** we obtain the trienone **519**, which in turn arises from the aldehyde **520**. The Robinson annulation of a protected form of the sugar methyl ketone **521** should give the C-ring synthon **520**. The "chiral template" for this synthesis is glucose.

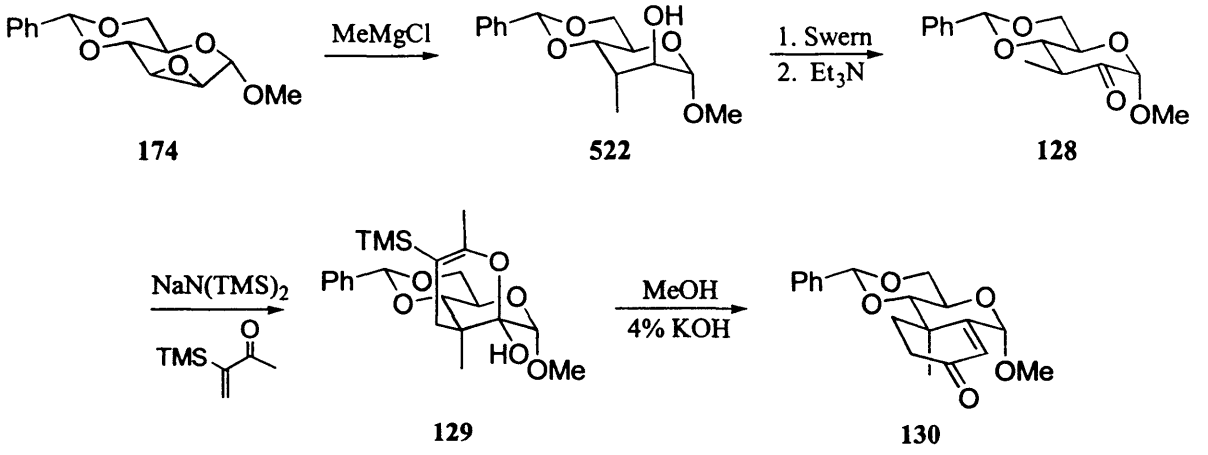


518 **519** **520**

521 **Glucose**

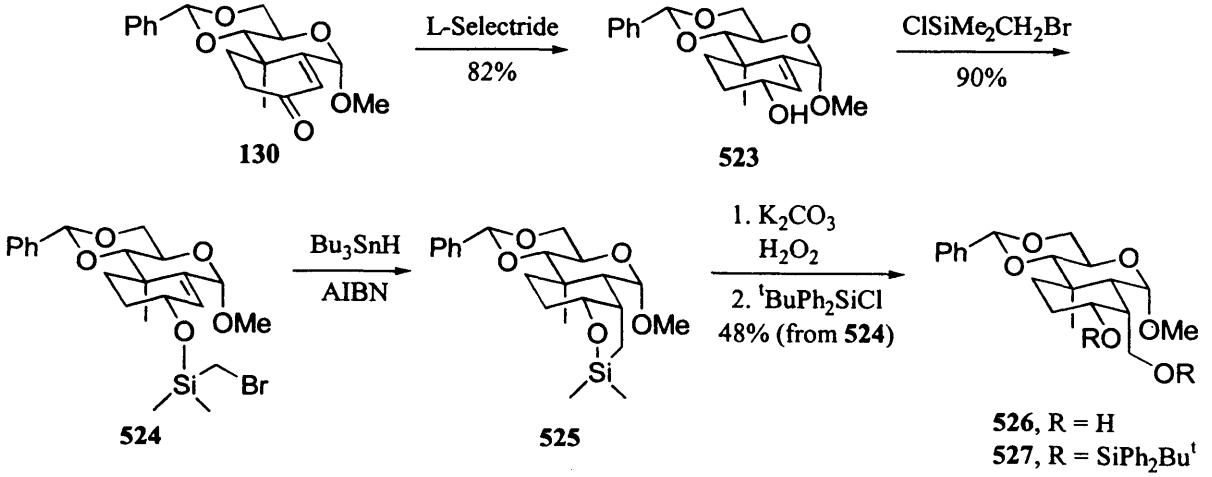
Scheme 89

The starting point for the synthesis was the known β-epoxide **174**,[60] which was selectively opened with methylmagnesium chloride to give the alcohol **522** (Scheme 90). Swern oxidation of alcohol **522** furnished a ketone which, upon treatment with triethylamine, epimerized to give ketone **128**. The methyl ketone **128** was treated with sodium bis(trimethylsilyl)amide, and the resulting enolate reacted with 3-trimethylsilyl-3-buten-2-one[158] to afford the alcohol **129**, which gave the Robinson annulation product **130** upon treatment with 4% methanolic potassium hydroxide.[41]



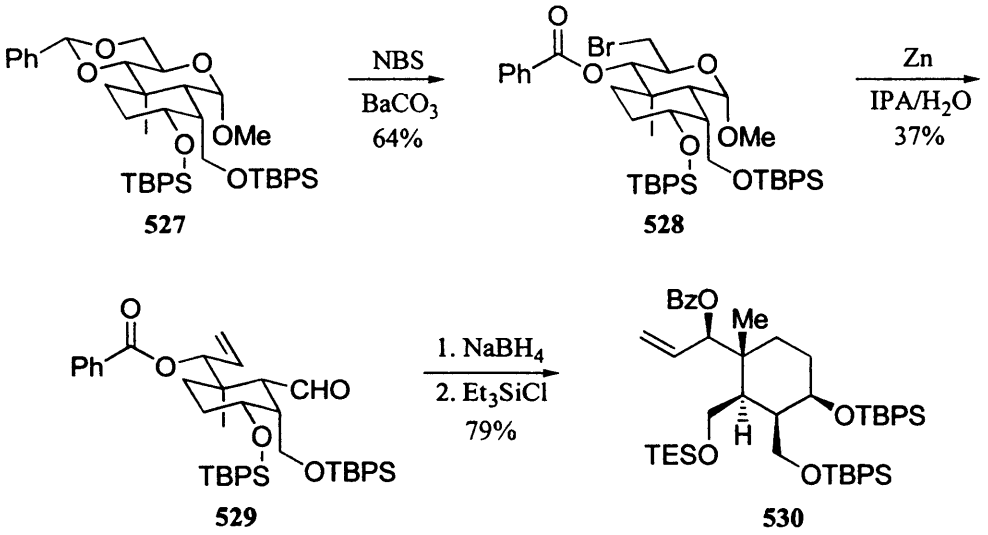
Scheme 90

Reduction of the cyclohexenone **130** with L-Selectride® furnished the allylic alcohol **523**. Silylation of the allylic alcohol **523** proceeded smoothly to yield the silyl ether **524**, which was subsequently treated with tributyltin hydride to give the tetracyclic siloxane **525**. Tamao-Kumada oxidation of **525** followed by protection of the subsequent diol **526** produced the *bis* silyl ether **527** (Scheme 91).[159]



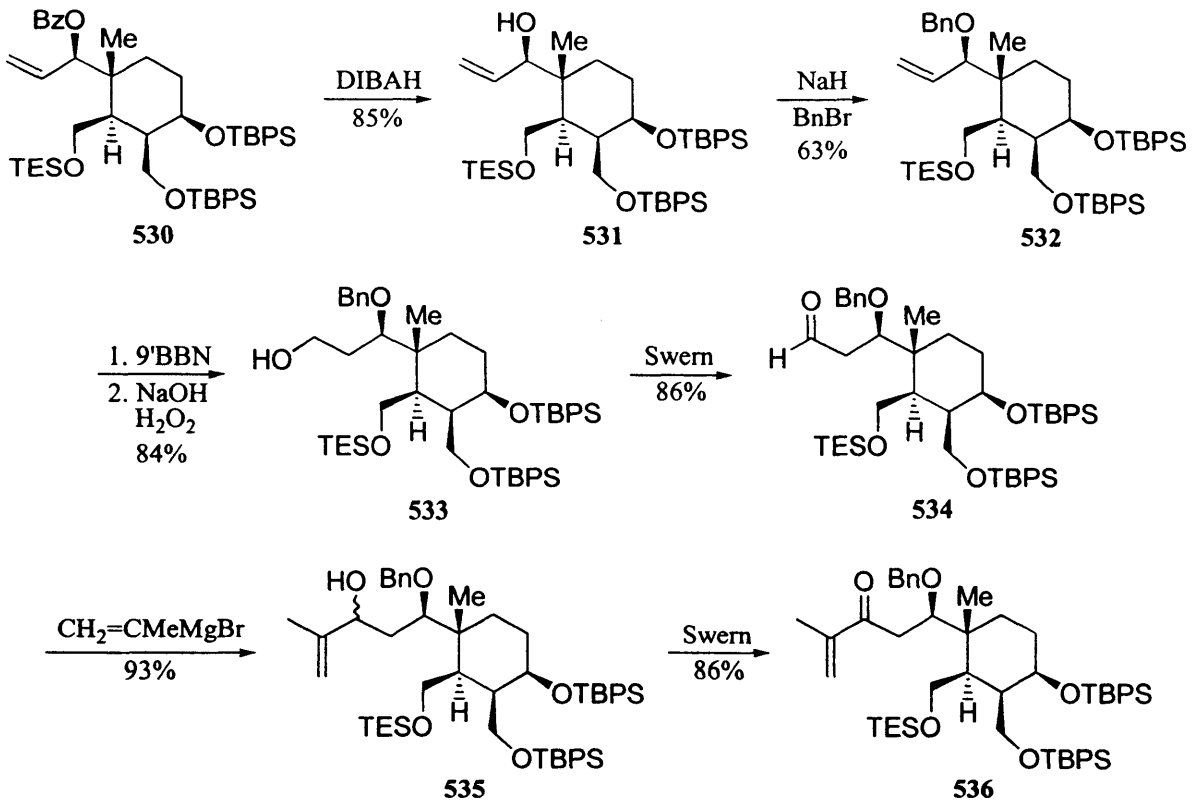
Scheme 91

Having used the protected carbohydrate ring as a "chiral template" it was then necessary to fragment the sugar ring, leaving behind a chiral functionalized cyclohexane C-ring synthon. The first step was to react the protected diol **527** with NBS following the work of Hanessian[63] to give the bromo ester **528**. Treatment of **528** with activated zinc produced the aldehyde **529** in a Vasella elimination.[30a] Reduction and protection of the aldehyde **529** gave the required chiral C-ring synthon **530** in good yield (Scheme 92).[160]



Scheme 92

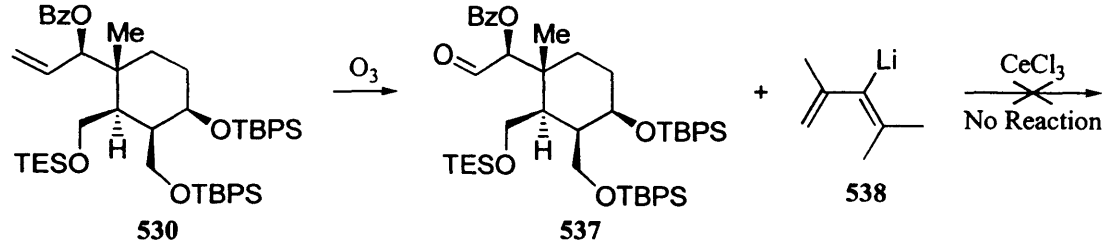
Reduction of the benzoyl group of **530** by reaction with DIBAH gave the alcohol **531**, which was reacted with sodium hydride and benzyl bromide to give C-ring synthon **532** (Scheme 93). This conversion from a benzoyl to a benzyl group was shown to be necessary in a model study, where hydroboration of an allylic benzoate led to destruction of the starting material.[161] Hydroboration of olefin **532** followed by oxidation gave the primary alcohol **533**, which afforded the aldehyde **534** upon Swern oxidation. Isopropenylmagnesium bromide was added to aldehyde **534** to produce the allylic alcohols **535** as a 2:1 mixture of diastereoisomers. Swern oxidation of both isomers yielded the enone **536**.



Scheme 93

5.8.1 Approaches Towards Diene Construction

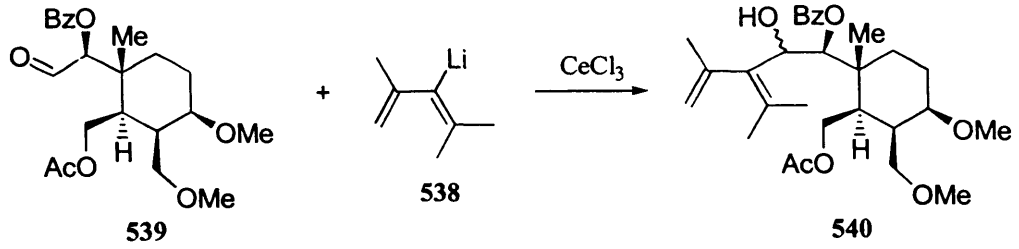
Early attempts at constructing the diene focused on attaching the diene as a single unit. Ozonolysis of the C-ring synthon **530** furnished the aldehyde **537** (Scheme 94). The reaction of aldehyde **537** with the lithiated diene **538**,[162] in the presence of $CeCl_3$, met with failure. This was thought to be due to the remote steric hindrance of the three silyl protecting groups lowering the reactivity of the aldehyde **537**.[163]



Scheme 94

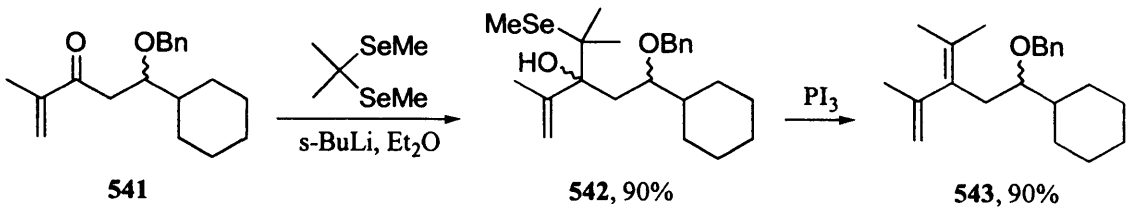
Replacing the bulky TBPS protecting groups with methyl groups, and the TES protecting group with an acetyl group, produced a more reactive aldehyde **539**.[164] Addition of the lithiated diene **538** furnished the alcohols **540** as a 2:1 mixture of diastereoisomers.

This result demonstrates that remote steric hindrance by the silyl protecting groups is an important factor in determining the reactivity of the aldehyde. Clearly the methyl groups in **540** are not ideal protecting groups, and their removal to construct the oxetane ring would be very difficult.



The more recent approaches towards diene construction have followed the methods used in the synthesis of alkylated taxane model **517** (Scheme 88), where the use of selenium chemistry helped to build the diene in a stepwise fashion. Initial attempts to use selenium chemistry in the chiral route were unsuccessful, due to the failure of $Me_2CLiSePh$ to add effectively and then eliminate to form a diene. However, in 1995 Williams and co-workers adapted the synthesis described in Scheme 88 to construct the diene moiety, in their approach to the biosynthetic intermediate taxadienes **418** and **419**.[165] The authors found that the sterically less demanding selenium reagent $Me_2CLiSeMe$ was a more effective nucleophile than $Me_2CLiSePh$.

The lithiation of 2,2-bis(methylseleno)propane, following the work of Krief,[156] proved to be an extremely unpredictable reaction. However, after a great deal of work by Dr. Andrew Wood, suitable conditions for acetal cleavage were found (s-butyllithium in diethyl ether). The addition of $Me_2CLiSeMe$ to model enone **541** gave the alcohols **542** as a 2:1 mixture of diastereoisomers. Subsequent treatment with PI_3 produced the diene **543**, thus completing the invaluable enone to diene conversion (Scheme 95). Unfortunately, several attempts by Dr. Andrew Wood to add $Me_2CLiSeMe$ to the chiral enone **536** met with failure.[161]

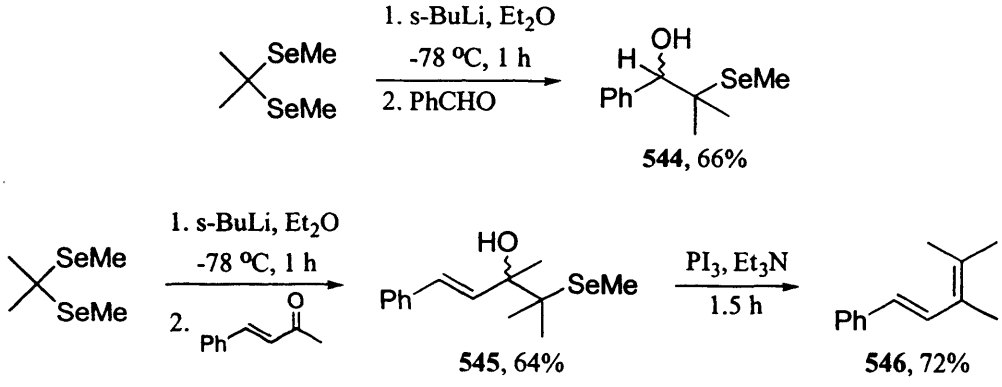


Scheme 95

5.8.2 **Results and Discussion**

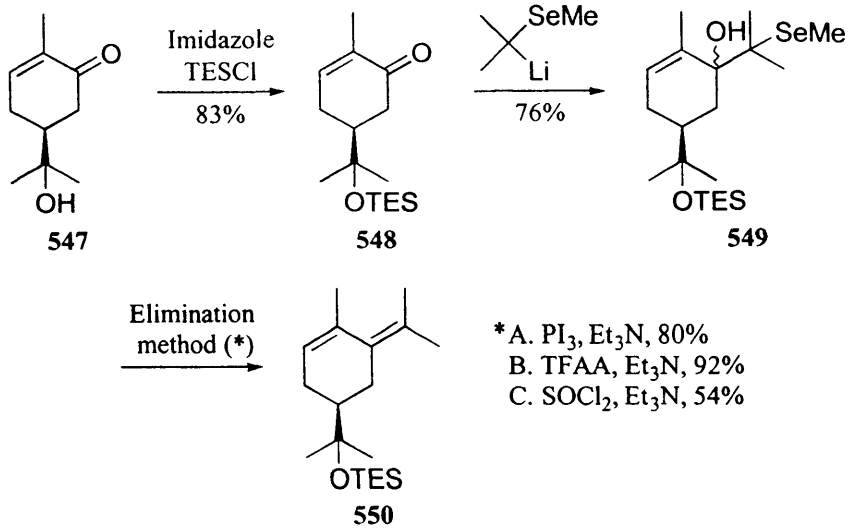
On starting work on this project it became very clear, firstly that progress through the route relied upon a constant supply of starting materials, and secondly that any one chemical step could not be too low yielding in this linear synthesis.

Having painstakingly replenished the supply of enone **536**, via the numerous chemical steps from β-epoxide **174**, we decided that it would be a good idea to carry out the selenium chemistry on a series model compounds to test the viability of the procedure. Benzaldehyde and *trans*-4-phenyl-3-buten-2-one were chosen as simple model systems. Successful nucleophilic additions were achieved to give the corresponding β-hydroxyalkyl selenides **544**[166] and **545**. Subsequent treatment of **545** with PI_3 gave the diene **546** (Scheme 96).



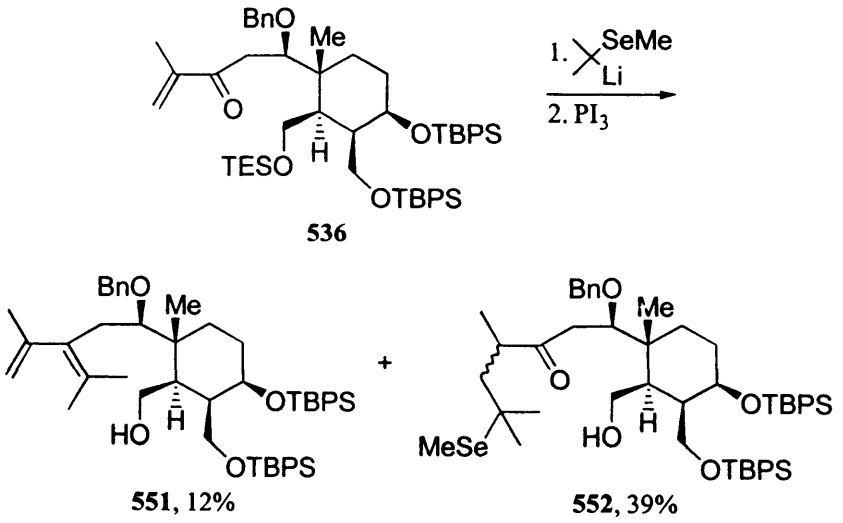
Scheme 96

Another model enone system was selected to test the selenium chemistry *and* the various different elimination methods (Scheme 97). Protection of the alcohol **547** gave the desired silyl ether **548**. Nucleophilic addition of $Me_2CLiSeMe$ produced the β-hydroxyalkyl selenides **549** as a *ca.* 1:1 mixture of diastereoisomers. Elimination using PI_3 proved to be the cleanest method for constructing the diene **550**. Trifluoroacetic anhydride gave the highest yield of **550**, yet impurities were seen by ^1H NMR, even after flash chromatography.



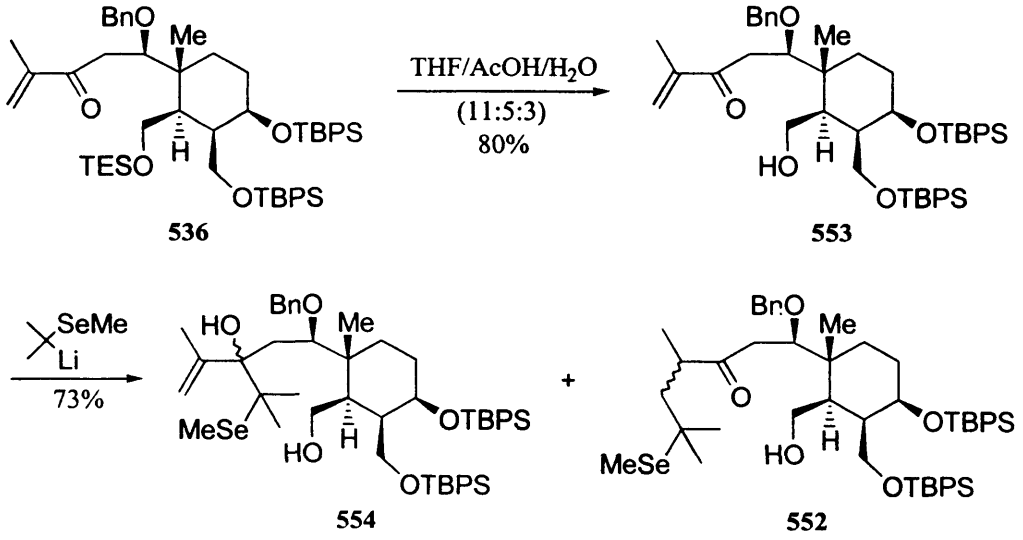
Scheme 97

Confident that the selenium chemistry was working, we applied these methods to the conversion of the chiral enone **536** to a diene. The selenium addition reaction was carried out concurrently on *trans*-4-phenyl-3-buten-2-one, to ensure that lithiation of the selenium acetal was achieved. After several attempts, the enone to diene conversion was accomplished, but with limited success. Treatment of the enone **536** with five equivalents of $Me_2CLiSeMe$, followed by reaction with PI_3 gave the desired diene **551** (12%) along with the Michael-type addition products **552** (39%). Evidence for the formation of **552** can be seen in the ^1H and ^{13}C NMR spectra, where the olefinic CH_2 signals are no longer present. Also, from the mass spectrum (FAB) of **552**, the *m/z* 1013 (MNa^+) peak is observed.



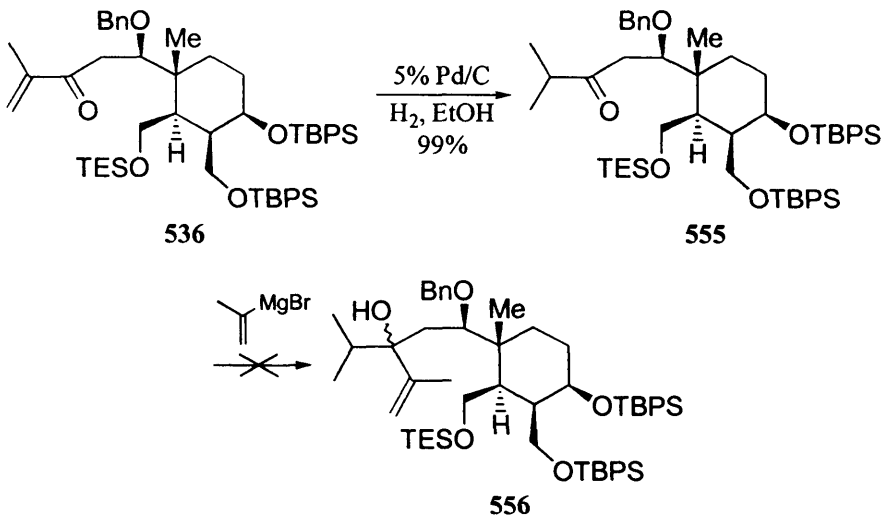
From this result we can deduce, firstly that 1,4 addition to the enone **536** competes preferentially with 1,2 addition (to the C=O), and secondly that treatment with PI_3 leads to deprotection of the triethylsilyl ether. This competing 1,2/1,4 addition was not observed in the model study undertaken by Dr. Andrew Wood[161] (Scheme 95) or in the model enone **548**. After lengthy discussion, it was decided that selective deprotection of the TES group of enone **536** would provide a less hindered substrate, therefore improving the chance of increasing the 1,2:1,4 addition ratio.

Deprotection of the enone **536** gave the desired alcohol **553** in good yield (Scheme 98).[167] Subsequent addition of $Me_2CLiSeMe$ furnished the β-hydroxyalkyl selenides **554** and the Michael-type addition products **552**, in a *ca.* 1:1 ratio (only partial separation of products was achieved). Unfortunately, the reaction of a mixture of **552** and **554** with PI_3 met with failure. In hindsight, it would have been more sensible to react a pure sample of **554** with PI_3.



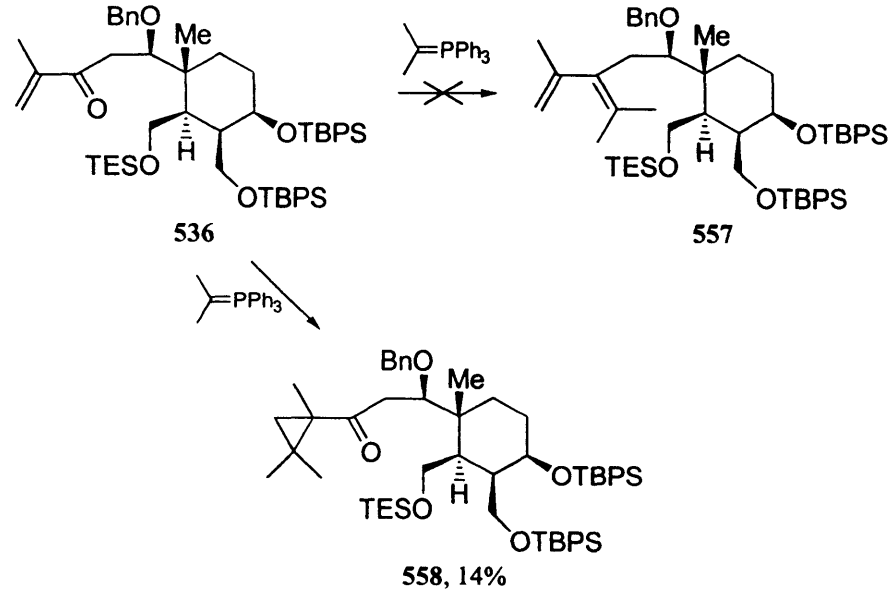
Scheme 98

Having experienced very little success with the selenium chemistry, we decided to explore other avenues in the pursuit of enone to diene conversion. It was thought that a Grignard addition reaction, followed by the elimination of water, could provide the desired diene moiety. Hydrogenation of the double bond of enone **536** gave the desired ketone **555** in excellent yield (Scheme 99). It was hoped that the addition of isopropenyl Grignard to the ketone **555** would produce the tertiary alcohol **556**. However, several attempts to carry out this Grignard reaction were unsuccessful, with only starting material recovered in each case.



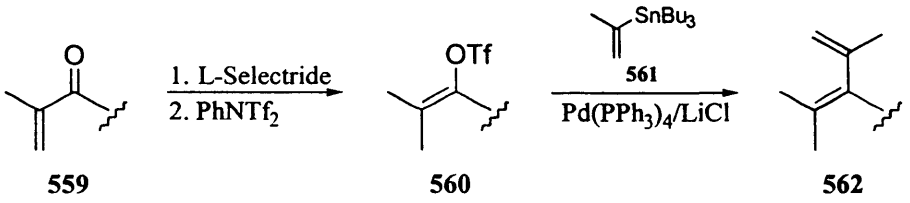
Scheme 99

Another method available for constructing the required diene is a Wittig reaction. However, treatment of the enone **536** with isopropyltriphenylphosphorane, generated from isopropyltriphenylphosphonium iodide and butyllithium,[168] did not produce the diene **557**. The only identifiable product was the cyclopropane **558** (14%), resulting from Michael-type addition to the enone **536** (Scheme 100). Evidence for the formation of **558** can be seen in the ^{1}H NMR spectrum, where the olefinic proton signals are no longer present. Also, two new methyl singlets have appeared at δ 1.10 and δ 1.25.



Scheme 100

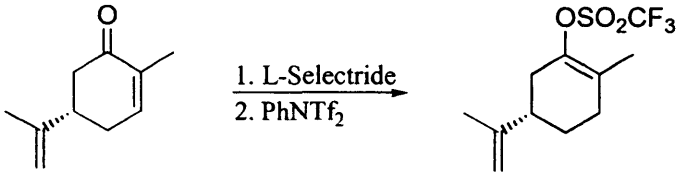
From analyzing these results it became apparent that the carbonyl group of the enone **536** is extremely sterically hindered. Consequently, 1,4 addition to the enone **536** competes preferentially with 1,2 addition. So, at this point we asked the question: Could a premeditated 1,4 nucleophilic addition still provide a route to the required diene? After searching the literature, a possible solution was found. Conjugate reduction of the enone **559** with L-Selectride®, followed by quenching the resulting enolate with *N*-phenyltriflimide would provide the vinyl triflate **560**.[169] Palladium-catalyzed Stille coupling of the vinyl triflate **560** with isopropenylstannane **561** would furnish the required diene **562** (Scheme 101).[170]



559 **560** **562**

Scheme 101

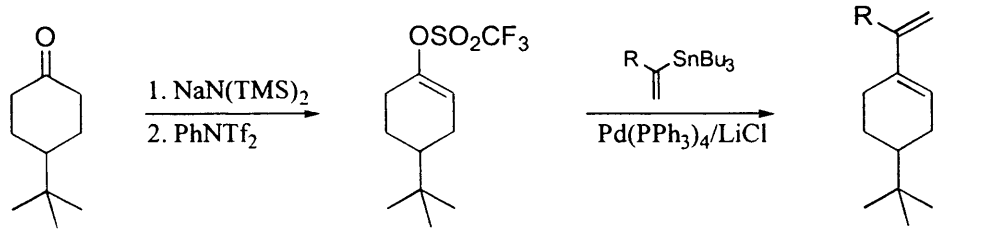
To test the efficacy of this chemistry, model studies were undertaken. Conjugate reduction of (*R*)-Carvone **563** with L-Selectride®, followed by quenching the resulting enolate with *N*-phenyltriflimide, gave the vinyl triflate **564** in good yield.[169b] Unfortunately, attempts to couple the vinyl triflate **564** with isopropenylstannane **561** were unsuccessful.



563 **564**, 83%

At this point we decided to choose a simple model system to test the Stille coupling reaction. Treatment of 4-*tert*-butylcyclohexanone **565** with sodium bis(trimethylsilyl)amide, followed by quenching the resulting enolate with *N*-phenyltriflimide, gave the vinyl triflate **566** (Scheme 102).[171] Palladium-catalyzed Stille coupling of the vinyl triflate **566** with vinyltributylstannane furnished the diene **567** in good yield.[170] The equivalent reaction with isopropenylstannane **561**, generated from

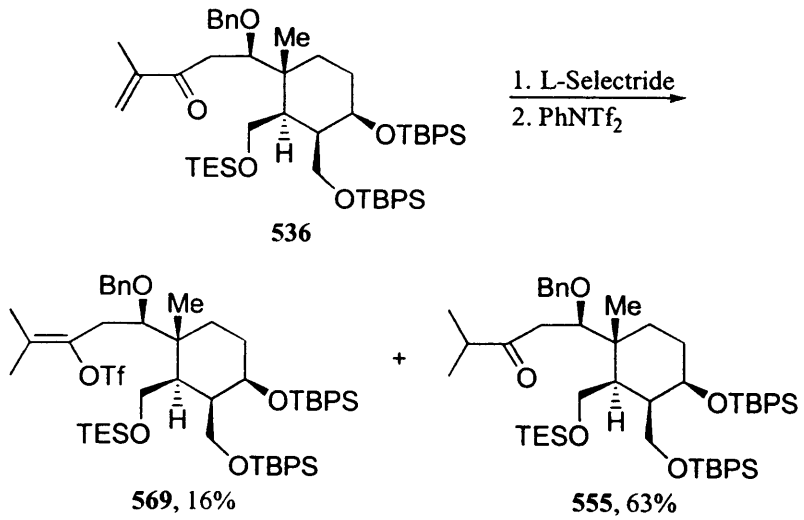
isopropenylmagnesium bromide and tributyltin chloride,[172] gave the desired diene **568**,[173] again in good yield.



565 **566**, 53% **567**, R = H, 73%
568, R = Me, 67%

Scheme 102

With these results in hand, we applied these methods to the conversion of the chiral enone **536** to a diene. Conjugate reduction of the enone **536** with L-Selectride®, followed by quenching the resulting enolate with *N*-phenyltriflimide, gave the vinyl triflate **569** (16%) and the reduced product **555** (63%). From this result we can deduce that the remote steric hindrance of the three silyl protecting groups is impeding the trapping of the enolate with *N*-phenyltriflimide, and therefore on aqueous work-up, protonation of the enolate gives the reduced product **555**. Evidence for the formation of **569** can be seen in the ^{1}H NMR spectrum, where the olefinic proton signals are no longer present. Also, two new methyl singlets have appeared at δ 1.55 and δ 1.60. Attempts to produce the vinyl triflate **569** from ketone **555**, using LDA and *N*-phenyltriflimide, met with failure.



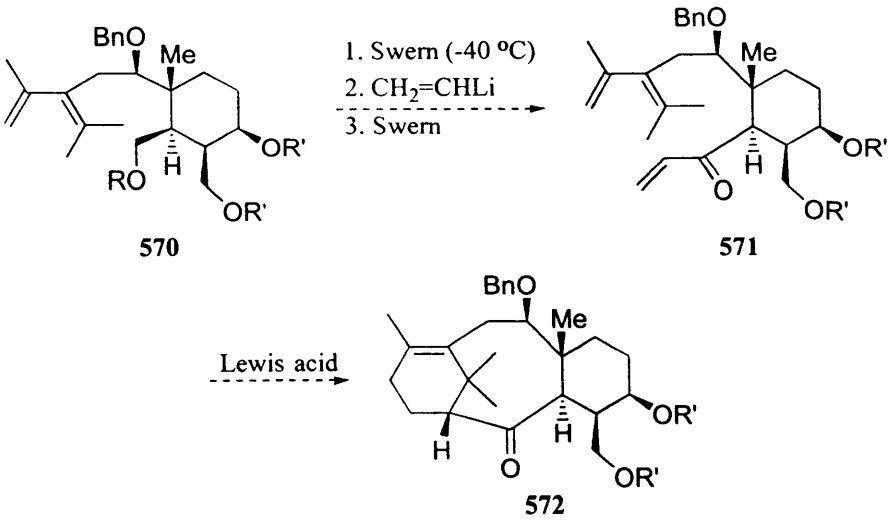
5.8.3 **Future Work**

Obviously it is necessary to pursue a successful method for the enone to diene conversion, in the synthetic route towards a chiral taxoid. To achieve this goal, certain changes could be made to improve the chances of enone to diene conversion:

- the three silyl protecting groups could be replaced with smaller, less hindering protecting groups, to make the carbonyl group of the enone more accessible to nucleophilic attack.

- introducing the C-ring diol functionality at a later stage in the synthetic route would eliminate the need for bulky hydroxyl protecting groups, and therefore could improve the reactivity of the carbonyl group of the enone.

Implementing either of these changes may improve the results of the selenium-based chemistry. The outcome of the Wittig and vinyl triflate chemistry may also be more desirable on eliminating the remote steric hindrance. Alternatively, utilizing the hard silicon reagent $Me_2CLiSiMe_3$, instead of the softer selenium reagent $Me_2CLiSeMe$, may improve the ratio of 1,2:1,4 nucleophilic addition. If a reasonable yield of the diene (e.g. **570**) is accomplished, the chiral taxoid is only a few steps away. Conversion to an aldehyde, utilizing a Swern Oxidation at -40 °C,[161] followed by addition of vinyllithium and subsequent oxidation, would furnish the trienone **571**. The intramolecular Diels-Alder reaction of a highly functionalized chiral intermediate **571**, to produce the chiral taxoid **572**, could then be tested (Scheme 103).



570 **571** **572**

Scheme 103

5.9 Summary

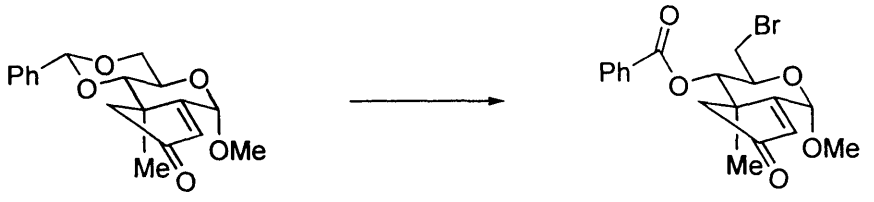
Model studies proved that both the selenium and Stille chemistry are viable methods for enone to diene conversion. However, the conversion of the enone moiety of advanced C-ring synthon **536** into a diene met with a very limited amount of success, with Michael-type addition providing unwanted by-products. This suggests that removing the remote steric hindrance in **536** may improve the reactivity of the carbonyl group.

EXPERIMENTAL

GENERAL EXPERIMENTAL

The large-scale synthesis of intermediates in the chiral taxoid route proved to be a time consuming process, and therefore experimental procedures for compounds prepared previously have been included. All reactions were performed under an atmosphere of nitrogen (unless otherwise stated) and solvent extractions were dried with anhydrous magnesium sulphate. Tetrahydrofuran and benzene were distilled from sodium-benzophenone. Diethyl ether was distilled from lithium aluminium hydride. Chloroform was distilled from phosphorus pentoxide and stored over molecular sieves. Dichloromethane was distilled from calcium hydride. Petroleum ether refers to the 40-60 °C boiling fraction. Phosphate buffer solution (pH = 7) was prepared by dissolving potassium dihydrogen phosphate (8.95 g) and sodium hydroxide (1.53 g) in water (100 mL). Thin Layer Chromatography (TLC) analysis was performed using silica gel 60 F_{254} aluminium TLC plates, Merck 5554. Flash column chromatography was carried out using sorbsil C-60 silica gel, 40-60 μm. The chromatotron used was the Harrison Research model 7924T, and the plates used were made from silica gel 60 PF_{254} with $CaSO_4$. Melting points were measured using a Kofler hotstage and are uncorrected. Elemental analyses were carried out by Butterworth Laboratories, Teddington, Middlesex. Infrared (IR) spectra were recorded using a Perkin Elmer 298 IR spectrometer; peaks are referred to as strong (s), medium (m) or weak (w). Optical rotations were measured using a Perkin Elmer 341 polarimeter. Mass spectra were recorded on a Kratos Concept Sector mass spectrometer. ^1H and ^{13}C NMR spectra were recorded on a Bruker ARX 250 (250 MHz ^1H, 62.9 MHz ^{13}C), Bruker AM 300 (300 MHz ^1H, 75 MHz ^{13}C), or Bruker DRX 400 (400 MHz ^1H, 100.6 MHz ^{13}C) spectrometer. NMR spectra recorded in $CDCl_3$ were calibrated to $CHCl_3$ (^1H, δ 7.27; ^{13}C, δ 77.4), all chemical shifts were taken directly from the spectra, and *J* values are given in hertz.

Methyl (*R*)-4-*O*-Benzoyl-6-*C*-bromo-2,3,6-trideoxy-3-*C*-methyl-3,2-*C*-(2'-oxapropan-1'-yl-3'-ylidene)-α-D-*arabino*-hexopyranoside (185).

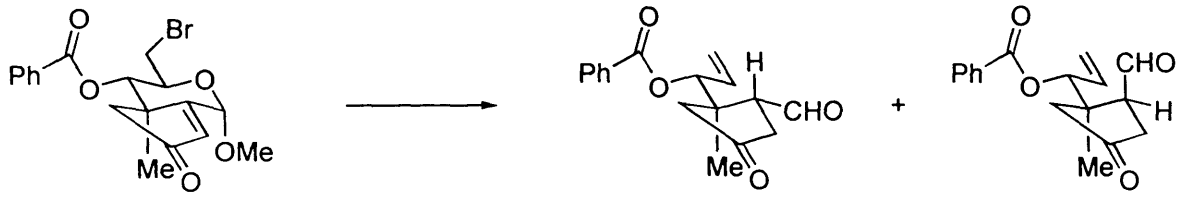


179 185

Barium carbonate (1.03 g, 5.22 mmol) and *N*-bromosuccinimide (203 mg, 1.14 mmol) were added sequentially to a solution of enone **179** (300 mg, 0.95 mmol) in dry carbon tetrachloride (30.0 mL). The resulting solution was stirred at reflux overnight. The barium carbonate was removed by filtration, washed with dichloromethane (2 × 100 mL), the combined organic layers washed with water (2 × 100 mL), saturated sodium chloride solution (100 mL), dried, and evaporated to dryness. Chromatography on silica gel with petroleum ether-diethyl ether (1:1) as the eluent yielded **185** as a white solid (269 mg, 72%): mp 131-132 °C; R_f 0.63, diethyl ether-petroleum ether (2:1); 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* 18.7, 9b-H), 3.37 (1H, dd, *J* 7.6, 11.0, 6a-H), 3.46 (1H, obscured dd, *J* 2.5, 11.0, 6b-H), 3.77 (3H, s, OMe), 4.36 (1H, ddd, *J* 2.5, 7.6, 9.8, 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 (2H, *m*-Ph), 7.57 (1H, *p*-Ph), 7.99 (2H, *o*-Ph); δ_C (62.9 MHz, $CDCl_3$) 20.1 (CH_3, C3-Me), 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), 127.0 (CH, C7), 127.7 (CH, Ph), 128.5 (CH, Ph), 128.8 (CH, Ph), 132.9 (C, Ph), 164.2 (CO, OBz), 174.0 (C, C2), 205.0 (C, C8).

This is a literature compound.[161]

(1*R*,1'*R*,2'*R*)-Benzoic acid 1-(2'-formyl-1'-methyl-4'-oxo-cyclopentyl)-allyl ester (187) and (1*R*,1'*R*,2'*S*)-Benzoic acid 1-(2'-formyl-1'-methyl-4'-oxo-cyclopentyl)-allyl ester (188).

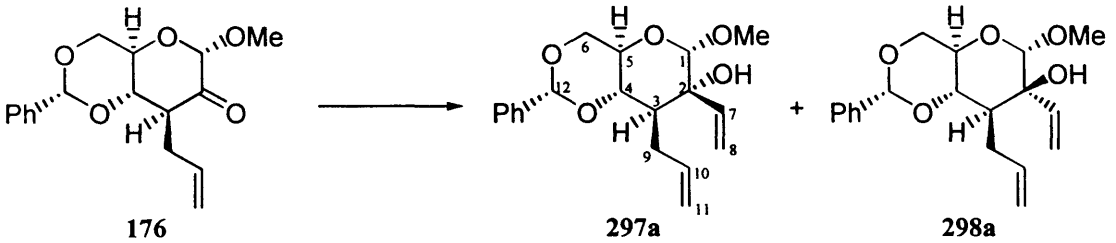


Zinc shot (100 g) was activated by washing sequentially with 2M hydrochloric acid (6 × 50 mL), water (5 × 60 mL), 10% w/v aqueous potassium carbonate solution (50 mL), water (4 × 70 mL), isopropanol (2 × 60 mL) and ether (3 × 60 mL). The bromo ester **185** (356 mg, 0.90 mmol) was heated under reflux with the activated zinc (7.66 g, 0.117 mol) in isopropanol : water (20:2 mL) for 22 h. The zinc was removed by filtration, washed with diethyl ether (3 × 40 mL), the combined organic layers washed with saturated sodium chloride solution (2 × 40 mL), dried, and evaporated to dryness. Separation by the chromatotron technique on a 2 mm plate with petroleum ether-diethyl ether (2:1) as the eluent yielded starting material **185** (64 mg, 18%), **187** as a colourless oil (100 mg, 39%), and a 1:1 mixture of **187** and **188** (58 mg, 23%): **187** - R_f 0.47, diethyl ether-petroleum ether (2:1); $[\alpha]^{18}_D$ - 80.0° (*c* 1.2, $CHCl_3$); υ_{max} (CH_2Cl_2)/cm^{-1} 3050w, 2920m, 2840w, 1745s, 1725s, 1715s, 1600w, 1450m, 1245s, 1105m, 1095s; δ_H (250 MHz, $CDCl_3$) 1.17 (3H, s, C1'-Me), 2.20 (1H, d, *J* 17.6, 5'α-H), 2.37 (1H, dd, *J* 8.8, 19.5, 3'β-H), 2.70 (1H, d, *J* 17.6, 5'β-H), 2.84 (1H, ddd, *J* 1.5, 10.3, 19.5, 3'α-H), 3.32 (1H, ddd, *J* 1.4, 8.8, 10.3, 2'-H), 5.44 (1H, d, *J* 10.4, 1_{cis}-H), 5.51 (1H, d, *J* 17.0, 1_{trans}-H), 5.76 (1H, d, *J* 7.2, 3-H), 5.93 (1H, ddd, *J* 7.2, 10.4, 17.0, 2-H), 7.42-7.67 (3H, Ph), 8.00-8.09 (2H, Ph), 9.98 (1H, d, *J* 1.4, C*H*O); δ_C (62.9 MHz, $CDCl_3$) 19.9 (CH_3, C1'-Me), 36.6 (CH_2, C5'), 46.8 (C, C1'), 49.2 (CH_2, C3'), 52.3 (CH, C2'), 79.3 (CH, C3), 121.6 (CH_2, C1), 129.1 (CH, C2), 129.9 (C, Ph), 130.0 (CH, Ph), 132.4 (CH, Ph), 134.0 (CH, Ph), 165.7 (CO, OBz), 201.1 (CH, C*H*O), 213.6 (C, C4'); *m/z* (CI) 304 (MNH_4^+, 100%) (found MH^+, 304.1549; $C_{17}H_{22}NO_4$ requires 304.1549). Anal. Found: C, 70.76; H, 6.62. $C_{17}H_{18}O_4$ requires C, 71.31; H, 6.34%.

188 - δ_C (62.9 MHz, $CDCl_3$) 25.8 (CH_3, C1'-Me), 38.1 (CH_2, C5'), 47.5 (C, C1'), 48.6 (CH_2, C3'), 57.9 (CH, C2'), 78.8 (CH, C3), 121.1 (CH_2, C1), 129.9 (CH, C2), 130.2 (C,

Ph), 130.4 (CH, Ph), 132.7 (CH, Ph), 133.9 (CH, Ph), 165.0 (CO, OBz), 200.6 (CH, C*H*O), 214.4 (C, C4').

Methyl (*R*)-4,6-*O*-Benzylidene-2-*C*-ethenyl-3-deoxy-3-*C*-propenyl-α-D-glucopyranoside (297a) and Methyl (*R*)-4,6-*O*-Benzylidene-2-*C*-ethenyl-3-deoxy-3-*C*-propenyl-α-D-mannopyranoside (298a).

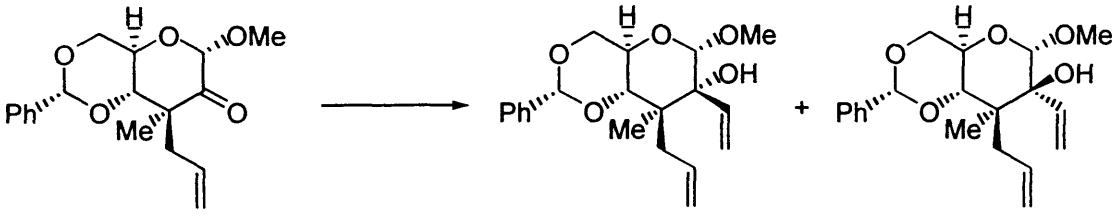


176 **297a** **298a**

Vinylmagnesium chloride (5.70 mL, 9.60 mmol, 15% wt. solution in THF) was added dropwise to an ice-cooled stirred solution of the ketone **176** (2.00 g, 6.58 mmol) in dry THF (7.0 mL). The solution was heated under reflux for 2 h and allowed to cool to room temperature, then quenched by portionwise addition to ice/water (300 mL). The resulting mixture was extracted into diethyl ether (2 × 150 mL), and the combined organic layers were washed with water (2 × 150 mL), followed by saturated sodium chloride solution (150 mL), dried, and evaporated to leave a yellow oil. Chromatography on silica gel with petroleum ether-diethyl ether (4:1) as the eluent yielded **297a** as a colourless oil (711 mg, 33%) and **298a** as a colourless oil (1.16 g, 53%): **297a** - R_f 0.58, petroleum ether-diethyl ether (1:1); $[\alpha]^{20}_D$ + 58.8° (*c* 5.9, $CHCl_3$); υ_{max} ($CHCl_3$)/cm^{-1} 3570w, 3010m, 2930m, 1640w, 1205s, 1065s, 1000s; δ_H (250 MHz, $CDCl_3$) 2.09-2.43 (3H, 3-H and 9-H), 2.61 (1H, s, O*H*), 3.33-3.46 (1H, m, 4-H), 3.36 (3H, s, overlapping, OMe), 3.68 (1H, t, *J* 9.8, 6ax-H), 3.82 (1H, dt, *J* 4.4, 9.8, 5-H), 4.23 (1H, dd, *J* 4.4, 9.8, 6eq-H), 4.29 (1H, s, 1-H), 4.91 (1H, d, *J* 10.1, 11-H_{cis}), 5.00 (1H, dd, *J* 1.1, 17.2, 11-H_{trans}), 5.31 (1H, dd, *J* 1.6, 11.0, 8-H_{cis}), 5.45 (1H, s, 12-H), 5.56 (1H, dd, *J* 1.6, 17.2, 8-H_{trans}), 5.91-6.10 (2H, 7-H and 10-H), 7.27-7.51 (5H, Ph); δ_C (62.9 MHz, $CDCl_3$) 31.4 (CH_2, C9), 46.3 (CH, C3), 55.7 (CH_3, OMe), 64.9 (CH, C5), 69.7 (CH_2, C6), 75.9 (C, C2), 80.9 (CH, C4), 101.9 (CH, C12), 103.2 (CH, C1), 115.3 (CH_2, C11), 117.4 (CH_2, C8), 126.5 (CH, Ph), 128.6 (CH, Ph), 129.3 (CH, Ph), 136.4 (CH, C10), 138.1 (C, Ph), 139.4 (CH, C7); *m/z* (FAB) 333 (MH^+, 39%) (found MH^+, 333.1703; $C_{19}H_{25}O_5$ requires 333.1702).

298a - R_f 0.46, petroleum ether-diethyl ether (1:1); $[\alpha]^{20}_D$ + 12.9° (*c* 10.35, $CHCl_3$); υ_{max} ($CHCl_3$)/cm^{-1} 3570w, 3010m, 2930m, 1640w, 1205s, 1065s, 1000s; δ_H (250 MHz, $CDCl_3$) 2.08-2.40 (3H, 3-H and 9-H), 2.33 (1H, s, overlapping, O*H*), 3.25 (3H, s, OMe), 3.68-3.91 (3H, 4-H, 5-H and 6ax-H), 4.09 (1H, s, 1-H), 4.18 (1H, dd, *J* 4.4, 9.8, 6eq-H), 4.85-5.04 (2H, 11-H), 5.18 (1H, d, *J* 11.0, 8-H_{cis}), 5.36 (1H, d, *J* 17.3, 8-H_{trans}), 5.45 (1H, s, 12-H), 5.80-6.07 (2H, 7-H and 10-H), 7.22-7.49 (5H, Ph); δ_C (62.9 MHz, $CDCl_3$) 30.6 (CH_2, C9), 42.7 (CH, C3), 55.6 (CH_3, OMe), 65.1 (CH, C5), 69.7 (CH_2, C6), 77.9 (C, C2), 79.0 (CH, C4), 102.1 (CH, C12), 104.5 (CH, C1), 115.4 (CH_2, C11), 116.3 (CH_2, C8), 126.6 (CH, Ph), 128.6 (CH, Ph), 129.2 (CH, Ph), 138.4 (C, Ph), 138.8 (CH, C10), 140.7 (CH, C7); *m/z* (FAB) 333 (MH^+, 72%) (found MH^+, 333.1701; $C_{19}H_{25}O_5$ requires 333.1702).

Methyl (*R*)-4,6-*O*-Benzylidene-2-*C*-ethenyl-3-deoxy-3-*C*-methyl-3-*C*-propenyl-α-D-glucopyranoside (297b) and Methyl (*R*)-4,6-*O*-Benzylidene-2-*C*-ethenyl-3-deoxy-3-*C*-methyl-3-*C*-propenyl-α-D-mannopyranoside (298b).



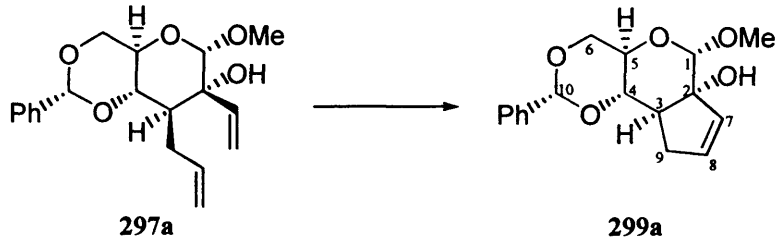
177 **297b** **298b**

Vinylmagnesium chloride (2.00 mL, 3.37 mmol, 15% wt. solution in THF) was added dropwise to an ice-cooled stirred solution of the ketone **177** (729 mg, 2.29 mmol) in dry THF (6.0 mL). The solution was heated under reflux for 2 h and allowed to cool to room temperature, then quenched by dropwise addition of water (20 mL). The resulting mixture was diluted with water (50 mL), extracted into diethyl ether (2 × 75 mL), and the combined organic layers were washed with water (50 mL), followed by saturated sodium chloride solution (50 mL), dried, and evaporated to leave a yellow oil. Chromatography on silica gel with petroleum ether-diethyl ether (3:1) as the eluent yielded **297b** as a colourless oil (518 mg, 65%) and **298b** as a colourless oil (118 mg, 15%): **297b** - R_f 0.62, petroleum ether-diethyl ether (1:1); $[\alpha]^{20}_D$ + 26.6° (*c* 0.7, $CHCl_3$); υ_{max} ($CHCl_3$)/cm^{-1} 3570w, 3010m, 2930m, 1640w, 1205s, 1065s, 1000s; δ_H (250 MHz, $CDCl_3$) 1.23 (3H, s, C3-Me), 2.13-2.32 (2H, m, 9-H), 2.71 (1H, d, *J* 1.3, O*H*), 3.37 (3H, s, OMe), 3.55 (1H, d, *J* 9.8, 4-H), 3.71 (1H, t, *J* 10.1, 6ax-H), 3.95 (1H, ddd, *J* 5.0, 9.8, 10.1, 5-H), 4.27 (1H, s, 1-H), 4.30

(1H, dd, overlapping, *J* 5.0, 10.1, 6eq-H), 4.88-5.00 (2H, m, 11-H), 5.25 (1H, dd, *J* 1.9, 11.0, 8-H_{cis}), 5.49 (1H, s, 12-H), 5.56 (1H, dd, *J* 1.9, 17.2, 8-H_{trans}), 5.90-6.24 (2H, 7-H and 10-H), 7.28-7.53 (5H, Ph); δ_C (62.9 MHz, $CDCl_3$) 14.2 (CH_3, C3-Me), 41.9 (CH_2, C9), 44.1 (C, C3), 56.3 (CH_3, OMe), 60.4 (CH, C5), 70.0 (CH_2, C6), 76.8 (C, C2), 82.9 (CH, C4), 101.9 (CH, C12), 105.0 (CH, C1), 115.5 (CH_2, C11), 116.7 (CH_2, C8), 126.6 (CH, Ph), 128.6 (CH, Ph), 129.3 (CH, Ph), 136.7 (CH, C10), 138.3 (C, Ph), 138.7 (CH, C7); *m/z* (FAB) 347 (MH^+, 20%) (found MH^+, 347.1858; $C_{20}H_{27}O_5$ requires 347.1859).

298b - R_f 0.38, petroleum ether-diethyl ether (1:1); υ_{max} ($CHCl_3$)/cm^{-1} 3570w, 3010m, 2930m, 1640w, 1205s, 1065s, 1000s; δ_H (250 MHz, $CDCl_3$) 1.26 (3H, s, C3-Me), 2.12-2.48 (3H, 9-H and O*H*), 3.36 (3H, s, OMe), 3.72-3.90 (1H, m, 5-H), 3.94-4.10 (2H, 4-H and 6ax-H), 4.15 (1H, s, 1-H), 4.30 (1H, dd, *J* 5.0, 10.1, 6eq-H), 4.92-5.10 (2H, m, 11-H), 5.32 (1H, d, *J* 10.0, 8-H_{cis}), 5.44 (1H, d, *J* 17.0, 8-H_{trans}), 5.58 (1H, s, 12-H), 5.97-6.19 (1H, m, 10-H), 6.24 (1H, dd, *J* 10.0, 17.0, 7-H), 7.30-7.56 (5H, Ph); δ_C (62.9 MHz, $CDCl_3$) 16.3 (CH_3, C3-Me), 40.7 (CH_2, C9), 43.3 (C, C3), 56.2 (CH_3, OMe), 60.8 (CH, C5), 69.9 (CH_2, C6), 79.0 (C, C2), 80.5 (CH, C4), 101.9 (CH, C12), 106.3 (CH, C1), 116.0 (CH_2, C11), 117.2 (CH_2, C8), 126.5 (CH, Ph), 128.6 (CH, Ph), 129.2 (CH, Ph), 137.6 (CH, C10), 138.0 (CH, C7), 138.4 (C, Ph); *m/z* (FAB) 347 (MH^+, 34%) (found MH^+, 347.1859; $C_{20}H_{27}O_5$ requires 347.1859).

Methyl (*R*)-4,6-*O*-Benzylidene-2,3-*C*-(propene-1-ylidene-3-yl)-3-deoxy-α-D-glucopyranoside (299a).

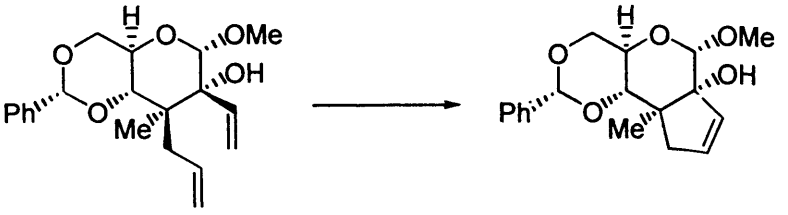


297a **299a**

Nitrogen gas was bubbled through a solution of the diene **297a** (106 mg, 0.32 mmol) in dry benzene (10 mL) for 2-3 minutes. The catalyst **196b** (8 mg, 0.0097 mmol, 3.0 mol%) was added and the solution heated at 60 °C for 48 h. The solvent was removed under reduced pressure to leave a dark brown oil. Chromatography on silica gel with petroleum ether-diethyl ether (3:1 to 2:1) as the eluent yielded starting material **297a** as a colourless oil (79 mg, 75%) and **299a** as a white solid (15 mg, 15%): mp 148-150 °C (petroleum

ether/diethyl ether); R_f 0.15, petroleum ether-diethyl ether (1:1); $[\alpha]^{20}_D$ + 28.5° (*c* 0.9, $CHCl_3$); υ_{max} ($CHCl_3$)/cm^{-1} 3540w, 3010m, 2940m, 1205s, 1085s, 1015s; δ_H (400 MHz, $CDCl_3$) 2.35 (1H, dt, *J* 5.0, 9.8, 3-H), 2.38-2.45 (1H, m, overlapping, CH*H*, 9-H), 2.80-2.89 (1H, m, C*H*H, 9-H), 2.86 (1H, s, overlapping, O*H*), 3.12 (1H, t, *J* 9.8, 4-H), 3.53 (3H, s, OMe), 3.66 (1H, t, *J* 10.3, 6ax-H), 3.90 (1H, ddd, *J* 5.1, 9.8, 10.3, 5-H), 4.31 (1H, dd, *J* 5.1, 10.3, 6eq-H), 4.76 (1H, s, 1-H), 5.47 (1H, s, 10-H), 5.78-5.83 (1H, m, 7-H), 6.17-6.22 (1H, m, 8-H), 7.33-7.52 (5H, Ph); δ_C (100.6 MHz, $CDCl_3$) 35.2 (CH_2, C9), 48.0 (CH, C3), 55.8 (CH_3, OMe), 61.8 (CH, C5), 69.7 (CH_2, C6), 81.5 (CH, C4), 83.5 (C, C2), 100.2 (CH, C10), 102.4 (CH, C1), 126.6 (CH, Ph), 128.7 (CH, Ph), 129.5 (CH, Ph), 133.7 (CH, C8), 138.0 (C, Ph), 138.0 (CH, C7); *m/z* (CI) 305 (MH^+, 100%) (found MH^+, 305.1388; $C_{17}H_{21}O_5$ requires 305.1389). Anal. Found: C, 64.36; H, 6.68. $C_{17}H_{20}O_5$ requires C, 67.09; H, 6.62%.

Methyl (*R*)-4,6-*O*-Benzylidene-2,3-*C*-(propene-1-ylidene-3-yl)-3-deoxy-3-*C*-methyl-α-D-glucopyranoside (299b).

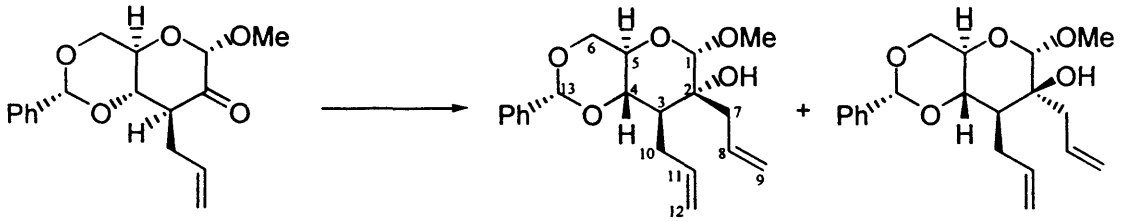


297b **299b**

Nitrogen gas was bubbled through a solution of the diene **297b** (124 mg, 0.36 mmol) in dry benzene (10 mL) for 2-3 minutes. The catalyst **196b** (10 mg, 0.012 mmol, 3.4 mol%) was added and the solution heated at 60 °C for 17 h. The solvent was removed under reduced pressure to leave a dark brown oil. Chromatography on silica gel with petroleum ether-diethyl ether (2:1) as the eluent yielded **299b** as a white solid (112 mg, 98%): mp 107-108 °C (petroleum ether/diethyl ether); R_f 0.21, petroleum ether-diethyl ether (1:1); $[\alpha]^{20}_D$ + 39.5° (*c* 5.95, $CHCl_3$); υ_{max} ($CHCl_3$)/cm^{-1} 3540w, 3010m, 2940m, 1205s, 1085s, 1015s; δ_H (250 MHz, $CDCl_3$) 1.31 (3H, s, C3-Me), 2.38 (1H, dt, *J* 2.1, 16.8, CH*H*, 9-H), 2.52 (1H, dd, *J* 1.6, 16.8, C*H*H, 9-H), 2.81 (1H, s, O*H*), 3.33 (1H, d, *J* 9.9, 4-H), 3.47 (3H, s, OMe), 3.69 (1H, t, *J* 10.3, 6ax-H), 3.93 (1H, ddd, *J* 5.1, 9.9, 10.3, 5-H), 4.31 (1H, dd, *J* 5.1, 10.3, 6eq-H), 4.71 (1H, s, 1-H), 5.47 (1H, s, 10-H), 5.74-5.84 (1H, m, 7-H), 6.09-6.19 (1H, m, 8-H), 7.32-7.57 (5H, Ph); δ_C (62.9 MHz, $CDCl_3$) 13.4 (CH_3, C3-Me), 43.1 (CH_2, C9), 48.3

(C, C3), 56.0 (CH_3, OMe), 58.8 (CH, C5), 69.8 (CH_2, C6), 82.6 (CH, C4), 82.9 (C, C2), 101.2 (CH, C10), 102.1 (CH, C1), 126.6 (CH, Ph), 128.6 (CH, Ph), 129.4 (CH, Ph), 134.6 (CH, C8), 137.9 (CH, C7), 138.3 (C, Ph); *m/z* (FAB) 319 (MH^+, 26%) (found MH^+, 319.1545; $C_{18}H_{23}O_5$ requires 319.1546). Anal. Found: C, 67.68; H, 6.92. $C_{18}H_{22}O_5$ requires C, 67.91; H, 6.96%.

Methyl (*R*)-4,6-*O*-Benzylidene-2-*C*-propenyl-3-deoxy-3-*C*-propenyl-α-D-glucopyranoside (300) and Methyl (*R*)-4,6-*O*-Benzylidene-2-*C*-propenyl-3-deoxy-3-*C*-propenyl-α-D-mannopyranoside (301).

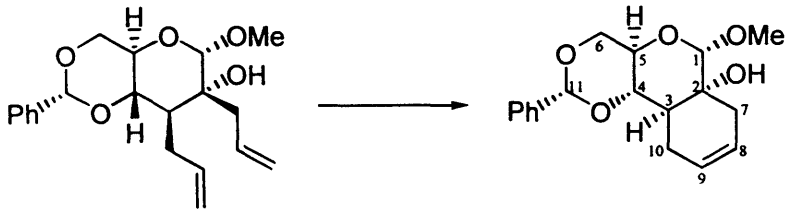


Allylmagnesium chloride (9.94 mL, 19.88 mmol, 2M solution in THF) was added dropwise to an ice-cooled stirred solution of the ketone **176** (2.00 g, 6.58 mmol) in dry THF (7.0 mL). The solution was heated under reflux for 2 h and allowed to cool to room temperature, then quenched by portionwise addition to ice/water (300 mL). The resulting mixture was treated with saturated ammonium chloride solution (30 mL), extracted into diethyl ether (2 × 150 mL), and the combined organic layers were washed with water (300 mL), followed by saturated sodium chloride solution (300 mL), dried, and evaporated to leave a yellow oil. Chromatography on silica gel with petroleum ether-diethyl ether (4:1) as the eluent yielded **300** as a colourless oil (1.68 g, 74%) and **301** as a colourless oil (344 mg, 15%): **300** - R_f 0.68, petroleum ether-diethyl ether (1:1); $[\alpha]^{20}_D$ + 75.9° (*c* 4.8, $CHCl_3$); υ_{max} ($CHCl_3$)/cm^{-1} 3570w, 3010m, 2930m, 1640w, 1205s, 1070s, 1000s; δ_H (250 MHz, $CDCl_3$) 2.32-2.78 (6H, 3-H, 7-H, 10-H and O*H*), 3.60 (3H, s, OMe), 3.64 (1H, dd, overlapping, *J* 9.1, 10.7, 4-H), 3.88-4.05 (2H, 5-H and 6ax-H), 4.40-4.49 (1H, m, 6eq-H), 4.68 (1H, s, 1-H), 5.10-5.40 (4H, 9-H and 12-H), 5.70 (1H, s, 13-H), 6.05-6.33 (2H, 8-H and 11-H), 7.53-7.69 (5H, Ph); δ_C (62.9 MHz, $CDCl_3$) 31.3 (CH_2, C10), 36.6 (CH_2, C7), 46.6 (CH, C3), 55.7 (CH_3, OMe), 64.8 (CH, C5), 69.8 (CH_2, C6), 74.7 (C, C2), 81.1 (CH, C4), 101.0 (CH, C1), 101.9 (CH, C13), 115.3 (CH_2, C9), 119.0 (CH_2, C12), 126.5 (CH,

Ph), 128.6 (CH, Ph), 129.2 (CH, Ph), 133.6 (CH, C11), 138.1 (C, Ph), 139.3 (CH, C8); *m/z* (FAB) 347 (MH^+, 34%) (found MH^+, 347.1858; $C_{20}H_{27}O_5$ requires 347.1859).

301 - R_f 0.40, petroleum ether-diethyl ether (1:1); $[\alpha]^{20}_D$ + 9.6° (*c* 5.8, $CHCl_3$); υ_{max} ($CHCl_3$)/cm^{-1} 3570w, 3010m, 2930m, 1640w, 1205s, 1070s, 1000s; δ_H (250 MHz, $CDCl_3$) 2.00-2.16 (2H, 3-H and O*H*), 2.26-2.59 (4H, 7-H and 10-H), 3.33 (3H, s, OMe), 3.64-3.91 (3H, 4-H, 5-H and 6ax-H), 4.22 (1H, dd, *J* 4.1, 9.8, 6eq-H), 4.25 (1H, s, overlapping, 1-H), 4.92-5.22 (4H, 9-H and 12-H), 5.50 (1H, s, 13-H), 5.71-6.10 (2H, 8-H and 11-H), 7.25-7.52 (5H, Ph); δ_C (62.9 MHz, $CDCl_3$) 29.4 (CH_2, C10), 41.5 (CH_2, C7), 43.6 (CH, C3), 55.3 (CH_3, OMe), 65.1 (CH, C5), 69.7 (CH_2, C6), 76.4 (C, C2), 78.7 (CH, C4), 102.1 (CH, C1), 102.9 (CH, C13), 115.9 (CH_2, C9), 119.7 (CH_2, C12), 126.5 (CH, Ph), 128.6 (CH, Ph), 129.2 (CH, Ph), 133.1 (CH, C11), 138.3 (C, Ph), 139.1 (CH, C8); *m/z* (FAB) 347 (MH^+, 60%) (found MH^+, 347.1859; $C_{20}H_{27}O_5$ requires 347.1859).

Methyl (*R*)-4,6-*O*-Benzylidene-2,3-*C*-(but-2-ene-1,4-diyl)-3-deoxy-α-D-glucopyranoside (302).

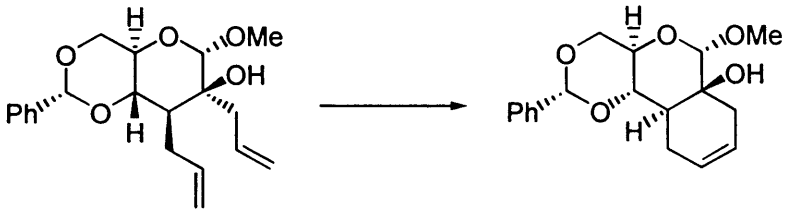


300 **302**

Nitrogen gas was bubbled through a solution of the diene **300** (101 mg, 0.29 mmol) in dry benzene (10 mL) for 2-3 minutes. The catalyst **196b** (8 mg, 0.0097 mmol, 3.3 mol%) was added and the solution heated at 60 °C for 17 h. The solvent was removed under reduced pressure to leave a dark brown oil. Chromatography on silica gel with petroleum ether-diethyl ether (3:1 to 2:1) as the eluent yielded **302** as a white solid (83 mg, 89%): mp 142-143 °C (petroleum ether/diethyl ether); R_f 0.19, petroleum ether-diethyl ether (1:1); $[\alpha]^{20}_D$ + 33.6° (*c* 8.3, $CHCl_3$); υ_{max} ($CHCl_3$)/cm^{-1} 3570w, 3010m, 2920m, 1205s, 1060s, 1000s; δ_H (250 MHz, $CDCl_3$) 1.98–2.13 (1H, m, CH*H*, 7-H), 2.19-2.58 (5H, 3-H, C*H*H, 7-H, 10-H and O*H*), 3.41 (1H, dd, *J* 9.1, 10.7, 4-H), 3.50 (3H, s, OMe), 3.68-3.86 (2H, 5-H and 6ax-H), 4.27 (1H, dd, *J* 3.5, 9.1, 6eq-H), 4.32 (1H, s, 1-H), 5.51 (1H, s, 11-H), 5.61-5.79 (2H, 8-H and 9-H), 7.34-7.54 (5H, Ph); δ_C (62.9 MHz, $CDCl_3$) 18.8 (CH_2, C10), 30.8 (CH_2, C7), 38.2 (CH, C3), 54.4 (CH_3, OMe), 63.7 (CH, C5), 68.3 (CH_2, C6), 69.1 (C, C2), 76.1

(CH, C4), 100.6 (CH, C11), 101.8 (CH, C1), 121.4 (CH, C8), 123.5 (CH, C9), 125.1 (CH, Ph), 127.2 (CH, Ph), 127.9 (CH, Ph), 136.6 (C, Ph); *m/z* (FAB) 319 (MH^+, 100%) (found MH^+, 319.1547; $C_{18}H_{23}O_5$ requires 319.1546). Anal. Found: C, 67.75; H, 7.05. $C_{18}H_{22}O_5$ requires C, 67.91; H, 6.96%.

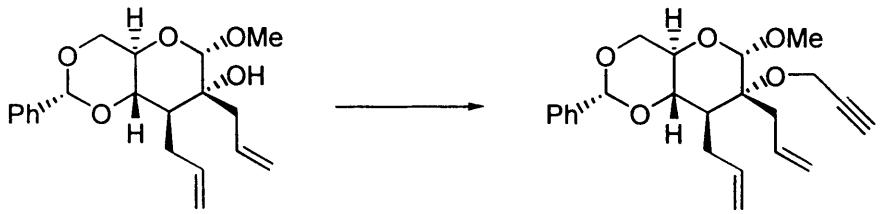
Methyl (*R*)-4,6-*O*-Benzylidene-2,3-*C*-(but-2-ene-1,4-diyl)-3-deoxy-α-D-mannopyranoside (303).



301 **303**

Nitrogen gas was bubbled through a solution of the diene **301** (86 mg, 0.25 mmol) in dry benzene (10 mL) for 2-3 minutes. The catalyst **196b** (8 mg, 0.0097 mmol, 3.9 mol%) was added and the solution heated at 60 °C for 17 h. The solvent was removed under reduced pressure to leave a dark brown oil. Chromatography on silica gel with petroleum ether-diethyl ether (3:1 to 2:1) as the eluent yielded **303** as a colourless oil (63 mg, 80%): R_f 0.13, petroleum ether-diethyl ether (1:1); $[\alpha]^{18}_D$ + 8.8° (*c* 6.0, $CHCl_3$); υ_{max} ($CHCl_3$)/cm^{-1} 3570w, 3010m, 2920m, 1205s, 1060s, 1000s; δ_H (250 MHz; $CDCl_3$) 1.86 (1H, dd, *J* 4.4, 18.2, CH*H*, 7-H), 1.94-2.10 (1H, m, CH*H*, 10-H), 2.04 (1H, s, overlapping, O*H*), 2.16 (1H, dt, *J* 5.2, 10.6, 3-H), 2.40-2.55 (1H, m, C*H*H, 10-H), 2.51-2.67 (1H, m, overlapping, C*H*H, 7-H), 3.41 (3H, s, OMe), 3.65 (1H, t, *J* 10.6, 4-H), 3.76-3.94 (1H, t, *J* 9.0, 6ax-H; 1H, m, overlapping, 5-H), 4.25 (1H, dd, *J* 3.6, 9.0, 6eq-H), 4.39 (1H, s, 1-H), 5.53 (1H, s, 11-H), 5.54-5.68 (1H, m, 8-H), 5.70-5.82 (1H, m, 9-H), 7.30-7.53 (5H, Ph); δ_C (62.9 MHz, $CDCl_3$) 24.4 (CH_2, C10), 34.3 (CH_2, C7), 37.6 (CH, C3), 55.5 (CH_3, OMe), 64.5 (CH, C5), 69.7 (CH_2, C6), 71.9 (C, C2), 80.2 (CH, C4), 102.3 (CH, C11), 103.3 (CH, C1), 123.5 (CH, C8), 126.1 (CH, C9), 126.5 (CH, Ph), 128.6 (CH, Ph), 129.3 (CH, Ph), 138.2 (C, Ph); *m/z* (FAB) 319 (MH^+, 34%) (found MH^+, 319.1544; $C_{18}H_{23}O_5$ requires 319.1546).

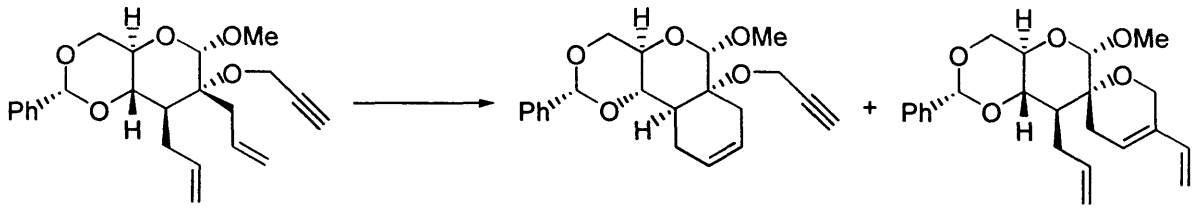
Methyl (*R*)-4,6-*O*-Benzylidene-2-*C*-propenyl-2-*O*-propargyl-3-deoxy-3-*C*-propenyl-α-D-glucopyranoside (304).



A suspension of sodium hydride (46.5 mg, 60% dispersion in mineral oil, 1.16 mmol) in dry THF (3.0 mL) was heated under reflux for 1.25 h. Diene **300** (200 mg, 0.58 mmol) in dry THF (5.0 mL) was added dropwise to the reaction mixture at 0 °C, then the reaction was heated under reflux for 1.5 h. A solution of propargyl bromide (129 μL, 80% wt. solution in toluene, 1.16 mmol) and DMPU (100 μL) in dry THF (3.0 mL) was added dropwise to the reaction mixture at 0 °C, then the reaction was heated under reflux for 4 h. A spatula end of potassium iodide was added to the reaction mixture (to make the more reactive propargyl iodide), then the reaction was heated at reflux overnight. At this point, because the reaction was slow, further portions of sodium hydride (46.5 mg, 60% dispersion in mineral oil, 1.16 mmol) and propargyl bromide (129 μL, 80% wt. solution in toluene, 1.16 mmol) were added to the reaction mixture at room temperature, then the reaction was heated under reflux for 5 h. The mixture was allowed to cool to room temperature, then quenched by portionwise addition to ice/water (100 mL). The resulting mixture was extracted with diethyl ether (2 × 75 mL), the combined organic layers washed with saturated sodium chloride solution (100 mL), dried, and evaporated to leave a brown oil. Chromatography on silica gel with petroleum ether-diethyl ether (7:1) as the eluent yielded starting material **300** as a colourless oil (66 mg, 33%) and **304** as a colourless oil (124 mg, 56%): R_f 0.44, petroleum ether-diethyl ether (4:1); δ_H (250 MHz, $CDCl_3$) 2.15-2.69 (6H, 3-H, 7-H, 12-H and 13-H), 3.39 (3H, s, OMe), 3.59 (1H, t, *J* 9.8, 4-H), 3.69-3.90 (2H, 5-H and 6ax-H), 4.16 (1H, dd, *J* 2.2, 15.1, CH*H*, 10-H), 4.25 (1H, dd, *J* 3.3, 9.0, 6eq-H), 4.49 (1H, dd, *J* 2.5, 15.1, C*H*H, 10-H), 4.57 (1H, s, 1-H), 4.90-5.20 (4H, 9-H and 15-H), 5.53 (1H, s, 16-H), 5.90-6.13 (2H, 8-H and 14-H), 7.30-7.55 (5H, Ph); δ_C (62.9 MHz, $CDCl_3$) 31.8 (CH_2, C13), 38.6 (CH_2, C7), 40.2 (CH, C3), 53.1 (CH_2, C10), 55.3 (CH_3, OMe), 64.6 (CH, C5), 69.9 (CH_2, C6), 73.1 (C, C2), 79.5 (C, C11), 81.8 (CH, C12), 82.4 (CH, C4), 101.9 (CH, C1), 102.1 (CH, C16), 115.8 (CH_2, C9), 118.7 (CH_2, C15), 126.4

(CH, Ph), 128.6 (CH, Ph), 129.2 (CH, Ph), 133.9 (CH, C14), 138.0 (C, Ph), 138.6 (CH, C8); *m/z* (FAB) 385 (MH^+, 27%) (found MH^+, 385.2016; $C_{23}H_{29}O_5$ requires 385.2015).

Methyl (*R*)-4,6-*O*-Benzylidene-2,3-*C*-(but-2-ene-1,4-diyl)-2-*O*-propargyl-3-deoxy-α-D-glucopyranoside (306) and Methyl (*R*)-4,6-*O*-Benzylidene-2(*R*)-spiro(2,6'-5',6'-dihydro-2'H-3'-ethenyl-pyran)-3-*C*-propenyl-2,3-dideoxy-α-D-glucopyranoside (307).



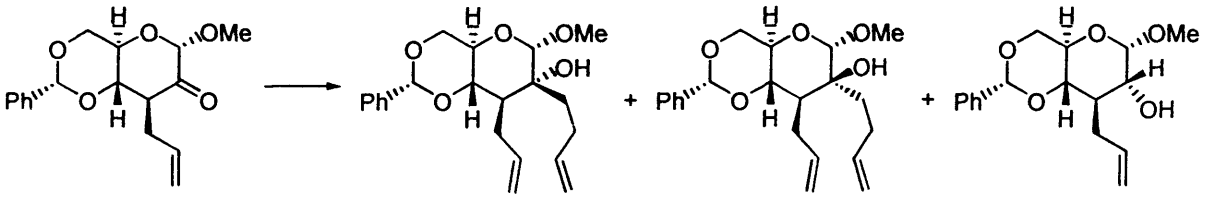
304 **306** **307**

Nitrogen gas was bubbled through a solution of **304** (123 mg, 0.32 mmol) in dry benzene (10 mL) for 2-3 minutes. The catalyst **196b** (16 mg, 0.0195 mmol, 6.1 mol%) was added and the solution heated at 60 °C for 6.5 h. The solvent was removed under reduced pressure to leave a dark brown oil. Chromatography on silica gel with petroleum ether-diethyl ether (4:1) as the eluent yielded **306** as a white solid (51 mg, 45%) and **307** as a white solid (24 mg, 20%): **306** - R_f 0.30, petroleum ether-diethyl ether (4:1) (ran twice); $[\alpha]^{20}_D$ + 16.2° (*c* 2.3, $CHCl_3$); υ_{max} ($CHCl_3$)/cm^{-1} 3310w, 3010m, 2920w, 1205s, 1090s, 1060s; δ_H (250 MHz, $CDCl_3$) 2.14-2.56 (6H, 3-H, 7-H, 10-H and 13-H), 3.47 (3H, s, OMe), 3.47 (1H, t, overlapping, *J* 9.9, 4-H), 3.71 (1H, t, *J* 10.1, 6ax-H), 3.75-3.89 (1H, m, overlapping, 5-H), 4.21 (1H, dd, *J* 2.5, 15.7, CH*H*, 11-H), 4.25 (1H, dd, overlapping, *J* 3.5, 9.1, 6eq-H), 4.38 (1H, dd, *J* 2.2, 15.7, C*H*H, 11-H), 4.52 (1H, s, 1-H), 5.50 (1H, s, 14-H), 5.53-5.77 (2H, 8-H and 9-H), 7.30-7.54 (5H, Ph); δ_C (62.9 MHz, $CDCl_3$) 20.4 (CH_2, C10), 29.3 (CH_2, C7), 36.1 (CH, C3), 51.3 (CH_2, C11), 55.1 (CH_3, OMe), 64.3 (CH, C5), 69.3 (CH_2, C6), 73.3 (C, C2), 75.5 (C, C12), 77.4 (CH, C4), 81.4 (CH, C13), 101.7 (CH, C14), 102.2 (CH, C1), 121.7 (CH, C8), 125.3 (CH, C9), 126.1 (CH, Ph), 128.3 (CH, Ph), 129.0 (CH, Ph), 137.6 (C, Ph); *m/z* (FAB) 357 (MH^+, 22%) (found MH^+, 357.1702; $C_{21}H_{25}O_5$ requires 357.1702).

307 - R_f 0.45, petroleum ether-diethyl ether (4:1) (ran twice); $[\alpha]^{20}_D$ + 75.9° (*c* 2.3, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.18-2.36 (2H, CH*H*, 10-H and CH*H*, 11-H), 2.37-2.45 (1H, m, 3-H), 2.49-2.60 (2H, C*H*H, 10-H and C*H*H, 11-H), 3.44 (1H, dd, *J* 9.3, 11.2, 4-H), 3.47 (3H, s, OMe), 3.72 (1H, t, *J* 10.3, 6ax-H), 3.81-3.90 (1H, m, 5-H), 4.22-4.31 (2H, 6eq-H and

CH*H*, 7-H), 4.40 (1H, br d, *J* 16.1, C*H*H, 7-H), 4.64 (1H, s, 1-H), 4.89-5.09 (4H, 13-H and 15-H), 5.54 (1H, s, 16-H), 5.76-5.83 (1H, m, 9-H), 5.96-6.09 (1H, m, 12-H), 6.27 (1H, dd, *J* 11.1, 17.9, 14-H), 7.32-7.54 (5H, Ph); δ_C (100.6 MHz, $CDCl_3$) 26.9 (CH_2, C10), 31.3 (CH_2, C11), 44.2 (CH, C3), 55.6 (CH_3, OMe), 60.8 (CH_2, C7), 64.9 (CH, C5), 69.7 (CH_2, C6), 75.1 (C, C2), 80.8 (CH, C4), 98.9 (CH, C1), 101.9 (CH, C16), 111.8 (CH_2, C13), 115.1 (CH_2, C15), 123.8 (CH, C9), 126.4 (CH, Ph), 128.6 (CH, Ph), 129.2 (CH, Ph), 134.8 (C, C8), 135.8 (CH, C14), 138.0 (C, Ph), 139.1 (CH, C12); *m/z* (FAB) 385 (MH^+, 5%) (found MH^+, 385.2013; $C_{23}H_{29}O_5$ requires 385.2015).

Methyl (*R*)-4,6-*O*-Benzylidene-2-*C*-but-3-enyl-3-deoxy-3-*C*-propenyl-α-D-glucopyranoside (308), Methyl (*R*)-4,6-*O*-Benzylidene-2-*C*-but-3-enyl-3-deoxy-3-*C*-propenyl-α-D-mannopyranoside (309) and Methyl (*R*)-4,6-*O*-Benzylidene-3-deoxy-3-*C*-propenyl-α-D-glucopyranoside (310).



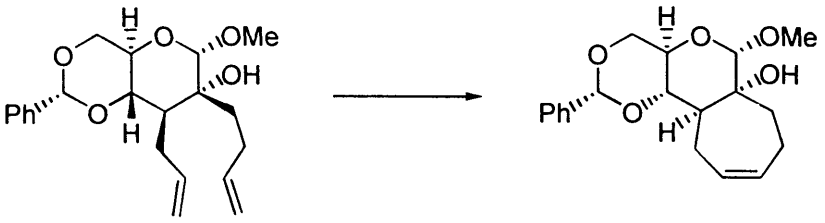
Anhydrous cerium(III) chloride (2.03 g, 8.23 mmol) in dry diethyl ether (4.0 mL) was stirred at room temperature for 1.5 h. In another flask, 4-bromo-1-butene (0.835 mL, 8.23 mmol) in dry diethyl ether (5.0 mL) was added dropwise to magnesium turnings (220 mg, 9.05 mmol) in dry diethyl ether (4.0 mL) at 0 °C. This mixture was stirred at 0 °C for 0.25 h and then at room temperature for 1 h. The cerium(III) chloride mixture was cooled to -78 °C, the freshly prepared Grignard added dropwise via a cannula, and the resulting mixture stirred at -78 °C for 2 h. Ketone **176** (500 mg, 1.64 mmol) in dry diethyl ether (6.0 mL) was added dropwise via a cannula to the cooled (-78 °C) reaction mixture. The mixture was stirred at -40 °C for 1.5 h, then added portionwise to ice/water (150 mL) and saturated ammonium chloride solution (50 mL). The mixture was extracted into dichloromethane (2 × 100 mL), and the combined organic layers were washed with saturated sodium chloride solution (200 mL), dried, and evaporated to leave a yellow oil. Chromatography on silica gel with petroleum ether-diethyl ether (3:1 to 2:1) as the eluent yielded **308** as a colourless oil (120 mg, 20%), **309** as a colourless oil (39 mg, 7%) and the reduced product **310** as a white solid (252 mg, 50%): **308** - R_f 0.60, petroleum ether-diethyl ether (1:1); $[\alpha]^{20}_D$ +

43.1° (*c* 2.1, $CHCl_3$); υ_{max} ($CHCl_3$)/cm^{-1} 3560w, 3010m, 2940m, 1640w, 1205s, 1075s, 1000s; δ_H (250 MHz, $CDCl_3$) 1.62-1.88 (2H, m, 7-H), 2.00-2.61 (5H, 3-H, 8-H and 11-H), 2.30 (1H, d, overlapping, *J* 1.6, O*H*), 3.40-3.57 (1H, m, 4-H), 3.47 (3H, s, overlapping, OMe), 3.65-3.90 (2H, 5-H and 6ax-H), 4.28 (1H, dd, *J* 3.2, 8.7, 6eq-H), 4.55 (1H, s, 1-H), 4.90-5.20 (4H, 10-H and 13-H), 5.53 (1H, s, 14-H), 5.78-6.18 (2H, 9-H and 12-H), 7.32-7.57 (5H, Ph); δ_C (62.9 MHz, $CDCl_3$) 27.5 (CH_2, C11), 30.9 (CH_2, C8), 31.3 (CH_2, C7), 46.8 (CH, C3), 55.8 (CH_3, OMe), 64.9 (CH, C5), 69.8 (CH_2, C6), 74.7 (C, C2), 81.2 (CH, C4), 100.7 (CH, C14), 101.9 (CH, C1), 115.1 (CH_2, C10), 115.1 (CH_2, C13), 126.5 (CH, Ph), 128.6 (CH, Ph), 129.2 (CH, Ph), 138.0 (C, Ph), 139.1 (CH, C12), 139.5 (CH, C9); *m/z* (FAB) 361 (MH^+, 32%) (found MH^+, 361.2015; $C_{21}H_{29}O_5$ requires 361.2015).

309 - R_f 0.24, petroleum ether-diethyl ether (1:1); υ_{max} ($CHCl_3$)/cm^{-1} 3560w, 3010m, 2940m, 1640w, 1205s, 1075s, 1000s; δ_H (250 MHz, $CDCl_3$) 1.60-2.63 (7H, 3-H, 7-H, 8-H and 11-H), 1.86 (1H, s, overlapping, O*H*), 3.40 (3H, s, OMe), 3.65-3.96 (3H, 4-H, 5-H and 6ax-H), 4.25 (1H, dd, *J* 3.3, 9.3, 6eq-H), 4.38 (1H, s, 1-H), 4.90-5.20 (4H, 10-H and 13-H), 5.55 (1H, s, 14-H), 5.72-6.16 (2H, 9-H and 12-H), 7.29-7.56 (5H, Ph); δ_C (62.9 MHz, $CDCl_3$) 27.2 (CH_2, C11), 29.2 (CH_2, C8), 36.2 (CH_2, C7), 43.8 (CH, C3), 55.3 (CH_3, OMe), 64.9 (CH, C5), 69.7 (CH_2, C6), 76.7 (C, C2), 78.4 (CH, C4), 102.2 (CH, C14), 102.5 (CH, C1), 115.1 (CH_2, C10), 116.2 (CH_2, C13), 126.5 (CH, Ph), 128.6 (CH, Ph), 129.2 (CH, Ph), 138.2 (C, Ph), 138.7 (CH, C12), 139.2 (CH, C9); *m/z* (FAB) 361 (MH^+, 28%) (found MH^+, 361.2015; $C_{21}H_{29}O_5$ requires 361.2015).

310 - mp 139-140 °C (petroleum ether/diethyl ether); $[\alpha]^{20}_D$ + 71.0° (*c* 0.52, $CHCl_3$); δ_H (250 MHz, $CDCl_3$) 1.92 (1H, d, *J* 11.0, O*H*), 2.02-2.18 (1H, m, 3-H), 2.42-2.58 (2H, m, 7-H), 3.32 (1H, dd, *J* 9.0, 10.8, 4-H), 3.46 (3H, s, OMe), 3.54 (1H, dt, *J* 3.8, 11.0, 2-H), 3.67 (1H, t, J 10.0, 6ax-H), 3.76 (1H, overlapping, ddd, *J* 4.0, 9.0, 10.0, 5-H), 4.27 (1H, dd, *J* 4.0, 10.0, 6eq-H), 4.68 (1H, d, *J* 3.8, 1-H), 5.05-5.23 (2H, m, 9-H), 5.48 (1H, s, 10-H), 5.84-6.06 (1H, m, 8-H), 7.29-7.57 (5H, Ph); δ_C (62.9 MHz, $CDCl_3$) 30.3 (CH_2, C7), 42.5 (CH, C3), 55.7 (CH_3, OMe), 64.1 (CH, C5), 69.7 (CH_2, C6), 70.2 (CH, C2), 78.6 (CH, C4), 99.8 (CH, C1), 101.8 (CH, C10), 118.2 (CH_2, C9), 126.5 (CH, Ph), 128.7 (CH, Ph), 129.3 (CH, Ph), 135.1 (CH, C8), 138.0 (C, Ph); *m/z* (FAB) 307 (MH^+, 54%) (found MH^+, 307.1546; $C_{17}H_{23}O_5$ requires 307.1546). Anal. Found: C, 65.94; H, 7.12. $C_{17}H_{22}O_5$ requires C, 66.65; H, 7.24%.

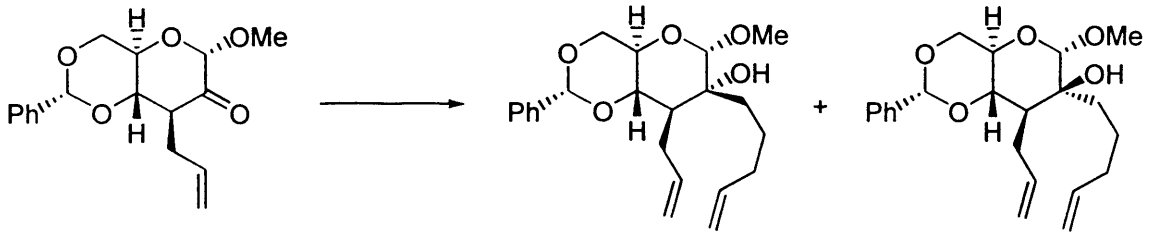
Methyl (*R*)-4,6-*O*-Benzylidene-2,3-*C*-(pent-3-ene-1,5-diyl)-3-deoxy-α-D-glucopyranoside (311).



308 **311**

Nitrogen gas was bubbled through a solution of the diene **308** (120 mg, 0.33 mmol) in dry benzene (10 mL) for 2-3 minutes. The catalyst **196b** (10 mg, 0.012 mmol, 3.6 mol%) was added and the solution heated at 60 °C for 17 h. The solvent was removed under reduced pressure to leave a dark brown oil. Chromatography on silica gel with petroleum ether-diethyl ether (3:1) as the eluent yielded **311** as a white solid (96 mg, 87%): mp 113-114 °C (petroleum ether/diethyl ether); R_f 0.32, petroleum ether-diethyl ether (1:1); $[\alpha]^{20}_D$ - 30.0° (*c* 3.6, $CHCl_3$); υ_{max} ($CHCl_3$)/cm^{-1} 3560w, 3010m, 2940m, 1710w, 1205s, 1120s, 1060s; δ_H (250 MHz, $CDCl_3$) 1.40–1.59 (1H, m, CH*H*, 7-H), 1.77-2.09 (2H, C*H*H, 7-H and CH*H*, 8-H), 2.09-2.22 (1H, m, 3-H), 2.24–2.43 (1H, m, CH*H*, 11-H), 2.49 (1H, d, *J* 2.1, O*H*), 2.54-2.83 (2H, C*H*H, 8-H and C*H*H, 11-H), 3.45 (3H, s, OMe), 3.62-3.90 (3H, 4-H, 5-H and 6ax-H), 4.13 (1H, s, 1-H), 4.27 (1H, dd, *J* 3.8, 9.3, 6eq-H), 5.48 (1H, s, 12-H), 5.68-5.85 (1H, m, 10-H), 5.93-6.10 (1H, m, 9-H), 7.31-7.57 (5H, Ph); δ_C (62.9 MHz, $CDCl_3$) 21.2 (CH_2, C11), 21.5 (CH_2, C8), 31.9 (CH_2, C7), 42.8 (CH, C3), 55.7 (CH_3, OMe), 65.3 (CH, C5), 69.8 (CH_2, C6), 75.1 (C, C2), 76.7 (CH, C4), 101.9 (CH, C12), 105.6 (CH, C1), 126.5 (CH, Ph), 128.6 (CH, Ph), 129.3 (CH, Ph), 129.8 (CH, C10), 133.7 (CH, C9), 138.2 (C, Ph); *m/z* (FAB) 333 (MH^+, 41%) (found MH^+, 333.1703; $C_{19}H_{25}O_5$ requires 333.1702). Anal. Found: C, 68.65; H, 7.26. $C_{19}H_{24}O_5$ requires C, 68.66; H, 7.28%.

Methyl (*R*)-4,6-*O*-Benzylidene-2-*C*-pent-4-enyl-3-deoxy-3-*C*-propenyl-α-D-glucopyranoside (312) and Methyl (*R*)-4,6-*O*-Benzylidene-2-*C*-pent-4-enyl-3-deoxy-3-*C*-propenyl-α-D-mannopyranoside (313).



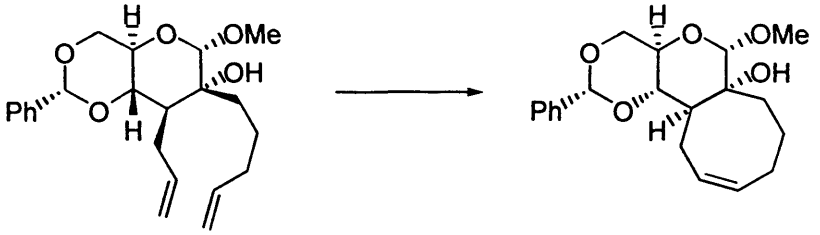
176 312 313

Anhydrous cerium(III) chloride (2.03 g, 8.23 mmol) in dry diethyl ether (4.0 mL) was stirred at room temperature for 1.5 h. In another flask, 5-bromo-1-pentene (0.975 mL, 8.23 mmol) in dry diethyl ether (5.0 mL) was added dropwise to magnesium turnings (220 mg, 9.05 mmol) in dry diethyl ether (4.0 mL) at 0 °C. This mixture was stirred at 0 °C for 0.25 h and then at room temperature for 1 h. The cerium(III) chloride mixture was cooled to -78 °C, the freshly prepared Grignard added dropwise via a cannula, and the resulting mixture stirred at -78 °C for 2 h. Ketone **176** (500 mg, 1.64 mmol) in dry diethyl ether (6.0 mL) was added dropwise via a cannula to the cooled (-78 °C) reaction mixture. The mixture was stirred at -40 °C for 2 h, then added portionwise to ice/water (150 mL) and saturated ammonium chioride solution (50 mL). The mixture was extracted into dichloromethane (2 × 100 mL), and the combined organic layers were washed with saturated sodium chloride solution (200 mL), dried, and evaporated to leave a yellow oil. Chromatography on silica gel with petroleum ether-diethyl ether (3:1 to 1:1) as the eluent yielded **312** as a colourless oil (465 mg, 76%) and the reduced product **310** as a white solid (83 mg, 16%): **312** - R_f 0.56, petroleum ether-diethyl ether (1:1); $[\alpha]^{20}_D$ + 47.3° (*c* 4.3, $CHCl_3$); υ_{max} ($CHCl_3$)/cm^{-1} 3570w, 3010m, 2940m, 1640w, 1205s, 1075s, 1000s; δ_H (250 MHz, $CDCl_3$) 1.22-1.78 (4H, 7-H and 8-H), 2.00-2.58 (5H, 3-H, 9-H and 12-H), 2.22 (1H, s, overlapping, O*H*), 3.46 (3H, s, OMe), 3.46 (1H, t, *J* 9.9, 4-H), 3.68-3.88 (2H, 5-H and 6ax-H), 4.26 (1H, dd, *J* 3.1, 8.6, 6eq-H), 4.54 (1H, s, 1-H), 4.89-5.13 (4H, 11-H and 14-H), 5.53 (1H, s, 15-H), 5.73-6.17 (2H, 10-H and 13-H), 7.30-7.56 (5H, Ph); δ_C (62.9 MHz, $CDCl_3$) 22.4 (CH_2, C8), 31.1 (CH_2, C9), 31.3 (CH_2, C12), 34.7 (CH_2, C7), 46.9 (CH, C3), 55.7 (CH_3, OMe), 64.9 (CH, C5), 69.8 (CH_2, C6), 74.9 (C, C2), 81.2 (CH, C4), 100.9 (CH, C1), 101.9 (CH, C15), 115.1 (CH_2, C14), 115.2 (CH_2, C11), 126.4 (CH, Ph), 128.6 (CH, Ph), 129.2 (CH,

Ph), 138.0 (C, Ph), 138.9 (CH, C13), 139.5 (CH, C10); *m/z* (FAB) 375 (MH^+, 19%) (found MH^+, 375.2172; $C_{22}H_{31}O_5$ requires 375.2172).

313 (obtained as a colourless oil in a 7% yield from a *normal* Grignard reaction) - R_f 0.39, petroleum ether-diethyl ether (1:1); $[\alpha]^{20}_D$ + 32.6° (*c* 1.8, $CHCl_3$); υ_{max} ($CHCl_3$)/cm^{-1} 3570w, 3010m, 2940m, 1640w, 1205s, 1075s, 1000s; δ_H (250 MHz, $CDCl_3$) 1.20-1.76 (4H, 7-H and 8-H), 1.82 (1H, s, O*H*), 1.95-2.61 (5H, 3-H, 9-H and 12-H), 3.37 (3H, s, OMe), 3.66-3.93 (3H, 4-H, 5-H and 6ax-H), 4.25 (1H, dd, *J* 3.1, 8.8, 6eq-H), 4.35 (1H, s, 1-H), 4.92-5.17 (4H, 11-H and 14-H), 5.54 (1H, s, 15-H), 5.71-6.13 (2H, 10-H and 13-H), 7.30-7.56 (5H, Ph); δ_C (62.9 MHz, $CDCl_3$) 21.9 (CH_2, C8), 29.2 (CH_2, C9), 34.5 (CH_2, C12), 36.6 (CH_2, C7), 43.7 (CH, C3), 55.4 (CH_3, OMe), 64.9 (CH, C5), 69.7 (CH_2, C6), 76.7 (C, C2), 78.4 (CH, C4), 102.1 (CH, C1), 102.6 (CH, C15), 115.2 (CH_2, C14), 116.2 (CH_2, C11), 126.4 (CH, Ph), 128.6 (CH, Ph), 129.2 (CH, Ph), 138.2 (C, Ph), 138.7 (CH, C13), 138.9 (CH, C10); *m/z* (FAB) 375 (MH^+, 45%) (found MH^+, 375.2172; $C_{22}H_{31}O_5$ requires 375.2172).

Methyl (*R*)-4,6-*O*-Benzylidene-2,3-*C*-(hex-4-ene-1,6-diyl)-3-deoxy-α-D-glucopyranoside (314).

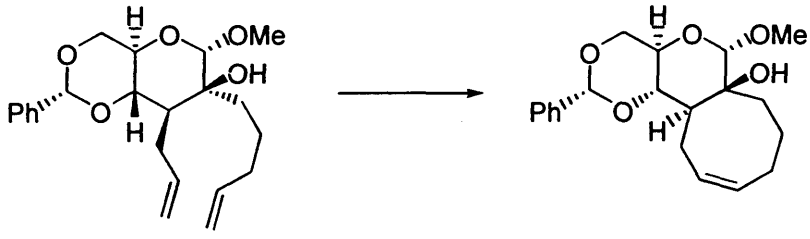


312 **314**

Nitrogen gas was bubbled through a solution of the diene **312** (144 mg, 0.39 mmol) in dry benzene (10 mL) for 2-3 minutes. The catalyst **196b** (10 mg, 0.012 mmol, 3.2 mol%) was added and the solution heated at 60 °C for 17 h. More catalyst **196b** (10 mg, 0.012 mmol, 3.2 mol%) was added and the solution heated at 60 °C for a further 48 h. The solvent was removed under reduced pressure to leave a dark brown oil. Chromatography on silica gel with petroleum ether-diethyl ether (4:1) as the eluent yielded starting material **312** as a colourless oil (43 mg, 30%) and **314** as a white solid (69 mg, 52%): mp 109-110 °C (petroleum ether/diethyl ether); R_f 0.40, petroleum ether-diethyl ether (1:1); $[\alpha]^{17}_D$ - 79.1° (*c* 2.4, $CHCl_3$); υ_{max} ($CHCl_3$)/cm^{-1} 3560w, 3010m, 2940m, 1205s, 1130s, 1060s; δ_H (400 MHz; $CDCl_3$) 1.39 (1H, dd, *J* 4.1, 11.0, CH*H*, 7-H), 1.44–1.56 (1H, m, CH*H*, 8-H), 1.93-

2.11 (3H, C*H*H, 7-H; C*H*H, 8-H and CH*H*, 9-H), 2.19-2.33 (2H, CH*H*, 12-H and 3-H), 2.26 (1H, s, overlapping, O*H*), 2.49-2.61 (1H, m, C*H*H, 9-H), 2.65 (1H, dd, *J* 8.4, 12.5, C*H*H, 12-H), 3.42 (3H, s, OMe), 3.60 (1H, dd, *J* 9.2, 10.8, 4-H), 3.71 (1H, t, *J* 9.6, 6ax-H), 3.79 (1H, ddd, *J* 4.1, 9.2, 9.6, 5-H), 4.17 (1H, s, 1-H), 4.25 (1H, dd, *J* 4.1, 9.6, 6eq-H), 5.53 (1H, s, 13-H), 5.68-5.78 (1H, m, 10-H), 5.80-5.90 (1H, m, 11-H), 7.31-7.54 (5H, Ph); δ_C (100.6 MHz, $CDCl_3$) 20.9 (CH_2, C12), 24.4 (CH_2, C8), 26.2 (CH_2, C9), 30.8 (CH_2, C7), 46.2 (CH, C3), 55.6 (CH_3, OMe), 65.3 (CH, C5), 69.9 (CH_2, C6), 74.7 (C, C2), 78.1 (CH, C4), 102.0 (CH, C13), 107.3 (CH, C1), 126.5 (CH, Ph), 128.7 (CH, Ph), 129.2 (CH, C11), 129.3 (CH, Ph), 132.7 (CH, C10), 138.1 (C, Ph); *m/z* (FAB) 347 (MH^+, 10%) (found MH^+, 347.1858; $C_{20}H_{27}O_5$ requires 347.1859). Anal. Found: C, 69.35; H, 7.35. $C_{20}H_{26}O_5$ requires C, 69.34; H, 7.56%.

Methyl (*R*)-4,6-*O*-Benzylidene-2,3-*C*-(hex-4-ene-1,6-diyl)-3-deoxy-α-D-mannopyranoside (315).

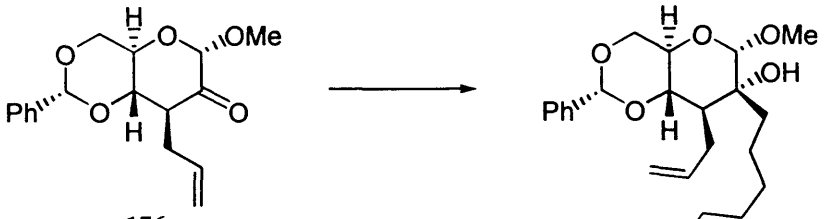


313 **315**

Nitrogen gas was bubbled through a solution of the diene **313** (42 mg, 0.11 mmol) in dry benzene (7 mL) for 2-3 minutes. The catalyst **196b** (8 mg, 0.010 mmol, 9.1 mol%) was added and the solution heated at 60 °C for 17 h and at 80 °C for a further 24 h. The solvent was removed under reduced pressure to leave a dark brown oil. Chromatography on silica gel with petroleum ether-diethyl ether (3:1) as the eluent yielded starting material **313** as a colourless oil (20 mg, 48%) and **315** as a white solid (10 mg, 26%): R_f 0.30, petroleum ether-diethyl ether (1:1); $[\alpha]^{19}_D$ + 47.5° (*c* 0.5, $CHCl_3$); υ_{max} ($CHCl_3$)/cm^{-1} 3560w, 3010m, 2940m, 1205s, 1130s, 1060s; δ_H (400 MHz; $CDCl_3$) 1.58 (2H, m, CH*H*, 7-H and CH*H*, 8-H), 1.80 (2H, m, C*H*H, 7-H and C*H*H, 8-H), 2.00 (1H, s, O*H*), 2.14 (2H, m, CH*H*, 9-H and 3-H), 2.41 (3H, m, C*H*H, 9-H and 12-H), 3.41 (3H, s, OMe), 3.63 (1H, dd, *J* 9.2, 11.0, 4-H), 3.80 (1H, t, *J* 9.6, 6ax-H), 3.87 (1H, ddd, *J* 4.1, 9.2, 9.6, 5-H), 4.12 (1H, s, 1-H), 4.27 (1H, dd, *J* 4.1, 9.6, 6eq-H), 5.56 (1H, s, 13-H), 5.68 (1H, m, 10-H), 5.92 (1H, m, 11-H), 7.37-7.53 (5H, Ph); δ_C (100.6 MHz, $CDCl_3$) 21.5 (CH_2, C12), 24.1 (CH_2, C8), 25.9 (CH_2,

C9), 33.7 (CH_2, C7), 45.9 (CH, C3), 55.8 (CH_3, OMe), 65.2 (CH, C5), 69.7 (CH_2, C6), 75.9 (C, C2), 78.5 (CH, C4), 102.4 (CH, C13), 106.3 (CH, C1), 126.5 (CH, Ph), 128.6 (CH, Ph), 129.3 (CH, Ph), 131.1 (CH, C11), 131.5 (CH, C10), 138.2 (C, Ph); *m/z* (FAB) 347 (MH^+, 100%) (found MH^+, 347.1859; $C_{20}H_{27}O_5$ requires 347.1859).

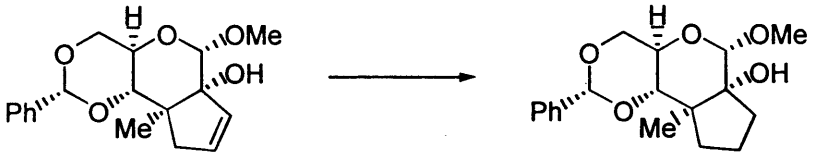
Methyl (*R*)-4,6-*O*-Benzylidene-2-*C*-hex-5-enyl-3-deoxy-3-*C*-propenyl-α-D-glucopyranoside (316).



Anhydrous cerium(III) chloride (2.03 g, 8.23 mmol) in dry diethyl ether (4.0 mL) was stirred at room temperature for 1.5 h. In another flask, 6-bromo-1-hexene (1.00 g, 6.13 mmol) in dry diethyl ether (5.0 mL) was added dropwise to magnesium turnings (220 mg, 9.05 mmol) in dry diethyl ether (4.0 mL) at 0 °C. This mixture was stirred at 0 °C for 0.25 h and then at room temperature for 1 h. The cerium(III) chloride mixture was cooled to -78 °C, the freshly prepared Grignard added dropwise via a cannula, and the resulting mixture stirred at -78 °C for 2 h. Ketone **176** (500 mg, 1.64 mmol) in dry diethyl ether (6.0 mL) was added dropwise via a cannula to the cooled (-78 °C) reaction mixture. The mixture was stirred at -40 °C for 2 h, then added portionwise to ice/water (150 mL) and saturated ammonium chloride solution (50 mL). The mixture was extracted into dichloromethane (2 × 100 mL), and the combined organic layers were washed with saturated sodium chloride solution (200 mL), dried, and evaporated to leave a yellow oil. Chromatography on silica gel with petroleum ether-diethyl ether (3:1) as the eluent yielded **316** as a colourless oil (350 mg, 55%) and the reduced product **310** as a white solid (139 mg, 28%): **316** - R_f 0.65, petroleum ether-diethyl ether (1:1); $[\alpha]^{20}_D$ + 35.5° (*c* 3.1, $CHCl_3$); υ_{max} ($CHCl_3$)/cm^{-1} 3570w, 3010m, 2930m, 2860w, 1640w, 1205s, 1120s, 1070s, 1000s; δ_H (250 MHz, $CDCl_3$) 1.20-1.78 (6H, 8-H, 9-H and 10-H), 2.00-2.58 (5H, 3-H, 7-H and 13-H), 2.22 (1H, s, overlapping, O*H*), 3.46 (3H, s, OMe), 3.46 (1H, t, overlapping, *J* 9.5, 4-H), 3.68-3.88 (2H, 5-H and 6ax-H), 4.20-4.32 (1H, m, 6eq-H), 4.53 (1H, s, 1-H), 4.90-5.13 (4H, 12-H and 15-H), 5.53 (1H, s, 16-H), 5.73-6.16 (2H, 11-H and 14-H), 7.30-7.57 (5H, Ph); δ_C

(62.9 MHz, $CDCl_3$) 22.7 (CH_2, C8), 30.1 (CH_2, C9), 31.3 (CH_2, C10), 31.6 (CH_2, C13), 34.2 (CH_2, C7), 46.8 (CH, C3), 55.7 (CH_3, OMe), 64.9 (CH, C5), 69.8 (CH_2, C6), 74.9 (C, C2), 81.3 (CH, C4), 100.9 (CH, C1), 101.9 (CH, C16), 114.9 (CH_2, C15), 115.0 (CH_2, C12), 126.5 (CH, Ph), 128.6 (CH, Ph), 129.2 (CH, Ph), 138.1 (C, Ph), 139.2 (CH, C14), 139.6 (CH, C11); *m/z* (FAB) 389 (MH^+, 33%) (found MH^+, 389.2328; $C_{23}H_{33}O_5$ requires 389.2328).

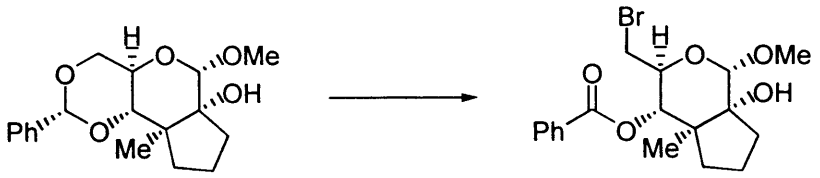
Methyl (*R*)-4,6-*O*-Benzylidene-2,3-*C*-(propane-1,3-diyl)-3-deoxy-3-*C*-methyl-α-D-glucopyranoside (333).



299b **333**

A solution of the olefin **299b** (100 mg, 0.31 mmol) in dry ethanol (5.0 mL) was degassed several times with nitrogen. The catalyst (Palladium, 5% on carbon, 10 mg) was added, the mixture degassed several times with hydrogen, then allowed to stir under a positive pressure of hydrogen (balloon) for 17 h. At this point the mixture was filtered through a plug of celite under reduced pressure, and the residue washed with ethanol (3 × 5 mL). The filtrate was concentrated under reduced pressure to yield **333** as a pale yellow oil (100 mg, 99%): δ_H (250 MHz, $CDCl_3$) 1.20 (3H, s, C3-Me), 1.60-2.24 (6H, 7-H, 8-H and 9-H), 2.70 (1H, br s, O*H*), 3.37 (1H, d, *J* 9.7, 4-H), 3.43 (3H, s, OMe), 3.69 (1H, t, *J* 10.2, 6ax-H), 3.92 (1H, ddd, *J* 5.0, 9.7, 10.2, 5-H), 4.31 (1H, dd, *J* 5.0, 10.2, 6eq-H), 4.51 (1H, s, 1-H), 5.52 (1H, s, 10-H), 7.31-7.57 (5H, Ph); δ_C (62.9 MHz, $CDCl_3$) 14.3 (CH_3, C3-Me), 19.9 (CH_2, C9), 35.0 (CH_2, C8), 35.9 (CH_2, C7), 49.4 (C, C3), 56.1 (CH_3, OMe), 59.6 (CH, C5), 70.0 (CH_2, C6), 80.4 (CH, C4), 81.3 (C, C2), 101.9 (CH, C10), 102.1 (CH, C1), 126.6 (CH, Ph), 128.6 (CH, Ph), 129.3 (CH, Ph), 138.3 (C, Ph); *m/z* (FAB) 321 (MH^+, 6%) (found MH^+, 321.1702; $C_{18}H_{25}O_5$ requires 321.1702).

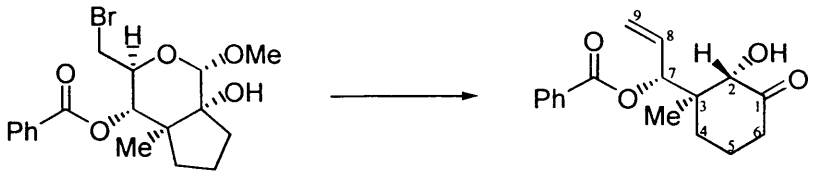
Methyl (*R*)-4-*O*-Benzoyl-6-*C*-bromo-2,3-*C*-(propane-1,3-diyl)-3,6-dideoxy-α-D-glucopyranoside (334).



333 **334**

Barium carbonate (247 mg, 1.25 mmol) and *N*-bromosuccinimide (61 mg, 0.34 mmol) were added sequentially to a solution of **333** (100 mg, 0.31 mmol) in dry chloroform (10 mL). The mixture was heated under reflux for 17 h, allowed to cool to room temperature, barium carbonate removed by filtration and the residue washed with dichloromethane (2 × 10 mL). The filtrate was washed with water (2 × 30 mL), dried and concentrated under reduced pressure to leave a yellow oil. Chromatography on silica gel with petroleum ether-diethyl ether (3:1) as the eluent yielded **334** as a colourless oil (93 mg, 75%): R_f 0.32, petroleum ether-diethyl ether (1:1); $[\alpha]^{20}_D$ + 78.6° (*c* 4.3, $CHCl_3$); υ_{max} ($CHCl_3$)/cm^{-1} 3570w, 3010m, 2970m, 1720s, 1270s, 1205s, 1070s; δ_H (250 MHz, $CDCl_3$) 1.26 (3H, s, C3-Me), 1.53-1.97 (5H, CH*H*, 7-H, 8-H and 9-H), 2.15-2.38 (1H, m, C*H*H, 7-H), 2.64 (1H, d, *J* 2.3, O*H*), 3.33-3.49 (2H, m, 6-H), 3.52 (3H, s, OMe), 4.16 (1H, ddd, *J* 2.9, 7.8, 10.3, 5-H), 4.61 (1H, s, 1-H), 5.04 (1H, d, *J* 10.3, 4-H), 7.47 (2H, *m*-Ph), 7.61 (1H, *p*-Ph), 8.05 (2H, *o*-Ph); δ_C (62.9 MHz, $CDCl_3$) 14.6 (CH_3, C3-Me), 19.7 (CH_2, C9), 33.2 (CH_2, C6), 35.5 (CH_2, C8), 35.9 (CH_2, C7), 51.0 (C, C3), 56.3 (CH_3, OMe), 67.4 (CH, C5), 72.6 (CH, C4), 81.1 (C, C2), 101.4 (CH, C1), 129.0 (CH, Ph), 129.8 (C, Ph), 130.2 (CH, Ph), 133.9 (CH, Ph), 166.3 (CO, OBz); *m/z* (FAB) 398/400 (M^+, 1%), 105 ($PhCO^+$, 96) (found M^+, 398.0729; $C_{18}H_{23}O_5Br$ requires 398.0729).

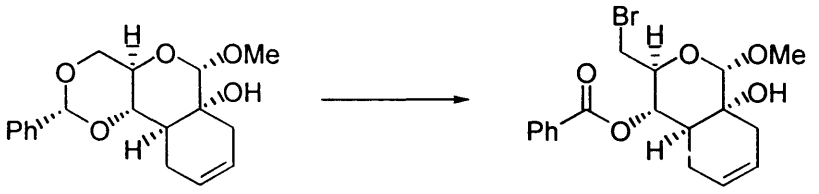
(1*R*,1'*R*,2'*S*)-Benzoic acid 1-(2'-hydroxy-1'-methyl-3'-oxo-cyclohexyl)-allyl ester (336).



334 336

Zinc powder (60 g) was activated by washing sequentially with 2M hydrochloric acid (6 × 30 mL), water (5 × 35 mL), 10% w/v aqueous potassium carbonate solution (30 mL), water (4 × 40 mL), isopropanol (2 × 35 mL) and diethyl ether (3 × 35 mL). The bromo compound **334** (214 mg, 0.54 mmol) was heated under reflux with the activated zinc (4.56 g, 0.070 mol) in isopropanol : water (16:1.6 mL) for 48 h. The zinc was removed by filtration, washed with diethyl ether (2 × 50 mL), the combined organic layers washed with water (100 mL), saturated sodium chloride solution (100 mL), dried, and evaporated to leave a colourless oil. Chromatography on silica gel with petroleum ether-diethyl ether (3:1) as the eluent yielded **336** as a colourless oil (83 mg, 54%): R_f 0.28, petroleum ether-diethyl ether (1:1); $[\alpha]^{20}_D$ + 57.3° (*c* 1.8, $CHCl_3$); υ_{max} ($CHCl_3$)/cm^{-1} 3500w, 3010m, 2950m, 1720s, 1610w, 1270s, 1205s, 1110s; δ_H (400 MHz, $CDCl_3$) 0.86 (3H, s, C3-Me), 1.76-1.91 (2H, 4α-H and 5α-H), 2.03-2.15 (1H, m, 5β-H), 2.15-2.23 (1H, m, 4β-H), 2.35-2.47 (1H, m, 6β-H), 2.52-2.60 (1H, m, 6α-H), 3.56 (1H, d, *J* 4.1, O*H*), 4.25 (1H, dd, *J* 1.2, 4.1, 2-H), 5.34 (1H, dt, *J* 1.3, 10.6, H-9_{cis}), 5.41 (1H, dt, *J* 1.4, 17.1, H-9_{trans}), 5.67 (1H, d, *J* 6.7, 7-H), 5.94 (1H, ddd, *J* 6.7, 10.6, 17.1, 8-H), 7.39 (2H, *m*-Ph), 7.61 (1H, *p*-Ph), 8.13 (2H, *o*-Ph); δ_C (100.6 MHz, $CDCl_3$) 15.3 (CH_3, C3-Me), 21.7 (CH_2, C5), 29.1 (CH_2, C4), 39.1 (CH_2, C6), 48.0 (C, C3), 77.9 (CH, C2), 78.1 (CH, C7), 119.7 (CH_2, C9), 128.9 (CH, Ph), 130.0 (CH, Ph), 130.7 (C, Ph), 132.6 (CH, C8), 133.4 (CH, Ph), 165.5 (CO, OBz), 211.6 (C, C1); *m/z* (FAB) 289 (MH^+, 56%), 311 (MNa^+, 45) (found MH^+, 289.1440; $C_{17}H_{21}O_4$ requires 289.1440).

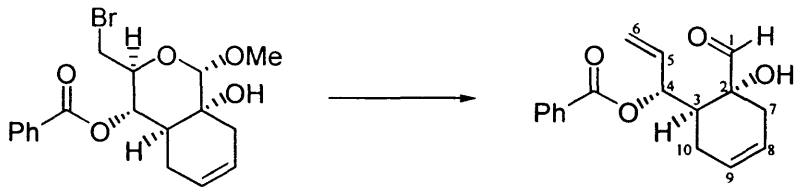
Methyl (*R*)-4-*O*-Benzoyl-6-*C*-bromo-2,3-*C*-(but-2-ene-1,4-diyl)-3,6-dideoxy-α-D-glucopyranoside (339).



302 **339**

Barium carbonate (248 mg, 1.26 mmol) and *N*-bromosuccinimide (61 mg, 0.34 mmol) were added sequentially to a solution of **302** (100 mg, 0.31 mmol) in dry chloroform (10 mL). The mixture was heated under reflux for 16 h, allowed to cool to room temperature, barium carbonate removed by filtration and the residue washed with diethyl ether (2 × 25 mL). The filtrate was concentrated under reduced pressure to leave a yellow oil. Chromatography on silica gel with dichloromethane-diethyl ether (97.5:2.5) as the eluent yielded starting material **302** as a white solid (21 mg, 21%) and **339** as a colourless oil (48 mg, 38%): R_f 0.50, dichloromethane-diethyl ether (9:1); $[\alpha]^{20}_D$ + 66.7° (*c* 2.8, $CHCl_3$); υ_{max} ($CHCl_3$)/cm^{-1} 3570w, 3010m, 2920w, 1725s, 1610w, 1270s, 1205s, 1055s; δ_H (250 MHz, $CDCl_3$) 1.83-2.68 (6H, 3-H, 7-H, 10-H and *OH*), 3.39-3.52 (2H, m, 6-H), 3.57 (3H, s, OMe), 4.02 (1H, ddd, *J* 2.5, 7.9, 10.2, 5-H), 4.43 (1H, s, 1-H), 5.04 (1H, t, *J* 10.2, 4-H), 5.57-5.76 (2H, 8-H and 9-H), 7.48 (2H, *m*-Ph), 7.62 (1H, *p*-Ph), 8.05 (2H, *o*-Ph); δ_C (62.9 MHz, $CDCl_3$) 20.3 (CH_2, C10), 30.4 (CH_2, C7), 31.5 (CH_2, C6), 38.4 (CH, C3), 54.6 (CH_3, OMe), 69.0 (C, C2), 69.3 (CH, C5), 69.8 (CH, C4), 100.9 (CH, C1), 122.0 (CH, C8), 122.6 (CH, C9), 127.5 (CH, Ph), 128.2 (C, Ph), 128.8 (CH, Ph), 132.5 (CH, Ph), 164.6 (CO, OBz); *m/z* (EI) 396/398 (M^+, 2%), 105 ($PhCO^+$, 100) (found M^+, 396.0572; $C_{18}H_{21}O_5Br$ requires 396.0572).

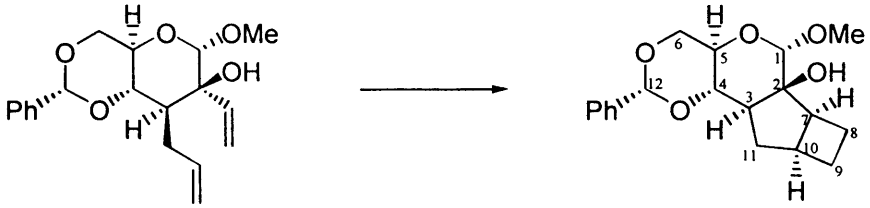
(1*S*,1'*S*,6'*R*)-Benzoic acid 1-(6'-formyl-6'-hydroxy-cyclohex-3'-enyl)-allyl ester (340).



339 **340**

Zinc powder (60 g) was activated by washing sequentially with 2M hydrochloric acid (6 × 30 mL), water (5 × 35 mL), 10% w/v aqueous potassium carbonate solution (30 mL), water (4 × 40 mL), isopropanol (2 × 35 mL) and diethyl ether (3 × 35 mL). The bromo compound **339** (155 mg, 0.39 mmol) was heated under reflux with the activated zinc (3.32 g, 0.051 mol) in isopropanol : water (10:1 mL) for 5 h. The zinc was removed by filtration, washed with diethyl ether (2 × 50 mL), the combined organic layers washed with water (100 mL), saturated sodium chloride solution (100 mL), dried, and evaporated to leave a colourless oil. Chromatography on silica gel with petroleum ether-diethyl ether (3:1) as the eluent yielded **340** as a colourless oil (56 mg, 50%): R_f 0.54, diethyl ether-petroleum ether (2:1); δ_H (250 MHz, $CDCl_3$) 2.18 (1H, dd, *J* 5.0, 17.6, CH*H*, 7-H), 2.40-2.80 (4H, 3-H, C*H*H, 7-H and 10-H), 3.95 (1H, s, O*H*), 5.19-5.33 (2H, m, 6-H), 5.66-5.97 (3H, 4-H, 5-H, 8-H) 6.06-6.16 (1H, m, 9-H), 7.43 (2H, *m*-Ph), 7.56 (1H, *p*-Ph), 7.95 (2H, *o*-Ph), 9.81 (1H, s, C*H*O); δ_C (62.9 MHz, $CDCl_3$) 24.8 (CH_2, C10), 36.7 (CH_2, C7), 47.2 (CH, C3), 71.3 (CH, C4), 76.2 (C, C2), 117.0 (CH_2, C6), 123.8 (CH, C8), 126.8 (CH, C9), 128.9 (CH, Ph), 129.9 (CH, Ph), 130.0 (C, Ph), 133.6 (CH, Ph), 134.9 (CH, C5), 165.2 (CO, OBz), 202.2 (CH, *C*HO); *m/z* (FAB) 287 (MH^+, 9%), 309 (MNa^+, 21) (found MH^+, 287.1281; $C_{17}H_{19}O_4$ requires 287.1283).

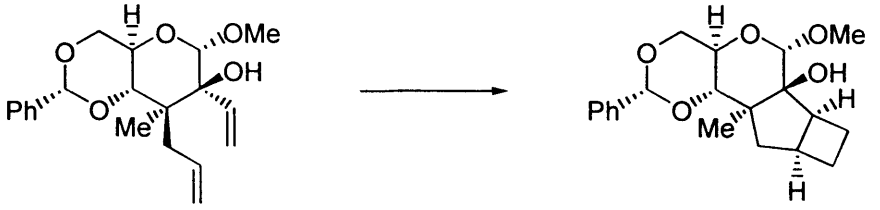
(2*R*,4a*R*,6*S*,6a*S*,6b*S*,8a*S*,9a*S*,9b*S*)-6-Methoxy-2-phenyl-octahydro-1,3,5-trioxa-cyclobuta[3,4]cyclopenta[1,2-*a*]naphthalen-6a-ol (392a).



298a **392a**

$(CF_3SO_3Cu)_2.C_6H_6$ (10 mg, 0.020 mmol, 5 mol%) was added to a solution of diene **298a** (140 mg, 0.42 mmol) in dry benzene (10 mL), in a quartz photolysis tube, water-cooled by a cold finger extending into the solution. Irradiation was carried out at 254 nm, using a Rayonet™ photochemical reactor, for 6 h. The reaction mixture was diluted with diethyl ether (40 mL) and washed with aqueous ammonia solution (35%, 2 × 20 mL). The organic layer was washed with water (20 mL), dried and concentrated under reduced pressure to leave a yellow oil. Chromatography on silica gel with petroleum ether-diethyl ether (3:1) as the eluent yielded **392a** as a white solid (121 mg, 86%): mp 101-103 °C (ethanol); R_f 0.36, petroleum ether-diethyl ether (1:1); $[\alpha]^{20}_D$ + 34.2° (*c* 4.1, $CHCl_3$); υ_{max} ($CHCl_3$)/cm^{-1} 3580w, 3010w, 2940m, 2870w, 1090s, 1060s, 1030s; δ_H (400 MHz, $CDCl_3$) 1.58 (1H, dt, *J* 5.7, 12.3, CH*H*, 11-H), 1.81 (1H, m, CH*H*, 9-H), 1.97-2.08 (3H, C*HH*, 8-H and 3-H), 2.15 (1H, br s, O*H*), 2.15-2.29 (2H, overlapping, C*H*H, 9-H and C*H*H, 11-H), 2.73-2.84 (2H, 7-H and 10-H), 3.42 (3H, s, OMe), 3.70 (1H, ddd, *J* 4.7, 9.2, 10.2, 5-H), 3.87 (1H, t, *J* 10.2, 6ax-H), 3.88 (1H, dd, overlapping, *J* 9.2, 11.0, 4-H), 4.31 (1H, dd, *J* 4.7, 10.2, 6eq-H), 4.60 (1H, s, 1-H), 5.59 (1H, s, 12-H), 7.33-7.55 (5H, Ph); δ_C (100.6 MHz, $CDCl_3$) 17.2 (CH_2, C8), 29.4 (CH_2, C9), 33.6 (CH_2, C11), 37.1 (CH, C10), 42.7 (CH, C7), 48.0 (CH, C3), 55.6 (CH_3, OMe), 65.1 (CH, C5), 69.6 (CH_2, C6), 81.4 (CH, C4), 81.9 (C, C2), 102.3 (CH, C12), 102.9 (CH, C1), 126.6 (CH, Ph), 128.7 (CH, Ph), 129.3 (CH, Ph), 138.2 (C, Ph); *m/z* (FAB) 333 (MH^+, 15%) (found MH^+, 333.1703; $C_{19}H_{25}O_5$ requires 333.1702). Anal. Found: C, 68.75; H, 7.32. $C_{19}H_{24}O_5$ requires C, 68.66; H, 7.28%.

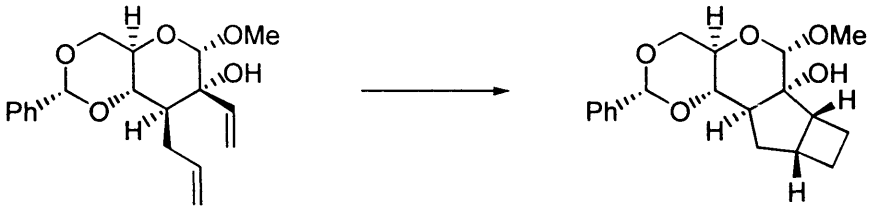
(2*R*,4a*R*,6*S*,6a*S*,6b*S*,8a*S*,9a*S*,9b*S*)-6-Methoxy-9a-methyl-2-phenyl-octahydro-1,3,5-trioxa-cyclobuta[3,4]cyclopenta[1,2-*a*]naphthalen-6a-ol (392b).



298b **392b**

$(CF_3SO_3Cu)_2.C_6H_6$ (22 mg, 0.044 mmol, 13 mol%) was added to a solution of diene **298b** (118 mg, 0.34 mmol) in dry benzene (10 mL), in a quartz photolysis tube, water-cooled by a cold finger extending into the solution. Irradiation was carried out at 254 nm, using a Rayonet™ photochemical reactor, for 22 h. The reaction mixture was diluted with diethyl ether (40 mL) and washed with aqueous ammonia solution (35%, 2 × 20 mL). The organic layer was washed with water (20 mL), dried and concentrated under reduced pressure to leave a yellow oil. Chromatography on silica gel with petroleum ether-diethyl ether (3:1) as the eluent yielded **392b** as a colourless oil (21 mg, 18%): R_f 0.50, petroleum ether-diethyl ether (1:1); $[\alpha]^{20}_D$ - 59.2° (*c* 2.1, $CHCl_3$); υ_{max} ($CHCl_3$)/cm^{-1} 3580w, 3010w, 2940m, 2870w, 1090s, 1060s, 1030s; δ_H (250 MHz, $CDCl_3$) 0.93 (3H, s, C3-Me), 1.72-1.94 (4H, CH*H*, 8-H, CH*H*, 9-H and C*HH*, 11-H), 2.00-2.26 (2H, C*H*H, 8-H and C*H*H, 9-H), 2.57 (1H, s, O*H*), 2.57-2.69 (1H, m, 7-H), 2.80-3.00 (1H, m, 10-H), 3.50 (3H, s, OMe), 3.79 (1H, ddd, *J* 4.1, 9.1, 9.8, 5-H), 3.87 (1H, t, *J* 9.8, 6ax-H), 4.23 (1H, d, *J* 9.1, 4-H), 4.33 (1H, dd, *J* 4.1, 9.8, 6eq-H), 4.71 (1H, s, 1-H), 5.58 (1H, s, 12-H), 7.29-7.54 (5H, Ph); δ_C (100.6 MHz, $CDCl_3$) 15.8 (CH_3, C3-Me), 17.4 (CH_2, C8), 28.4 (CH_2, C9), 37.2 (CH, C10), 42.5 (CH_2, C11), 42.9 (CH, C7), 51.6 (C, C3), 57.2 (CH_3, OMe), 66.9 (CH, C5), 70.1 (CH_2, C6), 82.2 (C, C2), 82.7 (CH, C4), 102.1 (CH, C1), 103.3 (CH, C12), 126.7 (CH, Ph), 128.6 (CH, Ph), 129.3 (CH, Ph), 138.4 (C, Ph); *m/z* (FAB) 347 (MH^+, 12%) (found MH^+, 347.1859; $C_{20}H_{27}O_5$ requires 347.1859).

(2*R*,4a*R*,6*S*,6a*R*,6b*R*,8a*R*,9a*S*,9b*S*)-6-Methoxy-2-phenyl-octahydro-1,3,5-trioxa-cyclobuta[3,4]cyclopenta[1,2-*a*]naphthalen-6a-ol (393a).

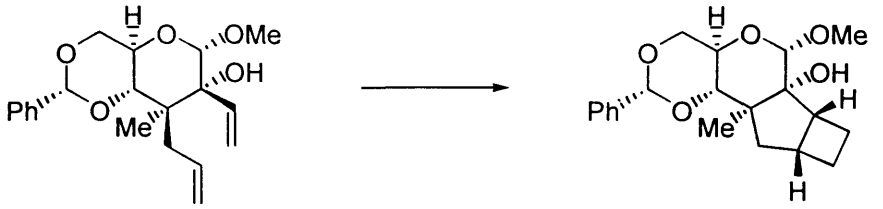


297a

393a

$(CF_3SO_3Cu)_2.C_6H_6$ (23 mg, 0.046 mmol, 13 mol%) was added to a solution of diene **297a** (118 mg, 0.36 mmol) in dry benzene (10 mL), in a quartz photolysis tube, water-cooled by a cold finger extending into the solution. Irradiation was carried out at 254 nm, using a Rayonet™ photochemical reactor, for 5.5 h. The reaction mixture was diluted with diethyl ether (40 mL) and washed with aqueous ammonia solution (35%, 2 × 20 mL). The organic layer was washed with water (20 mL), dried and concentrated under reduced pressure to leave a yellow oil. Chromatography on silica gel with petroleum ether-diethyl ether (4:1) as the eluent yielded **393a** as a colourless oil (101 mg, 86%): R_f 0.52, petroleum ether-diethyl ether (1:1); $[\alpha]^{20}_D$ + 4.3° (*c* 1.0, $CHCl_3$); υ_{max} ($CHCl_3$)/cm^{-1} 3580w, 3010w, 2940m, 2870w, 1090s, 1060s, 1030s; δ_H (400 MHz, $CDCl_3$) 1.74-1.90 (2H, CH*H*, 9-H and CH*H*, 11-H), 1.94-2.07 (1H, m, CH*H*, 8-H), 2.13-2.34 (4H, 3-H, C*H*H, 8-H, C*H*H, 9-H and C*H*H, 11-H), 2.71 (1H, s, O*H*), 2.75-2.83 (1H, m, 7-H), 2.83-2.95 (1H, m, 10-H), 2.96 (1H, dd, overlapping, *J* 9.7, 10.5, 4-H), 3.48 (3H, s, OMe), 3.65 (1H, t, *J* 10.3, 6ax-H), 3.80 (1H, ddd, *J* 4.8, 9.7, 10.3, 5-H), 4.28 (1H, dd, *J* 4.8, 10.3, 6eq-H), 4.46 (1H, s, 1-H), 5.45 (1H, s, 12-H), 7.32-7.54 (5H, Ph); δ_C (62.9 MHz, $CDCl_3$) 16.6 (CH_2, C8), 28.6 (CH_2, C9), 34.1 (CH_2, C11), 36.3 (CH, C10), 44.0 (CH, C7), 52.7 (CH, C3), 55.8 (CH_3, OMe), 62.8 (CH, C5), 69.8 (CH_2, C6), 78.9 (CH, C4), 80.9 (C, C2), 100.5 (CH, C1), 102.2 (CH, C12), 126.6 (CH, Ph), 128.7 (CH, Ph), 129.4 (CH, Ph), 138.1 (C, Ph); *m/z* (FAB) 333 (MH^+, 18%) (found MH^+, 333.1703; $C_{19}H_{25}O_5$ requires 333.1702).

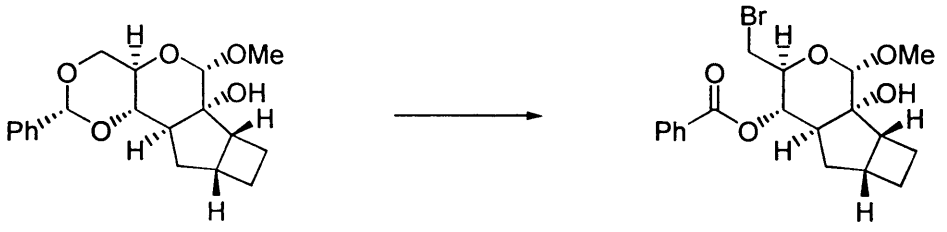
(2*R*,4a*R*,6*S*,6a*R*,6b*R*,8a*R*,9a*S*,9b*S*)-6-Methoxy-9a-methyl-2-phenyl-octahydro-1,3,5-trioxa-cyclobuta[3,4]cyclopenta[1,2-*a*]naphthalen-6a-ol (393b).



297b **393b**

$(CF_3SO_3Cu)_2.C_6H_6$ (20 mg, 0.040 mmol, 14 mol%) was added to a solution of diene **297b** (96 mg, 0.28 mmol) in dry benzene (10 mL), in a quartz photolysis tube, water-cooled by a cold finger extending into the solution. Irradiation was carried out at 254 nm, using a Rayonet™ photochemical reactor, for 6 h. The reaction mixture was diluted with diethyl ether (40 mL) and washed with aqueous ammonia solution (35%, 2 × 20 mL). The organic layer was washed with water (20 mL), dried and concentrated under reduced pressure to leave a yellow oil. Chromatography on silica gel with petroleum ether-diethyl ether (3:1) as the eluent yielded **393b** as a colourless oil (85 mg, 89%): R_f 0.69, petroleum ether-diethyl ether (1:1); $[\alpha]^{20}_D$ + 13.6° (*c* 7.0, $CHCl_3$); υ_{max} ($CHCl_3$)/cm^{-1} 3580w, 3010w, 2940m, 2870w, 1090s, 1060s, 1030s; δ_H (250 MHz, $CDCl_3$) 1.20 (3H, s, C3-Me), 1.50 (1H, dd, *J* 6.3, 13.2, CH*H*, 11-H), 1.60-1.82 (1H, m, CH*H*, 9-H), 1.86-2.09 (1H, m, CH*H*, 8-H), 2.12-2.31 (3H, C*H*H, 8-H, C*H*H, 9-H and C*H*H, 11-H), 2.70-2.98 (2H, 7-H and 10-H), 2.75 (1H, s, overlapping, O*H*), 3.11 (1H, d, *J* 9.4, 4-H), 3.42 (3H, s, OMe), 3.62 (1H, t, *J* 10.1, 6ax-H), 3.86 (1H, ddd, *J* 5.0, 9.4, 10.1, 5-H), 4.27 (1H, dd, *J* 5.0, 10.1, 6eq-H), 4.37 (1H, s, 1-H), 5.44 (1H, s, 12-H), 7.28-7.55 (5H, Ph); δ_C (62.9 MHz, $CDCl_3$) 14.3 (CH_3, C3-Me), 16.9 (CH_2, C8), 28.2 (CH_2, C9), 35.5 (CH, C10), 43.4 (CH_2, C11), 45.7 (CH, C7), 53.3 (C, C3), 56.1 (CH_3, OMe), 59.3 (CH, C5), 70.0 (CH_2, C6), 80.1 (CH, C4), 80.3 (C, C2), 101.8 (CH, C1), 102.1 (CH, C12), 126.6 (CH, Ph), 128.6 (CH, Ph), 129.3 (CH, Ph), 138.3 (C, Ph); *m/z* (FAB) 347 (MH^+, 20%) (found MH^+, 347.1858; $C_{20}H_{27}O_5$ requires 347.1859).

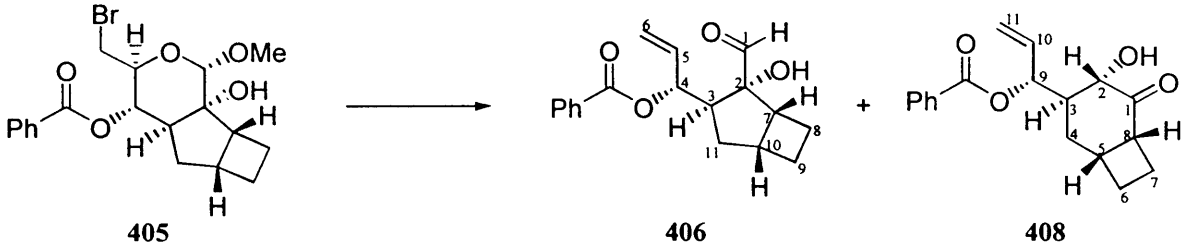
(2a*R*,2b*R*,3*S*,5*S*,6*S*,6a*S*,7a*R*)-Benzoic acid 5-bromomethyl-2b-hydroxy-3-methoxy-decahydro-4-oxa-cyclobuta[*a*]inden-6-yl ester (405).



393a **405**

Barium carbonate (552 mg, 2.80 mmol) and *N*-bromosuccinimide (137 mg, 0.77 mmol) were added sequentially to a solution of **393a** (232 mg, 0.70 mmol) in dry chloroform (30 mL). The mixture was heated under reflux for 23 h, allowed to cool to room temperature, barium carbonate removed by filtration and the residue washed with dichloromethane (2 × 20 mL). The filtrate was washed with water (2 × 50 mL), dried and concentrated under reduced pressure to leave a yellow oil. Chromatography on silica gel with petroleum ether-diethyl ether (3:1) as the eluent yielded **405** as a colourless oil (211 mg, 73%): R_f 0.62, petroleum ether-diethyl ether (1:1); $[\alpha]^{20}_D$ + 54.3° (*c* 1.1, $CHCl_3$); υ_{max} ($CHCl_3$)/cm^{-1} 3580w, 2950m, 1725s, 1275s, 1115s, 1030s; δ_H (250 MHz, $CDCl_3$) 1.61-2.47 (7H, 3-H, 8-H, 9-H and 11-H), 2.65 (1H, s, O*H*), 2.76-2.98 (2H, 7-H and 10-H), 3.35 (1H, dd, *J* 8.2, 11.0, CH*H*, 6-H), 3.47 (1H, dd, *J* 2.5, 11.0, C*H*H, 6-H), 3.57 (3H, s, OMe), 4.10 (1H, ddd, *J* 2.5, 8.2, 9.8, 5-H), 4.53 (1H, s, 1-H), 4.64 (1H, dd, *J* 9.1, 9.8, 4-H), 7.47 (2H, *m*-Ph), 7.59 (1H, *p*-Ph), 8.04 (2H, *o*-Ph); δ_C (62.9 MHz, $CDCl_3$) 16.6 (CH_2, C8), 27.5 (CH_2, C9), 32.9 (CH_2, C11), 35.3 (CH_2, C6), 35.9 (CH, C10), 43.7 (CH, C7), 52.4 (CH, C3), 56.0 (CH_3, OMe), 69.7 (CH, C5), 71.7 (CH, C4), 80.5 (C, C2), 100.2 (CH, C1), 128.9 (CH, Ph), 129.8 (C, Ph), 130.2 (CH, Ph), 133.9 (CH, Ph), 166.4 (CO, OBz); *m/z* (EI) 410/412 (M^+, 1%), 105 ($PhCO^+$, 84) (found M^+, 410.0728; $C_{19}H_{23}O_5Br$ requires 410.0729).

(1*S*,1'*R*,3'*S*,4'*R*,5'*R*)-Benzoic acid 1-(4'-formyl-4'-hydroxy-bicyclo[3.2.0]hept-3'-yl)-allyl ester (406) and (1*S*,1'*R*,3'*R*,4'*S*,6'*R*)-Benzoic acid 1-(4'-hydroxy-5'-oxo-bicyclo[4.2.0]oct-3'-yl)-allyl ester (408).



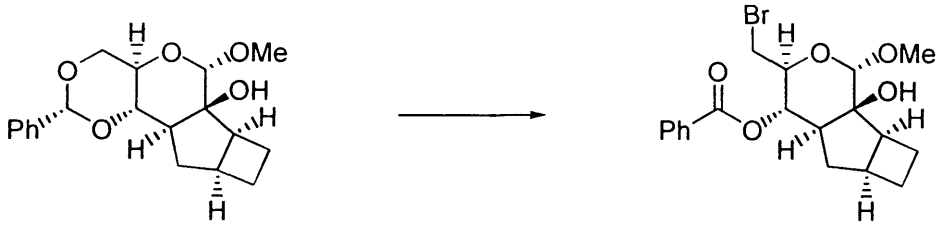
405 406 408

Zinc powder (60 g) was activated by washing sequentially with 2M hydrochloric acid (6 × 30 mL), water (5 × 35 mL), 10% w/v aqueous potassium carbonate solution (30 mL), water (4 × 40 mL), isopropanol (2 × 35 mL) and diethyl ether (3 × 35 mL). The bromo compound **405** (200 mg, 0.49 mmol) was heated under reflux with the activated zinc (4.14 g, 0.063 mol) in isopropanol : water (20:2 mL) for 2.5 h. The zinc was removed by filtration, washed with diethyl ether (3 × 25 mL), the combined organic layers washed with water (2 × 50 mL), saturated sodium chloride solution (50 mL), dried, and evaporated to leave a colourless oil. Chromatography on kieselgel silica with petroleum ether-diethyl ether (4:1 to 3:1) as the eluent yielded **406** as a colourless oil (42 mg, 29%) and **408** as a colourless oil (43 mg, 29%): **406** - R_f 0.49, petroleum ether-diethyl ether (1:1); $[\alpha]^{20}_D$ - 38.9° (*c* 1.6, $CHCl_3$); υ_{max} ($CHCl_3$)/cm^{-1} 3510w, 3030m, 2960m, 1715s, 1610w, 1275s, 1115m; δ_H (250 MHz, $CDCl_3$) 1.69-1.93 (2H, CH*H*, 8-H and CH*H*, 9-H), 2.08-2.37 (3H, C*H*H, 8-H, C*H*H, 9-H and CH*H*, 11-H), 2.38-2.58 (1H, m, 3-H), 2.64-2.77 (1H, m, 7-H), 2.90-3.05 (1H, m, 10-H), 3.12 (1H, ddd, *J* 3.6, 6.9, 13.4, C*H*H, 11-H), 3.41 (1H, s, O*H*), 5.19-5.38 (2H, m, 6-H), 5.67-5.75 (1H, m, 4-H), 5.83-6.01 (1H, m, 5-H), 7.44 (2H, *m*-Ph), 7.58 (1H, *p*-Ph), 7.99 (2H, *o*-Ph), 9.52 (1H, s, C*H*O); δ_C (100.6 MHz, $CDCl_3$) 18.5 (CH_2, C8), 26.2 (CH_2, C9), 31.2 (CH_2, C11), 34.8 (CH, C10), 42.0 (CH, C7), 51.6 (CH, C3), 72.5 (CH, C4), 86.5 (C, C2), 117.5 (CH_2, C6), 128.9 (CH, Ph), 129.9 (CH, Ph), 130.3 (C, Ph), 133.6 (CH, Ph), 135.5 (CH, C5), 165.2 (CO, OBz), 200.3 (CH, C1); *m/z* (FAB) 301 (MH^+, 5%), 323 (MNa^+, 7) (found MH^+, 301.1440; $C_{18}H_{21}O_4$ requires 301.1440).

408 - R_f 0.46, petroleum ether-diethyl ether (1:1); $[\alpha]^{20}_D$ + 5.5° (*c* 1.0, $CHCl_3$); υ_{max} ($CHCl_3$)/cm^{-1} 3490w, 3020w, 2940m, 1725s, 1715s, 1610w, 1275s, 1115s; δ_H (400 MHz, $CDCl_3$) 1.72-2.30 (7H, 3-H, 4-H, 6-H and 7-H), 2.87-2.97 (1H, m, 8-H), 3.20-3.31 (1H, m, 5-H), 3.87 (1H, br s, O*H*), 4.05 (1H, dd, *J* 1.3, 11.5, 2-H), 5.23-5.38 (2H, m, 11-H), 5.86-

5.98 (1H, m, 10-H), 6.04-6.10 (1H, m, 9-H), 7.48 (2H, *m*-Ph), 7.60 (1H, *p*-Ph), 8.11 (2H, *o*-Ph); δ_C (100.6 MHz, $CDCl_3$) 23.0 (CH_2, C7), 25.2 (CH_2, C6), 25.6 (CH_2, C4), 36.6 (CH, C5), 45.4 (CH, C3), 45.5 (CH, C8), 73.8 (CH, C9), 76.0 (CH, C2), 117.2 (CH_2, C11), 128.9 (CH, Ph), 130.1 (CH, Ph), 130.7 (C, Ph), 133.5 (CH, Ph), 135.1 (CH, C10), 165.7 (CO, OBz), 215.2 (C, C1); *m/z* (FAB) 301 (MH^+, 15%), 323 (MNa^+, 13).

(2a*S*,2b*S*,3*S*,5*S*,6*S*,6a*S*,7a*S*)-Benzoic acid 5-bromomethyl-2b-hydroxy-3-methoxy-decahydro-4-oxa-cyclobuta[*a*]inden-6-yl ester (409).



392a **409**

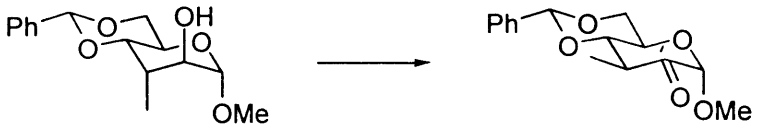
Barium carbonate (542 mg, 2.75 mmol) and *N*-bromosuccinimide (135 mg, 0.76 mmol) were added sequentially to a solution of **392a** (228 mg, 0.69 mmol) in dry chloroform (30 mL). The mixture was heated under reflux for 23 h, allowed to cool to room temperature, barium carbonate removed by filtration and the residue washed with dichloromethane (2 × 20 mL). The filtrate was washed with water (2 × 50 mL), dried and concentrated under reduced pressure to leave a yellow oil. Chromatography on silica gel with petroleum ether-diethyl ether (3:1) as the eluent yielded **409** as a colourless oil (204 mg, 72%): R_f 0.60, petroleum ether-diethyl ether (1:1); υ_{max} ($CHCl_3$)/cm^{-1} 3580w, 2950m, 1725s, 1275s, 1115s, 1030s; δ_H (300 MHz, $CDCl_3$) 1.63-2.27 (7H, 3-H, 8-H, 9-H and 11-H), 2.33 (1H, s, O*H*), 2.63-2.80 (2H, 7-H and 10-H), 3.41 (3H, s, OMe), 3.44 (1H, dd, overlapping, *J* 6.7, 11.0, CH*H*, 6-H), 3.52 (1H, dd, *J* 2.5, 11.0, C*H*H, 6-H), 3.83 (1H, ddd, *J* 2.5, 6.7, 10.2, 5-H), 4.59 (1H, s, 1-H), 5.29 (1H, t, *J* 10.2, 4-H), 7.37 (2H, *m*-Ph), 7.49 (1H, *p*-Ph), 7.94 (2H, *o*-Ph); δ_C (75.8 MHz, $CDCl_3$) 17.3 (CH_2, C8), 29.1 (CH_2, C9), 33.1 (CH_2, C11), 34.5 (CH_2, C6), 36.9 (CH, C10), 42.3 (CH, C7), 48.8 (CH, C3), 55.9 (CH_3, OMe), 70.6 (CH, C5), 73.7 (CH, C4), 81.0 (C, C2), 102.1 (CH, C1), 128.9 (CH, Ph), 130.0 (C, Ph), 130.1 (CH, Ph), 133.8 (CH, Ph), 165.9 (CO, OBz).

Methyl (*R*)-4,6-*O*-benzylidene-3-deoxy-3-*C*-methyl-α-D-altropyranoside (522).

174 **522**

Methylmagnesium chloride (3M solution in THF, 320.0 mL, 0.96 mol) was added dropwise to a stirred suspension of the epoxide **174** (50.0 g, 0.19 mol) in dry THF (200 mL), while cooling the reaction flask in ice. The reaction mixture was heated under gentle reflux for 5 h, then stirred at room temperature overnight. The reaction was quenched by the addition of the reaction mixture to ice/water (750 mL) in several portions. This mixture was extracted with diethyl ether (2 × 600 mL), the combined organic layers washed with saturated sodium chloride solution (400 mL), dried, and evaporated to leave a thick yellow oil. Chromatography on silica gel with petroleum ether-ethyl acetate (1:1) as eluent yielded a white solid, which was redissolved in diethyl ether, and petroleum ether (60-80 °C) added until the solution became cloudy and the product began to crystallize out of solution. The product was filtered off under vacuum, washed with petroleum ether (60-80 °C), and dried in a vacuum oven overnight at room temperature to give **522** as a white crystalline solid (23.86 g, 45%): δ_H (250 MHz, $CDCl_3$) 1.23 (3H, d, *J* 7.5, C3-Me), 2.10 (1H, br s, O*H*), 2.35 (1H, br m, 3-H), 3.38 (3H, s, OMe), 3.65-4.40 (5H, 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, Ph).
This is a literature compound and method.[60]

Methyl (*R*)-4,6-*O*-benzylidene-3-deoxy-3-*C*-methyl-α-D-*arabino*-hexopyranosid-2-ulose (128).



522 **128**

Dimethyl sulphoxide (10.1 mL, 0.14 mol) in dry dichloromethane (140.0 mL) was added dropwise to a stirred solution of trifluoroacetic anhydride (15.1 mL, 0.11 mol) in dry dichloromethane (40.0 mL) at -78 °C. After allowing the solution to stir for 0.25 h, a solution of the alcohol **522** (20.0 g, 71.35 mmol) in dry dichloromethane (20.0 mL) was

added dropwise and the reaction allowed to stir for 1.2 h. Triethylamine (28.8 mL, 0.21 mol) was added and the solution allowed to warm to room temperature overnight. The reaction mixture was diluted with dichloromethane (400 mL), washed with 1M aqueous hydrochloric acid (2 × 100 mL), and saturated aqueous sodium hydrogen carbonate (2 × 200 mL). The dichloromethane layer was dried and evaporated to leave a brown solid. Chromatography on silica gel with petroleum ether-ethyl acetate (4:1) as the eluent yielded **128** as a white crystalline solid (12.22 g, 62%): mp 124-125 °C (lit.[60] mp 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, 10.3, 6eq-H), 4.66 (1H, s, 1-H), 5.55 (1H, s, 10-H), 7.41-7.54 (5H, Ph); δ_C (75 MHz, $CDCl_3$) 8.8 (CH_3, C3-Me), 46.2 (CH, C3), 55.6 (CH_3, OMe), 64.2 (CH, C5), 69.0 (CH_2, C6), 82.5 (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.[60]

1-(Bromovinyl)trimethylsilane.

Trimethylsilane (50.0 g, 0.50 mol) was cooled to -70 °C (dry ice/acetone bath) and bromine (28.4 mL, 0.55 mol) added dropwise over 1.5 h. The mixture was allowed to slowly warm to room temperature and the pale yellow solution cooled in ice. Diethylamine (300 mL, 2.90 mol) was added dropwise to this solution. 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, the precipitate of diethylamine hydrobromide removed by filtration, and the solid washed with diethyl ether (3 × 100 mL). The filtrate was washed with 100 mL portions of 10% aqueous hydrochloric acid until the aqueous layer remained acidic. When the washing was complete and the aqueous layer remained acidic, the yellow/orange colour of the organic phase transferred to the aqueous phase. The organic layer was then washed with water (100 mL) followed by saturated aqueous sodium chloride (200 mL). The organic layer was dried and the diethyl ether removed from the solution by distillation at atmospheric pressure. The remaining pale yellow solution containing the product was distilled under reduced pressure using Kugelrohr apparatus. The bromide was

obtained as a clear colourless liquid which was light sensitive (44.80 g, 50%): bp 48-50 °C at 50 mbar; δ_H (90 MHz, $CDCl_3$) 0.15 (9H, s, $Si(CH_3)_3$), 6.60 (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.[158]

3-Trimethylsilyl-3-buten-2-ol.

A few crystals of iodine and approximately 2.0 - 3.0 mL of a solution of the bromide (46.16 g, 0.26 mol) in dry THF (66.0 mL) were added sequentially to a suspension of magnesium turnings (8.77 g, 0.36 mol) in dry THF (45.0 mL). Once the reaction was initiated, the remainder of the bromide solution was added dropwise while maintaining a gentle reflux. When addition was complete (*ca.* 45 minutes) the reaction was heated under reflux for a further hour. The reaction was then cooled in an ice bath and a solution of acetaldehyde (21.6 mL, 0.39 mol) in dry THF (17.0 mL) added dropwise with stirring. The reaction was heated under reflux at 70 °C for 1 h. The reaction mixture was added to ice/water (1000 mL) in several portions. This mixture was quenched by adding saturated aqueous ammonium chloride (65 mL) slowly in several portions. The mixture was extracted with diethyl ether (4 × 200 mL), the combined organic extracts washed with saturated aqueous sodium chloride (200 mL), dried and the diethyl ether (and some THF) removed by distillation at atmospheric pressure, leaving the crude product as a yellow liquid (71.90 g, >100%).

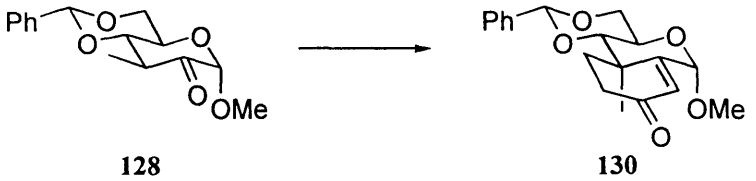
This is a literature compound and method.[158]

3-Trimethylsilyl-3-buten-2-one.

Jones' reagent (70.0 mL) was added dropwise to a cooled (0 °C) solution of the allylic alcohol (71.90 g crude, assume 100% from previous reaction = 37.18 g, 0.26 mol) in acetone (440 mL). The solution changed from yellow to green and finally red/brown at the end point. After addition was complete the reaction was stirred at 0 °C for 0.5 h then saturated aqueous sodium metabisulphite (75.0 mL) added to destroy any excess chromic acid. Water (200 mL) and diethyl ether (400 mL) were added and the reaction stirred until the Cr^{3+} salts dissolved. The aqueous and diethyl ether layers were separated and the aqueous layer extracted with diethyl ether (2 × 150 mL). The diethyl ether layer and extracts were combined, washed with water (4 × 200 mL), 10% aqueous potassium carbonate (4 × 150 mL) and finally saturated aqueous sodium chloride (2 × 200 mL). The organic layer was dried and the diethyl ether removed on a rotary evaporator at atmospheric pressure (water bath temperature 40 °C). The last traces of diethyl ether were removed by distillation under reduced pressure. The remaining yellow liquid was distilled using Kugelrohr apparatus to give a pale yellow liquid (17.20 g, 46%): δ_H (90 MHz, $CDCl_3$) 0.00 (9H, s, $SiMe_3$), 2.20 (3H, s, CH_3), 6.03 (1H, s, Me_3Si-C=CH_aH_b), 6.37 (1H, s, Me_3Si-C=CH_aH_b).

This is a literature compound.[158]

(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 (130).



128 **130**

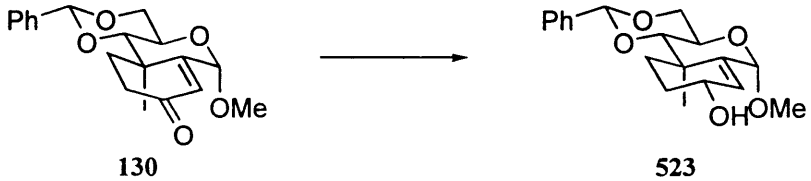
Sodium bis(trimethylsilyl)amide (1M solution in THF, 19.0 mL, 19.00 mmol) was added dropwise to a cooled solution of the ketone **128** (4.81 g, 17.28 mmol) in dry THF (20.0 mL) and the reaction stirred at 0 °C for 1 h. 3-Trimethylsilyl-3-buten-2-one (3.44 g, 24.18

mmol) was added dropwise and the solution allowed to warm to room temperature and stirred for a further hour. The mixture was poured into water (200 mL) and extracted into diethyl ether (2 × 200 mL). The combined organic extracts were washed with saturated aqueous sodium chloride (200 mL), dried and evaporated to leave a deep yellow oil (12.8 g), which was used without any further purification in the next step.

A solution of the intermediate in methanol (100 mL) containing aqueous potassium hydroxide (4% solution, 12.0 mL, 8.57 mmol) was heated at 80 °C for 2 h. The methanol was removed under reduced pressure, the residue dissolved in diethyl ether (400 mL), washed with saturated aqueous sodium chloride (2 × 150 mL), dried and evaporated to dryness. Chromatography on silica gel with petroleum ether-ethyl acetate (4:1) as the eluent yielded the enone **130** as an off-white foam (4.34 g, 76%): 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, d, 2-H) overlapping with 3.41 (3H, s, OMe), 3.72 (1H, t, *J* 10.2, 6ax-H), 4.20 (1H, dt, *J* 5.2, 9.7, 7-H), 4.35 (1H, dd, *J* 5.2, 10.2, 6eq-H), 4.89 (1H, s, 9-H), 5.55 (1H, s, 4-H), 5.87 (1H, s, 11-H), 7.33-7.49 (5H, Ph); δ_C (75 MHz, $CDCl_3$) 16.6 (CH_3, C1-Me), 33.5 (CH_2, C14), 34.6 (CH_2, C13), 37.8 (C, C1), 55.2 (CH_3, OMe), 59.7 (CH, C7), 69.1 (CH_2, C6), 85.3 (CH, C2), 101.5 (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.[41]

(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 (523).



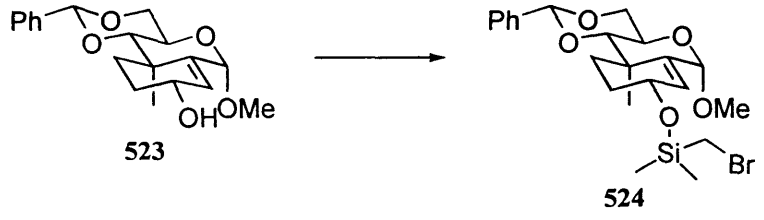
130 **523**

A solution of **130** (17.35 g, 52.52 mmol) in dry THF (200.0 mL) was cooled to -78 °C. L-Selectride® (1M solution in THF, 52.52 mL, 52.52 mmol) was added dropwise to this solution and the reaction was then stirred at -78 °C for 1.5 h. The reaction was allowed to warm to room temperature, water (280 mL) was added and the reaction stirred at room temperature for 0.5 h. The reaction mixture was extracted with diethyl ether (3 × 200 mL),

the combined organic extracts washed with saturated aqueous sodium chloride (3 × 150 mL), dried and concentrated under reduced pressure to leave a yellow oil. Chromatography on silica gel with petroleum ether-ethyl acetate (6:4) as the eluent yielded the allylic alcohol **523** as a white foam (14.25 g, 82%): 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* 2.5, 9.5, 14.3), 1.73 (1H, br s, O*H*), 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, OMe), 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, Ph); δ_C (75 MHz, $CDCl_3$) 19.0 (CH_3, C1-Me), 28.2 (CH_2, C14), 34.4 (CH_2, C13), 37.3 (C, C1), 54.9 (CH_3, OMe), 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.[159]

(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 (524).

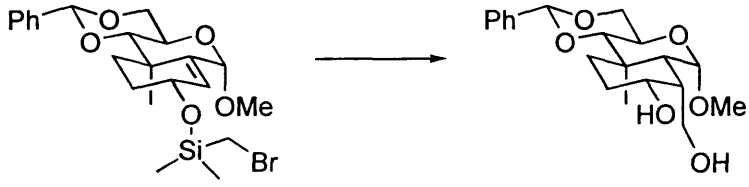


(Bromomethyl)chlorodimethylsilane (17.03 mL, 124.9 mmol) was added dropwise to a solution of allylic alcohol **523** (37.74 g, 113.5 mmol) and triethylamine (28.47 mL, 204.3 mmol) in dry dichloromethane (480.0 mL) over 15 minutes. The reaction was stirred at room temperature for 2.5 h. The reaction mixture was concentrated under reduced pressure and the residue dissolved in diethyl ether (500 mL). Any remaining residue was dissolved in water (1000 mL). The aqueous layer was extracted with diethyl ether (300 mL), the combined diethyl ether extracts washed with saturated aqueous sodium chloride (2 × 300 mL), dried and concentrated under reduced pressure to give an orange syrup. Chromatography on silica gel with diethyl ether basified with 0.1% triethylamine as the eluent yielded the silyl ether **524** as a pale yellow oil (49.65 g, 90%): 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* 10.0, 2-

H), 3.45 (3H, s, OMe), 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, Ph); δ_C (75 MHz, $CDCl_3$) -2.4 (CH_3, $SiMe_2$), 16.2 (CH_3, C1-Me), 18.9 (CH_2, CH_2Br), 28.1 (CH_2, C14), 34.4 (CH_2, C13), 37.2 (C, C1), 54.9 (CH_3, OMe), 60.3 (CH, C7), 68.6 (CH, C2), 69.6 (CH_2, C6), 86.8 (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, C11), 137.8 (C), 138.8 (C).

This is a literature compound and method.[159]

(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 (526).



524 **526**

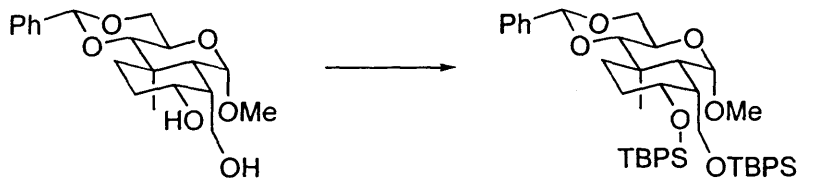
Sodium cyanoborohydride (16.13 g, 255.9 mmol), tribuyltin chloride (2.79 mL, 10.27 mmol) and AIBN (1.69 g, 10.27 mmol) were added sequentially to a solution of silyl ether **524** (49.65 g, 102.7 mmol) in dry *tert*-butanol (500 mL). The reaction mixture was heated under reflux (90 °C) for 4 h. The reaction was cooled to room temperature and poured into water (200 mL), the product extracted into diethyl ether (2 × 500 mL), the combined diethyl ether layers washed with water (2 × 200 mL), dried and evaporated to dryness. The resulting white solid **525** was used directly in the next step without further purification.

Potassium carbonate (14.24 g, 103.2 mmol) was added to a solution of the intermediate white solid **525** in THF/methanol (1:1; 500 mL), followed by the cautious dropwise addition of hydrogen peroxide (30% aqueous solution, 58.37 mL, 515.0 mmol). The reaction was heated under reflux for 16 h, cooled to room temperature and concentrated under reduced pressure. The resulting residue was poured into saturated aqueous sodium chloride (500 mL) and the product extracted into ethyl acetate (3 × 200 mL). 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 **526** as a waxy solid (19.94 g, 53%): δ_H (300 MHz, $CDCl_3$) 1.50 (1H, br t, *J* 5.1, 10.1, 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, OMe), 3.49 (2H, br s, O*H*), 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, 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), 47.8 (CH, C10), 55.1 (CH_3, OMe), 60.2 (CH_2, CH_2OH), 60.3 (CH, C7), 69.5 (CH_2, C6), 74.6 (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, Ph).

This is a literature compound and method.[159]

(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 (527).



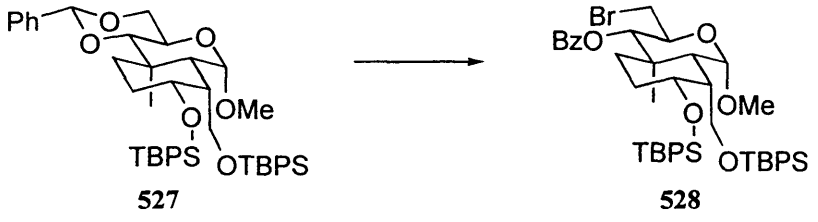
526 527

Diol **526** (19.94 g, 54.71 mmol), imidazole (14.90 g, 218.9 mmol) and 4-(dimethylamino) pyridine (334 mg, 2.73 mmol) were dissolved in dry dichloromethane (130 mL). This solution was cooled in an ice bath and *tert*-butylchlorodiphenylsilane (42.7 mL, 164.2 mmol) added dropwise. The reaction was then stirred at room temperature for 3 days. A small amount of imidazole was added to ensure the reaction was basic then the reaction was quenched by the cautious addition of methanol (100 mL), diluted with dichloromethane (1200 mL) and this solution washed with water (3 × 400 mL), followed by saturated aqueous sodium chloride (2 × 300 mL), dried and concentrated under reduced pressure to give a yellow oil. Chromatography on silica gel with petroleum ether-ethyl acetate (95:5) as the eluent yielded the protected diol **527** as a white foam (44.40 g, 96%): δ_H (250 MHz, $CDCl_3$) 0.97 (1H, m, 14a-H), 1.12 (3H, s, C1-CH_3), 1.21 (9H, s, ^{t}Bu), 1.23 (9H, s, ^{t}Bu), 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, 7-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, 6eq-H overlapping 9-H), 5.49 (1H, s, 4-H), 7.38-7.52 (17H, Ph), 7.84-

7.93 (8H, 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 (2 × CH, C10 and C11), 54.9 (CH_3, OMe), 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 (15 × CH, Ph), 138.5 (C, Ph).

This is a literature compound.[160]

(1*R*,2*S*,3*S*,5*S*,6*R*,7*R*,8*R*)-2-Benzoyloxy-3-bromomethyl-8-*tert*butyldiphenylsiloxy-7-*tert*-butyldiphenylsiloxymethyl-5-methoxy-1-methyl-4-oxabicyclo[4.4.0]-decane (528).

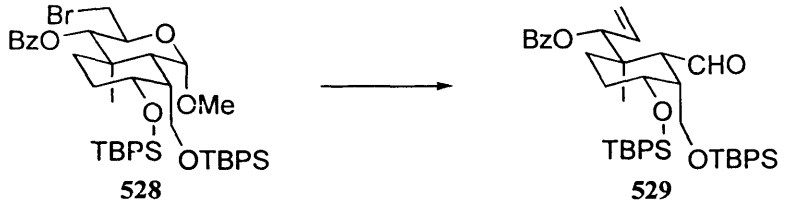


527 **528**

Barium carbonate (57.29 g, 290.3 mmol) and *N*-bromosuccinimide (11.27 g, 63.32 mmol) were added sequentially to a solution of **527** (44.40 g, 52.78 mmol) in dry carbon tetrachloride (600 mL). The reaction was heated at 80 °C overnight, allowed to cool to room temperature, barium carbonate removed by filtration and the residue washed with dichloromethane (2 × 250 mL). The filtrate was washed with water (2 × 300 mL), dried and evaporated to dryness. Chromatography on silica gel with petroleum ether-ethyl acetate (20:1) as the eluent yielded the bromo ester **528** as a white foam (31.18 g, 64%): δ_H (250 MHz, $CDCl_3$) 0.72-0.91 (2H, m), 0.94 (3H, s, C1-CH_3), 0.96 (9H, s, ^{t}Bu), 0.97 (9H, s, ^{t}Bu), 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, ddd, *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, 9.4, 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, Ph), 7.57-7.66 (8H, Ph), 7.81-7.84 (2H, Ph); 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 (2 × CH, C6 and C7), 55.0 (CH_3, OMe), 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 (7 × CH, Ph), 134.7-135.1 (4 × C, Ph), 136.4 (3 × CH, Ph), 166.0 (C, CO).

This is a literature compound.[160]

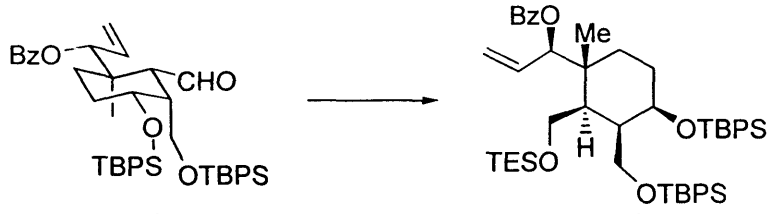
(1*R*,1'*R*,2'*R*,3'*R*,4'*R*)-1'-Methyl-2'-formyl-3'-*tert*-butyldiphenylsiloxymethyl-4'-*tert*-butyldiphenylsiloxy-1-cyclohexyl-2-propenyl-1-benzoate (529).



528 **529**

Zinc (510 g, 7.80 mol) was activated by washing with 2M aqueous hydrochloric acid (6 × 250 mL), water (5 × 300 mL), 10% aqueous potassium carbonate (250 mL), water (4 × 350 mL), isopropanol (2 × 300 mL) and finally diethyl ether (3 × 300 mL). Activated zinc (288.1 g, 4.41 mol) was added to a solution of **528** (31.18 g, 33.89 mmol) in isopropanol : water (900:102 mL). The reaction was heated under reflux for 5 h, cooled to room temperature and stirred overnight. The zinc removed by filtration and washed with diethyl ether (3 × 250 mL). The filtrate was concentrated under reduced pressure, the resulting residue dissolved in diethyl ether (800 mL), washed with water (2 × 400 mL), followed by saturated aqueous sodium chloride (300 mL), dried and evaporated to dryness. Chromatography on silica gel with petroleum ether-dichloromethane (1:1) as the eluent yielded the aldehyde **529** as a white foam (10.23 g, 37%): δ_H (250 MHz, $CDCl_3$) 0.87 (9H, s, ^{t}Bu), 0.89 (9H, s, ^{t}Bu), 1.04 (3H, s, C1'-CH_3), 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-H), 5.42-5.67 (2H, 1-H and 2-H), 7.05-7.51 (23H, Ph), 7.89 (2H, Ph), 10.05 (1H, d, *J* 5.0, C*H*O); 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_2, C3), 127.9-130.1 (7 × CH, Ph), 130.5 (C, Ph), 132.4 (CH, Ph), 133.2 (CH, Ph), 133.6-134.3 (4 × C, Ph), 136.0-136.5 (4 × CH, Ph), 165.9 (C, CO), 205.0 (CH, CHO). This is a literature compound.[160]

(1*R*,1'*R*,2'*R*,3'*R*,4'*R*)-1'-Methyl-2'-triethylsiloxymethyl-3'-*tert*-butyldiphenylsiloxymethyl-4'-*tert*-butyldiphenylsiloxy-1-cyclohexyl-2-propenyl-1-benzoate (530).



529 **530**

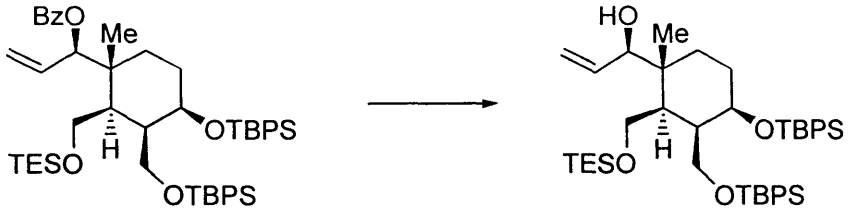
Aldehyde **529** (10.23 g, 12.64 mmol) was dissolved in isopropanol : methanol (380:152 mL). This solution was cooled in an ice bath and sodium borohydride (1.913 g, 50.57 mmol) was added in several portions. The reaction was stirred at room temperature overnight. The solvent was removed under reduced pressure, the residue dissolved in dichloromethane (500 mL), washed with water (2 × 450 mL), followed by saturated aqueous sodium chloride (500 mL), dried and concentrated under reduced pressure to give a white solid which was used directly in the next reaction.

Imidazole (2.16 g, 31.73 mmol) and chlorotriethylsilane (4.25 mL, 25.32 mmol) were added sequentially to a solution of the crude alcohol (10.31 g, 12.64 mmol) in dry dichloromethane (150 mL). The reaction was stirred for 4 days at room temperature. A small amount of imidazole was added to ensure the reaction was basic, then the reaction was diluted with dichloromethane (500 mL). This solution was washed with water (2 × 300 mL), followed by saturated aqueous sodium chloride (400 mL), dried and concentrated under reduced pressure to give a colourless oil. Chromatography on silica gel with petroleum ether-diethyl ether (30:1) as the eluent yielded **530** as a white foam (9.25 g, 79% over two steps): δ_H (250 MHz, $CDCl_3$) 0.45 (6H, q, *J* 8.0, CH_3CH_2Si), 0.83 (9H, t, *J* 8.0, CH_3CH_2Si), 0.92 (9H, s, ^{t}Bu), 0.96 (10H, s, ^{t}Bu 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, 3-H), 5.77-5.93 (2H, m, 1-H and 2-H), 7.25-7.50 (15H, Ph), 7.58-7.67 (8H, Ph), 7.94 (2H, d with fine splitting, *J* 7.1, Ph); δ_C (62.9 MHz, $CDCl_3$) 4.2 (CH_2, CH_3CH_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 (6 × CH, Ph), 130.1 (C, Ph), 132.7 (CH, Ph or C2), 133.0 (CH, C2 or Ph), 133.2-134.1 (3 × C, Ph), 135.4-135.9 (3 × CH, Ph), 165.6 (C, CO).

This is a literature compound.[160]

(3*R*,1'*R*,2'*R*,3'*R*,4'*R*)-4'-*tert*-Butyldiphenylsiloxy-3'-*tert*-butyldiphenylsiloxymethyl-3-hydroxy-1'-methyl-2'-triethylsiloxymethyl-3-cyclohexyl-propene (531).

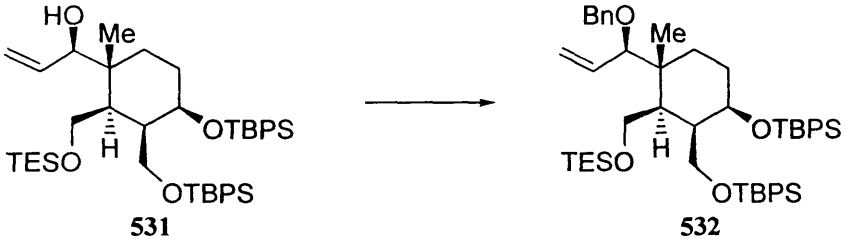


530 **531**

Diisobutylaluminium hydride (1.5M solution in toluene, 20.0 mL, 30 mmol) was added to a cooled (-78 °C) solution of **530** (9.25 g, 9.99 mmol) in dry dichloromethane (300 mL). The reaction was stirred at -78 °C for 2.5 h, quenched with isopropanol (35 mL) and saturated sodium sulphate solution (20 mL), and allowed to warm to room temperature. The gelatinous solid was filtered through celite and washed with dichloromethane (3 × 150 mL). The organic filtrate was washed with water (500 mL), followed by saturated aqueous sodium chloride (300 mL), dried and evaporated to dryness. Chromatography on silica gel with petroleum ether-diethyl ether (97.5:2.5) as the eluent yielded the alcohol **531** as a colourless oil (7.00 g, 85%): R_f 0.33, petroleum ether-diethyl ether (4:1); δ_H (250 MHz, $CDCl_3$) 0.45 (6H, q, *J* 7.6, CH_3CH_2Si), 0.80 (3H, s, C1'-CH_3), 0.82 (9H, t, overlapping, *J* 7.6, CH_3CH_2Si), 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, O*H*), 3.67 (1H, apparent d, *J* 11.3, 3-H), 3.83 (4H, m, 2 × CH_2OSi), 4.06 (1H, m, 4'-H), 5.01 (1H, d, *J* 10.1, 1_{cis}-H), 5.05 (1H, d, overlapping, *J* 17.3, 1_{trans}-H), 5.71 (1H, ddd, *J* 6.8, 10.1, 17.3, 2-H), 7.18-7.56 (20H, Ph); δ_C (62.9 MHz, $CDCl_3$) 3.6 (CH_2, CH_3CH_2Si), 5.7 (CH_3, CH_3CH_2Si), 17.2 (CH_3, C1'-Me), 18.1 (2 × C, ^{t}Bu), 26.0 (CH_2 and 2 × CH_3, ^{t}Bu and C6' or C5'), 28.7 (CH_2, C6' or C5'), 38.9 (C, C1'), 44.3 (2 × CH, C3' and C2'), 62.0 (CH_2, C2'-CH_2OSi), 64.1 (CH_2, C3'-CH_2OSi), 76.0 (CH, C3 or C4'), 76.2 (CH, C4' or C3), 115.6 (CH_2, C1), 126.4-126.6 (3 × CH, Ph), 128.5 (CH, Ph), 128.6 (CH, Ph), 132.6-133.3 (3 × C, Ph), 134.5-134.7 (3 × CH, Ph), 135.9 (CH, C2).

This is a literature compound.[161]

(3*R*,1'*R*,2'*R*,3'*R*,4'*R*)-4'-*tert*-Butyldiphenylsiloxy-3'-*tert*-butyldiphenylsiloxymethyl-1'-methyl-3-benzyloxy-2'-triethylsiloxymethyl-3-cyclohexyl-propene (532).

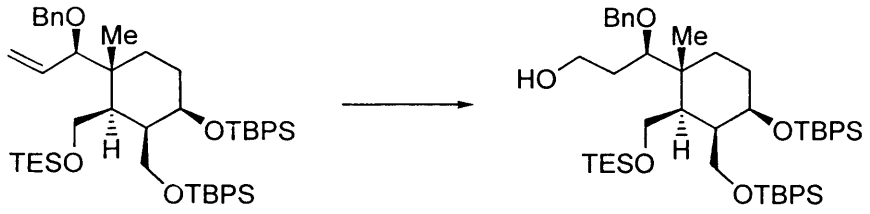


531 **532**

A solution of the alcohol **531** (5.34 g, 6.50 mmol) in dry THF (34.0 mL) was added dropwise to a suspension of sodium hydride (233 mg, 95% dry, 0.12 mmol) in dry THF (8.0 mL), cooled to 0 °C with stirring. The reaction mixture was allowed to stir for 2 h. Benzyl bromide (1.20 mL, 10.09 mmol) was added dropwise and the reaction allowed to stir at reflux for 68 h. The reaction was cooled in ice, and ethanol (5 mL) added to destroy the excess sodium hydride. The reaction mixture was poured into ice/water (500 mL), the aqueous layer was extracted with diethyl ether (2 × 250 mL) and the combined organic layers washed with saturated aqueous sodium chloride (2 × 100 mL), dried and evaporated to dryness. Chromatography on silica gel with petroleum ether-diethyl ether (98:2) as the eluent yielded **532** as a colourless oil (3.72 g, 63%): R_f 0.25, petroleum ether-diethyl ether (98:2); δ_H (250 MHz, $CDCl_3$) 0.42 (6H, q, *J* 7.9, CH_3CH_2Si), 0.80 (9H, t, *J* 7.9, CH_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, 9.4, C*H*HOSi), 3.72 (1H, d obscured, *J* 4.1, CH*H*OSi) overlapping 3.72 (2H, m, CH_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-H_{cis}), 5.62 (1H, ddd, *J* 1.6, 10.1, 17.3, 2-H), 7.14-7.99 (25H, 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, ^{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, C5' or C6'), 40.6 (C, C1'), 43.4 (CH, C2'), 44.9 (CH, C3'), 61.9 (CH_2, CH_2OSi), 65.3 (CH_2, CH_2OSi), 68.9 (CH, C4'), 70.8 (CH_2, CH_2Ph), 82.3 (CH, C3), 119.6 (CH_2, C1), 127.6-128.6 (7 × CH, Ph), 129.9 (CH, Ph or C2), 129.9 (CH, C2 or Ph), 134.2-135.0 (4 × C, Ph), 135.9-136.6 (5 × CH, Ph), 139.7 (C, Ph).

This is a literature compound.[161]

(3*R*,1'*R*,2'*R*,3'*R*,4'*R*)-4'-*tert*-Butyldiphenylsiloxy-3'-*tert*-butyldiphenylsiloxymethyl-1'-methyl-3-benzyloxy-2'-triethylsiloxymethyl-3-cyclohexyl-propan-1-ol (533).

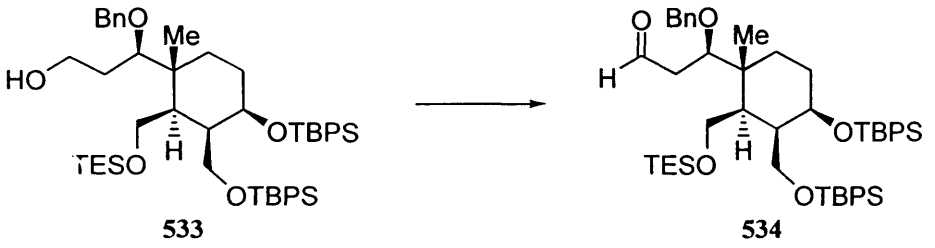


532 533

9'BBN (0.5M solution in hexanes, 24.5 mL, 12.25 mmol) was added dropwise to a solution of **532** (3.72 g, 4.08 mmol) in dry THF (20 mL), cooled to 0 °C with stirring. The resulting solution was warmed to 30 °C and held at this temperature for 19 h with stirring. The reaction was quenched (care) by the addition of sodium hydroxide (13.5 mL, 6N solution) followed by hydrogen peroxide (13.5 mL, 30% w/v solution in water), and the solution allowed to stir overnight. The solution was diluted with water (200 mL) and diethyl ether (200 mL). The layers were separated and the aqueous layer extracted with diethyl ether (100 mL). The combined organic layers were washed with saturated aqueous sodium chloride (2 × 100 mL), dried and evaporated to dryness. Chromatography on silica gel with petroleum ether-ethyl acetate (95:5) as the eluent yielded **533** as a colourless oil (3.17 g, 84%): R_f 0.30, petroleum ether-ethyl acetate (95:5); δ_H (250 MHz, $CDCl_3$) 0.43 (6H, q, *J* 8.0, CH_3CH_2Si), 0.79 (9H, t, *J* 8.0, CH_3CH_2Si), 0.89 (9H, s, ^{t}Bu) overlapping 0.89 (3H, s, C1'-CH_3), 0.94 (9H, s, ^{t}Bu), 1.22-1.35 (2H, m), 1.40-1.62 (7H, m), 3.59 (4H, m, 2 × CH_2OSi), 3.78 (3H, m, 4'-H and CH_2OH), 3.97 (1H, br s, 3-H), 4.37 (1H, d, *J* 11.3, CHHPh), 4.46 (1H, d, *J* 11.3, CHHPh), 7.10-7.54 (25H, 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, ^{t}Bu), 19.8 (C, ^{t}Bu), 20.6 (CH_3, C1'-Me), 26.1 (CH_2, C6' or C5'), 27.4 (CH_3, ^{t}Bu), 27.6 (CH_3, ^{t}Bu), 29.5 (CH_2, C5' or C6'), 33.3 (CH_2, C2), 41.7 (C, C1'), 43.5 (CH, C2'), 45.0 (CH, C3'), 61.5 (CH_2, CH_2OSi), 61.8 (CH_2, CH_2OSi), 65.3 (CH_2, C1), 69.0 (CH, C4'), 75.0 (CH_2, CH_2Ph), 78.8 (CH, C3), 127.6-130.0 (8 × CH, Ph), 134.0-134.8 (4 × C, Ph), 136.0-136.6 (4 × CH, Ph), 139.3 (C, Ph).

This is a literature compound.[161]

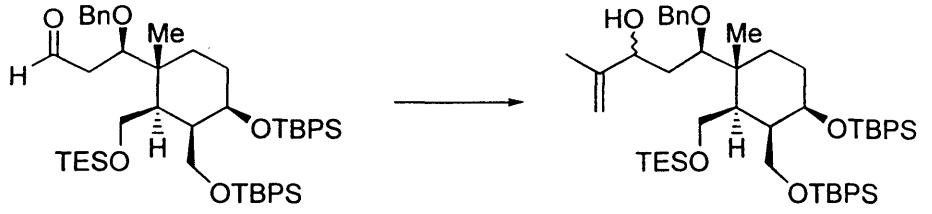
(3*R*,1'*R*,2'*R*,3'*R*,4'*R*)-4'-*tert*-Butyldiphenylsiloxy-3'-*tert*-butyldiphenylsiloxymethyl-1'-methyl-3-benzyloxy-2'-triethylsiloxymethyl-3-cyclohexyl-propanal (534).



Dimethyl sulphoxide (0.71 mL, 10.01 mmol) in dry dichloromethane (2.0 mL) was added dropwise to a stirred solution of oxalyl chloride (0.44 mL, 5.04 mmol) in dry dichloromethane (3.0 mL) at -78 °C. After allowing the reaction to stir for 0.25 h, a solution of the alcohol **533** (3.10 g, 3.34 mmol) in dry dichloromethane (15.0 mL) was added dropwise and the reaction allowed to stir for 1.2 h. Triethylamine (2.79 mL, 20.02 mmol) was added and the reaction allowed to warm to room temperature. The reaction mixture was diluted with diethyl ether (300 mL) and water (100 mL). The combined organic layers were washed with saturated aqueous sodium chloride (2 × 100 mL) and water (100 mL), dried and evaporated to dryness. Chromatography on silica gel with petroleum ether-ethyl acetate (97.5:2.5) as the eluent yielded **534** as a colourless oil (2.65 g, 86%): R_f 0.30, petroleum ether-ethyl acetate (97.5:2.5); 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, ^{t}Bu), 1.03 (3H, s, C1'-CH_3), 1.06 (9H, s, ^{t}Bu), 1.30-1.45 (2H, m), 1.55-1.80 (4H, m), 2.62 (2H, m, 2-H), 3.71 (1H, m, 4'-H), 3.81-4.01 (4H, m, 2 × CH_2OSi), 4.20 (1H, m, 3-H), 4.38 (1H, d, *J* 11.3, C*H*HPh), 4.51 (1H, d, *J* 11.3, CH*H*Ph), 7.21-7.66 (25H, Ph), 9.80 (1H, s, 1-H); δ_C (62.9 MHz, $CDCl_3$) 5.0 (CH_2, CH_3CH_2Si), 7.5 (CH_3, CH_3CH_2Si), 19.7 (C, ^{t}Bu), 19.8 (C, ^{t}Bu), 20.7 (CH_3, C1'-Me), 26.0 (CH_2, C6' or C5'), 27.4 (CH_3, ^{t}Bu), 27.7 (CH_3, ^{t}Bu), 29.4 (CH_2, C5' or C6'), 41.5 (C, C1'), 43.5 (CH, C2'), 45.1 (CH, C3'), 46.3 (CH_2, C2), 65.1 (CH_2, CH_2OSi), 66.3 (CH_2, CH_2OSi), 69.1 (CH, C4'), 73.9 (CH_2, CH_2Ph), 75.2 (CH, C3), 127.7-130.1 (9 × CH, Ph), 134.0-134.8 (4 × C, Ph), 136.0-136.6 (4 × CH, Ph), 139.2 (C, Ph), 201.9 (CH, C1).

This is a literature compound.[161]

(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 (535).



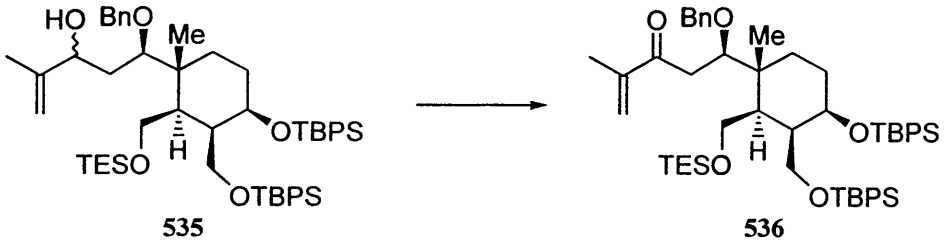
534 **535**

Isopropenylmagnesium bromide (0.5M solution in THF, 6.0 mL, 3.00 mmol) was added dropwise to a solution of the aldehyde **534** (2.65 g, 2.86 mmol) in dry THF (10 mL) at 0 °C. After 0.25 h the reaction was quenched by the addition of water (20 mL). The reaction mixture was diluted with diethyl ether (50 mL), the combined organic layers washed with saturated aqueous sodium chloride (2 × 15 mL), water (25 mL), dried and evaporated to dryness. Chromatography on silica gel with petroleum ether-ethyl acetate (9:1) as the eluent yielded **535** as a colourless oil (2.59 g, 93%), which was a *ca.* 2:1 mixture of diastereoisomers: Major isomer - R_f 0.40, petroleum ether-ethyl acetate (9:1); δ_H (250 MHz, $CDCl_3$) 0.69 (6H, q, *J* 8.2, CH_3CH_2Si), 1.06 (9H, t, *J* 8.2, CH_3CH_2Si), 1.15 (9H, s, ^{t}Bu), 1.17 (9H, s, ^{t}Bu) overlapping 1.18 (3H, s, C1'-CH_3), 1.60-2.00 (9H, 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, Ph); δ_C (62.9 MHz, $CDCl_3$) 7.0 (CH_2, CH_3CH_2Si), 9.5 (CH_3, CH_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, C5' or C6'), 38.7 (CH_2, C4), 43.7 (C, C1'), 45.3 (CH, C2'), 46.8 (CH, C3'), 63.8 (CH_2, CH_2OSi), 67.4 (CH_2, CH_2OSi), 71.4 (CH, C4' or C3), 75.3 (CH, C3 or C4'), 77.1 (CH_2, CH_2Ph), 79.7 (CH, C5), 112.2 (CH_2, C1), 129.5-132.0 (9 × CH, Ph), 136.1-136.9 (4 × C, Ph), 138.1-138.6 (4 × CH, Ph), 141.9 (C, Ph), 151.1 (C, C2).

Minor isomer - R_f 0.35, petroleum ether-ethyl acetate (9:1); δ_H (250 MHz, $CDCl_3$) 0.66 (6H, q, *J* 7.9, CH_3CH_2Si), 1.04 (9H, t, *J* 7.9, CH_3CH_2Si), 1.10 (9H, s, ^{t}Bu), 1.14 (9H, s, ^{t}Bu) overlapping 1.17 (3H, s, C1'-CH_3), 1.50-2.00 (8H, m) overlapping 1.74 (3H, s, C2-

CH_3), 2.79 (1H, br s, O*H*), 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, Ph); δ_C (62.9 MHz, $CDCl_3$) 6.7 (CH_2, CH_3CH_2Si), 9.1 (CH_3, CH_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, C5' or C6'), 38.3 (CH_2, C4), 44.0 (C, C1'), 45.3 (CH, C2'), 46.4 (CH, C3'), 63.4 (CH_2, CH_2OSi), 67.0 (CH_2, CH_2OSi), 71.0 (CH, C4' or C3), 76.5 (CH_2, CH_2Ph), 77.1 (CH, C3 or C4'), 82.2 (CH, C5), 113.1 (CH_2, C1), 129.1-131.7 (7 × CH, Ph), 135.6-136.5 (4 × C, Ph), 137.7-138.2 (4 × CH, Ph), 140.6 (C, Ph), 149.5 (C, C2).
These are literature compounds.[161]

(5*R*,1'*R*,2'*R*,3'*R*,4'*R*)-4'-*tert*-Butyldiphenylsiloxy-3'-*tert*-butyldiphenylsiloxymethyl-2,1'-dimethyl-5-benzyloxy-2'-triethylsiloxymethyl-5-cyclohexyl-pent-1-en-3-one (536).

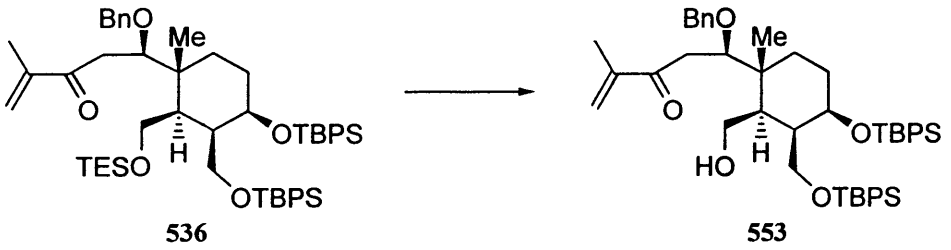


Dimethyl sulphoxide (0.57 mL, 8.03 mmol) in dry dichloromethane (2.0 mL) was added dropwise to a stirred solution of oxalyl chloride (0.35 mL, 4.01 mmol) in dry dichloromethane (2.0 mL) at -78 °C. After allowing the reaction to stir for 0.25 h, a solution of the alcohol **535** (2.59 g, 2.67 mmol) in dry dichloromethane (10.0 mL) was added dropwise and the reaction allowed to stir for 1.2 h. Triethylamine (2.23 mL, 16.00 mmol) was added and the reaction allowed to warm to room temperature. The reaction mixture was diluted with diethyl ether (300 mL) and water (200 mL). The combined organic layers were washed with saturated aqueous sodium chloride (2 × 100 mL) and water (100 mL), dried and evaporated to dryness. Chromatography on silica gel with petroleum ether-ethyl acetate (95:5) as the eluent yielded **536** as a colourless oil (2.23 g, 86%): R_f 0.45, petroleum ether-ethyl acetate (95:5); δ_H (250 MHz, $CDCl_3$) 0.47 (6H, q, *J* 7.9, CH_3CH_2Si), 0.81 (9H, t, *J* 7.9, CH_3CH_2Si), 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), 3.58-3.72 (2H, m), 3.78-3.94 (3H, 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, Ph); δ_C (62.9 MHz, $CDCl_3$) 3.5 (CH_2, CH_3CH_2Si), 5.9 (CH_3, CH_3CH_2Si), 16.8 (CH_3, C1'-Me), 18.1 (C, ^{t}Bu), 18.3 (C, ^{t}Bu), 19.4 (CH_3, C2-Me), 26.6 (CH_2, C6' or C5'), 27.9 (CH_3, ^{t}Bu), 28.0 (CH_3, ^{t}Bu), 31.0 (CH_2, C5' or C6'), 38.1 (CH_2, C4), 40.3 (C, C1'), 41.8 (CH, C2'), 43.4 (CH, C3'), 60.2 (CH_2, CH_2OSi), 63.6 (CH_2, CH_2OSi), 67.9 (CH, C4'), 72.5 (CH_2, CH_2Ph), 75.2 (CH, C5), 123.9 (CH_2, C1), 126.0-128.5 (9 × CH, Ph), 132.5-133.3 (4 × C, Ph), 134.5-135.0 (4 × CH, Ph), 138.3 (C, Ph), 143.8 (C, C2), 200.0 (C, C3).

This is a literature compound.[161]

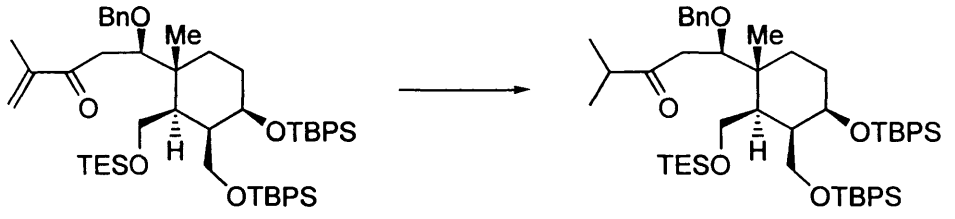
(5*R*,1'*R*,2'*R*,3'*R*,4'*R*)-4'-*tert*-Butyldiphenylsiloxy-3'-*tert*-butyldiphenylsiloxymethyl-2,1'-dimethyl-5-benzyloxy-2'-hydroxymethyl-5-cyclohexyl-pent-1-en-3-one (553).



A solution of enone **536** (366 mg, 0.38 mmol) in THF/acetic acid/water (11:5:3, 20 mL) was stirred overnight at room temperature. The mixture was poured into excess saturated aqueous sodium carbonate (100 mL), extracted with diethyl ether (2 × 50 mL), the combined organic layers washed with water (20 mL) and phosphate buffer (pH = 7, 10 mL), dried and evaporated to dryness. Chromatography on silica gel with petroleum ether-ethyl acetate (9:1) as the eluent yielded **553** as a colourless oil (259 mg, 80%): R_f 0.45, petroleum ether-ethyl acetate (9:1); δ_H (250 MHz, $CDCl_3$) 0.95 (9H, s, ^{t}Bu), 0.98 (9H, s, ^{t}Bu), 1.14 (3H, s, C1'-CH_3), 1.40-1.75 (4H, m), 1.83 (3H, s, C2-CH_3), 2.13 (1H, br s, O*H*), 2.69 (1H, br d, *J* 17.4, 4a-H), 3.07 (1H, dd, *J* 7.4, 17.4, 4b-H), 3.52 (1H, m), 3.78-3.90 (5H, m), 4.29 (2H, m) overlapping 4.33 (1H, d, *J* 11.3, C*H*HPh), 4.41 (1H, d, *J* 11.3, CH*H*Ph), 5.73 (1H, br s, 1a-H), 5.95 (1H, br s, 1b-H), 7.15-7.64 (25H, Ph); δ_C (62.9 MHz, $CDCl_3$) 18.2 (CH_3, C1'-Me), 19.6 (C, ^{t}Bu), 19.7 (C, ^{t}Bu), 19.9 (CH_3, C2-Me), 27.3 (CH_3, ^{t}Bu), 27.5 (CH_3, ^{t}Bu), 28.8 (CH_2, C6' or C5'), 39.9 (CH_2, C5' or C6'), 40.9 (CH, C2'), 41.1 (C, C1'), 42.9 (CH, C3'), 59.6 (CH_2, C4), 64.5 (CH_2, CH_2OSi), 66.3 (CH_2, CH_2OH), 70.2 (CH, C4'), 73.7 (CH_2, CH_2Ph), 77.0 (CH, C5), 125.4 (CH_2, C1), 127.6-130.4 (9 × CH, Ph),

132.7-134.0 (4 × C, Ph), 136.0-136.5 (4 × CH, Ph), 139.5 (C, Ph), 145.1 (C, C2), 201.1 (C, C3); *m/z* (FAB) 875 (MNa^+, 100%), 853 (MH^+, 41).

(5*R*,1'*R*,2'*R*,3'*R*,4'*R*)-4'-*tert*-Butyldiphenylsiloxy-3'-*tert*-butyldiphenylsiloxymethyl-2,1'-dimethyl-5-benzyloxy-2'-triethylsiloxymethyl-5-cyclohexyl-pentan-3-one (555).



536 555

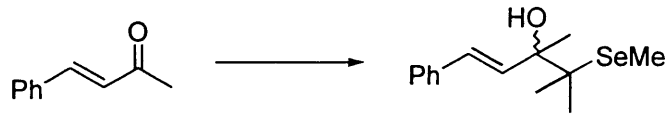
A solution of the enone **536** (107 mg, 0.11 mmol) in dry ethanol (5.0 mL) was degassed several times with nitrogen. The catalyst (palladium, 5% on carbon, 10 mg) was then added, the mixture degassed several times with hydrogen, then allowed to stir under a positive pressure of hydrogen (balloon) for 16 h. At this point the mixture was filtered through a plug of celite under reduced pressure, and the residue washed with ethanol (3 × 5 mL). The filtrate was then concentrated under reduced pressure to yield **555** as a colourless oil (107 mg, 99%): δ_H (250 MHz, $CDCl_3$) 0.79 (6H, q, *J* 7.7, CH_3CH_2Si), 1.15 (9H, t, *J* 7.7, CH_3CH_2Si), 1.21 (9H, s, ^{t}Bu), 1.21 (3H, d, overlapping, *J* 3.4, C2-CH_3), 1.23 (3H, d, *J* 3.4, C2-CH_3), 1.25 (3H, s, C1'-CH_3), 1.26 (9H, s, ^{t}Bu), 1.52-2.20 (6H, m), 2.62-2.85 (2H, m), 3.01 (1H, dd, *J* 8.5, 17.2, CH*H*, 4-H), 3.88-4.26 (5H, m), 4.53-4.62 (1H, m), 4.61 (1H, d, overlapping, *J* 11.3, C*H*HPh), 4.69 (1H, d, *J* 11.3, CH*H*Ph), 7.35-7.90 (25H, Ph); δ_C (62.9 MHz, $CDCl_3$) 4.9 (CH_2, CH_3CH_2Si), 7.4 (CH_3, CH_3CH_2Si), 18.3 (CH_3, C2-Me), 18.4 (CH_3, C2-Me), 19.6 (C, ^{t}Bu), 19.8 (C, ^{t}Bu), 20.8 (CH_3, C1'-Me), 26.4 (CH_2, C6' or C5'), 27.4 (CH_3, ^{t}Bu), 27.6 (CH_3, ^{t}Bu), 29.4 (CH_2, C5' or C6'), 41.3 (C, C1'), 42.2 (CH_2, C4), 42.3 (CH, C2'), 43.2 (CH, C2), 44.9 (CH, C3'), 61.6 (CH_2, CH_2OSi), 65.1 (CH_2, CH_2OSi), 69.3 (CH, C4'), 74.2 (CH_2, CH_2Ph), 76.4 (CH, C5), 127.5-130.0 (9 × CH, Ph), 134.0-134.8 (4 × C, Ph), 136.0-136.5 (4 × CH, Ph), 139.8 (C, Ph), 214.2 (C, C3); *m/z* (FAB) 991 (MNa^+, 26%).

2-Methyl-2-methylselenyl-1-phenyl-propan-1-ol (544).

544

A solution of 2,2-bis(methylseleno)propane (230 mg, 1.00 mmol) in dry diethyl ether (1.0 mL) was stirred at -78 °C. s-BuLi (1.3M solution in cyclohexane, 0.77 mL, 1.00 mmol) was added dropwise and the reaction allowed to stir at -78 °C for 1 h. Benzaldehyde (106 mg, 1.00 mmol) in dry diethyl ether (1.0 mL) was added and the reaction allowed to stir at -78 °C for 1 h. The reaction was quenched by the addition of saturated aqueous ammonium chloride (5.0 mL), diluted with diethyl ether (15 mL), the combined organic layers washed with water (10 mL) and saturated aqueous sodium chloride (2 × 10 mL), dried and evaporated to dryness. Chromatography on silica gel with petroleum ether-diethyl ether (4:1) as the eluent yielded **544** as a colourless oil (160 mg, 66%): R_f 0.50, petroleum ether-diethyl ether (4:1); δ_H (250 MHz, $CDCl_3$) 1.10 (3H, s, Me), 1.21 (3H, s, Me), 1.77 (3H, s, MeSe), 3.07 (1H, s, O*H*), 4.37 (1H, s, C*H*OH), 7.07-7.23 (5H, Ph).
This is a literature compound.[166]

***trans*-4-Methyl-4-methylselenyl-3-methyl-1-phenyl-pent-1-en-3-ol (545).**

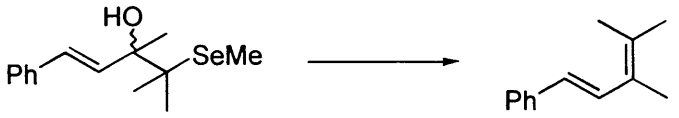


545

A solution of 2,2-bis(methylseleno)propane (230 mg, 1.00 mmol) in dry diethyl ether (1.0 mL) was stirred at -78 °C. s-BuLi (1.3M solution in cyclohexane, 0.77 mL, 1.00 mmol) was added dropwise and the reaction allowed to stir at -78 °C for 1 h. *trans*-4-Phenyl-3-buten-2-one (146 mg, 1.00 mmol) in dry diethyl ether (1.0 mL) was added and the reaction allowed to stir at -78 °C for 1 h. The reaction was quenched by the addition of saturated aqueous ammonium chloride (5.0 mL), diluted with diethyl ether (15 mL), the combined organic layers washed with water (10 mL) and saturated aqueous sodium chloride (2 × 10 mL), dried and evaporated to dryness. Chromatography on silica gel with petroleum ether-diethyl ether (4:1) as the eluent yielded **545** as a colourless oil (180 mg, 64%): R_f 0.41,

petroleum ether-diethyl ether (4:1); δ_H (250 MHz, $CDCl_3$) 1.33 (3H, s, Me), 1.37 (3H, s, Me), 1.41 (3H, s, Me), 1.86 (3H, s, MeSe), 2.61 (1H, s, O*H*), 6.36 (1H, d, *J* 16.0, 2-H), 6.59 (1H, d, *J* 16.0, 1-H), 7.08-7.31 (5H, Ph); δ_C (62.9 MHz, $CDCl_3$) 5.0, 24.3, 25.9 and 26.1 (4 × CH_3), 53.0 (C, C4), 78.3 (C, C3), 126.7-133.9 (5 × CH, C1, C2 and Ph), 137.5 (C, Ph).

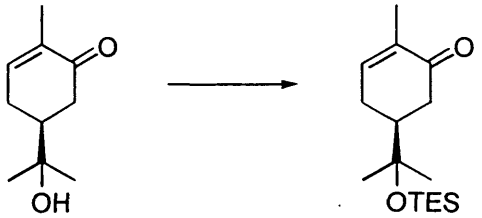
trans-(3,4-Dimethyl-penta-1,3-dienyl)-benzene (546).



545 **546**

A solution of the alcohol **545** (368 mg, 1.30 mmol) and triethylamine (0.70 mL, 5.02 mmol) in dry dichloromethane (6.0 mL) was added dropwise to a stirred solution of phosphorus triiodide (948 mg, 2.30 mmol) in dry dichloromethane (6.0 mL) at 0 °C. The reaction was stirred for 1.5 h and then filtered through a plug of silica gel. The silica gel was washed with petroleum ether-diethyl ether (4:1, 200 mL), the combined organic layers washed with water (80 mL) and saturated aqueous sodium chloride (2 × 50 mL), dried and evaporated to dryness. Chromatography on silica gel with petroleum ether-diethyl ether (99:1) as the eluent yielded the diene **546** as a colourless oil (160 mg, 72%): R_f 0.62, petroleum ether; δ_H (250 MHz, $CDCl_3$) 1.92-2.12 (9H, 3s, 3 × Me), 6.60 (1H, d, *J* 16.0, 2-H), 7.25-7.60 (6H, Ph and 1-H); δ_C (62.9 MHz, $CDCl_3$) 14.8, 21.0 and 22.6 (3 × CH_3), 126.5-129.0 (5 × CH, C1, C2 and Ph), 129.0 and 133.0 (C, C3 and C4), 139.2 (C, Ph).

(*S*)-(+)-5-(1-Triethylsiloxy-1-methylethyl)-2-methyl-2-cyclohexen-1-one (548).

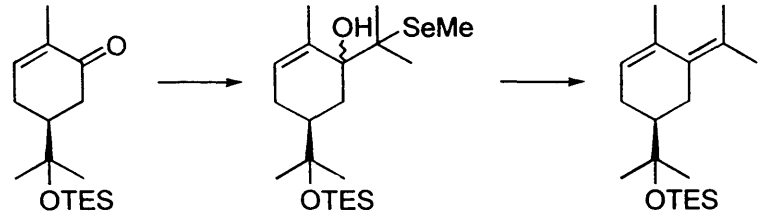


547 **548**

Imidazole (1.11 g, 16.30 mmol) and chlorotriethylsilane (2.20 mL, 13.11 mmol) were added sequentially to a solution of the alcohol **547** (1.10 g, 6.54 mmol) in dry

dichloromethane (15.0 mL) at 0 °C. The reaction was stirred overnight at room temperature. A small amount of imidazole was added to make sure the reaction was basic, then the reaction was diluted with dichloromethane (50 mL). This solution was washed with water (2 × 50 mL), followed by saturated aqueous sodium chloride (50 mL), dried and evaporated to dryness. Chromatography on silica gel with petroleum ether-diethyl ether (85:15) as the eluent yielded **548** as a colourless oil (1.54 g, 83%): R_f 0.60, petroleum ether-diethyl ether (4:1); δ_H (250 MHz, $CDCl_3$) 0.53 (6H, q, *J* 7.9, CH_3CH_2Si), 0.89 (9H, t, *J* 7.9, CH_3CH_2Si), 1.16 (3H, s, Me), 1.17 (3H, s, Me), 1.70 (3H, s, C2-Me), 1.93 (1H, m, 5-H), 2.09-2.43 (3H, m), 2.53 (1H, ddd, *J* 1.3, 3.6, 16.1, 4-H), 6.69 (1H, d, *J* 1.3, 3-H); δ_C (62.9 MHz, $CDCl_3$) 7.1 (CH_2, CH_3CH_2Si), 7.4 (CH_3, CH_3CH_2Si), 15.9 (CH_3, C2-Me), 27.5 (CH_2, C6), 27.9 (CH_3, C7-Me), 28.1 (CH_3, C7-Me), 40.0 (CH_2, C4), 47.7 (CH, C5), 74.1 (C, C7), 135.3 (C, C2), 145.6 (CH, C3), 201.0 (C, C1).

(*S*)-(+)-5-(1-Triethylsiloxy-1-methylethyl)-2-methyl-3-isopropylidene-1-cyclohexene (550).

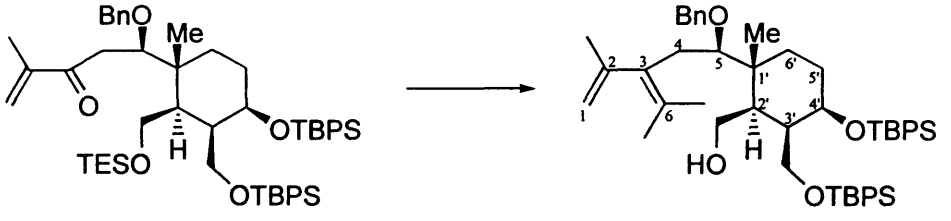


A solution of 2,2-bis(methylseleno)propane (253 mg, 1.10 mmol) in dry diethyl ether (1.0 mL) was stirred at -78 °C. s-BuLi (1.3M solution in cyclohexane, 0.85 mL, 1.10 mmol) was added dropwise and the reaction allowed to stir at -78 °C for 1.5 h. Enone **548** (282 mg, 1.00 mmol) in dry diethyl ether (2.0 mL) was added and the reaction allowed to stir at -78 °C for 1.5 h. The reaction was quenched by the addition of water (5.0 mL), diluted with diethyl ether (15 mL), the combined organic layers washed with water (10 mL) and saturated aqueous sodium chloride (2 × 10 mL), dried and evaporated to dryness. Chromatography on silica gel with petroleum ether-diethyl ether (4:1) as the eluent yielded **549** as a colourless oil (317 mg, 76%), which was a *ca.* 1:1 mixture of diastereoisomers. Alcohol **549** was used directly in the next reaction.

A solution of the alcohol **549** (104 mg, 0.25 mmol) and triethylamine (0.09 mL, 0.65 mmol) in dry dichloromethane (1.0 mL) was added dropwise to a stirred solution of

phosphorus triiodide (118 mg, 0.29 mmol) in dry dichloromethane (1.0 mL) at 0 °C. The reaction was stirred for 1.5 h, poured into saturated aqueous sodium hydrogen carbonate (10 mL) and extracted with diethyl ether (2 × 10 mL). The combined organic layers were washed with saturated aqueous sodium hydrogen carbonate (2 × 10 mL) and saturated aqueous sodium chloride (10 mL), dried and evaporated to dryness. Chromatography on silica gel with petroleum ether-diethyl ether (98:2) as the eluent yielded the diene **550** as a colourless oil (61 mg, 80%): R_f 0.88, petroleum ether-diethyl ether (95:5); δ_H (250 MHz, $CDCl_3$) 0.50 (6H, q, *J* 7.9, CH_3CH_2Si), 0.88 (9H, t, *J* 7.9, CH_3CH_2Si), 1.09 (3H, s, C7-Me), 1.12 (3H, s, C7-Me), 1.40-1.64 (2H, m), 1.69 (3H, s, C2-Me), 1.78 (3H, s, C8-Me), 1.90-2.13 (2H, m) overlapping 1.90 (3H, s, C8-Me), 2.68 (1H, d, *J* 10.7, H-6), 5.41 (1H, s, H-1); δ_C (62.9 MHz, $CDCl_3$) 7.5 (CH_2, CH_3CH_2Si), 7.8 (CH_3, CH_3CH_2Si), 23.0 (CH_3, C8-Me), 23.7 (CH_3, C8-Me), 24.9 (CH_3, C2-Me), 27.0 (CH_3, C7-Me), 28.3 (CH_3, C7-Me), 28.8 and 30.7 (2 × CH_2, C4 and C6), 47.6 (CH, C5), 75.4 (C, C7), 125.6, 132.7 and 134.9 (3 × C, C2, C3 and C8), 128.1 (CH, C1).

(5*R*,1'*R*,2'*R*,3'*R*,4'*R*)-4'-*tert*-Butyldiphenylsiloxy-3'-*tert*-butyldiphenylsiloxymethyl-2,1'-dimethyl-5-benzyloxy-2'-hydroxymethyl-5-cyclohexyl-3-isopropylidene-pent-1-ene (551).

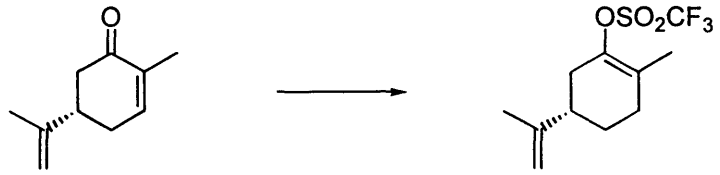


536 **551**

A solution of 2,2-bis(methylseleno)propane (713 mg, 3.10 mmol) in dry diethyl ether (3.1 mL) was stirred at -78 °C. s-BuLi (1.3M solution in cyclohexane, 2.00 mL, 2.60 mmol) was added dropwise and the reaction allowed to stir at -78 °C for 1.75 h. Enone **536** (510 mg, 0.53 mmol) in dry diethyl ether (1.4 mL) was added and the reaction allowed to stir at -78 °C for 4 h. The reaction was quenched by the addition of water (20 mL), diluted with diethyl ether (20 mL), the combined organic layers washed with water (20 mL) and saturated aqueous sodium chloride (2 × 20 mL), dried and evaporated to dryness. Chromatography on silica gel with petroleum ether-ethyl acetate (95:5) as the eluent

yielded a mixture of several products as a colourless oil (589 mg, 101%): R_f 0.34-0.52, petroleum ether-ethyl acetate (95:5). This mixture was used directly in the next reaction.
A solution of the crude addition product (560 mg, 0.51 mmol) and triethylamine (0.284 mL, 2.04 mmol) in dry dichloromethane (4.0 mL) was added dropwise to a stirred solution of phosphorus triiodide (426 mg, 1.03 mmol) in dry dichloromethane (3.0 mL) at 0 °C. The reaction was stirred for 3 h, poured into saturated aqueous sodium hydrogen carbonate (50 mL) and extracted with diethyl ether (2 × 50 mL). The combined organic layers were washed with saturated aqueous sodium hydrogen carbonate (50 mL) and saturated aqueous sodium chloride (50 mL), dried and evaporated to dryness. Chromatography on silica gel with petroleum ether-ethyl acetate (95:5) as the eluent yielded the diene **551** as a colourless oil (55 mg, 12%), along with the unwanted Michael-type addition product **552** as a white foam (206 mg, 39%): **551** - R_f 0.32, petroleum ether-ethyl acetate (95:5); $[\alpha]^{20}_D$ - 15.0° (*c* 4.5, $CHCl_3$); δ_H (250 MHz, $CDCl_3$) 0.84 (9H, s, ^{t}Bu), 0.95 (9H, s, ^{t}Bu), 1.06 (4H, m), 1.18 (3H, s, C1'-CH_3), 1.57 (6H, s, C6-CH_3), 1.60 (3H, s, C2-CH_3), 1.80-2.11 (3H, m), 2.56 (1H, dd, *J* 10.4, 14.2, 4-H), 3.38-3.92 (4H, m) overlapping 3.78 (1H, d, *J* 10.1, C*H*HPh) and 3.86 (1H, d, *J* 10.1, CH*H*Ph), 4.09 (1H, br s, O*H*), 4.24 (1H, d, *J* 10.4, H-5), 4.54 (1H, d, *J* 4.4, 1a-H), 4.57 (1H, d, *J* 4.4, 1b-H), 4.90 (1H, m), 7.08-7.60 (25H, Ph); δ_C (62.9 MHz, $CDCl_3$) 19.6 (C, ^{t}Bu), 19.6 (C, ^{t}Bu), 20.2 (CH_3, C1'-Me or C2-Me), 20.9 (CH_3, C2-Me or C1'-Me), 22.7 (CH_3, C6-Me), 23.6 (CH_3, C6-Me), 27.5 (CH_3, ^{t}Bu), 27.5 (CH_3, ^{t}Bu), 29.0 (CH_2, C6' or C5'), 30.1 (CH_2, C6' or C5'), 30.8 (CH, C2'), 32.1 (CH_2, C4), 40.9 (CH, C3'), 41.4 (C, C1'), 43.3 (CH, C4'), 60.0 (CH_2, *C*H_2OSi), 64.6 (CH_2, *C*H_2OH), 71.0 (CH, C5), 75.1 (CH_2, *C*H_2Ph), 114.9 (CH_2, C1), 127.4-130.3 (11 × CH, Ph), 132.8-135.2 (6 × C, Ph and C3), 135.9-136.5 (4 × CH, Ph), 140.0 (C, C2), 146.8 (C, C6); *m/z* (FAB) 901 (MNa^+, 100%), 879 (MH^+, 9).

2-Methyl-5-(2-propenyl)cyclohexenyl triflate (564).



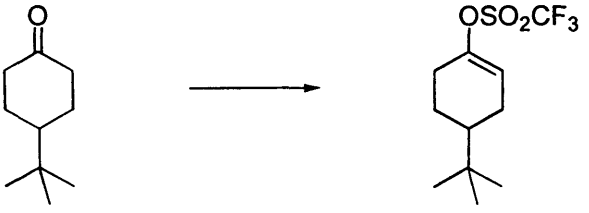
563 **564**

A solution of (*R*)-Carvone (900 mg, 6.00 mmol) in dry THF (10.0 mL) was added dropwise to a solution of L-Selectride® (1M solution in THF, 6.6 mL, 6.60 mmol) in dry

THF (40.0 mL) at -78 °C, via a cannula. The reaction was stirred at -78 °C for 2 h, solid *N*-phenyltriflimide (2.15 g, 6.02 mmol) added and the resulting solution allowed to warm to room temperature overnight. After this period the reaction was diluted with hexane (150 mL) and washed with water (2 × 50 mL). The combined aqueous layers were back-extracted with hexane (2 × 25 mL). The combined organic layers were then washed with 10% sodium hydroxide solution (2 × 50 mL), saturated aqueous sodium chloride (2 × 50 mL), dried and evaporated to dryness. Chromatography on silica gel with petroleum ether-diethyl ether (99:1) as the eluent yielded the triflate **564** as a colourless oil (1.42 g, 83%): R_f 0.20, hexane; δ_H (250 MHz, $CDCl_3$) 1.40-1.60 (1H, m), 1.69-1.87 (1H, m), 1.75 (3H, s, overlapping, vinyl-CH_3), 1.77 (3H, s, overlapping, vinyl-CH_3), 2.08-2.44 (5H, m), 4.72-4.82 (2H, m, vinyl-CH_2); δ_C (62.9 MHz, $CDCl_3$) 16.8 (CH_3), 21.0 (CH_3), 27.1 (CH_2), 30.8 (CH_2), 33.0 (CH_2), 42.3 (CH), 110.3 (vinyl-CH_2), 118.8 (q, *J* 319, CF_3), 126.5 (C), 142.8 (C), 147.6 (C); *m/z* (EI) 284 (M^+, 19%) (found M^+, 284.0695; $C_{11}H_{15}O_3F_3S$ requires 284.0694).

This is a literature compound.[169b]

4-*tert*-butylcyclohexenyl triflate (566).



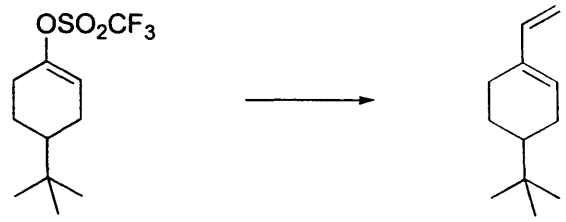
565 **566**

Sodium bis(trimethylsilyl)amide (1M solution in THF, 6.6 mL, 6.60 mmol) was added dropwise to a cooled solution of the ketone **565** (926 mg, 6.00 mmol) in dry THF (5.0 mL) at -78 °C. The reaction was stirred at -78 °C for 2 h, solid *N*-phenyltriflimide (2.15 g, 6.02 mmol) added and the resulting solution allowed to warm to room temperature overnight. After this period the reaction mixture was poured into water (100 mL) and extracted into diethyl ether (2 × 100 mL). The combined organic layers were then washed with saturated aqueous sodium chloride (100 mL), dried and evaporated to dryness. Chromatography on silica gel with petroleum ether-diethyl ether (99:1) as the eluent yielded the triflate **566** as a colourless oil (913 mg, 53%): δ_H (250 MHz, $CDCl_3$) 0.90 (9H, s, ^tBu), 1.20-1.50 (2H, m), 1.75-2.58 (5H, m), 5.65-5.80 (1H, m, vinyl-H); δ_C (62.9 MHz, $CDCl_3$) 24.5 (CH_2), 25.7

(CH_2), 27.5 (CH_3, ^tBu), 28.9 (CH_2), 32.4 (C, ^tBu), 43.3 (CH), 118.8 (CH, vinyl), 118.9 (q, *J* 321, CF_3), 149.6 (C, vinyl).

This is a literature compound.[171]

1-Vinyl-4-*tert*-butylcyclohex-1-ene (567).

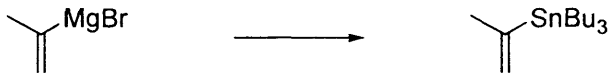


566 **567**

A solution of triflate **566** (291 mg, 1.02 mmol) and vinyltributylstannane (297 μL, 1.02 mmol) in dry THF (2.5 mL) was added dropwise, via a cannula, to a slurry of LiCl (129 mg, 3.04 mmol) and $Pd(PPh_3)_4$ (24 mg, 0.021 mmol, 2.0 mol%) in dry THF (2.5 mL), under an atmosphere of argon. The resulting mixture was heated under reflux for 17 h, cooled to room temperature, and diluted with hexane (30 mL). The resulting solution was washed sequentially with water (30 mL), 10% ammonium hydroxide solution (30 mL), water (30 mL) and saturated aqueous sodium chloride (30 mL). The organic layer was then dried and concentrated to leave a yellow oil. Chromatography on silica gel with petroleum ether as the eluent yielded the diene **567** as a colourless oil (122 mg, 73%): R_f 0.66, hexane; δ_H (250 MHz, $CDCl_3$) 0.91 (9H, s, ^tBu), 1.07-1.40 (3H, m), 1.80-2.45 (4H, m), 4.91 (1H, d, *J* 10.8, CH=CH*H*), 5.07 (1H, d, *J* 17.4, CH=C*H*H), 5.72-5.83 (1H, m, vinyl-H), 6.38 (1H, dd, *J* 10.8, 17.4, C*H*=CH_2); δ_C (62.9 MHz, $CDCl_3$) 24.1 (CH_2), 25.6 (CH_2), 27.6 (CH_3, ^tBu), 27.8 (CH_2), 32.6 (C, ^tBu), 44.7 (CH), 110.1 (CH_2, vinyl), 130.4 (CH, vinyl), 136.4 (C, vinyl), 140.1 (CH, vinyl); *m/z* (EI) 164 (M^+, 47%) (found M^+, 164.1564; $C_{12}H_{20}$ requires 164.1565).

This is a literature compound.[170]

Isopropenyltributylstannane (561).

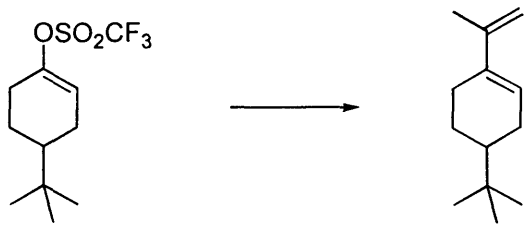


561

Tributyltin chloride (3.62 mL, 13.30 mmol) was added dropwise to a solution of isopropenylmagnesium bromide (0.5M solution in THF, 40.0 mL, 20.00 mmol) at 0 °C. The mixture was allowed to stir at 0 °C for 0.5 h, then at reflux for 35 h. At this point the mixture was allowed to cool to room temperature, then quenched by portionwise addition to saturated ammonium chloride solution (150 mL). The resulting mixture was extracted into diethyl ether (2 × 100 mL), the combined organic layers washed with saturated aqueous sodium chloride (100 mL), dried and the diethyl ether (and some THF) removed by distillation at atmospheric pressure. The remaining pale yellow solution containing the product was distilled under reduced pressure using Kugelrohr apparatus. The stannane **561** was obtained as a colourless liquid (3.33 g, 75%): bp 118-120 °C/15mm; δ_H (250 MHz, $CDCl_3$) 0.77-1.05 (6H, m, $(CH_3CH_2CH_2CH_2)_3Sn$), 0.90 (9H, t, overlapping, *J* 7.2, $(CH_3CH_2CH_2CH_2)_3Sn$), 1.24-1.59 (12H, m, $(CH_3CH_2CH_2CH_2)_3Sn$), 1.97 (3H, t, *J* 1.6, (J_{SnH} 21.6) vinyl-CH_3), 5.09 (1H, sextet, *J* 1.5, (J_{SnH} 31.2) vinyl-H), 5.69 (1H, sextet, *J* 1.7, (J_{SnH} 69.5) vinyl-H); δ_C (62.9 MHz, $CDCl_3$) 9.5 (CH_2, ^{n}Bu), 14.0 (CH_3, ^{n}Bu), 27.6 (CH_3, vinyl-CH_3), 27.8 (CH_2, ^{n}Bu), 29.4 (CH_2, ^{n}Bu), 125.9 (CH_2, vinyl), 150.6 (C, vinyl); *m/z* (FAB) 331 (M^+, 6%).

This is a literature compound.[172]

1-Isopropenyl-4-*tert*-butylcyclohex-1-ene (568).



566 **568**

A solution of triflate **566** (311 mg, 1.09 mmol), isopropenyltributylstannane (360 mg, 1.09 mmol) and DMPU (400 μL) in dry THF (5.0 mL) was added dropwise, via a cannula, to a slurry of LiCl (300 mg, 7.08 mmol) and $Pd(PPh_3)_4$ (50 mg, 0.043 mmol, 4.0 mol%) in dry

THF (5.0 mL), under an atmosphere of argon. The resulting mixture was heated under reflux for 72 h, cooled to room temperature, and diluted with hexane (40 mL). The resulting solution was washed sequentially with water (30 mL), 10% ammonium hydroxide solution (30 mL), water (30 mL) and saturated aqueous sodium chloride (30 mL). The organic layer was then dried and concentrated to leave a yellow oil. Chromatography on silica gel with petroleum ether as the eluent yielded the diene **568** as a colourless oil (130 mg, 67%): R_f 0.55, hexane; δ_H (250 MHz, $CDCl_3$) 0.74 (9H, s, ^{t}Bu), 0.93-1.20 (3H, m), 1.56-2.32 (4H, m), 1.75 (3H, s, overlapping, Me), 4.68 (1H, br s, CH_3C=CH*H*), 4.80 (1H, br s, CH_3C=C*H*H), 5.70-5.79 (1H, m, vinyl-H); δ_C (62.9 MHz, $CDCl_3$) 21.0 (CH_3), 24.7 (CH_2), 27.3 (CH_2), 27.5 (CH_3, ^{t}Bu), 27.6 (CH_2), 32.5 (C, ^{t}Bu), 44.3 (CH), 110.0 (CH_2, vinyl), 125.5 (CH, vinyl), 136.9 (C, vinyl), 143.9 (C, vinyl); *m/z* (EI) 178 (M^+, 35%) (found M^+, 178.1721; $C_{13}H_{22}$ requires 178.1722).

This is a literature compound[173] but not a literature method.

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APPENDIX

X-RAY CRYSTALLOGRAPHY DATA

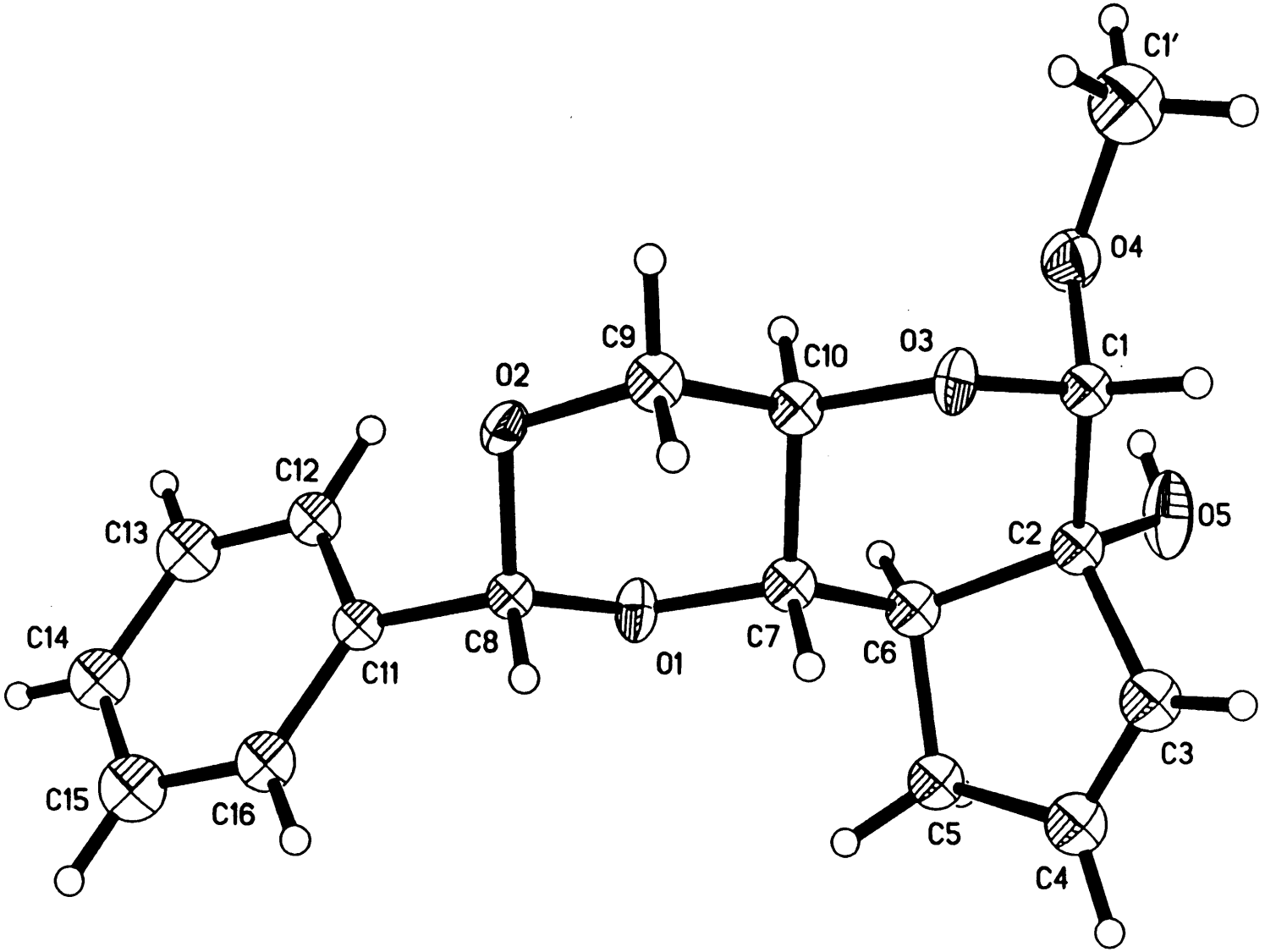

Figure 3. X-ray crystal structure of cyclopentene **299a**

Table 1. Crystal data and structure refinement for 1.

Identification code	1
Empirical formula	$C_{17}H_{20}O_5$
Formula weight	304.33
Temperature	190(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_12_12_1$
Unit cell dimensions	a = 5.258(3) Å alpha = 90° b = 8.856(4) Å beta = 90° c = 32.99(2) Å gamma = 90°
Volume, Z	1536.2(14) $Å^3$, 4
Density (calculated)	1.316 Mg/m^3
Absorption coefficient	0.096 mm^{-1}
F(000)	648
Crystal size	0.57 x 0.09 x 0.08 mm
θ range for data collection	2.61 to 23.49°
Limiting indices	$-1 \le h \le 5$, $-9 \le k \le 9$, $-29 \le l \le 36$
Reflections collected	1619
Independent reflections	1363 (R_{int} = 0.0457)
Absorption correction	Not applied
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1362 / 0 / 118
Goodness-of-fit on F^2	1.029
Final R indices [I>2σ(I)]	R1 = 0.0828, wR2 = 0.1745
R indices (all data)	R1 = 0.1956, wR2 = 0.2401
Absolute structure parameter	-3(8)
Largest diff. peak and hole	0.344 and -0.335 $eÅ^{-3}$

Table 2. Atomic coordinates [x 10^4] and equivalent isotropic displacement parameters [$Å^2$ x 10^3] for 1. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U(eq)
O(1)	-1532(15)	9066(8)	8458(2)	36(2)
O(2)	985(15)	6897(7)	8523(2)	32(2)
O(3)	2492(15)	9444(8)	9353(2)	34(2)
O(4)	-529(17)	9682(8)	9861(2)	48(2)
C(1')	826(30)	8966(16)	10187(3)	68(4)
O(5)	-2302(20)	12269(12)	9639(3)	53(3)
C(1)	1124(23)	10488(12)	9605(3)	32(3)
C(2)	-480(24)	11609(13)	9362(3)	35(3)
C(3)	1007(27)	12901(13)	9186(3)	44(3)
C(4)	33(26)	13339(14)	8851(3)	46(3)
C(5)	-2138(24)	12378(12)	8702(3)	41(3)
C(6)	-1781(26)	10997(12)	8974(3)	38(3)
C(7)	-151(25)	9834(12)	8768(3)	34(3)
C(8)	51(22)	8027(12)	8251(3)	26(3)
C(9)	2470(24)	7532(12)	8840(3)	36(3)
C(10)	876(24)	8684(12)	9067(3)	33(3)
C(11)	-1471(22)	7268(12)	7929(3)	30(3)
C(12)	-3422(24)	6304(12)	8038(3)	36(3)
C(13)	-4873(27)	5646(14)	7737(3)	52(4)
C(14)	-4398(26)	5908(14)	7331(3)	49(4)
C(15)	-2385(27)	6861(14)	7219(4)	55(4)
C(16)	-948(24)	7535(12)	7522(3)	42(3)

Table 3. Bond lengths [Å] and angles [°] for 1.

O(1)-C(8)	1.416(11)	O(1)-C(7)	1.428(12)
O(2)-C(9)	1.423(12)	O(2)-C(8)	1.430(11)
O(3)-C(1)	1.436(12)	O(3)-C(10)	1.436(12)
O(4)-C(1)	1.408(12)	O(4)-C(1')	1.436(14)
O(5)-C(2)	1.446(14)	C(1)-C(2)	1.529(14)
C(2)-C(3)	1.50(2)	C(2)-C(6)	1.551(14)
C(3)-C(4)	1.279(13)	C(4)-C(5)	1.51(2)
C(5)-C(6)	1.529(13)	C(6)-C(7)	1.50(2)
C(7)-C(10)	1.517(13)	C(8)-C(11)	1.490(13)
C(9)-C(10)	1.518(13)	C(11)-C(12)	1.382(14)
C(11)-C(16)	1.392(13)	C(12)-C(13)	1.380(14)
C(13)-C(14)	1.383(13)	C(14)-C(15)	1.40(2)
C(15)-C(16)	1.39(2)		

C(8)-O(1)-C(7)	110.9(8)	C(9)-O(2)-C(8)	112.0(8)
C(1)-O(3)-C(10)	112.6(9)	C(1)-O(4)-C(1')	111.5(10)
O(4)-C(1)-O(3)	109.3(8)	O(4)-C(1)-C(2)	107.7(9)
O(3)-C(1)-C(2)	113.1(8)	O(5)-C(2)-C(3)	106.3(10)
O(5)-C(2)-C(1)	107.3(9)	C(3)-C(2)-C(1)	114.2(10)
O(5)-C(2)-C(6)	111.8(10)	C(3)-C(2)-C(6)	100.1(8)
C(1)-C(2)-C(6)	116.6(10)	C(4)-C(3)-C(2)	110.9(12)
C(3)-C(4)-C(5)	114.5(12)	C(4)-C(5)-C(6)	99.6(10)
C(7)-C(6)-C(5)	110.7(9)	C(7)-C(6)-C(2)	111.2(10)
C(5)-C(6)-C(2)	105.1(9)	O(1)-C(7)-C(6)	111.1(10)
O(1)-C(7)-C(10)	109.1(8)	C(6)-C(7)-C(10)	111.7(8)
O(1)-C(8)-O(2)	110.8(7)	O(1)-C(8)-C(11)	108.7(9)
O(2)-C(8)-C(11)	108.4(8)	O(2)-C(9)-C(10)	109.0(9)
O(3)-C(10)-C(7)	108.8(8)	O(3)-C(10)-C(9)	108.2(9)
C(7)-C(10)-C(9)	109.1(8)	C(12)-C(11)-C(16)	120.1(10)
C(12)-C(11)-C(8)	119.5(9)	C(16)-C(11)-C(8)	120.4(10)
C(13)-C(12)-C(11)	119.0(10)	C(12)-C(13)-C(14)	121.7(13)
C(13)-C(14)-C(15)	119.4(12)	C(16)-C(15)-C(14)	118.7(11)
C(15)-C(16)-C(11)	121.0(12)		

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters [$Å^2$ x 10^3] for 1.

The anisotropic displacement factor exponent takes the form:

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

	U11	U22	U33	U23	U13	U12
O(1)	35(5)	32(4)	40(4)	-14(4)	-3(4)	4(4)
O(2)	39(5)	20(4)	36(4)	-2(3)	-4(4)	-6(4)
O(3)	31(5)	30(4)	40(4)	-12(4)	-4(4)	-6(5)
O(4)	55(6)	45(5)	45(4)	-1(4)	5(5)	-11(5)
O(5)	38(6)	59(6)	63(6)	-36(5)	11(5)	7(6)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for 1.

	x	y	z	U(eq)
H(1'A)	-352(30)	8427(16)	10356(3)	102
H(1'B)	1687(30)	9719(16)	10345(3)	102
H(1'C)	2049(30)	8273(16)	10077(3)	102
H(1A)	2342(23)	11050(12)	9771(3)	39
H(3A)	2443(27)	13326(13)	9305(3)	53
H(4A)	618(26)	14181(14)	8710(3)	56
H(5B)	-1959(24)	12126(12)	8417(3)	49
H(5C)	-3770(24)	12861(12)	8746(3)	49
H(6A)	-3440(26)	10560(12)	9042(3)	46
H(7A)	1295(25)	10351(12)	8643(3)	40
H(8A)	1484(22)	8565(12)	8128(3)	31
H(9A)	3970(24)	8015(12)	8729(3)	44
H(9B)	3020(24)	6742(12)	9025(3)	44
H(10A)	-528(24)	8182(12)	9209(3)	40
H(12A)	-3754(24)	6102(12)	8309(3)	43
H(13A)	-6204(27)	5010(14)	7810(3)	63
H(14A)	-5404(26)	5456(14)	7133(3)	59
H(15A)	-2020(27)	7038(14)	6947(4)	67
H(16A)	385(24)	8174(12)	7452(3)	51
H(5A)	-2952(534)	11649(300)	9742(68)	239(140)

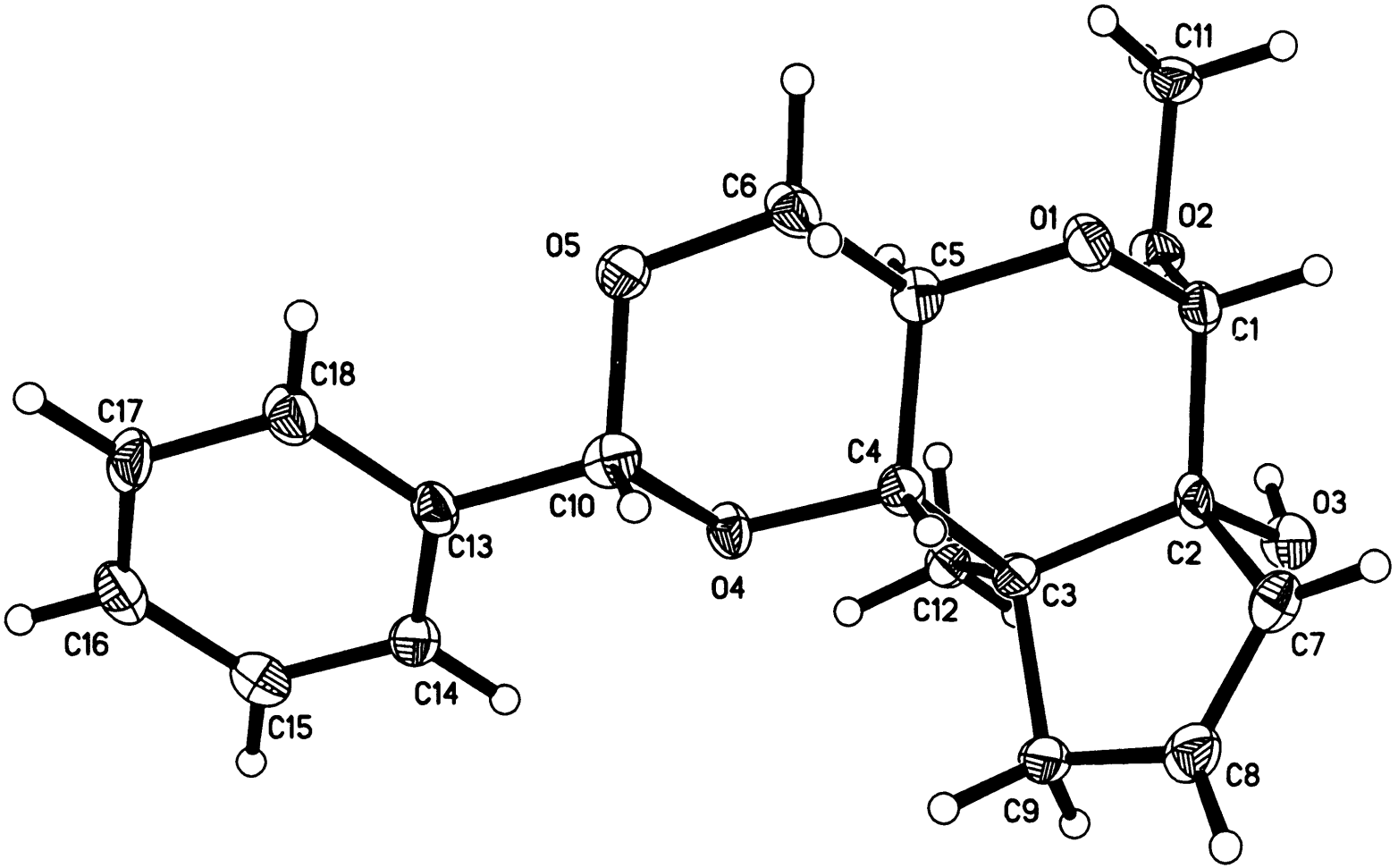

Figure 4. X-ray crystal structure of cyclopentene **299b**

Table 1. Crystal data and structure refinement for 1.

Identification code	9913
Empirical formula	$C_{18}H_{22}O_5$
Formula weight	318.36
Temperature	200(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Unit cell dimensions	a = 7.502(2) Å alpha = 90° b = 10.384(2) Å beta = 90° c = 20.758(5) Å gamma = 90°
Volume, Z	1617.1(7) $Å^3$, 4
Density (calculated)	1.308 Mg/m^3
Absorption coefficient	0.095 mm^{-1}
F(000)	680
Crystal size	0.43 x 0.31 x 0.27 mm
θ range for data collection	1.96 to 24.49°
Limiting indices	$-1 \le h \le 8$, $-1 \le k \le 12$, $-1 \le l \le 24$
Reflections collected	2006
Independent reflections	1864 (R_{int} = 0.0361)
Absorption correction	Not applied
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1864 / 0 / 209
Goodness-of-fit on F^2	1.023
Final R indices [$I>2\sigma(I)$]	R1 = 0.0590, wR2 = 0.1295
R indices (all data)	R1 = 0.0958, wR2 = 0.1508
Absolute structure parameter	3(3)
Largest diff. peak and hole	0.248 and -0.256 $eÅ^{-3}$

Table 2. Atomic coordinates [x 10^4] and equivalent isotropic displacement parameters [$Å^2$ x 10^3] for 1. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U(eq)
O(1)	-1634(5)	10045(3)	4183(2)	33(1)
O(2)	-561(5)	11807(3)	3594(2)	30(1)
O(3)	1833(6)	12476(3)	4462(2)	35(1)
O(4)	2130(5)	7950(3)	3818(2)	29(1)
O(5)	-508(5)	6955(3)	3478(2)	33(1)
C(1)	-806(7)	11279(5)	4207(3)	28(1)
C(2)	1038(7)	11224(5)	4515(3)	28(1)
C(3)	2298(7)	10137(5)	4247(3)	27(1)
C(4)	1170(7)	8925(5)	4169(3)	27(1)
C(5)	-583(7)	9148(5)	3826(3)	28(1)
C(6)	-1590(7)	7887(5)	3793(3)	33(1)
C(7)	1047(8)	10930(5)	5232(3)	34(1)
C(8)	2483(8)	10256(5)	5391(3)	37(2)
C(9)	3599(8)	9928(5)	4815(3)	34(1)
C(10)	1156(7)	6785(5)	3798(3)	30(1)
C(11)	-2191(7)	12065(6)	3260(3)	39(2)
C(12)	3252(8)	10481(5)	3623(2)	30(1)
C(13)	2227(7)	5794(5)	3432(2)	28(1)
C(14)	4059(8)	5926(5)	3351(3)	32(1)
C(15)	5010(8)	4999(6)	3017(3)	38(2)
C(16)	4149(9)	3936(6)	2770(3)	41(2)
C(17)	2336(8)	3784(5)	2857(3)	36(2)
C(18)	1371(8)	4716(5)	3183(3)	35(1)

Table 3. Bond lengths [Å] and angles [°] for 1.

O(1)-C(1)	1.425(6)	O(1)-C(5)	1.427(6)
O(2)-C(1)	1.399(6)	O(2)-C(11)	1.431(6)
O(3)-C(2)	1.434(6)	O(4)-C(10)	1.414(6)
O(4)-C(4)	1.440(6)	O(5)-C(6)	1.422(6)
O(5)-C(10)	1.425(6)	C(1)-C(2)	1.525(8)
C(2)-C(7)	1.520(8)	C(2)-C(3)	1.574(7)
C(3)-C(12)	1.523(7)	C(3)-C(4)	1.526(7)
C(3)-C(9)	1.545(7)	C(4)-C(5)	1.514(7)
C(5)-C(6)	1.513(7)	C(7)-C(8)	1.327(8)
C(8)-C(9)	1.498(8)	C(10)-C(13)	1.510(7)
C(13)-C(18)	1.389(7)	C(13)-C(14)	1.392(8)
C(14)-C(15)	1.384(8)	C(15)-C(16)	1.377(8)
C(16)-C(17)	1.381(8)	C(17)-C(18)	1.385(8)

C(1)-O(1)-C(5)	111.4(4)	C(1)-O(2)-C(11)	113.7(4)
C(10)-O(4)-C(4)	111.0(4)	C(6)-O(5)-C(10)	111.7(4)
O(2)-C(1)-O(1)	112.2(4)	O(2)-C(1)-C(2)	106.1(4)
O(1)-C(1)-C(2)	112.1(4)	O(3)-C(2)-C(7)	104.8(4)
O(3)-C(2)-C(1)	108.2(4)	C(7)-C(2)-C(1)	114.9(5)
O(3)-C(2)-C(3)	111.9(4)	C(7)-C(2)-C(3)	101.5(4)
C(1)-C(2)-C(3)	115.1(4)	C(12)-C(3)-C(4)	111.3(4)
C(12)-C(3)-C(9)	112.6(4)	C(4)-C(3)-C(9)	108.4(4)
C(12)-C(3)-C(2)	114.5(4)	C(4)-C(3)-C(2)	107.2(4)
C(9)-C(3)-C(2)	102.2(4)	O(4)-C(4)-C(5)	107.7(4)
O(4)-C(4)-C(3)	110.9(4)	C(5)-C(4)-C(3)	113.9(4)
O(1)-C(5)-C(4)	109.6(4)	O(1)-C(5)-C(6)	108.2(4)
C(4)-C(5)-C(6)	108.8(4)	O(5)-C(6)-C(5)	108.9(4)
C(8)-C(7)-C(2)	110.6(5)	C(7)-C(8)-C(9)	112.1(5)
C(8)-C(9)-C(3)	102.9(4)	O(4)-C(10)-O(5)	111.1(4)
O(4)-C(10)-C(13)	108.9(4)	O(5)-C(10)-C(13)	108.5(4)
C(18)-C(13)-C(14)	119.3(5)	C(18)-C(13)-C(10)	119.3(5)
C(14)-C(13)-C(10)	121.3(5)	C(15)-C(14)-C(13)	120.1(6)
C(16)-C(15)-C(14)	120.1(6)	C(15)-C(16)-C(17)	120.3(6)
C(16)-C(17)-C(18)	119.9(6)	C(17)-C(18)-C(13)	120.2(5)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters [$Å^2$ x 10^3] for 1.

The anisotropic displacement factor exponent takes the form:

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

	U11	U22	U33	U23	U13	U12
O(1)	25(2)	25(2)	48(2)	-6(2)	4(2)	1(2)
O(2)	30(2)	23(2)	37(2)	8(2)	-6(2)	2(2)
O(3)	40(3)	22(2)	43(2)	4(2)	-2(2)	-4(2)
O(4)	27(2)	20(2)	39(2)	-4(2)	6(2)	-2(2)
O(5)	28(2)	24(2)	46(2)	-1(2)	-4(2)	-3(2)
C(1)	26(3)	23(3)	36(3)	-7(3)	2(3)	1(3)
C(2)	30(3)	11(2)	42(3)	-5(2)	2(3)	0(3)
C(3)	22(3)	22(3)	35(3)	-4(2)	-4(3)	-3(3)
C(4)	27(3)	24(3)	30(3)	-2(3)	1(3)	2(3)
C(5)	27(3)	27(3)	32(3)	1(3)	6(3)	-4(3)
C(6)	18(3)	25(3)	55(4)	-1(3)	4(3)	-2(3)
C(7)	41(4)	27(3)	33(3)	-4(3)	-1(3)	-5(3)
C(8)	47(4)	25(3)	38(3)	-1(3)	-10(3)	-2(3)
C(9)	34(3)	24(3)	45(3)	-4(3)	-14(3)	3(3)
C(10)	33(3)	24(3)	32(3)	8(3)	-2(3)	-7(3)
C(11)	35(3)	32(3)	49(4)	1(3)	-16(3)	6(3)
C(12)	27(3)	23(3)	39(3)	-3(2)	-1(3)	-3(3)
C(13)	34(3)	20(3)	31(3)	3(3)	0(3)	5(3)
C(14)	33(3)	27(3)	36(3)	1(3)	-4(3)	-1(3)
C(15)	31(3)	41(3)	43(4)	4(3)	0(3)	6(3)
C(16)	50(4)	33(3)	39(4)	2(3)	1(3)	16(4)
C(17)	49(4)	17(3)	42(3)	-1(3)	-4(3)	-5(3)
C(18)	34(3)	26(3)	45(3)	2(3)	2(3)	2(3)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for 1.

	x	y	z	U(eq)
H(3)	1637(78)	12771(28)	4103(12)	53
H(1A)	-1560(7)	11861(5)	4460(3)	34
H(4A)	908(7)	8586(5)	4600(3)	32
H(5A)	-365(7)	9476(5)	3391(3)	34
H(6A)	-1880(7)	7595(5)	4224(3)	39
H(6B)	-2694(7)	8004(5)	3557(3)	39
H(7A)	167(8)	11188(5)	5520(3)	40
H(8A)	2765(8)	10014(5)	5810(3)	44
H(9A)	4006(8)	9042(5)	4832(3)	41
H(9B)	4623(8)	10494(5)	4782(3)	41
H(10A)	945(7)	6479(5)	4238(3)	36
H(11A)	-1930(7)	12424(6)	2844(3)	58
H(11B)	-2892(7)	12665(6)	3504(3)	58
H(11C)	-2846(7)	11277(6)	3207(3)	58
H(12A)	3949(8)	11246(5)	3686(2)	44
H(12B)	2388(8)	10630(5)	3290(2)	44
H(12C)	4019(8)	9784(5)	3499(2)	44
H(14A)	4646(8)	6638(5)	3521(3)	38
H(15A)	6232(8)	5093(6)	2958(3)	46
H(16A)	4791(9)	3318(6)	2544(3)	49
H(17A)	1764(8)	3057(5)	2697(3)	43
H(18B)	148(8)	4621(5)	3236(3)	42

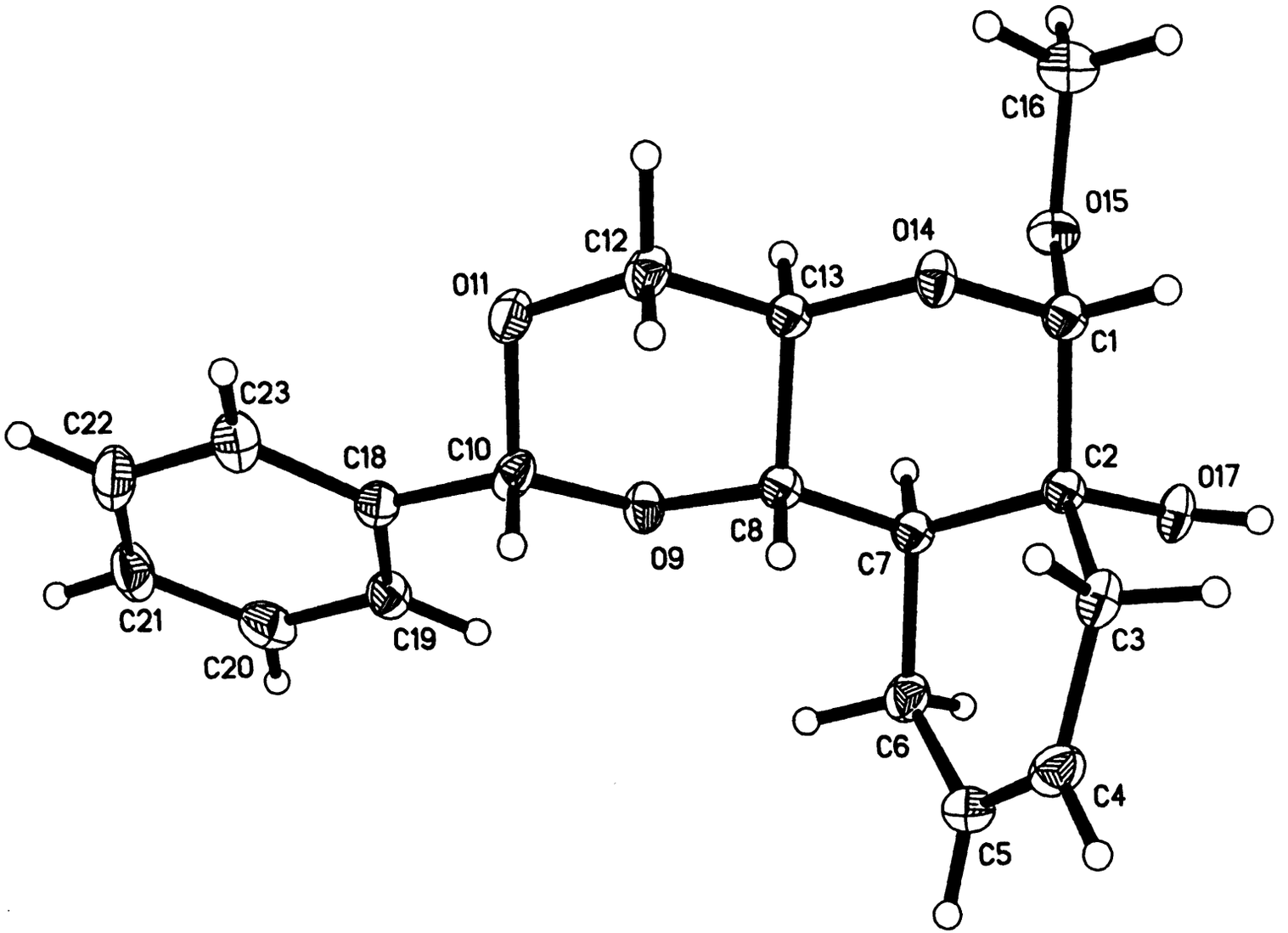

Figure 5. X-ray crystal structure of cyclohexene **302**

Table 1. Crystal data and structure refinement for 1.

Identification code	1
Empirical formula	$C_{18}H_{22}O_5$
Formula weight	318.36
Temperature	190(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1$
Unit cell dimensions	a = 8.547(1) Å alpha = 90° b = 6.403(1) Å beta = 105.24(1)° c = 15.206(2) Å gamma = 90°
Volume, Z	802.9(2) $Å^3$, 2
Density (calculated)	1.317 Mg/m^3
Absorption coefficient	0.095 mm^{-1}
F(000)	340
Crystal size	0.40 x 0.24 x 0.05 mm
θ range for data collection	2.78 to 24.00°
Limiting indices	$-1 \le h \le 9$, $-1 \le k \le 7$, $-17 \le l \le 17$
Reflections collected	1810
Independent reflections	1641 (R_{int} = 0.0129)
Absorption correction	Not applied
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1641 / 1 / 183
Goodness-of-fit on F^2	1.036
Final R indices [I>2σ(I)]	R1 = 0.0450, wR2 = 0.0862
R indices (all data)	R1 = 0.0764, wR2 = 0.0995
Absolute structure parameter	1(2)
Largest diff. peak and hole	0.219 and -0.184 $eÅ^{-3}$

Table 2. Atomic coordinates [x 10^4] and equivalent isotropic displacement parameters [$Å^2$ x 10^3] for 1. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U(eq)
O(9)	9118(3)	-2451(5)	2653(2)	28(1)
O(11)	11768(3)	-1852(5)	2535(2)	32(1)
O(14)	9010(3)	1668(4)	978(2)	27(1)
O(15)	7079(3)	-114(5)	-138(2)	30(1)
O(17)	4609(3)	947(5)	610(2)	30(1)
C(1)	7349(5)	1571(8)	488(3)	27(1)
C(2)	6254(5)	1252(8)	1135(3)	26(1)
C(3)	6370(5)	3199(7)	1734(3)	30(1)
C(4)	5749(5)	2852(9)	2550(3)	37(1)
C(5)	5472(5)	975(8)	2854(3)	37(1)
C(6)	5730(5)	-1008(8)	2403(3)	33(1)
C(7)	6743(5)	-713(7)	1711(3)	25(1)
C(8)	8548(5)	-564(7)	2175(3)	25(1)
C(10)	10782(4)	-2218(8)	3133(3)	28(1)
C(12)	11300(4)	13(8)	2012(3)	31(1)
C(13)	9525(5)	-195(7)	1493(3)	25(1)
C(16)	7924(5)	137(9)	-829(3)	42(1)
C(18)	11342(5)	-4180(8)	3672(3)	28(1)
C(19)	10249(6)	-5504(7)	3902(3)	32(1)
C(20)	10812(6)	-7213(9)	4471(3)	42(1)
C(21)	12449(6)	-7577(9)	4798(3)	44(1)
C(22)	13526(6)	-6281(9)	4544(3)	47(2)
C(23)	12996(6)	-4566(8)	3985(3)	41(1)

Table 3. Bond lengths [Å] and angles [°] for 1.

O(9)-C(10)	1.425(4)	O(9)-C(8)	1.428(5)
O(11)-C(10)	1.412(4)	O(11)-C(12)	1.433(5)
O(14)-C(1)	1.421(4)	O(14)-C(13)	1.431(5)
O(15)-C(1)	1.418(5)	O(15)-C(16)	1.431(5)
O(17)-C(2)	1.436(5)	C(1)-C(2)	1.539(5)
C(2)-C(7)	1.527(6)	C(2)-C(3)	1.532(6)
C(3)-C(4)	1.488(6)	C(4)-C(5)	1.331(7)
C(5)-C(6)	1.486(6)	C(6)-C(7)	1.540(6)
C(7)-C(8)	1.521(5)	C(8)-C(13)	1.511(5)
C(10)-C(18)	1.507(6)	C(12)-C(13)	1.521(5)
C(18)-C(19)	1.374(6)	C(18)-C(23)	1.390(6)
C(19)-C(20)	1.399(6)	C(20)-C(21)	1.376(6)
C(21)-C(22)	1.369(7)	C(22)-C(23)	1.389(7)

C(10)-O(9)-C(8)	109.5(3)	C(10)-O(11)-C(12)	111.7(3)
C(1)-O(14)-C(13)	111.8(3)	C(1)-O(15)-C(16)	112.5(3)
O(15)-C(1)-O(14)	110.5(3)	O(15)-C(1)-C(2)	108.0(3)
O(14)-C(1)-C(2)	111.2(3)	O(17)-C(2)-C(7)	106.7(4)
O(17)-C(2)-C(3)	110.0(4)	C(7)-C(2)-C(3)	111.4(3)
O(17)-C(2)-C(1)	109.5(3)	C(7)-C(2)-C(1)	110.8(3)
C(3)-C(2)-C(1)	108.4(4)	C(4)-C(3)-C(2)	113.1(4)
C(5)-C(4)-C(3)	124.0(5)	C(4)-C(5)-C(6)	123.3(4)
C(5)-C(6)-C(7)	112.8(4)	C(8)-C(7)-C(2)	107.8(3)
C(8)-C(7)-C(6)	112.1(3)	C(2)-C(7)-C(6)	112.0(4)
O(9)-C(8)-C(13)	107.8(3)	O(9)-C(8)-C(7)	110.6(4)
C(13)-C(8)-C(7)	111.6(3)	O(11)-C(10)-O(9)	111.8(3)
O(11)-C(10)-C(18)	109.3(3)	O(9)-C(10)-C(18)	108.9(4)
O(11)-C(12)-C(13)	108.0(3)	O(14)-C(13)-C(8)	111.1(3)
O(14)-C(13)-C(12)	109.4(4)	C(8)-C(13)-C(12)	108.2(3)
C(19)-C(18)-C(23)	120.1(5)	C(19)-C(18)-C(10)	120.8(4)
C(23)-C(18)-C(10)	118.9(4)	C(18)-C(19)-C(20)	119.6(4)
C(21)-C(20)-C(19)	120.5(5)	C(22)-C(21)-C(20)	119.4(5)
C(21)-C(22)-C(23)	121.1(5)	C(22)-C(23)-C(18)	119.3(5)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters [$Å^2$ x 10^3] for 1.

The anisotropic displacement factor exponent takes the form:

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

	U11	U22	U33	U23	U13	U12
O(9)	24(2)	25(2)	31(2)	4(2)	3(1)	-1(1)
O(11)	24(2)	31(2)	40(2)	8(2)	8(1)	5(2)
O(14)	22(2)	21(2)	36(2)	8(2)	3(1)	-2(1)
O(15)	30(2)	30(2)	33(2)	-3(2)	11(1)	-6(2)
O(17)	18(2)	27(2)	40(2)	1(2)	-2(1)	2(2)
C(3)	24(2)	24(3)	40(3)	1(2)	4(2)	0(2)
C(4)	37(3)	36(3)	37(3)	-9(3)	11(2)	4(3)
C(5)	38(3)	44(3)	34(2)	3(3)	16(2)	5(3)
C(6)	25(3)	36(3)	40(3)	7(3)	11(2)	2(2)
C(10)	16(2)	32(3)	33(2)	-7(2)	2(2)	0(2)
C(12)	19(2)	32(3)	42(3)	6(3)	8(2)	-1(2)
C(16)	44(3)	45(4)	41(3)	-3(3)	19(2)	-4(3)
C(18)	29(2)	27(3)	27(2)	-6(2)	4(2)	3(2)
C(19)	40(3)	24(3)	31(2)	2(2)	8(2)	6(2)
C(20)	59(3)	36(3)	35(3)	2(3)	18(3)	-1(3)
C(21)	55(3)	38(3)	33(3)	6(3)	0(2)	17(3)
C(22)	37(3)	50(4)	44(3)	2(3)	-3(2)	11(3)
C(23)	41(3)	39(3)	38(3)	0(3)	0(2)	5(3)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for 1.

	x	y	z	U(eq)
H(17)	4169(3)	1982(5)	413(2)	36
H(1)	7047(5)	2879(8)	152(3)	33
H(3A)	7494(5)	3638(7)	1932(3)	36
H(3B)	5756(5)	4320(7)	1372(3)	36
H(4)	5543(5)	4018(9)	2866(3)	44
H(5)	5097(5)	901(8)	3374(3)	45
H(6A)	4684(5)	-1594(8)	2092(3)	40
H(6B)	6275(5)	-1998(8)	2865(3)	40
H(7)	6564(5)	-1923(7)	1303(3)	30
H(8)	8734(5)	597(7)	2610(3)	30
H(10)	10889(4)	-1038(8)	3555(3)	34
H(12A)	11964(4)	199(8)	1589(3)	37
H(12B)	11448(4)	1218(8)	2412(3)	37
H(13)	9396(5)	-1390(7)	1077(3)	30
H(16A)	7705(5)	-1037(9)	-1235(3)	63
H(16B)	9068(5)	222(9)	-549(3)	63
H(16C)	7566(5)	1395(9)	-1165(3)	63
H(19)	9142(6)	-5267(7)	3681(3)	38
H(20)	10074(6)	-8109(9)	4629(3)	50
H(21)	12820(6)	-8693(9)	5189(3)	53
H(22)	14632(6)	-6553(9)	4748(3)	56
H(23)	13740(6)	-3685(8)	3823(3)	49

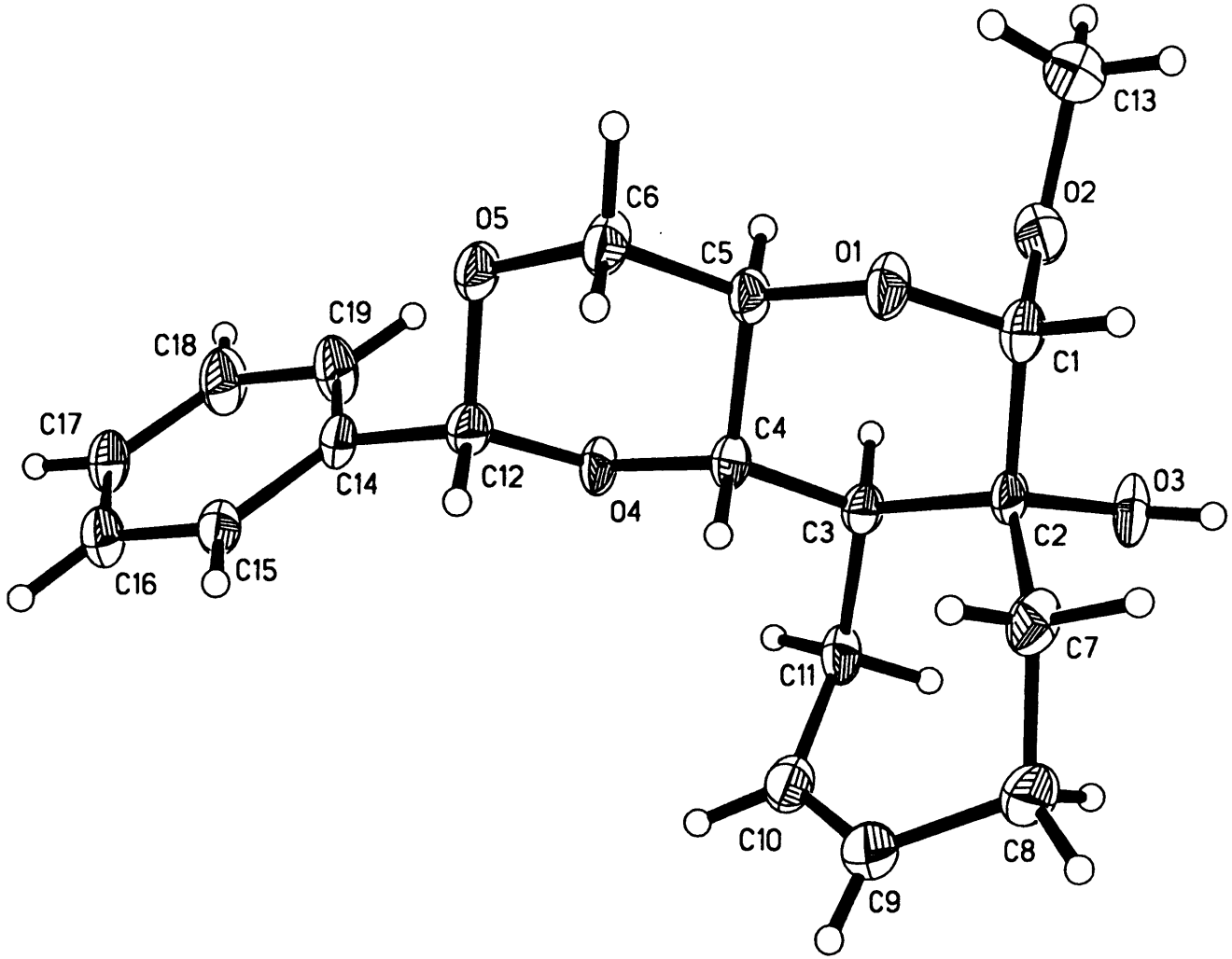

Figure 6. X-ray crystal structure of cycloheptene **311**

Table 1. Crystal data and structure refinement for 1.

Identification code	9914
Empirical formula	$C_{19}H_{24}O_5$
Formula weight	332.38
Temperature	200(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1$
Unit cell dimensions	a = 11.850(2) Å alpha = 90° b = 5.5655(12) Å beta = 97.12(2)° c = 13.000(3) Å gamma = 90°
Volume, Z	850.8(3) $Å^3$, 2
Density (calculated)	1.297 Mg/m^3
Absorption coefficient	0.093 mm^{-1}
F(000)	356
Crystal size	0.48 x 0.43 x 0.11 mm
θ range for data collection	2.19 to 25.00°
Limiting indices	$0 \le h \le 14$, $-1 \le k \le 6$, $-15 \le l \le 15$
Reflections collected	2072
Independent reflections	1973 (R_{int} = 0.0510)
Absorption correction	Not applied
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1973 / 1 / 219
Goodness-of-fit on F^2	1.059
Final R indices [$I>2\sigma(I)$]	R1 = 0.0618, wR2 = 0.1454
R indices (all data)	R1 = 0.0875, wR2 = 0.1705
Absolute structure parameter	1(3)
Extinction coefficient	0.036(8)
Largest diff. peak and hole	0.282 and -0.289 $eÅ^{-3}$

Table 2. Atomic coordinates [x 10^4] and equivalent isotropic displacement parameters [$Å^2$ x 10^3] for 1. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U(eq)
O(1)	9802(3)	5618(8)	2430(2)	40(1)
O(2)	10373(3)	9456(10)	1963(3)	49(1)
O(3)	8743(3)	10004(8)	438(3)	48(1)
O(4)	7423(3)	7854(8)	3698(2)	35(1)
O(5)	8586(3)	5449(8)	4870(2)	41(1)
C(1)	9811(5)	7336(12)	1614(4)	40(2)
C(2)	8614(4)	8068(12)	1135(3)	34(1)
C(3)	7941(4)	8971(11)	2006(3)	31(1)
C(4)	8008(4)	7055(11)	2843(3)	30(1)
C(5)	9220(4)	6530(12)	3261(4)	34(1)
C(6)	9263(4)	4632(13)	4091(4)	42(2)
C(7)	8079(5)	5981(13)	487(4)	44(2)
C(8)	6886(5)	6408(16)	-86(4)	53(2)
C(9)	5962(5)	6316(15)	608(4)	50(2)
C(10)	5889(5)	7829(14)	1371(4)	43(2)
C(11)	6729(4)	9807(12)	1634(4)	39(1)
C(12)	7449(4)	5930(12)	4438(3)	34(1)
C(13)	11553(5)	9150(20)	2313(5)	70(3)
C(14)	6797(4)	6685(11)	5303(4)	34(1)
C(15)	5950(4)	5201(14)	5565(4)	42(2)
C(16)	5339(5)	5824(13)	6377(4)	44(2)
C(17)	5583(5)	7861(14)	6931(4)	46(2)
C(18)	6425(5)	9353(15)	6667(4)	53(2)
C(19)	7025(5)	8795(14)	5850(4)	51(2)

Table 3. Bond lengths [Å] and angles [°] for 1.

O(1)-C(1)	1.429(7)	O(1)-C(5)	1.443(6)
O(2)-C(1)	1.402(8)	O(2)-C(13)	1.426(7)
O(3)-C(2)	1.429(7)	O(4)-C(12)	1.437(7)
O(4)-C(4)	1.451(5)	O(5)-C(12)	1.419(6)
O(5)-C(6)	1.441(6)	C(1)-C(2)	1.531(7)
C(2)-C(7)	1.526(9)	C(2)-C(3)	1.546(6)
C(3)-C(4)	1.518(7)	C(3)-C(11)	1.530(7)
C(4)-C(5)	1.501(7)	C(5)-C(6)	1.507(8)
C(7)-C(8)	1.532(8)	C(8)-C(9)	1.503(8)
C(9)-C(10)	1.313(9)	C(10)-C(11)	1.496(9)
C(12)-C(14)	1.502(7)	C(14)-C(15)	1.375(8)
C(14)-C(19)	1.382(9)	C(15)-C(16)	1.395(7)
C(16)-C(17)	1.355(10)	C(17)-C(18)	1.373(9)
C(18)-C(19)	1.385(7)		

C(1)-O(1)-C(5)	111.6(4)	C(1)-O(2)-C(13)	114.2(6)
C(12)-O(4)-C(4)	108.2(4)	C(12)-O(5)-C(6)	111.4(3)
O(2)-C(1)-O(1)	111.7(4)	O(2)-C(1)-C(2)	106.7(5)
O(1)-C(1)-C(2)	112.8(4)	O(3)-C(2)-C(7)	107.0(4)
O(3)-C(2)-C(1)	106.9(4)	C(7)-C(2)-C(1)	108.8(5)
O(3)-C(2)-C(3)	108.9(5)	C(7)-C(2)-C(3)	115.8(4)
C(1)-C(2)-C(3)	108.9(4)	C(4)-C(3)-C(11)	113.8(4)
C(4)-C(3)-C(2)	108.1(5)	C(11)-C(3)-C(2)	114.6(4)
O(4)-C(4)-C(5)	108.0(4)	O(4)-C(4)-C(3)	110.3(4)
C(5)-C(4)-C(3)	111.0(4)	O(1)-C(5)-C(4)	108.8(4)
O(1)-C(5)-C(6)	108.2(5)	C(4)-C(5)-C(6)	109.9(4)
O(5)-C(6)-C(5)	108.0(5)	C(2)-C(7)-C(8)	116.4(6)
C(9)-C(8)-C(7)	113.6(5)	C(10)-C(9)-C(8)	123.6(6)
C(9)-C(10)-C(11)	122.7(5)	C(10)-C(11)-C(3)	114.9(5)
O(5)-C(12)-O(4)	110.2(4)	O(5)-C(12)-C(14)	108.0(4)
O(4)-C(12)-C(14)	108.8(5)	C(15)-C(14)-C(19)	119.0(5)
C(15)-C(14)-C(12)	118.5(5)	C(19)-C(14)-C(12)	122.5(5)
C(14)-C(15)-C(16)	120.1(6)	C(17)-C(16)-C(15)	120.9(6)
C(16)-C(17)-C(18)	119.2(5)	C(17)-C(18)-C(19)	120.9(7)
C(14)-C(19)-C(18)	119.9(6)		

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters [$Å^2$ x 10^3] for 1.

The anisotropic displacement factor exponent takes the form:

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

	U11	U22	U33	U23	U13	U12
O(1)	48(2)	47(3)	29(2)	4(2)	16(2)	11(2)
O(2)	46(2)	61(3)	43(2)	-1(2)	12(2)	-10(2)
O(3)	62(2)	54(3)	32(2)	14(2)	26(2)	12(2)
O(4)	41(2)	43(2)	25(2)	2(2)	16(2)	6(2)
O(5)	42(2)	57(3)	25(2)	2(2)	12(1)	6(2)
C(1)	48(3)	47(4)	29(3)	-5(3)	14(2)	2(3)
C(2)	33(3)	49(4)	22(2)	-2(3)	12(2)	5(3)
C(3)	36(3)	33(3)	25(2)	-5(3)	8(2)	1(3)
C(4)	38(3)	31(3)	23(2)	-2(2)	12(2)	3(3)
C(5)	35(3)	43(4)	26(2)	-1(3)	13(2)	4(3)
C(6)	47(3)	52(4)	29(2)	9(3)	13(2)	18(3)
C(7)	55(3)	46(4)	33(3)	-11(3)	12(2)	10(3)
C(8)	53(3)	71(5)	37(3)	-17(4)	8(2)	0(4)
C(9)	40(3)	67(5)	42(3)	4(4)	3(3)	1(4)
C(10)	43(3)	54(4)	32(3)	3(3)	7(2)	7(3)
C(11)	44(3)	45(4)	32(2)	4(3)	18(2)	7(3)
C(12)	37(3)	39(4)	27(2)	-2(3)	8(2)	1(3)
C(13)	46(3)	111(8)	54(4)	9(5)	3(3)	-15(5)
C(14)	43(3)	38(4)	23(2)	5(3)	11(2)	-2(3)
C(15)	47(3)	49(4)	29(2)	4(3)	9(2)	-10(3)
C(16)	49(3)	48(4)	38(3)	3(3)	19(2)	-4(3)
C(17)	56(4)	56(4)	31(3)	1(3)	22(3)	0(4)
C(18)	70(4)	56(5)	38(3)	-9(3)	24(3)	-6(4)
C(19)	60(4)	54(5)	43(3)	-3(4)	29(3)	-5(4)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for 1.

	x	y	z	U(eq)
H(3)	9021(50)	9497(22)	-67(23)	71
H(1A)	10209(5)	6633(12)	1069(4)	48
H(3A)	8352(4)	10374(11)	2316(3)	37
H(4A)	7648(4)	5580(11)	2550(3)	36
H(5A)	9593(4)	7999(12)	3545(4)	40
H(6A)	8964(4)	3127(13)	3795(4)	51
H(6B)	10042(4)	4371(13)	4396(4)	51
H(7A)	8045(5)	4603(13)	939(4)	53
H(7B)	8580(5)	5563(13)	-22(4)	53
H(8A)	6869(5)	7968(16)	-420(4)	64
H(8B)	6732(5)	5203(16)	-624(4)	64
H(9A)	5412(5)	5122(15)	490(4)	60
H(10A)	5290(5)	7664(14)	1765(4)	51
H(11A)	6467(4)	10798(12)	2170(4)	47
H(11B)	6747(4)	10808(12)	1025(4)	47
H(12A)	7108(4)	4482(12)	4102(3)	41
H(13A)	11878(5)	10669(20)	2538(5)	106
H(13B)	11932(5)	8541(20)	1755(5)	106
H(13C)	11643(5)	8033(20)	2880(5)	106
H(15A)	5784(4)	3780(14)	5201(4)	50
H(16A)	4756(5)	4828(13)	6539(4)	53
H(17A)	5186(5)	8244(14)	7482(4)	56
H(18A)	6594(5)	10757(15)	7043(4)	64
H(19A)	7581(5)	9839(14)	5670(4)	61

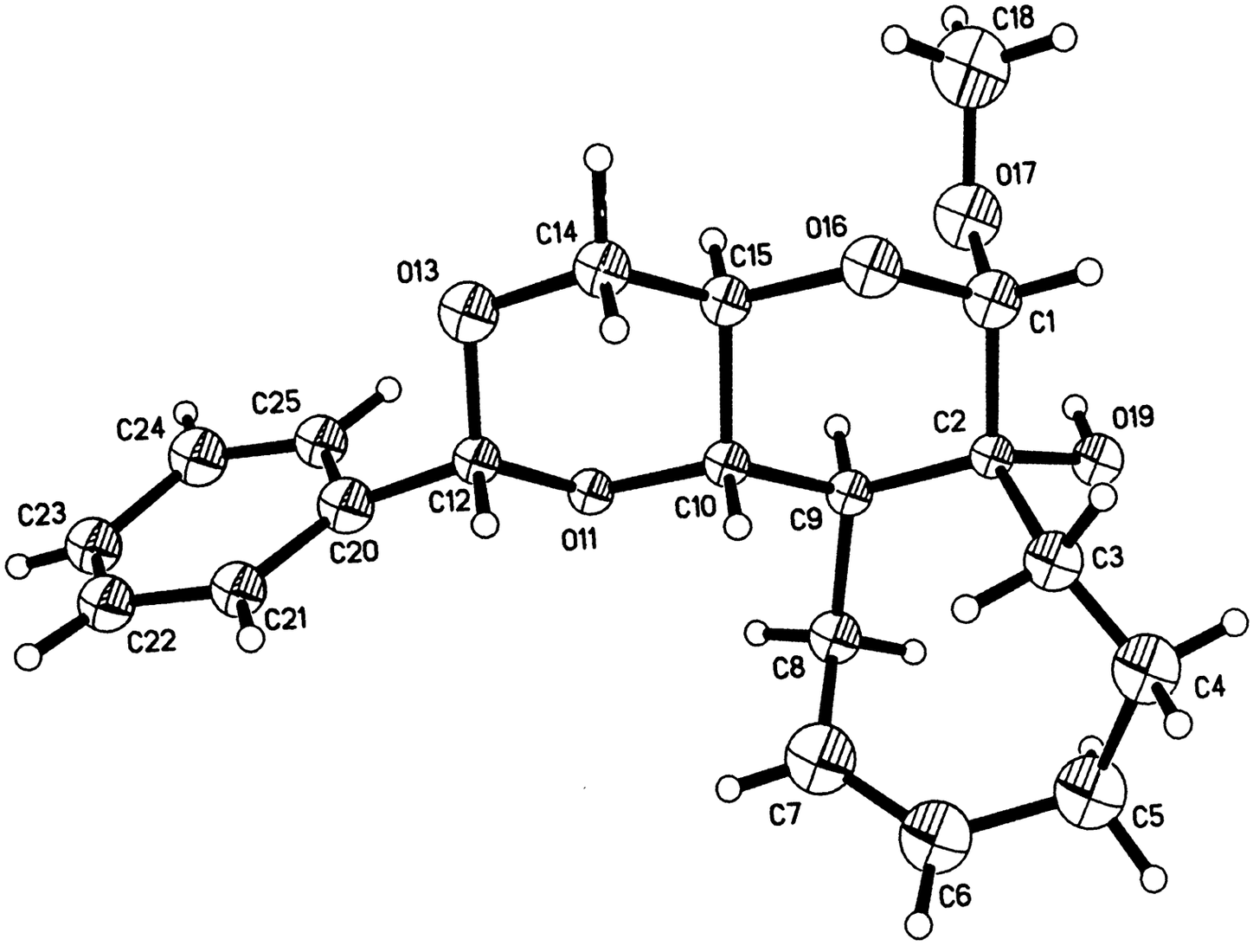

Figure 7. X-ray crystal structure of cyclooctene **314**

Table 1. Crystal data and structure refinement for 1.

Identification code	9840
Empirical formula	$C_{20}H_{26}O_5$
Formula weight	346.41
Temperature	190(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1$
Unit cell dimensions	a = 11.796(5) Å alpha = 90° b = 5.592(3) Å beta = 93.92(4)° c = 13.675(9) Å gamma = 90°
Volume, Z	899.9(8) $Å^3$, 2
Density (calculated)	1.278 Mg/m^3
Absorption coefficient	0.091 mm^{-1}
F(000)	372
Crystal size	0.24 x 0.21 x 0.04 mm
θ range for data collection	2.99 to 25.01°
Limiting indices	$0 \le h \le 12$, $-6 \le k \le 6$, $-14 \le l \le 14$
Reflections collected	2308
Independent reflections	2156 (R_{int} = 0.1117)
Absorption correction	Not applied
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2156 / 1 / 102
Goodness-of-fit on F^2	1.079
Final R indices [$I>2\sigma(I)$]	R1 = 0.2145, wR2 = 0.4649
R indices (all data)	R1 = 0.3515, wR2 = 0.6043
Absolute structure parameter	9(10)
Largest diff. peak and hole	1.216 and -1.206 $eÅ^{-3}$

Table 2. Atomic coordinates [x 10^4] and equivalent isotropic displacement parameters [$Å^2$ x 10^3] for 1. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U(eq)
O(11)	7465(13)	6733(25)	3716(9)	32(4)
O(13)	8554(14)	4288(29)	4817(10)	51(5)
O(16)	9979(14)	4647(29)	2535(10)	50(5)
O(17)	10546(17)	8539(36)	2189(13)	69(6)
O(19)	9086(13)	8939(27)	650(9)	43(4)
C(1)	10039(23)	6413(44)	1763(17)	49(7)
C(2)	8888(19)	7062(36)	1328(14)	29(5)
C(3)	8399(22)	4942(46)	660(16)	49(6)
C(4)	7880(25)	5294(53)	-190(19)	65(8)
C(5)	6715(28)	6906(65)	-243(22)	79(9)
C(6)	6000(28)	6086(59)	583(21)	76(9)
C(7)	6141(28)	6991(61)	1515(22)	76(9)
C(8)	6948(20)	8819(44)	1795(16)	45(6)
C(9)	8160(19)	7939(40)	2118(15)	34(5)
C(10)	8126(19)	6030(38)	2919(15)	32(5)
C(12)	7486(19)	4936(39)	4418(14)	33(5)
C(14)	9257(20)	3537(43)	4069(15)	43(6)
C(15)	9313(19)	5443(41)	3350(15)	37(6)
C(18)	11633(27)	8096(68)	2580(22)	92(11)
C(20)	6696(22)	5675(44)	5173(17)	48(7)
C(21)	5887(20)	4088(46)	5477(15)	45(6)
C(22)	5305(22)	4722(46)	6340(16)	49(6)
C(23)	5471(24)	6826(48)	6821(18)	53(7)
C(24)	6363(23)	8419(54)	6548(18)	59(7)
C(25)	6931(22)	7801(43)	5702(15)	45(6)

Table 3. Bond lengths [Å] and angles [°] for 1.

O(11)-C(12)	1.39(2)	O(11)-C(10)	1.44(3)
O(13)-C(12)	1.39(2)	O(13)-C(14)	1.42(3)
O(16)-C(1)	1.45(3)	O(16)-C(15)	1.47(3)
O(17)-C(18)	1.38(3)	O(17)-C(1)	1.44(3)
O(19)-C(2)	1.43(2)	C(1)-C(2)	1.49(3)
C(2)-C(9)	1.51(3)	C(2)-C(3)	1.58(3)
C(3)-C(4)	1.29(3)	C(4)-C(5)	1.64(4)
C(5)-C(6)	1.53(4)	C(6)-C(7)	1.37(4)
C(7)-C(8)	1.43(4)	C(8)-C(9)	1.55(3)
C(9)-C(10)	1.53(3)	C(10)-C(15)	1.52(3)
C(12)-C(20)	1.50(3)	C(14)-C(15)	1.45(3)
C(20)-C(21)	1.39(3)	C(20)-C(25)	1.41(3)
C(21)-C(22)	1.45(3)	C(22)-C(23)	1.36(3)
C(23)-C(24)	1.45(4)	C(24)-C(25)	1.42(4)

C(12)-O(11)-C(10)	110(2)	C(12)-O(13)-C(14)	111(2)
C(1)-O(16)-C(15)	114(2)	C(18)-O(17)-C(1)	111(2)
O(17)-C(1)-O(16)	108(2)	O(17)-C(1)-C(2)	108(2)
O(16)-C(1)-C(2)	112(2)	O(19)-C(2)-C(1)	105(2)
O(19)-C(2)-C(9)	111(2)	C(1)-C(2)-C(9)	110(2)
O(19)-C(2)-C(3)	104(2)	C(1)-C(2)-C(3)	110(2)
C(9)-C(2)-C(3)	117(2)	C(4)-C(3)-C(2)	123(2)
C(3)-C(4)-C(5)	118(3)	C(6)-C(5)-C(4)	108(3)
C(7)-C(6)-C(5)	123(3)	C(6)-C(7)-C(8)	123(3)
C(7)-C(8)-C(9)	116(2)	C(2)-C(9)-C(10)	109(2)
C(2)-C(9)-C(8)	117(2)	C(10)-C(9)-C(8)	111(2)
O(11)-C(10)-C(15)	107(2)	O(11)-C(10)-C(9)	113(2)
C(15)-C(10)-C(9)	111(2)	O(13)-C(12)-O(11)	116(2)
O(13)-C(12)-C(20)	113(2)	O(11)-C(12)-C(20)	107(2)
O(13)-C(14)-C(15)	109(2)	C(14)-C(15)-O(16)	110(2)
C(14)-C(15)-C(10)	110(2)	O(16)-C(15)-C(10)	107(2)
C(21)-C(20)-C(25)	120(2)	C(21)-C(20)-C(12)	120(2)
C(25)-C(20)-C(12)	119(2)	C(20)-C(21)-C(22)	118(2)
C(23)-C(22)-C(21)	123(3)	C(22)-C(23)-C(24)	120(3)
C(25)-C(24)-C(23)	117(3)	C(20)-C(25)-C(24)	123(3)

Symmetry transformations used to generate equivalent atoms:

Table 4. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for 1.

	x	y	z	U(eq)
H(19)	9384(13)	10071(27)	949(9)	65
H(1)	10505(23)	5802(44)	1252(17)	58
H(3B)	9031(22)	3881(46)	559(16)	59
H(3A)	7880(22)	4058(46)	1044(16)	59
H(4B)	7693(25)	3743(53)	-475(19)	78
H(4A)	8411(25)	6052(53)	-604(19)	78
H(5B)	6902(28)	8588(65)	-167(22)	95
H(5A)	6296(28)	6686(65)	-872(22)	95
H(6)	5447(28)	4925(59)	449(21)	91
H(7)	5689(28)	6387(61)	1989(22)	92
H(8B)	6660(20)	9725(44)	2330(16)	54
H(8A)	6998(20)	9905(44)	1247(16)	54
H(9)	8559(19)	9315(40)	2422(15)	41
H(10)	7791(19)	4572(38)	2625(15)	38
H(12)	7155(19)	3511(39)	4094(14)	40
H(14B)	8946(20)	2102(43)	3755(15)	51
H(14A)	10014(20)	3175(43)	4352(15)	51
H(15)	9662(19)	6869(41)	3659(15)	44
H(18A)	11953(27)	9541(68)	2860(22)	137
H(18B)	12092(27)	7543(68)	2073(22)	137
H(18C)	11612(27)	6896(68)	3081(22)	137
H(21)	5724(20)	2671(46)	5140(15)	54
H(22)	4794(22)	3633(46)	6575(16)	59
H(23)	5014(24)	7244(48)	7322(18)	63
H(24)	6556(23)	9785(54)	6910(18)	71
H(25)	7479(22)	8838(43)	5488(15)	54

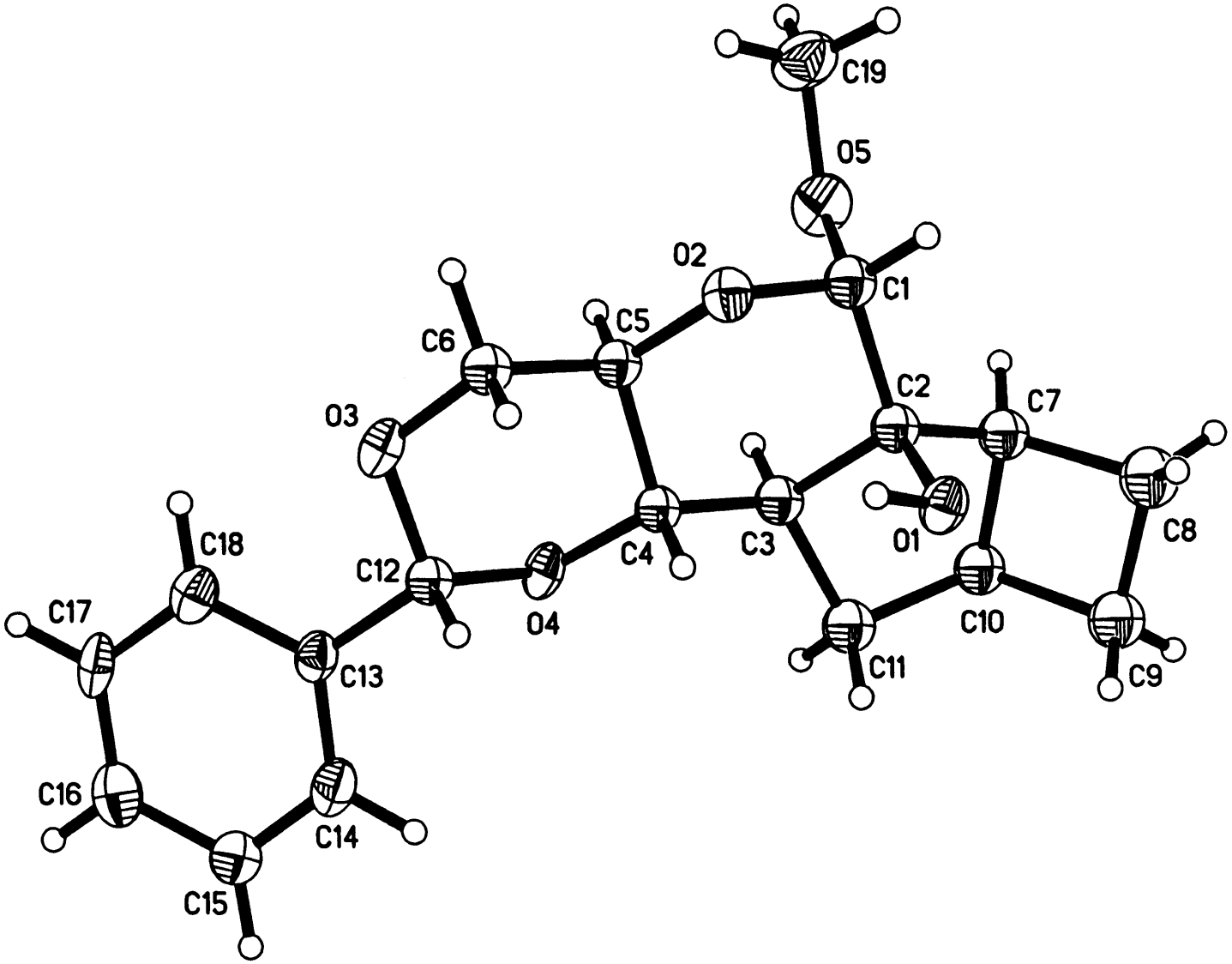

Figure 12. X-ray crystal structure of **392a**

Table 1. Crystal data and structure refinement for 1.

Identification code	1
Empirical formula	$C_{19}H_{24}O_5$
Formula weight	332.38
Temperature	190(2) K
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group	$P\bar{1}$
Unit cell dimensions	a = 8.467(2) Å alpha = 90.40(3)° b = 10.304(3) Å beta = 109.34(3)° c = 10.464(5) Å gamma = 101.30(2)°
Volume, Z	842.2(5) $Å^3$, 2
Density (calculated)	1.311 Mg/m^3
Absorption coefficient	0.094 mm^{-1}
F(000)	356
Crystal size	0.54 x 0.24 x 0.12 mm
θ range for data collection	3.62 to 23.99°
Limiting indices	$-9 \le h \le 0$, $-11 \le k \le 11$, $-10 \le l \le 11$
Reflections collected	2368
Independent reflections	2368 (R_{int} = 0.0000)
Absorption correction	Not applied
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2366 / 3 / 313
Goodness-of-fit on F^2	1.091
Final R indices [I>2σ(I)]	R1 = 0.0628, wR2 = 0.1494
R indices (all data)	R1 = 0.0815, wR2 = 0.1699
Absolute structure parameter	0(2)
Largest diff. peak and hole	0.263 and -0.309 $eÅ^{-3}$

Table 2. Atomic coordinates [x 10^4] and equivalent isotropic displacement parameters [$Å^2$ x 10^3] for 1. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U(eq)
O(1)	9161(6)	1632(5)	2922(5)	41(1)
O(2)	6695(6)	3125(5)	2863(5)	38(1)
O(3)	8443(7)	6009(5)	5300(5)	42(1)
O(4)	9795(6)	4302(5)	6262(5)	40(1)
O(5)	5155(7)	1263(6)	3528(7)	56(2)
C(1)	6355(10)	1706(8)	2913(8)	43(2)
C(2)	8051(9)	1298(8)	3710(8)	39(2)
C(3)	8848(9)	2022(7)	5134(8)	40(2)
C(4)	9101(9)	3505(7)	4967(7)	34(2)
C(5)	7391(9)	3815(7)	4173(7)	37(2)
C(6)	7615(9)	5293(7)	3983(8)	39(2)
C(7)	7986(10)	-153(8)	4020(8)	45(2)
C(8)	8621(12)	-1070(10)	3223(10)	60(2)
C(9)	10348(11)	-839(9)	4354(9)	56(2)
C(10)	9605(10)	-109(8)	5270(9)	47(2)
C(11)	10380(10)	1363(8)	5790(9)	49(2)
C(12)	10007(9)	5667(7)	5980(7)	37(2)
C(13)	10904(9)	6529(7)	7317(8)	38(2)
C(14)	12550(10)	6502(8)	8047(9)	48(2)
C(15)	13441(11)	7304(9)	9253(10)	54(2)
C(16)	12645(12)	8188(9)	9672(9)	55(2)
C(17)	10979(11)	8245(7)	8913(9)	50(2)
C(18)	10118(10)	7419(7)	7747(8)	42(2)
C(19)	3487(11)	1366(11)	2717(12)	65(3)
O(1A)	6362(6)	2579(5)	7150(5)	44(1)
O(2A)	5720(6)	4540(5)	8751(5)	39(1)
O(3A)	9516(6)	6274(5)	11496(5)	41(1)
O(4A)	9795(5)	4070(4)	11171(5)	33(1)
O(5A)	4057(6)	2784(5)	9468(5)	40(1)
C(1A)	4744(9)	3214(7)	8463(7)	36(2)
C(2A)	5910(9)	2268(7)	8343(7)	35(2)
C(3A)	7477(8)	2438(7)	9620(7)	32(2)
C(4A)	8417(8)	3868(7)	9903(7)	32(2)
C(5A)	7159(9)	4700(7)	9990(7)	36(2)
C(6A)	8072(9)	6147(7)	10281(8)	40(2)
C(7A)	5186(9)	774(7)	8229(7)	39(2)
C(8A)	4753(11)	-78(9)	6864(9)	53(2)
C(9A)	6424(11)	-605(9)	7491(9)	54(2)
C(10A)	6789(9)	157(7)	8873(8)	40(2)
C(11A)	8351(9)	1310(7)	9424(7)	39(2)
C(12A)	10625(8)	5431(7)	11425(7)	31(1)
C(13A)	12061(8)	5623(7)	12780(7)	34(2)
C(14A)	12530(8)	4566(8)	13501(7)	38(2)
C(15A)	13783(9)	4776(9)	14782(9)	51(2)
C(16A)	14593(9)	6058(9)	15318(9)	48(2)
C(17A)	14143(11)	7117(9)	14589(9)	57(2)
C(18A)	12902(10)	6931(8)	13327(8)	46(2)
C(19A)	2840(10)	3543(8)	9602(9)	49(2)

Table 3. Bond lengths [Å] and angles [°] for 1.

O(1)-C(2)	1.439(9)	O(2)-C(5)	1.421(8)
O(2)-C(1)	1.439(9)	O(3)-C(12)	1.395(9)
O(3)-C(6)	1.442(9)	O(4)-C(12)	1.428(9)
O(4)-C(4)	1.458(8)	O(5)-C(1)	1.382(9)
O(5)-C(19)	1.411(11)	C(1)-C(2)	1.543(11)
C(2)-C(7)	1.526(11)	C(2)-C(3)	1.534(11)
C(3)-C(4)	1.520(10)	C(3)-C(11)	1.542(11)
C(4)-C(5)	1.509(9)	C(5)-C(6)	1.520(10)
C(7)-C(8)	1.537(12)	C(7)-C(10)	1.543(12)
C(8)-C(9)	1.519(13)	C(9)-C(10)	1.566(12)
C(10)-C(11)	1.545(12)	C(12)-C(13)	1.529(10)
C(13)-C(14)	1.355(11)	C(13)-C(18)	1.386(10)
C(14)-C(15)	1.399(13)	C(15)-C(16)	1.381(12)
C(16)-C(17)	1.384(13)	C(17)-C(18)	1.377(12)
O(1A)-C(2A)	1.443(8)	O(2A)-C(1A)	1.424(9)
O(2A)-C(5A)	1.437(9)	O(3A)-C(12A)	1.416(8)
O(3A)-C(6A)	1.426(9)	O(4A)-C(12A)	1.420(8)
O(4A)-C(4A)	1.429(8)	O(5A)-C(1A)	1.396(9)
O(5A)-C(19A)	1.451(8)	C(1A)-C(2A)	1.549(9)
C(2A)-C(3A)	1.519(10)	C(2A)-C(7A)	1.529(10)
C(3A)-C(4A)	1.507(9)	C(3A)-C(11A)	1.541(10)
C(4A)-C(5A)	1.516(9)	C(5A)-C(6A)	1.516(10)
C(7A)-C(10A)	1.561(10)	C(7A)-C(8A)	1.566(11)
C(8A)-C(9A)	1.555(12)	C(9A)-C(10A)	1.548(12)
C(10A)-C(11A)	1.537(10)	C(12A)-C(13A)	1.513(10)
C(13A)-C(14A)	1.376(11)	C(13A)-C(18A)	1.413(11)
C(14A)-C(15A)	1.391(11)	C(15A)-C(16A)	1.383(13)
C(16A)-C(17A)	1.378(14)	C(17A)-C(18A)	1.372(13)

C(5)-O(2)-C(1)	112.8(5)	C(12)-O(3)-C(6)	111.4(5)
C(12)-O(4)-C(4)	107.7(5)	C(1)-O(5)-C(19)	112.6(7)
O(5)-C(1)-O(2)	112.6(6)	O(5)-C(1)-C(2)	109.4(7)
O(2)-C(1)-C(2)	108.3(6)	O(1)-C(2)-C(7)	108.1(6)
O(1)-C(2)-C(3)	111.2(6)	C(7)-C(2)-C(3)	102.2(6)
O(1)-C(2)-C(1)	106.4(6)	C(7)-C(2)-C(1)	118.0(6)
C(3)-C(2)-C(1)	111.0(6)	C(4)-C(3)-C(2)	107.7(6)
C(4)-C(3)-C(11)	121.4(6)	C(2)-C(3)-C(11)	102.2(6)
O(4)-C(4)-C(5)	108.7(5)	O(4)-C(4)-C(3)	112.8(6)
C(5)-C(4)-C(3)	108.5(5)	O(2)-C(5)-C(4)	111.3(6)
O(2)-C(5)-C(6)	107.7(6)	C(4)-C(5)-C(6)	109.4(6)
O(3)-C(6)-C(5)	108.4(6)	C(2)-C(7)-C(8)	120.2(7)
C(2)-C(7)-C(10)	104.1(6)	C(8)-C(7)-C(10)	89.8(6)
C(9)-C(8)-C(7)	90.6(7)	C(8)-C(9)-C(10)	89.6(7)
C(11)-C(10)-C(7)	107.6(7)	C(11)-C(10)-C(9)	120.6(7)
C(7)-C(10)-C(9)	88.6(6)	C(3)-C(11)-C(10)	101.9(6)
O(3)-C(12)-O(4)	111.8(5)	O(3)-C(12)-C(13)	109.6(6)
O(4)-C(12)-C(13)	109.0(6)	C(14)-C(13)-C(18)	118.9(7)
C(14)-C(13)-C(12)	119.5(6)	C(18)-C(13)-C(12)	121.3(7)
C(13)-C(14)-C(15)	121.6(7)	C(16)-C(15)-C(14)	118.9(8)
C(17)-C(16)-C(15)	119.8(9)	C(16)-C(17)-C(18)	120.0(7)
C(17)-C(18)-C(13)	120.7(7)	C(1A)-O(2A)-C(5A)	112.4(5)
C(12A)-O(3A)-C(6A)	112.3(5)	C(12A)-O(4A)-C(4A)	109.9(5)
C(1A)-O(5A)-C(19A)	112.7(6)	O(5A)-C(1A)-O(2A)	113.1(6)
O(5A)-C(1A)-C(2A)	107.8(5)	O(2A)-C(1A)-C(2A)	109.1(5)
O(1A)-C(2A)-C(3A)	112.0(5)	O(1A)-C(2A)-C(7A)	107.9(6)
C(3A)-C(2A)-C(7A)	102.0(6)	O(1A)-C(2A)-C(1A)	106.9(5)
C(3A)-C(2A)-C(1A)	110.4(5)	C(7A)-C(2A)-C(1A)	117.7(6)
C(4A)-C(3A)-C(2A)	110.5(6)	C(4A)-C(3A)-C(11A)	122.0(6)
C(2A)-C(3A)-C(11A)	103.7(5)	O(4A)-C(4A)-C(3A)	111.2(5)

O(4A)-C(4A)-C(5A)	108.1(5)	C(3A)-C(4A)-C(5A)	107.7(5)
O(2A)-C(5A)-C(4A)	111.4(5)	O(2A)-C(5A)-C(6A)	109.7(6)
C(4A)-C(5A)-C(6A)	108.9(5)	O(3A)-C(6A)-C(5A)	108.6(6)
C(2A)-C(7A)-C(10A)	104.5(6)	C(2A)-C(7A)-C(8A)	120.4(6)
C(10A)-C(7A)-C(8A)	89.8(6)	C(9A)-C(8A)-C(7A)	89.4(6)
C(10A)-C(9A)-C(8A)	90.8(6)	C(11A)-C(10A)-C(9A)	120.0(6)
C(11A)-C(10A)-C(7A)	107.5(6)	C(9A)-C(10A)-C(7A)	89.8(6)
C(10A)-C(11A)-C(3A)	100.6(5)	O(3A)-C(12A)-O(4A)	112.8(5)
O(3A)-C(12A)-C(13A)	107.2(5)	O(4A)-C(12A)-C(13A)	108.8(5)
C(14A)-C(13A)-C(18A)	119.7(7)	C(14A)-C(13A)-C(12A)	122.0(6)
C(18A)-C(13A)-C(12A)	118.4(7)	C(13A)-C(14A)-C(15A)	120.6(7)
C(16A)-C(15A)-C(14A)	119.5(9)	C(17A)-C(16A)-C(15A)	120.0(8)
C(18A)-C(17A)-C(16A)	121.4(8)	C(17A)-C(18A)-C(13A)	118.8(8)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters [$Å^2$ x 10^3] for 1.

The anisotropic displacement factor exponent takes the form:

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

	U11	U22	U33	U23	U13	U12
O(1)	48(3)	39(3)	43(3)	6(2)	25(2)	13(2)
O(2)	45(3)	34(3)	36(3)	10(2)	14(2)	10(2)
O(3)	54(3)	36(3)	47(3)	10(2)	25(3)	21(2)
O(4)	54(3)	28(3)	47(3)	12(2)	23(2)	19(2)
O(5)	55(3)	47(3)	75(4)	16(3)	38(3)	6(3)
C(13)	45(4)	30(4)	47(4)	6(3)	26(4)	10(3)
C(14)	56(5)	37(4)	58(5)	6(4)	26(4)	18(4)
C(15)	48(4)	46(5)	68(6)	3(4)	17(4)	11(4)
C(16)	74(6)	45(5)	48(5)	2(4)	23(4)	11(4)
C(17)	75(6)	30(4)	59(5)	2(4)	36(5)	21(4)
C(18)	55(4)	38(4)	46(5)	14(3)	27(4)	17(3)
C(19)	45(5)	69(6)	89(7)	8(5)	32(5)	14(4)
O(1A)	52(3)	45(3)	39(3)	-4(2)	25(2)	4(2)
O(2A)	39(3)	38(3)	43(3)	8(2)	15(2)	12(2)
O(3A)	44(3)	33(3)	51(3)	-5(2)	20(2)	11(2)
O(4A)	30(2)	30(3)	38(3)	4(2)	10(2)	7(2)
O(5A)	36(3)	44(3)	46(3)	6(2)	20(2)	15(2)
C(13A)	34(3)	36(4)	41(4)	1(3)	22(3)	9(3)
C(14A)	33(4)	44(4)	37(4)	-2(3)	11(3)	9(3)
C(15A)	37(4)	65(6)	59(6)	5(4)	22(4)	19(4)
C(16A)	37(4)	60(6)	49(5)	-4(4)	16(3)	11(4)
C(17A)	48(5)	61(6)	58(5)	-22(5)	22(4)	-2(4)
C(18A)	51(4)	40(4)	46(5)	-7(3)	20(4)	3(3)
C(19A)	51(5)	51(5)	61(5)	11(4)	33(4)	22(4)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for 1.

	x	y	z	U(eq)
H(1)	9137(6)	2519(5)	2621(5)	61
H(1B)	5935(10)	1290(8)	1985(8)	52
H(3A)	8033(9)	1790(7)	5618(8)	48
H(4A)	9883(9)	3743(7)	4454(7)	41
H(5A)	6594(9)	3566(7)	4672(7)	45
H(6A)	8308(9)	5532(7)	3411(8)	47
H(6B)	6509(9)	5515(7)	3547(8)	47
H(7A)	6927(10)	-579(8)	4170(8)	54
H(8A)	7995(12)	-1984(10)	3088(10)	72
H(8B)	8682(12)	-742(10)	2371(10)	72
H(9A)	11260(11)	-271(9)	4128(9)	67
H(9B)	10683(11)	-1649(9)	4704(9)	67
H(10A)	9372(10)	-654(8)	5976(9)	57
H(11A)	10761(10)	1478(8)	6773(9)	59
H(11B)	11333(10)	1716(8)	5485(9)	59
H(12A)	10729(9)	5831(7)	5410(7)	44
H(14A)	13100(10)	5936(8)	7738(9)	57
H(15A)	14552(11)	7243(9)	9765(10)	65
H(16A)	13226(12)	8743(9)	10461(9)	66
H(17A)	10440(11)	8841(7)	9191(9)	60
H(18A)	8997(10)	7459(7)	7244(8)	51
H(19A)	2702(11)	1048(11)	3185(12)	98
H(19B)	3155(11)	842(11)	1872(12)	98
H(19C)	3469(11)	2277(11)	2543(12)	98
H(1A)	6991(6)	3526(5)	7418(5)	65
H(1AB)	3807(9)	3155(7)	7595(7)	43
H(3AA)	7055(8)	2223(7)	10375(7)	39
H(4AA)	8854(8)	4140(7)	9167(7)	39
H(5AA)	6746(9)	4425(7)	10738(7)	43
H(6AA)	8444(9)	6446(7)	9530(8)	48
H(6AB)	7302(9)	6689(7)	10391(8)	48
H(7AA)	4317(9)	538(7)	8663(7)	47
H(8AA)	3717(11)	-761(9)	6647(9)	64
H(8AB)	4745(11)	446(9)	6097(9)	64
H(9AA)	6226(11)	-1561(9)	7527(9)	65
H(9AB)	7279(11)	-300(9)	7071(9)	65
H(10B)	6656(9)	-439(7)	9573(8)	48
H(11C)	8941(9)	1508(7)	8773(7)	47
H(11D)	9151(9)	1128(7)	10276(7)	47
H(12B)	11101(8)	5693(7)	10707(7)	38
H(14B)	12003(8)	3704(8)	13128(7)	46
H(15B)	14073(9)	4058(9)	15275(9)	61
H(16B)	15442(9)	6207(9)	16170(9)	58
H(17B)	14693(11)	7976(9)	14960(9)	68
H(18B)	12619(10)	7654(8)	12841(8)	55
H(19D)	2407(10)	3211(8)	10303(9)	73
H(19E)	1909(10)	3461(8)	8757(9)	73
H(19F)	3398(10)	4461(8)	9836(9)	73