# Photoannulation and Ring Closing Metathesis of Carbohydrate Derivatives


University *of* Leicester

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*Doctor of Philosophy*

*At the University of Leicester*

*by*

William D. Barker

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 "Photoannulation and Ring Closing Metathesis of Carbohydrate Derivatives" is based on work conducted by the author in the Department of Chemistry at the University of Leicester between the period October 1997 to September 2000.

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

Signed: ..... Date: .....

Parts of this work have been published:

*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.Engl.*, **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.

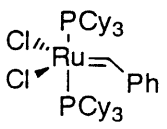
*Stereoselective Preparation of Enantiomerically Pure Annulated Carbohydrates Using Ring-Closing Metathesis*; David J. Holt, William D. Barker, Paul R. Jenkins, Jagannath Panda, and Subrata Ghosh, *J.Org.Chem.*, **2000**, *65*, 482.

# Abstract

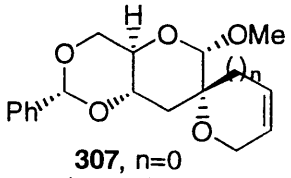
## Photoannulation and Ring Closing Metathesis of Carbohydrate Derivatives by William D. Barker


The 'chiron approach' is a well-recognised technique for converting carbohydrates and other naturally occurring compounds into new chiral target molecules. The success of this area of chemistry can be attributed to the vast array of novel methods for transforming carbohydrates that have been developed over the last 50 years. Chapter 1 describes some of the key discoveries and pioneers within the field of carbohydrate annulation

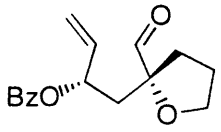
As part of the Jenkins groups' on-going studies into the development of new methods for carbohydrate annulation, we have demonstrated the ease in which simple carbohydrate derivatives can be cyclised by Ring Closing Metathesis (RCM). Using Grubbs ruthenium catalyst **176b**, we have cyclised a range of substrates derived from D-glucose to give annulated products such as **307**. Some of the adducts have been reduced by well known methodology to give chiral fragments such as **348** which may be used as a 'chiron' in further synthesis (Chapter 2).




**176b**

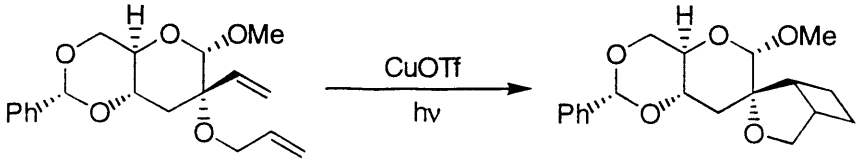



**307**, n=0
also n=1,2,3



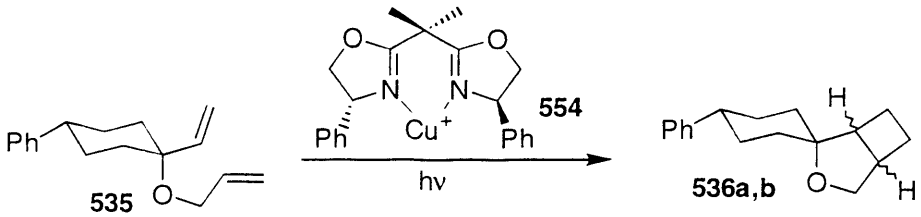

**348**

We have also utilised the copper (I) triflate catalysed intramolecular [2+2] photocycloaddition reaction to cyclise a range of carbohydrate derivatives such as **306** to afford enantiomerically pure products **400** and this represents a novel method to add to the increasingly wide range of techniques for annulating carbohydrates.




**306** **400**

To further extend the scope of the catalysed [2+2] photochemical ring closure reaction, we have investigated a variety of reagents in an attempt to make it an asymmetric catalytic process. The achiral diene **535** can be cyclised in the presence of a number of chiral catalysts such as **554** to give two enantiomeric tricyclic products **536a** and **536b**, which can be quantitatively analysed by chiral hplc. The chiral catalyst should favour one enantiomer over the other. We have considered a variety of substrates, reagents and reaction conditions, and the results are reported in chapter 4.



# Acknowledgements

First and foremost I would like to thank my supervisor Dr. Paul Jenkins for his assistance, endless enthusiasm and constant flow of new ideas over the last three years. Two other members of staff who deserve thanks are Prof. Paul Cullis and Dr. Sandeep Handa who have gone out of their way to encourage, teach and befriend.

I am grateful to all my friends and colleagues past (Chi-kit, Dave and Roger) and present (the usual suspects, they know who they are), for the exceptional atmosphere within the lab, promoting hard work in a very relaxed and friendly environment. I am also indebted to all the technical staff (again, past and present), as without them I don't think anything would ever get done!

Finally, I would like to thank three very special people, my Mother and Father and my girlfriend Carol, because they are always there for me.

# Contents

# Abbreviations

| | |
|---|---|
| Ac | acetyl |
| acac | acetylacetonate |
| ADMET | acyclic diene metathesis |
| AIBN | azobisisobutyrylnitrile |
| AIDS | Aquired Immuno Deficiency Syndrome |
| Bn | benzyl |
| Bz | benzoyl |
| CSA | camphor sulfonic acid |
| Cy | cyclohexyl |
| DBU | 1,8-diazabicyclo[5.4.0]undec-7-ene |
| DCM | dichloromethane |
| de | diastereomeric excess |
| DEAD | diethylazodicarboxylate |
| DIBAL | diisobutylaluminium hydride |
| DMAP | 4-dimethylaminopyridine |
| DMF | *N,N*-dimethylformamide |
| DMPU | 1,3-dimethyltetrahydro-2(1*H*)-pyrimidone |
| DMSO | dimethylsulfoxide |
| DPPE | bis (diphenylphosphino)ethane |
| ee | enantiomeric excess |
| EI | electron ionisation |
| ES | electrospray |
| FAB | fast atom bombardment |
| FG | functional group |
| GLC | gas liquid chromatography |
| HMPA | hexamethylphosphoric triamide |
| HPLC | high performance liquid chromatography |
| HOMO | highest occupied molecular orbital |
| IPA | propan-2-ol |
| *J* | coupling constant |
| LAH | lithium aluminium hydride |

| | |
|---|---|
| LDA | lithium diisopropylamide |
| LUMO | lowest unoccupied molecular orbital |
| MCPBA | *meta*-chloroperbenzoic acid |
| Mes | mesitaldehyde |
| Ms | mesyl |
| NBS | *N*-bromosuccinimide |
| NCS | *N*-chlorosuccinimide |
| NMO | *N*-morpholine oxide |
| NMR | nuclear magnetic resonance |
| nOe | nuclear Overhauser effect |
| PMB | *para*-methoxybenzyl |
| RCM | ring closing metathesis |
| ROMP | ring opening metathesis polymerisation |
| rt | room temperature |
| TBDMS | *tert*-butyldimethylsilyl |
| TBDPS | *tert*-butyldiphenylsilyl |
| TBS | tributylsilyl |
| Tf | trifluoromethanesulfonyl |
| THF | tetrahydrofuran |
| TMS | trimethylsilyl |
| TPS | triphenylsilyl |
| Tr | triphenyl methyl |
| Ts | *para*-toluenesulfonyl |
| TSA | toluene sulfonic acid |
| UV | ultra violet |

# Chapter 1

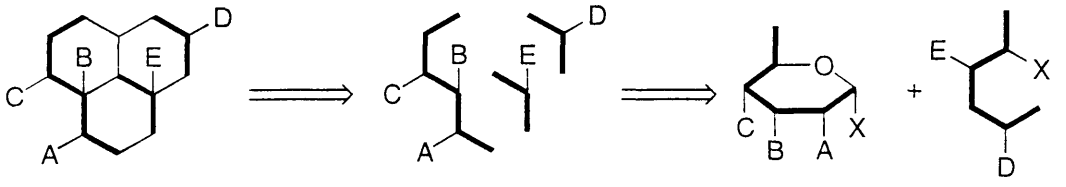
# Carbohydrate Annulation:

# A brief overview.

## 1.1 Introduction:

The synthetic organic chemist has tackled the challenge of producing enantiomerically pure compounds with a variety of tactics, a common theme however, is the necessity of optically pure reagents or starting material. When natural products are used in such a synthesis, the source of this chirality is the vast array of compounds produced by enzymatic processes in nature. Within the carbohydrate family of compounds, one can find many of the attributes often required by the organic chemist when preparing target chiral compounds. For example, they are cheap, come in a variety of cyclic and acyclic forms and they also contain a wealth of functional, stereochemical and conformational features making them susceptible to chemical manipulation. Carbohydrates are particularly useful in the synthesis of target molecules which contain several oxygen substituents.

The first step in any synthesis is to consider the target molecule by retrosynthetic analysis. When analysing a molecule in this manner, it is sometimes possible to locate a fragment with attributes that may be derived from a carbohydrate. Usually, this fragment must be 'decoded' from the target molecule to realise how it may be incorporated. The decoded fragments have been labelled 'chirons' by Hanessian.[1] Scheme 1 illustrates how the target molecule has been decoded and broken down into three chirons. These chirons can be derived through a series of chemical manipulations from the naturally occurring starting materials labelled 'chiral templates'.



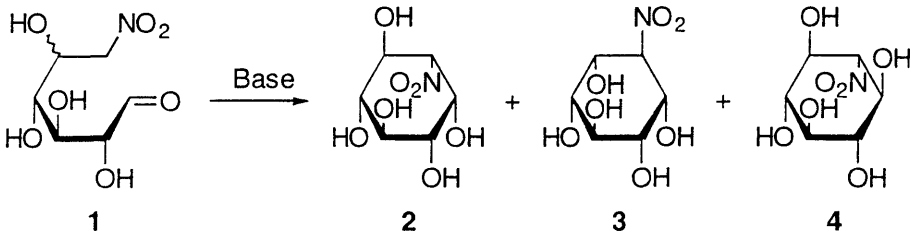

**Scheme 1**

A key element of the chiron approach to producing target molecules is the wide range of methods available for preparing chiral carbocyclic, heterocyclic and acyclic compounds. The stereochemical advantages offered by a carbohydrate, lie not only in their inherent chirality but also the various conformations that they may exist in. The task of the synthetic chemist is to utilise the chirality present to prepare new chiral compounds.

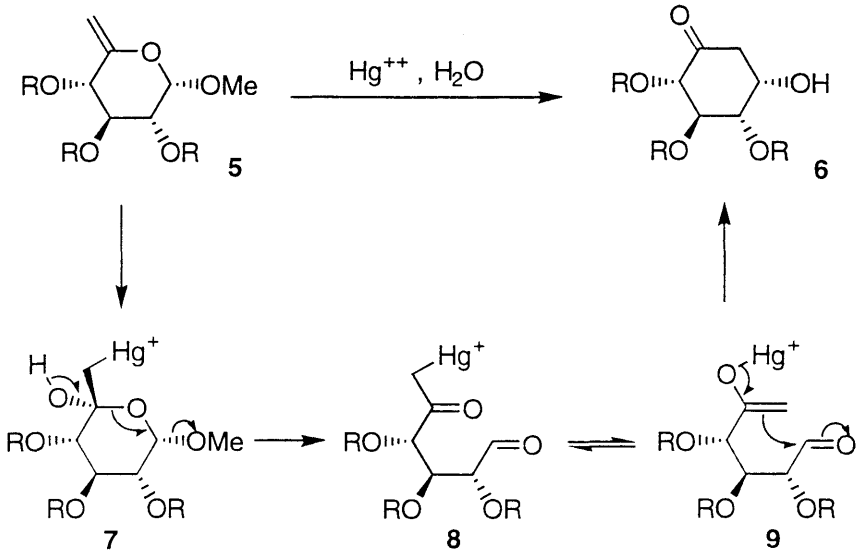
This thesis describes investigations into new methods for the annulation of carbohydrates, to further extend the wide range of target molecules available from sugars.

## 1.2 Carbocycles from Carbohydrates

Carbocyclic targets derived from carbohydrates have been studied extensively since the first rational sugar to chiral cyclohexane conversion was reported by Fischer in 1948. Base catalysed intramolecular aldol-like cyclisation of nitro sugar **1** yielded nitroinositols **2-4**.[2]




The field has expanded rapidly over the last 30 years, with a ground breaking convenient and general procedure for the conversion of carbohydrates such as **5** into cyclohexane analogues **6**, reported by Ferrier in 1979 (Scheme 2).[3]

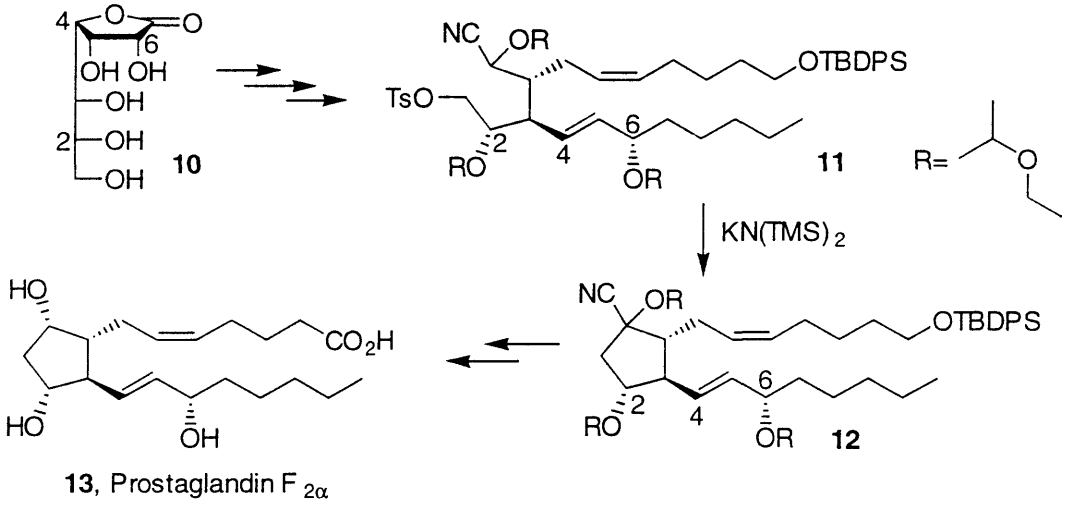



**Scheme 2**

The D-glucose derived olefin **5** is hydroxymercuriated furnishing **7**; this unstable hemiacetal spontaneously condenses methanol to afford acyclic dicarbonyl **8**. The

dicarbonyl can tautomerise to **9**, which undergoes aldol condensation to yield cyclohexanone **6**.

A milestone in carbohydrate chemistry was realised when Stork published an elegant synthesis of prostaglandin $F_{2\alpha}$.[4] Scheme 3 illustrates this extremely efficient synthesis, as all five chiral centres of the starting material **10**, are used to furnish the stereochemical attributes of the product **13**.[5] Two of the chiral hydroxyl groups are used for the stereospecific generation of the *trans* double bond, two are retained in the final product and one has been transposed to a carbon chiral centre via a Claisen rearrangement. The key ring closure step is an $S_N2$ displacement of the tosylate by the nitrile-stabilised anion of **11**, which furnishes chiral cyclopentane **12**.




**Scheme 3**

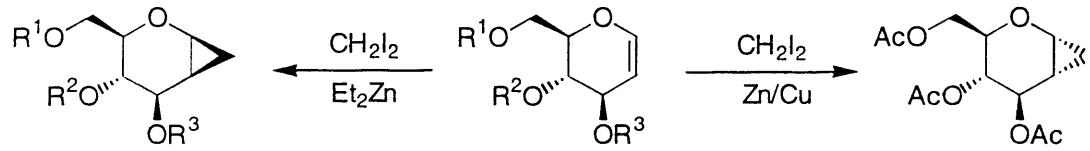
The two-featured reactions (Schemes 2 and 3) represent two discrete methods for the preparation of carbocycles from carbohydrates. In the first example (Scheme 2), all six of the sugar carbon atoms are incorporated into the new ring of the product, which gives a "carbohydrate-like" compound. We find it convenient to classify this reaction an F-type reaction (after Ferrier). In the second example however (Scheme 3), all six of the carbon atoms from the starting material are present in the product, but only three are present in the new ring resulting in a "carbohydrate-unlike" product. We choose to label this reaction, where between one and five carbon atoms from the original sugar are incorporated into the new ring, an S-type reaction (after Stork).

It is clear that an almost infinitely wide range of products are available from carbohydrates, by ring closing an acyclic sugar or by building new functionality onto a sugar that will facilitate ring closure. In the next section of this overview, we will explore some of the methods utilised for ring closing carbohydrates, paying particular

attention to 5- and 6-membered carbocyclic rings, as they have been studied the most extensively over the last 20 years.[6]

### 1.2.1 3- and 4-Membered Carbocycles from Carbohydrates.

The incorporation of the cyclopropane ring into carbohydrates provides an interesting mixture of strained and reactive 3-membered rings with the inherent optical activity of carbohydrates. The most popular cyclopropanation reaction involves the addition of a dihaloalkane to a 1,2 unsaturated carbohydrate or glycal, in a Simmons Smith carbenoid addition.[7] Glycals **14** undergo cyclopropanation in the presence of diiodomethane and diethyl zinc to give a range of products **15** in yields of up to 96% and diastereoselectivity of over 250:1. The *syn* diastereoisomer is formed due to co-ordination of the zinc to the allylic $OR^3$ group.[8]



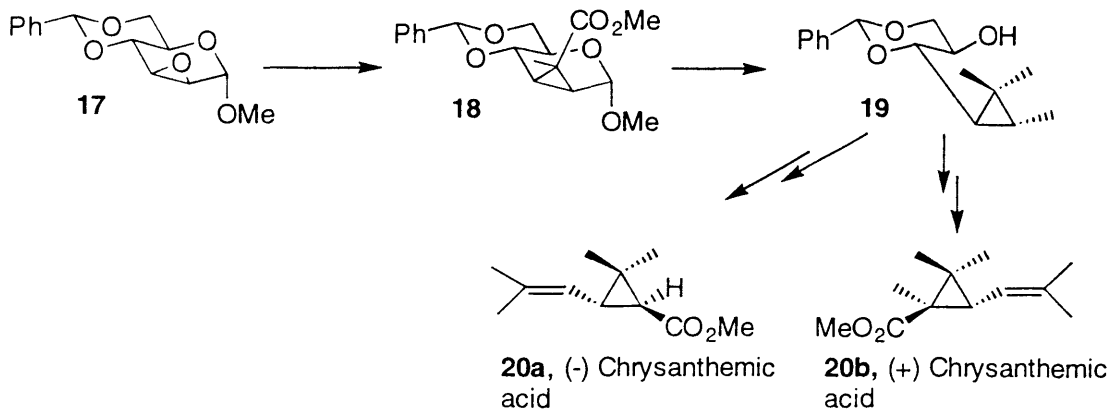

**15a**, $R^1$, $R^2$, $R^3$ = Me
**15b**, $R^1$, $R^2$, $R^3$ = Bn
**15c**, $R^1$ = TMS; $R^2$, $R^3$ = H

**14**

**16**

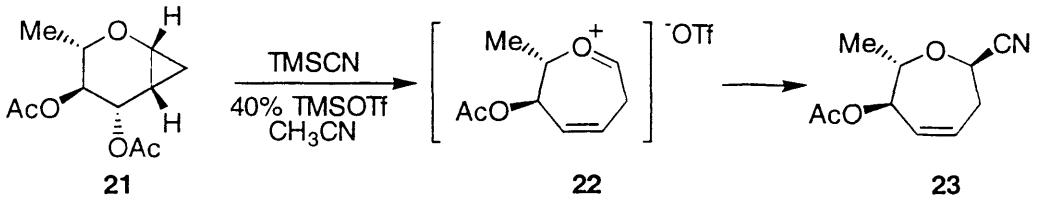
Lorica and co-workers reported that the *anti* cyclopropane adduct **16**, was the major product of the carbenoid addition to **14** in 38% yield, under similar conditions. The stereoselectivity was attributed to the steric hindrance of the upper face of the sugar by the acetate protecting groups; thus it appears that a suitable protecting group is critical for a stereodirected cyclopropanation.[9]

A total synthesis of (+) and (-) chrysanthemic acid **20a** and **20b**, reported by Fitzsimmons and Fraser-Reid illustrates how a cyclopropane ring is annulated onto the glucose derived epoxide **17** via a phosphonate anion (Scheme 4). The carbohydrate moiety **18** is then modified to give fragment **19**, which can be transformed into **20a** and **20b**.[10]



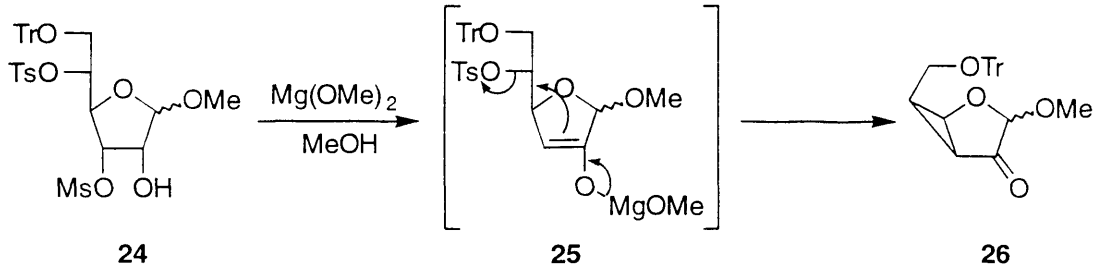

**Scheme 4**

The high reactivity of cyclopropanes makes them excellent substrates for ring expansion reactions, Scheme 5 illustrates how oxepane **23** is afforded with excellent diastereoselectivity when **21** is treated with trimethylsilylcyanide and trimethylsilyltriflate. This reaction is thought to occur through the intermediate **22**.[11]



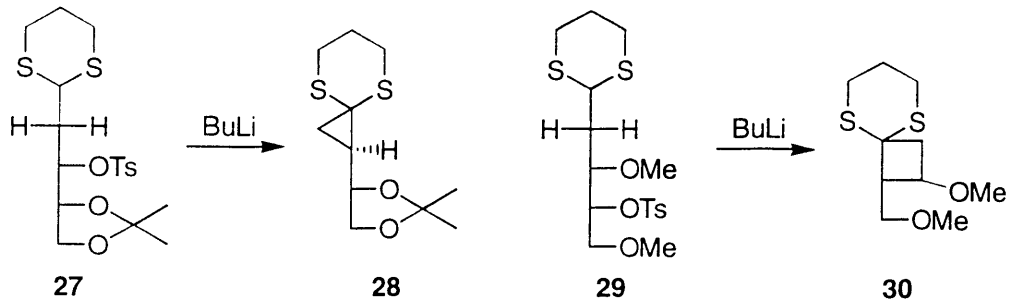

**Scheme 5**

An example of intramolecular cyclopropanation was reported by Kawana and co-workers.[12] Treatment of the protected D-glucose moiety **24** with magnesium methoxide results in a rearrangement/elimination to give furanose **25**, spontaneous intramolecular displacement of the tosylate affords **26** in 70% yield (Scheme 6).



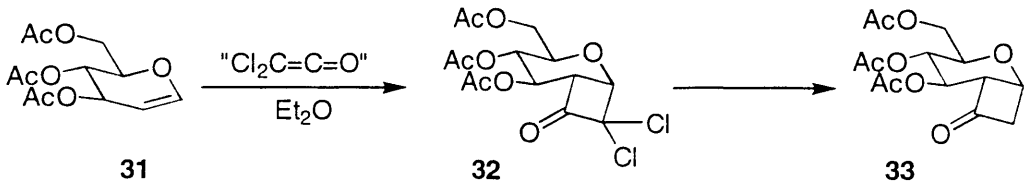

**Scheme 6**

Another cyclopropanation via intramolecular displacement of the tosyl ether of acyclic dithiane **27** yields chiral cyclopropane derivative **28** in 73% yield overall.




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

Interestingly, when the dithiane derivative **29** is treated under the same conditions, the cyclobutane product **30** was afforded in only 18% yield. Generally cyclobutanes are not common products of the intramolecular nucleophilic displacement reaction.[13] Carbohydrate derived cyclobutane adducts are commonly obtained via a [2+2] photochemical process, although there are only a handful of examples.[14] This photochemical process is discussed extensively in chapter 2. Another successful cyclobutanation reaction proposed by Redlich *at al.* involves the thermally allowed [2+2] cycloaddition of a ketene to a carbohydrate derived enol ether (Scheme 7).[15] The reaction of 3,4,6-tri-O-acetyl-D-glucal **31**, with dichloroketene (generated in situ from trichloroacetyl chloride and Zn/Cu couple) afforded **32** in 95% yield. Dichloro-sugar derivative **32** was reduced with zinc in acetic acid to afford cyclobutanone **33** in 58% yield. The dichloro- intermediate **32** is the only observed product of the cycloaddition, as the ketene will preferentially approach from the less hindered α face of the glycal.




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

**Scheme 7**

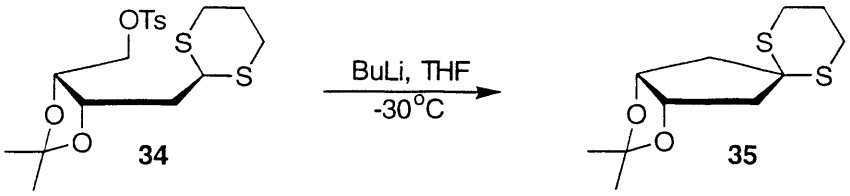
All of the above reactions are S-type reactions as only two of the sugar carbon atoms are incorporated into the product. The topographical features of many cyclic carbohydrates tend to promote selectivity when a new ring is annulated onto it. This has led to the synthesis of a wide range of enantiomerically pure 3- and 4-membered carbocycles bound to carbohydrates, which lend themselves to further manipulation.

### 1.2.2 5-Membered Carbocycles from Carbohydrates.

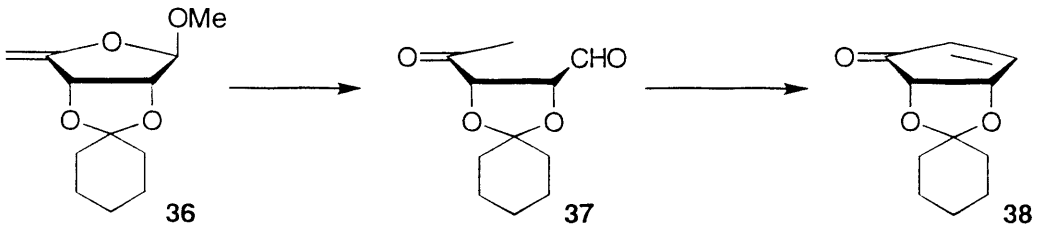
30 years elapsed between the first carbohydrate to cyclohexane conversion and the analogous cyclopentane synthesis, however, to date there are as many if not more examples available in the literature.[6] Most reactions employed by synthetic chemists for a carbohydrate to cyclopentane conversion involve intramolecular nucleophilic displacement of a suitable leaving group. The nucleophilic species is usually a carbanion α to a stabilising carbonyl, phosphonate or nitro group.

### 1.2.2a Carbanion Cyclisations

**F-Type:** A dithiane-stabilised anion can also be used to effect ring closure as Krohn and Borner demonstrated.[16] Treatment of the dithiane **34** with butyl lithium at -30°C affords the cyclopentane product **35** in 71% yield.



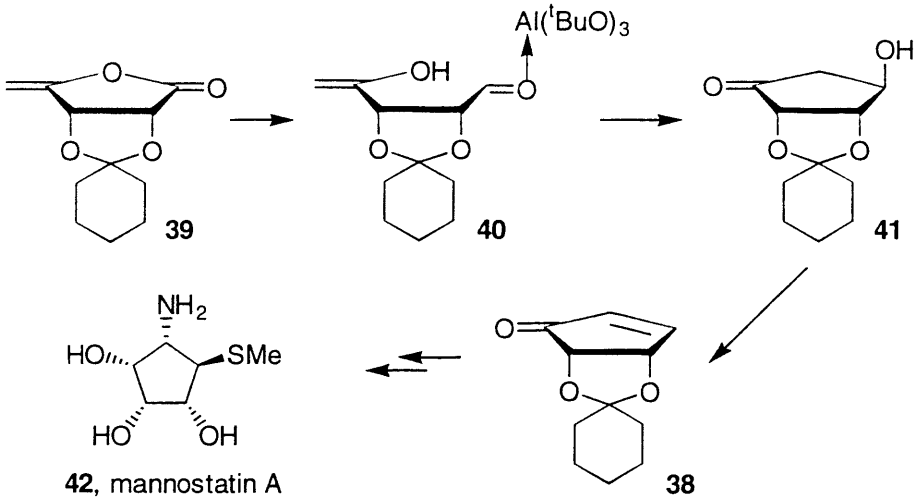

The first example of an aldol type ring closure of a 1,4-dicarbonyl compound derived from a carbohydrate was described by Moffat *et al.* The unsaturated glycoside **36** derived from α-D-ribo-hexofuranos-3-ulose was selectively hydrolysed to 1,4 dicarbonyl **37**. Cyclisation to give enone **38** was effected by stirring with neutral alumina at 100°C (Scheme 8).[17]




**Scheme 8**

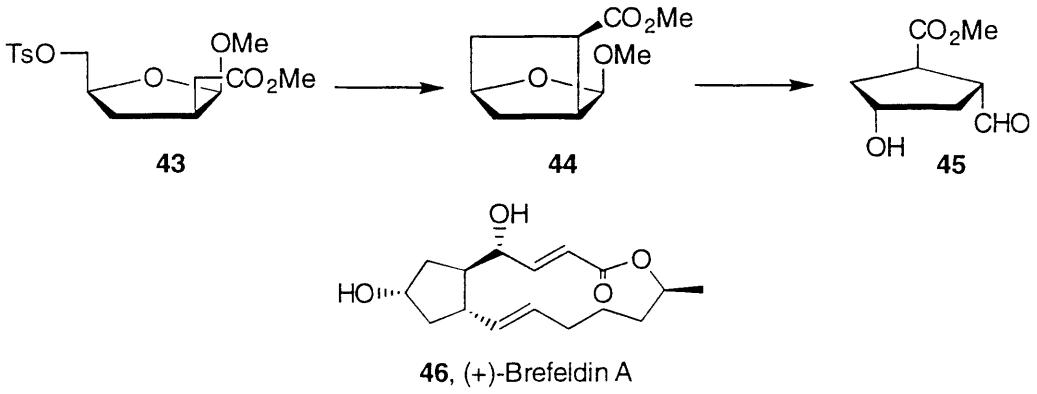
There are now many other examples of the 1,4-dicarbonyl aldol ring closure despite the reaction being kinetically unfavourable.[6] A similar reaction utilising enol lactone **39** derived from D-ribose, was developed by Bélanger and Prasit (Scheme 9).[18] Treatment

of **39** with lithium tri-*tert*-butoxy aluminium hydride affords the intermediate **40**, which cyclises spontaneously on quenching with ammonium chloride to furnish **41**. Dehydration with mesyl chloride affords **38** which was used as a chiron in the total synthesis of mannostatin A **42**, a glycoprotein processing inhibitor.




**Scheme 9**

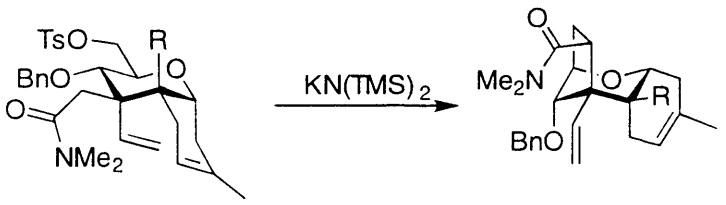
**S-Type:** Attempts by Ohuri and Kuruhara, to synthesise the biologically active macrocyclic lactone (+)-brefeldin A **46**, illustrate an S-type carbanion ring closure and can be seen in Scheme 10. Tosyl furanose **43**, synthesised from D-allofuranoside in six steps was deprotonated with lithium hexamethyl disilazide; subsequent intramolecular displacement of the tosyl ester afforded bicyclic compound **44** in 90% yield. The carbohydrate moiety was hydrolysed, furnishing cyclopentane **45**, with functionality and stereochemistry corresponding to the left-hand end of Brefeldin A **46**.[19]




**Scheme 10**

Fraser-Reid and co-workers illustrated the excellent stereocontrol afforded when synthesising carbohydrate based polycyclic systems. *Cis* fused, conformationally

mobile, oxadecalin **47**, derived from D-glucose, was treated with potassium hexamethyldisilazide to furnish tricyclic trichothecene derivative **48** as a single diastereoisomer.[20]

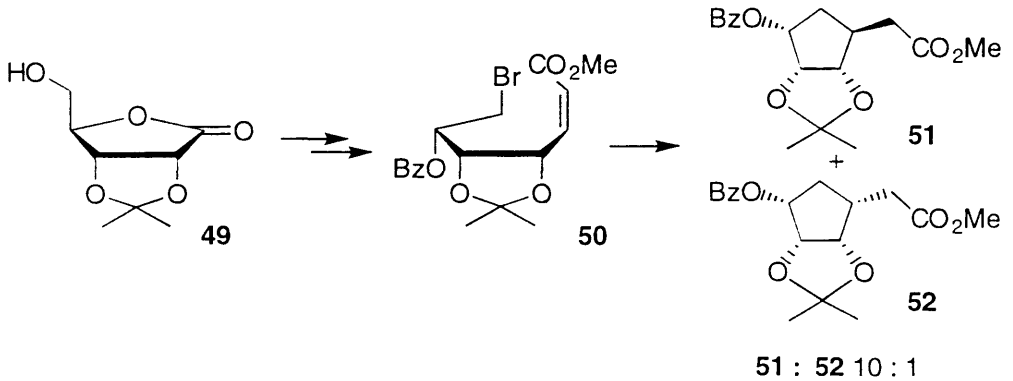



**47** R = $CO_2Me$ **48**

### 1.2.2b Radical Cyclisations

Radical cyclisations of carbohydrate derivatives have only been around since 1985, however since then, it has been demonstrated convincingly that they are highly suited to the formation of cyclopentane rings.[6]

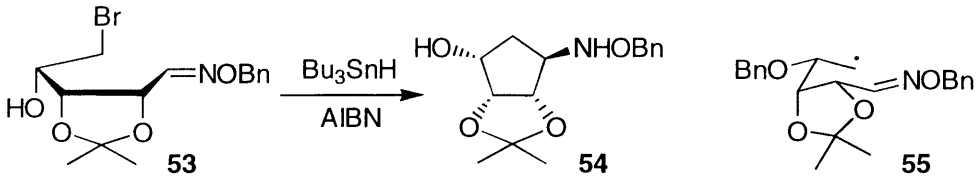
**F-type:** Wilcox and Tomasco have prepared a series of unsaturated bromo esters such as **50**, derived from D-ribono-γ-lactone acetal **49**.[21] When **50** is treated with tributyl tin hydride and AIBN cyclopentane derivatives **51** and **52** are afforded in 89% yield and a diastereomeric product ratio of 10:1 (Scheme 11). The exo product is the major diastereoisomer, which is expected if the 5-exo-trig radical cyclisation proceeds via a "chairlike" transition state as originally proposed by Beckwith *et al.*[22]




**51 : 52** 10 : 1

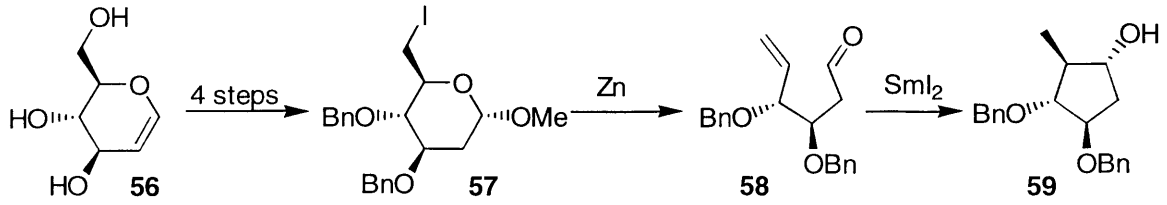
**Scheme 11**

A (70:30 syn:anti) mixture of bromo oxime ether **53**, readily prepared from 5-bromo-5-deoxy-2,3-O-isopropyliden-α-D-ribopyranoside was treated with $Bu_3SnH$ and AIBN, which afforded exo product **54** exclusively in 75% yield in this work described by Marco-Contelles *at al.*[23]



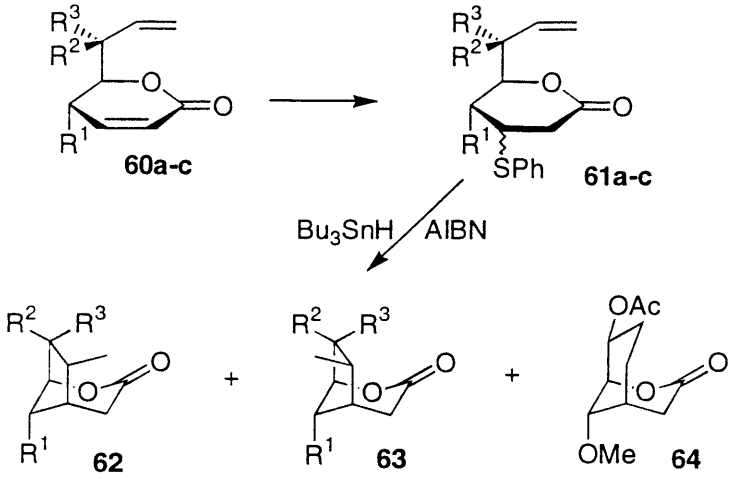

Again the observed product is the expected diastereoisomer if the reaction proceeds through the "chair like" transition state **55**, with the substituents at C2 and C4 (with respect to the radical centre) preferentially occupying quasiequatorial positions. The alternative "boat like" transition state is thermodynamically less favourable.

Holzapfel and co-workers reported a novel general cyclisation of 5-hexenals such as **58**, using $SmI_2$ as the radical initiator (Scheme 12).[24] Iodo glucopyranoside **57** was prepared from D-glucal **56** in four high yielding steps, and was converted via a zinc assisted Vasella fragmentation into 5-hexenal **58**. The ring closure was effected by treatment with $SmI_2$ in butanol at -78°C, to afford cyclopentanol **59** as a single diastereoisomer.




**Scheme 12**

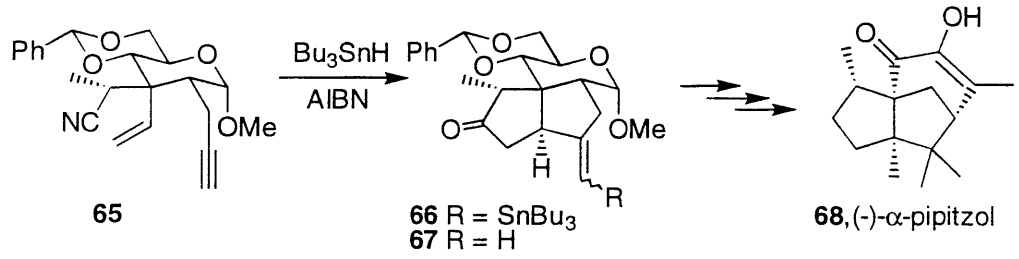
**S-Type:** To date there are many examples of the S-type radical ring closure of carbohydrate derivatives due to the relative ease in which a radical initiator and/or trap can be constructed onto the sugar unit. López and co-workers have demonstrated how the carbohydrate derived unsaturated lactones **60a-c**, can be converted to the thioethers **61a-c** by conjugate addition of benzene thiol in the presence of $NEt_3$ (Scheme 13). The cyclisation of **61a-c** is brought about by treatment with tributyl tin hydride and AIBN to give diastereomeric adducts **62** and **63**. In the case of **61b**, some 6-endo-trig addition is observed yielding **64** as well as the expected 5-exo-trig adducts **62** and **63**.[25]




| | $R^1$ | $R^2$ | $R^3$ | 62 : 63 : 64 | % yield |
|---|---|---|---|---|---|
| **a** | OMe | OAc | H | 4 1 0 | 92 |
| **b** | OMe | H | OAc | 1.2 2.5 1 | 78 |
| **c** | Me | H | Me | 1 1 0 | 72 |

**Scheme 13**

An extremely elegant serial radical cyclisation reported by Fraser-Reid *et al.* can be seen in Scheme 14.[26] The tributyl tin hydride induced serial radical cyclisation of **65** gave quadricyclic carbohydrate derivative **66**, which on stirring with silica gel afforded **67**. Further manipulation led to the isolation of the naturally occurring (-)-α-pipitzol **68**.

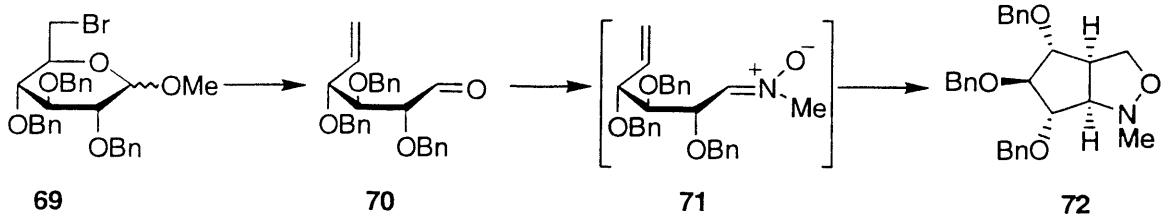



**Scheme 14**

### 1.2.2c Cycloaddition Reactions

**F-Type:** Vasella has demonstrated the utility of the nitrone [3+2] cycloaddition reaction on converting carbohydrates to cyclopentane based bicycles.[27] In a similar manner to the samarium iodide example above (Scheme 12), 6-bromo-6-deoxyglucopyranoside **69** is reduced on treatment with zinc and ethanol to give 5-hexenal **70**, as illustrated in Scheme 15. The reaction of **70** with N-methylhydroxylamine affords the unsaturated

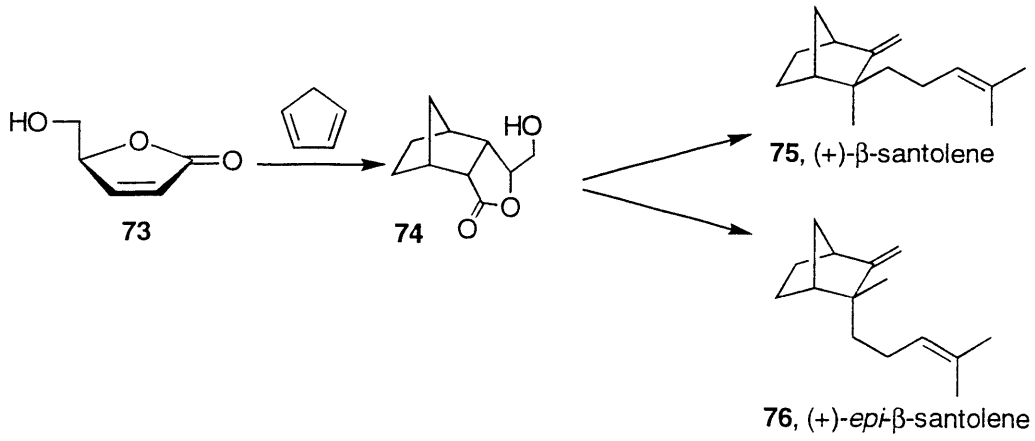
nitrone **71**, which spontaneously cyclises to furnish the 2-aza-3-oxabicyclo-[3.3.0]-octane derivative **72** in 80% yield overall.




**69** **70** **71** **72**

**Scheme 15**

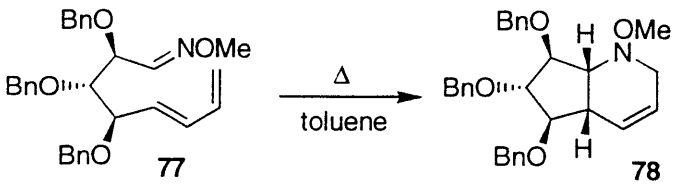
**S-Type:** There have been several examples of carbohydrate derivatives being used as the dienophile in a [4+2] cycloaddition reaction. One excellent example reported by Tokano *et al.* is described in Scheme 16. The D-mannitol derived buten-2-olide **73** reacts with cyclopentadiene to give exclusively the crystalline endo product **74**. This tricyclic compound served as a convenient starting material for the elegant synthesis of both (+)-β-santolene **75** and (+)-β-epi-santolene **76**, well known constituents of East Indian sandalwood oil.[28]




**73** **74**

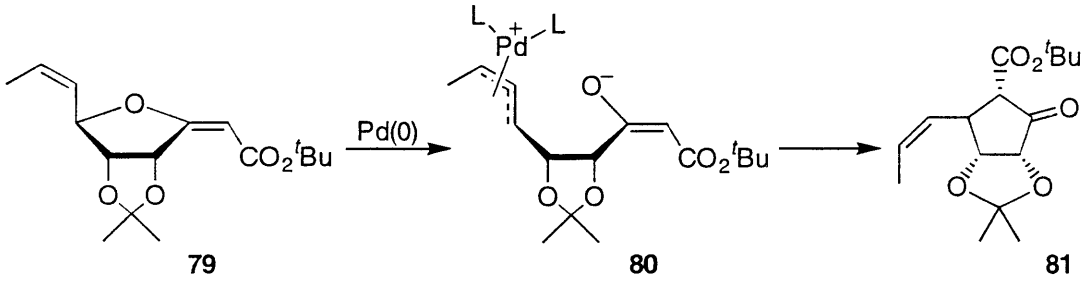
**Scheme 16**

Herczegh *et al.* have utilised the Diels-Alder methodology to cyclise 1,3,8-nonatrienes derived from carbohydrates in an intramolecular ring closure. Due to the nature of the reaction the products necessarily incorporate new five and six membered carbocyclic units. However, oxime **77** can be cyclised in toluene at 160°C to give the *cis* fused azaindene derivative **78** as a single diastereoisomer.[29]



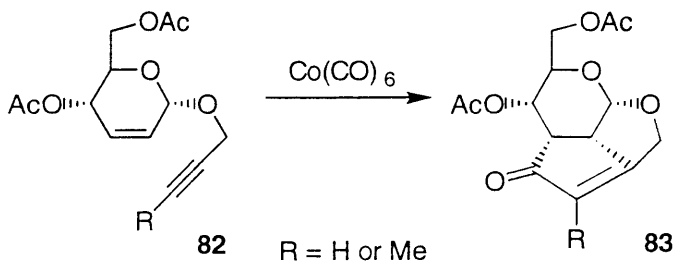

### 1.2.2d Metal Assisted Cyclisations

**F-Type:** While we have already seen functionalised cyclohexanes are readily prepared from carbohydrates on treatment with mercury (II) chloride (Scheme 2), there are no analogous routes to cyclopentanes. In fact the metal mediated F-type ring closure is quite rare. One example reported by Trost and Runge involves the treatment of 1,6-diene **79** with Pd (0), which results in the enolate Palladium complex **80**, ring closure affords the thermodynamically favoured cyclopentane adduct **81** (Scheme 17).[30]




**Scheme 17**

**S-Type:** Marco-Contelles has demonstrated that a variety of carbohydrate based 1-hepten-6-ynes can be converted into tricyclic compounds using Pauson-Khand methodology. The D-glucose derived ene-yne **82** can be cyclised in the presence of $Co(CO)_6$ to give tricycle **83** exclusively. The stereoselection arises from the propargylic side chain being tethered to the bottom face of the sugar, thus the alkyne moiety reacts with the bottom face of the olefin to give the observed isomer.[31]

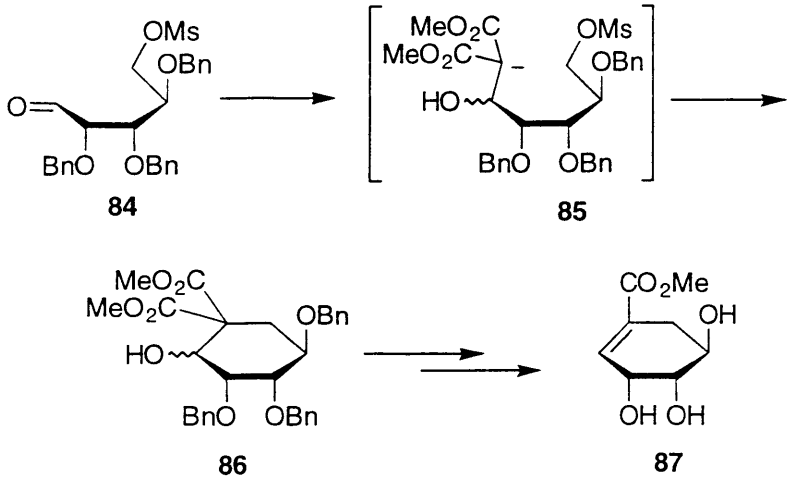



R = H or Me

### 1.2.3 6-Membered Carbocycles from Carbohydrates

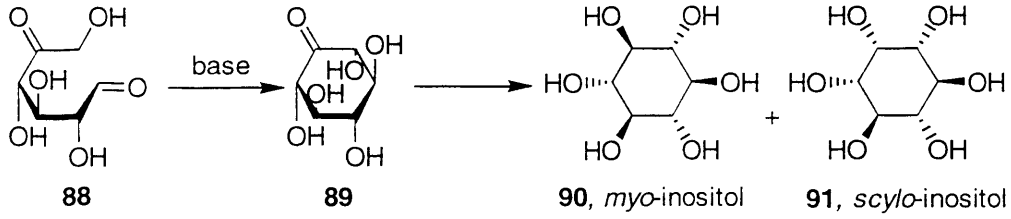
#### 1.2.3a Carbanion Cyclisations

**F-Type:** F-type cyclohexane derivatives can be synthesised from carbohydrates in a very similar manner to the cyclopentane examples seen above. Again most conversions have involved intramolecular nucleophilic displacement by carbanions or carbanion equivalents, however the 6-membered products require that the nucleophilic and electrophilic moieties of the substrate are in a 1,6 relationship. A general approach reported by Suami, illustrated in Scheme 18, indicates how a malonate ester anion reacts with an aldehydopentose **84** to effect a 2-carbon chain extension. This results in intermediate **85** which cyclises to give polyoxygented cyclohexane **86** in 43% yield. Reduction followed by deprotection affords methyl shikimate **87**.[32]




**Scheme 18**

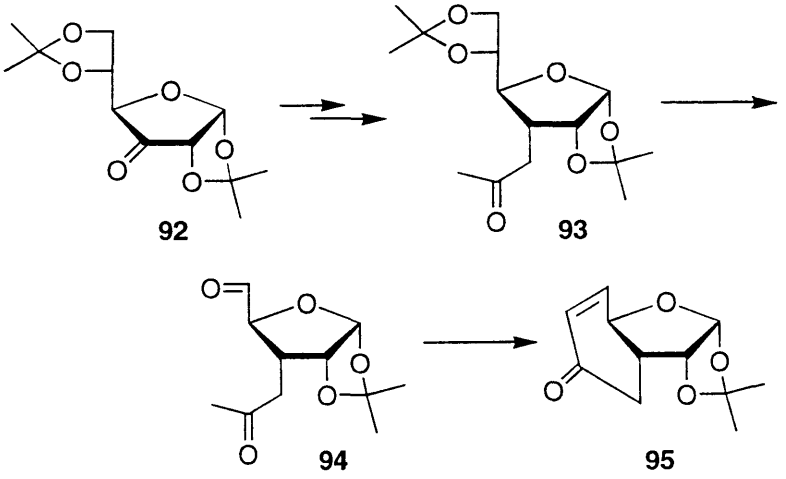
The aldol cyclisation has also been successfully utilised to bring about ring closure. Kiely and Fletcher converted D-xylo-hexos-5-ulose **88** into inososе **89** (Scheme 19) by treatment with a base. Reduction of the ketone moiety with sodium borohydride afforded *myo*- and *scylo*-inositol (**90** and **91** respectively).[33]




**Scheme 19**

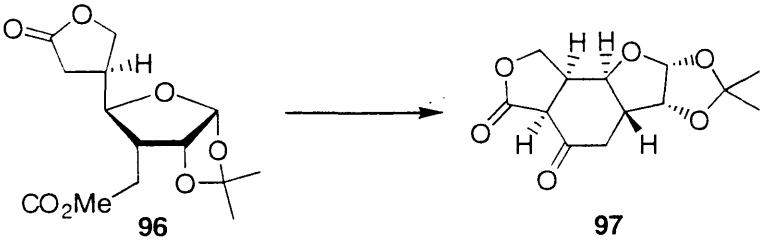
Reactions such as this provide exceptionally efficient and general methods for the conversion of sugars into inositols, which have recently been found to have interesting biological activity.[34]

**S-Type:** The branched chain (S-type) ring closure is not as well defined as the cyclopentane analogues with fewer examples reported, although considerable attention has been paid to the 1,5 dicarbonyl cyclisation. Scheme 20 outlines one fine example; D-glucose derived ketone **92** was converted to **93** by Wittig methodology, partial deprotection and periodate cleavage of the exposed diol afforded **94** which was cyclised in 45% yield by treatment with DBU then acetic anhydride and pyridine to afford *trans* fused cyclohexane derivative **95**.[35]




**Scheme 20**

In a similar manner, Fraser-Reid and co-workers prepared 1,7-dicarbonyl **96** from D-glucose, which furnished keto-lactone **97** in 91% yield upon Dieckmann cyclisation with potassium *tert*-butoxide.[36]

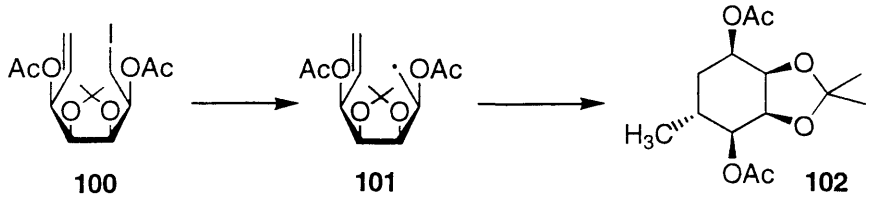


### 1.2.3b Radical Cyclisations

**F-Type:** There are fewer examples of the F-type radical ring closure resulting in 6-membered rings than the analogous cyclopentanes. In the main this is because most common carbohydrates do not offer the opportunity to produce the required 1,6-heptenyl radical required for the favoured exo cyclisation.[6] This point is exemplified when considering the 5-hexenyl radical species **98** which can cyclise easily, whereas the 6-heptenyl species **99** requires a chain extension of common six carbon carbohydrates.

**98** **99**

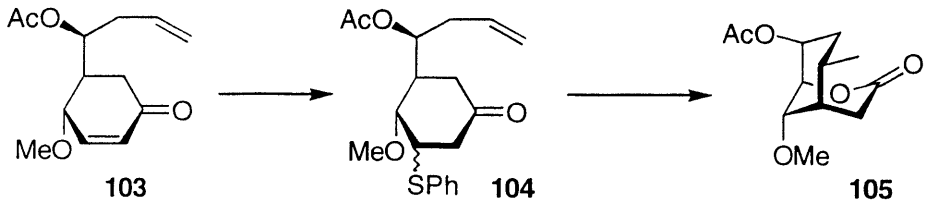
An example of this process, developed by Redlich *et al.*, can be seen in Scheme 21 and involves the generation of a radical at C-7 of several 1,2-dideoxyhept-1-enol derivatives. D-allo-iodide derivative **100** was treated with tributyl tin hydride and AIBN to initiate the radical **101** which cyclises stereospecifically furnishing **102** in 87% yield.[37]




**100** **101** **102**

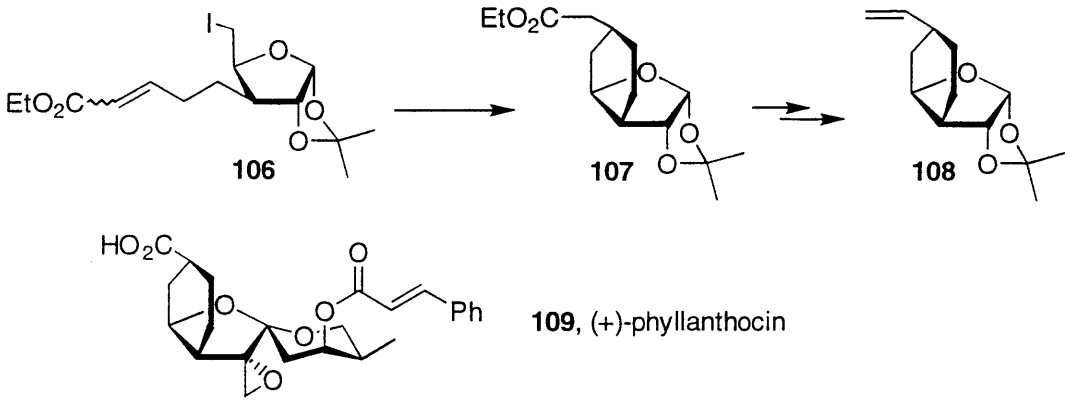
**Scheme 21**

**S-Type:** The S-type reaction is far more common, as the radical trap can easily be constructed into a side chain of a carbohydrate. Scheme 22 illustrates a continuation of the work carried out by López and co-workers, which was described earlier in Scheme 13.[25] The epimeric products **104** were formed on reaction of the homoallylic branched glucal **103** with benzyl thiol and triethylamine. Subsequent treatment of the thiol epimers **104** with tributyl tin hydride and AIBN afforded the 6-membered carbocycle **105** in 77% yield together with a trace amount of the C-8 epimer.




**Scheme 22**

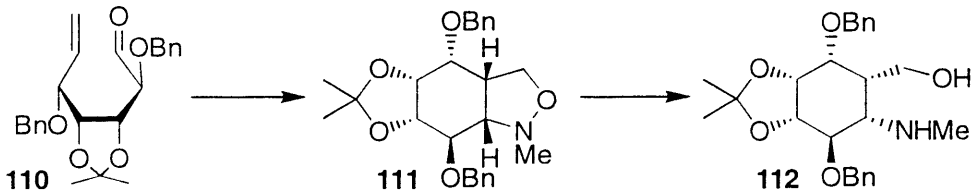
In another exceptional natural product synthesis reported by Fraser-Reid *et al.*, the 5-iodopentose derivative **106**, synthesised by Wittig methodology from the corresponding aldehyde, cyclised to afford bicycle **107** and its epimer in 85% yield (Scheme 23). The epimeric ratio was 9:1 in favour of the desired (illustrated) product **107**, which was converted into (+)-phyllanthocin **109**, an anti-leukaemia plant product, via key intermediate **108**.[38]




**Scheme 23**

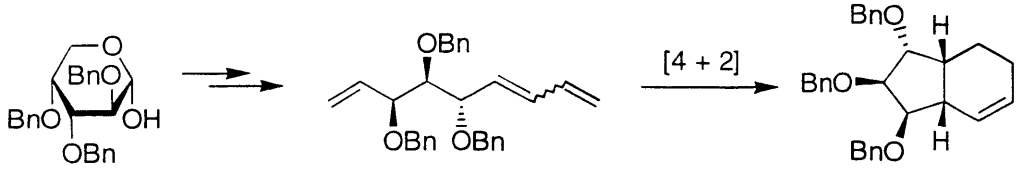
### 1.2.3c Cycloaddition Reactions:

**F-Type:** The [3+2] cycloaddition has not been exploited to any great extent in the synthesis of cyclohexane derivatives from carbohydrates. One rare example (Scheme 24), proposed by Gillhouley introduces the nitrone species onto enal **110**, derived from 2,3:5,6-di-O-isopropylidene-D-mannose, by reaction with N-methylhydroxyl amine. Subsequent cycloaddition affords **111** and the other possible diastereoisomer in a 6:1 ratio, hydrogenolysis of the N-O bond yields carbasugar **112**.[39]




**Scheme 24**

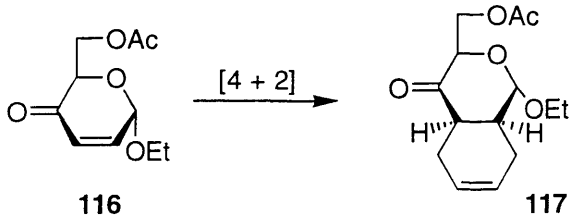
The [4+2] cycloaddition reactions of sugar derivatives containing both the diene and dienophile moieties are well-established processes. In a similar manner to a ring closure described earlier, the nonatriene **114** (9:1 mixture of E and Z isomers) was prepared from the D-aribinose derivative **113** in three steps (Scheme 25). Subsequent intramolecular Diels-Alder reaction afforded the *cis* fused bicyclic product **115**.[29]




**113** **114** **115**

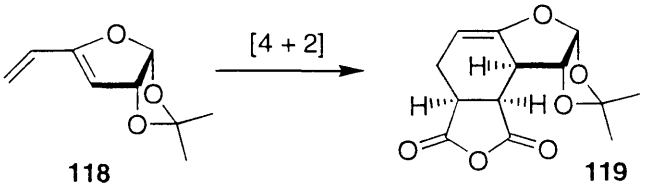
**Scheme 25**

**S-Type:** Fraser-Reid sparked significant impetus in the intramolecular [4+2] cycloaddition reaction of carbohydrates when he developed a method for cyclising a sugar based olefin with a diene. The Diels-Alder addition of 1,3 butadiene to the sugar derived dienophile **116**, at -60°C, in dichloromethane with an excess of aluminium chloride gave **117** exclusively in 81% yield.[40]




**116** **117**

Fraser-Reid also led the way in utilising the conjugated diene moiety of a sugar derivative in a cycloaddition reaction with a dienophile. Hexafuranose derived diene **118** was successfully cyclised with maleic anhydride in a Diels-Alder reaction to yield quadricyclic compound **119**.[41]

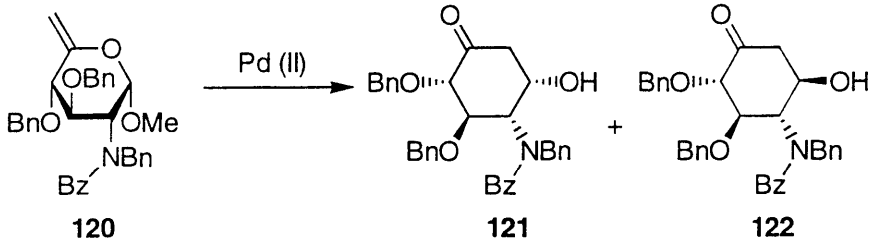



**118** **119**

There are now many examples of cycloadditions of carbohydrate derived conjugated dienes and dienophiles, giving a wide range of adducts, including many natural products.[29]

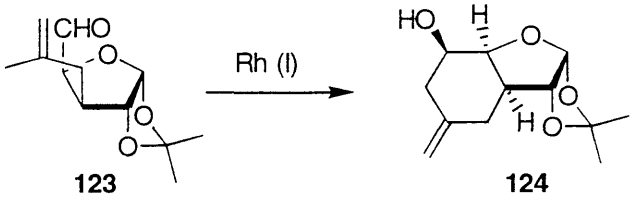
### 1.2.3d Metal Assisted Cyclisations

**F-Type:** As we have already seen, mercury (II) chloride can be used to cyclise a wide variety of hexose sugars, however it was Adams that first reported that an analogous reaction could be effected using Pd (II) in the presence of aqueous sulphuric acid.[42] Whilst the mechanism is not fully understood, it gives similar results to the mercury mediated process, for example hexose **120** was converted to cyclohexanone **121** and **122** in 70% yield, in a 3:2 ratio of diastereoisomers, on treatment with palladium (II) chloride.




**120** **121** **122**

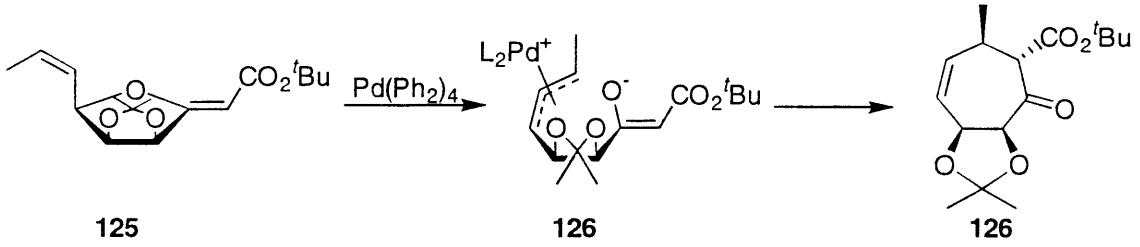
**S-Type:** Gable and Benz have demonstrated that 5-hexenals undergo an 'ene' type reaction in the presence of rhodium (I). For example the hexenal **123** cyclises in dichloromethane in the presence of a catalytic amount of $[(Ph_3P)_2RhCl]_2$ under an atmosphere of ethene, to furnish *cis* fused cyclohexane **124**.[43]




**123** **124**

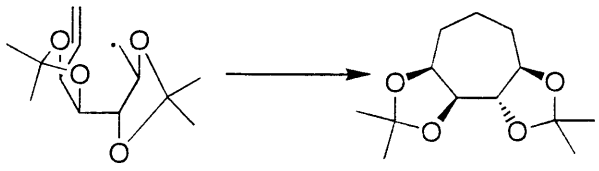
### 1.2.4 7- and 8-Membered Carbocycles from Carbohydrates

7-Membered rings are quite uncommon within the field of carbohydrate annulation, in fact there are only a few examples reported. One example illustrated in Scheme 26, follows work seen previously (Scheme 17), where the $Pd^{+}$-$\pi$ enolate complex **126** of carbohydrate derivative **125**, ring closes to furnish the 7-membered endo product **127** in 64% yield. The authors conclude that the preferred 5-membered exo product is not formed as steric influences inhibit cyclisation.[30]



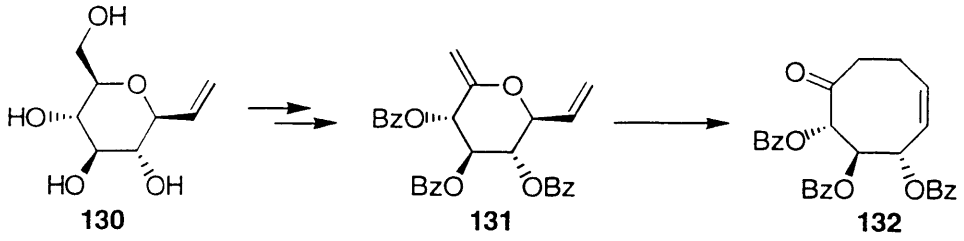

**Scheme 26**

Another ring closure outlined earlier (Scheme 21) also gives a 7-membered product when an alternative carbohydrate reagent is used as described below. 6-Heptenyl radical species **128**, derived from D-gulose, underwent an endo cyclisation to afford functionalised cycloheptane **129** in 81% yield. The authors have again suggested that the transition state of the endo ring closure can accommodate the trans dioxalane ring better than the transition state associated with the exo ring closure.[37]




**128** **129**

A novel example reported by Werschkun and Thiem illustrates how a Claisen type rearrangement can be utilised to afford a cyclo-octane product as depicted in Scheme 27. The substituted carbohydrate **131**, derived from vinyl glycoside **130**, underwent the Claisen rearrangement in refluxing xylene to furnish the cyclo-octanoid product **132** in 60% yield.[44]

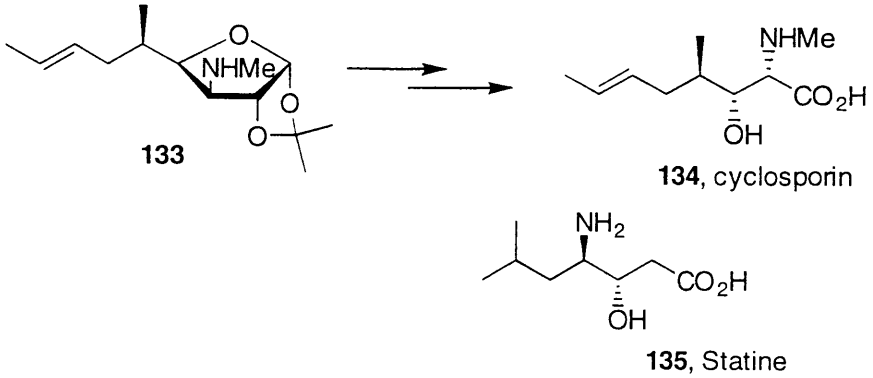



**Scheme 27**

7- And 8-membered carbohydrate derivatives are more commonly obtained from the ring expansion of smaller rings.[14]

## 1.3 Acyclic and Macrocyclic Products from Carbohydrates

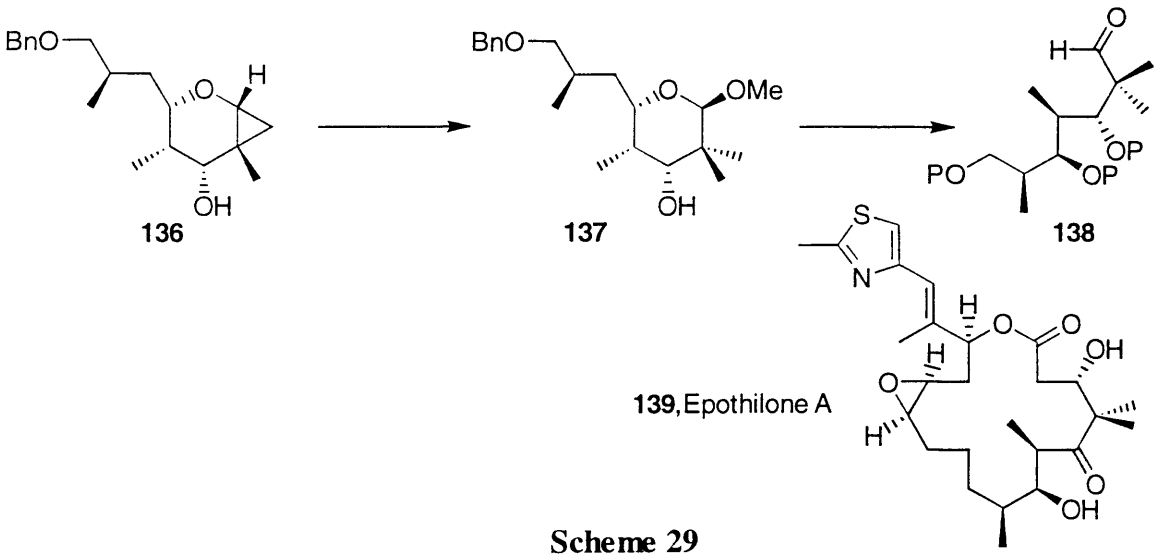
Carbohydrates are well suited for producing functionalised carbon chains, due to the ease of ring opening of cyclic sugar moieties by hydrolysis. For example a variety of unusual amino acids can be synthesised from carbohydrates; D-glucose derivative **133** can be converted to the immunosuppressive peptide cyclosporin **134**, by deprotection of the 5-membered acetal, periodate cleavage of the resulting diol followed by oxidation (Scheme 28).[45] γ-Amino acid statine **135**, has also been synthesised from D-glucose in a similar manner.




**Scheme 28**

There are many examples of complex macrocyclic substrates that have sugars glycosidically bound to them, however acyclic carbohydrates have also been used as chirons in the synthesis of macrocycles. The inherent functionality of carbohydrates makes them particularly useful as chiral fragments in the synthesis of macrocycles, with some more complicated syntheses using three or more 'chirons' derived from sugars.[14] A relatively simple example demonstrated by Danishefsky, utilises the sugar-cyclopropane moiety **136** as the template (Scheme 29). Ring opening of the

cyclopropane ring with N-iodosuccinimide followed by reduction furnishes sugar moiety **137**, subsequent protection and ring opening yields acyclic fragment **138** which was used in the total synthesis of epothilone A **139**.[46]

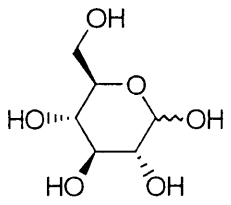



**Scheme 29**

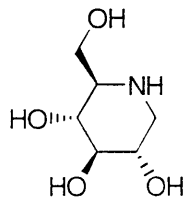
## 1.4 Heterocyclic Sugar Derivatives

### 1.4.1 Nitrogen Heterocycles from Carbohydrates

There has been considerable interest shown in "carbohydrate-like" nitrogen heterocycles or azasugars, over the last 10 years due to their potent biological activity. For example many polyhydroxylated piperidines are efficient and specific inhibitors of the stereochemically corresponding glycosidase enzymes, thus deoxynojirimycin **141** is a glucosidase inhibitor, effectively and irreversibly blocking the binding site of the glucosidase enzyme (Figure 1). Consequently these compounds have important implications for anticancer and antiviral chemotherapy, as they block key enzymes required for cell replication and growth.[14]



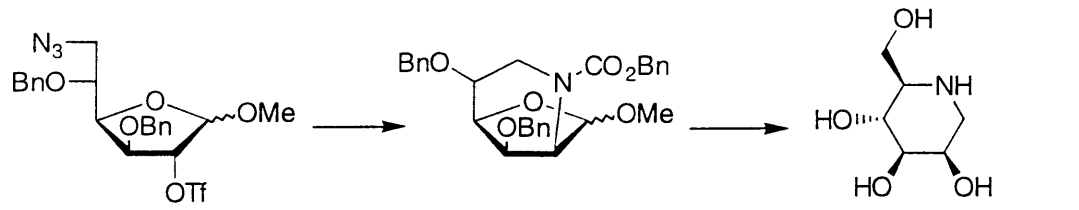

**140**, D-Glucose




**141**, Deoxynojirimycin

**Figure 1**

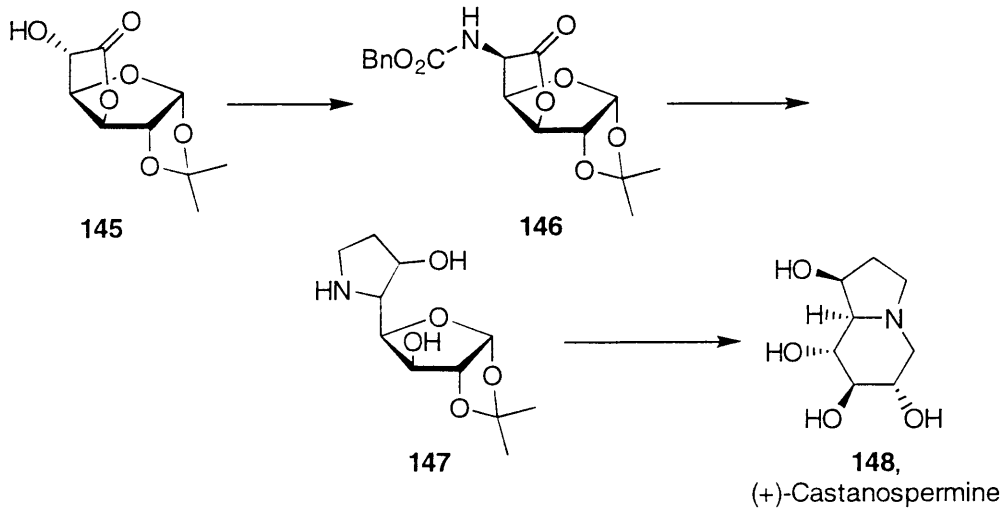
An isomer of **141**, deoxymannojirimycin **144**, a mannosidase inhibitor has been prepared by Fleet *et al.* from D-glucose and is illustrated below in Scheme 30. The azide functionality of D-glucose derivative **142** is reduced to an amine, which cyclises via an intramolecular nucleophilic displacement of the triflate ester to afford bicycle **143**. Ring opening of the sugar moiety followed by deprotection furnishes **144** in 65% yield overall.[47]




**142** **143** **144**, Deoxymannojirimycin

**Scheme 30**

The introduction of a nitrogen atom into a carbohydrate is often facilitated by exploitation of the reactivity of the anomeric oxygen. (+) Castanospermine **148**, an indolizidine plant alkaloid that inhibits glycosidases and shows anticancer, antiviral and anti-AIDS activity has been synthesised in this manner (Scheme 31). 1,2-O-Isopropylidene-α-D-glucofuranurono-6,3-lactone **145** is converted into protected amino carbohydrate derivative **146** in four steps. Ring opening followed by a ring closure and deprotection affords **147** which cyclises onto the anomeric centre by reductive amination to furnish castanospermine **148** in 61% yield.[48]

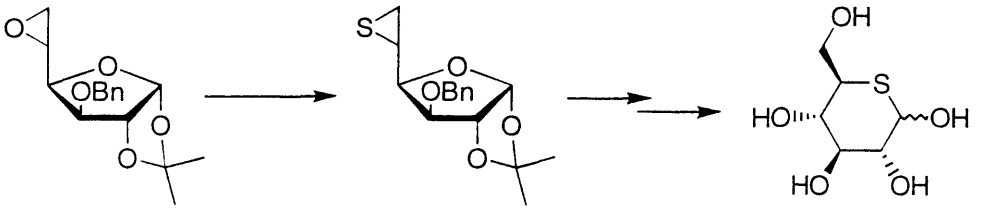



**145** **146** **147** **148**, (+)-Castanospermine

**Scheme 31**

### 1.4.2 Sulphur Heterocycles from Carbohydrates

Sulphur heterocycles have also been prepared from carbohydrate reagents, although there are far fewer examples than the analogous nitrogen or oxygen based heterocycles. Scheme 32 depicts how the episulphide **150**, formed on reaction of 5,6-anhydro-L-ido-compound **149** with thiourea, can be cyclised in 85% yield, by treatment with potassium acetate in acetic acid. Subsequent deprotection affords 5-thio-D-glucose **151** which has been reported to be a reversible sterilant of the male rat.[49]




**149** **150** **151**, 5-thioglucose

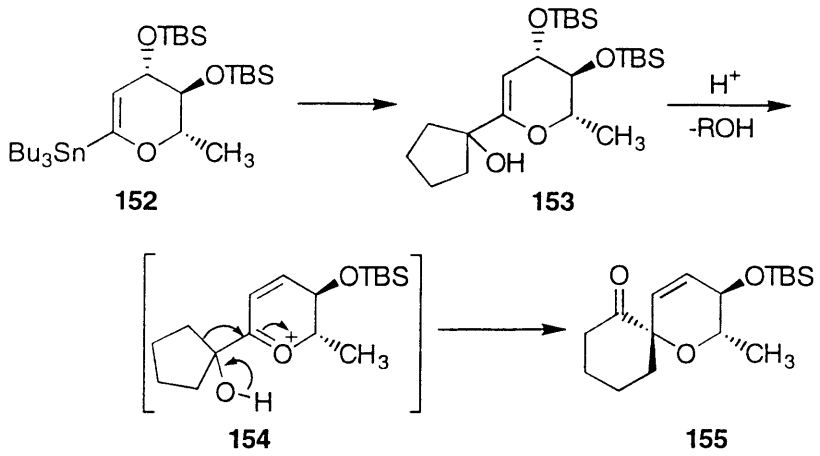
**Scheme 32**

Due to natures ability to generate complicated polyhydroxylated chiral compounds, most attention of the synthetic chemist has been focussed on producing oxygen-substituted heterocycles. However, because of their similarities with naturally occurring sugars and their abundance in the literature, the methods for cyclising O-heterocycles will not be discussed here.

## 1.5 Spirocyclic Products from Carbohydrates

Within the field of natural product synthesis, spirocyclic systems are important structural features. They are encountered in many different classes of compounds, ranging from relatively simple bicyclic systems in the dactyloxenes to very complicated molecules such as polyether antibiotics. To date, there have been very few reports of reactions of carbohydrates yielding spiro-annulated ring systems.

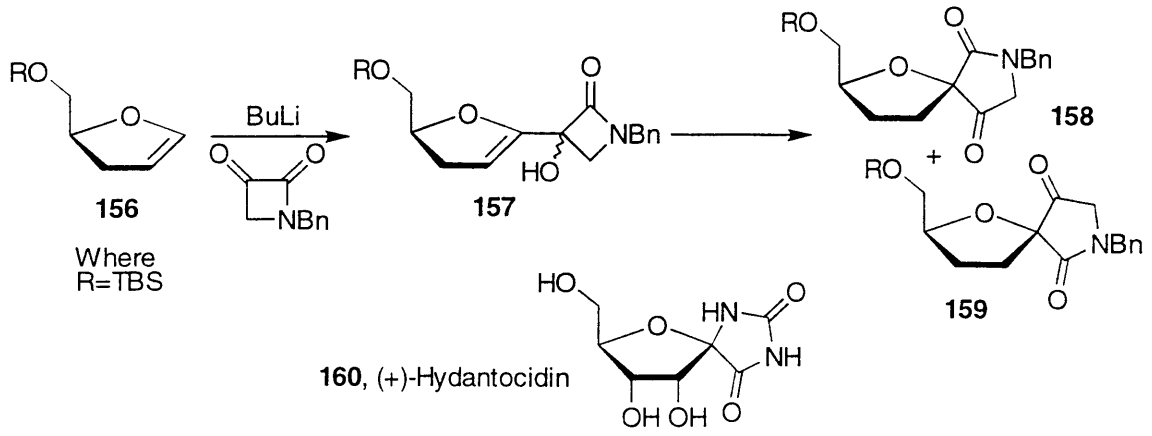
Paquette, Dullweber and Cowgill have demonstrated a unique acid catalysed rearrangement that affords carbocycles spiro bound to carbohydrate moieties (Scheme 33).[50] Exposure of the vinyl lithium reagent, generated by transmetallation of **152** with $^{t}$BuLi, to cyclopentanone afforded **153**. When stirred at room temperature for 30 hours with a catalytic amount of camphor sulfonic acid, **153** was transformed into **155** exclusively in 81% yield.




**Scheme 33**

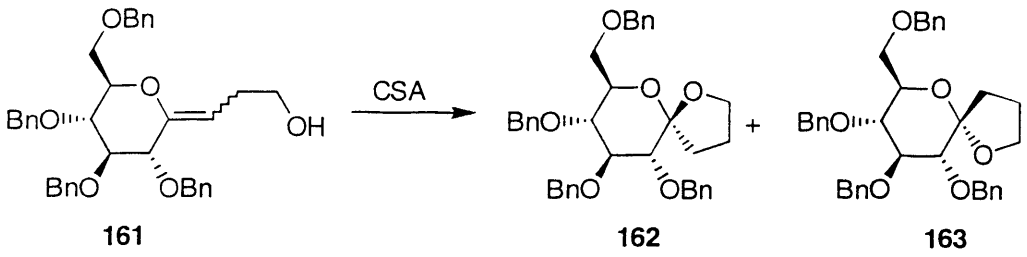
The unique stereoselectivity is proposed to arise from the migration of the methylene carbon to the axial surface of the pyran ring in intermediate **154**.

Paquette has utilised this methodology in a further publication, to afford heterocyclic spirocycles, architecturally similar to highly toxic herbicides such as (+)-hydantocidin **160** (Scheme 34).[51] Sugar moiety **156** is treated with butyl lithium, to afford a vinyl lithium reagent which reacts with the N-benzyl cyclobutadione derivative, to furnish **157** in 64% yield. Stirring with a catalytic amount of acid affords **158** and **159** in 51% yield and 2:1 ratio.



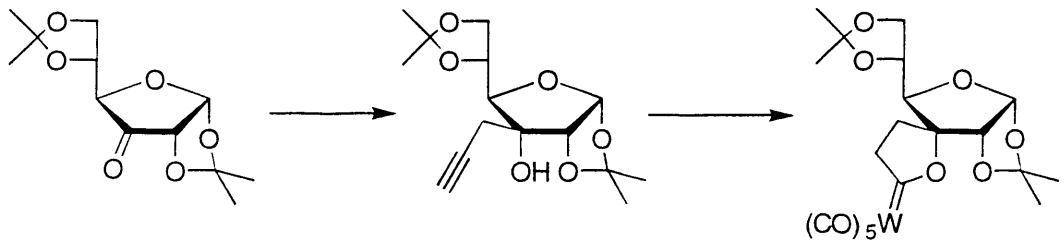

**Scheme 34**

Taylor *et al.* have described a synthesis of a variety of spirocyclic ethers, derived in a similar manner to the examples above. The protected exo glycal **161** was stirred in methanol with a catalytic amount of camphor sulfonic acid at rt, and afforded spiroacetals **162** and **163** in a 3:7 ratio and 75% combined yield.[52] The group has also reported a number of N-heterocyclic spirocycles.




**161** **162** **163**

Dötz and co-workers have used chromium and tungsten complexes to afford enantiomerically pure spirocyclic ethers as described in Scheme 35.[53] D-Glucose derived ketone **92** is treated with a propargyl Grignard reagent to afford **164** which is efficiently cyclised on treatment with tungsten hexacarbonyl to furnish the psicocarbene complex **165** in 71% yield.




**92** **164** **165**

**Scheme 35**

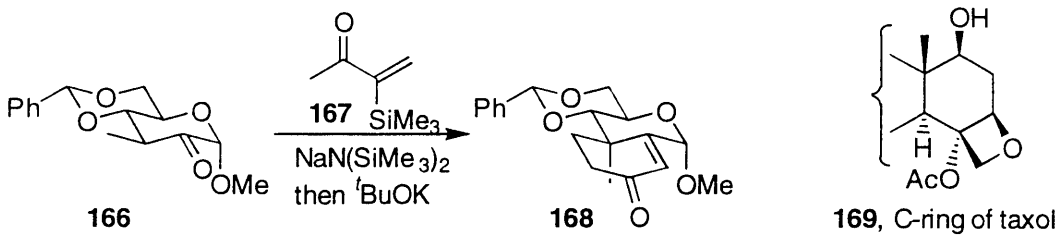
The process is stereospecific as the propargyl group only adds via the top face due to the increased steric bulk on the bottom face.

## 1.6 Summary

It is clear from the abundant examples present in the literature that the use of carbohydrates in producing chiral fragments for further synthesis is an extremely powerful method. However, to be effective, it is important that the starting materials are readily available and cheap, also the synthetic steps to attain a target need to be efficient (high yielding), not too numerous, and inexpensive. The reactions involved need to be selective, affording the appropriate product which should be easily purified, and the overall operations must be applicable on a reasonably large scale. On the whole carbohydrate annulation meets most of these demanding criteria, although there is a need to improve efficiency in almost every area.

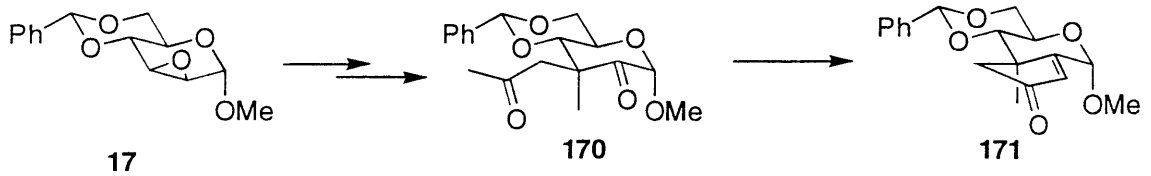
## 1.7 Previous Work at Leicester:

The Jenkins group has been interested in carbohydrate annulation for some time, and has made several important contributions to the field, for example the first Robinson annulation performed on a carbohydrate.[54] In work directed towards the synthesis of the C-ring of Taxol® **169**, the methyl ketone carbohydrate **166**, undergoes Robinson annulation with an enone **167** in the presence of sodium hexamethyl disilazide then potassium-*tert*-butoxide, to afford cyclohexaannulated sugar **168** (Scheme 36).




**Scheme 36**

The Jenkins group has also been responsible for developing new protocol for the stereoselective conversion of D-glucose into an enantiomerically pure cyclopentanone.[55] D-Glucose derived epoxide **17**, was converted into 1,4-dicarbonyl **170** in four high yielding steps, **170** was cyclised by treatment with potassium *tert*-butoxide, affording cyclopentanone **171** in 90% yield (Scheme 37).




**Scheme 37**

Other recent work includes radical cyclisations of cyclohexa-annulated carbohydrates,[56] and more recently; we have been developing an S-type reductive amination ring closure of 1,4 and 1,5 dicarbonyl derivatives to afford potential glycosidase inhibitors. Thus far we have made several important contributions to the field of carbohydrate annulation, concentrating on the S-type ring closure of D-glucose derivatives. Our continuing aim is to develop other, more general methods for ring closing carbohydrate derivatives, and the results of our latest findings are reported in this thesis.

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# Chapter 2

# Ring Closing Metathesis of Carbohydrate Derivatives

## 2.1 Introduction:

New C-C bond formation is a testing problem for the synthetic chemist, with few universally general methods available to date. The advent of olefin metathesis has provided us with a powerful new tool to address this challenge. Working by a unique carbon skeleton rearrangement, olefin metathesis induces both the cleavage and formation of C-C double bonds, and its broad applicability has attracted attention from both academic and industrial scientists.

Olefin metathesis can be classified into three discrete categories (Figure 2); (A) Ring Opening Metathesis Polymerisation (ROMP); (B) Ring Closing Metathesis (RCM); (C) Acyclic Cross Metathesis, which can be a polymerisation process (ADMET), depending on the nature of the substrate.[1]

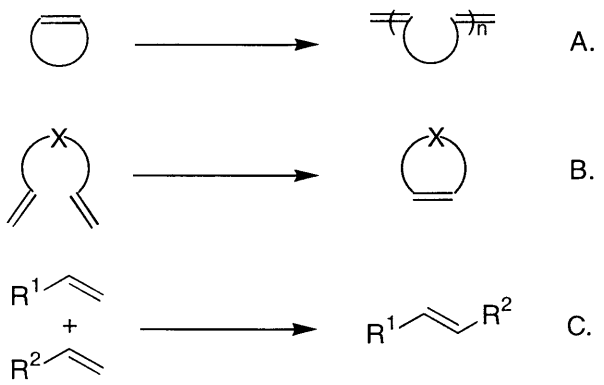
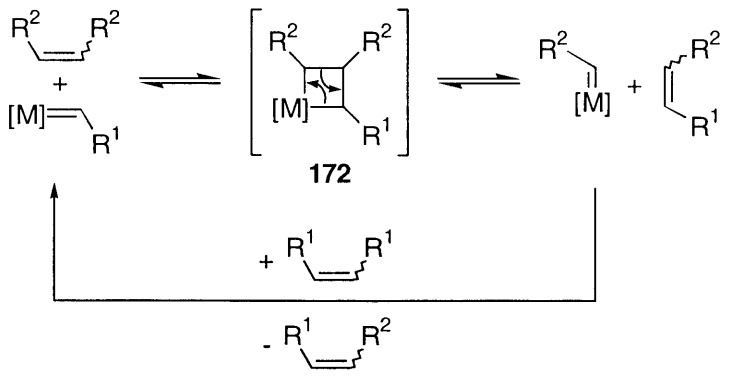



**Figure 2**

Despite the fundamental differences in these three classes of metathesis reaction, it is thought that they all proceed via a common metallacyclobutane intermediate **172** (Scheme 38), as first postulated by Chauvin *et al.*[2]



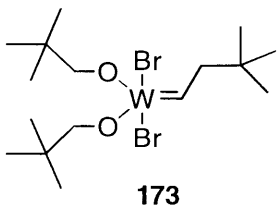

**Scheme 38**

According to this universally accepted model, olefin metathesis proceeds by a [2+2] cycloaddition between a C-C double bond and a metal-carbene complex, followed by cycloreversion.

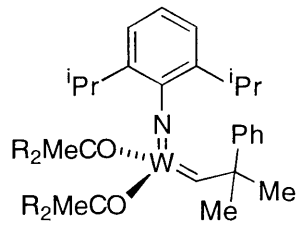
### 2.1.1 Well-Defined Catalyst Systems

The concept of olefin metathesis was first developed as a polymerisation reaction, as Anderson and Merckling described the catalytic polymerisation of norbornene by a complex Ti (II) compound in 1955.[3] Interest in metathesis remained almost exclusively confined to this area for many years, and although largely ignored by the synthetic chemist, it found many industrial applications. One classical industrial example is the Phillips triolefin process, where propene is converted into a mixture of ethene and but-2-ene.[4]

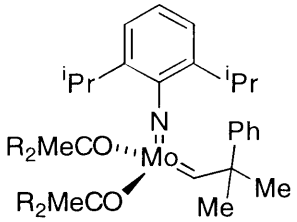
There have been a vast number of catalyst systems developed for industrial processes, however most of these have been ill-defined multi-component systems.[5] The first well defined homogeneous catalysts **173** and **174a,b**, developed by Osborn[6] and Schrock[7] respectively in 1988, initiated a wave of interest within the field of organic synthesis (Figure 3). The tungsten-alkylidene complexes **173** and **174a,b** were obtained by thermal abstraction of an α-hydrogen from the alkyl moiety, leading to a stable metallo-carbene type species. Further work by Schrock and co-workers introduced the alkylidene-molybdenum catalyst **175a,b**,[8] in 1990, which was shortly followed by the pioneering work of Grubbs *et al.* as they described the preparation of ruthenium-alkylidene catalysts such as **176a,b**.[9]



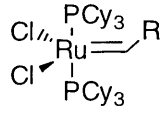

**173**




**174a**, R = Me
**174b**, R = $CF_3$



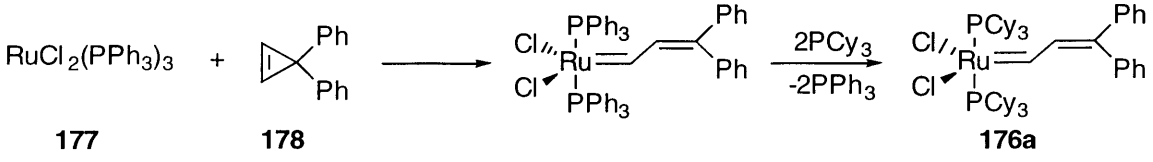

**175a**, R = Me
**175b**, R = $CF_3$

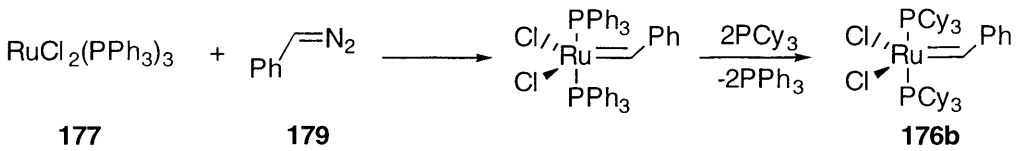



**176a**, R = $CH{=}CPh_2$
**176b**, R = Ph

**Figure 3**

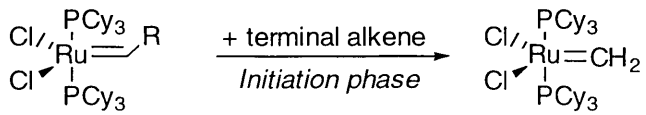
Since the early 1990's, these catalysts, notably **175** and **176** have drawn considerable attention, as they exhibit high reactivity in a variety of ROMP, RCM and ADMET processes under mild conditions. Grubbs' catalyst **176b** has received particularly close scrutiny, and has been utilised extensively in a range of reactions due to its excellent inherent tolerance for an array of polar functional groups. Its catalytic activity isn't significantly reduced by the presence of air, moisture or slight impurities in solvents and it can be conveniently stored on the bench for a number of weeks, making it an extremely attractive reagent for a variety of syntheses. Another feature of this catalyst is the relative ease in which it can be prepared, for example the ruthenium-vinylidene complex **176a** is prepared by reaction of $RuCl_2(PPh_3)_3$ **177** with 3,3-diphenyl-cyclopropene **178** followed by ligand exchange with tricyclohexylphosphine (Scheme 39). The closely related Ru-benzylidene carbene complex **176b** was prepared in a similar manner using phenyldiazomethane **179** instead of cyclopropane.[1]




**Scheme 39**

In a formal sense, these alkylidene-transition metal complexes such as **176a,b** are correctly referred to as initiators, as they must first be converted into catalytically active metal-carbene complexes such as **180**. This is achieved by alkylidene exchange with a double bond in the first turnover of the catalytic cycle. It is believed that the active complex **180** is the propagating species in solution.



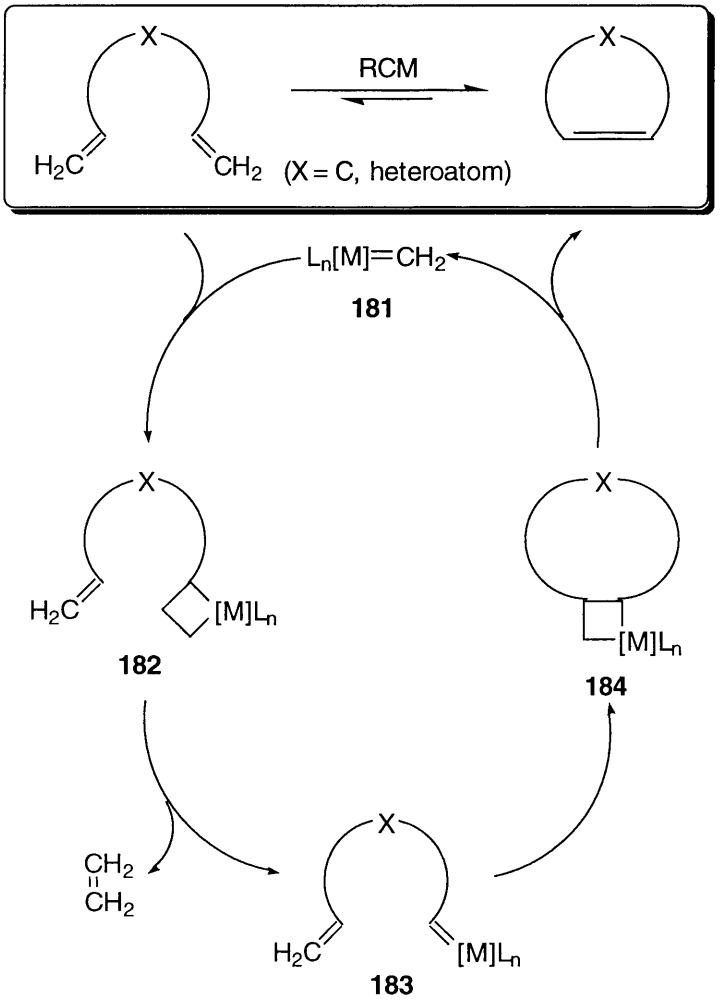

**176a**, R = $CH{=}CPh_2$
**176b**, R = Ph

**180**

The recent advances in olefin metathesis catalysis have drawn considerable attention, and the abundance of examples of ROMP, RCM and ADMET processes in the recent literature pays tribute to the pioneers in the field. However, due to the increasingly large range of syntheses described in the literature, we will only be discussing the areas of metathesis relevant to our own work, which to date has focussed on ring closure reactions.

## 2.2 Ring Closing Metathesis

Ring Closing Metathesis is an extremely powerful tool for the formation of unsaturated cyclic systems from acyclic dienes. An extension of the generally accepted Chauvin mechanism for olefin metathesis, illustrates how an RCM reaction proceeds via a sequence of alternating [2+2] cycloadditions and cycloreversions between the metal-alkylidene and a metallacyclobutane species (Scheme 40).[1]




**Scheme 40**

Once the catalyst $L_nM=CH_2$ **181** has been generated *in situ* from the relevant initiator, a [2+2] cycloaddition between the alkylidene and a terminal olefin affords metallacyclobutane **182**, subsequent cycloreversion affords metal-alkylidene **183** with the generation of ethene. A second [2+2] cycloaddition gives the ring closed intermediate **184**, which again undergoes a [2+2] cycloreversion to give the cyclic olefin and regenerates the catalytic species. Although the intricate details of the mechanism are not fully understood, kinetic studies of an RCM reaction using **176b** as the catalyst, have ascertained that the metal complex loses a phosphine ligand, in order to accommodate the cyclobutane moiety. On complete cyclisation the free phosphine ligand is scavenged from the solution.[10]

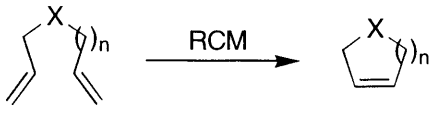
All metathetic processes are in principle reversible, however the RCM reaction proceeds to give a cyclised product for several reasons:[11]

- RCM inadvertently cuts one molecule into two, and is therefore entropically favourable.
- The equilibrium is constantly shifted towards the cyclic product if a volatile olefin such as ethene is the by-product.
- If a product has a more highly substituted double bond than the substrate, the reverse reaction is kinetically hindered due to the catalyst's sensitivity to steric factors.
- ADMET can compete with RCM of a diene substrate, but is reduced if the reaction is performed at high dilution.

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

### 2.2.1 Medium Sized (5-8) Ring Formation

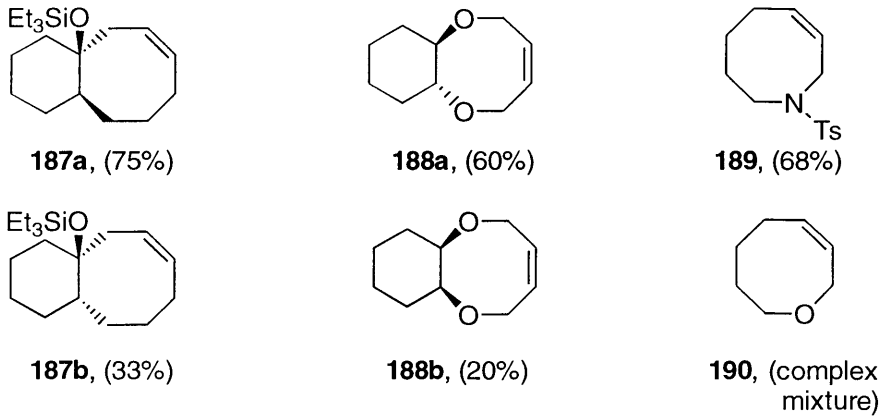
Although the first example of catalytic RCM was reported by Tsuji in 1980,[12] its emergence as a valuable tool can be traced through a series of papers in the early 1990's where Grubbs and co-workers demonstrated the high yielding ring closing of diolefins to furnish 5-, 6- and 7-membered rings **186**. Using the ruthenium catalyst **176b**, they were able to effect cyclisation of a number of dienes **185** with diverse functionality.[13]




**185** **186**

Where X = O, NR, CHR
n = 1,2,3

Since these early contributions, the synthesis of 5-, 6-, and 7-membered rings using RCM methodology has evolved into a general method due to the facile nature of the reaction. Ring closure of larger rings can be more complicated, as the polymerisation process ROMP, can compete with RCM as it releases the ring strain present in many medium sized ring products. In the case of 8-membered rings, it is generally accepted that a conformational predisposition favouring ring closure, such as the Thorpe-Ingold effect or hydrogen bonding, is required to overcome the competition.[11] This is clear when considering the 8-membered products, synthesised by reaction of the appropriate diene with ruthenium catalyst **176b**, illustrated in Figure 4.[14]




**187a**, (75%) **188a**, (60%) **189**, (68%)

**187b**, (33%) **188b**, (20%) **190**, (complex mixture)

**Figure 4**

It is clear from products **187a** and **188a** that the RCM is favoured when the *trans* fused product is formed. The analogous products **187b** and **188b** are less favoured due to the increased strain of the *cis* fused system. The heteroatom present in examples **189** and **190** can also influence the product, as the nitrogen containing heterocycle **189** is cyclised in 68% yield, whereas the analogous more flexible ether **190** is not isolated. Despite this added complexity, the 8-membered ring product is still fairly well documented in the literature, particularly within the field of natural product synthesis, which will be discussed extensively later.

Further systematic investigation by Grubbs and co-workers, has uncovered a limitation of the Ru catalyst **176b**. Table 1 illustrates how the activity of **176b** is

eclipsed by the superior catalytic activity of Schrock's Mo catalyst **175b** when cyclising highly substituted dienes **191**, **193** and **195** to furnish tri and tetrasubstituted olefins **192**, **194**, **196**.[15]

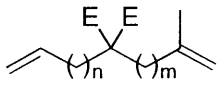
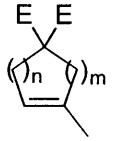
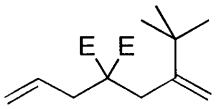
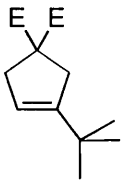
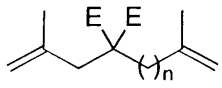
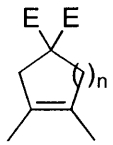
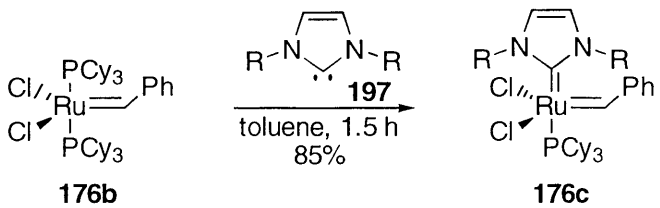
| Substrate | | Product | | Yield | |
|---|---|---|---|---|---|
| | | | | **176b** | **175b** |
|  | **191a**, n=1, m=1<br>**191b**, n=1, m=2<br>**191c**, n=2, m=2 |  | **192a**<br>**192b**<br>**192c** | 93%<br>97%<br>96% | 100%<br>100%<br>100% |
|  | **193** |  | **194** | 0% | 96% |
|  | **195a**, n=1<br>**195b**, n=2 |  | **196a**<br>**196b** | 0%<br>0% | 93%<br>61% |

**Table 1:** Formation of tri- and tetrasubstituted alkenes by RCM; comparison of the efficiency of catalysts **175b** and **176b** (E=COOMe).

Although the trisubstituted products **192** are formed in almost quantitative yield by both catalysts, the Ru catalyst **176b** is not as effective when ring closing bulky *gem* substituted substrates such as **193**, and *gem* disubstituted dienes **195**. The ruthenium catalyst compensates for this lower intrinsic reactivity by an increased tolerance towards functional groups when compared to Mo catalyst **175b**. Obviously a system combining the positive features of each catalyst is highly desirable, and a recent contribution by Grubbs *et al.* goes some way to providing a solution. Reaction of ruthenium catalyst **176b** with imadazole moiety **197**, furnishes N,N-disubstituted-2,3-dihydro-1H-imidazol-2-ylidene ruthenium complex **176c** in 85% yield after recrystallisation.[16]




**176b** **176c**

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

This new generation Ru complex does catalyse the ring closure of tri and tetrasubstituted cycloalkenes, which were beyond the domain of the original catalyst **176b**. In terms of stability, compound **176c** is even more robust than the dicyclohexylphosphine catalyst **176b**, with a very similar tolerance towards an array of polar functional groups.

Fürstner and co-workers have described a comparative investigation of the reactivity of metathesis catalysts **175b**, **176b** and **176c**, in the key ring closure step of dienes **198**, **200**, and **202** to afford the naturally occurring conduritol derivatives **199**, **201** and **203** respectively (Table 2).[17]

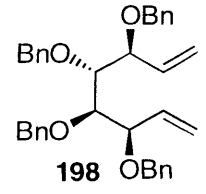
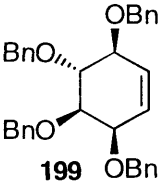
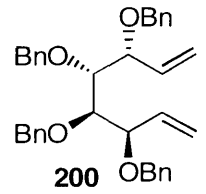
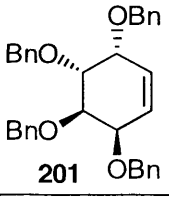
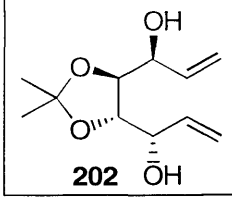
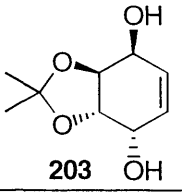
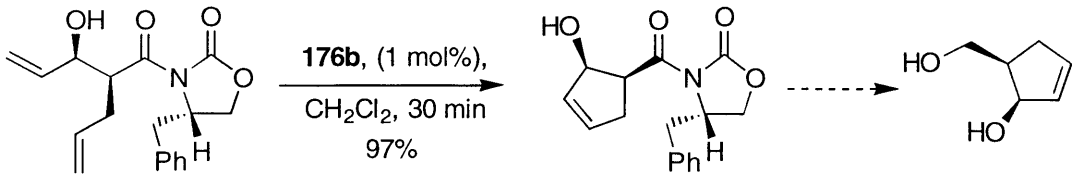
| Substrate | Catalyst | Mol% | Time (h) | Product | Yield (%) |
|---|---|---|---|---|---|
|  **198** | **175b** | 5 | 1 |  **199** | 92 |
| | **176b** | 5 | 60 | | 32 |
| | **176c** | 5 | 2 | | 89 |
|  **200** | **175b** | 5 | 1 |  **201** | 91 |
| | **176c** | 5 | 3 | | 85 |
|  **202** | **175b** | 20 | 20 |  **203** | 0 |
| | **176b** | 5 | 2 | | 0 |
| | **176c** | 1.5 | 2 | | 69 |

**Table 2:** Comparative investigations of the reactivity of different metathesis initiators **175b**, **176b** and **176c**.

The new ruthenium catalyst **176c** and Schrock's molybdenum catalyst **175b** are far more effective than **176b** for the ring closure of the bulky tetrabenzylated dienes **198** and **200**, to afford cyclohexene derivatives **199** and **201** respectively. However, when the unprotected diol **202** is treated with the three catalysts, ring closure to furnish **203** is only effected by the new Ru catalyst **176c**, clearly demonstrating its superiority in this type of ring closure.

The remarkable tolerance to a wide variety of functional groups and heteroatoms has been a key factor in the success of the ruthenium catalysts **176b** and **176c**. For example they are compatible with ethers, silyl ethers, acetals, esters, amides, carbamates, sulfonamides and silanes to name but a few, making them particularly

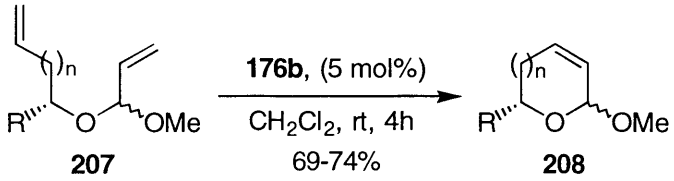
attractive for synthetic purposes. Crimmins and co-workers have illustrated how highly functionalised chiral diene **204**, formed by aldol methodology, was cyclised to afford cyclopentanol **205** on exposure to ruthenium catalyst **176b** in dichloromethane.[18] Cyclopentanol **205** is a key intermediate in the synthesis of chiral nucleosides such as **206** (Scheme 41).




**204** **205** **206**

**Scheme 41**

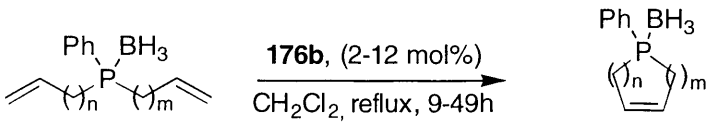
Rutjes and co-workers have demonstrated the value of **176b** in the synthesis of α,α substituted dihydropyrans. Ring closure of dienes **207** is effected by treatment with 5 mol% of catalyst **176b** to afford dihydropyrans **208** in 69-74% yield, these oxygen heterocycles can be used in the synthesis of a variety of natural products.[19]




**207** **208**

Where R = $CO_2Me$, $CH_2OBn$
n=1,2

Further evidence for the remarkable tolerance of ruthenium catalysts to functional groups has been demonstrated by Gouverneur *et al.* as **176b** and **176c** are used to effectively cyclise a number of dienes, such as **209** bearing borane and phosphane functionality, to afford cyclic phosphanes such as **210**, in yields ranging from 63-95%.[20]

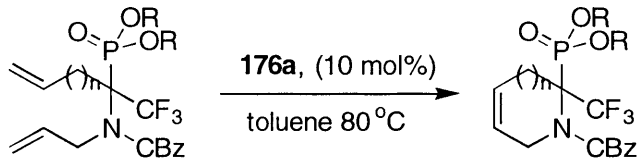



**209** **210**

Where n = 1,2, m = 1,2

The authors, have reported that the larger ring heterocycles where n = m = 2, require a higher concentration of catalyst to react, which was added in 2 mol% portions until the reaction had proceeded to a satisfactory end point.

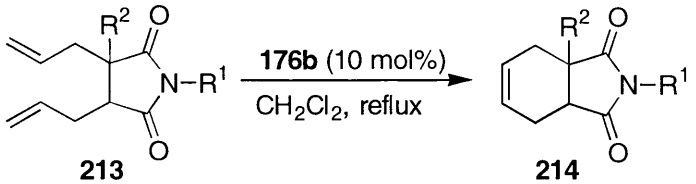
Dixneuf and Osipov have also demonstrated this exceptional functional group tolerance, by applying ruthenium catalysed RCM to α-$CF_3$ substituted, α-aminophosphonates such as **211**. Ring closure was effected by treatment with Ru catalyst **176a** in toluene, yielding cyclic products **212** in approximately 70% yield.[21]




**211** **212**

Where n = 1 or 2

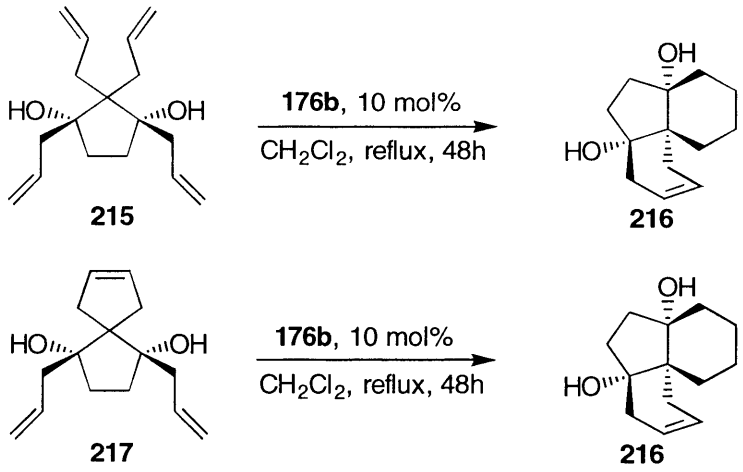
A limitation of the Ru catalysts **176a,b** and **c**, is that their intrinsic activity is reduced by free amines, hence the amine in the above example must be suitably protected before reaction. However, the Ru catalyst **176** activity is not affected by amide functionality, as Dyatkin has demonstrated. In the example below, the diene moiety **213** is successfully cyclised to the bicycle **214** in greater than 95% yield when treated with 10 mol% Ru catalyst **176b**. An interesting observation of this reaction is that when $R^2$ = allyl, none of the spirocyclic product is observed, even though the two ring closure reactions are in direct competition.[22]



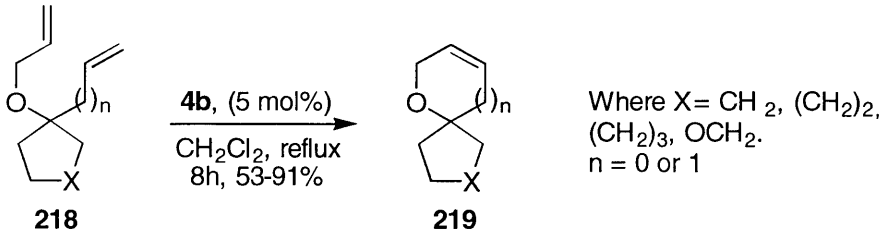

**213** **214**

Where $R^1$ = alkyl, aryl,
$R^2$ = alkyl, aryl, allyl.

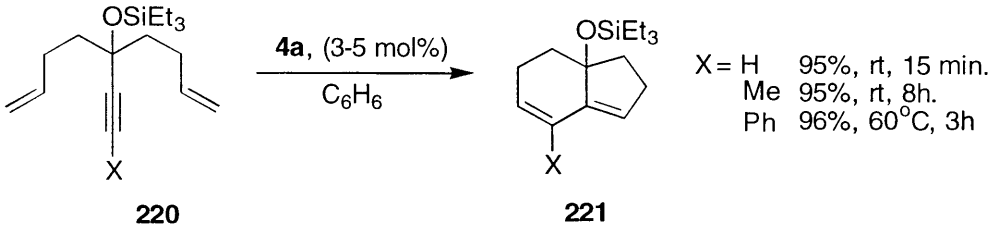
Harrity and co-workers have demonstrated that bicyclic and tricyclic angularly fused systems are formed in preference to spirocyclic systems when the two processes are in competition in a tandem RCM reaction.[23] Tetraene **215** is cyclised via RCM to give *cis-cis* fused tricycle **216** in 72% yield, with no evidence of the 5-membered spirocyclic moiety formed. Further studies illustrate how the spirocyclic compound **217** cyclises to give the same tricyclic product **216** in 85% yield, thus confirming that the fused ring is thermodynamically favoured over the spirocyclic system.




Maier and Bugl have been able to furnish a number of spirocyclic ethers utilising RCM. Diene moieties **218** prepared by Grignard addition to the relevant ketone (e.g. cyclohexanone), followed by O-alkylation with allyl bromide, were cyclised in refluxing dichloromethane in the presence of 5 mol% of **176b** furnishing oxa-spirocycles **219**.[23]

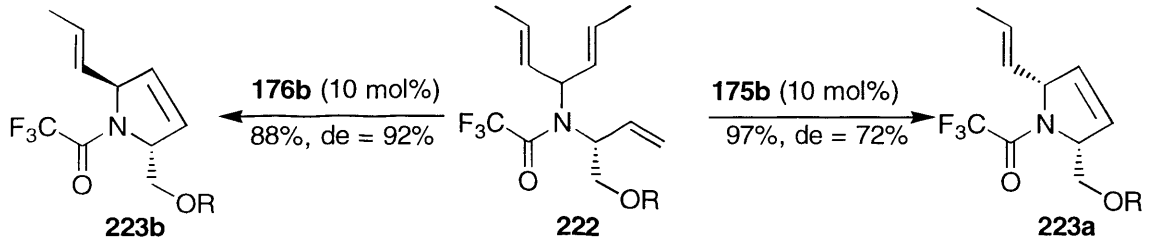



The tandem metathesis RCM reaction, where tetraene **215** gives exclusively the tricycle **216**, was first described by Grubbs *et al.* as they demonstrated that fused bicycles could be generated via Ru-carbene catalysed double RCM of acyclic dienynes, where the acetylene moiety acts as a metathesis relay. Dienyne **220** is successfully cyclised in benzene in the presence of Ru catalyst **176b** to afford bicycle **221**.[25]

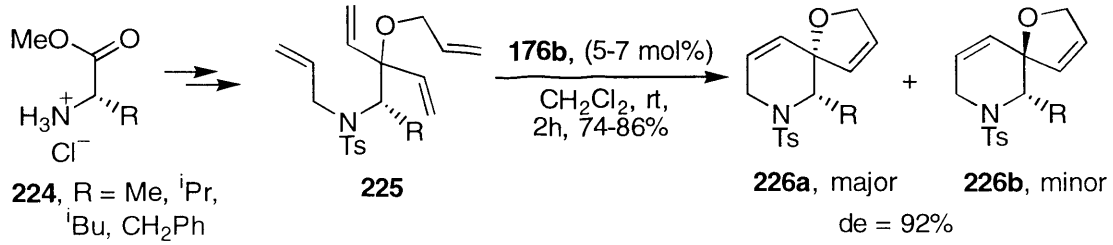


## 2.2.2 Asymmetric Ring Closing Metathesis

Due to the increasing synthetic potential of ring closing metathesis, the need for stereoselective RCM is also becoming important. Most of the examples of diastereoselective RCM described to date have used an existing chiral centre to control the direction of cyclisation of pro-chiral dienes. For example Blechert and co-workers have found that enantiopure triene **222** does undergo selective RCM in the presence of Mo catalyst **175b**, to afford predominantly the *syn* product **223a** with 72% de.[26] In this type of reaction it is important that the catalyst reacts with the olefin adjacent to the chiral centre first, rather than the prochiral olefins, and this is achieved by increasing the substitution of the latter olefin moieties. Somewhat surprisingly, when **222** is treated with the ruthenium catalyst **176b**, the *anti* product **223b** is preferred. The authors attribute this "catalyst specificity" to the different spatial arrangement of the respective ligands in each complex during the cyclisation.

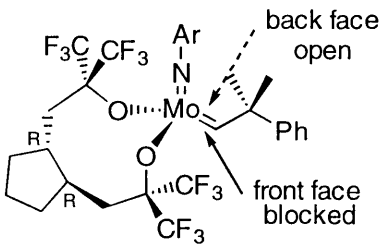



An example of double RCM furnishing spirocyclic products has been reported recently by Wallace *et al.*[27] Chiral tetraenes **225**, prepared from amino acid derivatives **224**, were successfully cyclised to give chiral spirocycles **226a** and **226b** on treatment with Ru cat **176b** at rt for two hours (Scheme 42). The ring closure reaction proceeds with impressive diastereoselectivity, strongly in favour of **226a**, and the observed diastereoselectivity is not affected by the size of the alkyl substituent R.



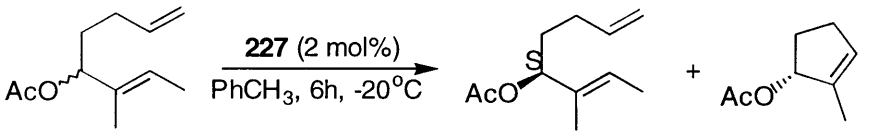

**Scheme 42**

Grubbs and co-workers have developed a chiral catalyst for RCM that has been successfully utilised for the kinetic resolution of a racemate.[28] The chiral alkylidene **227** (Figure 5) displays similar reactivity to Schrock's Mo catalyst **175b** in both RCM and ROMP processes. However, due to the different steric properties of the two faces of the chiral catalyst, one enantiomer of the substrate reacts faster than the other (kinetic resolution). The best resolution achieved with this catalyst is about 48% e.e. when cyclising racemic diene **228** to give 38% of the unreacted (S) diene **228a**, and 62% of the cyclised (R) product **229**.



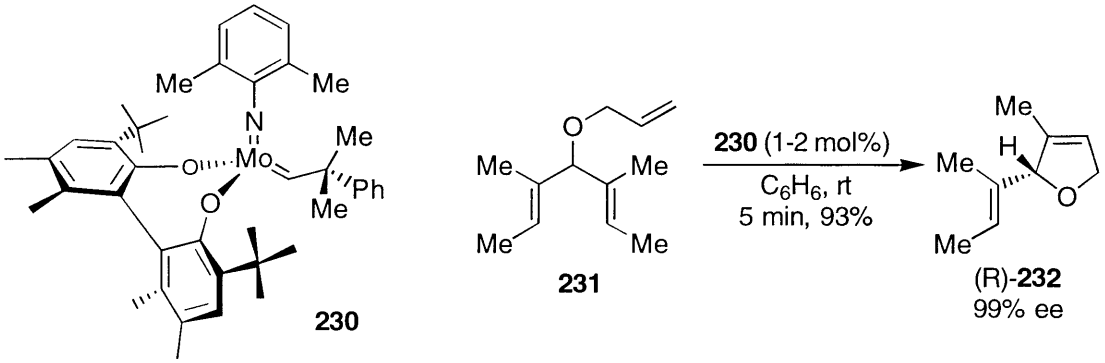

**227**
Where Ar = 2,6-$^{i}Pr_2C_6H_3$

**Figure 5**




**228** **228a**, 38%, 48% ee **229**, 62%

A recent example by Hoveyda and Schrock provides an attractive extension to this strategy.[29] Chiral Mo alkylidene catalyst **230**, was used for catalytic enantioselective desymmeterisation of achiral trienes such as **231**, which on cyclisation afforded chiral heterocycles such as **232** in high yield and remarkable stereoselectivity.

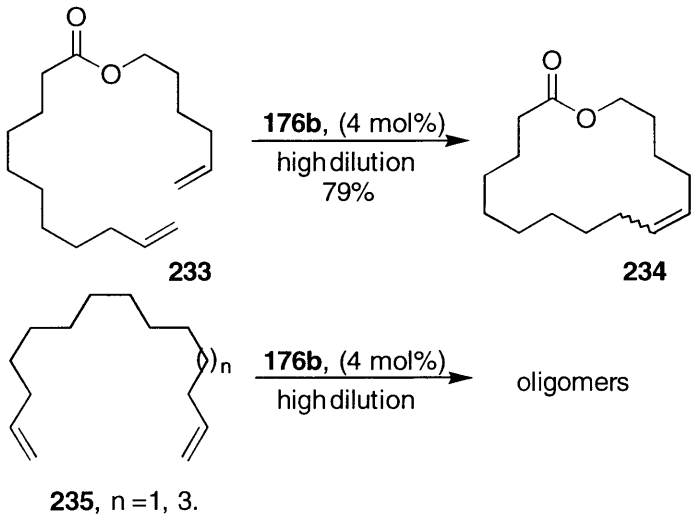



## 2.2.3 Macrocyclic Ring Closing Metathesis (≥ 9)

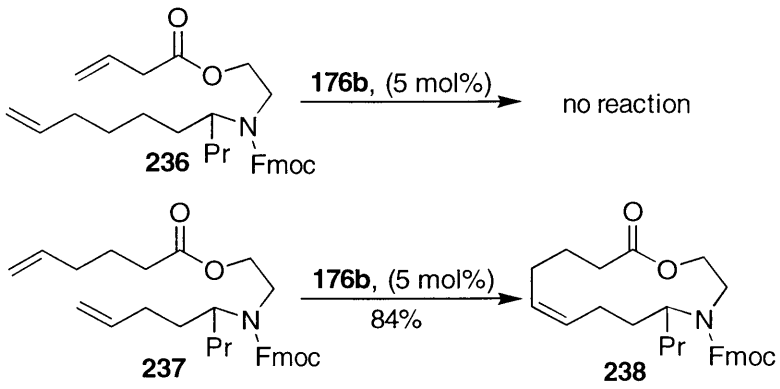
As we saw earlier, in the case of 8-membered rings, one of the major considerations for RCM in the synthesis of highly flexible ring systems is the conformational predisposition of the starting material for favourable intramolecular

cyclisation. Unlike the earlier examples however, macrocyclic RCM is better understood, with a set of parameters clearly defining the limitations of the reaction:[11]

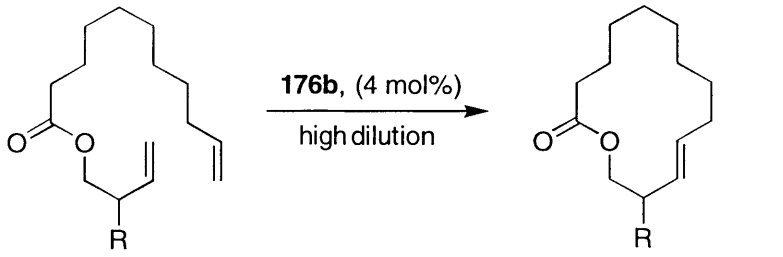
- The presence of a polar functional group (ester amide, ketone, ether, sulfonamide, urethane etc.) is a fundamental requirement for smooth macrocyclisation by RCM. This is outlined below, as 18-membered acyclic lactone **233** cleanly cyclises to afford 16-membered cyclic lactone **234** in good yield, whereas the analogous carbon chain **235** affords a mixture of oligomers.




- The site of ring closure is a key issue. This factor is illustrated below, as diene **236** does not cyclise, but by changing the site of reaction, **237** ring closes to give the 13-membered heterocycle **238** in excellent yield.




- Steric hindrance close to the double bonds significantly lowers the yield of the cyclisation, as the comparison between **240a** and **240b** illustrates.

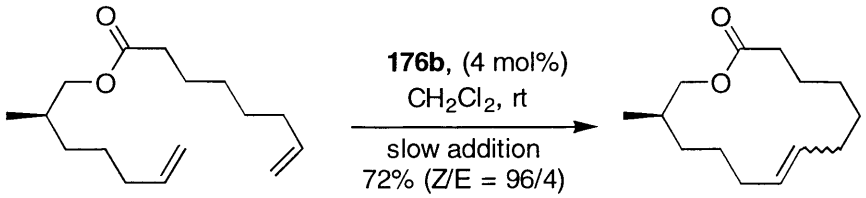



**239**

**240a**, R = H (52%)
**240b**, R = Me (10%)

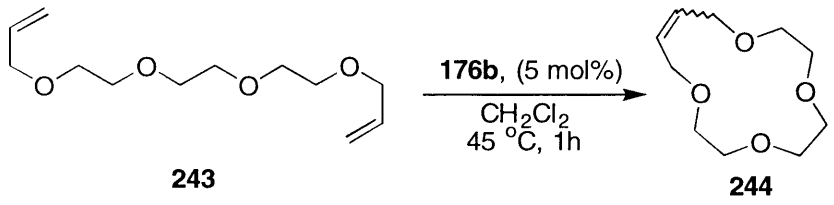
Once again, the RCM of large rings is in direct competition with polymerisation processes; however, the rate of oligomerisation can be significantly reduced by lowering the concentration of the diene in solution, or by slow addition of the substrate to the reaction mixture.

Despite these limitations, RCM is rapidly becoming recognised as one of the simplest and most reliable methods for the formation of large rings. For example Fürstner and Langemann have demonstrated the ease in which 14 membered lactone **242** can be cyclised from the highly flexible 1-15 diene **241** under slow addition conditions in the presence of **176b**.[30]




**241** **242**

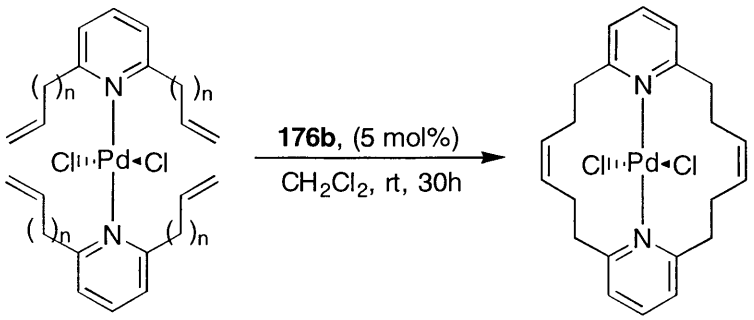
Template directed RCM of macrocycles has been found to not only promote intramolecular reaction, but the pre-coordination can affect the stereoselectivity of the reaction. Grubbs and co-workers have found that the pre-organisation of linear oligo-oxy ethylenic diene **243** around a complimentary metal ion provides a favourable conformation that enhances cyclisation and stereocontrol to give exclusively the *cis* cyclic crown ether **244**. Of the variety of metals tested, $Li^+$ gave the best results.[31]




**243** **244**

no template: 39% (38:62 Z/E)
$LiClO_4$ (5 eq.): >95% (100:0 Z/E)

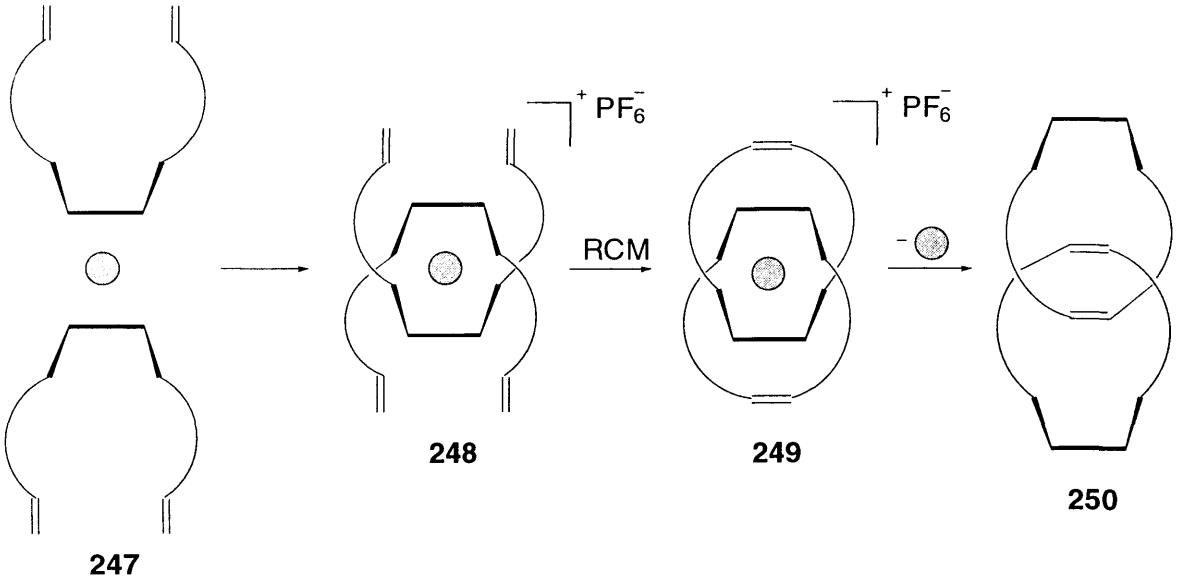
Lambert and Ng have reported an extension of this work, where the pre-coordinated bis-pyridine diene complexes **245a,b** were prepared by reacting 2 equivalents of the pyridine diene with *trans* $[PdCl_2(PhCN)_2]$.[32] On treatment with Ru catalyst **176b**, tetraene complex **245b** was successfully cyclised to give the 18 membered macrocycle **246** exclusively in 80% yield. However, when bis-pyridine diene complex **245a** was treated under the same conditions, none of the cyclised product was observed, the authors have attributed this lack of reaction to the development of excessive ring strain.




**245a**, n = 1
**245b**, n = 2

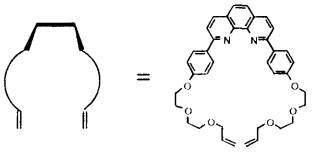
**246**

Grubbs *et al.* have also utilised a variation of this methodology to prepare a number of interlocked molecular rings, or catenanes as they are commonly known. Intertwined complex **248**, obtained from the complexation of two equivalents of bidentate ligand **247** with copper (I), was cleanly cyclised to form the 32-membered [2]-catenane complex **249** in remarkably high yield (Scheme 43). Subsequent demetallation with potassium cyanide furnished the [2] catenane **250**.[33]




RCM - **176b** (5 mol%), $CH_2Cl_2$, rt, 6 h, 92% (trans:cis = 98:2)

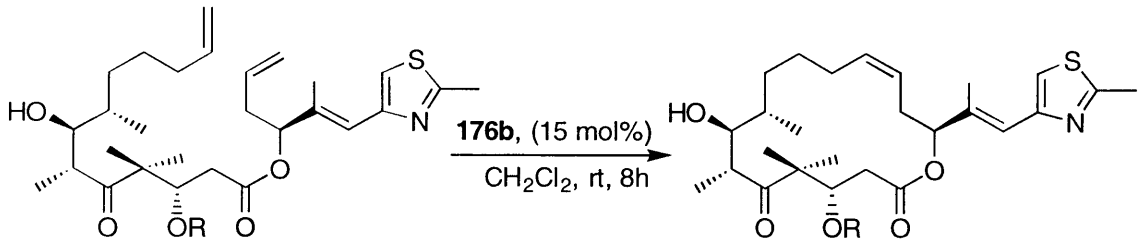
○ = $Cu^+$



**Scheme 43**

## 2.2.4 Natural Product Synthesis using Ring Closing Metathesis

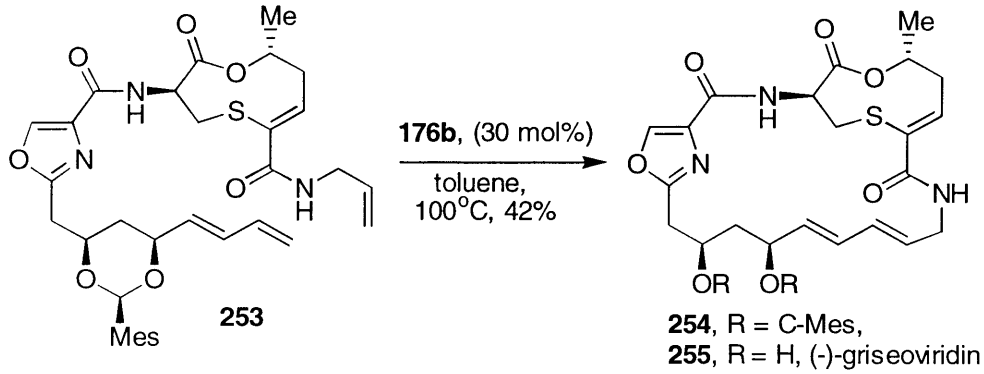
The power of olefin metathesis in forming macrocycles has culminated in the synthesis of complex biologically active macrocyclic natural products, including Epothilone A, which along with many derivatives has been prepared by a number of research groups.[34] The first formal synthesis of Epothilone A, which utilises RCM for the key ring closure step, was reported by Nicolaou *et al.*[35] The cyclisation of acyclic diene **251** was effected by treatment with the Ru catalyst **176b** in DCM, affording the 16-membered macrocycle **252** as a 10:7 mixture of the *Z* and *E* isomers respectively in 85% overall yield. The major *Z* product was separated and the new olefin moiety was selectively epoxidised. Subsequent deprotection afforded Epothilone A **139**.




**251**, where R = TBS

**252**

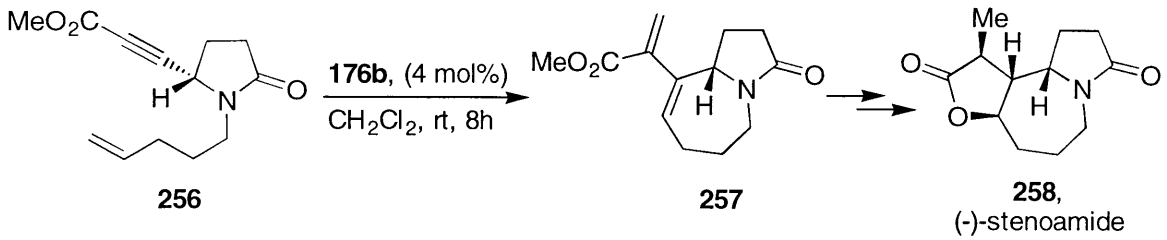
A recent communication by Meyers *et al.* illustrates the novel synthesis of (-)-griseoviridin **255**, a powerful naturally occurring antibiotic.[36] Allyl amide **253**, obtained in 22 linear steps from (S)-malic acid, was successfully cyclised with Ru catalyst **176b** to give **254** in 42% yield. The poor yield was compensated by the fact that the required *trans* geometry was the exclusive product of the ring closure. Subsequent deprotection of **254** furnished (-)-griseoviridin **255** in 68% yield.




**253**

**254**, R = C-Mes,
**255**, R = H, (-)-griseoviridin

Kinoshita and Mori have used RCM to effect ring closure of an enyne in an elegant synthesis of the insecticidal tricyclic alkaloid (-)-stenoamide **258**. Chiral enyne **256**, prepared from pyroglutamate, was cyclised in the presence of a catalytic amount of **176b** to afford bicycle **257** in good yield (Scheme 44). This bicyclic vinyl ester represents a key intermediate in the synthesis of **258**.[37]



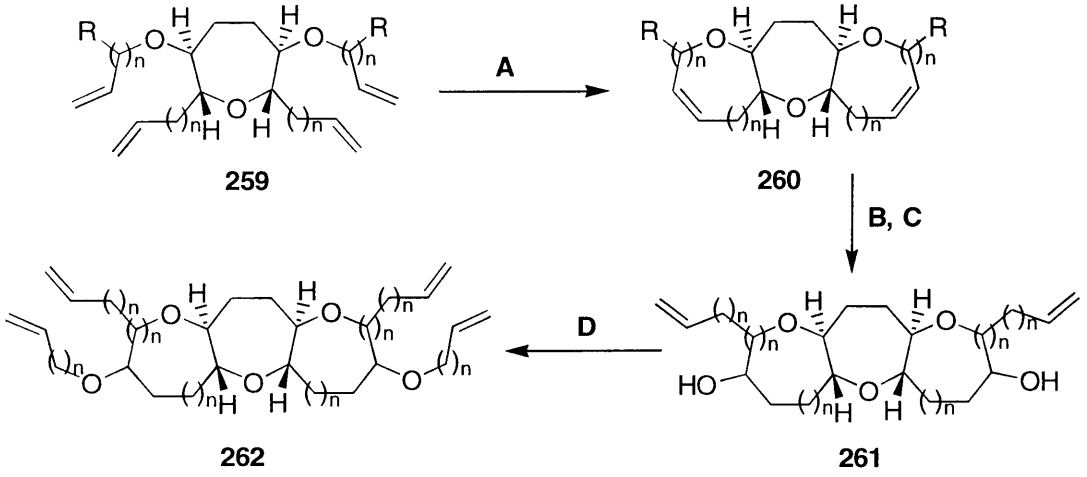

**256**

**257**

**258**,
(-)-stenoamide

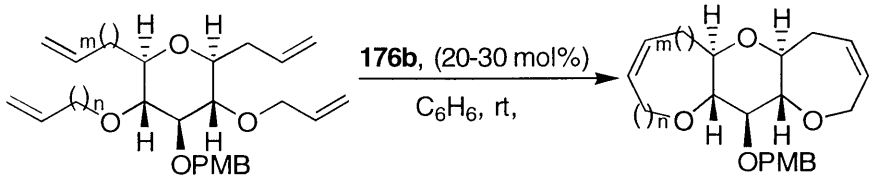
**Scheme 44**

Polycyclic ethers continue to provide interesting synthetic targets as a consequence of their architectural complexity and potent biological activity. Clark and Hamelin have designed a novel strategy for the efficient construction of polycyclic ethers using RCM in the ring closure step.[38] Scheme 45 illustrates the potentially infinite stepwise construction of polycyclic ethers, where step A involves ring closing metathesis across the diene moieties of **259**. Step B is a functionalisation of the new ring systems in **260**, step C is a side chain functionalisation to afford **261** and step D represents the introduction of a new side chain to regenerate a tetraene **262**. This type of synthesis could theoretically produce a whole library of polycyclic ethers.




**Scheme 45**

Their preliminary results in this area can be seen below, where tetraenes **263**, prepared from D-glucal, were cyclised in the presence of Grubbs' ruthenium catalyst **176b** to afford polycyclic ethers **264a-d**.



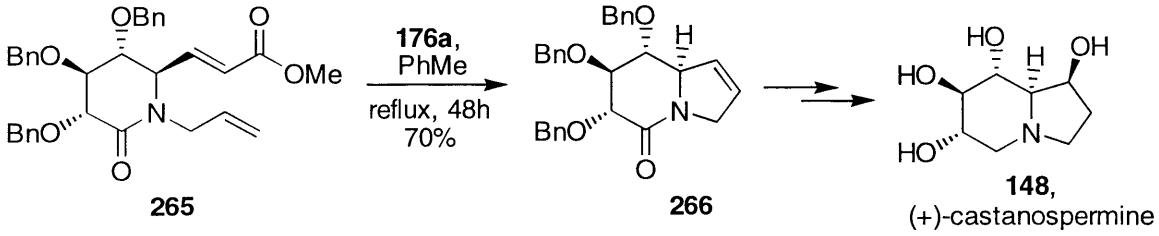

**263**

**264a**, n=0, m=1, 71%
**264b**, n=1, m=1, 88%
**264c**, n=1, m=2, 77%
**264d**, n=3, m=1, 65%

## 2.3 Ring Closing Metathesis of Carbohydrate Derivatives

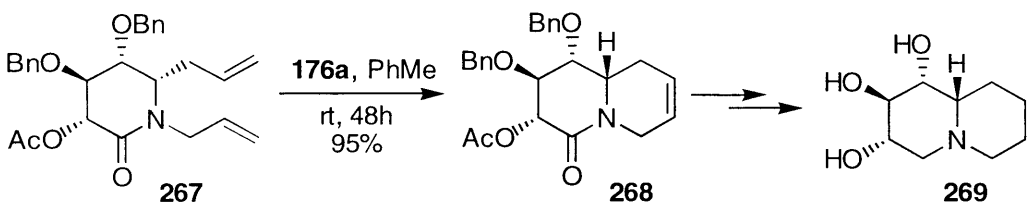
The above case represents an example of a carbohydrate-derived substrate undergoing RCM to furnish a new chiral tricycle. As we have already seen in Chapter 1, carbohydrates provide an excellent template for a variety of syntheses due to their intrinsic functionality and chirality. The advent of well defined catalysts for RCM, and in particular the functional group tolerant catalysts such as **176**, has generated huge interest within the field of carbohydrate chemistry leading to a variety of carbo- and heterocyclic products and many total syntheses.

Overkleeft *et al.* have reported an attractive total synthesis of the polyhydroxylated alkaloid castanospermine **148**.[39] The aza-sugar **265**, derived from tetrabenzyl-glucopyranoside, was treated with Ru catalyst **176a** in refluxing toluene for 48 hours to afford the azabicycle **266** in 70% yield (Scheme 46). The harsh reaction conditions are necessary to facilitate the cleavage of the acrylic ester group in the cyclisation, as opposed to a molecule of ethene, which is the common more volatile by-product of RCM. Selective dihydroxylation of the new double bond followed by reduction and deprotection afforded castanospermine **148**.



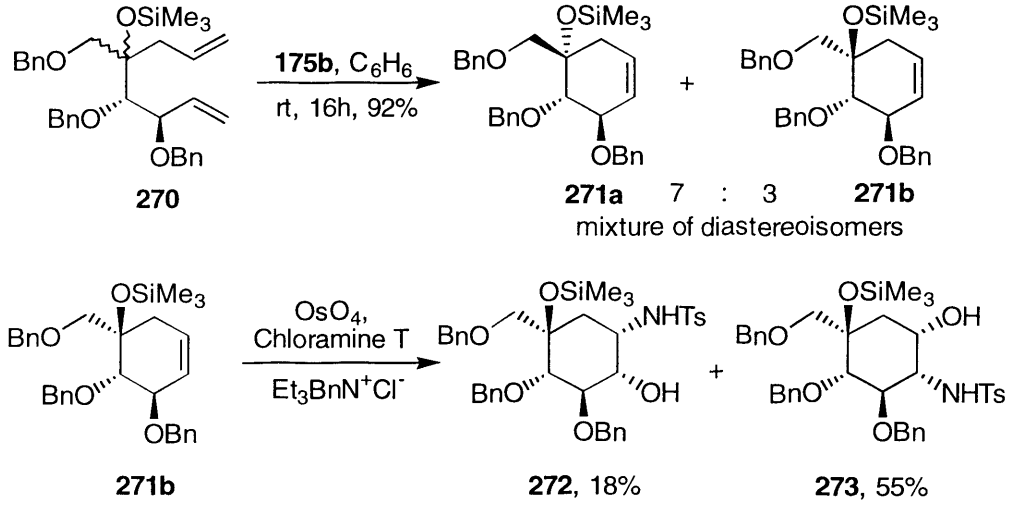

**Scheme 46**

The same group have also reported a synthesis of a 6,6-azabicycle **269**, using similar techniques.[40] Diene **267**, similarly derived from tetrabenzyl-glucopyranoside underwent RCM in toluene at rt in the presence of **176a**, to afford azabicycle **268** in 95% yield. Reduction and deprotection furnishes chiral quinolizidine derivative **269** in 56% yield (Scheme 47).



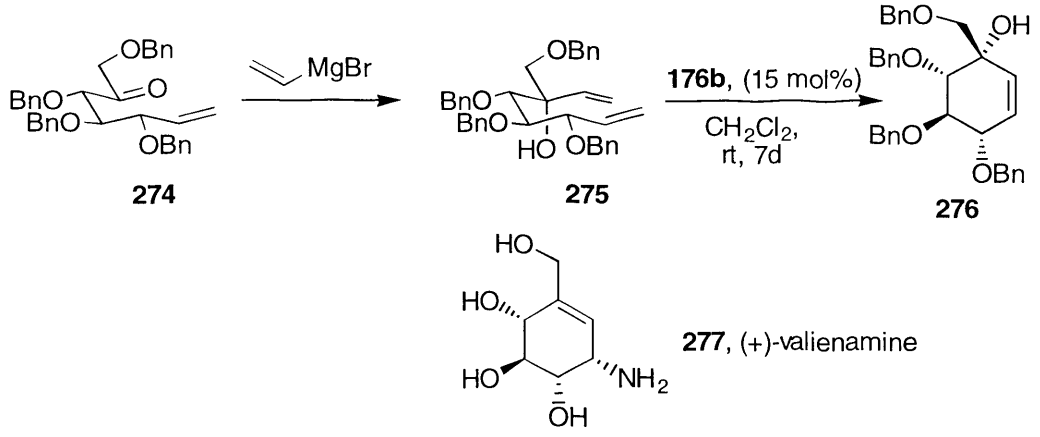

**Scheme 47**

Ring closing metathesis methodology has also been successfully utilised to furnish carbocycles derived from carbohydrates. Scheme 48 illustrates a short and concise, but somewhat inefficient synthesis of valiolamine, a potent glycosidase inhibitor. Diene **270**, easily prepared from D-aribinose, was treated with Mo catalyst **175b** to afford diastereomeric isomers **271a** and **271b** in 92% yield. The mixture was separated by HPLC and the minor isomer **271b** was subjected to *cis*-aminohydroxylation to afford key intermediate **272** and its regioisomer **273** in 73% combined yield.[41]



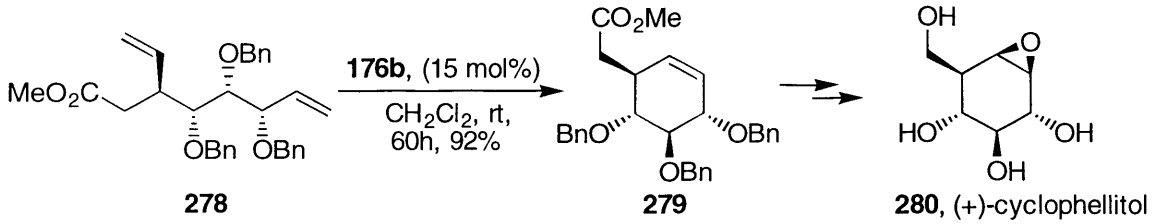

**Scheme 48**

A much more efficient synthesis of (+)-valienamine **277**, a close derivative of valiolamine, has recently been described by Vasella and co-workers and is depicted in Scheme 49.[42] D-Glucose derived acyclic ketone **274** was alkylated with a vinyl Grignard reagent to afford **275**, which undergoes RCM in the presence of Ru catalyst **176b**, to yield the chiral carbocycle **276** in 58% yield. Compound **276** was then converted to (+)-valienamine **277** in three further steps with an overall yield of 47%.




**Scheme 49**

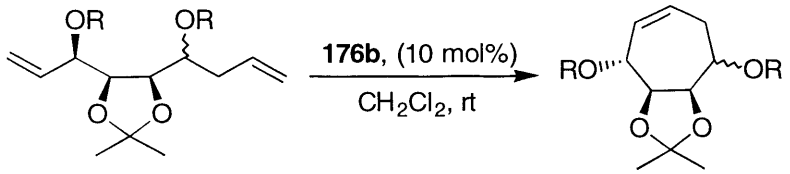
Ziegler and Wang have described a direct synthesis of the β-glucosidase inhibitor (+)-cyclophellitol **280**, from the carbohydrate precursor D-xylose.[43] Ru catalysed RCM of the diene **278** led to the efficient formation of cyclohexene **279** in 92% yield. Further chemical manipulation afforded enantiomerically pure (+)-cyclophellitol **280** (Scheme 50).




**278** **279** **280**, (+)-cyclophellitol

**Scheme 50**

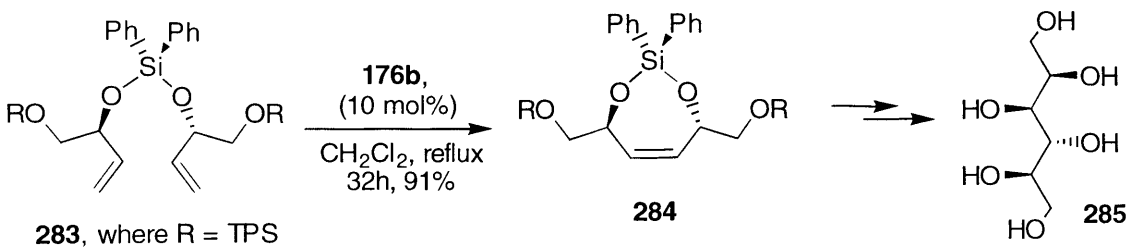
A very recent communication by Marco-Contelles and Opazo has established the ease in which polyhydroxylated cycloheptane rings can be derived from carbohydrates. The RCM of acyclic 1,8-nonadienes **281a-c**, easily prepared from D-mannose, was mediated by a 10 mol% solution of Ru catalyst **176b** in DCM at rt, affording cycloheptanols **282a-c**.[44]




**281a**,C6 S, where R =H
**281b**,C6 R, R =Ac
**281c**,C6 R, R =Bn

**282a**, (85%, 6h)
**282b**, (95%, 1h)
**282c**, (90%, 40min)

RCM has also been applied to the preparation of carbohydrates from simple chiral olefins. For example Scheme 51 illustrates how Evans and Murthy have developed an interesting silicon tethered RCM procedure for the synthesis of $C_2$ symmetric 1,4-diol **284**, from simple starting material **283**.[45] Dihydroxylation of the new olefinic moiety by the Sharpless protocol and removal of the protecting groups affords the reduced carbohydrate D-altitrol **285**.



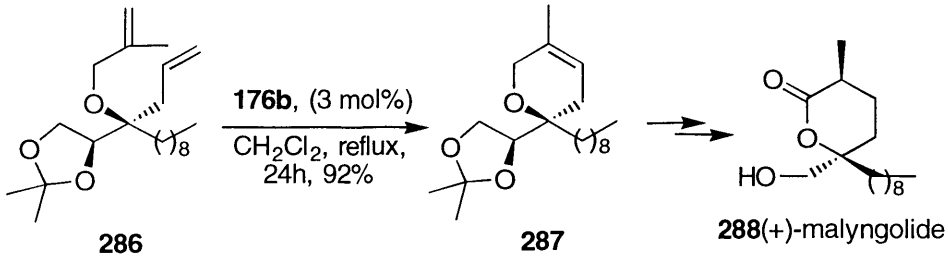

**283**, where R = TPS

**284**

**285**

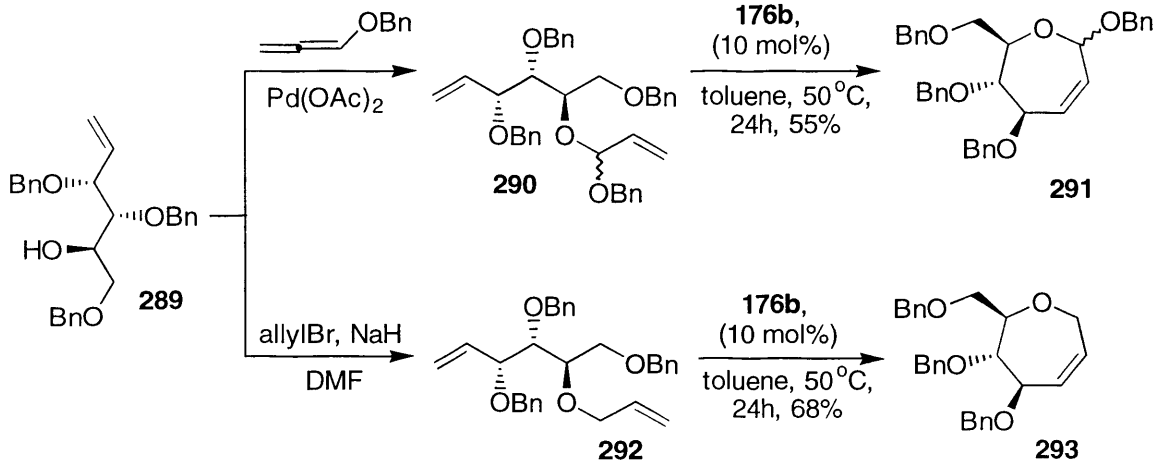
**Scheme 51**

Due to the polyhydroxylated nature of carbohydrates, there are many examples of oxa-cyclic compounds constructed using RCM in the cyclisation step, as illustrated by the synthesis of (+)-malyngolide **288**, an antibiotic isolated from marine algae (Scheme 52). In this case Ru catalyst **176b**, was used to ring close the diene **286**, derived from D-erythrulose, to give the dihydropyran **287** in 92% yield. Further functionalisation and reduction over three steps affords (+)-malyngolide **288**.[46]




**Scheme 52**

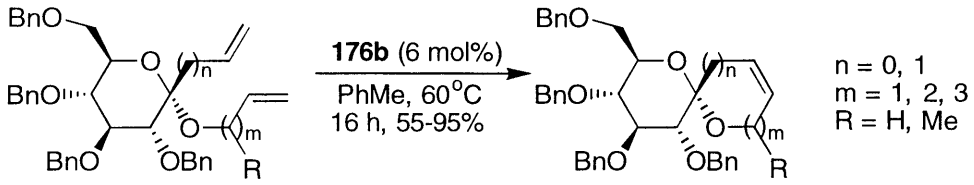
A novel and versatile route to highly functionalised chiral oxepines, based on the RCM of various protected glucofuranoses has been reported by van Boom *et al.* Benzylated tetraol **289**, easily prepared from 2,3,5-tri-O-benzyl-D-aribinofuranose via Wittig methodology, was further alkylated to furnish dienes **290** and **292**. Cyclisation of dienes **290** and **292** was effected with Ru catalyst **176b** affording oxepines **291** and **293** respectively (Scheme 53).[47]




**Scheme 53**

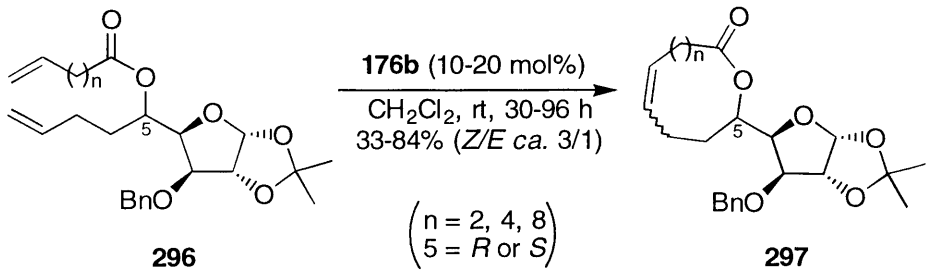
The same group have also described the synthesis of several unsaturated spiroacetals **295**, conformationally congruous to the semi-rigid dioxa-spiroacetal function, which is a common characteristic of many natural products.[48] The terminal alkene-O-alkene moiety on the anomeric centre of dienes **294**, was readily achieved in three steps from perbenzylated D-glucono-1,5-lactone. RCM of dienes **294** was effected

by treatment with Grubbs' Ru catalyst **176b**, resulting in 5-, 6-, 7- and 8-membered spiroacetals **295**.



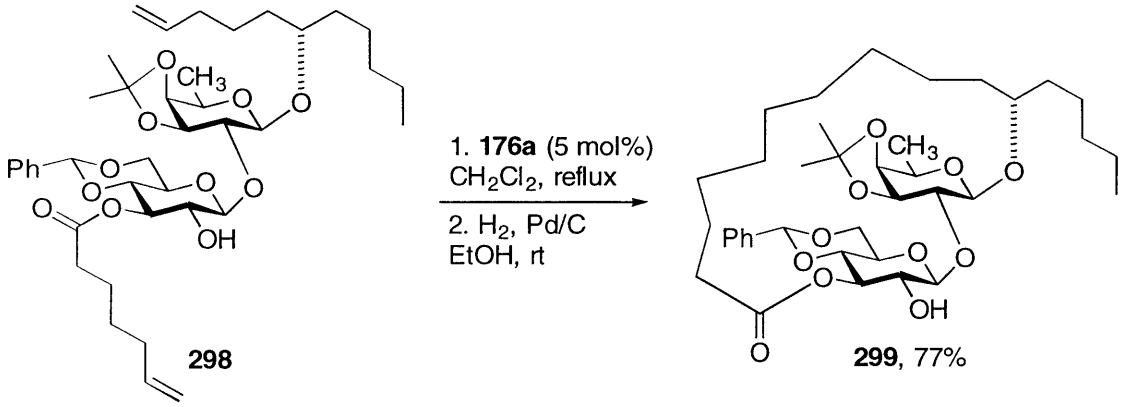

**294** **295**

In connection with their studies of the naturally occurring annonceous acetogenins, Gesson and co-workers have studied the formation of macrocyclic lactones from carbohydrate derivatives by RCM. Dienes **296** were obtained from diacetone-D-glucofuranose, by Grignard alkylation followed by condensation with the corresponding carboxylic acid. Cyclisation on heating with **176b** in DCM furnished 9-15-membered lactones **297** in moderate to good yield.[49]




**296** **297**

Fürstner and Muller have also utilised RCM instead of the more common method of macrolactonisation as the cyclisation step in their synthesis of the disaccharide fragment of trichlorin A **299**. Trichlorin A exhibits significant cytotoxic properties against cultured P-388, and human breast cancer cell lines.[50] The key disaccharide intermediate **298** was prepared via a multistep process and was cyclised by treatment with Ru catalyst **176a** to afford the19-membered lactone as a mixture of *E* and *Z* isomers. The isomeric mixture was subsequently hydrogenated furnishing trichlorin A fragment **299**.

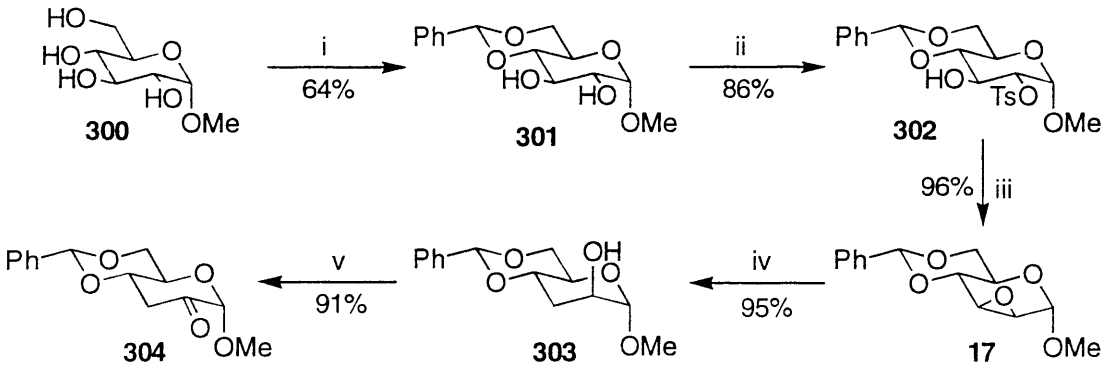



## 2.4 Summary

It is clear that over the last four years ring closing metathesis has evolved into an extremely powerful tool for the synthetic chemist, and during this time many novel syntheses involving one of the well defined catalyst systems have been reported. The technique has been successfully applied within the field of carbohydrate chemistry, with many novel examples demonstrating its potential. During the last three years, we have contributed to expanding the scope of the RCM reaction by using it as a method for producing enantiomerically pure fused and spiro bound, carbo- and oxa-cyclic rings annulated to a carbohydrate template. The results of our findings are reported below.

## 2.5 Results and Discussion[51, 52]

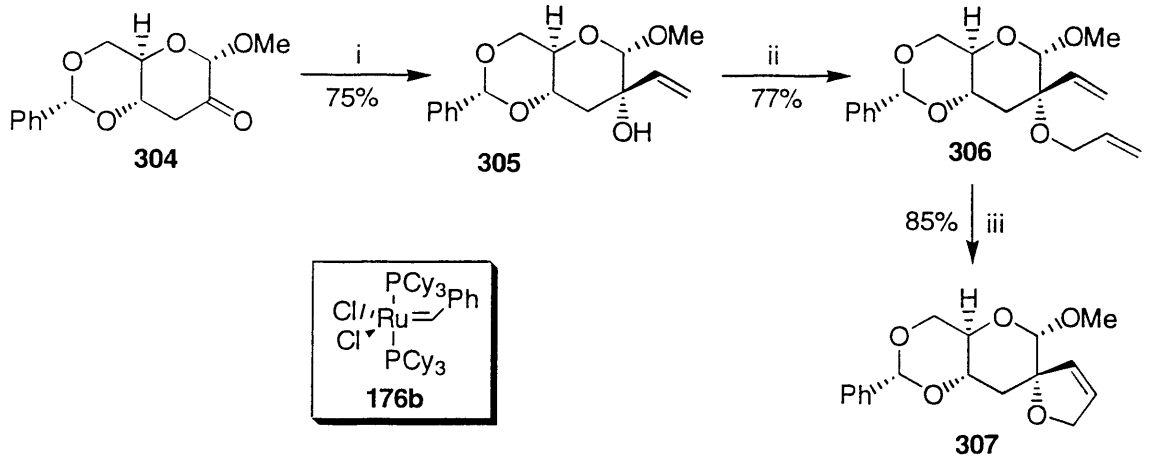
As part of our continuing program of investigating carbohydrate annulation, which has focussed on techniques of annulating D-glucose based derivatives, we have once again opted to start with the cheap and readily available methyl-α-D-glucopyranoside **300** (Scheme 54). Acetal protection of the C-4 and C-6 hydroxyl groups with benzaldehyde dimethyl acetal effectively locks the sugar moiety into it's pyranosidic form in a fairly rigid chair-chair conformation **301**.[53] Reaction of the diol **301** with *p*-toluene sulfonyl chloride furnishes the C-2 tosyl ether **302** exclusively.[54] Deprotonation of the remaining hydroxyl group effects an intramolecular nucleophilic tosyloxy displacement furnishing the "up-epoxide" **17** in 96% yield.[55] Treatment of the epoxide with lithium aluminium hydride affords alcohol **303** exclusively via an axial nucleophilic attack from the hydride species. Swern oxidation of the alcohol **303** affords the ketone moiety **304**,[56] which served as a convenient precursor for our RCM studies.




**Scheme 54,** Reagents and Conditions: i, benzaldehyde dimethyl acetal, DMF, p-toluene sulfonic acid, 65°C, 3h; ii, p-toluene sulfonyl chloride, $CH_2Cl_2$, DMAP, $Et_3N$, rt, 2.5h; iii, NaH, DMF, 0°C then 2.5h rt; iv, $LiAlH_4$, THF, 0°C then 4h reflux; v, DMSO, $(COCl)_2$, $CH_2Cl_2$, -78°C, then $Et_3N$, 24h.

All of the products in the above scheme are white crystalline solids that were easily prepared and purified on a large scale by recrystallisation. Scheme 55 illustrates how the ketone **304** was converted into a spirocyclic annulated carbohydrate via RCM. The ketone moiety **304** was treated with vinyl magnesium chloride to afford allylic alcohol **305** in 75% yield. Interestingly, only one diastereoisomer was isolated from the reaction mixture, which was assumed to be **305**, arising from preferential axial attack of the Grignard reagent. Deprotonation of the alcohol moiety of **305** with sodium hydride followed by O-alkylation with allyl bromide furnished diene **306** as a white crystalline solid in excellent yield. RCM was effected by dissolving the diene **306** in dry benzene, which was subsequently de-gassed, Ru catalyst **176b** (2 mol%) was added to the

solution which was stirred at 60°C overnight. Removal of the solvent by evaporation gave a black oil, which was purified by column chromatography to yield **307** as a white solid.




**Scheme 55,** Reagents and Conditions: i, $H_2C$=CHMgCl, THF, reflux, 4h; ii, NaH, THF, 0°C, then reflux 2h, then $H_2C$=$CHCH_2Br$, DMPU, reflux, 4h; iii, **176b** (2 mol%), benzene, 60°C, 18h.

Pure dihydrofuran derivative **307** was recrystallised from petrol and ether, and the resulting crystals were analysed by X-ray diffraction to confirm our proposed structure (Figure 6).

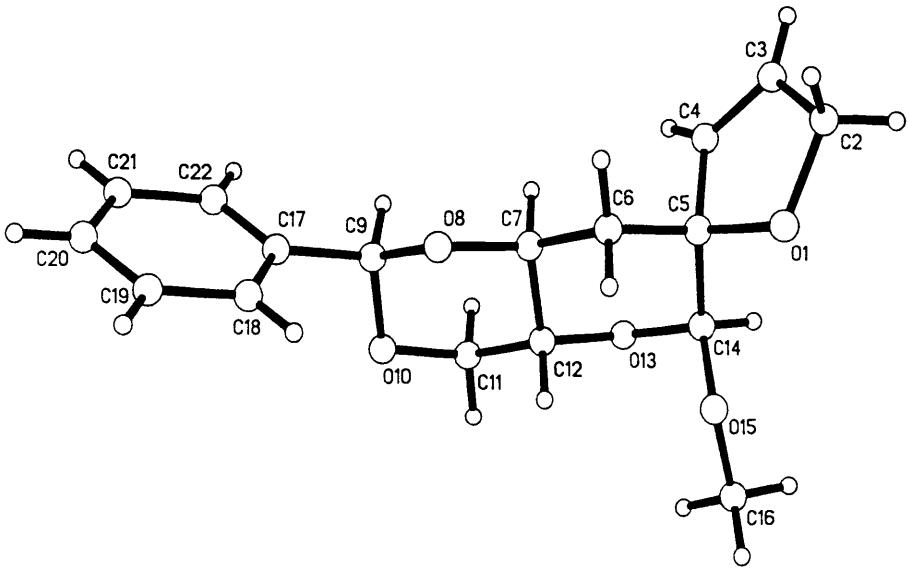
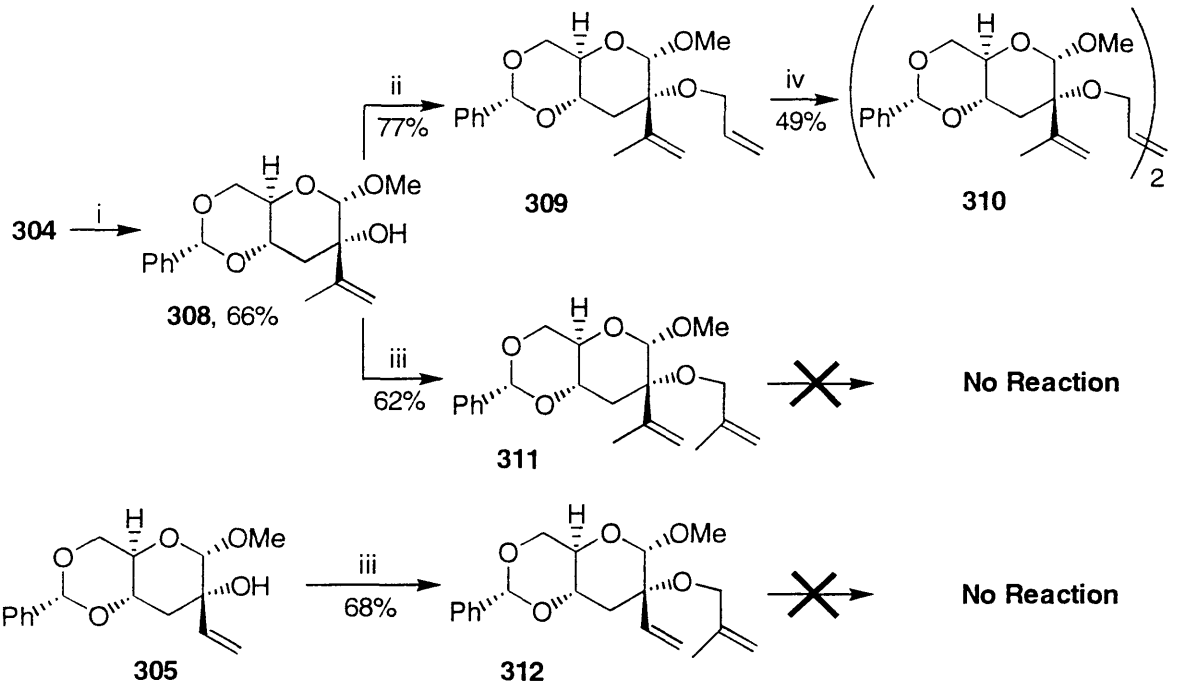



**Figure 6** X-Ray structure of spirocyclic dihydrofuran **307**.

A series of methyl functionalised dienes **309**, **311** and **312** (Scheme 56), were prepared in a similar manner to that described above. Ketone **304** was treated with isopropyl magnesium bromide to afford methyl substituted allylic alcohol **308**. Separate reaction of alcohol **308** with allyl bromide and methallyl chloride afforded dienes **309**

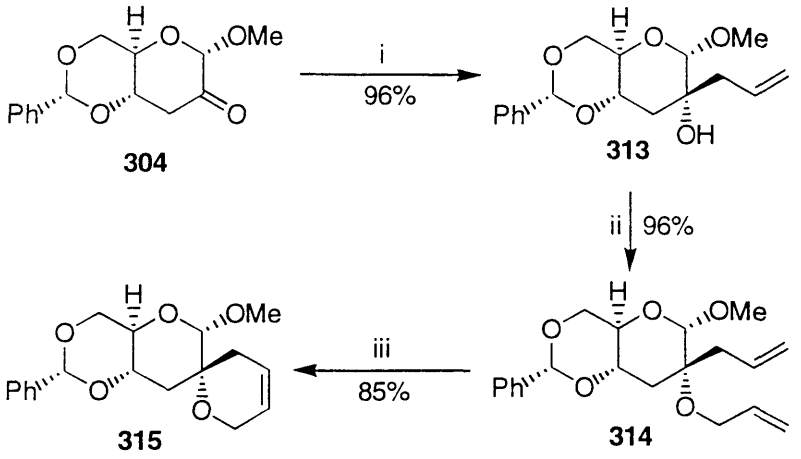
and **311** respectively. The third diene **312**, was prepared by alkylation of allylic alcohol **305** with methallyl chloride. The three tri- and tetrasubstituted dienes **309**, **311** and **312** were treated with Ru catalyst **176b**, however none of the substrates cyclised, with **311** and **312** being quantitatively recovered and diene **309** undergoing an ADMET reaction to afford the dimer **310**, with 23% recovered starting material.




**Scheme 56,** Reagents and Conditions: i, $H_2C=C(CH_3)MgBr$, THF, -78°C then rt 4h; ii, NaH, THF, 0°C, then reflux 2h, then $H_2C=CHCH_2Br$, DMPU, reflux, 4h; iii, NaH, THF, 0°C, then reflux 2h, then $H_2C=C(CH_3)CH_2Cl$, KI, DMPU, reflux, 4h; iv, **176b** (2 mol%), benzene, 60°C, 18h.

The lack of reaction of the tetrasubstituted diene **311** was by no means a surprise, but we did expect at least some ring closure of the trisubstituted dienes **309** and **312**. On reflection, we can assume that the bulk and rigidity of the sugar template reduces the reactivity of the vinyl olefin towards RCM.

Homoallylic alcohol **313** (Scheme 57), was prepared by reaction of ketone **304** with allyl magnesium chloride, and was again the only product isolated from the reaction mixture. Once again this is the expected diastereoisomer if the ketone is to undergo the more favoured axial attack. Alcohol **313** was similarly O-alkylated by reaction with sodium hydride, then allyl bromide to afford diene **314**, which was converted to dihydropyran derivative **315** in excellent yield by RCM.




**Scheme 57,** Reagents and Conditions: i, $H_2C{=}CHCH_2MgCl$, THF, reflux, 4h; ii, NaH, THF, 0°C, then reflux 2h, then $H_2C{=}CHCH_2Br$, DMPU, reflux, 4h; iii, **176b** (2 mol%), benzene, 60°C, 18h.

An X-ray crystal structure (Figure 7) was obtained to once again confirm the configuration at C-2 of dihydropyran derivative **315**.

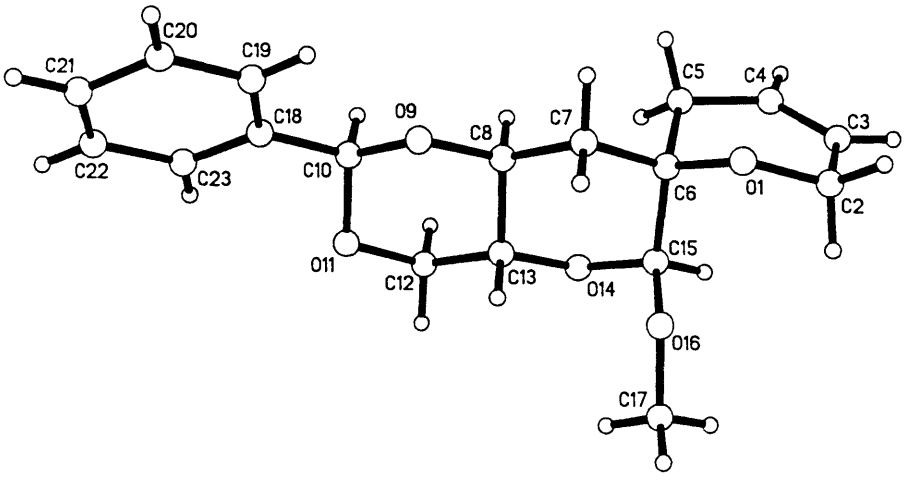
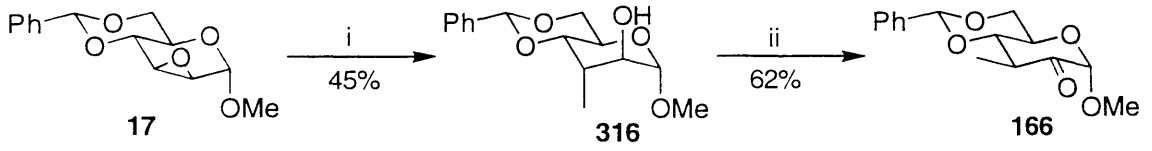


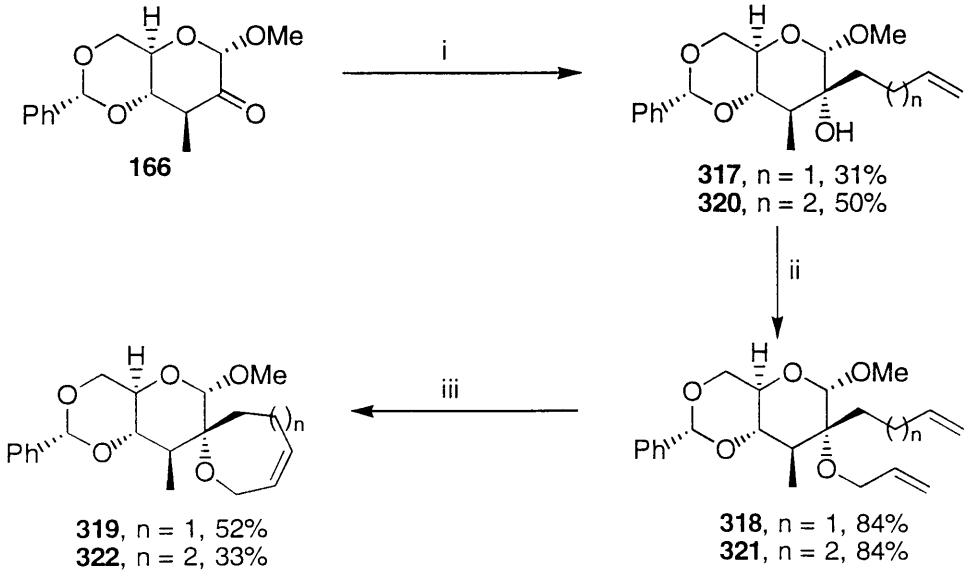

**Figure 7** X-Ray structure of spirocyclic dihydropyran **315**.

In an attempt to extend the scope of the work we modified the sugar moiety by reacting the original epoxide **17** with methyl magnesium chloride to afford methyl alcohol **316** (Scheme 58). Swern oxidation yielded **166**, with epimerisation of the methyl group at C-3 occurring during the basic work up of the reaction.[55]



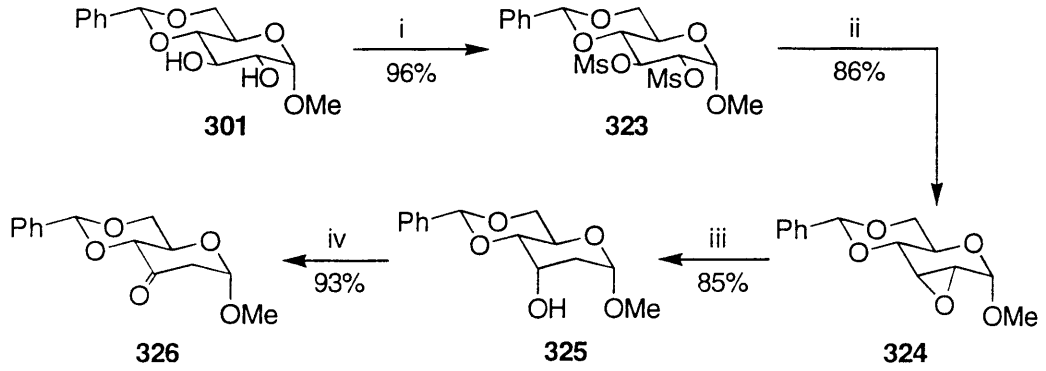

**Scheme 58,** Reagents and Conditions: i, MeMgCl, THF, reflux, 5h; ii, DMSO, $(COCl)_2$, $CH_2Cl_2$, −78°C, then $Et_3N$, 24h

Reaction of freshly prepared butenyl magnesium chloride with ketone **166** resulted in an inseparable mixture of products, the major constituent of which was believed to be a reduced product arising from a hydride reduction of the ketone. However, there is literature precedent stating that 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.[57] In the event, reaction of freshly prepared butenyl magnesium bromide and cerium (III) chloride with ketone **166** afforded alcohol **317** as a significant constituent of the reaction mixture (31%), together with 22% of the same unwanted reduced product and 27% recovered starting material (Scheme 59). Alkylation of the alcohol **317** afforded diene **318**, which was cleanly cyclised by RCM furnishing **319** in 52% yield with 22% recovered starting material. The chain extended olefin **320** was prepared in a similar manner from reaction of pentenyl magnesium bromide with methyl ketone **166** to afford alcohol **320** in 50% yield with 25% recovered starting material and 18% reduced product, and subsequent O-alkylation afforded diene **321**. The RCM reaction was much slower than the previous cases and an increased reaction time and catalyst loading (15 mol%) afforded 8-membered spirocyclic oxacycle **322** in a modest 33% yield with 36% recovered starting material.



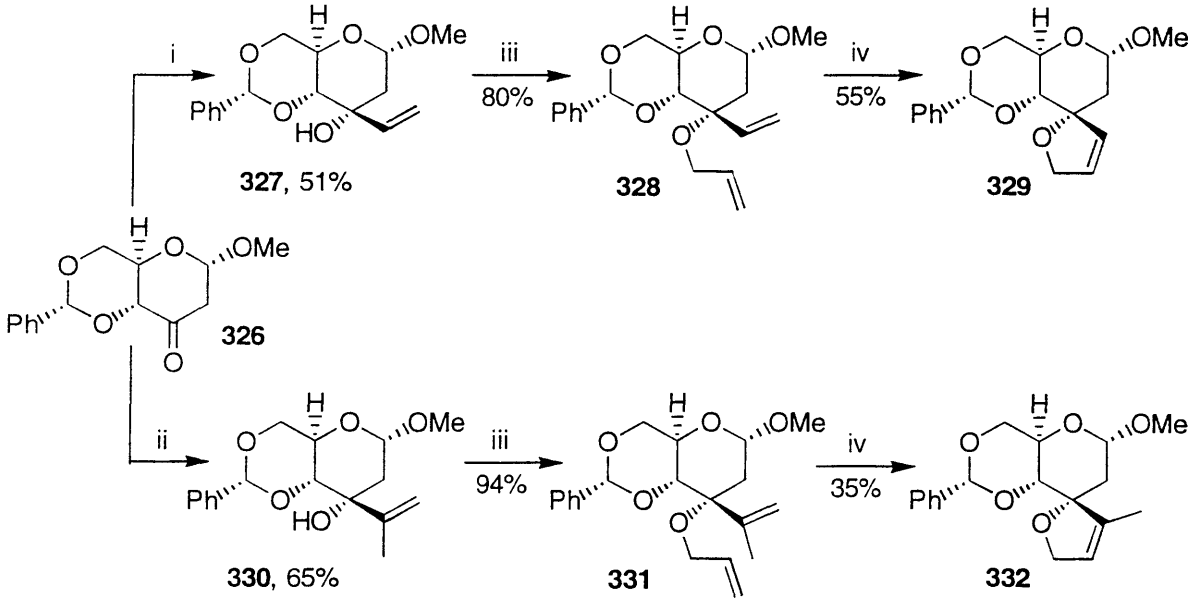

**Scheme 59,** Reagents and Conditions: i, $H_2C{=}CH(CH_2)_nCH_2MgBr.CeCl_3$, $Et_2O$, -40°C, 2h then rt 18h; ii, NaH, THF, 0°C. then reflux 2h, then $H_2C{=}CHCH_2Br$, DMPU, reflux, 4h; iii, **176b** (7-15 mol%), benzene, 60°C, 18h.

To further broaden the scope of the spirocyclic RCM of α-D-glucose derivatives, we prepared C-3 ketone **326** from protected alcohol **301** via four well-documented steps (Scheme 60). Protected diol **301** reacted with mesyl chloride to afford the dimesyl compound **323** in quantitative yield. Reduction of the crude dimesylate afforded the "down-epoxide" **324**,[58] which was ring opened by treatment with LAH. Again the axial alcohol **325** was the only observed product, and this was easily oxidised by Swern protocol to afford C-3 ketone **326**.[59]




**Scheme 60,** Reagents and Conditions: i, MsCl, $CH_2Cl_2$, $NEt_3$, 0°C then rt 18h; ii, MeONa, $CH_2Cl_2$, 4°C, 4d; iii, $LiAlH_4$, THF, 0°C then 4h reflux; iv, DMSO, $(COCl)_2$, $CH_2Cl_2$, -78°C, then $Et_3N$, 24h.

The C-3 ketone **326** was separately alkylated by Grignard addition of vinyl magnesium chloride and isopropyl magnesium bromide to afford allylic alcohols **327** and **330** respectively (Scheme 61). Interestingly the products were both found to arise from equitorial attack of the Grignard species, which is not the common product of such an addition, but is expected when considering the steric factors affecting both faces of the rigid sugar template.[60] The nucleophilic species must attack from an angle of 120° behind the ketone, and approach from the top face is less hindered than the underside of the ketone, which has an axial proton at C-5, and the methoxy and phenyl moieties restricting access. O-Alkylation is effected by treatment with sodium hydride, then allyl bromide to afford dienes **328** and **331** in 51% and 65% yield respectively. RCM of diene **328** proceeds easily furnishing dihydrofuran **329** in fair yield, however the reaction of the analogous trisubstituted diene **331** is not so efficient, but by increasing the concentration of the Ru catalyst and the reaction time, spirocycle **332** was afforded in 35% yield with 51% recovered starting material.




**Scheme 61,** Reagents and Conditions: i, $H_2C$=CHMgCl, THF, reflux, 4h; ii, $H_2C$=C($CH_3$)MgBr, THF, 0°C then rt 18h; iii, NaH, THF, 0°C, then reflux 2h, then $H_2C$=$CHCH_2$Br, DMPU, reflux, 4h; iii, **176b** (2-8 mol%), benzene, 60°C, 18h.

Once again the stereochemistry was confirmed by X-ray crystallography and the X-ray structure of **332** can be seen in Figure 8.

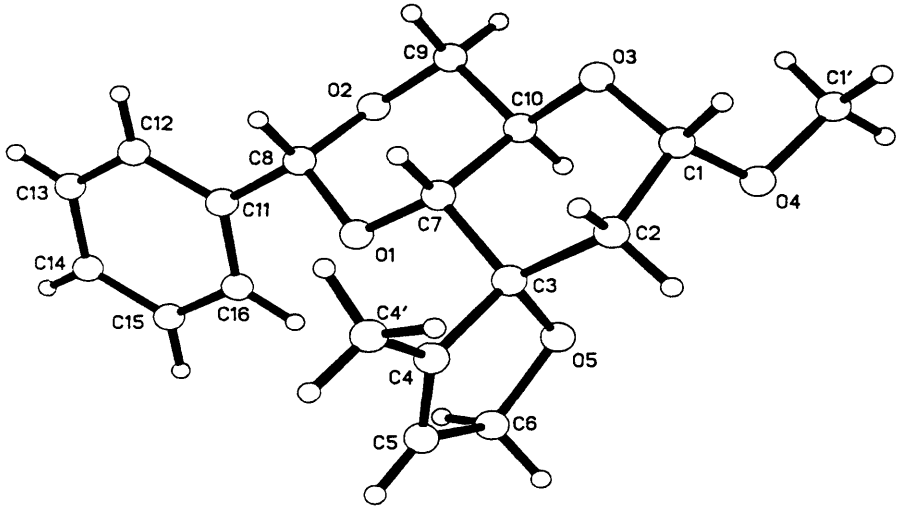
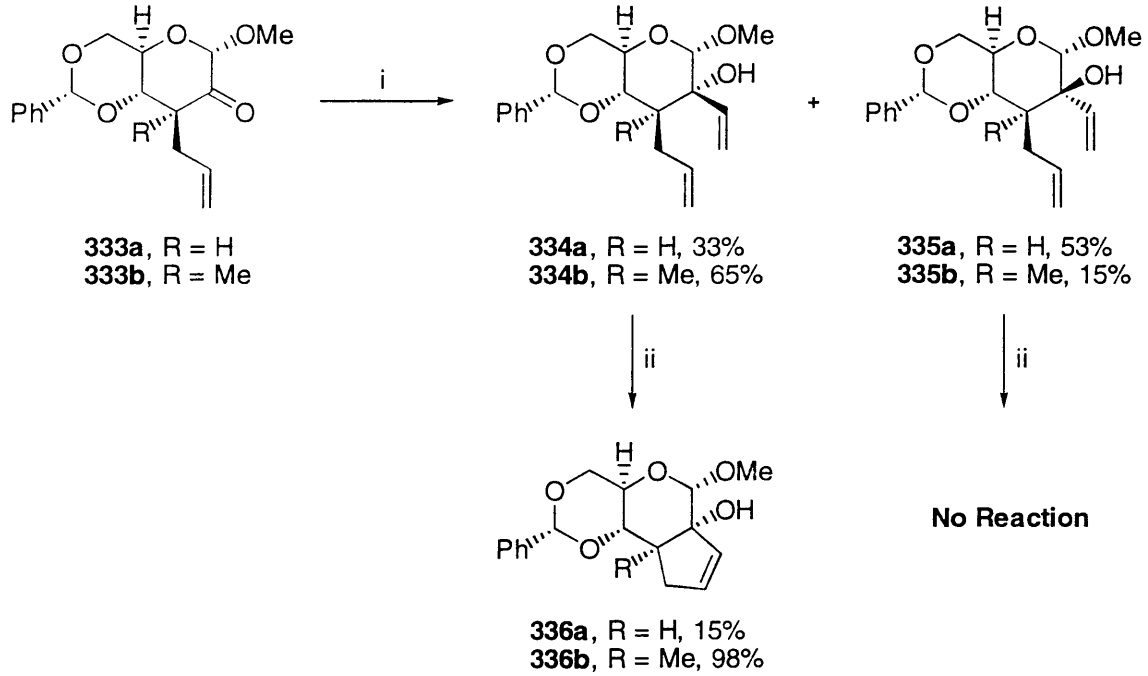



**Figure 8** X-Ray structure of methyl substituted spirocyclic dihydropyran **332.**

A co-worker, Dr David Holt has extended this work by utilising RCM to furnish *cis* and *trans* fused carbocycles.[61] Ketone **333a,b**, again derived from methyl-α-D-glucopyranoside, afforded *cis* and *trans* dienes **334a,b** and **335a,b** on reaction with vinyl magnesium chloride (Scheme 62). *Cis* dienes **334a** and **334b** underwent RCM in 15% and 98% yields to afford cyclopentene derivatives **336a** and **336b** respectively. The improvement in yield when R = Me, is attributed to the Thorpe-Ingold effect,

where the quaternary centre restricts the number of degrees of freedom of the side chain, thus providing some conformational predisposition favouring ring closure.[62] *Trans* dienes **335a** and **335b** would not cyclise under any conditions, probably because of the steric strain associated with the *trans* fused 5-6-ring system of the product.




**333a**, R = H
**333b**, R = Me

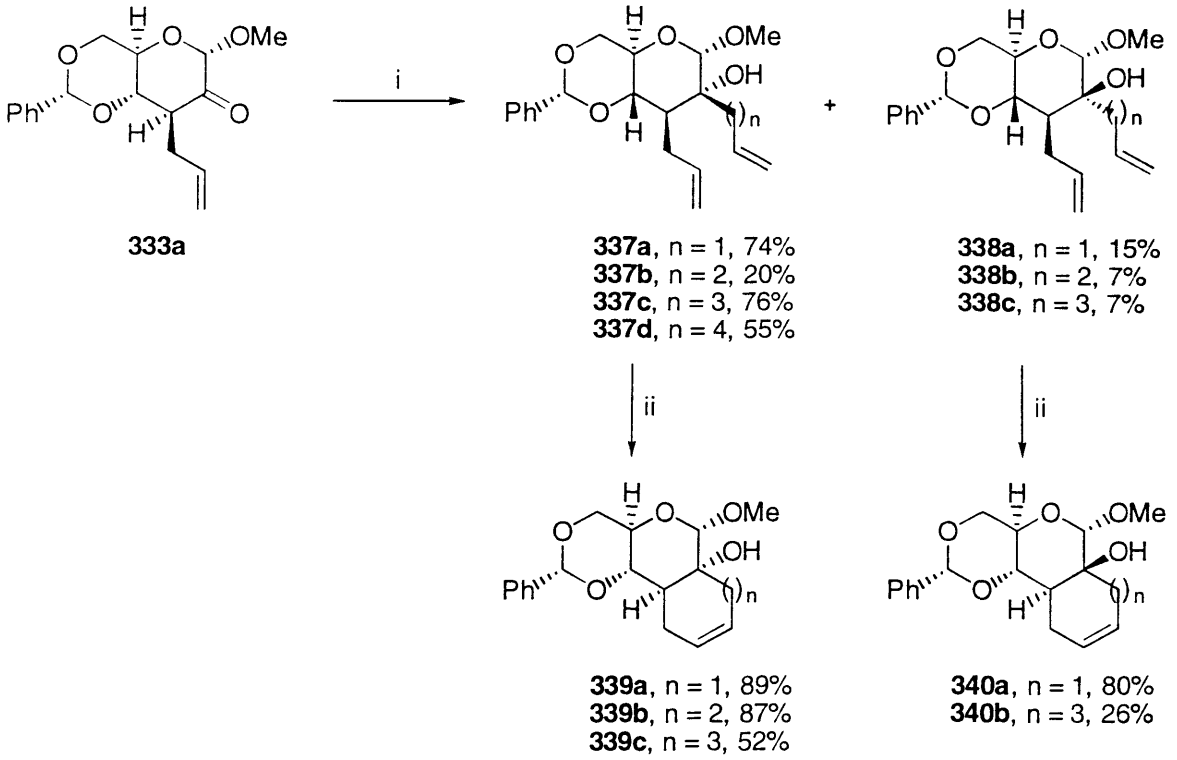
**334a**, R = H, 33%
**334b**, R = Me, 65%

**335a**, R = H, 53%
**335b**, R = Me, 15%

**336a**, R = H, 15%
**336b**, R = Me, 98%

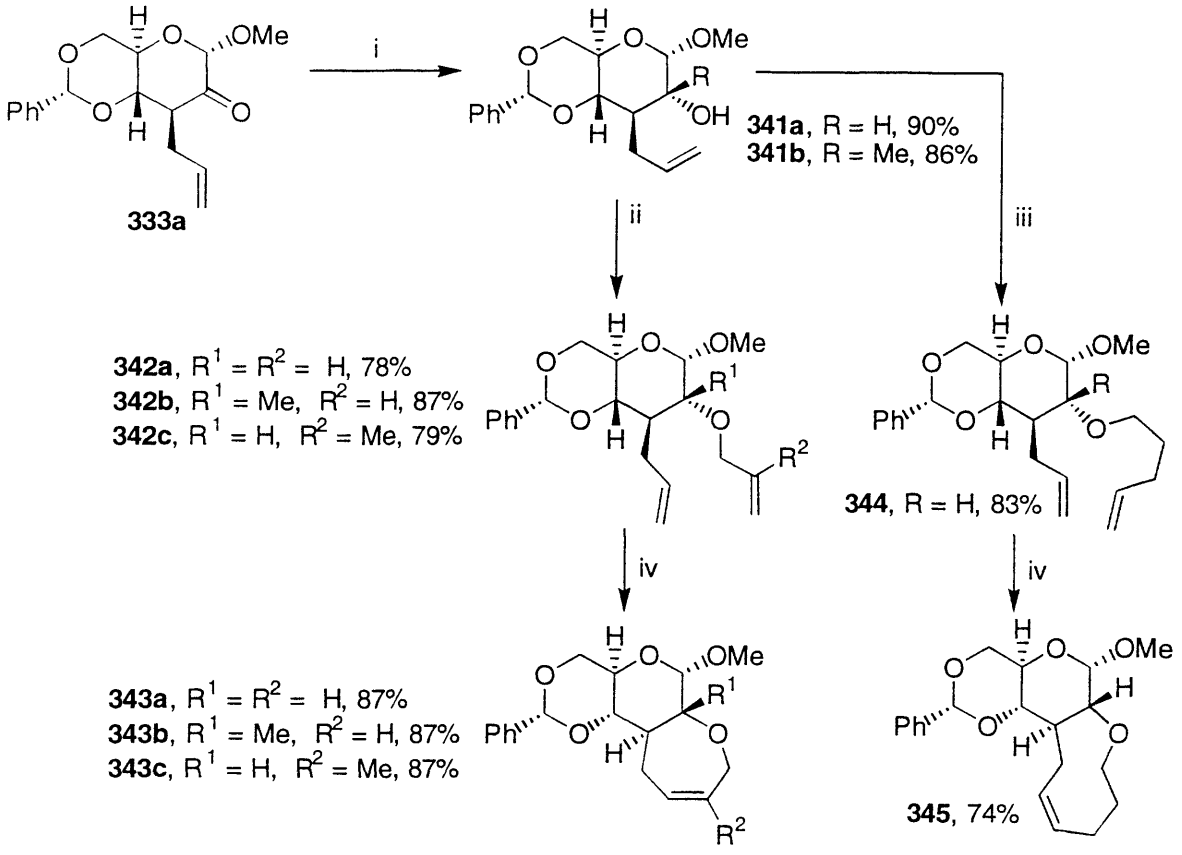
**Scheme 62**, Reagents and Conditions: i, $H_2C$=CHMgCl, THF, reflux, 2 h; ii, **176b** (3 mol%), benzene, 60°C, 48 h for **336a** and 17 h for **336b**.

Dr David Holt was able to demonstrate the general applicability of this reaction by forming 6-, 7- and 8-membered fused carbocyclic analogues (Scheme 63). Reaction of the ketone **333a** with the appropriate Grignard reagent afforded *cis* and *trans* dienes **337a-d** and **338a-c**. RCM of the dienes furnished 6-, 7- and 8-membered carbocycles **339a-c** and **340a,b** in moderate to excellent yield. However, diene **337d** could not be cyclised under any of our RCM conditions indicating an upper limit of an 8-membered ring in this type of reaction. Most of Dr David Holt's products have been analysed by X-ray crystallography, thus confirming the stereochemistry.




**Scheme 63,** Reagents and Conditions: i, $H_2C{=}CHCH_2MgCl$, THF, reflux 2h, for **337a**, $H_2C{=}CH(CH_2)_nMgBr.CeCl_3$, diethyl ether, -40°C, 2 h, for **337b-d**; ii, **176b** (6-9 mol%), benzene, 60-80°C, 41-65 h.

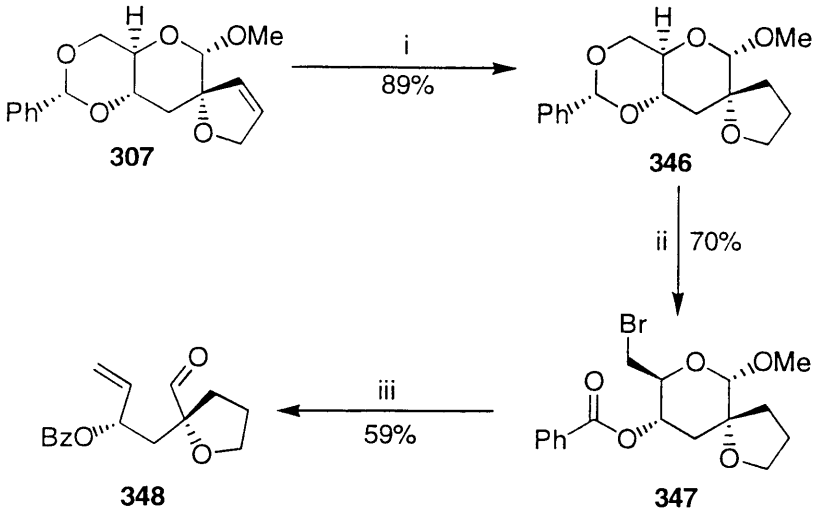
A study into the synthesis of medium ring oxygen-containing heterocyclic annulated sugars, via RCM, was carried out within the research group of our Indian collaborator, Professor Subrata Ghosh, by Jagannath Panda. The addition of lithium aluminium hydride or methyl lithium to ketone **333a** produced alcohols **341a** and **341b** in 90 and 86% yield respectively (Scheme 64). Conversion to the ethers **342a-c** was achieved in 78-87% yield and the three RCM reactions occurred in 87% yield coincidentally, to afford oxepine derivatives **343a-c**. Alcohol **341a** was converted into the ether **344** in 83% yield, which gave the oxo-cyclononene **345** in 74% yield, as a product of RCM.




**Scheme 64,** Reagents and Conditions: i, **341a** - $LiAlH_4$, THF, 0°C, then 3 h reflux; **341b** - MeLi, THF, 0°C, then 6h rt; ii, NaH, THF, HMPA, $H_2C{=}CR^2CH_2Br$, 2h reflux; iii, NaH, THF, HMPA, $H_2C{=}CH(CH_2)_3Br$, 2h reflux; iv, **176b** (4 mol%), benzene, 60°C, 6-14h.

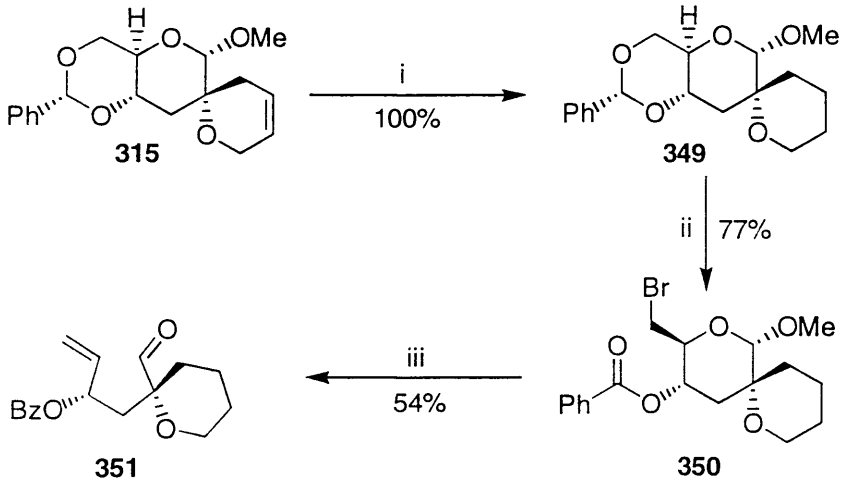
The successful formation of the 9-membered heterocyclic ring **345** is in stark contrast to the failure of RCM in the case of the carbon containing analogue, **337d**. One difference between the two substrates is that in **337d** the chains are *cis* and in **344** they are *trans*. Another reason for 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 the ease in which carbohydrate derived 5-, 6-, 7- and 8-membered spiro-heterocycles are formed by RCM, we turned our attention to fragmenting some of the derivatives to furnish enantiomerically pure oxa-cycles. Reaction of the dihydrofuran carbohydrate derivative **307** with NBS under a variety of conditions resulted in an inseparable mixture of brominated products. We attributed this anomaly to the reaction of the NBS radical species with the allylic position on the dihydrofuran unit. Hydrogenation of **307** furnished tetrahydrofuran derivative **346** quantitatively, and this saturated substrate was effectively brominated with NBS to give bromo ester **347** in 70% yield. Reduction of the brominated sugar **347** with zinc dust afforded chiral fragment **348**, formed by a Vasella type elimination (Scheme 65).




**Scheme 65,** Reagents and conditions: i, $H_2$, MeOH, 5% Pd/C, rt, 18h; ii, NBS, $BaCO_3$, $CHCl_3$, reflux, 18h; iii, Activated Zn, IPA:$H_2O$ (10:1), reflux, 2h.

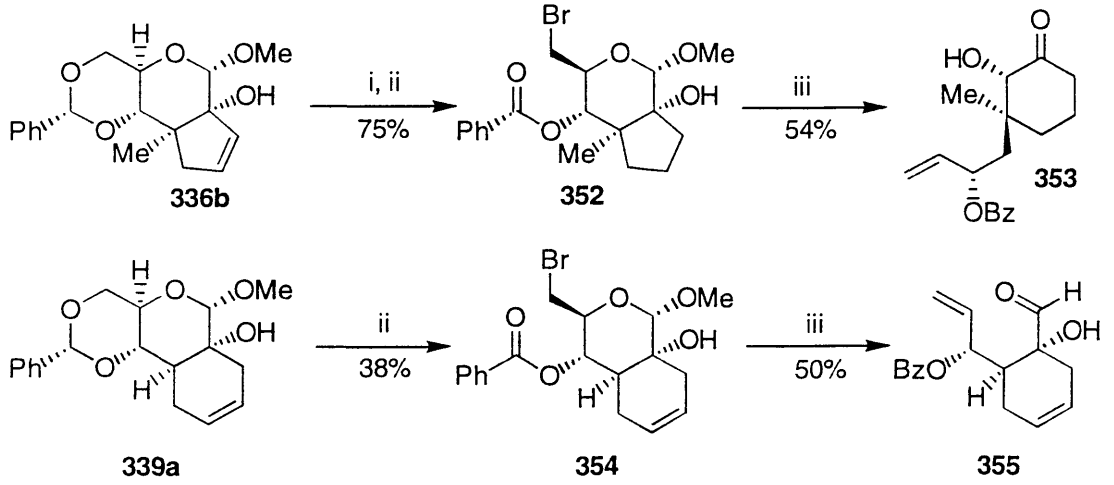
Tetrahydropyran derivative **315** underwent a similar process; reduction of the double bond afforded saturated hexahydropyran derivative **349**, treatment with NBS furnished bromoester **350** which was also fragmented by reduction with zinc dust to afford enantiomerically pure hexahydropyran derivative **351** in good yield (Scheme 66).




**Scheme 66,** Reagents and conditions: i, $H_2$, MeOH, 5% Pd/C, rt, 18h; ii, NBS, $BaCO_3$, $CHCl_3$, reflux, 18h; iii, Activated Zn, IPA:$H_2O$ (10:1), reflux, 2h.

The olefinic and aldehyde moieties of the new chiral fragments **348** and **351** (Scheme 65 and 66), are now poised for a ring closure reaction seen previously in Scheme 12 (Chapter 1). However, attempts to cyclise **348** and **351** to form spirocyclopentane products by $SmI_2$ mediated radical ring closure all failed.

Dr David Holt has also demonstrated the ease in which chiral carbocyclic compounds can be derived from his RCM products. *Cis* fused cyclopentane **336b** was reduced to give a saturated cyclopentane derivative, which reacts with NBS to afford bromoester **352** in 75% yield over both steps (Scheme 67). Reaction with zinc dust gave the surprise enantiomerically pure cyclohexanone product **353**, which is the result of a Lewis acid promoted 1 carbon ring expansion. The cyclohexane carbohydrate derivative **339a** was directly brominated to give **354**, and Vasella elimination gave the expected aldehyde **355** in 50% yield.




**Scheme 67,** 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.

## 2.5.1 Conclusion

We have demonstrated the remarkable stereocontrol afforded when synthesising a variety of acyclic dienes from carbohydrate precursors. We have shown the scope and limitations of the RCM reaction when synthesising a wide range of carbohydrate derived spiro-oxacycles. Two co-workers have also shown the ease in which fused carbocyclic and oxacyclic carbohydrate derivatives can be synthesised by RCM methodology. In an attempt to utilise these cyclic compounds in further synthesis, we have fragmented them to furnish enantiomerically pure, highly functionalised chiral fragments. Although there is room for further investigation, we have demonstrated with a wide variety of examples the wealth of chiral cyclic products available from simple carbohydrate precursors e.g. methyl-α-D-glucose, using RCM.

## 2.6 References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# Chapter 3

# Copper (I) Triflate Catalysed [2+2] Photochemical Ring Closure of Carbohydrate Derivatives

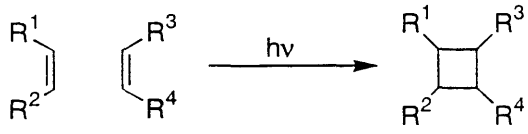
## 3.1 Introduction:

The first [2+2] photocycloaddition reaction was reported by Ciamicin in 1908, when he observed that carvone **356** was converted to carvone camphor **357** on prolonged exposure to "Italian sunlight".[1] The distinctive smell of each isomer led to this discovery, however Buchi confirmed the isomerisation when he reinvestigated the reaction some five decades later.[2]


**356** Carvone

**357** Carvone camphor

Since this discovery the field has expanded very rapidly, and at present there are thousands of examples of light mediated processes including geometric isomerisation, hydrogenation, oxidation and the [2+2] cycloaddition. The [2+2] photocycloaddition reaction is perhaps the most valuable to the synthetic chemist as it is an extremely powerful tool for C-C bond formation. This bond formation is a concerted process where the two $\pi$ bonds from two unconjugated olefin moieties are converted to two new $\sigma$ bonds in a cyclobutane product after absorbing energy from a source of radiation.[3]




The [2+2] ring closure differs from most other common pericyclic reactions, such as the Diels-Alder reaction, in that it is a suprafacially disallowed thermal process. There are two discrete types of [2+2] cycloaddition reactions: the first has already been encountered in chapter 1, (Scheme 7), where a ketene can add to an olefin in an antarafacial ring closure. The other type of [2+2] ring closure is between two simple olefins, or an olefin and an enone, where the system requires excitation by the absorption of photons of light to allow the reaction to proceed.

According to frontier molecular orbital theory, the Highest Occupied Molecular Orbital (HOMO) of one olefin moiety must overlap with the Lowest Unoccupied Molecular Orbital (LUMO) of the other for the reaction to take place in a suprafacial manner. Figure 9 illustrates the HOMO and LUMO of two ethene molecules in their unexcited state, and in this case the orbitals cannot overlap as the two left-hand lobes are of opposing symmetry.

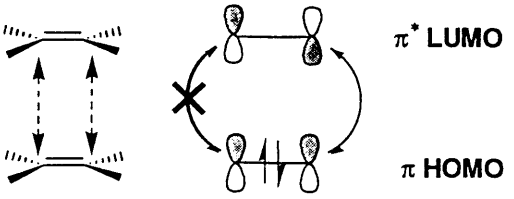



**Figure 9**

However upon the excitation of an electron from a $\pi$ to a $\pi^*$ orbital of one olefin moiety (Figure 10), by the absorption of energy, the lobes of the HOMO and LUMO from the separate olefins can now overlap. The two overlapping orbitals are $\pi^*$ orbitals which results in the breaking of the $\pi$ bonds whilst forming new $\sigma$ bonds in a concerted manner.

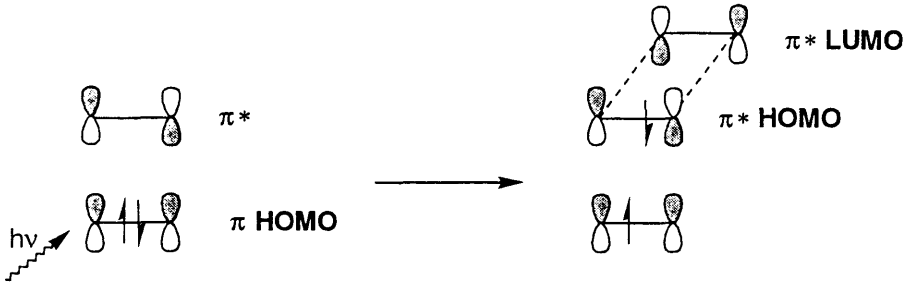



**Figure 10**

The most common [2+2] photocycloaddition reaction occurs when the LUMO of an olefin can overlap with the HOMO of an excited enone. The excited enone is more stable than an excited olefin, and can therefore react more easily, such as the previous case of carvone isomerising to carvone camphor. Typically alkenes are transparent in the spectroscopic region where enones absorb light energy, so for a [2+2] cycloaddition between two simple olefin moieties, it is necessary to add an extra activating component to the reaction mixture, thus changing the energy absorbing properties of the alkene.[4]

## 3.2 Homogeneous Transition Metal Catalysed Photochemical Cycloaddition Reactions

For many years it has been known that a variety of metals interact with a multitude of substrates and alter their intrinsic light absorption properties. Two classic cases are the importance of magnesium in photosynthesis and the role that silver plays in many photographic processes. But perhaps of more interest to the organic chemist are the interactions of metals with organic substrates within a homogeneous solution. For example many transition metal catalysts are known to promote *cis-trans* photoisomerisation of C-C double bonds.[5] In this chapter we are examining [2+2] photocycloaddition reactions and indeed, the homogeneous transition metal catalyst plays an important role in this type of reaction.

The inherent orbital properties of transition metals allow them to co-ordinate to a number of different species, and in many cases the resulting complex has different properties than any of its parts. An example of this phenomenon affecting the photochemical properties of a substrate can be seen in Figure 11. The reaction where norbornene **358** is dimerised to give unsaturated products **359a** and **359b** in the presence of copper (I) bromide was proposed by Trecker, Henry and McKeown in 1965 and was the first example of a transition metal catalysed photocycloaddition of a monoene. The adjacent UV spectrum illustrates how an ethereal solution of copper (I) bromide and the norbornene (NB) absorbs light at around 240nm, whereas the separate components are effectively transparent in this region. The absorption of light results in excitation of an electron within the olefin moiety, allowing the photocycloaddition to take place.[6]

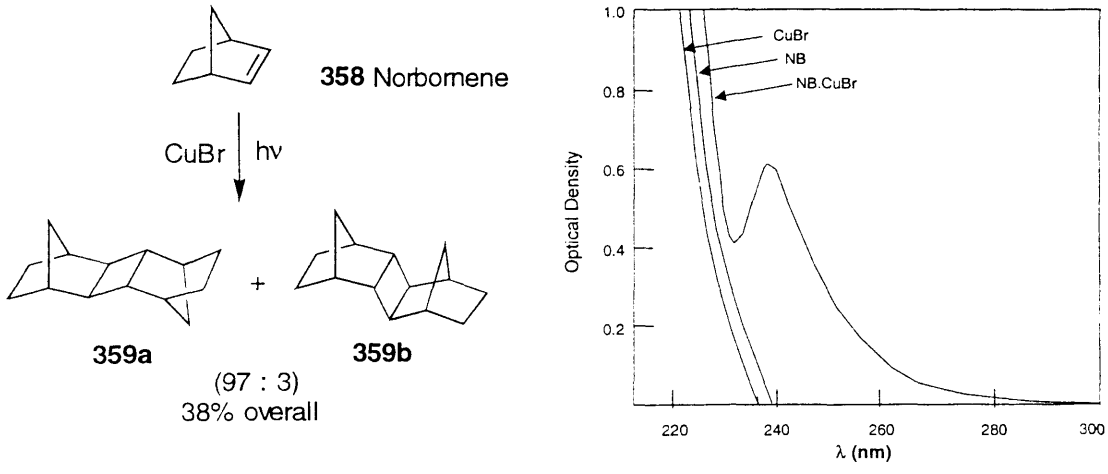
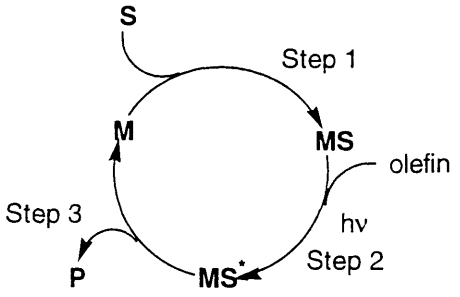



**Figure 11**

This activation process is catalytic with respect to the transition metal and Scheme 68 illustrates the cycle:




**Scheme 68**

The three steps involved are quite straightforward:

Step 1. The substrate(s) **S** $\pi$ bonds co-ordinate to the metal **M** to give the homogeneous complex **MS.**

Step 2. The co-ordinated complex **MS** absorbs hv to give the excited state species **MS***

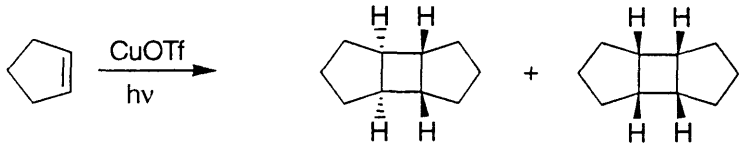
Step 3. The excited substrate cyclises in an intramolecular reaction, or with a second olefin to give the product **P** which can no longer co-ordinate to **M** thus allowing it to rejoin and complete the catalytic cycle.

The overall process is very fast and the actual mechanistic details are not fully understood, however when the radiation source is removed from the reaction, the whole cycle stops.[5]

### 3.2.1 Copper (I) Triflate Catalysed [2+2] Photocyclisation Reactions

Many transition metals catalyse the inter and intramolecular [2+2] photocyclisations, although copper (I) salts and in particular copper (I) triflate are more successful than most. In fact, when copper triflate is used as a catalyst the above reaction (Figure 11) proceeds to give a yield of 88%, more than double the yield obtained when CuBr is used as catalyst.[7] Another major advantage of using CuOTf is illustrated below where copper triflate catalyses the photodimerisation of cyclopentene **360** to give *trans* fused and *cis* fused products **361a** and **361b** in 32% yield overall.

When copper bromide or copper chloride are used the reaction does not proceed and the starting material is recovered.

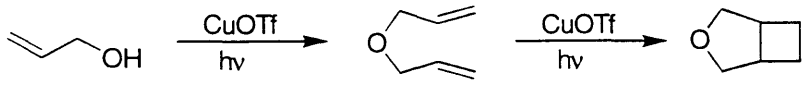



**360** **361a**, 30% **361b**, 2%

The reason for the improvement in efficiency of the catalyst can be attributed to the ease of dissociation of the counter ion. The halide counter ions tend to compete with the alkene for co-ordination with the copper, thus reducing the number of olefin moieties the copper can co-ordinate to, the copper triflate however can dissociate more easily, due to the stability of the counter ion, thus allowing co-ordination of up to four Cu-alkene bonds.

### 3.2.2 Intramolecular [2+2] Photocycloaddition Reactions

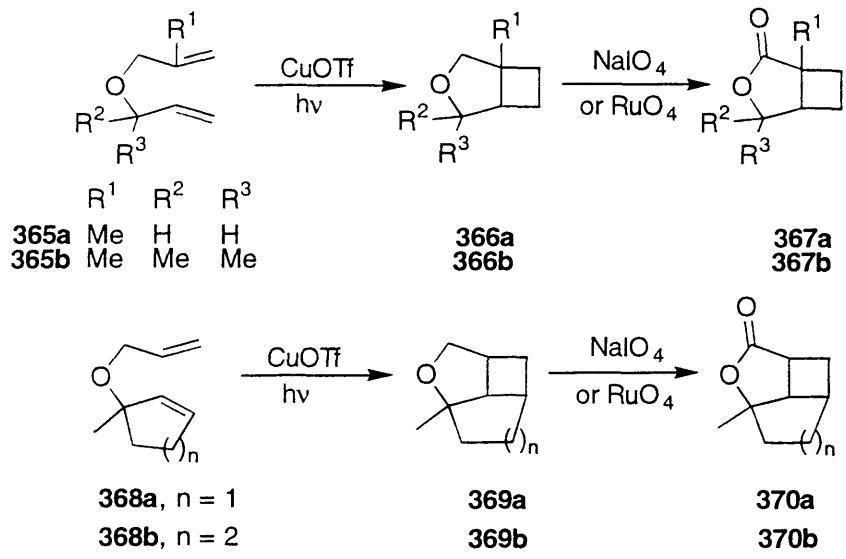
A serendipitous result, in this work by Evers and Mackor yielded the first photocyclisation of two acyclic C-C double bonds (Scheme 69).[8] An attempt to dimerise allyl alcohol **362** resulted in a light mediated displacement reaction giving diallyl ether **363**, which consequentially underwent a copper triflate catalysed intramolecular [2+2] photocycloaddition to furnish bicycle **364**.




**362** **363** **364**

**Scheme 69**

The synthetic utility and generality of this process was illustrated by Salomon and Ghosh, when they synthesised a wide range of bicyclic and tricyclic lactones (Scheme 70).[5] A number of alkyl substituted cyclic and acyclic diallyl ethers **365a,b** and **368a,b** were irradiated at 254nm in the presence of copper triflate to give bicycles **366a,b** and tricycles **369a,b** respectively. These cyclic products were all selectively oxidised with $NaIO_4$ or $RuO_4$ to give bi/tri cyclic lactones **367a,b** and **370a,b**.

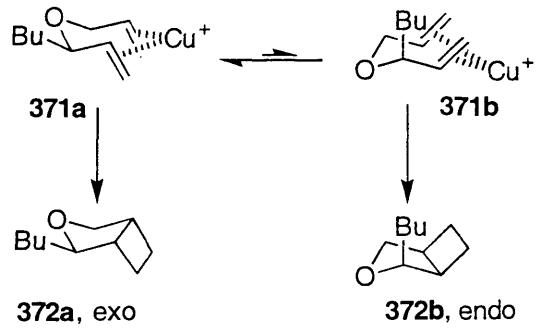



| | $R^1$ | $R^2$ | $R^3$ | | |
|---|---|---|---|---|---|
| **365a** | Me | H | H | **366a** | **367a** |
| **365b** | Me | Me | Me | **366b** | **367b** |

**368a**, n = 1 **369a** **370a**
**368b**, n = 2 **369b** **370b**

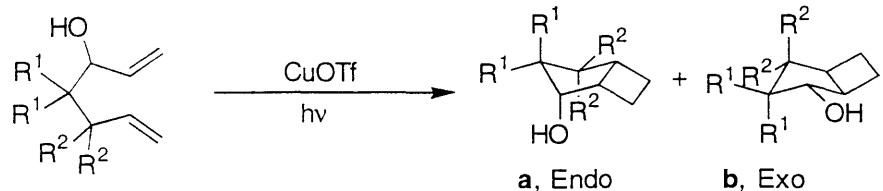
**Scheme 70**

A degree of stereocontrol was observed when using bulky side chains, for example butyl substituted 1,6 diene **371** (Scheme 71). In this case the transition state of the ring closure dictates the stereocontrol of the reaction. A pseudo chair type transition state, with the two olefin moieties co-ordinated to the copper can exist in two conformations **371a** or **371b**. The bulky alkyl side chain will be favoured in an equatorial position. This results in the thermodynamically preferred exo epimer **372a** being formed exclusively in preference to the endo **372b**.




**Scheme 71**

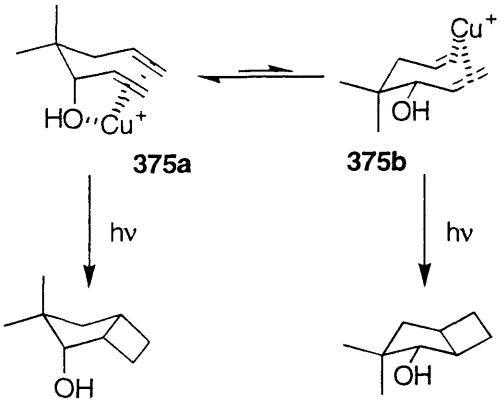
An extension of this work by Salomon and Ghosh that utilises the CuOTf catalysed photocyclisation to afford bicyclic carbocycles, has also been reported. Again [2+2] photocyclisation of dienes **373**, **375**, and **377** results in bicyclic heptan-2-ols **374**, **376** and **378** respectively.[9]




**373**, $R^1$ = H, $R^2$ = H.
**375**, $R^1$ = Me, $R^2$ = H.
**377**, $R^1$ = H, $R^2$ = Me.

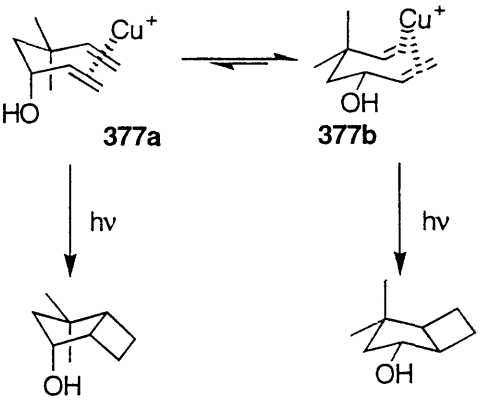
| | **a**, Endo | | **b**, Exo |
|---|---|---|---|
| **374**, | 9 | : | 1 |
| **376**, | 9 | : | 1 |
| **378**, | 3 | : | 4 |

In contrast to the previous examples, the reaction conditions for the ring closure of **373** and **375** favour the formation of the thermodynamically less stable endo epimer products **374** and **375** respectively. This selectivity arises from the copper (I) acting preferentially as a tridentate ligand, co-ordinating to the hydroxyl group and the alkene moieties, as illustrated in Scheme 72a. This results in a shift in the equilibrium, giving an excess of the endo product **376a**.




**376a** Endo 9 : 1 Exo **376b**

**Scheme 72a**



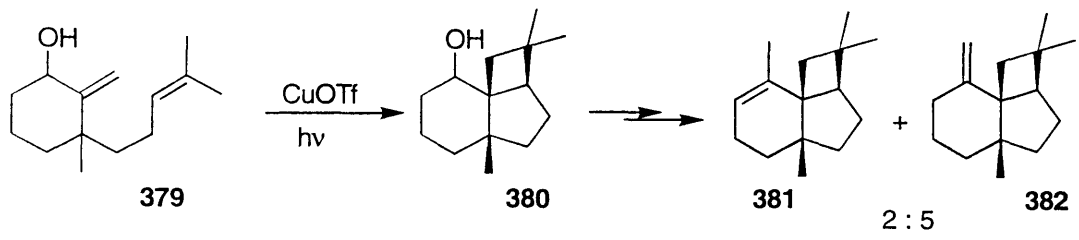

**378a** Endo 3 : 4 Exo **378b**

**Scheme 72b**

Scheme 72b reinforces this reasoning, illustrating the endo:exo preference obtained on cyclisation of **377**. In this example the axial methyl group sterically hinders the co-ordination of the copper (I) to the hydroxyl group resulting in a slight excess of the thermodynamically favoured exo epimer **378b**.

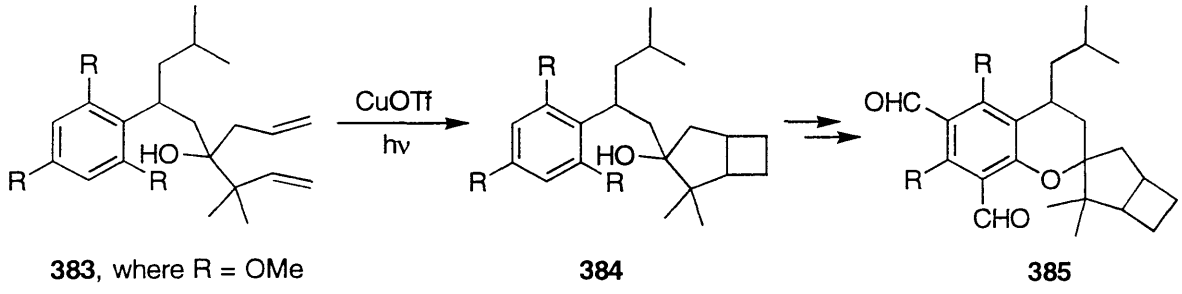
### 3.2.3 Natural Product Synthesis using Cu (I) Catalysed Photochemical Ring Closure

The above methodology has also been utilised to synthesise natural products, for example the sesquiterpenes α and β panasinsene **381** and **382**, extracts from root ginger, are derived from cyclohexanol **379** (Scheme 73). Intramolecular photocycloaddition of **379** furnishes tricycle **380** in 55% yield; this cycloaddition is facially selective giving only the *cis* stereochemistry. Cyclic alcohol **380** is a mixture of diasteroisomers, and the authors conclude that the hydroxyl group does not co-ordinate to the copper during the ring closure to obtain this stereochemistry.[10] Further oxidation followed by alkylation and dehydration led to **381** and **382** in a 5:2 ratio in 50% yield overall from **380**.




**Scheme 73**

Salomon *et al.* disproved the structure of putative (±) robustadial sesquiterpene phenols such as **385** (Scheme 74). Copper catalysed [2+2] photocyclisation of **383** furnished bicyclo [3.2.0] heptyl ring system **384** in 75% yield; further ring closure followed by formylation gave three of the four possible diastereoisomers of **385**. None of the derivatives corresponded to the natural products, which have subsequently been proven to have a bicyclo [3.1.1] heptylpinane ring system.[11]

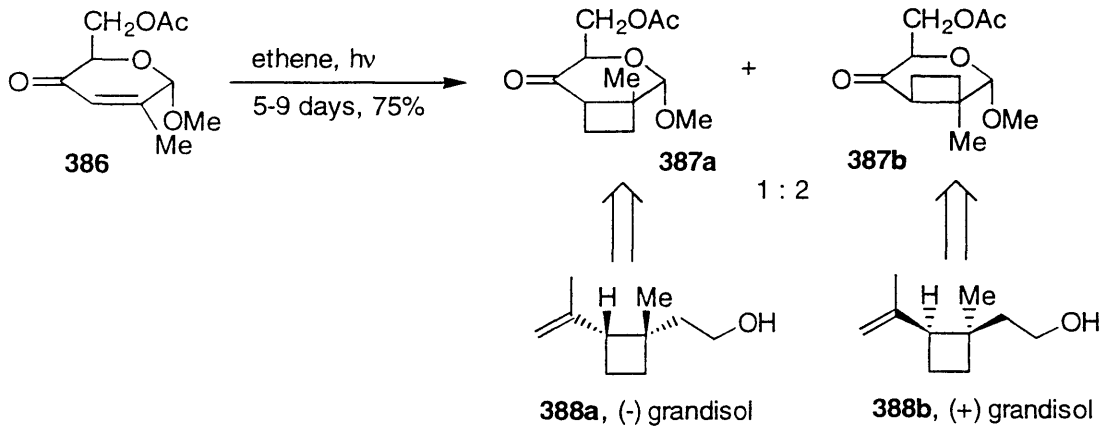



**383**, where R = OMe **384** **385**

**Scheme 74**

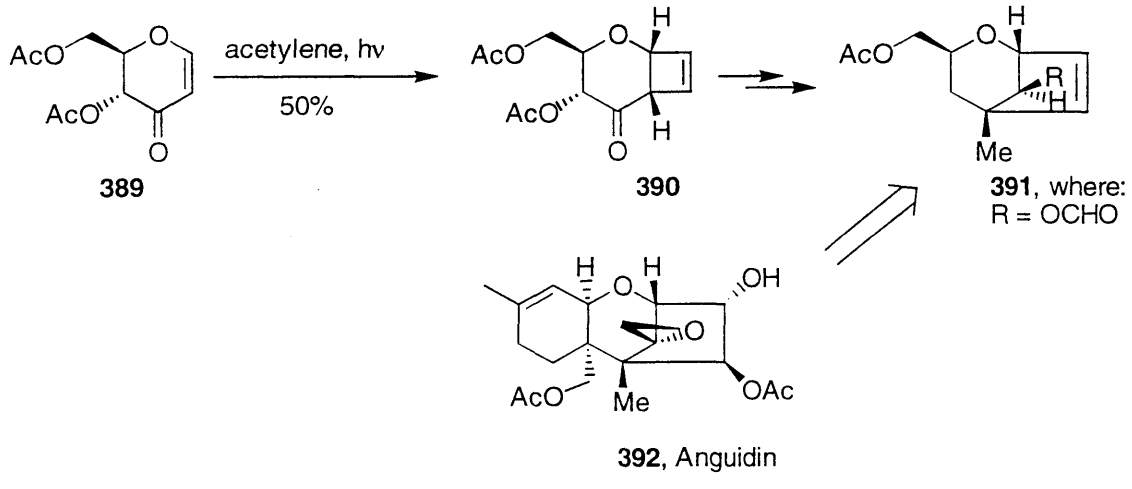
## 3.3 [2+2] Photocycloaddition Reactions of Carbohydrate Derivatives

Light mediated [2+2] photocycloaddition reactions have been used extensively in the synthesis of natural products,[12] however there are few examples of their utility in reactions involving carbohydrates. Fraser-Reid and co-workers successfully prepared the two isomers **387a** and **387b** (Scheme 75) from the intermolecular [2+2] photoaddition of ethene to 2,3-dideoxy-2-C-methyl-α-D-glycero-hex-2-enopyranosid-4-ulose **386**. Each diastereoisomer represents a synthetic building block for the naturally occurring pheromone (-) grandisol **388a** and its enantiomer **388b**.[13]



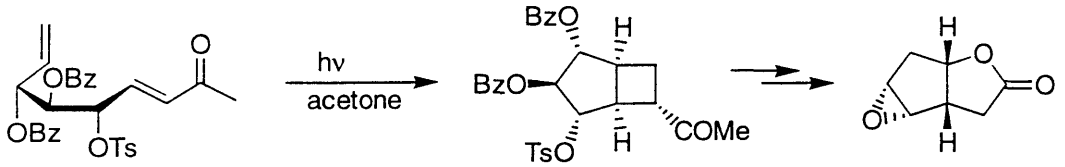

**Scheme 75**

Another example of intermolecular [2+2] photocycloaddition to a sugar derived enone was proposed by Fetizon *et al.* in their attempts to synthesise a class of natural products known as trichothecenes. This diverse family of mycotoxins exhibits a wide range of biological activity including anticancer activity. Photocycloaddition of acetylene to enone **389** in acetone gave the cyclobutene adduct **390** in 50% yield (Scheme 76). Deacetoxylation followed by alkylation with methyl lithium then ring expansion yielded **391** which is a 'chiron' with correct stereochemistry for the B and C rings of anguidin **392** and other related trichothecenes.[14] Somewhat surprisingly, in this reaction sequence, cyclobutene **390**, is the only diastereoisomer reported, although there is no rational explanation for the observed stereochemistry.




**Scheme 76**

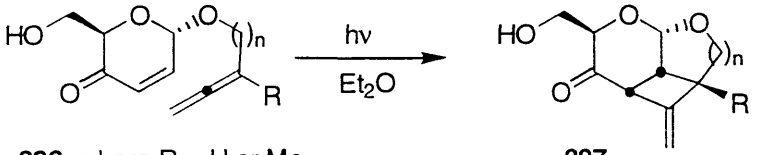
An elegant synthesis of epoxy lactone **395** (Scheme 77), a synthetic precursor to several prostaglandins was reported by Ferrier and co-workers. This example represents the first intramolecular [2+2] photocycloaddition, between the olefin and enone moieties of sugar fragment **393** to furnish chiral bicyclic ketone **394**. Once again in this ring closure, only one diastereoisomer is isolated, in this case however, this is because the new fused 4-membered ring is effectively *trans* to the bulky tosyl and benzoyl groups on adjacent carbons.[15] The bicyclic compound is again manipulated to give chiral epoxy lactone **395** in five further steps.




**393** **394** **395**

**Scheme 77**

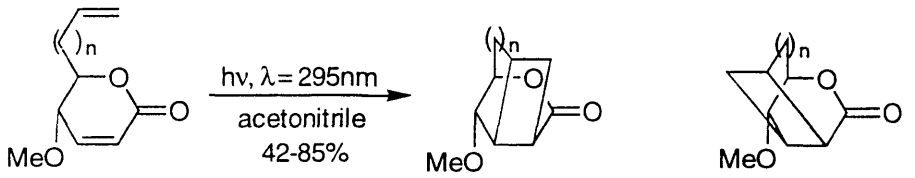
A report by Tenaglia and Barillé, illustrates how an allene moiety can add to the enone **396** derived from D-glucose, via intramolecular ring closure, in a regiospecific and stereoselective manner. The allene moiety will only cyclise to give the terminal olefin, which is the exo product, and the stereoselectivity arises from the tether linking the olefin to the α face of the sugar resulting in only one observed diastereoisomer **397**.[16]




**396**, where R = H or Me and n = 1 or 2.

**397**

Gómez and López have utilised the [2+2] photocycloaddition reaction to create a range of carbocyclic lactones such as **399a** and **399b**, from a variety of lactones derived from carbohydrates. The intramolecular ring closure of **398**, gives two regioisomers, where the olefin adds 'head to head' with the enone to give **399a**, or 'head to tail' with the enone resulting in **399b**. The ratio of these regioisomers depends largely on the length of the olefinic tether.[17]



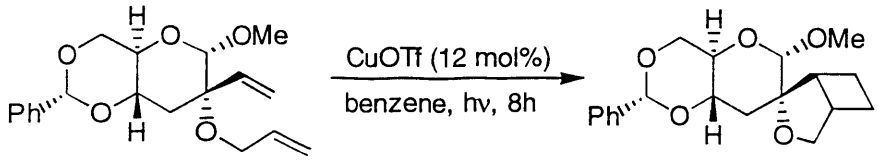

**398**, where n= 0,1 or 2 **399a**, major **399b**, minor

## 3.4 Summary

All of the carbohydrate based ring closure reactions described above, have been the addition of an olefin to an excited enone. As stated earlier, enone excitation is possible under UV conditions, and therefore the reactions described thus far do not need to be catalysed. We wanted to extend the versatility of the [2+2] cycloaddition reaction within the field of carbohydrate chemistry to include simple olefin-olefin cyclisations using copper (I) triflate to catalyse the reaction. The results of our study are reported below.

## 3.5 Results and Discussion[18]

As a continuation of our studies into new methods for carbohydrate annulation, we utilised some of the dienes prepared for ring closing metathesis, in the previous chapter, to test the viability of the copper (I) triflate mediated [2+2] photocyclisation of sugar derivatives. The carbohydrate derived diene **306** was prepared by methods described in the previous chapter, and was dissolved in a 12 mol% CuOTf solution in diethyl ether, and irradiated at 254nm for 8 hours in a water cooled quartz tube in a Rayonet® photochemical reactor. A crude NMR of the reaction mixture showed a complicated mixture of deprotected fragments of the substrate **306**. On repeating the experiment under the same conditions, using benzene as the solvent instead of ether, the spirocyclic ether product **400** was obtained exclusively in 62% yield, with 14% recovered starting material.




**306** **400**

This result was somewhat surprising, as there are 2 possible diastereoisomers that could be formed in this reaction, depending on the facial selectivity of the ring closure. However, we could find no trace of the other diastereoisomer and analysis of the crude reaction mixture with $^{1}H$ and $^{13}C$ NMR and HPLC indicated that the only components in the mixture were the isolated product **400** and unreacted starting material. The product **400** was a white crystalline solid and was analysed by X-Ray crystallography (Figure 12), and the configuration of the unknown stereogenic centres were confirmed by comparison with the unchanged chiral centres.

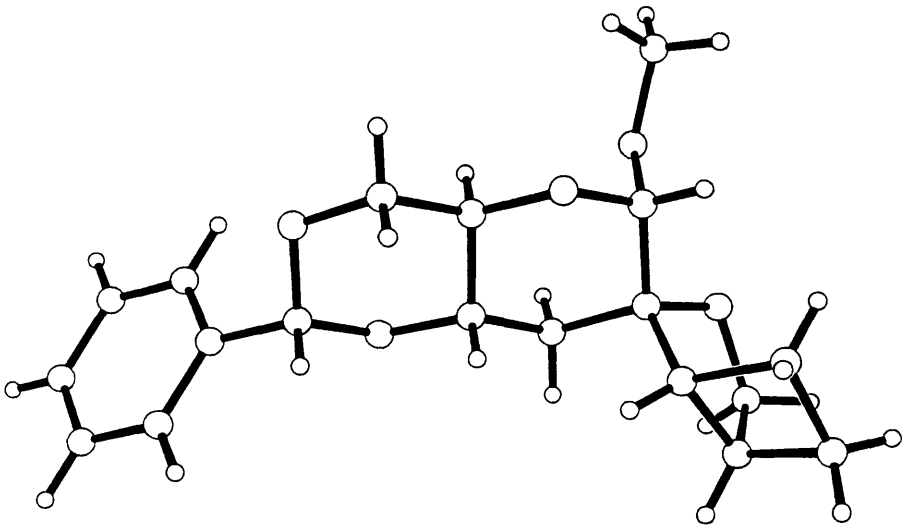
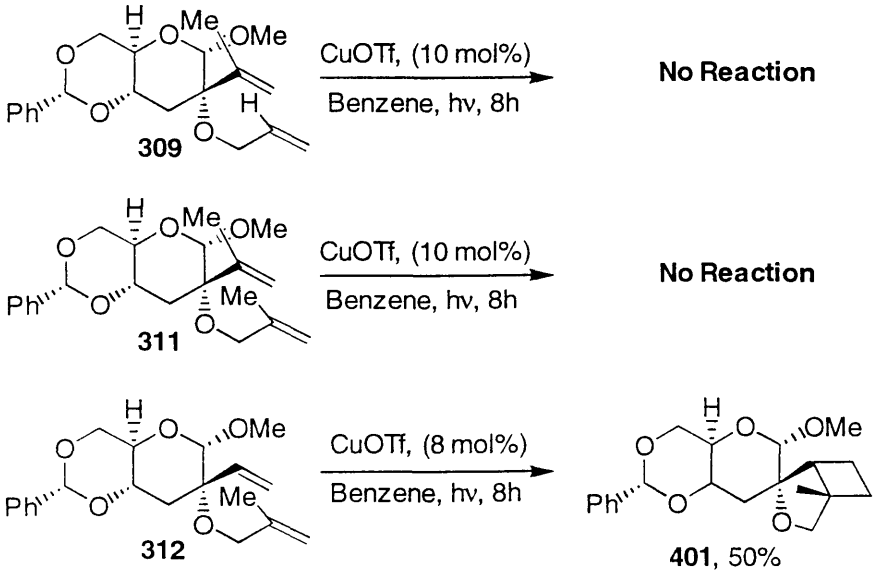


**Figure 12**, X-Ray structure of spirocyclic ether **400**.

The methyl substituted dienes **309**, **311** and **312**, prepared by the methods described in chapter 2 were all irradiated under the same photocyclisation reaction conditions. Alkyl substituted dienes **309** and **311** were recovered from the reaction mixture in quantitative yield. The probable reason for these reactions not proceeding is the presence of the methyl group on the rigid vinyl olefin. The extra bulk probably restricts the rotation, thus preventing the vinyl olefin occupying a position where it may react with the somewhat 'freer' ether tethered olefin.



The analogous alkyl substituted diene **312** cyclised in the presence of copper triflate to furnish the spirocyclic ether **401** in 50% yield with 29% recovered starting material. The isolated product was once again the only observed product in the reaction mixture, and again on purification and recrystallisation, the configuration of **401** was confirmed by X-Ray crystallography (Figure 13).

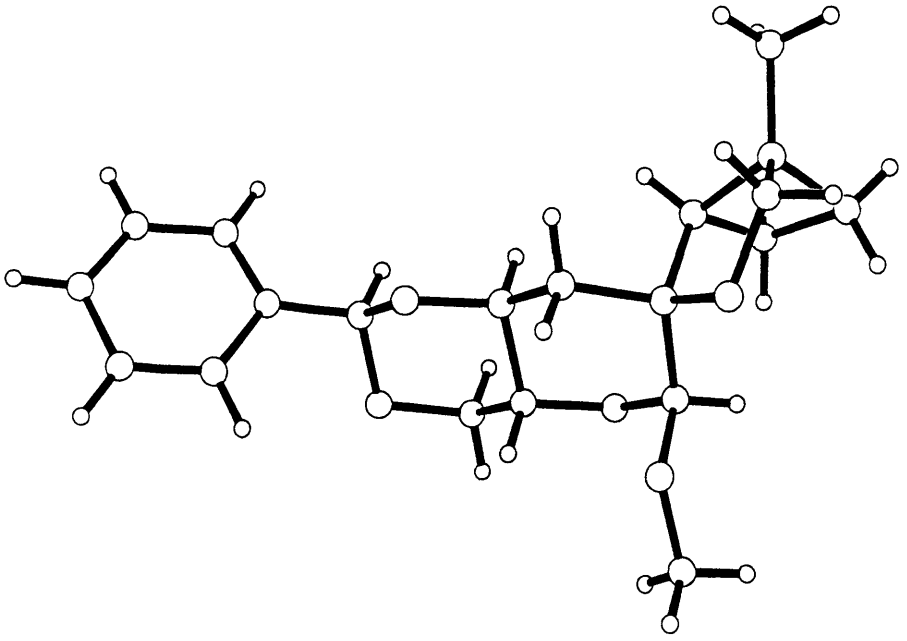
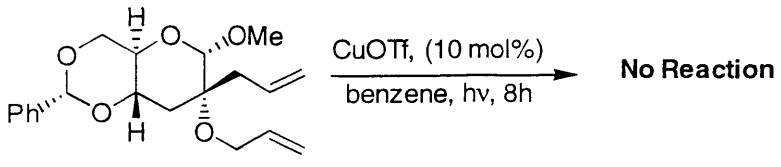


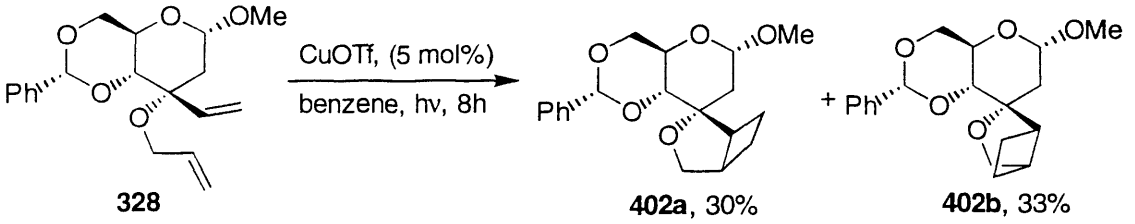
**Figure 13** X-Ray crystal structure of spirocyclic ether **401**

Attempts to cyclise a 6-membered spirocycle from 1,7-diene **314** were unsuccessful, and the starting material was again recovered virtually quantitatively. In this case, we believe that the additional degrees of freedom afforded by the extended olefin chain, make it less likely that the $Cu^{+}$ will bind to both olefin moieties simultaneously, which is a requirement of this type of reaction.[5] Although there are many examples of ring closure reactions involving 1,6-diene substrates and 1,7-enones within the literature, there is no precedent for the cyclisation of the 1,7-dienes.



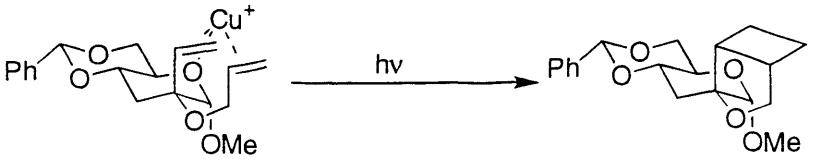

**314**

When C-3 diene **328** was subjected to the same photocyclisation conditions as described above, the two diastereomeric products **402a** and **402b** were formed in an approximately 1:1 ratio in 63% yield overall. The diastereoisomers were separated by column chromatography and their respective configurations were confirmed by nOe comparison.




**328** **402a**, 30% **402b**, 33%

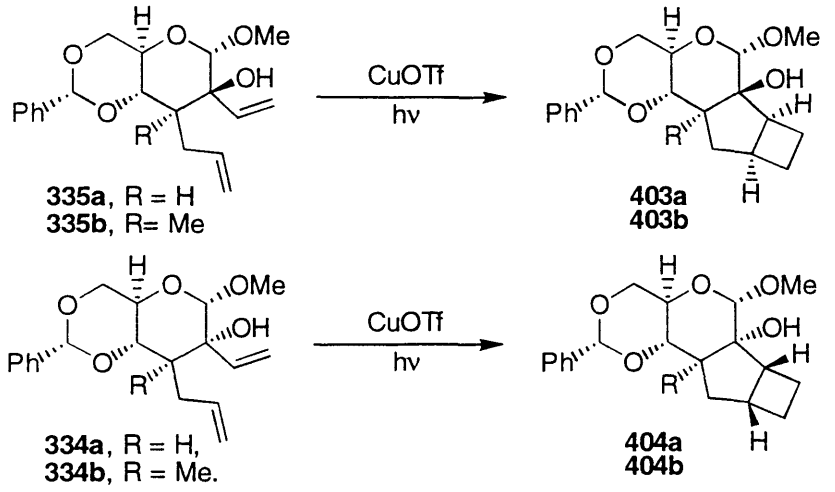
In order to rationalise the stereochemical outcome of the above reactions, we returned to the work of Salomon and Ghosh[8] (Scheme 72a), where they obtain an excess of the thermodynamically less favoured product due to tridentate co-ordination of the $Cu^+$ catalyst to a local hydroxyl group as well as the olefin moieties involved in the ring closure. Applying these arguments to our system, we hypothesise that the copper co-ordinates to the anomeric oxygen of diene **306** as well as the olefins. This preferred tridentate intermediate can absorb hv and the [2+2] photocyclisation occurs to give the observed product **400**.




**306** **400**

This hypothesis is reinforced when considering the lack of selectivity observed in the ring closure of diene **328**. In this case, the olefin moieties are too remote for co-ordination to any of the sugar ring oxygen atoms, thus resulting in an approximately 1:1 mixture of diastereoisomers.

The scope of this reaction was extended by a co-worker, Dr. David Holt, as he successfully cyclised a number of carbohydrate derived dienes **335a,b** and **334a,b** to give both *cis* and *trans* fused carbocyclic products **403a,b** and **404a,b** exclusively.



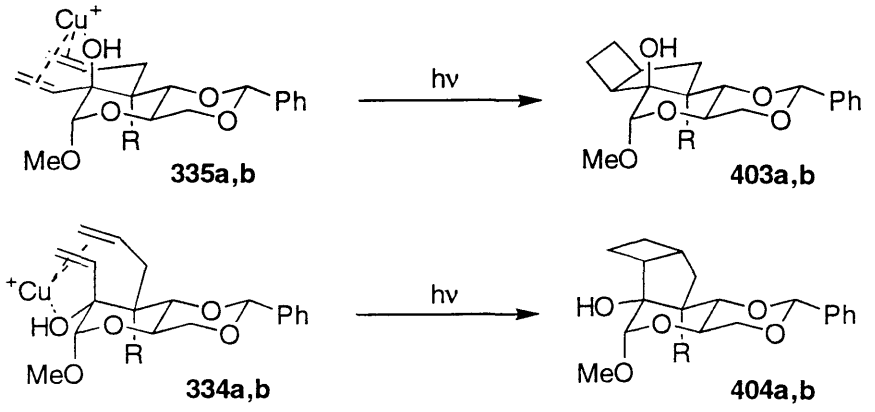

**335a**, R = H
**335b**, R= Me

**403a**
**403b**

**334a**, R = H,
**334b**, R = Me.

**404a**
**404b**

Once again Dr. Holt observed a similar stereocontrol in the ring closure reaction resulting in enantiomerically pure products in each case. These results could be rationalised in a similar manner to those reported above, thus providing more evidence for our hypothesis.[19]




**335a,b**

**403a,b**

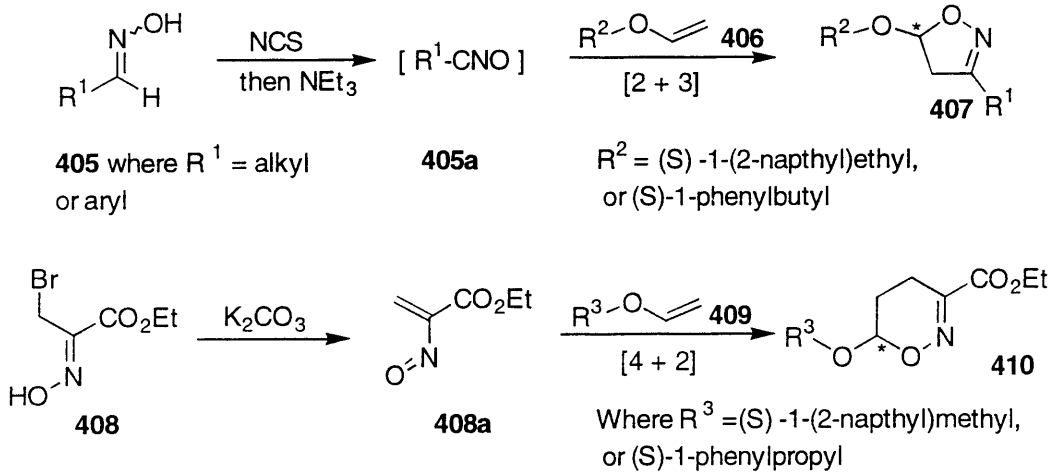
**334a,b**

**404a,b**

By forming the preferred tridentate ligand system, the axial hydroxyl group in dienes **335a** and **335b**, will direct the ring closure to give the observed products **403a** and **403b**, whereas the equatorial hydroxyl group in diene systems **334a** and **334b**, will direct the ring closure to give **404a** and **404b**, which are also the observed products. The stereochemistry of ring closed products **403** and **404** were confirmed by X-ray crystallography.

### 3.5.1 Studies into Cu (I) Catalysed [2+2] Photocycloaddition Reactions involving Heteroatoms

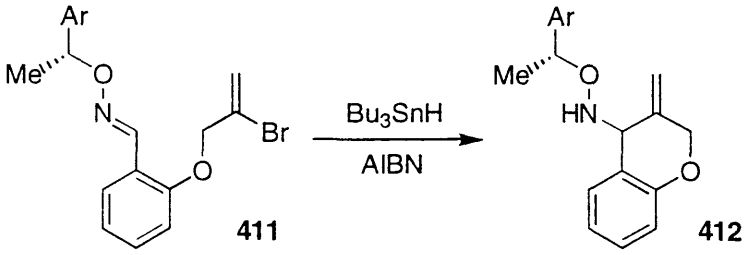
The Jenkins group has been interested in techniques for the ring closing of heteroatom containing substrates for some time. An investigation into the intermolecular [3+2] cycloaddition of nitrile oxides **405** with homochiral ethers **406** yielded a range of isoxazoles **407** (scheme 78). Six membered oxazines e.g. **410** can be synthesised via the [4+2] heterocycloaddition of nitrosoalkene **408** to the vinyl ethers e.g. **409**.[20]



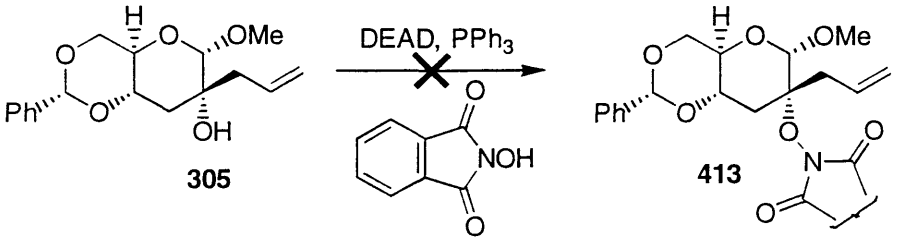

**Scheme 78**

The diastereoselectivity of each cycloaddition depends on the size and configuration of the homochiral vinyl ether, and ranges from 1.1:1 – 4:1 for the isoxazole **407**, and ~6:1 for the oxazine **410**.

Other work undertaken by the Jenkins group has involved the intramolecular radical cyclisation of chiral oxime ethers.[21] Chiral oxime ether **411**, conveniently prepared from N-hydroxy phthalimide in 3 steps, following the method described by Grochowski and Jurczac,[22] was treated with $Bu_3SnH$ and AIBN, resulting in a radical ring closure which furnished alkoxy amine **412** in 68% yield. The product was obtained as a 1:1 mixture of diastereoisomers.

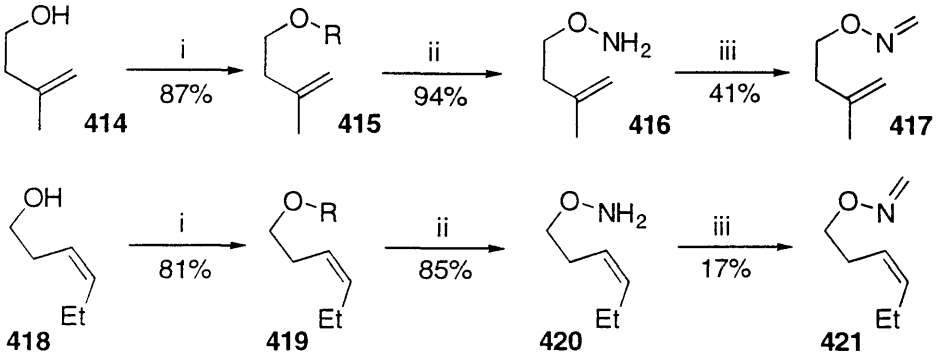



We wanted to evaluate the prospect of applying the previously described [2+2] photocycloaddition methodology to intramolecularly ring close a carbohydrate derivative bearing olefin and oxime ether substituents. To investigate this unique area we needed to develop a test system. Unfortunately our attempts to convert the tertiary alcohol **313** to the hydroxylamine type function **413** by reaction with N-hydroxy phthalimide all failed.




The reaction with N-hydroxy phthalimide is a Mitsunobu type displacement, and the steric bulk and rigidity of the sugar template, and the nature of the tertiary hydroxyl-leaving group, make this $S_N2$ displacement reaction extremely unfavourable.

To test the viability of the cycloaddition reaction, we decided to synthesise some much simpler model systems (Scheme 79). In the same fashion as above, homoallylic alcohols **414** and **418** reacted with N-hydroxy phthalimide in a Mitsunobu displacement reaction to furnish **415** and **419** in 87% and 81% respectively. Treatment of these substrates with hydrazine gave hydroxylamine ethers **416** and **420**, which upon reaction with formaldehyde afforded **417** and **421**.




**Scheme 79,** Reagents and conditions: i, N-hydroxyphthalimide, $PPh_3$. DEAD, THF, rt, 24h; ii, $NH_2NH_2.H_2O$, MeOH, reflux, 2h; iii, $H_2C{=}O$ 39% solution in $H_2O$, MeOH, rt, 18h.

The yields of the latter steps are quite low due to the volatility of the substrates. Purification by distillation proved inadequate; column chromatography was employed more successfully, but unfortunately resulted in large losses due to evaporation.

The attempted cyclisation reactions of oxime ether-olefin substrates **417** and **421** failed under the same conditions used to cyclise the 1,6-diene substrates. The reaction of **417** and **421** in benzene or $Et_2O$ with 10% CuOTf and UV radiation gave homoallyl alcohols **414** and **418** respectively, as the oxime ether tether was cleaved. These inherently negative results led us to cease work in this area.

### 3.5.2 Conclusions

We have demonstrated the remarkable stereocontrol afforded when cyclising a number of unactivated 1,6-diene carbohydrate derivatives using copper (I) triflate as the catalyst. To the best of our knowledge this is a unique reaction,[18] and we hope to use these results in further asymmetric synthesis. Attempts to increase the scope of this reaction to the [2+2] cycloaddition of an olefin with an oxime ether, were not successful.

## 3.6 References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# Chapter 4

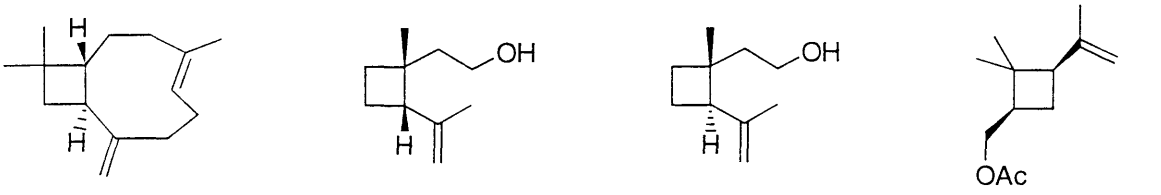
# Studies into Catalytic Asymmetric Cyclobutanation

## 4.1 Introduction:

In the previous chapter, we looked at how the stereocontrol of a reaction was achieved in the copper (I) catalysed [2+2] photochemical ring closure of a number of sugar derivatives. Using the co-ordinating ability of heteroatoms present within the sugar moiety to direct the ring closure, it was possible to obtain just one of the two available diasteroisomers. This intramolecular stereocontrol has been very useful within the realm of our carbohydrate annulation research, but requires a rigid hydroxylated template to induce any selectivity in an intramolecular ring closure of a diene. Therefore we wanted to expand the scope of the reaction, for the efficient stereoselective [2+2] cyclisations of other dienes, without relying on intramolecular influences. To date there are no universally efficient methods for generating enantiomerically pure 4 membered rings.[1]

## 4.2 The Cyclobutanation Reaction

The necessity of such a reaction is clear when considering the wide range of chiral natural products that contain the cyclobutane unit. For example β-caryophyllene **422** (Figure 14), a major component of fragrant oils found in spices such as cloves and cinnamon. Many derivatives of this important compound are used as constituents of fragrances in the cosmetics industry.[2] Some of the relatively simple examples of cyclobutane systems found in nature include grandisol **388**, fragranol **423**, which is the *trans* isomer of grandisol, and planococcyl acetate **424**.

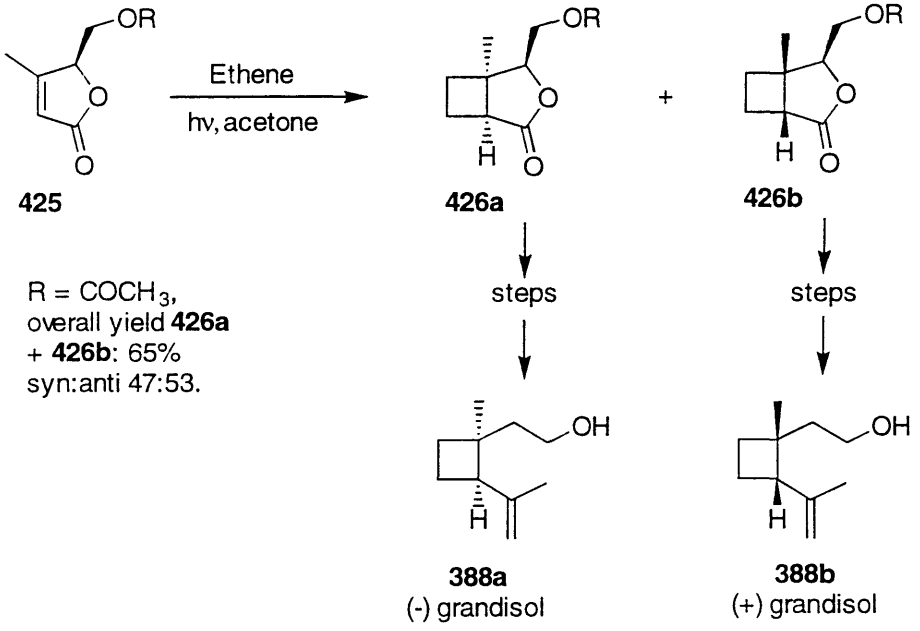



**422** caryophyllene | **388** grandisol | **423** fragranol | **424** plannococcyl acetate

**Figure 14**

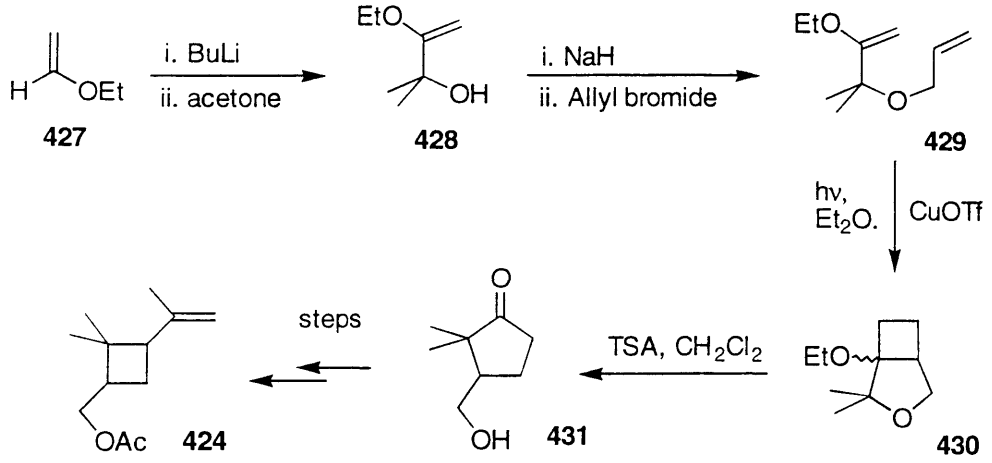
The latter three compounds are perhaps the most studied of the cyclobutane ring containing natural products, as they have been identified as important pheromones. For example grandisol is the major component of 'grandlüre', which is the sex attractant of

the male cotton boll weevil, an unwanted pest affecting cotton crops in the USA.[3] Grandisol has been prepared a number of times in racemic[4] and optically active forms.[5] However most of the chiral syntheses rely on the resolution of two diastereoisomers formed in a [2+2] photocyclisation step. One such route carried out by Font and co-workers[6] involves an intermolecular [2+2] photocyclisation of enone **425** with ethene, leading to two diastereoisomers **426a,b** in an approximately 1:1 ratio, which are separated by flash column chromatography (Scheme 80). The resulting isomers **426a** and **426b** were converted to the naturally occurring (-) grandisol **388a** and its enantiomer (+) grandisol **388b** after six subsequent steps.




**Scheme 80**

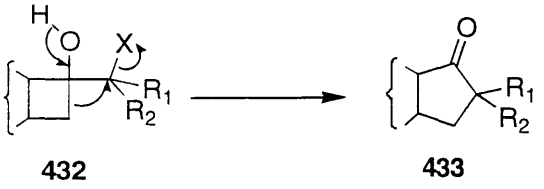
Planococcyl acetate **424** is a pheromone of the citrus mealy bug, and has also been the target of many syntheses.[7] An interesting preparation by Patra and Ghosh[8] can be seen in Scheme 81. Butyl lithium deprotonates the ethyl vinyl ether **427** to give ethoxy vinyl lithium, which reacts with acetone to afford alcohol **428**, alkylation of the alcohol with allyl bromide gives the diene **429**, which undergoes photochemical ring closure under standard conditions to give the bicyclic compound **430**. The acid catalysed ring expansion of the cyclobutane adduct **430** affords the cyclopentanone **431**. This cyclopentanone is a key intermediate from a previous formal synthesis, which converts **431** into planococcyl acetate **424** via a ring contraction step resulting in a *cis:trans* ratio of 2:1.[7]



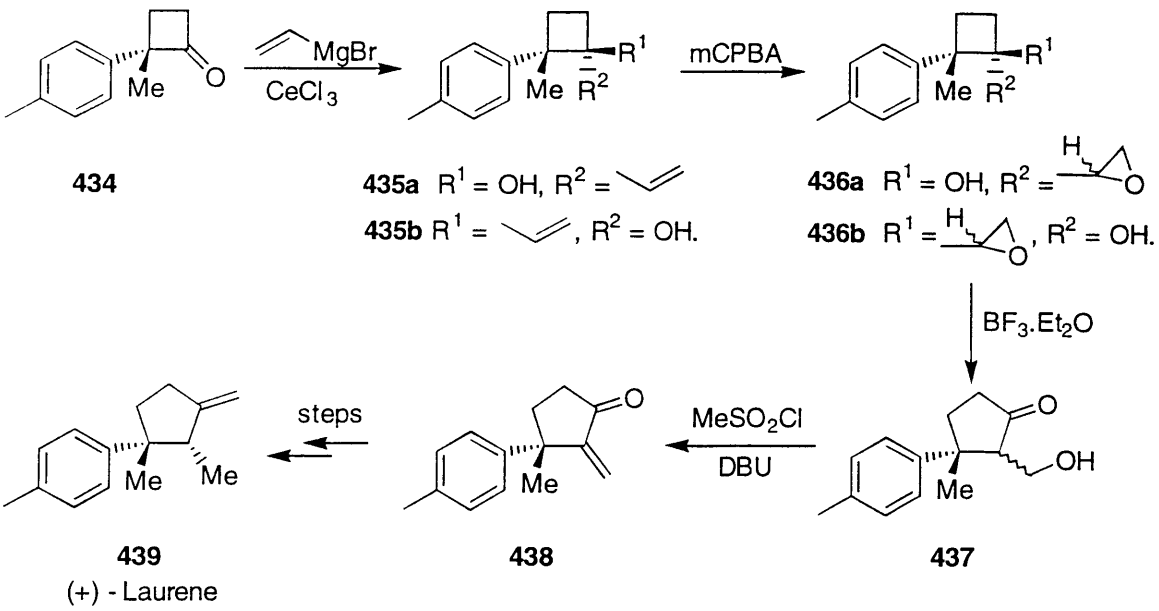

**Scheme 81**

### 4.2.1 Ring Expansion of Cyclobutane Adducts:

The one carbon ring expansion of bicycle **430** to give cyclopentanone **431** illustrated in Scheme 81 above, represents another major role that the cyclobutane ring system can play within organic synthesis. The basic concept of this process requires the loss of a suitable leaving group X from cyclobutanol **432**, with concomitant migration of a C-C bond to give the ring expanded cyclopentanone **433**.[9] The first total synthesis of (+)-laurene **439**, (Scheme 82) isolated from the marine red algae *laurencia elate*, illustrates this technique perfectly.[10] Fukumoto and co-workers took cyclobutanone **434**, derived from the thermally allowed [2+2] cycloaddition between a ketene and an olefin, and reacted it with vinyl magnesium bromide to afford the diastereomeric alcohols **435a** and **435b**. Epoxidation of the olefin with *m*CPBA resulted in the key cyclobutanol isomers **436a** and **436b**. Treatment of both diastereoisomers with the Lewis acid $BF_3.Et_2O$ in THF at -78°C afforded the ring expanded cyclopentanone **437** in 80% yield. The two diastereoisomers were dehydrated with a base to give the olefin **438** which was converted to (+)-laurene **439** in five further steps.

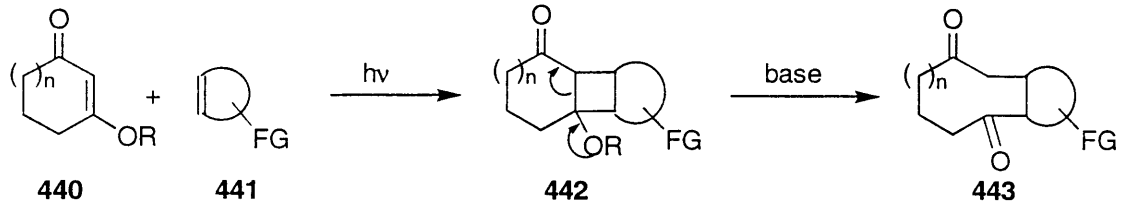



**432** **433**



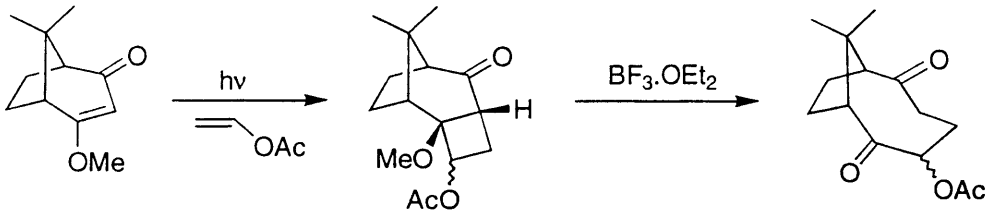

**Scheme 82**

Another application of the cyclobutane derivatives is ring expansion to form medium sized rings, first reported by de Mayo.[11] This process consists of a [2+2] photocycloaddition reaction between enol ethers such as **440** (Scheme 83) and olefins **441**, followed by a retro-aldol fragmentation of the photoadduct **442** to yield the functionalised medium sized ring **443**.




**Scheme 83**

This reaction is highly versatile, with respect to both reaction substrates, and has been utilised for both inter and intra molecular ring closure reactions to yield functionalised cyclo-octanoid ring systems.[12] Fetizon has reported the reaction between bicyclic enone **444** (Scheme 84) and vinyl acetate to yield the diastereoisomeric adduct **445**, which undergoes a retro aldol ring opening in the presence of a Lewis acid to give the functionalised 8-membered ring **446**, a precursor for Fetizon's model taxane studies.[13]




**444** **445** **446**

**Scheme 84**

It is clear that a general method for asymmetric [2+2] ring closure would be an invaluable tool, not only for chiral targets with a 4-membered ring system, but also larger rings that are accessible through ring expansion. We decided to explore the viability of reagent controlled asymmetric catalysis after its success in many other celebrated areas, such as epoxidation, hydroxylation, hydrogenation, cyclopropanation and aziridination.

## 4.3 Asymmetric Catalysis:

Until the early 1970's the resolution of racemates was the primary method for obtaining chiral molecules. Equation 1 (Figure 15) illustrates the separation of enantiomers from a racemic mixture where the enantiomers are signified by opposing flags.

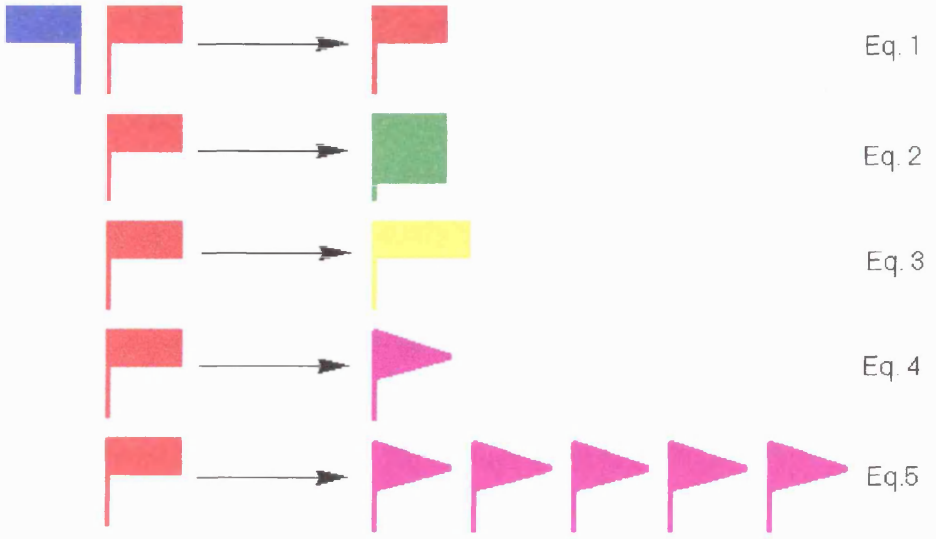



**Figure 15**

Equation 2 shows how an already chiral molecule can be 'transformed' through chemical manipulations to a chiral target. We have seen this method used extensively in chapters 1, 2 and 3, where carbohydrate derivatives undergo chemical transformations, often keeping their original chirality. 'Intramolecular chirality transfer' (equation 3) describes how chirality from one part of a molecule can help control the stereochemistry of a new centre being formed within the same molecule. Again we have seen examples of this in chapter 3. 'Inter-molecular chirality transfer' (equation 4) is the first example of asymmetric induction. In this case a chiral molecule is added to a reaction mixture in a stoichiometric amount and it 'controls' the stereochemistry of a new species formed within the reaction. Equation 5 illustrates classical 'asymmetric catalysis'; whereby a small amount of a chiral, man-made catalyst controls the stereochemical centres of a large number of products within a chemical reaction. To achieve efficient chiral amplification, the chemist must design catalytic systems that discriminate precisely between groups, atoms or faces within an achiral molecule.[14]

A variety of chiral metal complexes have been the most effective asymmetric catalysts to date, as they tend to not only promote stereoselectivity, but quite often they also activate a reagent to allow it to react under milder conditions. Figure 16 illustrates how a transition metal might bond to a simple olefin in a co-ordination process. The olefin $\pi$ electrons are donated into an empty orbital of the metal species forming a $\sigma$ bond. The metal in turn back donates its d-orbital electrons into the olefins $\pi^*$ orbitals to form a $\pi$ type bond. The olefin is thus 'activated' by the formal electron promotion from the $\pi$ bonding orbital to the $\pi^*$ antibonding orbital. Consequently the transition metal can 'accelerate', or reduce the activation energy of a chemical reaction. However it is the chiral ligands bound to the metal that promote asymmetric induction onto a substrate. The ligands around the metal are usually 'endowed' with a certain configuration and conformation, which allows the metal to interact with the reagents in a fixed position. On reaction, the product has gained the stereochemical attributes effectively forced upon it by the chiral metal complex. Obviously the reaction mechanism is far more complicated than is explained above. The bias required to achieve the stereoselectivity within a reaction arises from subtle differences in the transition states of the reacting species. This bias may be less than a 1kJ/mol difference in transition state energies, but a well designed chiral metal complex will differentiate between diastereomeric transition states with an accuracy of over 10kJ/mol.[14]

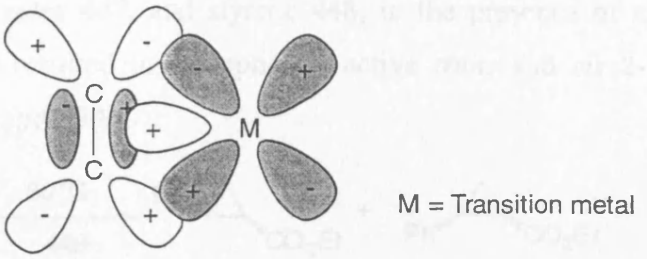
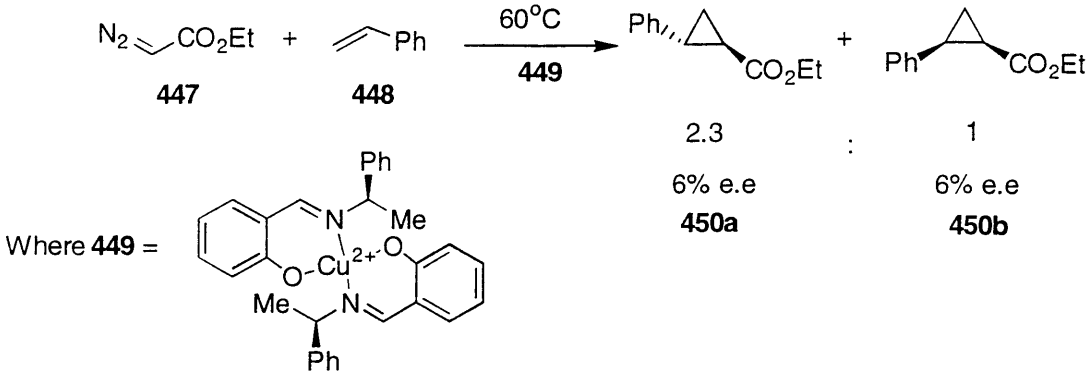


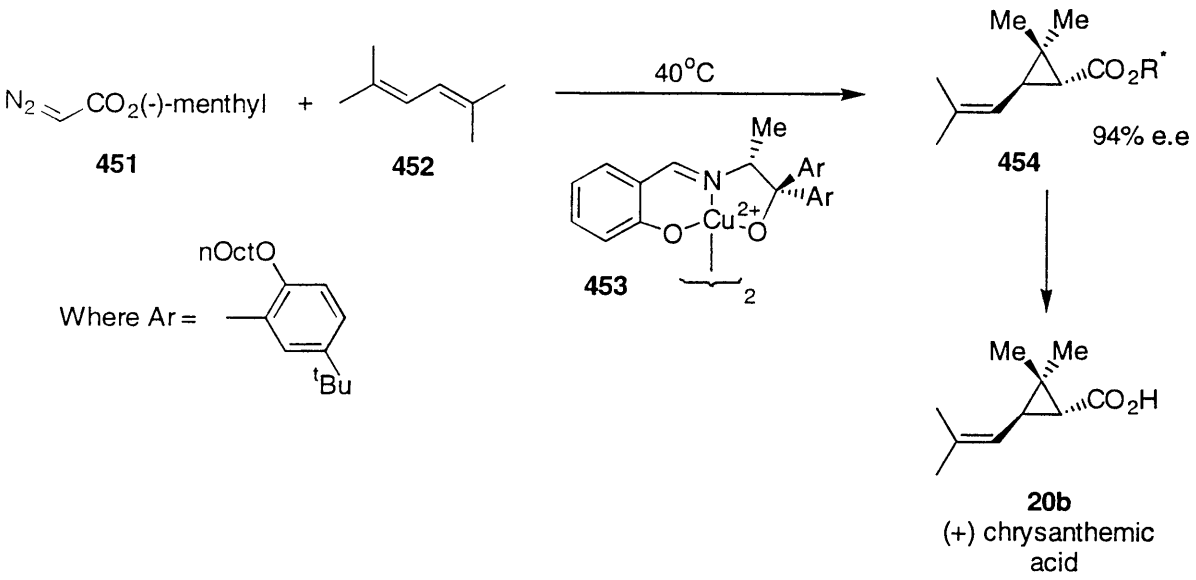

**Figure 16**

### 4.3.1 The Catalytic Asymmetric Cyclopropanation Reaction:

The first recognised example of a transition metal catalysed reaction in the homogeneous phase was reported by Nozaki *et al.* in 1966.[15] The reaction between a carbene species, derived from diazo ester **447,** and styrene **448**, in the presence of a copper (II)-Schiff base complex **449** resulted in the optically active *trans* and *cis* 2-phenylcyclopropanecarboxylate **450a** and **450b**.

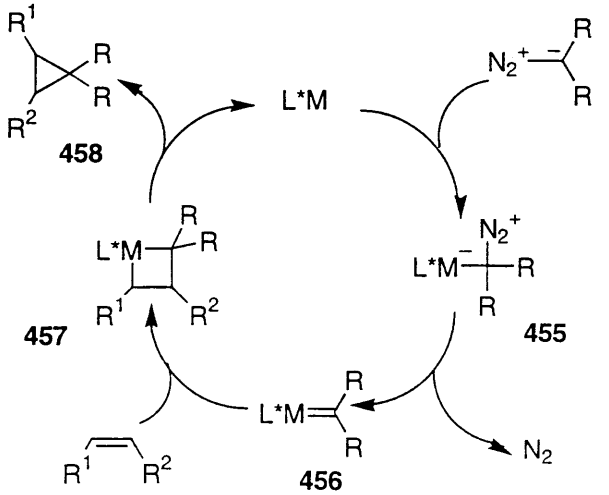



Although the above selectivities are very low, the results sparked huge interest within the field of asymmetric transition metal catalysis. Rapid progress was made within the field, and the systematic screening of the chiral Schiff base – copper catalyst systems yielded a number of important cyclopropane derivatives. Scheme 85 illustrates the synthesis of (+) chrysanthemic acid **20b**, a powerful insecticide. This work was carried out by Aratani and co-workers in the 1970's.[16] The chiral diazo acetate **451**, forms the metallo-carbene on reaction with copper with its salicylimine ligand **453**. The reaction with diene **452** proceeds at 40°C to give the required product **454** with an enantiomeric excess well over 90%. Quite clearly there are two chiral influences involved in this reaction, the chiral salicylimine ligand and the chiral auxiliary ester, both of them promoting the observed stereochemistry. The chiral ester is then easily hydrolysed to give (+)-chrysanthemic acid **20b**.




**Scheme 85**

The catalytic cyclopropanation reaction proceeds via the cycle shown in Scheme 86. To date the metal (M) has usually been a copper (I) or (II) salt, due to its intrinsic ability to direct ligand functionality towards a bound substrate, although a few other metals, in particular rhodium, have also been utilised to some effect.[17] M reacts with the diazo compound to form an unstable intermediate **455**, which rapidly loses $N_2$ to form metallo-carbene **456**; this is presumably the driving force for the catalytic cycle. Reaction with an olefin forms the metallocyclobutane **457**, which can rearrange to release the cyclopropane **458** and regenerate the catalyst. It is thought that the chiral bias is provided in the transition state leading to the formation of the metallocyclobutane **457**.[14]




**Scheme 86**

Major advances in the enantioselectivity of the cyclopropanation reaction were realised when Pfaltz *et al.* introduced a metal complex, based on a chiral semicorrin **459** (Figure 17).[18] The well designed semicorrins, afforded excellent selectivities in the cyclopropanation of styrene with a whole range of diazoacetates. This discovery was followed shortly by the introduction of bis (oxazoline) – copper complexes by Masamune and co-workers.[19] The bis oxazoline **460** was the work of Evans *et al.* and

when used in conjunction with 2,2-di-tert-butyl-4-methyl phenyl diazoacetate and a variety of olefins, results in cyclopropanes with selectivities of over 99% e.e.[20] Other particularly efficient ligands for the cyclopropanation reaction include the optically active bipyridyl ligands developed by Katsuki, such as **461**,[21] and the more recent $C_2v$ Schiff base ligands such as **462**, proposed by Jacobsen.[22] The latter ligands provide much cheaper and synthetically simpler alternatives whilst attaining practically quantitative selectivity in many reported cyclopropanation reactions.

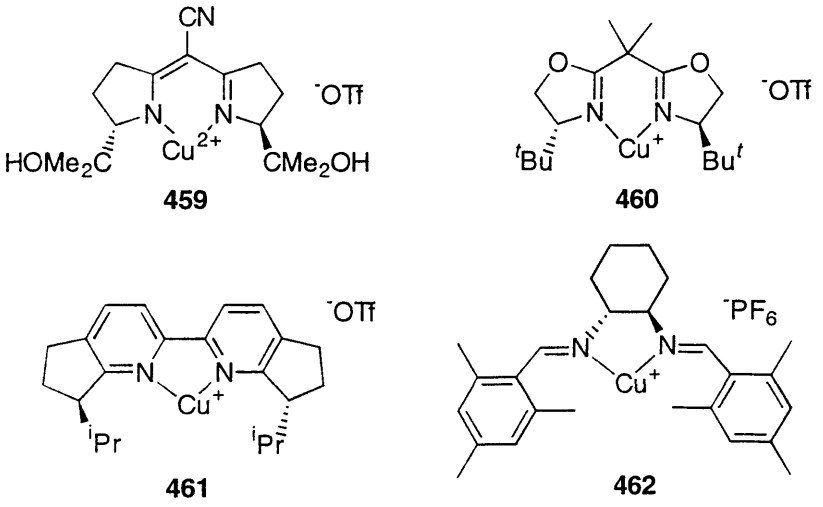
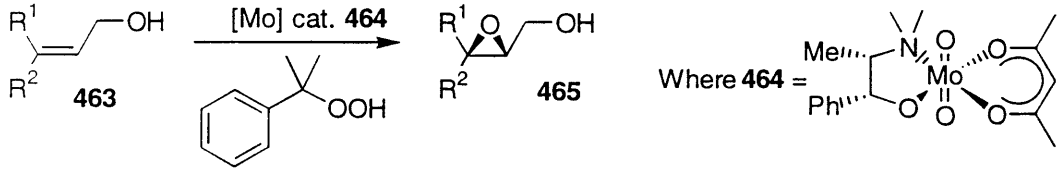



**Figure 17**

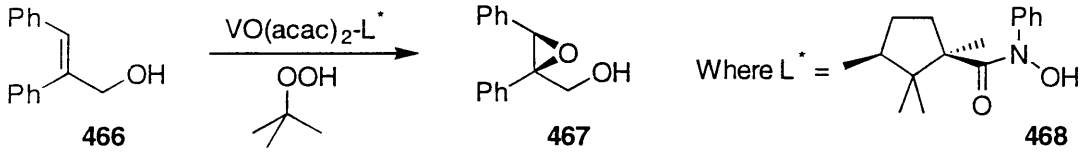
The diversity of this field is now huge, with many different types of ligands and metals being used to produce a whole range of effectively enantiopure cyclopropanes that can often be used in synthesis.

### 4.3.2 The Catalytic Asymmetric Epoxidation Reaction:

Perhaps the biggest breakthrough in the field of asymmetric catalysis in the last 25 years is the development of the epoxidation of allylic alcohols. The first catalytic asymmetric epoxidations were published simultaneously by two different groups, although the principles of the reactions and reagents were very similar. Yamada *et al*, from the university of Tokyo, proposed that the allylic alcohol **463**, where $R^1$ and $R^2$ are alkyl or allyl, could be asymmetrically oxidised with cumene hydroperoxide in the presence of the chiral molybdenum catalyst **464**.[23] The epoxide **465** was obtained in low to moderate chemical yield, 33-56% depending on $R^1$ and $R^2$, and with a fairly low enantiomeric excess of between 10 and 33%.

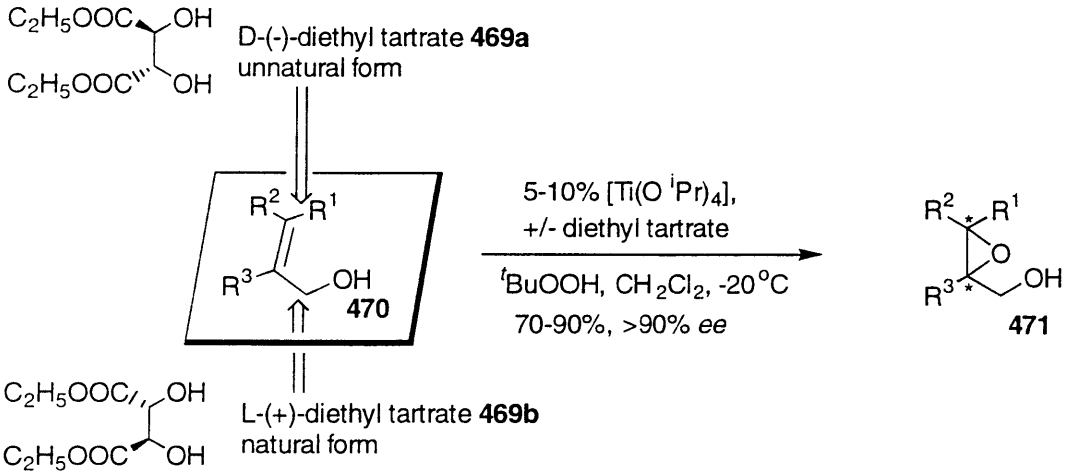



The following article in the same journal described how Sharpless *et al* of Massachusetts Institute of Technology, obtained similar selectivities when they epoxidised a variety of allylic alcohols using a chiral vanadium catalyst.[24] A summary of the results proposed by Sharpless is outlined below. The best induction (50% e.e.) was attained in the epoxidation of *E*-α-phenylcinnamyl alcohol **466**, in the presence of a chiral vanadium complex to give oxirane **467**, with a yield of up to 100% . The chiral ligands used to promote the asymmetry in these reactions were hydroxamic acids such as **468**: N-phenylcamphor-hydroxyamic acid, which is thought to act as bi-dentate ligand, and the oxidising agent is *tert* butyl hydroperoxide.




These two results sparked huge interest within the field, as from a synthetic perspective; the epoxide is an extremely versatile building block. Both carbons of an epoxide are activated towards nucleophilic attack, and in an unsymmetrical epoxide, the regiochemistry of the product can often be predicted. The ring opening of epoxides is also usually highly stereoselective, often creating two adjacent stereogenic centres.[25]

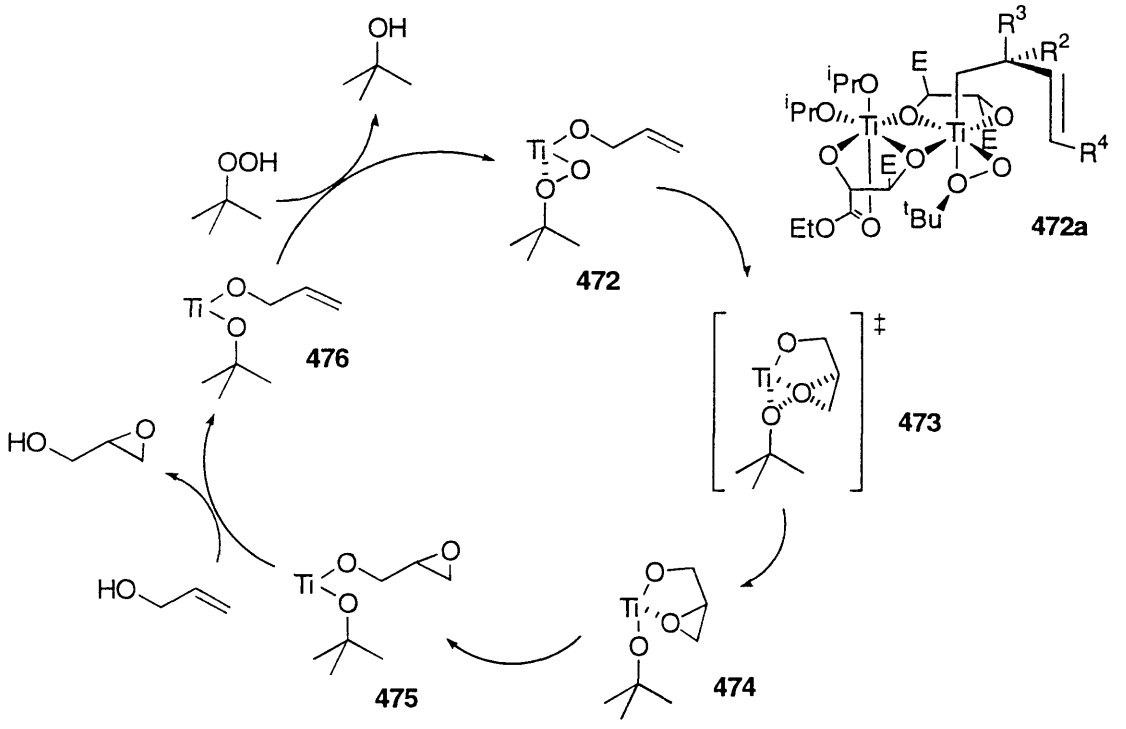
The main stumbling block for research into this field, was the difficulty in developing chiral ligands that would be stable to the relatively harsh conditions of the oxidation. A major breakthrough within the area proposed by Sharpless and co-workers in 1980 still stands as one of the most important reactions in asymmetric catalysis.[14] The versatile oxidation of allylic alcohols using a 1:1 Ti (IV) tetraisopropoxide-diethyl tartrate mixture as the chiral catalyst system resulted in epoxides in 70-90% chemical yield and enantiomeric excesses of over 90%. Scheme 87 illustrates the general reaction, where the chiral diethyl tartrates **469a** and **469b** can recognise the *re* or *si* face of the allylic alcohol **470**, and can direct the oxidation depending on the configuration of the ligand, leading to the chiral epoxide **471**.




**Scheme 87**

The original procedure required a stoichiometric amount of the tartrate complexed Ti promoter, but more recently with the introduction of molecular sieves to 'mop up' water liberated in the reaction, the Ti complex can be used in catalytic amounts.[14]

The proposed mechanism by which the catalytic cycle proceeds is illustrated in Scheme 88. The titanium complex **472** comprises the tertiary butyl hydroperoxide (TBHP) and the allylic alkoxide groups as ligands. It is thought that the alkyl peroxide is electrophilically activated by its bidentate co-ordination to the Ti centre. Oxygen transfer via the transition state **473**, affords the bound epoxide **474** which opens out to give **475**. In this complex the alkoxide products are replaced by an allylic alcohol to give **476**, then TBHP to regenerate **472** and complete the catalytic cycle. This is a simplified mechanism as the reactive titanium tartrate species is believed to be dimeric such as proposed structure **472a**.[25] This structure is consistent with the observed stereochemistry, but the whole area is not fully understood and this putative hypothesis remains contraversial.[14]




**Scheme 88**

The Sharpless epoxidation is sensitive to chirality already present within allylic alcohols and thus allows relatively easy kinetic resolution. The kinetics of such reactions have been studied extensively, but the basic principal is illustrated in Figure 18. In the case of **477** on the left, an oxygen atom can be delivered more easily to the bottom face than to the top face due to the extra steric bulk of $R_4$. The reverse is true for the other enantiomer **478**. This makes it possible to resolve the enantiomers by reacting a racemic mixture with 0.5 equivalents of TBHP in the presence of the Ti catalyst. One enantiomer will react quickly, to form the desired epoxide product, whereas the other enantiomer will remain largely unchanged.[25]

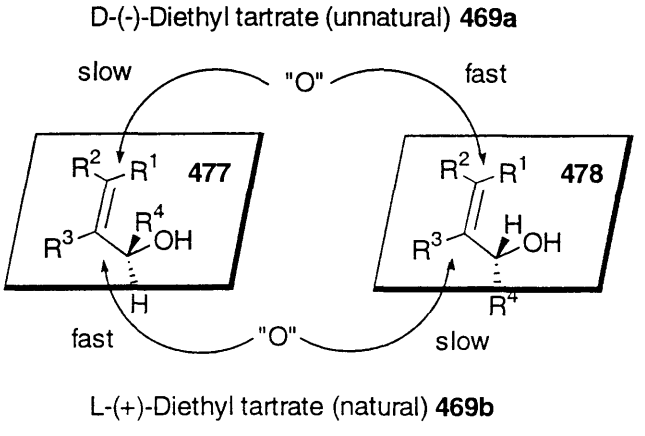
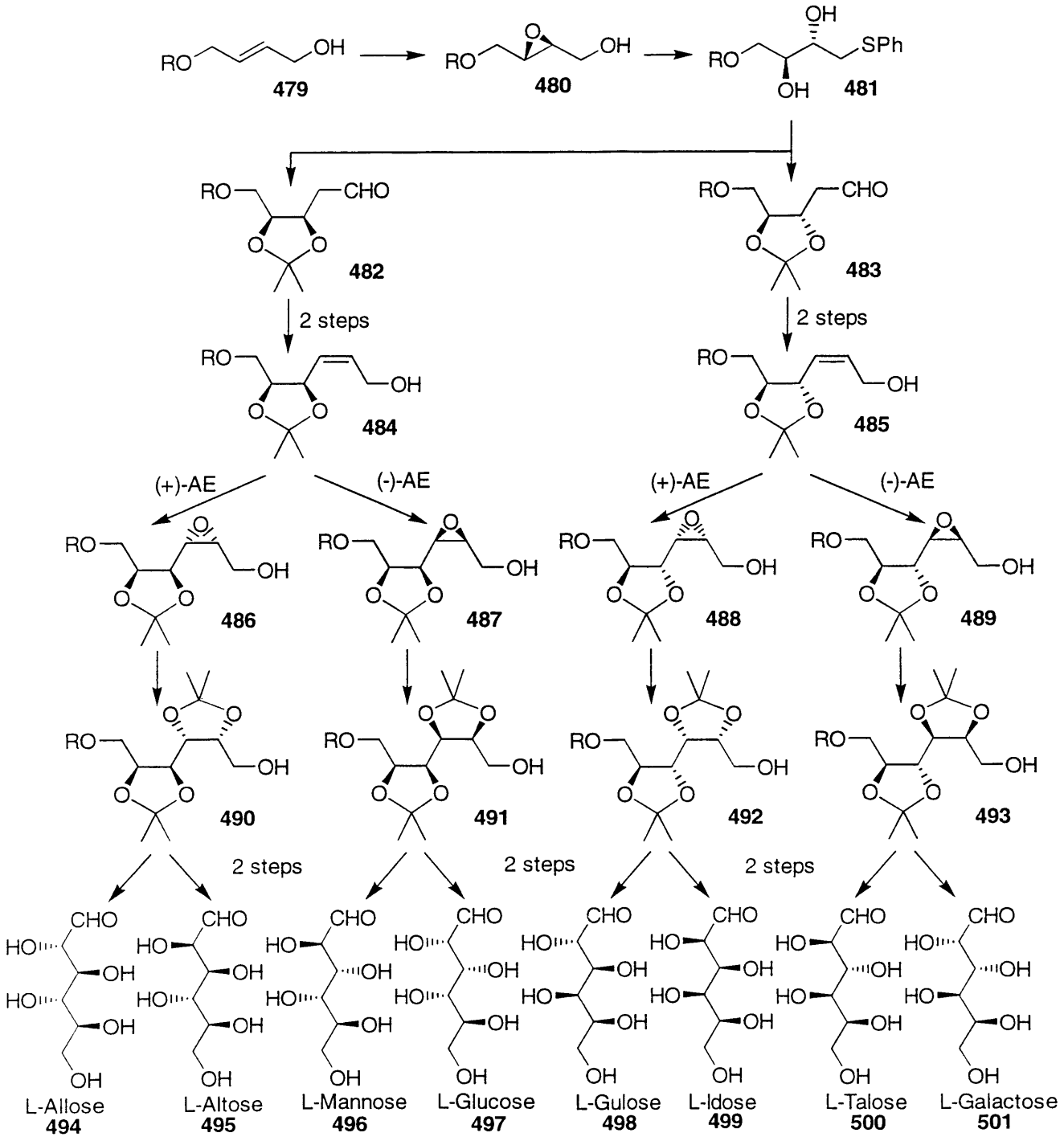



**Figure 18**

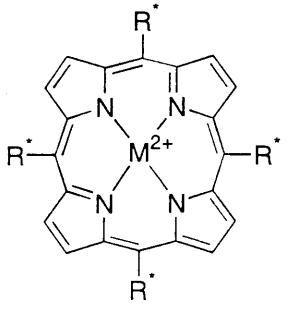
The reagent control method discussed previously has been utilised to great effect in the total synthesis of all eight of the unnatural L-hexoses **494-501** (Scheme 89).[26] This route proposed by Sharpless *et al* provides an extremely elegant illustration of the utility of the epoxidation of allylic alcohols to yield stereochemically complex, chiral polyoxygenated products.



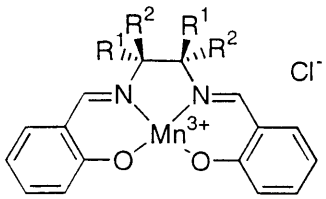

**Scheme 89**

Allylic alcohol **479** is oxidised to give the chiral epoxide **480** which is converted to the thiol **481** via a nucleophilic ring opening using a thiolate anion and subsequent Payne rearrangement. Oxidation of **481** to a sulfoxide, followed by a Pummerer reaction, then reduction using DIBAL, followed by protection of the diol with acetone results in the aldehyde **482**, which can be epimerised to give the diastereomeric aldehyde **483**. Alkylation followed by reduction gives allylic alcohols **484** and **485**. A further asymmetric epoxidation of **484** and **485** gives the epoxides **486**, **487**, **488** and **489**. Similar conversion to the thiol, transformation to the diol then protection, affords the protected tetraols **490-493**, oxidation followed by epimerisation of half of each of the respective tetraols then deprotection results in all eight of the unnatural hexoses **494-501**. The reaction conditions can also be tailored to make all eight naturally occurring hexoses.

The Sharpless Ti catalysts do not promote enantioselective epoxidation onto simple olefins as effectively. In fact there are few good methods for the asymmetric epoxidation of olefins, one of the better techniques described by Groves and Meyers in 1983 attempts to mimic natures methods.[27] They used the chiral porphyrin **502** (Figure 19), where M = $Fe^{2+}$ or $Mn^{2+}$ to introduce an oxygen atom, which is thought to proceed via a radical addition. Other effective catalysts include the Manganese salen complex **503**, proposed by Kochi and co-workers.[28] The latter $Mn^{3+}$ salen type complexes are particularly efficient and can achieve enantiomeric excesses of well over 90%. Systematic variation of the Manganese environment, both electronic and steric has led to effective catalysts for a wide range of olefin epoxidations.[29] The manganese salen type ligands are of particular interest as, like the Schiff base ligands mentioned earlier, they are relatively cheap and simple to synthesise.




**502**

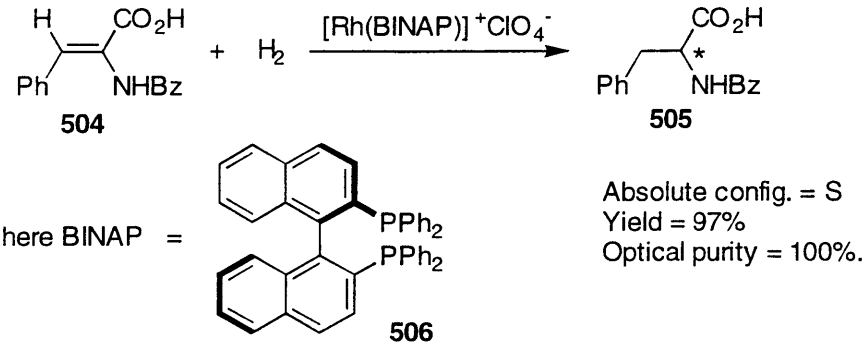



**503**

**Figure 19**

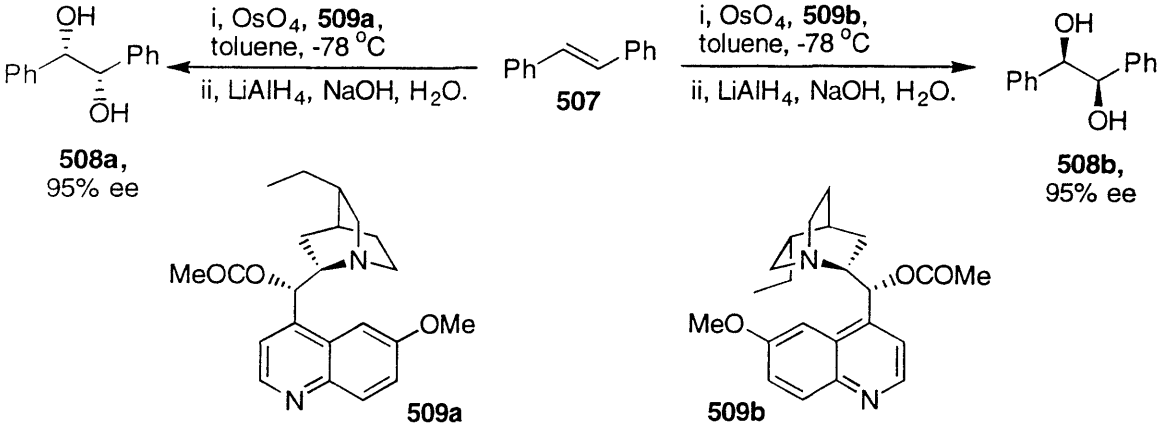
### 4.3.3 Other Catalytic Asymmetric Reactions:

Over the last 25 years, catalytic asymmetric processes using transition metals have improved enormously. Many more reactions have been developed, and these include: hydrogenation of olefins, hydroxylation of olefins and aziridination to name but a few. For the large number of transition state metal catalysts developed, there are an even larger number of ligands available. Some of the more sophisticated ligands have been discussed already, but these lists are by no means exhaustive. For example phosphino type ligands such as BINAP® **506**, are extremely effective ligands for the hydrogenation of olefins, when used in conjunction with a number of metals.

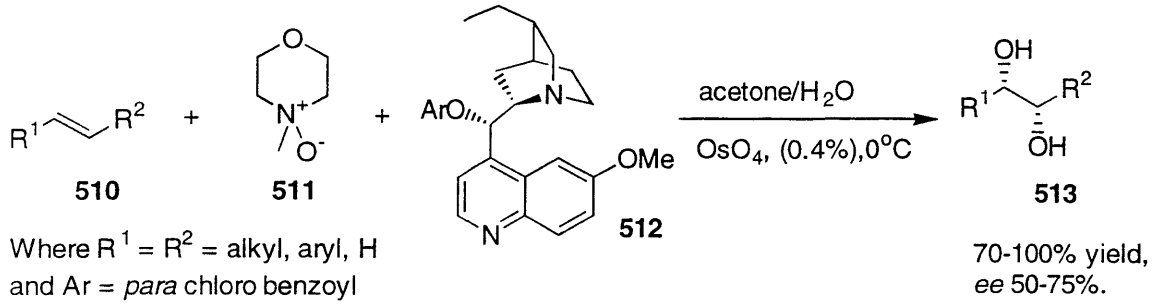



In this example, (R) BINAP (**506**) is bound to Rhodium, which effectively catalyses the hydrogenation of a variety of α-(benzoylamino) acrylic acids. The olefin **504** is converted to the functionalised amino acid **505** in excellent yield and essentially quantitative optical yield.[30]

The role of the ligand is not always as straight forward as described previously. For example in the case of the osmium tetroxide catalysed dihydroxylation of olefins, the choice of ligand can affect the rate of reaction. Osmium tetroxide is well established as a reliable reagent for converting an olefin into a *cis* diol. However in 1936, Criegee reported that certain amines can accelerate the reaction of $OsO_4$ with olefins.[31] In 1980 it was found that by using chiral amines such as quinuclidines **509a** and **509b** in conjunction with $OsO_4$, it was possible to oxidise olefin **507** to afford chiral diols **508a** and **508b** respectively with excellent selectivities.[32]




Although this, and other early examples use a stoichiometric amount of the metal, a catalytic system was soon developed and reported in 1988 by Sharpless *et al.*[33] By incorporating a co-oxidant into the reaction mixture, it is possible to re-oxidise the reduced $OsO_4$ after it has reacted with an olefin moiety. A cheap and readily available oxidising agent such as NMO **511** used in excess, in conjunction with catalytic amounts of the osmium tetroxide and a chiral quinuclidine **512** can oxidise a variety of olefins **510** to afford *cis* diols **513**, in excellent yields with fair selectivities.




Again this field has advanced rapidly in the last 12 years and with improved understanding of the catalytic cycle, many asymmetric dihydroxylation reactions have been reported with enantiomeric excesses well over 90%. These reactions are extremely efficient due to the previously mentioned acceleration of the reaction by the very ligands that affect the configuration of the product.[34]

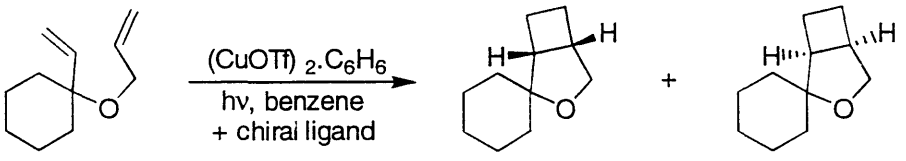
## 4.4 Summary

This extremely brief discussion of transition metal catalysed asymmetric reactions does not do the field justice, however it is clear from the few examples above that this class of reaction represents an invaluable tool to the synthetic organic chemist

industrially as well as academically. The field is advancing and expanding extremely rapidly, and although few of the presently available processes are general, more reactions with broader ranges of substrate specificities and scope are certain to be developed.[14]

## 4.5 Catalytic Asymmetric Cyclobutanation:

We have already seen that the Cu (I) triflate catalysed [2+2] photocyclisation of carbohydrate derivatives is a diastereoselective process. The aim of this new study is to extend the scope of this diastereoselectivity to simple non-carbohydrates, and thus develop a general catalytic asymmetric cyclobutanation reaction. From chapter 3 we have already learnt that the copper (I) catalyst can direct ring closure by intramolecular co-ordination to an oxygen atom present within the sugar ring. We reasoned that it might be possible to set up a catalytic asymmetric ring closure if we could develop a catalytic cycle involving a chiral ligand co-ordinated to the Cu (I). To test the viability of this reaction we needed a model system, preferably an achiral diene, such as **514**, which will create two new chiral centres upon cyclisation.




**514** **515a** **515b**

We want to be able to control the amounts of the two enantiomeric products **515a** and **515b** formed, by using a chiral catalyst. In order to attain any level of enantiomeric excess in this reaction, we first need to understand the co-ordination chemistry of copper (I). This subject area has been reviewed extensively,[35] and it is known that copper (I) complexes are generally co-ordinated in such a manner that the ligands are arranged tetrahedrally.[35a] In a copper (I) catalysed photochemical ring closure reaction, the $\pi$ electrons from each olefin fill two of the co-ordination sites. The other two sites are thought to be filled by molecules of the solvent.[36] In our previous work, we postulated that one of these 'free' solvent sites was replaced by a hetero-atom present within our carbohydrate derivative.[37] In this project however, we propose that the vacant sites will be filled by a bidentate ligand such as the bis oxazoline displayed in our working hypothesis (Figure 20).

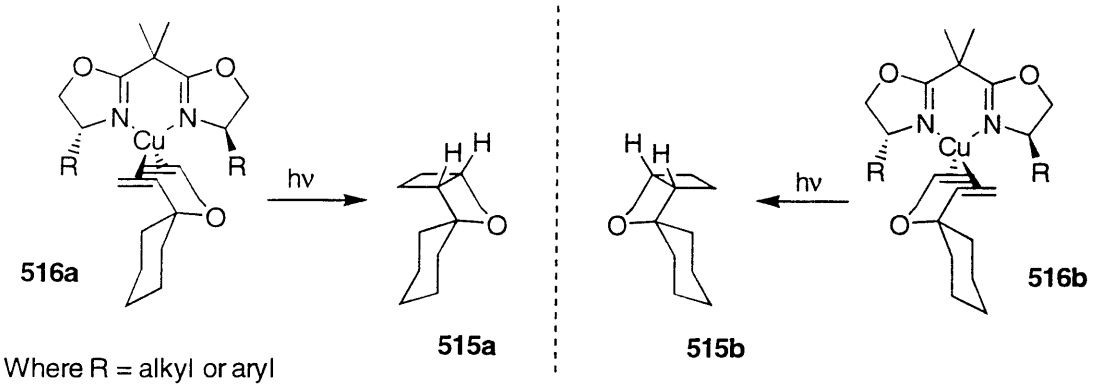
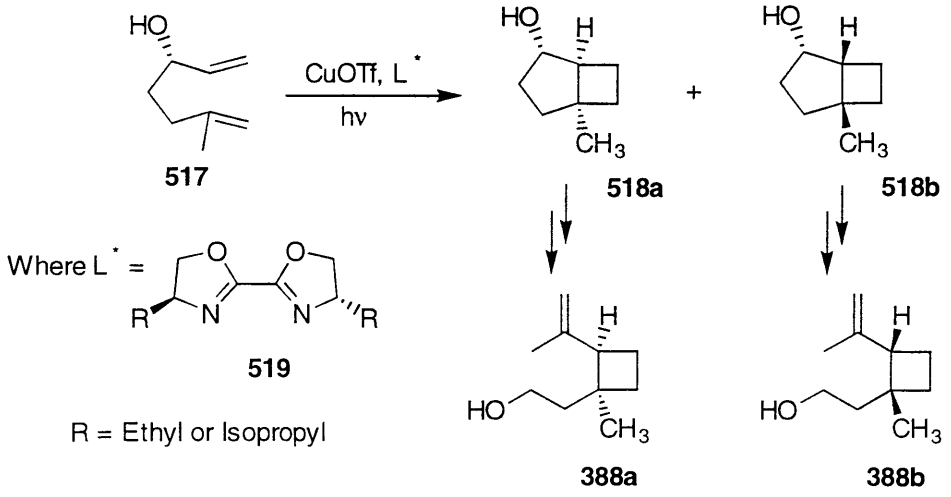



**Figure 20**

From the model it appears likely that the favoured complex **516b** will preferentially form product **515b**. This selectivity should arise from the proximity of the cyclohexane ring in **516a** (coming out of the plane of the paper), to the bulky R group (also coming out of the plane of the paper), thus resulting in a more strained conformation when compared to **516b**. This argument predicts that **515b** will be the major enantiomer formed on cyclobutanation.

A literature search revealed only one previous study within this area.[38] The research was directed towards a stereoselective synthesis of grandisol, and was carried out by Mattay and Langer, and is summarised in Scheme 90.




**Scheme 90**

The optically active diene **517** was irradiated in the presence of copper (I) triflate, and a number of chiral bidentate nitrogen containing ligands. The resulting diastereoisomers **518a** and **518b** could be separated by preparative HPLC and the enantiomeric excesses

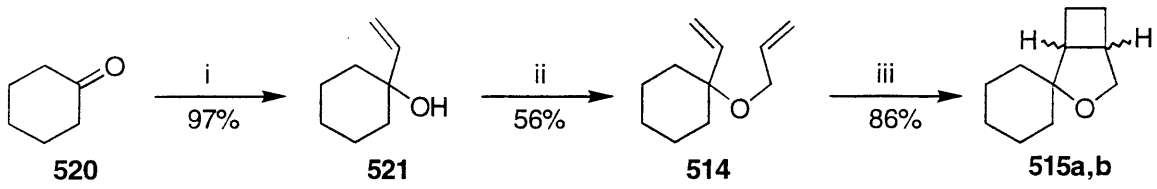
determined by chiral GLC. Their study found that only bis oxazoline derivatives **519**, induced any selectivity, and this was very low (less than 5%). All other ligands that they evaluated did not exhibit any selectivity. The resulting cyclobutane derivatives were converted into (-) grandisol **388a** and (+) grandisol **388b** after further chemical manipulation.

The authors proposed three possibilities for the lack of stereoselectivity: (a) The chiral ligands are not suitable to induce enantioselectivity, (b) the affinity of the copper ion to the diene moiety is decreased by the chiral ligand and (c) the chiral copper complex exhibits low reactivity compared to the copper ion co-ordinated to the solvent molecules. A comprehensive UV/vis. spectroscopic study of the co-ordinated and uncoordinated copper species led them to report that the reactivity of the copper-diene moiety is reduced by the chiral ligand, due to changes within the co-ordination sphere of the metal.

Although these results are inherently negative, we wanted to investigate further. This was achieved by carefully selecting and evaluating a wide range of substrates, ligands, transition metals and reaction conditions.

## 4.6 Results and Discussion:

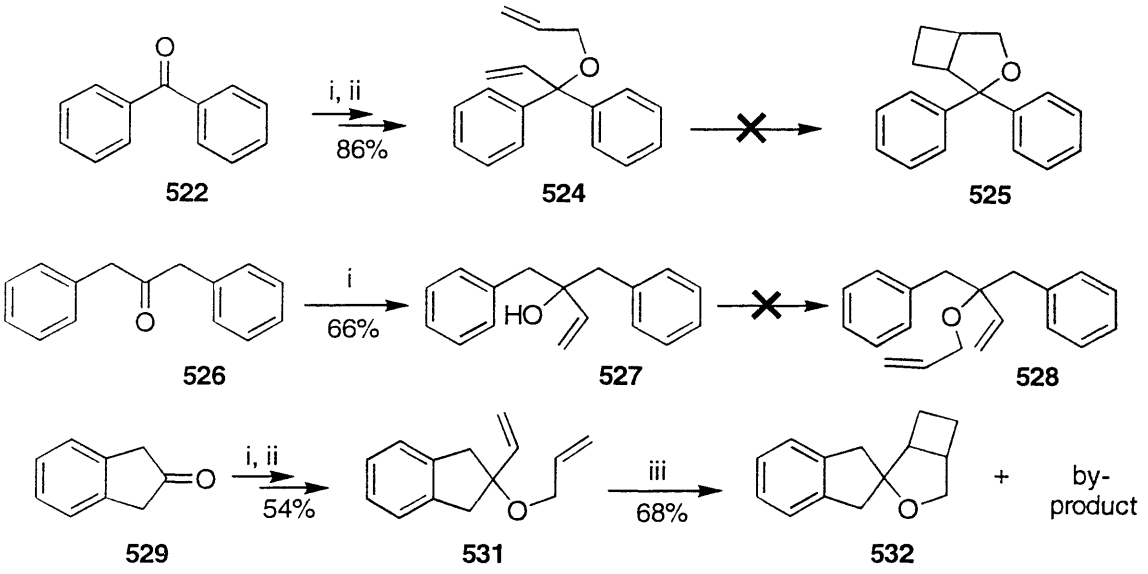
Due to the novel nature of this new area of work, it was necessary to evaluate a number of 1,6-diene systems, to find a suitable candidate to test the efficiency of the asymmetric cyclobutanation reaction. For simplicity, we thought that the ideal diene would have no chiral centres before the photochemical ring closure, with new chiral centres being created in the product. The relative molecular mass of the starting material was also a consideration, as volatile compounds are particularly difficult to purify. The synthesis of the first model system investigated can be seen in Scheme 91. The readily available, inexpensive starting material cyclohexanone **520**, was alkylated with a vinyl Grignard reagent to give the alcohol **521**, this was deprotonated with sodium hydride and further alkylated with allyl bromide to afford the 1,6-diene **514** in 54% yield overall. The diene substrate **514** undergoes ring closure to give enantiomers **515a** and **515b** in 86% yield upon irradiation at 254nm in the presence of copper triflate.




**Scheme 91,** Reagents and conditions: i, $H_2C{=}CHMgCl$, THF, reflux, 4h; ii, NaH, THF, reflux, 2h, then $CH_2{=}CHCH_2Br$, DMPU, 4h; iii, $(CuOTf)_2.C_6H_6$, $Et_2O$, 24h.

Unfortunately the resulting enantiomers were inseparable by chiral capillary gas chromatography, making the calculation of enantiomeric excesses impossible by this method. Due to the lack of functionality of the products, we were unable to find any other quantitative methods to distinguish between the two enantiomers.

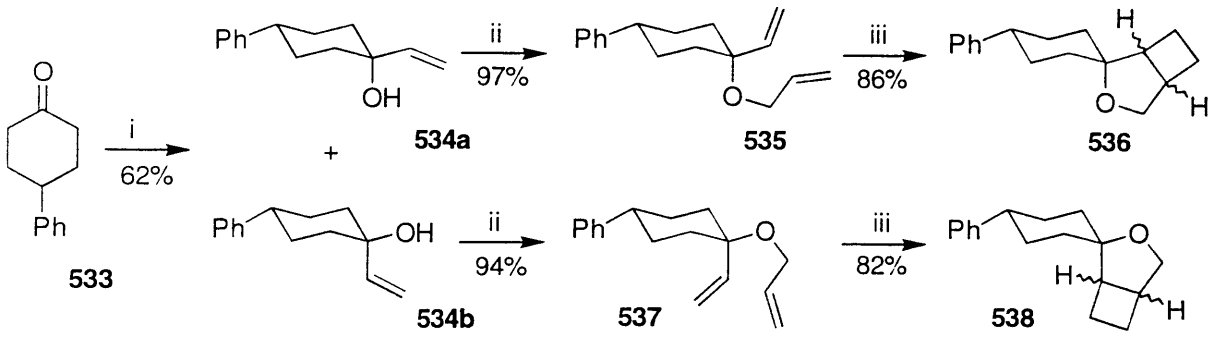
It was thought that the best technique for resolving such enantiomers would be by chiral HPLC, and the most effective method for detecting the resolved products would be by incorporating a chromophore into the molecule, thus rendering it UV active. A number of problems were encountered when trying to find a suitable system containing one or more chromophores, and these are summarised in Scheme 92.




**Scheme 92** Reagents and conditions: i, $H_2C$=CHMgCl, THF, reflux, 4h; ii, NaH, THF, reflux, 2h, then $CH_2$=$CHCH_2Br$, DMPU, 4h; iii, $(CuOTf)_2.C_6H_6$, $Et_2O$, 24h.

The first system was derived from benzophenone **522** and the reaction with a vinyl Grignard reagent gave an allylic alcohol **523** which was O-alkylated affording the 1,6-diene **524** in 86% overall yield. The difficulty with this model arose when the diene was irradiated in the presence of copper triflate, as the cyclised product **525** could not be isolated when the reaction was run in diethyl ether, benzene or THF. The resultant mixture of products was inseparable, and indistinguishable by NMR, and was thought to arise from reactions involving a stable doubly benzylic radical formed on cleavage of the C-O bond. To overcome this problem we extended the carbon chain between the phenyl groups, as seen in the second example. The ketone **526** was alkylated with vinyl magnesium chloride, to give the allylic alcohol **527** but attempts to further alkylate the alcohol were unsuccessful, probably due to steric crowding around the hydroxyl group. Another diene candidate **531** was synthesised from the indanone **529**, in a similar manner to the previous examples. The 1,6-diene was irradiated in the presence of copper triflate, and the product **532** was observed, along with another inseparable and unidentifiable by-product. We were able to resolve the enantiomers of the required product using chiral HPLC, but the added complexity arising from the presence of the unwanted by product made the chromatograph particularly troublesome to interpret. The calculation of enantiomeric excesses would be very difficult as the signals from the by-product obscured the required product signals using a range of eluents.

The candidate that alleviated all of these problems can be seen in Scheme 93.




**Scheme 93,** Reagents and conditions: i, $H_2C$=CHMgCl, THF, reflux, 4h; ii, NaH, THF, reflux, 2h, then $CH_2$=$CHCH_2Br$, DMPU, 4h; iii, $(CuOTf)_2.C_6H_6$, $Et_2O$, 24h.

Phenylcyclohexanone **533** was alkylated with vinyl magnesium chloride to give allylic alcohols **534a** and **534b** in an approximately 1:1 mixture and 62% yield. The *cis* and *trans* products were separable by column chromatography, although the configurations at C-1 were unknown. The correct configurations were determined by nOe studies. Figure 21 illustrates how the olefinic proton displays an intense nOe signal with the axial protons of C-2 in the case of the *cis* system **534a**. Whereas the olefinic proton of the *trans* alcohol **534b** shows distinctive nOe signals with the axial protons on C-3.

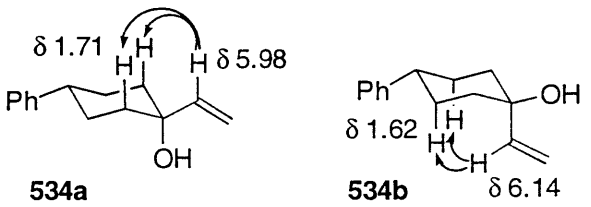



**Figure 21**

Both alcohols were O-alkylated as described previously, to give the dienes **535** and **537** in excellent yields. These dienes both undergo ring closure upon irradiation in the presence of copper triflate to afford cyclobutane derivatives **536** and **538** respectively, in high yield.

Chiral HPLC analysis of **538**, derived from the *trans* alcohol, resulted in only one peak as the enantiomers were not resolved. However, analysis of **536** gave two separate peaks in a 1:1 ratio from the resolved enantiomers, and a sample chromatograph is displayed in Figure 22.

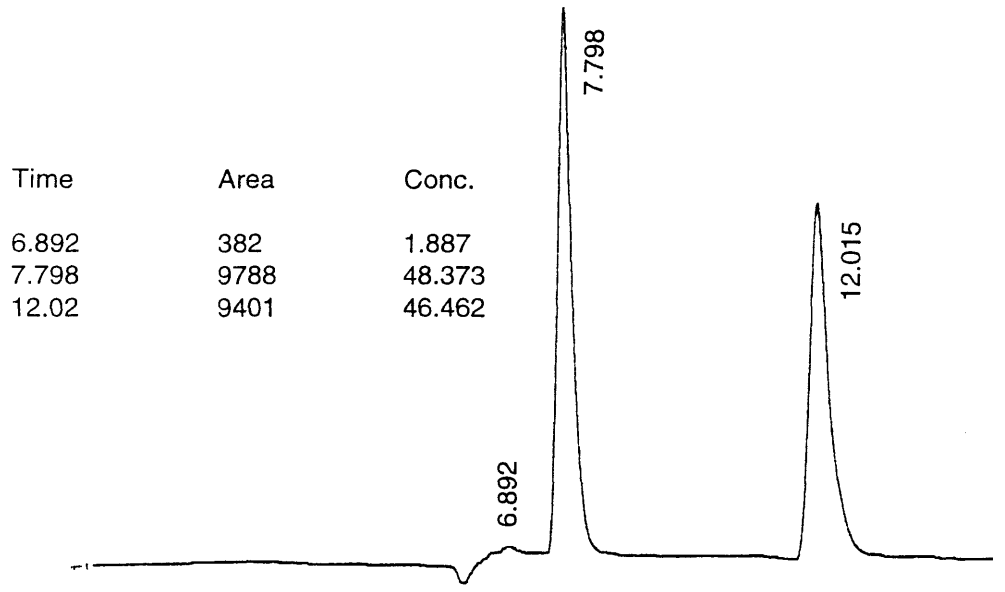



**Figure 22,** HPLC chromatograph of racemic spiro tricycle **536**

With a suitable candidate in hand, it was possible to initiate the investigation into asymmetric cyclobutanation. A number of chiral ligands, already proven to successfully promote asymmetry in other catalytic reactions were obtained and can be seen in Figure 23.

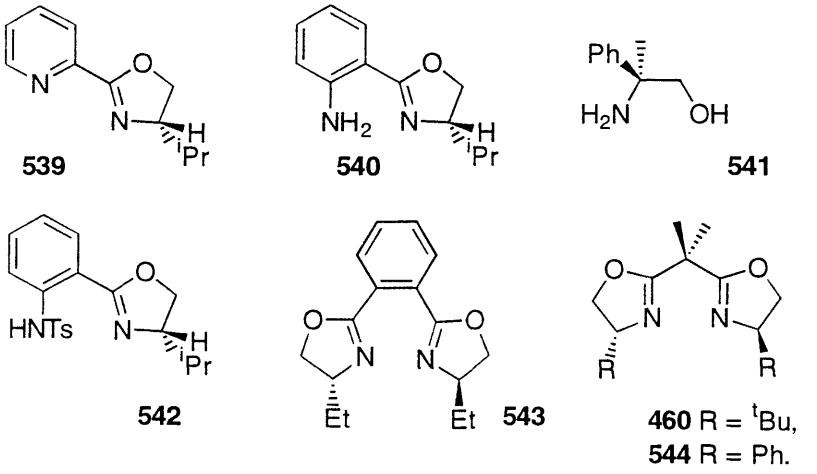
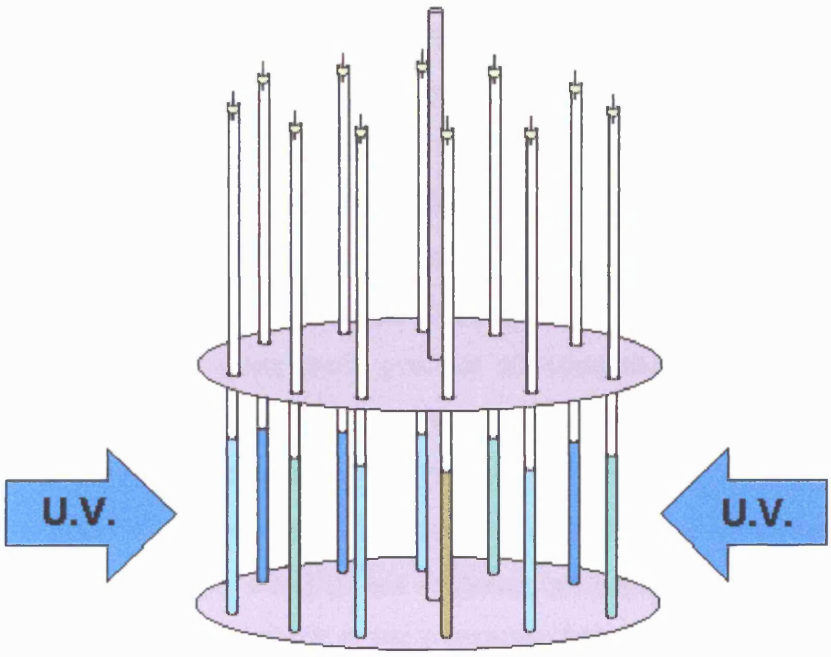



**Figure 23**

The ligands **539-543**[39] were kindly donated by the group of Dr D.L. Davis from the inorganic section of Leicester University, and ligands **460** and **544**[20,30] were obtained from a commercial supplier.[40] The screening process was quite simple, but time consuming, and involved changing a number of variables including solvent, ligand and

stoichiometry. The solvents used were dry diethyl ether, benzene, THF, dichloromethane, and acetonitrile, although acetonitrile was ruled out immediately as it prevented the photochemical reaction occurring entirely. This was probably due to the solvent molecules forming strong bonds to the copper catalyst, thus reducing its activity. Dichloromethane was also rejected as it encouraged the formation of unknown by




products, probably due its instability under UV light.

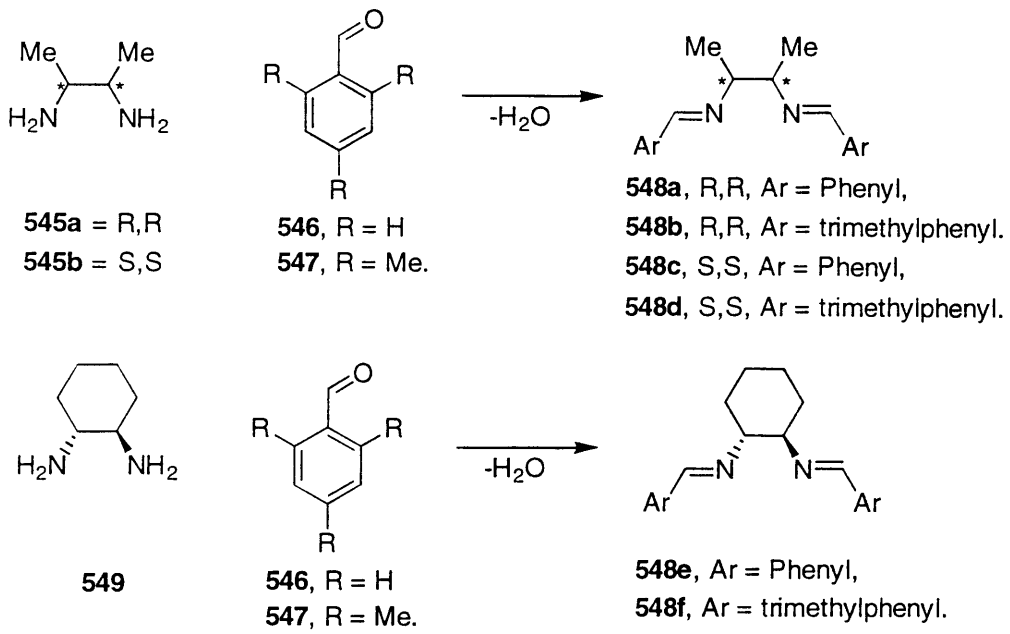
**Figure 24**

Figure 24 is a schematic diagram of the high throughput photochemical reacting system that we developed for the screening purposes. The diene moiety could be dissolved in the desired solvent and a catalytic amount of the copper triflate-chiral ligand solution could be added to it through the septum at the top of each vessel. The sealed quartz tubes could then be irradiated at 254nm for 24 hours under a positive pressure of $N_2$. After a number of experiments it was found that a reaction mixture comprising a 1:1 copper to ligand ratio, significantly reduced the reaction progress; in fact the furthest any reaction proceeded was ~4%. When a 2:1 ligand to metal complex was used, the photochemical reaction was almost non-existent. This led us to reduce the ligand stoichiometry, in order to allow the reaction to proceed, whilst maintaining a large proportion of the complexed copper within the reaction mixture. All of the following results were obtained using a copper to ligand ratio of between 2:1 and 2:1.4 unless

otherwise stated. With this in mind, the diene **535** was screened against ligands **539-544** and **460** using the three solvents mentioned earlier.

After irradiation for 24h, the reaction mixtures were each filtered through a pad of silica, and the respective solvents evaporated. The samples were then re-dissolved in a 10:1 mixture of hexane : propan-2-ol and assayed by chiral HPLC. The initial crude results were encouraging, as each sample displayed an excess of one enantiomer of between 1.1:1 and 2.3:1, (actual crude data is tabulated in appendix 1A). However, none of the samples were pure, as the reactions hadn't gone to completion, and the starting material peak on the HPLC chromatograph overlapped with the major enantiomer of the product, possibly affecting the results. Some of the reaction that did proceed to a satisfactory end point (>80% complete), displayed a significant excess of one enantiomer over the other, when analysed by HPLC, however this could have been due to additional impurities in the crude product affecting the results. Some of the more promising reactions were scaled up (irradiated in the large-scale photochemical reactor), and the products purified by column chromatography, and once again analysed by chiral HPLC. In every case the enantiomers were calculated to be in a ratio of 1:1, i.e. a racemic mixture. To further confirm this evidence, we carried out the same experiments using the S,S enantiomer of the R,R bis oxazoline **544** as the ligand. On work up and purification, the HPLC chromatographs were almost identical to those obtained with the initial ligand. Overall these results effectively proved that the ligands **539-544** and **460** did not affect the stereoselectivity of the photochemical ring closure of diene **535**.

On returning to the literature, we found that the series of chiral Schiff base ligands described earlier in this chapter, were extremely effective ligands when used in conjunction with copper (I) in a number of different asymmetric reactions. The stable diimine Schiff base ligands **548a-f** were all prepared by the dehydration of aldehydes **546** and **547** with the chiral amines **545a,b** and **549**.[41]




The diene **535** was screened against the Schiff bases **548a-f** and the aforementioned solvents in a similar manner to that described previously, and the crude results can be seen summarised in appendix 1B. Once again we were hampered by the overlapping starting material peak on the HPLC trace, but we were able to establish that no selectivity was obtained by comparing results obtained with the opposing enantiomers of the Schiff base ligands e.g. **548b** and **548d**. Some of the reactions were also scaled up and purified before reanalysis confirmed racemic mixtures.

At this point we decided to diversify into chiral phosphine ligands, to see if the ligands chelating atom had any effect on the reaction. The commercially available ligands R, R BINAP **506**, R, R CHIRAPHOS **550** and R PROPHOS **551** (Figure 25)[30,42] were all tested, but again very similar trends were observed.

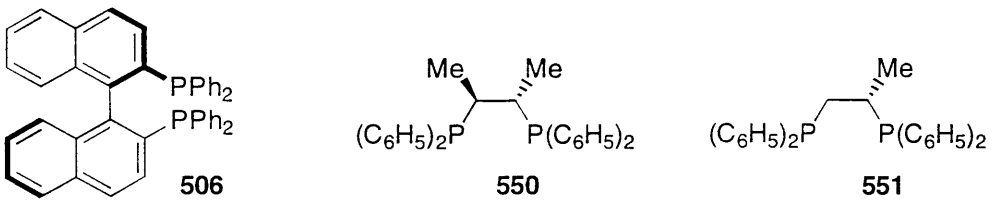



**Figure 25**

At this stage we decided to re-evaluate our model system, and when comparing it to those already reported,[38] we realised that the methyl group present in the Langer and Mattay system (Scheme 90) could have a bearing on the outcome of the reaction.

Figure 26 illustrates how the additional bulk of an alkyl or aryl substituent on one of the olefin moieties may interact better with $C_2v$ chiral ligand. In this case **553b** will be formed preferentially over **553a** due to the proximity of the substituents R and R' in the case of the co-ordinated complex**552a**.

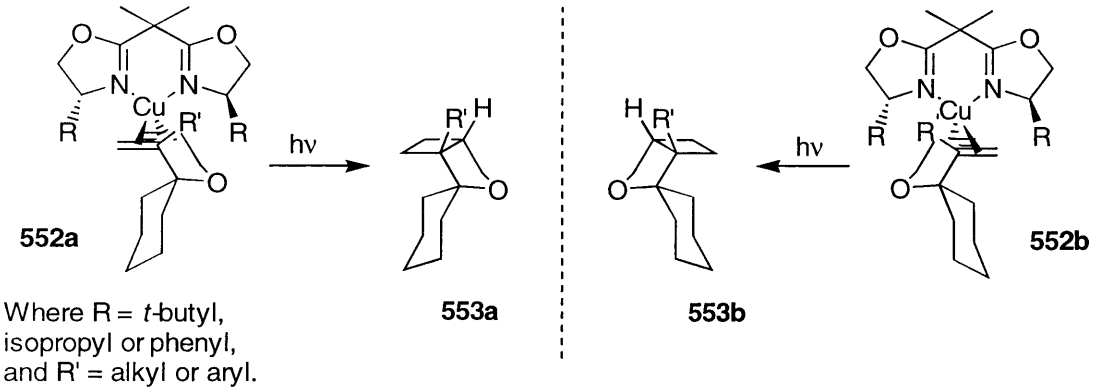
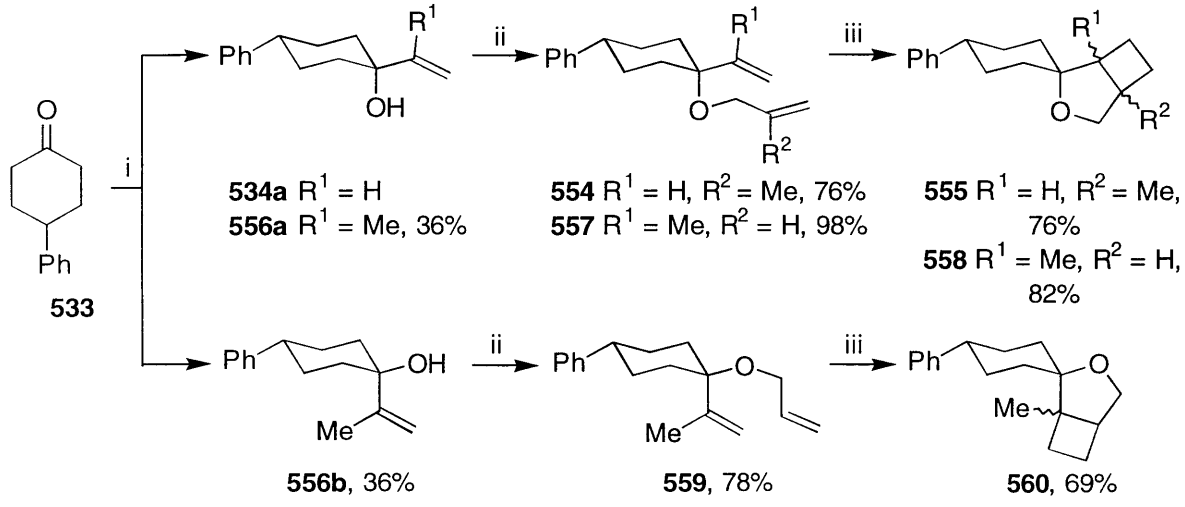



**Figure 26**

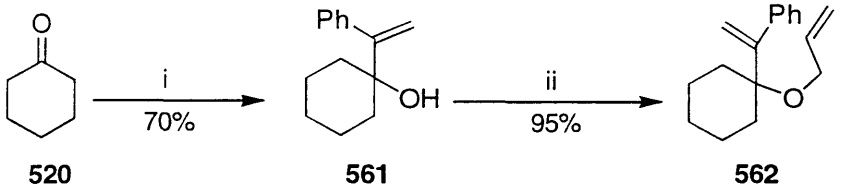
A number of methyl substituted dienes **554**, **557** and **559** (Scheme 94) bearing methyl functionality were prepared in a similar manner to previously described from alcohols **534a**, **556a** and **556b**, and each were subjected to hν in the presence of copper triflate co-ordinated to a variety of ligands: Pfaltz ligand **544**, diimine ligand **548f**, phosphino ligand **550** and L-diethyl tartrate **496b**.




**Scheme 94,** Reagents and conditions: i, $H_2C$=CRMgBr, THF, reflux, 4h; ii, NaH, THF, reflux, 2h, then $CH_2$=$CRCH_2Br$, DMPU, 4h; iii, $(CuOTf)_2.C_6H_6$, $Et_2O$, hν, 24h.

The reactions were all carried out in the large scale photochemistry reaction vessels and the products **555** and **558** were isolated, and purified by column chromatography to ensure accurate measurement of enantiomeric excess and in every case the ratio of enantiomers was effectively 1:1. The enantiomers of product **560** were inseparable by

HPLC, as was observed in the case of the unsubstituted *trans* alcohol derived analogue **538**. To investigate the effect of a larger substituent, we synthesised **562** (Scheme 95), by Grignard addition of phenyl magnesium bromide to cyclohexanone **520** to afford **561**, followed by O-alkylation using allyl bromide to give **562** in 67% yield overall.




**520** **561** **562**

**Scheme 95,** Reagents and Conditions: i, α-bromostyrene, Mg, THF, 0°C to rt 20h; ii, ii, NaH, THF, reflux, 2h, then $CH_2$=$CHCH_2Br$, DMPU, 4h.

Unfortunately, the photocyclisation in the presence of CuOTf afforded a wide range of inseparable by-products, probably due to the vinyl aromatic functionality, allowing radical reactions to take place easily under the reaction conditions.

One interesting factor that we noticed during the screening of the previous reactions, was that when L-diethyl tartrate **469b** was used as a ligand the reaction proceeded much further than in most of the other cases, and the phosphino ligands needed longer to react than any others. In an attempt to rationalise these results, we decided to monitor the kinetics of the cyclisation reactions. To do this we went back to the original simple diene substrate **514**, as the reaction progress could be followed by capillary GLC. By removing an aliquot of the reaction mixture at regular intervals of time, and analysing the sample, it is possible to see the consumption of the diene and formation of the spiro-cyclohexane tricycle as a function of time. The results of this study can be seen in Figure 27.

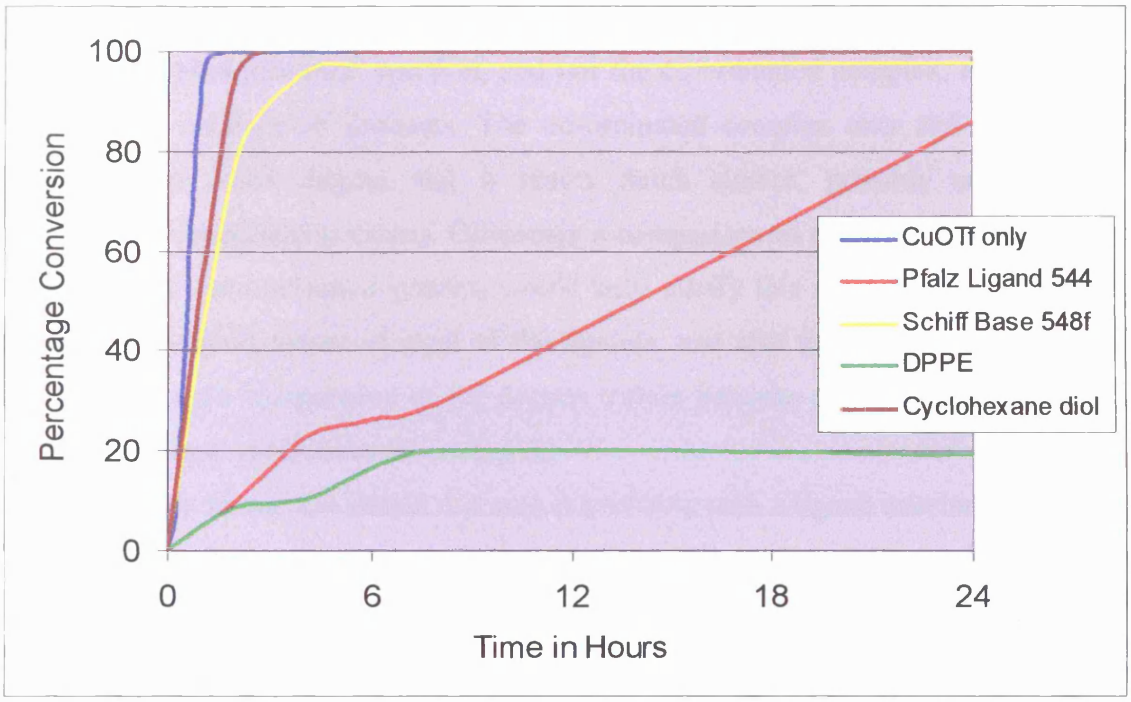



**Figure 27,** Kinetic plot of the photochemical ring closure of diene **514** in the presence of a slight excess of Cu(I) catalyst with a variety of ligands.

Quite clearly the uncoordinated copper species (indicated by the blue line) reacts at a much faster rate than any of the other co-ordinated species. The Schiff base ligand (yellow line) reacts faster than the bis oxazoline ligand (red line), which in turn reacts faster than the phosphine ligand (green line). This fairly dramatic change in the rate of reaction upon addition of the ligand, leads us to think that the ligand and metal are in an equilibrium with the strongest bound ligands slowing the reaction more than the less tightly bound.

$$[CuL_n]^+ \rightleftharpoons Cu^+ + nL$$

Using a hard soft acid and base argument, it appears that the phosphino ligand, being the softest, would bind the inherently soft copper (I) metal atom the tightest. When nitrogen is used as the co-ordinating atom, the copper (I) wouldn't be bound so tight, as nitrogen is slightly harder than phosphorous. To back up this hypothesis, the same rate determining experiment was carried out using cyclohexane diol as the co-ordinating ligand. The oxygen atoms that co-ordinate the metal are quite hard, and would lead to a fairly loosely bound complex. This appears to be the case, as the brown plot (Figure 27) shows that the reaction is slowed much less than the previous examples.

This leads us to propose that it is only the excess of free copper in solution that catalyses the photochemical reaction, and not the co-ordinated complex, thus resulting in a racemic mixture of products. The co-ordinated complex may still catalyse the reaction to a small degree, but it reacts much slower, possibly producing an undetectable enantiomeric excess. Obviously a comparison of the UV spectra of the co-ordinated and uncoordinated systems would help clarify this reasoning. Unfortunately due to the aromatic nature of most of the ligands, and also the absorptions associated with the aromatic components of the copper triflate benzene complex, the results of a UV spectroscopic study were inconclusive.

The key to success within this area is probably with a ligand accelerated reaction similar to the dihydroxylation reaction discussed earlier, and unfortunately the ligands tested so far dramatically reduce the rate of reaction. We thought that by changing the counter ion of the original copper salt, the rate of the uncoordinated reaction would be slower, and this in turn may make the co-ordinated complex more competitive, leading to a higher degree of asymmetric induction. Figure 28 shows that the change in counter ion does significantly slow the photochemical reaction where copper (I) triflate is denoted by the blue line, copper (I) cyanide by the yellow line and copper (I) bromide dimethyl sulfide by the red line.

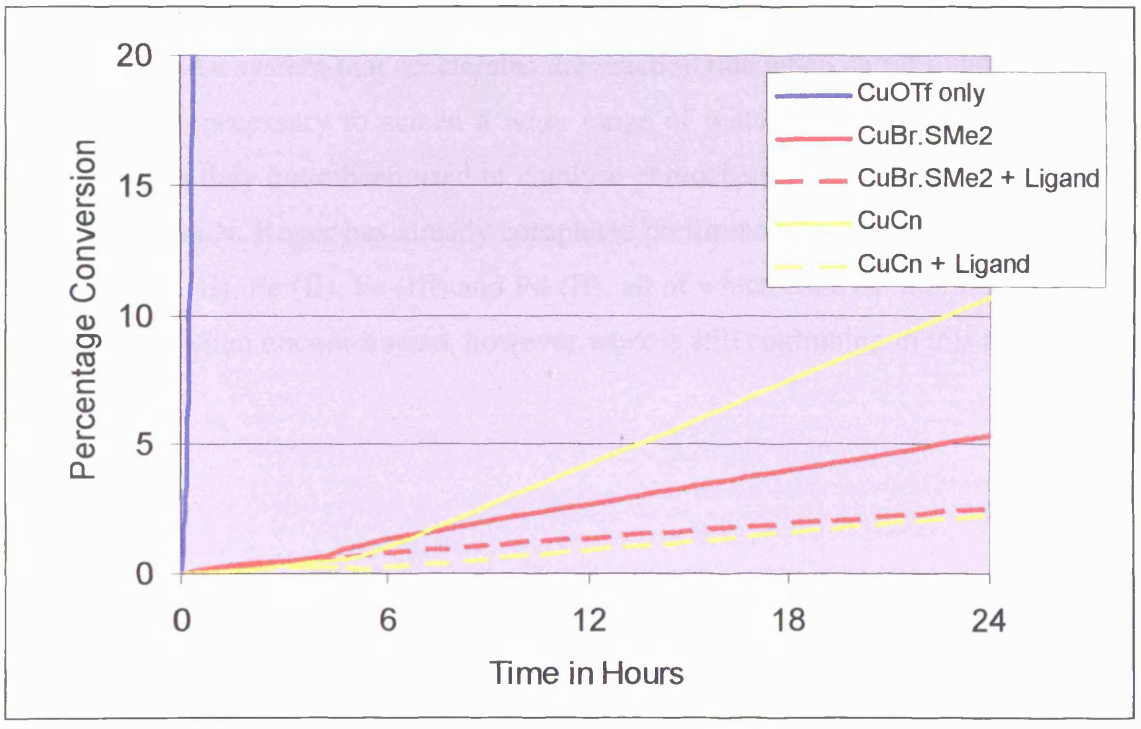



**Figure 28,** Kinetic plot of the photochemical ring closure of diene **514** in the presence of Cu (I) catalyst with a variety counter ions where the ligand is **548f**.

However, when the metal is co-ordinated to a ligand, in this example the Schiff base **548f**, the copper (I) cyanide (broken yellow line) is much slower than the uncoordinated metal, the reaction only 2.5% complete after 24h. The same is true for the co-ordinated copper (I) bromide dimethyl sulfide (broken red line).

### 4.6.1 Conclusions

We have seen from chapter 3 that it is possible to control the diastereoselectivity of a photochemical [2+2] ring closure reaction by intramolecular influences. In this study however, we have not been able to control the stereochemical outcome using intermolecular means. From the literature[38] and our own findings, it is clear that upon co-ordination, the copper (I) catalyst used for the ring closure, is deactivated with respect to catalysing the reaction. We have demonstrated that it is likely that the uncoordinated copper (I) present in solution is responsible for cyclising the large majority, if not all of the product formed in the photochemical ring closure.

### 4.6.2 Future Work:

To find a system that accelerates the reaction rate when chiral ligands are added, it is probably necessary to screen a wide range of metals. $Ag^+$ and $Rh^+$ are potential candidates, as they have been used to catalyse photochemical reactions in the past.[34] A colleague Miss N. Roper has already completed preliminary tests on a number of metals including Cu (II), Fe (II), Fe (III) and Pd (II), all of which catalyse the ring closure to a small degree when uncoordinated, however work is still continuing in this area.

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# Chapter 5

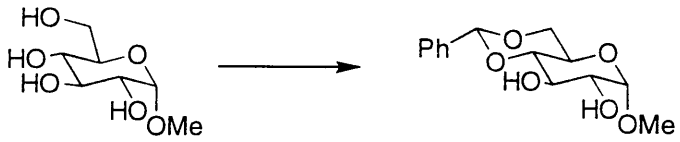
# Experimental

## 5.1 General Experimental

The synthesis of some compounds on a large scale proved to be laborious, and therefore experimental procedures for compounds prepared previously have been included where modifications to the published procedure have been employed, or little or no data for compounds was available. All reactions were performed under an atmosphere of nitrogen (unless otherwise stated) 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. 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 C60 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 $CaSO_4$. HPLC was performed using a Shimadzu LC-6 liquid chromatograph with a Daicel® Chiralcel OD-H chiral column. GLC was carried out using a Perkin Elmer Autosystem XL gas chromatograph with a P.E. elite series 5 column 30.0×0.25μL. 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), weak (w) or broad (br.). 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.

## 5.2 Experimental

### Methyl-(*R*)-4,6-*O*-benzylidene-α-D-glucopyranoside (301)

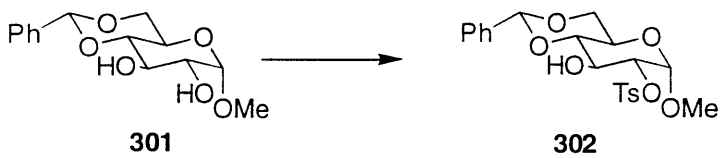



**300** **301**

Methyl-α-D-glucopyranoside **300** (68.0g, 0.35mol), benzaldehyde dimethyl acetal (52.8mL, 0.35mol), dry DMF (400mL), and *para*-toluene sulfonic acid monohydrate (200mg, 1.05mmol), were placed in a flask fitted with a water condenser attached to a water pump. The solution was then heated (65°C) under vacuum, for 3h. The DMF was then removed under reduced pressure and the resulting white solid dispersed in sodium hydrogen carbonate solution (560mL water, 11g carbonate), on a hot water bath. After cooling, the product was filtered, washed with water (400mL), and dried *in vacuo* overnight over phosphorous pentoxide. The white solid was recrystallised from isopropanol (180mL) and pyridine (3.0mL) to give **301** (62.95g, 64%): mp 160-161°C (lit.[1] mp 166-167°C); $\delta_H$ (250 MHz; $CDCl_3$) 3.41 (3H, s, OMe), 3.44 (1H, obscured t, *J* 10.3, 4-H), 3.57 (1H, dd, *J* 3.9, 9.1, 2-H), 3.73 (2H, dt, t, overlapping, *J* 4.3, 10.3, *J* 10.3, 5-H, 6ax-H), 3.89 (1H, t, *J* 9.1, 3-H), 4.26 (1H, dd, *J* 4.3, 10.3, 6eq-H), 4.72 (1H, d, *J* 3.9, 1-H), 5.49 (1H, s, 7-H), 7.32-7.53 (5H, m, Ph); $\delta_C$ (62.9 MHz, $CDCl_3$) 55.8 ($CH_3$, OMe), 62.8 (CH, C5), 69.3 ($CH_2$, C6), 71.5 (CH, C3), 73.1 (CH, C2), 81.4 (CH, C4), 100.4 (CH, C7), 102.3 (CH, C1), 126.8, (CH, Ph), 128.8 (CH, Ph), 129.0 (CH, Ph), 137.6 (C, Ph).

This is a literature compound.[1]

### Methyl-(*R*)-4,6-*O*-benzylidene-2-*O*-p-toluenesulphonyl-α-D-glucopyranoside (302)



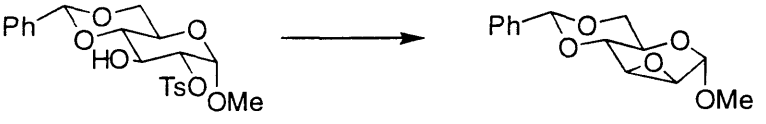

**301** **302**

Methyl 4,6-*O*-benzylidene-α-D-glucopyranoside **301** (30.0g, 0.11mol), was dissolved in dry dichloromethane (300mL). To this solution was added *N,N*-dimethyl-4-

aminopyridine (2.6g, 0.02mol), and triethylamine (44mL, 0.32mol). This solution was cooled to 0°C and *para*-toluenesulfonyl chloride (22.29g, 0.12mol), added in portions. The reaction mixture was left to stir at 0°C for 15min and then at room temperature for 2h. The reaction was quenched by the addition of water (250mL), extracted into dichloromethane (2x200mL), dried and evaporated to dryness. The resultant yellow syrup was dissolved in isopropanol (40mL), and concentrated. This addition and concentration was repeated until a white foam was obtained. The product was then finally precipitated by the addition of hot isopropanol, the white solid was filtered, washed with isopropanol and dried *in vacuo* to give a white crystalline solid **302** (41.47g, 86%): mp 149-151°C (lit.[2] 153-155°C); $\delta_H$ (250 MHz; $CDCl_3$) 2.40 (3H, s, Ts-Me), 3.42 (3H, s, OMe), 3.47 (1H, t, *J* 9.3, 4-H), 3.70 (1H, t, *J* 9.3, 6ax-H), 3.89 (1H, dt, *J* 9.3, 4.4, 5-H), 4.10 (1H, t, *J* 9.3, 3-H), 4.24 (1H, dd, *J* 9.3, 4.4, 6eq-H), 4.42 (1H, dd, *J* 9.3, 3.8, 2-H), 4.82 (1H, d, *J* 3.8, 1-H), 5.49(1H, s, 7-H), 7.35 (5H, m, Ph), 7.48 (2H, m, m-Ts), 7.84 (2H, m, o-Ts); $\delta_C$ (62.9 MHz, $CDCl_3$) 22.0 ($CH_3$, Ts), 56.3 ($CH_3$, OMe), 62.8 (CH, C5), 68.8 (CH, C3), 69.1 ($CH_2$, C6), 80.1 (CH, C2), 81.3 (CH, C4), 98.8 (CH, C7), 102.2 (CH, C1), 126.7 (CH, Ph), 128.4 (CH, Ts), 128.9 (CH, Ph), 129.6 (CH, Ph), 130.2 (CH, Ts), 133.6 (C, Ts), 137.4 (C, Ph), 146.0 (C, Ts).

This is a literature compound.[2]

**Methyl-(*R*)-2,3-anhydro-4,6-*O*-benzylidene-α-D-mannopyranoside (17)**




**302** **17**

The tosylate **302** (40.75g, 0.093mol), was dissolved in dry DMF (322mL), and cooled to 0°C in an ice bath. Sodium hydride (80% dispersion in paraffin oil, 3.08g, 0.1mol) was added portionwise and the reaction stirred at room temperature for 2h. Ethanol (32mL) was added with cooling and the resulting solution poured into ice/water (160mL). The resulting white precipitate was filtered and dried under suction for 1h. The solid was recrystallised from isopropanol (120mL) to give a white crystalline solid **17** (23.56g, 96%): mp 143-145°C (lit.[3] 143-145°C): $\delta_H$ (250MHz; $CDCl_3$) 3.00 (1H, d, *J* 3.8, 2-H), 3.30 (3H, s, OMe), 3.37 (1H, obscured, 4-H), 3.54 (3H, overlapping, 3-H, 5-H, 6ax-H), 4.15 (1H, m, 6eq-H), 4.74 (1H, s, 1-H), 5.40 (1H, s, 7-H), 7.31-7.50 (5H, m,

Ph); $\delta_C$ (62.9 MHz, $CDCl_3$) 50.9 (CH, C3), 54.2 (CH, C2), 56.1 ($CH_3$, OMe), 62.1 (CH, C5), 69.8 ($CH_2$, C6), 75.3 (CH, C4), 97.3 (CH, C7), 102.8 (CH, C1), 126.6, (CH, Ph), 128.9 (CH, Ph), 129.7 (CH, Ph), 137.5 (C, Ph).

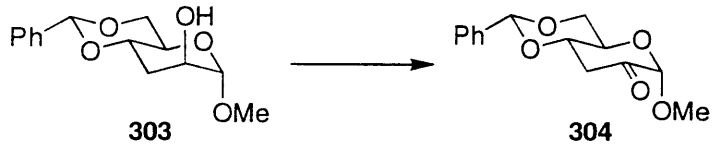
This is a literature compound.[3]

**Methyl-(*R*)-4,6-*O*-benzylidene-3-deoxy-α-D-*aribino*-hexopyranoside (303)**


Methyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-mannopyranoside **17** (10.0g, 38mmol) was dissolved in dry THF (230mL) and the stirred solution was cooled to 0°C. Lithium aluminium hydride (2.9g, 76mmol) was added portionwise and once the vigorous reaction had subsided, the solution was heated to reflux temperature for 5h. The reaction mixture was cooled in an ice bath and water (2.9mL) was added dropwise to destroy unreacted LAH. A 15% solution of sodium hydroxide (2.9mL) followed by water (8.7mL) were added dropwise. The resulting dispersion was diluted with diethyl ether (200mL) and filtered. The organic phase was washed with brine (200mL), dried and evaporated to give white solid **303** (9.5g, 95%), which was used without further purification. A small sample was purified by recrystallisation from petroleum ether and diethyl ether: mp 105-106°C (lit.[4] 111-112°C); $\delta_H$ (250MHz, $CDCl_3$) 2.02 (1H, t, 3ax-H), 2.05 (1H, dd, overlapping, 3eq-H), 2.44 (1H, br s, O*H*), 3.39 (3H, s, OMe), 3.74-3.98 (4H, overlapping, 2-H, 4-H, 5-H, 6ax-H), 4.22 (1H, dd, *J* 2.9, 8.2, 6eq-H), 4.50 (1H, d, *J* 0.95, 1-H), 5.59 (1H, s, 7-H), 7.32-7.59 (5H, m, Ph); $\delta_C$ (62.9 MHz, $CDCl_3$) 32.4 ($CH_2$, C3), 55.3 ($CH_3$, OMe), 65.4 (CH, C2), 68.8 (CH, C5), 69.7 ($CH_2$, C6), 74.3 (CH, C4), 101.2 (CH, C1), 102.5 (CH, C7), 126.6, (CH, Ph), 128.7 (CH, Ph), 129.5 (CH, Ph), 137.9 (C, Ph).

This is a literature compound.[4]

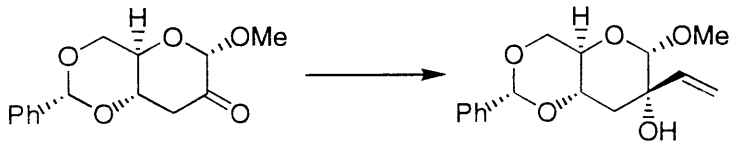
**Methyl-(*R*)-4,6-*O*-benzylidene-3-deoxy-α-D-*erythro*-hexopyranosid-2-ulose (304)**




Oxalyl chloride (1.1mL, 12.2mmol) in dry dichloromethane (10mL) was added dropwise to a cooled solution of dimethyl sulfoxide (1.73mL, 24.2mmol) in dry dichloromethane (17mL). Once addition was complete, the mixture was stirred for 20 mins at -78°C, then a solution of alcohol **303** (2.7g, 10.1mmol) in dry dichloromethane (15mL) was added dropwise, whilst maintaining the temperature at -78°C. On complete addition, the solution was stirred at -78°C for 3h. Triethylamine (15mL, 0.1mol) was then added dropwise, and the solution allowed to warm to room temperature. The reaction mixture was diluted with dichloromethane (100mL) and then washed with 1M hydrochloric acid (2x50mL) followed by saturated sodium hydrogen carbonate (2x50mL) and then brine (100mL). The organic layer was dried and evaporated to give a yellow solid. This was recrystallised from hot propanol (8mL) to give yellow crystalline solid **304** (2.45g, 91%): mp 114-115°C (lit.[4] 114-115°C); $\delta_H$ (250MHz, $CDCl_3$) 2.89 (1H, t, *J* 3.0, 3eq-H), 2.96 (1H, overlapping, 3ax-H), 3.51 (3H, OMe), 3.79 (1H, t, *J* 10.4, 6ax-H), 3.87 (1H, ddd, overlapping, *J* 3.0, 4.8, 10.4, 4-H), 4.16 (1H, dt, *J* 4.8, 10.4, 5-H), 4.40 (1H, dd, *J* 4.8, 10.4, 6eq-H), 4.58 (1H, s, 1-H), 5.58 (1H, s, 7-H), 7.34-7.56 (5H, m, Ph); $\delta_C$ (62.9 MHz, $CDCl_3$) 43.2 ($CH_2$, C3), 56.1 ($CH_3$, OMe), 64.5 (CH, C5), 69.5 ($CH_2$, C6), 76.9 (CH, C4), 101.0 (CH, C1), 101.9 (CH, C7), 126.6, (CH, Ph), 128.8 (CH, Ph), 129.7 (CH, Ph), 137.3 (C, Ph), 199.2 (C, C2).

This is a literature compound.[4]

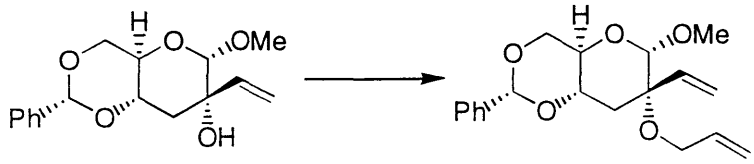
**Methyl-(*R*)-4,6-*O*-benzylidene-3-deoxy-2-*C*-ethenyl-α-D-glucopyranoside (305).**




Vinylmagnesium chloride (20.60 mL, 34.70 mmol, 15% wt. solution in THF) was added dropwise to an ice-cooled solution of the ketone **304** (1.85 g, 7.00 mmol) in dry THF (10.0 mL). The solution was then heated to reflux for 4 h and allowed to cool to

room temperature, then quenched by dropwise addition of saturated ammonium chloride solution (30 mL). The resulting mixture was extracted into diethyl ether (2 × 100 mL), and the combined organic layers were 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 (4:1) as the eluent yielded **305** as a colourless oil (1.35 g, 75%): $R_f$ 0.13, petroleum ether-diethyl ether (1:1); $[\alpha]^{20}_D$ + 76.5° (*c* 3.45, $CHCl_3$); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 3550m, 2900w, 1400w, 1110s, 1050s, 1030m; $\delta_H$ (300 MHz, $CDCl_3$) 1.95 (1H, t, *J* 11.5, 3ax-H), 2.09 (1H, dd, *J* 4.2, 11.5, 3eq-H), 2.63 (1H, d, *J* 0.6, O*H*), 3.39 (3H, s, OMe), 3.52-3.62 (1H, m, overlapping, 4-H), 3.68 (1H, t, *J* 9.1, 6ax-H), 3.68-3.76 (1H, m, overlapping, 5-H), 4.20 (1H, dd, *J* 3.5, 9.1, 6eq-H), 4.35 (1H, s, 1-H), 5.23 (1H, dd, *J* 1.3, 10.9, 8-$H_{cis}$), 5.43 (1H, s, 9-H), 5.47 (1H, dd, *J* 1.3, 17.4, 8-$H_{trans}$), 6.03 (1H, ddd, *J* 0.6, 10.9, 17.4, 7-H), 7.32-7.52 (5H, Ph); $\delta_C$ (75.8 MHz, $CDCl_3$) 39.1 ($CH_2$, C3), 55.8 ($CH_3$, OMe), 64.7 (CH, C5), 69.8 ($CH_2$, C6), 72.6 (C, C2), 76.0 (CH, C4), 102.2 (CH, C9), 102.3 (CH, C1), 116.5 ($CH_2$, C8), 126.6 (CH, Ph), 128.8 (CH, Ph), 129.6 (CH, Ph), 137.8 (C, Ph), 139.1 (CH, C7); *m/z* (FAB) 293 ($MH^+$, 52), found $MH^+$, 293.1389; $C_{16}H_{21}O_5$ requires 293.1389.

**Methyl-(*R*)-4,6-*O*-benzylidene-2-*C*-ethenyl-3-deoxy-2-*O*-propenyl-α-D-glucopyranoside (306).**

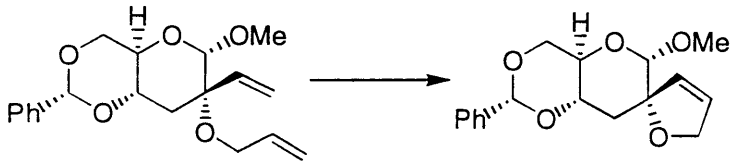



**305** **306**

Sodium hydride (169 mg, 60% dispersion in mineral oil, 4.23 mmol) was added portionwise to an ice-cooled solution of alcohol **305** (1.18 g, 4.00 mmol) in dry THF (30.0 mL). The resulting mixture was heated to reflux for 2 h and allowed to cool to room temperature. Allyl bromide (710 μL, 8.20 mmol) and DMPU (400 μL) were then added, the mixture was heated to reflux for 4 h, allowed to cool to room temperature, and quenched by addition of water (10 mL). The resulting mixture was then extracted into diethyl ether (2 × 50 mL), the combined organic layers washed with saturated sodium chloride solution (50 mL), dried, and evaporated to leave a yellow solid. Chromatography on silica gel with petroleum ether-diethyl ether (3:1) as the eluent

yielded **306** as a white solid (1.03 g, 77%): mp 146-147°C; $R_f$ 0.52, petroleum ether-diethyl ether; $[\alpha]^{20}_D$ + 75.1° (*c* 2.48, $CHCl_3$); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 3050s, 2950m, 2300m, 1425m br, 1260s; $\delta_H$ (301 MHz, $CDCl_3$) 2.16 (1H, dd, *J* 4.6, 11.5, 3eq-H), 2.25 (1H, t, *J* 11.5, 3ax-H), 3.52 (3H, s, OMe), 3.67 (1H, ddd, *J* 4.4, 4.6, 11.5, 4-H), 3.76 (1H, t, *J* 9.4, 6ax-H), 3.85 (1H, dd, *J* 4.4, 9.4, 5-H), 3.91 (1H, ddt, *J* 1.4, 5.5, 11.5, C*H*H 9-H), 4.02 (1H, ddt, *J* 1.4, 5.5, 11.5, CH*H* 9-H), 4.31 (1H, dd, *J* 4.4, 9.4, 6eq-H), 4.72 (1H, s, 1-H), 5.18 (1H, ddd, *J* 1.4, 3.6, 10.5, 11-$H_{cis}$), 5.32 (1H, ddd, *J* 1.4, 3.6, 16.5, 11-$H_{trans}$), 5.51 (1H, dd, *J* 1.7, 7.2, 8-$H_{cis}$), 5.53 (1H, s, 12-H), 5.54 (1H, dd, *J* 1.7, 13.7, 8-$H_{trans}$), 5,95 (1H, dd, overlapping, 7-H), 5.87-6.02 (1H, m, overlapping, 10-H), 7.32-7.59 (5H, Ph); $\delta_C$ (75.8 MHz, $CDCl_3$) 36.7 ($CH_2$, C3), 55.4 ($CH_3$, OMe), 64.0 ($CH_2$, C9), 64.8 (CH, C5), 69.8 ($CH_2$, C6), 76.2 (CH, C4), 77.5 (C, C2), 100.3 (CH, C1), 102.3 (CH, C12), 116.9 ($CH_2$, C8), 118.8 ($CH_2$, C11), 126.6 (CH, Ph), 128.8 (CH, Ph), 129.5 (CH, Ph), 135.5 (CH, C10), 137.8 (C, Ph), 139.1 (CH, C7); *m/z* (FAB) 333 ($MH^+$, 100); elemental analysis found: C, 68.43; H, 7.08. $C_{19}H_{24}O_5$ requires C, 68.66; H, 7.28%.

**Methyl-(*R*)-4,6-*O*-benzylidene-2,3-dideoxy-2(*S*)-spiro(2,5'-2',5'-dihydrofuran)-α-D-glucopyranoside (307).**

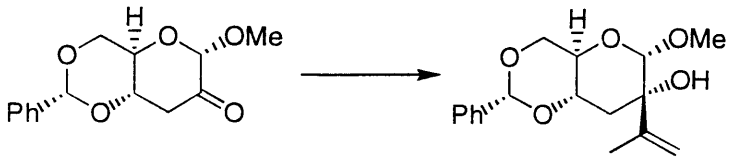



**306** **307**

Nitrogen gas was bubbled through a solution of the diene **306** (223 mg, 0.67 mmol) in benzene (10 mL) for 2-3 minutes. The catalyst **176b** (10 mg, 0.012 mmol, 1.4 mol%) was then added and the solution heated at 60°C for 36 h. The solvent was then 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 **307** as a white solid (173 mg, 85%): mp 86-87°C; $R_f$ 0.12, petroleum ether-diethyl ether (1:1); $[\alpha]^{14}_D$ + 47.8° (*c* 5.8, $CHCl_3$); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 2760m br, 1450w, 1380m, 1050s; $\delta_H$ (250 MHz; $CDCl_3$) 2.02 (1H, dd, *J* 4.1, 11.3, 3eq-H), 2.35 (1H, t, *J* 11.3, 3ax-H), 3.48 (3H, s, OMe), 3.63 (1H, ddd, *J* 4.1, 9.0, 11.3, 4-H), 3.77 (1H, t, *J* 9.4, 6ax-H), 3.86 (1H, ddd, overlapping, *J* 3.8, 9.0, 9.4, 5-H), 4.31 (1H, dd, *J* 3.8, 9.4, 6eq-H), 4.39 (1H, s, 1-H), 4.63-4.77 (2H, m, 9-H), 5.54 (1H, s, 10-H), 6.02-6.15 (2H, overlapping, 7-H and 8-H), 7.30-7.57 (5H, Ph);

$\delta_C$ (62.9 MHz, $CDCl_3$) 36.5 ($CH_2$, C3), 55.5 ($CH_3$, OMe), 64.3 (CH, C5), 69.9 ($CH_2$, C6), 75.2 ($CH_2$, C9), 77.2 (CH, C4), 89.5 (C, C2), 102.2 (CH, C10), 102.3 (CH, C1), 126.6 (CH, Ph), 128.7 (CH, Ph), 129.2 (CH, C8), 129.5 (CH, Ph), 130.4 (CH, C7), 137.9 (C, Ph); *m/z* (FAB) 305 ($MH^+$, 47), found $MH^+$, 305.1389; $C_{17}H_{21}O_5$ requires 305.1389; elemental analysis found: C, 66.97; H, 6.66. $C_{17}H_{20}O_5$ requires C, 67.09; H, 6.62%.

**Methyl-(*R*)-4,6-*O*-benzylidene-3-deoxy-2-*C*-(1-methylethenyl)-α-D-glucopyranoside (308)**

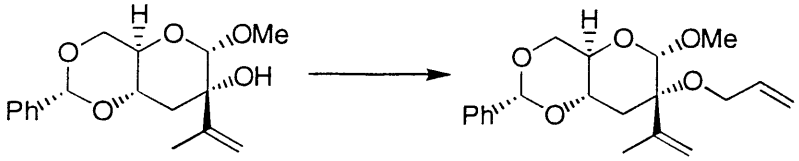



**304** **308**

Isopropenylmagnesium bromide (19.00 mL, 9.50 mmol, 0.5 M solution in THF) was added dropwise to a cooled (-78°C) solution of the ketone **304** (500 mg, 1.9 mmol) in dry THF (40.0 mL). The solution was then stirred at -50°C for 4 h and allowed to warm to room temperature, then quenched by dropwise addition of saturated ammonium chloride solution (40 mL). The resulting mixture was extracted into diethyl ether (2 × 120 mL), and the combined organic layers were washed with saturated sodium chloride solution (150 mL), dried, and evaporated to leave a yellow solid. Chromatography on silica gel with petroleum ether-diethyl ether (3:1) as the eluent yielded **308** as a white solid (381 mg, 66%): mp 76-76°C; $R_f$ 0.24, petroleum ether-diethyl ether (1:1); $[\alpha]^{20}_D$ + 71.0° (*c* 4.2, $CHCl_3$); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 3520m, 2950m br, 1450m, 1375m br, 1110s, 1050s; $\delta_H$ (250MHz, $CDCl_3$) 1.88 (1H, t, overlapping, *J* 12.0, 3ax-H), 1.88 (3H, s, 9-H), 2.34 (1H, dd, *J* 4.1, 12.0, 3eq-H), 2.73 (1H, s, O*H*), 3.48 (3H, s, OMe), 3.55 (1H, ddd, *J* 4.1, 8.9, 12.0, 4-H), 3.69 (1H, t, overlapping, *J* 9.7, 6ax-H), 3.77 (1H, ddd, *J* 4.0, 8.9, 9.7, 5-H), 4.25 (1H, dd, *J* 4.0, 9.7, 6eq-H), 4.68 (1H, s, 1-H), 5.09 (1H, s, 8-$H_{cis}$), 5.18 (1H, s, 8-$H_{trans}$), 5.47 (1H, s, 10-H), 7.29-7.58 (5H, m, Ph); $\delta_C$ (62.9MHz, $CDCl_3$) 19.2 ($CH_3$, C9), 36.4 ($CH_2$, C3), 55.7 ($CH_3$, OMe), 65.4 (CH, C5), 69.8 ($CH_2$, C6), 74.0 (C, C2), 76.0 (CH, C4), 101.7 (CH, C1), 102.2 (CH, C10), 114.1 ($CH_2$, C8), 126.6 (CH, Ph), 128.7 (CH, Ph), 129.5 (CH Ph), 137.9 (C, Ph), 145.3 (C, C7); *m/z* (FAB) 307

($MH^+$, 86); elemental analysis found C 66.64, H 7.23, $C_{17}H_{22}O_5$ requires C 66.15, H 7.16.

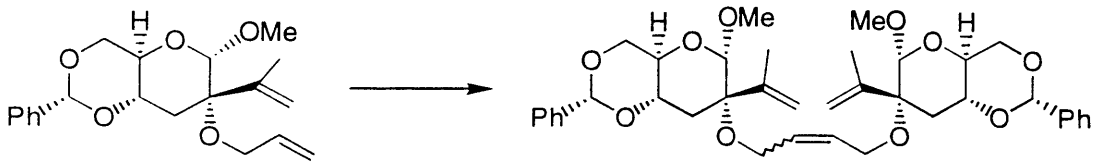
**Methyl-(*R*)-4,6-*O*-benzylidene-3-deoxy-2-*C*-(1-methylethenyl)-2-*O*-propenyl-α-D-glucopyranoside (309)**




**308** **309**

Sodium hydride (137 mg, 60% dispersion in mineral oil, 3.40 mmol) was added portionwise to an ice-cooled solution of alcohol **308** (525 mg, 1.70 mmol) in dry THF (20.0 mL). The resulting mixture was heated to reflux for 2 h and allowed to cool to room temperature. Allyl bromide (300 μL, 3.40 mmol) and DMPU (200 μL) were then added, the mixture was heated to reflux for 4 h, allowed to cool to room temperature, and quenched by addition of water (10 mL). The resulting mixture was then extracted into diethyl ether (2 × 100 mL), the combined organic layers washed with saturated sodium chloride solution (150 mL), dried, and evaporated to leave a yellow oil. Chromatography on silica gel with petroleum ether-diethyl ether (3:1) as the eluent yielded **309** as a white solid (455 mg, 77%): mp 151-153°C; $R_f$ 0.45, petroleum ether-diethyl ether (1:1); $[\alpha]^{20}_D$ + 78.6° (*c* 4.9, $CHCl_3$); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 2900m br, 1450m, 1390m, 1100m br, 1050s; $\delta_H$ (301.5MHz, $CDCl_3$) 1.79 (3H, s, 9-H), 2.07 (1H, t, *J* 12.0, 3ax-H), 2.26 (1H, dd, *J* 3.9, 12.0, 3eq-H), 3.48 (3H, s, OMe), 3.54 (1H, dd, *J* 3.9, 9.2, 4-H), 3.68 (1H, t, *J* 10.1, 6ax-H), 3.73-3.86 (3H, 5-H, 10-H), 4.24 (1H, dd, *J* 4.5, 10.1, 6eq-H), 4.88 (1H, s, 1-H), 5.12 (1H, dd, *J* 1.5, 10.2, 12-$H_{trans}$), 5.20 (1H, s, 8-$H_{cis}$) 5.26 (1H, s, 8-$H_{trans}$), 5.29 (1H, m, overlapping, 12-$H_{cis}$), 5.48 (1H, s, 13-H), 5.88 (1H, ddd, *J* 5.4, 10.2, 11-H); $\delta_C$ (75.8MHz, $CDCl_3$) 18.6 ($CH_3$, C9), 33.1 ($CH_2$, C3), 54.9 ($CH_3$, OMe), 63.3 ($CH_2$, C10), 65.1 (CH, C5), 69.5 ($CH_2$, C6), 75.5 (CH, C4), 78.6 (C, C2), 99.1 (CH, C13), 101.8 (CH, C1), 116.3 ($CH_2$, C12), 117.0 ($CH_2$, C8), 126.2 (CH, Ph), 128.3 (CH, Ph), 129.1 (CH, Ph), 134.8 (CH, C11), 137.2 (C, Ph), 143.1 (C, C7); *m/z* (FAB) 347 ($MH^+$, 53); elemental analysis found C 69.17, H 7.54, $C_{20}H_{26}O_5$ requires C 69.34, H 7.56.

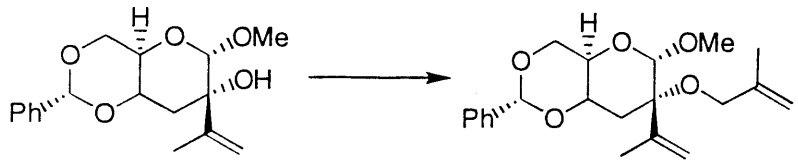
**1,4-Bis-(Methyl (*R*)-4,6-*O*-benzylidene-3-deoxy-2-*C*-(1-methylethenyl)-α-D-glucopyranosid-2-*O*-yl)-but-2-ene (310)**



**309** **310**

Nitrogen gas was bubbled through a solution of the diene **309** (167 mg, 0.49 mmol) in benzene (10 mL) for 2-3 minutes. The catalyst **176b** (10 mg, 0.012 mmol, 2.5 mol%) was then added and the solution heated at 60°C for 24 h. The solvent was then 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 **309** (30mg, 23%) and **310** as a white foam (81 mg, 49%): $R_f$ 0.31, petroleum ether-diethyl ether (1:1); $[\alpha]^{20}_D$ + 81.3° (*c* 3.8, $CHCl_3$); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 3000m, 2940m, 2860m, 1680w, 1450m, 1360m, 1100s; $\delta_H$ (250 MHz, $CDCl_3$) 1.71 (6H, Me, Me'), 1.98 (2H, t, *J* 11.6, 3ax-H, 3ax'-H), 2.16 (1H, dd, *J* 3.5, 11.6, 3eq-H, 3eq'-H), 3.39 (6H, s, OMe, OMe'), 3.46 (2H, dt, overlapping, *J* 3.5, 11.6, 4-H, 4'-H), 3.59 (2H, t, *J* 10.1, 6ax-H, 6ax'H), 3.66-3.81 (6H, overlapping, 5-H, 5'-H, 10-H, 10'-H), 4.16 (2H, dd, *J* 4.1, 10.1, 6eq-H, 6eq'-H), 4.79 (2H, s, 1-H, 1'-H), 5.14 (2H, br. s, 8-$H_{cis}$, 8'-$H_{cis}$), 5.21 (2H, br. s, 8-$H_{trans}$, 8'-$H_{trans}$), 5.40 (2H, s, 12-H, 12'-H), 5.67 (br. s, 11-H, 11'-H), 7.30-7.54 (10H, m, Ph, Ph'); $\delta_C$ (62.9 MHz, $CDCl_3$) 19.0 ($CH_3$, Me, Me'), 33.5 ($CH_2$, C3, C3'), 55.3 ($CH_3$, OMe, OMe'), 62.9 ($CH_2$, C10, C10'), 65.6 (CH, C5, C5'), 69.9 ($CH_2$, C6, C6'), 76.0 (CH, C4, C4'), 79.1 (C, C2, C2'), 99.5 (CH, C1, C1'), 102.3 (CH, C12, C12'), 117.5 ($CH_2$, C8, C8'), 126.7 (CH, Ph, Ph'), 128.7 (CH, Ph, Ph'), 129.3 (CH, C11, C11'), 129.5 (CH, Ph, Ph'), 137.9 (C, Ph, Ph'), 143.5 (C, C7, C7'); *m/z* (FAB) 687 ($MNa^+$, 100%) 665 ($MH^+$, 62%), found $MH^+$, 665.33265; $C_{38}H_{49}O_{10}$ requires 665.33257.

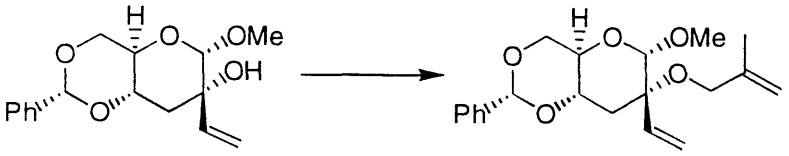
**Methyl-(*R*)-4,6-*O*-benzylidene-3-deoxy-2-*C*-(1-methylethenyl)-2-*O*-(2-methylpropenyl)-α-D-glucopyranoside (311)**




**308** **311**

Sodium hydride (88 mg, 60% dispersion in mineral oil, 2.20 mmol) was added portionwise to an ice-cooled solution of alcohol **308** (350 mg, 1.15 mmol) in dry THF (10.0 mL). The resulting mixture was heated to reflux for 2 h and allowed to cool to room temperature. 1-Chloro-2-methylprop-2-ene (200 μL, 2.30 mmol), DMPU (200 μL) and potassium iodide (10mg) were then added, the mixture was heated to reflux for 4 h, allowed to cool to room temperature, and quenched by addition of water (5 mL). The resulting mixture was then extracted into diethyl ether (2 × 75 mL), the combined organic layers washed with saturated sodium chloride solution (150 mL), dried, and evaporated to leave a yellow oil. Chromatography on silica gel with petroleum ether-diethyl ether (3:1) as the eluent yielded **311** as a colourless oil (253 mg, 62%): mp 82-83°C; $R_f$ 0.52, petroleum ether-diethyl ether (1:1); $[\alpha]^{20}_D$ + 65.1° (*c* 4.2, $CHCl_3$); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 2900m br, 1450m, 1380m, 1100s br, 1050s; $\delta_H$ (250MHz, $CDCl_3$) 1.73 (3H, s, 9-H), 1.79 (3H, s, 13-H), 2.10 (1H, t, *J* 11.9, 3ax-H), 2.27 (1H, dd, *J* 3.9, 11.9, 3eq-H), 3.47 (3H, s, OMe), 3.55 (1H, overlapping, m, 4-H), 3.72 (1H, t, 9.8, 6ax-H), 3.60-3.87 (3H, m, 5-H, 10-H), 4.24 (1H, dd, *J* 4.4, 9.8, 6eq-H), 4.83 (1H, br. s, 12-$H_{cis}$), 4.89 (1H, s, 1-H), 4.99 (1H, br. s, 12-$H_{trans}$), 5.22 (1H, br. s, 8-$H_{cis}$), 5.29 (1H, br. s, 8-$H_{trans}$), 5.48 (1H, s, 14-H), 7.32-7.55 (5H, m, Ph); $\delta_C$ (62.9MHz, $CDCl_3$) 18.6 ($CH_3$, C9), 19.7 ($CH_3$, C13) 33.1 ($CH_2$, C3), 54.9 ($CH_3$, OMe), 65.2 (CH, C5), 65.8 ($CH_2$, C10), 69.5 ($CH_2$, C6), 75.6 (CH, C4), 78.5 (C, C2), 99.2 (CH, C14), 101.9 (CH, C1), 111.3 ($CH_2$, C12), 116.8 ($CH_2$, C8), 126.2 (CH, Ph), 128.3 (CH, Ph), 129.1 (CH, Ph), 137.5 (C, Ph), 142.1 (CH, C11), 143.2 (C, C7); *m/z* (FAB) 347 ($MH^+$, 53); elemental analysis found C 69.51, H 7.78, $C_{21}H_{28}O_5$ requires C 69.98, H 7.83.

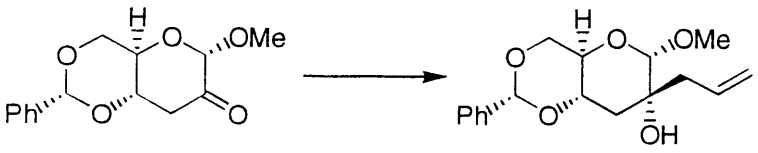
**Methyl-(*R*)-4,6-*O*-benzylidene-3-deoxy-2-*C*-ethenyl-2-*O*-(2-methylpropenyl)-α-D-glucopyranoside (312)**



**305** **312**

Sodium hydride (160 mg, 60% dispersion in mineral oil, 4.00 mmol) was added portionwise to an ice-cooled solution of alcohol **305** (700 mg, 2.40 mmol) in dry THF (20.0 mL). The resulting mixture was heated to reflux for 2 h and allowed to cool to room temperature. 1-Chloro-2-methylprop-2-ene (400 μL, 4.60 mmol), DMPU (200 μL) and potassium iodide (10mg) were then added, the mixture was heated to reflux for 4 h, allowed to cool to room temperature, and quenched by addition of water (10 mL). The resulting mixture was then extracted into diethyl ether (2 × 75 mL), the combined organic layers washed with saturated sodium chloride solution (150 mL), dried, and evaporated to leave a yellow oil. Chromatography on silica gel with petroleum ether-diethyl ether (3:1) as the eluent yielded **312** as a colourless oil (564 mg, 68%): mp 105-106.5°C; $R_f$ 0.68, petroleum ether-diethyl ether (1:1); $[\alpha]^{20}_D$ + 51.7° (*c* 4.9, $CHCl_3$); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 2960m br, 1450m, 1375m, 1090s, 1050s; $\delta_H$ (250MHz, $CDCl_3$) 2.03 (1H, dd, *J* 4.6, 11.5, 3eq-H), 2.15 (1H, t, *J* 11.5, 3ax-H), 3.41 (3H, s, OMe), 3.54 (1H, ddd, 4.6, 9.0, 11.5, 4-H), 3.59 (1H, t, overlapping, *J* 9.5, 6ax-H), 3.68-3.80 (3H, overlapping, 5H, 9-H), 4.29 (1H, dd, *J* 4.1, 9.5, 6eq-H), 4.60 (1H, s, 1-H), 4.77 (1H, br. s, 11-$H_{cis}$), 4.93 (1H, br. s, 11-$H_{trans}$), 5.37 (1H, dd, overlapping, *J* 1.0, 11.0, 8-$H_{cis}$), 5.43 (1H, s, overlapping, 13-H), 5.43 (1H, dd, overlapping, *J* 1.0, 17.8, 8-$H_{trans}$), 5.83 (1H, dd, *J* 11.0, 17.8, 7-H), 7.25-7.28 (5H, m, Ph); $\delta_C$ (100MHz, $CDCl_3$) 20.1 ($CH_3$, C12), 36.6 ($CH_2$, C3), 55.4 ($CH_3$, OMe), 64.8 (CH, C5), 66.5 ($CH_2$, C9), 69.8 ($CH_2$, C6), 76.1 (CH, C4), 77.3 (C, C2), 100.5 (CH, C1), 102.3 (CH, C13), 111.7 ($CH_2$, C8), 120.0 ($CH_2$, C11), 126.6 (CH, Ph), 128.7 (CH, Ph), 129.5 (CH, Ph), 137.9 (C, Ph), 139.2 (CH, C7), 142.8 (C, C10); *m/z* (ES) 369 ($MNa^+$, 100); elemental analysis found C 69.20, H 7.58, $C_{20}H_{26}O_5$ requires C 69.34, H 7.56.

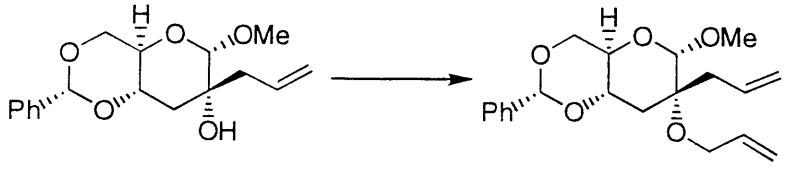
**Methyl-(*R*)-4,6-*O*-benzylidene-3-deoxy-2-*C*-propenyl-α-D-glucopyranoside (313).**



**304** **313**

Allylmagnesium chloride (1.00 mL, 2.00 mmol, 2 M solution in THF) was added dropwise to an ice-cooled solution of the ketone **304** (224 mg, 0.85 mmol) in dry THF (10.0 mL). The solution was then heated to reflux for 4 h and allowed to cool to room temperature, then quenched by dropwise addition of saturated ammonium chloride solution (5 mL). The resulting mixture was then diluted with water (50 mL), extracted into diethyl ether (2 × 50 mL), and the combined organic layers were 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 (3:1) as the eluent yielded **313** as a colourless oil (260 mg, 96%): $R_f$ 0.16, petroleum ether-diethyl ether (1:1); $[\alpha]^{20}_D$ + 51.6° (*c* 3.64, $CHCl_3$); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 3580m, 2940m, 1450m, 1395m, 1100s, 1050s; $\delta_H$ (250MHz, $CDCl_3$) 1.85 (1H, t, *J* 11.8, 3ax-H), 2.17 (1H, dd, *J* 4.3, 11.8, 3eq-H), 2.35-2.48 (2H, m, 7-H), 2.51 (1H, br s, O*H*) 3.46 (3H, s, OMe), 3.51-3.62 (1H, m, 4-H), 3.68-3.82 (2H, overlapping, 5-H and 6eq-H), 4.62 (1H, dd, *J* 10.7, 16.1, 6ax-H), 4.34 (1H, s, 1-H), 5.12-5.18 (1H, m, 9-$H_{trans}$), 5.21 (1H, br s, 9-$H_{cis}$), 5.52 (1H, s, 10-H), 5.87-6.05 (1H, m, 8-H), 7.30-7.56 (5H, Ph); $\delta_C$ (75.8 MHz, $CDCl_3$) 37.0 ($CH_2$, C3), 40.9 ($CH_2$, C7), 55.4 ($CH_3$, OMe), 64.3 (CH, C5), 69.4 ($CH_2$, C6), 72.0 (C, C2), 75.5 (CH, C4), 101.9 (CH, C1), 102.0 (CH, C10), 118.8 ($CH_2$, C9), 126.2 (CH, Ph), 128.3 (CH, Ph), 129.1 (CH, Ph), 132.5 (CH, C8), 137.4 (C, Ph); *m/z* (FAB) 347 ($MH^+$, 52), found $MH^+$, 347.1858; $C_{17}H_{23}O_5$ requires 347.1859.

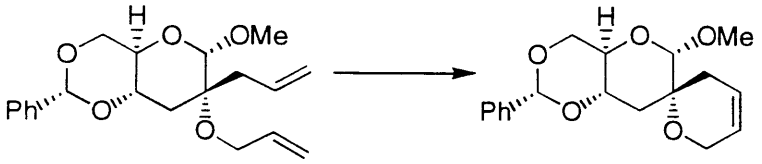
**Methyl-(*R*)-4,6-*O*-benzylidene-3-deoxy-2-*C*-propenyl-2-*O*-propenyl-α-D-glucopyranoside (314).**




**313** **314**

Sodium hydride (60 mg, 60% dispersion in mineral oil, 1.50 mmol) was added portionwise to an ice-cooled solution of alcohol **313** (215 mg, 0.70 mmol) in dry THF (15.0 mL). The resulting mixture was heated to reflux for 2 h and allowed to cool to room temperature. Allyl bromide (130 μL, 1.50 mmol) and DMPU (200 μL) were then added, the mixture was heated to reflux for 4 h, allowed to cool to room temperature, and quenched by addition of water (5 mL). The resulting mixture was then extracted into diethyl ether (2 × 25 mL), the combined organic layers washed with 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 **314** as a colourless oil (232 mg, 96%): $R_f$ 0.46, petroleum ether-diethyl ether (1:1); $[\alpha]^{20}_D$ + 35.4° (*c* 4.42, $CHCl_3$); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 2940m br, 1450m, 1380s, 1100s, 1050s; $\delta_H$ (250MHz, $CDCl_3$) 2.01-2.18 (2H, m, 3-H), 2.39-2.62 (2H, m, 7-H), 3.43 (3H, s, OMe), 3.53-3.66 (1H, m, 4-H), 3.73 (1H, t, *J* 10.4, 6ax-H) 3.78 (1H, dd, *J* 3.8, 10.4, 5-H), 3.96 (1H, ddt, *J* 1.5, 5.4, 12.1 CH*H* 10-H), 4.10 (1H, ddt, *J* 1.5, 5.4, 12.1, C*H*H 10-H), 4.25 (1H, dd, *J* 3.8, 10.4, 6eq-H), 4.43 (1H, s, 1-H), 5.14 (1H, dd, *J* 1.6, 3.1 9-$H_{cis}$), 5.14-5.22 (2H, overlapping, 9-$H_{trans}$ and 12-$H_{cis}$), 5.27 (1H, ddd, *J* 1.7, 3.4, 17.2, 12-$H_{trans}$), 5.51 (1H, s, 13-H), 5.77-5.99 (2H, overlapping, 8-H and 11-H), 7.30-7.56 (5H, Ph); $\delta_C$ (62.9 MHz, $CDCl_3$) 33.2 ($CH_2$, C3), 38.7 ($CH_2$, C7), 55.5 ($CH_3$, OMe), 63.8 ($CH_2$, C10) 64.8 (CH, C5), 69.9 ($CH_2$, C6), 76.1 (CH, C4), 77.0 (C, C2), 102.3 (CH, C13), 102.4 (CH, C1), 116.5 ($CH_2$, C12), 119.8 ($CH_2$, C9), 126.7 (CH, Ph), 128.7 (CH, Ph), 129.1 (CH, Ph), 132.7 (CH, C8),135.7 (CH, C11) 137.9 (C, Ph); *m/z* (FAB) 307 ($MH^+$, 28), found $MH^+$, 307.1545; $C_{20}H_{27}O_5$ requires 307.1546.

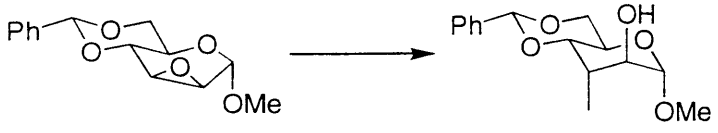
**Methyl-(*R*)-4,6-*O*-benzylidene-2,3-dideoxy-2(*S*)-spiro(2,6'-5',6'-dihydro-2'H-pyran)- α-D-glucopyranoside (315).**



**314** **315**

Nitrogen gas was bubbled through a solution of the diene **314** (148 mg, 0.43 mmol) in benzene (10 mL) for 2-3 minutes. The catalyst **176b** (20 mg, 0.024 mmol, 3.4 mol%) was then added and the solution heated at 60°C for 36 h. The solvent was then 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 **315** as a white solid (116 mg, 85%): mp 69-70°C; $R_f$ 0.19, petroleum ether-diethyl ether (1:1); $[\alpha]^{14}_D$ + 93.5° (*c* 9.2, $CHCl_3$); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 2940m br, 1450w, 1380m, 1090s, 1055s; $\delta_H$ (400 MHz; $CDCl_3$) 2.09-2.17 (2H, m, 3-H), 2.25–2.33 (1H, m, CH*H* 7-H), 2.37-2.45 (1H, m, C*H*H 7-H), 3.51 (3H, s, OMe), 3.66 (1H, dt, *J* 6.3, 9.8, 4-H), 3.76 (1H, t, *J* 9.8, 6ax-H), 3.86 (1H, dt, *J* 4.4, 9.8, 5-H), 4.15-4.27 (2H, m, 10-H), 4.30 (1H, dd, *J* 4.4, 9.8, 6eq-H), 4.66 (1H, s, 1-H), 5.56 (1H, s, 11-H), 5.76-5.85 (2H, 8-H and 9-H), 7.32-7.55 (5H, Ph); $\delta_C$ (62.9 MHz, CDCl3) 32.6 ($CH_2$, C7), 36.4 ($CH_2$, C3), 55.6 ($CH_3$, OMe), 61.6 ($CH_2$, C10), 64.8 (CH, C5), 69.8 ($CH_2$, C6), 72.5 (C, C2), 76.0 (CH, C4), 100.1 (CH, C11), 102.3 (CH, C1), 122.1 (CH, C8), 126.2 (CH, C9), 126.6 (CH, Ph), 128.7 (CH, Ph), 129.5 (CH, Ph), 137.8 (C, Ph); *m/z* (FAB) 319 ($MH^+$, 88), found $MH^+$, 319.1545; $C_{18}H_{22}O_5$ requires 319.1546; elemental analysis found: C, 67.80; H, 6.73. $C_{18}H_{22}O_5$ requires C, 67.91; H, 6.96%.

**Methyl-(*R*)-4,6-*O*-benzylidene-3-deoxy-3-*C*-methyl-α-D-altropyranoside (316).**

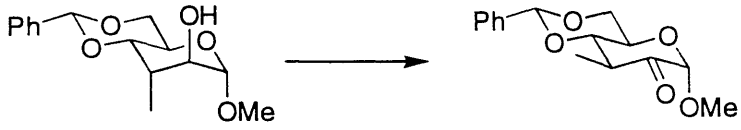


**17** **316**

Methylmagnesium chloride (3M solution in THF, 320.0 mL, 0.96 mol) was added dropwise to a stirred suspension of the epoxide **17** (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 crystallise 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 **316** as a white crystalline solid (23.86 g, 45%): mp 109-110°C; $\delta_H$ (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.[3]

**Methyl (*R*)-4,6-*O*-benzylidene-3-deoxy-3-*C*-methyl-α-D-*arabino*-hexopyranosid-2-ulose (166).**



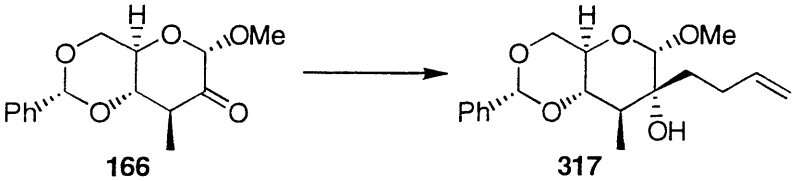

**316** **166**

Oxalyl chloride (7.72 mL, 85.6 mmol) in dry dichloromethane (40.0 mL) was added dropwise to a stirred solution of dimethyl sulfoxide (12.2 mL, 0.17 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 **316** (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) then brine (2 × 200mL). 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 **166** as a white crystalline solid (12.22 g, 62%): mp 124-125 °C (lit.[3] mp 125.5-126 °C); $\delta_H$ (300 MHz, $CDCl_3$) 1.25 (3H, d, *J* 6.4, C3-Me), 3.09 (1H,

d, *J* 11.4, 3-H), 3.46 (1H, dd, *J* 10.3, 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, 10.3, 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); $\delta_C$ (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.[3]

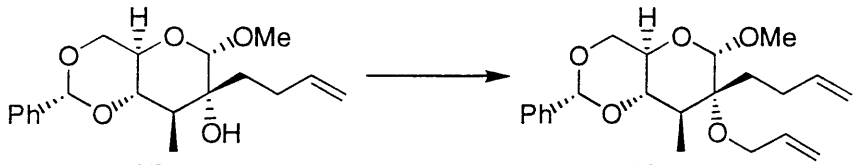
**Methyl-(*R*)-4,6-*O*-benzylidene-2-*C*-but-3'-enyl-3-deoxy-3-*C*-methyl-α-D-glucopyranoside (317)**




Anhydrous cerium (III) chloride (4.2 g, 17.0 mmol) in dry diethyl ether (20.0 mL) was stirred at room temperature for 1.5 h. In another flask, 4-bromo-1-butene (1.84 mL, 18.0 mmol) in dry diethyl ether (5.0 mL) was added dropwise to magnesium turnings (450 mg, 18.8 mmol) and a crystal of $I_2$ in dry diethyl ether (5.0 mL) at 0 °C. This mixture was stirred at 0 °C for 1 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 **166** (1.0 g, 3.6 mmol) in dry diethyl ether (20.0 mL) was added dropwise via a cannula to the cooled (−78 °C) reaction mixture. The mixture was stirred at -78 °C for 2 h, then at rt overnight, and then added portionwise to ice/water (200 mL) and saturated ammonium chloride solution (150 mL). The mixture was extracted into dichloromethane (2 × 200 mL), and the combined organic layers were washed with saturated sodium chloride solution (300 mL), dried, and evaporated to leave a yellow oil. Chromatography on silica gel with petroleum ether-diethyl ether (3:1) as the eluent yielded starting material **166** as a white solid (270 mg, 27%), **317** as a colourless oil (373 mg, 31%) and a reduced product as a white solid (220 mg): $R_f$ 0.22, petroleum ether-diethyl ether (1:1); $[\alpha]^{20}_D$ + 28.2° (*c* 14.5, $CHCl_3$); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 3580s, 2970s br, 1648m, 1460m, 1360m, 1055s; $\delta_H$ (250 MHz, $CDCl_3$) 1.07 (3H, d, *J* 6.7, C3-Me), 1.61-1.82 (2H, m, 7-

H), 2.03-2.33 (2H, m, overlapping, 8-H), 2.17 (1H, dq, *J* 6.7, 11.2, 3-H), 2.22 (1H, d, *J* 1.8, O*H*), 3.29 (1H, dd, *J* 8.9, 11.2, 4-H), 3.43 (3H, s, OMe), 3.71 (1H, t, *J* 9.9, 6ax-H), 3.77 (1H, m, overlapping, 5-H), 4.20-4.26 (1H, m, 6eq-H), 4.54 (1H, s, 1-H), 4.97 (1H, m, 10-$H_{cis}$), 5.06 (1H, m, 10-$H_{trans}$), 5.48 (1H, s, 11-H), 5.72-5.93 (1H, m, 9-H), 7.31-7.51 (5H, m, Ph); $\delta_C$ (62.9 MHz, $CDCl_3$) 9.2 ($CH_3$, C3-Me), 27.6 ($CH_2$, C7), 30.2 ($CH_2$ C8), 41.4 (CH, C3), 55.8 ($CH_3$, OMe), 64.9 (CH, C5), 69.7 ($CH_2$, C6), 74.1 (C, C2), 81.0 (CH, C4), 100.9 (CH, C1), 102.0 (CH, C11), 114.9 ($CH_2$, C10), 126.5 (CH, Ph), 128.8 (CH, Ph), 129.3 (CH, Ph), 138.1 (C, Ph), 139.2 (CH, C9); *m/z* (FAB) 335 ($MH^+$, 56), found $MH^+$, 335.18575; $C_{19}H_{27}O_5$ requires 335.18575.

**Methyl-(*R*)-4,6-*O*-benzylidene-2-*C*-but-3'-enyl-3-deoxy-3-*C*-methyl-2-*O*-propenyl-α-D-glucopyranoside (318)**

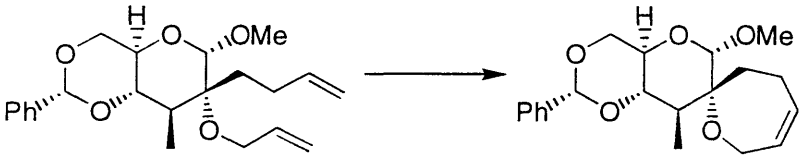



**317** **318**

Sodium hydride (17.7 mg, 60% dispersion in mineral oil, 0.44 mmol) was added portionwise to an ice-cooled solution of alcohol **317** (74 mg, 0.22 mmol) in dry THF (10.0 mL). The resulting mixture was heated to reflux for 2 h and allowed to cool to room temperature. Allyl bromide (38 μL, 0.44 mmol) and DMPU (50 μL) were then added, the mixture was heated to reflux for 4 h, allowed to cool to room temperature, and quenched by addition of water (2 mL). The resulting mixture was then extracted into diethyl ether (2 × 50 mL), the combined organic layers washed with saturated sodium chloride solution (75 mL), dried, and evaporated to leave a yellow oil. Chromatography on silica gel with petroleum ether-diethyl ether (6:1) as the eluent yielded **318** as a colourless oil (69 mg, 84%): $R_f$ 0.67, petroleum ether-diethyl ether (1:1); $[\alpha]^{20}_D$ + 45.3° (*c* 3.6, $CHCl_3$); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 2960s br, 1650w, 1460m, 1380m, 1065s; $\delta_H$ (250 MHz, $CDCl_3$) 1.27 (3H, d, *J* 6.7, C3-Me), 1.88-2.11 (2H, m, 7-H), 2.26-2.44 (1H, m, CH*H* 8-H), 2.46-2.70 (1H, m, C*H*H 8-H) 2.87 (1H, dq, *J* 6.7, 11.0, 3-H), 3.64 (3H, s, OMe), 3.66 (1H, dd, overlapping, *J* 9.0, 11.0, 4-H), 3.96 (1H, t, *J* 9.0, 6ax-H), 4.05 (1H, dt, *J* 4.1, 9.0, 5-H), 4.21 (1H, ddt, *J* 1.6, 5.0, 13.1, CH*H* 11-H), 4.47 (1H, dd, *J* 4.1, 9.0, 6eq-H), 4.57 (1H, ddt, *J* 1.6, 5.0, 13.1, *CH*H 11-H), 4.83 (1H, s, 1-H), 5.21 (1H, m, 10-$H_{cis}$), 5.29 (1H, m, 10-$H_{trans}$), 5.32 (1H, m, 13-$H_{cis}$), 5.50 (1H,

dddd, *J* 1.8, 4.0, 5.7, 17.2, 13-$H_{trans}$), 5.75 (1H, s, 14-H), 6.01-6.22 (2H, overlapping, 9-H, 12-H), 7.31-7.51 (5H, m, Ph); $\delta_C$ (62.9 MHz, $CDCl_3$) 9.9 ($CH_3$, C3-Me), 27.8 ($CH_2$, C7), 32.4 ($CH_2$, C8), 35.5 (CH, C3), 55.3 ($CH_3$, OMe), 64.6 ($CH_2$, C11), 64.7 (CH, C5), 69.9 ($CH_2$, C6), 78.8 (C, C2), 81.9 (CH, C4), 102.1 (CH, C1), 102.5 (CH, C14), 114.8 ($CH_2$, C10), 114.9 ($CH_2$, C13), 126.5 (CH, Ph), 128.6 (CH, Ph), 129.3 (CH, Ph), 136.6 (CH, C9), 138.2 (C, Ph), 139.5 (CH, C12); *m/z* (FAB) 375 ($MH^+$, 100), found $MH^+$, 375.21712; $C_{22}H_{31}O_5$ requires 375.21712.

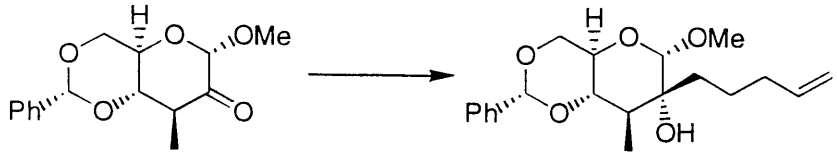
**Methyl-(*R*)-4,6-*O*-benzylidene-3-*C*-methyl-2*S*-spiro(2,7'-1'-oxacyclohept-3'-ene)-α-D-glucopyranoside (319)**




**318** **319**

Nitrogen gas was bubbled through a solution of the diene **318** (65 mg, 0.17 mmol) in benzene (5 mL) for 2-3 minutes. The catalyst **176b** (14 mg, 0.017 mmol, 10 mol%) was then added and the solution heated at 60°C for 36h. The solvent was then 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 **318** as a colourless oil (14 mg, 22%) and **319** as a colourless oil (31 mg, 52%): $R_f$ 0.30, petroleum ether-diethyl ether (1:1); $[\alpha]^{14}_D$ + 38.0° (*c* 2.8, $CHCl_3$); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 3450w br, 2940w, 2880w, 1450w, 1370w, 1100m, 1070m; $\delta_H$ (400 MHz; $CDCl_3$) 1.17 (3H, d, *J* 12.1, C3-Me) 1.90 (1H, dq, *J* 9.3, 12.1, 3-H), 2.22 (2H, m, 8-H), 2.39 (1H, m, CH*H* 7-H), 2.52 (1H, m, C*H*H 7-H), 3.28 (1H, dd, *J* 9.3, 10.2, 4-H), 3.47 (3H, s, OMe), 3.72 (1H, t, *J* 10.2, 6ax-H), 3.84 (1H, dt, *J* 4.6, 10.2, 5-H), 4.25 (1H, dd, overlapping, *J* 4.6, 10.2, 6eq-H), 4.25-4.32 (1H, m, CH*H* 11-H), 4.34-4.42 (1H, m, C*H*H 11-H), 4.72 (1H, s, 1-H), 5.50 (1H, s, 12-H), 5.55 (1H, m, 9-H), 5.74 (1H, m, 10-H), 7.32-7.52 (5H, Ph); $\delta_C$ (100 MHz, $CDCl_3$) 9.1 ($CH_3$, C3-Me), 24.9 ($CH_2$, C8), 31.6 ($CH_2$, C7), 40.1 (CH, C3), 54.9 ($CH_3$, OMe), 63.8 ($CH_2$, C11), 64.3 (CH, C5), 69.5 ($CH_2$, C6), 78.3 (C, C2), 81.2 (CH, C4), 101.2 (CH, C1), 101.8 (CH, C12), 126.1 (CH, Ph), 128.3 (CH, Ph), 128.9 (CH, C9), 129.2 (CH, Ph), 130.1 (CH, C10), 137.7 (C, Ph); *m/z* (FAB) 347 ($MH^+$, 100), 369 ($MNa^+$, 26), found $MH^+$, 347.18589; $C_{20}H_{27}O_5$ requires 347.18585.

**Methyl-(*R*)-4,6-*O*-benzylidene-3-deoxy-3-*C*-methyl-2-*C*-pent-4'-enyl-α-D-glucopyranoside (320)**

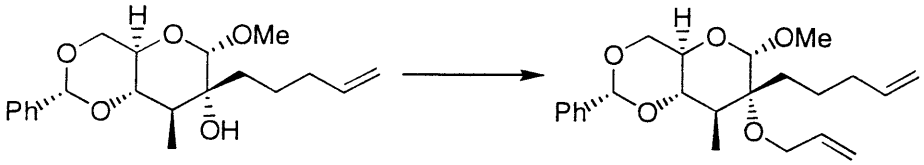


**166** **320**

Anhydrous cerium (III) chloride (2.49 g, 10.1 mmol) in dry diethyl ether (10.0 mL) was stirred at room temperature for 1.5 h. In another flask, 5-bromo-1-pentene (1.19 mL, 10.1 mmol) in dry diethyl ether (5.0 mL) was added dropwise to magnesium turnings (300 mg, 12.0 mmol) and a crystal of $I_2$ in dry diethyl ether (5.0 mL) at 0 °C. This mixture was stirred at 0 °C for 1 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 **166** (500 mg, 1.79 mmol) in dry diethyl ether (10.0 mL) was added dropwise via a cannula to the cooled (-78 °C) reaction mixture. The mixture was stirred at -78 °C for 2 h, then at rt overnight, and then added portionwise to ice/water (100 mL) and saturated ammonium chloride solution (100 mL). The mixture was extracted into dichloromethane (2 × 100 mL), and the combined organic layers were washed with saturated sodium chloride solution (100 mL), dried, and evaporated to leave a yellow oil. Chromatography on silica gel with petroleum ether-diethyl ether (3:1) as the eluent yielded starting material **166** as a white solid (33 mg, 7%), **320** as a colourless oil (309 mg, 50%) and a reduced product as a white solid (45 mg): $R_f$ 0.18, petroleum ether-diethyl ether (1:1); $[\alpha]^{20}_D$ + 36.0° (*c* 8.4, $CHCl_3$); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 3560s, 2940s br, 1680m, 1450m, 1360m, 1055s; $\delta_H$ (250 MHz, $CDCl_3$) 1.07 (3H, d, *J* 6.9, C3-Me), 1.31-1.75 (4H, overlapping, 7-H, 8-H), 2.02-2.19 (3H, overlapping, 9-H, 3-H), 2.20 (1H, d, *J* 1.4, O*H*), 3.29 (1H, dd, *J* 8.7, 9.8, 4-H), 3.43 (3H, s, OMe), 3.70 (1H, t, overlapping, *J* 9.8, 6ax-H), 3.75 (1H, dt, overlapping, *J* 3.6, 9.8, 5-H), 4.23 (1H, dd, *J* 3.6, 9.8, 6eq-H), 4.54 (1H, s, 1-H), 4.98-5.08 (2H, overlapping, 11-$H_{cis}$, 11-$H_{trans}$), 5.49 (1H, s, 12-H), 5.74-5.91 (1H, m, 10-H), 7.31-7.51 (5H, m, Ph); $\delta_C$ (62.9 MHz, $CDCl_3$) 9.2 ($CH_3$, C3-Me), 22.5 ($CH_2$, C5), 30.4 ($CH_2$, C7), 34.7 ($CH_2$ C9), 41.5 (CH, C3), 55.7 ($CH_3$, OMe), 64.9 (CH, C5), 69.8 ($CH_2$, C6), 74.2 (C, C2), 81.1 (CH, C4), 101.0 (CH, C1), 102.0 (CH, C12), 115.1 ($CH_2$, C11), 126.5 (CH, Ph), 128.6 (CH, Ph), 129.3 (CH, Ph), 138.1

(C, Ph), 138.9 (CH, C10); *m/z* (FAB) 349 ($MH^+$, 34), found $MH^+$, 349.20156; $C_{20}H_{29}O_5$ requires 349.20150.

**Methyl-(*R*)-4,6-*O*-benzylidene-3-deoxy-3-*C*-methyl-2-*C*-pent-4'-enyl-2-*O*-propenyl-α-D-glucopyranoside (321)**

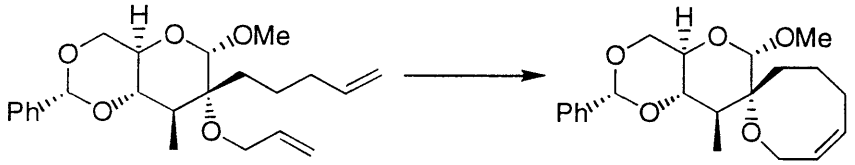



**320** **321**

Sodium hydride (124 mg, 60% dispersion in mineral oil, 3.1 mmol) was added portionwise to an ice-cooled solution of alcohol **320** (107 mg, 0.31 mmol) in dry THF (10.0 mL). The resulting mixture was heated to reflux for 2 h and allowed to cool to room temperature. Allyl bromide (54 μL, 0.62 mmol) and DMPU (50 μL) were then added, the mixture was heated to reflux for 4 h, allowed to cool to room temperature, and quenched by addition of water (10 mL). The resulting mixture was then extracted into diethyl ether (2 × 50 mL), the combined organic layers washed with saturated sodium chloride solution (75 mL), dried, and evaporated to leave a yellow oil. Chromatography on silica gel with petroleum ether-diethyl ether (8:1) as the eluent yielded **321** as a colourless oil (101 mg, 84%): $R_f$ 0.58, petroleum ether-diethyl ether (1:1); $[\alpha]^{20}_D$ + 50.9° (*c* 4.9, $CHCl_3$); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 2940s br, 1650w, 1450m, 1360m, 1070s; $\delta_H$ (250 MHz, $CDCl_3$) 1.06 (3H, d, *J* 6.6, C3-Me), 1.42-1.85 (1H, m, C*H*H 8-H), 1.62-1.85 (3H, overlapping, CH*H* 8-H, 7-H),2.06-2.17 (2H, m, 9-H), 2.66 (1H, dq, *J* 6.6, 10.8, 3-H), 3.44 (3H, s, OMe), 3.45 (1H, dd, 9.4, 10.8, 4-H), 3.76 (1H, t, *J* 9.4, 6ax-H), 3.86 (1H, dt, *J* 4.1, 9.4, 5-H), 4.00 (1H, ddt, *J* 1.6, 5.0, 13.3, CH*H* 12-H), 4.27 (1H, dd, *J* 4.1, 9.4, 6eq-H), 4.35 (1H, ddt, *J* 1.6, 5.0, 13.3, C*H*H 12-H), 4.62 (1H, s, 1-H), 5.02 (1H, m, 11-$H_{cis}$), 5.08 (1H, m, 11-$H_{trans}$), 5.12 (1H, m, 14-$H_{cis}$), 5.31 (1H, dq, *J* 1.6, 17.2, 14-$H_{trans}$), 5.55 (1H, s, 15-H), 5.79-5.94 (1H, m, overlapping, 10-H), 5.88-6.02 (1H, overlapping, 13-H), 7.32-7.54 (5H, m, Ph); $\delta_C$ (62.9 MHz, $CDCl_3$) 9.9 ($CH_3$, C3-Me), 22.7 ($CH_2$, C8), 32.7 ($CH_2$, C7), 34.9 ($CH_2$, C9), 35.6 (CH, C3), 55.3 ($CH_3$, OMe), 64.6 ($CH_2$, C12), 64.9 (CH, C5), 69.9 ($CH_2$, C6), 78.2 (C, C2), 81.9 (CH, C4), 102.1 (CH, C1), 102.6 (CH, C15), 114.8 ($CH_2$, C11), 115.0 ($CH_2$, C14), 126.5 (CH,

Ph), 128.6 (CH, Ph), 129.3 (CH, Ph), 136.7 (CH, C10), 138.2 (C, Ph), 139.1 (CH, C13); *m/z* (FAB) 389 ($MH^+$, 40), found $MH^+$, 389.23289; $C_{23}H_{33}O_5$ requires 389.23280.

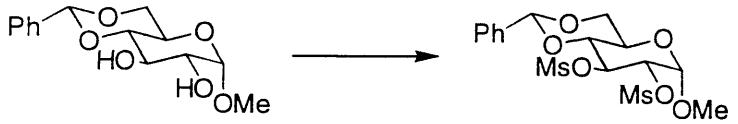
**Methyl-(*R*)-4,6-*O*-benzylidene-2,3-dideoxy-3-*C*-methyl-2(*S*)-spiro(2,8'-1'-oxacyclooct-3'-ene)-α-D-glucopyranoside (322)**



**321** **322**

Nitrogen gas was bubbled through a solution of the diene **321** (87 mg, 0.22 mmol) in benzene (5 mL) for 2-3 minutes. The catalyst **176b** (38 mg, 0.045 mmol, 20 mol%) was then added and the solution heated at 60°C for 60 h. The solvent was then 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 **321** as a colourless oil (31 mg, 36%) and **322** as a colourless oil (26 mg, 33%): $R_f$ 0.32, petroleum ether-diethyl ether (1:1); $[\alpha]^{14}_D$ + 29.7° (*c* 1.0, $CHCl_3$); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 2940m, 2880w, 1760m, 1460w, 1370w, 1120m, 1065m; $\delta_H$ (400 MHz; $CDCl_3$) 1.23 (3H, d, *J* 7.0, C3-Me), 1.56-1.68 (1H, m, CH*H* 8-H), 1.85-2.70 (3H, m, C*H*H 8-H, 9-H), 2.20-2.28 (1H, m, C*H*H 7-H), 2.40 (1H, dq, *J* 7.0, 11.2, 3-H), 2.69-2.81 (1H, m, CH*H* 7-H), 3.40 (1H, dd, *J* 8.9, 11.2, 4-H), 3.47 (3H, s, OMe), 3.74 (1H, t, *J* 10.4, 6ax-H), 3.83 (1H, ddd, *J* 4.3, 8.9, 10.4, 5-H), 4.15 (1H, m, CH*H* 12-H), 4.26 (1H, dd, *J* 4.3, 10.4, 6eq-H), 4.35 (1H, m, C*H*H 12-H), 4.71 (1H, s, 1-H), 5.55 (1H, s, 13-H), 5.63-5.77 (2H, m, 10-H, 11-H), 7.32-7.51 (5H, Ph); $\delta_C$ (100 MHz, $CDCl_3$) 10.0 ($CH_3$, C3-Me), 24.5 ($CH_2$, C8), 25.6 ($CH_2$, C7), 30.7 ($CH_2$, C9), 40.4 (CH, C3), 55.4 ($CH_3$, OMe), 63.2 ($CH_2$, C12), 64.6 (CH, C5), 69.9 ($CH_2$, C6), 80.6 (C, C2), 81.6 (CH, C4), 101.5 (CH, C1), 102.2 (CH, C13), 126.5 (CH, Ph), 128.6 (CH, Ph), 128.9 (CH, C10), 129.3 (CH, Ph), 131.3 (CH, C11), 138.1 (C, Ph); *m/z* (FAB) 361 ($MH^+$, 64), found $MH^+$, 361.20141; $C_{21}H_{29}O_5$ requires 361.20150.

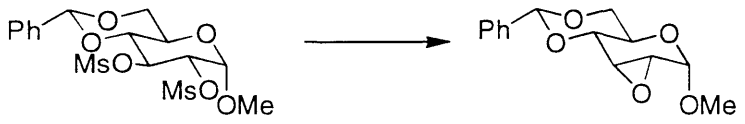
**Methyl-(*R*)-4,6-*O*-benzylidene-2,3-di-*O*-methylsulphonyl-α-D-glucopyranoside (323)**




**301** **323**

Protected diol **301** (40.0g, 142.0mmol), was dissolved in dry dichloromethane (200mL) and triethylamine (50.0mL, 264mmol) and cooled in an ice bath. Methanesulfonyl chloride (23mL, 296.0mmol) was added dropwise and the solution was allowed to warm to room temperature and left to stir for 18h. The reaction was quenched by the addition of water (800mL), extracted into dichloromethane (2x250mL), dried and evaporated to dryness. The resultant yellow solid **323** (60.0g, 96%) was used without further purification. A small sample was purified by re-crystallisation from $CHCl_3$: mp 167-169°C (lit.[5] 163-165°C): $\delta_H$ (250MHz, $CDCl_3$) 2.97 (3H, s, Ms-Me), 3.19 (3H, s, Ms-Me), 3.49 (3H, s, OMe), 3.77 (2H, overlapping, 4-H, 6ax-H), 3.94 (1H, dt, *J* 4.7, 10.0, 5-H), 4.34 (1H, dd, *J* 4.7, 10.0, 6eq-H), 4.63 (1H, dd, *J* 3.7, 9.6, 2-H), 5.02 (1H, d, *J* 3.7, 1-H), 5.08 (1H, t, overlapping, *J* 9.6, 3-H), 5.55 (1H, s, 7-H), 7.36-7.53 (5H, m, Ph); $\delta_C$ (62.9 MHz, $CDCl_3$) 39.2 ($CH_3$, Ms), 39.4 ($CH_3$, Ms), 56.5 ($CH_3$, OMe), 62.7 (CH, C5), 69.1 ($CH_2$, C6), 76.2 (CH, C3), 76.9 (CH, C2), 79.5 (CH, C4), 99.3 (CH, C1), 102.5 (CH, C7), 126.5, (CH, Ph), 128.9 (CH, Ph), 130.0 (CH, Ph), 136.7 (C, Ph).
This is a literature compound.[5]

**Methyl-(*R*)-2,3-anhydro-4,6-*O*-benzylidene-α-D-allopyranoside (324)**




**323** **324**

Sodium metal (10.0g, 0.43mol) was added cautiously to dry methanol (140mL) with cooling (0°C), on complete addition a cooled solution of the dimesylate **323** (41.6g, 95mmol) in dry DCM (200mL) was added via a cannula and solution was allowed to stand in a refrigerator with occasional stirring for 6 days. The resulting solution was poured into water (100mL) to which saturated potassium carbonate (150mL) was added. The precipitated product was extracted into dichloromethane (2x125mL), dried and

evaporated to dryness. The solid was redissolved in dichloromethane and isopropanol added to precipitate a white crystalline solid **324** (21.6g, 86%): mp 199-200°C (lit.[5] 199-200°C); $\delta_H$ (250MHz; $CDCl_3$) 3.47 (3H, s, OMe), 3.45-3.51 (2H, overlapping, 2-H, 4-H), 3.69 (1H, t, *J* 10.2, 3-H), 3.96 (1H, dd, *J* 1.5, 9.1, 6ax-H), 4.08 (1H, dt, *J* 5.6, 9.1, 5-H), 4.24 (1H, dd, 5.6, 9.1, 6eq-H), 4.87 (1H, d, *J* 2.6, 1-H), 5.56 (1H, s, 7-H), 7.30-7.53 (5H, m, Ph); $\delta_C$ (62.9 MHz, $CDCl_3$) 51.1 (CH, C3), 53.5 (CH, C2), 56.3 ($CH_3$, OMe), 60.5 (CH, C5), 69.3 ($CH_2$, C6), 78.3 (CH, C4), 95.7 (CH, C1) 103.2 (CH, C7), 126.7, (CH, Ph), 128.7 (CH, Ph), 129.6 (CH, Ph), 137.6 (C, Ph).
This is a literature compound.[5]

**Methyl-(*R*)-4,6-*O*-benzylidene-2-deoxy-α-D-*ribo*-hexopyranoside (325)**


**324** **325**

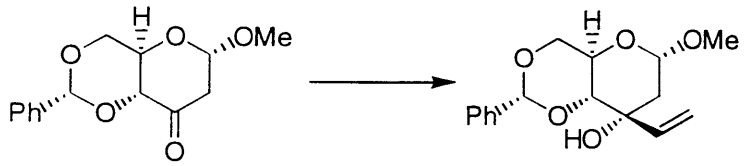
Methyl-4,6-*O*-benzylidene-2,3-anhydro-α-D-alloside **324** (11.5g, 44mmol) was dissolved in dry THF (200mL) and the stirred solution was cooled to 0°C. Lithium aluminium hydride (2.57g, 67mmol) was added portionwise and once the vigorous reaction had subsided, the solution was heated to reflux temperature for 5h. The reaction mixture was cooled in an ice bath and water (2.6mL) was added dropwise to destroy unreacted LAH. A 15% solution of sodium hydroxide (2.6mL) followed by water (7.8mL) were added dropwise. The resulting dispersion was diluted with diethyl ether (200mL) and filtered. The organic phase was washed with brine (200mL), dried and evaporated to give white solid **325** (10.43g, 91%), which was used without further purification. A small sample was purified by recrystallisation from petroleum ether and diethyl ether: mp 119-120°C (lit.[6] 118-120°C); $\delta_H$ (250MHz, $CDCl_3$) 1.95 (1H, dt, *J* 3.7, 14.9, 2ax-H), 2.14 (1H, dd, *J* 3.2, 14.9, 2eq-H), 3.05 (1H, d, *J* 6.6, O*H*), 3.38 (3H, s, OMe), 3.56 (1H, dd, *J* 2.8, 9.4, 6ax-H), 3.74 (1H, t, *J* 9.4, 6eq-H) 4.12-4.33 (3H, overlapping, 3-H, 4-H, 5-H), 4.75 (1H, d, *J* 3.2, 1-H), 5.60 (1H, s, 7-H), 7.29-7.52 (5H, m, Ph); $\delta_C$ (62.9 MHz, $CDCl_3$) 35.9 ($CH_2$, C2), 55.8 ($CH_3$, OMe), 58.6 (CH, C3), 65.4 (CH, C5), 69.8 ($CH_2$, C6), 80.1 (CH, C4), 99.0 (CH, C1), 102.5 (CH, C7), 126.7, (CH, Ph), 128.6 (CH, Ph), 129.5 (CH, Ph), 137.9 (C, Ph).
This is a literature compound.[6]

**Methyl-(*R*)-4,6-*O*-benzylidene-2-deoxy-α-D-*erythro*-hexopyranosid-3-ulose (326)**


**325** **326**

Oxalyl chloride (4.06mL, 45.6mmol) in dry dichloromethane (20mL) was added dropwise to a cooled solution of dimethyl sulfoxide (6.61mL, 93mmol) in dry dichloromethane (40mL). Once addition was complete, the mixture was stirred for 20 mins at -78°C, then a solution of alcohol **325** (10.34g, 38.8mmol) in dry dichloromethane (40mL) was added dropwise, whilst maintaining the temperature at –78°C. On complete addition, the solution was stirred at -78°C for 3h. Triethylamine (30mL, 0.2mol) was then added dropwise, and the solution allowed to warm to room temperature. The reaction mixture was diluted with dichloromethane (150mL) and then washed with 1M hydrochloric acid (2x100mL) followed by saturated sodium hydrogen carbonate (2x90mL) and then brine (150mL). The organic layer was dried and evaporated to give a brown solid. This was recrystallised from petroleum ether and dichloromethane to give yellow crystalline solid **326** (9.61g, 93%): mp 160-161°C (lit.[6] 176-178°C); $\delta_H$ (250MHz, $CDCl_3$) 2.61 (1H, d, *J*, 14.6, 2eq-H), 2.82 (1H, dd, *J* 4.7, 14.6, 2ax-H), 3.46 (3H, s, OMe), 3.89 (1H, t, *J* 10.1, 6ax-H), 4.10 (1H, dt, *J* 4.5, 10.1, 6eq-H), 4.29 (1H, m, 4-H), 4.34 (1H, dd, *J* 4.5, 10.1, 5-H), 5.10 (1H, d, *J* 4.7, 1-H), 5.56 (1H, s, 7-H), 7.29-7.47 (5H, m, Ph); $\delta_C$ (62.9 MHz, $CDCl_3$) 46.8 ($CH_2$, C2), 55.4 ($CH_3$, OMe), 65.5 (CH, C5), 69.8 ($CH_2$, C6), 83.4 (CH, C4), 101.0 (CH, C1), 102.4 (CH, C7), 126.8, (CH, Ph), 128.7 (CH, Ph), 129.7 (CH, Ph), 137.1 (C, Ph), 198.1 (C, C3).
This is a literature compound.[6]

**Methyl-(*R*)-4,6-*O*-benzylidene-2-deoxy-3-*C*-vinyl-α-D-*allo*-hexopyranosid-3-ulose (327)**

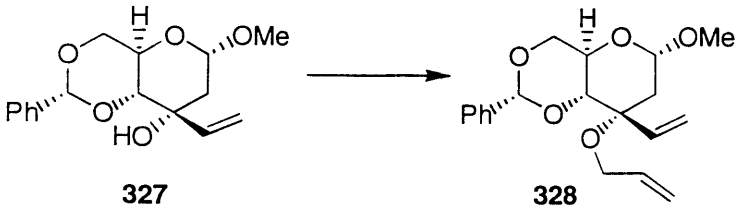



**326** **327**

To a solution of ketone **326** (2.2g, 8.33mmol) in THF (20mL) cooled in an ice bath, was added vinyl magnesium chloride 15% solution in THF (19.4mL, 32.6mmol) dropwise. On complete addition, the solution was heated to reflux temperature for 4h. The unreacted vinyl magnesium chloride was destroyed by careful addition of saturated ammonium chloride solution (30mL), and the mixture diluted with diethyl ether (150mL). The solution was washed with brine (100mL), dried and evaporated to give a brown solid which was recrystallised in petroleum ether and diethyl ether to give **327** as a white crystalline product (1.34g, 55%): mp 161-164°C (lit.[7] 163-167°C); $\delta_H$ (250MHz, $CDCl_3$) 1.99 (2H, overlapping, 2ax-H, 2eq-H), 3.37 (1H, s, O*H*), 3.45 (3H, s, OMe), 3.58 (1H, d, *J* 10.1, 4-H), 3.78 (1H, t, *J* 10.2, 6ax-H), 4.21 (1H, dt, *J* 5.1, 10.1, 5-H), 4.34 (1H, dd, *J* 5.1, 10.2, 6cq-H), 4.83 (1H, m, 1-H), 5.21 (1H, dd, *J* 1.3, 10.9, 7-$H_{cis}$), 5.44 (1H, dd, *J* 1.3, 17.3, 8-$H_{trans}$), 5.59 (1H, s, 9-H), 5.89 (1H, dd, *J* 10.9, 17.3, 8-H), 7.32-7.52 (5H, m, Ph); $\delta_C$ (75.8 MHz, $CDCl_3$) 42.6 ($CH_2$, C2), 57.9 ($CH_3$, OMe), 61.9 (CH, C5), 71.7 ($CH_2$, C6), 73.4 (C, C3), 84.6 (CH, C4), 100.9 (CH, C1), 104.3 (CH, C9), 117.5 ($CH_2$, C8), 128.7, (CH, Ph), 130.6 (CH, Ph), 131.4 (CH, Ph), 139.8 (C, Ph), 143.1 (CH, C7).

This is a literature compound.[7]

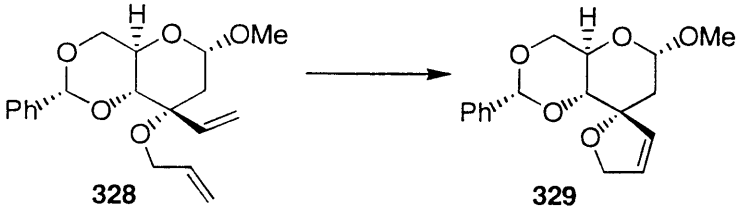
**Methyl-(*R*)-4,6-*O*-benzylidene-2-deoxy-3-*C*-ethenyl-3-*O*-propenyl-α-D-allopyranoside (328).**




**327** **328**

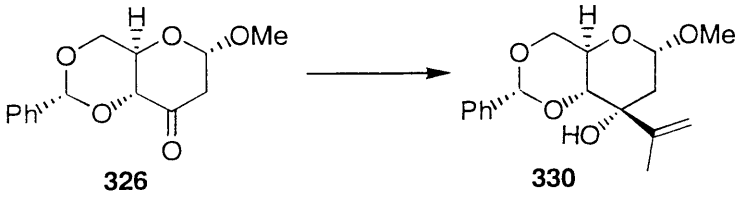
Sodium hydride (250 mg, 80% dispersion in mineral oil, 8.33 mmol) was added portionwise to an ice-cooled solution of alcohol **327** (1.22 g, 4.18 mmol) in dry THF (25.0 mL). The resulting mixture was heated to reflux for 2 h and allowed to cool to room temperature. Allyl bromide (680 μL, 7.86 mmol) and DMPU (200 μL) were then added, the mixture was heated to reflux for 4 h, allowed to cool to room temperature, and quenched by addition of water (15 mL). The resulting mixture was then extracted into diethyl ether (2 × 75 mL), the combined organic layers washed with saturated sodium chloride solution (150 mL), dried, and evaporated to leave a brown oil. Chromatography on silica gel with petroleum ether-diethyl ether (4:1) as the eluent yielded **328** as a colourless oil (1.11 g, 80%): $R_f$ 0.52, petroleum ether-diethyl ether (1:1); $[\alpha]^{20}_D$ + 79.9° (*c* 5.6, $CHCl_3$); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 2900w br, 1390m, 1255s, 1100s, 1050s; $\delta_H$ (250MHz, $CDCl_3$) 1.77 (1H, dd, *J* 4.6, 14.8, 2eq-H), 2.17 (1H, d, *J* 14.8, 2ax-H), 3.28 (3H, s, OMe), 3.52 (1H, d, *J* 9.2, 4-H), 3.61 (1H, t, *J* 10.3, 6ax-H), 3.89-4.05 (2H, m, 9-H), 4.22 (1H, dd, *J* 5.4, 10.3, 6eq-H), 4.34 (1H, ddd, *J* 5.4, 9.2, 10.3, 5-H), 4.64 (1H, d, *J* 4.6, 1-H), 5.00 (1H, ddd, *J* 1.9, 3.5, 8.8, 11-$H_{cis}$), 5.16 (1H, dd, *J* 0.9, 3.8, 8-$H_{cis}$), 5.21 (1H, overlapping, 8-$H_{trans}$), 5.25 (1H, overlapping, 11-$H_{trans}$), 5.41 (1H, s, 12-H), 5.79-5.97 (2H, overlapping, 7-H and 10-H), 7.30-7.57 (5H, Ph); $\delta_C$ (62.9 MHz, $CDCl_3$) 36.9 ($CH_2$, C2), 55.7 ($CH_3$, OMe), 59.3 (CH, C5), 65.7 ($CH_2$, C9), 69.9 ($CH_2$, C6), 75.0 (C, C3), 83.8 (CH, C4), 98.5 (CH, C1), 102.5 (CH, C12), 115.3 ($CH_2$, C8), 117.0 ($CH_2$, C11), 126.7 (CH, Ph), 128.6 (CH, Ph), 129.3 (CH, Ph), 136.6 (C, C7), 138.3 (C, Ph), 139.0 (CH, C10); *m/z* (FAB) 333 ($MH^+$, 48), found $MH^+$, 333.17029; $C_{19}H_{25}O_5$ requires 333.17020.

**Methyl-(*R*)-4,6-*O*-benzylidene-2,3-dideoxy-3(*R*)-spiro(3,5'-2',5'-dihydrofuran)-α-D-allopyranoside (329).**




Nitrogen gas was bubbled through a solution of the diene **328** (416 mg, 1.25 mmol) in benzene (20 mL) for 2-3 minutes. The catalyst **176b** (11 mg, 0.013 mmol, 1.1 mol%) was then added and the solution heated at 60°C for 36 h. The solvent was then 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 **329** as a white solid (230 mg, 55%): mp 155-157°C; $R_f$ 0.32, petroleum ether-diethyl ether (1:1); $[\alpha]^{20}_D$ + 202.1° (*c* 2.76, $CHCl_3$); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 2900m br, 1750m, 1360m; $\delta_H$ (301 MHz, $CDCl_3$)1.98 (1H, dd, *J* 1.2, 14.9, 2eq-H), 2.05 (1H, dd, *J* 4.2, 14.9, 2ax-H), 3.35 (3H, s, OMe), 3.46 (1H, dt, *J* 2.9, 9.4, 4-H), 3.57-3.69 (1H, m, 5-H), 4.18-4.30 (2H, m, H-6), 4.62-4.76 (3H, overlapping, 9-H and 1-H), 5.42 (1H, dt, *J* 2.4, 6.0, 8-H), 5.45 (1H, s, 10-H), 5.95 (1H, dt, *J* 1.5, 6.0, 7-H), 7.32-7.55 (5H, Ph); $\delta_C$ (62.9 MHz, $CDCl_3$) 40.3 ($CH_2$, C2), 56.0 ($CH_3$, OMe), 60.0 (CH, C5), 69.8 ($CH_2$, C6), 77.4 ($CH_2$, C9), 81.4 (CH, C4), 87.2 (c, C3), 98.5 (CH, C1), 102.1 (CH, C10), 126.6 (CH, Ph), 128.5 (CH, Ph), 128.9 (CH, C7), 129.2 (CH, Ph), 130.3 (CH, C8), 138.3 (C, Ph); *m/z* (FAB) 305 ($MH^+$, 46), found $MH^+$, 305.13891; $C_{17}H_{21}O_5$ requires 305.13891.

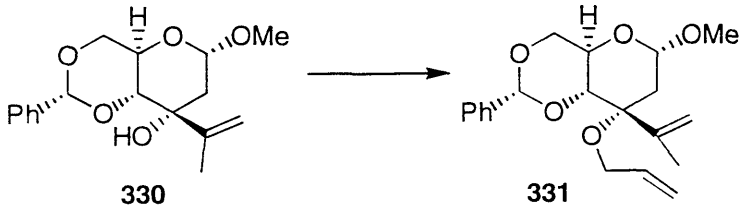
**Methyl-(*R*)-4,6-*O*-benzylidene-2-deoxy-3-*C*-(1-methylethenyl)-α-D-allopyranoside (330).**




Isopropenylmagnesium bromide (25.00 mL, 12.50 mmol, 0.5 M solution in THF) was added dropwise to a cooled (-78°C) solution of the ketone **326** (921 mg, 3.50 mmol) in dry THF (40.0 mL). The solution was then stirred at -50°C for 4 h and allowed to warm

to room temperature, then quenched by dropwise addition of saturated ammonium chloride solution (40 mL). The resulting mixture was extracted into diethyl ether (2 × 100 mL), and the combined organic layers were washed with saturated sodium chloride solution (100 mL), dried, and evaporated to leave a yellow solid. Chromatography on silica gel with petroleum ether-diethyl ether (3:1) as the eluent yielded **330** as a white solid (694 mg, 65%): mp 74-75°C; $R_f$ 0.24, petroleum ether-diethyl ether (1:1); $[\alpha]^{20}_D$ + 117.2° (*c* 7.23, $CHCl_3$); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 3500m br, 2940m, 1640w, 1450m, 1380m; $\delta_H$ (250MHz, $CDCl_3$) 1.83 (3H, d, *J* 0.7, 9-H), 1.95 (1H, dd, *J* 1.3, 14.9, 2eq-H), 2.05 (1H, dd, *J* 3.9, 14.9, 2ax-H), 3.37 (1H, s, O*H*), 3.39 (3H, s, OMe), 3.78 (1H, t, *J* 10.0, 6ax-H), 3.78 (1H, m, 4-H), 4.21 (1H, dt, *J* 5.1, 10.0, 5-H), 4.34 (1H, dd, *J* 5.1, 10.0, 6eq-H), 4.79 (1H, dd, *J* 1.3, 3.9, 1-H), 4.97 (1H, quintet, *J* 0.7, 8-$H_{trans}$), 5.24 (1H, d, *J* 0.7, 8-$H_{cis}$), 5.58 (1H, s, 10-H), 7.32-7.55 (5H, Ph); $\delta_C$ (62.9 MHz, $CDCl_3$) 19.7 ($CH_3$, C9), 40.2 ($CH_2$, C2), 55.8 ($CH_3$, OMe), 60.0 (CH, C5), 69.8 ($CH_2$, C6), 73.3 (C, C3), 80.9 (CH, C4), 99.1 (CH, C1), 102.2 (CH, C10), 113.0 ($CH_2$, C8), 126.6 (CH, Ph), 128.5 (CH, Ph), 129.3 (CH, Ph), 137.9 (C, Ph), 146.9 (C, C7); *m/z* (ES) 329 ($MNa^+$, 100); elemental analysis found C 66.53, H 7.20, $C_{17}H_{22}O_5$ requires C 66.65, H 7.24.

**Methyl-(*R*)-4,6-*O*-benzylidene-2-deoxy-3-*C*-(1-methylethenyl)-3-*O*-propenyl-α-D-allopyranoside (331).**

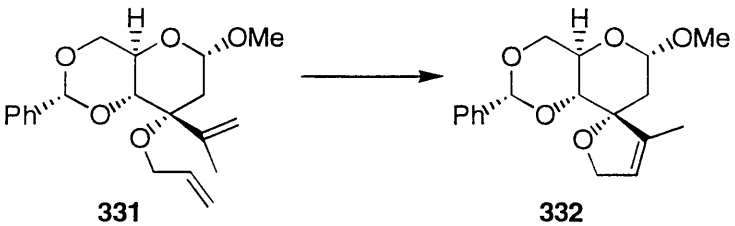



**330** **331**

Sodium hydride (240 mg, 80% dispersion in mineral oil, 8.00 mmol) was added portionwise to an ice-cooled solution of alcohol **330** (610 mg, 2.00 mmol) in dry THF (30.0 mL). The resulting mixture was heated to reflux for 2 h and allowed to cool to room temperature. Allyl bromide (344 μL, 4.00 mmol) and DMPU (200 μL) were then added, the mixture was heated to reflux for 4 h, allowed to cool to room temperature, and quenched by addition of water (10 mL). The resulting mixture was then extracted into diethyl ether (2 × 50 mL), the combined organic layers washed with saturated sodium chloride solution (100 mL), dried, and evaporated to leave a yellow oil. Chromatography on silica gel with petroleum ether-diethyl ether (5:1) as the eluent

yielded **331** as a colourless oil (650 mg, 94%): $R_f$ 0.45, petroleum ether-diethyl ether (1:1); $[\alpha]^{20}_D$ + 77.0° (*c* 9.64, $CHCl_3$); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 3000m, 2940m, 2860m, 1680w, 1450m, 1360m, 1100s; $\delta_H$ (250MHz, $CDCl_3$) 1.80 (3H, d, *J* 0.7, 9-H), 1.86 (1H, dd, *J* 4.7, 14.8, 2ax-H), 2.23 (1H, dd, *J* 0.7, 14.8, 2eq-H), 3.37 (3H, s, OMe), 3.71 (1H, t, *J* 8.9, 6ax-H), 3.87 (1H, d, *J* 8.9, 4-H), 4.01 (1H, ddt, *J* 1.6, 5.3, 13.1, CH*H* 10-H), 4.18 (1H, ddt, *J* 1.6, 4.9, 13.1, C*H*H 10-H), 4.31 (1H, dt, *J* 5.3, 8.9, 5-H), 4.42 (1H, dd, *J* 5.3, 8.9, 6eq-H), 4.71 (1H, d, *J* 4.7, 1-H), 5.04-5.11 (2H, overlapping, 8-$H_{cis}$ and 12-$H_{cis}$), 5.13 (1H, br s, 8-$H_{trans}$), 5.30 (1H, ddd, *J* 1.8, 3.7, 17.2, 12-$H_{trans}$), 5.49 (1H, s, 13-H), 5.89-6.06 (1H, m, 11-H), 7.35-7.55 (5H, Ph); $\delta_C$ (62.9MHz, $CDCl_3$) 19.7 ($CH_3$, C9), 39.4 ($CH_2$, C2), 55.8 ($CH_3$, OMe), 59.4 (CH, C5), 66.9 ($CH_2$, C10), 70.0 ($CH_2$, C6), 77.7 (C, C3), 83.3 (CH, C4), 98.6 (CH, C1), 102.3 (CH, C13), 114.9 ($CH_2$ C8), 115.4 ($CH_2$, C12), 126.5 (CH, Ph), 128.6 (CH, Ph), 129.2 (CH, Ph), 136.6 (CH, C11), 138.3 (C, Ph), 145.3 (C, C7); *m/z* (FAB) 347 ($MH^+$, 48), found $MH^+$, 347.18585; $C_{20}H_{27}O_5$ requires 347.19592.

**Methyl-(*R*)-4,6-*O*-benzylidene-2,3-dideoxy-3(*R*)-spiro(3,5'-2',5'-dihydro-4'-methyl-furan)- α-D-allopyranoside (332).**

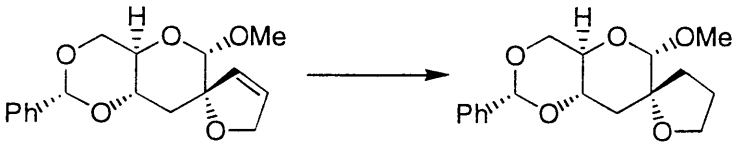



**331** **332**

Nitrogen gas was bubbled through a solution of the diene **331** (90 mg, 0.26 mmol) in benzene (8 mL) for 2-3 minutes. The catalyst **176b** (10 mg, 0.012 mmol, 4.6 mol%) was then added and the solution heated at 60°C for 36 h. The solvent was then 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 **331** as a colourless oil (46 mg, 51%) and **332** as a white solid (29 mg, 35%): mp 147-149°C; $R_f$ 0.35, petroleum ether-diethyl ether (1:1); $[\alpha]^{20}_D$ + 137.9° (*c* 3.84, $CHCl_3$); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 2900m br, 1720w, 1440w, 1360m; $\delta_H$ (250MHz, $CDCl_3$) 1.71 (3H, dd, *J* 2.2, 3.8, 10-H), 1.93 (1H, dd, *J* 0.7, 14.6, 2eq-H), 2.14 (1H, dd, *J* 4.7, 14.6, 2ax-H), 3.42 (3H, s, OMe), 3.53-3.72 (2H, m, 4-H, 5-H), 4.25-4.40 (2H, m, 6-H), 4.57-4.71 (2H, m, 9-H), 4.78 (1h, d, *J* 4.7, 1-H), 5.51 (1H, s, 11-H), 5.64 (1H, m, 8-H), 7.30-7.55 (5H, Ph);

$\delta_C$ (100MHz, $CDCl_3$) 12.3 ($CH_3$, C10), 38.2 ($CH_2$, C2), 56.1 ($CH_3$, OMe), 59.9 (CH, C5), 69.9 ($CH_2$, C6), 75.2 ($CH_2$, C9), 79.2 (CH, C4), 87.9 (C, C3), 98.8 (CH, C1), 102.2 (CH, C11), 124.4 (CH, C8), 126.6 (CH, Ph), 128.5 (CH, Ph), 129.2 (CH, Ph), 135.1 (C, C7), 138.4 (C, Ph); *m/z* (ES) 341 ($MNa^+$, 100); elemental analysis found C 67.83, H 7.07, $C_{18}H_{22}O_5$ requires C 67.90, H 6.96.

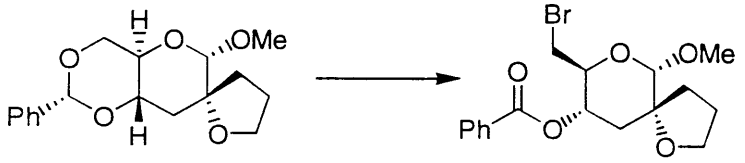
**Methyl-(*R*)-4,6-*O*-benzylidene-2,3-dideoxy-2(*S*)-spiro(2,5'-2',3',4',5'-tetrahydrofuran)-α-D-glucopyranoside (346).**




**307** **346**

To a solution of olefin **307** (363mg, 1.19mmol), in methanol (25 mL), was added 5% Palladium on carbon catalyst (30mg). The solution was stirred under an atmosphere of hydrogen for 48 h. The solution was filtered through celite, diluted with ether (150mL), washed with brine (2 × 100 mL), and the organic layer dried and evaporated. Chromatography on silica gel with petroleum ether-diethyl ether (2:1) as the eluent yielded **346** as a colourless oil (323 mg, 89%): $R_f$ 0.22, petroleum ether-diethyl ether (1:1); $[\alpha]^{20}_D$ +67.8° (*c* 8.64, $CHCl_3$); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 2920m, 2875m, 1450m, 1380m, 1050s; $\delta_H$ (250MHz, $CDCl_3$) 1.77-2.14 (5H, overlapping, 3eq-H, 8-H and 7-H), 2.26 (1H, t, *J* 11.7, 3ax-H), 3.43 (3H, s, OMe), 3.51 (1H, ddd, *J* 4.3, 8.8, 11.7, 4-H), 3.70 (1H, t, *J* 8.7, 6ax-H), 3.68-3.94 (3H, overlapping, 5-H and 9-H), 4.25 (1H, dd, *J* 4.1, 8.7, 6eq-H), 4.26 (1H, s, 1-H), 5.51 (1H, s, 10-H), 7.31-7.53 (5H, Ph); $\delta_C$ (62.9 MHz, $CDCl_3$) 26.1 ($CH_2$, C7), 35.8 ($CH_2$, C8), 36.5 ($CH_2$, C3), 55.5 ($CH_3$, OMe), 64.3 (CH, C5), 68.2 ($CH_2$, C9), 69.9 ($CH_2$, C6), 77.7 (CH, C4), 82.3 (C, C2), 102.2 (CH, C1), 102.2 (CH, C10), 126.6 (CH, Ph), 128.6 (CH, Ph), 129.5 (CH, Ph), 137.9 (C, Ph); *m/z* (FAB) 307 ($MH^+$, 11), found $MH^+$, 307.15449; $C_{17}H_{23}O_5$ requires 307.15455.

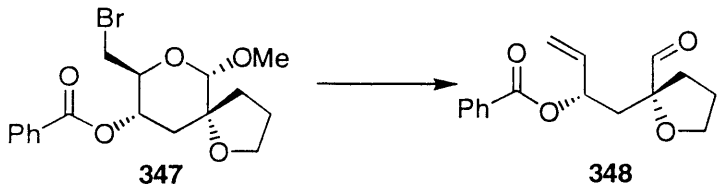
**Methyl-(*R*)-4-*O*-benzoyl-6-*C*-bromo-2(*S*)-spiro(2,5'-2',3',4',5'-tetrahydrofuran)-2,3,6-trideoxy-α-D-glucopyranoside (347).**




**346** **347**

Barium carbonate (835 mg, 4.24 mmol) and N-bromosuccininmide (207 mg, 1.16 mmol) were added sequentially to a solution of **436** (323 mg, 1.06 mmol) in dry chloroform (40 mL). The mixture was then heated to reflux for 4 h. The mixture was allowed to cool to room temperature, barium carbonate removed by filtration and the residue washed with diethyl ether (2 × 50 mL). The filtrate was concentrated under reduced pressure to leave a yellow oil. Chromatography on silica gel with toluene-diethyl ether (3:1) as the eluent yielded **347** as a white solid (285 mg, 70%): mp 104.5-106°C; $R_f$ 0.48, petroleum ether-diethyl ether (1:1); $[\alpha]^{20}_D$ +89.6° (*c* 2.87, $CHCl_3$); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 3000m br, 1720s, 1450w, 1260s; $\delta_H$ (250MHz, $CDCl_3$) 1.84-2.13 (4H, overlapping, 7-H and 8-H), 2.13 (1H, dd, overlapping, *J* 5.3, 11.3, 3eq-H), 2.24 (1H, t, *J* 11.3, 3ax-H), 3.44 (1H, dd, *J* 7.1, 11.0, CH*H* 6-H), 3.54 (3H, s, OMe), 3.59 (1H, dd, *J* 2.4, 11.0, C*H*H 6-H), 3.78-3.95 (2H, m, 9-H), 4.07 (1H, ddd, *J* 2.4, 7.1, 9.6, 5-H), 4.37 (1H, s, 1-H), 4.95 (1H, ddd, *J* 5.3, 9.6, 11.3, 4-H), 7.42-7.63 (3H, m, Ph), 8.00 (2H, m, o-Ph); $\delta_C$ (62.9 MHz, $CDCl_3$) 26.1 ($CH_2$, C7), 32.9 ($CH_2$, C8), 35.1 ($CH_2$, C3), 35.8 ($CH_2$, C6), 55.8 ($CH_3$, OMe), 68.5 ($CH_2$, C9), 69.6 (CH, C5), 70.4 (CH, C4), 81.7 (C, C2), 101.8 (CH, C1), 128.9 (CH, Ph), 129.9 (CH, Ph), 130.1 (CH, Ph), 133.8 (C, Ph), 165.7 (C, C10); *m/z* (ES) 407 and 409 ($MNa^+$, 100); elemental analysis found C 52.91, H 5.42, $C_{17}H_{21}O_5Br$ requires C 53.00, H 5.49.

**(2*R*, 4*S*)-4-*O*-benzoyl-2-spiro(2,5'-2',3',4',5'-tetrahydrofuran)hex-5-enal (348).**



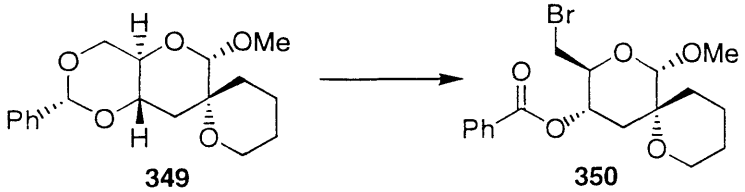

Zinc powder (60 g) was activated by washing with 2M hydrochloric acid (6 × 30 mL), water (5 × 35 mL), 10% w/v aqueous potassium carbonate solution (30 mL), water (4 × 40 mL), isopropanol (2 × 35 mL) and diethyl ether (3 × 35 mL). The bromo compound **347** (233 mg, 0.59 mmol) was heated to reflux with the activated zinc (5.08 g, 77.6 mol) in isopropanol : water (15:1.5 mL) for 3.5 h. The zinc was removed by filtration, washed with diethyl ether (2 × 50 mL), the combined organic layers washed with water (150 mL), saturated sodium chloride solution (150 mL), dried, and evaporated to leave a colourless oil. Chromatography on silica gel with petroleum ether-diethyl ether (3:1) as the eluent yielded **348** as a colourless oil (96 mg, 59%): $R_f$ 0.36, petroleum ether-diethyl ether (1:1); $[\alpha]^{20}_D$ -52.9° (*c* 3.99, $CHCl_3$); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 2900w br, 1715s, 1240w, 1095m; $\delta_H$ (250MHz, $CDCl_3$) 1.76-2.18 (4H, overlapping, 7-H and 8-H), 1.94 (1H, overlapping, dd, *J* 6.3, 14.5, CH*H* 3-H) 2.50 (1H, dd, *J* 10.6, 14.5, C*H*H 3-H), 3.83-4.06 (2H, m, 9-H), 5.18 (1H, dt, *J* 1.0, 10.4, 6-$H_{cis}$) 5.32 (1H, dt, *J* 1.0, 17.1, 6-$H_{trans}$) 5.66-5.77 (1H, m, 5-H), 5.87 (1H, ddd, *J* 6.3, 10.6, 16.7, 4-H), 7.34-7.68 (3H, Ph), 8.01 (2H, o-Ph), 9.58 (1H, s, 1-H); $\delta_C$ (62.9 MHz, $CDCl_3$) 25.8 ($CH_2$, C7), 34.5 ($CH_2$, C8), 42.1 ($CH_2$, C3), 69.6 ($CH_2$, C9), 71.8 (CH, C4), 87.7 (C, C2), 117.3 ($CH_2$, C6), 128.8 (CH, Ph), 130.1 (CH, Ph), 130.4 (C, Ph), 133.4 (CH, Ph), 136.4 (CH, C5), 165.5 (C, C10), 205.2 (CH, C1); *m/z* (ES) 297 ($MNa^+$, 82), found 275.1283; $C_{16}H_{19}O_4$ requires 275.1283.

**Methyl-(*R*)-4,6-*O*-benzylidene-2,3-dideoxy-2(*S*)-spiro(2,6'-2',3',5',6'-tetrahydropyran)-α-D-glucopyranoside (349).**


**315** **349**

To a solution of olefin **315** (1.43g, 4.5mmol), in methanol (30 mL), was added 5% Palladium on carbon catalyst (132mg). The solution was stirred under an atmosphere of hydrogen for 48 h. The solution was filtered through celite, diluted with ether (200mL), washed with brine (2 × 150 mL), and the organic layer dried and evaporated, to give a colourless oil **349** (1.48g, 100%), which was used without further purification: $R_f$ 0.16, petroleum ether-diethyl ether (1:1); $[\alpha]^{20}_D$ + 37.8° (*c* 3.71, $CHCl_3$); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 2975s, 1460m, 1390m; $\delta_H$ (250 MHz, $CDCl_3$) 1.52-1.64 (2H, m, 8-H), 1.65-1.81 (4H, overlapping, 7-H, 9-H), 1.97 (1H, t, *J* 11.8, 3ax-H), 2.30 (1H, dd, *J* 4.4, 11.8, 3eq-H), 3.48 (3H, s, OMe), 3.61 (1H, ddd, *J* 4.4, 9.4, 11.8, 4-H), 3.66-3.77 (3H, overlapping, 10-H, 6ax-H), 3.82 (1H, dt, *J* 4.4, 9.4, 5-H), 4.26 (1H, dd, *J* 4.4, 9.4, 6eq-H), 4.66 (1H, s, 1-H), 5.53 (1H, s, 11-H), 7.29-7.54 (5H, m, Ph); $\delta_C$ (62.9 MHz, $CDCl_3$) 18.8 ($CH_2$, C8), 25.4 ($CH_2$, C9), 31.8 ($CH_2$, C7), 34.0 ($CH_2$, C3), 55.2 ($CH_3$, OMe), 62.0 ($CH_2$, C10), 64.6 (CH, C5), 69.5 ($CH_2$, C6), 73.3 (C, C2), 75.7 (CH, C4), 100.8 (CH, C1), 102.0 (CH, C11), 126.2 (CH, Ph), 128.3 (CH, Ph), 129.1 (CH, Ph), 137.4 (C, Ph); *m/z* (FAB) 321 ($MH^+$, 34), found $MH^+$, 321.17024; $C_{18}H_{25}O_5$ requires 321.17020.

**Methyl-(*R*)-4-*O*-benzoyl-6-*C*-bromo-2(*S*)-spiro(2,6'-2',3',5',6'-tetrahydropyran)-2,3,6-trideoxy-α-D-glucopyranoside (350).**

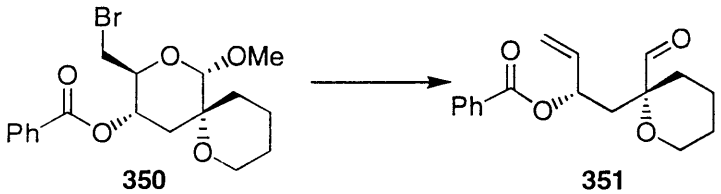



**349** **350**

Barium carbonate (3.78g, 19.2mmol) and N-bromosuccininmide (940mg, 5.27mmol) were added sequentially to a solution of **349** (1.53g, 4.8mmol) in dry chloroform (50 mL). The mixture was then heated to reflux for 18h. The mixture was allowed to cool to room temperature, barium carbonate removed by filtration and the residue washed with

diethyl ether (2 × 150 mL). The filtrate was concentrated under reduced pressure to leave a yellow oil. Chromatography on silica gel with petroleum ether-diethyl ether (2:1) as the eluent yielded **350** as a colourless oil (1.48g, 77%): $R_f$ 0.39, petroleum ether-diethyl ether (1:1); $[\alpha]^{20}_D$ + 56.2° (*c* 9.64, $CHCl_3$); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 2980m br, 1760s, 1460m, 1275m; $\delta_H$ (250 MHz, $CDCl_3$) 1.51-1.64 (2H, m, 8-H), 1.69-1.87 (4H, overlapping, 7-H, 9-H), 1.95 (1H, t, *J* 11.7, 3ax-H), 2.55 (1H, dd, *J* 5.2, 11.7, 3eq-H), 3.46 (1H, dd, *J* 6.9, 11.0, CH*H* 6-H), 3.56 (3H, s, OMe), 3.60 (1H, dd, overlapping, *J* 2.5, 11.0, C*H*H 6-H), 3.70 (2H, t, *J* 5.4, 10-H), 4.09 (1H, ddd, *J* 2.5, 6.9, 9.6, 5-H), 4.69 (1H, s, 1-H), 5.02 (1H, ddd, *J* 5.2, 9.6, 11.7, 4-H), 7.40-7.67 (3H, m, Ph), 7.95-8.10 (2H, m, o-Ph); $\delta_C$ (62.9 MHz, $CDCl_3$) 19.1 ($CH_2$, C8), 25.8 ($CH_2$, C9), 31.6 ($CH_2$, C7), 33.0 ($CH_2$, C3), 33.0 ($CH_2$, C6), 55.8 ($CH_3$, OMe), 62.5 ($CH_2$, C10), 69.2 (CH, C5), 70.0 (CH, C4), 73.2 (C, C2), 101.1 (CH, C1), 128.9 (CH, Ph), 129.9 (C, Ph), 130.2 (CH, Ph), 133.8 (CH, Ph), 165.8 (C, C11); *m/z* (FAB) 399, 401 ($MH^+$, 32), found $MH^+$, 399.08070; $C_{18}H_{24}O_5Br$ requires 399.08071.

**(2*R*, 4*S*)-4-*O*-benzoyl-2-spiro(2,6'-2',3',5',6'-tetrahydropyran)hex-5-enal (351)**

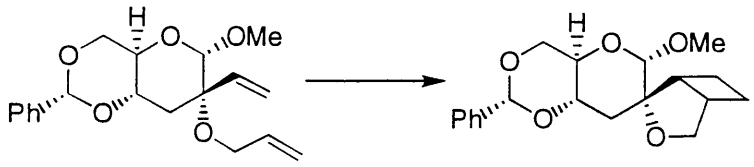



**350** **351**

The bromo compound **350** (1.40g, 3.5mmol) was heated to reflux with the activated zinc (11.45g, 175mmol) in isopropanol : water (60:6 mL) for 1h. The zinc was removed by filtration, washed with diethyl ether (2 × 200mL), the combined organic layers washed with water (300 mL), saturated sodium chloride solution (300 mL), dried, and evaporated to leave a colourless oil. Chromatography on silica gel with petroleum ether-diethyl ether (3:1) as the eluent yielded **351** as a colourless oil (552 mg, 54%): $R_f$ 0.46, petroleum ether-diethyl ether (1:1); $[\alpha]^{20}_D$ + 3.9° (*c* 2.1, $CHCl_3$); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 2960m, 2860w, 1720s, 1455m, 1275s; $\delta_H$ (250 MHz, $CDCl_3$) 1.54-1.95 (5H, m, CH*H* 7-H, 8-H, 9-H), 2.22 (1H, ddd, *J* 2.8, 7.6, 16.3, C*H*H 7-H), 2.30 (1H, d, *J* 2.8, C*H*H 3-H), 2.40 (1H, dd, *J* 10.3, 14.9, CH*H* 3-H), 3.89 (1H, m, CH*H* 10-H), 4.08 (1H, m, C*H*H 10-H), 5.37 (1H, d, *J* 10.0, 6-$H_{cis}$), 5.50 (1H, d, *J* 16.3, 6-$H_{trans}$), 5.93 (1H, m, 4-H), 6.04 (1H, ddd, overlapping, *J* 6.2, 10.0, 16.3, 5-H), 7.32-7.48 (3H, m, Ph), 8.02-8.18 (2H, m,

o-Ph), 9.85 (1H, s, 1-H); $\delta_C$ (62.9 MHz, $CDCl_3$) 20.3 ($CH_2$, C8), 25.4 ($CH_2$, C9), 31.6 ($CH_2$, C7), 43.2 ($CH_2$, C3), 65.0 ($CH_2$, C10), 70.7 (CH, C4), 80.3 (C, C2), 117.3 ($CH_2$, C6), 128.8 (CH, Ph), 130.1 (CH, Ph), 130.4 (C, Ph), 133.5 (CH, Ph), 136.4 (CH, C5), 165.5 (C, C11), 207.1 (CH, C1); *m/z* (ES) 311 ($MNa^+$, 100).

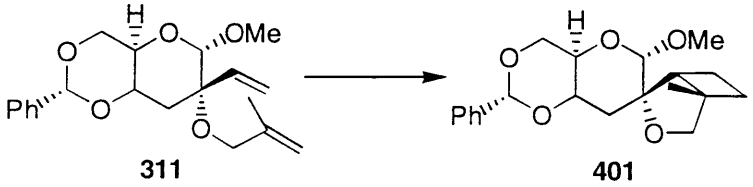
**Methyl (*R*)-4,6-*O*-benzylidene-2,3-dideoxy-2(*S*)-spiro(2,7'-3'(*R*), 6'(*R*)-1'-oxa-bicyclo-[3.2.0]-heptane)- α-D-glucopyranoside (400)**




**306** **400**

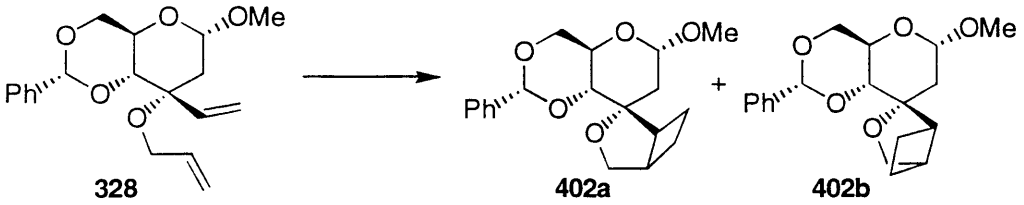
$(CF_3SO_3Cu)_2.C_6H_6$ (10 mg, 0.020 mmol, 6 mol%) was added to a solution of diene **306** (208 mg, 0.33 mmol) in dry benzene (10 mL), in a quartz photolysis tube, water-cooled by a cold finger extending into the solution. Irradiation was carried out at 254 nm, using a Rayonet™ photochemical reactor, for 8 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 solid. Chromatography on silica gel with petroleum ether-diethyl ether (3:1) as the eluent yielded **400** as a white solid (143 mg, 86%): mp 141.5-143°C; $R_f$ 0.26, petroleum ether-diethyl ether (1:1); $[\alpha]^{20}_D$ + 36.6° (*c* 3.3, $CHCl_3$); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 2900m br, 1410m, 1250s, 1080m br, 890s; $\delta_H$ (250MHz, $CDCl_3$) 1.67 (1H, m, CH*H* 9-H), 1.87 (2H, m, 3-H), 2.01 (2H, m, 8-H), 2.22 (1H, m, C*H*H 9-H), 2.93-3.16 (2H, m, 7-H, 10-H), 3.49 (1H, m, overlapping, 4-H), 3.49 (3H, s, OMe), 3.70 (1H, t, *J* 10.1, 6ax-H), 3.80-3.98 (3H, overlapping, 11-H, 5-H), 4.24 (1H, dd, *J* 4.4, 10.1, 6eq-H), 4.67 (1H, s, 1-H), 5.50 (1H, s, 12-H), 7.30-7.55 (5H, m, Ph); $\delta_C$ (62.9MHz, $CDCl_3$) 19.6 ($CH_2$, C8), 24.1 ($CH_2$, C9), 32.7 ($CH_2$, C3), 39.1 (CH, C10), 45.6 (CH, C7), 55.4 ($CH_3$, OMe), 64.1 (CH, C5), 69.9 ($CH_2$, C6), 73.1 ($CH_2$, C11), 77.4 (CH, C4), 83.8 (C, C2), 99.6 (CH, C1), 102.3 (CH, C12), 126.6 (CH, Ph), 128.7 (CH, Ph), 129.5 (CH, Ph), 137.8 (C, Ph); *m/z* (FAB) 333 ($MH^+$, 56), 301 ($MH^+$, -MeOH, 100); elemental analysis found C 68.46, H 7.22, $C_{19}H_{24}O_5$ requires C 68.66, H 7.30.

**Methyl (*R*)-4,6-*O*-benzylidene-2,3-dideoxy-2(*S*)-spiro(2,7'-3'(*R*), 6'(*R*)-3'-methyl-1'-oxa-bicyclo-[3.2.0]-heptane)- α-D-glucopyranoside (401)**




$(CF_3SO_3Cu)_2.C_6H_6$ (10 mg, 0.020 mmol, 4 mol%) was added to a solution of diene **311** (165 mg, 0.47 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 solid. Chromatography on silica gel with petroleum ether-diethyl ether (3:1) as the eluent yielded starting material **311** as a white solid (48 mg, 29%) and **401** as a white solid (83 mg, 50%): mp 165.5-167°C; $R_f$ 0.29, petroleum ether-diethyl ether (1:1); $[\alpha]^{20}_D$ + 11.2° (*c* 4.9, $CHCl_3$); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 2940s br, 1450m, 1395m, 1100s; $\delta_H$ (250MHz, $CDCl_3$) 1.25 (3H, s, 11-H), 1.71-1.99 (6H, overlapping, 3-H, 8-H, 9-H), 2.54 (1H, m, 7-H), 3.42 (3H, s, OMe), 3.46 (1H, m, overlapping, 4-H), 3.51 (1H, d, *J* 9.1, CH*H* 12-H), 3.63 (1H, t, *J* 10.2, 6ax-H), 3.76 (1H, ddd, overlapping, *J* 4.4, 8.6, 5-H), 3.79 (1H, d, *J* 9.1, C*H*H 12-H), 4.17 (1H, dd, *J*, 4.4, 10.2, 6eq-H), 4.58 (1H, s, 1-H), 5.45 (1H, s, 13-H), 7.22-7.55 (5H, m, Ph); $\delta_C$ (62.9MHz, $CDCl_3$) 16.1 ($CH_2$, C9), 24.9 ($CH_3$, C11), 30.7 ($CH_2$, C8), 31.3 ($CH_2$, C3), 46.8 (C, C10), 51.4 (CH, C7), 55.4 ($CH_3$, OMe), 64.1 (CH, C5), 69.8 ($CH_2$, C6), 77.9 (CH, C4), 78.7 ($CH_2$, C12), 84.2 (C, C2), 99.8 (CH, C1), 102.4 (CH, C13), 126.6 (CH, Ph), 128.8 (CH, Ph), 129.5 (CH, Ph), 137.8 (C, Ph); *m/z* (ES) 369 ($MNa^+$, 100); elemental analysis found C 69.34, H 7.56, $C_{20}H_{26}O_5$ requires C 69.35, H 7.35.

**Methyl (*R*)-4,6-*O*-benzylidene-2,3-dideoxy-3(*R*)-spiro(3,7'-3'(*R*), 6'(*R*)-1'-oxa-bicyclo-[3.2.0]-heptane)-α-D-glucopyranoside (402a) and Methyl (*R*)-4,6-*O*-benzylidene-3(*R*)-2,3-dideoxy-spiro(3,7'-3'(*S*), 6'(*S*)-1'-oxa-bicyclo-[3.2.0]-heptane)-α-D-glucopyranoside (402b)**



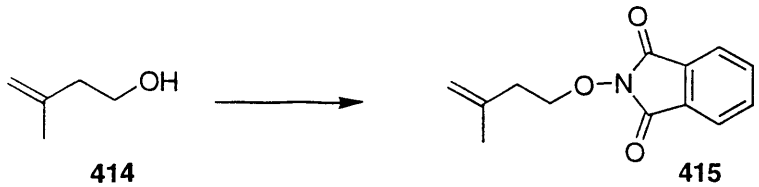

$(CF_3SO_3Cu)_2.C_6H_6$ (10 mg, 0.020 mmol, 5 mol%) was added to a solution of diene **328** (147 mg, 0.45 mmol) in dry benzene (10 mL), in a quartz photolysis tube, water-cooled by a cold finger extending into the solution. Irradiation was carried out at 254 nm, using a Rayonet™ photochemical reactor, 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 solid. Chromatography by chromatatron with chloroform-ethyl acetate (4:1) as the eluent yielded **402a** as a white solid (48 mg, 33%) and **402b** as a white solid (40 mg, 30%): **402a:** mp 141-143°C; $R_f$ 0.36, petroleum ether-diethyl ether (1:1); $[\alpha]^{20}_D$ + 87.9° (*c* 4.2, $CHCl_3$); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 2950m, 1450w, 1390m, 1100s, 1050s; $\delta_H$ (400MHz, $CDCl_3$) 1.72 (1H, m, CH*H* 8-H, or CH*H* 9-H), 1.85 (1H, dd, *J* 4.6, 14.6, 2ax-H), 1.95 (1H, m, CH*H* 8-H, or CH*H* 9-H), 2.03 (1H, m, C*H*H 8-H, or C*H*H 9-H), 2.19 (1H, m, C*H*H 8-H, or C*H*H 9-H), 2.21 (1H, dd, overlapping, *J* 0.6, 14.6, 2eq-H), 2.93-2.98 (2H, m, 7-H, 10-H), 3.46 (3H, s, OMe), 3.47 (1H, m, overlapping, 4-H), 3.69 (1H, t, *J* 11.7, 6ax-H), 3.97 (1H, d, *J* 8.0, 5-H), 4.31 (1H, m, overlapping, 6eq-H), 4.31 (2H, d, 11-H), 4.79 (1H, d, *J* 4.6, 1-H), 5.45 (1H, s, 12-H), 7.35-7.58 (5H, m, Ph); $\delta_C$ (100.6MHz, $CDCl_3$) 18.4 ($CH_2$, C8), 24.8 ($CH_2$, C9), 36.8 ($CH_2$, C2), 40.2 (CH, C10), 46.9 (CH, C7), 56.0 ($CH_3$, OMe), 59.6 (CH, C5), 69.7 ($CH_2$, C6), 77.8 ($CH_2$, C11), 81.3 (C, C3), 86.3 (CH, C4), 98.8 (CH, C1), 102.4 (CH, C12), 126.4 (CH, Ph), 128.6 (CH, Ph), 129.3 (CH, Ph), 138.3 (C, Ph); *m/z* (ES) 355 ($MNa^+$, 100); elemental analysis found C 68.58, H 6.88, $C_{19}H_{24}O_5$ requires C 68.66, H 7.30.

**402b:** mp 168-169°C; $R_f$ 0.25, petroleum ether-diethyl ether (1:1); $[\alpha]^{20}_D$ + 58.3° (*c* 4.6, $CHCl_3$); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 2960m br, 1390m, 1200m, 1100s; $\delta_H$ (400MHz, $CDCl_3$)

1.61 (1H, dd, *J* 4.6, 14.8, 2ax-H), 1.79 (1H, m, CH*H* 8-H, or CH*H* 9-H), 2.01 (1H, dd, *J* 0.8, 14.8, 2eq-H), 1.98-2.12 (2H, m, CH*H* 8-H, and/or CH*H* 9-H), 2.54-2.66 (2H, m, C*H*H 8-H, or C*H*H 9-H, 7-H), 2.95 (1H, m 10-H), 3.38 (3H, s, OMe), 3.71-3.79 (2H, overlapping, 5-H, 4-H), 4.01 (1H, dd, *J* 3.4, 9.3, 6ax-H), 4.07 (1H, dd, *J* 7.0, 9.3, 6eq-H), 4.35 (2H, m, 11-H), 4.66 (1H, d, *J* 4.6, 1-H), 5.61 (1H, s, 12-H), 7.38-7.57 (5H, m, Ph); $\delta_C$ (100.6MHz, $CDCl_3$) 20.6 ($CH_2$, C8), 24.1 ($CH_2$, C9), 38.6 ($CH_2$, C2), 39.2 (CH, C10), 48.7 (CH, C7), 55.9 ($CH_3$, OMe), 60.6 (CH, C5), 70.2 ($CH_2$, C6), 73.8 ($CH_2$, C11), 81.4 (C, C3), 81.5 (CH, C4), 98.8 (CH, C1), 101.9 (CH, C12), 126.5 (CH, Ph), 128.5 (CH, Ph), 129.1 (CH, Ph), 138.3 (C, Ph); *m/z* (ES) 355 ($MNa^+$, 100); elemental analysis found C 68.41, H 7.27, $C_{19}H_{24}O_5$ requires C 68.66, H 7.30.

Configuration of diastereoisomers was confirmed by 2-D NOESY experiments. **402a** showed a significant nOe signal between 7-H and 4-H, whereas **402b** showed a significant nOe signal between 7-H and 2ax-H.

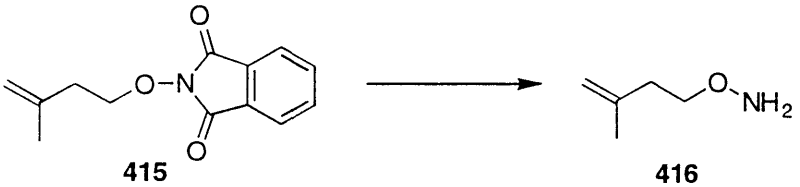
### *N*-(3-Methyl-butenoxy)-phthalimide (415)




**414** **415**

Diethyl-aza-dicarboxylate (4.02 mL, 25.5 mmol) was added dropwise to an ice-cooled solution of N-hydroxyphthalamide (3.84 g, 23.2 mmol), alcohol **414** (2.0g, 23.2 mmol) and triphenyl phosphine (6.09g, 23.2 mmol) in dry THF (40mL). The resulting mixture was stirred at rt for 18 h, then diluted with diethyl ether (200 mL), washed with brine (2 × 100mL), dried and evaporated to give a yellow oil. Chromatography on silica gel with petroleum ether : diethyl ether (2 : 1) as eluent yielded **415** as a colourless oil (4.64g, 87%): $R_f$ 0.31, petroleum ether-diethyl ether (1:1); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 3520m, 2990s br, 1800s, 1740s, 1380s; $\delta_H$ (250 MHz, $CDCl_3$) 1.87 (3H, s, 3-H), 2.59 (2H, t, *J* 6.9, 4-H), 4.37 (2H, t, *J* 6.9, 5-H), 4.90 (2H, br s, overlapping, 1-$H_{cis}$, 1-$H_{trans}$), 7.77-7.93 (4H, m, Ph); $\delta_C$ (62.9MHz, $CDCl_3$) 22.7 ($CH_3$, C3), 36.3 ($CH_2$, C4), 74.1 ($CH_2$, C5), 112.5 ($CH_2$, C1), 123.6 (CH, Ph), 129.1 (C, Ph), 134.7 (CH, Ph), 141.2 (C, C2), 163.5 (C, C6); *m/z* (FAB) 232 ($MH^+$, 66), found $MH^+$, 232.09736; $C_{13}H_{14}NO_3$ requires 232.09737.

**_N_-(3-Methyl-butenyl)-hydroxylamine (416)**



**415** **416**

Hydrazine monohydrate (1.07 mL, 22.1 mmol) was added dropwise to a solution of aryl olefin **415** (4.64g, 20.1 mmol) in MeOH (50mL), and the mixture was stirred at reflux for 2h. The solid precipitate was removed by filtration washed with MeOH (2 × 20mL) and the solvent evaporated. The resulting oil was taken up into diethyl ether (50mL), filtered through a pad of silica, dried and the solvent evaporated to give **416** as a colourless oil (2.18g, 94%): $R_f$ 0.20, petroleum ether-diethyl ether (1:1); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 2980m br, 1795m, 1735s, 1360m, 1180m; $\delta_H$ (250 MHz, $CDCl_3$) 1.76 (3H, s, 3-H), 2.31 (2H, t, *J* 6.7, 4-H), 3.78 (2H, t, *J* 6.7, 5-H), 4.74 (1H, s, 1-$H_{cis}$) 4.76 (1H, s, 1-$H_{trans}$), 5.30 (2H, br s, $NH_2$); $\delta_C$ (62.9MHz, $CDCl_3$) 22.8 ($CH_3$, C3), 37.0 ($CH_2$, C4), 74.2 ($CH_2$, C5), 111.9 ($CH_2$, C1), 143.1 (C, C2); *m/z* (ES) 102 ($MH^+$, 100), 85 ($MH^+$–$NH_3$, 47), 55 ($MH^+$–$CH_2ONH_3$, 73).

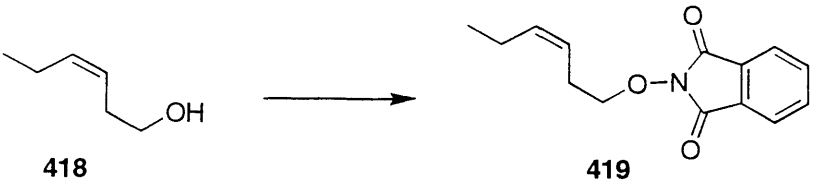
**Formaldehyde-*O*-(3-methyl-butenyl)-oxime (417)**

**416** **417**

Formaldehyde solution (1.26 mL, 39% solution in $H_2O$, 16.4 mmol) was added dropwise to a solution of hydroxylamine **416** (1.85g, 16.4 mmol) in MeOH (10mL) and the mixture stirred at rt for 18h. The solvent was removed by evaporation and the resulting oil taken up in diethyl ether (75 mL), washed with brine (50 mL), dried and evaporated to give a brown oil. Chromatography on silica gel with petroleum ether : diethyl ether (4 : 1) as eluent afforded **417** as a colourless oil (754mg, 41%): $R_f$ 0.35, petroleum ether-diethyl ether (1:1); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 2990m br, 1740m, 1375m, 1110m, 910s; $\delta_H$ (250 MHz, $CDCl_3$) 1.76 (3H, s, 3-H), 2.38 (2H, t, *J* 6.9, 4-H), 4.19 (2H, t, *J* 6.9, 5-H), 4.76 (1H, t, *J* 11.0, 1-$H_{cis}$), 4.77 (1H, t, *J* 11.0, 1-$H_{trans}$), 6.40 (1H, d, *J* 8.5, 6-$H_{cis}$), 6.99 (1H, d, *J* 8.5, 6-$H_{trans}$); $\delta_C$ (62.9MHz, $CDCl_3$) 23.0 ($CH_3$, C3), 37.4

($CH_2$, C4), 72.7 ($CH_2$, C5), 112.1 ($CH_2$, C1), 137.2 ($CH_2$, C6), 142.6 (C, C2); *m/z* (ES) 114 ($MH^+$, 70), 69 ($MH^+$–$CH_2ONH_3$, 100).

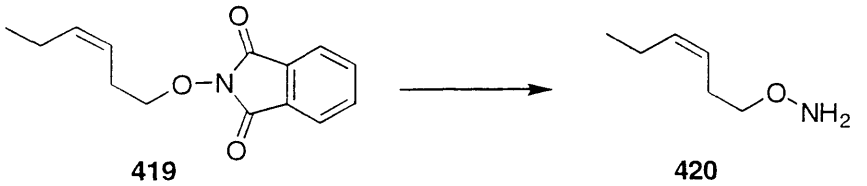
**N-[(Z)-hex-3-enoxy]-phthalimide (419)**




**418** **419**

Diethyl-aza-dicarboxylate (8.7 mL, 54.9 mmol) was added dropwise to an ice-cooled solution of N-hydroxyphthalamide (8.36 g, 49.9 mmol), alcohol **418** (5g, 49.9 mmol) and triphenyl phosphine (13.1g, 49.9 mmol) in dry THF (100mL). The resulting mixture was stirred at rt for 18 h, then diluted with diethyl ether (400 mL), washed with brine (2 × 200mL), dried and evaporated to give a yellow solid. Chromatography on silica gel with petroleum ether : diethyl ether (1 : 1) as eluent yielded **419** as a waxy white solid (9.95g, 81%): mp 40-41°C; $R_f$ 0.28, petroleum ether-diethyl ether (1:1); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 3520w, 2975s, 1995m, 1740s, 1370m; $\delta_H$ (250 MHz, $CDCl_3$) 0.97 (3H, t, *J* 7.6, 1-H), 2.08 (2H, quintet, *J* 7.6, 2-H), 2.57 (2H, quintet, *J* 7.1, 5-H), 4.20 (2H, t, *J* 7.1, 6-H), 5.35-5.59 (2H, overlapping, 3-H, 4-H), 7.73-7.88 (4H, m, Ph); $\delta_C$ (62.9MHz, $CDCl_3$) 14.5 ($CH_3$, C1), 21.0 ($CH_2$, C2), 26.8 ($CH_2$, C5), 78.1 ($CH_2$, C6), 123.2 (CH, C3), 123.8 (CH, Ph), 129.3 (C, Ph), 134.8 (CH, Ph), 135.2 (CH, C4), 163.9 (C, C7); *m/z* (FAB) 246 ($MH^+$, 93), found $MH^+$, 246.11307; $C_{14}H_{16}NO_3$ requires 246.11302.

**N-[(Z)-hex-3-enyl]-hydroxylamine (420)**

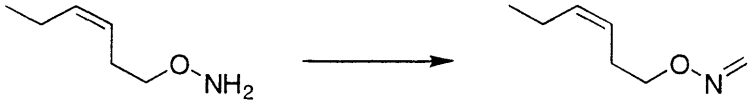



**419** **420**

Hydrazine monohydrate (0.55 mL, 11.2 mmol) was added dropwise to a solution of aryl olefin **419** (2.67g, 10.9 mmol) in MeOH (50mL), and the mixture was stirred at reflux for 2h. The solid precipitate was removed by filtration washed with MeOH (2 × 20mL) and the solvent evaporated. The resulting oil was taken up into diethyl ether (50mL), filtered through a pad of silica, dried and the solvent evaporated to give **420** as a

colourless oil (1.06g, 85%): $R_f$ 0.28, petroleum ether-diethyl ether (1:1); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 2900s br, 2250m, 1960w, 1590m, 1280m; $\delta_H$ (250 MHz, $CDCl_3$) 1.12 (3H, t, *J* 7.6, 1-H), 2.22 (2H, quintet, *J* 7.6, 2-H), 2.48 (2H, quintet, *J* 6.9, 5-H), 3.81 (2H, t, *J* 6.9, 6-H), 5.41-5.69 (2H, overlapping, 3-H, 4-H), 5.52 (2H, s, $NH_2$); $\delta_C$ (62.9MHz, $CDCl_3$) 14.5 ($CH_3$, C1), 20.9 ($CH_2$, C2), 26.9 ($CH_2$, C5), 75.2 ($CH_2$, C6), 125.1 (CH, C3), 133.9 (CH, C4); *m/z* (ES) 116 ($MH^+$, 100), 83 ($MH^+$–$H_3NO$, 21), 69 ($MH^+$–$H_3NOCH_2$, 38), 55 ($MH^+$–$H_3NOCH_2CH_2$, 70).

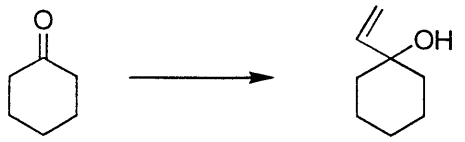
**Formaldehyde-*O*-[(*Z*)-hex-3-enyl]-oxime (421)**




**420** **421**

Formaldehyde solution (0.70 mL, 39% solution in $H_2O$, 9.13 mmol) was added dropwise to a solution of hydroxylamine **420** (1.05g, 9.13 mmol) in MeOH (10mL) and the mixture stirred at rt for 18h. The solvent was removed by evaporation and the resulting oil taken up in diethyl ether (75 mL), washed with brine (50 mL), dried and evaporated to give a brown oil. Chromatography on silica gel with petroleum ether : diethyl ether (2 : 1) as eluent afforded **421** as a colourless oil (201mg, 17%): $R_f$ 0.36, petroleum ether-diethyl ether (1:1); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 2980s, 2880s, 1450w, 1385m, 1110s; $\delta_H$ (250 MHz, $CDCl_3$) 0.97 (3H, t, *J* 7.5, 1-H), 2.17 (2H, dquintet, *J* 0.7, 7.5, 2-H), 2.40 (2H, quintet, *J* 6.9, 5-H), 4.08 (2H, t, *J* 6.9, 6-H), 5.28-5.41 (1H, m, 3-H), 5.43-5.56 (1H, m, 4-H), 6.41 (1H, d, *J* 8.5, 7-$H_{cis}$), 7.01 (1H, d, *J* 8.5, 7-$H_{trans}$); $\delta_C$ (62.9MHz, $CDCl_3$) 14.6 ($CH_3$, C1), 21.0 ($CH_2$, C2), 27.6 ($CH_2$, C5), 73.9 ($CH_2$, C6), 124.6 (CH, C3), 134.5 (CH, C4), 137.2 ($CH_2$, C7); *m/z* (ES) 128 ($MH^+$, 41), 83 ($MH^+$–$CH_2NHO$, 54), 55 ($MH^+$–$C_3H_6NHO$, 100).

**1-Vinyl-cyclohexanol (521)**

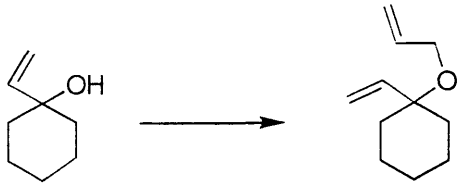



**520** **521**

Vinylmagnesium chloride (122 mL, 204 mmol, 15% wt. solution in THF) was added dropwise to an ice-cooled solution of cyclohexanone **520** (10.0 g, 102 mmol) in dry THF (20.0 mL). The solution was then heated to reflux for 4 h and allowed to cool to room temperature, then quenched by dropwise addition of saturated ammonium chloride solution (60 mL). The resulting mixture was extracted into diethyl ether (2 × 300 mL), and the combined organic layers were washed with saturated sodium chloride solution (500 mL), dried, and evaporated to yielded **521** as a pale yellow oil (12.54g, 97%), which was used without further purification: $R_f$ 0.13, petroleum ether-diethyl ether (1:1); $\delta_H$ (250 MHz, $CDCl_3$) 1.20-1.73 (10H, overlapping, 2-H, 3-H, 4-H), 5.02 (1H, dd, *J* 1.2, 10.8, 6-$H_{cis}$), 5.24 (1H, dd, *J* 1.2, 17.4, 6-$H_{trans}$), 5.97 (1H, dd, *J* 10.8, 17.4, 5-H); $\delta_C$ (62.9 MHz, $CDCl_3$) 22.4 ($CH_2$, C3), 25.9 ($CH_2$, C4), 37.9 ($CH_2$, C2), 72.1 (C, C1), 111.8 ($CH_2$, C6), 146.4 (CH, C5).

This is a literature compound.[8]

**1-Allyloxy-1-vinyl-cyclohexane (514)**



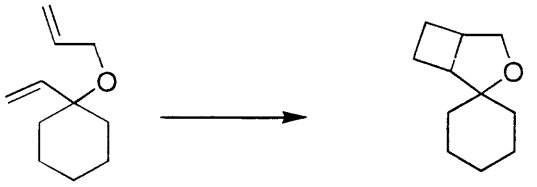

**521** **514**

Sodium hydride (3.9 g, 60% dispersion in mineral oil, 98 mmol) was added portionwise to an ice-cooled solution of alcohol **521** (10.14 g, 80 mmol) in dry THF (30.0 mL). The resulting mixture was heated to reflux for 2 h and allowed to cool to room temperature. Allyl bromide (7.7 mL, 92 mmol) and DMPU (200 μL) were then added, the mixture was heated to reflux for 4 h, allowed to cool to room temperature, and quenched by addition of water (30 mL). The resulting mixture was then extracted into diethyl ether (2 × 250 mL), the combined organic layers washed with saturated sodium chloride solution

(250 mL), dried, and evaporated to leave a pale yellow oil. Chromatography on silica gel with neat toluene as the eluent yielded **514** as a colourless oil (7.43 g, 56%): $R_f$ 0.62, petroleum ether-diethyl ether; $\delta_H$ (250 MHz, $CDCl_3$) 1.40-2.06 (10H, overlapping, 2-H, 3-H, 4-H), 4.01 (2H, dt, *J* 1.5, 5.5, 7-H), 5.32 (1H, dq, *J* 1.5, 10.3, 9-$H_{cis}$), 5.36 (1H, dd, *J* 1.4, 17.4, 6-$H_{trans}$), 5.38 (1H, dd, *J* 1.4, 11.3, 6-$H_{cis}$), 5.50 (1H, dq, *J* 1.5, 17.2, 9-$H_{trans}$), 5.97 (1H, dd, *J* 11.3, 17.4, 5-H), 6.15 (1H, m, 8-H); $\delta_C$ (62.9 MHz, $CDCl_3$) 22.2 ($CH_2$, C3), 26.2 ($CH_2$, C4), 34.8 ($CH_2$, C2), 63.2 ($CH_2$, C7), 76.3 (C, C1), 114.9 ($CH_2$, C6), 115.9 ($CH_2$, C9), 136.5 (CH, C8), 143.6 (CH, C5).

This is a literature compound.[8]

### (±) 2-cyclohexyl-oxabicyclo-[3.2.0]-heptane (515)

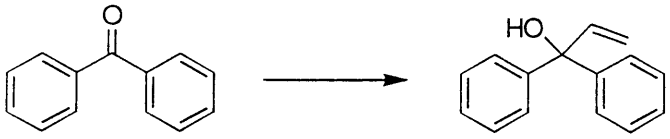


**514** (+/-) **515**

$(CF_3SO_3Cu)_2.C_6H_6$ (10 mg, 0.020 mmol, 3 mol%) was added to a solution of diene **514** (121 mg, 0.73 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 8 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 solid. Chromatography on silica gel with petroleum ether-diethyl ether (7:1) as the eluent yielded **515** as a colourless oil (104 mg, 86%): $R_f$ 0.82, petroleum ether-diethyl ether (1:1); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 2940s, 2865m, 1760s, 1450m, 1195w; $\delta_H$ (400 MHz, $CDCl_3$) 1.22-1.36 (3H, overlapping, CH*H* 3-H, CH*H* 4-H), 1.36-1.47 (3H, overlapping, C*H*H 3-H, C*H*H 4-H), 1.53-1.72 (5H, overlapping, 2-H, CH*H* 7-H), 1.82-1.93 (1H, overlapping, m, C*H*H 6-H), 1.90-2.02 (1H, overlapping, m, CH*H* 6-H), 2.17 (1H, m, C*H*H 7-H), 2.70 (1H, q, *J* 6.9, 5-H), 2.91 (1H, m, 8-H), 3.74 (1H, dd, *J* 1.4, 11.0, CH*H* 9-H), 3.83 (1H, dd, *J* 5.9, 11.0, C*H*H 9-H); $\delta_C$ (100 MHz, $CDCl_3$) 18.4 ($CH_2$, C6), 23.0 ($CH_2$, C4), 23.7 ($CH_2$, C7), 23.8 ($CH_2$, C2), 26.0 ($CH_2$, C3), 31.8 ($CH_2$, C2'), 33.4 ($CH_2$, C3'), 38.9 (CH, C5), 44.8 (CH, C8), 71.4 ($CH_2$, C9),

83.6 (C, C1); *m/z* (EI) 166 ($M^+$, 17%), found $M^+$ 166.13576; $C_{11}H_{18}O$ requires 166.13577.

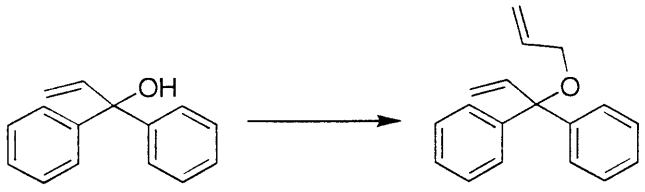
**1,1-Diphenyl-prop-2-en-1-ol (523)**




**522** **523**

Vinylmagnesium chloride (66 mL, 110 mmol, 15% wt. solution in THF) was added dropwise to an ice-cooled solution of benzophenone **522** (10.0 g, 55 mmol) in dry THF (10.0 mL). The solution was then heated to reflux for 4 h and allowed to cool to room temperature, then quenched by dropwise addition of saturated ammonium chloride solution (50 mL). The resulting mixture was extracted into diethyl ether (2 × 300 mL), and the combined organic layers were washed with saturated sodium chloride solution (500 mL), dried, and evaporated to leave a yellow oil. Chromatography on silica gel with petroleum ether-diethyl ether (5:2) as the eluent yielded **523** as a colourless oil (9.01 g, 78%): $R_f$ 0.22, petroleum ether-diethyl ether (1:1); $\delta_H$ (250 MHz, $CDCl_3$) 3.14 (1H, br. s, O*H*), 5.58 (1H, dd, overlapping, *J*, 1.1, 10.3, 3-$H_{cis}$), 5.59 (1H, dd, overlapping, *J* 1.1, 17.4, 3-$H_{trans}$), 6.78 (1H, dd, *J* 10.3, 17.4, 2-H), 7.46-7.63 (10H, m, Ph); $\delta_C$ (62.9 MHz, $CDCl_3$) 79.9 (C, C1), 114.5 ($CH_2$, C3), 127.4 (CH, Ph), 127.7 (CH, Ph), 128.6 (CH, Ph), 144.0 (CH, C2), 146.2 (C, Ph).
This is a literature compound.[9]

**1-Allyloxy-1,1-diphenyl-prop-2-ene (524)**




**523** **524**

Sodium hydride (5.12g, 60% dispersion in mineral oil, 128mmol) was added portionwise to an ice-cooled solution of alcohol **523** (6.12 mg, 29.0 mmol) in dry THF (50.0 mL). The resulting mixture was heated to reflux for 2 h and allowed to cool to

room temperature. Allyl bromide (8.46 mL, 93 mmol) and DMPU (100 μL) were then added, the mixture was heated to reflux for 18h, allowed to cool to room temperature, and quenched by addition of water (50 mL). The resulting mixture was then extracted into diethyl ether (2 × 250 mL), the combined organic layers washed with saturated sodium chloride solution (300 mL), dried, and evaporated to leave a brown oil. KügelRohr Distillation at 115°C, 0.36 mbar, yielded **524** as a pale yellow oil (5.40 g, 74%): $R_f$ 0.62, petroleum ether-diethyl ether (1:1); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 2940s, 4860m, 1730m, 1450m; $\delta_H$ (250 MHz, $CDCl_3$) 3.76 (2H, dt, *J* 1.8, 4.8, 4-H), 5.12 (1H, dq, *J* 1.8, 10.3, 6-$H_{cis}$), 5.21 (1H, dd, *J* 1.4, 17.2, 3-$H_{trans}$), 5.32 (1H, dd, *J* 1.4, 10.7, 3-$H_{cis}$), 5.37 (1H, dq, *J* 1.8, 17.2, 6-$H_{trans}$), 5.92 (1H, m, 5-H), 6.44 (1H, dd, *J* 10.7, 17.2, 2-H), 7.16-7.41 (10H, overlapping, Ph); $\delta_C$ (62.9MHz, $CDCl_3$) 65.3 ($CH_2$, C4), 84.7 (C, C1), 115.8 ($CH_2$, C3 or C6), 116.7 ($CH_2$, C6 or C3), 127.8 (CH, Ph), 128.3 (CH, Ph), 128.4 (CH, Ph), 135.8 (CH, C5), 140.8 (CH, C2), 144.5 (CH, Ph); *m/z* (EI) 250 ($M^+$, 30), found $M^+$, 250.13580; $C_{18}H_{18}O$ requires 250.13577.

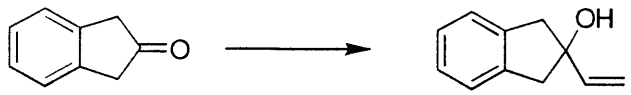
**1,3-Diphenyl-2-vinyl-2-propanol (527)**


**526** **527**

Vinylmagnesium chloride (38.4 mL, 64.5 mmol, 15% wt. solution in THF) was added dropwise to an ice-cooled solution of the dibenzyl ketone **526** (9.60 g, 45.7 mmol) in dry THF (10.0 mL). The solution was then heated to reflux for 4 h and allowed to cool to room temperature, then quenched by dropwise addition of saturated ammonium chloride solution (40 mL). The resulting mixture was extracted into diethyl ether (2 × 250 mL), and the combined organic layers were washed with saturated sodium chloride solution (250 mL), dried, and evaporated to leave a brown oil. Chromatography on silica gel with petroleum ether-diethyl ether (5:2) as the eluent yielded **527** as a pale green oil (7.17 g, 66%): $R_f$ 0.15, petroleum ether-diethyl ether (1:1); $\delta_H$ (250 MHz, $CDCl_3$) 2.90 (4H, s, 1-H, 1'-H), 3.71 (1H, s, O*H*), 4.91 (1H, dd *J* 1.4, 17.2, 4-$H_{trans}$), 5.01 (1H, dd, *J* 1.4, 10.8, 4-$H_{cis}$), 5.93 (1H, dd, *J* 10.8, 17.2, 3-H), 7.11-7.33 (10H, m, Ph); $\delta_C$ (62.9 MHz, $CDCl_3$) 47.9 ($CH_2$, C1), 76.0 (C, C2), 114.1 ($CH_2$, C4), 127.0 (CH, Ph), 128.5 (CH, Ph), 131.3 (CH, Ph), 137.1 (C, Ph), 143.6 (CH, C3).

This is a literature compound.[10]

**2-Vinyl-indan-2-ol (530)**

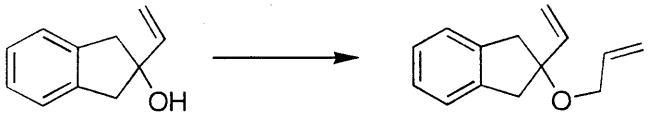



**529** **530**

Vinylmagnesium chloride (28.8 mL, 48 mmol, 15% wt. solution in THF) was added dropwise to an ice-cooled solution of the ketone **529** (3.19 g, 24 mmol) in dry THF (10.0 mL). The solution was then heated to reflux for 2 h and allowed to cool to room temperature, then quenched by dropwise addition of saturated ammonium chloride solution (25 mL). The resulting mixture was extracted into diethyl ether (2 × 100 mL), and the combined organic layers were washed with saturated sodium chloride solution (150 mL), dried, and evaporated to leave a yellow oil. Chromatography on silica gel with petroleum ether-diethyl ether (2:1) as the eluent yielded starting material **529** (730mg, 23%) and **530** as a white solid (735 mg, 19%): $R_f$ 0.17, petroleum ether-diethyl ether (1:1); $\delta_H$ (250 MHz, $CDCl_3$) 3.00 (1H, br. s, O*H*), 3.23 (2H, d, *J* 16.3, CH*H* 2-H), 3.44 (2H, d, *J* 16.3, C*H*H 2-H), 5.40 (1H, dd, *J* 1.3, 10.8, 4-$H_{cis}$), 5.66 (1H, dd, *J* 1.3, 17.3, 4-$H_{trans}$), 6.43 (1H, dd, *J* 10.8, 17.3, 3-H), 7.41-7.53 (4H, m, Ph); $\delta_C$ (62.9 MHz, $CDCl_3$) 47.7 ($CH_2$, C2), 82.6 (C, C1), 113.0 ($CH_2$, C4), 125.3 (CH, Ph), 127.1 (CH, Ph), 141.5 (C, Ph), 143.3 (CH, C3).

This is a literature compound[11] but not a literature method.

**2-Allyloxy-2-vinyl-indane (531)**




**530** **531**

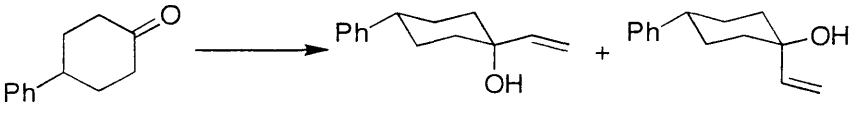
Sodium hydride (690 mg, 60% dispersion in mineral oil, 17.3 mmol) was added portionwise to an ice-cooled solution of alcohol **530** (693 mg, 4.33 mmol) in dry THF (20.0 mL). The resulting mixture was heated to reflux for 2 h and allowed to cool to room temperature. Allyl bromide (1.43 mL, 17.3 mmol) and DMPU (200 μL) were then added, the mixture was heated to reflux for 4 h, allowed to cool to room temperature, and quenched by addition of water (10 mL). The resulting mixture was then extracted into diethyl ether (2 × 50 mL), the combined organic layers washed with saturated

sodium chloride solution (75 mL), dried, and evaporated to leave a brown oil. Chromatography on silica gel with petroleum ether-diethyl ether (4:1) as the eluent yielded **531** as a colourless oil (710 mg, 82%): $R_f$ 0.52, petroleum ether-diethyl ether (1:1); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 3060m, 2930m, 1760s, 1420m, 1080s; $\delta_H$ (250 MHz, $CDCl_3$) 3.12 (2H, d, *J* 15.8, 2-H), 3.14 (2H, d, *J* 15.8, 2-H'), 3.89 (2H, dt, *J* 1.6, 5.3, 5-H), 5.07 (1H, dq, *J* 1.6, 10.3, 7-$H_{cis}$), 5.15 (1H, dd, *J* 1.2, 10.8, 4-$H_{cis}$), 5.18 (1H, dd, *J* 1.2, 17.7, 4-$H_{trans}$), 5.20 (1H, dq, *J* 1.6, 17.2, 7-$H_{trans}$), 5.87 (1H, ddd, *J* 5.3, 10.3, 17.2, 6-H), 6.00 (1H, dd, *J* 10.8, 17.7, 3-H); $\delta_C$ (62.9MHz, $CDCl_3$) 43.8 ($CH_2$, C2), 65.8 ($CH_2$, C5), 87.7 (C, C1), 115.2 ($CH_2$, C4), 116.3 ($CH_2$, C7), 124.9 (CH, Ph), 127.0 (CH, Ph), 141.3 (CH, C6), 141.6 (C, Ph), 143.7 (CH, C3); *m/z* (EI) 200 ($M^+$, 23), found $M^+$, 200.12016; $C_{14}H_{16}O$ requires 200.12012.

**Example of the procedure for small scale asymmetric cyclobutanation reaction:**

To a suspension of $(CF_3SO_3Cu)_2.C_6H_6$ (2mg, 4μmol) in dry diethyl ether (0.5mL) was added to a solution of Pfaltz ligand **460** (1.3mg, 4.4μmol, 0.55 eq.) in ether (0.5mL) and the resulting mixture stirred under $N_2$ at rt for 1h. Diene **514** (10mg, 0.06mmol) was added to the solution, which was subsequently injected into a 2mL quartz photolysis tube and subjected to hν at 254nm for 24h. The resulting solution was filtered through a pad of celite then silica, the solvent removed by evaporation, and the crude product re-dissolved in a suitable solvent system (10:1) hexane : IPA, and analysed by HPLC.

***cis*-4-Phenyl-1-vinyl-cyclohexan-1-ol (534a) and *trans*-4-Phenyl-1-vinyl-cyclohexan-1-ol (534b)**




**533** **534a** **534b**

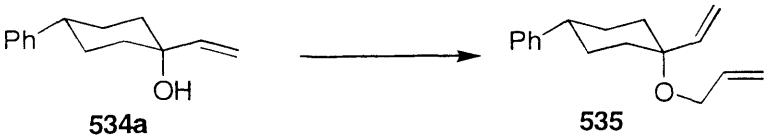
Vinylmagnesium chloride (50.0 mL, 85.6 mmol, 15% wt. solution in THF) was added dropwise to an ice-cooled solution of the ketone **533** (4.53 g, 26.0 mmol) in dry THF (10.0 mL). The solution was then heated to reflux for 18 h and allowed to cool to room temperature, then quenched by dropwise addition of saturated ammonium chloride

solution (50 mL). The resulting mixture was extracted into diethyl ether (2 × 200 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 (4:1) as the eluent yielded **534a** as a white solid (1.46 g, 28%) and **534b** as a white solid (1.79g, 34%): **534a:** mp 44-45°C; $R_f$ 0.31, petroleum ether-diethyl ether (1:1); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 3600m, 2940s, 2860m, 1495m, 1450s; $\delta_H$ (400MHz, $CDCl_3$) 1.61 (2H, dt, *J* 4.6, 14.8, 2ax-H), 1.71 (2H, d, *J* 4.6, 2eq-H), 1.74 (2H, d, *J* 3.5, 3eq-H), 1.92 (2H, dq, *J* 3.5, 12.5, 3ax-H), 2.47 (1H, tt, *J* 3.1, 12.5, 4-H), 5.03 (1H, d, *J* 12.5, 6-$H_{cis}$), 5.28 (1H, d, *J* 17.3, 6-$H_{trans}$), 5.98 (1H, dd, *J* 12.5, 17.3, 5-H), 7.16-7.31 (5H, m, Ph); $\delta_C$ (100MHz, $CDCl_3$) 29.5 ($CH_2$, C2), 37.8 ($CH_2$, C3), 44.1 (CH, C4), 71.4 (C, C1), 111.7 ($CH_2$, C6), 126.4 (CH, Ph), 127.1 (CH, Ph), 128.8 (CH, Ph), 147.3 (CH, C5), 147.7 (C, Ph); *m/z* (EI) 202 ($MH^+$, 28), found $M^+$, 202.13575; $C_{14}H_{18}O$ requires 202.13577; elemental analysis found C 82.64, H 9.04, $C_{21}H_{28}O_5$ requires C 83.12, H 8.97.

**534b:** mp 93-95°C; $R_f$ 0.24, petroleum ether-diethyl ether (1:1); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 3600m, 2940m, 1495m, 1455m; $\delta_H$ (400MHz, $CDCl_3$) 1.54-1.67 (4H, overlapping, 2ax-H, 3ax-H), 1.84 (2H, m, 3eq-H), 1.98 (2H, m, 2eq-H), 2.07 (1H, s, O*H*), 2.56 (1H, tt, *J* 2.3, 7.3, 4-H), 5.22 (1H, d, *J* 11.6, 6-$H_{cis}$), 5.48 (1H, d, *J* 15.0, 6-$H_{trans}$), 6.14 (1H, dd, *J* 11.6, 15.0, 5H), 7.12-7.38 (5H, m, Ph); $\delta_C$ (100MHz, $CDCl_3$) 31.7 ($CH_2$, C2), 39.2 ($CH_2$, C3), 43.9 (CH, C4), 72.2 (C, C1), 114.7 ($CH_2$, C6), 126.5 (CH, Ph), 127.3 (CH, Ph), 128.8 (CH, Ph), 143.2 (CH, C5), 146.9 (C, Ph); *m/z* (EI) 202 ($MH^+$, 5), found $M^+$, 202.13573; $C_{14}H_{18}O$ requires 202.13577; elemental analysis found C 81.40, H 8.69, $C_{21}H_{28}O_5$ requires C 83.12, H 8.97.

Configuration of diastereoisomers was confirmed by 2-D NOESY experiments. **534a** showed a significant nOe signal between olefinic proton 5-H and 2ax-H, whereas **534b** showed a significant nOe signal between olefinic proton 5-H and 3ax-H.

### *cis*-1-Allyloxy-4-phenyl-1-vinyl-cyclohexane (535)




**534a** **535**

Sodium hydride (530 mg, 60% dispersion in mineral oil, 13.3 mmol) was added portionwise to an ice-cooled solution of alcohol **534a** (1.167 g, 5.78 mmol) in dry THF (20.0 mL). The resulting mixture was heated to reflux for 2 h and allowed to cool to room temperature. Allyl bromide (0.97 mL, 11.6 mmol) and DMPU (200 μL) were then added, the mixture was heated to reflux for 18 h, allowed to cool to room temperature, and quenched by addition of water (10 mL). The resulting mixture was then extracted into diethyl ether (2 × 100 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 (4:1) as the eluent yielded **535** as a colourless oil (1.36 g, 97%): $R_f$ 0.62, petroleum ether-diethyl ether (1:1); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 3060m, 2940s, 2860m, 1725s, 1450m, 1260s; $\delta_H$ (250MHz, $CDCl_3$) 1.50 (2H, dt, *J* 2.4, 13.2, 2ax-H), 1.69 (2H, m, 3ax-H), 1.85 (2H, dt, *J* 3.9, 12.6, 3eq-H), 1.99 (2H, m, 2eq-H), 2.49 (1H, tt, *J* 3.9, 11.9, 4-H), 3.82 (2H, dt, *J* 1.6, 5.3, 7-H), 5.10-5.21 (3H, overlapping, 9-$H_{cis}$, 6-$H_{trans}$, 6-$H_{cis}$), 5.32 (1H, dq, *J* 1.6, 17.0, 9-$H_{trans}$), 5.83 (1H, dd, *J* 11.0, 18.1, 5-H), 5.95 (1H, m, 8-H), 7.12-7.33 (5H, m, Ph); $\delta_C$ (62.9MHz, $CDCl_3$) 29.4 ($CH_2$, C2), 34.6 ($CH_2$, C3), 44.2 (CH, C4), 63.4 ($CH_2$, C7), 75.5 (C, C1), 114.6 ($CH_2$, C6), 116.0 ($CH_2$, C9), 126.4 (CH, Ph), 127.2 (CH, Ph), 128.8 (CH, Ph), 136.4 (CH, C8), 144.2 (CH, C5), 147.8 (C, Ph); *m/z* (EI) 242 ($M^+$, 8), found $M^+$, 242.16707; $C_{17}H_{22}O$ requires 242.16705.

### (±) 2-(*cis*-4'-phenyl-cyclohexyl)-oxabicyclo-[3.2.0]-heptane (536)

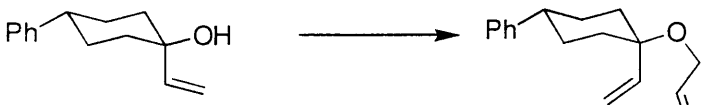

**535** (+/-) **356**

$(CF_3SO_3Cu)_2.C_6H_6$ (10 mg, 0.020 mmol, 3 mol%) was added to a solution of diene **535** (145 mg, 0.60 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 8 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 solid. Chromatography on silica gel with petroleum ether-diethyl ether (6:1) as the eluent yielded **536** as a colourless oil (133 mg, 92%): $R_f$

0.62, petroleum ether-diethyl ether (1:1); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 2940s, 2875m, 1760w, 1730w, 1495m, 1445m; $\delta_H$ (400 MHz, $CDCl_3$) 1.11 (1H, dt, *J* 3.0, 14.4, 2eq'-H), 1.40 (1H, dt, *J* 5.0, 13.4, 2eq-H), 1.58-1.72 (2H, overlapping, CH*H* 7-H, 3ax'-H), 1.74-1.93 (5H, overlapping, 3ax-H, 3eq'-H, 2ax'-H, 6-H), 1.98-2.09 (2H, overlapping, 3eq-H, 2ax-H), 2.18 (1H, m, C*H*H 7-H), 2.48 (1H, tt, *J* 4.0, 11.8, 4-H), 2.56 (1H, q, *J* 7.5, 5-H), 2.92 (1H, m, 8-H), 3.79 (2H, m, 9-H), 7.12-7.32 (5H, m, Ph); $\delta_C$ (100 MHz, $CDCl_3$) 18.8 ($CH_2$, C3), 24.4 ($CH_2$, C7), 29.6 ($CH_2$, C3'), 31.2 ($CH_2$, C6), 32.1 ($CH_2$, C2), 33.2 ($CH_2$, C2'), 39.2 (CH, C8), 44.7 (CH, C4), 47.9 (CH, C5), 72.2 ($CH_2$, C9), 82.2 (C, C1), 126.3 (CH, Ph), 127.4 (CH, Ph), 128.7 (CH, Ph), 147.9 (C, Ph); *m/z* (EI) 242 ($M^+$, 9%), found $M^+$ 242.16708; $C_{17}H_{22}O$ requires 242.16707.

HPLC was performed using a Daicel® chiralcel OD-H column, running a 10:1 hexane : IPA mixture as the eluent at a flow rate of 0.5 mL/min. The UV detector was set at 520nm and recorded the starting material at retention time 6.9 min, one enantiomer at 7.84 min and the other enantiomer at 12.31 min.

**_trans_-1-Allyloxy-4-phenyl-1-vinyl-cyclohexane (537)**

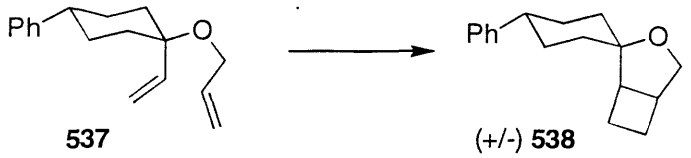



**534b** **537**

Sodium hydride (530 mg, 60% dispersion in mineral oil, 13.3 mmol) was added portionwise to an ice-cooled solution of alcohol **534b** (1.35 g, 6.68 mmol) in dry THF (20.0 mL). The resulting mixture was heated to reflux for 2 h and allowed to cool to room temperature. Allyl bromide (1.11 mL, 13.3 mmol) and DMPU (200 μL) were then added, the mixture was heated to reflux for 18 h, allowed to cool to room temperature, and quenched by addition of water (10 mL). The resulting mixture was then extracted into diethyl ether (2 × 100 mL), the combined organic layers washed with saturated sodium chloride solution (150 mL), dried, and evaporated to leave a brown oil. Chromatography on silica gel with petroleum ether-diethyl ether (5:1) as the eluent yielded **537** as a colourless oil (1.52 g, 94%): $R_f$ 0.59, petroleum ether-diethyl ether (1:1); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 3050m, 2940s, 2870m, 1730m, 1260s; $\delta_H$ (250MHz, $CDCl_3$) 1.49-1.77 (4H, overlapping, 2ax-H, 3ax-H), 1.86 (2H, br dd, *J* 3.1, 11.7, 3eq-H), 2.10 (2H, br d, *J* 11.7, 2eq-H), 2.59 (1H, tt, *J* 3.1, 11.7, 4-H), 3.88 (2H, dd, *J* 0.45, 5.5, 7-H),

5.09 (1H, dd, *J* 1.2, 10.3, 9-$H_{cis}$), 5.26 (1H, dd, *J* 1.2, 17.0, 9-$H_{trans}$), 5.31 (1H, d, *J* 17.1, 6-$H_{trans}$), 5.41 (1H, d, *J* 10.8, 6-$H_{cis}$), 5.76 (1H, dd, *J* 10.8, 17.6, 5-H), 5.91 (1H, ddd, *J* 5.5, 10.3, 17.0, 8-H), 7.12-7.33 (5H, m, Ph); $\delta_C$ (62.9MHz, $CDCl_3$) 31.3 ($CH_2$, C2), 35.9 ($CH_2$, C3), 44.1 (CH, C4), 63.3 ($CH_2$, C7), 77.0 (C, C1), 116.3 ($CH_2$, C9), 118.1 ($CH_2$, C6), 126.5 (CH, Ph), 127.2 (CH, Ph), 128.8 (CH, Ph), 136.5 (CH, C5), 140.2 (CH, C8), 147.0 (C, Ph); *m/z* (EI) 242 ($M^+$, 7); found $M^+$, 242.16704; $C_{17}H_{22}O$ requires 242.16705.

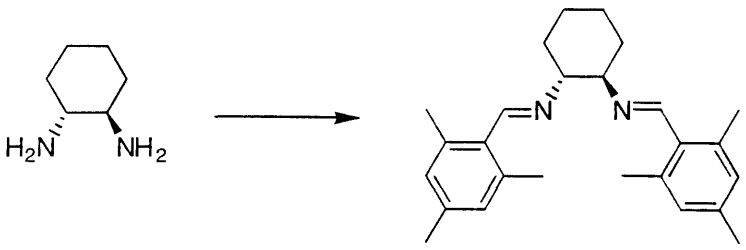
**(±) 2-(*trans*-4'-phenyl-cyclohexyl)-oxabicyclo-[3.2.0]-heptane (538)**




**537** (+/-) **538**

$(CF_3SO_3Cu)_2.C_6H_6$ (10 mg, 0.020 mmol, 3 mol%) was added to a solution of diene **537** (136 mg, 0.56 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 8 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 solid. Chromatography on silica gel with petroleum ether-diethyl ether (8:1) as the eluent yielded **538** as a colourless oil (116 mg, 85%): $R_f$ 0.59, petroleum ether-diethyl ether (1:1); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 2940s, 2860m, 1605w, 1500m, 1455m, 1085s; $\delta_H$ (250 MHz, $CDCl_3$) 1.29 (1H, dt, *J* 3.0, 12.1, 2eq-H), 1.32-1.51 (2H, overlapping, 2eq'-H, 3eq-H), 1.62-1.79 (3H, overlapping, 3eq'-H, 3ax-H, CH*H* 6-H), 1.80-2.12 (5H, overlapping, CH*H* 7-H, C*H*H 6-H, 3ax'-H, 2ax'-H, 2ax-H), 2.19 (1H, m, C*H*H 7-H), 2.54 (1H, tt, *J* 3.7, 11.7, 4-H), 2.92-3.03 (2H, overlapping, 5-H, 8-H), 3.75 (1H, d, *J* 9.0, CH*H* 9-H), 3.87 (1H, dd, *J* 5.5, 9.0, C*H*H 9-H), 7.17-7.30 (5H, m, Ph); $\delta_C$ (62.9 MHz, $CDCl_3$) 19.1 ($CH_2$, C3'), 23.9 ($CH_2$, C3), 32.1 ($CH_2$, C2), 32.3 ($CH_2$, C6), 32.4 ($CH_2$, C2'), 34.5 ($CH_2$, C7), 39.5 (CH, C8), 42.1 (CH, C5), 44.1 (CH, C4), 71.9 ($CH_2$, C9), 84.4 (C, C1), 126.4 (CH, Ph), 127.2 (CH, Ph), 128.7 (CH, Ph), 147.1 (C, Ph); *m/z* (EI) 242 ($M^+$, 10%), found $M^+$ 242.16706; $C_{17}H_{22}O$ requires 242.16707.

**Sample Schiff Base synthesis: *N,N*-Bis(2,4,6-trimethyl-benzylidene)-cyclohexane-1,2-diimine (548f)**

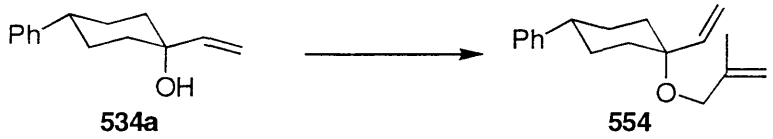


549 548f

Diamine **549** (78mg, 0.70 mmol) in MeOH (5 mL) was heated to reflux and mesitaldehyde (206 μL, 1.40 mmol) added dropwise. The solution was heated at reflux for 1h then at rt overnight, the white precipitate was collected by filtration and dried *in vacuo* to yield **548f** as a white solid (160mg, 60%): $\delta_H$ (400 MHz, $CDCl_3$) 1.46-1.55 (2H, m, CH*H* 3-H), 1.77-1.91 (6H, m, C*H*H 3-H, 2-H), 2.22 (6H, s, *p*-Ph-Me), 2.25 (12H, s, *o*-Ph-Me), 3.37-3.96 (2H, m, 1-H), 6.76 (4H, s, *m*-Ph), 8.54 (2H, s, 4-H); $\delta_C$ (100 MHz, $CDCl_3$) 20.7 ($CH_3$, *p*-Ph-Me), 21.1 ($CH_3$, *o*-Ph-Me), 24.6 ($CH_2$, C3), 33.7 ($CH_2$, C2), 75.7 (CH, C1), 129.2 (CH, Ph), 131.1 (C, Ph), 137.4 (C, Ph), 138.3 (C, Ph), 160.3 (CH, C4).

This is a literature compound.[12]

***cis*-1-(2-Methylallyloxy)-4-phenyl-1-vinyl-cyclohexane (554)**

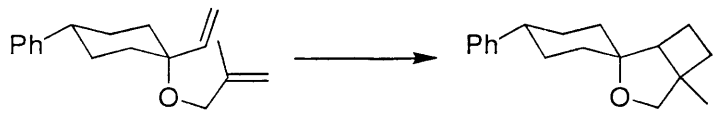


534a 554

Sodium hydride (182 mg, 60% dispersion in mineral oil, 4.55 mmol) was added portionwise to an ice-cooled solution of alcohol **534a** (460 mg, 2.28 mmol) in dry THF (20.0 mL). The resulting mixture was heated to reflux for 2 h and allowed to cool to room temperature. 3-Bromo-2-methyl-propene (459 μL, 4.55 mmol) and DMPU (200 μL) were then added, the mixture was heated to reflux for 18 h, allowed to cool to room temperature, and quenched by addition of water (10 mL). The resulting mixture was then extracted into diethyl ether (2 × 100 mL), the combined organic layers washed with saturated sodium chloride solution (100 mL), dried, and evaporated to leave a yellow oil. Chromatography on silica gel with petroleum ether-diethyl ether (6:1) as the eluent

yielded **554** as a colourless oil (444 mg, 76%): $R_f$ 0.55, petroleum ether-diethyl ether (1:1); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 2940s br, 2860s, 1610m, 1495m, 1450m; $\delta_H$ (250MHz, $CDCl_3$) 1.50 (2H, dt, *J* 3.9, 13.4, 2ax-H), 1.69 (2H, m, 3ax-H), 1.79 (3H, s, 10-H), 1.87 (2H, dt, *J* 3.6, 12.6, 3eq-H), 2.02 (2H, m, 2eq-H), 2.50 (1H, tt, *J* 3.6, 11.9, 4-H), 3.70 (2H, s, 7-H), 4.87 (1H, q, *J* 1.1, 9-$H_{cis}$), 5.07 (1H, d, *J* 1.1, 9-$H_{trans}$), 5.15 (1H, dd, *J* 1.3, 10.8, 6-$H_{cis}$), 5.17 (1H, dd, *J* 1.3, 18.1, 6-$H_{trans}$), 5.84 (1H, dd, *J* 10.8, 18.1, 5-H), 7.12-7.32 (5H, m, Ph); $\delta_C$ (62.9MHz, $CDCl_3$) 20.4 ($CH_3$, C10), 29.4 ($CH_2$, C2), 34.5 ($CH_2$, C3), 44.3 (CH, C4), 66.0 ($CH_2$, C7), 75.1 (C, C1), 111.2 ($CH_2$, C6), 114.6 ($CH_2$, C9), 126.3 (CH, Ph), 127.3 (CH, Ph), 128.7 (CH, Ph), 143.8 (C, C8), 144.2 (CH, C5) 147.8 (C, Ph); *m/z* (EI) 256 ($M^+$, 11), found $M^+$, 256.18271, $C_{18}H_{24}O$ requires 256.18272.

**(±) 2-(*cis*-4'-phenyl-cyclohexyl)-6-methyl-oxabicyclo-[3.2.0]-heptane (555)**



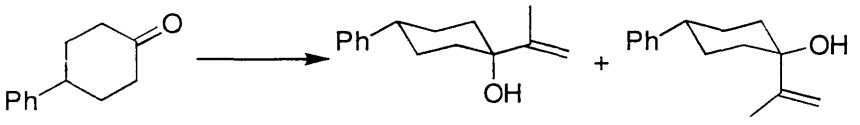

**554** (+/-) **555**

$(CF_3SO_3Cu)_2.C_6H_6$ (10 mg, 0.020 mmol, 3 mol%) was added to a solution of diene **554** (148 mg, 0.58 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 8 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 solid. Chromatography on silica gel with petroleum ether-diethyl ether (8:1) as the eluent yielded **555** as a colourless oil (125 mg, 85%): $R_f$ 0.68, petroleum ether-diethyl ether (1:1); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 2940s, 2860m, 1605w, 1495m, 1450m, 1025s; $\delta_H$ (250 MHz, $CDCl_3$) 1.44 (1H, dt, *J* 3.7, 10.1, 2eq-H), 1.54 (3H, s, C8-Me), 1.65 (1H, dt, *J* 4.8, 12.6, 2eq'-H), 1.89 (1H, m, 3ax-H), 2.01-2.43 (10H, overlapping, 3eq-H, 3'-H, 2ax-H, 2ax'-H, 6-H, 7-H, 5-H), 2.76 (1H, tt, *J* 3.9, 11.7, 4-H), 3.75 (1H, d, *J* 9.2, CH*H* 9-H), 4.02 (1H, d, *J* 9.2, C*H*H 9-H), 7.38-7.53 (5H, m, Ph); $\delta_C$ (62.9 MHz, $CDCl_3$) 15.2 ($CH_2$, C3), 24.4 ($CH_3$, C8-Me), 29.6 ($CH_2$, C3'), 30.9 ($CH_2$, C6), 31.0 ($CH_2$, C7), 32.8 ($CH_2$, C2), 34.1 ($CH_2$, C2'), 44.7 (CH, C4), 46.4 (C, C8), 53.6 (CH, C5), 77.0 ($CH_2$, C9), 82.9 (C, C1), 126.3 (CH, Ph), 127.4 (CH, Ph), 128.7

(CH, Ph), 147.9 (C, Ph). *m/z* (EI) 256 ($M^+$, 9%), found $M^+$ 256.18267; $C_{18}H_{24}O$ requires 256.18272.

HPLC was performed using a Daicel® chiralcel OD-H column, running a 10:1 hexane : IPA mixture as the eluent at a flow rate of 0.5 mL/min. The UV detector was set at 520nm and recorded the starting material at retention time 6.78 min, one enantiomer at 7.24 min and the other enantiomer at 10.21 min.

**_cis_-4-Phenyl-1-(1-methyl-ethenyl)-cyclohexan-1-ol (556a) and _trans_-4-Phenyl-1-(1-methyl-ethenyl)-cyclohexan-1-ol (556b)**




**533** **556a** **556b**

2-Bromo-propene (1.68 mL, 18.9 mmol) in dry THF (10.0 mL) was added dropwise to magnesium turnings (502 mg, 20.7 mmol) and a crystal of $I_2$ in dry THF (10.0 mL) at 0 °C. This mixture was stirred at 0 °C for 1 h and then at room temperature for 1 h. Ketone **533** (3.0 g, 17.2 mmol) in dry THF (10.0 mL) was added dropwise via a cannula to the cooled (0 °C) reaction mixture. The solution was stirred at rt for 18 h, then quenched by dropwise addition of saturated ammonium chloride solution (50 mL). The resulting mixture was extracted into diethyl ether (2 × 100 mL), and the combined organic layers were washed with 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 **556a** as a white solid (1.32 g, 36%) and **556b** as a white solid (1.32g, 36%): **556a:** mp 52-54°C; $R_f$ 0.30, petroleum ether-diethyl ether (1:1); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 3600m, 2940s, 2860m, 1695m, 1495m, 1450m; $\delta_H$ (400MHz, $CDCl_3$) 1.50 (1H, br s, O*H*), 1.78-1.87 (6H, overlapping, 2ax-H, 3ax-H, 2eq-H), 1.90 (3H, d, *J* 0.6, 7-H), 1.95-2.06 (2H, m, 3eq-H), 2.55 (1H, tt, *J* 3.3, 12.2, 4-H), 4.89 (1H, t, *J* 0.6, 6-$H_{cis}$), 5.12 (1H, d, *J* 0.6, 6-$H_{trans}$), 7.21-7.40 (5H, m, Ph); $\delta_C$ (100MHz, $CDCl_3$) 19.4 ($CH_3$, C7), 29.8 ($CH_2$, C2), 36.5 ($CH_2$, C3), 44.3 (CH, C4), 73.4 (C, C1), 109.5 ($CH_2$, C6), 126.4 (CH, Ph), 127.3 (CH, Ph), 128.8 (CH, Ph), 147.7 (C, Ph), 152.8 (C, C5); *m/z* (EI) 216 ($M^+$, 10), found $M^+$, 216.15141; $C_{15}H_{20}O$ requires 216.15142; elemental analysis found C 83.46, H 9.22, $C_{15}H_{20}O$ requires C 83.28, H 9.32.

**556b:** mp 84-85°C; $R_f$ 0.22, petroleum ether-diethyl ether (1:1); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 3600m, 2940s, 2860m, 1455s, 1050s; $\delta_H$ (400MHz, $CDCl_3$) 1.56-1.75 (4H, overlapping, 3ax-H, 3eq-H), 1.87-1.97 (6H, overlapping, 2ax-H, O*H*, 7-H), 2.29 (2H, m, 2eq-H), 2.67 (1H, tt, *J* 4.0, 11.0, 4-H), 5.13 (1H, t, *J* 0.8, 6-$H_{cis}$), 51.7 (1H, s, 6-$H_{trans}$), 7.20-7.48 (5H, m, Ph); $\delta_C$ (100MHz, $CDCl_3$) 19.3 ($CH_3$, C7), 31.7 ($CH_2$, C2), 36.8 ($CH_2$, C3), 43.9 (CH, C4), 73.9 (C, C1), 113.6 ($CH_2$, C6), 126.5 (CH, Ph), 127.3 (CH, Ph), 128.7 (CH, Ph), 146.9 (C, Ph), 147.5 (C, C5); *m/z* (EI) 216 ($M^+$, 4), found $M^+$, 216.15149; $C_{15}H_{20}O$ requires 216.15142; elemental analysis found C 82.82, H 9.30, $C_{15}H_{20}O$ requires C 83.28, H 9.32.

Configuration of diastereoisomers was confirmed by 2-D NOESY experiments. **556a** showed a significant nOe signal between methyl protons 7-H and 2ax-H, whereas **556b** showed a significant nOe signal between methyl protons 7-H and 3ax-H.

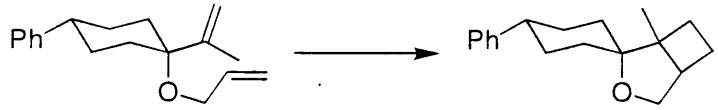
***cis*-1-Allyloxy-1-(1-methylvinyl)-4-phenyl-cyclohexane (557)**


**556a** **557**

Sodium hydride (404 mg, 60% dispersion in mineral oil, 10.1 mmol) was added portionwise to an ice-cooled solution of alcohol **556a** (1.09 g, 5.05 mmol) in dry THF (45.0 mL). The resulting mixture was heated to reflux for 2 h and allowed to cool to room temperature. Allyl bromide (0.87 mL, 10.4 mmol) and DMPU (200 μL) were then added, the mixture was heated to reflux for 2 h, allowed to cool to room temperature, and quenched by addition of water (10 mL). The resulting mixture was then extracted into diethyl ether (2 × 100 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 (10:1) as the eluent yielded **557** as a colourless oil (1.20 g, 98%): $R_f$ 0.57, petroleum ether-diethyl ether (1:1); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 2940s, 2860m, 1645m, 1605m, 1450m; $\delta_H$ (250MHz, $CDCl_3$) 1.89 (2H, dt, *J* 3.9, 13.3, 2ax-H), 1.69 (2H, m, 3ax-H), 2.14 (3H, s, 7-H), 2.25 (2H, dq, *J* 3.9, 12.0, 3eq-H), 2.49 (2H, dq, *J* 3.9, 14.2, 2eq-H), 2.87 (1H, tt, *J* 3.9, 12.0, 4-H), 4.07 (2H, dt, *J* 1.4, 5.3, 8-H), 5.31 (1H, s, 6-$H_{cis}$), 5.35 (1H, q, *J* 1.4, 6-$H_{trans}$), 5.51 (1H, dq, *J* 1.4, 10.3, 10-$H_{cis}$), 5.70 (1H, dq, *J* 1.4, 17.2, 10-$H_{trans}$), 6.34 (1H, ddt, *J* 5.3, 10.3, 17.2,

9-H), 7.45-7.63 (5H, m, Ph); $\delta_C$ (62.9MHz, $CDCl_3$) 18.9 ($CH_3$, C7), 29.8 ($CH_2$, C2), 33.8 ($CH_2$, C3), 44.5 (CH, C4), 63.1 ($CH_2$, C8), 77.1 (C, C1), 112.6 ($CH_2$, C6), 116.0 ($CH_2$, C10), 126.4 (CH, Ph), 127.3 (CH, Ph), 128.8 (CH, Ph), 136.3 (CH, C9), 147.8 (C, Ph), 149.5 (C, C5); *m/z* (EI) 256 ($M^+$, 14), found $M^+$, 256.18267; $C_{18}H_{24}O$ requires 256.18272.

**(±) 2-(*cis*-4'-phenyl-cyclohexyl)-3-methyl-oxabicyclo-[3.2.0]-heptane (558)**




**557** (+/-) **558**

$(CF_3SO_3Cu)_2.C_6H_6$ (10 mg, 0.020 mmol, 5 mol%) was added to a solution of diene **557** (105 mg, 0.41 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 8 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 solid. Chromatography on silica gel with petroleum ether-diethyl ether (6:1) as the eluent yielded **558** as a colourless oil (96 mg, 91%): $R_f$ 0.65, petroleum ether-diethyl ether (1:1); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 3400br. w, 2940s, 2860m, 1605w, 1495m, 1000m; $\delta_H$ (250 MHz, $CDCl_3$) 1.37-1.54 (3H, overlapping, 2eq'-H, 2eq-H, 3eq'-H), 1.42 (3H, s, C5-Me), 1.56-1.69 (1H, m, CH*H* 7-H), 1.70-1.94 (2H, overlapping, 3ax'-H, 3eq-H), 1.95-2.20 (4H, overlapping, 6-H, 2ax-H, 2ax'-H), 2.37-2.77 (4H, overlapping, C*H*H 7-H, 3ax-H, 4-H, 8-H), 3.99 (1H, dd, *J* 1.4, 9.4, C*H*H 9-H), 4.10 (1H, dd, *J* 7.1, 9.4, CH*H* 9-H), 7.37-7.52 (5H, m, Ph); $\delta_C$ (62.9 MHz, $CDCl_3$) 19.7 ($CH_3$, C5-Me), 21.9 ($CH_2$, C3), 27.2 ($CH_2$, C7), 28.5 ($CH_2$, C3'), 29.3 ($CH_2$, C6), 29.5 ($CH_2$, C2'), 31.0 ($CH_2$, C2), 44.4 (CH, C4), 44.7 (CH, C8), 51.6 (C, C5), 71.4 ($CH_2$, C9), 83.8 (C, C1), 126.3 (CH, Ph), 127.4 (CH, Ph), 128.7 (CH, Ph), 147.9 (C, Ph); *m/z* (EI) 256 ($M^+$, 14%), $M^+$ 256.18262; $C_{18}H_{24}O$ requires 256.18272.

HPLC was performed using a Daicel® chiralcel OD-H column, running a 10:1 hexane : IPA mixture as the eluent at a flow rate of 0.5 mL/min. The UV detector was set at 520nm and recorded the starting material at retention time 6.71 min, one enantiomer at 7.01 min and the other enantiomer at 9.86 min.

**_trans_-1-Allyloxy-1-(1-methylvinyl)-4-phenyl-cyclohexane (559)**


**556b** **559**

Sodium hydride (404 mg, 60% dispersion in mineral oil, 10.1 mmol) was added portionwise to an ice-cooled solution of alcohol **556b** (1.09 g, 5.05 mmol) in dry THF (45.0 mL). The resulting mixture was heated to reflux for 2 h and allowed to cool to room temperature. Allyl bromide (0.87 mL, 10.1 mmol) and DMPU (200 μL) were then added, the mixture was heated to reflux for 2 h, allowed to cool to room temperature, and quenched by addition of water (10 mL). The resulting mixture was then extracted into diethyl ether (2 × 100 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 (10:1) as the eluent yielded **559** as a colourless oil (1.01 g, 78%): $R_f$ 0.55, petroleum ether-diethyl ether (1:1); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 3400m br, 2960s, 2875m, 1680m, 1610m, 1060s; $\delta_H$ (250MHz, $CDCl_3$) 1.55-1.79 (4H, overlapping, 2ax-H, 3ax-H), 1.83 (3H, d, *J* 0.5, 7-H), 1.94 (2H, br d, *J* 10.3, 3eq-H), 2.35 (2H, m, 2eq-H), 2.71 (1H, m, 4-H), 3.85 (2H, dd, *J* 1.4, 5.5, 8-H), 5.15 (1H, d, *J* 0.5, 6-$H_{cis}$), 5.18 (1H, dq, *J* 1.4, 10.3, 10-$H_{cis}$), 5.33 (1H, q, *J* 0.5, 6-$H_{trans}$), 5.34 (1H, dq, overlapping, *J* 1.4, 17.2, 10-$H_{trans}$), 6.00 (1H, m, 9-H), 7.20-7.38 (5H, m, Ph); $\delta_C$ (62.9MHz, $CDCl_3$) 19.0 ($CH_3$, C7), 31.2 ($CH_2$, C2), 34.3 ($CH_2$, C3), 44.3 (CH, C4), 63.1 ($CH_2$, C8), 78.9 (C, C1), 116.2 ($CH_2$, C6), 116.7 ($CH_2$, C10), 126.4 (CH, Ph), 127.3 (CH, Ph), 128.7 (CH, Ph), 136.8 (CH, C9), 143.9 (CH, C5), 147.0 (C, Ph); *m/z* (EI) 256 ($MH^+$, 12), found $M^+$, 256.18290; $C_{18}H_{24}O$ requires 256.18272.

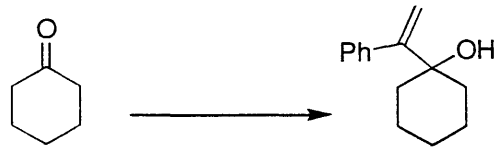
**(±) 2-(_trans_-4'-phenyl-cyclohexyl)-3-methyl-oxabicyclo-[3.2.0]-heptane (560)**


**559** (+/-) **560**

$(CF_3SO_3Cu)_2.C_6H_6$ (10 mg, 0.020 mmol, 5 mol%) was added to a solution of diene **559** (95 mg, 0.38 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 8 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 solid. Chromatography on silica gel with petroleum ether-diethyl ether (6:1) as the eluent yielded **560** as a colourless oil (90 mg, 95%): $R_f$ 0.55, petroleum ether-diethyl ether (1:1); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 3400br. w, 2945s, 2875m, 1500m, 1450m, 1000m; $\delta_H$ (250 MHz, $CDCl_3$) 1.44 (3H, s, C5-Me), 1.48-2.22 (10H, overlapping, 2-H, 6-H, 3'-H, 3eq-H, CH*H* 7-H), 2.31-2.49 (3H, overlapping, 3ax-H, C*H*H 7-H, 8-H), 2.99 (1H, m, 4-H), 3.86 (1H, dd, *J* 1.6, 9.4, CH*H* 9-H), 4.04 (1H, ddd, *J* 0.9, 6.9, 9.4, C*H*H 9-H), 7.21-7.41 (5H, m, Ph); $\delta_C$ (62.9 MHz, $CDCl_3$) 21.3 ($CH_2$, C3), 21.4 ($CH_3$, C5-Me), 27.3 ($CH_2$, C2), 28.3 ($CH_2$, C3'), 28.6 ($CH_2$, C2'), 28.8 ($CH_2$, C6), 29.1 ($CH_2$, C7), 40.2 (CH, C8), 45.6 (CH, C4), 51.7 (C, C5), 71.1 ($CH_2$, C9), 83.8 (C, C1), 126.1 (CH, Ph), 127.5 (CH, Ph), 128.6 (CH, Ph), 146.3 (C, Ph): *m/z* (EI) 256 ($M^+$, 11%), found $M^+$ 256.18267; $C_{18}H_{24}O$ requires 256.18272.

**1-(1-Phenylvinyl)-cyclohexanol (561)**




**520** **561**

α-Bromostyrene (1.28 mL, 9.8 mmol) in dry THF (10.0 mL) was added dropwise to magnesium turnings (251 mg, 10.3 mmol) and a crystal of $I_2$ in dry THF (10.0 mL) at 0 °C. This mixture was stirred at 0 °C for 1 h and then at room temperature for 2 h. Ketone **520** (0.99mL, 9.6 mmol) in dry THF (10.0 mL) was added dropwise via a cannula to the cooled (0 °C) reaction mixture. The solution was stirred at rt for 20 h, then quenched by dropwise addition of saturated ammonium chloride solution (50 mL). The resulting mixture was extracted into diethyl ether (2 × 100 mL), and the combined organic layers were washed with saturated sodium chloride solution (150 mL), dried, and evaporated to leave a yellow oil. Chromatography on silica gel with petroleum ether-diethyl ether (7:2) as the eluent yielded **561** as a colourless oil (1.38 g, 70%): $R_f$ 0.18, petroleum ether-diethyl ether (1:1); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 3600m, 2960s, 2860m,

1790m, 1450m; $\delta_H$ (250MHz, $CDCl_3$) 1.11-1.20 (1H, br m, O*H*), 1.40-1.72 (10H, overlapping, 2-H, 3-H, 4-H), 5.01 (1H, d, *J* 1.6, 6-$H_{cis}$), 5.42 (1H, d, *J* 1.6, 6-$H_{trans}$), 5.30-5.39 (5H, m, Ph); $\delta_C$ (62.9MHz, $CDCl_3$) 22.5 ($CH_2$, C3), 25.9 ($CH_2$, C4), 37.1 ($CH_2$, C2), 73.9 (C, C1), 113.7 ($CH_2$, C6), 127.2 (CH, Ph), 128.0 (CH, Ph), 129.4 (CH, Ph), 142.0 (C, Ph), 157.4 (C, C5); *m/z* (EI) 202 ($M^+$, 32), found $M^+$, 202.13580; $C_{14}H_{18}O$ requires 202.13577.

**1-Allyloxy-1-(2-phenylvinyl)-cyclohexane (562)**


**561** **562**

Sodium hydride (490 mg, 60% dispersion in mineral oil, 12.3 mmol) was added portionwise to an ice-cooled solution of alcohol **561** (1.23 g, 6.09 mmol) in dry THF (20.0 mL). The resulting mixture was heated to reflux for 2 h and allowed to cool to room temperature. Allyl bromide (0.63 mL, 7.31 mmol) and DMPU (100 μL) were then added, the mixture was heated to reflux for 18 h, allowed to cool to room temperature, and quenched by addition of water (10 mL). The resulting mixture was then extracted into diethyl ether (2 × 100 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 (10:1) as the eluent yielded **562** as a pale green oil (1.39 g, 95%): $R_f$ 0.44, petroleum ether-diethyl ether (1:1); $\nu_{max}$ ($CHCl_3$)/$cm^{-1}$ 3090w, 2940s, 2860m, 1450m, 1050s, 920s; $\delta_H$ (250MHz, $CDCl_3$) 1.14-1.32 (1H, m, CH*H* 4-H), 1.36-1.71 (7H, overlapping, C*H*H 4-H, 3-H, CH*H* 2-H), 1.79-1.89 (2H, m, C*H*H 2-H), 3.88 (2H, dt, *J* 1.4, 5.5, 7-H), 5.13 (1H, dq, *J* 1.4, 10.3, 9-$H_{cis}$), 5.28 (1H, d, *J* 1.4, 6-$H_{cis}$), 5.30 (1H, d, *J* 1.4, 6-$H_{trans}$), 5.32 (1H, dq, overlapping, *J* 1.4, 17.2 9-$H_{trans}$), 5.97 (1H, m, 8-H), 7.12-7.41 (5H, m, Ph); $\delta_C$ (62.9MHz, $CDCl_3$) 22.6 ($CH_2$, C3), 26.3 ($CH_2$, C4), 34.7 ($CH_2$, C2), 62.9 ($CH_2$, C7), 78.1 (C, C1), 116.2 ($CH_2$, C6), 117.3 ($CH_2$, C9), 127.4 (CH, Ph), 128.2 (CH, Ph), 129.0 (CH, Ph), 136.0 (CH, C8), 142.2 (C, Ph), 151.9 (C, C5); *m/z* (EI) 242 ($M^+$, 8), found $M^+$, 242.16698; $C_{17}H_{22}O$ requires 242.16707.

**Example of the procedure for the determination of the rate of cyclobutanation**

To a suspension of $(CF_3SO_3Cu)_2.C_6H_6$ (5mg, 10μmol) in dry diethyl ether (1mL) was added to a solution of Pfaltz ligand **548f** (3.3mg, 11μmol) in ether (1mL) and the resulting mixture stirred under $N_2$ at rt for 1h. Diene **514** (30mg, 0.018mmol) in diethyl ether (8mL) was combined with the freshly prepared catalyst, and the mixture added to a water cooled quartz photolysis tube. Irradiation was carried out at 254nm using a Rayonet™ photochemical reactor for 8h. A 1mL aliquot of the reaction mixture was removed at regular time intervals, and replaced with diethyl ether. Each aliquot was filtered through a pad of celite then silica, then the solvent removed by evaporation. The resulting oils were re-dissolved in ether and separately analysed by glc.

GLC measurements were recorded using a PE elite series 5 30.0×2.5μL column, with a column temperature of 180°C, an injector temperature of 250°C, a detector temperature of 280°C, an air flow rate of 300mL/min, a $H_2$ flow rate of 30mL/min, a He flow rate of 1mL/min and a split ratio of 50:1. The starting material had a retention time of 1.65 min and the product came at 6.44 min.

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# Appendices

## Appendix 1A: Crude Asymmetric Cyclobutanation Results

Crude results of small scale attempted asymmetric cyclobutanation reaction of diene **536** using ligands **539-544** and **460**. Percentage of starting material (S.M) consumed during the reaction was determined from crude NMR experiments by observing loss of olefinic protons. The ratio of peaks corresponding to the enantiomers, was calculated by chiral hplc using Daicel® Chiralcel OD-H chiral column and a mixture of hexane:IPA (10:1) as eluent.

| Entry | Ligand | Solvent | Time | % S.M. consumed Determined by NMR | Observed Ratio of Peaks (HPLC) |
|---|---|---|---|---|---|
| 1 | **539** | Benzene | 24h | 29% | **1.3 : 1** |
| 2 | **539** | THF | 24h | 79% | **1 : 1** |
| 3 | **539** | $Et_2O$ | 24h | 74% | **1.2 : 1** |
| 4 | **540** | Benzene | 24h | 50% | **1.3 : 1** |
| 5 | **540** | $Et_2O$ | 24h | 79% | **1.2 : 1** |
| 6 | **541** | Benzene | 24h | 25% | **2.2 : 1** |
| 7 | **541** | THF | 24h | 80% | **1.3 : 1** |
| 8 | **541** | $Et_2O$ | 24h | 53% | **1.4 : 1** |
| 9 | **542** | Benzene | 24h | 42% | **1.4 : 1** |
| 10 | **542** | THF | 24h | 80% | **1 : 1** |
| 11 | **542** | $Et_2O$ | 24h | 74% | **1.2 : 1** |
| 12 | **543** | Benzene | 24h | 35% | **1.1 : 1** |
| 13 | **543** | THF | 24h | 63% | **1.2 : 1** |
| 14 | **543** | $Et_2O$ | 24h | 87% | **1 : 1** |
| 15 | **460** | Benzene | 24h | 38% | **1.3 : 1** |
| 16 | **460** | THF | 24h | 25% | **1.4 : 1** |
| 17 | **460** | $Et_2O$ | 24h | 18% | **2.3 : 1** |
| 18 | **544** | Benzene | 24h | 44% | **1.6 : 1** |
| 19 | **544** | THF | 24h | 76% | **1.4 : 1** |
| 20 | **544** | $Et_2O$ | 24h | 86% | **1.3 : 1** |

## Appendix 1B: Crude Asymmetric Cyclobutanation Results

Crude results of small scale attempted asymmetric cyclobutanation reaction of diene **536** using diimine ligands **548a-f**. Percentage of starting material (S.M) consumed during the reaction was determined from crude NMR experiments by observing loss of olefinic protons. The ratio of peaks corresponding to the enantiomers, was calculated by chiral hplc using Daicel® Chiralcel OD-H chiral column and a mixture of hexane:IPA (10:1) as eluent.

| Entry | Ligand | Solvent | Time | % S.M. Consumed Determined by NMR | Observed Ratio of Peaks (HPLC) |
|---|---|---|---|---|---|
| 21 | **548a** | Benzene | 24h | 18% | **2 : 1** |
| 22 | **548a** | THF | 24h | 0% | - |
| 23 | **548a** | $Et_2O$ | 24h | 23% | **1.6 : 1** |
| 24 | **548b** | Benzene | 24h | 40% | **2 : 1** |
| 25 | **548b** | THF | 24h | 41% | **2 : 1** |
| 26 | **548b** | $Et_2O$ | 24h | 95% | **2 : 1** |
| 27 | **548c** | Benzene | 24h | 34% | **1.8 : 1** |
| 28 | **548c** | THF | 24h | 83% | **1.1 : 1** |
| 29 | **548c** | $Et_2O$ | 24h | 96% | **2 : 1** |
| 30 | **548d** | Benzene | 24h | 30% | **2 : 1** |
| 31 | **548d** | THF | 24h | 63% | **1.4 : 1** |
| 32 | **548d** | $Et_2O$ | 24h | 54% | **1.7 : 1** |
| 33 | **548e** | Benzene | 24h | 30% | **3.2 : 1** |
| 34 | **548e** | THF | 24h | 43% | **1.7 : 1** |
| 35 | **548e** | $Et_2O$ | 24h | 77% | **1.5 : 1** |
| 36 | **548f** | Benzene | 24h | 20% | **2.3 : 1** |
| 37 | **548f** | THF | 24h | 10% | **1.6 : 1** |
| 38 | **548f** | $Et_2O$ | 24h | 23% | **1.9 : 1** |

## Appendix 2: Conferences and Lectures Attended

### Appendix 2A: Postgraduate Module CH501: Research Techniques.

This is a compulsory first year module that covers the following topics:

| Semester | Activity | Convenor/Lecturer (s) |
|---|---|---|
| 1 | Safety/Security | Mrs Sutherland |
| 1 | Introduction to Key Techniques | Mr Lee |
| | | Dr Eaton |
| | | Dr Fawcett |
| | | Dr Griffith |
| 1 | Use of the Library | Dr Lloyd |
| | | Ms Wilson |
| 1 | NMR Techniques I: 1D NMR | Dr Griffith |
| 1 | NMR Techniques II: 2D NMR | Dr Griffith |
| 2 | NMR Techniques III: The nOe Effect | Dr Griffith |
| 2 | Advanced Interpretation of Spectra | Dr Griffith |
| 2 | Lecture Presentations | Prof Holloway |
| 2 | Chemdraw and Molecular Modelling | Prof Cullis |
| 2 | Applications of 'Endnote' | Dr Davies |
| 2 | Advanced Scientific Writing | Dr Malpass |
| | | Mr Clark |

## Appendix 2B: Additional Modules taken during Postgraduate Training

| Year | Semester | Module | Module Title | Convenor | Attendance/ Assessment |
|---|---|---|---|---|---|
| 1 | 1 | CH 314 | Bioinorganic | Dr Lloyd | Pass |
| 1 | 2 | BS 106 | Introductory Physiology | | Pass |

## Appendix 2C: Lecture and Seminar Attendance - University of Leicester

This list covers formal lectures and seminars; group meetings, problem seminars and similar activities are not included here.

| Date | Dept | Lecturer | Title |
|---|---|---|---|
| 7/10/97 | Chem | Prof Nigel Simpkins (Nott) | New Assymetric Chemistry with Chiral Bases |
| 14/10/97 | Chem | Dr Martin Wills (Warwick) | Asymmetric catalysis |
| 17/10/97 | Chem | Dr Tim Gallagher (Bristol) | Synthesis of β Lactams |
| 23/11/97 | Chem | Dr Mike Sutcliffe (Leics) | Proteins; Modelling, Structure Calcs. |
| 29/11/97 | Chem | Mr Frank Friere (Leics) | New Sugar Chemistry |
| 4/11/97 | Chem | Dr Nigel Walsh (Pfizer) | Synthetic studies on Avermectin |
| 12/11/97 | Chem | Prof S. Ghosh (Calcutta) | Cyclopentanones; a Stereocontrolled Approach |
| 10/12/97 | Chem | Prof Brian Cox (Astra Zeneca) | Bigger and Better Reactions |
| 11/12/97 | Chem | Prof David Crout (Warwick) | Carbohydrates in biological systems; More than simply sweet |
| 11/12/97 | Chem | Dr David Ager (Monsanto) | Large scale synthesis of amino acids |
| 20/1/98 | Chem | Prof Christina Moberg (Sweden) | Chiral pyridine ligands in assymetric catalysis |
| 26/2/98 | Chem | Prof Barry Potter (Bath) | Synthetic chemistry in cellular signalling (inositols) |
| 2/3/98 | Chem | Prof Steve Davis | Assymetric synthesis of aldehydes and ketones |
| 9-13/3/98 | Chem | Prof Sabine Laschat (Braunschweig) | Organometallic reagents in organic synthesis; A short course |
| 19/3/98 | Chem | Prof C.D. Garner (Manchester) | Synthesis of Oxomolybdoenzyme cofactors |
| 6/5/98 | Chem | Dr David O'Hagan | Fluorinated natural products |
| 13/5/98 | Chem | Prof Stan Roberts (Liverpool) | Assymetric synthesis using natural and non-natural biocatalysts |
| 21/5/98 | Chem | Prof Alan Ferst (Cambridge Centre of Protein Engineering) | Protein Folding |
| 5/10/98 | Chem | Prof M.F. Hawthorne (UCLA) | Neutron capture by Boron 10 nucleii, the basis of a cell specific binary therapy for cancer |
| 6/10/98 | Chem | Prof. J. Mann (Reading) | The magic bullet and attempts to find it |
| 26/10/98 | Chem | Prof. B. Johnson (Cambridge) | The shape of things to come |

| | | | |
|---|---|---|---|
| 27/10/98 | Chem | Dr G. Tughan (Glaxo Wellcome) | Careers Lecture |
| 30/11/98 | Chem | Dr A. Stuart (Leicester) | Fluorinated Phosphinates |
| 10/12/98 | Chem | Dr C. Schofield (Dyson Lab.) | Stereoelectronics of enzyme catalysis and inhibition |
| 13/1/99 | Chem | Prof R. Stoodley (UMIST) | Stereocommunications through glycosidic bonds |
| 25/1/99 | Chem | Dr M. Winter (Sheffield) | Chemistry on the www |
| 3/2/99 | Chem | Prof R. Hubbard (York) | Modelling protein structure, function and dynamics |
| 17/2/99 | Chem | Dr M. Abraham (UCL) | Hydrogen and the blood brain barrier |
| 1/3/99 | Chem | Prof P. Atkins (Oxford) | The book, the disk and the future |
| 22/4/99 | Chem | Prof T. Katsuki (Fukuoka) | Studies on asymmetric catalysis |
| 19/5/99 | Chem | Prof. J. Murphy (Styrathclyde) | RSC lecture |
| 19/10/99 | Chem | Dr. Steve Marsden (London) | New synthetic methods using main group chemistry |
| 26/10/99 | Chem | Prof. John Boukouvalos (Laval University, Quebec) | Total synthesis of architecturally novel products of biomedical importance |
| 11/11/99 | Chem | Dr. Roger Thornley (Norwich) | Time resolved IR spectra of N-cycle enzymes |
| 15/11/99 | Chem | Prof. David Sherrington (Strathclyde) | Polymer supported asymmetric alkene epoxidation catalysts |
| 25/11/00 | Chem | Prof. Tom Hudlicky (Florida State University) | Recent advances in chemoenzymatic synthesis of natural products |
| 26/01/00 | Chem | Prof. Ron Grigg (Leeds) | Recent advances in catalytic cascade reactions |
| 3/04/00 | Chem | Prof. David Leigh (Warwick) | Molecules with moving parts: The race for molecular machinery |
| | Chem | Prof. Jean-Paul Sauvage (Strasbourg) | Porphyrin stoppered rotaxanes as models of the photosythesis reaction |
| 17/05/00 | Chem | Dr. Stephen Clark (Nottingham) | Synthesis of terpene derived polycyclic Natural products using metal carbenoids |
| 10/07/00 | Chem | Prof. Murata (Osaka, Japan) | Determination of stereochemistry for acyclic natural products |
| 24/07/00 | Chem | Prof. Takeshi Nakai (Tokyo, Japan) | Organometallic reagents in organic synthesis |

## Appendix 2D: Conference Attendance and Presentation of Lectures and Posters

| Date(s) | Meeting/ Conference | Place | Lecture/ Poster |
|---|---|---|---|
| 22/10/97 | Loughborough half day meeting of Organic Synthesis | Loughborough | - |
| 16/12/97 | Modern Aspects of Stereochemistry (31$^{st}$ Symposium) | Sheffield | - |
| 31/3/98 | RSC East Midlands Meeting 1998 | Sheffield | - |
| 5-10/8/98 | Brazilian meeting of Organic Synthesis | San Pedro, Brazil | P |
| 11/11/98 | Loughborough half day meeting of Organic Synthesis | Loughborough | - |
| 7/12/98 | Modern Aspects of Stereochemistry (32$^{nd}$ Symposium) | Sheffield | - |
| 6/1/99 | RSC Bioorganic Symposium | Leicester | P |
| 14/4/99 | RSC East Midlands Conference | Leicester | P |
| 12/5/99 | Organic Chemistry Symposium | Loughborough | - |
| 5/12/99 | Pfizer Organic Chemistry Poster Symposium | London | P |
| 24/11/00 | Loughborough half day meeting of Organic Synthesis | Loughborough | - |
| 14/12/99 | Modern Aspects of Stereochemistry (33$^{rd}$ Symposium) | Sheffield | - |
| 31/5/00 | RSC East Midlands Conference | Leicester | P |

## Appendix 3: X-Ray Crystallographic Data

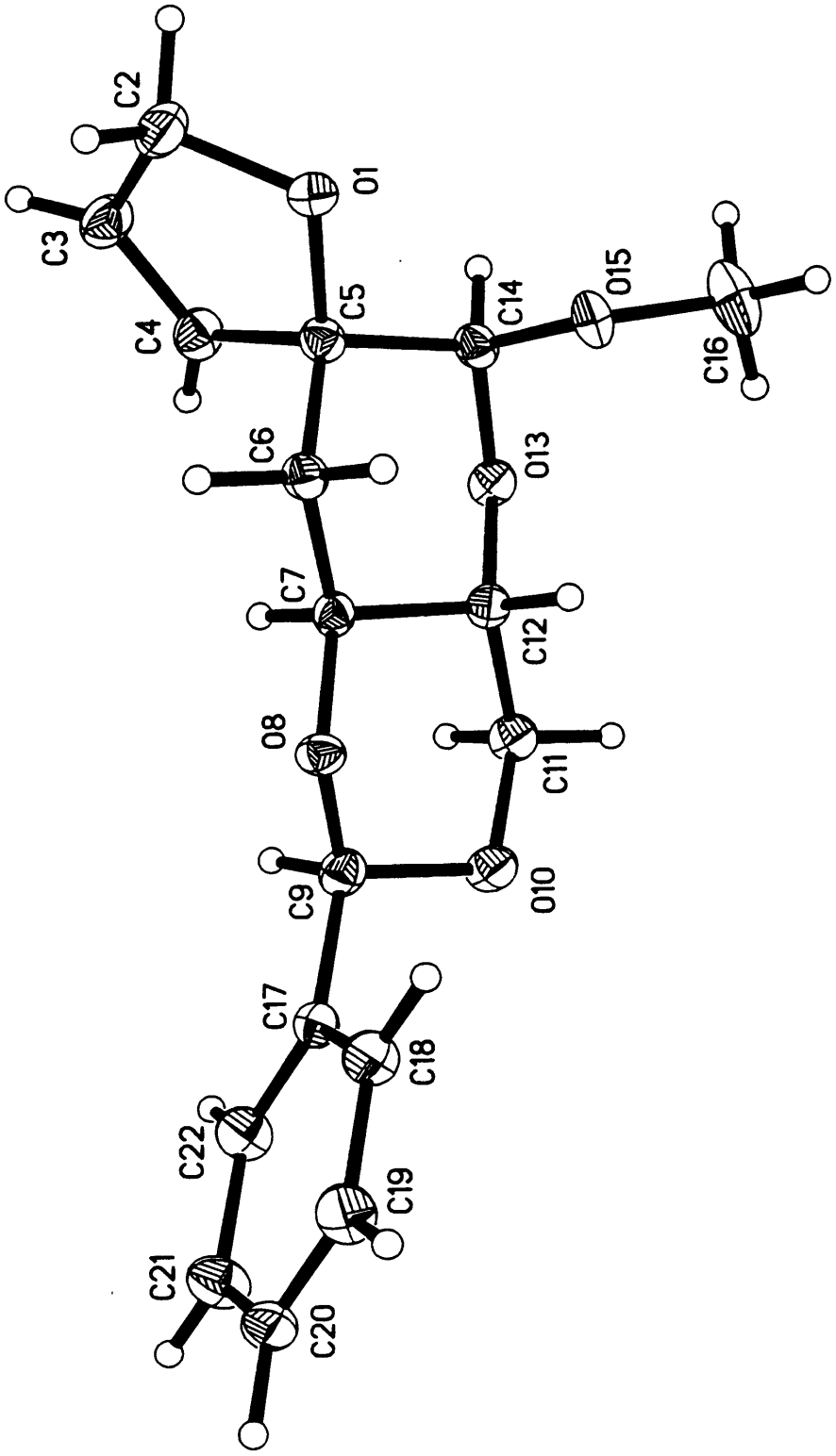


Table 1. Crystal data and structure refinement for 1.

| | |
|---|---|
| Identification code | 9825 |
| Empirical formula | $C_{18}H_{17}O_5$ |
| Formula weight | 313.32 |
| Temperature | 190(2) K |
| Wavelength | 0.71073 Å |
| Crystal system | Monoclinic |
| Space group | $P2_1$ |
| Unit cell dimensions | a = 9.505(4) Å alpha = 90°<br>*b* = 7.907(2) Å beta = 98.05(2)°<br>*c* = 10.319(2) Å gamma = 90° |
| Volume, Z | 768.0(4) $Å^3$, 2 |
| Density (calculated) | 1.355 $Mg/m^3$ |
| Absorption coefficient | 0.099 $mm^{-1}$ |
| F(000) | 330 |
| Crystal size | 0.77 x 0.72 x 0.61 mm |
| θ range for data collection | 1.99 to 28.82° |
| Limiting indices | $0 \le h \le 11$, $-1 \le k \le 9$, $-12 \le l \le 12$ |
| Reflections collected | 1616 |
| Independent reflections | 1553 ($R_{int}$ = 0.0546) |
| Absorption correction | Not applied |
| Refinement method | Full-matrix least-squares on $F^2$ |
| Data / restraints / parameters | 1553 / 1 / 200 |
| Goodness-of-fit on $F^2$ | 1.132 |
| Final R indices [I>2σ(I)] | R1 = 0.0497, wR2 = 0.1319 |
| R indices (all data) | R1 = 0.0550, wR2 = 0.1373 |
| Absolute structure parameter | -1.4(23) |
| Extinction coefficient | 0.044(6) |
| Largest diff. peak and hole | 0.238 and -0.266 $eÅ^{-3}$ |

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) | 6242(3) | 4503(4) | 6585(3) | 33(1) |
| O(8) | 7073(3) | 7395(4) | 2586(3) | 29(1) |
| O(10) | 8613(3) | 6171(5) | 1270(3) | 34(1) |
| O(13) | 8870(3) | 3813(4) | 4345(3) | 30(1) |
| O(15) | 6794(3) | 2391(5) | 4667(3) | 34(1) |
| C(2) | 6416(6) | 5554(8) | 7745(5) | 42(1) |
| C(3) | 7843(6) | 6337(8) | 7764(5) | 41(1) |
| C(4) | 8337(5) | 6019(7) | 6654(4) | 36(1) |
| C(5) | 7255(5) | 5015(6) | 5754(4) | 30(1) |
| C(6) | 6546(5) | 6086(6) | 4599(4) | 29(1) |
| C(7) | 7642(5) | 6399(6) | 3703(4) | 27(1) |
| C(9) | 8142(5) | 7716(6) | 1805(4) | 32(1) |
| C(11) | 9239(5) | 5058(7) | 2294(5) | 34(1) |
| C(12) | 8189(5) | 4738(6) | 3233(4) | 28(1) |
| C(14) | 7893(5) | 3401(6) | 5247(4) | 28(1) |
| C(16) | 7236(6) | 736(8) | 4351(7) | 58(2) |
| C(17) | 7597(5) | 8877(6) | 694(4) | 29(1) |
| C(18) | 6203(5) | 8681(7) | 52(4) | 35(1) |
| C(19) | 5723(5) | 9746(7) | -986(5) | 41(1) |
| C(20) | 6568(6) | 10988(7) | -1385(5) | 40(1) |
| C(21) | 7952(6) | 11200(8) | -743(5) | 45(1) |
| C(22) | 8435(5) | 10123(7) | 303(5) | 40(1) |

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

| | | | |
|---|---|---|---|
| O(1)-C(5) | 1.435(6) | O(1)-C(2) | 1.448(6) |
| O(8)-C(9) | 1.406(6) | O(8)-C(7) | 1.438(5) |
| O(10)-C(9) | 1.437(6) | O(10)-C(11) | 1.439(5) |
| O(13)-C(12) | 1.436(5) | O(13)-C(14) | 1.442(6) |
| O(15)-C(14) | 1.383(6) | O(15)-C(16) | 1.427(7) |
| C(2)-C(3) | 1.488(8) | C(3)-C(4) | 1.322(7) |
| C(4)-C(5) | 1.511(6) | C(5)-C(14) | 1.536(6) |
| C(5)-C(6) | 1.539(6) | C(6)-C(7) | 1.507(6) |
| C(7)-C(12) | 1.517(6) | C(9)-C(17) | 1.503(7) |
| C(11)-C(12) | 1.507(7) | C(17)-C(22) | 1.364(7) |
| C(17)-C(18) | 1.405(6) | C(18)-C(19) | 1.388(7) |
| C(19)-C(20) | 1.368(8) | C(20)-C(21) | 1.398(7) |
| C(21)-C(22) | 1.401(7) | | |

| | | | |
|---|---|---|---|
| C(5)-O(1)-C(2) | 108.9(4) | C(9)-O(8)-C(7) | 109.7(3) |
| C(9)-O(10)-C(11) | 110.9(3) | C(12)-O(13)-C(14) | 111.8(3) |
| C(14)-O(15)-C(16) | 113.5(4) | O(1)-C(2)-C(3) | 104.4(4) |
| C(4)-C(3)-C(2) | 110.1(5) | C(3)-C(4)-C(5) | 109.8(5) |
| O(1)-C(5)-C(4) | 103.7(4) | O(1)-C(5)-C(14) | 107.4(4) |
| C(4)-C(5)-C(14) | 112.2(4) | O(1)-C(5)-C(6) | 111.1(4) |
| C(4)-C(5)-C(6) | 111.9(4) | C(14)-C(5)-C(6) | 110.2(4) |
| C(7)-C(6)-C(5) | 107.5(3) | O(8)-C(7)-C(6) | 111.6(3) |
| O(8)-C(7)-C(12) | 109.0(3) | C(6)-C(7)-C(12) | 110.6(4) |
| O(8)-C(9)-O(10) | 110.9(4) | O(8)-C(9)-C(17) | 110.4(4) |
| O(10)-C(9)-C(17) | 108.6(4) | O(10)-C(11)-C(12) | 109.4(3) |
| O(13)-C(12)-C(11) | 109.5(3) | O(13)-C(12)-C(7) | 108.8(3) |
| C(11)-C(12)-C(7) | 110.3(4) | O(15)-C(14)-O(13) | 111.5(4) |
| O(15)-C(14)-C(5) | 108.4(4) | O(13)-C(14)-C(5) | 110.7(4) |
| C(22)-C(17)-C(18) | 119.4(4) | C(22)-C(17)-C(9) | 120.9(4) |
| C(18)-C(17)-C(9) | 119.6(4) | C(19)-C(18)-C(17) | 118.9(5) |
| C(20)-C(19)-C(18) | 121.6(4) | C(19)-C(20)-C(21) | 119.8(5) |
| C(20)-C(21)-C(22) | 118.5(5) | C(17)-C(22)-C(21) | 121.7(4) |

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) | 38(2) | 34(2) | 30(2) | 1(2) | 11(2) | -4(2) |
| O(8) | 30(2) | 30(2) | 26(1) | 6(2) | 4(1) | 6(2) |
| O(10) | 35(2) | 37(2) | 29(2) | 3(2) | 3(1) | 13(2) |
| O(13) | 28(2) | 32(2) | 29(2) | 2(2) | 1(1) | 7(2) |
| O(15) | 35(2) | 21(2) | 44(2) | -5(2) | 1(2) | -1(2) |
| C(2) | 49(3) | 43(3) | 34(2) | -7(2) | 11(2) | 4(3) |
| C(3) | 50(3) | 44(3) | 28(2) | -4(2) | 0(2) | 3(3) |
| C(4) | 36(2) | 38(3) | 33(2) | -3(2) | -3(2) | -2(2) |
| C(5) | 29(2) | 29(3) | 30(2) | 1(2) | 2(2) | -2(2) |
| C(6) | 31(2) | 26(2) | 31(2) | 3(2) | 6(2) | 6(2) |
| C(7) | 29(2) | 25(2) | 25(2) | -1(2) | 0(2) | 1(2) |
| C(9) | 31(2) | 34(3) | 29(2) | -2(2) | 1(2) | 1(2) |
| C(11) | 33(2) | 35(3) | 34(2) | 4(2) | 3(2) | 11(2) |
| C(12) | 30(2) | 27(2) | 25(2) | 1(2) | -2(2) | 4(2) |
| C(14) | 30(2) | 24(2) | 30(2) | 2(2) | 0(2) | 1(2) |
| C(16) | 50(3) | 30(3) | 93(5) | -8(3) | 7(3) | 0(3) |
| C(17) | 30(2) | 27(3) | 27(2) | 0(2) | 2(2) | -1(2) |
| C(18) | 30(2) | 37(3) | 36(2) | 1(2) | -3(2) | -3(2) |
| C(19) | 34(2) | 39(3) | 43(3) | 2(3) | -11(2) | 6(2) |
| C(20) | 49(3) | 35(3) | 34(2) | 7(2) | 1(2) | 12(3) |
| C(21) | 43(3) | 41(3) | 48(3) | 10(3) | 3(3) | -6(3) |
| C(22) | 34(2) | 40(3) | 42(3) | 3(2) | -3(2) | -2(2) |

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

| | x | y | z | U(eq) |
|---|---|---|---|---|
| H(2A) | 6378(6) | 4865(8) | 8541(5) | 50 |
| H(2B) | 5667(6) | 6431(8) | 7690(5) | 50 |
| H(3A) | 8327(6) | 6973(8) | 8471(5) | 49 |
| H(4A) | 9238(5) | 6368(7) | 6453(4) | 44 |
| H(6A) | 5720(5) | 5477(6) | 4126(4) | 35 |
| H(6B) | 6211(5) | 7173(6) | 4920(4) | 35 |
| H(7A) | 8457(5) | 7026(6) | 4201(4) | 32 |
| H(9A) | 8966(5) | 8265(6) | 2354(4) | 38 |
| H(11A) | 10111(5) | 5579(7) | 2765(5) | 41 |
| H(11B) | 9504(5) | 3975(7) | 1912(5) | 41 |
| H(12A) | 7373(5) | 4063(6) | 2784(4) | 33 |
| H(14A) | 8421(5) | 2778(6) | 6008(4) | 34 |
| H(16A) | 6411(6) | 88(8) | 3945(7) | 87 |
| H(16B) | 7667(6) | 162(8) | 5151(7) | 87 |
| H(16C) | 7934(6) | 819(8) | 3739(7) | 87 |
| H(18A) | 5599(5) | 7834(7) | 323(4) | 42 |
| H(19A) | 4785(5) | 9608(7) | -1431(5) | 49 |
| H(20A) | 6215(6) | 11704(7) | -2096(5) | 48 |
| H(21A) | 8552(6) | 12055(8) | -1011(5) | 53 |
| H(22A) | 9371(5) | 10266(7) | 752(5) | 47 |

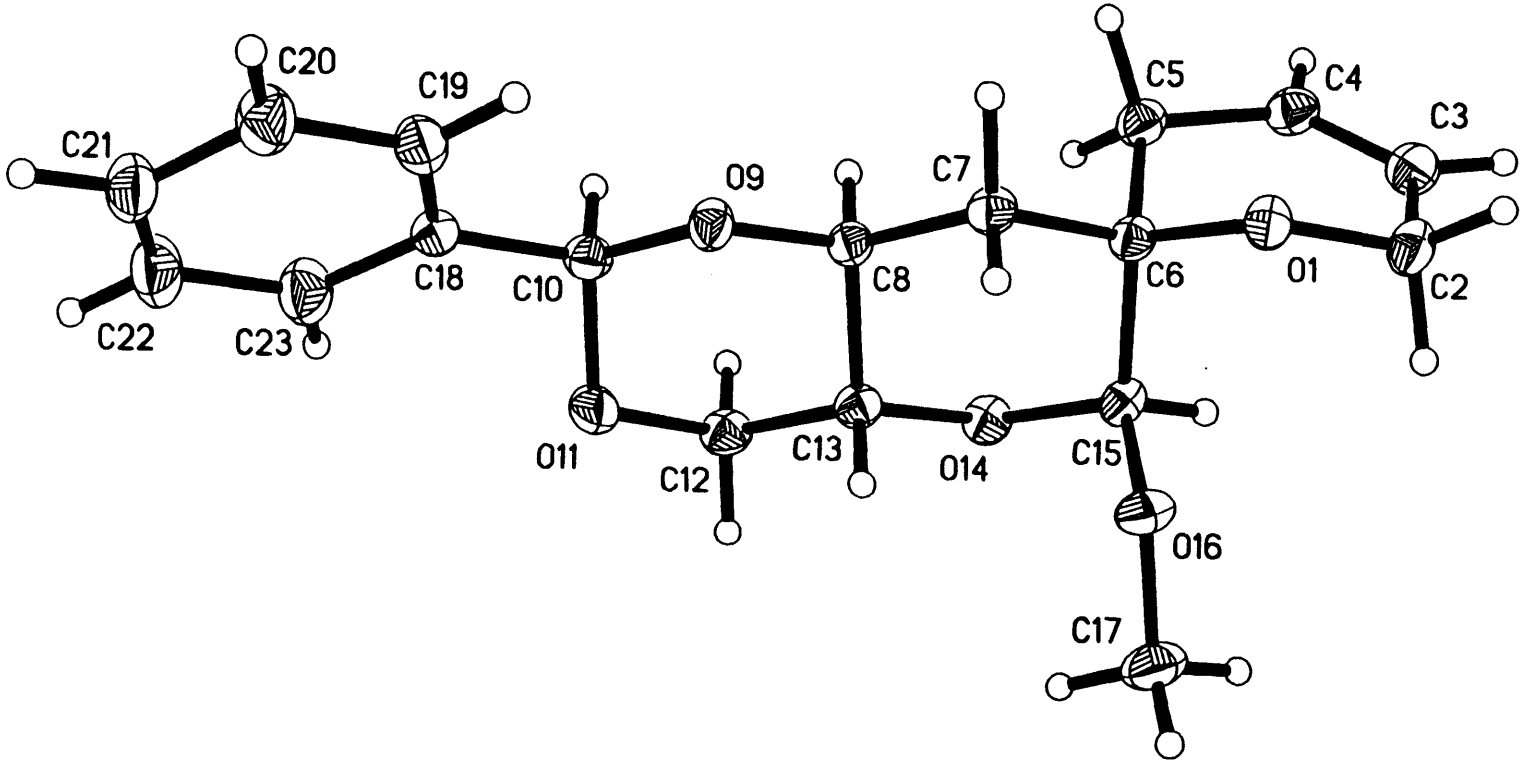

C20
C19
C21
C18
C10
09
C8
C7
C5
C4
C3
C6
01
C2
C22
C23
011
C12
C13
014
C15
016
C17

Table 1. Crystal data and structure refinement for 1.

| | |
|---|---|
| Identification code | 9837 |
| 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 | $a$ = 7.178(2) Å alpha = 90°<br>$b$ = 7.844(2) Å beta = 101.37(2)°<br>$c$ = 14.863(3) Å gamma = 90° |
| Volume, Z | 820.5(3) $Å^3$, 2 |
| Density (calculated) | 1.289 $Mg/m^3$ |
| Absorption coefficient | 0.093 $mm^{-1}$ |
| F(000) | 340 |
| Crystal size | 0.51 x 0.44 x 0.20 mm |
| θ range for data collection | 2.80 to 24.99° |
| Limiting indices | $0 \le h \le 8$, $-1 \le k \le 9$, $-17 \le l \le 17$ |
| Reflections collected | 1938 |
| Independent reflections | 1791 ($R_{int}$ = 0.0172) |
| Absorption correction | Not applied |
| Refinement method | Full-matrix least-squares on $F^2$ |
| Data / restraints / parameters | 1791 / 1 / 208 |
| Goodness-of-fit on $F^2$ | 1.082 |
| Final R indices [I>2σ(I)] | R1 = 0.0327, wR2 = 0.0778 |
| R indices (all data) | R1 = 0.0406, wR2 = 0.0838 |
| Absolute structure parameter | 0.0(13) |
| Largest diff. peak and hole | 0.149 and -0.145 $eÅ^{-3}$ |

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) | 4515(2) | 3959(3) | 943(1) | 32(1) |
| C(2) | 5146(4) | 2847(4) | 303(2) | 38(1) |
| C(3) | 3734(4) | 2662(4) | -569(2) | 40(1) |
| C(4) | 1964(4) | 3207(4) | -656(2) | 37(1) |
| C(5) | 1237(3) | 3969(4) | 133(2) | 35(1) |
| C(6) | 2599(3) | 3686(3) | 1056(2) | 29(1) |
| C(7) | 2291(3) | 4978(3) | 1779(2) | 31(1) |
| C(8) | 386(3) | 4656(3) | 2041(2) | 29(1) |
| O(9) | 99(2) | 5809(2) | 2743(1) | 33(1) |
| C(10) | -1686(4) | 5479(4) | 2980(2) | 32(1) |
| O(11) | -1792(2) | 3809(3) | 3327(1) | 36(1) |
| C(12) | -1582(4) | 2545(4) | 2649(2) | 35(1) |
| C(13) | 310(3) | 2839(4) | 2386(2) | 28(1) |
| O(14) | 541(2) | 1673(2) | 1665(1) | 31(1) |
| C(15) | 2349(3) | 1859(3) | 1416(2) | 29(1) |
| O(16) | 3846(2) | 1558(3) | 2150(1) | 36(1) |
| C(17) | 3903(4) | -155(4) | 2497(2) | 51(1) |
| C(18) | -1999(4) | 6735(4) | 3706(2) | 33(1) |
| C(19) | -923(4) | 8200(4) | 3873(2) | 40(1) |
| C(20) | -1224(4) | 9335(4) | 4545(2) | 47(1) |
| C(21) | -2599(4) | 9010(5) | 5051(2) | 49(1) |
| C(22) | -3691(5) | 7571(5) | 4877(2) | 57(1) |
| C(23) | -3397(4) | 6428(5) | 4202(2) | 50(1) |

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

| | | | |
|---|---|---|---|
| O(1)-C(2) | 1.429(3) | O(1)-C(6) | 1.434(3) |
| C(2)-C(3) | 1.486(4) | C(3)-C(4) | 1.322(4) |
| C(4)-C(5) | 1.499(4) | C(5)-C(6) | 1.535(3) |
| C(6)-C(7) | 1.525(3) | C(6)-C(15) | 1.552(4) |
| C(7)-C(8) | 1.515(3) | C(8)-O(9) | 1.426(3) |
| C(8)-C(13) | 1.519(4) | O(9)-C(10) | 1.418(3) |
| C(10)-O(11) | 1.415(3) | C(10)-C(18) | 1.510(4) |
| O(11)-C(12) | 1.443(3) | C(12)-C(13) | 1.503(3) |
| C(13)-O(14) | 1.442(3) | O(14)-C(15) | 1.426(3) |
| C(15)-O(16) | 1.393(3) | O(16)-C(17) | 1.437(4) |
| C(18)-C(23) | 1.379(4) | C(18)-C(19) | 1.380(4) |
| C(19)-C(20) | 1.387(4) | C(20)-C(21) | 1.378(4) |
| C(21)-C(22) | 1.369(5) | C(22)-C(23) | 1.392(5) |

| | | | |
|---|---|---|---|
| C(2)-O(1)-C(6) | 115.1(2) | O(1)-C(2)-C(3) | 112.9(2) |
| C(4)-C(3)-C(2) | 122.1(2) | C(3)-C(4)-C(5) | 121.9(2) |
| C(4)-C(5)-C(6) | 112.5(2) | O(1)-C(6)-C(7) | 105.0(2) |
| O(1)-C(6)-C(5) | 109.3(2) | C(7)-C(6)-C(5) | 112.2(2) |
| O(1)-C(6)-C(15) | 110.9(2) | C(7)-C(6)-C(15) | 109.1(2) |
| C(5)-C(6)-C(15) | 110.2(2) | C(8)-C(7)-C(6) | 109.6(2) |
| O(9)-C(8)-C(7) | 110.5(2) | O(9)-C(8)-C(13) | 109.2(2) |
| C(7)-C(8)-C(13) | 109.7(2) | C(10)-O(9)-C(8) | 109.5(2) |
| O(11)-C(10)-O(9) | 112.1(2) | O(11)-C(10)-C(18) | 108.5(2) |
| O(9)-C(10)-C(18) | 109.1(2) | C(10)-O(11)-C(12) | 111.2(2) |
| O(11)-C(12)-C(13) | 107.5(2) | O(14)-C(13)-C(12) | 109.7(2) |
| O(14)-C(13)-C(8) | 109.2(2) | C(12)-C(13)-C(8) | 109.0(2) |
| C(15)-O(14)-C(13) | 111.8(2) | O(16)-C(15)-O(14) | 112.3(2) |
| O(16)-C(15)-C(6) | 107.6(2) | O(14)-C(15)-C(6) | 110.9(2) |
| C(15)-O(16)-C(17) | 113.7(2) | C(23)-C(18)-C(19) | 119.3(3) |
| C(23)-C(18)-C(10) | 119.7(3) | C(19)-C(18)-C(10) | 121.0(2) |
| C(18)-C(19)-C(20) | 120.2(3) | C(21)-C(20)-C(19) | 120.3(3) |
| C(22)-C(21)-C(20) | 119.6(3) | C(21)-C(22)-C(23) | 120.4(3) |
| C(18)-C(23)-C(22) | 120.2(3) | | |

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:

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

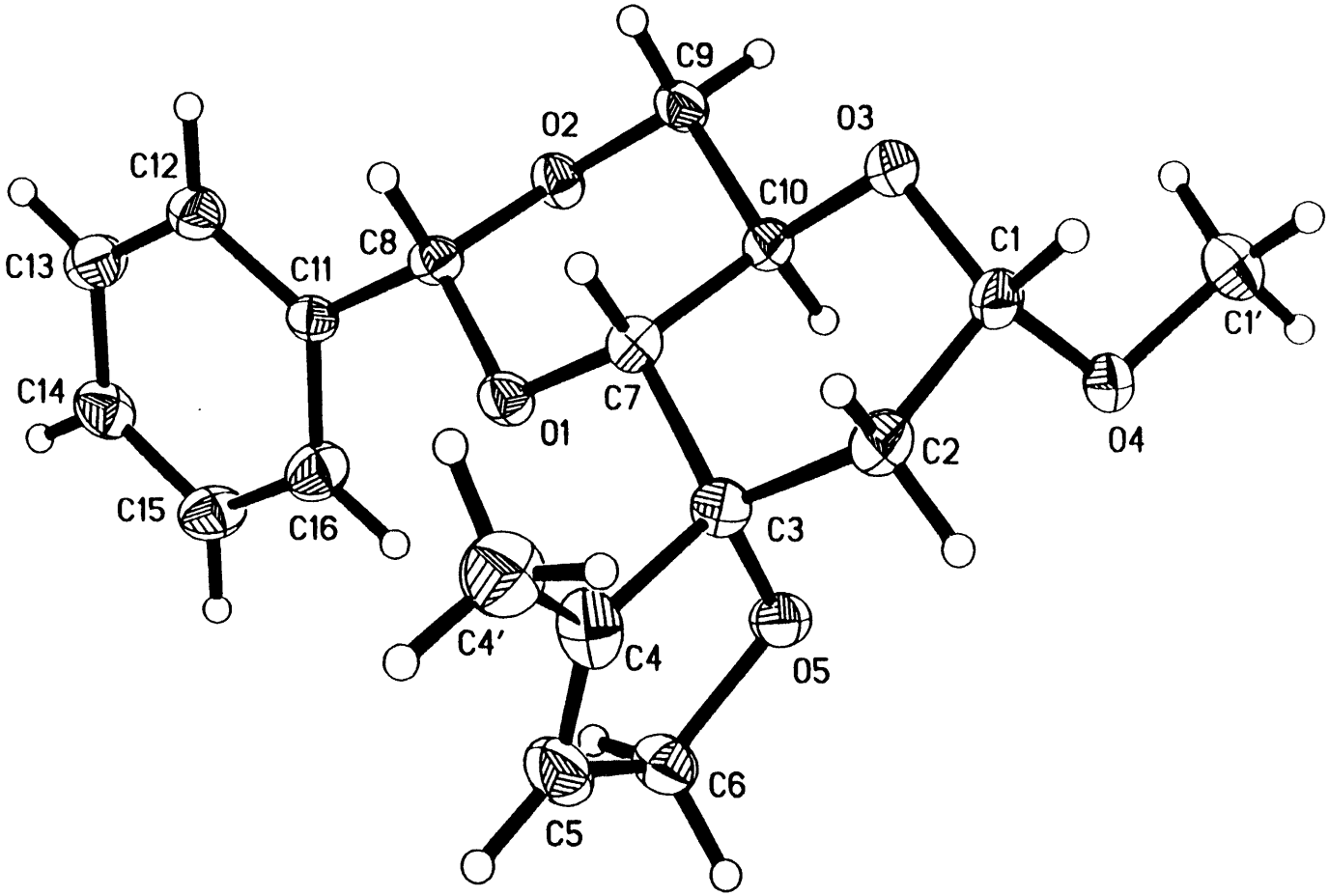
| | U11 | U22 | U33 | U23 | U13 | U12 |
|---|---|---|---|---|---|---|
| O(1) | 31(1) | 27(1) | 42(1) | -6(1) | 12(1) | -5(1) |
| C(2) | 37(1) | 34(2) | 46(1) | -6(1) | 13(1) | 4(1) |
| C(3) | 51(2) | 30(1) | 40(1) | -5(1) | 13(1) | 0(1) |
| C(4) | 44(2) | 29(1) | 36(1) | -2(1) | 4(1) | 2(1) |
| C(5) | 35(1) | 27(1) | 42(1) | 2(1) | 8(1) | 2(1) |
| C(6) | 28(1) | 23(2) | 37(1) | -1(1) | 8(1) | -1(1) |
| C(7) | 35(1) | 20(1) | 40(1) | -3(1) | 11(1) | -4(1) |
| C(8) | 33(1) | 24(1) | 33(1) | -1(1) | 10(1) | -1(1) |
| O(9) | 35(1) | 27(1) | 40(1) | -5(1) | 15(1) | -2(1) |
| C(10) | 31(1) | 32(2) | 35(1) | 5(1) | 8(1) | 1(1) |
| O(11) | 41(1) | 31(1) | 37(1) | 2(1) | 13(1) | -3(1) |
| C(12) | 38(1) | 25(1) | 42(1) | 1(1) | 9(1) | -4(1) |
| C(13) | 28(1) | 24(1) | 33(1) | 1(1) | 5(1) | -2(1) |
| O(14) | 31(1) | 23(1) | 40(1) | -4(1) | 6(1) | -6(1) |
| C(15) | 26(1) | 24(1) | 37(1) | -2(1) | 5(1) | 2(1) |
| O(16) | 33(1) | 28(1) | 45(1) | 7(1) | 1(1) | 0(1) |
| C(17) | 50(2) | 35(2) | 66(2) | 18(2) | 10(2) | 9(2) |
| C(18) | 33(1) | 34(2) | 31(1) | 4(1) | 7(1) | 7(1) |
| C(19) | 45(1) | 39(2) | 37(1) | -1(1) | 13(1) | -1(1) |
| C(20) | 53(2) | 47(2) | 41(2) | -9(2) | 9(1) | 0(2) |
| C(21) | 56(2) | 54(2) | 39(1) | -8(2) | 14(1) | 10(2) |
| C(22) | 56(2) | 62(2) | 61(2) | -4(2) | 33(2) | 3(2) |
| C(23) | 46(2) | 52(2) | 57(2) | -3(2) | 22(1) | -1(2) |

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

| | x | y | z | U(eq) |
|---|---|---|---|---|
| H(2A) | 5412(4) | 1709(4) | 587(2) | 46 |
| H(2B) | 6348(4) | 3294(4) | 164(2) | 46 |
| H(3A) | 4115(4) | 2137(4) | -1080(2) | 48 |
| H(4A) | 1129(4) | 3112(4) | -1235(2) | 44 |
| H(5A) | -11(3) | 3457(4) | 160(2) | 41 |
| H(5B) | 1046(3) | 5209(4) | 28(2) | 41 |
| H(7A) | 3319(3) | 4873(3) | 2328(2) | 38 |
| H(7B) | 2325(3) | 6148(3) | 1533(2) | 38 |
| H(8A) | -646(3) | 4821(3) | 1489(2) | 35 |
| H(10A) | -2710(4) | 5628(4) | 2423(2) | 39 |
| H(12A) | -2619(4) | 2656(4) | 2104(2) | 42 |
| H(12B) | -1633(4) | 1385(4) | 2905(2) | 42 |
| H(13A) | 1352(3) | 2658(4) | 2932(2) | 34 |
| H(15A) | 2436(3) | 1026(3) | 916(2) | 35 |
| H(17A) | 4985(4) | -278(4) | 3010(2) | 76 |
| H(17B) | 4042(4) | -955(4) | 2008(2) | 76 |
| H(17C) | 2722(4) | -400(4) | 2709(2) | 76 |
| H(19A) | 28(4) | 8432(4) | 3526(2) | 47 |
| H(20A) | -478(4) | 10342(4) | 4657(2) | 57 |
| H(21A) | -2789(4) | 9779(5) | 5519(2) | 59 |
| H(22A) | -4654(5) | 7352(5) | 5218(2) | 68 |
| H(23A) | -4162(4) | 5433(5) | 4084(2) | 60 |

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

| | x | y | z | U(eq) |
|---|---|---|---|---|
| H(2A) | 5412(4) | 1709(4) | 587(2) | 46 |
| H(2B) | 6348(4) | 3294(4) | 164(2) | 46 |
| H(3A) | 4115(4) | 2137(4) | -1080(2) | 48 |
| H(4A) | 1129(4) | 3112(4) | -1235(2) | 44 |
| H(5A) | -11(3) | 3457(4) | 160(2) | 41 |
| H(5B) | 1046(3) | 5209(4) | 28(2) | 41 |
| H(7A) | 3319(3) | 4873(3) | 2328(2) | 38 |
| H(7B) | 2325(3) | 6148(3) | 1533(2) | 38 |
| H(8A) | -646(3) | 4821(3) | 1489(2) | 35 |
| H(10A) | -2710(4) | 5628(4) | 2423(2) | 39 |
| H(12A) | -2619(4) | 2656(4) | 2104(2) | 42 |
| H(12B) | -1633(4) | 1385(4) | 2905(2) | 42 |
| H(13A) | 1352(3) | 2658(4) | 2932(2) | 34 |
| H(15A) | 2436(3) | 1026(3) | 916(2) | 35 |
| H(17A) | 4985(4) | -278(4) | 3010(2) | 76 |
| H(17B) | 4042(4) | -955(4) | 2008(2) | 76 |
| H(17C) | 2722(4) | -400(4) | 2709(2) | 76 |
| H(19A) | 28(4) | 8432(4) | 3526(2) | 47 |
| H(20A) | -478(4) | 10342(4) | 4657(2) | 57 |
| H(21A) | -2789(4) | 9779(5) | 5519(2) | 59 |
| H(22A) | -4654(5) | 7352(5) | 5218(2) | 68 |
| H(23A) | -4162(4) | 5433(5) | 4084(2) | 60 |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O3
C12
C10
C8
C1
C13
C11
C1'
C14
C7
O1
O4
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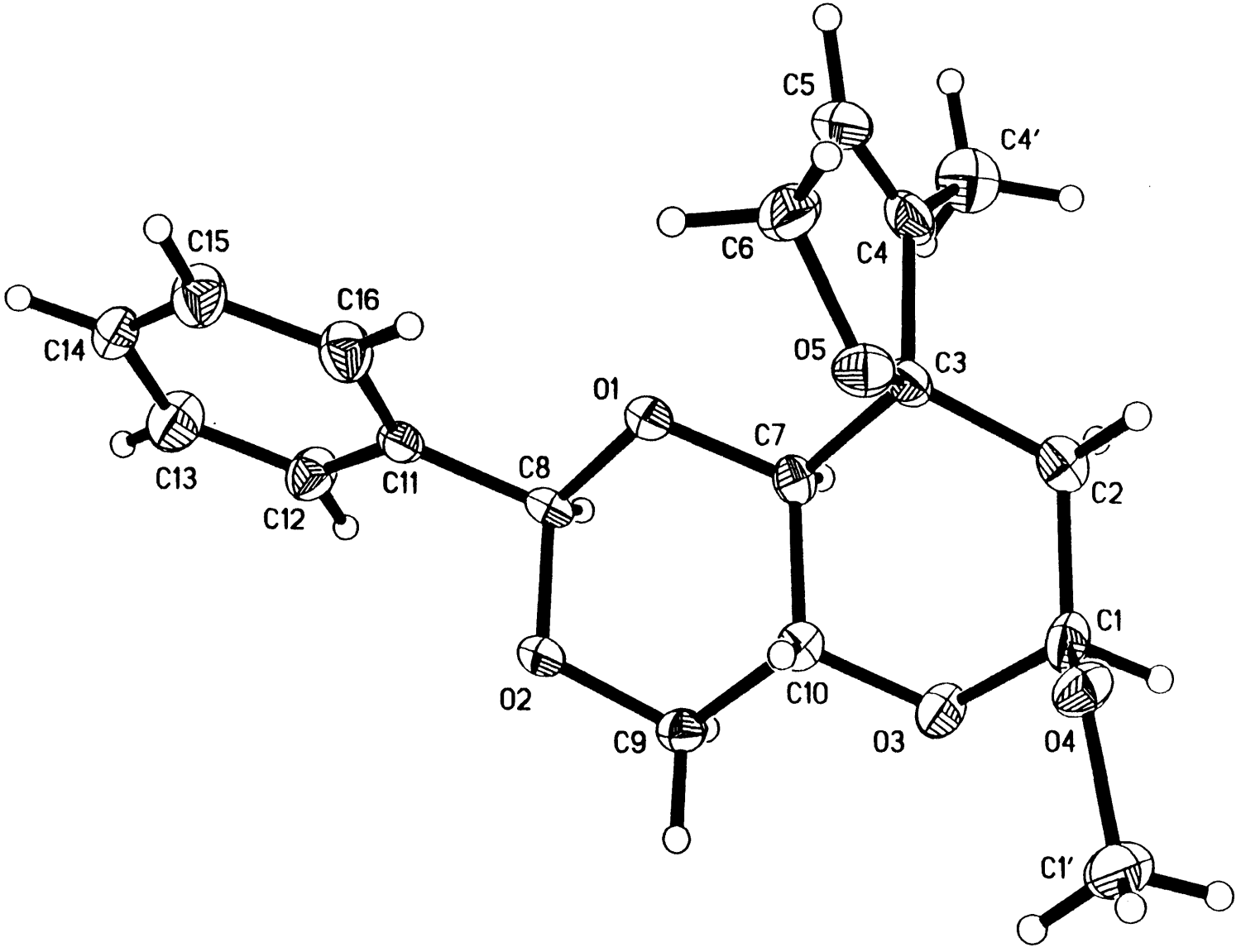
C16
C3
C4'
C4
O5
C6
C5


C5
C4'
C6
C4
C15
C16
C14
O5
C3
O1
C7
C13
C11
C8
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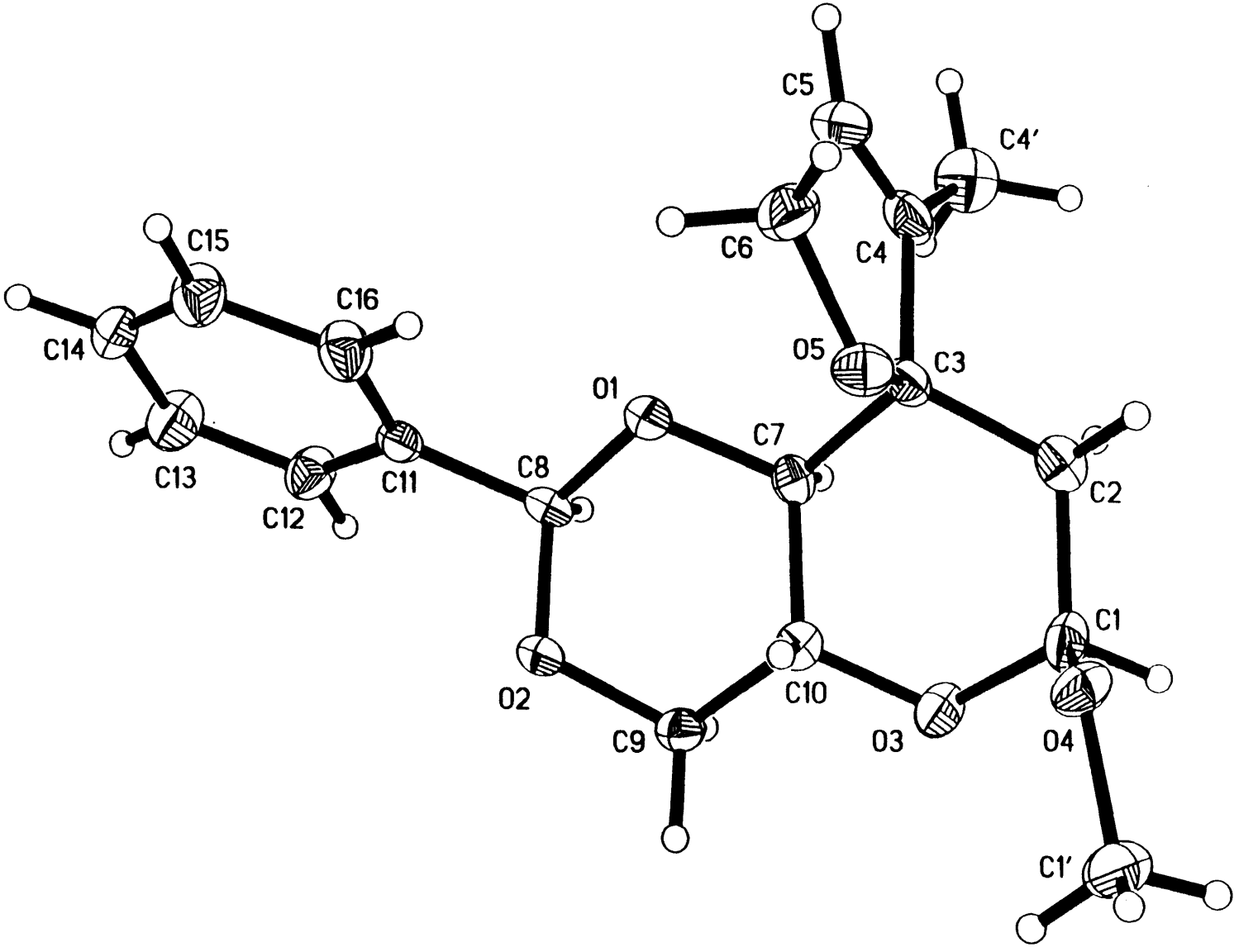
C1
O2
C10
C9
O3
O4
C1'


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

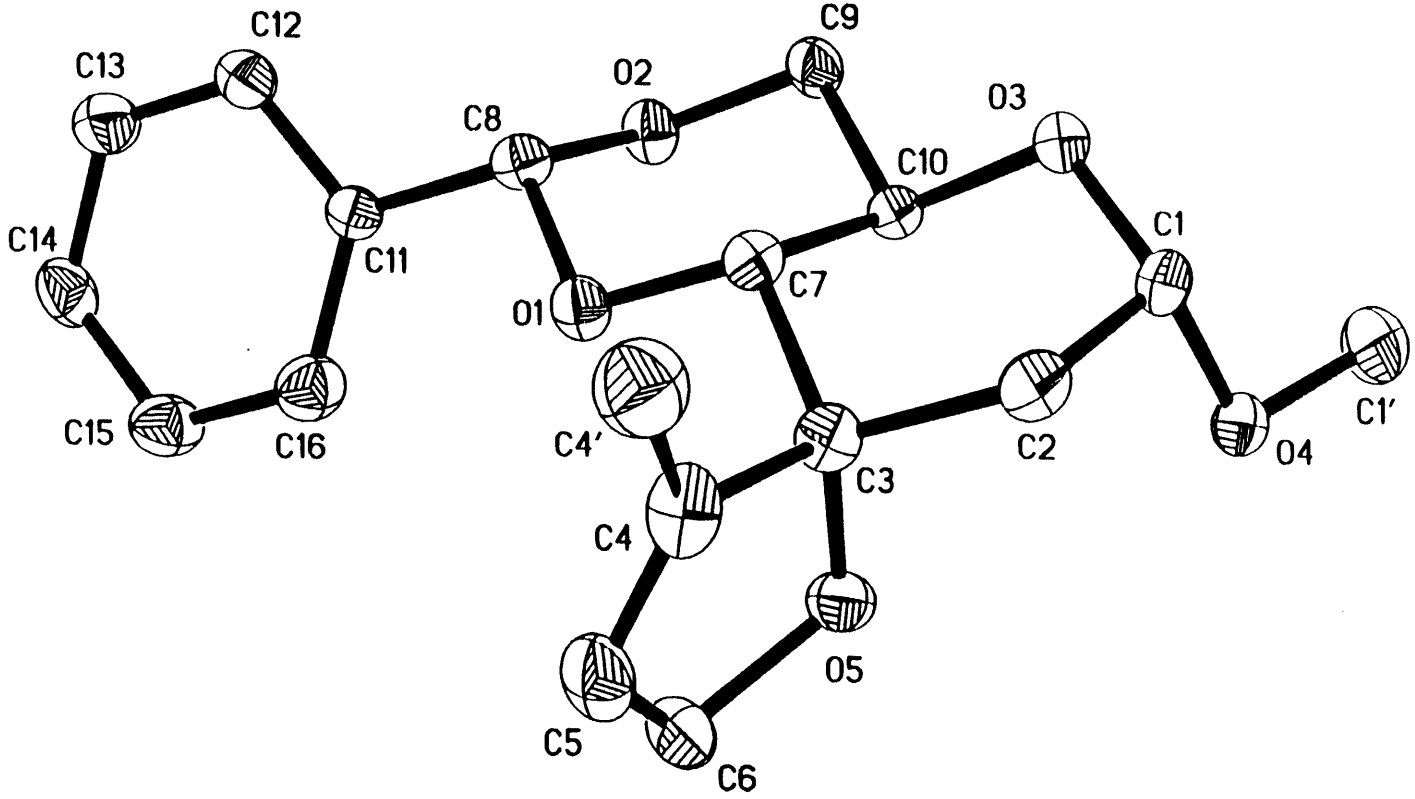
C12
C13
C9
O2
C8
O3
C10
C14
C11
C1
O1
C7
C15
C16
C4'
C2
C1'
O4
C3
C4
O5
C5
C6

Table 1. Crystal data and structure refinement for 1.

| | |
|---|---|
| Identification code | 9894 |
| 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 | $a$ = 5.649(2) Å alpha = 90°<br>$b$ = 13.000(4) Å beta = 90°<br>$c$ = 21.85(2) Å gamma = 90° |
| Volume, Z | 1605(2) $Å^3$, 4 |
| Density (calculated) | 1.318 $Mg/m^3$ |
| Absorption coefficient | 0.096 $mm^{-1}$ |
| F(000) | 680 |
| Crystal size | 0.78 x 0.21 x 0.17 mm |
| θ range for data collection | 1.82 to 25.02° |
| Limiting indices | $0 \le h \le 6$, $-15 \le k \le 1$, $-1 \le l \le 26$ |
| Reflections collected | 1910 |
| Independent reflections | 1847 ($R_{int}$ = 0.0578) |
| Absorption correction | Not applied |
| Refinement method | Full-matrix least-squares on $F^2$ |
| Data / restraints / parameters | 1847 / 0 / 201 |
| Goodness-of-fit on $F^2$ | 0.993 |
| Final R indices [I>2σ(I)] | R1 = 0.0630, wR2 = 0.1432 |
| R indices (all data) | R1 = 0.1050, wR2 = 0.1763 |
| Absolute structure parameter | -3(3) |
| Extinction coefficient | 0.010(3) |
| Largest diff. peak and hole | 0.355 and -0.340 $eÅ^{-3}$ |

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) | 90(7) | 10125(3) | 10152(2) | 34(1) |
| O(2) | 833(7) | 8461(2) | 9798(2) | 33(1) |
| O(3) | -985(7) | 8305(3) | 11386(2) | 37(1) |
| O(4) | -4955(7) | 8559(3) | 11636(2) | 38(1) |
| O(5) | -4180(7) | 10444(3) | 10766(2) | 38(1) |
| C(1) | -2637(10) | 8828(5) | 11766(3) | 37(2) |
| C(1') | -5448(12) | 7496(4) | 11768(3) | 50(2) |
| C(2) | -2362(11) | 9993(4) | 11727(3) | 36(1) |
| C(3) | -1983(11) | 10450(4) | 11097(3) | 33(1) |
| C(4) | -1306(9) | 11579(4) | 11112(2) | 44(2) |
| C(4') | 672(9) | 11979(4) | 11497(2) | 62(2) |
| C(5) | -2625(13) | 12081(5) | 10727(3) | 52(2) |
| C(6) | -4409(12) | 11388(4) | 10424(3) | 48(2) |
| C(7) | -173(10) | 9783(4) | 10767(2) | 30(1) |
| C(8) | 1702(10) | 9490(4) | 9828(2) | 29(1) |
| C(9) | 689(11) | 8025(4) | 10398(2) | 34(1) |
| C(10) | -998(10) | 8666(4) | 10779(2) | 30(1) |
| C(11) | 1962(9) | 9865(4) | 9188(2) | 29(1) |
| C(12) | 4006(12) | 9623(5) | 8867(3) | 41(2) |
| C(13) | 4257(12) | 9922(5) | 8268(3) | 51(2) |
| C(14) | 2504(12) | 10475(5) | 7978(3) | 45(2) |
| C(15) | 507(12) | 10721(5) | 8295(3) | 49(2) |
| C(16) | 230(12) | 10415(5) | 8896(3) | 45(2) |

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

| | | | |
|---|---|---|---|
| O(1)-C(8) | 1.418(6) | O(1)-C(7) | 1.423(6) |
| O(2)-C(8) | 1.426(6) | O(2)-C(9) | 1.430(6) |
| O(3)-C(10) | 1.407(6) | O(3)-C(1) | 1.423(7) |
| O(4)-C(1) | 1.386(7) | O(4)-C(1') | 1.439(6) |
| O(5)-C(3) | 1.436(7) | O(5)-C(6) | 1.442(6) |
| C(1)-C(2) | 1.525(8) | C(2)-C(3) | 1.516(8) |
| C(3)-C(4) | 1.518(7) | C(3)-C(7) | 1.522(7) |
| C(4)-C(5) | 1.300(8) | C(4)-C(4') | 1.49 |
| C(5)-C(6) | 1.504(9) | C(7)-C(10) | 1.525(7) |
| C(8)-C(11) | 1.490(8) | C(9)-C(10) | 1.515(7) |
| C(11)-C(16) | 1.369(8) | C(11)-C(12) | 1.386(8) |
| C(12)-C(13) | 1.373(8) | C(13)-C(14) | 1.379(9) |
| C(14)-C(15) | 1.362(9) | C(15)-C(16) | 1.380(8) |
| | | | |
| C(8)-O(1)-C(7) | 110.9(4) | C(8)-O(2)-C(9) | 110.4(4) |
| C(10)-O(3)-C(1) | 112.8(4) | C(1)-O(4)-C(1') | 112.6(5) |
| C(3)-O(5)-C(6) | 109.5(4) | O(4)-C(1)-O(3) | 112.2(5) |
| O(4)-C(1)-C(2) | 109.6(5) | O(3)-C(1)-C(2) | 112.1(5) |
| C(3)-C(2)-C(1) | 117.0(5) | O(5)-C(3)-C(4) | 103.5(4) |
| O(5)-C(3)-C(2) | 109.5(5) | C(4)-C(3)-C(2) | 113.2(5) |
| O(5)-C(3)-C(7) | 109.9(4) | C(4)-C(3)-C(7) | 113.1(5) |
| C(2)-C(3)-C(7) | 107.6(5) | C(5)-C(4)-C(4') | 128.3(4) |
| C(5)-C(4)-C(3) | 109.1(5) | C(4')-C(4)-C(3) | 122.6(3) |
| C(4)-C(5)-C(6) | 111.6(5) | O(5)-C(6)-C(5) | 102.9(5) |
| O(1)-C(7)-C(3) | 109.8(4) | O(1)-C(7)-C(10) | 110.2(4) |
| C(3)-C(7)-C(10) | 109.2(4) | O(1)-C(8)-O(2) | 110.3(4) |
| O(1)-C(8)-C(11) | 109.9(4) | O(2)-C(8)-C(11) | 107.3(4) |
| O(2)-C(9)-C(10) | 108.7(4) | O(3)-C(10)-C(9) | 109.3(4) |
| O(3)-C(10)-C(7) | 109.4(4) | C(9)-C(10)-C(7) | 108.8(4) |
| C(16)-C(11)-C(12) | 118.6(5) | C(16)-C(11)-C(8) | 122.6(5) |
| C(12)-C(11)-C(8) | 118.8(5) | C(13)-C(12)-C(11) | 120.2(6) |
| C(12)-C(13)-C(14) | 120.8(6) | C(15)-C(14)-C(13) | 118.9(6) |
| C(14)-C(15)-C(16) | 120.7(6) | C(11)-C(16)-C(15) | 120.8(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) | 42(2) | 26(2) | 33(2) | -2(2) | 6(2) | 2(2) |
| O(2) | 43(2) | 22(2) | 34(2) | -4(2) | 4(2) | -2(2) |
| O(3) | 34(2) | 40(2) | 37(2) | 10(2) | 6(2) | 5(2) |
| O(4) | 30(2) | 35(2) | 48(2) | 11(2) | 5(2) | -2(2) |
| O(5) | 33(2) | 34(2) | 47(2) | 1(2) | -2(2) | 4(2) |
| C(1) | 35(3) | 46(4) | 30(3) | 6(3) | 9(3) | 5(3) |
| C(1') | 54(4) | 36(3) | 61(4) | 10(3) | 6(4) | -3(3) |
| C(2) | 33(3) | 38(3) | 38(3) | -6(3) | 1(3) | 0(3) |
| C(3) | 38(3) | 28(3) | 34(3) | -8(3) | 1(3) | -2(3) |
| C(4) | 61(4) | 34(3) | 39(3) | -16(3) | 10(4) | -11(4) |
| C(5) | 71(5) | 30(3) | 55(4) | 0(3) | 16(4) | 4(4) |
| C(6) | 54(4) | 41(3) | 49(3) | 12(3) | 5(3) | 10(4) |
| C(7) | 30(3) | 33(3) | 26(3) | -4(2) | -2(3) | -1(3) |
| C(8) | 30(3) | 22(2) | 36(3) | -7(3) | -2(3) | 1(3) |
| C(9) | 41(3) | 24(3) | 38(3) | 2(2) | 5(3) | 4(3) |
| C(10) | 26(3) | 32(3) | 31(3) | 2(2) | 0(3) | 0(3) |
| C(11) | 33(3) | 23(3) | 32(3) | -4(2) | 1(3) | 1(3) |
| C(12) | 41(3) | 43(4) | 40(3) | 8(3) | 1(3) | 7(3) |
| C(13) | 45(4) | 56(4) | 51(4) | 9(3) | 7(4) | 12(4) |
| C(14) | 60(4) | 43(3) | 31(3) | 7(3) | 3(3) | 6(4) |
| C(15) | 47(4) | 58(4) | 40(4) | 1(3) | -6(3) | 12(4) |
| C(16) | 42(3) | 52(4) | 39(3) | -3(3) | 3(3) | 7(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(1A) | -2316(10) | 8625(5) | 12190(3) | 45 |
| H(1'A) | -7069(12) | 7347(4) | 11670(3) | 75 |
| H(1'B) | -5178(12) | 7366(4) | 12195(3) | 75 |
| H(1'C) | -4426(12) | 7065(4) | 11528(3) | 75 |
| H(2A) | -3768(11) | 10305(4) | 11902(3) | 43 |
| H(2B) | -1033(11) | 10191(4) | 11983(3) | 43 |
| H(4'A) | 2060(9) | 11573(4) | 11421(2) | 93 |
| H(4'B) | 258(9) | 11897(4) | 11920(2) | 93 |
| H(4'C) | 1042(9) | 12689(4) | 11423(2) | 93 |
| H(5A) | -2483(13) | 12782(5) | 10647(3) | 62 |
| H(6A) | -5996(12) | 11667(4) | 10459(3) | 58 |
| H(6B) | -4036(12) | 11285(4) | 9996(3) | 58 |
| H(7A) | 1354(10) | 9837(4) | 10977(2) | 36 |
| H(8A) | 3246(10) | 9498(4) | 10033(2) | 35 |
| H(9A) | 2244(11) | 8018(4) | 10586(2) | 41 |
| H(9B) | 121(11) | 7322(4) | 10373(2) | 41 |
| H(10A) | -2601(10) | 8617(4) | 10610(2) | 36 |
| H(12A) | 5211(12) | 9257(5) | 9059(3) | 50 |
| H(13A) | 5627(12) | 9749(5) | 8056(3) | 61 |
| H(14A) | 2682(12) | 10677(5) | 7572(3) | 54 |
| H(15A) | -682(12) | 11099(5) | 8105(3) | 58 |
| H(16A) | -1150(12) | 10585(5) | 9105(3) | 53 |

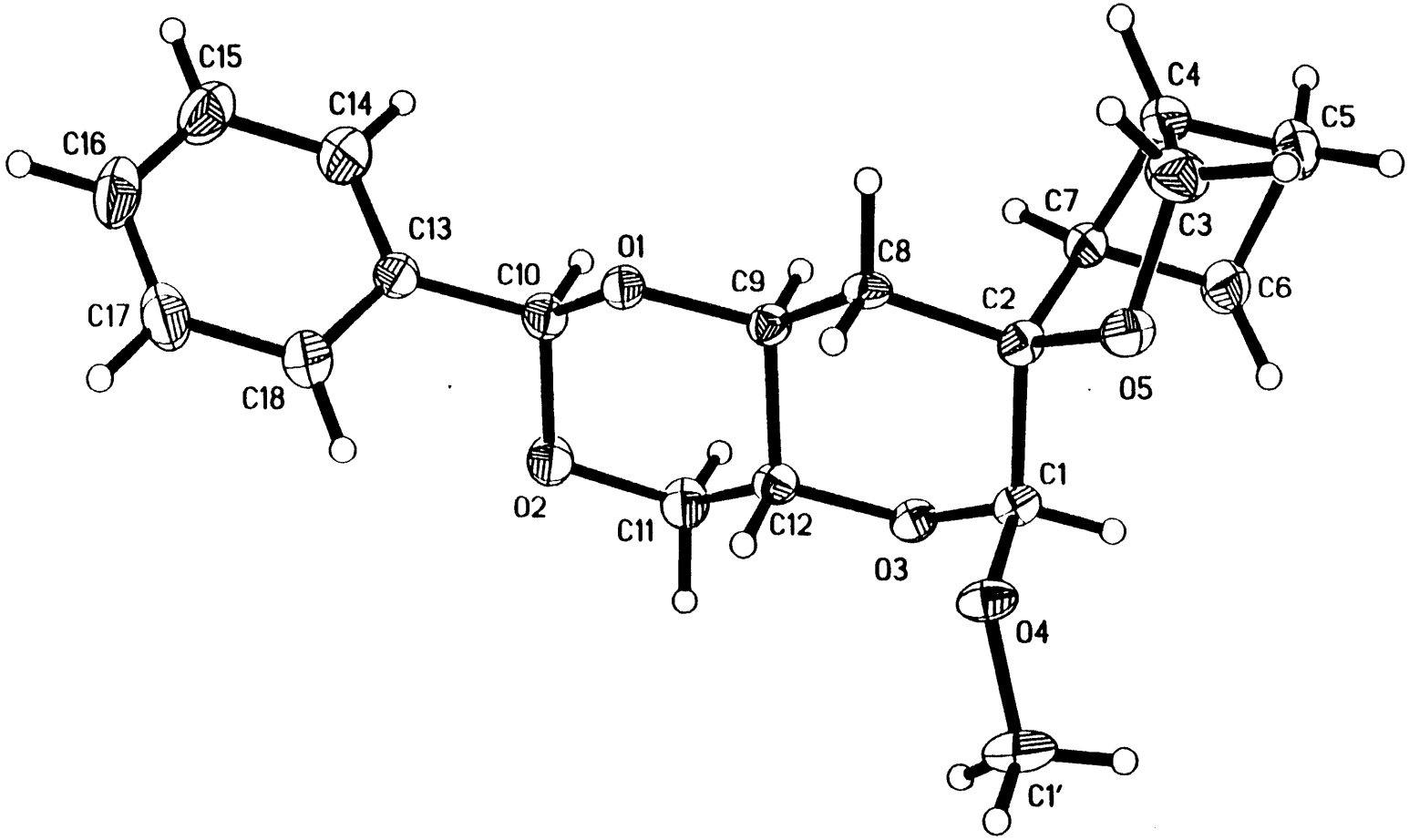
C15
C14
C16
C13
C17
C18
C10
O1
C9
C8
C7
C4
C5
C3
C6
C2
O5
O2
C11
C12
C1
O3
O4
C1'

Table 1. Crystal data and structure refinement for 1.

| | |
|---|---|
| Identification code | 9803 |
| Empirical formula | $C_{19}H_{24}O_5$ |
| Formula weight | 332.38 |
| Temperature | 190(2) K |
| Wavelength | 0.71073 Å |
| Crystal system | Monoclinic |
| Space group | $P2_1$ |
| Unit cell dimensions | $a$ = 5.7623(7) Å alpha = 90°<br>$b$ = 12.574(2) Å beta = 99.873(13)°<br>$c$ = 12.028(2) Å gamma = 90° |
| Volume, Z | 858.6(2) Å$^3$, 2 |
| Density (calculated) | 1.286 Mg/m$^3$ |
| Absorption coefficient | 0.092 mm$^{-1}$ |
| F(000) | 356 |
| Crystal size | 0.62 x 0.62 x 0.17 mm |
| θ range for data collection | 3.24 to 25.00° |
| Limiting indices | $-1 \le h \le 6$, $-1 \le k \le 14$, $-14 \le l \le 14$ |
| Reflections collected | 1999 |
| Independent reflections | 1729 ($R_{int}$ = 0.0122) |
| Absorption correction | Semi-empirical based on psi scan data |
| Max. and min. transmission | 0.582 and 0.551 |
| Refinement method | Full-matrix least-squares on $F^2$ |
| Data / restraints / parameters | 1729 / 1 / 217 |
| Goodness-of-fit on $F^2$ | 1.061 |
| Final R indices [$I>2\sigma(I)$] | R1 = 0.0299, wR2 = 0.0736 |
| R indices (all data) | R1 = 0.0323, wR2 = 0.0751 |
| Absolute structure parameter | -0.2(11) |
| Largest diff. peak and hole | 0.157 and -0.178 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) | 975(3) | 1262(1) | 1930(1) | 32(1) |
| O(2) | 2278(3) | 2577(1) | 3273(1) | 45(1) |
| O(3) | 277(2) | 3868(1) | 570(1) | 31(1) |
| O(4) | -3742(2) | 3663(1) | -109(1) | 34(1) |
| O(5) | -3028(2) | 2354(1) | -1785(1) | 37(1) |
| C(1) | -1488(3) | 3645(2) | -394(2) | 29(1) |
| C(2) | -1075(3) | 2554(2) | -891(2) | 29(1) |
| C(3) | -2273(5) | 1569(2) | -2513(2) | 51(1) |
| C(4) | 358(5) | 1706(2) | -2465(2) | 46(1) |
| C(5) | 1116(5) | 2528(3) | -3288(2) | 58(1) |
| C(6) | 1278(5) | 3388(2) | -2378(2) | 50(1) |
| C(7) | 1052(4) | 2519(2) | -1490(2) | 34(1) |
| C(8) | -930(4) | 1690(2) | 21(2) | 29(1) |
| C(9) | 881(4) | 2011(2) | 1022(2) | 29(1) |
| C(10) | 2740(4) | 1567(2) | 2849(2) | 37(1) |
| C(11) | 2192(5) | 3392(2) | 2437(2) | 43(1) |
| C(12) | 308(4) | 3097(2) | 1446(2) | 32(1) |
| C(1') | -4520(4) | 4713(2) | 73(3) | 47(1) |
| C(13) | 2779(4) | 756(2) | 3772(2) | 36(1) |
| C(14) | 4551(5) | 8(2) | 3973(2) | 51(1) |
| C(15) | 4522(6) | -768(3) | 4802(2) | 60(1) |
| C(16) | 2735(6) | -782(3) | 5414(2) | 58(1) |
| C(17) | 966(6) | -42(3) | 5216(2) | 56(1) |
| C(18) | 988(5) | 730(2) | 4399(2) | 47(1) |

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

| | | | |
|---|---|---|---|
| O(1)-C(10) | 1.421(3) | O(1)-C(9) | 1.437(2) |
| O(2)-C(10) | 1.411(3) | O(2)-C(11) | 1.430(3) |
| O(3)-C(12) | 1.430(3) | O(3)-C(1) | 1.433(3) |
| O(4)-C(1) | 1.400(2) | O(4)-C(1') | 1.424(3) |
| O(5)-C(3) | 1.435(3) | O(5)-C(2) | 1.439(2) |
| C(1)-C(2) | 1.531(3) | C(2)-C(7) | 1.525(3) |
| C(2)-C(8) | 1.536(3) | C(3)-C(4) | 1.517(4) |
| C(4)-C(5) | 1.545(4) | C(4)-C(7) | 1.556(3) |
| C(5)-C(6) | 1.531(4) | C(6)-C(7) | 1.549(3) |
| C(8)-C(9) | 1.507(3) | C(9)-C(12) | 1.513(3) |
| C(10)-C(13) | 1.505(3) | C(11)-C(12) | 1.514(3) |
| C(13)-C(14) | 1.379(4) | C(13)-C(18) | 1.379(3) |
| C(14)-C(15) | 1.397(4) | C(15)-C(16) | 1.365(4) |
| C(16)-C(17) | 1.370(5) | C(17)-C(18) | 1.382(4) |

| | | | |
|---|---|---|---|
| C(10)-O(1)-C(9) | 110.0(2) | C(10)-O(2)-C(11) | 112.2(2) |
| C(12)-O(3)-C(1) | 112.4(2) | C(1)-O(4)-C(1') | 112.5(2) |
| C(3)-O(5)-C(2) | 107.2(2) | O(4)-C(1)-O(3) | 111.0(2) |
| O(4)-C(1)-C(2) | 108.8(2) | O(3)-C(1)-C(2) | 110.8(2) |
| O(5)-C(2)-C(7) | 103.3(2) | O(5)-C(2)-C(1) | 107.1(2) |
| C(7)-C(2)-C(1) | 113.6(2) | O(5)-C(2)-C(8) | 110.5(2) |
| C(7)-C(2)-C(8) | 111.6(2) | C(1)-C(2)-C(8) | 110.3(2) |
| O(5)-C(3)-C(4) | 107.7(2) | C(3)-C(4)-C(5) | 116.2(2) |
| C(3)-C(4)-C(7) | 103.3(2) | C(5)-C(4)-C(7) | 88.8(2) |
| C(6)-C(5)-C(4) | 90.2(2) | C(5)-C(6)-C(7) | 89.5(2) |
| C(2)-C(7)-C(6) | 118.4(2) | C(2)-C(7)-C(4) | 104.5(2) |
| C(6)-C(7)-C(4) | 89.1(2) | C(9)-C(8)-C(2) | 109.1(2) |
| O(1)-C(9)-C(8) | 111.2(2) | O(1)-C(9)-C(12) | 108.5(2) |
| C(8)-C(9)-C(12) | 110.5(2) | O(2)-C(10)-O(1) | 111.7(2) |
| O(2)-C(10)-C(13) | 108.9(2) | O(1)-C(10)-C(13) | 108.0(2) |
| O(2)-C(11)-C(12) | 108.2(2) | O(3)-C(12)-C(9) | 109.8(2) |
| O(3)-C(12)-C(11) | 109.3(2) | C(9)-C(12)-C(11) | 108.5(2) |
| C(14)-C(13)-C(18) | 119.3(2) | C(14)-C(13)-C(10) | 120.5(2) |
| C(18)-C(13)-C(10) | 120.1(2) | C(13)-C(14)-C(15) | 120.1(2) |
| C(16)-C(15)-C(14) | 119.7(3) | C(15)-C(16)-C(17) | 120.4(3) |
| C(16)-C(17)-C(18) | 120.2(3) | C(13)-C(18)-C(17) | 120.3(3) |

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) | 43(1) | 24(1) | 29(1) | -1(1) | 5(1) | -3(1) |
| O(2) | 71(1) | 29(1) | 33(1) | -5(1) | 4(1) | -7(1) |
| O(3) | 32(1) | 22(1) | 38(1) | 0(1) | 6(1) | -4(1) |
| O(4) | 26(1) | 24(1) | 55(1) | -3(1) | 14(1) | -1(1) |
| O(5) | 33(1) | 34(1) | 41(1) | -7(1) | -3(1) | 4(1) |
| C(1) | 25(1) | 26(1) | 37(1) | 2(1) | 6(1) | 0(1) |
| C(2) | 25(1) | 26(1) | 33(1) | -1(1) | 0(1) | 0(1) |
| C(3) | 54(2) | 50(2) | 46(1) | -17(1) | -4(1) | 6(1) |
| C(4) | 55(2) | 46(2) | 35(1) | -3(1) | 3(1) | 19(1) |
| C(5) | 67(2) | 74(2) | 34(1) | 7(1) | 12(1) | 23(2) |
| C(6) | 55(2) | 54(2) | 45(1) | 12(1) | 21(1) | 9(1) |
| C(7) | 35(1) | 37(1) | 30(1) | 3(1) | 5(1) | 9(1) |
| C(8) | 32(1) | 20(1) | 36(1) | -5(1) | 9(1) | -1(1) |
| C(9) | 31(1) | 24(1) | 32(1) | 0(1) | 8(1) | -1(1) |
| C(10) | 45(1) | 33(1) | 32(1) | -3(1) | 5(1) | -3(1) |
| C(11) | 62(2) | 28(1) | 38(1) | -3(1) | 4(1) | -11(1) |
| C(12) | 37(1) | 24(1) | 37(1) | -1(1) | 12(1) | -4(1) |
| C(1') | 37(1) | 27(1) | 81(2) | -8(1) | 23(1) | 2(1) |
| C(13) | 46(1) | 32(1) | 29(1) | -3(1) | 2(1) | -2(1) |
| C(14) | 53(2) | 51(2) | 49(1) | 4(1) | 7(1) | 6(1) |
| C(15) | 67(2) | 50(2) | 58(2) | 11(2) | -6(1) | 10(2) |
| C(16) | 82(2) | 50(2) | 36(1) | 9(1) | -6(1) | -14(2) |
| C(17) | 74(2) | 59(2) | 37(1) | 2(1) | 16(1) | -9(2) |
| C(18) | 56(2) | 45(2) | 39(1) | 2(1) | 11(1) | 3(1) |

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

| | x | y | z | U(eq) |
|---|---|---|---|---|
| H(1A) | -1404(3) | 4200(2) | -981(2) | 35 |
| H(3A) | -3114(5) | 1667(2) | -3296(2) | 62 |
| H(3B) | -2618(5) | 846(2) | -2259(2) | 62 |
| H(4A) | 1288(5) | 1030(2) | -2386(2) | 55 |
| H(5A) | 2645(5) | 2361(3) | -3517(2) | 69 |
| H(5B) | -108(5) | 2670(3) | -3956(2) | 69 |
| H(6A) | -52(5) | 3898(2) | -2498(2) | 60 |
| H(6B) | 2807(5) | 3767(2) | -2241(2) | 60 |
| H(7A) | 2567(4) | 2349(2) | -981(2) | 41 |
| H(8A) | -2485(4) | 1603(2) | 255(2) | 35 |
| H(8B) | -481(4) | 1002(2) | -282(2) | 35 |
| H(9A) | 2462(4) | 2042(2) | 786(2) | 35 |
| H(10A) | 4307(4) | 1578(2) | 2599(2) | 44 |
| H(11A) | 3739(5) | 3453(2) | 2189(2) | 52 |
| H(11B) | 1815(5) | 4084(2) | 2754(2) | 52 |
| H(12A) | -1264(4) | 3076(2) | 1692(2) | 38 |
| H(1'A) | -6100(4) | 4685(2) | 270(3) | 70 |
| H(1'B) | -4564(4) | 5133(2) | -616(3) | 70 |
| H(1'C) | -3430(4) | 5044(2) | 692(3) | 70 |
| H(14A) | 5795(5) | 20(2) | 3547(2) | 61 |
| H(15A) | 5741(6) | -1285(3) | 4939(2) | 72 |
| H(16A) | 2718(6) | -1306(3) | 5981(2) | 70 |
| H(17A) | -280(6) | -60(3) | 5640(2) | 67 |
| H(18A) | -236(5) | 1244(2) | 4269(2) | 56 |

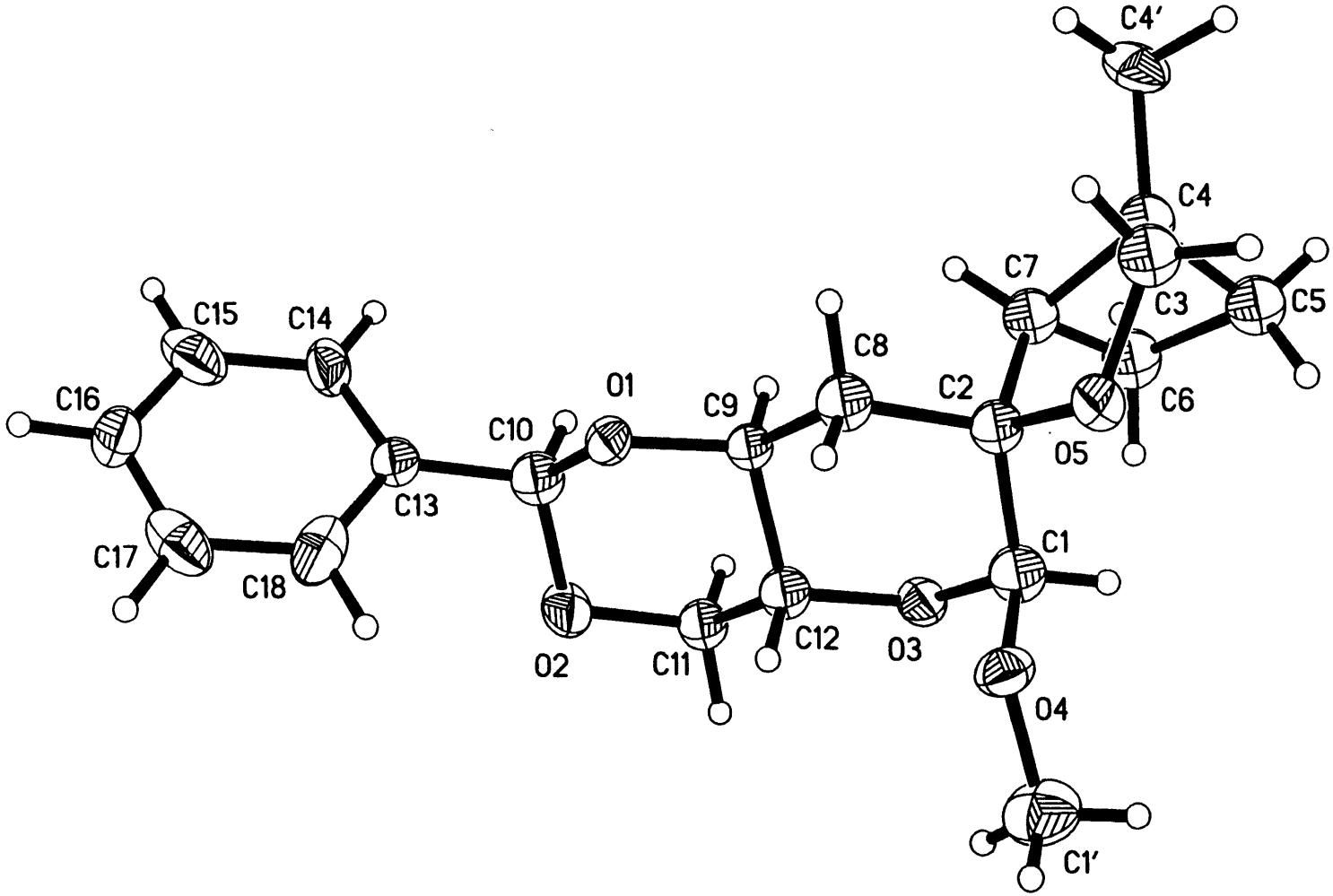
C4'
C4
C7
C3
C5
C15
C14
C8
C16
O1
C9
C2
C6
C10
O5
C13
C1
C17
C18
O2
C11
C12
O3
O4
C1'

Table 1. Crystal data and structure refinement for 1.

| | |
|---|---|
| Identification code | 1 |
| Empirical formula | $C_{20}H_{26}O_5$ |
| Formula weight | 346.41 |
| Temperature | 190(2) K |
| Wavelength | 0.71073 Å |
| Crystal system | Orthorhombic |
| Space group | $P2_12_12_1$ |
| Unit cell dimensions | $a$ = 10.716(3) Å alpha = 90°<br>$b$ = 11.797(2) Å beta = 90°<br>$c$ = 14.485(4) Å gamma = 90° |
| Volume, Z | 1831.1(8) $Å^3$, 4 |
| Density (calculated) | 1.257 $Mg/m^3$ |
| Absorption coefficient | 0.089 $mm^{-1}$ |
| F(000) | 744 |
| Crystal size | 0.57 x 0.13 x 0.12 mm |
| θ range for data collection | 2.23 to 23.50° |
| Limiting indices | $-1 \le h \le 12$, $-13 \le k \le 1$, $-16 \le l \le 1$ |
| Reflections collected | 1925 |
| Independent reflections | 1813 ($R_{int}$ = 0.0533) |
| Absorption correction | Not applied |
| Refinement method | Full-matrix least-squares on $F^2$ |
| Data / restraints / parameters | 1809 / 0 / 162 |
| Goodness-of-fit on $F^2$ | 1.084 |
| Final R indices [I>2σ(I)] | R1 = 0.1213, wR2 = 0.3145 |
| R indices (all data) | R1 = 0.2143, wR2 = 0.4113 |
| Absolute structure parameter | 5(9) |
| Extinction coefficient | 0.011(5) |
| Largest diff. peak and hole | 0.528 and -0.483 $eÅ^{-3}$ |

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) | 2367(11) | 7149(9) | 8313(7) | 41(3) |
| O(2) | 1923(13) | 8933(10) | 7653(8) | 55(4) |
| O(3) | 2312(11) | 9314(9) | 10129(7) | 44(3) |
| O(4) | 4377(12) | 8871(10) | 10619(8) | 50(3) |
| O(5) | 3588(13) | 7069(10) | 11548(8) | 53(3) |
| C(1) | 3056(17) | 8782(17) | 10823(13) | 54(5) |
| C(1') | 4851(23) | 9965(16) | 10676(16) | 79(7) |
| C(2) | 2762(16) | 7537(15) | 10882(12) | 44(4) |
| C(3) | 3030(17) | 6170(17) | 12051(14) | 58(5) |
| C(4) | 1643(18) | 6534(16) | 12133(13) | 53(5) |
| C(4') | 733(22) | 5571(16) | 12279(14) | 73(7) |
| C(5) | 1436(20) | 7597(16) | 12782(13) | 59(5) |
| C(6) | 835(20) | 8175(18) | 11908(13) | 64(6) |
| C(7) | 1392(18) | 7294(16) | 11258(13) | 53(5) |
| C(8) | 2924(17) | 6957(15) | 9944(12) | 50(5) |
| C(9) | 2184(16) | 7562(14) | 9216(10) | 36(4) |
| C(10) | 1591(19) | 7765(16) | 7677(13) | 51(5) |
| C(11) | 1727(17) | 9459(16) | 8546(11) | 46(5) |
| C(12) | 2545(17) | 8831(15) | 9231(11) | 45(5) |
| C(13) | 1694(16) | 7277(15) | 6756(12) | 41(4) |
| C(14) | 734(20) | 6727(16) | 6336(11) | 52(5) |
| C(15) | 893(24) | 6287(18) | 5467(15) | 77(7) |
| C(16) | 1936(22) | 6389(17) | 4979(14) | 62(6) |
| C(17) | 2925(23) | 6989(18) | 5372(15) | 71(7) |
| C(18) | 2763(23) | 7420(18) | 6239(14) | 68(6) |

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

| | | | |
|---|---|---|---|
| O(1)-C(9) | 1.41(2) | O(1)-C(10) | 1.44(2) |
| O(2)-C(10) | 1.42(2) | O(2)-C(11) | 1.45(2) |
| O(3)-C(1) | 1.43(2) | O(3)-C(12) | 1.44(2) |
| O(4)-C(1') | 1.39(2) | O(4)-C(1) | 1.45(2) |
| O(5)-C(3) | 1.42(2) | O(5)-C(2) | 1.42(2) |
| C(1)-C(2) | 1.50(3) | C(2)-C(8) | 1.53(2) |
| C(2)-C(7) | 1.59(3) | C(3)-C(4) | 1.55(3) |
| C(4)-C(4') | 1.51(3) | C(4)-C(7) | 1.58(3) |
| C(4)-C(5) | 1.58(3) | C(5)-C(6) | 1.58(3) |
| C(6)-C(7) | 1.52(3) | C(8)-C(9) | 1.50(2) |
| C(9)-C(12) | 1.55(2) | C(10)-C(13) | 1.46(2) |
| C(11)-C(12) | 1.52(2) | C(13)-C(14) | 1.36(2) |
| C(13)-C(18) | 1.38(3) | C(14)-C(15) | 1.37(3) |
| C(15)-C(16) | 1.33(3) | C(16)-C(17) | 1.40(3) |
| C(17)-C(18) | 1.37(3) | | |

| | | | |
|---|---|---|---|
| C(9)-O(1)-C(10) | 109.8(12) | C(10)-O(2)-C(11) | 110.9(13) |
| C(1)-O(3)-C(12) | 111.4(13) | C(1')-O(4)-C(1) | 114(2) |
| C(3)-O(5)-C(2) | 112.2(14) | O(3)-C(1)-O(4) | 112(2) |
| O(3)-C(1)-C(2) | 111(2) | O(4)-C(1)-C(2) | 107(2) |
| O(5)-C(2)-C(1) | 107(2) | O(5)-C(2)-C(8) | 111.0(14) |
| C(1)-C(2)-C(8) | 111(2) | O(5)-C(2)-C(7) | 105.8(13) |
| C(1)-C(2)-C(7) | 113(2) | C(8)-C(2)-C(7) | 109(2) |
| O(5)-C(3)-C(4) | 104(2) | C(4')-C(4)-C(3) | 115(2) |
| C(4')-C(4)-C(7) | 115(2) | C(3)-C(4)-C(7) | 105(2) |
| C(4')-C(4)-C(5) | 115(2) | C(3)-C(4)-C(5) | 114(2) |
| C(7)-C(4)-C(5) | 90.2(14) | C(6)-C(5)-C(4) | 85.6(14) |
| C(7)-C(6)-C(5) | 92(2) | C(6)-C(7)-C(4) | 87.6(14) |
| C(6)-C(7)-C(2) | 117(2) | C(4)-C(7)-C(2) | 103(2) |
| C(9)-C(8)-C(2) | 111(2) | O(1)-C(9)-C(8) | 114.4(13) |
| O(1)-C(9)-C(12) | 108.2(13) | C(8)-C(9)-C(12) | 108.6(14) |
| O(2)-C(10)-O(1) | 111(2) | O(2)-C(10)-C(13) | 110(2) |
| O(1)-C(10)-C(13) | 110.1(14) | O(2)-C(11)-C(12) | 106.9(14) |
| O(3)-C(12)-C(11) | 107.2(14) | O(3)-C(12)-C(9) | 110.6(13) |
| C(11)-C(12)-C(9) | 108.6(14) | C(14)-C(13)-C(18) | 116(2) |
| C(14)-C(13)-C(10) | 123(2) | C(18)-C(13)-C(10) | 121(2) |
| C(13)-C(14)-C(15) | 120(2) | C(16)-C(15)-C(14) | 124(3) |
| C(15)-C(16)-C(17) | 118(2) | C(18)-C(17)-C(16) | 118(2) |
| C(17)-C(18)-C(13) | 124(2) | | |

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) | 56(7) | 28(6) | 38(6) | -5(5) | 6(6) | 4(6) |
| O(2) | 88(10) | 35(6) | 42(7) | 9(6) | 1(7) | 7(7) |
| O(3) | 56(8) | 33(6) | 42(6) | -1(6) | 8(6) | 1(6) |
| O(4) | 56(7) | 38(7) | 58(8) | -7(7) | 5(7) | -10(6) |
| O(5) | 72(8) | 45(7) | 42(7) | 4(6) | 0(7) | -6(7) |
| C(1') | 91(18) | 46(12) | 99(18) | -9(13) | 7(15) | 1(14) |
| C(4') | 100(17) | 44(11) | 74(15) | 28(12) | -15(15) | -11(12) |
| C(14) | 71(13) | 53(12) | 31(10) | 5(10) | -2(10) | 4(11) |
| C(15) | 102(19) | 53(13) | 77(16) | 22(13) | 38(15) | 9(14) |
| C(16) | 85(16) | 52(13) | 48(12) | -11(11) | 3(12) | -2(13) |
| C(17) | 80(16) | 63(14) | 71(15) | 24(13) | 30(13) | 24(14) |
| C(18) | 90(16) | 57(13) | 58(13) | -13(11) | -18(13) | 9(13) |

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

| | x | y | z | U(eq) |
|---|---|---|---|---|
| H(1A) | 2887(17) | 9139(17) | 11421(13) | 65 |
| H(1'A) | 5726(23) | 9956(16) | 10533(16) | 118 |
| H(1'B) | 4733(23) | 10251(16) | 11290(16) | 118 |
| H(1'C) | 4422(23) | 10444(16) | 10244(16) | 118 |
| H(3A) | 3409(17) | 6092(17) | 12656(14) | 69 |
| H(3B) | 3108(17) | 5458(17) | 11722(14) | 69 |
| H(4'A) | -99(22) | 5868(16) | 12321(14) | 109 |
| H(4'B) | 937(22) | 5178(16) | 12839(14) | 109 |
| H(4'C) | 783(22) | 5054(16) | 11768(14) | 109 |
| H(5A) | 858(20) | 7468(16) | 13287(13) | 71 |
| H(5B) | 2199(20) | 7953(16) | 12995(13) | 71 |
| H(6A) | -70(20) | 8168(18) | 11917(13) | 77 |
| H(6B) | 1144(20) | 8935(18) | 11797(13) | 77 |
| H(7A) | 810(18) | 6974(16) | 10805(13) | 64 |
| H(8A) | 3800(17) | 6956(15) | 9774(12) | 60 |
| H(8B) | 2647(17) | 6176(15) | 9985(12) | 60 |
| H(9A) | 1296(16) | 7496(14) | 9369(10) | 44 |
| H(10A) | 722(19) | 7702(16) | 7881(13) | 62 |
| H(11A) | 857(17) | 9403(16) | 8725(11) | 55 |
| H(11B) | 1956(17) | 10254(16) | 8524(11) | 55 |
| H(12A) | 3426(17) | 8922(15) | 9066(11) | 54 |
| H(14A) | -28(20) | 6650(16) | 6636(11) | 62 |
| H(15A) | 231(24) | 5893(18) | 5205(15) | 93 |
| H(16A) | 2005(22) | 6070(17) | 4394(14) | 74 |
| H(17A) | 3670(23) | 7092(18) | 5054(15) | 86 |
| H(18A) | 3413(23) | 7836(18) | 6496(14) | 82 |