STUDIES TOWARD THE TOTAL SYNTHESIS OF PHYLLAEMBLIC ACID

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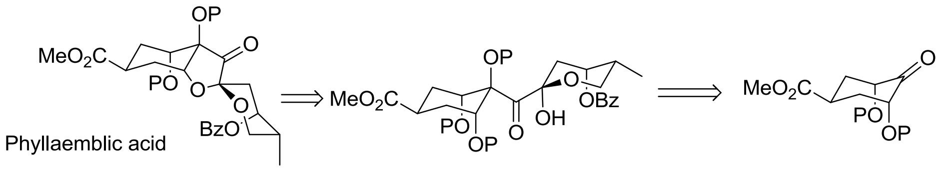
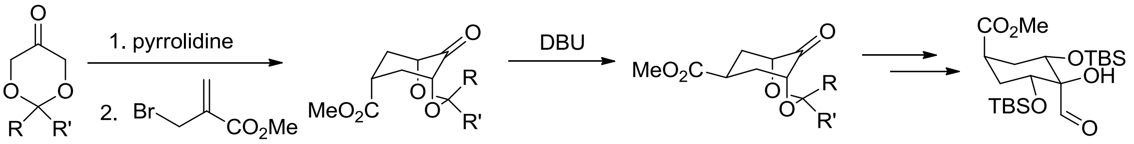
Abstract

Phyllaemblic acid is a highly oxygenated natural product isolated along with a number of related compounds from the roots of *Phyllanthis emblica* L. by Zhang *et al.* in 2000. The roots of this shrub have been used by the people in south-east Asia as an antiscorbutic and in the treatment of diverse ailments, especially those associated with the digestive organs. A total synthesis has yet to be reported.



A concise sequence has been developed which rapidly furnishes a range of *meso* bridged bicyclic ketones, in good yield and with complete diastereocontrol, utilizing on an α,α’-annelation reaction of 1,3-dioxan-5-ones. The bicyclic systems are shown to adopt chair-boat conformations in both solution and in the solid state. Single diastereomers are obtained in two cases with two different substituents. Stereochemical outcomes have been rationalized using steric and stereoelectronic arguments.



Carbon-carbon bond formation at the ketone carbonyl in these bicyclic systems is shown to be problematic. Ortho-acetal hydrolysis and diol reprotection as a *bis*-TBS ether provides a monocyclic system with increased ketone reactivity, allowing elaboration to an α-hydroxyaldehyde of appropriate stereochemistry for future application in a synthesis of the natural product. Preliminary studies towards this goal on a simplified model system are reported.

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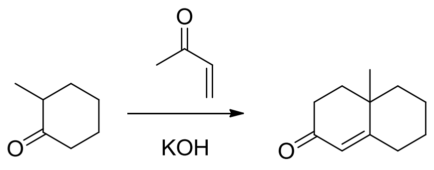
Abbreviations

Ac	- acetyl
aq	- aqueous
DABCO	- 1,4-diazabicyclo[2.2.2]octane
DCM	- dichloromethane
dd	- doublet of doublets
DMF	- dimethylformamide
DMSO	- dimethyl sulfoxide
dt	- doublet of triplets
EI	- electron ionisation
EtOAc	- Ethyl acetate
eqv	- equivalents
ES	- electrospray ionisation
h	- hour(s)
HWE	- Horner-Wadsworth-Emmons
HR	- high resolution
IR	- infra-red
*m*CPBA	- *meta*-chloroperbenzoic acid
MS	- mass spectrum
NMR	- nuclear magnetic resonance
nOe	- nuclear overhauser effect
GOESY	- gradient enhanced nuclear overhauser effect spectroscopy
R_f	- retention factor
rt	- room temperature
SM	- starting material
PENDANT	- polarization enhancement nurtured during attached nucleus testing
pTSA	- para-toluenesulfonic acid
TEA	- Triethylamine
THF	- tetrahydrofuran
TLC	- thin layer chromatography

Chapter One: Review of α,α'-annelation chemistry

1.1 Definition and history

An annelation is a reaction whereby a new ring structure is formed onto an existing molecule with the addition of two new bonds, specifically where one molecule already contains a ring. An annulation reaction is the same except that the condition of an existing ring is negated, but often the two terms are used interchangeably.[1] As a result annelation reactions are a broad category of reactions ranging from the well-known Robinson annelation to various cycloadditions. The Robinson annelation is where an α,β-unsaturated cyclic ketone is constructed from a ketone or aldehyde and methyl vinyl ketone, originally discovered in 1935 (Scheme 1).[2]



1 **2**

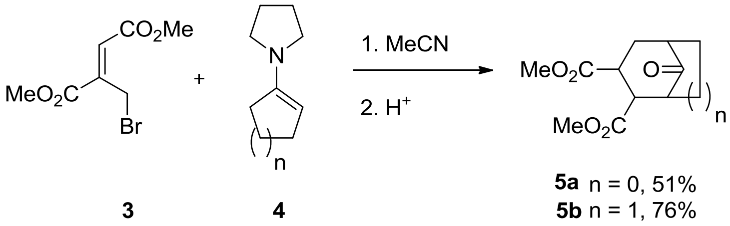
Scheme 1

This particular annelation and various related ones, exploit the relatively acidic α-hydrogens of carbonyl compounds in order to achieve bond formation through a Michael addition and subsequent aldol condensation.

An α,α’-annelation reaction is a specific subtype that involves forming a new ring joined at the two differing α positions of a ketone. This type of annelation has the useful feature that it retains the carbonyl functionality in the product, available for further synthetic transformations such as nucleophilic additions, reductions, olefinations and radical chemistry. This chapter is dedicated to the review of this particular subtype of annelation reactions, with a focus on the use of enamines to effect these transformations.

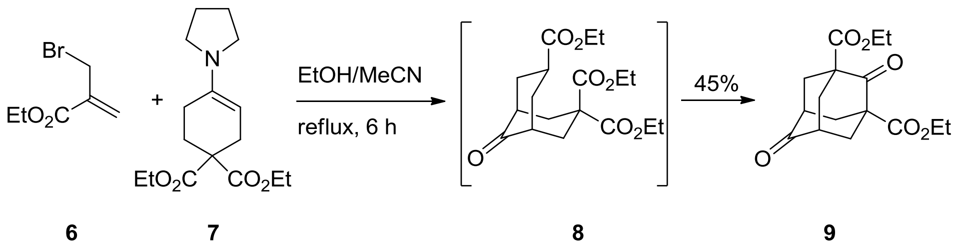
1.2 Lawton type α,α'-annelation reactions

Since the 1950s, enamines have become important compounds in organic chemistry, frequently being used as alternatives to enolates.[3] Enamines often applied to alkylation and acylation of ketones and aldehydes using a variety of reactive electrophiles.[4,5] In 1966 Lawton and co-workers[6] modified traditional enamine chemistry to achieve a double alkylation of a ketone. This technique was first reported in the synthesis of a set of bicylic keto-diesters from dimethyl γ-bromomesaconate and the pyrrolidine enamines of cyclopentanone and cyclohexanone (Scheme 2).



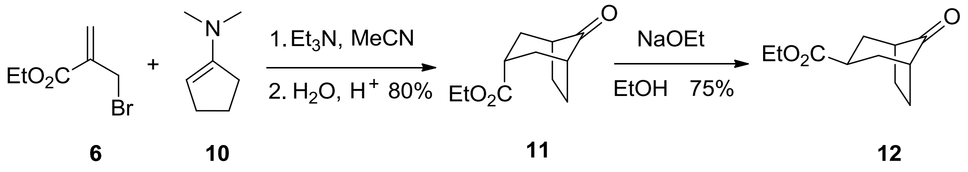
Scheme 2

Since this original publication, a number of related bicyclic systems have been constructed by adapting this methodology. Lawton and co-workers were not the only group to utilise this methodology, Stetter *et al.* applied it to the synthesis of a number of adamantane based structures, but did not isolate the bicycle **8** and obtained the cyclized product **9** instead. The first examples came shortly after Lawton's first paper on the subject (Scheme 3).[7,8]



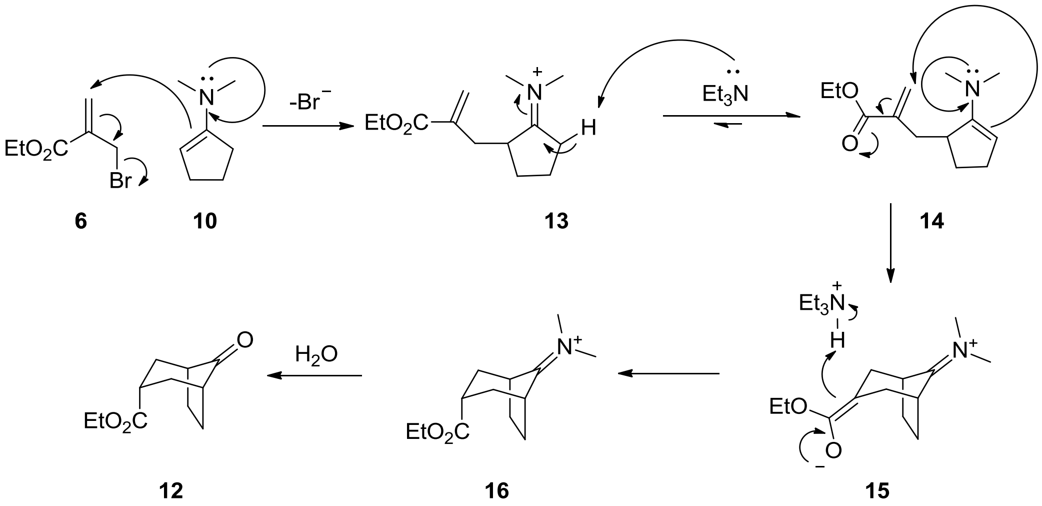
Scheme 3

In 1969 the synthesis of [3.2.1]-bicyclooctanone **12** was published by Lawton and co-workers.[9] In the presence of triethylamine, enamine **10** reacted with a *bis*-electrophile **6**, to give a bridged bicyclic ring structure **11** in a single step and in high yield (Scheme 4). They determined that the reaction was highly *endo* selective, placing the ester group axial on the six membered ring. As this was the undesired stereoisomer, epimerization was performed with sodium ethoxide in ethanol, which afforded **12** in good yield.



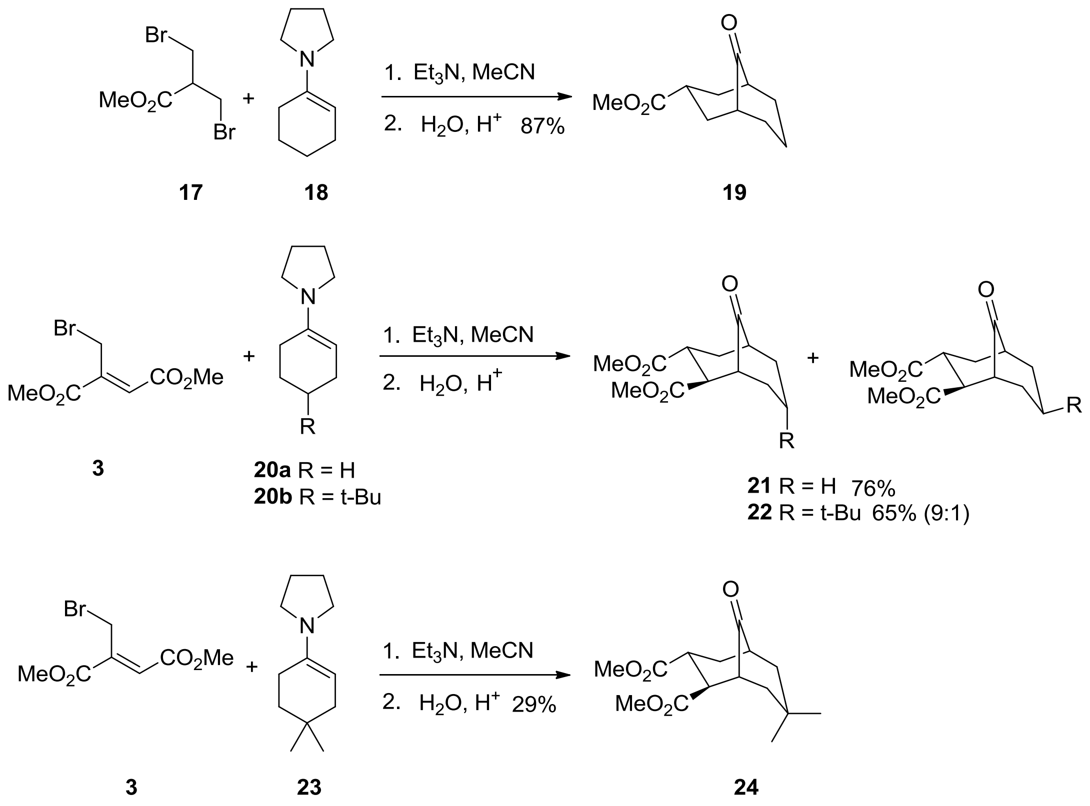
Scheme 4

The reaction mechanism was proposed to be a sequence of *C*-alkylation, tautomerism and a Michael reaction in which the *bis*-electrophile **6** acts as the annelating agent (Scheme 5). Stoichiometric triethylamine is added to the reaction mixture to facilitate enamine equilibration once the *C*-alkylation step has taken place, the resulting ammonium salt then re-protonates the enolate from the less hindered top face, resulting in the observed kinetic product following iminium hydrolysis under acidic conditions.



Scheme 5

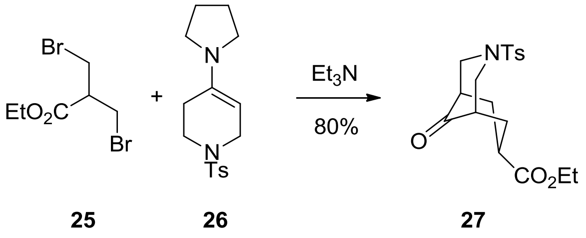
In 1970, Lawton reported the synthesis of several bicyclo[3.3.1]nonanone derivatives using this *α,α'*-annelation strategy (Scheme 6).[10] The α,α'-annelation reactions were carried out using at least one equivalent of base, refluxing overnight in anhydrous acetonitrile, with the final iminium hydrolysis step also performed at reflux under acidic conditions.



Scheme 6

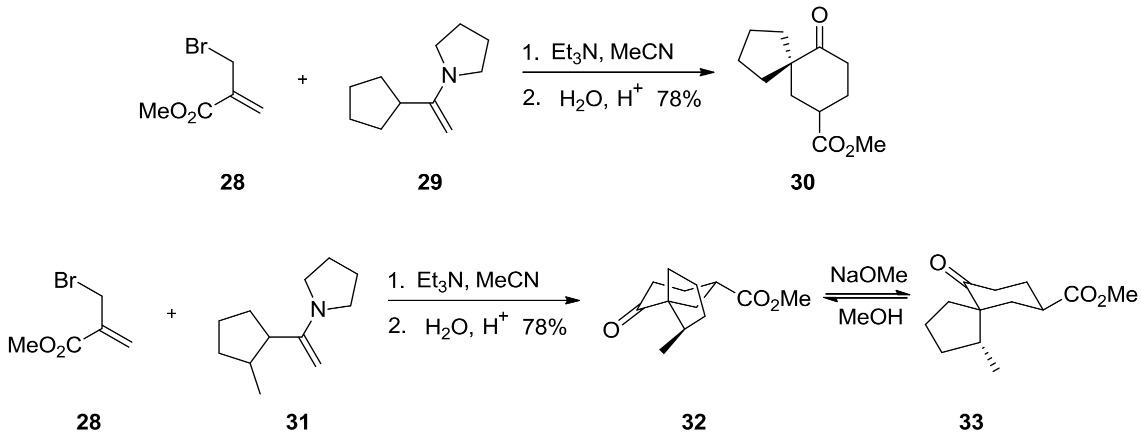
Substantial work was done to determine the configurations of these derivatives from epimerisation and lactonisation studies. The conformations of each bicyclic product were considered and a chair-boat type conformation was proposed to be the likely transition state during the Michael addition step. Significantly, the reaction of the pyrrolidine enamine of 4-*tert*-butylcyclohexanone with dimethyl γ-bromomesaconate allowed for two possible diastereomers depending upon the configuration of the tertiary butyl group, one of which appeared heavily favoured over the other. Lawton *et al.* theorized that the conformations of the transitions states during the reaction, and hence their relative energy, were responsible for the disparity. He describes that after the kinetic protonation the ester moiety must be axial and when the tertiary butyl group is equatorial, it is locked as a chair. Therefore when the tertiary butyl group is axial a boat conformation is much more energetically feasible and leads to the major product of **22** in Scheme 6.

The first example to produce a bicyclo[3.3.1]nonane which incorporated a heteroatom in the ring system was reported by Speckamp *et al.* in 1970.[11] Enamine **26** was reacted with **25** in the presence of triethylamine to give the adduct **27** in 80% yield (Scheme 7). These systems were then elaborated to produce aza-adamantanes as an example of this methodology's application.[12]



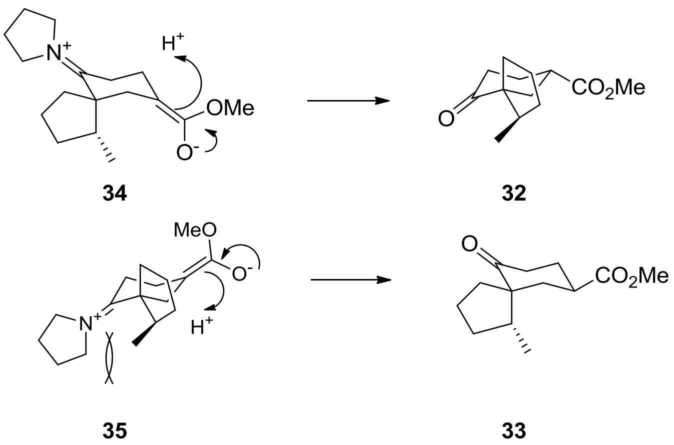
Scheme 7

Lawton demonstrated that α,α'-annelation reactions could also be applied to the synthesis of spirocyclic systems too, by forming the enamine from a ketone with a ring structure at the alpha position of the carbonyl group (Scheme 8).[13] The conditions employed for these reactions were similar to those previously published.



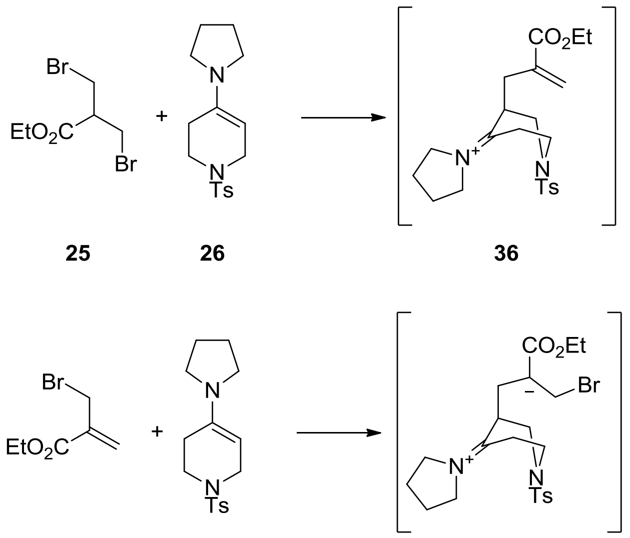
Scheme 8

In addition to demonstrating the utility of the reaction to create these aforementioned spirocycles, it allowed for further probing into the mechanism of the reaction. A methyl group on the existing ring on enamine **31** creates the possibility of two diastereomers as products. However, only one was observed. Epimerisation, under thermodynamic conditions, of **32** resulted in a mixture of **32** and **33** in a 3:7 ratio, respectively. This is suggestive that the transition state following the Michael addition step in the *α,α'*-annelation reaction favours the kinetic product since epimerisation, under thermodynamic control, leads to the alternate diastereomer as the major product. Thus, it was theorized that the steric interactions between the methyl group on the cyclopentane ring and the pyrrolidine moiety in the transition state (approaching **35**) were unfavourable, since otherwise it would have led to **33** being the product of the α,α'-annelation (Scheme 9).



Scheme 9

Speckamp *et al.* reported their continued work on aza-bicyclo[3.3.1]nonanes the following year, also revealing some mechanistic insight to the reaction, specifically the iminium-enamine equilibrium.[14] They proposed that the iminium ion resulting from initial *C*-alkylation would force the piperidine ring into a boat conformation, stabilised by an interaction of the electron deficient iminium with the electron rich oxygens in the tosyl group. They discovered that depending on the identity of the annelating agent, whether or not the iminium-enamine equilibrium required mediation by an external base. With dibromoester **25** as the annelating agent the reaction required the use of 2.2 equivalents of triethylamine to implement the ring closure. In the case of the bromoester **6** however, they proposed that that if the addition occurred in a Michael fashion it could intermolecularly mediate the equilibrium, allowing for ring closure (Scheme 10). Notably, conformational analysis was undertaken on these bicycles and it was determined that they adopt a chair-boat conformation in solution, determined by NMR techniques.

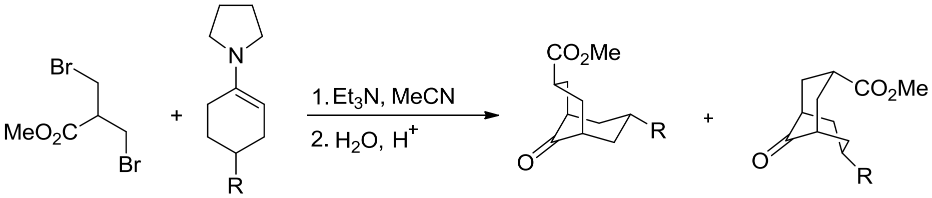


25 **26** **36**

6 **26** **37**

Scheme 10

In 1974, contrary to Lawton's investigations on the mechanistic details of *α,α'*-annelation reactions, Peters and co-workers reported some results that could not be explained by Lawton's description of the mechanism.[15] Enamines of substituted cyclohexanones were subjected to the standard reaction conditions in the presence of the *bis*-electrophile **17** to afford diastereomeric mixtures of *endo* bridged bicycles in 81-89% combined yield. Predictions based on Lawton's findings would suggest that **40** would be the dominating product, but it was in fact the other diastereomer **39** that was marginally preferred in each case (Scheme 11).

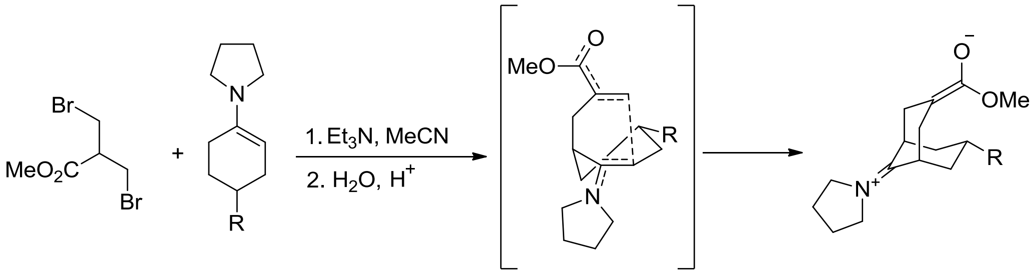


17 **38a** R = H
38b R = Me
38c R = i-Pr
38d R = t-Bu

39 **a** R = H **40**
b R = Me 63:37
c R = i-Pr 60:40
d R = t-Bu 59:41

Scheme 11

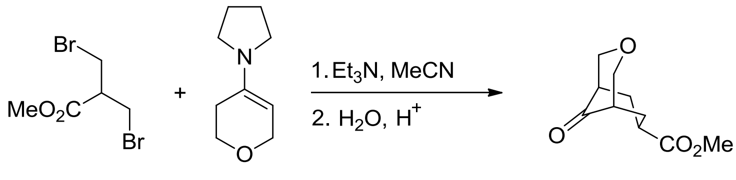
Peters *et al.* proposed that the transition state did not exist in a chair-boat conformation given the lack of significant preference for either diastereomer. They instead suggested that the reaction could proceed through an alternate half-chair transition state to arrive at the major product following kinetic protonation and hydrolysis (Scheme 12). The minor product was accounted for by inducing an iminium-enamine equilibrium where the alternate enamine proceeded *via* a boat conformation, with the R group positioned pseudoequatorial.



17 **38** **41** **42**

Scheme 12

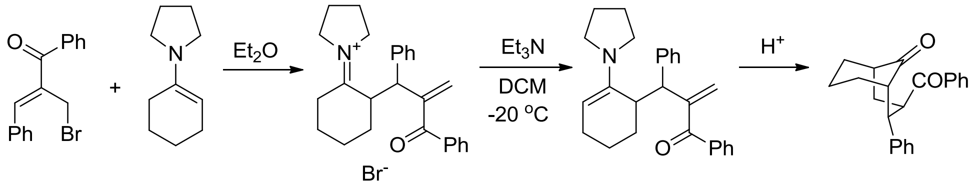
Not long after their work on substituted bicyclo[3.3.1]nonanes, Peters and co-workers reported the second example of heteroatom incorporation into the ring structure in 1976 when they published work on electron impact studies of oxabicyclo[3.3.1]nonanes.[16] The enamine of 4-oxacyclohexanone was synthesised and reacted with a *bis*-electrophile to give **44** in 76% yield (Scheme 13).



17 **43** **44**

Scheme 13

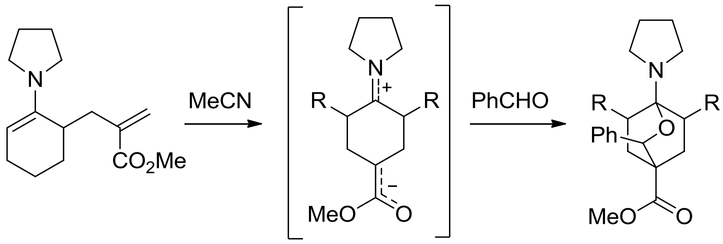
Gompper and Ulrich investigated Cope rearrangements with 1,4-dipoles in the same year, focusing on *α,α'*-annelation reaction intermediates.[17] They were able to synthesise and isolate iminium ions by reacting enamines with *bis*-electrophiles (Scheme 14). They were then able to isolate the enamines following *C*-alkylation at low temperatures, before affecting cyclisation and subsequent hydrolysis.



45 **18** **46** **47** **48**

Scheme 14

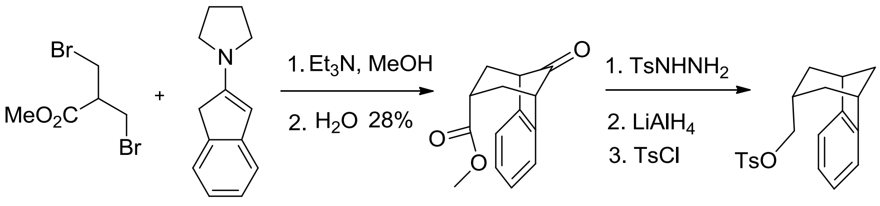
They were also able to demonstrate that the zwitter ion intermediate formed following Michael addition and before protonation was able to undergo polar Cope rearrangements (Scheme 15), providing more evidence for the mechanism of the *α,α'*-annelation reaction.



49 **50** **51**

Scheme 15

Lawton and co-workers also returned to α,α’-annelation chemistry in 1976,[18] this time as part of a study into solvolysis of benzobicyclo[3.2.1]octenylmethyl tosylates such as **54** derived from the corresponding esters. The α,α’-annelations were carried out under somewhat milder conditions than had previously been employed: refluxing in methanol for 3 h followed by a non-acidic hydrolysis giving a low yield of 28% (Scheme 16).

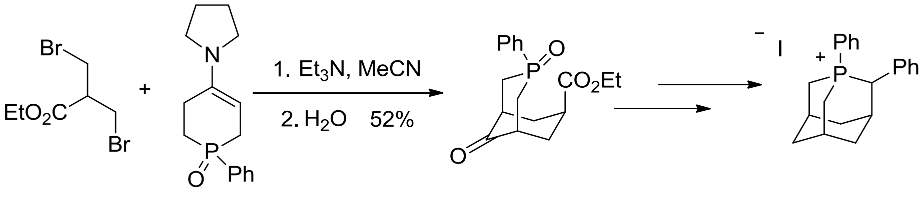


17 **52** **53** **54**

Scheme 16

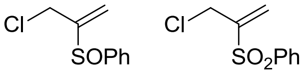
Variable temperature ^{1}H-NMR showed *endo* tosylate isomer **53** to exist predominately in the chair form (as drawn in Scheme 16), even though it was suggested that a boat conformation would have been more stable due to the severe diaxial steric clashin **53**.

In 1983 Bickelhaupt and co-workers used an *α,α’*-annelation approach to construct 1-phosphaadamantane **56** in 52% yield from enamine **55** (Scheme 17).[19] As in previous examples, the well-established *endo* selectivity of the reaction was exploited to rapidly construct the adamantane ring system. The conditions were notably milder than in previous *α,α*'-annelations, with the addition of the annelating agent **25** carried out at -30 ^{o}C, and the reaction allowed to stand at room temperature for 2 h and the solvents subsequently evaporated before being dissolved in water and stirred for 14 h to affect iminium hydrolysis.



Scheme 17

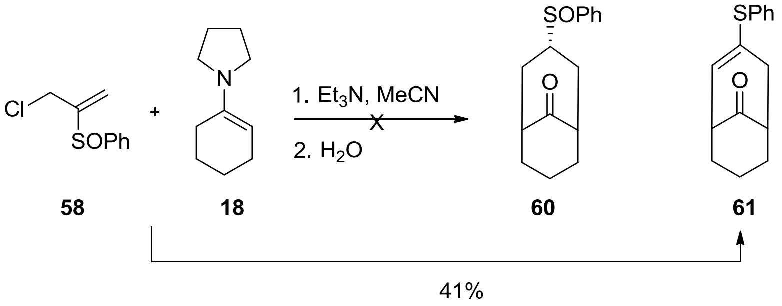
At this point it is necessary to point out that in all of the examples so far presented the variety in annelating agents is quite small, typically one of two types is used throughout. Firstly and most commonly, bromoesters and secondly enones, both of which are capable of alkylation followed by Michael addition, or *vice versa*. In 1984 Anzeveno and co-workers in contrast developed sulfur-based annelating agents and successfully used them in α,α'-annelation reactions to form bicyclic keto-sulfones.[20] A sulfoxide and sulfone were synthesised and reacted with sample enamines under typical conditions (Figure 1).



58 **59**

Figure 1. Alternate annelating agents

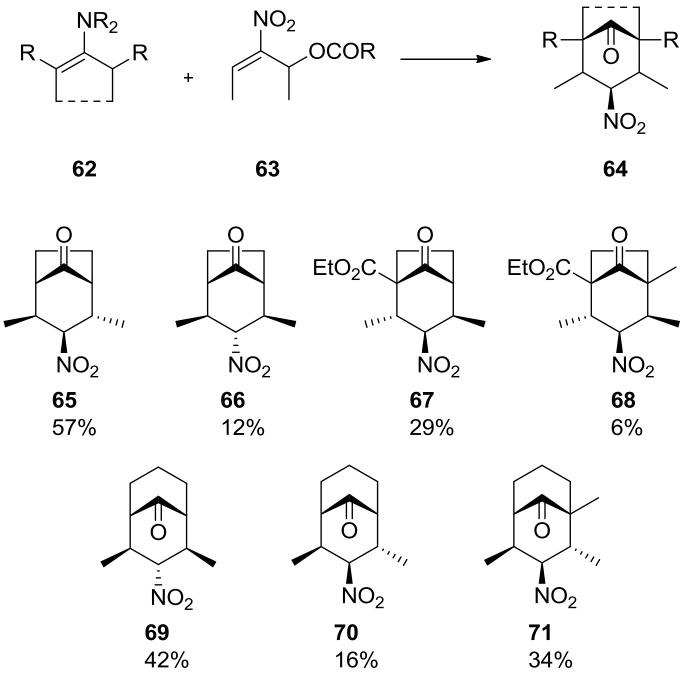
Notably, the sulfinyl annelating agent did not give the corresponding keto-sulfoxide bicycle when subjected to the reaction conditions. Instead it was discovered that a Pummerer type reaction had taken place under the reaction conditions to give the unexpected thioenol **61** (Scheme 18).



Scheme 18

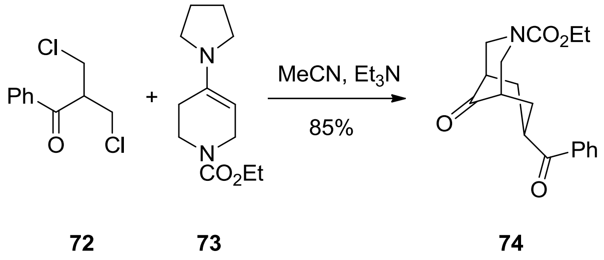
α,α’-Annelations involving the sulfone in contrast afforded the expected bicyclic keto-sulfone products in good yields (51-84%). Unusually however, these reactions had no preference for *endo* products, the reason for which was not commented upon.

In 1990 Seebach *et al.* applied *α,α’*-annelation to carbocylisations of nitroallylic esters.[21] The conditions used here were considerably different than those used previously. The nitroallylic annelating agents **63** were cooled to -78 °C and the enamine added, after which the mixture was stirred for 15 h at rt, acetonitrile then added and the reaction refluxed for 8 h before acidic hydrolysis. Yields were variable and dependent on the substrate used, ranging from 6-57% of any single diastereomer (Scheme 19).



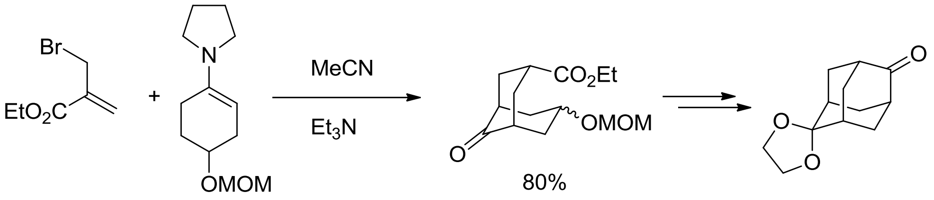
Scheme 19

Another example of an aza-bicycle constructed using an α,α’-annelation reaction was reported in 1992 by Nemes and co-workers.[22] They employed conditions significantly milder than most, initially adding the reagents to warm acetonitrile (30-40 °C) then allowing the reaction to stand at rt for 12 h before water being added for hydrolysis (Scheme 20).



Scheme 20

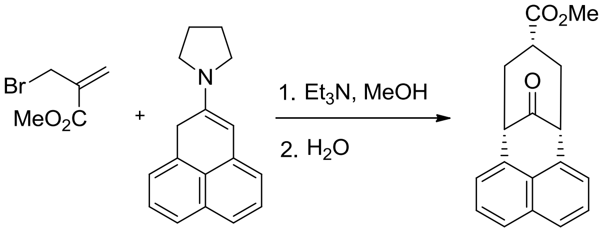
Kaganove and co-workers reported the successful synthesis of adamantane-2,6-dione and the related mono-ketal in 1994.[23] They applied the α,α’-annelation methodology to construct the bulk of the molecular architecture as several groups before had done. The bicyclic structure **76** was formed in 80% yield as a mixture of diastereomers employing similar conditions as reported by Stetter *et al.* (Scheme 21).



6 **75** **76** **77**

Scheme 21

In 1997, Lawton and co-workers once again used *α,α'*-annelation chemistry in order to study aromatic stacking in folded architectures through hydrogen bonding.[24] Similar harsh conditions were employed as in previous work to afford the *endo* product **79** in 76% yield (Scheme 22).



28 **78** **79**

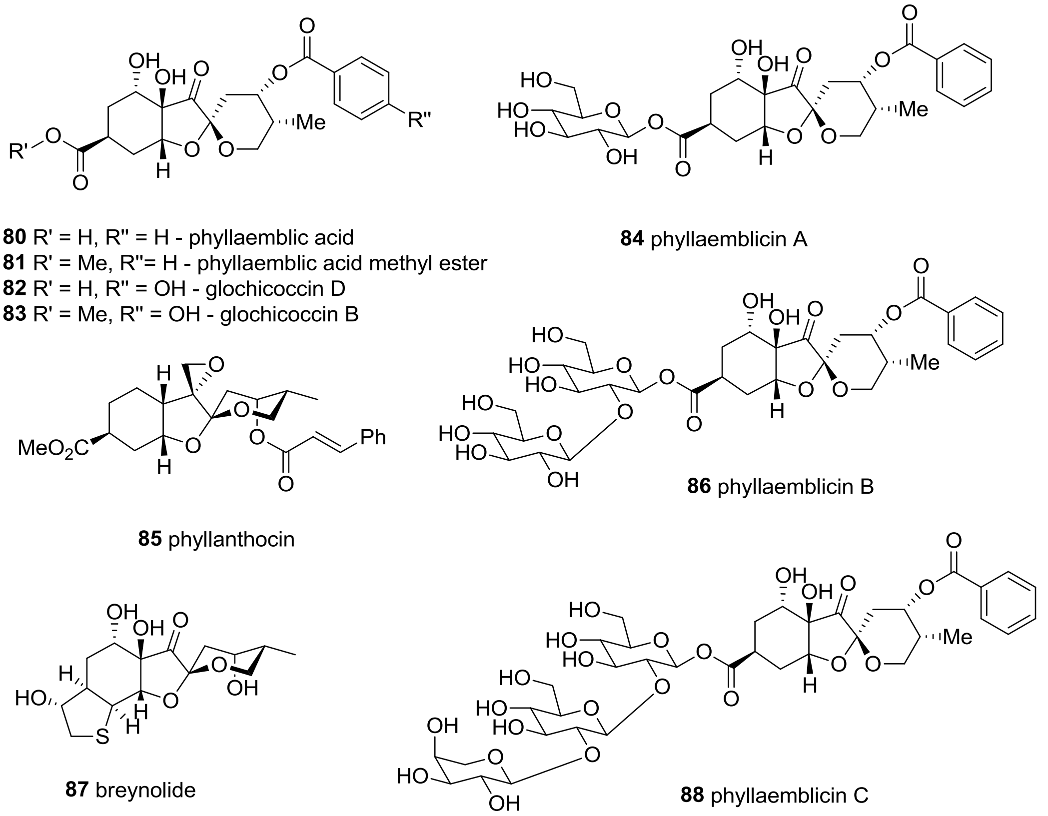
Scheme 22

1.4 Summary of Lawton type α,α'-annelation reactions

From Lawton's original paper on the novel α,α'-annelation from being published up to now, a significant number of examples using this methodology have been reported. Considerable work has been undertaken to probe the mechanism of the reaction and detailed analysis of the conformational considerations arising from the multi-cyclic products of α,α’-annelation reactions. Overall, the yields reported for this transformation are generally quite promising and it is somewhat surprising that the reaction is not more widely used, particularly in target synthesis. The precise reaction conditions for these types of transformations are notably similar throughout, typically heating the reagents in polar solvents over a number of hours and affecting final protonation and hydrolysis under acidic conditions, some precedent however exists for milder conditions to be employed. The main advantage of this reaction is that it allows for the creation of complex cyclic systems, often with excellent stereocontrol from relatively simple starting materials containing common functional groups, quickly and cheaply. To this point, the range of substrates synthesised remains somewhat limited, typically carbocycles or those with a single heteroatom incorporated into the ring.

1.5 Previous α,α’-Annelation Chemistry within the Grainger Group

The Grainger group first became interested in the α,α’-annelation reaction in 2003. In particular, α,α’-annelation reactions applied to 1,3-dioxan-5-ones, since their usefulness as starting materials in many synthetic applications including natural product syntheses is well documented. It was hoped that α,α’-annelations of such systems would allow a rapid route into oxygen containing bicycles suitable for further elaboration. A group of natural products were identified as possible targets in which to employ a strategy based around the above concept (Figure 2). Phyllaemblic acid **80** and its methyl ester **81** became the focus of the research as to date their total synthesis remain elusive. Glochicoccin B **82** and D **83** respectively were later discovered later in 2007[25] and have very similar structures to phyllaemblic acid **80** and so any synthesis of **80** could be modified to obtain these natural products as well.



80 R' = H, R'' = H - phyllaemblic acid
81 R' = Me, R''= H - phyllaemblic acid methyl ester
82 R' = H, R'' = OH - glochicoccin D
83 R' = Me, R'' = OH - glochicoccin B

84 phyllaemblicin A

85 phyllanthocin

86 phyllaemblicin B

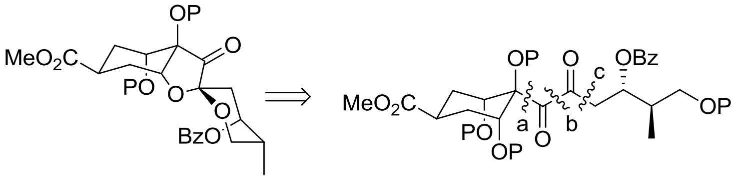
87 breynolide

88 phyllaemblicin C

Figure 2. Phyllaemblic acid and related Natural products

Phyllaemblic acid **80** is a highly oxygenated norbisabolane sesquiterpene that was isolated along with a number of related compounds from the roots of *Phyllanthis emblica* (alternative names include emblic myrobalan, Malacca tree and Indian gooseberry) by Zhang *et al.* in 2000.[26] The roots of this shrub has been used by the people in south-east Asia as an antiscorbutic and in the treatment of diverse ailments, especially those associated with the digestive system. Two classes of compounds were isolated, the aglycons phyllaemblic acid **80** and its methyl ester **81** and the glycosides phyllaembins A **84**, B **86** and C **88**. The glycosides of certain structurally related natural products, namely breynolide **87** and phyllanthocin **85,** are known to have significant medicinal properties. The former is a potent oral hypocholesterolemic and the later has anti-tumour properties. Studies have shown that phyllaemblic acid **80** and phyllaemblicin A **84** can inhibit protein kinases, whilst the glycosides phyllaemblicins B **86** and C **88** remain untested.[27] Aside from its potential as a medicinal target, phyllaemblic acid's structural features are also of significant synthetic interest; it contains a highly oxygenated spirocyclic acetal ring system which is *cis*-fused to a functionalized cyclohexane ring. Syntheses of similar compounds containing the common spirocyclic acetal ring moiety have been reported, including phyllanthocin **85** and berynolide **87**.[28,29,30]

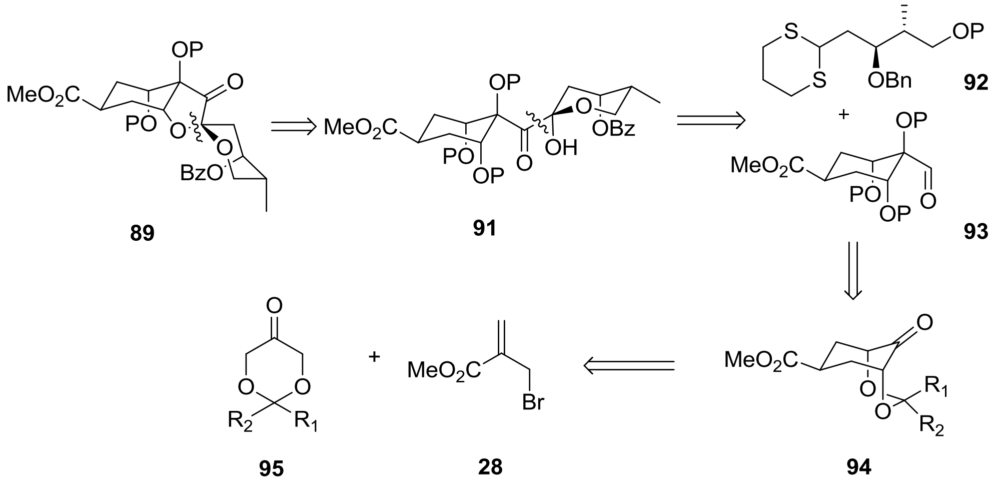
Retrosynthetic analysis of phyllaemblic acid **81**, its derivatives and glochicoccins B **82** and D **83** reveals a latent symmetry in the carbocyclic portion of these natural products, upon disconnection at the spirocyclic acetal from the cyclohexane ring system (demonstrated with **89** in Scheme 23). This inherent symmetry suggests a different route that can be employed towards the synthesis of these natural products separate to the approaches previously used in the construction of phyllanthocin **85** or breynolide **87**.



89 **90**

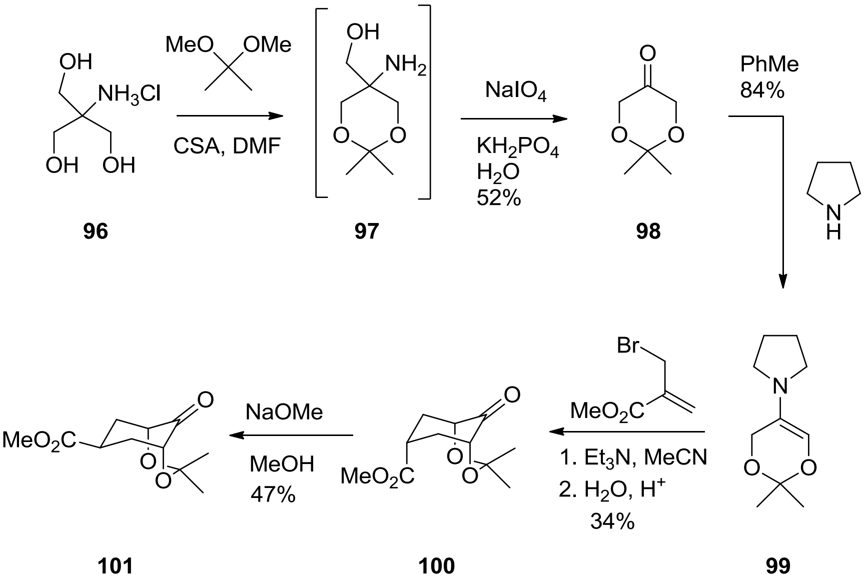
Scheme 23

A *meso* compound **94** where two hydroxyls are protected simultaneously could be derived from a corresponding protected ketone **95**[31,32] utilising an α,α'-annelation reaction. This strategy uses the diol protecting group to lock the stereochemistry of the two hydroxyl groups efficiently in a single step. Further elaboration of such an intermediate as **94** to the natural product was envisaged from a number of possible disconnections shown in Scheme 23. Disconnection of phyllaemblic acid methyl ester **81** leads to a *meso* aldehyde **93** that could be coupled with a dithiane **92** to give **91** and with further manipulation, finally phyllaemblic acid methyl ester **81** and the corresponding acid **80** (Scheme 24).[33,34]



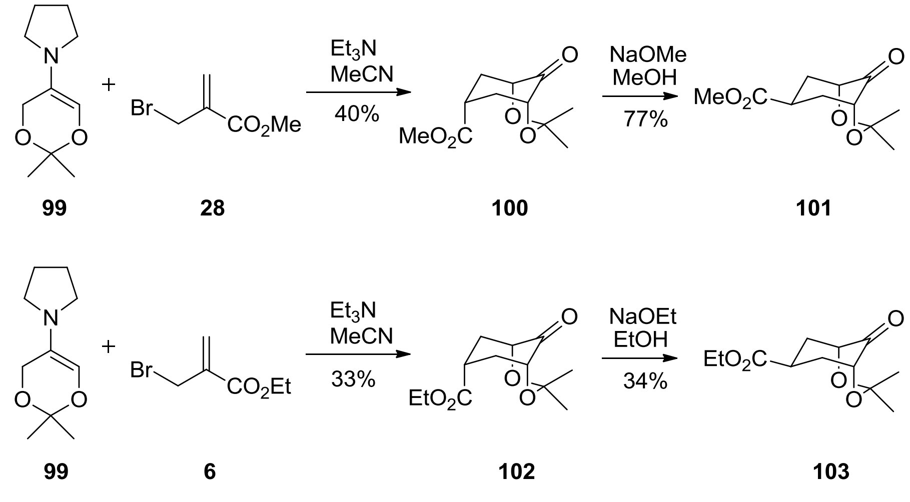
Scheme 24

Tisselli constructed the ketone **98** from commercially available *tris*-hydroxyaminomethane hydrochloride **96** using a known approach.[32,35] Its pyrrolidine enamine was then synthesised and coupled successfully to methyl-1-bromomethyl acrylate affording the bicyclic product **100** in a modest yield of 34% (Scheme 25).[36] Later, Carlisle further optimised this route resulting in a small increase in the yield of this α,α’-annelation step to 40%.[37] Both employed quite harsh conditions similar to that of majority of the literature; refluxing acetonitrile for 5-18 h followed by acidic hydrolysis. As with previous experiments shown by Lawton *et al.*, the ester group was positioned axially; the opposite to the required equatorial orientation in the natural product. So, epimerization of **100** with sodium methoxide afforded **101** with the correct stereochemistry in place.



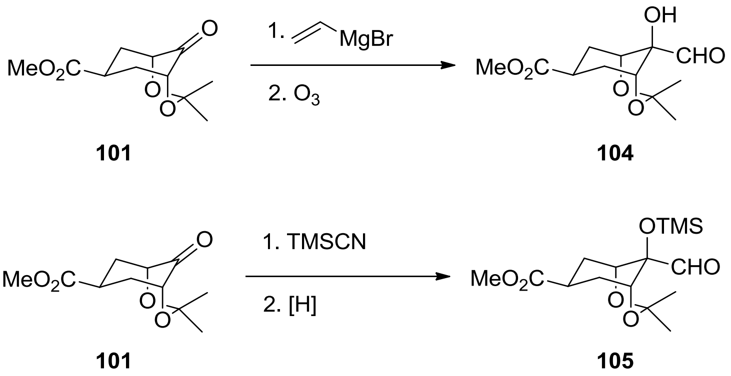
Scheme 25

Carlisle worked on both the methyl and ethyl esters, with comparable results for the α,α’-annelation steps. However, the epimerisation steps showed some disparity between the two variants and more generally suffered from being quite unreliable in practice, thus in need of refinement for a long synthetic endeavour (Scheme 26).



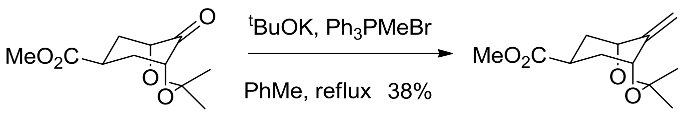
Scheme 26

With small quantities of the *exo* esters **101** and **103** available, attention turned to elaborating these systems towards the natural products. However, it was quickly determined that these rigid bicycles were unreactive to reactions targeted at the ketone, with a view to achieving carbon-carbon bond formation. It had been hoped that if vinyl magnesium bromide or vinyl lithium could be selectively added to the correct face of the ketone, this would provide a rapid route to the desired *meso* aldehyde **104** for further elaboration, *via* an ozonolysis. If the kinetic selectivity proved to be in the opposite sense to that required for the natural product, it was envisaged that a complementary thermodynamic strategy could be employed, for example by reversible addition of a cyanide nucleophile (Scheme 27). However, repeated Grignard and organolithium nucleophilic additions using a variety of conditions were completely unsuccessful.



Scheme 27

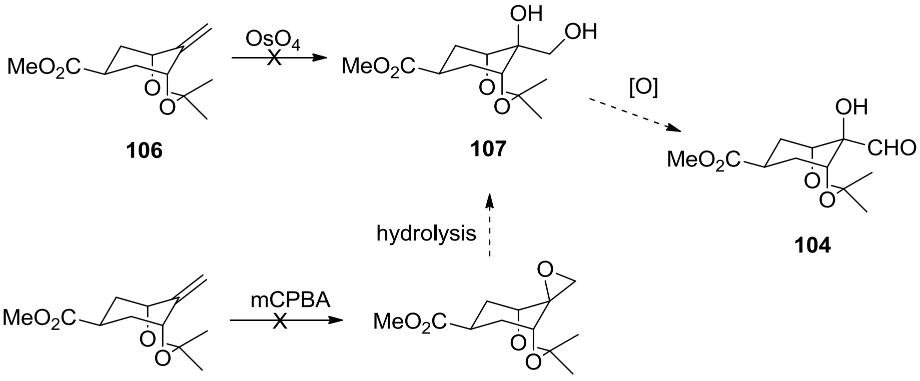
A strategy based on olefination chemistry was therefore devised as an alternate route towards the natural product. Unfortunately, a similar result was obtained when a Wittig reaction utilising the ylide formed by treatment of trimethylphosphonium bromide was initially attempted. However following some optimisation work, it was found that the Wittig reaction under forcing condition was partially successful; the potassium ylide was formed in refluxing toluene, and **101** then added at 80 °C, although the yield of terminal alkene **106** was low (Scheme 28). The high temperatures required suggest that a high energy transition state exists and is a significant barrier to reaction.



101 **106**

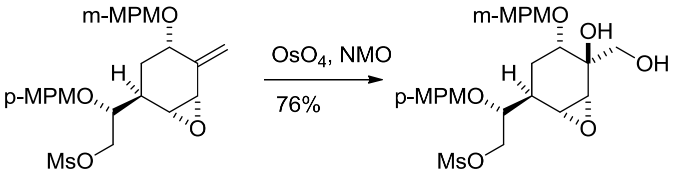
Scheme 28

This alkene **106** can be considered as a possible intermediate towards the *meso* aldehyde **104**, if it can be further functionalised by dihydroxylation or epoxidation (Scheme 29).



Scheme 29

Significantly, Burke and co-workers dihydroxylated a similar *exo*-cyclic alkene **109** in their total synthesis of breynolide with complete stereocontrol.[29] With this precedence, it was hoped that this would be an effective strategy to introduce the required oxygen functionality with the correct stereochemistry (Scheme 30).

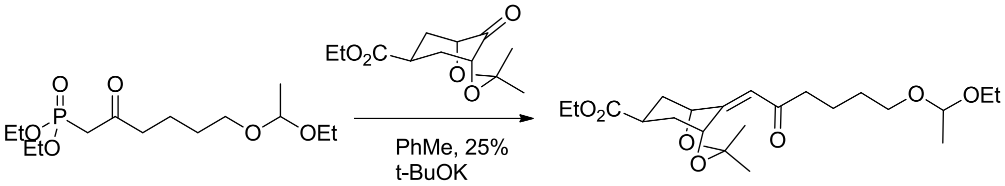


109 **110**

Scheme 30

Carlisle attempted to dihydroxylate **106** using the conditions used by Burke[38] and also under Sharpless phase transfer conditions, but both unfortunately failed to produce any reaction at all.[39] Similarly, attempted epoxidation using *m*-chloroperbenzoic acid resulted only in recovery of the starting material.

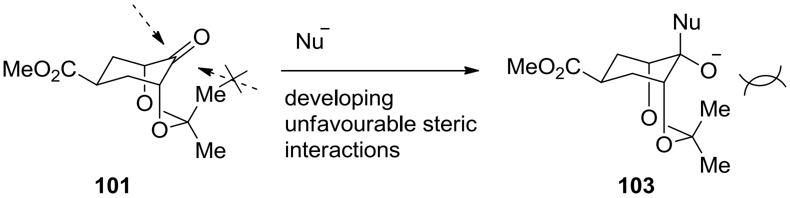
Horner-Wadsworth-Emmons (HWE) coupling reactions were also carried out in the hope that the more reactive phosphonate would improve the yields. Although reactions using the phosphonates of protected δ-valerolactones occurred, they too were poor yielding (25%) and the resulting product **112** was again unreactive to dihydroxylation and epoxidation (Scheme 31).



111 **112**

Scheme 31

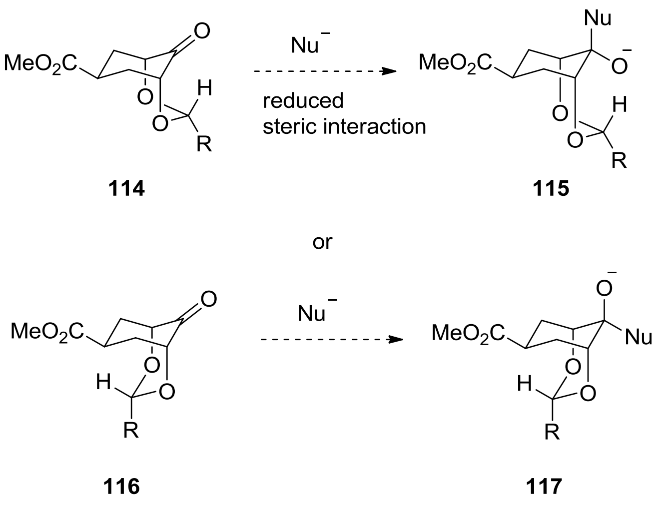
In light of the lack of reactivity and poor yields in constructing ketone **101** it was envisaged that an alternate protecting group strategy could be utilised that would increase the ketone group reactivity. In ketone **101** there are two methyl groups which block attack by nucleophiles from the bottom face in the chair-boat conformation that these bicyclic systems adopt. However, attack from the top face is also unfavourable as a result of the carbon centre moving from sp^2 to sp^3 during the course of the reaction (Scheme 32).



101 **103**

Scheme 32

This is a plausible explanation for the lack of reactivity of this system. The partially successful olefination reactions may be due to the sp^3 carbon formed upon addition of the phosphonate being immediately converted back to the sp^2 centre by elimination to the alkene, therefore releasing the strain. To minimise this strain the “offending” methyl group could be replaced with hydrogen (Scheme 33). This would decrease the steric clash between the diol protecting group and any reaction at the carbonyl whilst maintaining a degree of steric hindrance towards nucleophilic attack from the bottom face of the ketone, if the dioxane ring were still to exist in a boat conformation. This in turn would depend upon which diastereomer, **114** or **116**, forms in the α,α’-annelation reaction. The alternate diastereomer **116** offers a potential chelation-assisted addition to the lower face of the ketone.



114 **115**

116 **117**

Scheme 33

Chapter Two: Diastereoselective α,α’-annelation reactions of 1,3-dioxan-5-ones

2.1 Aims and objectives

Following on from the work undertaken in the Grainger group by both Tisselli and Carlisle (see Chapter 1), a set of differently protected 1,3-dioxan-5-ones **98**, **118**, **119** and **120** were considered as potential starting points towards a total synthesis of phyllaemblic acid **80** and structurally related compounds (Figure 3). Bicyclic ketone **101** constructed previously in the group was found to have poor reactivity with respect to the carbonyl functionality. By varying both the steric and electronic characteristics of the protecting groups it was hoped to improve the reactivity as well as more generally demonstrating the scope of the α,α'-annelation reaction. Specifically, the susceptibility of the carbonyl group to nucleophilic attack following α,α'-annelation was expected to differ, depending on the precise conformation(s) of the resulting bicycle. With a more reactive bicyclic ketone the long term objective of constructing the natural product would be more feasible. Notably, the formations of more stereoisomers are also possible, starting from ketones **118-120**.

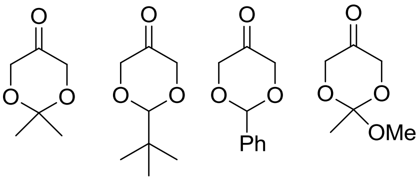
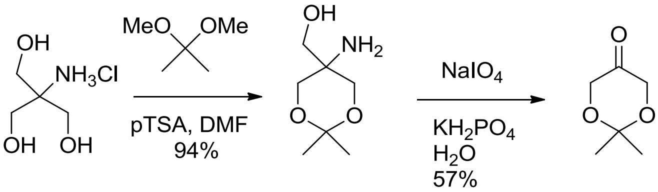


Figure 3. 1,3-Dioxan-5-ones of interest

2.2 Synthesis of the starting materials

Dioxanone **98**, previously investigated within the group, was synthesised by subjecting Trizma hydrochloride **96** to a two-step literature procedure (Scheme 34).[36]

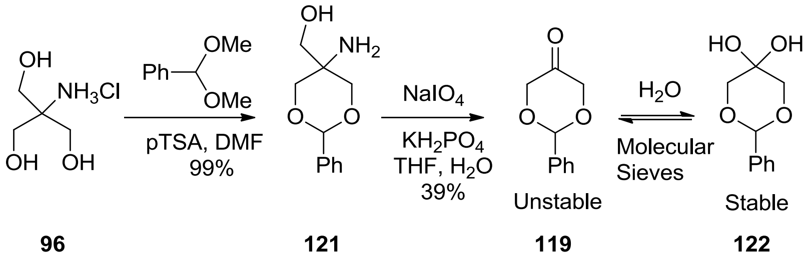


96 **97** **98**

Scheme 34

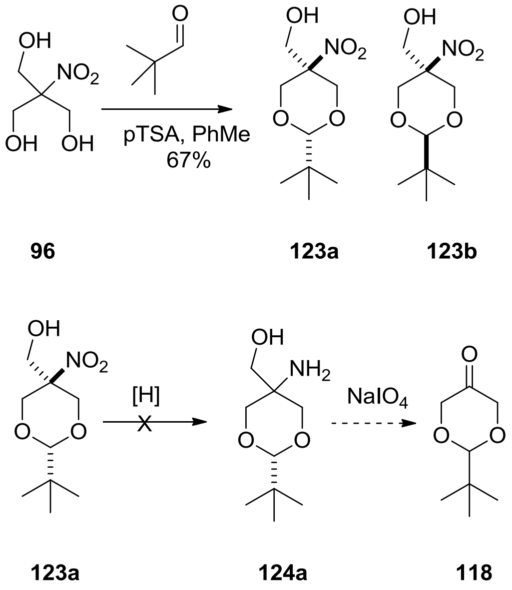
Initial attempts at synthesis proved to be frustrating, with solubility problems hampering efforts to construct the *β*-amino-alcohol intermediate **97**. Modification of the method by increasing the temperature and using a higher dilution in DMF allowed the reaction to proceed in high yield.[32] The subsequent oxidative cleavage with sodium periodate in water also proved problematic due to the highly polar and volatile nature of the product affecting both the extraction and purification stages. Continuous extraction was performed over two days, which improved recovery, and **98** was obtained in 57% yield after purification. Residual DMF from the acetal formation step made distillation impractical as the boiling points of each are similar (153 ^{o}C and 173 ^{o}C respectively).

Benzylidene acetal **119** was prepared in a similar manner to **98**: protection of both alcohol groups followed by oxidative cleavage**.** The more lipophilic phenyl substituent required the use of a mixed solvent system (1:1 THF:water) for good solubility in the oxidative cleavage step, but a continuous extraction was no longer required for good recovery. Interestingly, this compound proved to be unstable and decomposes even when stored at low temperatures. To combat this, the hydrate **122** instead was formed *via* recrystallization and this compound could be stored for months at room temperature without any significant degradation (Scheme 35).



Scheme 35

Attempts to prepare ketone **118** were not successful. Following a similar route to that described above for **98** and **119**, the literature requires that the nitro intermediates **123a** (major) and **123b** (minor) be first constructed, and then reduced to the corresponding β-amino-alcohols (Scheme 36).[31]



Scheme 36

The first step gave a 2:1 mixture of diastereomers **123a** and **123b** respectively, in 67% overall yield. X-ray crystallographic analysis of the minor diastereomer **123b** allowed for unambiguous assignment of relative stereochemistry but the results are not of significant quality for publication (Figure 4).

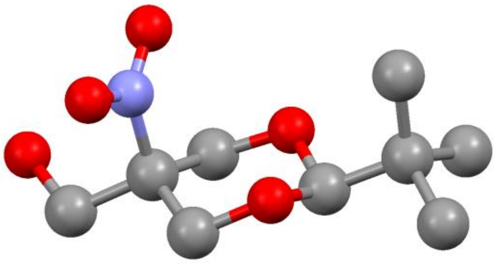
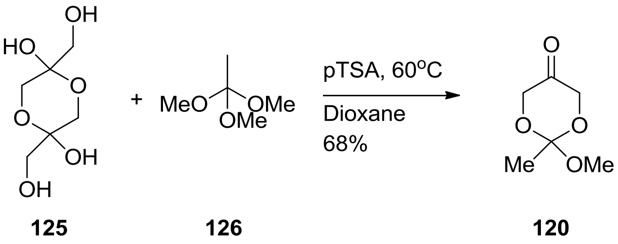


Figure 4. X-ray crystal structure of **123b**

Attempts to reduce the major isomer **123a** using $LiAlH_4$ and H_2/Raney Ni at atmospheric pressure were not successful, yielding products that were inconsistent with reported data for the desired compound **124**.[40,55] As a result this could not be elaborated to the desired dioxanone **118** for further study.

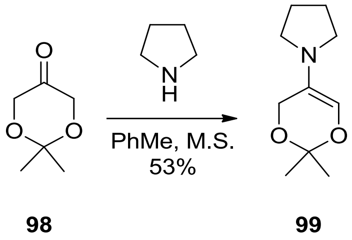
Ortho-acetal **120** was prepared according to an established procedure (Scheme 37).[41] Although the reaction proceeded in slightly lower yields than previously reported, it remains the fastest and most convenient way to obtain gram quantities of a 1,3-dioxan-5-one, out of the three acetals thus far presented.



Scheme 37

The next step was to form enamines of dioxanones **98**, **119** and **120** ready for coupling to a suitable *bis*-electrophile. Initial attempts to produce enamine **99** from **98** were successful albeit in modest yields, following the procedure outlined by Tisselli

(Scheme 38).[36] She described a procedure using dry toluene as solvent and 4Ǻ molecular sieves as a water trap, all at room temperature. The work-up included an acidic wash, which potentially risked partial/complete hydrolysis back of the enamine moiety to the starting material. It was observed that over time the success of this procedure declined dramatically; it was found subsequently that pyrrolidine required distillation before use in order to maximise the yield and simplify purification of the enamine. Enamine **99** itself proved to be unstable and had to be prepared immediately before use for successful results in the next step. Attempts to optimise this step included varying the temperature, the water trapping method, and the work-up. The results of these investigations are summarised in Table 1. They show that better yields are obtained under milder conditions and by avoiding aqueous work-ups but the overall yield remained disappointing.



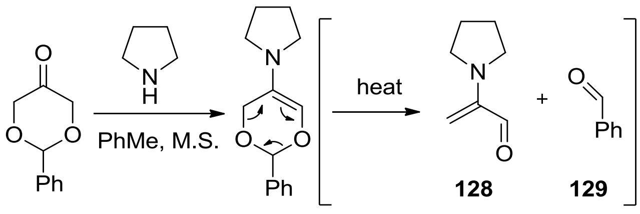
Scheme 38

Entry	Water Trapping Method	Temperature/^{o}C	Time/h	Yield(%)
1 [a]	*Dean Stark apparatus*	*100*	*24*	*0*
2	*Dean Stark apparatus*	*80*	*24*	*0*
3 [a]	4Å *molecular sieves*	*20*	*24*	*42*
4	4Å *molecular sieves*	*20*	*24*	*53*

[a] Acidic work-up.

Table 1. Preparation of enamine **99** from ketone **98**

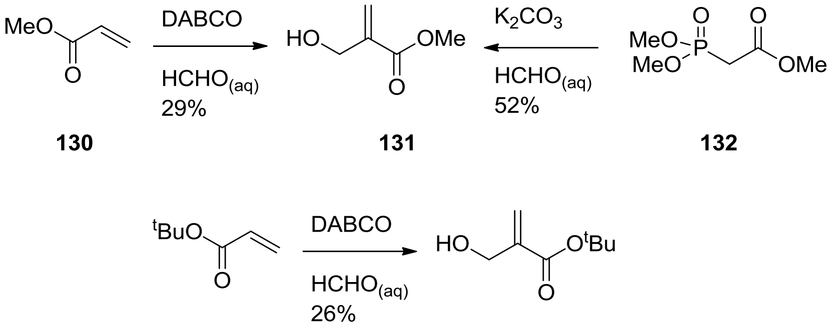
Synthesis of enamine **127** proved more problematic (Scheme 39). Firstly, the ketone **119** proved to be only sparingly soluble in toluene, and hence very little product formation was observed when the reaction was conducted in this solvent. The solvent was altered to MeCN in which **119** dissolved more readily, however the yield remained low at only 36% by crude mass recovery. Purification by distillation was impractical as the product appeared highly temperature sensitive, much more so than enamine **99**, and so an isolated yield could not be obtained. The instability of these enamines can be rationalised in terms of a possible retro hetero Diels-Alder reaction occurring at elevated temperatures.[42] The lower stability of **127**, the enamine of benzylidene acetal **119**, can therefore be explained by the conjugation of the carbonyl with the aromatic ring in benzaldehyde making it more thermodynamically stable, and thus favouring the retro hetero Diels-Alder reaction both in terms of enthalpy and entropy. The isolation of a pyrrolidine enamine of **120** was not pursued in light of developments in the use of **98** and **119** in a one-pot enamine formation – α,α’-annelation reaction (see Section 2.3).



119 **127** **128** **129**

Scheme 39

A series of *bis*-electrophiles were prepared for use in the α,α'-annelation step, with a view to determining an ideal annelating agent. Generation of allylic alcohols followed by halogenation provides a quick route to such compounds. Allylic alcohol **131** was prepared in two ways, firstly *via* a Baylis-Hillman reaction and secondly by using phosphonate **132** in a HWE style procedure (Scheme 40).[37,57]



130 **131** **132**

133 **134**

Scheme 40

The use of previously reported Baylis-Hillman procedures gave very slow reactions and poor yields. Although some optimisation work was undertaken the yield remained disappointing (Table 2). *tert*-Butyl ester **134** was prepared using a similar procedure. The best results were obtained with generally longer reaction times and a higher mol % of catalyst, and this was sufficient to enable the production of significant quantities of **131** on scale-up.

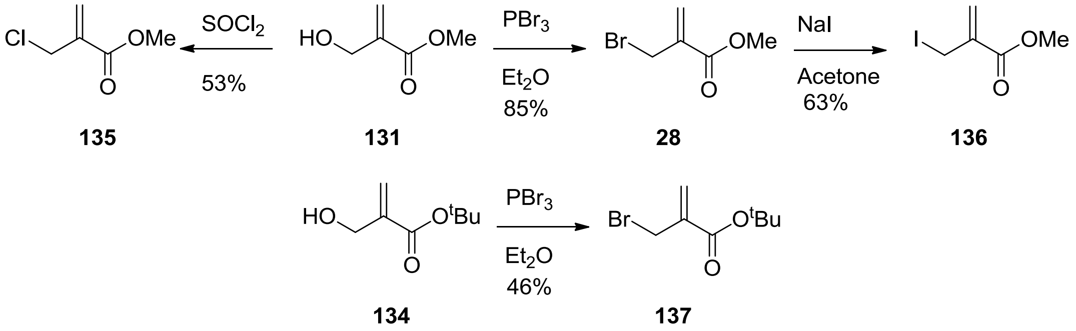
Entry	Ester	Temperature/^{o}C	Base	Time(h)	Yield(%)
1	***130***	*20*	*Imidazole*	*24*	*0*
2	***130***	*20*	*TEA*	*24*	*6*
3	***130***	*20*	*DABCO*	*24*	*11*
4	***130***	*20*	*DABCO*	*48*	*16*
5	***133***	*100*	*DABCO*	*16*	*26*
6	***130***	*100*	*DABCO*	*16*	*0*
7[a]	***130***	*20*	*DABCO*	*48*	*29*

[a] 2.0 equivalents of DABCO

Table 2. Baylis-Hillman reaction of methyl acrylate **130** with aqueous formaldehyde

The alternative HWE reaction, although higher yielding, suffers from inherently poor atom economy and uses more expensive starting materials, so is overall less satisfactory than the Baylis-Hillman reaction given the quantities of **131** needed.

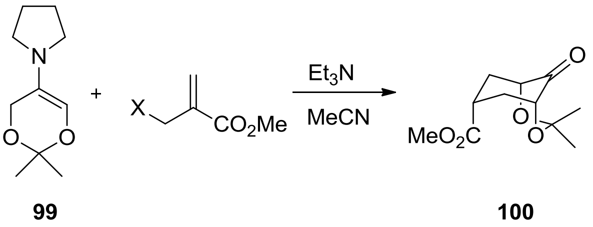
The chlorination of allyl alcohol **131** using direct addition of thionyl chloride gave the corresponding commercially available but expensive allyl chloride **135** in 53% yield after distillation. Bromination *via* the addition of PBr_3 gave the expensive allyl bromide **28** in 79% yield, but this was compound more sensitive compared with the chloride, decomposing slowly over time when stored at low temperatures. The very sensitive allyl iodide **136** was synthesised from the bromide in a Finkelstein reaction in 63% yield as a third annelating agent. Allyl bromide **137** was prepared from *tert*-butyl ester **134** in the same manner as for methyl ester **28**.



Scheme 41

2.3 The *α,α'*-annelation reaction

Work on the *α,α'*-annelation reaction began following the conditions set out by previous members of the Grainger group: typically the two coupling partners were stirred for several hours under refluxing conditions in acetonitrile before being subjected to an acidic iminium hydrolysis with heating.[36,37] The reaction described created a black solution when all the reagents were added and heated. The desired bridged bicylic ketone **100** was obtained in poor yield and the reaction itself was inconsistent. Further work has been done to improve both the yield and reproducibility of this transformation for ketones **98** and **119**, the results of which are summarised in Table 3.



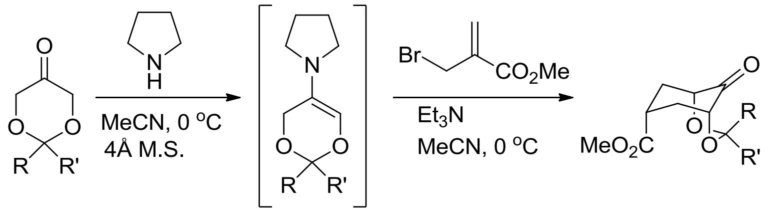
Scheme 42

Entry	Enamine	Allyl halide	Temperature (^oC)	Reaction Time (h)	Hydrolysis Time (h)	Yield (%)
1	***99***	***28***	*reflux*	*24*	*2*	*0*
2	***99***	***28***	*reflux*	*48*	*2*	*19*
3	***99***	***135***	*reflux*	*48*	*2*	*0*
4	***99***	***135***	*0- rt*	*24*	*2*	*17*
5	***99***	***28***	*0- rt*	*24*	*2*	*27*
6	***99***	***136***	*0- rt*	*24*	*2*	*0*
7	***99***	***28***	*0- rt*	*24*	*5*	*52*
8	***127***	***28***	*0- rt*	*24*	*5*	*24*

Table 3. Formation of bicyclic ketones **100** and **140**

Based on the observation that the enamines may be less stable at elevated temperatures, particularly **127**, the reaction was conducted at lower temperatures than previously studied (Table 3, Entries 1 - 3)**.** This resulted in increased yields over a shorter reaction period (Table 3, Entries 4 - 8)**.** Varying the identity of the allyl halide showed, as expected, that the allyl chloride **135** is less effective than the corresponding allyl bromide **28** under the same conditions (Table 3, Entries 4 and 5). The more stable allyl chloride **135** produced no desired products when the reaction was conducted under reflux, yet lowering the temperature allowed the reaction to proceed in 17% yield. This suggests that the stability of the enamines was one possible issue that could be depressing the yield. To investigate this hypothesis, the allyl iodide **136** was prepared for α,α’-annelation, as it could, in theory, react more rapidly with an enamine before any possible decomposition could take place, even at room temperature. Unfortunately, allyl iodide **136** did not appear to be a suitable substrate for this reaction possibly because it is unstable under these conditions (Table 3, Entry 6). It is known that the bicyclic ketone **101** is unreactive towards nucleophiles at the ketone carbonyl, possibly due to steric hindrance (see Section 1.5).[37] It is conceivable that the iminium ion formed in the reaction may also be less susceptible to nucleophilic attack; so hydrolysis was allowed to proceed for longer (Table 3, Entry 7) but still without addition of acid to mediate the transformation. This increased the yield of **100** to 52% after purification, now under much milder conditions than previously employed. The same reaction conditions were applied to the enamine **127** affording the ketone **140** as a single diastereomer in 24% yield (Table 3, Entry 8) whose configuration was determined by X-ray crystallography and nOe studies (see Section 2.5).

Enamine **127** could not be fully purified and was thus used crude in the reaction. Considering the time taken for purification of the enamines and potential loss of material a one-pot procedure to incorporate the enamine formation and *α,α’*-annelation steps was therefore devised. Given the improvement to the α,α’-annelation reaction and success of the enamine **127** as a substrate for the reaction (Table 3, Entry 8), where lack of purification of the **127** still allowed the reaction to proceed, this presented an opportunity to streamline and possibly improve the sequence. Ketone **119** was therefore subjected to a one-pot reaction sequence. Enamine formation was first affected at <10 °C, followed by addition of the annelating agent **28**. After 16 hours at <10 °C water was added and the hydrolysis step carried out over 5 hours at room temperature. In this way, the novel bicycle **140** was obtained in 41% yield over two steps; an overall increase of 32% on the separate reactions (Table 4, Entry 1). This methodology was then applied to the formation of dimethyl acetal **99**, which gave a similar 40% yield over two steps (Table 4, Entry 2). Further optimisation was undertaken to improve this procedure further, including variation of the water trapping method at the enamine formation stage and altering the base used for the α,α’-annelation step, but no further improvement was made (Table 4, Entries 3 - 6). These optimised conditions were then later applied to ortho-acetal **120** which gave the best yield of the three systems studied thus far, at 61% over two steps (Table 4, Entry 7). Scheme 43 summarises the best results obtained for each bicylic system.



98 R = R' = Me
119 R = H, R' = Ph
120 R = OMe, R' = Me

99 R = R' = Me
127 R = H, R' = Ph
139 R = OMe, R' = Me

100 R = R' = Me 40%
140 R = H, R' = Ph 41%
141 R = OMe, R' = Me 61%

Scheme 43

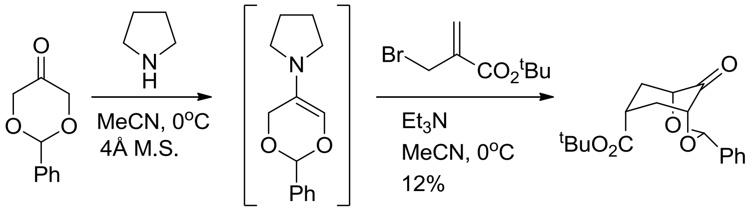
Entry	Ketone	Temperature (°C)	Base	Reaction Time (h)	Yield (%)
1	***119***	*0- rt*	*TEA*	*16*	*41*
2	***98***	*0- rt*	*TEA*	*16*	*40*
3	***98***	*0- rt*	*Hünigs*	*16*	*0*
4	***119***	*0- rt*	*Hünigs*	*16*	*33*
5[a]	***119***	*0- rt*	*TEA*	*16*	*0*
6[a]	***98***	*0- rt*	*TEA*	*16*	*0*
7	***120***	*0- rt*	*TEA*	*16*	*61*

[a] $MgSO_4$ used instead of 4Å molecular sieves

Table 4. Two step, one-pot α,α'-annelation

The products for the *α,α'*-annelations of the unsymmetrical ketones **98** and **119** are also of note as in each case only one diastereomer was ever observed. Stereochemical assignment is described in Section 2.5. A mechanistic interpretation of the possible origin of this observed diastereoselectivity is given in Section 2.6.

tert-Butyl ester **142** was synthesised in a reduced yield of 12% using the same conditions (Scheme 44). This reaction was only successful once and attempts to repeat it failed, the reason for which is unclear. The increased steric bulk of the *tert*-butyl group may possibly be hindering the ester moiety from being positioned pseudoaxially in the transition state for the Michael addition step, preventing ring closure, but this remains speculation.

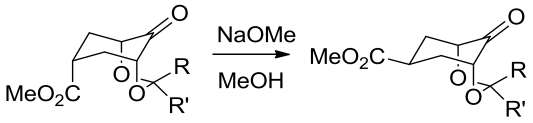


119 **127** **142**

Scheme 44

2.4 Epimerization studies

In order to determine the configurations and conformations of bicycles **100**, **140**, **141** and **142** epimerisation of the ester group was undertaken to aid NMR studies. Furthermore, the natural products described in Chapter 1 require this epimerisation step in order to match their stereochemistry. Epimerisation of esters on **100** and **140** using sodium methoxide in methanol, as reported by previous members of the Grainger group,[37] was investigated and afforded **101** and **143** in disappointing 35% and 12% yields, respectively (Scheme 45).

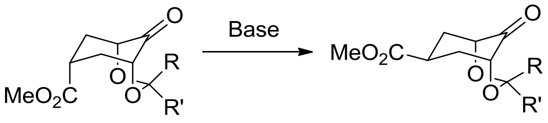


100 R' = R = Me
140 R' = Ph, R = H

101R' = R = Me 35%
143 R' = Ph, R = H 12%

Scheme 45

Although the explanation for the low yields in these reactions is not clear, one likely possibility is the result of decomposition of the starting material caused by the strongly nucleophilic sodium methoxide. Poor mass recovery obtained prior to purification supports this suggestion. Occasionally, some starting material was also recovered but the amount was insufficient for effective recycling given the low conversion and poor mass recovery. An investigation of alternative bases to carry out the epimerization was undertaken. More specifically, it was thought that using a weaker, non-nucleophilic base may increase the success of the reaction. A number of amines were screened under a variety of conditions (Table 5).



100 R = R'= Me
140 R = H, R' = Ph
141 R = OMe, R '= Me

101 R = R'= Me
143 R = H, R' = Ph
144 R = OMe, R '= Me

Scheme 46

Entry	Ketone	Base	Temperature (°C)	Solvent	Reaction Time (h)	Yield (%)
1	***100***	*DBU*	*rt*	*MeCN*	*48*	*0*
2	***100***	*DBU*	*reflux*	*MeCN*	*15*	*64*
3	***140***	*DBU*	*reflux*	*MeCN*	*15*	*52*
4	***140***	*DBU*	*reflux*	*PhMe*	*24*	*29*
5	***140***	*Hunig*	*reflux*	*MeCN*	*15*	*0*
6	***140***	*TEA*	*reflux*	*MeCN*	*24*	*trace*
7	***140***	*Proton sponge*	*reflux*	*MeCN*	*24*	*0*
8[a]	***100***	*DBU*	*65*	*MeCN*	*24*	*77*
9[a]	***140***	*DBU*	*65*	*MeCN*	*24*	*68*
10[a]	***141***	*DBU*	*65*	*MeCN*	*24*	*79*

[a] work-up stage removed

Table 5. Ester epimerization

DBU proved to be the most effective of the four bases screened, giving very consistent results and significant improvements in yield over sodium methoxide. Elevated temperatures were required for epimerisation to occur and *ca*. 60 °C was determined to be sufficient. Reactions tended to go to completion, as monitored by TLC analysis, in 12-24 h. However, yields in excess of 80% were not observed for any esters. Mass recovery before purification was lower than expected but still comparable with that of the final purified yield. In order to determine the loss of mass, the work up stage was removed and the reaction loaded directly onto a column, following concentration under reduced pressure. This led to a further improvement in the yield but failed to account for loss of material entirely. This therefore points to the origin of the mass loss occurring in the reaction itself. During column chromatography of **143**, small amounts of benzaldehyde were detected after the product had eluted. This indicates that deprotection of the acetal during the reaction or during chromatography may be occurring, with and the resulting diol too slow to elute, even in highly polar solvent mixtures of the mobile phase.

Subjecting benzylidene acetal **143** to the same reaction conditions but with omission of DBU resulted in 90% of the starting material being recovered after chromatography. Although not all of the mass was recovered in this instance, it still suggests that the majority of the missing material is being lost during the reaction itself, with possibly some mass also lost during the purification stage. Applying these conditions to the ortho-acetal **141** gave a comparable 79% yield of **144**. This compound is therefore obtained in a higher overall yield than the other two ketones **101** and **143**, making it the prominent candidate for later work towards the natural products described in Chapter 1. Epimerisation of *tert*-butyl ester **142** under these conditions resulted in a comparable 50% yield. Full characterisation data of this compound could not be obtained, however, due to subsequent decomposition in solution.

2.5 Conformation and configuration analysis of bridged bicyclic ketones

The configuration at each carbon for the bridged bicyclic ketones was determined through a combination of X-ray crystallography and GOESY experiments. X-ray crystal structures were obtained for acetonide **100** and benzylidene acetal **140** (Figures 5 and 6). These products from the α,α’-annelation steps all have the ester substituent positioned *syn* to the acetal. This is consistent with the results of similar carbocyclic and hetereocylic systems where the ester groups were revealed to be *endo*

(Chapter 1). In each system, the carbocyclic ring adopts a chair conformation whilst the dioxanone ring exists as a boat.

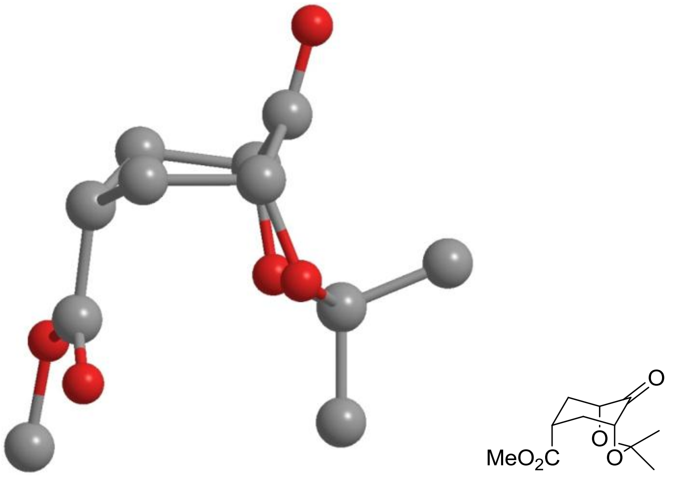


Figure 5. X-ray crystal structure of **100**

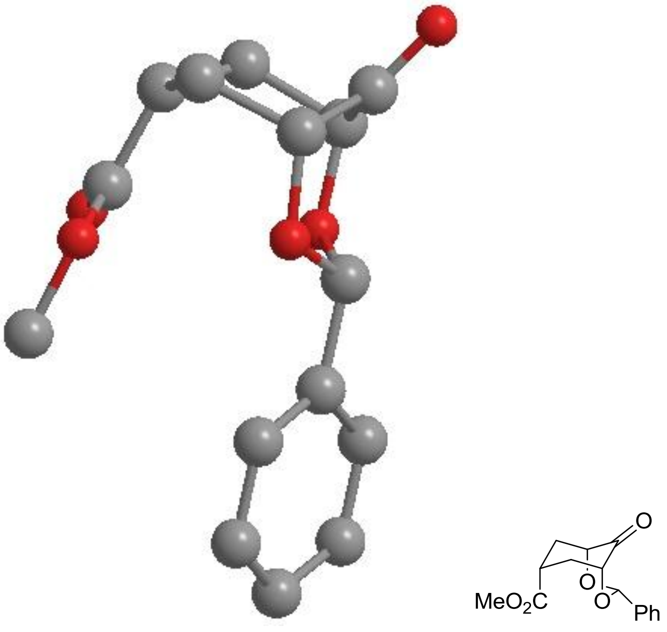


Figure 6. X-ray crystal structure of **140**

As in Figure 6 it can be seen that the phenyl group in **140** is positioned in a pseudoequatorial orientation on the dioxanone ring. Upon epimerization, X-ray crystal structures were obtained for all **101**,[37] **143** and **144** (Figures 7, 8 and 9). Again, in all cases the carbocyclic ring adopts a chair conformation whilst the dioxanone ring exists as a boat.

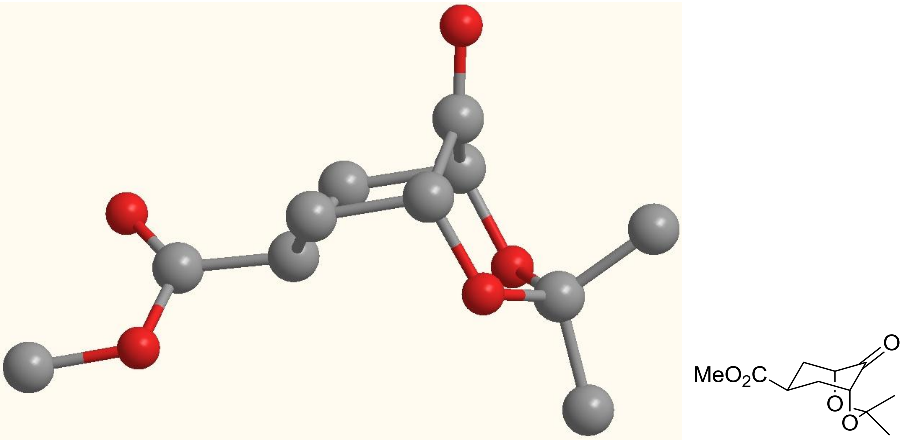


Figure 7. X-ray crystal structure of **101**

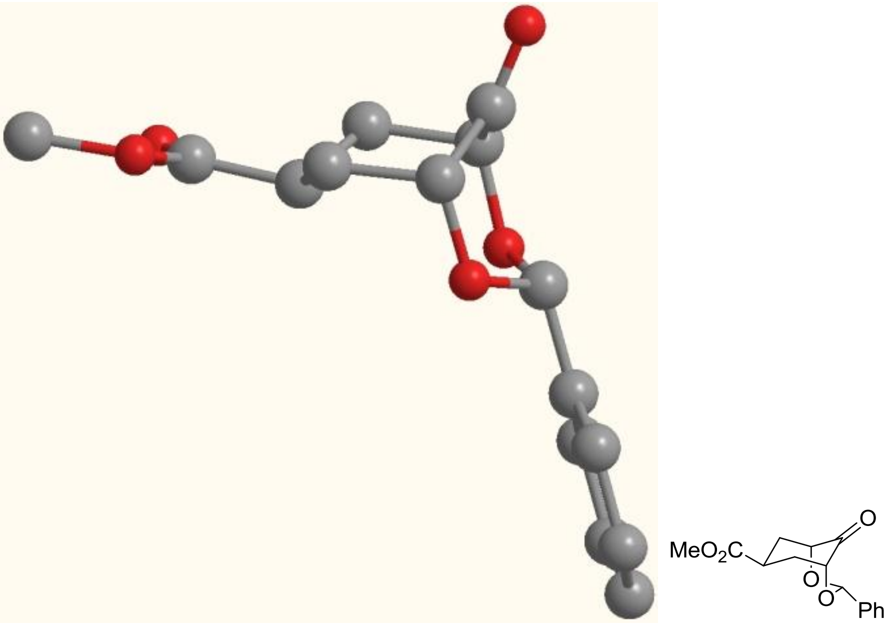


Figure 8. X-ray crystal structure of **143**

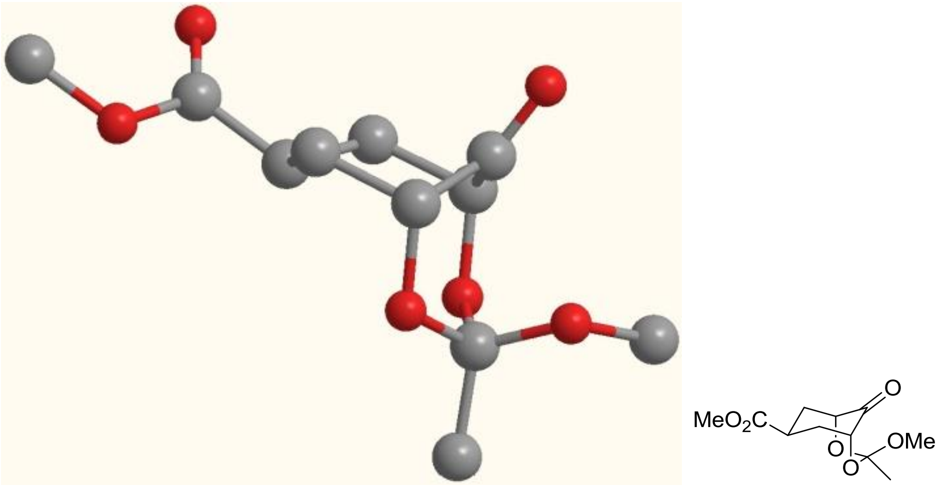
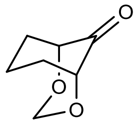


Figure 9. X-ray crystal structure of **144**

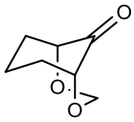
The X-ray crystal structure of ortho-acetal **144** also confirms the configuration at the acetal carbon formed in the *α,α'*-annelation reaction from **141** (Figure 9). The methoxy group occupies the pseudoaxial position on the dioxanone ring (flagpole position) and the methyl group is positioned in a pseudoequatorial fashion.

With relative stereochemistry determined, the conformations of these molecules were investigated. Knowledge of the conformation of these compounds is of great importance since the precise arrangement of the groups in space would have implications for subsequent reactivity of the carbonyl group and thus the potential utility of these compounds for further chemical transformations. There exists four principle conformations for the bicycles created in the *α,α'*-annelation reaction, which are shown in Figure 10, with the substituents removed for clarity.



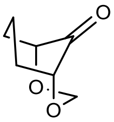
chair-chair

145



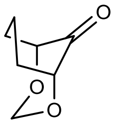
chair-boat

146



boat-boat

147



boat-chair

148

Figure 10. Principle conformations of 2,4-dioxabicyclo[3.3.1]nonanes

As X-ray analysis does not confer any information about conformation in solution, NMR studies were performed to extract this information. Analysis of GOESY data of *endo* ester **100** reveals a positive nOe between the α-hydrogens of the ketone and one of the methyl groups from the acetal. The other methyl group shows an nOe to the hydrogens of the methyl ester. This combination suggests a chair-boat conformation analogous to the X-ray crystal structure (Figure 11).

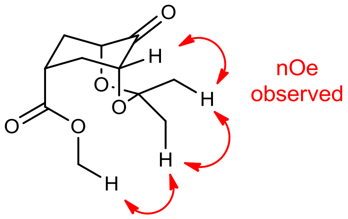


Figure 11. GOESY results for **100**

Similarly, the nOe correlations observed for benzylidene acetal **140** point to a chair-boat type conformation. The presence of a strong nOe from the benzylic hydrogen to the α-hydrogen of the ketone and the absence of an nOe from the α-hydrogens of the ketone to the α-hydrogen of the ester rules out either a boat-boat or chair-chair conformation given that the number of bonds between the two hydrogens is the same. Therefore, the conformation must either be a chair-boat or a boat-chair and the nOe pattern suggests a boat conformation for the dioxanone ring. The nOe pattern for the ortho-acetal **141** is analogous to **140** described above (Figure 12).

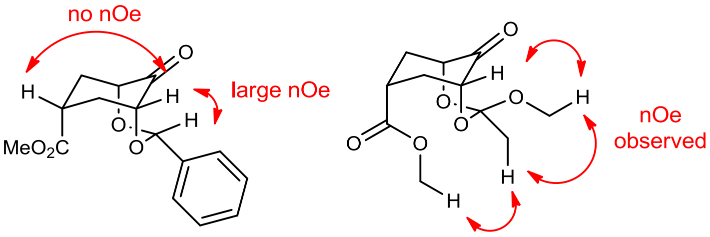


Figure 12. GOESY results for **140** and **141**

In the case of *exo* ester **101** the *J* coupling patterns suggest a chair conformation in the carbocycle ring. The axial proton α to the ester group is a triplet-of-triplets, with one large (13.4 Hz) and one smaller (4.6 Hz) coupling constant. The larger coupling constant is consistent with a *trans* diaxial arrangement of hydrogens in the ring. Also of note is the large shift (from 2.58 ppm to 3.55 ppm) of the proton α to the ester group compared to the *endo* ester **100**, which can be rationalised in terms of the anisotropy of the two axially orientated oxygens. In general, protons adjacent to carbonyl groups on six membered rings are shifted upfield when equatorial compared to axial.[43]

The other three *endo* esters **140-142** and their products following epimerisation have very similar ^{1}H NMR spectra compared to the *exo* and *endo* ketones **100** and **101** respectively, i.e. there is a large downfield shift (~ 1 ppm) of the proton α to the ester group between the *endo* and *exo* stereoisomers. This, along with the large *J* couplings for each epimerization products of **140-142** suggests a similar chair conformation for all four of the *exo* ester carbocycles and retention of the boat conformation of the dioxanone ring. As confirmation, GOESY experiments on *exo* ester **143** were carried out. The strong nOe between the α-hydrogens of the ketone and the benzylic hydrogen remains, whilst a smaller nOe is now detected to the α-hydrogen of the ester (Figure 13).

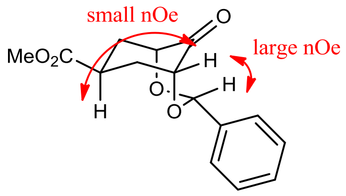
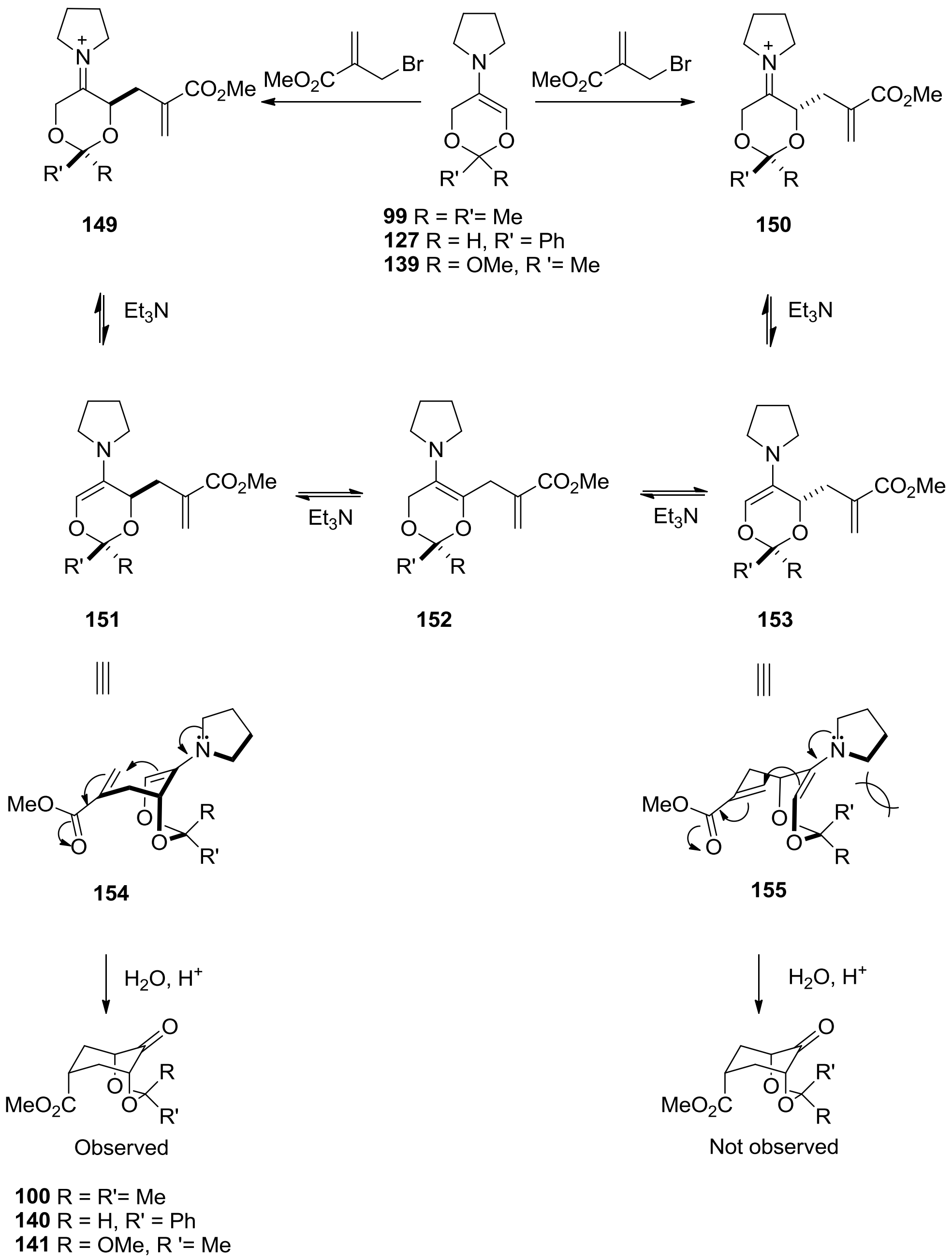


Figure 13. GOESY results for **143**

Finally, variable temperature NMR experiments on ketones **101**, **143** and **144** have shown no evidence of any averaging conformations at normal temperatures since the low temperature (down to -60 °C) ^{1}H-NMR spectra are near-identical to the room temperature experiments.

2.6 Mechanistic interpretation

The diastereoselectivity of the *α,α'*-annelation reactions can be rationalised by considering the Michael addition step in the mechanism after the initial *C*-alkylation of the enamine. Scheme 47 describes the evolution of the two diastereomers **151** and **153** from two different iminium ions **149** and **150** respectively, which are in equilibrium with one another. The subsequent Michael addition step has to occur *via* a boat conformation of the dioxane ring to avoid unfavourable *trans*-diaxial interactions that would arise in the alternate chair in order to orientate the ester group axially.[10]



Scheme 47

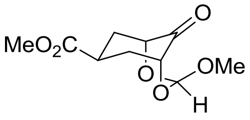
In the case of the benzyildene acetal the phenyl group would prefer to be in a pseudoequatorial position on the boat **154** (R’ = Ph) in order to avoid the very significant steric interaction between the flagpole phenyl group and the pyrrolidine ring in a boat conformation **155**. Since these two forms can interconvert under the reaction conditions, this therefore leads to **140** as the only observed product after kinetic protonation (from the least hindered top face, *anti* to the dioxane ring) and iminium hydrolysis. Similarly, the same steric argument can be applied to the ortho-acetal, though the magnitude of the interaction is reduced in this instance. However, in addition to the steric effect there may exist an added stabilisation by an anomeric effect with the flagpole methoxy group leading again to the single observed diastereomer **141**.

In addition to the assertion by Lawton *et al.* that the Michael addition step must take place with the ester group axial and thus a boat conformation must be adopted by the existing ring, Peters *et al.* proposed that the mechanism may instead proceed through an alternative half-chair transition state (see Section 1.2). Peters *et al.* based their explanation on the fact that the stereochemistry of their products of similar α,α'-annelation reactions were opposite to those expected based on the work by Lawton *et al.* The observed results from the systems investigated here are in accordance with the predictions made by Lawton rather than Peters.

2.7 Conclusions and future work

A set of four bridged bicycles have been synthesised utilising a one-pot enamine formation - *α,α'*-annelation sequence from 1,3-dioxan-5-ones in good overall yields and with complete diastereoselectivity. Determination of each bicycle's configuration and the mechanistic origin of the diastereoselectivities observed have been discussed. Conformations of each, both in solid and solution phase have been determined. Subsequent epimerization of these products has been undertaken and optimised and again, the products' conformations probed. Following epimerization, these *meso* ketones provide a good entry point into possible total synthesis of some natural products, in particular phyllaemblic acid **80** and its derivatives.

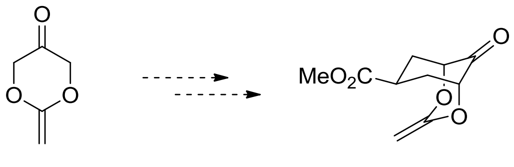
In order to further study the diastereoselectivity of the α,α’-annelation reactions of 1,3-dioxan-5-ones, it would be interesting to replace the methyl group of the ortho-acetal with a hydrogen atom to investigate the relative importance of sterics and stereoelectronic effects (Figure 14).



156

Figure 14. Proposed alternative ortho-ester

In addition, a methylene acetal **157** could be constructed with the aim to create a chair-chair conformation in the resulting bicyclic product **158**, with potentially interesting consequences on ketone reactivity. The lone pairs on the oxygens on the dioxanone ring may then influence nucleophilic addition reactions, possibly creating a preference for a nucleophile to attack the lower face of the ketone (Scheme 48).



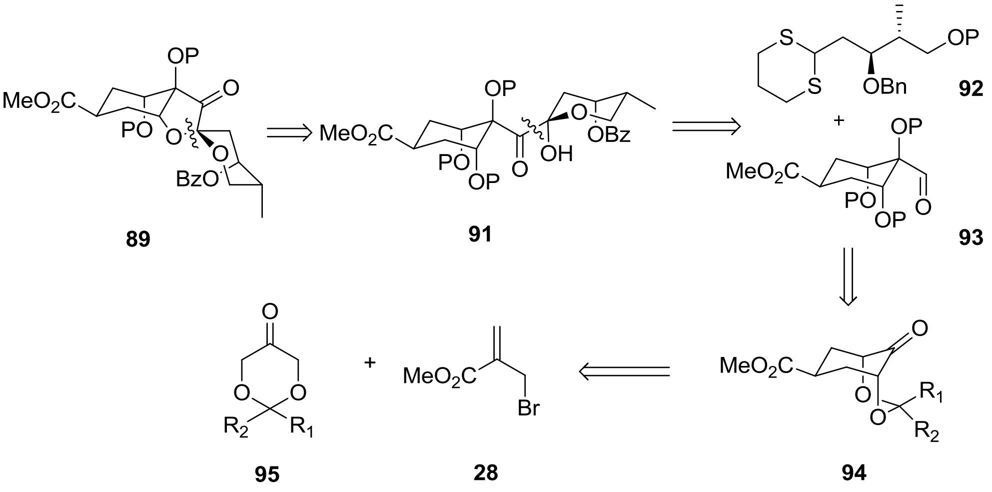
157 **158**

Scheme 48

Chapter Three: Synthetic approaches to phyllaembic acid its derivatives

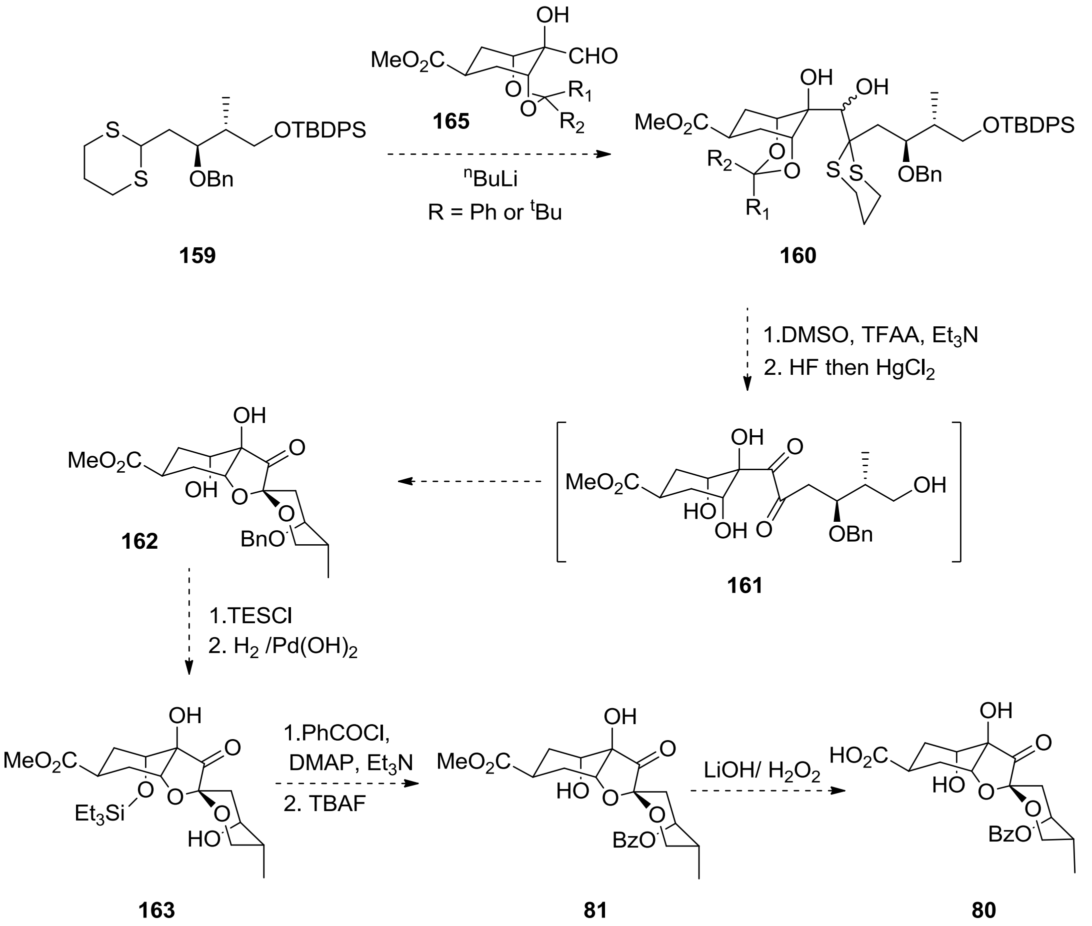
3.1 Aims and objectives

As discussed in Chapter 1, the development of α,α'-annelation reactions on 1,3-dioxan-5-ones could have application in the synthesis of certain natural products. As a result of the work carried out in Chapter 2, attention now turned toward the longer term objective of incorporating the work into a total synthesis project, specifically studies towards the total synthesis of phyllaemblic acid **80** and its structurally related compounds. Retrosynthetic analysis of **89** is briefly discussed in Section 1.4.



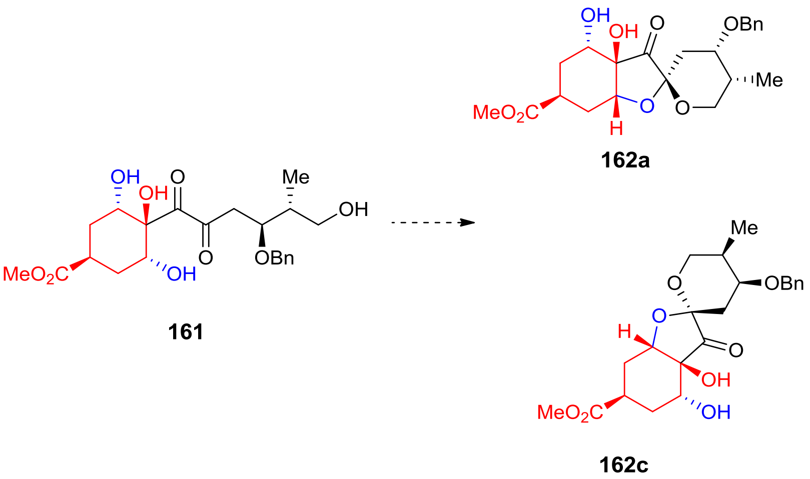
Scheme 49

meso Aldehyde **93** is one of two key intermediates in a potential total synthesis of phyllaemblic acid **80** and its derivatives. The forward synthesis is proposed in Scheme 50 utilising the diol protecting group strategy imbedded within the *α,α'*-annelation reaction. If carbon-carbon bond formation could be achieved at the ketone of the bridged bicycle **94** in good yield and stereocontrol, there exists a number of other ways to elaborate this to *meso* aldehyde **93**. The following forward reaction pathway from the coupling of a protected dithiane **159** and *meso* aldehyde **165** provides a reasonable starting point.



Scheme 50

This route allows for a potential convergent synthesis of phyllaemblic acid methyl ester **81** in 7 steps and phyllaemblic acid **80** in 8 steps from the *meso* aldehyde **165** and dithiane **159**.[33,34] One of the key steps in this route is the spiroacetal formation, which is inspired from Burke's synthesis of phyllanthocin, except in this case there exists the possibility of spiroacetalisation from either hydroxyl group leading to four possible diastereomeric spiroacetals.[29] However, it is thought that the dominant form would be the one required for phyllaemblic acid's construction (Scheme 51) as it is likely to be the thermodynamically preferred product based on previous spiroacetalisations in Nature, with a few notable exceptions.[44] The anomeric effect, non-bonding steric interactions caused by the methyl group placed equatorially on the tetrahydropyran ring and the possibility that the remaining hydroxyl can form an intramolecular hydrogen bond (in a six membered array) to the oxygen in the tetrahydrofuran ring may all contribute to the stability of diastereomers **162a** and **162d** over **162b** and **162c**. Energy minimisation calculations at the RHF 6-31G* level of theory have also been undertaken and suggests that the desired diastereomer **162a** being favoured by 2.9 kcal mol^{-1} over **162d**.[45]



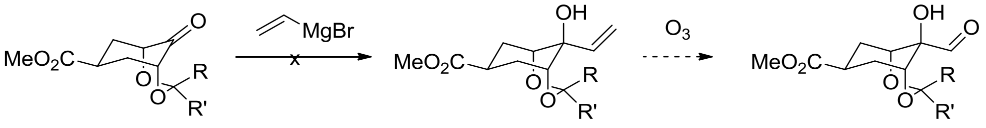
Scheme 51

With this precedent and computational results in hand, work began to elaborate the bridged bicyclic ketones described in Chapter 2 towards the natural products. If successful, their related glycosides could then be pursued and their potential as biological agents tested.

3.2 Nucleophilic addition reactions to the bridged bicycles

Previous attempts in the Grainger group to add both organolithium and Grignard reagents to the ketone of bicycle **101**, in order to achieve carbon-carbon bond formation, were fruitless (see section 1.4). Adaption of the diol protecting group as described in

Chapter 2 allowed for possible alternate reactivity at the ketone functionality. Firstly, vinylmagnesium bromide was chosen, as addition from the lower face would allow for subsequent ozonolysis or dihydroxylation and oxidative cleavage to afford a *meso* aldehyde suitable for coupling with dithiane **159** (Scheme 52). If attack occurred on the opposite face, there remains potential for the stereochemistry to be reversed *via* reforming an sp^2 centre at a later point. Unfortunately, no carbon-carbon bond formation was observed for any of the three bicyclic esters **101**, **143** or **144** with excess vinylmagnesium bromide (Table 6).



101 R = R' = Me
143 R = H, R' = Ph
144 R = OMe, R' = Me

164

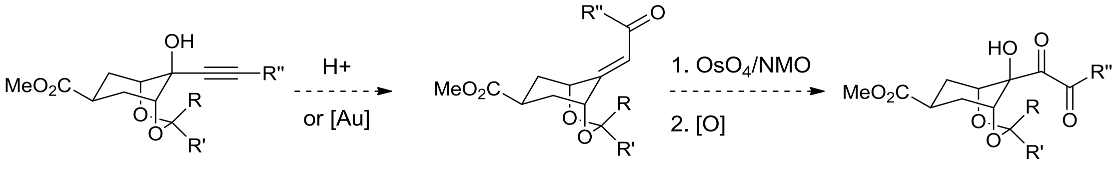
165

Scheme 52

Entry	Ketone	Nucleophile	Solvent	Temperature (^{o}C)	Result
1	***143***	$CH_2CHMgBr$	*THF*	*–78 - rt*	*SM*
2	***144***	$CH_2CHMgBr$	*THF*	*–78*	*decomposition*
3	***143***	$LiCCC_4H_9$	*THF*	*–78*	***169*** *(35%)*
4	***101***	$LiCCC_4H_9$	*THF*	*–78 - rt*	*SM*
5	***144***	$LiCCC_4H_9$	*THF*	*–78 - rt*	*decomposition*

Table 6: Attempted addition reactions to bicyclic ketones

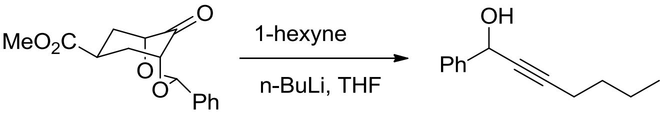
Alternatively, a Meyer–Schuster type rearrangement, promoted by either acid or a gold catalyst[46] was envisaged following addition of a suitable alkyne to the ketone. This would then have potential to be manipulated to a diketone **168** suitable for further manipulation to the natural product(s) (Scheme 53).



166 **167** **168**

Scheme 53

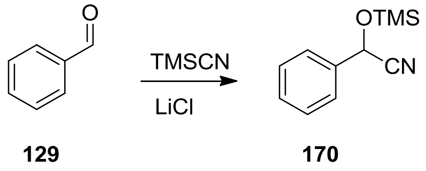
In a model study, attempted addition of hexynyl anions to bicyclic esters **101** and **144** resulted in starting materials being recovered or decomposition, respectively. In contrast, however, reaction with benzylidene acetal **143** afforded an unexpected product **169** (Scheme 54). Instead of alkyne addition to the ketone carbonyl, attack at the acetal carbon occurred, either directly or as a result of fragmentation/deprotection, though given the lack of any reactivity with acetals **101** and **104**, the former explanation is more convincing.



143 **169**

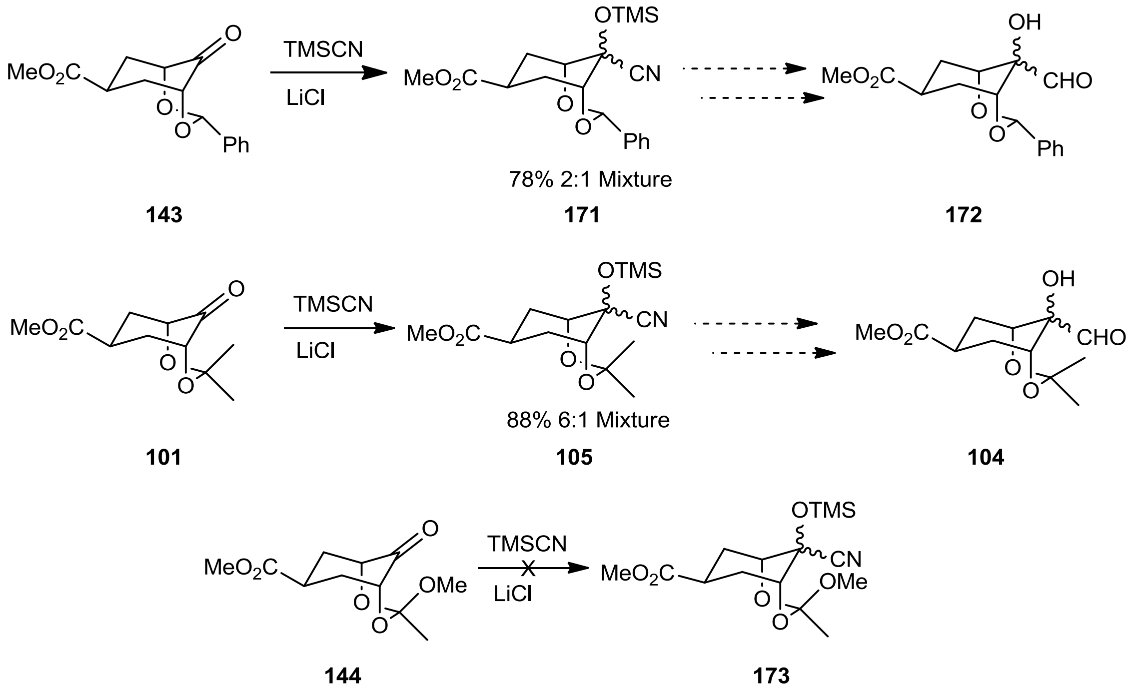
Scheme 54

In light of the failure of organometallic reagents to affect the necessary carbon-carbon bond formation despite alteration of the diol protecting group, an alternative route to a *meso* aldehyde **93** was devised *via* initial cyanohydrin formation. Firstly a test system was investigated (Scheme 55). Neat TMSCN was added to benzaldehyde, along with LiCl as a Lewis acid to afford the silyl protected cyanohydrin in quantitative yield.[47]



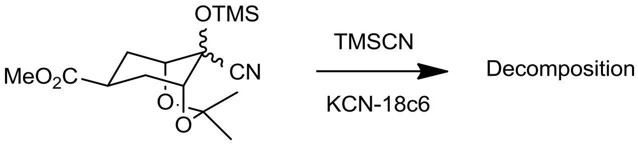
Scheme 55

These conditions were then applied to each of the three bicyclic esters **101**, **143** and **144**, to give diastereomeric mixtures in good yields. The ratio of stereoisomers observed depends on the identity of the diol protecting group (Scheme 56). Acetonide **101** showed the highest selectivity, possibly due to greater steric hindrance from the bottom of the ketone carbonyl. This cannot be confirmed since the identities of the major and/or minor stereoisomers could not be determined; nOe analysis was inconclusive and repeated attempts to grow a single crystal for X-ray analysis were unsuccessful. Interestingly, ortho-acetal **144** did not react to form a cyanohydrin under the same conditions as the other two acetals, but rather decomposition was observed, perhaps reflecting the sensitivity of the ortho-acetal towards Lewis acids.



Scheme 56

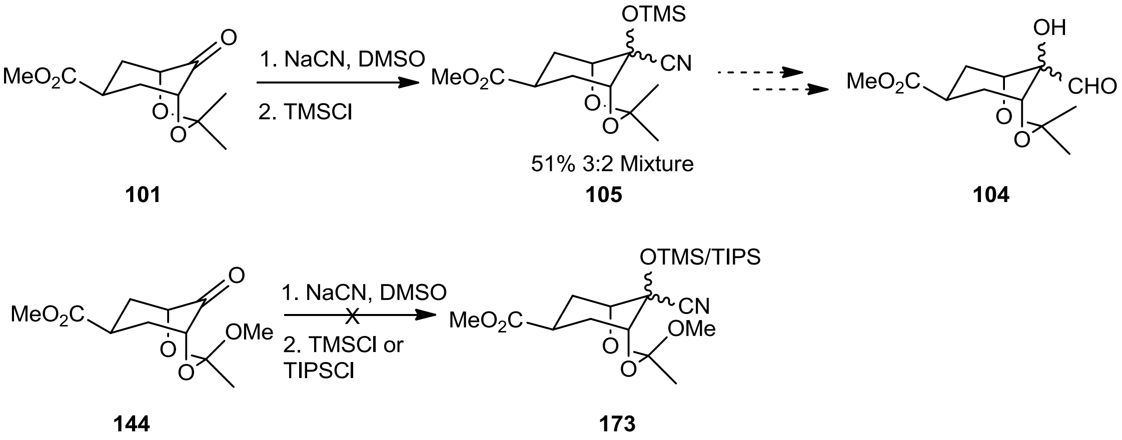
The silyl protected cyanohydrin mixture **105** was also subjected to reported thermodynamic equilibrium conditions in an attempt to alter the ratios of the stereoisomers present. Potentially, this could lead to one of two outcomes, either of which may be beneficial. Firstly, the ratio could increase to favour the major stereoisomer leading to an enhancement in the yield of the desired compound, assuming the major stereoisomer was indeed the desired compound. Alternatively, a reversal of the ratio, either partial or total, to favour the minor stereoisomer instead may be achieved in case the previous presumption that the major stereoisomer was the desired one was incorrect. It is presumed that if the chair-boat conformation were to be retained, the silyl protected hydroxyl would preferentially reside axially, to avoid the steric clash with the methyl groups from the acetal moiety. Unfortunately, subjecting the 6:1 mixture of **105** to Evans' conditions[48] caused decomposition to occur, resulting in loss of all of the starting material (Scheme 57).



105

Scheme 57

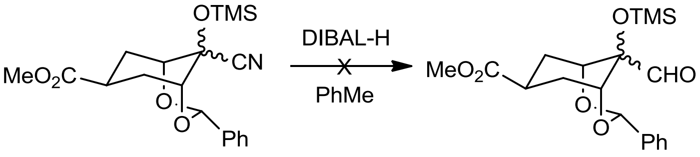
Notably, an alternate two step procedure[49] to form the protected cyanohydrins resulted in a reversal of the ratios, but in reduced overall yield (Scheme 58). With these complementary methods identified it is possible to tune the reaction to provide favourable ratios of the correct stereoisomer, to be identified further down the synthetic route. Ortho-acetal **144**, as in the previous cyanohydrin formation, remained incompatible to the reagents and/or conditions, leading to decomposition.



Scheme 58

With a reliable method for synthesizing silyl protected cyanohydrins in hand, attention turned to elaborating them to the target *meso* aldehyde **93.** It was envisaged that a reduction of the nitrile group in **171** with DIBAL-H would afford **174** in a single step, as a mixture of diastereomers (Scheme 59). The aldehyde proton would also potentially aid in nOe studies to determine the identities of the diastereomers. However, subjecting

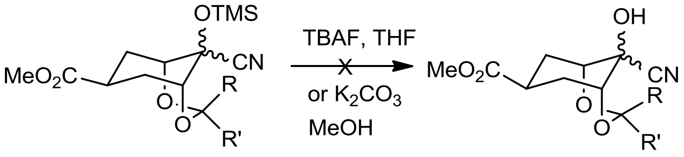
171 to increasing equivalents (3, 6 and 12) of DIBAL-H at low temperatures[50] resulted in a variety of products whose identities could not be determined.



171 **174**

Scheme 59

A brief study into deprotecting the OTMS group was undertaken. No deprotection of the silyl group was detected for **105** and **171** using TBAF or under base-catalysed methanolysis conditions.

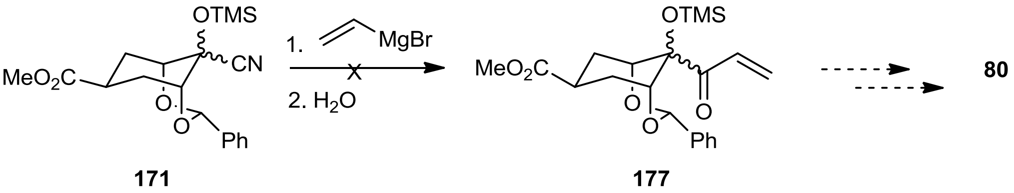


105 R = R' = Me
171 R = H, R' = Ph

175 R = R' = Me
176 R = H, R' = Ph

Scheme 60

An alternative way of introducing the carbonyl functionality from the nitrile was proposed *via* direct Grignard addition, initially forming an imine followed by subsequent hydrolysis (Scheme 61). Vinylmagnesium bromide was selected as the nucleophile due to its availability and potential for further alkene manipulation. Like previous Grignard additions, no addition was observed and only the starting material **171** was recovered.

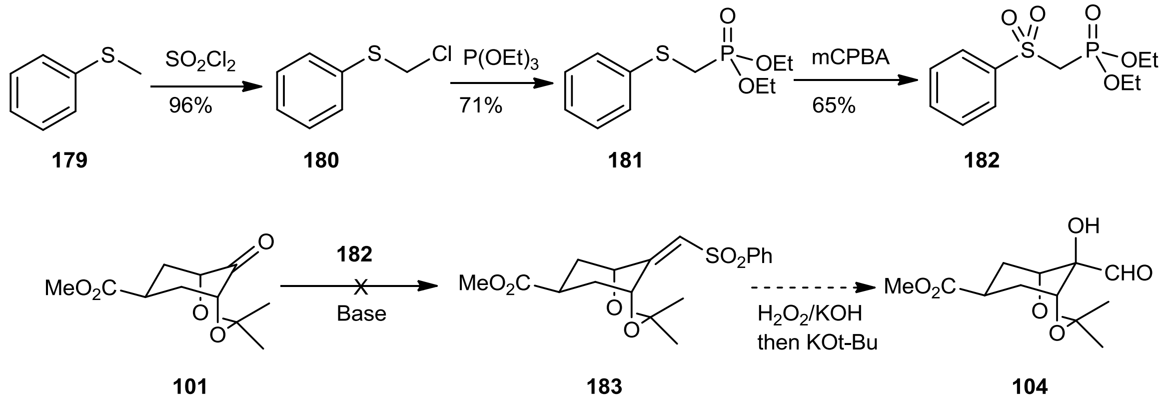


Scheme 61

3.3 Olefination reactions of the bridged bicycles

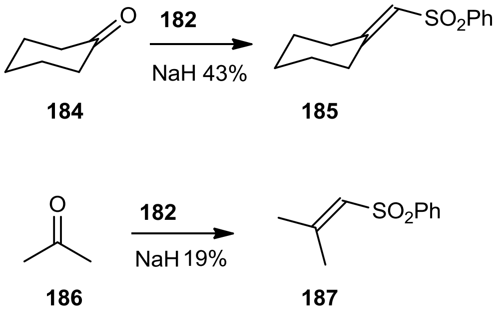
In order to elaborate the bicyclic ketones **101** to a *meso* aldehyde **93,** a new carbon-carbon bond must first be established. As discussed in previous sections, ketone **101** was quite unreactive to many carbon-carbon bond forming reactions. However, olefination chemistry proved partially successful in previous work.[37] As a result, Wittig reactions of the bicycles **101** and **143** were conducted. It was proposed that the *exo*-cyclic alkene could then be selectively dihydroxylated, or alternatively epoxidised, to a desired *meso* aldehyde **93**. Firstly, following on from previous experiments within the group, acetonide **101** was reacted with the ylide of Ph_3PMeBr with *n*-butyllithium, to give the desired alkene **106** in 16% yield compared to 38% previously reported with potassium *tert*-butoxide. Repeating the experiments with potassium potassium *tert*-butoxide gave no product formation at all. Previous work in the group had shown that **106** was resistant to dihydroxylation with OsO_4/NMO or under Sharpless conditions.[37] Renewed attempts to epoxidize **106** with *m*CPBA resulted in recovery of starting material (Scheme 29).

HWE reactions that utilise more reactive phosphonates were therefore examined. A vinyl sulfone **183** was proposed as a new precursor to *meso* aldehyde **104** (Scheme 63).



Scheme 62

Synthesis of the phosphonate **182** from thioanisole **179** was accomplished in 44% overall yield, comparable with the yield reported in the literature.[51,52] Two simple test systems, cyclohexanone and acetone, were first investigated to determine suitable conditions for the HWE reaction. For cyclohexanone, two bases were used to carry out this transformation, firstly sodium hydride, giving a modest yield of 43% for the vinyl sulfone **185**, and secondly *n*-butyllithium, with a similar yield of 39% (Scheme 64). The reaction with acetone was less successful, affording the vinyl sulfone **187** in 19% yield, presumably due to some water contamination in the substrate.



Scheme 63

Applying these conditions, utilizing sodium hydride as base, to the bicyclic ketone **101** resulted in no observable product formation by ^{1}H-NMR spectroscopy, with only starting materials recovered by column chromatography. Later, ortho-acetal **144** was subjected to the HWE conditions outlined above and although some enone formation was observed in the ^{1}H-NMR spectrum of the crude mixture, no product was isolated. The results of the HWE reactions are summarised in Table 7.

Entry	Ketone	Base	Solvent	Conditions	Result
1	***156***	*NaH*	*THF*	*16 h, 0 ^{o}C-rt*	*19%*
2	***184***	*NaH*	*THF*	*16 h, 0 ^{o}C-rt*	*43%*
3	***184***	*^{n}BuLi*	*THF*	*16 h, 0 ^{o}C-rt*	*39%*
4	***101***	*NaH*	*THF*	*16 h, 0 ^{o}C-rt*	*SM*
5	***101***	*NaH*	*THF*	*16 h, reflux*	*SM*
6	***144***	*NaH*	*THF*	*16 h, 0 ^{o}C-rt*	*trace*

Table 7. Attempted HWE reactions of ketones with phosphonate **182**

3.4 Alternate diol protecting group strategy

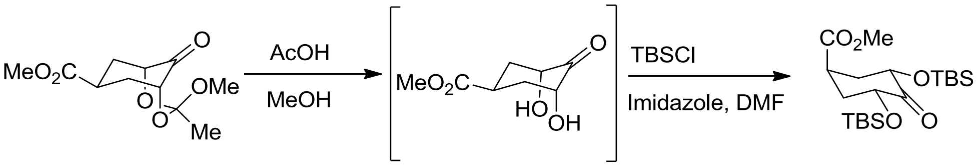
In light of the poor reactivity of the bicycles in general, it was decided that alternative cyclic and non-cyclic protecting groups for the hydroxyl groups should be investigated. The acetal group needs to be removed *following* annelation and subsequent epimerisation due to the need to retain the stereochemistry introduced during the annelation reaction. Initial attempts to deprotect the acetal groups were frustrating. The diol product was expected to be highly polar so both column chromatography and aqueous work ups were intentionally avoided. Small scale experiments using acids on

143 and **144** often resulted in no reaction, some even at elevated temperatures (Table 8). Eventually ortho-acetal **144** was found to be susceptible to extended methanolysis at elevated temperatures with acetic acid. The product was insoluble in several different organic solvents and the ^{1}H-NMR spectrum was very complicated, possibly owing to several different conformations in solution, dimerization and impurities. It is estimated based on mass recovery that the deprotection is close to 100% effective.

Entry	Ketone	Acid	Solvent	Conditions	Result
1	***144***	*pTSA*	*MeOH*	*24 h, rt*	*SM*
2	***143***	*Silica*	*MeOH*	*24 h, rt*	*SM*
3	***143***	*AcOH*	*MeOH*	*24 h, rt*	*SM*
4	***144***	*AcOH*	*MeOH*	*24 h, rt*	*SM*
5	***143***	*AcOH*	*MeOH*	*48 h, reflux*	*SM*
6	***144***	*AcOH*	*MeOH*	*48 h, reflux*	*quantitative*

Table 8. Deprotection of bicyclic ketones

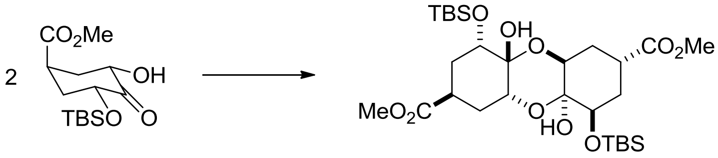
Attention turned to a non-cyclic protecting group. The diol **188** was used directly in a silyl protection step with *tert*-butyldimethylsilyl chloride, without further purification. This gave the monocyclic ketone **189** in 74% over two steps (Scheme 65).



144 **188** **189**

Scheme 64

Some early experiments occasionally afforded the monoprotected diol **190**, which was also isolated (Scheme 66). This exists as a tricyclic dimer **191** in solution as determined by ^{13}C-NMR, specifically the lack of a carbonyl peak corresponding to the ketone functionality. Mass spectrometry also supports the formation of the dimer. Increased equivalents of TBSCl were used to ensure protection of both hydroxyl groups to give **189**.



190 **191**

Scheme 65

X-ray crystallographic analysis of the fully protected diol **189** confirmed the retention of relative stereochemistry following deprotection and re-protection of the hydroxyl groups (Figure 15). The molecule exists in a chair conformation in the solid state, with the bulky *tert*-butyldimethylsilyloxy groups orientated equatorially and the ester group axial.

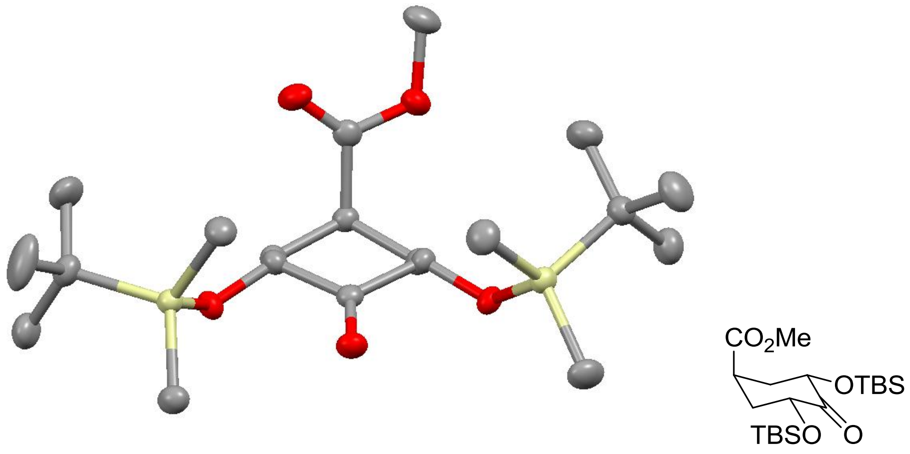
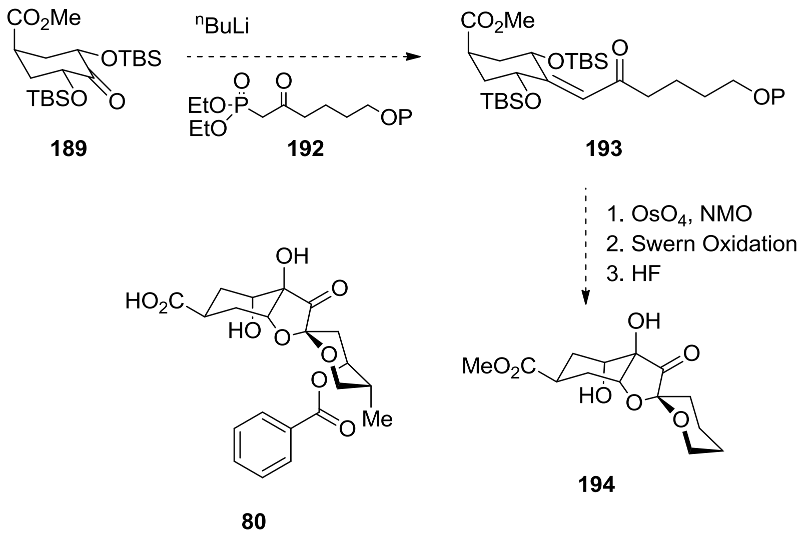


Figure 15. X-ray crystal structure of **189**

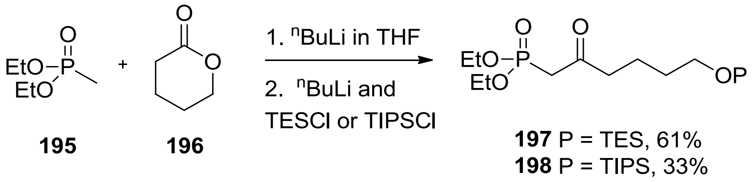
The ^{1}H-NMR of **189** also suggests this conformation is adopted in solution, signified by the lack of a large *J* coupling value of the α-hydrogen of the ester consistent with it residing equatorial on a chair. Further evidence of the chair conformation being adopted in solution is a large *J* coupling value of the α-hydrogens of the ketone, consistent with them being situated axially.

With ketone **189** in hand and its stereochemistry and conformation identified, previous methodology to effect carbon-carbon bond formation at the ketone moiety was re-investigated. Specifically, it was envisaged that HWE reaction with a simple phosphonate would potentially allow for the construction of a core structure **194** in as few as four steps from **189** (Scheme 67). This core structure **194** could then be adapted for a total synthesis of **80** by addition of further functionality on the phosphonate.



Scheme 66

Syntheses of two phosphonates, which varied by protecting group, were achieved in modest yields from δ-valerolactone and diethylmethylphosphonate (Scheme 68). Results of attempted formation of enone **193** from phosphonates **197** and **198** are given in Table 9.



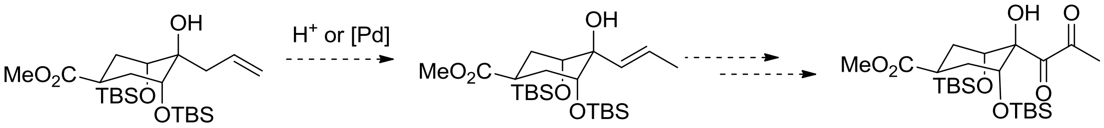
Scheme 67

Entry	Phosphonate	Base	Solvent	Conditions	Result
1	***197***	*^{t}BuOK*	*Toluene*	*16 h, 0 °C -rt*	*SM*
2	***197***	*NaH*	*THF*	*16h, 0 °C -rt*	*SM*
3	***197***	*^{n}BuLi*	*Toluene*	*24h, 0 °C - reflux*	*SM*
4	***198***	*^{n}BuLi*	*Toluene*	*24h, 0 °C- reflux*	*SM*
5	***198***	*DBU*	*MeCN*	*LiCl, 24h rt, 24h reflux*	*SM*
6	***198***	*tert-Amyl*	*THF*	*16 h, 0 °C -rt*	*SM*
7	***198***	*LHMDS*	*THF*	*6h -78 °C, 16h rt*	*SM*

Table 9. Attempted HWE reactions of monocyclic ketone **189**

A number of different bases, solvents and conditions were screened, but in each case no product formation was observed in any of the experiments undertaken. Although the steric hindrance of having a bicyclic ketone has been reduced, the bulky OTBS groups may still pose a significant steric obstacle to the approach of the relatively large phosphonate. The previous sulfone phosphonate **182** with NaH in THF was also trialled as before with the bicyclic ketones, but the same lack of reactivity was again observed.

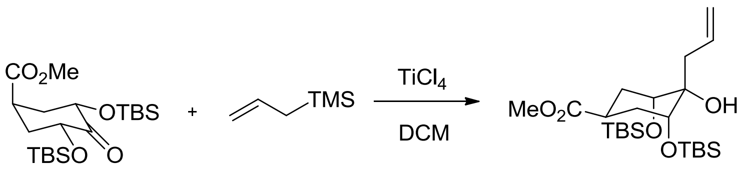
Encouraged by the Lewis acid assisted, TMSCN additions to bicyclic ketones **101** and **143** in Section 3.2, type II allylations were investigated on the monocylic ketone **189**. If addition of an allyl group could be achieved to the correct face of the ketone, a route to the natural product could be envisaged by double bond migration and subsequent oxidations (Scheme 69).



199 **200** **201**

Scheme 68

Allyltrimethylsilane in the presence of $TiCl_4$ was successfully added to the ketone functionality present in **189** to give homoallylic alcohol **203** as a single diastereomer in 58% yield (Scheme 70).



189 **202** **203**

Scheme 69

Unfortunately, nOe analysis on this molecule determined it to be the wrong stereoisomer needed for the construction of the natural products (Figure 16). An nOe is observed between the CH_2 group on the allyl chain with only one set of signals corresponding to the CH_2 groups on the ring. This is highly suggestive of the allyl chain residing axially on the ring. Furthermore, the α-hydrogen of the ester shows non-equivalent nOes to the CH_2 groups on the ring and a large *J* coupling value, both indicative of this hydrogen also residing axially. Thus, the α-hydrogen of the ester and the allyl chain must be on opposite sides of the ring, contrary to the desired configuration.

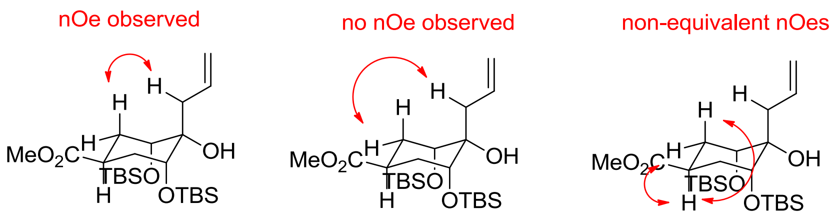
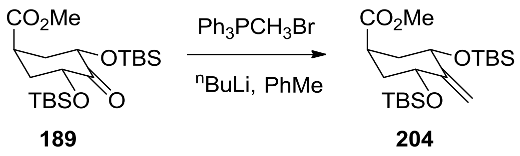


Figure 16. GOESY results of **203**

3.5 Construction of the *meso* aldehyde 207

Following the apparent resistance to HWE type chemistry to afford an enone capable of quickly leading to a possible core structure, work resumed on synthesising a *meso* aldehyde **93** described in Section 3.1 for a total synthesis of **80**. The Wittig reaction was revisited and a significant improvement in reactivity of the monocyclic silyl protected diol **189** over the three bicyclic acetals **101**, **143** and **144** was noticed (Table 10).

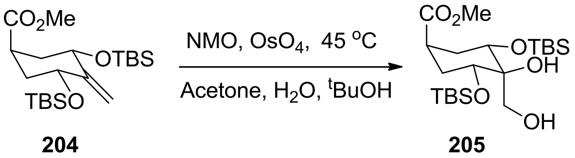


Scheme 70

Entry	Base	Solvent	Conditions	Result
1	*NaH*	*PhMe*	*16 h, 0 °C - rt*	*SM*
2	*NaH*	*DMSO*	*24h, reflux*	*SM*
3	*^{n}BuLi*	*PhMe*	*16h, 0 °C -rt*	*57%*
4	*tert-Amyl*	*PhMe*	*2h, reflux*	*decomposition*
5	*NaH*	*PhMe*	*16 h, 0 °C - rt*	*SM*

Table 10. Wittig reaction of **189**

Although the 57% yield obtained is modest, it does represent the best yield for a single product in carbon-carbon double bond formation from any of the ketones presented herein. The alkene **204** was subjected to dihydroxylation with OsO_4/NMO to afford the corresponding diol **205** in good yield and with complete stereocontrol.



Scheme 71

nOe analysis confirmed that the desired diol stereoisomer had been obtained, with the tertiary alcohol *syn* to the ester group (Figure 17, an OTBS group has been omitted for clarity). An nOe was observed between the CH_2 adjacent to the primary hydroxyl and one set of CH_2 signals on the ring, but not the other. This is consistent with the CH_2OH segment residing axially on a chair. The α-hydrogen of the ester group shows equal nOes to both CH_2 signals on the ring as well as a lack of a large *J* coupling value, suggesting an equatorial position on the ring.

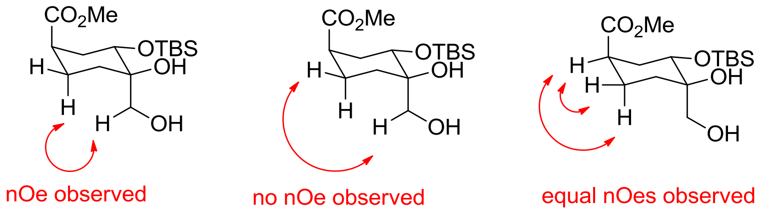
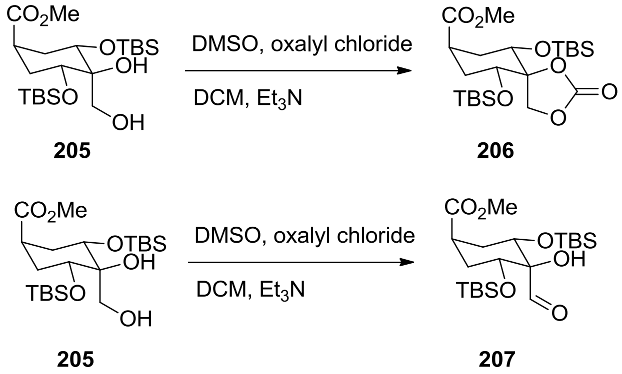


Figure 17. GOESY results for **205**

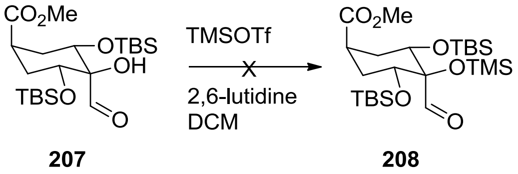
With the configuration and conformation of the diol now determined, the next step was oxidation to *meso* aldehyde **207**. Swern conditions were chosen to affect this transformation, however initial attempts afforded an undesired cyclic carbonate **206** in 39% yield (Scheme 73). This result was likely due to the direct reaction of the diol with oxalyl chloride instead of dimethylchlorosulfonium chloride. As a result, the time for dimethylchlorosulfonium chloride formation was increased during the experiment, giving the desired aldehyde **207** in 79% yield.



Scheme 72

3.6 Attempted coupling reactions with meso aldehyde 207

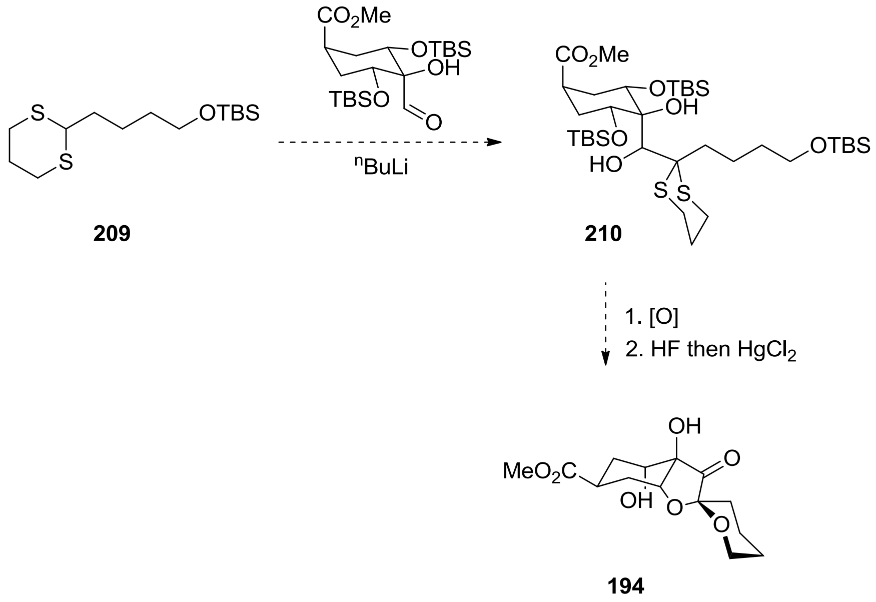
In order to better facilitate nucleophilic reactions at the aldehyde, protection of the tertiary alcohol with a TMS group was investigated. Trimethylsilyl triflate was added to the aldehyde **207** in DCM with 2,6-lutidine but no reaction was observed even with multiple equivalents of base and triflate, and extended reaction times of up to 5 days (Scheme 74).



Scheme 73

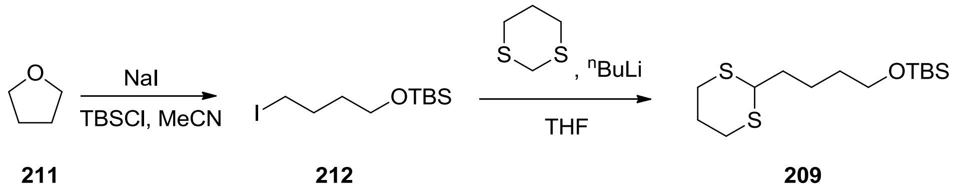
The lack of reactivity suggests that the tertiary alcohol may be sterically crowded, and protection at the diol stage may be more successful, where the tertiary alcohol had been shown to react (Scheme 73). This is likely aided by reaction of the primary alcohol group first, followed by an intramolecular attack. Since the primary alcohol must be free to be oxidised, several more steps would be needed to protect the tertiary alcohol whilst leaving the primary alcohol unprotected. With this in mind, the protection of the tertiary alcohol was abandoned.

As described in section 3.1, a *meso* aldehyde **93** could be reacted with a suitable dithiane to afford the natural products. A model system was devised to test the validity of such a reaction on novel aldehyde **207**. Successful carbon-carbon bond formation with a simple dithiane **209** with the correct carbon chain length would potentially allow for the synthesis of a core system **194** in three steps (Scheme 75).



Scheme 74

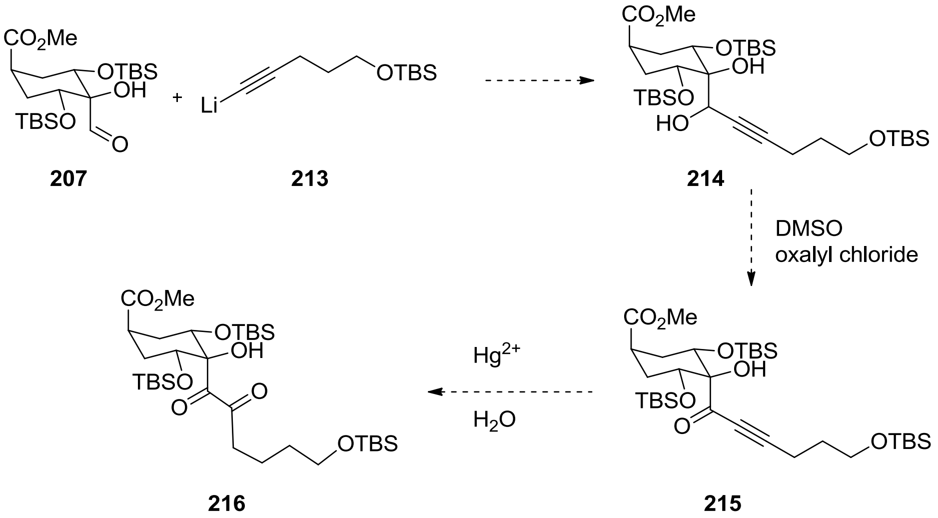
The dithiane **209** could be obtained in two steps from THF (Scheme 76). Treatment with NaI and TBSCl in a one-pot procedure afforded the desired iodide in 75% yield.[53] Displacement of the iodide with 1,3-dithiane gave **209** in a moderate 44% yield.



Scheme 75

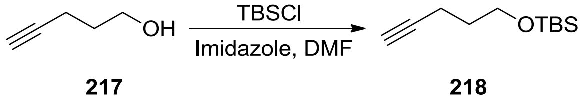
With both reagents available, coupling experiments began in earnest. Conditions were similar to those employed to synthesize dithiane **209**; initial deprotonation of **209** with *n*-butyllithium at -30 °C followed by addition of the electrophile. Unfortunately, no desired product was observed in any experiment and TLC analysis suggested little to no reaction was occurred.

The aldehyde remains in a crowded environment sterically, with two flanking OTBS groups hindering the approach of nucleophiles. However, the results described in this chapter suggest that carbon-carbon bond formation may still be achievable since ketone **189** has shown susceptibility to olefination and Lewis acid catalyzed addition. A new route was thus devised based on a potential hydration following an alkyne addition to aldehyde **207** (Scheme 77). This model system could also provide a short path to the core structure and eventual first generation synthesis of the natural products described in Chapter 1.



Scheme 76

Commercially available alkyne **217** was protected with TBSCl to **218** under standard conditions but with very low product formation of just 5% (Scheme 78). This, however, did provide enough material to test the coupling chemistry, the results of which are summarized in Table 11.



Scheme 77

Entry	Eqv. Of Nucleophile	Solvent	Conditions	Result
1	*2*	*DCM*	*–78 ^oC- rt, 24 h*	*SM*
2	*2*	*DCM*	*–78 ^oC -rt, 72 h*	*SM*
3	*2*	*THF*	*–78 ^oC - rt, 24 h*	*SM*
4	*2*	*THF*	*EtMgBr, –78 ^oC -rt, 24 h*	*SM*
5	*3*	*THF*	*CH_2=CHMgBr, –78 ^oC -rt, 24 h*	*SM*
6	*3*	*THF*	*–78 ^oC -rt, 2 eqv $BF_3.Et_2O$, 2 h*	*decomposition*
7	*1.5*	*THF*	*$CeCl_3$, 16 h, 0 ^oC -rt*	*SM*

Table 11. Attempted organometallic additions to **207**

Table 11, Entries 1-3 describe the addition of the alkynyllithium addition to the aldehyde in different solvents over different time periods but without positive results. Grignard reagents (Table 11, Entries 4 and 5) behaved similarly. Lewis acid catalysed addition, unlike in previous chemistry undertaken in Sections 3.2 and 3.4, lead to decomposition in this instance (Table 11, Entry 6). Finally, a cerium based reagent, known to be far less basic than organolithiums or Grignard reagents also failed to react with the aldehyde (Table 11, Entry 7).

3.7 Conclusions

Progress has been made on a number of synthetic strategies towards phyllaemblic acid **80** and its various derivatives and related compounds. The synthesis of the bridged bicyclic ketones, described in Chapter 2, have allowed for a robust and flexible approach towards these natural products. Specifically, there are multiple disconnections where the symmetry element remains a key component of a convergent synthesis, which is highly desirable in any synthetic endeavour.

Early work on keto-bridged dioxabicyclic ring systems proved frustrating, with low reactivity of the ketone functional group hindering progress from an early stage. Cyanohydrin formation showed the greatest promise for the development of a route incorporating the bicycles. However, the lack of stereoselectivity for some examples, difficulty in characterising the products and ultimately their resistance to further transformations led to a re-think of strategy. Once the acetal protecting group was removed in favour of two silyl protecting groups reactivity improved significantly. Although the synthesis of a *meso* ketone was now longer, the improvement in synthetic utility far outweighs that downside. The synthesis of the desired *meso* aldehyde **207** was achieved after a short series of moderate-good yielding steps. From this advanced intermediate only a small number of steps potentially remain towards the synthesis of a core structure, very closely resembling the target natural products. Modification of a core structure synthesis could conceivably yield a total synthesis or one or more of the natural products. Each route contains the key spiroacetalisation step which due to its lateness in the synthesis has not been investigated in this work.

Chapter Four: Experimental Section

4.1 General experimental

All reagents were obtained from commercial sources from Aldrich, Acros, or Fisher.

Proton and carbo nuclear magnetic resonance spectra were recorded using a Bruker AC-300 (300 MHz) AV-300 (300 MHz), AVIII300 (300 MHz), AMX-400 (400 MHz) or DRX-500 (500 MHz) spectrometers. Chemical shifts are quoted in parts per million (ppm) relative to the residual solvent peak: $CDCl_3$ (^{1}H, 7.26 ppm; ^{13}C, 77.0 ppm), D_6-Benzene (^{1}H, 7.16 ppm; ^{13}C, 128.4 ppm), D_6-DMSO (^{1}H, 2.50 ppm; ^{13}C, 39.5 ppm) and D_6-Acetone (^{1}H, 2.05 ppm; ^{13}C, 206.68 ppm). The terms expressed in parentheses in order are; number of equivalent nuclei, multiplicity, coupling constant (*J*) where appropriate and assignment. The following abbreviations are used; s - singlet, d - doublet, t - triplet, q - quartet, m - mutiplet, and br - broad.

Mass spectra were obtained on a Micromass LCT spectrometer utilising electrospray (ES) ionisation (and a methanol mobile phase), or on a VG ProSpec mass spectrometer utilising electron impact (EI) ionisation.

Infrared spectra were recorded neat or in nujol mull on a Perkin Elmer 1600 series FTIR or a Perkin Elmer FT-IR Paragon 1000 spectrometer.

Melting points were determined using open glass capillaries on a Gallenkamp melting point apparatus and are uncorrected.

Flash column chromatography was carried out using silica gel 60 (0.040-0.063 mm).

Analytical TLC analysis was performed on Merck Silica Gel 60 F_{254} plates, visualised by UV light, and Anisaldehyde or $KMnO_4$ solution with heating.

Solvents and reagents were subject to the following purification procedures:

Tetrahydrofuran was distilled from sodium and benzophenone.

Toluene was distilled from sodium.

Methanol was distilled from magnesium and iodine.

Chloroform dried over 4 Å molecular sieves.

Dichloromethane was distilled from calcium hydride.

Diethyl ether was distilled from calcium hydride.

Acetonitrile was distilled from $P_2O_{5.}$

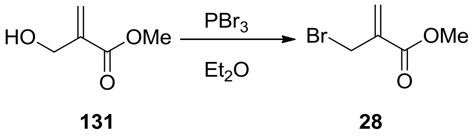
Pyrrolidine and triethylamine were distilled from either sodium metal or calcium hydride then stored over KOH pellets.

n-BuLi was titrated with menthol in the presence of 1-(biphenyl-4-yl)-3-phenyl-2-azapropene as indicator.

The following cold baths were utliased: 0 ^{o}C (ice/water), -78 ^{o}C (dry ice/acetone)

4.2 Experimental for Chapter Two

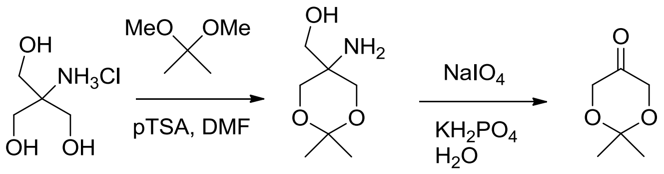
2-Bromomethyl-acrylic acid methyl ester 28



Synthesized using a modified literature procedure[54]

Phosphorus tribromide (8.37 g, 32.3 mmol) was added to a stirred solution of 2-hydroxymethyl-acrylic acid methyl ester (7.20 g, 62.0 mmol) in anhydrous diethyl ether (200 mL) at 0 ºC. The temperature was allowed to rise to rt and stirred for 4 h under an inert atmosphere. Distilled water (30 mL) was then added at 0 ^{o}C and the mixture extracted with hexane (3 × 50 mL). The organic layers were collected, washed with brine (50 mL) and dried over anhydrous $MgSO_4$, filtered and solvents removed under reduced pressure. Distillation under reduced pressure afforded the *title compound* as a colourless oil (8.79 g, 79%); bp 86 ^{o}C/20 Torr; ^{1}H NMR δ (300 MHz, $CDCl_3$) 3.77 (3H, s, CH_3), 4.14 (2H, s, CH_2), 5.93 (1H, s, C*H*), 6.29 (1H, s, C*H*); ^{13}C NMR δ (75.5 MHz, $CDCl_3$) 29.2 (CH_3), 52.2 (CH_2), 129.1 (CH), 137.2 (C), 165.2 (C); *m/z* (EI) 178 (M^+ 21%), 147 (27), 119 (23), 99 (100), 69 (13), 59 (43), 45 (7). Analytical data is in agreement with reported values.[54]

2,2-Dimethyl-1,3-dioxan-5-one 98



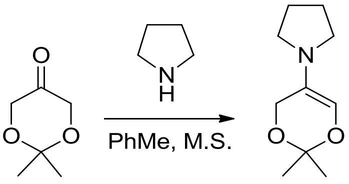
96 **97** **98**

Synthesized using a modified literature procedure[55]

2-Amino-2-hydroxymethyl-1,3-propandiol hydrochloride (38.5 g, 243 mmol), anhydrous *N*,*N*-dimethylformamide (200 mL), 2,2-dimethoxypropane (34.0 mL, 276 mmol) and *para*-toluenesulfonic acid (2.50 g, 13.1 mmol) were stirred together at 65 ^{o}C for 48 h. Triethylamine (1.77 mL) was added followed by removal of the solvent under reduced pressure. The residue was dissolved in ethyl acetate (600 mL) and triethylamine (28.0 ml) and stirred at room temperature for 2 h. The precipitate was filtered and the solvent was removed under reduced pressure affording the *ß*-amino alcohol as a white solid (31.0 g, 79%). This (7.50 g, 46.5 mmol) was then dissolved in distilled water (190 mL), KH_2PO_4 (6.24 g, 46.5 mmol) added and the solution was cooled to 0 ^{o}C. Then, an aqueous sodium periodate solution (9.97 g, 0.5 M) was added dropwise over 2 h whilst the temperature was maintained at 0-10 ^{o}C. The reaction was then allowed to warm to room temperature for 18 h. The organic layer was then extracted from the aqueous solution with dichloromethane *via* a continuous extractor for 48 h. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and the solvents removed under reduced pressure. The crude product was purified by flash column chromatography (1:1 diethyl ether/hexane) to afford the *title compound* as a volatile colourless oil (3.44 g, 57%); ^{1}H NMR δ (300 MHz, $CDCl_3$) 1.40 (6H, s, CH_3), 4.10 (4H, s, CH_2); ^{13}C NMR δ (75.5 MHz, $CDCl_3$) 23.4 (CH_3), 66.7 (CH_2), 100.0 (C), 207.8

(C); *m/z* (EI) 130 (M^+; 12%), 115 (27), 100 (30), 72 (39), 59 (8), 42 (100). Analytical data is in agreement with reported values.[55]

1-(2,2-Dimethyl-4H-1,3-dioxin-5-yl)-pyrrolidine 99

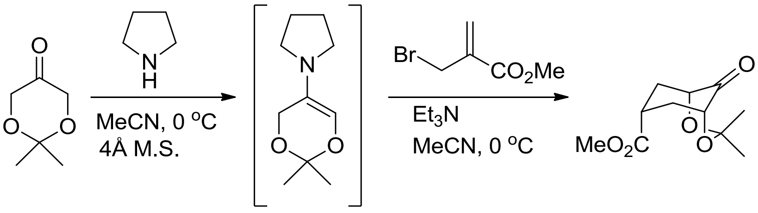


98 **99**

Synthesized using a modified literature procedure[36]

To a solution of 2,2-dimethyl-1,3-dioxan-5-one (0.99 g, 7.60 mmol) in dry toluene (7 ml) was added molecular sieves (4 Å, 1.90 g) and freshly distilled pyrrolidine (1.64 g, 23.0 mmol) under an inert atmosphere. The solution was stirred at room temperature overnight and then filtered, concentrated under reduced pressure and distilled to afford the *title compound* as a pale yellow oil (0.74 g, 53%); υ_{max} (neat)/cm^{-1} 1657, 1454, 1381, 1133, 840; ^{1}H NMR δ (300 MHz, CDCl$_3$) 1.43 (6H, s, CH$_3$), 1.83 (4H, quintet, *J* = 6.7 Hz, C*H*$_2$C*H*$_2$), 2.77 (4H, t, *J* = 6.7 Hz, C*H*$_2$NC*H*$_2$), 4.27 (2H, d, *J* = 1.3 Hz, OC*H*$_2$CN), 5.79 (1H, s, OC*H*CN); ^{13}C NMR δ (75.5 MHz, CDCl$_3$) 23.6 (CH$_2$), 24.0 (CH$_3$), 48.5 (CH$_2$), 60.2 (CH$_2$), 97.5 (C), 120.5 (CH), 125.1 (C); *m/z* (ES) 216 $[M + Na]^+$, 208, 184, 152, 126.

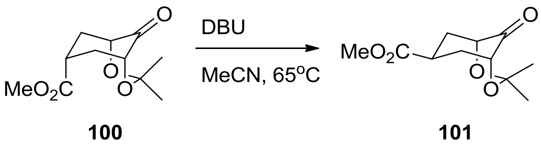
Methyl 3,3-dimethyl-9-oxo-2,4-dioxabicyclo[3.3.1]nonane-7α-carboxylate 100



98 **99** **100**

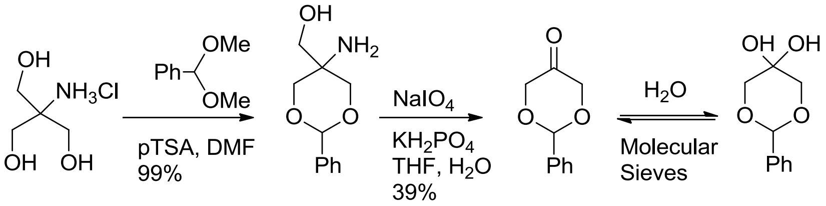
To an ice-cooled solution of 2,2-dimethyl-1,3-dioxan-5-one (0.501 g, 3.85 mmol) in anhydrous acetonitrile (10 mL) was added molecular sieves (4 Å, 4.00 g) and pyrrolidine (0.274 g, 3.85 mmol). The solution was stirred at 0 °C (external ice-bath temperature) for 5 h under an inert atmosphere. Triethylamine (0.39 g, 3.86 mmol) was added, followed by a solution of methyl α-(bromomethyl)acrylate (0.69 g, 3.85 mmol) in acetonitrile (30 mL) dropwise under an inert atmosphere. A precipitate quickly formed and re-dissolved. The resulting yellow solution was stirred for 16 h with gradual warming to room temperature. The solution was filtered to remove the molecular sieves, distilled water (40 mL) was added, and the resulting mixture was stirred at room temperature for 5 h. The mixture was then extracted with dichloromethane (3 × 40 mL), dried over anhydrous Na_2SO_4, filtered and solvents removed under reduced pressure. Purification by column chromatography (3:1 hexane:diethyl ether) afforded the *title compound* as a white solid (0.353 g, 40%): R_f 0.25 (1:1 hexane:diethyl ether); mp 65−67 °C; υ_{max} (nujol mull)/cm^{-1} 1745, 1456, 1023, 992; ^{1}H NMR δ (300 MHz, $CDCl_3$) 1.35 (3H, s, C*H*$_3$), 1.36 (3H, s, C*H*$_3$), 1.99 (2H, dd, *J* = 7.2, 14.4 Hz, C*H*$_2$), 2.58 (1H, t, *J* = 7.2 Hz, C*H*CO_2CH_3), 3.27 (2H, m, C*H*$_2$), 3.76 (3H, s, CO_2C*H*$_3$), 4.28 (2H, d, *J* = 3.9 Hz, C*H*CO); ^{13}C NMR δ (75.5 MHz, $CDCl_3$) 24.9 (CH_3), 27.9 (CH_3), 33.8 (CH), 38.8 (CH_2), 52.2 (CH_3), 76.8 (CH), 99.2 (C), 173.8 (C), 215.3 (C); *m/z* (EI) 229.1 $[M + H]^+$. Anal. Calc. for $C_{11}H_{16}O_5$: C, 57.88; H, 7.07. Found C, 57.77; H, 7.00.

Methyl 3,3-Dimethyl-9-oxo-2,4-dioxabicyclo[3.3.1]nonane-7β-carboxylate 101



Methyl 3,3-dimethyl-9-oxo-2,4-dioxabicyclo[3.3.1]nonane-7α-carboxylate (0.053 g, 0.232 mmol) was dissolved in acetonitrile (3 mL) followed by addition of DBU (0.035 g, 0.230 mmol). The reaction mixture was heated at 65 °C (external temperature) for 24 h, allowed to cool, and concentrated to approximately half volume. Column chromatography (4:1 hexane:diethyl ether) afforded the *title compound* as a white solid (0.041 g, 77%); R_f 0.47 (1:1 hexane:diethyl ether); mp 79−82 °C; υ_{max} (nujol mull)/cm^{-1} 1754, 1455, 1006, 964; ^{1}H NMR δ (300 MHz, $CDCl_3$) 1.42 (3H, s, CH_3), 1.50 (3H, s, CH_3), 1.93 (2H, t, J = 13.4 Hz, CH_2), 2.60 (2H, m, CH_2), 3.55 (1H, tt, J = 4.6, 12.6 Hz, C$H$$CO_2CH_3$), 3.67 (3H, s, $CO_2C$$H_3$), 4.28 (2H, d, J = 3.8 Hz, CHCO); ^{13}C NMR δ (75.5 MHz, $CDCl_3$) 25.0 (CH_3), 28.5 (CH_3), 33.0 (CH), 40.3 (CH_2), 52.0 (CH_3), 76.0 (CH), 98.7 (C), 174.2 (C), 214.0 (C); *m*/*z* (ES) 251.1 [M + Na]$^+$, HRMS (ES) [M + Na]$^+$ 251.0891, $C_{11}H_{16}O_5Na$ requires 251.0895.

2-Phenyl-1,3-dioxan-5-one 119



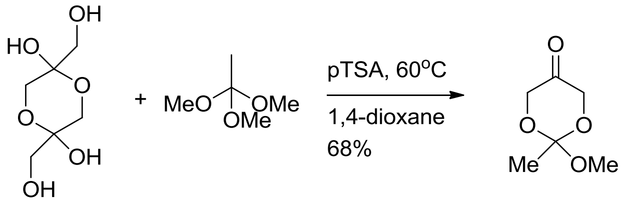
96 **121** **119** **122**

Synthesized using a modified literature procedure[55]

2-Amino-2-hydroxymethyl-1,3-propandiol hydrochloride (60.3 g, 381 mmol), anhydrous *N*,*N*-dimethylformamide (300 mL), 2,2-dimethoxypropane (47.9 mL, 381 mmol) and para-toluenesulfonic acid (3.45 g, 18.1 mmol) were stirred together at 65 °C for 48 h. Triethylamine (2.44 mL) was added followed by the removal of solvents under reduced pressure. The residue was dissolved in ethyl acetate (800 mL) and triethylamine (40 mL) and then stirred at rt for 2 h. The precipitate was filtered and the solvent was removed under reduced pressure affording as a white solid (71.9 g, 90%). 5-Amino-2-phenyl-1,3-dioxan-5-yl-methanol (56.94 g, 272 mmol) was then dissolved in 1:1 distilled water/THF (2 L), KH_2PO_4 (36.5 g, 272 mmol) added slowly and the solution was cooled to 0 °C. Then, an aqueous sodium periodate solution (58.3 g, 0.5 M) was added dropwise over 2 h whilst the temperature was maintained at 0-10 °C. The reaction gradually warmed to rt, and stirred for 18 h. The organic layer was then extracted from the aqueous solution with dichloromethane (10 x 200 mL). The combined organic layers were washed with brine and the solvents removed under reduced pressure. The crude product was then treated with an equivalent of water and recrystallized from hexane/$CHCl_3$ to afford the hydrate of the *title compound* as a white solid (37.1 g, 69%). ^1H NMR δ (300 MHz, C_6D_6) 3.86 (2H, d, J = 16.5 Hz, CH_2), 4.15 (2H, d, J = 16.5 Hz, CH_2), 5.38 (1H, s, PhCH), 7.26 (3H, m, PhH), 7.60 (2H, d, J = 9.0 Hz, PhH);

m/z (EI) 178 (M^+; 30%), 148 (100), 120 (47), 105 (96), 90 (42), 77 (25). Analytical data is in agreement with reported values.[56]

2-Methyl-2-methoxy-1,3-dioxan-5-one 120

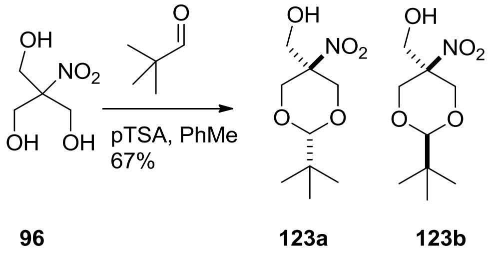


125 **126** **120**

Synthesized using a modified literature procedure[41]

Dimeric dihydroxyacetone (4.09 g, 22.7 mmol) and pTSA (50 mg, 263 μmol) were heated to 60 °C in 1,4-dioxane (200 mL) under an inert atmosphere. Ten minutes after the dimeric dihydroxyacetone was completely dissolved, trimethyl orthoacetate (60 mL, 57.0 g, 454 mmol) was added. The solution was stirred for 18 h at 60 °C and concentrated under reduced pressure. The resulting crude product underwent Kugelrohr distillation (140 °C/20 mmHg) to afford the *title compound* as a clear, colourless oil (3.88 g, 26.5 mmol, 58%); ^{1}H NMR δ (300 MHz, $CDCl_3$) 1.57 (3H, s, CH_3), 3.37 (3H, s, OCH_3), 4.16 (2H, m, CH_2), 4.33 (2H, m, CH_2). ^{13}C NMR δ (100 MHz, $CDCl_3$) 20.5 (CH_3), 51.3 (CH_3), 67.5 (CH_2), 112.3 (C), 204.5 (C). Analytical data is in agreement with reported values.[41]

cis /*trans*-2-tert-butyl-5-nitro-[1,3]dioxan-5-yl-methanol 123a and 123b

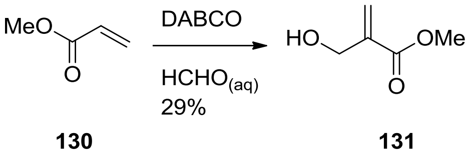


Synthesized using a modified literature procedure[32]

2-Hydroxymethyl-2-nitro-propane-1,3-diol (3.90 g, 25.8 mmol) was dissolved in anhydrous toluene (75 mL) and heated to 75 °C. Pivaldehyde (4.16 mL, 26.0 mmol) and *para*-toluenesulfonic acid (0.45 g, 2.37 mmol) were added and the mixture stirred for 24 h. Triethylamine (0.50 mL) was then added followed by the removal of solvents under reduced pressure, affording the *title compound* as a major/minor mixture which was then purified by column chromatography (1:1 hexane/diethyl ether) to elute firstly an orange solid (2.52 g, 44%); ^{1}H NMR δ (500 MHz, $CDCl_3$) 0.88 (9H, s, $C(CH_3)_3$), 1.89 (1H, t, J = 6.0 Hz, O*H*), 3.80-3.83 (4H, m, CH_2, CH_2OH), 4.13 (1H, s, *t*BuC*H*), 4.85 (2H, d, J = 12.7 Hz, CH_2). ^{13}C NMR δ (75.5 MHz, $CDCl_3$) 24.4 (CH_3), 34.9 (CH_2), 63.8 (CH_2), 68.4, 109.0. and then a white solid (1.30 g, 23%); ^{1}H NMR δ (500 MHz, $CDCl_3$) 0.92 (9H, s, $C(CH_3)_3$), 2.09 (1H, br, O*H*), 4.00 (2H, d, J = 11.5 Hz, CH_2), 4.11 (1H, s, t-BuC*H*), 4.28 (2H, br, CH_2OH), 4.42 (2H, d, J = 11.5 Hz, CH_2), ^{13}C NMR δ (75.5 MHz, $CDCl_3$) 24.4 (CH_3), 34.7 (CH_2), 62.5 (CH_2), 67.6 (CH_2), 83.0 (C), 108.2 (CH). Analytical data is in agreement with reported values. [32]

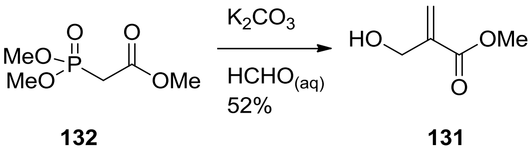
2-Hydroxymethyl-acrylic acid methyl ester 131

Method A[57]



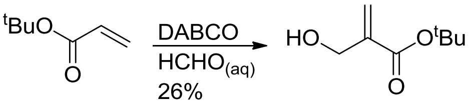
1,4-Dioxane (30 mL), methyl acrylate (30 mL, 332 mmol), and DABCO (7.60 g, 67.9 mmol) were added to an aqueous formaldehyde solution (30.0 g, 37% w/w) and the mixture stirred for 48 h at rt. NaCl (12.0 g) and diethyl ether (30 mL) were then added. The organic layers were separated and the product was extracted from the aqueous layer with diethyl ether (3 × 30 mL). These combined organic layers were washed with saturated NaCl solution (2 × 30 mL) and dried over $MgSO_4$. The solvents were removed under reduced pressure and the crude mixture was distilled under reduced pressure to afford the *title compound* as a colourless oil (11.20 g, 29%); bp 65-70 ^{o}C/1 mmHg; ^{1}H NMR δ (300 MHz, $CDCl_3$) 2.49 (1H, t, J = 6.5 Hz, OH), 3.77 (3H, s, CH_3), 4.32 (2H, d, J = 5.8 Hz, CH_2OH), 5.84 (1H, s, C*H*), 6.25 (1H, s, C*H*); ^{13}C NMR δ (75.5 MHz, $CDCl_3$) 51.9 (CH_3), 62.4 (CH_2), 125.8 (CH), 139.2 (C), 166.7 (C); *m/z* (EI) 115 ([M-H]$^+$ 15%), 99 (59), 87 (100), 59 (16), 55 (74), 45 (5). Analytical data is in agreement with reported values.[57]

Method B[58]



Trimethylphosphonoacetate (20.0 g, 110 mmol) was added to an aqueous formaldehyde solution (50 g, 37% w/w) and the mixture stirred at rt. An aqueous K_2CO_3 solution (30 g, saturated) was added dropwise at 0 ^{o}C over an hour and the reaction allowed to warm to rt for a further 3 h before saturated $NH_4Cl_{(aq)}$ (40 mL) was added. The mixture was then extracted with dichloromethane (3 x 50 mL), dried over anhydrous $MgSO_4$, filtered and solvents removed under reduced pressure. Distillation afforded the title compound as a colourless oil (6.20 g, 52%). Data as above.

2-Hydroxymethyl-acrylic acid *tert*-butyl ester 134



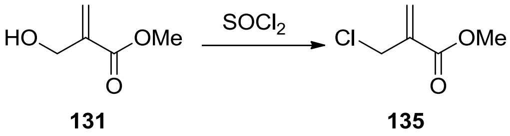
133 **134**

Synthesized using a modified literature procedure[59]

1,4-Dioxane (80 mL), *tert*-butyl acrylate (47 g, 367 mmol), and DABCO (4.11 g, 36.7 mmol) were added to an aqueous formaldehyde solution (30.0 g, 37% w/w) followed by further water (40 mL) and the resulting turbid mixture was stirred for 15 h at 100 ^{o}C. Diethyl ether (50 mL) was added, the organic layers separated and the product was extracted from the aqueous layer with diethyl ether (3 × 30 mL). These combined organic layers were washed with brine (2 × 30 mL) and then dried over anhydrous $MgSO_4$. The solvents were removed under reduced pressure and the crude mixture was distilled under reduced pressure to afford the *title compound* as a colourless oil (12.25 g, 21%); ^{1}H NMR δ (300 MHz, $CDCl_3$) 1.48 (9H, s, $C(CH_3)_3$), 2.60 (1H, br, O*H*), 3.77 (3H, s, CH_3), 4.26 (2H, s, CH_2OH), 5.73 (1H, s, C*H*), 6.13 (1H, s, C*H*); ^{13}C NMR δ

(75.5 MHz, $CDCl_3$) 28.0 (CH_3), 29.8 (CH_2), 83.4 (C), 128.1 (CH_2), 137.2 (C), 163.9 (C). Analytical data is in agreement with reported values.[60]

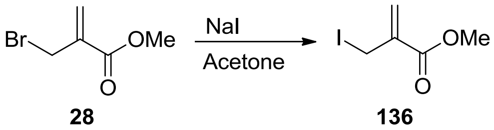
2-Chloromethyl-acrylic acid methyl ester 135



Synthesized using a modified literature procedure[61]

$SOCl_2$ (0.78 g, 6.51 mmol) was added dropwise to 2-hydroxymethyl-acrylic acid methyl ester (0.66 g, 5.69 mmol) and stirred at -10 °C for 15 minutes under an inert atmosphere. The temperature was allowed to gradually rise to 75 °C and stirred for a further 3 h. Hexane (5 mL) was then added dropwise at rt and the solvents removed under reduced pressure to give a colourless oil (0.41 g, 53%). ^1H NMR δ (300 MHz, $CDCl_3$) 3.75 (3H, s, CH_3), 4.24 (2H, s, CH_2Cl), 5.94 (1H, s, C*H*), 6.33 (1H, s, C*H*); ^{13}C NMR δ (75.5 MHz, $CDCl_3$) 40.3 (CH_3), 52.0 (CH_2), 128.5 (CH), 136.7 (C), 165.2 (C). Analytical data is in agreement with reported values.[61]

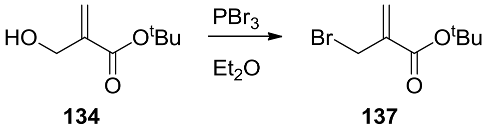
2-Idomethyl-acrylic acid methyl ester 136



Synthesized using a modified literature procedure[62]

Sodium iodide (0.75 g, 5.00 mmol) was dissolved in acetone (5 mL) and added to a stirred solution of 2-bromomethyl-acrylic acid methyl ester (0.42 g, 2.34 mmol) in acetone (10 mL). A white-yellow precipitate instantly formed, which was then diluted with diethyl ether (50 mL), washed with distilled water (20 mL) and brine (20 mL). The remains were then distilled by bulb-to-bulb distillation to give the unstable *title compound* as a yellow oil (0.19 g, 63%). ^{1}H NMR δ (300 MHz, CD_3CN) 3.76 (3H, s, C*H*$_3$), 4.17 (2H, s, C*H*$_2$), 6.00 (1H, s, C*H*), 6.13 (1H, s, C*H*); (EI) 226 ([M]$^+$ 60%), 195 (9), 167 (12), 127 (10), 99 (100), 69 (23), 59 (47); *m/z* (EI) 226 ([M]$^+$ 57%), 195 (11), 167 (13), 127 (11), 99 (100), 69 (24), 59 (45). Analytical data is in agreement with reported values.[63]

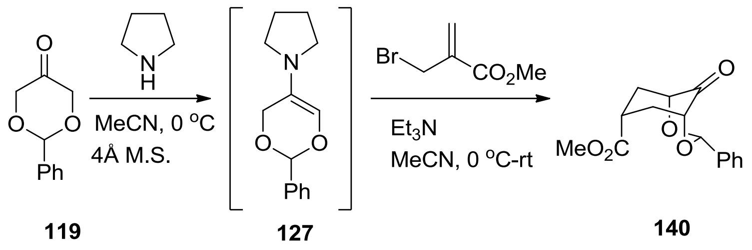
2-Bromomethyl-acrylic acid *tert*-butyl ester 137



Synthesized using a modified literature procedure[54,64]

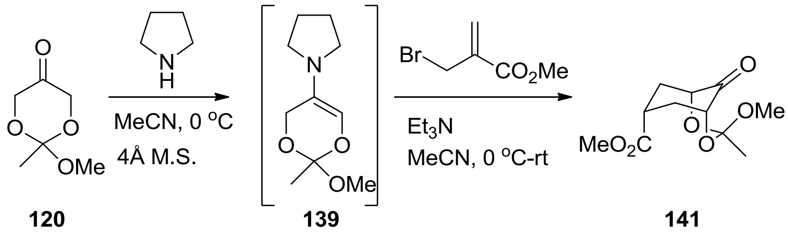
Phosphorus tribromide (0.85 g, 3.14 mmol) was added to a stirred solution of 2-hydroxymethyl-acrylic acid *tert*-butyl ester (0.92 g, 6.32 mmol) in anhydrous diethyl ether (20 mL) at 0 °C. The temperature was allowed to rise to rt and stirred for 4 h under an inert atmosphere. Distilled water (10 mL) was then added at 0 °C and the mixture extracted with hexane (3 × 20 mL). The organic layers were collected, washed with brine (20 mL) and dried over anhydrous $MgSO_4$, filtered and solvents removed under reduced pressure. Distillation *in vacuo* afforded the *title compound* as a colourless oil (0.74 g, 53%); bp 104 °C/0.1 mmHg ^{1}H NMR δ (300 MHz, $CDCl_3$) 1.50 (9H, s, (C*H*$_3$)3), 4.08 (2H, s, C*H*$_2$), 5.78 (1H, s, C*H*), 6.12 (1H, s, C*H*); ^{13}C NMR δ (75.5 MHz, $CDCl_3$) 28.0 (CH_3), 29.8 (CH_2), 83.4 (C), 128.1 (CH_2), 137.2 (C), 163.9 (C).

Methyl 9-Oxo-3α-phenyl-2,4-dioxabicyclo[3.3.1]nonane-7α-carboxylate 140



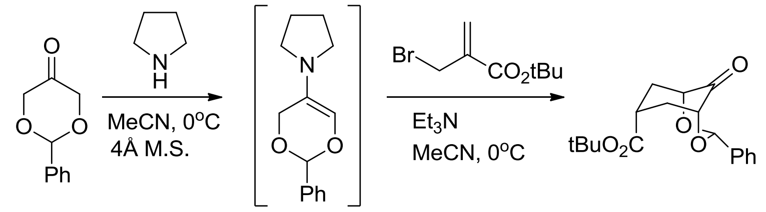
Prepared using the same method as **101** from 2-phenyl-1,3-dioxan-5-one (1.986 g, 11.15 mmol). Column chromatography (3:1 hexane:diethyl ether) the *title compound* was afforded as a white solid (1.22 g, 41%); R_f 0.26 (1:1 hexane:diethyl ether); mp 101−104 °C; υ_{max} (neat)/cm^{-1} 1747, 1718, 1456, 1016, 989; ^{1}H NMR δ (500 MHz, CDCl$_3$) 2.12 (2H, dd, J = 7.6, 15.2 Hz, CH_2), 2.68 (1H, t, J = 7.2 Hz, CHCO$_2$CH$_3$), 3.42−3.50 (2H, m, CH_2), 3.58 (3H, s, CO$_2$CH_3), 4.60 (2H, d, J = 3.9 Hz, CHCO), 5.70 (1H, s, PhCH), 7.35−7.51 (5H, m, Ph-H); ^{13}C NMR δ (75.5 MHz, CDCl$_3$) 33.7 (CH), 38.0 (CH$_2$), 52.1 (CH$_3$), 80.7 (CH), 98.5 (CH), 126.2 (CH), 128.2 (CH), 129.3 (CH), 136.3 (C), 173.6 (C), 212.9 (C); m/z (ES) 299.1 [M + Na]$^+$, HRMS (ES) [M + Na]$^+$ 299.0901, $C_{15}H_{16}O_5Na$ requires 299.0895.

Methyl 3β-Methoxy-3α-methyl-9-oxo-2,4-dioxabicyclo[3.3.1]nonane-7α-carboxylate 141



Prepared using the same method as **101** from 2-methyl-2-methoxy-1,3-dioxan-5-one (1.50 g, 10.3 mmol). Column chromatography (3:1 hexane:diethyl ether) afforded the *title compound* as a viscous, pale yellow oil (1.530 g, 61%); R_f 0.51 (1:1 hexane:diethyl ether); υ_{max} (neat)/cm^{-1}1731, 1441, 1046, 1010; ^{1}H NMR δ (300 MHz, $CDCl_3$) 1.41 (3H, s, C*H*$_3$), 1.97 (2H, dd, *J* = 7.1, 14.2 Hz, C*H*$_2$), 2.62 (1H, t, *J* = 7.0 Hz, C*H*CO_2CH_3), 3.19−3.25 (5H, m, OC*H*$_3$, C*H*$_2$), 3.75 (3H, s, CO_2C*H*$_3$), 4.16 (2H, d, *J* = 3.9 Hz, C*H*CO); ^{13}C NMR δ (100 MHz, $CDCl_3$) 19.7 (CH_3), 33.8 (CH), 36.4 (CH_2), 50.9 (CH_3), 51.9 (CH_3), 75.0 (CH), 111.8 (C), 173.5 (C), 207.8 (C); *m/z* (ES) 267.1 [M + Na]$^+$, HRMS (ES) [M + Na]$^+$ 267.0842, $C_{11}H_{16}O_6Na$ requires 267.0845.

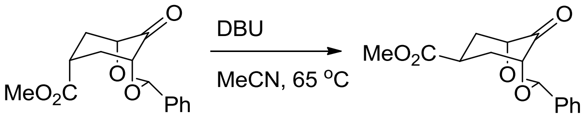
tert-Butyl 3β-*tert*-butlyoxy-3α-methyl-9-oxo-2,4-dioxabicyclo[3.3.1]nonane-7α-carboxylate 142



119 **127** **142**

Prepared using the same method as **101** from 2-phenyl-1,3-dioxan-5-one (0.400 g, 2.25 mmol). Column chromatography (3:1 hexane:diethyl ether) afforded the *title compound* as a white solid (80 mg, 12%); m.p. 140-143 °C; R_f 0.57 (1:1 hexane:diethyl ether); υ_{max} (neat)/cm^{-1}1745, 1727, 1451, 1100, 1017; ^{1}H NMR δ (300 MHz, CDCl$_3$) 1.23 (9H, s, C(C*H*$_3$)$_3$), 2.08 (2H, dd, *J* = 7.5, 10.1 Hz, C*H*$_2$), 2.56 (1H, t, *J* = 7.6 Hz, C*H*CO$_2$CH$_3$), 3.35–3.42 (2H, m, C*H*$_2$), 4.58 (2H, d, *J* = 3.7 Hz, C*H*CO) 5.72 (1H, s, PhC*H*) 7.29-7.56 (5H, m, Ph*H*); ^{13}C NMR δ (100 MHz, CDCl$_3$) 28.0 (CH$_3$), 34.6 (CH), 38.1 (CH$_2$), 80.7 (C), 80.8 (CH), 98.5 (CH), 126.6 (CH), 127.9 (CH), 129.0 (CH), 136.7 (C), 171.5 (C), 214.8 (C); *m/z* (ES) 341.2 [M + Na]$^+$, HRMS (ES) [M + Na]$^+$ 341.1370, $C_{18}H_{22}O_5Na$ requires 341.1365.

Methyl 9-Oxo-3α-phenyl-2,4-dioxabicyclo[3.3.1]nonane-7β-carboxylate 143

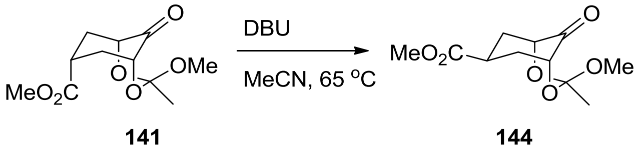


140 **143**

Methyl 9-oxo-3α-phenyl-2,4-dioxabicyclo[3.3.1]nonane-7α-carboxylate (0.062 g, 0.224 mmol) was dissolved in acetonitrile (3 mL) followed by addition of DBU (0.034

g, 0.223 mmol). The reaction mixture was heated at 65 °C (external temperature) for 24 h, allowed to cool, and concentrated to approximately half volume. Column chromatography (4:1 hexane:diethyl ether) afforded the *title compound* as a white solid (0.042 g, 68%); R_f 0.38 (1:1 hexane:diethyl ether); mp 113−116 °C; υ_{max} (neat)/cm^{-1} 1750, 1722, 1453, 1103, 1071; δ_H (300 MHz, CDCl$_3$) 2.08 (2H, t, *J*= 13.7 Hz, C*H*$_2$), 2.70−2.85 (2H, m, C*H*$_2$), 3.70 (3H, s, CO$_2$C*H*$_3$), 3.73 (1H, tt, *J* = 4.6, 12.5 Hz, C*H*CO$_2$CH$_3$), 4.59 (2H, d, *J* = 3.8 Hz, C*H*CO), 5.76 (1H, s, PhC*H*), 7.40−7.60 (5H, m, Ph-*H*); δ_c (75.5 MHz, CDCl$_3$) 33.1 (CH), 39.6 (CH$_2$), 52.1 (CH$_3$), 79.8 (CH), 98.0 (CH), 126.1 (CH), 128.4 (CH), 129.6 (CH), 136.4 (C), 174.1 (C), 211.7 (C); *m*/*z* (ES) [M + Na]$^+$ 299.1, HRMS (ES) [M + Na]$^+$ 299.0898, $C_{15}H_{16}O_5Na$ requires 299.0895.

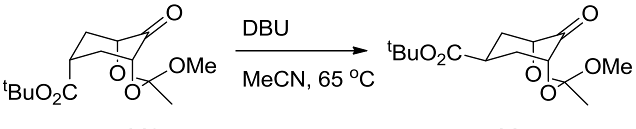
Methyl 3β-Methoxy-3α-methyl-9-oxo-2,4-dioxabicyclo[3.3.1]nonane-7β-carboxylate 144



Methyl 3β-methoxy-3α-methyl-9-oxo-2,4-dioxabicyclo[3.3.1]nonane-7α-carboxylate (1.300 g, 5.328 mmol) was dissolved in acetonitrile (50 mL) followed by addition of DBU (0.810 g, 5.329 mmol). The reaction mixture was heated at 65 °C (external temperature) for 24 h, allowed to cool, and concentrated to approximately half volume. Column chromatography (4:1 hexane:diethyl ether) afforded the *title compound* as a white solid (1.030 g, 79%); R_f 0.68 (1:1 hexane:diethyl ether); mp 34−36 °C; υ_{max} (neat)/cm^{-1} 1754, 1731, 1434, 1047, 918; δ_H (300 MHz, CDCl$_3$) 1.59 (3H, s, C*H*$_3$), 1.96 (2H, t, *J* = 13.6 Hz, C*H*$_2$), 2.62 (2H, m, C*H*$_2$), 3.27 (3H, s, OC*H*$_3$), 3.46 (1H, tt, *J* =

4.5, 12.5 Hz, C*H*CO_2CH_3), 3.71 (3H, s, CO_2CH_3), 4.20 (2H, d, *J* = 3.6 Hz, C*H*CO); δ_c (100 MHz, $CDCl_3$) 20.2 (CH_3), 33.2 (CH), 38.1 (CH_2), 50.9 (CH_3), 52.0 (CH_3), 74.5 (CH), 112.0 (C), 174.1 (C), 206.8 (C); *m/z* (ES) 267.1 $[M + Na]^+$, HRMS (ES) $[M + Na]^+$ 267.0850, $C_{11}H_{16}O_6Na$ requires 267.0845.

***tert*-Butyl 9-Oxo-3α-phenyl-2,4-dioxabicyclo[3.3.1]nonane-7β-carboxylate 145**

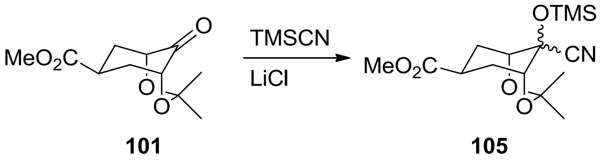


142 145

tert-Butyl 9-oxo-3α-phenyl-2,4-dioxabicyclo[3.3.1]nonane-7α-carboxylate (0.058 g, 0.182 mmol) was dissolved in acetonitrile (3 mL) followed by addition of DBU (0.030 g, 0.197 mmol). The reaction mixture was heated at 65 °C (external temperature) for 24 h, allowed to cool, and concentrated to approximately half volume. Column chromatography (4:1 hexane:diethyl ether) afforded the *title compound* as a white solid (0.029 g, 50%); ^{1}H NMR δ (300 MHz, $CDCl_3$) 1.44 (9H, s, $C(CH_3)_3$), 2.03 (2H, t, *J* = 13.7 Hz, C*H*$_2$), 2.70-2.80 (2H, m, C*H*$_2$), 3.99 (1H, dt, *J* = 4.6, 7.9 Hz, C*H*CO_2CH_3), 4.58 (2H, d, *J* = 3.7 Hz, C*H*CO) 5.76 (1H, s, PhC*H*) 7.41-7.56 (5H, m, Ph*H*); ^{13}C NMR δ (100 MHz, $CDCl_3$) 28.0 (CH_3), 33.6 (CH), 39.8 (CH_2), 79.8 (C), 81.1 (CH), 98.0 (CH), 126.1 (CH), 128.4 (CH), 129.6 (CH), 136.3 (C), 172.7 (C), 212.1 (C).

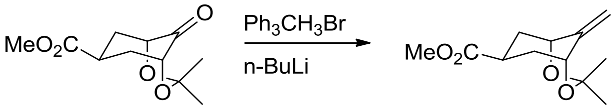
4.3 Experimental for Chapter Three

Methyl 9-cyano-3,3-dimethyl-9-((trimethylsilyl)oxy)-2,4-dioxabicyclo[3.3.1]nonane-7β-carboxylates 105a and 105b



Methyl 3,3-Dimethyl-9-oxo-2,4-dioxabicyclo[3.3.1]nonane-7α-carboxylate (44 mg, 0.19 mmol) was dissolved in TMSCN (1 mL), LiCl added (25 mg, 0.04 mmol) under an inert atmosphere. The mixture was stirred for 24 h at rt then a Kugelrohr distillation performed to remove the remaining TMSCN. The remaining residue was dissolved in chloroform (10 mL), filtered through celite, the filtrand washed with chloroform (3 x 5 mL) and the solvents removed under reduced pressure to afford a pale yellow solid of two diastereomers (56 mg, 6:1 ratio, 88%). Characterized as a mixture: ^{1}H NMR δ (300 MHz, $CDCl_3$) 0.05-0.29 (m, $Si(CH_3)_3$), 1.45-1.59 (m), 2.17-2.37 (m), 3.08-3.16 (m), 3.69 (3H, s (minor), $COCH_3$), 3.70 (3H, s (major), $COCH_3$), 4.33-4.34 (m); ^{13}C NMR δ (100 MHz, $CDCl_3$) -0.0, 26.5, 29.0, 31.7, 32.0, 50.9, 68.0, 71.1, 72.1, 97.7, 117.7, 173.4; *m/z* (ES) $[M + Na]^+$ 350.2; HRMS (ES) $[M + Na]^+$ 350.1390, $C_{15}H_{25}NO_5NaSi$ requires 350.1400.

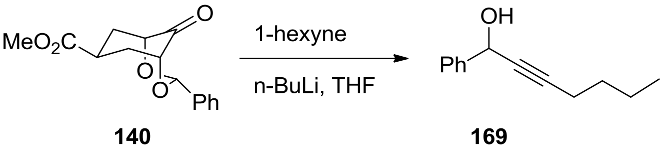
Methyl 3,3-dimethyl-9-methylene-2,4-dioxabicyclo[3.3.1]nonane-7α-ate 106



101 106

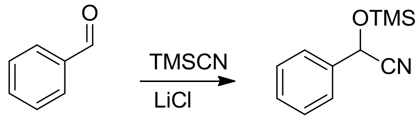
n-Butyllithium in hexanes (0.32 mL, 1.6 M) was added to a stirred solution of methyltriphenylphosphonium bromide (0.176 g, 0.49 mmol) in anhydrous toluene (4 mL), under an inert atmosphere at room temperature. Methyl 3,3-Dimethyl-9-oxo-2,4-dioxabicyclo[3.3.1]nonane-7α-carboxylate (0.11 g, 0.38 mmol) was added immediately after, forming a yellow solution. After 24 h the reaction was quenched with saturated aqueous ammonium chloride solution (1 mL) and the mixture extracted with diethyl ether (3 x 5 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and the solvents were removed under reduced pressure. Column chromatography (4:1 hexane:diethyl ether) afforded the *title compound* as a viscous oil (0.017 g, 0.06 mmol, 16%); R_f 0.79 (1:1 hexane:diethyl ether; υ_{max} (neat)/cm^{-1} 3053, 2978, 2911, 1729, 1590; ^{1}H NMR δ (300 MHz, $CDCl_3$) 1.32 (3H, s, CH_3), 1.47 (3H, s, CH_3), 1.58 (2H, t, *J* = 13.0 Hz, CH_2), 2.28 (2H, dt, *J* = 4.5, 14.0 Hz, CH_2), 3.32 (1H, tt, *J* = 4.5, 12.5 Hz, C*H*$COCH_3$), 3.61 (3H, s, COCH_3), 4.51 (2H, d, *J* = 3.0 Hz, COC*H*), 4.96 (2H, s, C=CH_2); ^{13}C NMR δ (100 MHz, $CDCl_3$) 28.1 (CH_3), 30.7 (CH_3), 34.8 (C), 39.1 (CH_3), 52.1 (CH_3), 72.9 (CH), 98.4 (C), 108.5 (CH_2), 146.6 (C), 176.3 (C); *m*/*z* (ES) $[M + Na]^+$ 297.1

1-Phenylhept-2-yn-1-ol 169[65]



n-Butyllithium in hexanes (0.36 mL, 1.60 M) was added slowly to a stirred solution of 1-hexyne in THF (3 mL). Methyl 9-Oxo-3α-phenyl-2,4-dioxabicyclo[3.3.1]nonane-7β-carboxylate (67 mg, 2.24 mmol) was added and the mixture stirred for 1 h, warmed to rt and stirred overnight. Saturated aqueous ammonium chloride solution (5 mL) was added and the mixture extracted with diethyl ether (3 x 5 mL). The combined organic extracts were dried over $MgSO_4$ and filtered. Solvents were removed under reduced pressure and the crude product was purified by column chromatography (15:85 diethyl ether:petrol) to afford the *title compound* as a colourless oil (16 mg, 35 %). ^{1}H NMR δ (300 MHz, $CDCl_3$) 0.88 (3H, m, CH_2CH_3), 1.55 (4H, m, $CH_2CH_2CH_3$), 2.23 (1H, br s, PhCHO*H*), 2.30 (2H, m, CCH_2CH_2), 5.46 (1H, s, PhC*H*OH), 7.21-7.45 (5H, m, Ph*H*); ^{13}C NMR δ (75.5 MHz, $CDCl_3$) 13.6 (CH_3), 18.7 (CH_2), 22.0 (CH_2), 30.6 (CH_2), 63.2 (CH), 79.9 (C), 87.7 (C), 126.6 (CH), 128.2 (CH), 129.0 (CH).

2-Phenyl-2-((trimethylsilyl)oxy)acetonitrile 170

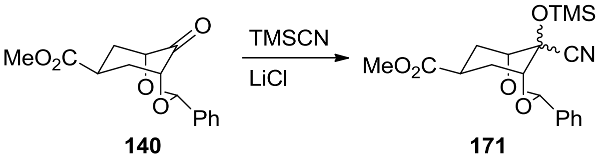


129 **170**

Synthesized using a modified literature procedure[47]

Benzaldehyde (0.5 mL, 4.9 mmol) was dissolved in TMSCN (1.5 mL), LiCl added (0.01 g) under an inert atmosphere. The mixture was stirred for 24 h at rt then a Kugelrohr distillation performed to remove the remaining TMSCN. The remaining residue was dissolved in (10 mL), filtered through celite, the filtrand washed with chloroform (3 x 5 mL) and the solvents removed under reduced pressure to afford the *title compound* in a racemic mixture as a colourless oil (quantitative). ^{1}H NMR δ (300 MHz, $CDCl_3$) 0.25 (9H, s, Si(CH_3)$_3$), 5.52 (1H, s, PhC*H*), 7.41-7.50 (5H, m, Ph*H*); ^{13}C NMR δ (100 MHz, $CDCl_3$) -0.0 (CH3), 63.9 (CH), 126.6 (CH), 129.2 (CH), 129.6 (CH), 138.4 (C).

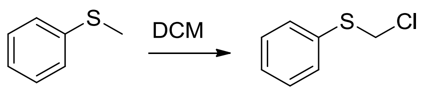
Methyl 9-cyano-3-phenyl-9-((trimethylsilyl)oxy)-2,4-dioxabicyclo[3.3.1]nonane-7β-carboxylates 171a and 171b



Methyl 9-oxo-3α-phenyl-2,4-dioxabicyclo[3.3.1]nonane-7β-carboxylate

(35 mg, 0.13 mmol) was dissolved in TMSCN (0.7 mL), LiCl added (42 mg) under an inert atmosphere. The mixture was stirred for 24 h at rt then a Kugelrohr distillation performed to remove the remaining TMSCN. The residue was dissolved in chloroform (10 mL), filtered through celite, the filtrand washed with chloroform (3 x 5 mL) and the solvents removed under reduced pressure to afford a pale yellow solid of two diastereomers (38 mg, 2:1 ratio, 78%). Characterized as a mixture: υ_{max} (neat)/cm^{-1} 2946, 1725, 1434, 1252; ^{1}H NMR δ (300 MHz, CDCl$_3$) 0.33-0.40 (m, Si(CH_3)$_3$), 2.02-2.49 (m), 3.21-3.23 (m), 3.69 (3H, s (major), COCH_3), 3.71 (3H, s (minor), COCH_3), 4.33-4.34 (m), 6.43 (1H, s (minor), PhC*H*), 6.75 (1H, s (major), PhC*H*), 7.38-7.54 (m, Ph*H*); ^{13}C NMR δ (100 MHz, CDCl$_3$) -0.0, 27.9, 30.4, 30.8, 32.0, 50.6, 50.8, 62.5, 72.3, 73.1, 89.9, 90.2, 120.5, 124.9, 125.0, 127.2, 128.1, 136.7, 137.9, 175.2, 178.0; *m*/*z* (ES) [M + Na]$^+$ 398.2; HRMS (ES) [M + Na]$^+$ 398.1406, $C_{19}H_{25}NO_5NaSi$ requires 398.1400.

Chloromethylsulfanyl-benzene 180

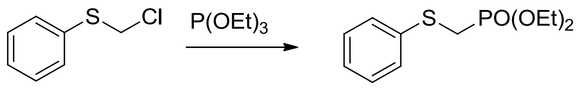


179 **180**

Synthesized using a modified literature procedure[66]

Thioanisole (3.50 g, 28.2 mmol) in DCM (25 mL) was heated to reflux and SO_2Cl_2 added dropwise in DCM under an inert atmosphere. After 4 h the solution cooled to rt and stirred overnight. DCM was removed under reduced pressure to afford the *title compound* as a colourless oil which required no further purification (4.32 g, 96%); ^{1}H NMR δ (300 MHz, $CDCl_3$) 4.87 (6H, s, CH_2), 7.26-7.47 (5H, m, Ph*H*); ^{13}C NMR δ (75.5 MHz, $CDCl_3$) 23.4 (CH_3), 66.7 (CH_2), 100.0 (C), 207.8 (C).

Phenylsulfanylmethylphosphonic acid diethyl ester 181



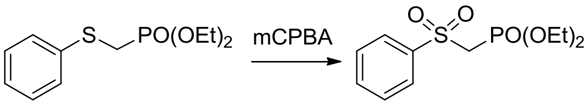
180 **181**

Synthesized using a modified literature procedure[67]

Chloromethylsulfanyl-benzene (4.30 g, 27.0 mmol) was added dropwise to neat $P(OEt)_3$ (4.50 g, 28.0 mmol) and heated to 110 °C for 48 h. The solution was allowed to cool to rt and $P(OEt)_3$ removed under reduced pressure (bp 160 °C/ 760 mmHg). The crude mixture was then purified by bulb-to-bulb distillation to give the *title compound* as a colourless oil (5.00 g, 71%). ^{1}H NMR δ (300 MHz, $CDCl_3$) 1.29 (6H, t, J = 7.1 Hz, PCH_2CH_3), 3.20 (2H, d, J = 14.1 Hz, PCH_2S), 4.13 (4H, doublet quintet, J = 7.1 Hz and 1.4 Hz, PCH_2CH_3), 7.21-7.45 (5H, m, Ph*H*); ^{13}C NMR δ (75.5 MHz, $CDCl_3$) 16.3 (d, J

= 5.7 Hz, CH_3), 28.5 (d, *J* = 148.1 Hz, CH_2), 62.7 (d, *J* = 6.2 Hz, CH_2), 126.7 (CH), 128.9 (CH), 129.5 (CH), 135.4 (CH).

Benzenesulfonylmethylphosphonic acid diethyl ester 182

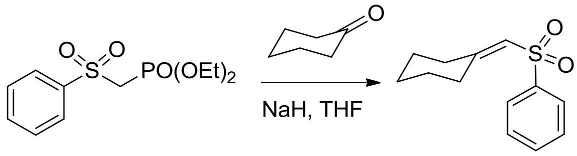


181 **182**

Synthesized using a modified literature procedure[52]

*m*CPBA (2.02 g, 11.7 mmol) was added in one portion to a stirred solution of phenylsulfanylmethylphosponic acid diethyl ester (1.00 g, 3.82 mmol) in DCM (55 mL) and stirred for 4 h at rt. The solution was washed with NaOH (60 mL, 0.1 M), distilled water (25 mL) and dried over anhydrous $MgSO_4$. This was then filtered and solvents removed under reduced pressure. Purification by column chromatography (9:1 EtOAc/hexane) afforded a colourless viscous oil (0.722 g, 65%) ^{1}H NMR δ (300 MHz, $CDCl_3$) 1.21 (6H, t, *J* = 7.1 Hz, PCH_2CH_3), 3.72 (2H, d, *J* = 16.8 Hz, PCH_2S), 4.07 (4H, doublet quintet, *J* = 7.1 Hz and 0.8 Hz, PCH_2CH_3), 7.25-7.94 (5H, m, Ph*H*); ^{13}C NMR δ (75.5 MHz, $CDCl_3$) 16.0 (d, *J* = 5.7 Hz, CH_3), 53.6 (d, *J* = 137.5 Hz, CH_2), 63.2 (d, *J* = 6.0 Hz, CH_2), 127.7 (CH), 128.9 (CH), 133.9 (CH), 139.8 (CH).

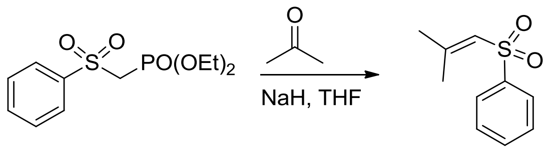
Cyclohexylidenemethanesulfonyl-benzene 185[68]



182 **185**

A slurry of anhydrous THF (5 ml) and NaH (15.0 mg, 0.62 mmol) was made at -20 °C followed by dropwise addition of benzenesulfonylmethyl-phosphonic acid diethyl ester (0.234 g, 0.80 mmol) which was left to stir slowly whilst warming to rt over 20 mins. Cyclohexanone (60 mg, 0.61 mmol) was added to the resulting clear yellow solution and the mixture heated to reflux overnight. The reaction was quenched with addition of distilled water (5 ml) and extracted with ethyl acetate (3 x 5 mL). Solvents removed under reduced pressure and purification by column chromatography (5:1 hexane:diethyl ether) afforded the *title compound* as a clear, colourless oil (62.1 mg, 43%); ^{1}H NMR δ (300 MHz, $CDCl_3$) 1.54-1.62 (6H, m, CH_2), 2.13-2.17 (2H, m, CH_2), 2.71 (2H, br s, CH_2), 6.15 (1H, s, $CHSO_2Ph$), 7.51-7.90 (5H, m, Ph*H*); ^{13}C NMR δ (75.5 MHz, $CDCl_3$) 25.6 (CH_2), 27.3 (CH_2), 28.2 (CH_2), 29.3 (CH_2), 37.5 (CH_2), 123.4 (CH), 126.9 (CH), 129.0 (CH), 132.8 (CH), 142.7 (C), 161.6 (C).

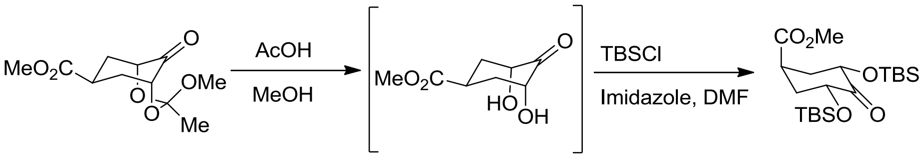
((2-Methylprop-1-en-1-yl)sulfonyl)benzene 187[69]



182 **185**

A slurry of anhydrous THF (5 mL) and NaH (15.0 mg, 0.62 mmol) was made at -20 °C followed by dropwise addition of benzenesulfonylmethyl-phosphonic acid diethyl ester (0.234 g, 0.80 mmol) which was left to stir slowly whilst warming to room temperature over 20 mins. Acetone (60 mg, 0.61 mmol) was added to the resulting clear yellow solution and the mixture heated to reflux overnight. After which the reaction was quenched with addition of distilled water (5 mL) and extracted with ethyl acetate. Solvents removed under reduced pressure and purification by column chromatography (5:1 hexane/diethyl ether) afforded the *title compound* as a clear, colourless oil (62.1 mg, 19%); ^{1}H NMR δ (300 MHz, $CDCl_3$) 1.89 (3H, s, CH_3), 2.16 (3H, s, CH_3), 6.17 (1H, s, C$H$$SO_2$Ph), 7.41-7.98 (5H, m, PhH); ^{13}C NMR δ 17.4 (CH_2), 25.3 (CH_3), 126.8 (CH), 128.0 (CH), 129.5 (CH), 133.1 (CH), 145.3 (C), 165.6 (C).

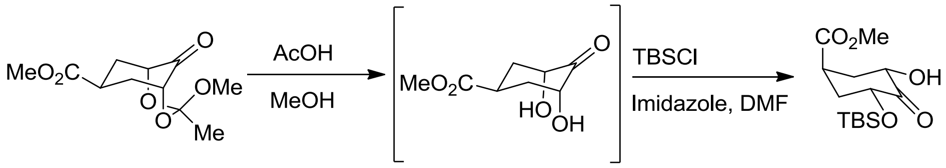
(1s,3R,5S)-Methyl 3,5-bis((*tert*-butyldimethylsilyl)oxy)-4-oxocyclohexane carboxylate 189



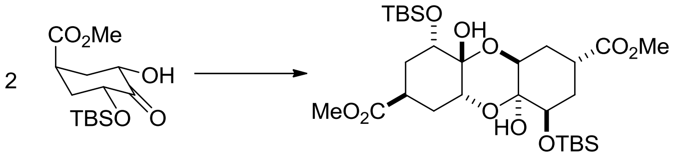
144 **188** **189**

Methyl 3β-methoxy-3α-methyl-9-oxo-2,4-dioxabicyclo[3.3.1]nonane-7β-carboxylate (1.00 g, 4.10 mmol) was dissolved in methanol (40 mL) followed by addition of acetic acid (0.23 mL, 4.10 mmol). The reaction mixture was refluxed for 48 h, allowed to cool, and the volatiles removed under reduced pressure. The resulting white, solid residue was then dissolved in anhydrous DMF (50 mL) followed by addition of imidazole (0.826 g, 12.25 mmol) and finally *tert*-butyldimethylsilyl chloride (1.48g, 9.8 mmol). and the mixture stirred at rt for 48 h under an inert atmosphere. The solution turned dark green and was diluted with DCM (50 mL), washed with distilled water (3 x 50 mL), brine (50 mL), dried over $MgSO_4$, filtered and solvents removed under reduced pressure. Column chromatography (9:1 hexane:diethyl ether) afforded the *title compound* as a white solid (1.268 g, 3.043 mmol, 74%); R_f 0.74 (4:1 hexane:diethyl ether); mp 56−58 °C; υ_{max} (neat)/cm^{-1} 1747, 1718, 1469, 1161, 991; ^{1}H NMR δ (400 MHz, $CDCl_3$) 0.02 (6H, s, 2 x CH_3), 0.12 (6H, s, 2 x CH_3), 0.90 (18H, s, C(CH_3)$_3$), 1.50 (2H, td, J = 5.4, 11.7 Hz, CH_2), 1.84 (2H, ddd, J = 5.4, 12.2, 13.2 Hz, CH_2), 2.57 (2H, ddd, J = 2.5, 6.2, 10.7 Hz, CH_2), 2.93 (1H, tt, J = 2.5, 5.3 Hz, C*H*CO_2CH_3), 3.78 (3H, s, CO_2CH_3), 4.36 (2H, dd, J = 6.1, 11.7 Hz, C*H*CO); ^{13}C NMR δ (100 MHz, $CDCl_3$) -5.5 (CH_3), -4.5 (CH_3), 18.5 (C), 25.8 (CH_3), 37.4 (CH), 38.8 (CH_2), 52.2 (CH_3), 74.4 (CH), 173.2 (C), 205.6 (C); *m*/*z* (ES) 439.2 [M + Na]$^+$, HRMS (ES) [M + Na]$^+$ 439.2332, $C_{11}H_{16}O_6Na$ requires 439.2312.

(1S,3R,5S)-Methyl 3-((*tert*-butyldimethylsilyl)oxy)-5-hydroxy-4-oxocyclohexane carboxylate dimer 191



144 **188** **190**

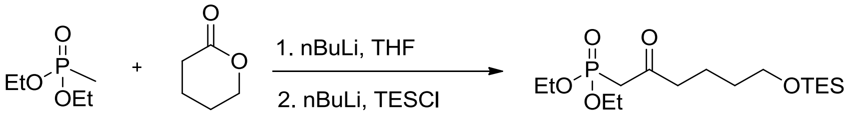


190 **191**

Methyl 3β-Methoxy-3α-methyl-9-oxo-2,4-dioxabicyclo[3.3.1]nonane-7β-carboxylate (98 mg, 0.40 mmol) was dissolved in methanol (5 mL) followed by addition of two drops of acetic acid. The reaction mixture was refluxed for 48 h, allowed to cool, and the volatiles removed under vacuum. The resulting white, solid residue was then dissolved in anhydrous DMF (3 mL) followed by addition of imidazole (67 mg, 1.00 mmol) and finally *tert*-butyldimethylsilyl chloride (60 mg, 0.40 mmol) and the mixture stirred at rt for 15 h under an inert atmosphere. The solution turned dark green and was diluted with DCM (10 mL), washed with distilled water (3 x 5 mL), brine (5 mL), dried over anhydrous $MgSO_4$, filtered and solvents removed under reduced pressure. Column chromatography (9:1 hexane:diethyl ether) afforded the *title compound* as a white solid (34 mg, 14%); R_f 0.14 (4:1 hexane:diethyl ether); mp 53−57 °C; υ_{max} (neat)/cm^{-1} 3541, 1754, 1731, 1438, 1043, 833; ^{1}H NMR δ (300 MHz, $CDCl_3$) 0.09 (6H, s, Si(CH_3)$_2$), 0.89 (9H, s, SiC(CH_3)$_3$), 1.55-1.70 (1H, m, $CH_{ax}H_{eq}$), 1.86 (1H, td, *J* = 5.6, 12.7 Hz, $CH_{ax}H_{eq}$), 1.95-2.05 (1H, m, $CH_{ax}H_{eq}$), 2.08-2.19 (1H, m, $CH_{ax}H_{eq}$), 2.75 (1H, m, C*H*CO_2CH_3),), 3.10 (1H, d, *J* = 1.5 Hz, CHO*H*), 3.70 (3H, s, OCH_3), 3.86 (1H, dd, *J* = 5.2, 10.9 Hz, C*H*CO), 4.01 (1H, dd, *J* = 4.2, 12.8 Hz, C*H*CO); ^{13}C NMR δ (100 MHz,

$CDCl_3$) -4.9 (CH_3), -4.6 (CH_3), 18.3 (C), 25.8 (CH_3), 28.1 (CH_2), 32.6 (CH_2), 36.6 (CH), 52.0 (CH_3), 68.2 (CH), 70.4 (CH), 94.6 (C), 174.7 (C); *m/z* (ES) 325.2 $[M + Na]^+$, 627.4 $[2M+2Na]^+$, HRMS (ES) $[M + Na]^+$ 325.1438, $C_{14}H_{26}O_5NaSi$ requires 325.1447.

Diethyl (2-oxo-6-((triethylsilanyl)oxy)hexyl)phosphonate 197

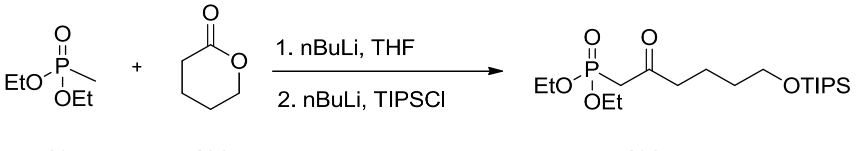


195 **196** **197**

Diethylmethylphosphonate (200 mg, 1.32 mmol) was dissolved in anhydrous tetrahydrofuran (10 mL) and cooled to -78 °C under an inert atmosphere. *n*-Butyllithium in hexanes (0.9 mL, 1.44 M) was added slowly and the mixture stirred for 1 h. δ-Valerolactone (130 mg, 1.30 mmol) was then added and the mixture stirred for 1 h, warmed to 0 °C and stirred overnight. The mixture was cooled back to -78 °C and *n*-butyllithium in hexanes (13.5 mL, 1.45 M) was added. The mixture was stirred for 1 h then triethylsilyl chloride (249 mg, 1.30 mmol) was added and the mixture allowed to gradually warm to room temperature overnight. Saturated aqueous ammonium chloride solution (10 mL) was added and the mixture extracted with diethyl ether (3 x 15 mL). The combined organic extracts were washed with saturated sodium bicarbonate (15 mL), water (10 mL) and brine (10 mL), dried over $MgSO_4$ and filtered. Solvents were removed under reduced pressure and the crude product was purified by column chromatography (1:1 ethyl acetate:hexane) to afford the *title compound* as a colourless oil (203 mg, 61 %). ^1H NMR δ (300 MHz, $CDCl_3$) 0.60 (6H, q, *J* = 8.0 Hz, $\mathrm{CH_3C}\mathit{H}_2\mathrm{Si}$), 0.96 (9H, t, *J* = 8.0 Hz, $\mathrm{C}\mathit{H}_3\mathrm{CH_2Si}$), 1.35 (6H, t, *J* 7.0 Hz, $\mathrm{C}\mathit{H}_3\mathrm{CH_2OP(O)}$), 1.71-1.62 (4H, m, CH_2CH_2), 2.67 (2H, t, *J* 7.0 Hz, $\mathrm{C(O)C}\mathit{H}_2\mathrm{CH_2}$), 3.09 (2H, d, *J* 23.0 Hz, $\mathrm{P(O)C}\mathit{H}_2\mathrm{C(O)}$), 3.62 (2H, t, *J* 6.5 Hz, $\mathrm{C}\mathit{H}_2\mathrm{OSi}$), 4.15 (2H, dq, *J* 7.0, 1.5 Hz,

$CH_3CH_2OP(O)$); *m*/*z* (EI) 337 (52%, M-Et). Analytical data is in agreement with reported values.[70]

Diethyl (2-oxo-6-((triisopropylsilyl)oxy)hexyl)phosphonate 198

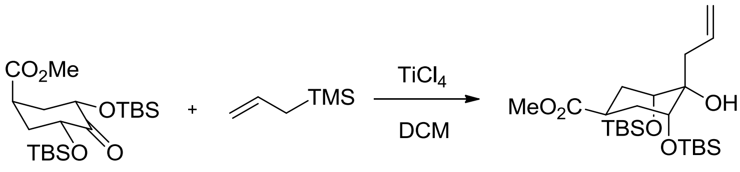


195 **196** **198**

Diethylmethylphosphonate (3.00 g, 19.7 mmol) was dissolved in anhydrous THF (150 mL) and cooled to -78 °C under an inert atmosphere. *n*-Butyllithium in hexanes (13.5 mL, 1.45 M) was added slowly and the mixture stirred for 1 h. δ-Valerolactone (1.97 g, 19.7 mmol) was then added and the mixture stirred for 1 h, warmed to 0 °C and stirred overnight. The mixture was cooled back to -78 °C and *n*-butyllithium in hexanes (13.5 mL, 1.45 M) was added. The mixture was stirred for 1 h until triisopropylsilyl chloride (3.78 g, 19.7 mmol) was added and the mixture allowed to gradually warm to rt overnight. Saturated aqueous ammonium chloride solution (30 mL) was added and the mixture extracted with diethyl ether (3 x 25 mL). The combined organic extracts were washed with saturated sodium bicarbonate (25 mL), water (20 mL) and brine (20 mL), dried over $MgSO_4$ and filtered. Solvents were removed under reduced pressure and the crude product was purified by column chromatography (1:1 ethyl acetate:hexane) to afford the *title compound* as a colourless oil (2.73 g, 34 %). R_f 0.15 (4:1 EtOAc); υ_{max} (neat)/cm^{-1} 2942, 2865, 1716, 1463, 1020; ^{1}H NMR δ (300 MHz, $CDCl_3$) 1.02 (3H, $SiCH(CH_3)_2$), 1.03 (18H, t, J = 3.9 Hz, $SiCH(CH_3)_2$), 1.31 (6H, t, J = 6.9 Hz, $CH_3CH_2OP(O)$), 1.60 (4H, m, CH_2CH_2), 2.63 (2H, t, J = 7.0 Hz, $C(O)CH_2CH_2$), 3.05 (2H, d, J = 22.8 Hz, $P(O)CH_2C(O)$), 3.66 (2H, t, J = 6.3 Hz, CH_2OSi), 4.12 (4H, dq, J =

8.1, 7.1 Hz, $CH_3CH_2OP(O)$); ^{13}C NMR δ (100 MHz, $CDCl_3$) 12.0 (CH_3), 16.3 (CH), 18.0 (CH_3), 20.0 (CH_2), 32.2 (CH_2), 41.7 (CH_2), 42.9 (CH_2), 43.9 (CH_2), 62.5 (CH_2), 63.0 (CH_2) 173.2 (C), 201.6 (C); *m/z* (ES) 431.1 $[M]^+$, HRMS (ES) $[M + Na]^+$ 431.2352, $C_{19}H_{41}O_5NaPSi$ requires 431.2359.

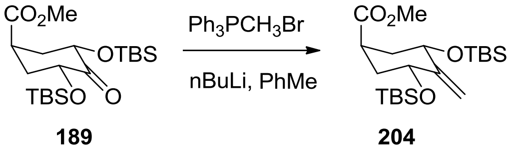
(1s,3R,4s,5S)-methyl 4-allyl-3,5-bis((*tert*-butyldimethylsilyl)oxy)-4-hydroxycyclohexanecarboxylate 203



189 **202** **203**

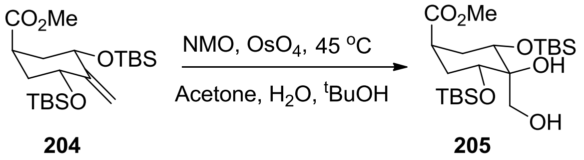
Titanium (IV) chloride in toluene (0.42 mL, 1.0 M) was added to a solution of (1s,3R,5S)-methyl 3,5-bis((*tert*-butyldimethylsilyl)oxy)-4-oxocyclohexane carboxylate (88 mg, 0.21 mmol) in DCM (2 mL) and cooled to -78 °C. Allyltrimethylsilane (121 mg, 1.05 mmol) was added to the mixture and allowed to gradually warm to room temperature overnight. Saturated ammonium chloride soltion (5 mL) was added to the mixture and the product extracted with diethyl ether (3 x 20 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and the solvents were removed under reduced pressure. Column chromatography (4:1 hexane:diethyl ether) afforded the *title compound* as a viscous liquid (60 mg, 58%); R_f 0.84 (4:1 hexane:diethyl ether); mp 56−58 °C; υ_{max} (neat)/cm^{-1} 2955, 2857, 1736, 1477, 1256; ^1H NMR δ (400 MHz, $CDCl_3$) 0.08 (12H, s, 4 x CH_3), 0.90 (18H, s, $C(CH_3)_3$), 1.88 (4H, m, 2 x CH_2), 2.32 (2H, d, *J* = Hz, CH_2), 2.73 (1H, s, CO*H*), 2.92 (1H, tt, *J* = 4.2, 8.2 Hz, $CHCO_2CH_3$), 3.68 (3H, s, CO_2CH_3), 3.71 (2H, dd, *J* = 3.5, 6.6 Hz, C*H*CO) 5.02-5.08 (2H, m, =C*H*), 5.75-5.88 (1H, m, =C*H*); ^{13}C NMR δ (100 MHz, $CDCl_3$) -4.7 (CH_3), -4.4 (CH_3), 18.2 (C), 26.0 (CH_3), 32.2 (CH_2), 33.4 (CH), 39.4 (CH_2), 51.7 (CH_3), 71.6 (CH), 73.4 (C), 117.7 (CH_2), 133.6 (CH_2), 176.0 (C); *m*/*z* (ES) 481.2 [M + Na]$^+$, HRMS (ES) [M + Na]$^+$ 481.2800, $C_{23}H_{46}O_5NaSi_2$ requires 481.2782.

(1s,3R,5S)-Methyl 3,5-bis((*tert*-butyldimethylsilyl)oxy)-4-methylenecyclohexanecarboxylate 204



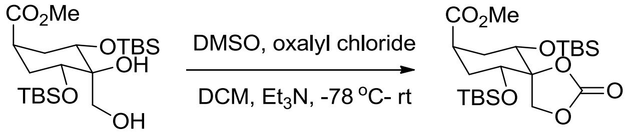
n-Butyllithium in hexanes (2.20 mL, 1.6 M) was added to a stirred solution of methyltriphenylphosphonium bromide (1.26 g, 3.53 mmol) in anhydrous toluene (30 mL), under an inert atmosphere at room temperature. (1s,3R,5S)-methyl 3,5-bis((*tert*-butyldimethylsilyl)oxy)-4-oxocyclohexane carboxylate (0.97 g, 2.33 mmol) was added immediately after, forming a yellow solution. After 24 h the reaction was quenched with saturated aqueous ammonium chloride solution (20 mL) and the mixture extracted with diethyl ether (3 x 30 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and the solvents were removed under reduced pressure. Column chromatography (95:5 hexane:diethyl ether) afforded the *title compound* as a white solid (0.547 g, 1.32 mmol, 57%); R_f 0.79 (1:1 hexane:diethyl ether); mp 29–31 °C; ^{1}H NMR δ (300 MHz, $CDCl_3$) 0.09 (6H, s, 2 x CH_3), 0.10 (6H, s, 2 x CH_3), 0.94 (18H, s, C(CH_3)$_3$), 1.50 (2H, td, *J* = 5.4, 11.7 Hz, CH_2), 2.37 (2H, m, CH_2), 2.85 (1H, tt, *J* = 2.6, 5.3 Hz, C*H*CO_2CH_3), 3.74 (3H, s, CO_2CH_3), 4.12 (2H, m, C*H*CCH_2) 5.1 (2H, t, *J* = 1.7 Hz, CH_2); ^{13}C NMR δ (100 MHz, $CDCl_3$) -5.18 (CH_3), -5.06 (CH_3), 18.4 (C), 25.8 (CH_3), 37.0 (CH), 37.8 (CH_2), 51.7 (CH_3), 69.3 (CH), 103.3 (C), 153.1 (CH_2), 175.0 (C); *m*/*z* (ES) 437.1 [M + Na]$^+$, HRMS (ES) [M + Na]$^+$ 437.2504, $C_{21}H_{42}O_4NaSi_2$ requires 437.2519.

(1s,3R,4r,5S)-Methyl 3,5-bis((*tert*-butyldimethylsilyl)oxy)-4-hydroxy-4-(hydroxymethyl)cyclohexane carboxylate 205



exo-Cyclic alkene **240** was dissolved in an acetone (1.5 mL), water (1.5 mL) and *tert*-butanol (0.75 mL) mixture. NMO (52 mg, 0.436 mmol, 1.1 equiv) was added followed by OsO_4 (2 drops, 4% v/w in water) and the misture heated to 45 ^{o}C for 2 h. Following completion of the reaction, the oxidant was quenched with sodium bisulfite (0.116 g, 0.611 mmol) and the mixture extracted with ethyl acetate (3 x 2 mL). The organic layers were collected, washed with 1 M $HCl_{(aq)}$ (3 mL) and brine (3 mL) then dried over anhydrous $MgSO_{4,}$ filtered and solvents removed under reduced pressure to afford the *title compound* as a white solid (0.136 g ,75%); R_f 0.26 (4:1 hexane:diethyl ether); mp 62−64 °C; υ_{max} (neat)/cm^{-1} 3493, 1724, 1472, 1069, 834; ^{1}H NMR δ (300 MHz, $CDCl_3$) 0.10 (6H, s, 2 x C*H*$_3$), 0.12 (6H, s, 2 x C*H*$_3$), 0.89 (18H, s, C(C*H*$_3$)$_3$), 1.61 (2H, td, *J* = 5.4, 11.7 Hz, C*H*$_2$), 2.21 (2H, m, C*H*$_2$), 2.76 (1H, tt, *J* = 2.4, 5.2 Hz, C*H*CO$_2$CH$_3$), 3.05 (1H, s, CO*H*), 3.16 (1H, t, *J* = 6.1 Hz, CH$_2$O*H*), 3.71 (3H, s, CO$_2$C*H*$_3$), 3.72 (2H, dd, *J* = 4.5, 11.4 Hz, C*H*COHCH$_2$OH) 3.92 (2H, d, *J* = 6.0 Hz, C*H*$_2$OH); ^{13}C NMR δ (100 MHz, $CDCl_3$) -4.87 (CH_3), 18.0 (C), 25.8 (CH_3), 32.7 (CH_2) 36.1 (CH), 51.9 (CH_3), 61.5 (CH_2), 74.2 (CH), 75.2 (C), 174.4 (C); *m/z* (ES) 471.4 [M + Na]$^+$, HRMS (ES) [M + Na]$^+$ 471.2567, $C_{21}H_{44}O_6NaSi_2$ requires 437.2574.

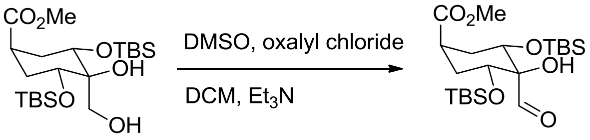
(5r,6R,8s,10S)-Methyl 6,10-bis((*tert*-butyldimethylsilyl)oxy)-2-oxo-1,3-dioxaspiro[4.5]decane-8-carboxylate 206



205 **206**

Dimethyl sulfoxide (0.05 mL, 0.65 mmol) was added dropwise to a solution of oxalyl chloride (0.22 mL, 2.52 mmol) in anhydrous dicholormethane (5 mL) at -60 ^{o}C and left to stir for 10 mins under an inert atmosphere. Then (1s,3R,4r,5S)-methyl 3,5-bis((*tert*-butyldimethylsilyl)oxy)-4-hydroxy-4-(hydroxymethyl)cyclohexanecarboxylate (0.120 g, 0.27 mmol) was added as a solution in anhydrous dicholormethane (0.4 mL) and left to stir for 30 mins at -60 ^{o}C. Triethylamine (0.11 mL, 0.81 mmol) was added and the mixture stirred for a further hour at -60 ^{o}C before being allowed to gradually warm to room temperature. Saturated aqueous ammonium chloride solution (1 mL) was added and the mixture extracted with diethyl ether (3 x 5 mL). The combined organic layers were washed with water (5 mL), dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure. Column chromatography (9:1 petrol:diethyl ether) afforded the *title compound* as a white solid (50 mg, 39%); R_f 0.80 (5:1 hexane:diethyl ether); mp 108−110 °C; υ_{max} (neat)/cm^{-1} 1785, 1732, 1463, 1089, 829; ^{1}H NMR δ (400 MHz, $CDCl_3$) 0.10 (6H, s, 2 x CH_3), 0.87 (18H, s, C(CH_3)$_3$), 2.30 (2H, m, CH_2), 2.70 (1H, m, C*H*CO_2CH_3), 3.74 (3H, s, CO_2CH_3 and 1H, s, CO*H*), 3.87 (2H, dd, *J* = 4.8, 12.2 Hz, C*H*CO) 4.39 (2H, s, CH_2OCO); ^{13}C NMR δ (100 MHz, $CDCl_3$) -5.05 (CH_3), -4.89 (CH_3), 15.25 (CH), 17.8 (C), 25.6 (CH_3), 30.3 (CH), 32.6 (CH_2), 52.1 (CH_3), 62.9 (CH_2), 68.9 (CH), 88.7 (C), 173.5 (C); *m*/*z* (ES) 497.2 [M + Na]$^+$, HRMS (ES) [M + Na]$^+$ 497.2353, $C_{22}H_{42}O_7NaSi_2$ requires 497.2367.

(1s,3R,4r,5S)-Methyl 3,5-bis((*tert*-butyldimethylsilyl)oxy)-4-formyl-4-hydroxycyclohexanecarboxylate 207

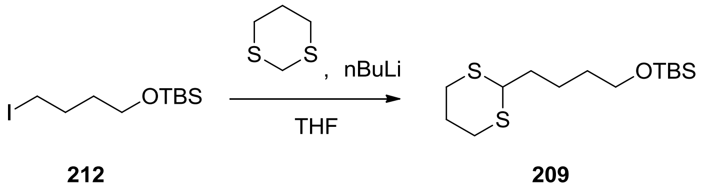


205 **207**

Synthesised using a modified procedure[71]

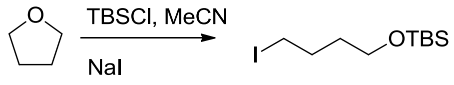
Dimethyl sulfoxide (0.39 mL, 4.03 mmol) was added dropwise to a solution of oxalyl chloride (0.22 mL, 2.52 mmol) in anhydrous dicholormethane (5 mL) at -78 ^{o}C and left to stir for 30 mins under an inert atmosphere. Then **205** (0.500 g, 1.01 mmol) was added as a solution in anhydrous DCM (5 mL) and left to stir for 45 mins at -78 ^{o}C. Triethylamine (0.84 mL, 6.04 mmol) was added and the mixture stirred for a further hour at -78 ^{o}C before being allowed to gradually warm to room temperature. Saturated aqueous ammonium chloride solution (10 mL) was added and the mixture extracted with diethyl ether (3 x 10 mL). The combined organic layers were washed with water (10 mL), dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure. Column chromatography (9:1 petrol:diethyl ether) afforded the *title compound* as a white solid (0.356 g, 79%); R_f 0.72 (5:1 hexane:diethyl ether); mp 90−93 °C; υ_{max} (neat)/cm^{-1} 3520, 1720, 1471, 1065, 832; ^{1}H NMR δ (400 MHz, $CDCl_3$) 0.03 (6H, s, 2 x CH_3), 0.04 (6H, s, 2 x CH_3), 0.82 (18H, s, C(CH_3)$_3$), 1.99 (2H, td, *J* = 5.1, 11.4 Hz, CH_2), 2.35 (2H, m, CH_2), 2.99 (1H, m, C*H*CO_2CH_3), 3.72 (3H, s, CO_2C*H*$_3$ and 1H, s, CO*H*), 3.83 (2H, dd, *J* = 4.5, 11.4 Hz, C*H*COHCHO) 9.90 (1H, d, *J* = 0.7 Hz, C*H*O); ^{13}C NMR δ (100 MHz, $CDCl_3$) -5.01 (CH_3), -4.88 (CH_3), 18.0 (C), 25.6 (CH_3), 33.4 (CH_2) 36.2 (CH), 52.0 (CH_3), 73.2 (CH), 83.1 (C), 174.1 (C), 202.1 (CH); *m*/*z* (ES) 469.3 [M + Na]$^+$, HRMS (ES) [M + Na]$^+$ 469.2432, $C_{21}H_{42}O_6NaSi_2$ requires 469.2418.

2-(4-*tert*-Butyldimethylsilyloxybutyl)-1,3-dithiane 209



1,3-dithiane (1.03 g, 8.59 mmol) was dissolved in anhydrous THF (50 mL) and cooled to -30 °C under an inert atmosphere. *n*-Butyllithium in hexanes (5.62 mL, 1.53 M) was added slowly and the mixture stirred for 1 h. *tert*-Butyl(4-iodobutoxy)dimethylsilane (3.00 g, 9.55 mmol) and was then added and the mixture stirred for 4 h. Saturated aqueous ammonium chloride solution (10 mL) was added and the mixture extracted with diethyl ether (3 x 15 mL). The combined organic extracts were washed with aqueous thiosulfate solution (15 mL), water (15 mL) and brine (20 mL), dried over $MgSO_4$ and filtered. Solvents were removed under reduced pressure and the crude product was purified by column chromatography (graduated 10:0 to 9:1 petrol/diethyl ether) to afford the *title compound* as a colourless oil (1.29 g, 44 %); ^{1}H NMR δ (300 MHz, $CDCl_3$) 0.05 (6H, s, 2 x CH_3), 0.87 (9H, s, C(CH_3)$_3$), 1.55 (2H, m, CH_2), 1.88 (2H, m, CH_2) 3.18 (2H, t, J = 6.8 Hz, CH_2), 3.18 (2H, t, J = 6.9 Hz, CH_2), ^{13}C NMR δ (100 MHz, $CDCl_3$) -5.3 (CH_3), 18.3 (C), 23.0 (CH_2), 26.0 (CH_3), 26.1 (CH_2), 30.5 (CH_2), 32.4 (CH_2), 35.3 (CH_2), 47.6 (CH), 61.9 (CH_2).

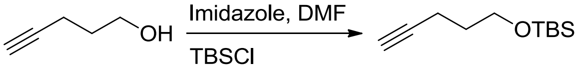
***tert*-Butyl(4-iodobutoxy)dimethylsilane 212**[53]



211 **212**

tert-Butyldimethylsilyl chloride (1.70 g, 11.2 mmol) was added in one portion to a stirred solution of sodium iodide (3.38 g, 22.5 mmol) in anhydrous THF (1.81 mL, 28.2 mmol) and stirred for 15 h at 55 ^{o}C under an inert atmosphere. Upon cooling, the solution was washed with distilled water (3 x 25 mL), thiosulfate solution (25 mL), dried over $MgSO_{4,}$ filtered and solvents removed under reduced pressure to leave the *title compound* as a colourless oil (2.66 g, 75%); ^{1}H NMR δ (300 MHz, $CDCl_3$) 0.05 (6H, s, 2 x CH_3), 0.87 (9H, s, $C(CH_3)_3$), 1.55 (2H, m, CH_2), 1.88 (2H, m, CH_2) 3.18 (2H, t, J = 6.8 Hz, CH_2), 3.18 (2H, t, J = 6.9 Hz, CH_2), ^{13}C NMR δ (100 MHz, $CDCl_3$) -5.3 (CH_3), 7.0 (CH_2), 18.3 (C), 25.9 (CH_3), 30.2 (CH_2), 33.5 (CH_2), 61.9 (CH_2).

tert-Butyldimethyl(pent-4-yn-1-yloxy)silane 218



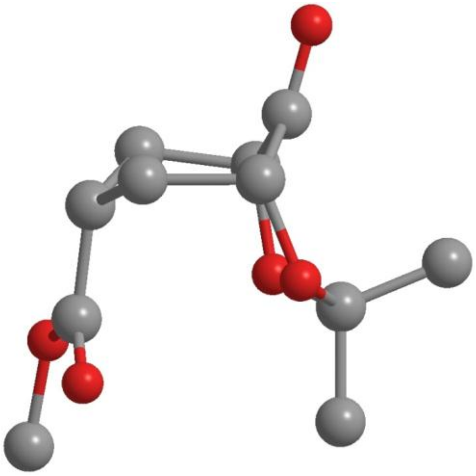
217 **218**

tert-Butyldimethylsilyl chloride (1.12 g, 7.44 mmol) was added in one portion to a stirred solution of imidazole (0.61 g, 8.93 mmol) and pent-4-yn-1-ol (0.50 g, 5.95 mmol) in anhydrous DMF (25 mL) and stirred for 15 h at rt under an inert atmosphere. The solution turned dark green and was diluted with DCM (25 mL), washed with distilled water (3 x 25 mL), brine (25 mL), dried over $MgSO_4$, filtered and solvents removed under reduced pressure. Purification by column chromatography (hexane) afforded the *title compound* as a colourless viscous oil (55 mg, 5%); ^{1}H NMR δ (300 MHz, $CDCl_3$) 0.05 (6H, s, 2 x CH_3), 0.84 (9H, s, C(CH_3)$_3$), 1.65 (2H, quintet, *J* = 6.7 Hz, CH_2), 1.88 (1H, s, CC*H*), 2.20 (2H, dt, *J* = 3.1, 6.9 Hz, CH_2), 3.60 (2H, s, CH_2); ^{13}C NMR δ (100 MHz, $CDCl_3$) -5.4 (CH_3), 14.8 (CH_2), 25.9 (CH_3), 29.1 (C), 31.5 (CH_2), 61.4 (CH_2), 68.2 (CH), 84.3 (C).

Appendices

5.1 X-ray data for 100

Recrystallised from $CDCl_3$



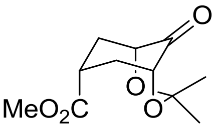


Table 1. Crystal data and structure refinement details.

Empirical formula	$C_{11}H_{16}O_5$	
Formula weight	228.24	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	$P\ \bar{1}$	
Unit cell dimensions	a = 7.9524(2) Å	α = 108.7380(10)°
	b = 8.2007(2) Å	β = 107.450(2)°
	c = 9.4468(2) Å	γ = 94.121(2)°
Volume	546.84(2) $Å^3$	
Z	2	
Density (calculated)	1.386 Mg / m^3	
Absorption coefficient	0.109 mm^{-1}	
F(000)	244	
Crystal	Block; Colourless	
Crystal size	0.10 × 0.09 × 0.08 mm^3	
θ range for data collection	3.74 – 27.48°	
Index ranges	$-10 \le h \le 10, -10 \le k \le 10, -12 \le l \le 12$	
Reflections collected	13210	
Independent reflections	2497 [R_{int} = 0.0379]	
Completeness to θ = 27.48°	99.1 %	
Absorption correction	Semi–empirical from equivalents	
Max. and min. transmission	0.9913 and 0.9891	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2497 / 0 / 148	
Goodness-of-fit on F^2	1.063	
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.0385, $wR2$ = 0.0874	
R indices (all data)	$R1$ = 0.0462, $wR2$ = 0.0936	
Largest diff. peak and hole	0.334 and –0.237 e $Å^{-3}$	

Diffractometer: *Bruker-Nonius APEX II* CCD camera (ϕ scans and ω scans to fill *asymmetric unit*). **Cell determination:** DirAx (Duisenberg, A.J.M.(1992). J. Appl. Cryst. 25, 92-96.) **Data collection:** Collect (Collect: Data collection software, R. Hooft, Nonius B.V., 1998). **Data reduction and cell refinement**: *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction**: Sheldrick, G. M. SADABS 2007/2 - Bruker Nonius area detector scaling and absorption correction. **Structure solution**: *SIR92* (Altomare, A., Cascarano, G., Giacovazzo, C. & Guagliardi, A, (1993) J. Appl. Cryst. 26, 343-350). **Structure refinement**: *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany). **Graphics:** *PLATON/PLUTON* (Spek, A. L. (1990). Acta Cryst. A46, C34).

Special details:

All hydrogen atoms were fixed as riding models with $U_{iso}(H) = 1.2*U_{eq}$(parent C) for methylene and methine groups and $U_{iso}(H) = 1.5*U_{eq}$(parent C) for methyl groups

Table 2. Atomic coordinates [× 10^4], equivalent isotropic displacement parameters [$Å^2 \times 10^3$] and site occupancy factors. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
O1	5239(1)	3270(1)	5348(1)	24(1)	1
O2	1106(1)	2799(1)	5927(1)	19(1)	1
O3	3338(1)	4156(1)	8412(1)	17(1)	1
O4	897(1)	357(1)	7954(1)	26(1)	1
O5	3452(1)	1422(1)	10051(1)	22(1)	1
C9	1805(2)	4382(2)	7281(1)	18(1)	1
C2	2409(2)	1972(2)	5327(1)	18(1)	1
C5	5368(2)	2158(2)	8244(2)	18(1)	1
C1	4235(2)	3131(2)	6068(2)	18(1)	1
C6	4816(2)	3769(2)	7860(1)	16(1)	1
C7	2505(2)	816(2)	8479(2)	19(1)	1
C11	2251(2)	5939(2)	6822(2)	22(1)	1
C4	3733(2)	648(2)	7498(2)	18(1)	1
C10	380(2)	4614(2)	8050(2)	24(1)	1
C8	2398(2)	1552(2)	11076(2)	27(1)	1
C3	2705(2)	310(2)	5734(2)	19(1)	1

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

O1–C1	1.2147(15)	C1–C6	1.5105(17)
O2–C9	1.4258(15)	C6–H6	1.0000
O2–C2	1.4355(14)	C7–C4	1.5203(17)
O3–C9	1.4284(15)	C11–H11A	0.9800
O3–C6	1.4385(14)	C11–H11B	0.9800
O4–C7	1.2058(16)	C11–H11C	0.9800
O5–C7	1.3496(15)	C4–C3	1.5412(17)
O5–C8	1.4438(15)	C4–H4	1.0000
C9–C10	1.5115(17)	C10–H10A	0.9800
C9–C11	1.5254(17)	C10–H10B	0.9800
C2–C1	1.5052(17)	C10–H10C	0.9800
C2–C3	1.5462(18)	C8–H8A	0.9800
C2–H2	1.0000	C8–H8B	0.9800
C5–C6	1.5373(17)	C8–H8C	0.9800
C5–C4	1.5424(17)	C3–H3A	0.9900
C5–H5A	0.9900	C3–H3B	0.9900
C5–H5B	0.9900		

C9–O2–C2	115.67(9)	C7–C4–H4	105.7
C9–O3–C6	115.03(9)	C3–C4–H4	105.7
C7–O5–C8	115.31(10)	C5–C4–H4	105.7
O2–C9–O3	109.58(10)	C9–C10–H10A	109.5
O2–C9–C10	105.53(10)	C9–C10–H10B	109.5
O3–C9–C10	106.05(10)	H10A–C10–H10B	109.5
O2–C9–C11	111.80(10)	C9–C10–H10C	109.5
O3–C9–C11	111.37(10)	H10A–C10–H10C	109.5
C10–C9–C11	112.18(11)	H10B–C10–H10C	109.5
O2–C2–C1	112.27(10)	O5–C8–H8A	109.5
O2–C2–C3	111.65(10)	O5–C8–H8B	109.5
C1–C2–C3	104.55(10)	H8A–C8–H8B	109.5
O2–C2–H2	109.4	O5–C8–H8C	109.5
C1–C2–H2	109.4	H8A–C8–H8C	109.5
C3–C2–H2	109.4	H8B–C8–H8C	109.5
C6–C5–C4	109.85(10)	C4–C3–C2	115.23(10)
C6–C5–H5A	109.7	C4–C3–H3A	108.5
C4–C5–H5A	109.7	C2–C3–H3A	108.5
C6–C5–H5B	109.7	C4–C3–H3B	108.5
C4–C5–H5B	109.7	C2–C3–H3B	108.5
H5A–C5–H5B	108.2	H3A–C3–H3B	107.5
O1–C1–C2	124.51(11)		
O1–C1–C6	123.62(11)		
C2–C1–C6	110.56(10)		
O3–C6–C1	111.72(9)		
O3–C6–C5	106.40(9)		
C1–C6–C5	103.36(10)		
O3–C6–H6	111.7		
C1–C6–H6	111.7		
C5–C6–H6	111.7		
O4–C7–O5	122.76(12)		
O4–C7–C4	125.63(12)		
O5–C7–C4	111.41(10)		
C9–C11–H11A	109.5		
C9–C11–H11B	109.5		
H11A–C11–H11B	109.5		
C9–C11–H11C	109.5		
H11A–C11–H11C	109.5		
H11B–C11–H11C	109.5		
C7–C4–C3	112.58(10)		
C7–C4–C5	113.29(10)		
C3–C4–C5	113.09(10)		

Table 4. Anisotropic displacement parameters [$Å^2 \times 10^3$]. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + \cdots + 2\,h\,k\,a^*\,b^*\,U^{12}]$.

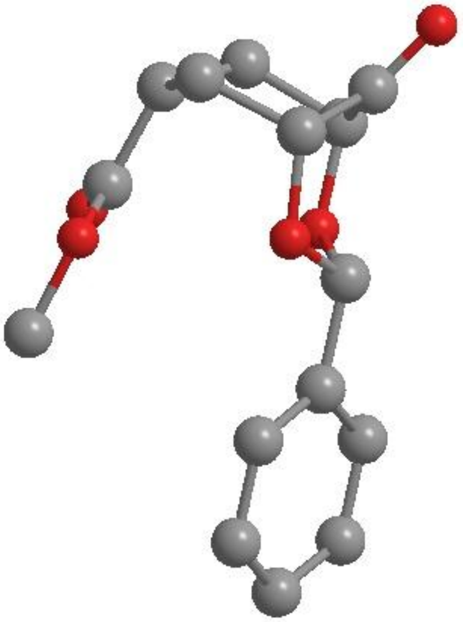
Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O1	25(1)	28(1)	24(1)	13(1)	14(1)	5(1)
O2	16(1)	18(1)	20(1)	3(1)	5(1)	2(1)
O3	18(1)	20(1)	16(1)	7(1)	7(1)	6(1)
O4	20(1)	29(1)	27(1)	10(1)	9(1)	−1(1)
O5	22(1)	30(1)	19(1)	12(1)	9(1)	6(1)
C9	17(1)	18(1)	16(1)	6(1)	4(1)	4(1)
C2	19(1)	20(1)	14(1)	4(1)	6(1)	3(1)
C5	16(1)	19(1)	19(1)	7(1)	6(1)	3(1)
C1	21(1)	16(1)	19(1)	8(1)	9(1)	5(1)
C6	14(1)	17(1)	18(1)	6(1)	6(1)	1(1)
C7	22(1)	15(1)	21(1)	9(1)	9(1)	3(1)
C11	26(1)	19(1)	23(1)	10(1)	7(1)	5(1)
C4	19(1)	15(1)	21(1)	7(1)	8(1)	4(1)
C10	24(1)	26(1)	26(1)	10(1)	13(1)	9(1)
C8	28(1)	35(1)	24(1)	15(1)	14(1)	9(1)
C3	19(1)	17(1)	18(1)	2(1)	7(1)	2(1)

Table 5. Hydrogen coordinates [$\times 10^4$] and isotropic displacement parameters [$Å^2 \times 10^3$].

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
H2	2000	1651	4146	22	1
H5A	5841	2465	9411	22	1
H5B	6329	1783	7817	22	1
H6	5837	4789	8372	20	1
H11A	3081	5681	6229	33	1
H11B	2812	6981	7786	33	1
H11C	1147	6154	6156	33	1
H4	4235	−433	7511	21	1
H10A	−739	4681	7289	36	1
H10B	777	5697	8988	36	1
H10C	176	3614	8371	36	1
H8A	1496	2272	10845	40	1
H8B	3184	2094	12189	40	1
H8C	1797	377	10888	40	1
H3A	1520	−431	5420	23	1
H3B	3372	−363	5086	23	1

5.2 X-ray data for 140

Recrystallised from diethyl ether



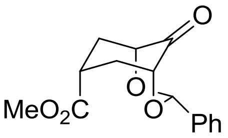


Table 1. Crystal data and structure refinement for 2008RG1.

Identification code	2008RG1	
Empirical formula	$C_{15} H_{16} O_5$	
Formula weight	276.28	
Temperature	120(2) K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	P 2(1)/n	
Unit cell dimensions	a = 13.33020(10) Å	α= 90°.
	b = 6.00180(10) Å	β= 101.7440(10)°.
	c = 16.81800(10) Å	γ = 90°.
Volume	1317.36(3) $Å^3$	
Z	4	
Density (calculated)	1.393 Mg/m^3	
Absorption coefficient	0.874 mm^{-1}	
F(000)	584	
Crystal size	0.24 x 0.19 x 0.10 mm^3	
Theta range for data collection	3.87 to 70.99°.	
Index ranges	-16<=h<=15, -7<=k<=7, -20<=l<=20	

Reflections collected	13286
Independent reflections	2503 [R(int) = 0.0182]
Completeness to theta = 70.99°	98.1 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9177 and 0.8176
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2503 / 0 / 183
Goodness-of-fit on F^2	1.054
Final R indices [I>2sigma(I)]	R1 = 0.0313, wR2 = 0.0781
R indices (all data)	R1 = 0.0318, wR2 = 0.0786
Extinction coefficient	0.0123(5)
Largest diff. peak and hole	0.284 and -0.292 e.Å^{-3}

Notes:

The hydrogen atoms were fixed as riding models.

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for 2008RG1. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	8199(1)	3091(2)	1545(1)	20(1)
C(2)	7978(1)	4756(2)	859(1)	20(1)
C(3)	6825(1)	5264(2)	740(1)	20(1)
C(4)	6183(1)	3133(2)	532(1)	18(1)
C(5)	6570(1)	1217(2)	1121(1)	18(1)
C(6)	7738(1)	848(2)	1273(1)	18(1)
C(7)	8655(1)	1685(2)	243(1)	17(1)
C(8)	6034(1)	2605(2)	-370(1)	18(1)
C(9)	5896(1)	-150(2)	-1382(1)	24(1)
C(10)	8845(1)	925(2)	-569(1)	18(1)
C(11)	9378(1)	2347(2)	-990(1)	22(1)
C(12)	9550(1)	1744(2)	-1748(1)	26(1)
C(13)	9190(1)	-281(2)	-2092(1)	27(1)
C(14)	8670(1)	-1710(2)	-1667(1)	25(1)
C(15)	8501(1)	-1120(2)	-904(1)	21(1)
O(1)	8560(1)	3573(1)	2245(1)	28(1)
O(2)	8156(1)	3785(1)	117(1)	20(1)
O(3)	8035(1)	124(1)	540(1)	18(1)
O(4)	5882(1)	4016(1)	-893(1)	26(1)
O(5)	6010(1)	422(1)	-532(1)	21(1)

Table 3. Bond lengths [Å] and angles [°] for 2008RG1.

C(1)-O(1)	1.2133(13)	C(7)-C(10)	1.5087(13)
C(1)-C(2)	1.5089(15)	C(7)-H(7)	1.0000
C(1)-C(6)	1.5118(15)	C(8)-O(4)	1.2077(13)
C(2)-O(2)	1.4400(12)	C(8)-O(5)	1.3367(13)
C(2)-C(3)	1.5391(14)	C(9)-O(5)	1.4480(12)
C(2)-H(2)	1.0000	C(9)-H(9A)	0.9800
C(3)-C(4)	1.5390(14)	C(9)-H(9B)	0.9800
C(3)-H(3A)	0.9900	C(9)-H(9C)	0.9800
C(3)-H(3B)	0.9900	C(10)-C(15)	1.3895(15)
C(4)-C(8)	1.5228(13)	C(10)-C(11)	1.3925(15)
C(4)-C(5)	1.5372(13)	C(11)-C(12)	1.3877(15)
C(4)-H(4)	1.0000	C(11)-H(11)	0.9500
C(5)-C(6)	1.5415(14)	C(12)-C(13)	1.3893(17)
C(5)-H(5A)	0.9900	C(12)-H(12)	0.9500
C(5)-H(5B)	0.9900	C(13)-C(14)	1.3881(17)
C(6)-O(3)	1.4366(11)	C(13)-H(13)	0.9500
C(6)-H(6)	1.0000	C(14)-C(15)	1.3932(15)
C(7)-O(3)	1.4070(12)	C(14)-H(14)	0.9500
C(7)-O(2)	1.4209(12)	C(15)-H(15)	0.9500

O(1)-C(1)-C(2)	124.16(10)	C(8)-C(4)-C(5)	116.41(8)
O(1)-C(1)-C(6)	124.19(10)	C(8)-C(4)-C(3)	110.73(8)
C(2)-C(1)-C(6)	110.77(8)	C(5)-C(4)-C(3)	112.12(8)
O(2)-C(2)-C(1)	110.67(8)	C(8)-C(4)-H(4)	105.5
O(2)-C(2)-C(3)	107.69(8)	C(5)-C(4)-H(4)	105.5
C(1)-C(2)-C(3)	105.36(8)	C(3)-C(4)-H(4)	105.5
O(2)-C(2)-H(2)	111.0	C(4)-C(5)-C(6)	114.18(8)
C(1)-C(2)-H(2)	111.0	C(4)-C(5)-H(5A)	108.7
C(3)-C(2)-H(2)	111.0	C(6)-C(5)-H(5A)	108.7
C(4)-C(3)-C(2)	111.07(8)	C(4)-C(5)-H(5B)	108.7
C(4)-C(3)-H(3A)	109.4	C(6)-C(5)-H(5B)	108.7
C(2)-C(3)-H(3A)	109.4	H(5A)-C(5)-H(5B)	107.6
C(4)-C(3)-H(3B)	109.4	O(3)-C(6)-C(1)	111.22(8)
C(2)-C(3)-H(3B)	109.4	O(3)-C(6)-C(5)	110.28(8)
H(3A)-C(3)-H(3B)	108.0	C(1)-C(6)-C(5)	104.92(8)

O(3)-C(6)-H(6)	110.1	C(7)-O(3)-C(6)	112.86(7)
C(1)-C(6)-H(6)	110.1	C(8)-O(5)-C(9)	115.22(8)
C(5)-C(6)-H(6)	110.1		
O(3)-C(7)-O(2)	110.59(8)		
O(3)-C(7)-C(10)	109.83(8)		
O(2)-C(7)-C(10)	107.06(8)		
O(3)-C(7)-H(7)	109.8		
O(2)-C(7)-H(7)	109.8		
C(10)-C(7)-H(7)	109.8		
O(4)-C(8)-O(5)	123.10(9)		
O(4)-C(8)-C(4)	123.19(9)		
O(5)-C(8)-C(4)	113.53(8)		
O(5)-C(9)-H(9A)	109.5		
O(5)-C(9)-H(9B)	109.5		
H(9A)-C(9)-H(9B)	109.5		
O(5)-C(9)-H(9C)	109.5		
H(9A)-C(9)-H(9C)	109.5		
H(9B)-C(9)-H(9C)	109.5		
C(15)-C(10)-C(11)	119.69(9)		
C(15)-C(10)-C(7)	122.15(9)		
C(11)-C(10)-C(7)	118.16(9)		
C(12)-C(11)-C(10)	120.28(10)		
C(12)-C(11)-H(11)	119.9		
C(10)-C(11)-H(11)	119.9		
C(11)-C(12)-C(13)	120.22(10)		
C(11)-C(12)-H(12)	119.9		
C(13)-C(12)-H(12)	119.9		
C(14)-C(13)-C(12)	119.46(10)		
C(14)-C(13)-H(13)	120.3		
C(12)-C(13)-H(13)	120.3		
C(13)-C(14)-C(15)	120.60(10)		
C(13)-C(14)-H(14)	119.7		
C(15)-C(14)-H(14)	119.7		
C(10)-C(15)-C(14)	119.73(10)		
C(10)-C(15)-H(15)	120.1		
C(14)-C(15)-H(15)	120.1		
C(7)-O(2)-C(2)	112.64(8)		

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2$x 10^3)for 2008RG1. The anisotropic displacement factor exponent takes the form: $-2\pi^2$[$h^2a^{*2}U^{11}$ + ... + 2 h k a* b* U^{12}]

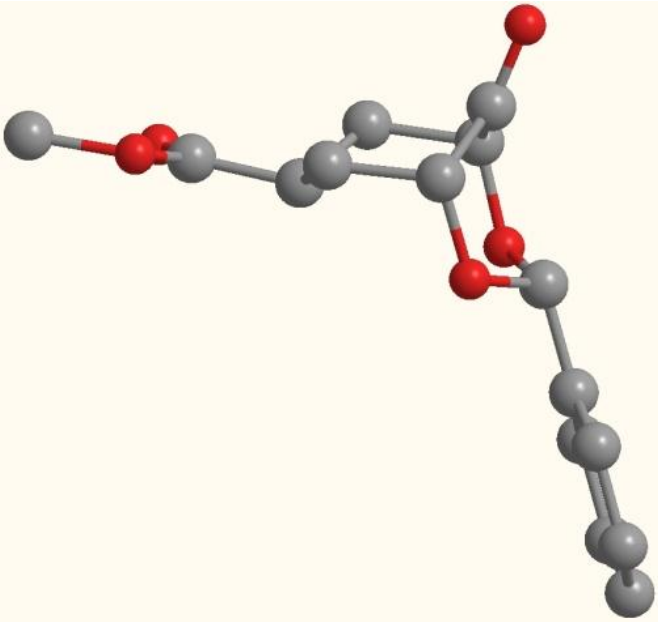
	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	18(1)	22(1)	19(1)	-4(1)	4(1)	3(1)
C(2)	24(1)	15(1)	20(1)	-5(1)	7(1)	-2(1)
C(3)	26(1)	15(1)	19(1)	-1(1)	7(1)	3(1)
C(4)	19(1)	17(1)	18(1)	1(1)	6(1)	3(1)
C(5)	22(1)	16(1)	16(1)	1(1)	6(1)	0(1)
C(6)	23(1)	17(1)	14(1)	1(1)	4(1)	3(1)
C(7)	18(1)	15(1)	19(1)	0(1)	4(1)	1(1)
C(8)	16(1)	19(1)	20(1)	2(1)	4(1)	2(1)
C(9)	27(1)	26(1)	16(1)	-3(1)	2(1)	1(1)
C(10)	16(1)	20(1)	17(1)	0(1)	2(1)	4(1)
C(11)	24(1)	21(1)	21(1)	0(1)	4(1)	1(1)
C(12)	28(1)	30(1)	20(1)	4(1)	8(1)	2(1)
C(13)	31(1)	33(1)	17(1)	-2(1)	6(1)	7(1)
C(14)	29(1)	24(1)	22(1)	-6(1)	4(1)	2(1)
C(15)	21(1)	21(1)	21(1)	-1(1)	5(1)	1(1)
O(1)	30(1)	34(1)	20(1)	-8(1)	1(1)	1(1)
O(2)	28(1)	16(1)	19(1)	0(1)	9(1)	4(1)
O(3)	23(1)	16(1)	17(1)	-2(1)	8(1)	0(1)
O(4)	35(1)	23(1)	20(1)	5(1)	5(1)	6(1)
O(5)	27(1)	19(1)	16(1)	-1(1)	3(1)	0(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^{2}x 10^3) for 2008RG1.

	x	y	z	U(eq)
H(2)	8394	6140	998	24
H(3A)	6680	5927	1244	23
H(3B)	6629	6362	297	23
H(4)	5486	3510	626	21
H(5A)	6222	-176	901	21
H(5B)	6373	1525	1647	21
H(6)	7950	-281	1713	21
H(7)	9323	1849	636	21
H(9A)	5252	471	-1688	35
H(9B)	5887	-1774	-1441	35
H(9C)	6472	467	-1592	35
H(11)	9625	3734	-758	26
H(12)	9915	2720	-2032	31
H(13)	9298	-685	-2614	32
H(14)	8428	-3101	-1899	30
H(15)	8151	-2113	-615	25

5.3 X-ray analysis of 143

Recrystalised from hexane



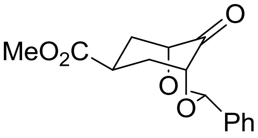


Table 1. Crystal data and structure refinement.

Identification code	**2008src0647**	
Empirical formula	$C_{15}H_{16}O_5$	
Formula weight	276.28	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1/n$	
Unit cell dimensions	a = 5.9584(3) Å	α = 90°
	b = 11.0045(4) Å	β = 91.2230(10)°
	c = 39.4196(18) Å	γ = 90°
Volume	2584.1(2) $Å^3$	
Z	8	
Density (calculated)	1.420 Mg / m^3	
Absorption coefficient	0.107 mm^{-1}	
F(000)	1168	
Crystal	Fragment; Colourless	
Crystal size	0.10 × 0.06 × 0.03 mm^3	
θ range for data collection	3.10 – 27.62°	
Index ranges	$-7 \leq h \leq 7$, $-14 \leq k \leq 14$, $-47 \leq l \leq 51$	
Reflections collected	23876	

Independent reflections	5901 [R_{int} = 0.0835]
Completeness to $\theta = 27.62°$	98.1 %
Absorption correction	Semi−empirical from equivalents
Max. and min. transmission	0.9968 and 0.9894
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5901 / 0 / 363
Goodness-of-fit on F^2	1.122
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.0989, $wR2$ = 0.1597
R indices (all data)	$R1$ = 0.1606, $wR2$ = 0.1879
Largest diff. peak and hole	0.467 and −0.444 e Å^{-3}

Diffractometer: *Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *asymmetric unit* sphere). **Cell determination:** DirAx (Duisenberg, A.J.M.(1992). J. Appl. Cryst. 25, 92-96.) **Data collection:** Collect (Collect: Data collection software, R. Hooft, Nonius B.V., 1998). **Data reduction and cell refinement**: *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307−326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction**: *SORTAV* (R. H. Blessing, Acta Cryst. A**51** (1995) 33–37; R. H. Blessing, J. Appl. Cryst. **30** (1997) 421−426). S**tructure solution**: *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) A**46** 467−473). S**tructure refinement**: *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany). **Graphics:** *ORTEP3 for Windows* (L. J. Farrugia, J. Appl. Crystallogr. 1997, 30, 565).

Special details:

Table 2. Atomic coordinates [× 10^4], equivalent isotropic displacement parameters [$Å^2 \times 10^3$] and site occupancy factors. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
C1	2503(6)	7829(4)	2836(1)	18(1)	1
C2	1526(6)	9074(4)	2732(1)	19(1)	1
C3	2094(6)	9355(4)	2365(1)	21(1)	1
C4	2829(6)	7790(4)	1962(1)	20(1)	1
C5	5551(7)	8092(4)	2408(1)	22(1)	1
C6	5044(6)	7756(4)	2775(1)	22(1)	1
C7	4649(7)	9356(4)	2353(1)	23(1)	1
C8	1966(6)	7484(4)	3192(1)	21(1)	1
C9	–965(7)	7276(4)	3585(1)	29(1)	1
C10	1783(6)	6800(4)	1751(1)	19(1)	1
C11	–312(6)	6310(4)	1817(1)	21(1)	1
C12	–1131(7)	5348(4)	1624(1)	24(1)	1
C13	167(7)	4855(4)	1371(1)	26(1)	1
C14	2254(7)	5343(4)	1301(1)	27(1)	1
C15	3038(7)	6323(4)	1490(1)	24(1)	1
C16	1723(6)	1099(4)	783(1)	17(1)	1
C17	–389(6)	1484(4)	581(1)	16(1)	1
C18	160(6)	2337(4)	286(1)	18(1)	1
C19	3311(6)	3644(4)	298(1)	17(1)	1
C20	4084(6)	1549(4)	270(1)	20(1)	1
C21	3628(6)	642(4)	560(1)	21(1)	1
C22	1865(7)	1657(4)	79(1)	20(1)	1
C23	1270(6)	134(4)	1047(1)	19(1)	1
C24	–1492(8)	–806(5)	1383(1)	36(1)	1
C25	4100(6)	4858(4)	432(1)	16(1)	1
C26	2644(7)	5841(4)	399(1)	20(1)	1
C27	3252(7)	6974(4)	521(1)	23(1)	1
C28	5356(7)	7144(4)	671(1)	23(1)	1
C29	6827(7)	6179(4)	699(1)	23(1)	1
C30	6206(6)	5033(4)	579(1)	20(1)	1
O1	1166(4)	8406(2)	2149(1)	21(1)	1
O2	4417(4)	7232(3)	2186(1)	21(1)	1
O3	5778(5)	10267(3)	2341(1)	34(1)	1
O4	3262(5)	7031(3)	3397(1)	31(1)	1
O5	–195(4)	7691(3)	3259(1)	24(1)	1
O6	1112(4)	3443(2)	418(1)	18(1)	1
O7	4760(4)	2709(2)	411(1)	18(1)	1
O8	1426(5)	1129(3)	–184(1)	28(1)	1
O9	2690(5)	–497(3)	1180(1)	29(1)	1
O10	–922(4)	63(3)	1118(1)	24(1)	1

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

C1–C8	1.495(6)	C16–C23	1.515(6)
C1–C6	1.540(5)	C16–C17	1.536(5)
C1–C2	1.541(5)	C16–C21	1.537(5)
C1–H1	1.0000	C16–H16	1.0000
C2–C3	1.526(6)	C17–C18	1.533(5)
C2–H2A	0.9900	C17–H17A	0.9900
C2–H2B	0.9900	C17–H17B	0.9900
C3–O1	1.448(5)	C18–O6	1.435(5)
C3–C7	1.524(5)	C18–C22	1.515(5)
C3–H3	1.0000	C18–H18	1.0000
C4–O2	1.419(5)	C19–O7	1.410(5)
C4–O1	1.420(5)	C19–O6	1.419(4)
C4–C10	1.499(6)	C19–C25	1.508(5)
C4–H4	1.0000	C19–H19	1.0000
C5–O2	1.447(5)	C20–O7	1.445(5)
C5–C7	1.506(6)	C20–C22	1.512(6)
C5–C6	1.531(6)	C20–C21	1.544(5)
C5–H5	1.0000	C20–H20	1.0000
C6–H6A	0.9900	C21–H21A	0.9900
C6–H6B	0.9900	C21–H21B	0.9900
C7–O3	1.209(5)	C22–O8	1.214(5)
C8–O4	1.213(5)	C23–O9	1.205(5)
C8–O5	1.339(5)	C23–O10	1.344(4)
C9–O5	1.448(5)	C24–O10	1.461(5)
C9–H9A	0.9800	C24–H24A	0.9800
C9–H9B	0.9800	C24–H24B	0.9800
C9–H9C	0.9800	C24–H24C	0.9800
C10–C15	1.387(6)	C25–C30	1.385(5)
C10–C11	1.390(5)	C25–C26	1.391(5)
C11–C12	1.388(6)	C26–C27	1.381(6)
C11–H11	0.9500	C26–H26	0.9500
C12–C13	1.385(6)	C27–C28	1.387(6)
C12–H12	0.9500	C27–H27	0.9500
C13–C14	1.387(6)	C28–C29	1.380(6)
C13–H13	0.9500	C28–H28	0.9500
C14–C15	1.387(6)	C29–C30	1.394(6)
C14–H14	0.9500	C29–H29	0.9500
C15–H15	0.9500	C30–H30	0.9500

C8–C1–C6	111.3(3)	C2–C1–H1	106.8
C8–C1–C2	112.9(3)	C3–C2–C1	110.0(3)
C6–C1–C2	111.8(3)	C3–C2–H2A	109.7
C8–C1–H1	106.8	C1–C2–H2A	109.7
C6–C1–H1	106.8	C3–C2–H2B	109.7

C1–C2–H2B	109.7
H2A–C2–H2B	108.2
O1–C3–C7	110.6(3)
O1–C3–C2	108.7(3)
C7–C3–C2	105.8(3)
O1–C3–H3	110.5
C7–C3–H3	110.5
C2–C3–H3	110.5
O2–C4–O1	110.3(3)
O2–C4–C10	107.1(3)
O1–C4–C10	110.4(3)
O2–C4–H4	109.7
O1–C4–H4	109.7
C10–C4–H4	109.7
O2–C5–C7	110.9(3)
O2–C5–C6	108.4(3)
C7–C5–C6	106.4(3)
O2–C5–H5	110.4
C7–C5–H5	110.4
C6–C5–H5	110.4
C5–C6–C1	110.5(3)
C5–C6–H6A	109.6
C1–C6–H6A	109.6
C5–C6–H6B	109.6
C1–C6–H6B	109.6
H6A–C6–H6B	108.1
O3–C7–C5	125.1(4)
O3–C7–C3	124.0(4)
C5–C7–C3	110.4(3)
O4–C8–O5	122.5(4)
O4–C8–C1	125.8(4)
O5–C8–C1	111.6(3)
O5–C9–H9A	109.5
O5–C9–H9B	109.5
H9A–C9–H9B	109.5
O5–C9–H9C	109.5
H9A–C9–H9C	109.5
H9B–C9–H9C	109.5
C15–C10–C11	119.5(4)
C15–C10–C4	117.5(4)
C11–C10–C4	122.8(4)
C12–C11–C10	120.0(4)
C12–C11–H11	120.0
C10–C11–H11	120.0
C13–C12–C11	120.0(4)
C13–C12–H12	120.0
C11–C12–H12	120.0
C12–C13–C14	120.5(4)
C12–C13–H13	119.8
C14–C13–H13	119.8
C15–C14–C13	119.2(4)
C15–C14–H14	120.4
C13–C14–H14	120.4
C10–C15–C14	120.8(4)
C10–C15–H15	119.6
C14–C15–H15	119.6
C23–C16–C17	113.2(3)
C23–C16–C21	108.0(3)
C17–C16–C21	113.5(3)
C23–C16–H16	107.3
C17–C16–H16	107.3
C21–C16–H16	107.3
C18–C17–C16	112.1(3)
C18–C17–H17A	109.2
C16–C17–H17A	109.2
C18–C17–H17B	109.2
C16–C17–H17B	109.2
H17A–C17–H17B	107.9
O6–C18–C22	110.4(3)
O6–C18–C17	109.6(3)
C22–C18–C17	105.2(3)
O6–C18–H18	110.5
C22–C18–H18	110.5
C17–C18–H18	110.5
O7–C19–O6	110.1(3)
O7–C19–C25	110.6(3)
O6–C19–C25	107.7(3)
O7–C19–H19	109.4
O6–C19–H19	109.4
C25–C19–H19	109.4
O7–C20–C22	110.8(3)
O7–C20–C21	109.8(3)
C22–C20–C21	104.7(3)
O7–C20–H20	110.5
C22–C20–H20	110.5
C21–C20–H20	110.5
C16–C21–C20	110.8(3)
C16–C21–H21A	109.5
C20–C21–H21A	109.5
C16–C21–H21B	109.5
C20–C21–H21B	109.5
H21A–C21–H21B	108.1

O8–C22–C20	124.0(4)
O8–C22–C18	124.2(4)
C20–C22–C18	111.1(3)
O9–C23–O10	123.6(4)
O9–C23–C16	124.6(3)
O10–C23–C16	111.8(3)
O10–C24–H24A	109.5
O10–C24–H24B	109.5
H24A–C24–H24B	109.5
O10–C24–H24C	109.5
H24A–C24–H24C	109.5
H24B–C24–H24C	109.5
C30–C25–C26	119.2(4)
C30–C25–C19	122.9(4)
C26–C25–C19	117.9(3)
C27–C26–C25	120.8(4)
C27–C26–H26	119.6
C25–C26–H26	119.6
C26–C27–C28	119.8(4)
C26–C27–H27	120.1
C28–C27–H27	120.1
C29–C28–C27	119.8(4)
C29–C28–H28	120.1
C27–C28–H28	120.1
C28–C29–C30	120.3(4)
C28–C29–H29	119.8
C30–C29–H29	119.8
C25–C30–C29	120.0(4)
C25–C30–H30	120.0
C29–C30–H30	120.0
C4–O1–C3	112.8(3)
C4–O2–C5	112.9(3)
C8–O5–C9	116.5(3)
C19–O6–C18	111.9(3)
C19–O7–C20	111.1(3)
C23–O10–C24	115.3(3)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters [$\text{Å}^2 \times 10^3$]. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + \cdots + 2\,h\,k\,a^*\,b^*\,U^{12}]$.

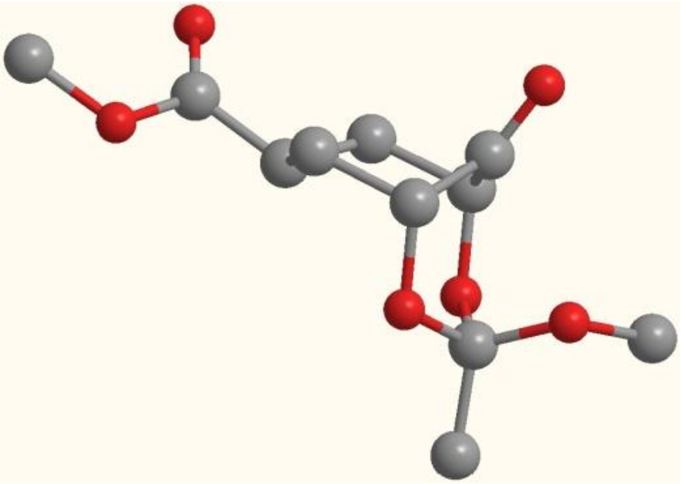
Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C1	16(2)	14(2)	25(2)	−2(2)	−1(2)	2(2)
C2	16(2)	20(2)	21(2)	−4(2)	2(2)	−1(2)
C3	20(2)	19(2)	26(2)	1(2)	0(2)	1(2)
C4	18(2)	22(2)	20(2)	1(2)	3(2)	3(2)
C5	20(2)	18(2)	27(2)	−4(2)	−1(2)	−4(2)
C6	16(2)	21(2)	28(2)	−3(2)	−2(2)	0(2)
C7	21(2)	27(2)	21(2)	−2(2)	5(2)	−3(2)
C8	18(2)	18(2)	28(2)	−2(2)	−1(2)	0(2)
C9	21(2)	42(3)	25(2)	9(2)	6(2)	−2(2)
C10	19(2)	21(2)	16(2)	3(2)	−2(2)	0(2)
C11	19(2)	24(2)	21(2)	3(2)	2(2)	4(2)
C12	21(2)	21(2)	29(2)	5(2)	−6(2)	−1(2)
C13	37(2)	26(2)	17(2)	−2(2)	−9(2)	0(2)
C14	33(2)	29(3)	20(2)	−1(2)	0(2)	−1(2)
C15	21(2)	33(3)	17(2)	4(2)	4(2)	−1(2)
C16	14(2)	16(2)	19(2)	−3(2)	0(2)	−3(2)
C17	16(2)	13(2)	19(2)	5(2)	0(2)	−3(2)
C18	15(2)	18(2)	21(2)	1(2)	0(2)	0(2)
C19	15(2)	21(2)	16(2)	3(2)	1(2)	0(2)
C20	20(2)	15(2)	24(2)	−3(2)	4(2)	−2(2)
C21	17(2)	17(2)	29(2)	3(2)	5(2)	1(2)
C22	26(2)	18(2)	16(2)	1(2)	4(2)	−7(2)
C23	14(2)	19(2)	24(2)	−5(2)	−2(2)	0(2)
C24	28(2)	41(3)	38(3)	23(2)	4(2)	−4(2)
C25	17(2)	16(2)	15(2)	0(2)	3(2)	−2(2)
C26	19(2)	23(2)	18(2)	4(2)	−1(2)	2(2)
C27	23(2)	24(2)	21(2)	3(2)	−3(2)	5(2)
C28	30(2)	17(2)	21(2)	−1(2)	4(2)	−7(2)
C29	21(2)	24(2)	23(2)	−3(2)	−1(2)	−6(2)
C30	19(2)	23(2)	18(2)	0(2)	3(2)	1(2)
O1	18(1)	19(2)	24(2)	−3(1)	0(1)	2(1)
O2	17(1)	20(2)	26(2)	−1(1)	−3(1)	2(1)
O3	32(2)	28(2)	42(2)	−1(2)	10(2)	−9(2)
O4	20(2)	43(2)	31(2)	14(2)	−1(1)	4(1)
O5	18(1)	32(2)	24(2)	5(1)	3(1)	2(1)
O6	15(1)	15(1)	25(2)	−3(1)	3(1)	−4(1)
O7	17(1)	15(2)	23(2)	−1(1)	0(1)	2(1)
O8	36(2)	28(2)	22(2)	−4(1)	4(1)	−8(1)
O9	22(2)	29(2)	36(2)	9(2)	1(1)	3(1)
O10	18(1)	30(2)	24(2)	10(1)	1(1)	−1(1)

Table 5. Hydrogen coordinates [× 10^4] and isotropic displacement parameters [$Å^2 \times 10^3$].

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
H1	1772	7210	2684	22	1
H2A	–124	9066	2757	23	1
H2B	2157	9714	2882	23	1
H3	1479	10166	2296	26	1
H4	3610	8380	1812	24	1
H5	7206	8073	2371	26	1
H6A	5848	8319	2931	26	1
H6B	5584	6922	2823	26	1
H9A	–360	6464	3633	44	1
H9B	–2609	7244	3582	44	1
H9C	–448	7841	3763	44	1
H11	–1183	6633	1995	26	1
H12	–2581	5027	1664	29	1
H13	–376	4178	1244	32	1
H14	3135	5010	1126	33	1
H15	4453	6671	1441	28	1
H16	2295	1834	907	20	1
H17A	–1152	751	490	20	1
H17B	–1435	1899	735	20	1
H18	–1220	2513	146	21	1
H19	3269	3662	44	21	1
H20	5267	1226	118	23	1
H21A	3212	–158	462	25	1
H21B	5010	534	700	25	1
H24A	–1005	–1621	1316	53	1
H24B	–3120	–806	1413	53	1
H24C	–734	–576	1596	53	1
H26	1215	5732	292	24	1
H27	2233	7636	501	27	1
H28	5783	7923	754	27	1
H29	8270	6296	801	27	1
H30	7228	4373	598	24	1

5.4 X-ray analysis of 144

Recrystaliszed from $CDCl_3$



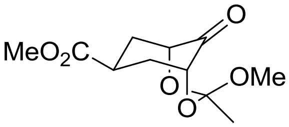


Table 1. Crystal data and structure refinement for TC228.

Identification code	TC228, 2009src0661	
Empirical formula	$C_{11} H_{16} O_6$	
Formula weight	244.24	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P\ 2_1/c$	
Unit cell dimensions	a = 5.98260(10) Å	α= 90°.
	b = 10.3401(2) Å	β= 96.097(2)°.
	c = 18.4246(4) Å	γ = 90°.
Volume	1133.31(4) $Å^3$	
Z	4	
Density (calculated)	1.431 Mg/m^3	
Absorption coefficient	0.117 mm^{-1}	
F(000)	520	
Crystal size	0.25 x 0.22 x 0.10 mm^3	
Theta range for data collection	2.97 to 27.48°.	
Index ranges	-7<=h<=7, -12<=k<=13, -23<=l<=23	
Reflections collected	14865	
Independent reflections	2600 [R(int) = 0.0402]	
Completeness to theta = 27.48°	99.8 %	
Absorption correction	Semi-empirical from equivalents	

Max. and min. transmission	0.9884 and 0.9713
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2600 / 0 / 157
Goodness-of-fit on F^2	1.082
Final R indices [I>2sigma(I)]	R1 = 0.0428, wR2 = 0.1119
R indices (all data)	R1 = 0.0529, wR2 = 0.1190
Largest diff. peak and hole	0.489 and -0.455 e.Å^{-3}

Notes:

The hydrogen atoms were fixed as riding models.

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^2x 10^3) for TC228. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	-4113(3)	3311(2)	-175(1)	27(1)
C(2)	-976(2)	3552(1)	714(1)	19(1)
C(3)	-230(2)	4043(1)	1477(1)	17(1)
C(4)	2297(2)	3789(1)	1671(1)	18(1)
C(5)	3260(2)	4505(1)	2365(1)	17(1)
C(6)	2649(2)	5915(1)	2234(1)	18(1)
C(7)	146(2)	6114(1)	2226(1)	18(1)
C(8)	-885(2)	5487(1)	1517(1)	18(1)
C(9)	983(2)	4930(1)	3327(1)	18(1)
C(10)	4423(3)	5649(2)	3993(1)	39(1)
C(11)	-79(3)	4261(2)	3931(1)	24(1)
O(1)	247(2)	3164(1)	280(1)	32(1)
O(2)	-3217(2)	3648(1)	561(1)	21(1)
O(3)	2232(2)	4003(1)	2983(1)	18(1)
O(4)	-716(2)	5467(1)	2837(1)	19(1)
O(5)	3920(2)	6717(1)	2023(1)	25(1)
O(6)	2376(2)	5990(1)	3567(1)	21(1)

Table 3. Bond lengths [Å] and angles [°] for TC228.

C(1)-O(2)	1.4480(17)	C(6)-C(7)	1.510(2)
C(1)-H(1A)	0.9800	C(7)-O(4)	1.4502(16)
C(1)-H(1B)	0.9800	C(7)-C(8)	1.5289(19)
C(1)-H(1C)	0.9800	C(7)-H(7)	1.0000
C(2)-O(1)	1.2079(18)	C(8)-H(8A)	0.9900
C(2)-O(2)	1.3441(17)	C(8)-H(8B)	0.9900
C(2)-C(3)	1.5170(18)	C(9)-O(4)	1.4010(16)
C(3)-C(4)	1.5387(19)	C(9)-O(3)	1.4071(17)
C(3)-C(8)	1.5473(19)	C(9)-O(6)	1.4190(17)
C(3)-H(3)	1.0000	C(9)-C(11)	1.507(2)
C(4)-C(5)	1.5355(19)	C(10)-O(6)	1.4269(18)
C(4)-H(4A)	0.9900	C(10)-H(10A)	0.9800
C(4)-H(4B)	0.9900	C(10)-H(10B)	0.9800
C(5)-O(3)	1.4470(16)	C(10)-H(10C)	0.9800
C(5)-C(6)	1.517(2)	C(11)-H(11A)	0.9800
C(5)-H(5)	1.0000	C(11)-H(11B)	0.9800
C(6)-O(5)	1.2157(18)	C(11)-H(11C)	0.9800

O(2)-C(1)-H(1A)	109.5	C(3)-C(4)-H(4A)	109.1
O(2)-C(1)-H(1B)	109.5	C(5)-C(4)-H(4B)	109.1
H(1A)-C(1)-H(1B)	109.5	C(3)-C(4)-H(4B)	109.1
O(2)-C(1)-H(1C)	109.5	H(4A)-C(4)-H(4B)	107.8
H(1A)-C(1)-H(1C)	109.5	O(3)-C(5)-C(6)	110.80(11)
H(1B)-C(1)-H(1C)	109.5	O(3)-C(5)-C(4)	109.24(11)
O(1)-C(2)-O(2)	123.16(13)	C(6)-C(5)-C(4)	105.56(11)
O(1)-C(2)-C(3)	125.84(13)	O(3)-C(5)-H(5)	110.4
O(2)-C(2)-C(3)	110.96(11)	C(6)-C(5)-H(5)	110.4
C(2)-C(3)-C(4)	110.07(11)	C(4)-C(5)-H(5)	110.4
C(2)-C(3)-C(8)	108.39(11)	O(5)-C(6)-C(7)	123.85(13)
C(4)-C(3)-C(8)	113.65(11)	O(5)-C(6)-C(5)	123.95(13)
C(2)-C(3)-H(3)	108.2	C(7)-C(6)-C(5)	110.76(11)
C(4)-C(3)-H(3)	108.2	O(4)-C(7)-C(6)	111.34(11)
C(8)-C(3)-H(3)	108.2	O(4)-C(7)-C(8)	108.83(11)
C(5)-C(4)-C(3)	112.54(11)	C(6)-C(7)-C(8)	105.06(11)
C(5)-C(4)-H(4A)	109.1	O(4)-C(7)-H(7)	110.5

C(6)-C(7)-H(7)	110.5
C(8)-C(7)-H(7)	110.5
C(7)-C(8)-C(3)	111.65(11)
C(7)-C(8)-H(8A)	109.3
C(3)-C(8)-H(8A)	109.3
C(7)-C(8)-H(8B)	109.3
C(3)-C(8)-H(8B)	109.3
H(8A)-C(8)-H(8B)	108.0
O(4)-C(9)-O(3)	111.31(11)
O(4)-C(9)-O(6)	104.85(11)
O(3)-C(9)-O(6)	110.15(11)
O(4)-C(9)-C(11)	108.92(11)
O(3)-C(9)-C(11)	107.79(12)
O(6)-C(9)-C(11)	113.85(12)
O(6)-C(10)-H(10A)	109.5
O(6)-C(10)-H(10B)	109.5
H(10A)-C(10)-H(10B)	109.5
O(6)-C(10)-H(10C)	109.5
H(10A)-C(10)-H(10C)	109.5
H(10B)-C(10)-H(10C)	109.5
C(9)-C(11)-H(11A)	109.5
C(9)-C(11)-H(11B)	109.5
H(11A)-C(11)-H(11B)	109.5
C(9)-C(11)-H(11C)	109.5
H(11A)-C(11)-H(11C)	109.5
H(11B)-C(11)-H(11C)	109.5
C(2)-O(2)-C(1)	116.12(11)
C(9)-O(3)-C(5)	113.60(10)
C(9)-O(4)-C(7)	112.94(10)
C(9)-O(6)-C(10)	114.96(11)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters (Å^{2}x 10^3)for TC228. The anisotropic displacement factor exponent takes the form: $-2\pi^2$[$h^2a^{*2}U^{11}$ + ... + 2 h k a* b* U^{12}]

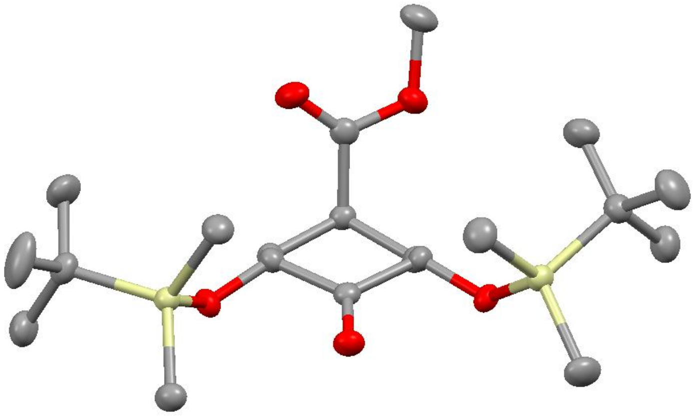
	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	28(1)	34(1)	17(1)	-3(1)	-1(1)	-3(1)
C(2)	21(1)	19(1)	17(1)	-1(1)	4(1)	-2(1)
C(3)	19(1)	16(1)	15(1)	-1(1)	5(1)	0(1)
C(4)	20(1)	18(1)	17(1)	-1(1)	4(1)	2(1)
C(5)	16(1)	18(1)	17(1)	1(1)	4(1)	0(1)
C(6)	21(1)	18(1)	14(1)	-2(1)	1(1)	-2(1)
C(7)	22(1)	15(1)	16(1)	1(1)	4(1)	2(1)
C(8)	19(1)	19(1)	16(1)	1(1)	1(1)	3(1)
C(9)	21(1)	16(1)	16(1)	-1(1)	1(1)	2(1)
C(10)	40(1)	29(1)	42(1)	-5(1)	-22(1)	5(1)
C(11)	30(1)	26(1)	18(1)	3(1)	7(1)	3(1)
O(1)	26(1)	50(1)	23(1)	-13(1)	7(1)	-2(1)
O(2)	20(1)	25(1)	17(1)	-2(1)	0(1)	0(1)
O(3)	23(1)	14(1)	19(1)	1(1)	6(1)	2(1)
O(4)	19(1)	21(1)	15(1)	3(1)	3(1)	3(1)
O(5)	27(1)	22(1)	27(1)	3(1)	4(1)	-7(1)
O(6)	24(1)	17(1)	19(1)	-2(1)	-2(1)	2(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^{2}x 10^3) for TC228.

	x	y	z	U(eq)
H(1A)	-3664	3966	-516	40
H(1B)	-5758	3272	-206	40
H(1C)	-3526	2465	-303	40
H(3)	-1070	3551	1829	20
H(4A)	2544	2848	1741	22
H(4B)	3117	4067	1258	22
H(5)	4929	4399	2443	21
H(7)	-219	7058	2229	21
H(8A)	-365	5952	1096	21
H(8B)	-2542	5562	1483	21
H(10A)	4083	5261	4454	58
H(10B)	5340	6427	4096	58
H(10C)	5251	5027	3723	58
H(11A)	-734	4908	4235	37
H(11B)	1067	3764	4232	37
H(11C)	-1262	3675	3720	37

5.5 X-ray analysis of 189

Recrystallised from diethyl ether



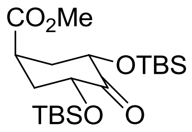


Table 1. Crystal data and structure refinement for TC506.

Identification code	TC506	
Empirical formula	$C_{20}H_{40}O_5Si_2$	
Formula weight	416.70	
Temperature	120(2) K	
Wavelength	1.54184 Å	
Crystal system	Orthorhombic	
Space group	$P\ 2_12_12_1$	
Unit cell dimensions	a = 10.9340(4) Å	α= 90°.
	b = 12.2156(5) Å	β= 90°.
	c = 18.4914(8) Å	γ = 90°.
Volume	2469.81(17) $Å^3$	
Z	4	
Density (calculated)	1.121 Mg/m^3	
Absorption coefficient	1.504 mm^{-1}	
F(000)	912	
Crystal size	0.30 x 0.30 x 0.24 mm^3	
Theta range for data collection	7.25 to 66.60°.	
Index ranges	-13<=h<=11, -14<=k<=14, -18<=l<=21	
Reflections collected	15847	
Independent reflections	4287 [R(int) = 0.0257]	

Completeness to theta = 66.60°	98.7 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.7142 and 0.6612
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4287 / 0 / 255
Goodness-of-fit on F^2	1.070
Final R indices [I>2sigma(I)]	R1 = 0.0259, wR2 = 0.0698
R indices (all data)	R1 = 0.0262, wR2 = 0.0700
Absolute structure parameter	0.018(15)
Largest diff. peak and hole	0.285 and -0.163 e.Å^{-3}

Notes:

The absolute structure has been determined from the diffraction data. The chirality of C(2) is S and that of C(6) is R.

The hydrogen atoms were fixed as riding models.

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for TC506. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	2457(1)	7196(1)	855(1)	20(1)
C(2)	2243(1)	8406(1)	1010(1)	22(1)
C(3)	1795(1)	8986(1)	332(1)	23(1)
C(4)	643(1)	8435(1)	37(1)	21(1)
C(5)	898(1)	7242(1)	-149(1)	22(1)
C(6)	1392(1)	6609(1)	499(1)	21(1)
C(7)	-433(1)	8544(1)	545(1)	23(1)
C(8)	-1576(2)	9770(1)	1250(1)	37(1)
C(9)	3151(2)	7884(1)	2670(1)	35(1)
C(10)	5407(1)	9092(2)	2096(1)	37(1)
C(11)	3078(1)	10381(1)	2460(1)	28(1)
C(12)	3474(2)	10589(2)	3242(1)	45(1)
C(13)	3533(2)	11323(1)	1988(1)	37(1)
C(14)	1680(2)	10355(1)	2428(1)	40(1)
C(15)	1502(2)	4779(1)	1749(1)	31(1)
C(16)	3428(1)	3935(1)	713(1)	29(1)
C(17)	714(1)	3453(1)	409(1)	28(1)
C(18)	711(2)	2402(2)	858(1)	57(1)
C(19)	-560(2)	3955(2)	415(1)	47(1)
C(20)	1056(2)	3178(2)	-367(1)	40(1)
O(1)	3387(1)	6734(1)	1023(1)	26(1)
O(2)	-1111(1)	7817(1)	719(1)	32(1)
O(3)	-545(1)	9572(1)	785(1)	29(1)
O(4)	3304(1)	8912(1)	1267(1)	25(1)
O(5)	1723(1)	5555(1)	276(1)	24(1)
Si(1)	3719(1)	9051(1)	2118(1)	23(1)
Si(2)	1847(1)	4460(1)	788(1)	21(1)

Table 3. Bond lengths [Å] and angles [°] for TC506.

C(1)-O(1)	1.2044(17)	C(11)-Si(1)	1.8790(15)
C(1)-C(6)	1.5174(18)	C(12)-H(12A)	0.9800
C(1)-C(2)	1.5233(19)	C(12)-H(12B)	0.9800
C(2)-O(4)	1.3982(16)	C(12)-H(12C)	0.9800
C(2)-C(3)	1.5206(19)	C(13)-H(13A)	0.9800
C(2)-H(2)	1.0000	C(13)-H(13B)	0.9800
C(3)-C(4)	1.5288(18)	C(13)-H(13C)	0.9800
C(3)-H(3A)	0.9900	C(14)-H(14A)	0.9800
C(3)-H(3B)	0.9900	C(14)-H(14B)	0.9800
C(4)-C(7)	1.5120(19)	C(14)-H(14C)	0.9800
C(4)-C(5)	1.5234(18)	C(15)-Si(2)	1.8587(15)
C(4)-H(4)	1.0000	C(15)-H(15A)	0.9800
C(5)-C(6)	1.5250(18)	C(15)-H(15B)	0.9800
C(5)-H(5A)	0.9900	C(15)-H(15C)	0.9800
C(5)-H(5B)	0.9900	C(16)-Si(2)	1.8482(15)
C(6)-O(5)	1.3996(16)	C(16)-H(16A)	0.9800
C(6)-H(6)	1.0000	C(16)-H(16B)	0.9800
C(7)-O(2)	1.2006(18)	C(16)-H(16C)	0.9800
C(7)-O(3)	1.3366(17)	C(17)-C(20)	1.521(2)
C(8)-O(3)	1.4384(19)	C(17)-C(19)	1.522(2)
C(8)-H(8A)	0.9800	C(17)-C(18)	1.528(2)
C(8)-H(8B)	0.9800	C(17)-Si(2)	1.8817(15)
C(8)-H(8C)	0.9800	C(18)-H(18A)	0.9800
C(9)-Si(1)	1.8605(16)	C(18)-H(18B)	0.9800
C(9)-H(9A)	0.9800	C(18)-H(18C)	0.9800
C(9)-H(9B)	0.9800	C(19)-H(19A)	0.9800
C(9)-H(9C)	0.9800	C(19)-H(19B)	0.9800
C(10)-Si(1)	1.8469(15)	C(19)-H(19C)	0.9800
C(10)-H(10A)	0.9800	C(20)-H(20A)	0.9800
C(10)-H(10B)	0.9800	C(20)-H(20B)	0.9800
C(10)-H(10C)	0.9800	C(20)-H(20C)	0.9800
C(11)-C(13)	1.528(2)	O(4)-Si(1)	1.6463(10)
C(11)-C(12)	1.531(2)	O(5)-Si(2)	1.6457(10)
C(11)-C(14)	1.531(2)		
O(1)-C(1)-C(6)	122.54(12)	O(1)-C(1)-C(2)	122.46(12)

C(6)-C(1)-C(2)	114.97(11)	O(3)-C(8)-H(8C)	109.5
O(4)-C(2)-C(3)	109.98(11)	H(8A)-C(8)-H(8C)	109.5
O(4)-C(2)-C(1)	111.42(11)	H(8B)-C(8)-H(8C)	109.5
C(3)-C(2)-C(1)	110.26(11)	Si(1)-C(9)-H(9A)	109.5
O(4)-C(2)-H(2)	108.4	Si(1)-C(9)-H(9B)	109.5
C(3)-C(2)-H(2)	108.4	H(9A)-C(9)-H(9B)	109.5
C(1)-C(2)-H(2)	108.4	Si(1)-C(9)-H(9C)	109.5
C(2)-C(3)-C(4)	110.75(11)	H(9A)-C(9)-H(9C)	109.5
C(2)-C(3)-H(3A)	109.5	H(9B)-C(9)-H(9C)	109.5
C(4)-C(3)-H(3A)	109.5	Si(1)-C(10)-H(10A)	109.5
C(2)-C(3)-H(3B)	109.5	Si(1)-C(10)-H(10B)	109.5
C(4)-C(3)-H(3B)	109.5	H(10A)-C(10)-H(10B)	109.5
H(3A)-C(3)-H(3B)	108.1	Si(1)-C(10)-H(10C)	109.5
C(7)-C(4)-C(5)	111.53(11)	H(10A)-C(10)-H(10C)	109.5
C(7)-C(4)-C(3)	112.40(11)	H(10B)-C(10)-H(10C)	109.5
C(5)-C(4)-C(3)	110.53(11)	C(13)-C(11)-C(12)	108.89(13)
C(7)-C(4)-H(4)	107.4	C(13)-C(11)-C(14)	108.55(14)
C(5)-C(4)-H(4)	107.4	C(12)-C(11)-C(14)	108.86(14)
C(3)-C(4)-H(4)	107.4	C(13)-C(11)-Si(1)	109.70(11)
C(4)-C(5)-C(6)	111.87(11)	C(12)-C(11)-Si(1)	110.85(11)
C(4)-C(5)-H(5A)	109.2	C(14)-C(11)-Si(1)	109.93(11)
C(6)-C(5)-H(5A)	109.2	C(11)-C(12)-H(12A)	109.5
C(4)-C(5)-H(5B)	109.2	C(11)-C(12)-H(12B)	109.5
C(6)-C(5)-H(5B)	109.2	H(12A)-C(12)-H(12B)	109.5
H(5A)-C(5)-H(5B)	107.9	C(11)-C(12)-H(12C)	109.5
O(5)-C(6)-C(1)	111.41(11)	H(12A)-C(12)-H(12C)	109.5
O(5)-C(6)-C(5)	109.01(10)	H(12B)-C(12)-H(12C)	109.5
C(1)-C(6)-C(5)	111.92(11)	C(11)-C(13)-H(13A)	109.5
O(5)-C(6)-H(6)	108.1	C(11)-C(13)-H(13B)	109.5
C(1)-C(6)-H(6)	108.1	H(13A)-C(13)-H(13B)	109.5
C(5)-C(6)-H(6)	108.1	C(11)-C(13)-H(13C)	109.5
O(2)-C(7)-O(3)	123.30(13)	H(13A)-C(13)-H(13C)	109.5
O(2)-C(7)-C(4)	125.60(13)	H(13B)-C(13)-H(13C)	109.5
O(3)-C(7)-C(4)	111.10(12)	C(11)-C(14)-H(14A)	109.5
O(3)-C(8)-H(8A)	109.5	C(11)-C(14)-H(14B)	109.5
O(3)-C(8)-H(8B)	109.5	H(14A)-C(14)-H(14B)	109.5
H(8A)-C(8)-H(8B)	109.5	C(11)-C(14)-H(14C)	109.5

H(14A)-C(14)-H(14C)	109.5
H(14B)-C(14)-H(14C)	109.5
Si(2)-C(15)-H(15A)	109.5
Si(2)-C(15)-H(15B)	109.5
H(15A)-C(15)-H(15B)	109.5
Si(2)-C(15)-H(15C)	109.5
H(15A)-C(15)-H(15C)	109.5
H(15B)-C(15)-H(15C)	109.5
Si(2)-C(16)-H(16A)	109.5
Si(2)-C(16)-H(16B)	109.5
H(16A)-C(16)-H(16B)	109.5
Si(2)-C(16)-H(16C)	109.5
H(16A)-C(16)-H(16C)	109.5
H(16B)-C(16)-H(16C)	109.5
C(20)-C(17)-C(19)	108.70(14)
C(20)-C(17)-C(18)	109.15(15)
C(19)-C(17)-C(18)	109.44(15)
C(20)-C(17)-Si(2)	109.46(11)
C(19)-C(17)-Si(2)	109.68(11)
C(18)-C(17)-Si(2)	110.38(11)
C(17)-C(18)-H(18A)	109.5
C(17)-C(18)-H(18B)	109.5
H(18A)-C(18)-H(18B)	109.5
C(17)-C(18)-H(18C)	109.5
H(18A)-C(18)-H(18C)	109.5
H(18B)-C(18)-H(18C)	109.5
C(17)-C(19)-H(19A)	109.5
C(17)-C(19)-H(19B)	109.5
H(19A)-C(19)-H(19B)	109.5
C(17)-C(19)-H(19C)	109.5
H(19A)-C(19)-H(19C)	109.5
H(19B)-C(19)-H(19C)	109.5
C(17)-C(20)-H(20A)	109.5
C(17)-C(20)-H(20B)	109.5
H(20A)-C(20)-H(20B)	109.5
C(17)-C(20)-H(20C)	109.5
H(20A)-C(20)-H(20C)	109.5
H(20B)-C(20)-H(20C)	109.5
C(7)-O(3)-C(8)	115.33(12)
C(2)-O(4)-Si(1)	126.85(9)
C(6)-O(5)-Si(2)	126.84(8)
O(4)-Si(1)-C(10)	104.92(7)
O(4)-Si(1)-C(9)	110.69(6)
C(10)-Si(1)-C(9)	111.47(8)
O(4)-Si(1)-C(11)	107.96(6)
C(10)-Si(1)-C(11)	110.90(8)
C(9)-Si(1)-C(11)	110.70(7)
O(5)-Si(2)-C(16)	108.43(6)
O(5)-Si(2)-C(15)	111.30(6)
C(16)-Si(2)-C(15)	109.55(7)
O(5)-Si(2)-C(17)	105.23(6)
C(16)-Si(2)-C(17)	111.18(7)
C(15)-Si(2)-C(17)	111.06(7)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2$x 10^3)for TC506. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	19(1)	25(1)	16(1)	1(1)	2(1)	0(1)
C(2)	19(1)	24(1)	22(1)	-2(1)	-1(1)	-2(1)
C(3)	21(1)	24(1)	22(1)	1(1)	-1(1)	-1(1)
C(4)	19(1)	25(1)	20(1)	2(1)	-2(1)	1(1)
C(5)	20(1)	25(1)	21(1)	-1(1)	-3(1)	1(1)
C(6)	21(1)	22(1)	21(1)	-2(1)	0(1)	2(1)
C(7)	21(1)	28(1)	21(1)	2(1)	-5(1)	4(1)
C(8)	33(1)	49(1)	29(1)	-9(1)	3(1)	11(1)
C(9)	40(1)	36(1)	31(1)	7(1)	-3(1)	-2(1)
C(10)	22(1)	52(1)	35(1)	-2(1)	-6(1)	3(1)
C(11)	28(1)	31(1)	26(1)	-3(1)	-1(1)	-1(1)
C(12)	58(1)	46(1)	31(1)	-10(1)	-5(1)	5(1)
C(13)	42(1)	30(1)	40(1)	-2(1)	-3(1)	-3(1)
C(14)	32(1)	40(1)	47(1)	-4(1)	6(1)	5(1)
C(15)	32(1)	37(1)	25(1)	0(1)	2(1)	-1(1)
C(16)	26(1)	29(1)	33(1)	3(1)	1(1)	3(1)
C(17)	27(1)	28(1)	30(1)	3(1)	-4(1)	-5(1)
C(18)	72(1)	40(1)	58(1)	18(1)	-29(1)	-28(1)
C(19)	24(1)	57(1)	60(1)	-14(1)	-4(1)	-6(1)
C(20)	37(1)	44(1)	39(1)	-12(1)	-4(1)	-10(1)
O(1)	20(1)	32(1)	28(1)	0(1)	-1(1)	4(1)
O(2)	24(1)	32(1)	40(1)	5(1)	7(1)	0(1)
O(3)	25(1)	31(1)	29(1)	-7(1)	1(1)	4(1)
O(4)	22(1)	30(1)	22(1)	-2(1)	-2(1)	-7(1)
O(5)	29(1)	21(1)	22(1)	-3(1)	0(1)	1(1)
Si(1)	20(1)	27(1)	21(1)	0(1)	-3(1)	-1(1)
Si(2)	20(1)	23(1)	21(1)	0(1)	0(1)	0(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^{2}x 10^3) for TC506.

	x	y	z	U(eq)
H(2)	1595	8469	1389	26
H(3A)	2445	8969	-41	27
H(3B)	1616	9761	446	27
H(4)	421	8817	-423	26
H(5A)	1500	7208	-549	26
H(5B)	133	6892	-319	26
H(6)	720	6541	863	26
H(8A)	-2335	9633	982	55
H(8B)	-1562	10532	1415	55
H(8C)	-1535	9279	1668	55
H(9A)	2255	7879	2665	53
H(9B)	3442	7962	3169	53
H(9C)	3457	7195	2467	53
H(10A)	5720	8397	1906	55
H(10B)	5721	9206	2587	55
H(10C)	5676	9694	1784	55
H(12A)	4366	10666	3263	67
H(12B)	3220	9971	3546	67
H(12C)	3090	11262	3419	67
H(13A)	3146	12007	2144	56
H(13B)	3322	11178	1482	56
H(13C)	4422	11388	2035	56
H(14A)	1374	9761	2735	60
H(14B)	1417	10232	1927	60
H(14C)	1352	11055	2599	60
H(15A)	2114	5292	1937	47
H(15B)	1522	4103	2035	47
H(15C)	688	5110	1784	47
H(16A)	3649	3866	201	44
H(16B)	3481	3216	946	44
H(16C)	3991	4444	951	44
H(18A)	504	2576	1361	85
H(18B)	1523	2064	840	85
H(18C)	103	1893	662	85

H(19A)	-1141	3445	192	70
H(19B)	-552	4642	141	70
H(19C)	-808	4102	915	70
H(20A)	474	2644	-562	60
H(20B)	1883	2869	-379	60
H(20C)	1032	3846	-661	60

Table 6. Torsion angles [°] for TC506.

O(1)-C(1)-C(2)-O(4)	8.39(18)
C(6)-C(1)-C(2)-O(4)	-173.83(11)
O(1)-C(1)-C(2)-C(3)	130.81(14)
C(6)-C(1)-C(2)-C(3)	-51.41(15)
O(4)-C(2)-C(3)-C(4)	179.32(11)
C(1)-C(2)-C(3)-C(4)	56.06(14)
C(2)-C(3)-C(4)-C(7)	65.68(15)
C(2)-C(3)-C(4)-C(5)	-59.64(14)
C(7)-C(4)-C(5)-C(6)	-69.35(14)
C(3)-C(4)-C(5)-C(6)	56.46(15)
O(1)-C(1)-C(6)-O(5)	-11.28(18)
C(2)-C(1)-C(6)-O(5)	170.94(10)
O(1)-C(1)-C(6)-C(5)	-133.62(13)
C(2)-C(1)-C(6)-C(5)	48.61(15)
C(4)-C(5)-C(6)-O(5)	-174.09(11)
C(4)-C(5)-C(6)-C(1)	-50.39(15)
C(5)-C(4)-C(7)-O(2)	-8.64(19)
C(3)-C(4)-C(7)-O(2)	-133.41(14)
C(5)-C(4)-C(7)-O(3)	171.32(11)
C(3)-C(4)-C(7)-O(3)	46.54(15)
O(2)-C(7)-O(3)-C(8)	-2.5(2)
C(4)-C(7)-O(3)-C(8)	177.53(11)
C(3)-C(2)-O(4)-Si(1)	146.02(10)
C(1)-C(2)-O(4)-Si(1)	-91.41(13)
C(1)-C(6)-O(5)-Si(2)	78.55(13)
C(5)-C(6)-O(5)-Si(2)	-157.45(9)
C(2)-O(4)-Si(1)-C(10)	151.48(11)
C(2)-O(4)-Si(1)-C(9)	31.12(13)
C(2)-O(4)-Si(1)-C(11)	-90.19(12)
C(13)-C(11)-Si(1)-O(4)	-57.35(12)
C(12)-C(11)-Si(1)-O(4)	-177.64(11)
C(14)-C(11)-Si(1)-O(4)	61.96(12)
C(13)-C(11)-Si(1)-C(10)	57.08(13)
C(12)-C(11)-Si(1)-C(10)	-63.21(14)
C(14)-C(11)-Si(1)-C(10)	176.38(11)
C(13)-C(11)-Si(1)-C(9)	-178.65(11)
C(12)-C(11)-Si(1)-C(9)	61.06(13)
C(14)-C(11)-Si(1)-C(9)	-59.35(13)

C(6)-O(5)-Si(2)-C(16)	-121.14(12)
C(6)-O(5)-Si(2)-C(15)	-0.58(13)
C(6)-O(5)-Si(2)-C(17)	119.81(12)
C(20)-C(17)-Si(2)-O(5)	61.69(12)
C(19)-C(17)-Si(2)-O(5)	-57.49(13)
C(18)-C(17)-Si(2)-O(5)	-178.15(13)
C(20)-C(17)-Si(2)-C(16)	-55.51(13)
C(19)-C(17)-Si(2)-C(16)	-174.68(12)
C(18)-C(17)-Si(2)-C(16)	64.66(15)
C(20)-C(17)-Si(2)-C(15)	-177.76(11)
C(19)-C(17)-Si(2)-C(15)	63.06(14)
C(18)-C(17)-Si(2)-C(15)	-57.60(15)

Symmetry transformations used to generate equivalent atoms:

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Stereoselective α,α′-Annelation Reactions of 1,3-Dioxan-5-ones

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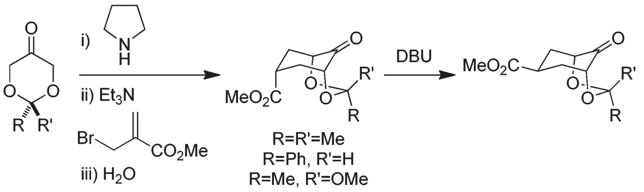
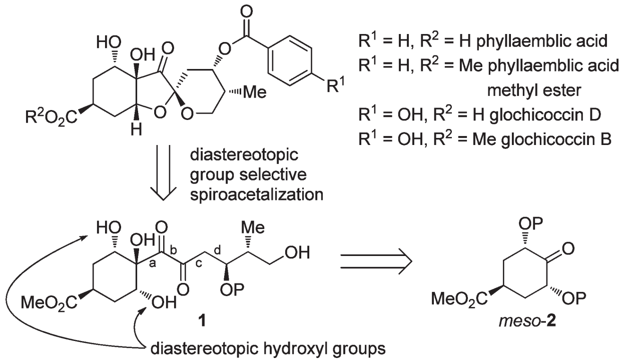


Pyrrolidine enamines derived from three 1,3-dioxan-5-ones undergo α,α′-annelation reactions with methyl α-(bromomethyl)acrylate to produce bridged 2,4-dioxabicyclo[3.3.1]-nonane ring systems with complete stereocontrol. Stereochemical outcomes have been rationalized based on steric and stereoelectronic interactions in intermediate boat-like conformations of the 1,3-dioxane ring and subsequent kinetic protonation to set an axial ester group on the cyclohexanone ring. Base-mediated ester epimerization provides the stereochemical array found in the highly oxygenated cyclohexane ring of phyllaemblic acid and glochicoccins B and D.

Phyllaemblic acid is a highly oxygenated, norbisabolane sesquiterpene isolated, along with its methyl ester and three ester glycosides, phyllaemblicins A−C, from the roots of *Phyllanthus emblica* L., a plant widely distributed in subtropical and tropical areas of China, India, Indonesia, and the Malay Peninsula.[1,2] The rhizomes of a related genus *Glochiddion coccineum*, also widely distributed in China, were found to contain the structurally similar glochicoccins B and D (Scheme 1).[3] Both these plants have long been used in traditional folk medicine by the indigenous people of these regions for the treatment of a range of ailments.

SCHEME 1. Retrosynthetic Analysis



Despite their potential biological activity, approaches toward the syntheses of these natural products have yet to be reported. Although structurally related to the extensively investigated phyllanthocins,[4] the presence of an additional alcohol functionality in the cyclohexane ring suggests a unique strategy can be adopted based on the presence of a latent symmetry element, revealed upon disconnection of the spiroacetal (Scheme 1). This functionality could conceivably arise through a plausible biomimetic spiroacetalization reaction, engaging one of the two diastereotopic hydroxyl groups on the cyclohexane ring of **1**.[5] The latent symmetry element can be exploited synthetically by further disconnection of **1** along any of the bonds a−d to two fragments of approximately equal complexity, only one of which need be chiral. We have targeted *meso*-2,4,6-trisubstituted cyclohexanone **2** as a suitable building block to investigate such an approach, and in this Note we report a concise, stereoselective synthesis of this system based on an α,α′-annelation reaction of 1,3-dioxan-5-ones.

The α,α′-annelation of enamines with *bis*electrophiles such as ethyl α-(bromomethyl)acrylate has been applied to the synthesis of a range of cyclic ketones with diverse application in organic chemistry.[6−8] The transformation shown in Scheme 2 is typical: a bridged bicyclic ring system is formed as a single stereoisomer, with the axial ester stereochemistry arising through in situ kinetic protonation from the less-hindered face, either of an ester enolate or in concert with C−C bond formation. Application of this methodology in the synthesis of **2** was envisaged

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