Studies Towards the Total Synthesis of Merrilactone A

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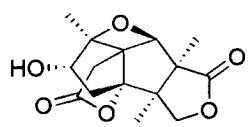
Abstract

Merrilactone A (**1**) is a pentacyclic sesquiterpene, first isolated in 2000 from the pericarps of *Illicium merrillianum* in 0.004% yield. It has been shown to promote neurite outgrowth in primary cultures of foetal rat cortical neurons at low micromolar concentrations. Compounds displaying such neurotrophic activities are of great interest as they could provide lead structures for the generation of small molecule, non-peptide neurotrophic agents with potential uses as therapeutics in the area of dementia. Structural elucidation of Merrilactone A revealed a compact, cage-like pentacyclic architecture of high molecular complexity, featuring seven stereocentres, five of which as contiguous fully substituted carbon atoms, two γ-lactones and a central oxetane ring.



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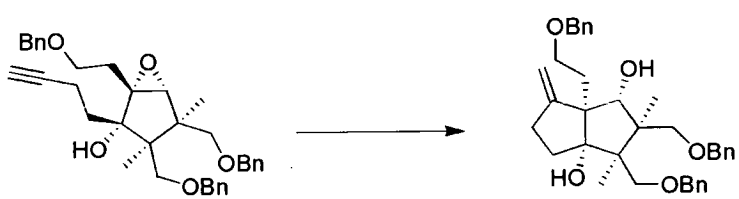
Described in this thesis are our research efforts directed towards developing a novel total synthesis of Merrilactone A. We investigated the feasibility of two distinct key reactions for the preparation of the natural product's core, a Paternò-Büchi photo-cyclisation and a titanium(III) mediated radical epoxide opening with *in situ* cyclisation. Employing the latter, we have devised a concise and novel synthesis of the entire carbon skeleton of Merrilactone A, culminating in the key transformation of epoxide (**234ββ**) into the carbo-bicycle (**233ββ**).



234ββ **233ββ**

In bicycle (**233ββ**), the entire carbon scaffold of the natural product has been realised and all functionality required for further elaboration into Merrilactone A has been put into place.

Declaration

This thesis was submitted in part fulfilment of the requirements for the Doctor of Philosophy at the University of Edinburgh. Unless otherwise stated, the work described in this thesis is original and has not been submitted previously in whole or in part for any degree or other qualification at this time or any other university.

Karsten Meyer

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Finally, I would like to thank my entire family for their constant support, encouragement and advice throughout my whole academic career. Thank you.

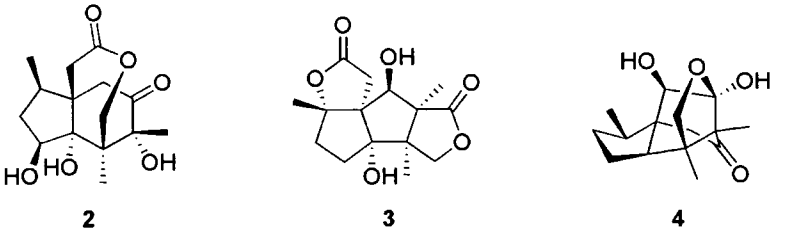
Gewidmet an Marlies und Uli, ohne Euch wäre diese Arbeit nicht möglich gewesen.

Contents

1. Introduction

1.1. Merrilactone A: Origin, Structure and Properties

The plant family *Illiciacae*'s single known genus member *Illicium* is an evergreen small tree or shrub, discovered disjunctively in eastern North America, Mexico, the West Indies and eastern Asia.[1] An area spanning southern China and northern Myanmar is home to the highest concentration of *Illicium* species where 35 of the 40 species described to date can be found. Members of the *Illicium* genus are exceptionally rich sources of complex natural products, such as the biosynthetically unique *Illicium* sesquiterpenes, and their distinctive ability to produce these intricate molecular architectures has been referred to as a chemical marker indicative of the *Illicium* genus. The *Illicium* sesquiterpenes, some of which possess intriguing biological activities such as neurotrophic properties, have been divided into three categories, based on their carbon skeletons. The largest class, the *seco*-prezizaane-type sesquiterpenes contains a number of sub-classes[2,3] while the other two categories, anislactone and *allo*-cedrane type sesquiterpenes feature as yet a much smaller number of compounds.[4,5] Pseudoanisatin (**2**), anislactone A (**3**) and 11-O-debenzoyltashironin (**4**), shown in Figure 1-1, are representative structures of each of the above categories.



2 **3** **4**

Figure 1-1 Compounds representing *seco*-prezizaane- (2), anislactone- (3) and *allo*-cedrane-type (4) sesquiterpenes

With its exceptional ability to produce an abundance of both the *seco*-prezizaane- and rare *allo*-cedrane-type sesquiterpenes, including the bio-synthetically important 11-O-debenzoyltashironin (**4**) and tashironin (**5**), *Illicium merrillianum* occupies a somewhat unique taxonomical position amongst the eastern Asian species of the

Illicium genus.[2] More importantly however, *I. merrillianum* was also found to produce a very large number of anislactone-type compounds such as anislactone A (**3**) and B (**6**) and merrilactones A (**1**), B (**7**) and C (**8**), characterised by a unique carbon skeleton consisting of two consecutive five-membered carbocycles fused to two γ-lactones (Figure 1-2).[6,7] To date, a total of 36 structurally novel sesquiterpenes, falling into all three categories, have been isolated from this species alone.

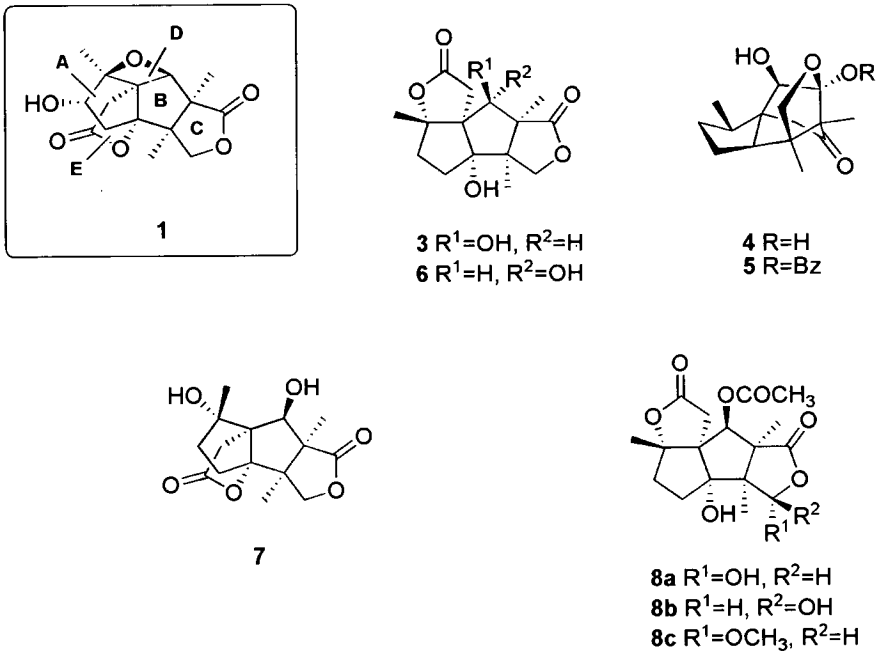


Figure 1-2 Structures of *Illicium* Sesquiterpenes isolated from *I. merrillianum*

Merrilactone A (**1**)* was first isolated in 2000 from the methanol extract of the dried pericarps of *Illicium merrillianum* in a 0.004% yield. Its structure was elucidated by means of extensive spectroscopic and X-ray crystallographic analysis and the absolute configuration was established using the modified Mosher's method.[7] Merrilactone A has a unique pentacyclic anislactone-type sesquiterpene structure, featuring a central oxetane ring and two γ-lactones as well as seven stereocentres, five contiguous fully substituted carbon atoms and a *cis*-arrangement of the two angular methyl groups at the B-C ring junctions. This densely oxygenated molecule

* An inconsistency in the labelling of the five rings of Merrilactone A is evident in the literature. Several different systems of labelling are in use, however, all labelling employed within this document is based on the assignment shown here.

forms a compact yet exceedingly complex cage-like structure, thereby presenting a highly attractive and challenging target for total synthesis. In addition to its intriguing molecular structure, Merrilactone A has also been shown to possess interesting biological activity. Displaying neurotrophic properties, Merrilactone A promotes neurite outgrowth in the primary cultures of foetal rat cortical neurons at very low concentrations, ranging from 10 to 0.1 μmol/L.[7]

1.2. Biological Activity: Neurotrophic Factors and Alzheimer's Disease

Neurotrophic factors (NTFs) are peptides which act as growth factors in the growth and maintenance of neurons in developing and adult vertebrate nervous systems. They regulate many aspects of neuronal structure and function and promote neuronal survival, as a deficiency in the necessary NTFs leads to programmed cell death and thus, in adulthood, NTFs are required to maintain neuronal functions. Furthermore, NTFs represent potential agents to counteract neuronal dysfunction and recent evidence has suggested that alterations in the levels of NTFs, due to age, genetic background or other factors might contribute to neuronal degradation processes. Based on this evidence, it has been postulated that a diminished endogenous neurotrophic support may lead to neuronal degeneration, characteristic of neurodegenerative diseases like Alzheimer's and Parkinson's disease.[8] Alzheimer's Disease (AD) is an age-related illness, affecting more then half a million people in the UK alone and is the most common cause of dementia among people over the age of 65, accounting for 55% of dementia cases. Around 5% of the population over the age of 65 and 20% over the age of 80 suffer from dementia.[9,10] AD is an irreversible and gradually occurring brain disorder, characterised by progressive memory loss, changes in behaviour and personality, decline in cognitive abilities and is accompanied by pathological changes in the brain. Initially, a breakdown of the synapses between nerve cells in the region of the brain responsible for memory, followed by the death of affected cells, leads to short term memory loss and hence an inability to perform even familiar tasks. Subsequent spread of the disease throughout

the cerebral cortex, the part of the brain controlling higher mental functions, such as language and reasoning, become affected, resulting in loss of language skills and diminished decision making abilities. Eventually, extended neuronal degeneration occurs, rendering patients irresponsive to external stimuli.[11] Three major pathological characteristics contribute to AD, however, their nature and possible roles in the development and progression of AD are as yet not fully understood.

- Amyloid Plaques were first discovered by Alois Alzheimer in 1906 and consist of insoluble protein fragments termed β-amyloids which are deposited between the brain's nerve cells. In AD, plaques first develop in areas of the brain responsible for memory and cognitive functions.[11,12]

- Neurofibrillary Tangles, also discovered by Alois Alzheimer, are abnormal depositions of twisted protein threads inside nerve cells. *Tau*-proteins, usually phosphorylated to a certain degree, bind to microtubules inside cells, thereby stabilising them. In AD, abnormal phosphorylations occur, leading to *Tau*-protein aggregations and a loss of cell stabilisation, eventually leading to tangle formation and cell death.[11]

- Brain atrophy has only been described over the past 3 decades and is defined as a gradual loss of connections between neurons, eventually leading to the neurons death, resulting in a shrinking of certain regions of the brain. In the final stages of AD, areas of significantly shrunk tissues are widespread throughout the brain.[11]

It is in the context of attempting to halt or reverse the effects of brain atrophy that the intracerebroventricular administration of NTFs has been shown to be promising.[13] NTF administration into rats has been shown to be effective in reversing age related spatial and reference memory deficiencies and amelioration in lesion-induced degeneration of basal forebrain cholinergic neurons in rats and primates has been reported.[14,15] Overall however, the use of natural, polypeptidal NTFs has led to poor performances *in vivo*, potentially due to the transport and pharmacostability issues usually associated with the administration of polypeptides. It is in the context of circumventing these inherent problems of polypeptidal NTFs that the discovery of

non-peptidal, small molecule neurotrophic agents holds great hope. It is therefore appropriate to explore and develop methods of preparing such agents in order to investigate in detail their biological functions and their usefulness in the treatment of neurodegenerative diseases.[16,17]

1.3. Previous Total Syntheses

It is not surprising that Merrilactone A's unique structure and intriguing biological properties have attracted the interest of a number of research groups leading to the publication of four total syntheses as well as three model studies to date. Although Anislactone B, abundant in *I. merrillianum*, can be converted into Merrilactone A *via* a three step sequence of dehydration, epoxidation and ring expansion in a 45% yield, the highly complex structure of the natural product clearly continues to present an exciting and challenging target for total synthesis.[3] Mirrored in the number of total syntheses achieved to date, as well as the model studies published so far, is the continuing interest in the development of novel synthetic pathways towards Merrilactone A. Presented in this chapter is a brief overview of the publications concerned with the synthesis of Merrilactone A which are available in the literature.

1.3.1. Danishefsky's total syntheses of Merrilactone A

1.3.1.1. Racemic total synthesis

In 2002, Danishefsky and Birman published the first total synthesis of Merrilactone A.[16] The 20 step, racemic approach yielded (±)-Merrilactone A in an impressive 10.7% overall yield, however, along their synthetic route, several issues of both of regio- and stereo- selectivity remained unsolved. Figure 1-3 shows the retrosynthetic approach adopted in this total synthesis.[†]

[†] Indicated in Figure 1-3 is the numbering of carbon atoms in Merrilactone A used throughout this document, based on Fukuyama *et al.*'s initial assignment.[7]

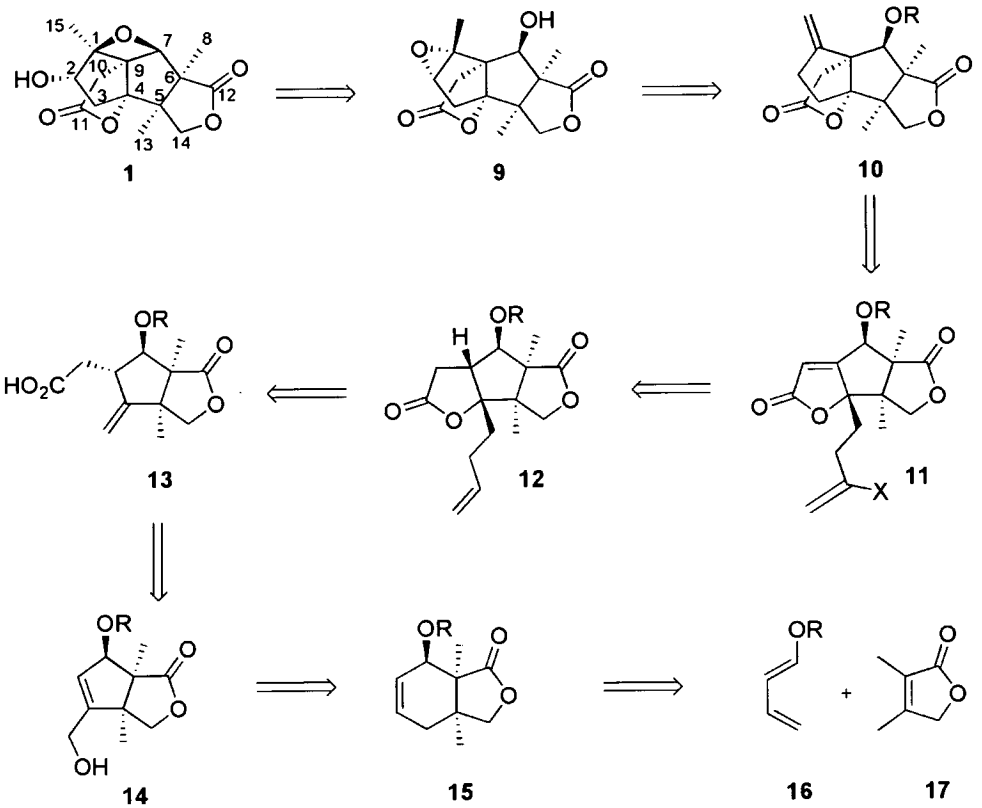
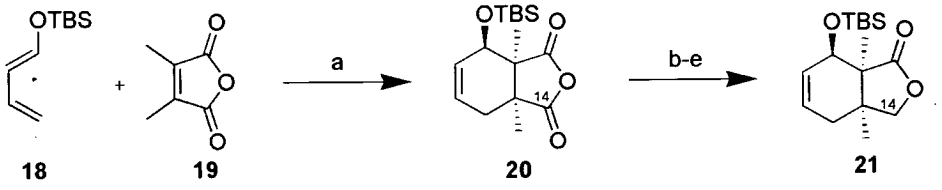


Figure 1-3 Danishefsky's retrosynthetic analysis of Merrilactone A

Merrilactone A's central oxetane motif is disconnected *via* a known, biomimetic *homo*-Payne-type rearrangement of epoxide (**9**), accessible from the *exo*-olefin (**10**) *via* alkene isomerisation followed by epoxidation.[3] Tetracycle (**10**) was anticipated to form by means of a free radical cyclisation of (**11**), creating a quaternary centre in a sterically crowded environment. Introduction of the required functionality for such an event *via* two fold oxidation of (**12**), suggested the γ,δ-unsaturated acid (**13**) as a key intermediate, to be elaborated into (**12**) *via* iodolactonisation. This substrate was believed to be accessible by a Claisen rearrangement *via* (**14**), which in turn could be prepared by a ring contraction of bicycle (**15**). The latter structure was suggestive of a Diels-Alder type reaction of diene (**16**) and dienophile (**17**).

In the forward synthesis, diene (**18**) reacts under Diels-Alder conditions with 2,3-dimethylmaleic anhydride (**19**) affording bicycle (**20**) in 74% yield (Figure 1-4). Due to the stereo—and regio-control incurred by the cyclo-addition reaction, three

stereocentres are set and two quaternary centres are created in a controlled manner in the very first step.

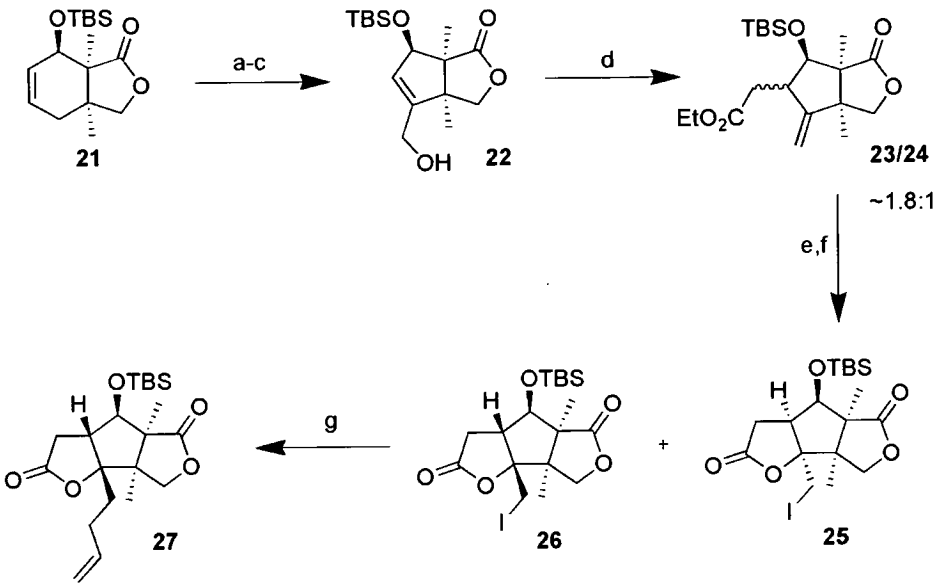


a) 165 °C, mesitylene, 74%; b) NaOMe, MeOH; c) $ClCO_2Me$, THF, then $NaBH_4$, MeOH, -35 °C; d) aq. LiOH; e) $LiBHEt_3$, THF, then TFA, DCM, 78% for 4 steps.

Figure 1-4 Diels-Alder reaction and regioselective C_{14} reduction

Regio-selective reduction of C_{14}[‡] under conventional reduction conditions yielded only complex mixtures and a somewhat tedious but high yielding four step circumvention was thus employed, eventually affording (**21**) in 78% yield from (**20**). A formal ring contraction was then carried out *via* a successive ring opening and ring closing sequence, initiated by ozonolysis of (**21**) with subsequent reductive workup (Figure 1-5). Aldol condensation of the resulting *di*-aldehyde and ensuing reduction then furnished the ring contracted bicyclic alcohol (**22**) in 94% yield. Employing an *ortho*-ester Claisen rearrangement, (**22**) was transformed into a diastereomeric mixture of esters (**23**) and (**24**) in a ~1.8:1 ratio. Hydrolysis of the ester mixture to the corresponding acids with subsequent iodolactonisation afforded two crystalline and chromatographically separable iodolactones (**25**) and (**26**) in 35% and 59% yield respectively. The desired diastereomer (**26**) then underwent a three carbon chain elongation *via* Keck's C-allylation protocol, yielding the tricyclic key intermediate (**27**).[18]

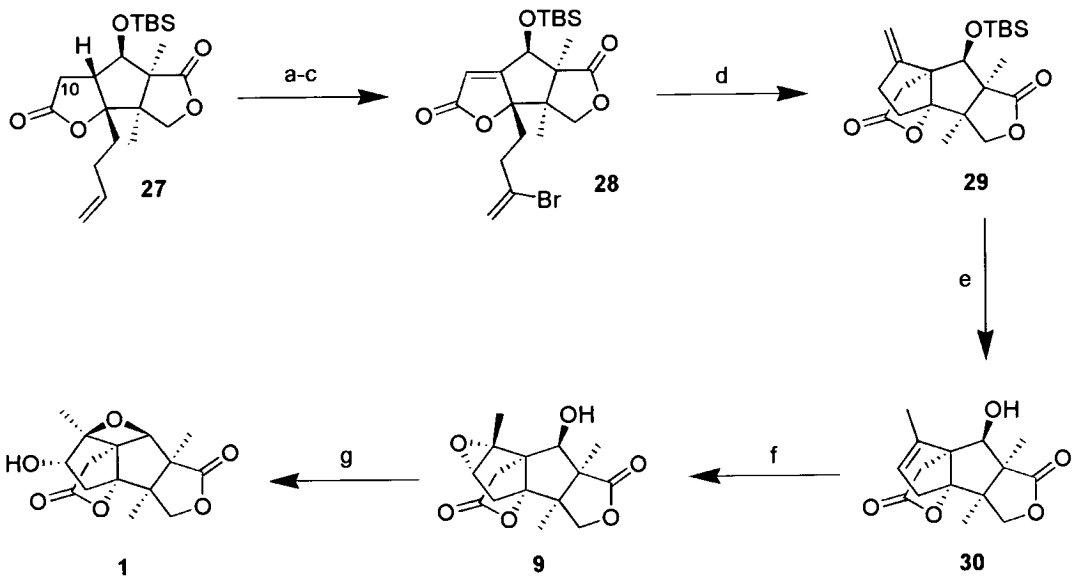
[‡] All numbering used within this document is based on future Merrilactone A numbering, as outlined in Figure 1-3 unless stated otherwise.



a) O_3, PPh_3, DCM/MeOH; b) $Bn_2NH{\cdot}TFA$, PhH, 65 °C, 94% over 2 steps; c) $NaBH_4$, DCM, MeOH, -78 °C, quant.; d) $MeC(OEt)_3$, mesitylene, PivOH, 135 °C, 92%; e) aq. LiOH, MeOH; f) I_2, $NaHCO_3$, THF, 59% **26** and 35% **25** over 2 steps; g) $AllylSnBu_3$, AIBN, PhH, 75%.

Figure 1-5 Johnson-*ortho*-ester reaction and Keck C-allylation

Two-fold oxidation of (**27**) was achieved by means of C_{10} selenylation, *via* an intermediate silyl ketene acetal, bromoselenylation of the pendant vinyl group and subsequent concurrent oxidative deselenation, yielding (**28**). With the stage set for the free radical cyclisation step, exposure of (**28**) to standard radical initiation conditions provided access to (**29**) in 90% yield. Subsequent isomerisation of the methylene group and deprotection led to β-alcohol (**30**). Although hydroxyl groups can often behave as *syn*-directing participating groups in epoxidations, in this case the congested nature of the β-face of the double bond was sufficient for the epoxidation to predominantly occur from the α-face (α/β epoxide = 3.5:1).[19] The total synthesis was then completed by conversion of the major isomer (**9**) into (±)-Merrilactone A (**1**) *via* an acid induced *homo*-Payne rearrangement (Figure 1-6).



a) LHMDS, TMSCl, PhSeCl; b) PhSeBr, MeCN; c) O_3, DCM, 1-hexene, PhH, NEt_3, reflux, 77% over 3 steps; d) Bu_3SnH, AIBN, PhH, 90%; e) $TsOH{\cdot}H_2O$, PhH, reflux, 98%; f) *m*CPBA, DCM, 3.5:1 ratio of α/β epoxide, quant.; g) $TsOH{\cdot}H_2O$, DCM, 71% over 2 steps.

Figure 1-6 Free radical cyclisation and *homo*-Payne rearrangement

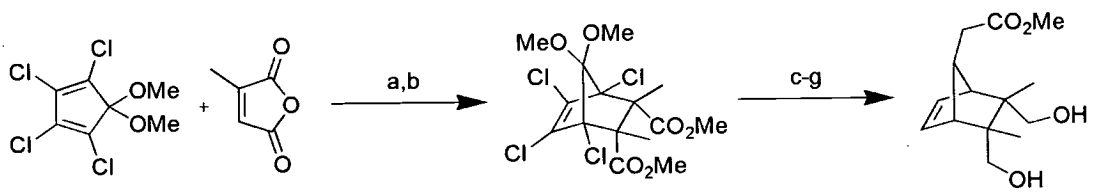
Whilst the accomplishment of this relatively short and high yielding total synthesis of Merrilactone A only two years after the characterisation of the natural product is an impressive feat, several selectivity issues are apparent which remain unresolved.

1.3.1.2. Asymmetric formal synthesis

Three years after publishing their racemic total synthesis of (±)-Merrilactone A, Danishefsky and co-workers reported a formal, asymmetric variant of this synthesis. In addressing the selectivity issues plaguing the racemic synthesis, access to either enantiomer of Merrilactone A was established.[17] The significantly modified approach focuses on a stereocontrolled synthesis of key intermediate (**26**, Figure 1-5), as the conversion of this compound into Merrilactone A had already been shown to be concise and efficient.[16] A substantial reconfiguration of the previously reported route was necessary to address a number of steps suffering from lack of selectivity or requiring multi-step circumventions, such as the regioselective C_{14} reduction, transforming (**20**) into (**21**) (see Figure 1-4) or the Claisen rearrangement of (**22**)

which yielded a mixture of the diastereomeric esters (**23**) and (**24**) in a ~1.8:1 ratio (Figure 1-5).

The starting point for the synthetic pathway was the *endo*-selective Diels-Alder reaction between diene (**31**) and the cyclic anhydride (**32**). Subsequent stereoselective methylation *via* lithiation furnished (**33**) in an 87% yield over two steps. The latter was then advanced to *meso*-compound (**34**) through a number of straightforward transformations, with an overall yield of 48% over five steps (Figure 1-7).

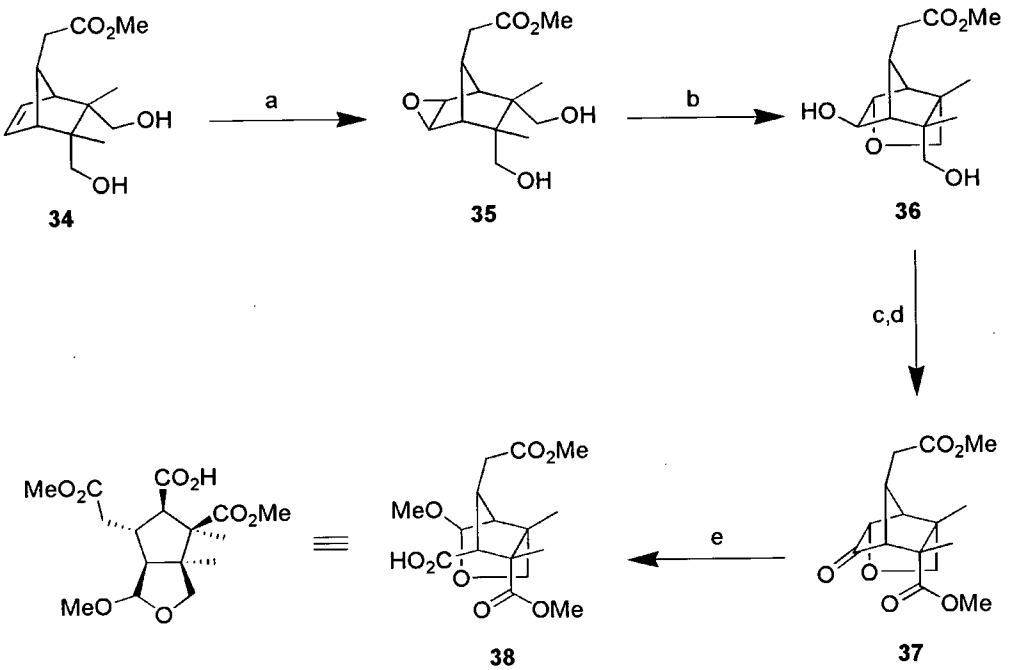


31 **32** **33** **34**

a) 180 °C, neat, then MeOH, reflux, PhH/MeOH, $TMSCHN_2$, 92%; b) LDA, HMPA, MeI, THF, -78 °C to RT, 95%; c) $LiAlH_4$, THF, reflux; d) Na, NH_3, THF/EtOH, 72% over 2 steps; e) 2,2-dimethoxy-propane, acetone, TsOH; f) NaH, $(EtO)_2POCH_2CO_2Et$, THF, 86% over 2 steps; g) Mg, MeOH, 77%.

Figure 1-7 *endo*-Diels Alder and conversion into *meso* 1,4-diol compound

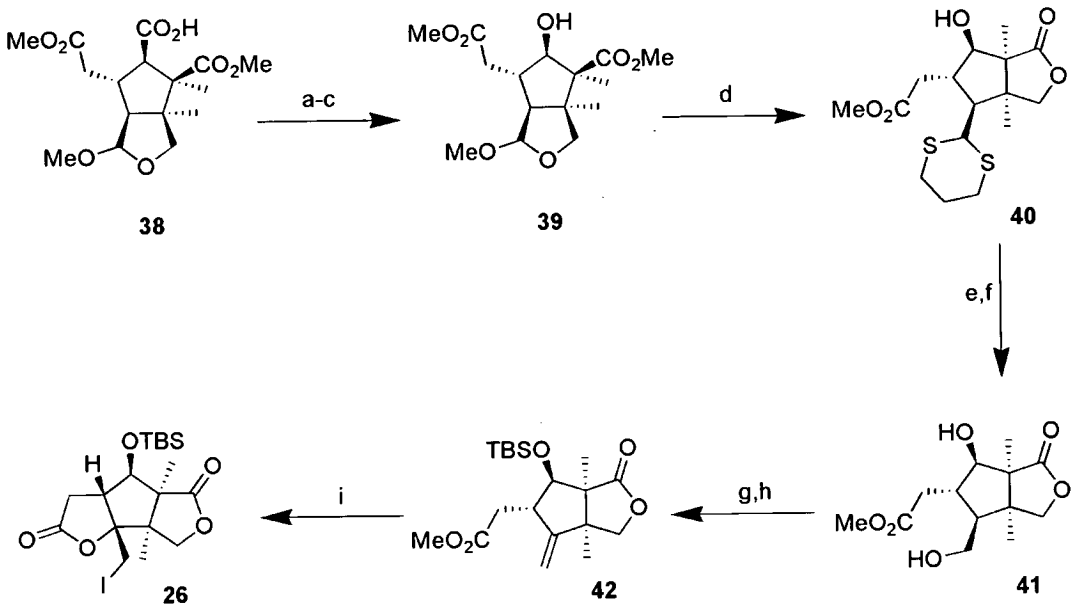
Desymmetrisation of the *meso*-intermediate (**34**) was achieved by exposure to dimethyldioxirane, leading to the discrete *exo*-epoxide (**35**) which in turn was the substrate for an asymmetric ring opening methodology. Upon treatment of (**35**) with a catalytic amount of (*S,S*)-[Co^{III}(salen)]-OAc, as described by Jacobsen and co-workers, enantioenriched tricycle (**36**) was formed in 86% yield and 86% ee.[20] The use of the *R,R*-Jacobsen catalyst afforded *ent*-(**36**), thereby opening up routes to either enantiomer of Merrilactone A. PDC mediated oxidation of the resulting diol (**36**) and successive esterification afforded ketoester (**37**) which underwent Baeyer-Villiger oxidation to furnish the carboxylic acid (**38**) in 63% yield over three steps (Figure 1-8).



a) DMDO, DCM; b) (S,S)-[Co^{III}(salen)]-OAc, -78 °C to -25 °C, THF, 86% for 2 steps; c) PDC, DMF; d) K_2CO_3, MeI, acetone, reflux, 70% over 2 steps; e) MMPP, MeOH, 0 °C to RT, 88%.

Figure 1-8 Regio- and enantio-controlled chemical degradation pathway

Carboxylic acid (**38**) was then transformed into the secondary alcohol (**39**) with retention of stereochemistry in a three step sequence with 58% yield. Lewis acid mediated opening of the methoxy-tetrahydrofuran ring moiety of (**39**) was achieved by trapping its masked aldehyde, prompting a lactonisation affording (**40**), which was then converted into diol (**41**). Upon exposure of (**41**) to the protocols of Grieco and co-workers, selective reaction at the primary alcohol provided a transient selenide which afforded the desired exocyclic olefin (**42**) after oxidative elimination.[21] The latter was hydrolysed and the resultant carboxylic acid underwent iodolactonisation, affording key intermediate (**26**) (Figure 1-9).



a) DCC, *m*CPBA, 0 °C to RT, 83%; b) PhH, reflux; c) K_2CO_3, MeOH, 70% for 2 steps; d) $BF_3{\cdot}OEt_2$, $HS(CH_2)_3SH$, DCM, 50%; e) $PhI(OCOCF_3)_2$, $MeCN/H_2O$, 50%; f) $NaBH_4$, MeOH, 0 °C; g) *o*-$NO_2C_6H_4SeCN$, Bu_3P, THF, then 30% H_2O_2, 86% for 2 steps; h) TBSOTf, NEt_3, DCM, 76%; i) LiOH, H_2O/MeOH, then I_2, aq. $NaHCO_3$/THF, 75%.

Figure 1-9 Synthesis of enantioenriched key intermediate

The advanced enantioenriched key intermediate (**26**) could then be converted into Merrilactone A *via* the methodology reported in Danishefsky and co-workers racemic total synthesis of Merrilactone A.[16] With this reconfigured synthetic route, the selectivity issues plaguing the previous route have been eradicated and for the first time allowed synthetic access to either enantiomer of the natural product. An overall yield of 6% over 21 steps was achieved for the synthesis of the key intermediate (**26**), thus completing the first formal asymmetric synthesis of (-)-Merrilactone A.

1.3.2. Hirama's total syntheses of Merrilactone A

1.3.2.1. Racemic total synthesis

In 2003, the second total synthesis of (±)-Merrilactone A was published by Hirama and co-workers.[22] Employing a novel synthetic strategy for the formation of the core of the natural product, the racemic total synthesis was completed in 27 steps with an overall yield of 1%. Shown in Figure 1-10 is the retrosynthetic approach adopted by Hirama and co-workers.

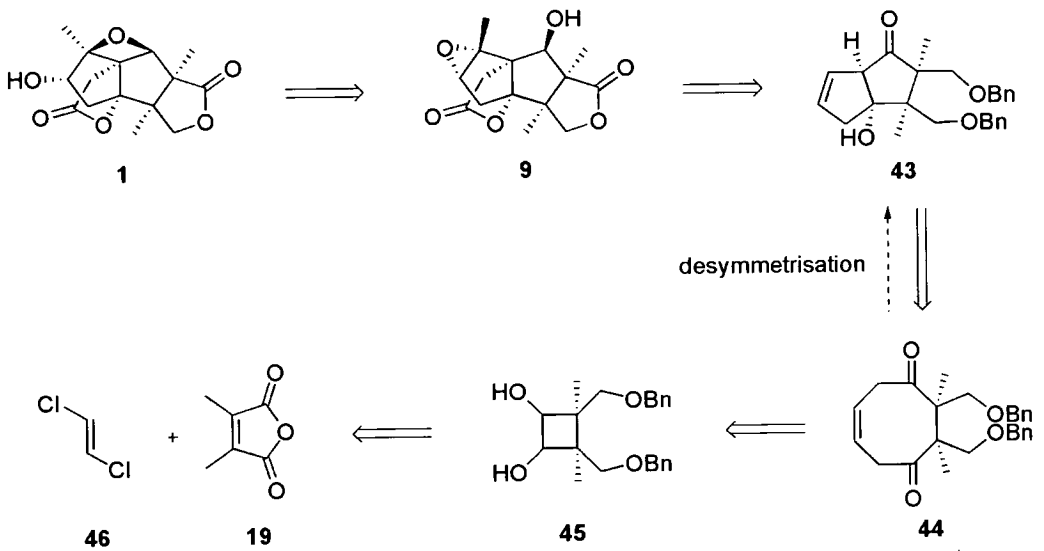
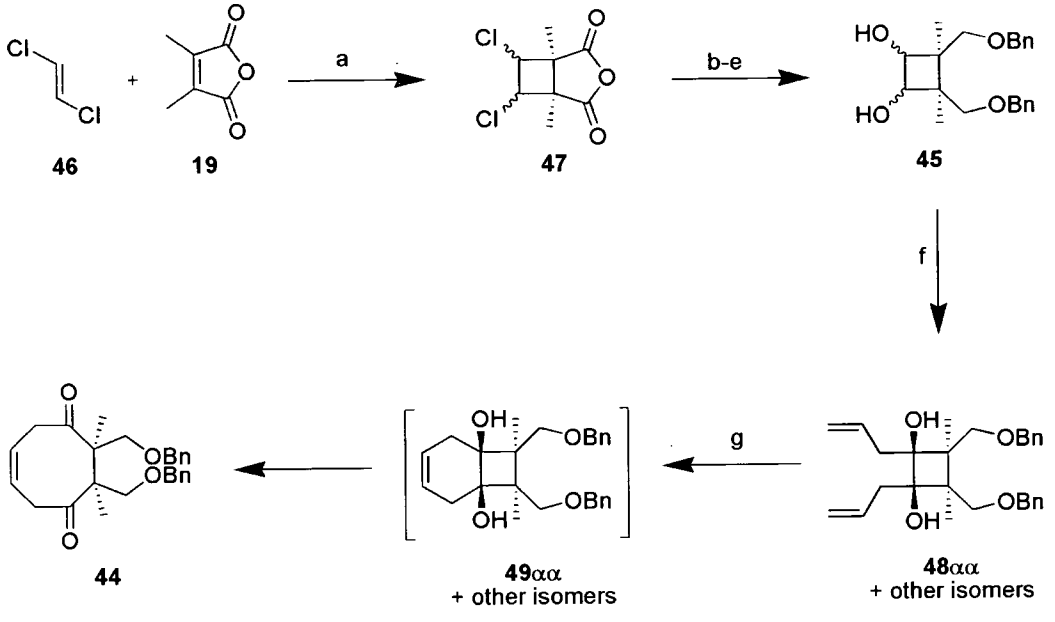


Figure 1-10 Hirama's retrosynthesis of Merrilactone A

Relying on the known and previously successfully employed *home*-Payne rearrangement to install the oxetane moiety in the final step of the synthesis, Merrilactone A (**1**) would be prepared from precursor (**9**), which in turn would arise *via* a multi-step sequence from bicycle (**43**). This *cis*-bicyclo[3.3.0]octane core was anticipated to be accessible *via* a pivotal desymmetrisation of the *meso*-diketone (**44**) by means of an intramolecular aldol reaction. The substrate (**44**) for this key step would arise from a double allylation, followed by ring closing metathesis and consecutive ring expansion from cyclobutane (**45**). The latter would in turn be accessible *via* a [2+2] photocyclisation of *di*-haloalkene (**46**) and cyclic anhydride (**19**).

In the forward synthesis, the [2+2] photocyclisation was achieved, as initially envisioned, by irradiation of substrates (**46**) and (**19**) in the presence of the photosensitiser benzophenone, affording (**47**) in a stereospecific manner with respect to the ring junction stereocentres. Subjecting the cycloadduct to reductive dechlorination, anhydride reduction, di-benzyl protection of the resulting diol and successive dihydroxylation furnished the *meso*-diol (**45**) in a 47% yield over three steps. A pair wise, symmetrical functionalisation of cyclobutane (**45**), consisting of a one-pot Swern oxidation and *in situ* double allylation then afforded a mixture of isomers of (**48**) in 78% yield. Here, the double *cis*-allylation was found to occur predominantly on the α-face, thereby effectively facilitating the following ring closing metathesis reaction of (**48αα**), giving rise to the bicyclic [4.2.0]octyl system (**49αα**). Treatment with $Pb(OAc)_4$ *in situ* then formed the eight membered ring system (**44**) in a 95% yield (Figure 1-11).

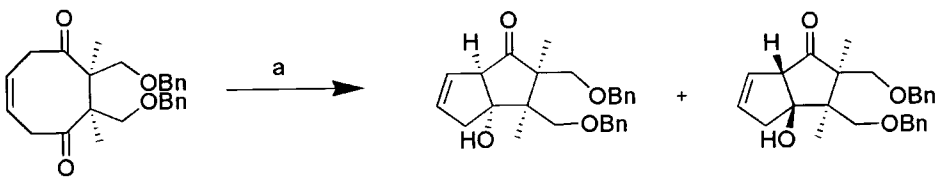


a) benzophenone, acetone, hν; b) Zn, TMSCl, Ac_2O, toluene, 85 °C; c) $LiAlH_4$, THF, 47% for 3 steps; d) BnBr, NaH, THF/DMF, 99%; e) OsO_4, NMO, $^tBuOMe/^tBuOH/H_2O$, 94%; f) $(COCl)_2$, DMSO, NEt_3, DCM, -78 °C, then allylmagnesium bromide, -78 °C, 10αα/10ββ/10αβ ratio 15:2.6:1, 78%; g) $(PCy_3)_2Cl_2Ru$=CHPh, DCM, reflux, then $Pb(OAc)_4$, 95%.

Figure 1-11 Synthesis of desymmetrisation substrate

In the total synthesis' key step, the *meso*-diketone (**44**) underwent a base-mediated intramolecular aldol reaction, facilitating the desymmetrisation of (**44**) and

furnishing the diastereomeric bicycles (**43**) and (**50**) in ratios reportedly dependant on the employed reaction conditions. A 3.1:1 ratio of desired diastereomer (**43**) over the undesired (**50**) was achieved using LHMDS at -100 °C in an 85% combined yield. By varying the conditions of the desymmetrisation reaction, access to the other diastereomer (**50**) was also found to be feasible (Figure 1-12).

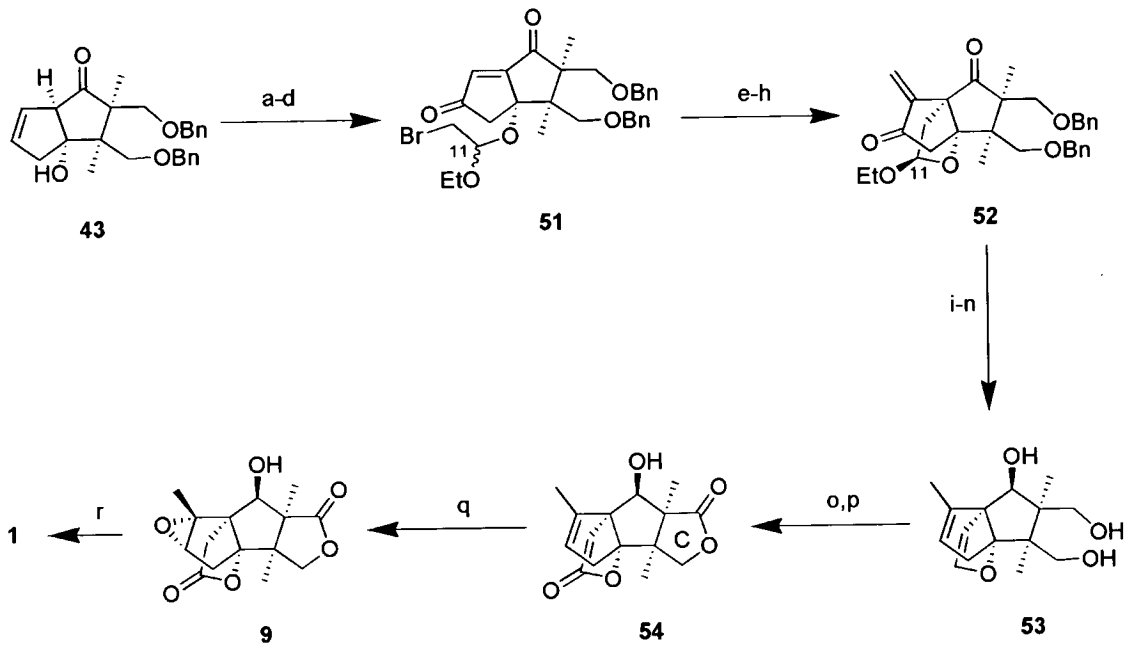


44 **43** **50**

a) LHMDS, THF, -100 °C, **43/50** ratio 3.1:1, 85%.

Figure 1-12 Desymmetrisation *via* intramolecular aldol reaction

Epoxidation of the desired aldol product (**43**) formed the α-epoxide, which was opened with DBU and following oxidation, an α-bromoacetal was appended to afford (**51**) in a 4:1 mixture of acetal diastereomers and an 38% yield over four steps. Radical cyclisation of (**51**) delivered a 5-exo-trig cyclised product in 71% yield in a 3.5:1 ratio of the desired acetal diastereomer over the undesired one at C_{11}. Conversion into the desired diastereomer could be achieved *via* treatment with CSA in 86%. Subsequent regioselective silyl enol ether formation and ensuing reaction with Eschenmoser's salt and *m*CPBA[23] produced exo-alkene (**52**) in 34% yield. Further chemical elaboration then led to triol (**53**) which, upon hydration and double Fetizon oxidation[24] of the diol, underwent lactonisation furnishing (**54**) in which ring C of the natural product had been introduced . Successive epoxidation afforded (**9**), the substrate for the final, acid induced Payne-type rearrangement to form Merrilactone A (**1**) (Figure 1-13).



a) *m*CPBA, DCM, 81%; b) DBU, DCM, -40 °C, 81%; c) IBX, DMSO, 94%; d) $BrCH_2CHBr(OEt)$, $PhNMe_2$, DCM, -78 °C to RT, 62%; e) Bu_3SnH, BEt_3/O_2, toluene, then CSA, EtOH, 71%; f) TMSOTf, DIPEA, DCM, -20 °C; g) $Me_2NCH_2^+I^-$, DCM; h) *m*CPBA, DCM, 70% over 3 steps; i) TFA/H_2O, 94%; j) MsCl, NEt_3, THF, 50 °C, 77%; k) LiBH(*s*-Bu)$_3$(L-Selectride), THF, MS, -78 °C then 2-Tf_2N-5-chloropyridine, -78 °C, 99%; l) $Pd(OAc)_2$, PPh_3, NBu_3, HCOOH, DMF, 40 °C, 89%; m) DIBALH, DCM, -78 °C, 88%; n) Na, NH_3, THF/EtOH, -78 °C, 100%; o) DOWEX 50WX2, THF/H_2O; p) Ag_2CO_3 on celite, toluene, 130 °C, 64% for 2 steps; q) DMDO, DCM, 96%; r) TsOH, DCM, 81%.

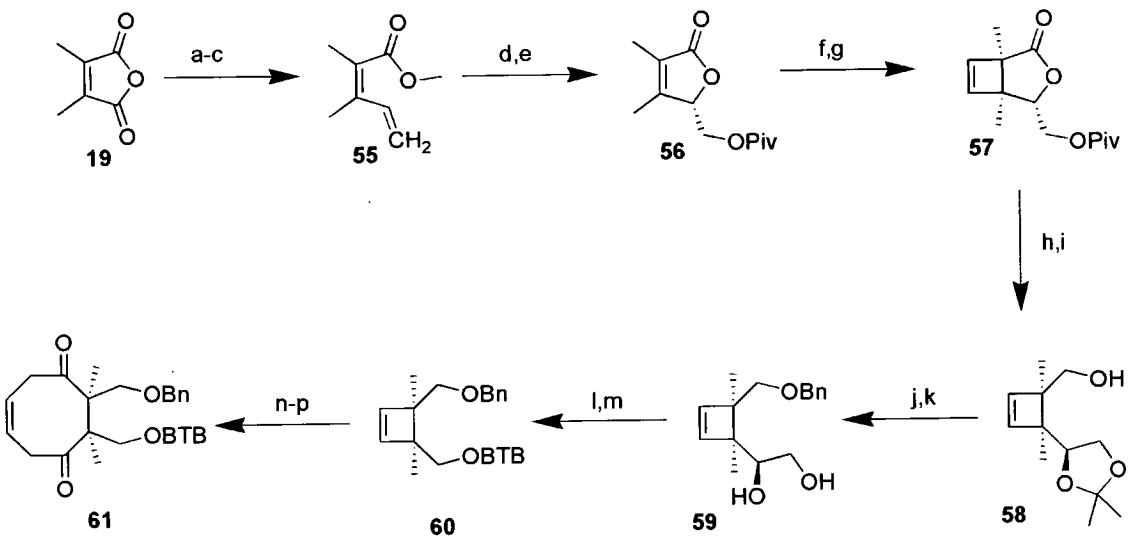
Figure 1-13 Completion of Merrilactone A synthesis

Hirama and co-workers total synthesis of Merrilactone A employs a key desymmetrisation reaction to install two of the central five-membered carbocycles. While the reported synthesis suffers from selectivity problems at several stages, the total synthesis of (±)-Merrilactone A was nonetheless achieved in 27 steps with an overall yield of 1%.

1.3.2.2. Asymmetric total synthesis

In 2006, Hirama *et. al.* presented an asymmetric version of their total synthesis of Merrilactone A.[25] In focusing on an enantioselective synthesis of an analogue of the desymmetrisation substrate (**44**) (Figure 1-12), the use of a bulky protecting group to induce long range stereo controlling effects in the intra molecular aldol reaction has been successfully demonstrated. In order to prepare an analogue of (**44**), in which the

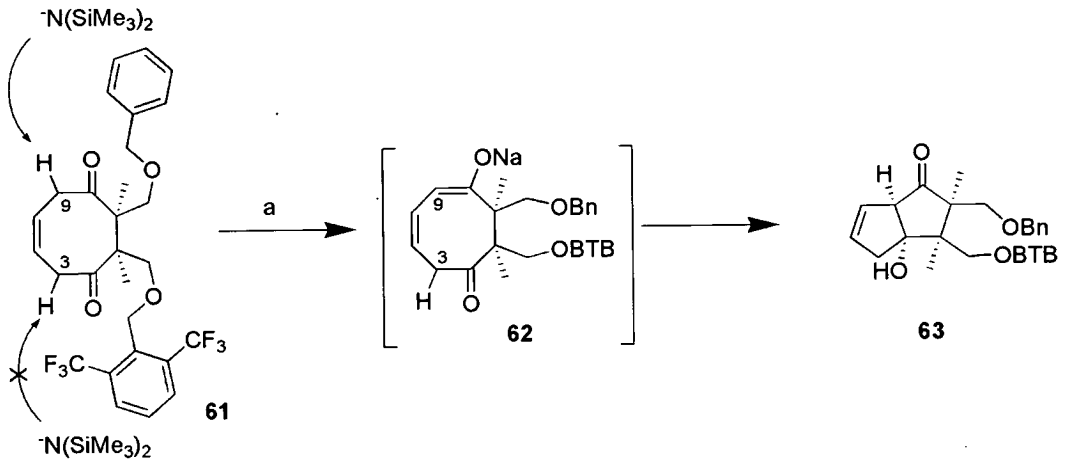
two pendant alcohol moieties are differentially protected, a novel route was developed, beginning with the partial reduction of dimethyl maleic anhydride (**19**), followed by Wittig olefination and esterification to furnish (**55**) in 68% over three steps. Sharpless asymmetric dihydroxylation proceeded with excellent enantio- and chemo-control and the resulting hydroxy-γ-lactone was protected as the pivaloate ester to afford (**56**). Photo-induced [2+2] addition of *cis*-1,2-dichloroethylene, followed by zinc mediated dechlorination then furnished bicycle (**57**). In order to install the desired differential protecting group pattern, (**57**) was reduced and the resulting 1,2-diol moiety protected as its propylidene acetal to afford (**58**), thus allowing mono-benzyl protection of the remaining primary alcohol. Subsequent removal of the acetal protecting group unmasked diol (**59**) which upon oxidative diol cleavage and *in situ* reduction followed by protection of the resulting primary alcohol as the *bis*-(trifluoromethyl)benzyl (BTB) ether furnished (**60**). Further elaboration into the aldol substrate (**61**) was achieved *via* steps analogous to those employed in the racemic synthesis (Figure 1-14, cf Figure 1-11).



a) $LiAlH(OtBu)_3$, DME, -15 °C to RT, 85%; b) $Ph_3PCH_3^+Br^-$, ^tBuOK, 0 °C to RT, 87%; c) MeI, K_2CO_3, THF, 50 °C, 92%, d) AD-mix-α, $^tBuOH/H_2O$, 0 °C, 65%, >99%ee after recrystallisation; e) PivCl, pyridine, DMAP, DCM, 99%; f) *cis*-dichloroethylene, MeCN, -20 °C, hν; g) Zn, Ac_2O, toluene, 120 °C h) $LiAlH_4$, Et_2O, 75% for 3 steps; i) $Me_2C(OMe)_2$, TsOH, DCM, 81%; j) BnBr, NaH, THF/DMF; k) 3M HCl, THF, 91% for 2 steps; l) $Pb(OAc)_4$, pyridine, DCM, -50 °C then DIBALH, -78 °C to -50 °C, 93%; m) BTBBr, KH, [18]crown-6, DMF; n) OsO_4, NMO, $^tBuOMe/^tBuOH/H_2O$, 94% over 2 steps; o) SO_3·py, DIPEA, DMSO, DCM, -15 °C then allylmagnesium bromide, -78 °C, ratio α/β 2.7:1, 78%; p) $[(PCy_3)_2Cl_2Ru{=}CHPh]$, DCM, reflux then $Pb(OAc)_4$, 97%.

Figure 1-14 Asymmetric synthesis of intramolecular aldol substrate

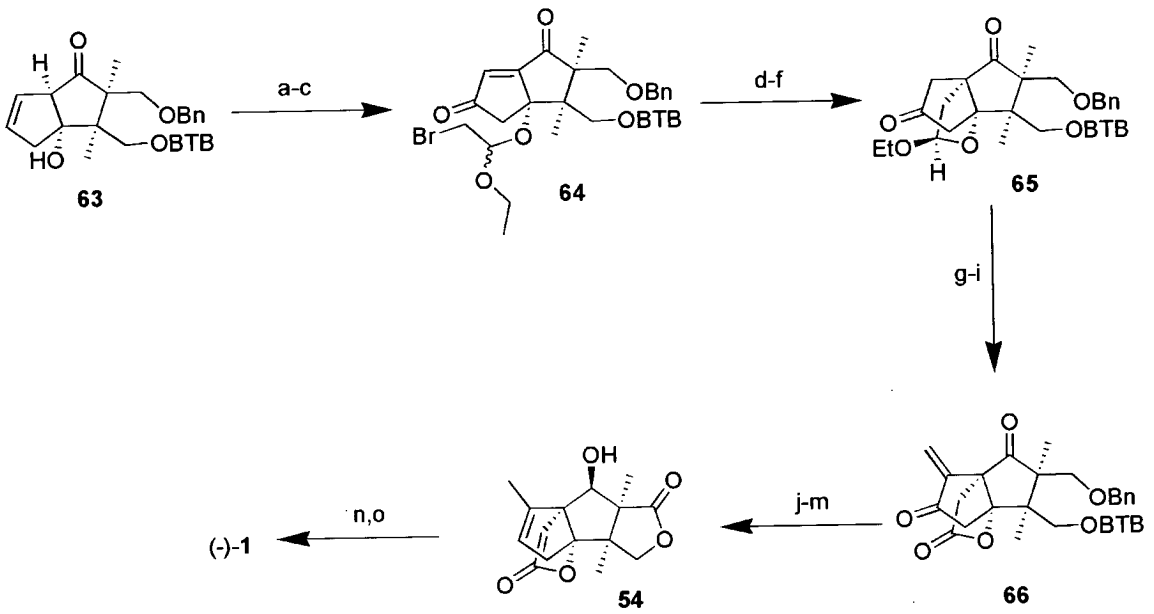
In order to achieve the desired regio-control in the key transformation, intermediate (**61**) was selectively deprotonated at C_9, the preference over C_3 arising from unfavourable long range steric interactions of the base with the trifluoromethyl substituents on the pendant BTB protecting group. The resulting sodium enolate (**62**) underwent a highly stereoselective transannular aldol reaction, furnishing the desired [3.3.0]octane system (**63**) as the major enantiomer in 75% yield, with the remaining three possible diastereomers accounting for a further 22% yield (Figure 1-15).



a) NaHMDS, THF, -100 °C, 97% overall, 75% yield for desired enantiomer **63**.

Figure 1-15 Asymmetric transannular aldol reaction

With a synthetic route to the enantiopure (**63**) established, the completion of the total synthesis closely followed the route developed in the racemic synthesis (cf. Figure 1-13). Compound (**63**) was thus elaborated into (-)-(**1**) in 15 steps as outlined in Figure 1-16.



a) *m*CPBA, DCM then florisil, DCM, 75%; b) IBX, DMSO, 91%, c) $BrCH_2CHBr(OEt)$, $PhNMe_2$, DCM, -78 °C to RT, 92%; d) Bu_3SnH, AIBN, toluene, 85 °C, 73%; e) $EtOSiMe_3$, $BF_3{\cdot}Et_2O$, DCM, 72%; f) Me_3SiOTf, NEt_3, DCM, -20 °C; g) $Me_2NCH_2{}^+I^-$, MeCN; h) *m*CPBA, DCM, 64% over 3 steps; i) *m*CPBA, $BF_3{\cdot}OEt_2$, DCM, 100%; j) $LiBH(^sBu)_3$, 2-Tf_2N-5-chloropyridine, THF, -78 °C, 73%; k) $Pd(OAc)_2$, PPh_3, NBu_3, HCOOH, DMF, 40 °C, 91%; l) Na, NH_3, THF/EtOH, -78 °C; m) Ag_2CO_3 on celite, toluene, 130 °C, 41% over 2 steps; n) DMDO, DCM, 91%; o) TsOH, DCM, 96%.

Figure 1-16 Completion of the asymmetric total synthesis

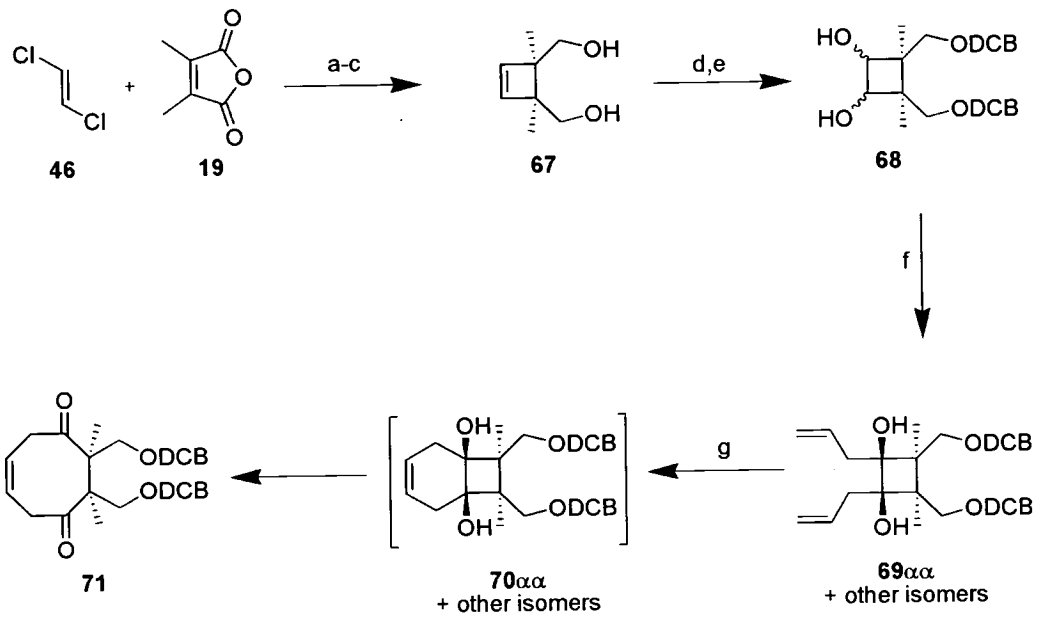
Hirama and co-workers have established the second asymmetric route to (-)-Merrilactone A and completed their total synthesis in 31 steps with an overall yield of 1%. In utilising the long range steric effects of a novel bulky protecting group, the selectivity issues experienced in their key intramolecular transannular aldol reaction in the racemic route could be overcome. The result represents an impressive regio- and stereoselective transformation, allowing the preparation of the key intermediate (**63**) as a single enantiomer.

1.3.2.3. Hirama's total synthesis of ent-(+)-Merrilactone A

Following Hirama and co-workers successful asymmetric synthesis of the natural enantiomer of Merrilactone A,[25] the group published a modified version of their synthesis in 2007, allowing the selective preparation of the unnatural enantiomer, *ent*-(+)-Merrilactone A.[26] Moving away from their previous strategy of employing

differentially protected alcohols to induce long range steric effects, the use of a chiral lithium amide base in the key transannular aldol reaction is demonstrated to effect selective deprotonation at C_9 over C_3, thereby giving rise to a novel desymmetrisation strategy. In circumventing the need for the differential protection of the pendant diol, the synthesis of the key aldol substrate could be achieved in analogy with the substrate preparation reported in the racemic total synthesis (cf. Figure 1-11), avoiding the lengthy and cumbersome route employed in the asymmetric total synthesis (cf. Figure 1-14).

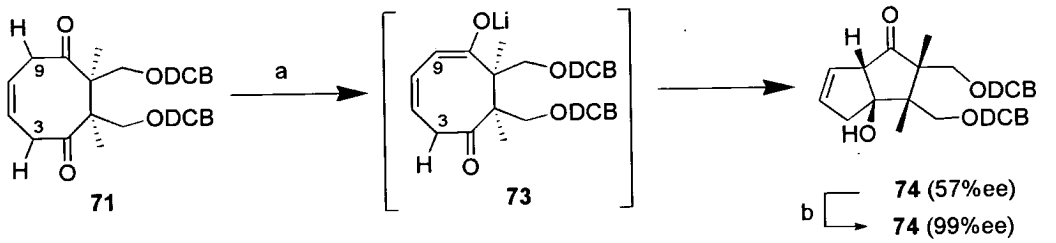
The synthetic sequence starts with the photochemical [2+2] reaction of 1,2-dichloroalkene (**46**) and 2,3-dimethylmaleic anhydride (**19**), followed by reductive dechlorination and anhydride reduction, furnishing diol (**67**). At this stage, the two hydroxyl moieties were protected as their respective 2,6-dichlorobenzyl (DCB) ethers, the protecting group that was found to give the greatest selectivity in the key aldol reaction. Subsequent dihydroxylation then afforded diol (**68**), which was further functionalised *via* a one pot Swern oxidation with subsequent Grignard addition of allylmagnesium bromide to the transient 1,2 dione. This furnished the desired diastereomer (**69αα**) over the undesired facial isomer in a 9:1 ratio. Ring closing metathesis and *in situ* treatment with $Pb(OAc)_4$ then afforded the key intermediate (**71**, Figure 1-17).



a) benzophenone, acetone, hν; b) Zn, TMSCl, Ac_2O, toluene, 85 °C; c) $LiAlH_4$, THF, 57% for 3 steps; d) DCBBr, NaH, THF/DMF; e) OsO_4, NMO, $^tBuOMe/^tBuOH/H_2O$, 91% over 2 steps; f) $(COCl)_2$, DMSO, NEt_3, DCM, -78 °C then allylmagnesium bromide, -78 °C, 10αα/10ββ ratio 9:1, 80%, g) $(PCy_3)_2Cl_2Ru$=CHPh, DCM, reflux, then $Pb(OAc)_4$, 95%. DCB = 2,6-Dichlorobenzyl

Figure 1-17 Preparation of DCB protected aldol substrate

The group's focus then turned to the development of methodology allowing the enantio-selective transformation of aldol substrate (**71**). A screen of a range of chiral lithium amide bases revealed (**72**) to afford the desired enantiomer in suitable selectivity over the other undesired enantio- and diastereomers. Thus, treatment of dione (**71**) with chiral base (**72**) led to selective deprotonation at C_9 over C_3, furnishing lithium enolate (**73**) which cyclised in a stereoselective fashion to afford the enantioenriched (**74**) in 79% yield and 57%ee. A diastereomeric ratio of 6:1 was observed and the desired enantiomer was formed in a 4.7:1 ratio over the undesired one. A single recrystallisation step with a yield of 53% increased the enantiomeric excess of (**74**) to 99%ee (Figure 1-18).



a) **71**, LiCl, THF, -78 °C, 79%; b) recrystallisation, 1:1 EtOAc/hexanes, 53%.

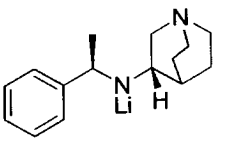


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Figure 1-18 Enantioselective transannular aldol reaction using chiral base

With a robust route to the enantio-pure key intermediate (**74**) in hand, the total synthesis of *ent*-(+)-Merrilactone A was completed in direct analogy with the steps employed in the racemic total synthesis, outlined in Figure 1-13 and the asymmetric variant described in Figure 1-16. The transformation of (**74**) into the unnatural enantiomer of Merrilactone A was thereby achieved in 16 steps and the total synthesis was achieved in 23 steps with an overall yield of 1.3%. With the synthesis complete, the biological activity of the unnatural enantiomer was investigated and, surprisingly, it was found to stimulate neurite outgrowth to a very similar extent as the natural enantiomer. This unexpected result presents a rare example of similar levels of biological activity being observed in both enantiomers of a natural product. Further studies into the mechanism of action are reportedly currently ongoing.

Hirama's group's total synthesis of the unnatural enantiomer of Merrilactone A presents the culmination of the group's efforts in developing their novel desymmetrisation strategy employed in the key intramolecular aldol reaction. Allowing the enantio-selective preparation of key intermediates *via* either selective deprotonation by means of chiral bases or the use of differential protection strategies provides a flexible approach towards the natural product.

1.3.3. Metha's racemic total synthesis

Singh and Mehta published results of a model study on a novel synthesis of the core of Merrilactone A in 2005.[27] The key steps which were developed as part of the model study formed the basis of the author's total synthesis of Merrilactone A, which was published in 2006.[28] In analogy with the previous two total syntheses, the installation of the oxetane motif is achieved in the final step *via* the known *homo*-Payne rearrangement. Mehta and Singh's retrosynthetic approach is outlined in Figure 1-19

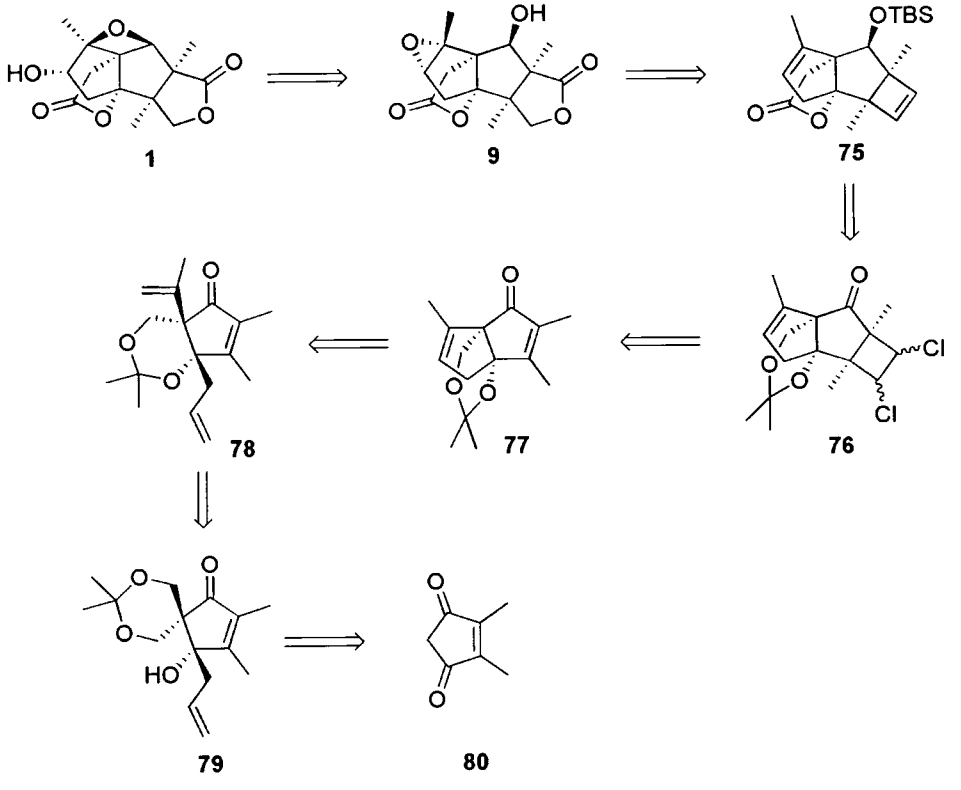
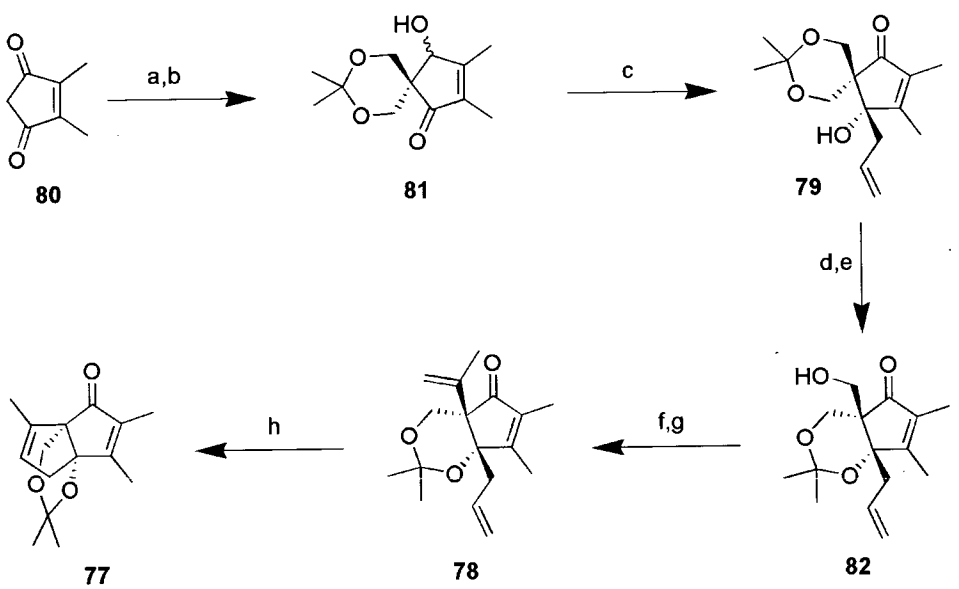


Figure 1-19 Mehta and co-workers retrosynthesis

Utilising the acid induced *homo*-Payne rearrangement in the final step of the synthesis of Merrilactone A (**1**), epoxide substrate (**9**) was envisaged to be accessible from (**75**) *via* ozonolysis. Tetracycle (**75**) would be formed from the [2+2] photo-addition product (**76**), in turn derived from (**77**). The latter would be prepared in a pivotal ring closing metathesis reaction of diene (**78**), synthesised *via* an acetonide

deprotection-protection sequence from (**79**). Further analysis delineated (**80**) as a suitable starting point for the total synthesis.

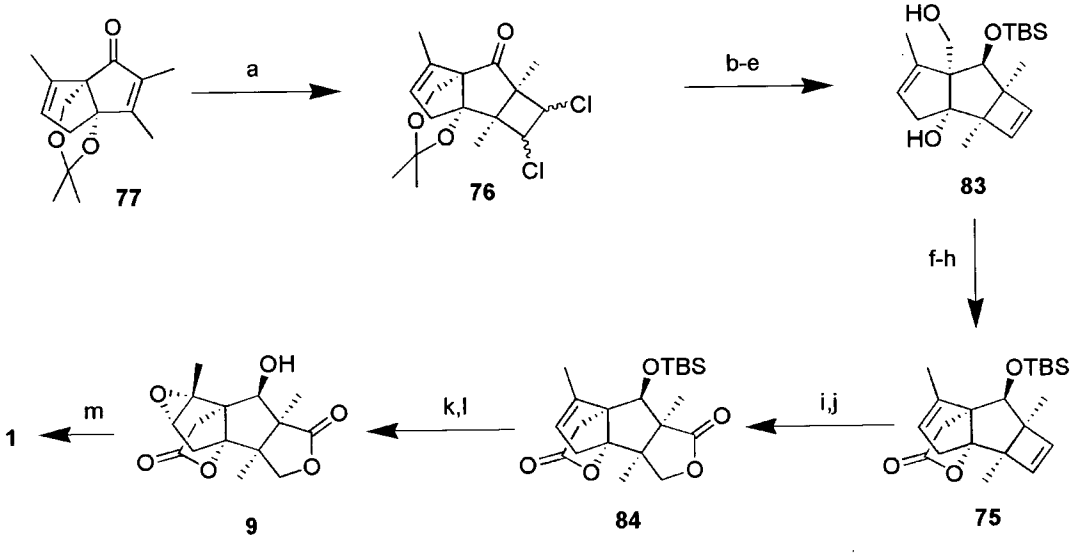
Initial elaboration of 1,4-dione (**80**) was carried out by a double hydroxylmethylation, followed by acetonide protection and Luche reduction, furnishing (**81**) in 77% yield over three steps. Successive allylation and re-oxidation then afforded hydroxyenone (**79**) in high yield. The latter was subjected to a key acetonide deprotection-protection sequence, setting up the four side arms on ring B for the subsequent sequential annulation of carbocycle C and the γ-lactone ring D. Thus, the deprotection of (**79**), followed by reprotection under equilibrating conditions afforded a 1:1 mixture of the desired (**82**) and (**79**), which could be readily recycled. The primary alcohol in (**82**) was then oxidised to the aldehyde, followed by methylation and a further oxidation, then allowing methylenation under Wittig conditions to afford (**78**) in 36% yield. The now *cis*-orientated allyl- and propenyl-side-chains underwent the key ring closing metathesis reaction on exposure to Grubbs' first generation catalyst, furnishing carbo-bicycle (**77**) in a moderate yield, setting the stage for the further elaboration towards Merrilactone A (Figure 1-20).[29]



a) DBU, 40% HCHO, THF, 0 °C, 95%; b) acetone, MS, Amberlyst-15 then $NaBH_4$, $CeCl_3$, 0 °C, 83%; c) $CeCl_3$, allylmagnesium chloride, -78 °C, then MnO_2, DCM, 81%; d) 2M HCl, THF/H_2O, 90%; e) acetone, MS, Amberlyst-15, 94%; f) PDC, DCM, then MeLi, Et_2O, 62%; g) PDC, DCM then Ph_3PCH_2Br, ^tBuOK, Et_2O, 55%; h) Grubbs' Catalyst I, DCM, reflux, 76%.

Figure 1-20 Synthesis of RCM substrate and metathesis reaction

The [2+2] cyclo-addition of key intermediate (**77**) with *trans*-1,2-dichloroethylene proceeded in 65% yield but with only a moderate degree of facial selectivity (2:1) in favour of the desired β-face isomer (**76**) over the undesired α-face diastereomer. After separation of the diastereomers, eliminative dehalogenation, DIBALH reduction and protection of the resulting alcohol with a TBS group was followed by acetonide deprotection to furnish the diol (**83**) in 54% yield over four steps. Advancing (**83**) *via* TPAP oxidation and Wittig methoxymethylenation followed by acid-mediated hydrolysis with concomitant intramolecular hemiacetal formation and subsequent oxidation then gave rise to γ-lactone (**75**). Next, elaboration of the cyclobutene ring of (**75**) into the second γ-lactone ring was facilitated by ozonolysis followed by *in situ* sodium borohydride reduction and successive oxidation to deliver the *bis*-lactone (**84**). Conversion of the latter into Merrilactone A (**1**) was carried out using established protocols[3] *via* TBS deprotection, followed by epoxidation to afford (**9**) and acid induced Payne-type rearrangement to complete the total synthesis of (**1**) (see Figure 1-21).



a) *trans*-dichloroethylene, *hν*, α/β face ratio 1:2, 65%; b) sodium naphthalenide, -60 °C, 70%; c) DIBALH, -78 °C, 95%; d) TBSOTf, NEt_3, DCM, 86%; e) 2M HCl, THF/H_2O, 95%; f) TPAP, DCM then $Ph_3PCH_2OCH_3$, ^tBuOK, THF, 54%; g) $HClO_4$, DCM/THF; h) PCC, DCM, 62 % for 2 steps; i) O_3, MeOH, -78 °C then $NaBH_4$, MeOH, -78 °C, 45%; j) PCC, DCM, 80%; k) TBAF, AcOH, THF, 85%; l) DMDO, 95%; m) TsOH, DCM, 80%.

Figure 1-21 Elaboration of key intermediate into Merrilactone A

In conclusion, Mehta and Singh have implemented a novel route to Merrilactone A and the preparation of the natural product was achieved in a 27 step sequence with an overall yield of 0.4%. While the synthesis shows potential for modifications that would allow an asymmetric approach, there remain problematic steps in the current synthesis, such as the lack of selectivity in the [2+2] cyclo-addition.

1.3.4. Frontier's racemic total synthesis

In 2007, Frontier's group published their total synthesis of (±)-Merrilactone A in a short communication,[30] followed in 2008 by a full account of their research leading to the completion of the synthesis.[31] Whilst relying on the now well established methodology to install the oxetane in the final step, Frontier's group have developed a remarkable synthetic route of the substrate required for the final rearrangement.

The retrosynthetic approach adopted is outlined in Figure 1-22. Conversion of the advanced intermediate (**30**) into the natural product was to be achieved *via* the proven epoxidation and *homo*-Payne rearrangement strategy. The introduction of the γ-lactone ring C was to be achieved at a late stage from alcohol (**85**). In turn, tricycle (**85**) would be prepared from (**86**) *via* a radical cyclisation strategy. Bicycle (**86**) would then be accessible from furan derivative (**87**) by means of a pivotal Nazarov cyclisation reaction. Further analysis then suggested (**88**), readily available from known aldehyde (**89**), as a suitable starting material for the preparation of (**87**).

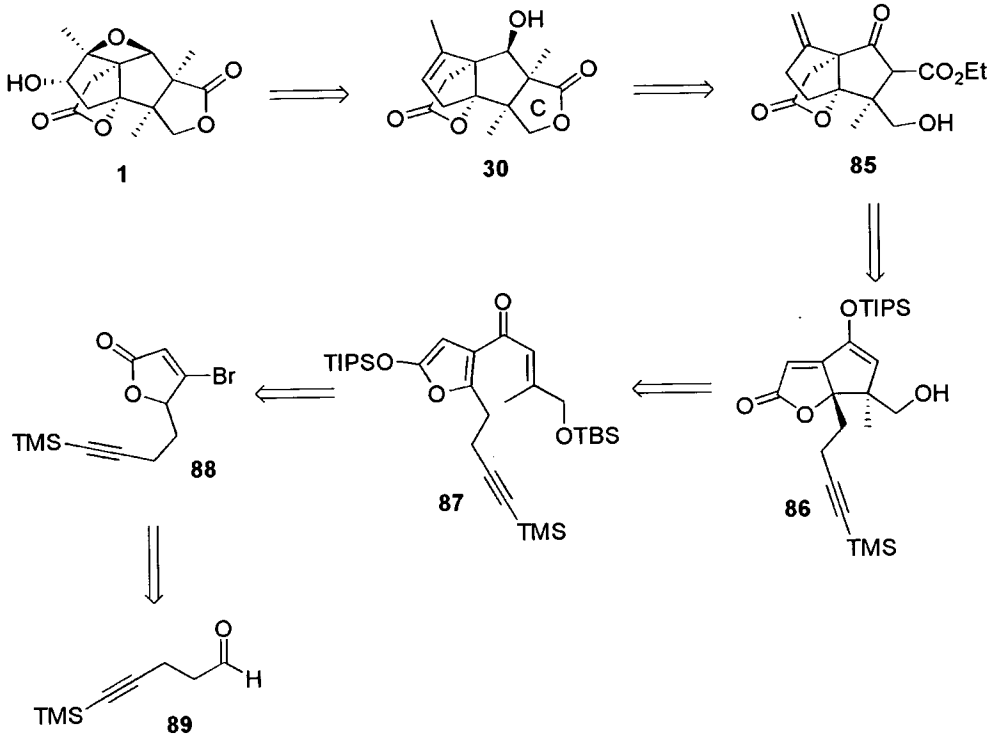
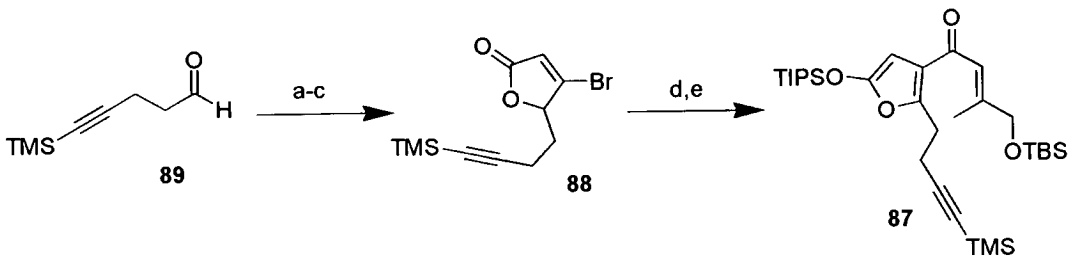


Figure 1-22 Frontier's retrosynthetic analysis

Outlined in Figure 1-23 is the synthetic route adopted towards the substrate for the key Nazarov reaction, beginning with the organometallic 1,2-addition of lithiated ethyl propiolate to known aldehyde (**89**). The resulting di-yne underwent lactonisation in the presence of a higher order stannyl cuprate and, following tin bromide exchange, the vinyl bromide (**88**) was obtained. Access to the required silyloxyfuran was then provided *via* treatment with triethylamine and triisopropylsilyl triflate in quantitative yield. Addition of the lithium anion of the silyloxyfuran to Weinreb amide (**90**) then furnished the advanced intermediate (**87**), setting the stage for the key Nazarov cyclisation.



a) ethyl propiolate, ^{n}BuLi, THF, -78 °C, 88%; b) $Bu_3Sn(Bu)(CN)CuLi_2$, THF/MeOH, -78 °C, 90%; c) Br_2, DCM, 93%; d) NEt_3, triisopropylsilyl triflate, DCM, -78 °C to 0 °C, quant.; e) ^{t}BuLi, Et_2O, then **90**, 82%.

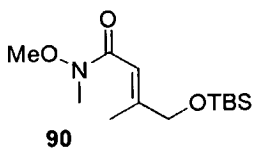


Figure 1-23 Synthesis of key Nazarov substrate

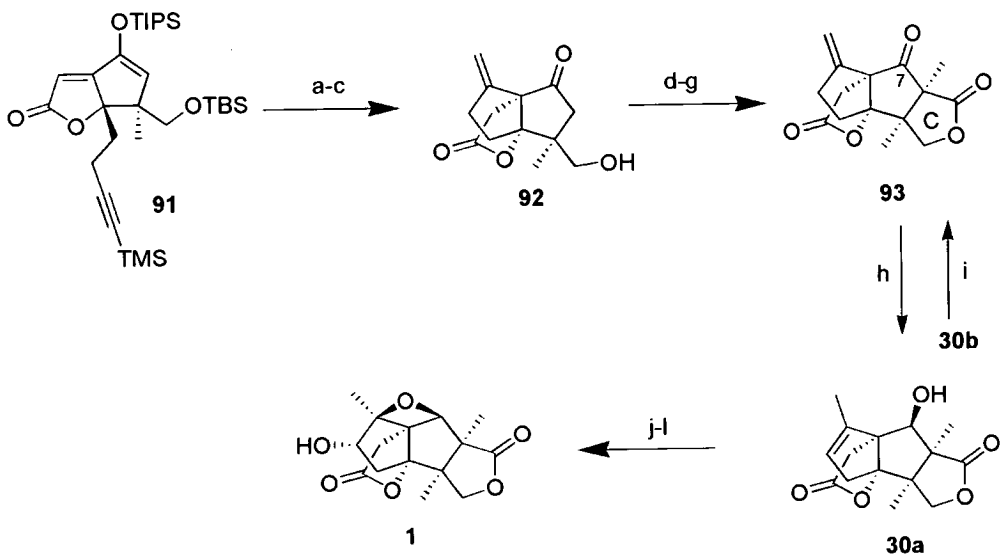
With the substrate for the pivotal Nazarov cyclisation in hand, the conditions developed on numerous model compounds closely related to (**87**) were applied to the actual substrate.[31] Treatment of silyloxyfuran (**87**) with a dicationic Iridium catalyst afforded a single diastereomer of the anticipated bicycle (**91**) in which C_4 and C_5 are introduced in a stereospecific manner due to the conrotatory nature of the 4π electrocyclic pathway of the Nazarov cyclisation (Figure 1-24).

a) $[Ir(CO)(Me)(dppe)(DIB)]^{2+}$-$(BAr^{f})^{-}_2$ (2 mol%), DCM, 87%

Figure 1-24 Nazarov cyclisation of silyloxyfuran

Following the successful Nazarov cyclisation, the resulting bicycle (**91**) was subjected to radical cyclisation conditions but the presence of the trimethylsilyl capped alkyne proved to inhibit the reaction. Thus, removal of the trimethylsilyl group provided the substrate for the tributyl tinhydride mediated radical cyclisation and following subsequent global fluoride induced silyl deprotection, alcohol (**92**) was

obtained. In a four step sequence, the right hand side γ-lactone ring C was then introduced *via* conversion of the alcohol into the corresponding carbonate, intramolecular nucleophilic lactonisation and subsequent methenylation to furnish the advanced intermediate (**93**). With the full carbon skeleton of the natural product in hand, a stereoselective reduction at C_7 would provide access to the secondary alcohol (**30a**), which has previously been transformed into Merrilactone A by Danishefsky and co-workers in their racemic total synthesis (cf. Figure 1-6). The reduction proved somewhat problematic as it only provided the desired facial selectivity for (**30a**) over (**30b**) in a 1.2:1 ratio. Re-oxidation and recycling of the undesired isomer (**30b**) had to be adopted in order to convert all material to the desired isomer (**30a**). The final three steps were then carried out in analogy with all previous total syntheses; isomerisation of the *exo*-alkene, stereoselective epoxidation and *homo*-Payne rearrangement to furnish racemic Merrilactone A (Figure 1-25).



a) $AgNO_3$, KCN, THF/EtOH/H_2O, 83%; b) AIBN, Bu_3SnH, PhH, reflux then TsOH, 91%; c) TBAF, THF, 99%; d) pyridine, DMAP, ethylchloroformate, 95%; e) NaH, THF; f) TsOH, PhH, reflux, 90% for 2 steps; g) NaH, MeI, HMPA, THF, 97%; h) $NaBH_4$, MeOH, ratio **30a/30b** 1.2:1, 93%; i) Dess-Martin periodinane, DCM, 98%; j) TsOH, PhH, reflux, 92%; k) *m*CPBA, DCM, l) TsOH, DCM, 68% over 2 steps.

Figure 1-25 Completion of the total synthesis

Frontier and co-workers have presented a concise, efficient and elegant total synthesis of Merrilactone A in only 17 steps with a highly impressive overall yield of

19%. Research aimed at the adaptation of the described route to allow an asymmetric total synthesis is reportedly ongoing at present.

1.4. Published Approaches towards Merrilactone A

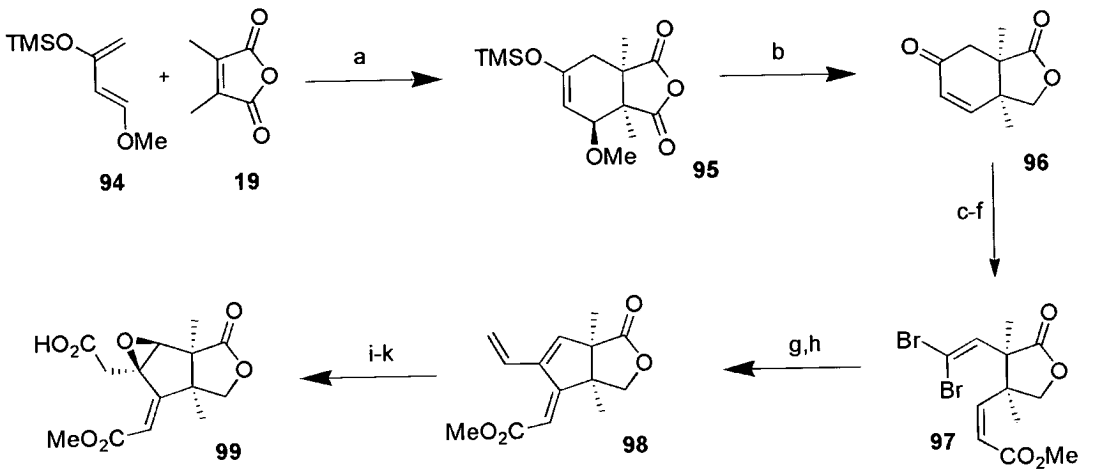
As well as the total syntheses detailed above, there have been a number of publications outlining novel approaches towards Merrilactone A.

1.4.1. Fukuyama's model studies 1+2

Since isolating and characterising Merrilactone A in 2000, Fukuyama's group has shown an interest in developing a total synthesis of the natural product. Two model studies have been published to date, a synthesis of the BC ring motif was reported in 2005[32] and in 2007, an approach for the synthesis of the AE ring system was disclosed.[33]

Outlined in Figure 1-26 is the group's approach to the BC ring system of Merrilactone A. Danishefsky's diene (**94**) underwent a Diels-Alder addition with dimethylmaleic anhydride (**19**), furnishing bicycle (**95**), which was regioselectively reduced using *Super Hydride* ($Li(C_2H_5)_3BH$), furnishing lactone (**96**). Subsequent reaction with $Pb(OAc)_4$, followed by acid hydrolysis furnished an intermediate alcohol which underwent oxidative cleavage upon treatment with $Pb(OAc)_4$ and the resulting aldehyde was transformed into dibromoalkene (**97**) *via* the Corey-Fuchs protocol. Next, both bromides were utilised in a stepwise, palladium catalysed coupling sequence consisting of a successive Stille and Heck coupling, affording the bicyclic system (**98**) in 48% yield. As both coupling steps utilised palladium(0) as the active catalytic species, an attempt was made to telescope the two steps into a one-pot procedure. This was found to be feasible when the toluene solution of the first Stille coupling was diluted with DMF and two equivalents of triethylamine were added in order to initiate the Heck reaction. Under such conditions, the one-pot procedure furnished bicycle (**98**) in a marginally improved yield of 52%. Finally, (**98**) was further functionalised *via* hydroboration, oxidation and subsequent epoxidation, affording the tricycle (**99**), which is reported to be under further investigation with respect to elaboration towards Merrilactone A. Fukuyama's model

study thus achieves the synthesis of the densely functionalised intermediate (**99**), representing the natural product's BC ring system, in 11 steps with a combined yield of 1.6%.

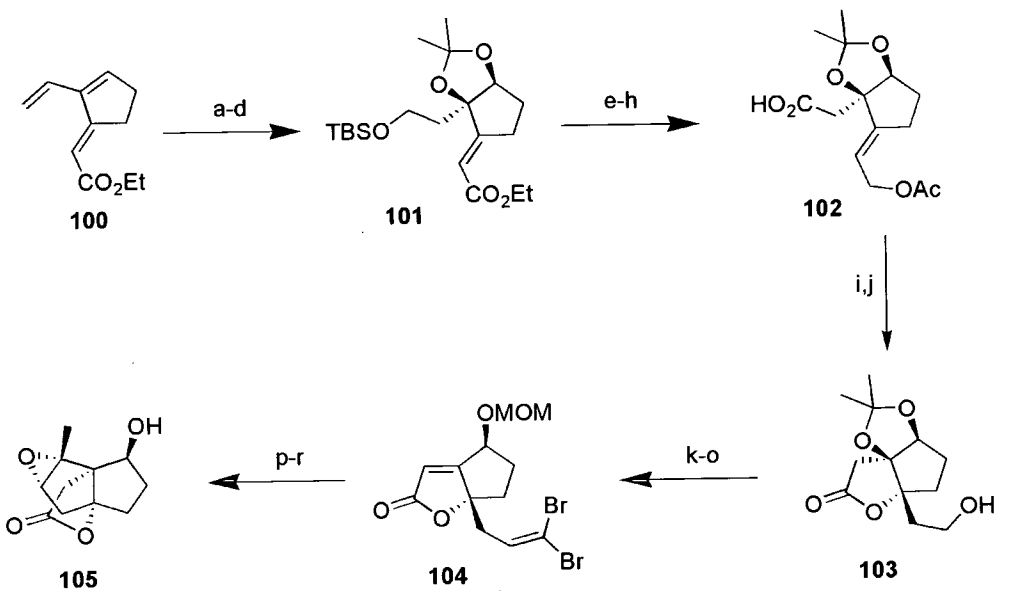


a) toluene, 150 °C, 63%; b) $Li(C_2H_5)_3BH$, THF, 74%; c) $Pb(OAc)_4$, PhH, reflux, 87%; d) TsOH, $MeOH/H_2O$, 100 °C, 72%; e) $Pb(OAc)_4$, PhH, MeOH, 76%; f) CBr_4, PPh_3, DCM, 74%; g) vinyltributyltin, Pd_2dba_3-CH_3CN 10mol%, trifurylphosphine 20mol%, toluene, 100 °C, 62%; h) $Pd(OAc)_2$ 20mol%, P(*o*-tol)$_3$, NEt_3, DMF, 100 °C, 78%; i) Sia_2BH, Et_2O, H_2O_2, 73%; j) PDC, DMF, 62%; k) *m*CPBA, DCM, 44%.

Figure 1-26 Fukuyama's model study of AB ring system

Fukuyama's second model study focuses on the development of a synthetic sequence allowing the preparation of Merrilactone A's AE ring system. The route began with hydroboration of triene (**100**), representing a simplified version of bicycle (**98**), followed by TBS protection of the resulting primary alcohol. Dihydroxylation and protection of the resulting diol then furnished acetonide (**101**). A four step sequence of DIBALH reduction, acetate protection, TBS deprotection and PDC oxidation then gave rise to acid (**102**). Following hydroboration of (**102**), the pivotal Tsuji-Trost reaction formed the desired γ-lactone (**103**). In order to set the scene for a Stille-Heck coupling sequence, already successfully employed in the first model study, (**103**) was oxidised and transformed into the desired dibromoalkene *via* the Corey-Fuchs protocol. Following acetal hydrolysis, protection of the resulting secondary alcohol and elimination of the tertiary hydroxyl moiety, the desired substrate (**104**) was obtained. In the event of subjecting (**104**) to the previously established reaction conditions for the Stille-Heck coupling sequence, no desired product could be

obtained. However, treatment with three equivalents of dimethyl lithium cuprate was found to effect the desired *mono*-methylation, followed by Michael type cyclisation to the conjugated lactone moiety. Finally, MOM deprotection followed by epoxidation furnished tricycle (**105**), in which the ABE ring system of Merrilactone A has been realised (Figure 1-27). Fukuyama's second model study thus allows access to the advanced intermediate (**105**) in 18 steps and 1.2% combined yield.



a) Sia_2BH, THF then aq. NaOH, H_2O_2, 88%; b) TBSCl, imidazole, DMF, 95%; c) OsO_4 3mol%, NMO, THF; d) 2,2-dimethoxypropane, TsOH, DCM, 56% over 2 steps; e) DIBALH, DCM; f) Ac_2O, DMAP, pyridine, 89% for 2 steps; g) TBAF, THF; h) PDC, DMF, 67% over 2 steps; i) $Pd(PPh_3)_4$, NaH, DMF, 75%; j) BH_3-THF complex, THF then aq NaOH, H_2O_2, 58%; k) Dess-Martin-periodinane, DCM, quant.; l) CBr_4, PPh_3, DCM, 64%; m) 1M HCl, THF, 71%; n) MOMCl, DIPEA, DCM, 76%; o) MsCl, NEt_3, DCM, 67%; p)Me_2CuLi, Et_2O, 78%; q) DOWEX 500WX2-100, MeOH, 88%; r) *m*CPBA, DCM, 66%.

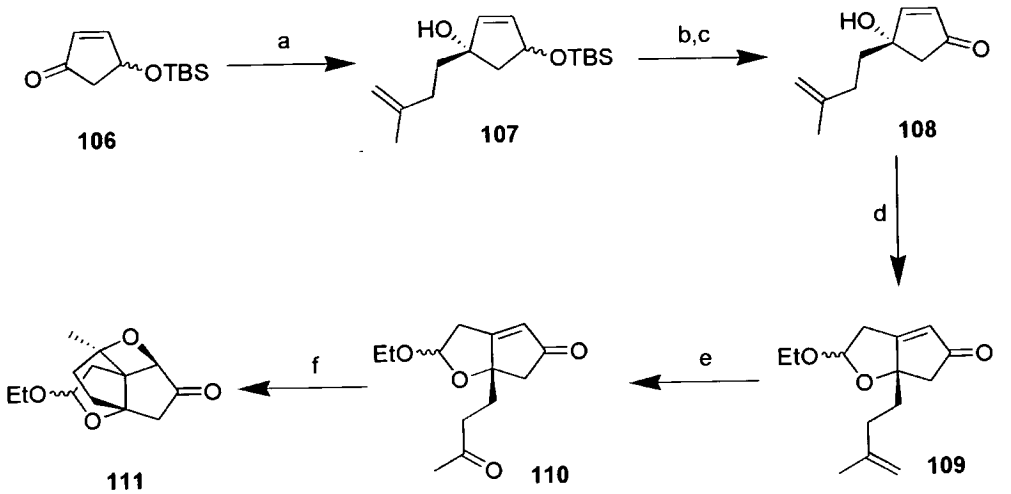
Figure 1-27 Fukuyama's model study of CD ring system

With their two published model studies, Fukuyama and co-workers have addressed the synthesis of both the left and right hand hemispheres of Merrilactone A in a straightforward and stepwise fashion. Research into combining the two approaches, leading to the total synthesis of the natural product, are reported to be currently in progress.

1.4.2. Greaney's model study

A radically different approach towards the total synthesis of Merrilactone A was presented by Greaney and co-workers in 2005.[34] Whilst all previously published total syntheses of the natural product relied on the installation of the central oxetane motif *via* a *homo*-Payne-type rearrangement as the final step, Greaney and co-workers employed an intramolecular [2+2] Paternò-Büchi photo-addition to facilitate the introduction of this key structural motif. The published model study focuses on the synthesis of an advanced tetracyclic oxetane core of Merrilactone A.

Starting with the silyl protected hydroxycyclopentenone (**106**), nucleophilic addition of lithiated 4-iodo-2-methyl-but-1-ene afforded alcohol (**107**) in 89% yield. The latter was deprotected and the resulting secondary alcohol oxidised to furnish hydroxyl-enone (**108**) in good yield. Next, a key palladium mediated domino oxy-/carbopalladation of (**108**) was carried out in neat ethyl vinyl ether, resulting in the formation of bicycle (**109**) in 65% yield. Ensuing oxidative cleavage of the *exo*-alkene then afforded photo-substrate (**110**). In the final step of the model study, (**110**) was exposed to UV radiation, resulting in an intramolecular [2+2] photo-addition of the pendant ketone and the electron deficient alkene to form tetracyclic oxetane (**111**) in 93% yield, thereby simultaneously setting three stereocentres and creating two rings. In (**111**), the oxa[3.3.3]propellane framework, representing the ABDE ring system of Merrilactone A, has been successfully realised (Figure 1-28).



a) 4-iodo-2-methylbut-1-ene, ^{t}BuLi, Et_2O, -78 °C, 89%; b) TBAF, THF; c) PDC, DCM, 62% over 2 steps; d) $Pd(OAc)_2$, ethylvinylether, 65%; e) OsO_4, $NaIO_4$, dioxane/H_2O, 47%; f) hν, MeCN, 93%.

Figure 1-28 Greaney and co-workers model study

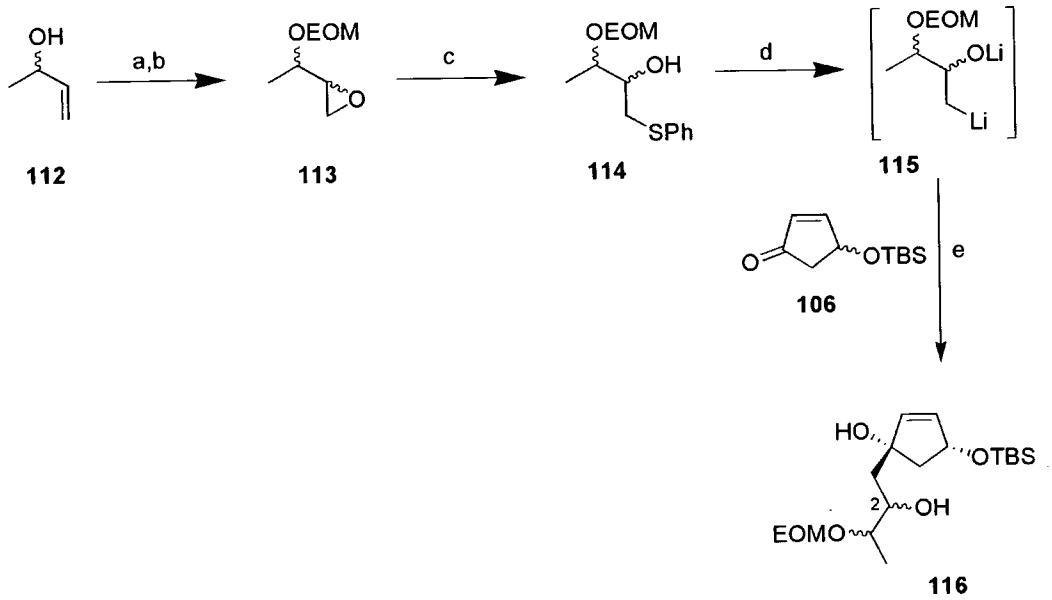
Greaney and co-workers have thus successfully demonstrated a novel approach towards the tetracyclic oxetane core of Merrilactone A, using a six step synthetic sequence with an overall yield of 16% for the preparation of the advanced intermediate (**111**).

1.5. Project Objectives

1.5.1. Previous unpublished work within project

In September of 2005, the Merrilactone A project had been running for a number of years, culminating in the publication of the model study in which the synthesis of the tetracyclic core of Merrilactone A was disclosed.[34] The contents of this paper have been discussed in Chapter 1.4.2 and the synthetic route employed has been outlined in Figure 1-28. As is evident from this publication, the feasibility of several key steps of a proposed total synthesis have been demonstrated, albeit on simplified model structures. Furthermore, the key transformations have been achieved in good to excellent yields, the nucleophilic addition proceeding in 89% yield, the oxy/carbo-palladation in 65% and the Paternò-Büchi reaction in 93% yield. However, two structural features of Merrilactone A were omitted in this model study; the hydroxyl functionality at C_2 as well as the γ-lactone ring C with its two angular methyl groups present at the *cis*-BC-ring junction.

The stereoselective introduction of the hydroxyl moiety at the C_2 position proved to be a significant synthetic challenge, possible solutions to which were investigated by Jone Iriondo-Alberdi.[35] As a late stage introduction of the alcohol was deemed to be undesirable, methodologies were investigated allowing the introduction of a suitably functionalised side-chain. Outlined in Figure 1-29 is the synthetic sequence which was established after extensive experimentation. The reaction of epoxide (**113**), readily prepared in 2 steps from but-3-en-2-ol (**112**), with thiophenyl afforded thioether (**114**) in 76% yield. Subsequent treatment of (**114**) with *tert*-butyl lithium and LDBB then afforded a solution of the lithium β-lithio-alkoxide which was trapped with cyclopentenone (**106**), thereby furnishing diol (**116**) in 67% yield. A satisfactory method for the early stage introduction of the C_2-hydroxyl moiety had thus been developed.



a) EOMCl, DIPEA, DMAP, DCM, 99%; b) *m*CPBA, DCM, 54%; c) PhSH, EtOH, reflux, 76%; d) Li, DBB, THF, -78 °C then ^{n}BuLi, -78 °C; e) **106**, THF, 67% over 2 steps.

Figure 1-29 Introduction of C_2-hydroxy-bearing side chain

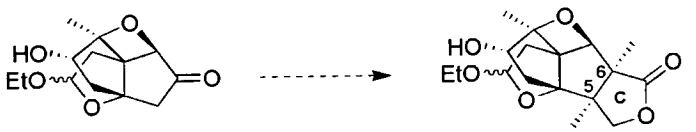
Following the successful introduction of the highly functionalised side-chain, an entry into an asymmetric synthesis was sought *via* the preparation of an enantiopure epoxide 2S-3R-(**113**) as well as R-(**106**). Both compounds were successfully prepared according to literature precedent, however, due to time constraints, no further work on this approach was undertaken at the time.

1.5.2. Project aim

The primary aim of the project remained the development of a total synthesis of Merrilactone A. The natural product's intriguing biological activity paired with its unique challenging structure means it remains a highly attractive target for total synthesis, despite the already published total syntheses.

With the preceding work carried out within the project allowing the synthesis of the advanced core of the natural product as well as addressing the introduction of the C_2 hydroxyl moiety, the initial aim of the project was to build on this route and thereby to achieve the total synthesis of the natural product. More specifically, the initial focus was on developing methodologies for the late stage annulation of the γ-

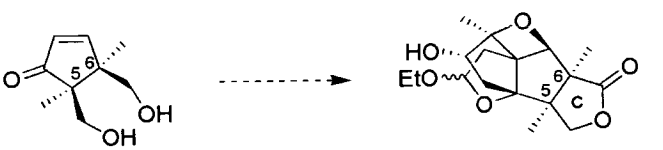
lactone ring C and the angular methyl substituents at C_5 and C_6, employing the carbonyl functionality present in tetracycle (**111**) as a functional handle. We anticipated that a combination of the established route to the tetracyclic core of Merrilactone A with the methodology allowing the introduction of the C_2 functionality would provide access to tetracycle (**117**). The carbonyl functionality would then provide the required functionality for the late stage annulation of the right hand side of the natural product, thus leading to the highly advanced intermediate (**118**, Figure 1-30).



117 **118**

Figure 1-30 Project aims I: Introduction of C-ring and angular methyl substituents

In the later stages of the project, the focus was to shift away from a late stage introduction of the right hand side of the molecule and instead an approach was sought to allow the formation of the two quaternary centres at C_5 and C_6 at the outset of the synthetic sequence (Figure 1-31). Developing a route to the key intermediate (**119**), in which a suitably functionalised carbon skeleton for the formation of lactone ring C is present in the form of the diol functionality, would allow the application of previously developed methodology to this system. In particular, applying the organometallic addition of the C_2-hydroxy containing functionality followed by the previously described oxy/carbo-palladation methodology and subsequent Paternò-Büchi photocyclisation would establish a novel route to the highly advanced intermediate (**118**).



119 **118**

Figure 1-31 Project aims II: Early stage annulation of ring C and angular methyl substituents

It was envisioned that if the two quaternary centres at C_5 and C_6 could be established in a stereospecific manner at an early stage of the total synthesis, the facial differentiation thereby generated could be exploited to direct the introduction of further chiral centres along the route, rather than relying on chiral reagents. Such an approach would allow the development of a synthetic route employing substrate control by facial differentiation to be employed to relay chiral information to parts of the molecule in which novel stereocentres are to be established.

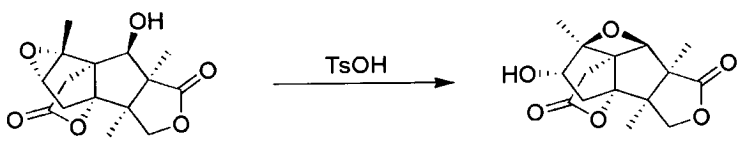
The development of such a route towards the right hand side of the natural product was performed with the aid of a number of synthetic approaches. Along the way, major reconfigurations of the previously established routes had to be implemented in order to allow for the more substituted and functionalised substrates to be advanced towards the natural product. The research carried out on each of the three adopted approaches will be presented in their own separate chapter, together with the appropriate retrosynthetic analyses (*vide infra*).

2. The Di-alkylation Approach

Our first approach was based firmly on the methodology previously developed within the project, discussed in chapter 1.4.2. Aiming at a late stage annulation of the γ-lactone ring C onto the tetracyclic core of Merrilactone A, we set out to develop a number of model systems in order to explore possible routes towards the construction of the right hemisphere of the natural product.

2.1. Retrosynthetic Analysis for the Di-alkylation Approach

All previous total syntheses of Merrilactone A have so far relied on the well established biomimetic *homo*-Payne rearrangement of epoxide (**9**), introducing the central oxetane motif in the final step (Figure 2-1).



9 **1**

Figure 2-1 Biomimetic *homo*-Payne rearrangement

We envisioned developing an alternative strategy, installing the oxetane ring in a pivotal Paternò-Büchi photo-cyclisation reaction. Such an approach would take advantage of the proven ability of [2+2] photoadditions to introduce quaternary stereocentres in sterically congested areas with high levels of stereocontrol. Our retrosynthesis employed in the di-alkylation approach, outlined in Figure 2-2, is therefore based around the formation of the tetracyclic core (**117**) *via* a key Paternò-Büchi reaction, in which two rings are formed and three stereocentres are set in a single step. Conversion of the photo-cyclisation product (**117**) into Merrilactone A (**1**) was then to be realised by exploiting the acidity of the ketone's α-position to carry out two consecutive alkylations, introducing both a methyl substituent as well as a functionalised one-carbon fragment. The introduced functionalisation is then to be used in order to construct the γ-lactone ring C. The substrate for the Paternò-Büchi reaction, bicycle (**120**), would in turn be prepared from cyclopentenone (**121**)

via an oxy/carbopalladation sequence, installing the scaffold for γ-lactone ring E. Disconnection of the highly functionalised side chain by means of an organometallic 1,2-addition then suggests the known simple cyclopentenone (**106**) as a suitable starting point for the total synthesis.

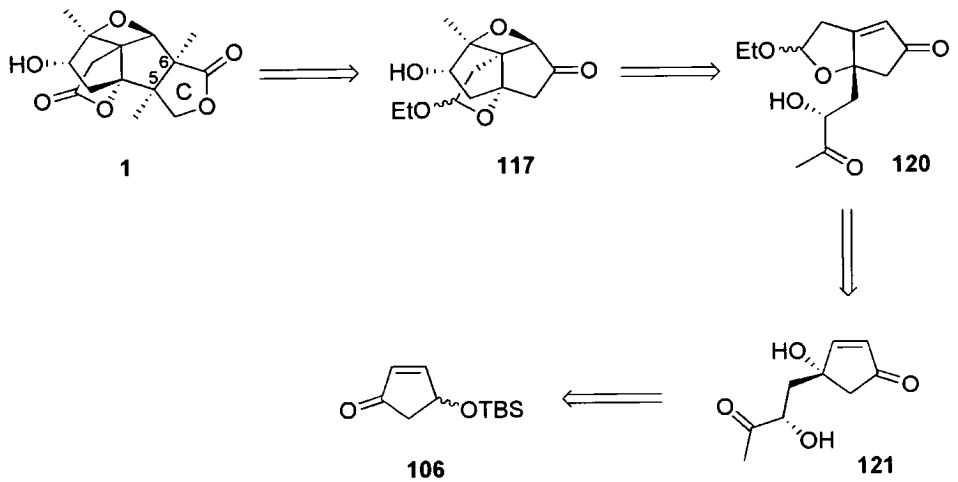


Figure 2-2: Retrosynthetic analysis for the di-alkylation approach

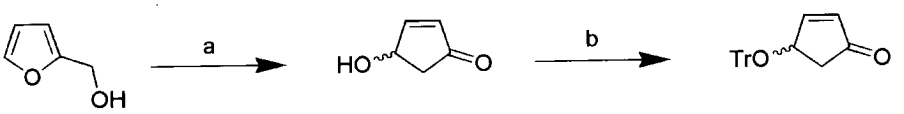
Of the four key transformations envisioned, the organometallic side-chain addition, oxy/carbopalladation sequence, Paternò-Büchi photocyclisation and late stage γ-lactone annulation, the former three have already been shown to be feasible (*vide supra*). The focus of the di-alkylation approach was thus to concentrate on the development of methodology allowing the introduction of the γ-lactone ring C and the two angular methyl substituents at C_5 and C_6 using the carbonyl functional handle present in tetracycle (**117**). Due to the highly advanced nature of substrate (**117**), model systems were to be used to develop a route which could then be applied to the natural product substrate.

2.2. Model System I: Simple Cyclopentenone

We began our investigation with a simplified model system, the trityl protected hydroxy-cyclopentenone (**124**), representing the central carbocycle B of Merrilactone A. The model system features a carbonyl moiety as the required functional handle, a protected secondary alcohol akin to the acetal moiety in tetracycle (**117**) and an

alkene, representing the required degree of unsaturation for the Paternò-Büchi reaction. Simultaneously, the complexity is kept to a minimum, allowing fast and effective access to the model substrate.

The two-step synthesis of the model system is outlined in Figure 2-3 and was adopted from a literature procedure.[36] A Bac-Piancatelli rearrangement of furfuryl alcohol (**122**) in slightly acidic aqueous medium afforded 4-hydroxycyclopentenone (**123**) and subsequent protection of the 4-hydroxy functionality as the trityl ether furnished the desired model system (**124**) in moderate yield. Although (**124**) was only isolated after extensive column chromatography, the two-step approach was amenable to efficient scale-up, enabling us to prepare large quantities of the desired model compound.



122 **123** **124**

a) hydroquinone, NaH_2PO_4, H_2O, 44%; b) TrCl, DMAP, NEt_3, DCM, 40%.

Figure 2-3 Synthesis of model system I

With the model system in hand, we explored several avenues towards the functionalisation of model system (**124**) *via* two successive alkylation reactions.

2.2.1. γ-Lactone formation via Horner-Wadsworth-Emmons reaction

A *bis*-alkylation of model system (**124**) consisting of a methylation followed by introduction of a functionalised side-arm would afford (**125**), setting up a cyclisation *via* intramolecular Horner-Wadsworth-Emmons (HWE) reaction yielding bicycle (**126**). Subsequent methylation and formation of lactone (**127**) *via* hydration would then give access to the desired γ-lactone ring with the angular methyl substituents in place (Figure 2-4).

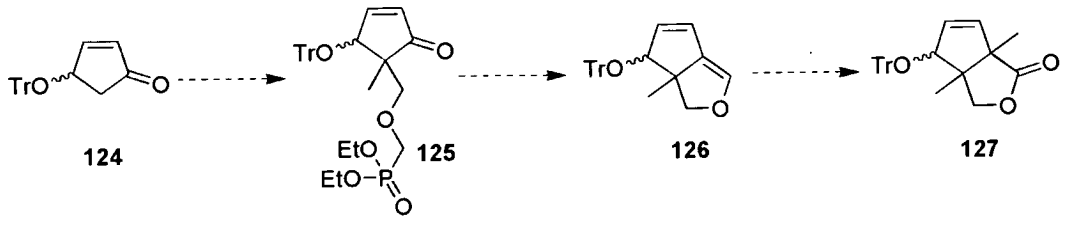
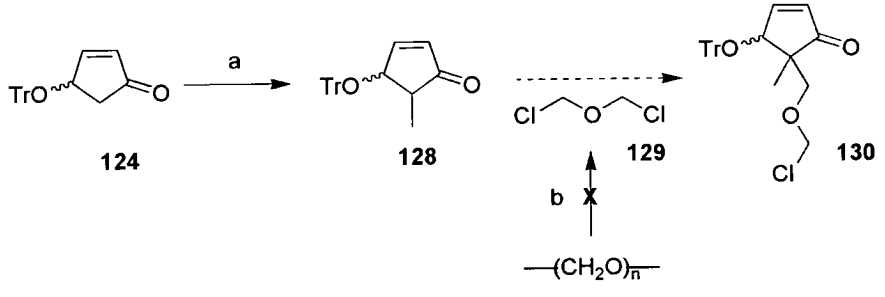


Figure 2-4 Proposed route to γ-lactone *via* HWE reaction

Initial work focused on the simple methylation of the lithium enolate of cyclopentenone (**124**), formed by treatment with freshly prepared LDA. Although subsequent addition of methyl iodide did indeed furnish the desired product (**128**), conversion was poor, affording the product in only 21% yield. A significant improvement could be achieved by the addition of DMPU as a co-solvent, raising the yield of the reaction to 49%. Next, it was anticipated that a second alkylation, in this instance using *bis*-chloromethylether (**129**) would afford the intermediate (**130**), which could be elaborated further into a HWE-type substrate. However, the preparation of the required *bis*-chloromethylether according to literature procedures could not be repeated in our hands and, taking into account the extreme toxicity of this particular compound, no further attempts to synthesise it were undertaken (Figure 2-5).[37]

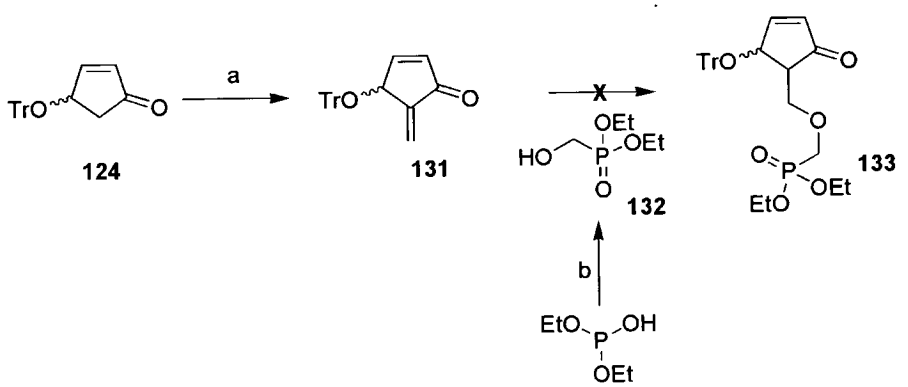


a) LDA, DMPU, MeI, THF, 49%; b) H_2SO_4, $ClSO_3H$.

Figure 2-5 Methylation of model system I

A slight modification in our approach then led us to investigate the introduction of an *exo*-methylene group using Eschenmoser's Salt, $[(CH_3)_2NCH_2]^+I^-$. As part of a total synthesis of Guanacastepene A, Danishefsky and co-workers reported the introduction of such a moiety in good yield by treatment of a lithium enolate with Eschenmoser's Salt, followed by an oxidative workup with *m*CPBA.[38] Application of

this methodology to our model system by preparation of the lithium enolate of (**124**) using LHMDS, followed by addition of Eschenmoser's Salt and successive elimination of the formed dimethylaminoethylene Mannich base product with *m*CPBA did indeed furnish the desired product (**131**). By analogy with the methylation reaction described above, the addition of DMPU as a co-solvent was again found to increase the yield, allowing the preparation of the *exo*-alkene (**131**) in 76% yield (Figure 2-6).



a) LHMDS, DMPU, THF, Eschenmoser's Salt, then *m*CPBA, $NaHCO_3$, DCM, 76%;
b) paraformaldehyde, NEt_3, 78%.

Figure 2-6 *exo*-Alkene *via* Eschenmoser's Salt

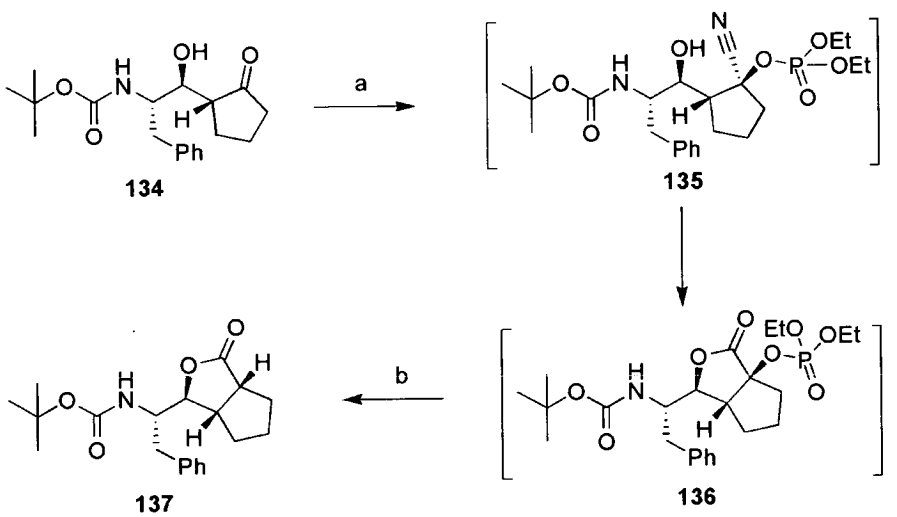
Next, further functionalisation was to be achieved by a hetero-Michael type reaction of phosphonate (**132**), which was readily prepared in a single step from commercially available diethyl phosphite in good yield.[39] Initially, treatment of phosphonate (**132**) with sodium hydride, followed by addition to (**131**) was attempted, however, recovery of starting material with a minor amount of decomposition was observed. Next, the *oxa*-Michael reaction was attempted using palladium(II) catalysis as literature precedent had shown this to be a viable catalyst in *aza*-Michael reactions, enabling the formation of β-aminoketones in high yields.[40] Furthermore, palladium(II) has been shown to effectively catalyse the *oxa*-Michael addition of benzyl alcohol to an enone in high yield.[41] However, in our case, exposure of a mixture of (**131**) and (**132**) to 10 mol% $PdCl_2(MeCN)_2$, even at elevated temperatures for prolonged periods of time, led only to decomposition of the starting materials with minor amounts of substrate recovery. Finally, it was attempted to employ a tributylphosphine catalyst to facilitate the reaction, as exemplified by Toste

and co-workers.[42] Disappointingly, after heating of enone (**131**) in a large excess of phosphonate (**132**) in the presence of 5 mol% tributylphosphine for two days, no reaction had occurred and quantitative recovery of starting materials was observed.

At this stage it was becoming apparent that the preparation of the desired substrate for the HWE reaction was not as straightforward as anticipated, with numerous literature methods proving ineffective and an alternative approach towards the construction of the γ-lactone *via* a di-alkylation methodology was sought.

2.2.2. *γ-Lactone formation via cyanation of β-hydroxy-ketone*

Our attention turned to methodology published by Cushman and co-workers, effecting lactonisation of a *β*-hydroxyketone upon treatment with lithium cyanide and diethyl phosphorocyanidate.[43] Exposing β-hydroxyketone (**134**) to such conditions formed the transient cyanohydrin species (**135**). *In situ* nucleophilic attack of the β-hydroxy functionality on the newly formed nitrile moiety and successive hydrolysis of the resulting imine then furnished lactone (**136**). Subsequent reduction of the phosphate functionality in (**136**) using samarium diiodide afforded the bicyclic γ-lactone (**137**) in satisfactory yield (Figure 2-7).



a) LiCN, diethylphosphorocyanidate, THF, 0 °C; b) SmI_2, THF/^{t}BuOH, 0 °C, 40% over 2 steps.

Figure 2-7 Cushman and co-workers lactonisation methodology

Adapting Cushman and co-workers methodology to our model system (**124**) would thus require the introduction of the prerequisite β-hydroxyketone motif, as exemplified by (**138**). Cyanohydrin formation would afford (**139**) and following lactonisation and phosphate reduction, the desired γ-lactone structure (**140**) should be formed (Figure 2-8).

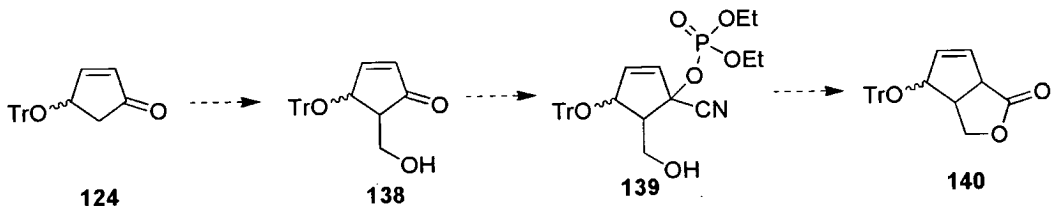


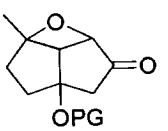
Figure 2-8 Proposed lactone synthesis *via* Cushman and co-workers methodology

Initial attempts towards the preparation of β-hydroxyketone (**138**) were made using aqueous formaldehyde solution in combination with either potassium carbonate or sodium bicarbonate in ethanol or THF.[44] Disappointingly, none were met with success and in all cases decomposition of the starting material was observed. Next, we shifted our attention to the use of masked formaldehyde equivalents, which had previously been successfully employed for the introduction of the functionality we required. β-Trimethylsilylethoxymethyl chloride (SEMCl) has been found to be a convenient formaldehyde equivalent and has been used for the trapping of ester- and ketone enolates to afford β-trimethylsilylethyl ethers of the products of the formal aldol reaction of formaldehyde in good to excellent yields.[45] Selective removal of the SEM protecting group using TBAF would then liberate the desired alcohol (**138**). To begin with, SEMCl was simply added to the lithium enolate of (**124**), which had been preformed using LHMDS. However, neither at -78 °C or after prolonged stirring at room temperature was any product formation observed. In an ensuing attempt, DMPU was added as a co-solvent in order to increase the reactivity of the lithium enolate and tetrabutylammonium iodide was added to the SEMCl to facilitate an *in situ* Finkelstein reaction, thereby increasing the reactivity of the electrophile. In spite of this, only starting material was present after prolonged stirring, first at -78 °C, then at room temperature. In a further attempt, ethoxymethylchloride (EOMCl) was employed as the formaldehyde equivalent; however, this reaction did not show any conversion into desired products either.

At this stage, it was decided to forsake work on the trityl-protected hydroxyl-cyclopentenone model compound (**120**). As only simple methylation and methenylation reactions were shown to be feasible and all further attempts at functionalising the model system were met without success, the development of the sought-after methodology was prevented. Whilst substrate recovery was possible in many instances, we also observed a substantial amount of decomposition in many reactions. We felt that the high density of reactive sites in the ring, including the disubstituted enone, the acidic proton in the γ-position and the two acidic α-protons could be responsible. An improved, second-generation model system would therefore have a reduced number of reactive sites on the central cyclopentenone ring whilst retaining the required functionalities and structural features to simulate the natural product substrate.

2.3. Model System II: Simplified Core

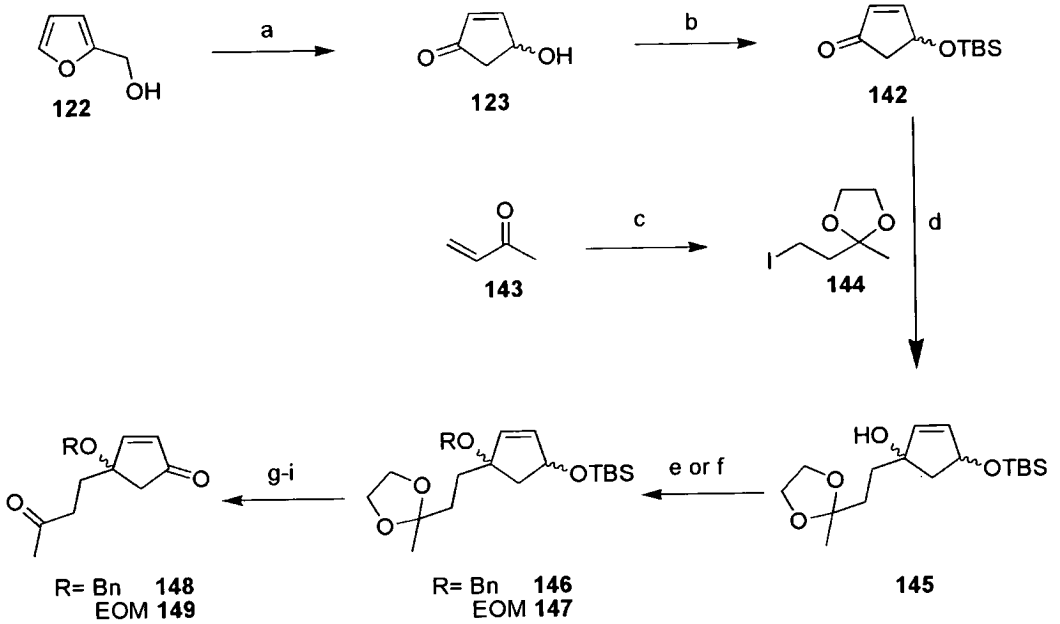
Whilst our mid term aim remained the adaptation of Cushman and co-workers methodology (cf. Figure 2-7) in order to develop a route for the late stage annulation of the γ-lactone ring C of Merrilactone A, the short term goal was the design of a second model system for the preparation of the required ketone β-hydroxy motif. We chose the tricyclic, oxetane-containing ketone (**141,** Figure 2-9) as our second model system for a number of reasons; as is evident from the structure, the number of reactive sites around the central, five-membered, ketone bearing ring has been reduced by the removal of the enone functionality, the acidic γ-proton in particular. Furthermore, the model system is much more closely related to the natural product substrate to which the methodology developed will eventually be employed, thus increasing the likelihood of a smooth transfer.



141

Figure 2-9 Model System II: Simplified core

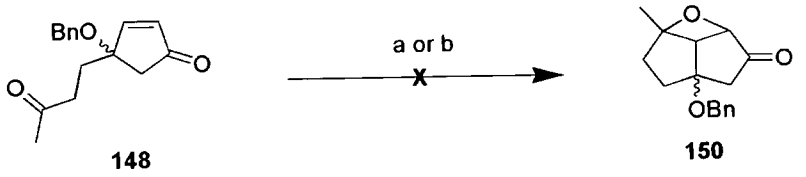
The synthetic route towards model system II is outlined in Figure 2-10, showing the preparation of the Paternò-Büchi substrate, which, upon irradiation was anticipated to undergo a [2+2] photocyclisation to afford the second generation model system, the tricycle (**141**).



a) hydroquinone, NaH_2PO_4, H_2O, 44%; b) TBSCl, DMAP, NEt_3, DCM, 48%; c) ethylene glycol, NaI, TMSCl, MeCN, 44%; d) **144**, ^tBuLi, Et_2O, 74%; e) BnBr, NaH, TBAI, THF, 78% **146**; f) EOMCl, DIPEA, DMAP, DCM, 92% **147**; g) TBAF, THF; h) PDC, DCM; i) HCl, THF, **148**: 82% over 3 steps, **149**: 62% over 3 steps.

Figure 2-10 Synthesis of Paternò-Büchi Substrate for formation of Model System II

Furfuryl alcohol (**122**) was heated in mildly acidic aqueous solution, promoting a Bac-Piancatelli rearrangement,[36] forming 4-hydroxycyclopentenone (**123**) in moderate yield. Subsequent protection of the 4-hydroxy group as the TBS-ether was carried out under standard conditions, affording (**142**) in a moderate yield.[46] Next, the iodoacetal (**144**) was prepared from methylvinyl ketone (**143**) in a one-pot reaction with trimethylsilyl chloride, methyl iodide and ethylene glycol in acetonitrile.[47] With iodoacetal (**144**) in hand, the stage was set for the key addition reaction. Lithium-iodide exchange, prompted by addition of *tert*-butyl lithium to (**144**) in THF at -78 °C, formed the organometallic nucleophile to which cyclopentenone (**142**) was added slowly, resulting in a clean formation of (**145**) in good yield. To begin with, the tertiary alcohol (**145**) was protected as a benzyl ether, affording (**146**) in 78% yield. Finally, a three step sequence of fluoride mediated TBS deprotection, oxidation of the resulting secondary alcohol with PDC in DCM and acetal deprotection using HCl in THF resulted in formation of Paternò-Büchi substrate (**148**) in a combined yield of 82% over three steps.



148 150

a) MeCN, hν, RT; b) MeCN/Acetone 9:1, hν, RT.

Figure 2-11 Paternò-Büchi reaction of benzyl protected substrate

The final step in the synthesis of model system II required (**148**) to undergo a Paternò-Büchi [2+2] photo-cyclisation to furnish the tricycle (**150**, Figure 2-11). After deoxygenating an acetonitrile solution of the photo-substrate (**148**) by bubbling a stream of nitrogen gas through it for 2 hours, irradiation was carried out with a 400W medium pressure mercury arc lamp through a Pyrex filter.

Mercury vapour lamps are regarded as the most useful sources of UV light for photochemical reactions due to their very high intensity combined with a long lifespan. The spectral output of mercury arc lamps ranges from 254nm to 580nm with a peak wavelength of 365nm. Metal vapour lamps emit radiation at discrete wavelengths only, corresponding to the spectral emissions of the metal used. Filters can be employed to remove undesired wavelengths and, in this case, a Pyrex filter was employed which only allows radiation of wavelengths of 280 nm or longer to pass through.

The electronically excited state of the carbonyl group participating in the Paternò-Büchi reaction is accessed *via* a $n \rightarrow \pi^*$ transition, forming an excited singlet state (S_1, Figure 2-12). In the case of the reaction of aliphatic ketones with electron rich olefins, two reaction pathways are available: reaction of the singlet excited state carbonyl group in a concerted manner with the olefin will proceed with retention of stereochemistry while the reaction of the triplet state excited carbonyl moiety (T_3), formed through intersystem crossing (ISC), proceeds *via* a bi-radical intermediate. Depending on the lifetime and stability of this intermediate, bond rotations may be possible which can influence the observed stereoselectivity depending on the relative timescales of the two processes, cyclisation and bond rotation.

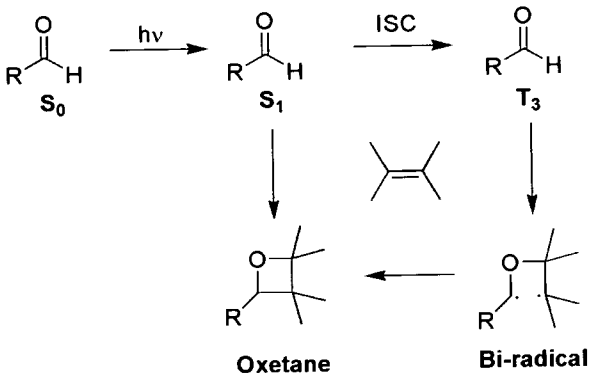


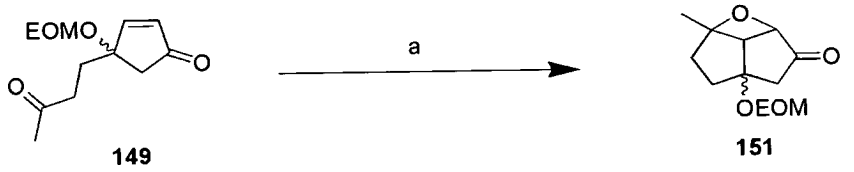
Figure 2-12 Mechanism of the Paternò-Büchi reaction

However, in the case of Paternò-Büchi reactions of electron deficient olefins, as is the case in our system, an additional reaction mechanism is possible. Due to the low electron density of the olefin, direct attack of the nπ* carbonyl oxygen atom is unfavourable. Electron transfer from the singlet excited carbonyl to the electron deficient olefin can however occur, forming an excited singlet complex. This *exciplex* may then react to form the oxetane ring in a stereospecific manner, not necessarily giving rise to the product expected to arise from a bi-radical intermediate with the highest stability.[48,49]

In the present case, the progress of the photoreaction of (**148**) was monitored by TLC analysis of aliquots taken from the vessel at half hour intervals and after three hours of UV irradiation, the reaction was stopped as no conversion of the starting material could be detected. Successive irradiation of the solution of (**148**) without a Pyrex filter led to complete decomposition of the starting material within 15 minutes of irradiation. Repeating the reaction in acetonitrile in the presence of 10% acetone as a photosensitiser was met with the same outcome. As the Paternò-Büchi reaction of very similar substrates, varying only in the protecting group of the tertiary alcohol, had previously been successfully achieved within the project, we believe that the failure of substrate (**148**) to cyclise can be explained by the presence of the benzyl group.[35] A possible explanation can be found in the potential of the aromatic benzyl moiety to quench the excited state of the carbonyl group, which is required for the photocyclisation to occur.[50] It was thus postulated that the introduction of a new

protecting group, unable to act as a quencher of electronically excited states would circumvent the encountered problem.

In consequence, the synthetic route outlined in Figure 2-10 was modified to incorporate a protecting group different from the previously employed benzyl group. Thus, addition product (**141**) was treated with ethoxymethylchloride in the presence of DMAP and diisopropylethylamine to afford the EOM-protected tertiary alcohol (**143**) in excellent yield. TBS deprotection, oxidation of the resulting secondary alcohol and finally acetal deprotection as previously described, afforded the EOM-protected Paternò-Büchi substrate (**149**) in 62% yield over three steps. With the new photo-substrate in hand, the first attempt to facilitate the [2+2] cyclisation, by irradiating the substrate through a pyrex filter in degassed acetonitrile, resulted in formation of the desired product (**151**) in 27% yield after purification by column chromatography.



149 151

a) hν, solvent, filter, RT

Solvent	Filter	Time (h)	Yield (%)
MeCN	Pyrex	1.5	27
MeCN, 10% acetone	Pyrex	1.5	26
EtOH	Pyrex	1.5	Decomposition
Toluene	Pyrex	1.5	35
Hexane	Pyrex	1.5	Decomposition
DCM	Pyrex	1.5	28
THF	Pyrex	1.5	Decomposition
MeCN	Uranium glass	7.5	33
Toluene	Uranium glass	7.5	34

Figure 2-13 Paternò-Büchi reactions of EOM-protected substrate

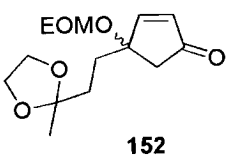
Following the successful formation of the desired model system II (**147**), a solvent screen was carried out, the results of which are summarised in Figure 2-13. Whilst using the Pyrex filter, very similar yields were observed in acetonitrile (with or without acetone), toluene or DCM after irradiating for 90 minutes. In ethanol, hexane and THF, only extensive decomposition was observed and no product formation could be detected. Due to the amount of decomposition observed, accompanying even the reactions in which product was formed, we decided to investigate the influence of the wavelength of light employed. This was achieved by the insertion of filters of differing materials into the photo reactor, surrounding the light source and thereby filtering out undesired wavelengths before the radiation passes through the reaction mixture. Due to the relatively low cut-off point of the initially employed Pyrex filter, allowing light of wavelengths of 280 nm or more to pass through, high

energy radiation passes through the solution containing the photo substrate. In order to reduce the energy of the emitted radiation, a uranium glass filter was employed, cutting off light with a wavelength of 330 nm or less, thereby providing lower energy radiation.[51] As expected, the rate of conversion in the case of the uranium glass filter was lower compared to the experiments using the Pyrex filter, leading to prolonged reaction times. Furthermore, the reactions carried out using lower energy radiation did prove to be much cleaner with less decomposition being observed, however, it was disappointing to note that no significant improvements in yield were observed.

As is evident from the Paternò-Büchi reactions outlined above, the formation of the model system II (**151**) has been shown to be feasible; however, the yields were only poor to moderate. As the photoreactions need to be carried out in high dilutions and only proceed with relatively poor conversion to the desired product, the synthesis of sufficient quantities of the required model compound (**151**) could not be achieved. Furthermore, the length of the synthesis of the required photo-substrates prohibited the use of such an approach as a model system. Due to these difficulties, it was decided to halt further investigations into the model compound (**151**) and instead explore the possibility of carrying out the annulation of the γ-lactone ring on the intermediate (**152**) which is prepared as part of the synthetic route to the photo-substrate (**149**).

2.4. Alkylation Reactions on Synthetic Intermediates

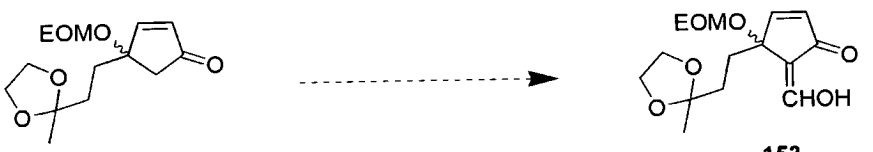
We believed that enone (**152,** Figure 2-14) would be more amenable to functionalisation in the α-position than the first model system, due to the lack of an acidic proton in the γ-position.



152

Figure 2-14 Substrate for formylation reactions

The aim remained the introduction of a hydroxy-methylene moiety in the α-position of cyclopentenone (**152**) *via* a formylation and successive reduction. This two stage process was deemed more likely to succeed than the already attempted direct introduction of the alcohol bearing sidearm. The synthesis of the substrate employed in these reactions has been outlined in Figure 2-10.



152 **153**

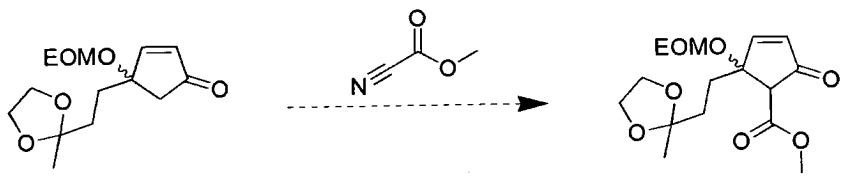
Base	Electrophile	Solvent	Conditions	Result
NaOMe	Ethyl formate	Et_2O	0 °C to RT	SM only
NaOMe	Ethyl formate	Et_2O	RT to 45 °C	SM only
NaOMe	Ethyl formate	MeOH	RT to 85 °C	SM + decomposition
NaH	Ethyl formate	Et_2O/EtOH	RT to 45 °C	SM only
LDA	Ethyl formate	THF	-78 °C to RT	decomposition
LDA	Ethyl formate	THF/DMPU	-78°C to RT	decomposition
LDA	DMF	THF	-78 °C to RT	decomposition
LDA	DMF	THF/DMPU	-78 °C to RT	decomposition
LHMDS	DMF	THF	-78 °C to RT	SM + decomposition
LHMDS	DMF	THF/DMPU	-78 °C to RT	SM + decomposition

Figure 2-15 Attempted formylations using ethyl formate or DMF

The conditions employed in the attempted formylations of (**152**), anticipated to form (**153**) are summarised in Figure 2-15. Treatment of cyclopentenones with sodium methoxide and ethyl formate had previously been described to facilitate the desired reaction,[52] however when substrate (**152**) was treated with freshly prepared sodium methoxide, no product formation was observed, either at room or elevated temperatures. Carrying out the reaction using sodium hydride as the base was also found to result in no conversion of starting material.[53] Subsequently, additions of

ethyl formate to the lithium enolate of (**152**) were attempted, in analogy with literature precedent,[54] yet, only decomposition of the starting material was observed. Finally, DMF was used instead of ethyl formate in a number of reactions, using LDA or LHMDS in THF and THF/DMPU mixtures, however, none showed any desired product formation, with decomposition being prevalent.

Following the unsuccessful attempts at formylating cyclopentenone (**152**) we turned our attention to a more stepwise approach towards the desired β-hydroxy-ketone structural motif. It was anticipated that an alkylation with Mander's reagent,[55] methyl cyanoformate, followed by reduction of the resulting ester would give access to the elusive target compound. The disadvantage of such an approach would be the unavoidable increase in the number of synthetic steps required due to the need to protect and later deprotect the cyclopentenone's carbonyl functionality in order to allow selective reduction of the ester. Nonetheless, the addition of two steps, which were assumed to be achievable in high yields were considered an acceptable drawback in order to reach the target compound. Outlined in Figure 2-16 are the conditions employed in the attempts to alkylate the model substrate (**152**) using Mander's reagent.



152 154

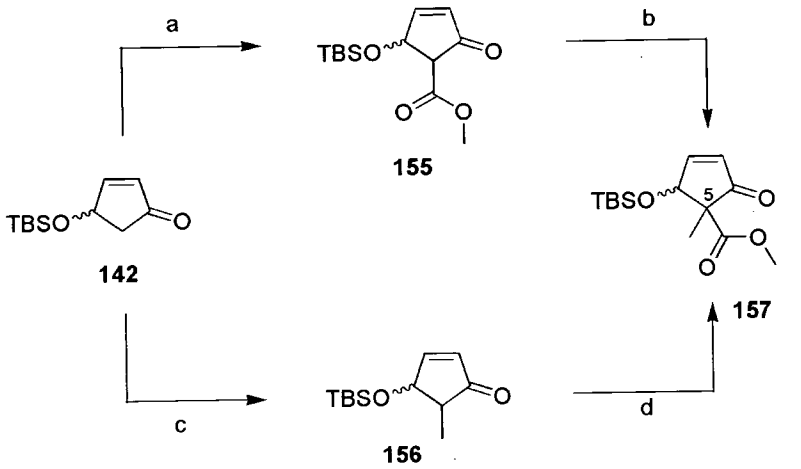
Base	Solvent	Conditions	Result
NaOMe	MeOH	RT to 85 °C	SM + decomposition
LDA	THF	-78 °C	SM only
LDA	THF/DMPU	-78 °C	SM + decomposition
LDA	THF/TPPA	-78 °C	SM only
LDA	THF/HMPA	-78 °C	SM only
LDA	THF/HMPA	-42 °C	SM + decomposition

Figure 2-16 Attempted alkylations using Mander's reagent

As is evident from the summary of results shown above, the addition of Mander's reagent to preformed enolates of (**152**) did not provide access to the desired 1,3-ketoester (**154**) as anticipated. Disappointingly, the functionalisation of the α-position of the model compound (**152**) could thus not be shown to be as straightforward as expected. It was at this stage that we decided to revisit a simpler model system to investigate the conditions required to successfully facilitate the alkylation using Mander's reagent.

2.5. Return to Simple Cyclopentenone – Mander's Reagent

To address the problems observed in attempting to alkylate the advanced intermediate (**152**) we decided to revisit the simple cyclopentenone model. We chose the TBS-protected 4-hydroxy cyclopentenone (**142**) previously prepared *en route* to the photocyclisation substrates (see Figure 2-10).



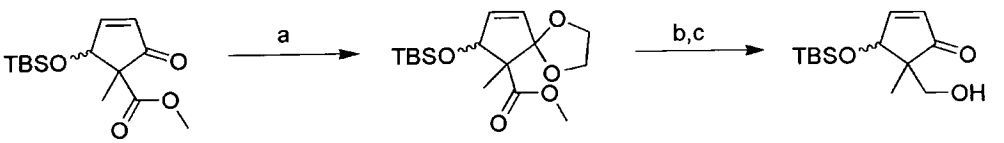
a) LHMDS, THF/HMPA, -78 °C, $NCCO_2Me$, 83%, single diastereomer; b) LHMDS, THF/HMPA, -78 °C, MeI, 63%, 9:1 ratio diastereomers; c) LHMDS, THF/HMPA, -78 °C, MeI, 52%, single diastereomer; d) LHMDS, THF/HMPA, -78 °C, $NCCO_2Me$, 54%, single diastereomer.

Figure 2-17 Cyclopentenone alkylation using Mander's reagent

Pleasingly, we found the alkylation reactions of cyclopentenone (**142**) proceeded with moderate to good yields, for both the reaction with methyl cyanoformate as well as methyl iodide. It has to be noted that the reactions were only successful in the presence of HMPA as a co-solvent, the use of neat THF as well as the addition of TPPA or DMPU as co-ordinating additives failed to give the desired results. Thus, treatment of the lithium enolate of (**142**), derived by slow addition of LHMDS, with Mander's reagent or methyl iodide afforded the mono-alkylated products (**155**) and (**156**) in 83% and 52% respectively. Only a single diastereomer was detected in each case. Next, a second alkylation step was required in order to set up the quaternary centre at C_5. In the case of the 1,3-ketoester (**155**), treatment with LHMDS afforded the lithium enolate which was quenched with methyl iodide to afford (**157**) in 63% yield in a 9:1 ratio of diastereomers. The presence of HMPA was again required in order to enable the reaction. The mono-methylated cyclopentenone (**156**) was elaborated into (**157**) *via* LHMDS deprotonation, followed by addition of Mander's reagent in the presence of HMPA, affording the desired product in 54% yield and as a single diastereomer. The spectroscopic data obtained from the single diastereomer formed in the transformation of (**156**) into (**157**) were identical with those obtained from the major diastereomer formed in the formation of (**157**) *via* (**155**). The relative

stereochemistry could not be established at this stage and the major diastereomer was used in the investigation of the next synthetic steps.

With a satisfactory route to 1,3-ketoester (**157**) in place, we turned our attention to the reduction of the ester moiety in order to access the desired 1,3-hydroxyketone motif. Protection of the enone carbonyl functionality in (**157**) was achieved *via* acetal formation using ethylene glycol under Dean-Stark conditions, furnishing (**158**) in a disappointingly low yield of 38%. Subsequent selective ester reduction using lithium aluminium hydride proceeded smoothly, however the following acetal deprotection step gave a very poor conversion to the desired 1,3-hydroxy ketone (**159**) with only a 42% yield realised over two steps.

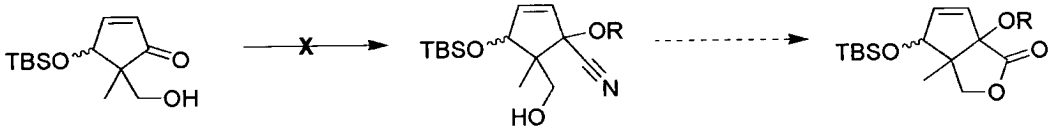


157 **158** **159**

a) ethylene glycol, TsOH, toluene, reflux, 38%; b) $LiAlH_4$, Et_2O, -78 °C; c) TsOH, THF, H_2O, 42% over 2 steps.

Figure 2-18 Synthesis of lactonisation *via* cyanation substrate

Despite the somewhat disappointing yields observed in the three step sequence of advancing (**157**) into (**159**), we moved on to investigate the feasibility of applying Cushman and co-workers lactonisation methodology to our model system.[43] Figure 2-19 outlines the conditions employed in attempting to generate the cyanohydrin required for the lactonisation reaction to take place.



159 160 R= H, TMS 161

Conditions	Result
Acetone Cyanohydrin, NaCN (cat.), H_2O	SM only
Acetone Cyanohydrin, NaCN (equiv), THF	1,4 addition of CN^-
TMSCN, ZnI_2, $CHCl_3$	SM only
TMSCN, ZnI_2, toluene, Δ	decomposition

Figure 2-19 Attempted cyanohydrin formation reactions

Initial attempts at forming cyanohydrin (**160**) were carried out in analogy with methodology published by Marquet and co-workers,[56] in which the treatment of a 1,3-hydroxy ketone motif with acetone cyanohydrin in the presence of catalytic sodium cyanide in aqueous conditions afforded the corresponding lactone *via* a transient cyanohydrin species. Disappointingly, when applied to our model system (**159**), no reaction could be observed and full recovery of starting materials was made. When we increased the amount of sodium cyanide employed from a catalytic amount to a slight excess and carried out the reaction under anhydrous conditions in THF, we observed the formation of a cyanide adduct believed to be the product of a conjugate 1,4-addition rather than the desired 1,2-addition product. Work by Evans and co-workers described the use of trimethylsilyl cyanide as an effective reagent for cyanohydrin formation, especially when catalysed by Lewis acids such as zinc iodide and in published work, specific reference is made to a preference for 1,2-addition over conjugate addition of the cyanide anion.[57] Additional support for the use of TMSCN and a Lewis acid catalyst can be found in the Organic Syntheses publication on the preparation of the cyanohydrin of *p*-benzoquinone, which proceeds exclusively in a 1,2-addition manner.[58] Thus, treatment of (**159**) with trimethylsilyl cyanide in the presence of catalytic zinc iodide in chloroform was anticipated to form lactone (**161**) *via* cyanohydrin (**160**). Disappointingly no conversion of the starting

material could be detected. Any attempts at forcing the reaction by means of increased temperature were met with rapid decomposition of the substrate.

Due to the lengthy and low yielding synthesis of the substrate (**159**), no further attempts at forming the lactone (**161**) were carried out.

2.6. Conclusions

Our initial aim when starting work on the di-alkylation approach was to develop methodology to employ the carbonyl functionality present on the central carbocycle of the core of Merrilactone A (**111**) to carry out a late stage annulation of the γ-lactone ring C as well as the two angular methyl groups at C_5 and C_6. Very early attempts at employing Horner-Wadsworth-Emmons-type chemistry in order to form the lactone ring were unsuccessful so our attention turned to the development of methodology that would allow us to form the desired lactone *via* a cyanohydrin intermediate derived from a 1,3-hydroxy-ketone motif. In order to prepare such a substrate, work was carried out on several model systems, starting with the attempted direct introduction of the desired 1,3-hydroxy ketone moiety *via* formylation reactions which proved unsuccessful. While the synthesis of a more complex model system, the simplified core model, was successful, the lengthy synthesis of the model system in combination with a low yielding [2+2] photo-cyclisation rendered this model system unsuitable for development of methodology. A brief attempt at functionalising intermediates *en route* to the simplified core model also proved unfruitful.

Success finally came when the simple, protected 4-hydroxycyclopentenone model system was revisited, this time with the intent of introducing the 1,3-hydroxy ketone motif *via* addition of Mander's reagent and successive methylation to set up the quaternary centre at C_5. While the desired key intermediate (**159**) was successfully synthesised *via* the developed sequence, the synthesis turned out to be lengthy, stepwise and low-yielding, affording the desired substrate in 7 steps with only a 1.5% yield. Furthermore, when the key cyanohydrin forming reaction could not be shown to be feasible on this substrate, the decision was made to abandon the

di-alkylation approach. We concluded that the late stage annulation of the right hand side of Merrilactone A *via* the methods explored would not be met with a desirable outcome. Our attention hence shifted towards an approach in which the introduction of the carbon skeleton of lactone ring C, as well as the two angular methyl groups, could be implemented early on in the synthesis. Furthermore, once such methodology had been developed, it was hoped that the synthetic route developed within the group and described earlier[34] would be readily transferable.

3. The [2+2] and Paternò-Büchi Approach

As a result of the difficulties encountered in the di-alkylation approach in attempting to introduce the γ-lactone ring C and the angular methyl substituents at C_5 and C_6 at a late stage, we decided to alter our approach. We aimed to introduce the right hand side of the natural product at an early stage in the synthesis and this called for the implementation of significant modifications to our retrosynthetic analysis, which is outlined in Figure 3-1. This chapter focuses on the realisation of this retrosynthesis, in particular the synthesis of a novel, key cyclopentenone intermediate and the challenges faced upon attempting to adapt previously developed methodology to this substrate.

3.1. Retrosynthesis

Disconnecting Merrilactone A's γ-lactone ring C to tetracycle (**162**) would allow the completion of the synthesis *via* a late stage lactonisation of an appropriately functionalised right hand side of the molecule *via* a regioselective oxidation. Due to the absence of the cyclopentenone motif in substrate (**163**), the oxy/carbo-palladation sequence previously employed in installing the second γ-lactone ring E would not be feasible. Alternatively, the formation of the ring could be achieved *via* capping of the tertiary alcohol in (**163**) with a suitably functionalised diazo side-chain, furnishing (**163a**), thus setting the scene for a carbene mediated C-H insertion reaction at C_9, allowing access to (**162**). The tricyclic [3.3.0]propellane structure (**163**) would in turn be derived from (**164**) *via* the previously successfully employed [2+2] Paternò-Büchi photo-cyclisation, forming ring A and D as well as setting three stereocentres around the oxetane ring in a single step. Photo-substrate (**164**) was anticipated to be synthesised in analogy with the established methodology of carrying out an organometallic side-chain addition to the highly substituted cyclopentenone (**165**). This would in turn be accessible *via* a regioselective Tiffeneau-Demjanov-type ring expansion of cyclobutane (**166**). Further disconnection established the ketene acetal (**167**) and 2,3-dimethylmaleic anhydride (**19**) as suitable substrates for an initial

[2+2] photo-cyclisation in which the relative stereochemistry at C_5 and C_6 would be set in a stereospecific *cis*-relationship in the very first step of the synthetic route.

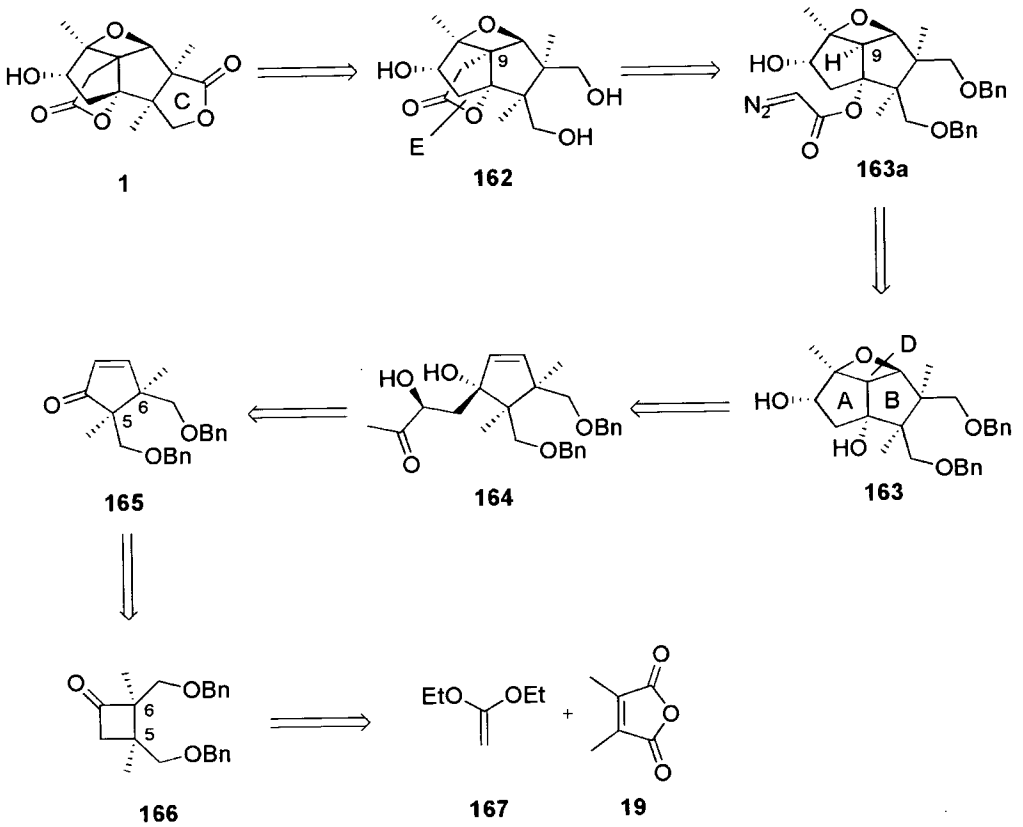


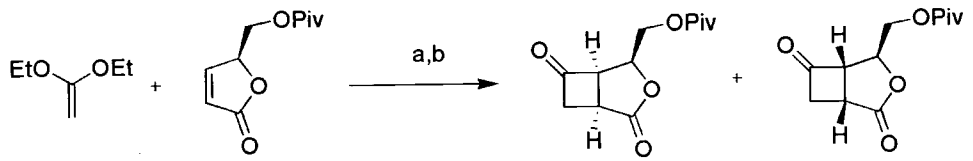
Figure 3-1 Retrosynthetic analysis for [2+2] and Paternò-Büchi Approach

As a result, introducing the carbon skeleton of the γ-lactone ring C and setting the *cis*-relation of the C_5 and C_6 methyl substituents at the very outset of the route should solve the problems encountered in implementing a late stage annulation of the right hand side of the natural product. Furthermore, the stereochemical environment generated in the initial, stereospecific [2+2] photo-cyclisation introduces a highly desirable differentiation between the two faces of cyclopentenone (**165**), to be exploited throughout the synthetic route to facilitate stereoselective transformations by means of substrate control.

3.1.1. An asymmetric [2+2] – scope for asymmetric synthesis

In addition to the ability of the [2+2] photoaddition reaction to stereospecifically build up significant levels of complexity in a single step, it could also represent a convenient entry into an asymmetric route of our envisioned total synthesis.

Rustullet and co-workers have reported an asymmetric intermolecular [2+2] photo-addition of ketene diethylacetal (**167**) with (*S*)-5-pivaloyloxymethyl-2(5*H*)-furanone (**168**) which, after acidic workup affords a separable 2:1 mixture of the *syn*- and *anti*- adducts (**169α**) and (**169β**) in 69% yield.[59]



167 **168** **169α** **169β**

a) hν, Et_2O, -20 °C; b) *p*TsOH, acetone, 56 °C, 69% over 2 steps.

Figure 3-2 Asymmetric photochemical [2+2] cycloaddition

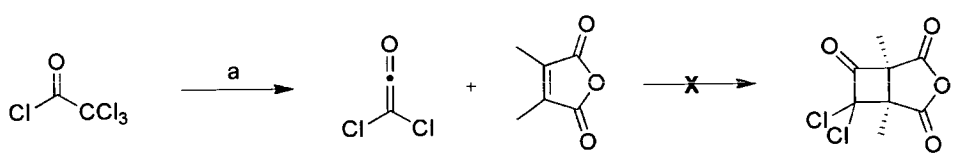
Such an approach could potentially be modified to suit our requirements, providing a direct and elegant entry into an asymmetric route which is to be investigated upon achieving our initial goal of developing a racemic total synthesis.

3.2. Synthesis of Key Cyclopentenone Intermediate (165)

Our first objective in this new approach was the development of a route to the novel cyclopentenone intermediate (**165**). This could be broken down into two stages, firstly the cycloaddition reaction, eventually furnishing cyclobutane (**166**) and subsequently, the development of a regioselective ring expansion reaction and oxidation to furnish the key cyclopentenone (**165**).

3.2.1. Thermal [2+2] cycloadditions

Addressing the initial [2+2] cycloaddition reaction, a number of thermal approaches were evaluated. Our first attempt was based on methodology published by Hassner and Krepski[60] as well as an Organic Synthesis preparation of cyclobutenone.[61] Described is the *in situ* generation of dichloroketene *via* zinc mediated dehalogenation and its subsequent [2+2] cyclo-addition reactions with olefins, ranging from uncongested terminal alkenes to highly sterically encumbered tetra-substituted olefins. Attempting to adapt this methodology to our substrates, we treated a mixture of activated zinc and 2,3-dimethylmaleic anhydride (**19**) with a combination of trichloroacetyl chloride (**170**) and phosphorus oxychloride before refluxing the resulting mixture in anhydrous ether (Figure 3-3). Disappointingly, no formation of the desired adduct (**172**) could be observed and full recovery of the cyclic anhydride (**19**) was made. Repeating the reaction sequence in anhydrous toluene in order to allow higher reaction temperatures was met with the same, unsatisfactory outcome.

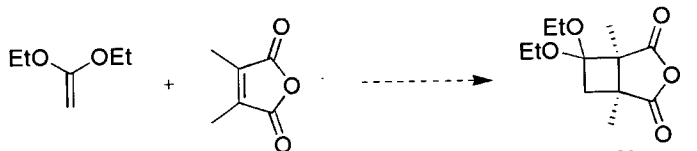


170 **171** **19** **172**

a) activated zinc, $POCl_3$, Et_2O, Δ

Figure 3-3 Attempted [2+2] cyclo-addition using dichloroketene

Our attention then turned to a number of literature reports, detailing the thermal cycloaddition reaction of ketene acetals with enoates. Bisacci and co-workers reported the reaction of diethyl ketene acetal with diethyl fumarate by simply heating the reagents in *tert*-butyl alcohol.[62] In addition, Takasu and co-workers published a method in which silyl enol ethers and acrylates undergo $TiCl_4$ catalysed cyclo-addition reactions and in a publication by Ahlam and co-workers, a fumarate is reported to undergo a [2+2] cyclisation with dimethyl ketene acetal in the presence of Et_2AlCl.[63,64] We carried out trial reactions representing each of these literature methods, employing 2,3-dimethylmaleic anhydride (**19**) and diethyl ketene acetal (**167**) as the substrates. The outcome of these reactions is summarised in Figure 3-4.



167 **19** **173**

Conditions	Result
t-butyl alcohol, 85 °C, 4 days	SM, side-products
$TiCl_4$ (20 mol%), DCM, - 78 °C to RT, 24 h	SM only
Et_2AlCl (2 equiv), toluene, -78 °C, 2 h	SM, decomposition

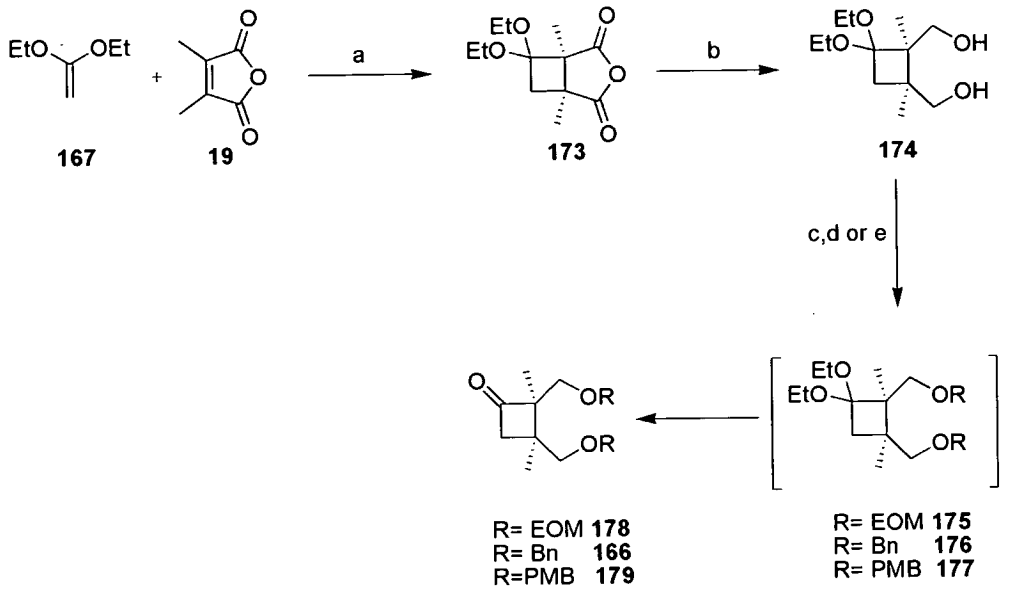
Figure 3-4 Attempted thermal cyclo-additions using diethyl ketene acetal

Heating the reagents in *tert*-butyl alcohol did not afford any desired product (**173**) but instead yielded several by-products, believed to arise from the ring-opening of the anhydride *via* transesterification with *tert*-butyl alcohol. Subsequent attempts at promoting the reaction using Lewis acids were equally unsuccessful, resulting in full recovery of starting materials when catalytic amounts of titanium tetrachloride were used or partial recovery of substrates with concurrent decomposition in the case of alkylaluminum chloride.

3.2.2. *Photochemical [2+2] route to cyclobutanone*

As our attempts at carrying out the thermal cycloaddition reaction proved unfruitful, we investigated a photochemical transformation, encouraged by reports in the literature in which ketene acetals reacted with α,β-unsaturated lactones upon exposure to UV radiation.[65] To our delight, we discovered that irradiating mixtures of 2,3-dimethylmaleic anhydride (**19**) and diethyl ketene acetal (**167**) in acetonitrile and acetone mixtures with a 400W medium pressure mercury vapour lamp through a pyrex filter did indeed furnish photoadduct (**173**) in good yield (Figure 3-5). Whilst the reaction proved very robust and reliable, one notable drawback was observed when attempting to scale up the reaction above 15 mmol of 2,3-dimethylmaleic anhydride (**19**), leading to a sharp drop-off in yields. Nevertheless, carrying out the synthesis of the photo-adduct (**173**) in batches and combining the crops of each reaction before subsequent steps rendered the reaction suitable for our purposes.

In establishing the novel, photochemical cyclo-addition of ketene diethyl acetate (**167**) and 2,3-dimethylmaleic anhydride (**19**), we have exploited the concerted nature of the [2+2] photocyclisation, creating the *cis*-ring junction in photoadduct (**173**) in a stereospecific manner. The correct relative stereochemistry at the two newly created quaternary centres at C_5 and C_6 is thereby established at the very outset, placing our synthetic route on sound stereochemical foundations.



a) hν, pyrex filter, MeCN/acetone 9:1, 10h, 91%; b) $LiAlH_4$, Et_2O, 91%; c) EOMCl, DIPEA, DCM, 0 °C to RT, then 1M HCl, THF, RT, 82% over steps; d) BnBr, NaH, TBAI, THF, RT, then 1M HCl, THF, RT, quantitative over 2 steps; e) PMBCl, TBAI, NaH, THF, RT, then 0.5M H_2SO_4, MeCN, 37% over 2 steps.

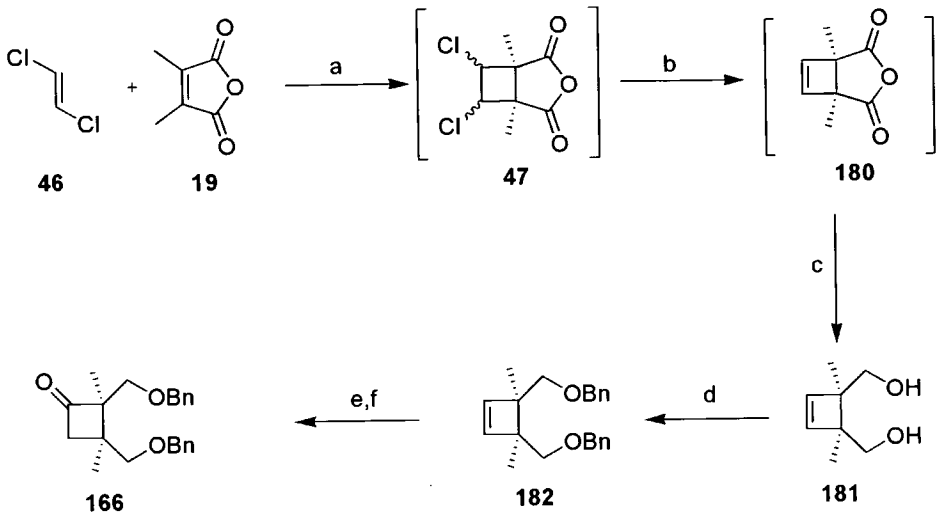
Figure 3-5 Photochemical [2+2] and elaboration into cyclobutanone

With photo-adduct (**173**) in hand, we initially attempted to carry out an acid-mediated acetal deprotection. Selectivity for the deprotection over anhydride hydrolysis and concomitant ring opening to the corresponding acid and ester derivatives could however not be attained. Instead, selective reduction of the anhydride was achieved using lithium aluminium hydride, furnishing diol (**174**) in high yields. Whilst on the one hand keen to avoid the use of benzyl protecting groups on the grounds of suspected quenching of excited states in photo-cyclisation reactions (*vide supra*), we also wanted to investigate the effect of a broad variety of diol protecting groups on the crucial ring expansion reaction. We therefore nonetheless prepared the benzyl protected cyclobutanone (**166**), *via* dibenzylation and subsequent acetal deprotection. The intermediate (**176**) was not isolated as it proved unstable. The EOM protected substrate (**178**) as well as the *para*-methoxybenzyl (PMB) analogue (**179**) were prepared *via* intermediates (**175**) and (**177**) in much the same way.

3.2.3. *Alternative route to cyclobutanone*

The synthesis of the ring expansion substrates *via* the route described in chapter 3.2.2 provides an elegant route to the desired cyclobutanone intermediates. However, the observed difficulty in scale up of the photo-cyclisation meant a batch-type synthesis of photo-adduct (**173**) had to be adopted. Hoping to address this issue, we developed a complementary method, based on a route to cyclobutene (**182**) employed by Hirama and Inoue in their racemic total synthesis of Merrilactone A (cf. Figure 1-11).[22]

Photochemical [2+2] cyclisation of 1,2-*trans*-dichloroethene (**46**) with 2,3-dimethylmaleic anhydride (**19**) afforded the bicyclic anhydride (**47**). Reductive dehalogenation with activated zinc then furnished the fused cyclobutene (**180**), which, after laborious workup procedures was reduced to the corresponding diol (**181**) in moderate yield over three steps. Dibenzyl protection then afforded cyclobutene (**182**) in quantitative yield. In Hirama and Inoue's total synthesis,[22] cyclobutene (**182**) forms the substrate for a sequence of pair wise, symmetrical functionalisations, however, our route departs from this literature precedent at this stage. A sequence of hydroboration and subsequent alkaline hydrogen peroxide oxidation afforded a diastereomeric mixture of secondary alcohols which was subsequently oxidised to the corresponding ketone using PDC, furnishing the desired benzyl protected cyclobutanone (**166**) in moderate yields (Figure 3-6).



a) hν, pyrex filter, benzophenone, acetone, 2.5 h, b) Zn dust, TMSCl, Ac_2O, toluene, 85 °C, 22 h; c) $LiAlH_4$, THF, 0 °C to RT, 20 h, 57% over 3 steps; d) BnBr, NaH, THF, DMF, quantitative yield; e) BH_3·THF, THF, 0 °C to RT, 18 h, then 3M NaOH, 30% H_2O_2, 76% yield; f) PDC, DCM, 0 °C to RT, 3 h, 57% yield.

Figure 3-6 Alternative preparation of ring expansion substrate (166)

Whilst the desired cyclobutanone (**166**) can be prepared *via* this route in larger batches than before, the synthesis is very labour intensive and time consuming, furnishing the desired intermediate (**166**) in 6 steps with a combined yield of only 25%. In comparison, the original and arguably more elegant route outlined in Figure 3-5 provides access to (**166**) in only 3 steps and a combined yield of 83%. Although the present route negates the need to carry out the initial photo-addition in batches, the lower yield and length of the route means that no significant advantage could be gained from employing this alternative approach.

With access to sufficient quantities of the desired cyclobutanones established *via* either of the described routes, we turned our attention to the development of the ring expansion methodology.

3.2.4. Regioselective Tiffeneau-Demjanov ring expansion

The Tiffeneau-Demjanov reaction is a carbocation rearrangement of β-aminoalcohols *via* diazotization, affording carbonyl compounds.[66] A plausible mechanism is outlined in Figure 3-7 and begins with the formation of diazonium compound (**184**)

from substrate (**183**) *via* treatment with dinitrogen trioxide, N_2O_3, formed by the formal condensation of two moles of sodium nitrite. Ring expansion with simultaneous loss of nitrogen then furnishes carbocation (**185**) which, accompanied by the loss of a proton, forms a one-carbon expanded, cyclic ketone (**186**).

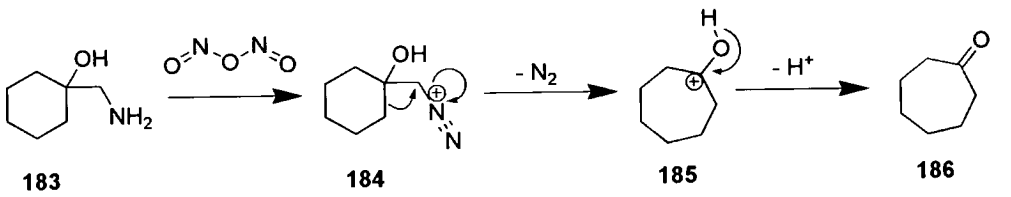


Figure 3-7 Tiffeneau-Demjanov rearrangement mechanism

In our case, a ketone rather than a β-amino alcohol waspresent in the substrate and hence the one-carbon fragment to be incorporated into the ring had to be introduced in a step preceding the rearrangement. This could be achieved by means of a nucleophilic attack of diazomethane onto a carbonyl group as exemplified by cyclohexanone (**187**, Figure 3-8). The thereby formed rearrangement substrate (**188**) then underwent a ring expansion, furnishing the reaction product (**186**). Several examples have been published in which this methodology has also been successfully employed in the expansion of cyclobutanones to cyclpentanones.[67,68]

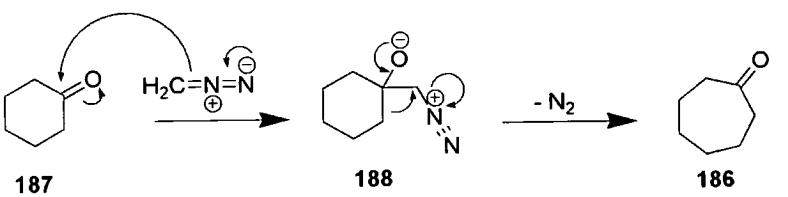


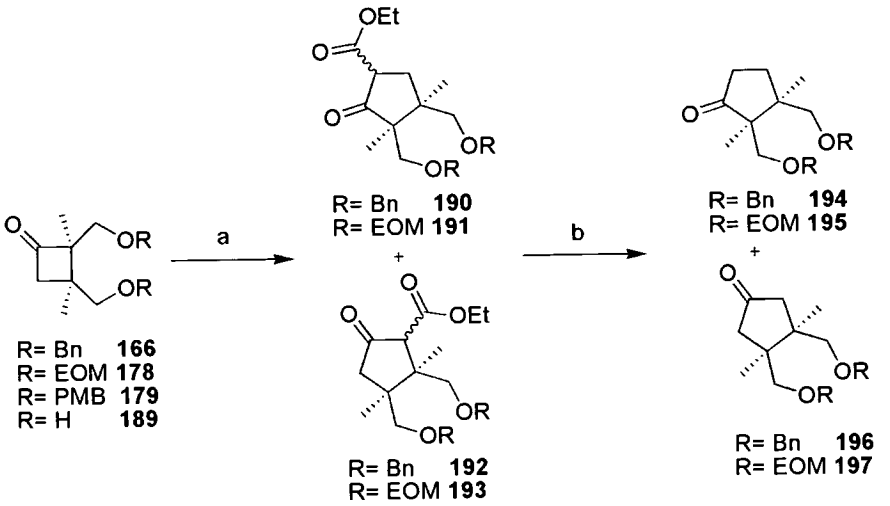
Figure 3-8 Modified Tiffeneau-Demjanov-type ring expansion

In the event of carrying out the ring expansion on our substrate (**166**) we opted to employ ethyl diazoacetate instead of diazomethane for a number of reasons. Firstly, the resulting 1,3-ketoester motif was to be employed at a later stage to allow further functionalisation (*vide infra*). Secondly, ethyl diazoacetate lacks diazomethane's unpleasant traits of explosiveness and difficulty of preparation and finally, literature precedent can be found describing a greater regioselectivity in the rearrangement step to be obtainable with this reagent when compared to diazomethane.[54] Due to the unsymmetrical nature of our substrate, the bond migration indicated in (**188**) can

occur on either side of the eventually formed carbonyl motif, thereby opening up reaction pathways to two regioisomeric products.

Outlined in Figure 3-9 are our attempts at carrying out the Tiffeneau-Demjanov-type ring expansion reaction on our cyclobutanone substrates. The newly formed stereocentre, flanked by the ketone and ester functionality is created without stereocontrol, thus forming diastereomeric mixtures of 1,3-ketoesters, complicating product characterisation. As a result, a subsequent decarboxylation step removes the ethyl ester functionality placed in the α-position, destroying the stereocentre and affording the simpler and much more readily characterised cyclopentanone structures shown.

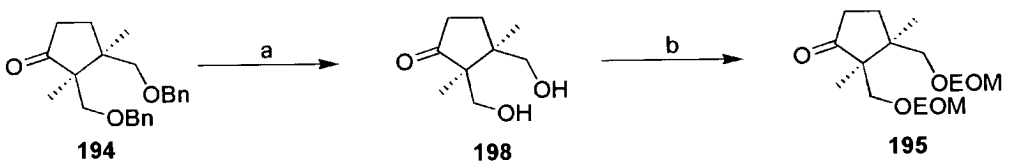
Initial experimentation saw the di-benzyl protected substrate (**166**), activated *via* antimony pentachloride addition, react with ethyl diazoacetate. After *in situ* decarboxylation of the intermediate (**190**), the desired regioisomer (**194**) was obtained exclusively, albeit in low yield. Employing boron trifluoride etherate as the Lewis acid resulted in a significant improvement in yield, furnishing a readily separable 9:1 ratio of the desired regio-isomeric ring expansion product (**194**) over the undesired isomer (**196**) in 75% yield. Next, we subjected the *bis*-EOM protected cyclobutanone (**178**) to these conditions and to our surprise, a complete reversal of regioselectivity was observed, yielding exclusively the undesired regioisomer (**197**) after decarboxylation of the intermediate (**193**). Attempting to carry out the ring expansion reaction on both the free diol (**189**) and the di-PMB protected substrate (**179**) resulted in extensive decomposition of the substrate and in the latter case, this was believed to be at least in part due to the deprotection of the PMB groups under the reaction conditions.[69]



Substrate	Conditions a	Conditions b	Yield	Result
166	Ethyl diazoacetate (2 eq), $SbCl_5$ (0.5 eq), DCM, -78 °C	DME, H_2O, 1M HCl, 90 °C, 24h	25%	**194**
166	Ethyl diazoacetate (5 eq), $BF_3{\cdot}Et_2O$ (5 eq), DCM, 0 °C	$MgCl_2{\cdot}6H_2O$, DMSO, 140 °C, 24h	75%	**194:196** 9:1
178	Ethyl diazoacetate (5 eq), $BF_3{\cdot}Et_2O$ (5 eq), DCM, 0 °C	$MgCl_2{\cdot}6H_2O$, DMSO, 140 °C, 24h	30%	**197**
179	Ethyl diazoacetate (2.5 eq), $BF_3{\cdot}Et_2O$ (5 eq), DCM, 0 °C	$MgCl_2{\cdot}6H_2O$, DMSO, 140 °C, 24h	Decomposition and suspected PMB deprotection	**n/a**
189	Ethyl diazoacetate (5 eq), $BF_3{\cdot}Et_2O$ (5 eq), DCM, 0 °C	n/a	Decomposition	**n/a**

Figure 3-9 Cyclobutanone ring expansion reaction

Although we initially wished to avoid the use of the benzyl protecting group due to its anticipated interference in the envisioned Paternò-Büchi step later on, the *bis*-benzyl protected substrate gave superior results in the ring expansion reaction. The preferred EOM protecting group only yielded the undesired regioisomer, an observation that we speculatively attributed to coordination effects resulting from the increased number of chelating oxygen atoms present in the EOM groups. Nonetheless, we decided to adopt both the benzyl protected cyclopentanone (**194**), accessible directly from the ring expansion step, as well as its EOM protected analogue (**195**) for the further development of our methodology. Due to the unavailability of the EOM protected cyclopentanone as a direct product from the Tiffeneau-Demjanov reaction, it was prepared in two steps from (**194**) *via* deprotection and reprotection, as shown in Figure 3-10. Removal of the benzyl protecting groups was carried out under standard hydrogenolysis conditions, affording diol (**198**) in excellent yield. Re-protection using EOMCl then afforded the desired cyclopentanone (**195**) in good yield.

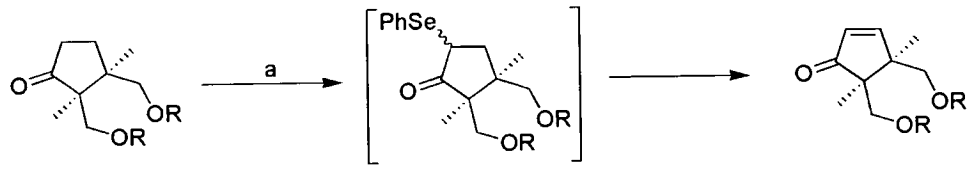


194 **198** **195**

a) $Pd(OH)_2$ (20%wt on C, 8wt% equiv), trace conc HCl, MeOH, H_2, 99%; DIPEA, EOMCl. DCM, 90%.

Figure 3-10 Synthesis of EOM protected cyclopentanone

In order to prepare the required cyclopentenone compounds, a final oxidative introduction of the enone functionality was required. This was achieved as outlined in Figure 3-11, beginning with the selenylation of the alkali metal enolates of (**194**) and (**195**) in the presence of HMPA. The resulting selenide species (**199**) and (**200**) then underwent an oxidative elimination upon treatment with hydrogen peroxide, affording the desired cyclopentenones (**165**) and (**201**) in moderate yields, providing access to the desired novel key intermediates.



R= Bn **194**
R= EOM **195**

R= Bn **199**
R= EOM **200**

R= Bn **165**
R= EOM **201**

a) **194**, KHMDS, PhSeCl, THF/HMPA, -78 °C to RT, then H_2O_2, DCM, 39%;
195, LHMDS, PhSeCl, THF/HMPA, -78 °C to RT, then H_2O_2, DCM, 51%.

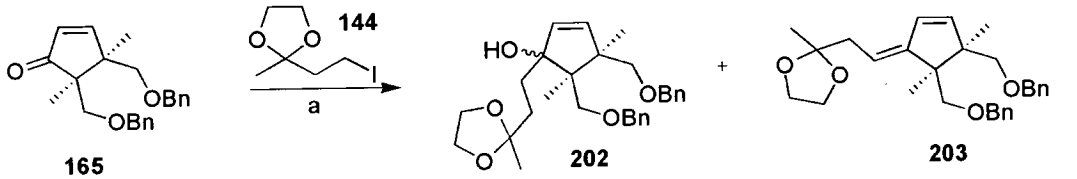
Figure 3-11 Synthesis of cyclopentenone intermediates

Described in this section is the development of our novel synthetic route to the densely functionalised key intermediates, the *bis*-benzyl protected cyclopentenone (**165**) and the *bis*-EOM protected cyclopentenone (**201**). In establishing this route, we have provided access to the central carbocycle B of Merrilactone A, featuring the required functionalisation for further elaboration towards the natural product. The carbonyl moiety represents the functional handle for the installation of a side-arm *via* organometallic addition and the olefin present is required for the eventual Paternò-Büchi photocyclisation. Furthermore, in line with our aim of introducing the right hand side of the molecule at an early stage, we have established the C_5 and C_6 quaternary centres, featuring the required *cis*-relation between the angular methyl substituents. The protected diol moiety represents the appropriately substituted carbon skeleton from which the γ-lactone ring C will be constructed at an advanced stage in the total synthesis *via* deprotection and subsequent regioselective oxidative lactonisation. The feasibility of such a transformation has been demonstrated in Inoue and Hirama's total synthesis of Merrilactone A where the γ-lactone ring C is constructed from the corresponding diol *via* a regio- and chemo-selective Fetizon oxidation.[22]

With the crucial cyclopentenone intermediates in hand, we set about attempting to apply the previously developed methodology of organometallic side-chain addition to these substrates.

3.3. Dioxolane Side-chain Addition

Employing the more readily accessible *bis*-benzyl protected cyclopentenone (**165**), we initially investigated the addition of the iodo-dioxolane side-chain (**144**) to our substrate, before intending to move on to the C_2-hydroxyl moiety containing side-chain (**115**, Figure 1-29). In direct analogy with the previously employed conditions for the introduction of the dioxolane side-chain (cf Figure 2-10), we treated the iodo-acetal (**144**) with *tert*-butyl lithium, prompting an iodide-lithium exchange. The resulting organometallic species then underwent a nucleophilic 1,2-addition onto cyclopentenone (**165,** Figure 3-12).



a) **144**, ^{t}BuLi, Et_2O, -78 °C to RT to -78 °C, then **165**, Et_2O, -78 °C to RT, 43% **202**, 37% **203**.

Figure 3-12 Dioxolane side-chain addition

Although the reaction furnished the desired adduct (**202**) as a single diastereomer in 43% yield, we also observed the formation of diene (**203**) in 37% yield, in which the tertiary alcohol formed in the addition reaction had eliminated. This caused major concern as the adducts arising from previous addition reactions of dioxolane side-chain (**144**) to the simpler cyclopentenone (**142**), shown in Figure 2-10, had not shown such a propensity towards elimination. Compared to the simpler addition product (**145**, Figure 2-10), the higher substituent density around the cyclopentenone ring in (**165**) appears to render the tertiary alcohol in the addition product (**202**) more prone to elimination.

Two plausible reaction pathways explaining the observed outcome can be postulated. The addition reaction could be highly stereoselective for the detected single diastereomer (**202**); however, this product is prone to elimination and is partially converted to diene (**203**) under the reaction and workup conditions, thus giving rise to the observed product distribution. Alternatively, a much lower degree of stereoselectivity is in operation, forming both possible tertiary alcohol

diastereomers of (**202**). The eventually isolated diastereomer would possess more resistance towards elimination compared to the necessarily less stable diastereomer, all of which would be converted into diene (**203**) *in situ*. From the experimentation carried out, no conclusive evidence favouring either pathway could be obtained. Furthermore, we were disappointed to find that even using a combination of 2D-NMR spectroscopy techniques such as COSY, HSQC and NOESY experiments, the relative stereochemistry at the newly created chiral centre in (**202**) could not be established with any confidence.

The addition reaction described above was consequently repeated using Grignard derivatives of dioxolane (**144**) in order to establish whether the use of an alternative organometallic species would result in an altered product distribution. However, obtaining the addition product (**202**) in 41% as a single diastereomer as well as the diene (**203**), in 16% yield offered no resolution to the encountered elimination issue, nor did it provided any further insight into the possible reaction pathways.

Turning our attention to the isolated addition product (**202**), we soon discovered an inherent instability of the tertiary alcohol prevailing in this compound also. Initial attempts to unmask the Paternò-Büchi photo-substrate *via* deprotection of the acetal group under both acidic and neutral conditions, employing iodine in acetone, resulted in elimination of the tertiary alcohol, affording moderate yields of diene (**203**) in each case.[70] Attempting to protect the labile tertiary alcohol with EOMCl and Hünig's base resulted in near quantitative formation of diene (**203**).

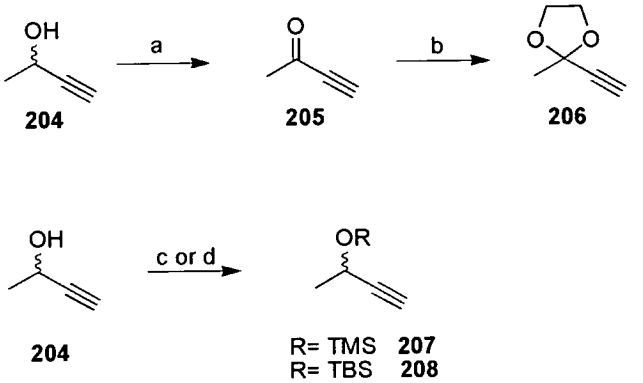
The encountered susceptibility towards elimination of the tertiary alcohol formed in the addition reaction with the dioxolane side-chain clearly presented a major setback to our plans to implement the previously developed methodology to our novel, highly substituted cyclopentenone substrate. The diene (**203**) formed in the addition reaction itself, as well as in a number of attempted functionalisation reactions of (**202**), could not be shown to have any synthetic use within our approach. We realised that in order to proceed with a side-chain addition reaction, as envisioned in our retrosynthesis, a structurally different organometallic nucleophile would have to be employed.

3.4. Propargylic Alcohol Side-chain Addition

In searching for a new side-chain to be employed in the 1,2-organometallic addition reaction, several structural features were identified as key requirements. As well as incorporating the carbonyl functionality required for the Paternò-Büchi reaction, the new reagent needed to be readily converted into an organometallic species. Furthermore, the C_2-hydroxyl moiety, or functionality allowing the installation thereof, needed to be present. Finally, an inherent inability or resistance towards the previously encountered elimination reactions was obviously essential.

It appeared that all the properties were evident in propargylic alcohol or propyn-one type structures; an alkyne motif, rendering elimination unfeasible as well as providing the functional handle for C_2-hydroxylation, acidity of the terminal alkyne proton suitable for lithiation, and availability of a carbonyl moiety by either deprotection or oxidation.

We therefore set about preparing several possible side-chains in order to probe their suitability for our purposes. Using 3-butyn-2-ol (**204**) as a common, commercially available starting material, we first envisioned the preparation of the dioxolane analogue (**206**). Jones oxidation of the propargylic alcohol gave rise to alkynone (**205**)[71] which was taken on without purification into an acetal protection step.[72] Although the resulting dioxolane side-chain (**206**) could be detected in the reaction mixture *via* ^{1}H NMR spectroscopy, only trace amounts could be isolated due to the product's very high volatility (Figure 3-13). Directly protecting the hydroxyl moiety in 3-butyn-2-ol as either the trimethylsilyl[73] or *tert*-butyldimethylsilyl[74] ether afforded compounds (**207**) and (**208**) in 87% and 83% yield respectively. Due to their non-volatile nature, the isolation and purification of these compounds was much more straightforward.



a) CrO_3, H_2SO_4/H_2O, 0 °C, 4 h; b) ethylene glycol, TsOH, $MgSO_4$, RT, 18 h, trace yields; c) HMDS, 110 °C, 18 h, 87%; d) TBSCl, imidazole, DCM, RT, 18 h, 83%.

Figure 3-13 Synthesis of propargylic side-chains

With the new side-chains in hand, we set about exploring the 1,2-addition reactions of their lithiated analogues which we hoped would give access to the synthetic route outlined in Figure 3-14.

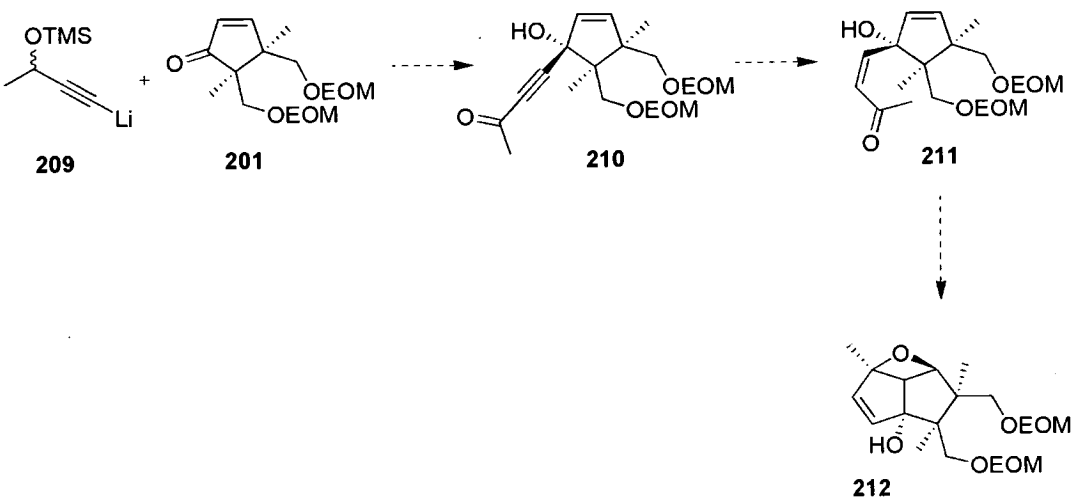


Figure 3-14 Envisioned synthetic sequence employing propargylic side-chains

The tertiary alcohol in (**210**), resulting from the organometallic addition of a lithiated side-chain (**209**) on cyclopentenone (**201**), should display resistance towards elimination. The side-chain's alkyne moiety would form the substrate for a subsequent partial hydrogenation, affording the *cis*-alkene containing Paternò-Büchi substrate (**211**). It was hoped that the sp^2-alkene geometry would provide adequate flexibility in the side-arm to allow positioning of its carbonyl functionality in

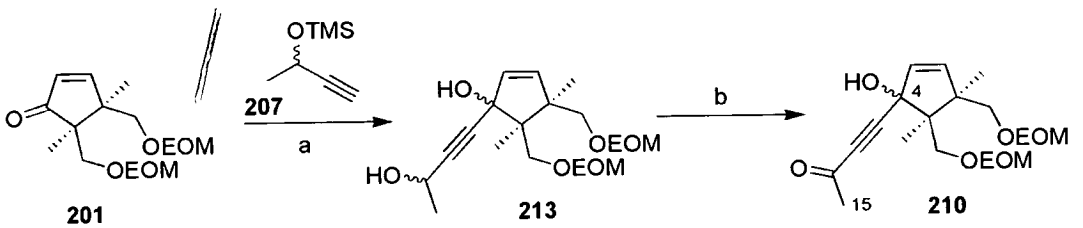
sufficient proximity to the cyclopentene ring's olefin in order to allow the [2+2] cyclo-addition to proceed, furnishing tricycle (**212**). The remaining olefin functionality would then be amenable to functionalisation of the C_2 position.

3.4.1. Propargylic alcohol additions on substrate

In implementing the addition of the new side-chain, we were keen to move away from the *bis*-benzyl protected cyclopentenone (**165**) for a couple of reasons. Firstly, the previously observed inhibition of the Paternò-Büchi photo-cyclisation and secondly, an anticipated improved stereocontrol in the side-chain addition step in the case of the *di*-EOM protected substrate (**201**). As we require the nucleophilic attack to occur on the same face as the protected diol, it was anticipated that the increased density of coordinating oxygen atoms in the EOM protecting groups would provide a chelation effect, directing the incoming organometallic species. A number of literature examples support our proposed chelation controlled addition and furthermore, even raise the possibility of eventually performing the addition reactions with the free diol moiety, avoiding the use of protecting groups altogether.[75,76]

We initially investigated the addition of the TMS-protected propargyl alcohol side-chain (**207**), as outlined in Figure 3-15. Deprotonation of terminal alkyne (**207**) using *n*-butyl lithium and following addition of cyclopentenone (**201**) affords the tertiary alcohol (**213**) in good yield after TMS deprotection during acidic workup. The side-chain (**207**) was prepared from racemic propargylic alcohol (**204**), resulting in a 1:1 mixture of diastereomers with respect to the secondary alcohol in (**213**). In order to establish the stereoselectivity of the addition step, the side-arm's chiral centre was destroyed in the subsequent manganese dioxide mediated oxidation, furnishing alkynone (**210**) in high yield. At this stage, the ratio of diastereomers formed in the addition reaction could readily be established as 8:1, based on the integration of two singlets at δ_{major} 2.32 ppm and δ_{minor} 2.35 ppm, arising from the CH_3 protons at C_{15}, the methyl group adjacent to the carbonyl functionality. However, the stereochemistry at C_4, the newly formed chiral centre, could not be

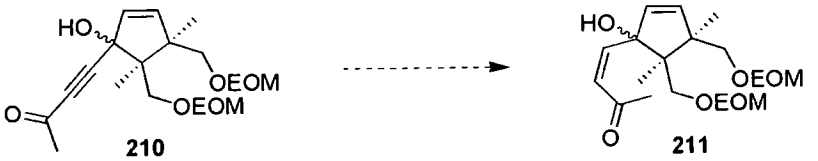
determined at this stage as the NOESY ^{1}H NMR spectrum proved non-conclusive. Whilst derivatisation with, for example *p*-bromobenzoyl chloride was a possibility in order to obtain a crystal structure, the scarcity of the material available led us to employ the material for methodology development in the hope that the relative stereochemistry could be readily elucidated after one of the subsequent steps.



a) **207**, ^{n}BuLi, THF, -78 °C, 1 h, then **201**, THF, -78 °C, 2 h, then 1 M HCl, RT, 30 min, 79%, 8:1 ratio of diastereomers; b) MnO_2, DCM, RT, 45 min, 74%, 8:1 ratio of diastereomers.

Figure 3-15 Addition of TMS-protected propargylic alcohol side-chain

Although at this stage it was unknown to us what the stereochemistry of (**210**) was, we nonetheless moved on to attempt the partial hydrogenations of the pendant alkyne, required in order to transform (**210**) into a Paternò-Büchi substrate. Figure 3-16 outlines the attempts carried out to partially hydrogenate the alkyne to the corresponding *Z*-alkene, using Lindlar's catalyst (palladium deposited on calcium carbonate, poisoned with lead acetate).[77]



Conditions	Results
2% w/w Lindlar's catalyst, H_2, trace quinoline, hexane, RT, 2 h	No reaction, full recovery of SM
10% w/w Lindlar's catalyst, H_2, THF, RT, 36 h	70% recovery of SM + decomposition
25% w/w Lindlar's catalyst, H_2, THF, RT, 4 h	decomposition

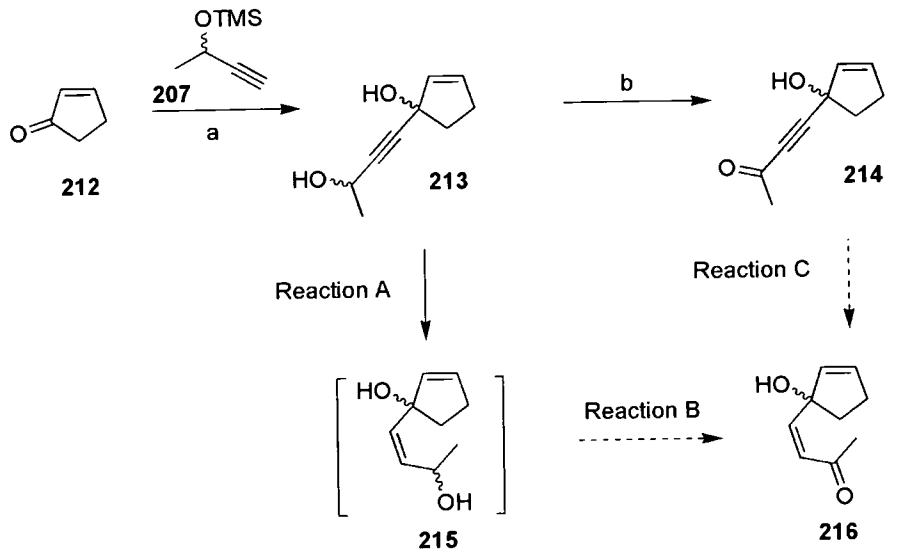
Figure 3-16 Lindlar hydrogenations on free tertiary alcohol

When alkyne (**210**) was exposed to low catalyst loadings in the presence of an additional catalyst poison, quinoline, and placed under a hydrogen atmosphere, no formation of product (**211**) could be detected and quantitative recovery of starting materials was made. Upon increasing the catalyst loading and removing any additional catalyst poisoning, we observed slow decomposition of the substrate into complex mixtures. An additional increase in catalyst loading eventually led to complete decomposition of starting materials with no detectable product formation.

Due to the advanced nature of the reaction substrate (**210**) we at this stage decided to employ a simple model system in order to establish a solution to the unexpectedly problematic partial reduction of the alkynone. Once a suitable methodology had been developed on a model system, we would return to our actual substrate (**210**) in order to elaborate the intermediate further towards the natural product.

3.4.2. Model system for propargyl alcohol side-chain

In order to develop the required methodology for the preparation of a Paternò-Büchi substrate containing the *cis*-enone side chain as depicted in Figure 3-14, we chose the simple cyclopentenone (**212**) as our model system. The initial addition of the TMS-protected propargylic side-chain (**207**) with subsequent silyl deprotection furnished the tertiary alcohol (**213**) in moderate yield. From this point, we attempted two reaction pathways in order to prepare the desired *cis*-enone containing substrate (**216**). The partial hydrogenation reactions were attempted on both the diol (**213**), formed in the addition reaction, as well as on the alkynone (**214**), derived from diol (**213**) *via* manganese dioxide oxidation (Figure 3-17).



a) **207**, ^{n}BuLi, -42 °C, THF, then **212**, THF, -42 °C, 2h, then 1 M HCl, 30 min, 38 %;
b) MnO_2, DCM, RT, 1.5 h, 52%.

Reaction	Conditions	Result
A	10 % Lindlar, H_2, MeOH	Over-reduction and product
A	10 % Pd($BaSO_4$), H_2, MeOH	Over-reduction and product
A	10 % Lindlar, H_2, MeOH, trace pyridine	Over-reduction and product
A	10 % Lindlar, H_2, EtOAc, trace pyridine	Over-reduction and product
A	10 % Pd($BaSO_4$), H_2, pyridine	SM only
B	MnO_2, DCM	Decomposition
B	PCC, DCM	Decomposition
C	10 % Lindlar, H_2, THF	Decomposition
C	10 % Pd($BaSO_4$), H_2, THF	Decomposition

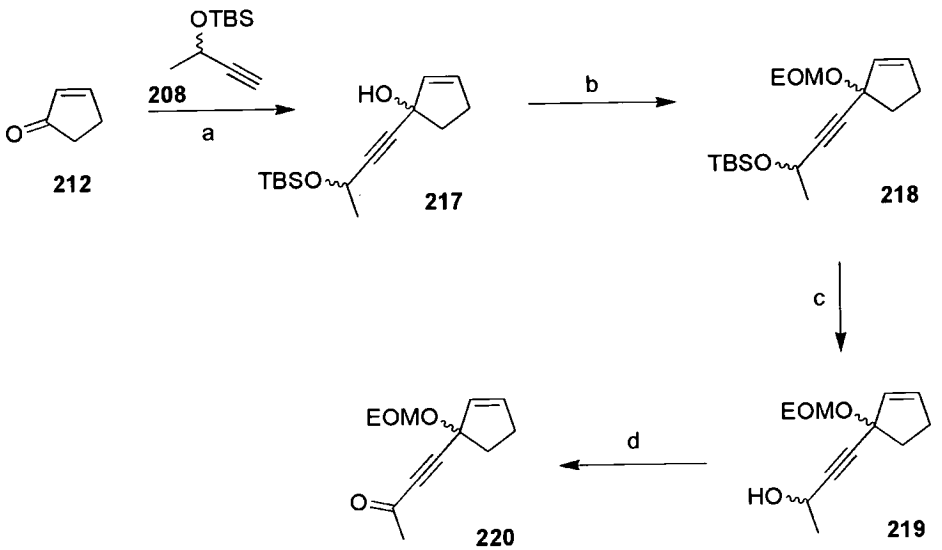
Figure 3-17 Partial Hydrogenation attempts on free tertiary alcohol model

Our attempts initially concentrated on the partial reduction of diol (**213**) and a number of conditions were employed, labelled *Reaction A* (Figure 3-17). Using Lindlar's catalyst as well as palladium barium sulfate, an alternative catalyst for partial reductions, we obtained inseparable mixtures, assigned tentatively by ^{1}H-NMR to contain the desired (**215**) as well as a compound in which the side-chain had been completely reduced to the alkane whilst leaving the cyclic olefin intact. Upon further poisoning of the catalysts by addition of trace amounts of pyridine, mixtures of the same composition were obtained. Carrying out the reactions in neat pyridine however did not lead to any consumption of starting material. Characterisation of (**215**) was not feasible due to the inseparable nature of the mixtures obtained and we attempted to carry out the required oxidation step, anticipated to form *cis*-enone (**216**). However, exposing the mixtures to either MnO_2 or PCC resulted in rapid consumption of the substrates, affording only complex mixtures. Moving on to attempt the partial reduction on the alkynone (**214**) we quickly discovered that the hydrogenation of this compound was also problematic, as outlined by the reactions labelled *Reaction C* (Figure 3-17). Placing (**214**) under a hydrogen atmosphere in the presence of either Lindlar's catalyst of palladium barium sulfate resulted in rapid consumption of the substrate furnishing complex mixtures from which no desired product could be isolated.

We suspected that the tertiary alcohol moiety present could be having an adverse effect, potentially allowing intramolecular cyclisation reactions upon revealing of the *cis*-enone functionality. In order to establish whether the hydroxyl moiety was indeed playing a detrimental part in the decomposition reactions, we set about synthesising analogous model compounds in which the tertiary alcohol would be protected.

Consequently, in order to allow a selective protection of the tertiary alcohol over the secondary alcohol present on the side-chain, we required the introduction of a side-arm containing a protecting group which would not be lost during the workup procedure. The TBS-protected propargylic alcohol (**208**) would stay intact under the conditions employed in the addition step and was therefore chosen. Outlined in Figure 3-18 is the synthesis of alcohol (**219**) and alkynone (**220**), the substrates on

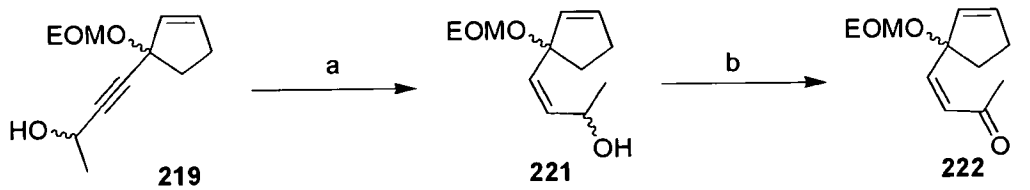
which the partial hydrogenation methodology was to be developed. Addition of lithiated TBS-protected 3-butyn-2-ol (**208**) to cyclopentenone (**212**) afforded tertiary alcohol (**217**) which was readily protected using EOMCl, affording (**218**). Next, the TBS-group was removed using TBAF affording the free alcohol (**219**) which was readily oxidised to afford alkynone (**220**) in good yield.



a) **208**, ^{n}BuLi, -42 °C, THF, then **212**, THF, -42 °C, 2h, 59%; b) EOMCl, DMAP, DIPEA, DCM, 40 °C, 18h, 88%; c) TBAF, THF, 1.5 h, 95%; d) MnO_2, DCM, RT, 1 h, 52%.

Figure 3-18 Synthesis of protected tertiary alcohol model

We first investigated the partial hydrogenation of the secondary alcohol (**219**) and the employed conditions are outlined in Figure 3-19.



219 221 222

Reaction	Conditions	Result
a	20 % Lindlar's catalyst, H_2, THF	Over-reduction
a	15 % Pd($BaSO_4$), H_2, THF, pyridine	Over-reduction
a	10 % Lindlar's catalyst, H_2, THF, pyridine	Complex mixture
a	10 % Lindlar's catalyst, H_2, EtOAc, 1-octene	55 % **221**
a	10 % Lindlar's catalyst, H_2, EtOAc, 1-octene, pyridine	57 % **221**
b	MnO_2, DCM	Decomposition
b	PCC, DCM	Decomposition
b	$(COCl)_2$, DMSO, NEt_3, DCM	11 % **222**

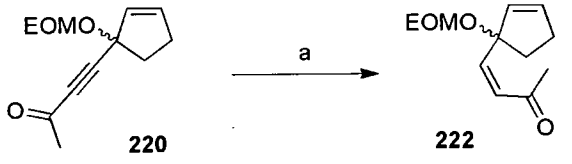
Figure 3-19 Partial hydrogenation of free alcohol on protected model system

Initial attempts at the partial hydrogenation of the alkyne were met with over-reduction, furnishing a fully saturated side-chain. Adding additional catalyst poison in the form of pyridine did not result in the desired moderation in catalyst reactivity, rendering it still too active to allow the isolation of the desired intermediary *cis*-olefin. A solution to this problem was eventually found when we employed a "sacrificial" olefin, 1-octene. In adding the terminal olefin, a hydrogenation substrate of higher susceptibility towards reduction than the desired reaction product, the internal alkene (**221**), is introduced. Thus, once the alkyne has been reduced to the *cis*-enone, the most reactive substrate for the catalyst to turn over is the sacrificial olefin. The presence of 1-octene thus provides a time window in which the alkyne reduction occurs without subsequent over-reduction to the alkane, allowing the isolation of the desired product (**221**) with careful monitoring of the reaction

progress. A further small increase in yield could be detected if a trace amount of pyridine is added to the reaction mixture, further moderating the catalyst activity.

With suitable conditions for the partial alkyne hydrogenation in hand, we turned our attention to the required oxidation of the secondary alcohol. The use of either manganese dioxide or PCC proved unsuitable, resulting in the formation of complex mixtures from which no desired product (**222**) could be isolated. It was however possible to convert alcohol (**221**) into enone substrate (**222**) *via* Swern oxidation, albeit in a very poor yield of 11%.

Hoping to develop a higher yielding route to *cis*-enone (**222**) we examined the partial hydrogenation of alkynone (**220**) in the presence of the sacrificial alkene. Pleasingly, the partial reduction proceeded smoothly, affording (**222**) in good yield, as outlined in Figure 3-20.



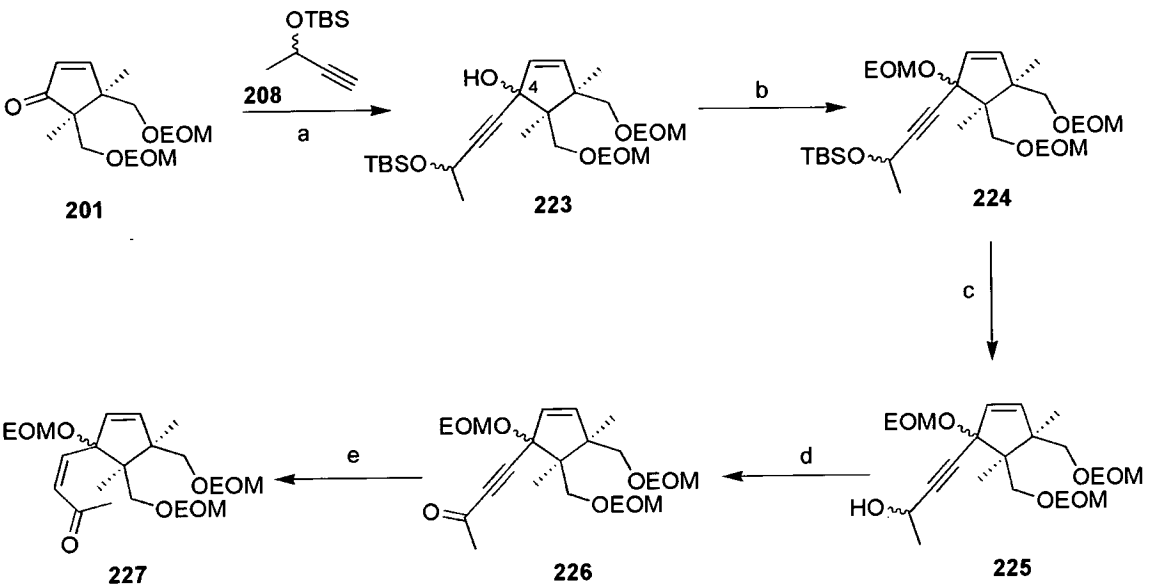
a) 10 % Lindlar's catalyst, H_2, EtOAc, pyridine, 1-octene, 63 %.

Figure 3-20 Partial hydrogenation of alkynone on protected model system

In using the cyclopentenone model system, we have developed the required methodology in order to achieve the partial hydrogenation of the alkyne bearing side-arm, furnishing the desired *cis*-enone motif. Subsequently, we set about applying the developed procedures to our advanced intermediate (**201**).

3.4.3. Propargylic side-chain addition on substrate revisited

With the methodology in hand to overcome our earlier problems in reducing the alkyne side-chain, we returned to our actual substrate to employ this new reaction sequence. When we applied the methodology, we were very pleased to find that it readily transferred onto the more complex substrate, even affording higher yields than those observed in the model system.



a) **208**, ^{n}BuLi, THF, -78 °C, 1 h, then **201**, THF, -78 °C to RT, 2 h, 80 %; b) EOMCl, DIPEA, DMAP, DCM, 40 °C, 18 h, 96%; c) TBAF, THF, RT, 1 h; d) MnO_2, DCM, RT, 1 h, 93% over 2 steps; e) 20 % Lindlar's catalyst, 1-octene, EtOAc, H_2, RT, 100 min, 92%.

Figure 3-21 Synthesis of Paternò-Büchi substrate featuring enone side-chain

In the event of treating the *bis*-EOM protected cyclopentenone (**201**) with lithiated (**208**), the tertiary alcohol (**223**) was formed in 80% yield and seemingly as a single diastereomer, established by both ^{1}H- and ^{13}C-NMR spectroscopy. This is surprising as even if the 1,2-addition proceeded highly stereoselectively, affording practically a single diastereomer with respect to C_4, the protected secondary alcohol on the side-arm originated from a racemic mixture of 3-butyn-2-ol and should in effect provide a 1:1 mixture of diastereomers of (**223**). Throughout the synthetic sequence outlined here, only a single diastereomer was observed right up to the product (**227**). Once again, the stereochemistry at C_4 could not be established at this stage.

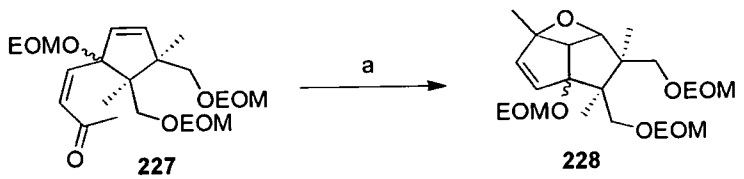
Subsequent protection of the resulting alcohol using EOMCl proceeded in high yield and the successive TBS-deprotection and oxidation to furnish alkynone (**226**) occurred as anticipated and in high yields, showing significant improvements over the yields achieved in the corresponding model system reactions. With the substrate for the partial hydrogenation in hand, we applied the previously developed methodology to the advanced intermediate (**226**) and to our delight, the desired *cis*-enone compound (**227**) was formed in 92% yield. Attempting to elucidate the

absolute configuration at C_4 at this stage unfortunately proved once again non-conclusive with no positive NOESY cross peaks allowing the assignment with any confidence.

Nonetheless, in developing the methodology outlined in this section, we had gained access to the advanced intermediate (**227**), which featured all the functionalisation required to advance the substrate to the natural product. This set the scene for the pivotal [2+2] Paternò-Büchi photocyclisation, anticipated to furnish the highly advanced core of Merrilactone A. Although the actual stereochemical configuration of the *cis*-enone (**227**) was unknown at this stage, we decided to use the material available to attempt to show the feasibility of the key photo reaction. We anticipated that, once the proof of concept had been made with a successful Paternò-Büchi reaction, we would elucidate the stereochemistry and, if necessary, investigate achieving the required selectivity of the organometallic 1,2-addition of (**208**) to (**201**), in which the crucial stereocentre at C_4 is set.

3.5. Paternò-Büchi Attempts and Side-chain Modifications

With photo-substrate (**227**) in hand, we investigated the pivotal [2+2] Paternò-Büchi photocyclisation, anticipated to form the tricyclic core of Merrilactone A (**228**). Outlined in Figure 3-22 are the conditions employed in the attempted photocyclisation of (**227**).



a) hν, solvent, pyrex filter, H_2O cooling

Solvent	Result
MeCN/Acetone 9:1	SM + Decomposition
Acetone	SM + Decomposition
Hexane	SM + Isomerisation
Toluene	SM + Isomerisation

Figure 3-22 Attempted Paternò-Büchi reaction of *cis*-enone substrate

Initial attempts were carried out in a 9:1 mixture of acetonitrile and acetone as well as neat acetone. After degassing the solutions of (**227**) with a stream of nitrogen gas, they were irradiated under water cooling with a 400 W medium pressure mercury arc lamp through a Pyrex filter. The progress of the reactions was monitored at regular intervals by TLC analysis but disappointingly, we could only observe the slow decomposition of the starting materials with no detectable product formation. Moving away from polar solvents, we employed hexane and toluene solutions of (**227**) in the photo reaction; however, no formation of the desired cyclisation product (**228**) was observed. The reactions were however much cleaner, suffering from less decomposition, readily allowing substrate recovery. When recovering the starting material, determined to be a single spot by TLC analysis, we observed the appearance of two new doublets in the olefin region of the ^{1}H-NMR spectrum. Although very weak, the new peaks were sufficiently separated from the signals arising from the *cis*-enone substrate to record their chemical shift and coupling constants. Appearing at δ 6.85 and 6.09 ppm with coupling constants of J= 16.0 Hz, we speculatively attributed these peaks to the enone-olefin protons of the *trans*-enone isomer of (**227**), potentially formed *via* photochemical isomerisation under the irradiation conditions. The enone-olefin peaks arising from the original photo-

substrate, the *cis*-enone (**227**) can be found at δ 5.96 and 6.71 ppm with coupling constants of J= 13.1 Hz. As only trace amounts of the compound responsible for the newly arisen peaks appeared to be formed even upon prolonged irradiation, no pure sample of this entity could be isolated for characterisation and thus our attribution of these peaks to the *trans*-enone isomer has to be a speculative one.

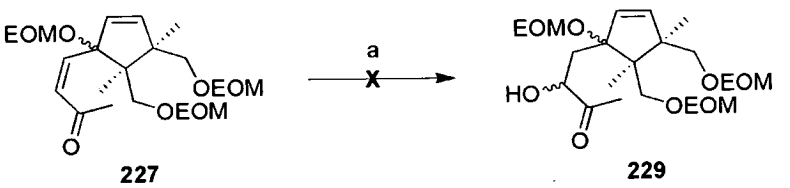
We had to conclude at this stage that the anticipated Paternò-Büchi reaction of substrate (**227**) was not feasible. It can be argued that the lack of reactivity observed could originate in geometrical constraints inherent within our substrate structure. In order for the cycloaddition to proceed, sufficient orbital overlap between the olefin and the electronically excited carbonyl motif has to occur. We have demonstrated previously that a side-arm containing two adjacent sp^3 carbon centres certainly displays enough flexibility in order to allow such spatial positioning of the carbonyl group in proximity to the olefin. In the current case however, the connecting side-arm features two adjacent sp^2 carbon atoms and the somewhat diminished flexibility of such a structural feature could thus prohibit the necessary alignment of functionalities to occur, hence preventing the desired reaction.

Moreover, a comparison of the electronic environments within our current substrate with the previous, successful photoaddition substrates brings to light a reversal of the electron densities of the reaction partners involved. The photosubstrates which in our hands have successfully undergone the desired Paternò-Büchi reaction featured the electronic excitation of an isolated carbonyl moiety which subsequently cyclises with the electron-deficient olefin part of a cyclic enone. In the case of our current substrate (**227**), the electronic excitation is required to occur on the carbonyl part of a conjugated, electron rich enone system in order to facilitate cyclisation with an isolated olefin. Although Paternò-Büchi reactions of substrates displaying the electronic nature present in our current case are known in the literature[78,79] such examples are quite rare, potentially suggesting an inherent lack of reactivity in cases of such particular electronic combinations of cyclisation partners.

In attempting to explain the lack of reactivity of our substrate (**227**) towards Paternò-Büchi cyclisation, both the electronic as well as the geometric arguments put

forth above seem to carry some weight. A detailed investigation of the governing factors resulting in the observed lack of reactivity however appears beyond the scope of this project.

We believed a possible solution could reside in the removal of the olefin component of the side-arm's enone functionality, addressing both the geometrical and electronic factors suspected to prevent the photo-cyclisation. Moving forward the transformation of the pendant alkene into the C_2-hydroxyl motif, initially envisioned to take place after the photo-addition, could possibly circumvent our problems. Surveying the literature, we found a rather limited number of examples of conversions of enone motifs into α-hydroxy ketone systems. Reported within these is the use of a Mn(III) catalyst in combination with phenylsilane and oxygen, forming α-hydroxy ketones from α,β-unsaturated ketones on a variety of substrates.[80,81] In applying this methodology to our substrate, we were hoping to transform (**227**) into (**229**), as outlined in Figure 3-23. Whilst we did not anticipate the hydroxyl functionality to be introduced with any stereocontrol, the product (**229**) would nonetheless provide us with an alternative substrate for the pivotal photoaddition step.



227 **229**

a) 3 % $Mn(dpm)_2$, $PhSiH_3$, O_2, 2-propanol, $P(OEt)_3$, 0 °C, 2h, then RT, 20 h.

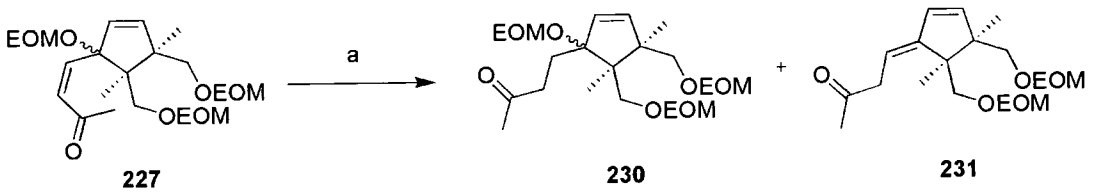
Figure 3-23 Attempted formation of α-hydroxy ketone photo-substrate

Upon treating enone (**227**) with the manganese (III) catalyst in the presence of phenylsilane and under an oxygen atmosphere, followed by reductive $P(OEt)_3$ workup resulted only in a complex mixture from which no desired product could be isolated.

Finally, in a last effort to at least demonstrate the feasibility of the key Paternò-Büchi reaction, we decided to remove the side-arm's unsaturation of substrate (**227**) altogether. In completely reducing the side-chain, we hoped to obtain

a substrate on which to demonstrate the feasibility of the photocyclisation of a substrate with the C_5 and C_6 quaternary centres in place. Before reducing the side-chain, we were aware of the possibility of forming a substrate prone to elimination in analogy with the previously observed eliminations. However, we hoped that the capping of the labile alcohol functionality, in our case as the EOM protected alcohol, would moderate such a tendency.

Our initial attempts at carrying out a conjugate reduction using the copper hydride cluster $[(Ph_3P)CuH]_6$, commonly known as Stryker's reagent, proved unfruitful, leading only to recovery of starting materials.[82] Changing the reductant to sodium dithionite[83] under basic, aqueous conditions did however lead to the consumption of the starting materials, as outlined in Figure 3-24.



227 **230** **231**

a) $Na_2S_2O_4$, $NaHCO_3$, H_2O, dioxane, 0 % **230**, 31 % **231**.

Figure 3-24 Enone side-chain reduction

We were highly disappointed to discover that although the conjugate reduction was feasible; the resulting (**230**) proved highly prone to elimination and was converted entirely into the corresponding elimination product, the diene (**231**), the only identifiable reaction product.

This result was clearly a major setback, effectively rendering our synthetic approach dependable on a key reaction whose feasibility could not be demonstrated. It had become clear at this stage that a major reconfiguration would be required in order to advance our synthetic route to allow the synthesis of the natural product and as a consequence, the Paternò-Büchi approach discussed in this chapter had to be abandoned.

3.6. Conclusions

Our primary goal in embarking on the [2+2] and Paternò-Büchi approach was the development of a total synthesis of Merrilactone A, featuring an early stage introduction of the natural product's right hand side. Following our retrosynthetic analysis, we established the cyclopentenone (**201**) as a crucial intermediate in such a novel approach. Featuring the two methyl substituents at the quaternary centres at C_5 and C_6 in the correct stereochemical *cis*-relation as well as *bis*-methylhydroxy substituents, which represents the carbon skeleton for the eventual formation of the γ-lactone ring C. Developing a synthetic route to the key intermediate (**201**) was thus our first challenge and early attempts at initiating our route using a thermal [2+2] photo-cyclisation proved troublesome. Switching to a photochemical transformation however allowed the high yielding, stereospecific formation of the C_5 and C_6 assembly at the very outset of our route in a single step. With the two important quaternary centres set, the elaboration of the photo-adduct into several cyclobutanone substrates for a regioselective Tiffeneau-Demjanov ring expansion was straightforward. The ring expansion reaction's regioselectivity proved highly dependant on the employed diol protection groups with the *bis*-benzyl protected substrate (**166**) affording the desired regiochemical outcome compared to the *bis*-EOM protected substrate which, surprisingly, afforded a complete reversal of regioselectivity. Further elaboration of the obtained cyclopentanones was straightforward, providing us with a robust route to the desired key intermediates, the cyclopentenones (**165**) and (**201**). In developing this route, we had thus achieved one of our goals of establishing a synthetic route to an advanced intermediate in which the early stage introduction of the right hand side of the molecule had been addressed.

With a route to such key substrates in hand, we set out to explore the application of methodology previously developed within the group, the organometallic 1,2-addition of a dioxolane side-chain. Whilst the reaction proceeded in high conversion, we were disappointed to find that the resulting tertiary alcohol species was highly unstable with respect to elimination, degrading readily into diene (**203**) which has no obvious synthetic use in our approach. Modifying our method to

allow the addition of a side-arm with a diminished propensity towards elimination, we introduced a protected propargylic alcohol chain, circumventing the previously observed problems. Further elaboration of the addition product *via* a partial hydrogenation afforded *cis*-enone (**227**), thus providing us with the desired Paternò-Büchi substrate which, upon UV irradiation, we anticipated to form the highly advanced tricyclic core of Merrilactone A (**228**). Disappointingly, the cyclo-addition reaction could not be shown to be feasible on this substrate and in attempts at modifying it, we detected a susceptibility towards elimination upon complete reduction of the side-chain, in analogy with the problems observed previously.

It was at this stage that the decision to abandon the Paternò-Büchi approach was made. It was becoming clear that in our hands, the required key [2+2] photo-cyclisation could not be achieved and hence a radically different approach towards the formation of the natural product would have to be implemented. Moving away from attempting to employ the Paternò-Büchi reaction as our key reaction would eventually require us to shift our attention towards the well established method of introducing the oxetane moiety *via* a *homo*-Payne type rearrangement reaction. The subsequent chapter shall be concerned with the development of a novel synthetic strategy, employing a different approach towards the formation of Merrilactone A's carbon skeleton.

4. The Radical Epoxide Opening Approach

The realisation that the Paternò-Büchi reaction would not present a viable route towards the total synthesis of Merrilactone A allowed us to investigate an alternative key transformation, which we believed could be employed in the synthesis of the natural product. We anticipated that a transition metal mediated radical epoxide opening with subsequent cyclisation could be employed in the formation of the carbocycle A. This would eventually provide us with a route towards a highly advanced intermediate, which has been shown in the literature to be readily converted into Merrilactone A *via* a *homo*-Payne type rearrangement. Such an approach would be based in part on the methodology developed previously, as outlined in Chapter 3, employing the product of the regioselective Tiffeneau-Demjanov ring expansion product as a substrate. The use of such an advanced intermediate would thus allow us a very quick entry into our novel approach.

Described within this chapter is our development of such a novel approach in which we have built upon the previously developed methodology in order to explore the radical epoxide opening methodology as a suitable key transformation in our natural product synthesis. The retrosynthetic analysis we conducted for the radical cyclisation approach is outlined below.

4.1. Retrosynthesis

Relying on the previously employed three-step transformation of (**232**) into Merrilactone A (**1**) *via* olefin isomerisation, stereoselective epoxidation and subsequent *homo*-Payne rearrangement, our synthesis was to focus on the preparation of the highly advanced intermediate (**232**).[3] The substrate for this three-step sequence would be available from bicycle (**233**) by means of a global benzyl deprotection and successive double Fetizon oxidation sequence, forming both γ-lactones, rings C and E in a regioselective manner.[22,24] The installation of carbocycle A was then envisioned to be achieved *via* a pivotal radical epoxide opening and cyclisation of (**234**), mediated by a low valent titanium complex, furnishing bicycle (**233**),

representing the entire carbon skeleton of the natural product. The substrate (**234**) for this key transformation would in turn be available from the densely substituted cyclopentenone (**235**) by means of a stereoselective epoxidation and subsequent installation of the pendant alkyne *via* 1,2-organometallic addition. A Tsuji-Trost reaction of cyclopentane (**236**) was believed to provide access to the substrate for such a reaction sequence. Cyclopentane (**236**) could then be further disconnected, *via* alkylation and transesterification to the product of the regioselective Tiffeneau-Demjanov ring expansion reaction (**190**), a known substance from our previous route. The initial steps of the synthesis would thus be carried out in direct analogy with the prior approach, beginning with the [2+2] photocyclisation of (**167**) and (**19**), the product of which is readily elaborated into the ring-expansion substrate, cyclobutanone (**166**).

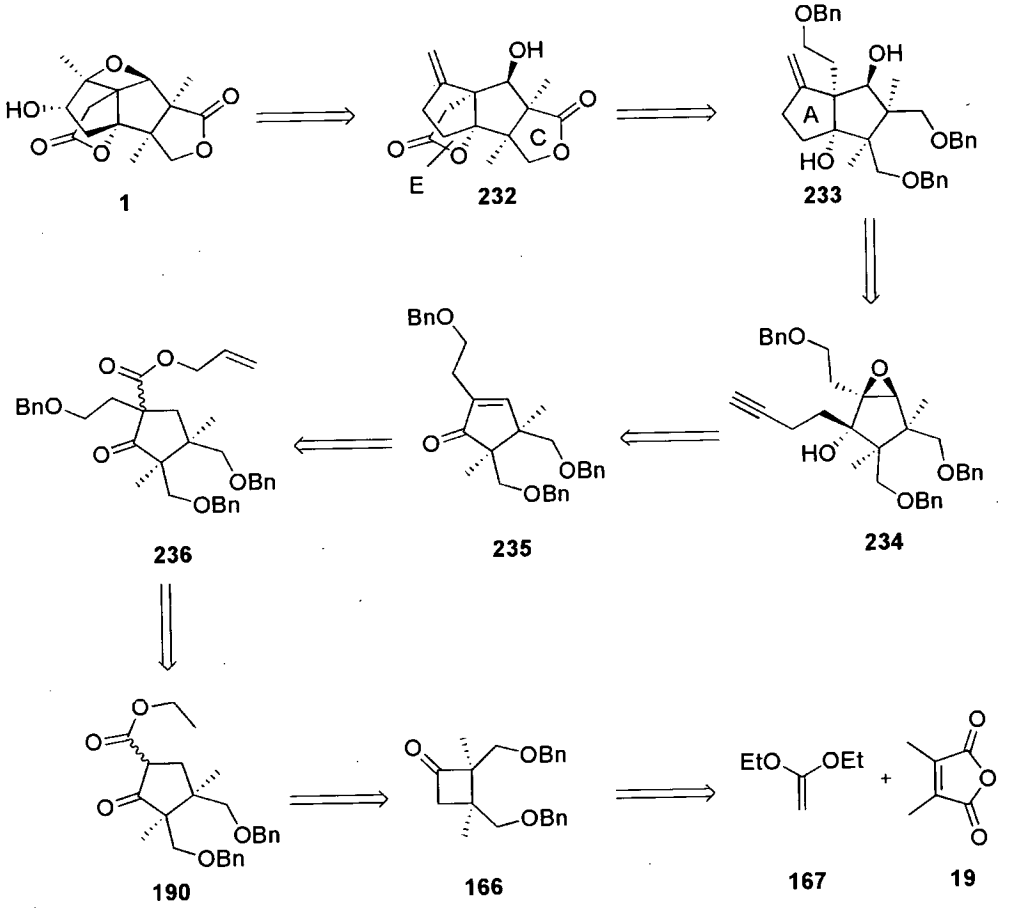


Figure 4-1 Retrosynthetic analysis for the radical cyclisation approach

As we would not be relying on the Paternò-Büchi reaction, the use of the benzyl protecting group throughout the entire synthetic sequence appeared feasible, negating the need to swap protecting groups at any stage. The stereoselectivity of the organometallic side-chain addition to the epoxide, derived from (**235**), was still anticipated to be achieved *via* chelation control, exploiting coordination effects of the incoming nucleophile to the epoxide and diol moiety, which were required to be introduced onto the same face of the cyclopentane ring. Furthermore, we were aware of the potentially problematic nature of the side-arm addition step due to the presence of an sp^3 carbon centre adjacent to the formed tertiary alcohol and the associated propensity towards elimination of such a motif. However, the saturated nature of the ring, due to the prior epoxidation step, was anticipated to render the addition product resistant towards elimination reactions. Preliminary trial reactions confirmed the stability of such a system (*vide supra*).

4.2. Synthesis of the Radical Cyclisation Substrate

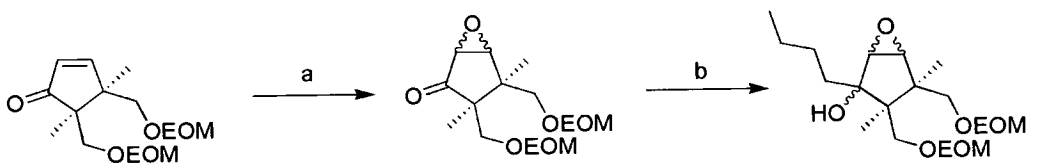
As outlined in our retrosynthetic analysis, a certain amount of overlap in the initial steps of the proposed synthetic route existed compared to the previously discussed approach. Thus, with access to the key cyclobutanone intermediate (**166**) already established, we were able to quickly start to develop our new route. Initially however, we wanted to establish the stability of the tertiary alcohol formed in the side-arm addition reaction, as this was anticipated to be potentially problematic.

4.2.1. Preliminary reactions

4.2.1.1. Stability of tertiary alcohol

In order to investigate the stability of the tertiary alcohol motif, flanked by an sp^3 carbon chain and a bicyclic epoxide, we employed the cyclopentenone (**201**), available from our previous approach. As our primary aim was to show the stability of the 1,2-addition product, we were not concerned with the stereoselectivities of these reactions and no attempts at separating the formed diastereomers were carried out.

Treating the *bis*-EOM-protected cyclopentenone (**201**) with aqueous alkaline hydroperoxide resulted in the clean transformation into the epoxide (**237**). The product was obtained as an inseparable mixture of diastereomers with respect to the facial selectivity of the epoxidation. Due to a lack of resolution of peaks in the ^{1}H-NMR spectrum, the exact ratio of isomers could not be established; however, the presence of two full sets of carbon signals in the ^{13}C-NMR spectrum of similar peak height suggested that only a low degree of stereoselectivity was in operation. Next, we treated the diastereomeric mixture of epoxides (**237**) with *n*-butyl lithium, resulting in 1,2-addition of an *n*-butyl chain to the cyclopentenone, furnishing tertiary alcohol (**238**). Two separable products were obtained in this case, established to be single diastereomers of the addition product, suggesting that the organometallic addition proceeded with a high degree of stereoselectivity and the diastereomers were isolated in an approximately 1:1 ratio. Most importantly however, the isolated tertiary alcohol addition products were found to be stable to both workup and purification conditions and showed no propensity towards elimination.



201 **237** **238**

a) H_2O_2 (30% w/w in H_2O), 1 M NaOH, MeOH, 0 °C, 99%; b) ^{n}BuLi, THF, -78 °C to RT, 91%.

Figure 4-2 Preliminary epoxidation and 1,2-addition reactions

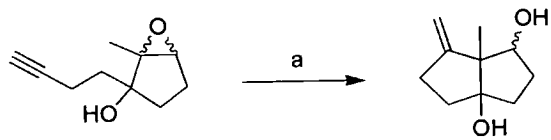
Consequently, before setting out to investigate the radical epoxide opening approach, we had established the feasibility of carrying out the 1,2-organometallic addition of a sp^3 carbon containing side-chain onto epoxide substrates such as (**237**).

4.2.1.2. Feasibility of radical cyclisation[§]

In addition to the preliminary reactions probing the stability of the side-chain addition product, we were also interested in demonstrating the feasibility of the key

[§] The preliminary reactions described in this section, the preparation of epoxide (**239**) as well as the radical cyclisation, were carried out by fellow group member Lei Shi.

transformation before dedicating substantial resources to such an approach. In the proposed radical epoxide opening and cyclisation reaction, a low valent titanium reagent derived in reductive manner from titanocene and zinc, facilitates the opening of the epoxide. The carbon based radical which is produced as a result cyclises onto the pendant alkyne, forming a new carbon-carbon bond in the process.[84] The mechanism and scope of the reaction will be discussed in chapter 4.3. In the event, titanocene dichloride was treated with zinc dust under strict exclusion of oxygen to form a low valent titanium(III) complex which, upon addition to the epoxide (**239**) facilitated the radical transformation into bicycle (**240**) in 62% yield.



239 **240**

a) Cp_2TiCl_2, Zn, THF, 62%.

Figure 4-3 Preliminary radical cyclisation feasibility study

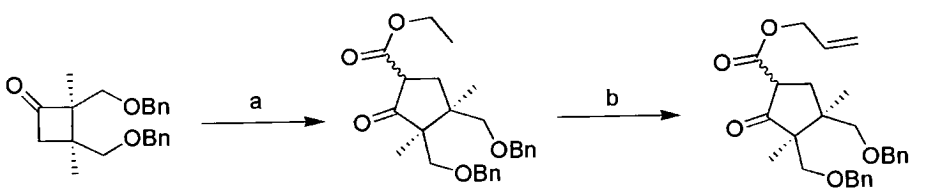
Pleasingly, we were thus able to demonstrate the viability of the new key transformation, albeit on a simpler model system.

The positive outcome of the two preliminary reactions, probing potentially problematic steps, provided us with sufficient confidence to initiate a full investigation of the proposed approach.

4.2.2. Ring expansion and transesterification

The cyclobutanone (**166**), available *via* the two methods outlined in chapter 3.2, formed the starting point for our investigations, allowing a very quick entry into the new route. We set about adapting the ring expansion methodology employed earlier to our new requirements. Employing ethyl diazoacetate had been shown to deliver the desired regioselectivity in the case of the *bis*-benzyl protected substrate (**166**) and the same reagent was to be employed here. In addition to providing access to the correct regioisomer, the product also features an essential functional handle in the form of the ethyl ester, placed in the α-position.

In the event of treating the cyclobutanone (**166**) with ethyl diazoacetate in the presence of boron trifluoro etherate afforded the ring-expanded cyclopentanone (**190**) in 88% yield. Although the formation of trace amounts of the undesired regioisomer was observed by TLC analysis, only the desired product was isolated. Subsequently, the 1,3-ketoester's ethyl ester functionality was trans-esterified by refluxing in the presence of a large excess of allylalcohol in toluene, furnishing the allylester (**241**) in high yield. This sets up our substrate for a future Tsuji-Trost reaction, anticipated to introduce an enone functionality into the cyclopentane motif (*vide infra*).



166 **190** **241**

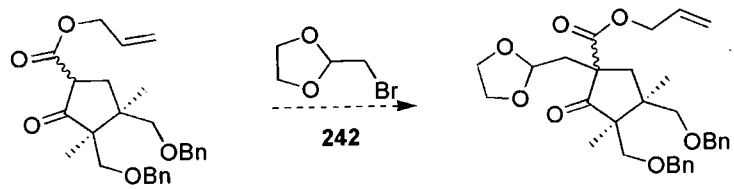
a) ethyl diazoacetate, $BF_3 \cdot Et_2O$, DCM, 0 °C, 88%; b) allyl alcohol, toluene, 120 °C, 85%.

Figure 4-4 Ring expansion and transesterification

In transforming the previously prepared cyclobutanone (**166**) into cyclopentanone (**241**) we had gained a very quick entry into our new synthetic route by employing methodology developed in a prior approach.

4.2.3. Alkylations of 1,3-ketoester

At this stage, the introduction of a quaternary centre at the 2-position of the 1,3-ketoester (**241**) needed to be addressed. We envisioned the introduction of a two carbon fragment, representing the carbon segment of γ-lactone E *via* an alkylation with an alkyl halide. As such, appropriate functionalisation had to be in place on the alkylating agent to allow the formation of the lactone at a later stage. Initial attempts at carrying out such a transformation were based around the commercially available 2-bromomethyl-1,3-dioxolane (**242**), featuring the required functionality as a masked aldehyde. Unfortunately, employing a range of conditions, no formation of the anticipated reaction product (**243**) could be achieved (Figure 4-5).



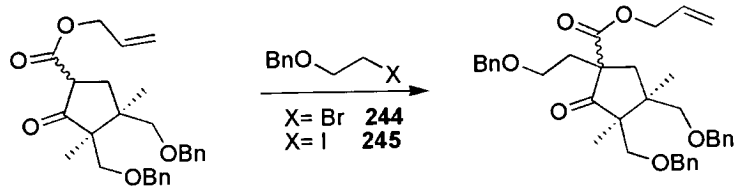
241 **243**

Conditions	Result
K_2CO_3, acetone, RT,18 h	SM only
K_2CO_3, acetone, reflux,40 h	SM only
K_2CO_3, MeCN, 85 °C, 18 h	SM only
K_2CO_3, KI, DMSO, 100 °C, 18 h	SM only
NaH, DMF, RT, 18 h	SM only
NaH, THF, 60 °C, 18 h	SM only
K_2CO_3, KI, DMF,120 °C,20 h	Complex mixture
K_2CO_3, KI, DMF,140 °C,24 h	Decomposition
Imidazole, TBAI, DMF, 140 °C, 24 h	Decomposition

Figure 4-5 Attempted alkylations using 2-bromomethyl-1,3-dioxolane

Moving away from alkylating agents featuring the lactonisation functionality in the appropriate oxidation state for the formation of a lactol, as exemplified by the 2-

bromomethyl-1,3-dioxolane (**242**), we investigated the use of masked hydroxyl-containing sidechains. Whilst evidently requiring a further adjustment in oxidation state to undergo lactonisation, we expected a more robust reagent, amenable to more forcing reaction conditions. We employed both benzyl-2-bromoethylether (**244**) and benzyl-2-iodoethylether (**245**) as alkylating agents; the former was obtained from a commercial supplier whereas the latter was prepared from ethylene glycol *via* mono-benzyl protection followed by iodination according to literature procedures.[85]



241 **236**

Conditions	X	Result
K_2CO_3, acetone, RT, 18 h	Br	SM only
K_2CO_3, KI, acetone, RT, 18 h	Br	SM only
K_2CO_3, KI, acetone, reflux, 18 h	Br	30 % yield
K_2CO_3, KI, DMF, 120 °C, 20 h	Br	Decomposition
K_2CO_3, acetone, reflux, 24 h	I	36 % yield
K_2CO_3, acetone, μ-wave, 100 °C, 20 min	I	Trace product
K_2CO_3, MeCN, μ-wave, 100 °C, 20 min	I	Decomposition
K_2CO_3, MeCN, 95 °C, 18 h, 0.39 M [**241**]	I	47% yield
K_2CO_3, MeCN, 95 °C, 18 h, 0.55 M [**241**]	I	76% yield

Figure 4-6 Alkylation using benzyl protected two carbon fragment

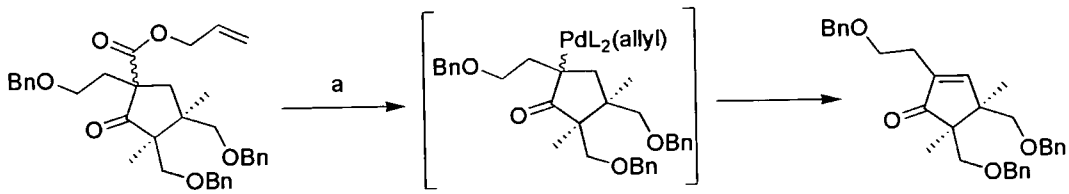
When initial attempts at alkylating cyclopentane (**241**) with benzyl-2-bromoethylether (**244**) were carried out at room temperature, no product formation could be observed. Addition of potassium iodide in order to facilitate an *in situ* Finkelstein reaction also proved unsuccessful. However, upon employing more thermally forcing conditions in refluxing acetone, yields of 30% of the desired

product (**236**) were achieved. Increasing the temperature further, by carrying out the reaction in DMF at 120 °C did not furnish the expected improvement in yield but instead resulted in decomposition of the substrate. Changing the alkylating agent to benzyl-2-iodoethylether (**245**) and carrying out the reaction under the previously successful conditions did eventually afford the product (**236**) in a slightly improved yield of 36%. Attempting to carry out the alkylation in the microwave proved unfruitful with only trace amounts of product formation being apparent. A significant improvement was eventually achieved when employing acetonitrile as the solvent and heating the reaction mixtures to 95 °C for 18 h. The reaction showed a marked dependence on the substrate concentration with the best yields observed in a 0.55 molar solution of the starting material in MeCN, furnishing product (**236**) in 76% yield.

Such conditions now allowed us to establish the quaternary carbon, centred within the 1,3-ketoester motif and in preparing such a structural feature, the stage was set for the subsequent Tsuji-Trost reaction.

4.2.4. Tsuji-Trost reaction

With the densely functionalised cyclopentanone (**236**) in hand, we intended to employ a Tsuji-Trost reaction to facilitate a decarboxylative unsaturation, furnishing the desired cyclopentenone (**235**). Introducing the enone functionality *via* a β-hydride elimination of the intermediate palladium species (**246**) would thus allow us to employ the ester functionality, originating in the ring expansion step in order to prepare the desired key intermediate (**235**).[86]



236 246 235

a) $Pd(OAc)_2$, PPh_3, MeCN, 95 °C, 5.5 h, 61%.

Figure 4-7 Tsuji-Trost reaction

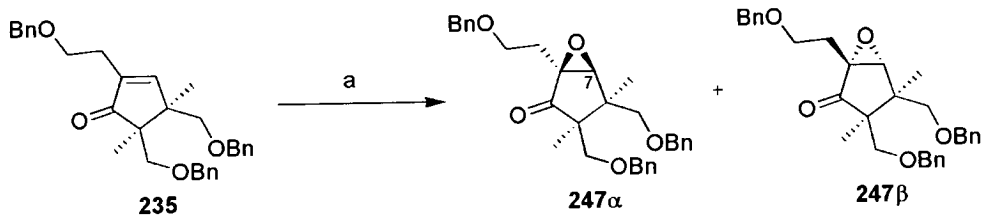
In the event of treating the substrate (**236**) with 10 mol% of palladium acetate and 10 mol% of triphenylphosphine in acetonitrile at 95 °C for 5.5 hours, we were delighted to observe the smooth formation of cyclopentenone (**235**) in 61% yield as well as the recovery of 22% of starting materials after column chromatography. Attempting to push the reaction through to completion by increasing the catalyst loading proved unsuccessful but the recovery of unreacted substrate proved straightforward and readily allowed recycling of the starting material.

In developing the synthetic route of (**235**), we have successfully integrated the functionality created in the ring expansion step into the synthetic route, as a functional handle for the introduction of the unsaturation into the carbocycle, required for the subsequent epoxidation reaction.

4.2.5. Epoxidation and 1,2-organometallic addition

With an efficient synthesis of cyclopentenone (**235**) established, we investigated the stereoselective epoxidation required to set up the radical epoxide opening and cyclisation reaction. As is evident from our retrosynthetic analysis, we require the epoxidation to occur on the same face of the cyclopentenone as the protected diol functionality, as exemplified by (**247α**). Such an event would introduce the desired stereochemistry at C_7, setting the scene for the late stage oxetane formation *via homo*-Payne rearrangement. Introducing the epoxide with such selectivity would also render the α-face of the resulting bicycle densely oxygenated, providing ample coordination sites for our proposed chelation controlled organometallic addition.

In the event of treating cyclopentenone (**235**) with alkaline hydroperoxide, a very clean epoxidation occurred in 84% yield, furnishing the two expected diastereomers in a 1.8:1 ratio of (**247α**) to (**247β**). Although the two isomers were readily separated chromatographically, the relative stereochemistry could not be established at this stage and the assignments indicated in Figure 4-8 are based on the elucidation of stereochemistry at a later stage (*vide infra*) and were assigned retrospectively.



235 **247α** **247β**

a) H_2O_2, 1M NaOH, MeOH, 0 °C, 18h, 84%, 1.8:1 ratio of α/β

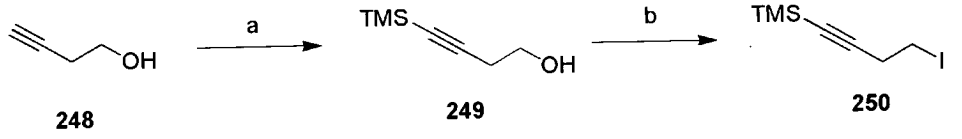
Figure 4-8 Epoxidation of cyclopentenone

The facial selectivity apparent in the epoxidation reaction slightly favoured the formation of (**247α**), in which the epoxide is introduced on the same face as the *bis*-benzyl protected diol. Constituting the correct stereochemistry with respect to our synthetic plan, this outcome was favourable to our requirements. However, as this stereochemical outcome was unknown to us at this stage, the formation of significant amounts of either diastereomer played to our advantage, allowing us to investigate the subsequent reactions on both isomers until the relative configuration could eventually be established.

Nonetheless, an improvement in the diastereoselectivity of the epoxidation was obviously still desirable, however, employing agents commonly known to afford greater stereoselectivity in epoxidation reactions failed to promote the reaction. Using *m*CPBA, *tert*-BuOOH and $VO(acac)_2$ in the presence of *tert*-BuOOH, no epoxidation product formation could be observed. This was speculatively attributed to the increased steric hindrance encountered by these larger epoxidation agents, impeding their approach.

With adequate quantities of either epoxide diastereomer in hand, we intended to carry out the introduction of a side-arm *via* organometallic addition. The side-

chain (**250**) to be introduced was prepared in two steps as is outlined Figure 4-9. Treating 3-butyn-1-ol (**248**) with *n*-butyl lithium and TMSCl furnished the intermediate alcohol (**249**) which was subsequently iodinated to afford the desired side-chain (**250**) in good yield.

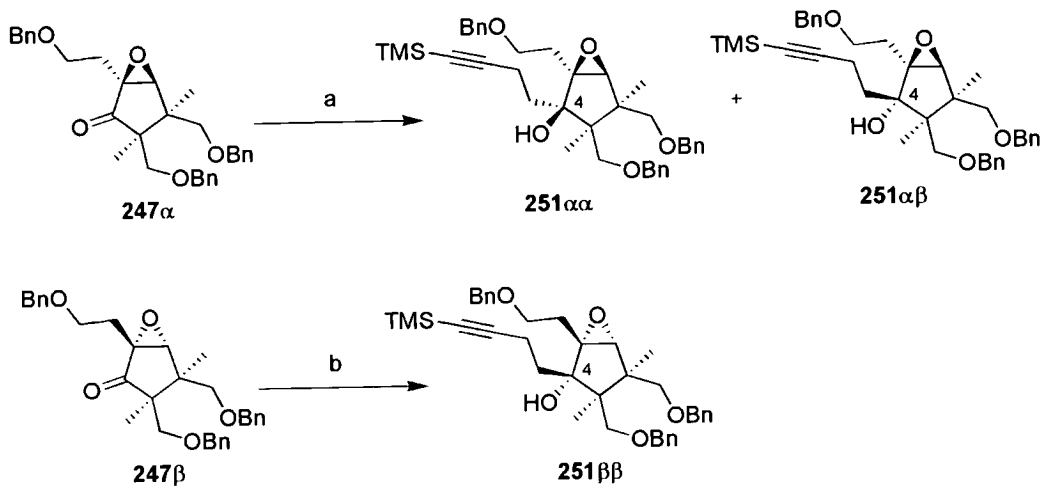


a) ^{n}BuLi, THF, -78 °C, then TMSCl, RT, 18 h; b) PPh_3, Imidazole, I_2, THF, RT, 1 h, 78% over 2 steps.

Figure 4-9 Synthesis of side-chain

Addition of *tert*-butyl lithium to side-chain (**250**) facilitated a lithium iodide exchange, and ensuing addition of bicycles (**247α**) or (**247β**) led to smooth addition reactions, as shown in Figure 4-10. In the case of the major epoxidation isomer (**247α**), the addition proceeded with moderate stereoselectivity, affording an inseparable 5:1 mixture of the major product (**251αα**) and the isomer arising from addition at the opposite face at C_4 (**251αβ**) as the minor product. The ratio of diastereomers was established on the de-silylated compound mixture of (**234αα**) and (**234αβ**) (see Figure 4-11) by comparison of the integration of the peaks in the ^{1}H-NMR spectrum of the two angular methyl substituents, C_8 and C_{13}, at δ_{major} 1.15 and 1.11 ppm and at δ_{minor} 1.20 and 1.02 ppm. Employing the same reaction conditions to the minor epoxidation isomer (**247β**) afforded the tertiary alcohol (**251ββ**) in good yield and as a single diastereomer.

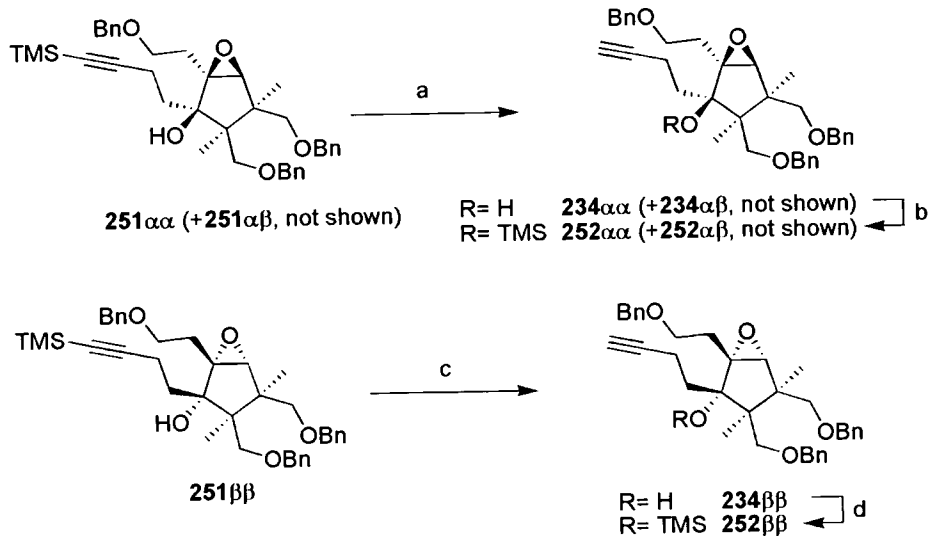
Pleasingly, we were thus able to introduce the desired side-arm in good yields and with moderate to excellent stereoselectivity. Furthermore, we were delighted to observe that no instability with respect to elimination of the formed tertiary alcohol seemed apparent, mirroring the results of our preliminary study.



a) **250**, ^{t}BuLi, Et_2O, -78 °C to RT, 2 h, 87%, 5:1 ratio of diastereomers (**251**αα:**251**αβ);
b) **250**, ^{t}BuLi, Et_2O, -78 °C to RT, 2 h, 81%, single diastereomer.

Figure 4-10 Organometallic side-chain addition

Next, the products of the organometallic addition reaction were treated with TBAF, removing the terminal alkyne protecting group, furnishing (**234αα/234αβ**) and (**234ββ**) in 92% and 91% yields respectively (Figure 4-11). Furthermore, in order to synthesise substrates for the key radical epoxide opening reaction in analogy with our preliminary study, in which a silyl-protected tertiary alcohol was present, we capped the free alcohol moiety in (**234αα/234αβ**) and (**234ββ**) using trimethylsilyl chloride. This afforded us with the substrates (**252αα/252αβ**) and (**252ββ**) in 54% and 73% yields respectively.



a) TBAF, THF, RT, 5 min, 92%; b) TMSCl, Imidazole, DMAP, DMF, 80 °C, 50 h, 54%; c) TBAF, THF, RT, 5 min, 91%; d) TMSCl, Imidazole, DMAP, DMF, 80 °C, 48 h, 73%.

Figure 4-11 From addition product to radical cyclisation substrate

In developing synthetic routes to the substrates (**252αα/252αβ**) and (**252ββ**) we have thus established access to the substrates for the pivotal radical epoxide opening and cyclisation reaction. The still inseparable mixture of (**252αα/252αβ**) consisted, as before, of a 5:1 mixture of **252αα** and **252αβ**.

4.3. Titanium Mediated Radical Epoxide Opening Reactions

The use of low valent titanium(III) complexes and *bis*(cyclopentadienyl) titanium(III) chloride (Cp_2TiCl) in particular as promoters of radical epoxide opening reactions first emerged in 1988 in a publication by Nugent and RajanBabu.[84,87] Described was the treatment of epoxide (**253**), tethered to a terminal alkene, with Cp_2TiCl, resulting in the formation of bicycle (**257**). The radical epoxide opening occurs with a high level of regioselectivity, furnishing the more substituted carbon radical, attributed to a combination of both the higher stability of such a radical as well as unfavourable steric interactions arising from the steric bulk of the titanocene(III) ligands upon the initial complexation to the epoxide.[88] The usual reactivity of the formed carbon-based radical towards radical traps can then be

exploited for carbon-carbon bond formations. In the present example, the radical (**254**) is trapped *via* a cyclisation with the tethered olefin, affording the carbon based radical (**255**) by means of a 5-exo-trig cyclisation. The hereby generated radical is subsequently quenched by a second equivalent of the Ti(III) reagent affording (**256**), which, upon acidic workup furnishes the bicycle (**257**) in 88% yield with a 90:10 endo/exo ratio, shown in Figure 4-12.

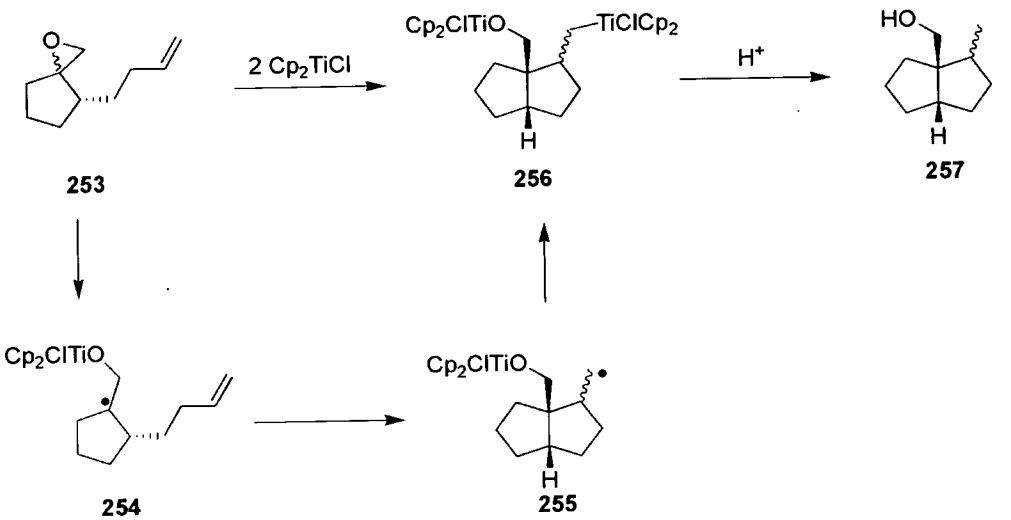


Figure 4-12 Nugent and RajanBabu's radical epoxide opening methodology

The Ti(III) mediated radical epoxide opening methodology was extended in scope when alkynes were added to the functionalities successfully employed as radical traps, allowing the reaction to proceed with no net loss in the number of functional groups. Clive and co-workers employed the methodology in their total synthesis of (±)-Ceratopicanol (**263**).[89,90] In direct analogy with the mechanism operating in Nugent's methodology, treatment of the tricyclic epoxide (**258**) with Cp_2TiCl led to regioselective, radical epoxide opening, furnishing the more substituted carbon based radical (**259**). 5-Exo-dig cyclisation of the radical with the tethered terminal alkyne then created a new carbon-carbon bond, resulting in intermediate radical (**260**). Quenching with a second equivalent of the titanocene reagent then afforded (**261**) which upon acidic workup furnished the desired product (**262**) in 82% yield. A further five steps transformed the product of the radical epoxide opening and cyclisation methodology into Ceratopicanol (**263**).

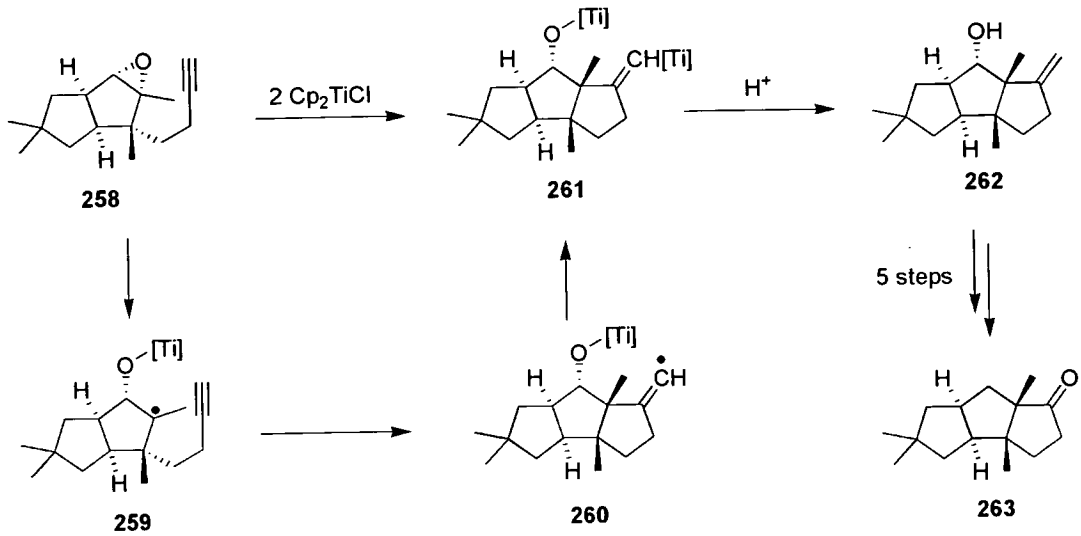
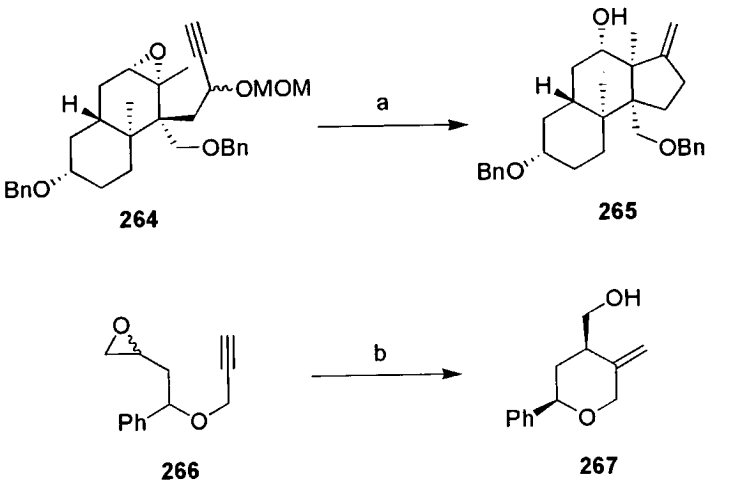


Figure 4-13 Clive and co-workers synthesis of (±)-Ceratopicanol

Further examples of the application of the radical epoxide opening methodology to cyclisations with alkynes can be found in the work of Toyota and co-workers and in a publication by Banerjee and Roy.[91,92] In Toyota and co-workers work, the tricyclic epoxide (**264**) underwent a highly stereoselective sequence of radical epoxide opening and subsequent 5-exo-dig cyclisation, affording the densely functionalised tricycle (**265**) as the sole product in high yield. Interestingly, the methoxymethyl ether functionality was removed under the reaction conditions. In a further example published by Banerjee and Roy, the epoxide (**266**), featuring a tethered propargyl ether, was opened in analogy with previous examples. The resulting carbon-based radical cyclised with the pendant alkyne in a 6-exo-dig reaction, thus forming the 6-membered cyclic ether (**267**). The stereoselectivity observed in this reaction was attributed to the preferred chair conformation which would be adopted by the radical intermediate formed by the initial epoxide opening.



a) Cp_2TiCl, 80%; b) Cp_2TiCl, 78%, 4.6:1 ratio

Figure 4-14 Toyota and Roy's examples of radical epoxide opening methodology

As the examples outlined within this section show, some literature precedent existed with respect to the application of the radical epoxide opening strategy towards the formation of 5-membered carbocycles bearing *exo*-alkenes. The successful formation of 6-membered rings using such methodology suggested that some flexibility towards the substrate scope is evident. However, no literature precedent could be found describing the reaction on substrates akin to our compounds, featuring a tertiary alcohol adjacent to the carbon based radical to be formed. Nonetheless, having demonstrated the feasibility of such a transformation on a simplified model system as one of our preliminary experiments, we were confident to be able to realise this methodology on our advanced intermediates.

4.4. Radical Epoxide Opening and Cyclisation

The preparation of the low valent titanium(III) reagent proved straightforward if conducted under strict exclusion of oxygen to prevent oxidation of the reagent. To a flask containing titanocene (Cp_2TiCl_2) and an excess of zinc powder as the reducing agent is simply added anhydrous and degassed THF under a constant purge of nitrogen. The colour of the resulting suspension changes over a period of about 20 minutes from a dark red colour to a bright green, confirming the formation of the

desired Ti(III) species. The entire mixture is then transferred into solutions of the reaction substrates with the formed $ZnCl_2$ and excess Zn dust appearing to have no detrimental effect on the reaction progress.

As our successful preliminary reactions had been carried out on a model system in which the tertiary alcohol was capped with a silyl group, we first attempted the methodology on substrates (**252αα/252αβ**) and (**252ββ**) in which the tertiary alcohol was protected with a TMS group. However, exposing either substrate to the titanium(III) reagent did not result in any product formation and TLC analysis showed the slow decomposition of the starting materials.

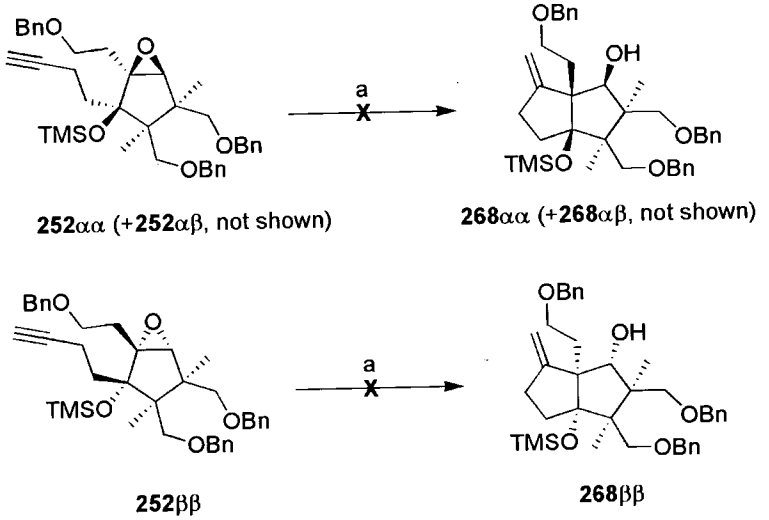
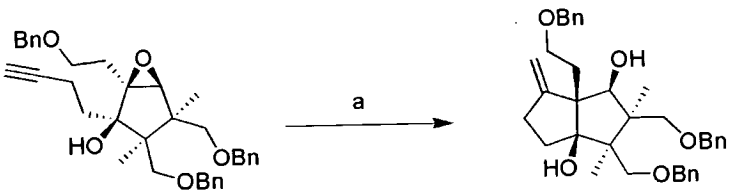


Figure 4-15 Radical cyclisation using protected tertiary alcohol

After the initial disappointment of the failed attempts at using the silyl protected tertiary alcohols (**252αα/252αβ**) and (**252ββ**) as the substrates for the radical reaction, we employed their precursors, the free tertiary alcohols (**234αα/234αβ**) and (**234ββ**) as alternative substrates. Due to the highly advanced nature of these substrates, their availability was very limited and for that reason, we initially focussed on the use of the more abundant (**234αα/234αβ**), the compounds arising from the major epoxidation diastereomer (**247α**).

In the event of exposing the inseparable 5:1 mixture of (**234αα**) and (**234αβ**) to $Cp_2Ti(III)Cl$ under the conditions outlined above, we were delighted to observe

the formation of reaction product (**233αα**) in 51% yield. Intriguingly, (**233αα**) was the sole product of the reaction with no recovery of (**234αβ**) or formation of (**233αβ**) being detectable (Figure 4-16). As the transformation was accompanied by a degree of decomposition evident by TLC analysis, we suspected that the minor substrate (**234αβ**) was unstable under the reaction conditions.

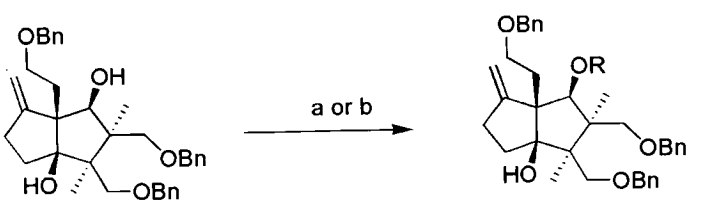


234αα (+**234αβ**, not shown) **233αα**

a) Cp_2TiCl_2, Zn, THF, N_2, RT, 22h, 51%, 61% by recovery.

Figure 4-16 Radical cyclisation of free tertiary alcohol – major epoxidation isomer

While the characterisation of the cyclisation product (**233αα**) was possible using 1D NMR spectroscopy techniques, its relative stereochemistry proved more difficult to elucidate. As diol (**233αα**) was formed as an oil, we acylated the secondary alcohol functionality as the *p*-bromobenzoyl (**269**) and 3,5-dinitrobenzoyl derivatives (**270**), as outlined in Figure 4-17. We hoped that the resulting esters would be formed as solids from which single crystals for X-ray crystallographic analysis could be obtained.



233αα

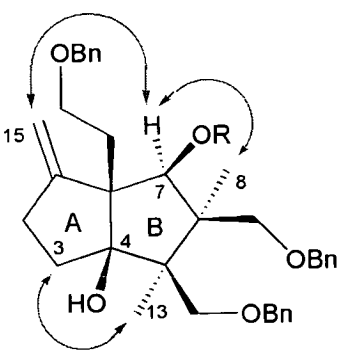
R= *p*-BrBz **269**
R= 3,5-*di*-NO_2Bz **270**

a) *p*BrBzCl, pyridine, 100 °C, 36 h, 54% **269**; b) 3,5-di-NO_2BzCl, pyridine, 100 °C, 3.5 h, 54% **270**.

Figure 4-17 Derivatisation of cyclisation product *via* acetylation

Although the esters were prepared successfully, no crystalline forms could be obtained even after numerous attempts at recrystallisations, freeze drying and

triturations. As the confirmation of the structure of the product (**233αα**) and its elucidation of relative stereochemistry was thus not possible *via* crystallographic methods, we turned our attention to 2D-NMR spectroscopy. The spectra recorded for the 3,5-dinitrobenzoyl derivative (**270**) proved to be the most suitable for the determination of the relative stereochemistry as it featured the clearest separation of peaks, allowing assignment of all signals using COSY and HSQC experiments. Shown in Figure 4-18 are the nOe interactions observed in the NOESY spectrum of (**270**). Strong correlation peaks indicate a close spatial arrangement between the single proton at C_7 and the methyl substituent at C_8, suggesting that the acylated secondary alcohol is on the same face as the *bis*-benzyl protected diol. This would suggest that the initial epoxidation had occurred on the desired face. However, upon inspection of the correlations between the proton at C_7 and the *exo*-alkene's methylene protons at C_{15}, we noted that such a *through space* interaction would only occur if ring A was on the same face of ring B as the two methyl substituents at C_8 and C_{13}. A further cross peak, correlating C_3 and C_{13} supported our suspicion that the incorrect stereochemistry across the A-B ring junction was present. Such a stereochemical arrangement, as shown in Figure 4-18, would have its roots in the organometallic addition step, in which the side-chain had evidently attacked from the opposite face with respect to the epoxide and diol, thereby creating the quaternary centre at C_4 with the incorrect stereochemistry.

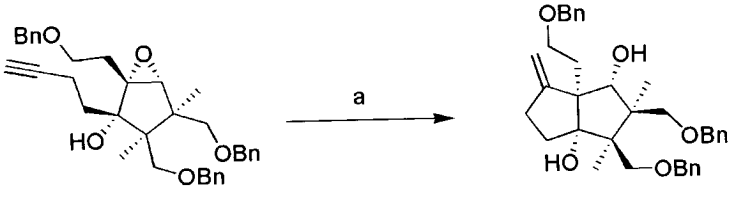


R= 3,5-di-NO_2Bz **270**

Figure 4-18 nOe-signals observed for radical cyclisation product (270)

This was a disappointment to us as it was clear that our hypothesised chelation controlled addition was not occurring. The stereoselectivity in the addition step appears to be controlled by the steric hindrance of the face featuring the diol and epoxide moiety. Perhaps though, this is not too surprising, considering the use of a lithium organometallic, not generally known to coordinate strongly to oxygen atoms. A stronger chelation effect would be expected with Grignard reagents, exploiting the higher affinity of magnesium for oxygen.[76] Whilst the formation of the undesired diastereomer of bicycle (**270**) and therefore (**233αα**) was a disappointment, we were nonetheless encouraged by the successful demonstration of our key transformation and we moved on to apply the methodology to the substrate (**234ββ**), arising from the minor epoxidation isomer (**247β**).

Applying the same conditions we had employed previously to the substrate (**234ββ**), derived from the minor epoxidation isomer, we were delighted to find that the reaction proceeded to furnish the bicyclic product (**233ββ**) in 46% yield as a single diastereomer. As before, the reaction was carried out under strict exclusion of oxygen throughout the course of the transformation. Initial formation of the low valent $Cp_2Ti(III)Cl$ reagent was achieved *via* treatment of titanocene with zinc dust and subsequent addition of this reagent to a solution of substrate (**234ββ**) in THF resulted in the rapid formation of the desired product (**233ββ**).



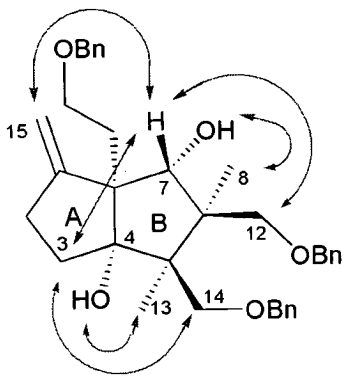
234ββ **233ββ**

a) Cp_2TiCl_2, Zn, THF, N_2, RT, 1.5 h, 46%.

Figure 4-19 Radical cyclisation of free tertiary alcohol – minor epoxidation isomer

Once we had successfully applied the pivotal radical epoxide opening and cyclisation methodology to our substrate (**234ββ**) to afford the advanced bicycle (**233ββ**), we set about demonstrating its relative stereochemistry. As before, the use of X-ray crystallography proved unfeasible, as (**233ββ**) was formed as an oil. Furthermore, the availability of only very small quantities of (**233ββ**) rendered the option of

derivatisation with a view of obtaining crystals unsuitable. Nonetheless, the elucidation of the relative stereochemistry was achieved by means of extensive 1D and 2D-NMR spectroscopy. Using 1D-^{1}H-NMR, ^{13}C-NMR and DEPT as well as HSQC and COSY 2D correlation spectroscopy allowed us to assign all the proton and carbon signals observed. This eventually permitted us to identify the cross peak interactions observed in the NOESY spectrum to specific and characteristic *through space* interactions, allowing us to determine the relative stereochemistry as outlined in Figure 4-20.



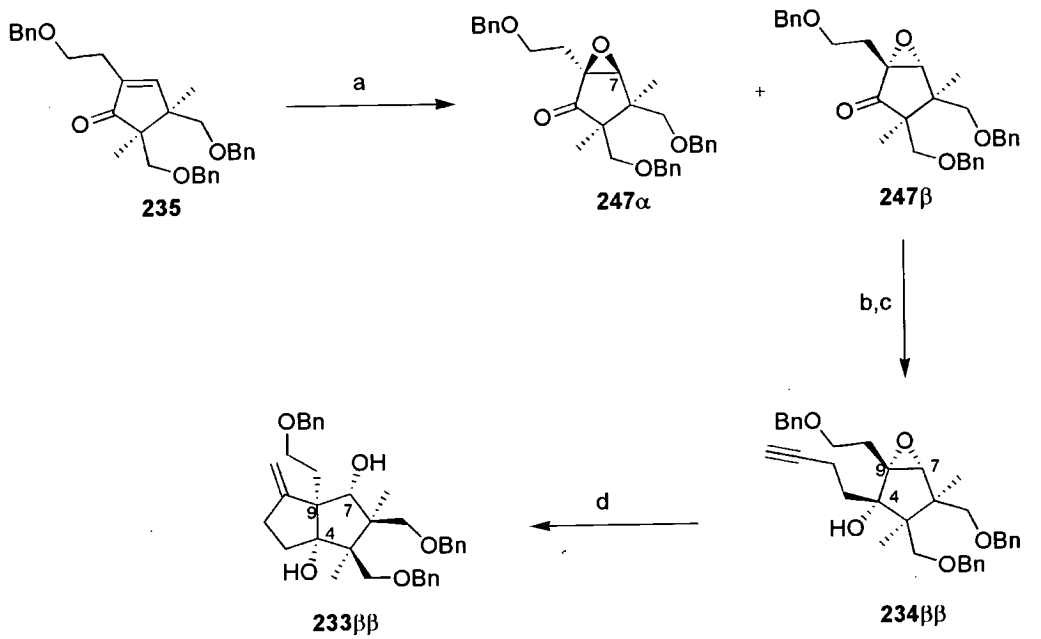
233ββ

Figure 4-20 nOe-signals observed for radical cyclisation product (233ββ)

The crucial stereochemical configuration to be assigned was the orientation of the tertiary alcohol functionality at C_4. If we could demonstrate its location to be on the same face of ring B as the methyl substituents at C_8 and C_{13}, we would simultaneously verify the correct orientation of ring A, due to the *cis*-arrangement of the formed ring junction. Such proof can be found in the nOe effect observed between the proton signals assigned to the methyl substituent C_{13} and the proton of the tertiary alcohol at C_4 as well as the nOe effect between C_3 and C_{14}. Both interactions strongly support our stereochemical assignment as indicated above. Next, we required to assign the stereochemistry of the newly formed secondary alcohol at C_7. As the substrate for the key radical reaction had been derived from the minor epoxidation isomer, we expected the alcohol to be located on the same face as the two methyl substituents, C_8 and C_{13}. This suspicion could indeed be confirmed by a number of nOe correlations observed between the protons present at the following

carbons: C_7 and C_{15}, C_3 and C_7, C_7 and C_{12} and C_7 (OH) and C_8. These interactions are outlined in Figure 4-20 and confirm the presence of the secondary alcohol on the opposite face of ring A with respect to the diol. Although this is the undesired orientation of the hydroxyl functionality, an inversion of the stereochemistry should be readily achievable, either *via* an oxidation/reduction sequence or a Mitsunobu inversion.

The assignment of stereochemistry outlined here forms the basis of the assignments of orientations employed since the initial epoxidation reaction. It thus seems appropriate to review how these assignments were made retrospectively. Described in Figure 4-21 is the synthetic sequence from the key cyclopentenone intermediate (**235**) up to the product of the pivotal radical epoxide opening reaction (**233βββ**) on which the relative stereochemistry was established.



a) H_2O_2, 1M NaOH, MeOH, 0 °C, 18h, 84%, 1.8:1 ratio of α/β; b) **250**, ^tBuLi, Et_2O, -78 °C to RT, 2 h, 81%, single diastereomer; c) TBAF, THF, RT, 5 min, 91%; d) Cp_2TiCl_2, Zn, THF, N_2, RT, 1.5 h, 46%.

Figure 4-21 Retrospective assignment of stereochemistry

Working back from the product (**233βββ**) of the radical reaction, we can assign the stereochemistry of the organometallic addition product (**234βββ**) to be as shown. The relative orientations at C_4 and C_7 are unchanged as they are set at the organometallic

addition and epoxidation step respectively. An inversion at C_9 is evident, the position on which the carbon centered radical is formed upon the opening of the epoxide. Due to the planar nature of such a radical, the formation of the carbon-carbon bond occurs with inversion of stereochemistry at C_9, allowing the formation of the A-B ring junction in a *cis*-relationship. With the stereochemical assignment of the tertiary alcohol at C_4 made as shown, the organometallic addition reaction, affording (**234ββ**) from (**247β**) must thus occur from the same face of ring A as the protected diol functionality, opposite to the epoxide. The facial selectivity of this addition reaction is thus likely to arise from the steric encumbrance created by the epoxide, adjacent to the carbonyl functionality in (**247β**) thereby blocking the lower face of the cyclopentenone. With the stereochemistry at C_7 determined to be as described, the epoxidation product (**247β**), which was employed in this synthetic sequence must therefore be the product in which the epoxidation had occurred on the cyclopentenone's opposite face with respect to the diol motif. Such an analysis can also be performed on the other epoxidation isomer, resulting in the eventual formation of the radical reaction product (**233αα**), retrospectively assigning the relative stereochemistry of epoxide (**247α**) to be as shown.

The product (**233ββ**) of the radical epoxide opening and cyclisation methodology represents the entire carbon skeleton of Merrilactone A, featuring all the required functionalisation to advance it to the natural product. With the relative stereochemistry at the tertiary alcohol and the *cis*-dimethyl substituents correctly introduced, a simple inversion of the secondary alcohol at C_7 would furnish the substrate for further elaboration towards the racemic total synthesis of the natural product.

4.5. Conclusions

In developing our approach towards the total synthesis of Merrilactone A, based on a pivotal radical epoxide opening and subsequent cyclisation methodology, we have successfully synthesised the entire carbon skeleton of the natural product. Building upon the previously developed route to the intermediate cyclobutanone (**166**), we

carried out a regioselective Tiffeneau-Demjanov ring expansion reaction. The thereby created 1,3-ketoester functionality was exploited for its acidity in the 2-position to facilitate an alkylating step, before employing the ester functionality in a Tsuji-Trost reaction. This simultaneously decarboxylated the 2-position and introduced the desired unsaturation into the carbocycle, furnishing the key intermediate, cyclopentenone (**235**). A subsequent epoxidation set up the forthcoming key reaction and permitted the addition of a side-chain, featuring sp^3 carbons adjacent to the formed tertiary alcohol, without concomitant elimination. Removal of the terminal alkyne protecting group then afforded the substrate for our new key transformation. The titanium(III) mediated radical epoxide opening reaction with *in situ* cyclisation with the tethered alkyne furnished the complete carbon skeleton of Merrilactone A (**233ββ**). As well as representing the entire carbon scaffold of the natural product, diol (**233ββ**) also features all necessary functionality to further advance the structure to the natural product.

The lack of stereoselectivity observed in the epoxidation of cyclopentenone (**235**) initially played to our advantage as it provided us with access to both product diastereomers. This allowed us to elucidate the stereochemistry at a later stage and assign it retrospectively to the epoxide isomers. With such an assignment made, it is now clearly desirable to address this low level of selectivity observed in the epoxidation step to favour the formation of the required diastereomer.

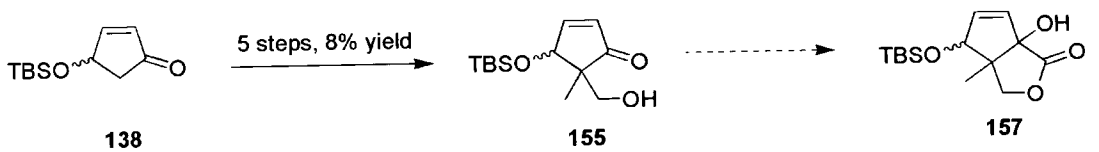
In the radical epoxide opening and cyclisation approach we have thus developed a synthetic route to the entire carbon skeleton of Merrilactone A (**233ββ**), allowing its preparation in 12 steps and with an overall yield of 3%. NMR characterisation spectra for the compounds along this route are presented in the appendix.

5. Conclusions and Future Work

The aim of this PhD project was to build upon the group's previous experience to work towards the total synthesis of Merrilactone A. Employing a number of approaches, we have significantly advanced the total synthesis project up to the stage of completing the entire carbon skeleton of the natural product.

5.1. Conclusions

In our initial work on the di-alkylation approach, outlined in chapter 2, we focussed on the direct extension of work previously carried out within our group. In attempting to implement a late stage annulation of the γ-lactone ring C, we hoped to elaborate Merrilactone A's tetracyclic core (**111**, Figure 1-28) into the natural product. Working on a simplified model system (**138**), we attempted to develop methodology for such a purpose. However, whilst the synthesis of the substrate (**155**) for the anticipated lactonisation *via* cyanation was achieved, the actual lactonisation step, expected to furnish (**157**) could not be shown to be feasible.

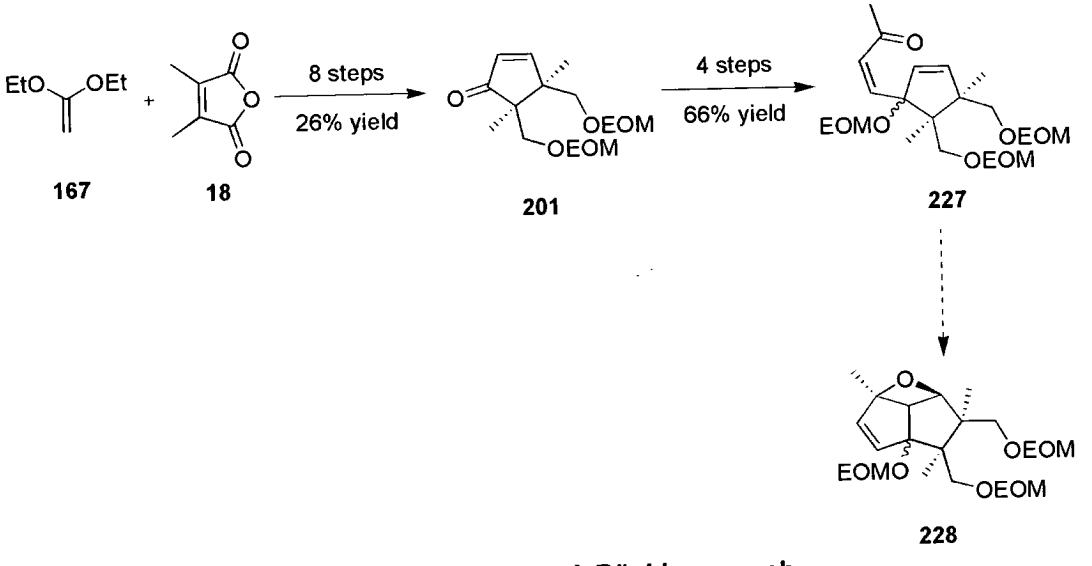


138 155 157

Figure 5-1 The Di-alkylation approach

With all our attempts at developing a synthesis featuring a late stage introduction of the γ-lactone ring C proving unsuccessful, we moved on to develop methodology allowing the introduction of the right hand side of the natural product at the very outset of the synthesis, as is outlined in chapter 3. As well as negating the encountered problems with a late stage annulation, such an approach would also generate a stereochemical differentiation of the two faces of the central carbocycle of the natural product, allowing the use of substrate control in order to develop stereoselective transformations. We developed a synthetic route to the key cyclopentenone intermediate (**201**) in which the two *cis*-methyl substituents at C_5 and C_6 have been introduced in a stereospecific manner at the very outset of the route.

Furthermore, the protected diol moiety represents the carbon skeleton of the γ-lactone ring C, readily convertible into the corresponding lactone *via* deprotection and selective oxidation. Subsequent attempts at employing previously developed methodology for the introduction of a dioxolane side chain proved unsuitable on this substrate due to the instability of the resulting tertiary alcohol with respect to elimination. Circumventing this problem by means of the use of a propargylic side-chain, eventually provided us with the advanced intermediate (**227**), representing the substrate for the pivotal Paternò-Büchi reaction anticipated to furnish (**228**). It came as a major disappointment that the key [2+2] photo-cyclisation could not be shown to be feasible and as such, we had to abandon the use of such a reaction as our key transformation.



167 **18** **201** **227** **228**

Figure 5-2 The Paternò-Büchi approach

Nonetheless, this allowed us to investigate the use of an alternative key transformation, a titanium(III) mediated radical epoxide opening reaction with *in situ* cyclisation onto a tethered alkyne. The research carried out on this approach is detailed in chapter 4. Entry into this approach was gained from a common intermediate with the previous approach, the cyclobutanone (**166**), which was synthesised from diethyl ketene acetal (**167**) and 2,3-dimethylmaleic anhydride (**18**) *via* a [2+2] photo-cyclisation, anhydride reduction, diol protection and subsequent acetal deprotection. Next, a regioselective Tiffeneau-Demjanov ring expansion reaction was implemented, giving rise to cyclopentanone (**190**). This was

transformed into cyclopentenone (**235**) *via* transesterification, alkylation and a Tsuji-Trost reaction. Following epoxidation, a side-chain was appended by means of an organometallic addition and following silyl deprotection, the advanced intermediate (**234βββ**) was formed. This represented the substrate for the pivotal radical epoxide opening and cyclisation reaction, which furnished (**233βββ**), the complete carbon skeleton of Merrilactone A.

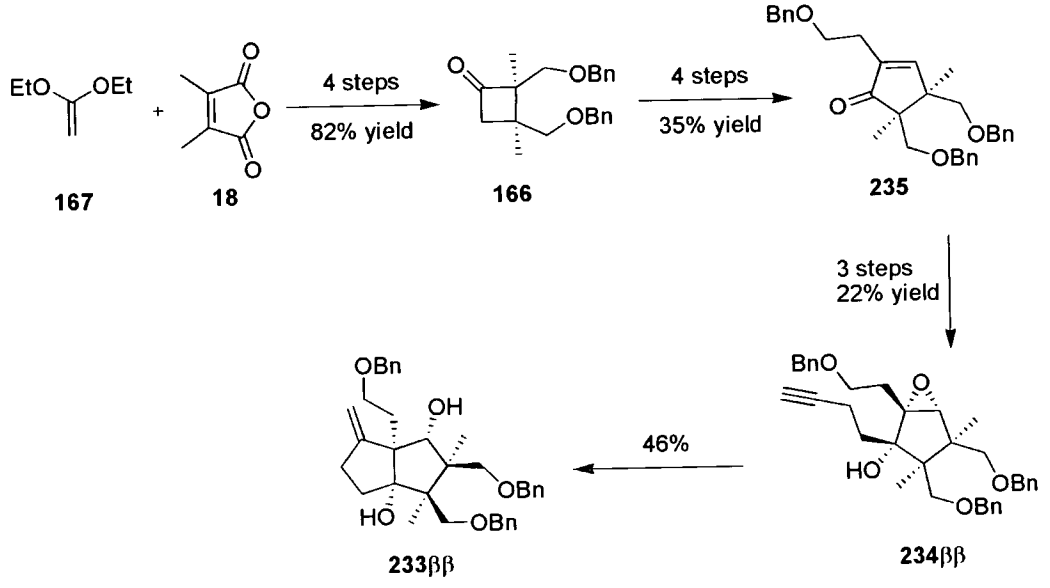


Figure 5-3 The radical epoxide opening and cyclisation approach

Although several issues of selectivity remain to be addressed along the synthetic route, we have nonetheless developed a novel approach towards Merrilactone A. The product of the radical reaction (**233βββ**) contains the entire carbon scaffold of the natural product and the correct relative stereochemistry with respect to the tertiary alcohol as well as the *cis*-di-methyl substituents has been established. The entire route to the highly advanced intermediate (**233βββ**) has been achieved in 12 steps with a combined yield of 3%.

5.2. Future Work

Whilst in synthesising (**233ββ**), we have achieved the preparation of the carbon scaffold of Merrilactone A, it is evident that some work still remains to be carried out to complete the total synthesis. Two major areas of work need to be addressed.

Firstly, the syntheses of the radical reaction substrate, as well as the key transformation itself need to be streamlined and optimised. In its current form, the synthetic sequence transforming the cyclopentenone (**235**) *via* epoxidation and organometallic addition into (**234ββ**) and the subsequent radical key reaction is unoptimised due to time constraints. Subjecting this sequence to a process of optimisation, both with respect to reaction yields and stereoselectivity would clearly be desirable.

Secondly, the elaboration of the product of the key radical reaction into the natural product has not yet been demonstrated. The remaining steps are outlined in Figure 5-4.

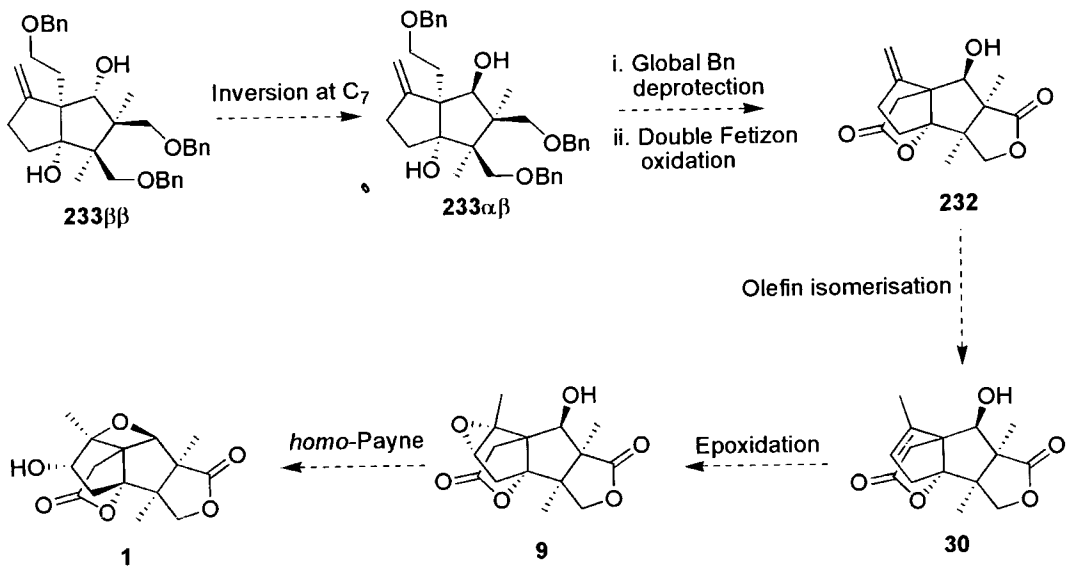


Figure 5-4 Future work required to complete the total synthesis

The preparation of (**233αβ**), in which the stereochemistry at C_7 is correct, could be achieved *via* an inversion of the secondary alcohol of the successfully prepared bicycle (**233ββ**). Alternatively, an optimised sequence of epoxidation, organometallic

side-chain addition and radical epoxide opening and cyclisation, in which the stereoselectivities of the reactions had been addressed appropriately could give rise to (**233αβ**) directly, negating the need for an inversion reaction. Next, a global benzyl deprotection under dissolving metal conditions, preserving the olefin functionality, would give rise to the substrate for a regioselective double Fetizon oxidation, furnishing tetracycle (**232**). The transformation of this *bis*-lactone into Merrilactone A has been well documented in the literature and the three step sequence of olefin isomerisation, stereoselective epoxidation and *homo*-Payne rearrangement has been achieved in high yields.

Work towards the completion of the total synthesis of Merrilactone A is currently ongoing within the group and research towards an asymmetric variant will commence upon completion of the racemic total synthesis.

6. Experimental

6.1. General Procedures

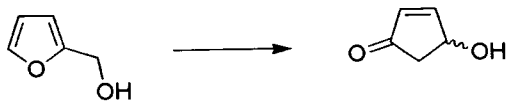
NMR spectra were recorded at ambient temperature on a Brüker DPX360 (360 MHz), Brüker AC250 (250MHz) or Varian Gemini-200 (200MHz) instruments and calibrated to residual solvent peaks: ^{1}H – $CDCl_3$, 7.26 ppm and ^{13}C – $CDCl_3$, 77.0 ppm. The ^{1}H-NMR data are presented as follows: chemical shift (in ppm on the δ scale), integration, multiplicity (s= singlet, d= doublet, t= triplet, q= quartet, m= multiplet), coupling constant (*J* in Hz) and structural assignment. The ^{13}C-NMR data are reported as ppm on the δ scale, followed by the structural assignment, based on DEPT spectra. IR spectra were recorded on a JASCO FT/IR-460 Plus instrument, using 4 mm sodium chloride discs. The wavelengths of the maximum absorbance (ν_{max}) are quoted in cm^{-1}. High resolution mass spectrometry was performed by the EPSRC National Mass Spectrometry Service Centre, Swansea, using Finnigan MAT 95XP and Finnigan MAT 900XLT instruments for FAB and ES analysis. The data are presented as the ionisation method, followed by the calculated and measured masses. TLC was performed on Merck 60 F254 silica plates and visualised by UV light and/or anisaldehyde* or potassium permanganate† stain. Compound purification was carried out by wet flash column chromatography, using Merck Kieselgel 60 (particle size 35-70) under positive pressure. Eluent constitution is quoted as ratios or percentages. All solvents were dried before use unless otherwise stated. Anhydrous solvents were obtained from a solvent purification system supplied by www.glasscontour.com or a PureSolv solvent purification system supplied by Innovative Technologies Inc. All other chemicals were purchased from a chemical supplier and used as received. All experiments were performed under an inert atmosphere of nitrogen gas under anhydrous conditions using oven dried glassware. Photoreactions were carried out in a photoreactor supplied by Photochemical

* Anisaldehyde stain was prepared by carefully adding concentrated sulphuric acid (10 mL) to a stirred ethanol solution (200 mL) of *p*-methoxybenzaldehyde (10 mL).
† Potassium Permanganate stain was prepared by dissolving potassium permanganate (3 g) and potassium carbonate (20 g) in sodium hydroxide (5%, 5 mL) and H_2O (300 mL).

Reactors Ltd., Reading, UK, using a 400 W medium pressure mercury vapour lamp under a N_2 atmosphere and water cooling.

6.2. Experimental Procedures

4-Hydroxycyclopent-2-enone (123)



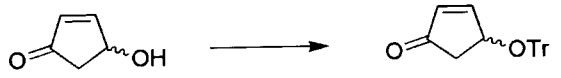
122 **123**

Furfuryl alcohol (**122**) (32.7 g, 333 mmol, 1 equiv) was dissolved in deionised water (1 L) and the resulting solution was deoxygenated with a stream of N_2 for 1 h. Following addition of hydroquinone (0.35 g, 3.18 mmol, 0.01 equiv) and sodium dihydrogenphosphate (1.63 g, 13.6 mmol, 0.04 equiv), the pH was adjusted to 4.1 by careful addition of 0.25 M orthophosphoric acid and the reaction mixture was then heated to reflux for 18 h. Formation of a thick brown oil was observed, which was dispersed by addition of 1,4-dioxane (200 mL) before returning the mixture to reflux for a further 23 h. After cooling to RT, the solution was washed with toluene and the aqueous layer was concentrated *in vacuo* to approximately 200 mL. The aqueous layer was extracted with EtOAc and the combined organic layers were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure to afford alcohol (**123**) as a brown oil (12.54 g, 38% yield). No further purification was undertaken.

^{1}H NMR (250 MHz, $CDCl_3$) δ 7.59 (1 H, dd, J= 2.35, 5.7 Hz, COCHC**H**), 6.22 (1 H, dd, J= 1.3, 5.7 Hz, COC**H**), 5.05 (1 H, m, C**H**OH), 2.78 (1 H, dd, $J_{AB,\,AX}$= 18.6, 6.1 Hz, C**H**$_2$), 2.28 (1 H, dd, $J_{AB,\,AX}$= 18.6, 2.2 Hz, C**H**$_2$).

The spectroscopic data were in agreement with those previously published.[36]

4-(Trityloxy)cyclopent-2-enone (124)



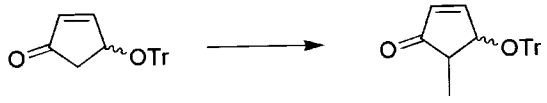
123 124

4-Hydroxycyclopent-2-enone (**123**) (5.00 g, 51.0 mmol, 1 equiv) was dissolved in DCM (150 mL) and tritylchloride (15.6 g, 56.1 mmol, 1.1 equiv), DMAP (250 mg, 2.0 mmol, 0.04 equiv) and triethylamine (10.7 mL, 76.5 mmol, 1.5 equiv) were added before heating the mixture to reflux for 24 h. Once cooled to RT, the mixture was washed with saturated NH_4Cl solution and water, dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. The resulting crude brown oil was absorbed onto silica and flash column chromatography (SiO_2, hexanes/EtOAc 9:1) afforded the title compound (**124**) as a yellow solid (6.88 g, 40% yield).

^{1}H NMR (250 MHz, $CDCl_3$) δ 7.77-7.68 (6 H, m, Ar**H**), 7.62-7.51 (9 H, m, Ar**H**), 7.06 (1 H, dd, *J*= 5.7, 2.2 Hz, COCHC**H**), 6.28 (1 H, dd, *J*= 5.7, 1.4 Hz, COC**H**), 5.06 (1 H, m, C**H**OC), 2.35-2.30 (2 H, m, C**H$_2$**).

The spectroscopic data were in agreement with those previously published.[93]

5-Methyl-4-(trityloxy)cyclopent-2-enone (128)



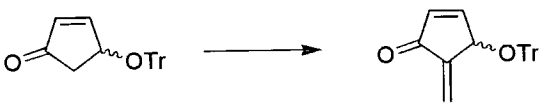
124 128

Diisopropylamine (50 μL, 0.35 mmol, 1.2 equiv) was dissolved in a mixture of distilled THF (4 mL) and DMPU (1 mL) and the resulting solution was cooled to -78 °C before addition of *n*-butyl lithium (0.2 mL, 1.6 M solution in hexanes, 0.32 mmol, 1.1 equiv). After stirring the mixture for 40 minutes at -78 °C, 4-(trityloxy)cyclopent-2-enone (**124**) (100 mg, 0.29 mmol, 1 equiv) in THF (3 mL) was added and the solution was stirred at -78 °C for 40 minutes before addition of methyl iodide (20 μL, 0.32 mmol, 1.1 equiv). Following stirring at -78 °C for an additional 90 minutes, the reaction mixture was poured into diethyl ether (10 mL), washed with

saturated NH_4Cl solution and H_2O, dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. Flash column chromatography (SiO_2, hexanes/EtOAc 9:1) afforded a single diastereomer of the title compound (**128**) as a yellow solid (50 mg, 49% yield).

^{1}H NMR (360 MHz, $CDCl_3$) δ 7.48-7.42 (6 H, m, Ar**H**), 7.31-7.20 (9 H, m, Ar**H**), 6.20 (1 H, dd, *J*= 5.9, 1.9 Hz, COCHC**H**), 5.88 (1 H, dd, *J*= 5.9, 1.9 Hz, COC**H**), 4.82 (1 H, m, C**H**OC), 2.39 (1 H, m, C**H**CH_3), 1.25 (3 H, d, *J*= 7.6 Hz, CH_3); **^{13}C NMR** (90 MHz, $CDCl_3$) δ 209.8 (**C**=O), 163.0 (COCH**C**H), 144.2 (**ArC**C), 132.6 (CO**C**H), 128.7 (**ArC**H), 128.1 (**ArC**H), 127.4 (**ArC**H), 87.9 ($OCAr_3$), 74.4 (**C**HOC), 45.7 (**C**HCH_3), 13.8 (CH_3); **IR** (thin film) ν 3058, 1716, 1092, 1051, 704 cm^{-1}; **HRMS** (FAB) *m/z* calcd for $C_{25}H_{23}O_2$ $[M+H]^+$ 355.1693, found 355.1697; **MP** 133-134 °C.

5-Methylene-4-(trityloxy)cyclopent-2-enone (131)



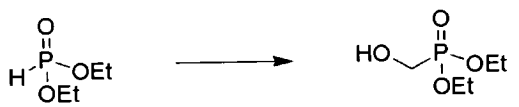
124 **131**

A solution of LHMDS (440 μL, 1.0 M in dry THF, 0.44 mmol, 1.5 equiv) in anhydrous THF (15 mL) and DMPU (5 mL) was cooled to -78 °C and 4-(trityloxy)cyclopent-2-enone (**124**) (500 mg, 1.47 mmol, 1 equiv) in dry THF (20 mL) was added dropwise *via* a cannula over 15 min. The resulting mixture was stirred at -78 °C for 60 min before transferring the mixture into a stirred suspension of Eschenmoser's Salt (681 mg, 3.68 mmol, 2.5 equiv) in dry THF (20 mL) *via* a cannula. The resulting solution was stirred at -78 °C for two hours before allowing to warm to RT and stirring for a further 30 min. The solution was then poured into a separating funnel containing Et_2O (50 ml) and saturated sodium bicarbonate solution (150 mL). The aqueous layer was extracted with DCM and the organic layers were combined and solvents removed *in vacuo*. The resulting yellow gum was taken up in DCM (50 mL) and treated with saturated sodium bicarbonate solution (15 mL). Under vigorous stirring, *m*CPBA (77%, 508 mg, 2.27 mmol, 1.5 equiv) was then added in one portion and the resulting mixture was stirred vigorously for 30 min

before separating the organic layer. The aqueous layer was extracted with DCM and the combined organic layers were dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Purification by flash column chromatography (SiO_2, DCM 100%) furnished the title compound (**131**) as a pale yellow solid (391 mg, 76% yield).

^{1}H NMR (360 MHz, $CDCl_3$) δ 7.58-7.51 (6 H, m, Ar**H**), 7.37-7.25 (9 H, m, Ar**H**), 6.32 (1 H, m, COCHC**H**), 6.19 (1 H, m, COC**H**), 6.12 (1 H, s, C**H**$_2$), 5.39 (1 H, s, C**H**$_2$), 5.12 (1 H, m, C**H**OC); **^{13}C NMR** (90 MHz, $CDCl_3$) δ 194.1 (**C**=O), 158.8 (COCH**C**H), 146.8 (**C**CH$_2$), 144.1 (**ArC**C), 136.0 (CO**C**H), 128.9 (**ArC**H), 128.1 (**ArC**H), 127.9 (**ArC**H), 118.8 (**C**H$_2$), 87.6 (O**C**Ar$_3$), 72.7 (**C**HOC); **IR** (thin film) ν 3057, 1712, 1089, 1033, 703 cm^{-1}; **MP** 78-79 °C.

Diethyl hydroxymethyl phosphonate (132)



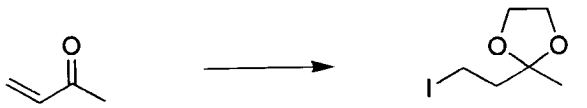
132

A mixture of diethyl phosphate (2.15 mL, 16.7 mmol, 1 equiv), paraformaldehyde (500 mg, 16.7 mmol, 1 equiv) and triethylamine (235 μL, 1.67 mmol, 0.1 equiv) was heated to 60 °C for 90 min. The resulting solution was poured into a separating funnel containing DCM and saturated NH_4Cl solution. Drying of the organic layer over $MgSO_4$, followed by filtration and solvent removal *in vacuo* yielded the title compound (**132**) as a pale yellow oil (2.19 g, 78% yield). No further purification was undertaken.

^{1}H NMR (200 MHz, CDCl3) δ 4.32-4.15 (4 H, m, C**H**$_2$CH$_3$), 3.97 (2 H, d, *J*= 6 Hz, C**H**$_2$OH), 1.41 (6 H, t, *J*= 8 Hz, CH$_2$C**H**$_3$).

The spectroscopic data were in agreement with those previously published.[39]

2-(2-iodoethyl)-2-methyl-1,3-dioxolane (144)



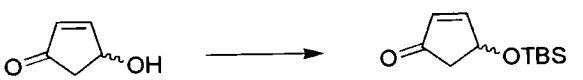
143 **144**

Me_3SiCl (32.9 mL, 257 mmol, 1.2 equiv) was added rapidly to a vigorously stirred solution of methyl vinyl ketone (**143**) (17.4 mL, 214 mmol, 1 equiv) and sodium iodide (38.5 g, 257 mmol, 1.2 equiv) in acetonitrile (600 mL). The resulting suspension was stirred vigorously for five minutes before rapid addition of ethylene glycol (14.3 mL, 257 mmol, 1.2 equiv). Following a further five minutes of vigorous stirring, the reaction mixture was poured into a separating funnel containing saturated $NaHCO_3$ solution (300 mL) and hexanes (600 mL). Three layers formed and the bottom, aqueous layer was discarded. The remaining two organic layers were washed first with 5% $Na_2S_2O_3$, then repeatedly with brine until only one organic layer remained. Drying over $MgSO_4$, filtration and removal of solvent *in vacuo* followed by flash column chromatography (SiO_2, hexanes/EtOAc 9:1) yielded dioxolane (**144**) as a light yellow oil (22.53 g, 44% yield).

^{1}H NMR (250 MHz, $CDCl_3$) δ 4.06-4.00 (4 H, m, OCH_2CH_2O), 3.30-3.18 (2 H, m, CH_2), 2.44-2.34 (2 H, m, CH_2), 1.40 (3 H, s, CH_3).

The spectroscopic data were in agreement with those previously published.[47]

***t*-Butyldimethylsiloxy-2-cyclopenten-1-one (142)**



123 **142**

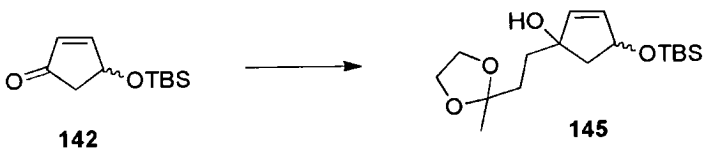
4-Hydroxycyclopent-2-enone (**123**) (13.6 g, 138 mmol, 1 equiv), triethylamine (50 mL, 360 mmol, 2.6 equiv) and DMAP (1.69g, 13.8 mmol, 0.1 equiv) were dissolved in dry DCM (150 mL) and cooled to 0 °C before addition of TBSCl (25.0g, 165 mmol, 1.2 equiv) in DCM (50 mL). The resulting mixture was then stirred at RT for 18 h before addition of H_2O (100 mL). After separation of the organic layer, the

aqueous phase was extracted with DCM and the combined organic layers were dried over $MgSO_4$, filtered and solvent removed under reduced pressure. Purification by flash column chromatography (SiO_2, EtOAc/petroleum ether (bp 40 – 60 °C) 0.5:9.5) yielded the cyclopentenone (**142**) as a yellow oil (14.18 g, 48% yield).

^{1}H NMR (250 MHz, $CDCl_3$) δ 7.33 (1 H, dd, *J*= 5.6, 2.2 Hz, COCHC**H**), 7.06 (1 H, dd, *J*= 5.6, 1.3 Hz, COC**H**), 4.86 (1 H, m, C**H**OSi), 2.58 (1 H, dd, $J_{AB, AX}$= 18.2, 6.0 Hz, $COCH_2$), 2.13 (1 H, dd, $J_{AB, AX}$= 18.2, 2.3 Hz, $COCH_2$), 0.78 (9 H, s, $SiC(CH_3)_3$), 0.02 (6 H, s, 2 x $SiCH_3$).

The spectroscopic data were in agreement with those previously published.[46]

4-(*t*-Butyldimethylsilyloxy)-1-(2-(2-methyl-1,3-dioxolan-2-yl)ethyl)cyclopent-2-enol (145)



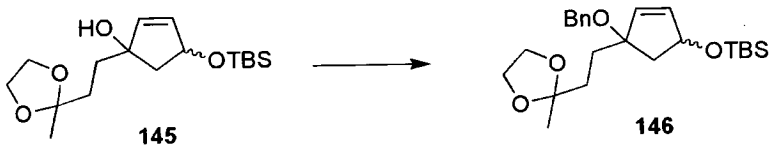
142 145

2-(2-iodoethyl)-2-methyl-1,3-dioxlane (**144**) (9.26 g, 38.2 mmol, 1.6 equiv) was dissolved in dry Et_2O (150 mL), cooled to -78 °C before dropwise addition of ^{t}butyl lithium (49.5 mL, 1.7 M in pentane, 84.1 mmol, 3.3 equiv). The resulting mixture was stirred at -78 °C for 1 h before warming to RT and stirring for an additional 1 h. The resulting solution was transferred into a solution of *t*-butyldimethylsiloxy-2-cyclopenten-1-one (**142**) (5.41 g, 25.5 mmol, 1 equiv) in dry Et_2O (75 mL) at -78 °C over a 2 h period. The resulting mixture was stirred at -78 °C for 30 min warmed to RT and decanted into a separating funnel containing saturated NH_4Cl solution (150 mL). The organic layer was washed with brine and H_2O, the aqueous layer extracted once with EtOAc before combining the organic layers, drying over $MgSO_4$, filtering and removing of the solvents under reduced pressure. Purification by flash column chromatography (SiO_2, hexanes/EtOAc 7:3) afforded a single diastereomer of alcohol (**145**) as a pale yellow oil (6.05 g, 74% yield).

^{1}H NMR (360 MHz, $CDCl_3$) δ 5.81 (1 H, dd, *J*= 5.6, 0.9 Hz, HC=C**H**), 5.77 (1 H, dd, *J*= 5.6, 1.9 Hz, **H**C=CH), 4.63 (1 H, m, C**H**OSi), 3.94-3.89 (4 H, m,

OCH_2CH_2O), 2.33 (1 H, m, CH_2COSi), 1.72-1.63 (5 H, m, CH_2COSi, 2 x CH_2), 1.29 (3 H, s, CH_3), 0.87 (9 H, s, $SiC(CH_3)$), 0.04 (6 H, s, 2 x $SiCH_3$); **^{13}C NMR** (90 MHz, $CDCl_3$) δ 138.7 (HC=CH), 135.3 (HC=CH), 109.8 (COO), 83.1 (COH), 75.2 (CHOSi), 64.6 (OCH_2CH_2O), 49.0 (CH_2COSi), 34.1 (CH_2), 33.7 (CH_2), 25.8 ($SiC(CH_3)_3$), 23.8 (CH_3), 18.1 (SiC), -4.7 (2 x $SiCH_3$); **IR** (thin film) ν 3444, 3056, 2954, 2884, 2857, 1745, 1715, 1373, 1253, 1071 cm^{-1}; **HRMS** (ES) *m/z* calcd for $C_{17}H_{36}NO_4Si$ $[M+NH_4]^+$ 346.2408, found 346.2407.

(4-(Benzyloxy)-4-(2-(2-methyl-1,3-dioxolan-2-yl)ethyl)cyclopent-2-enoloxy)(*t*-butyl)dimethylsilane (146)



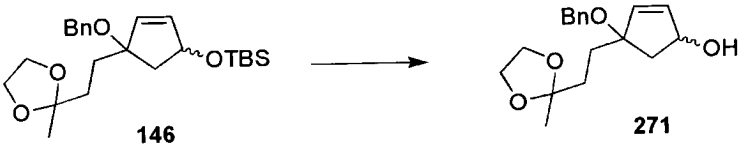
145 146

A solution of 4-(*t*-butyldimethylsilyloxy)-1-(2-(2-methyl-1,3-dioxolan-2-yl)ethyl) cyclopent-2-enol (**145**) (6.01 g, 18.3 mmol, 1 equiv) in dry THF (150 mL) was treated with sodium hydride (1.10 g, 60% in mineral oil, 27.5 mmol, 1.5 equiv) at 0 °C. The resulting mixture was warmed to RT and benzyl bromide (3.26 mL, 27.5 mmol, 1.5 equiv) and tetrabutylammonium iodide (3.38 g, 9.15 mmol, 0.5 equiv) were added. The reaction mixture was then stirred at 55 °C under nitrogen for 24 h, cooled to RT and a further 0.5 equiv of sodium hydride was added before heating to 70 °C for 18 h. Following addition of DCM (200 mL), the organic layer was washed with H_2O and brine before drying over $MgSO_4$, filtering and solvent removal *in vacuo*. Purification by flash column chromatography (SiO_2, hexanes/EtOAc 9:1) afforded cyclopentene (**146**) as a yellow oil (5.96 g, 78% yield).

^{1}H NMR (360 MHz, $CDCl_3$) δ 7.33-7.29 (5 H, m, ArH), 5.89 (1 H, dd, *J*= 5.6, 2.0 Hz, HC=CH), 5.79 (1 H, dd, *J*= 5.6, 1.1 Hz, HC=CH), 4.71 (1 H, m, CHOSi), 4.50 (1 H, d, J_{AB}= 12.2 Hz, $ArCH_2O$), 4.43 (1 H, d, J_{AB}= 12.2 Hz, $ArCH_2O$), 3.99-3.89 (4 H, m, OCH_2CH_2O), 2.29 (1 H, dd, $J_{AB,\ AX}$= 14.2, 7.3 Hz, CH_2COSi), 1.94 (1 H, dd, $J_{AB,\ AX}$= 14.2, 3.9 Hz, CH_2COSi), 1.76 (4 H, m, 2 x CH_2), 1.33 (3 H, s, CH_3), 0.92 (9 H, s, $SiC(CH_3)$), 0.11 (6 H, s, 2 x $SiCH_3$); **^{13}C NMR** (90 MHz, $CDCl_3$) δ 140.0

(**Ar**CCH_2O), 137.1 (**H**C=CH), 136.5 (HC=**C**H), 128.1 (**ArCH**), 127.0 (**ArCH**), 126.8 (**ArCH**), 110.0 (**C**OO), 88.7 ($COCH_2Ar$), 74.8 (**C**HOSi), 65.0 ($ArCH_2O$), 64.6 (OCH_2CH_2O), 43.7 (CH_2COSi), 34.7 (CH_2), 33.7 (CH_2), 25.8 ($SiC(CH_3)_3$), 23.8 (CH_3), 18.1 (Si**C**), -4.7 (2 x $SiCH_3$); **IR** (thin film) ν 2954, 2930, 2883, 2857, 1471, 1371, 1253, 1109, 1070, 836 cm^{-1}; **HRMS** (ES) *m/z* calcd for $C_{24}H_{38}NaO_4Si$ $[M+Na]^+$ 441.2432, found 441.2428.

4-(Benzyloxy)-4-(2-(2-methyl-1,3-dioxolan-2-yl)ethyl)cyclopent-2-enol (271)

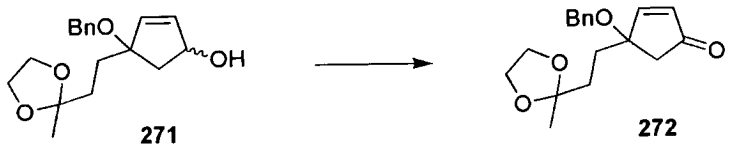


(4-(Benzyloxy)-4-(2-(2-methyl-1,3-dioxolan-2-yl)ethyl)cyclopent-2-enoloxy)(*t*-butyl)dimethylsilane (**146**) (5.80 g, 13.9 mmol, 1 equiv) was dissolved in dry THF (200 mL), TBAF (27.70 mL, 1 M in THF, 27.7 mmol, 2 equiv) was added and the resulting solution was stirred at RT under a N_2 atmosphere for 20 h. Saturated NH_4Cl solution (200 mL) was added and the mixture was transferred into a separating funnel containing Et_2O (200 mL). The organic layer was separated and the aqueous layer extracted with Et_2O. The organic layers were combined, dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Purification by flash column chromatography (SiO_2, hexanes/EtOAc 4:6) afforded the secondary alcohol (**271**) as a yellow oil (3.82 g, 91% yield).

^{1}H NMR (360 MHz, $CDCl_3$) δ 7.40-7.26 (5 H, m, Ar**H**), 6.04 (1 H, dd, *J*= 5.6, 2.1 Hz, **H**C=CH), 5.99 (1 H, dd, *J*= 5.6, 1.1 Hz, HC=C**H**), 4.74 (1 H, m, C**H**OH), 4.51 (1 H, d, J_{AB}= 11.7 Hz, OCH_2Ar), 4.46 (1 H, d, J_{AB}= 11.7 Hz, OCH_2Ar), 4.03-3.92 (4 H, m, OCH_2CH_2O), 2.38 (1 H, dd, $J_{AB,\ AX}$= 14.3, 7.3 Hz, CH_2CHOH), 1.98 (1 H, dd, $J_{AB,\ AX}$= 14.3, 3.9 Hz, CH_2CHOH), 1.85-1.75 (4 H, m, 2 x CH_2), 1.36 (3 H, s, CH_3); **^{13}C NMR** (90 MHz, $CDCl_3$) δ 139.4 (**Ar**CCH_2O), 137.8 (**H**C=CH), 136.6 (HC=**C**H), 128.2 (**ArCH**), 127.2 (**ArCH**), 127.1 (**ArCH**), 109.9 (**C**OO), 88.7 ($COCH_2Ar$), 74.8 (**C**HOH), 65.2 ($ArCH_2O$), 64.8 (OCH_2CH_2O), 43.7 (CH_2CHOH), 33.6 (CH_2), 33.5

(CH_2), 23.8 (CH_3); **IR** (thin film) ν 3408, 2959, 2880, 1709, 1376, 1259, 1068 cm^{-1}; **HRMS** (ES) *m/z* calcd for $C_{18}H_{28}NO_4$ $[M+NH_4]^+$ 322.2013, found 322.2015.

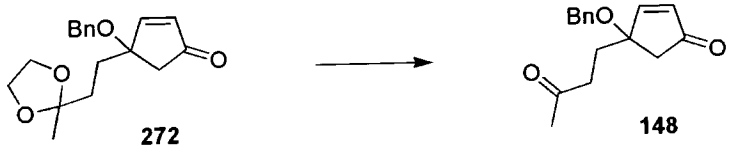
4-(Benzyloxy)-4-(2-(2-methyl-1,3-dioxolan-2-yl)ethyl)cyclopent-2-enone (272)



4-(Benzyloxy)-4-(2-(2-methyl-1,3-dioxolan-2-yl)ethyl)cyclopent-2-enol (**271**) (1.52 g, 5.01 mmol, 1 equiv) was dissolved in dry DCM (75 mL) and PDC (2.83 g, 7.51 mmol, 1.5 equiv) was added at 0 °C before stirring the reaction mixture at RT for 18 h. Filtration through a celite/silica/celite plug afforded cyclopentenone (**272**) as a yellow oil (1.28 g, 85% yield). No further purification was required.

^{1}H NMR (360 MHz, $CDCl_3$) δ 7.53 (1 H, d, *J*= 5.8 Hz, **H**C=CHCO), 7.40-7.30 (5 H, m, Ar**H**), 6.30 (1 H, d, *J*= 5.8 Hz, HC=C**H**CO), 4.47 (1 H, d, *J*= 11.5 Hz, Ar**CH$_2$**O), 4.40 (1 H, d, *J*= 11.5 Hz, Ar**CH$_2$**O), 4.03-3.95 (4 H, m, O**CH$_2$CH$_2$**O), 2.70 (1 H, d, J_{AB}= 18.6 Hz, CO**CH$_2$**), 2.47 (1 H, d, J_{AB}= 18.6 Hz, CO**CH$_2$**), 2.05-1.77 (4 H, m, 2 x **CH$_2$**), 1.37 (3 H, s, **CH$_3$**); **^{13}C NMR** (90 MHz, $CDCl_3$) δ 206.0 (**C**=O), 164.8 (**H**C=CHCO), 138.3 (**ArC**CH$_2$O), 135.6 (HC=**C**HCO), 128.4 (**ArC**H), 126.7 (**ArC**H), 127.1 (**ArC**H), 109.5 (**C**OO), 83.7 (**C**OCH$_2$Ar), 65.7 (Ar**CH$_2$**O), 64.7 (O**CH$_2$CH$_2$**O), 44.4 (**CH$_2$**CO), 33.4 (**CH$_2$**), 32.8 (**CH$_2$**), 23.9 (**CH$_3$**); **IR** (thin film) ν 2980, 2960, 2933, 2879, 1720, 1206, 1065 cm^{-1}; **HRMS** (ES) *m/z* calcd for $C_{18}H_{23}O_4$ $[M+H]^+$ 303.1591, found 303.1592.

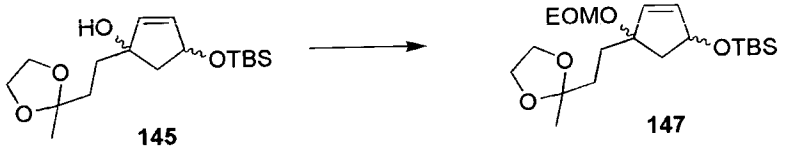
4-(Benzyloxy)-4-(3-oxobutyl)cyclopent-2-enone (148)



4-(Benzyloxy)-4-(2-(2-methyl-1,3-dioxolan-2-yl)ethyl)cyclopent-2-enone (**272**) (59 mg, 0.2 mmol, 1 equiv) was dissolved in THF (4 mL) and HCl (1 mL, 1 M) was added before stirring the reaction mixture at RT for 18 h. The solution was transferred into a separating funnel containing DCM (10 mL), organic layer separated, dried over $MgSO_4$, filtered and solvent removed under reduced pressure. Crude purified by flash colum chromatography (SiO_2, hexanes/EtOAc 1:1) to afford the title compound (**148**) as a yellow oil (50 mg, 98% yield).

^{1}H NMR (360 MHz, $CDCl_3$) δ 7.51 (1 H, d, *J*= 5.8 Hz, **H**C=CHCO), 7.40-7.30 (5 H, m, Ar**H**), 6.32 (1 H, d, *J*= 5.8 Hz, HC=C**H**CO), 4.42 (1 H, d, J_{AB}= 11.5 Hz, ArC**H**$_2$), 4.37 (1 H, d, J_{AB}= 11.5 Hz, ArC**H**$_2$), 2.75-2.63 (3 H, m, COC**H**$_2$, CH_3COC**H**$_2$), 2.43 (1 H, d, J_{AB}= 18.7 Hz, COC**H**$_2$), 2.20-2.13 (5 H, m, C**H**$_3$, $COCH_2$C**H**$_2$); **^{13}C NMR** (90 MHz, $CDCl_3$) δ 207.6 (**C**=O), 205.5 (**C**=O), 164.3 (**H**C=CH), 138.0 (**Ar**CCH_2O), 135.6 (HC=**C**H), 128.4 (**Ar**CH), 127.7 (**Ar**CH), 127.1 (**Ar**CH), 83.3 (ArCH_2O**C**), 65.7 (Ar**C**H_2O), 44.0 (CO**C**H_2), 38.2 (CH_3CO**C**H_2), 32.6 ($COCH_2$**C**H_2), 30.1 (**C**H_3); **IR** (thin film) ν 2928, 1718, 1354, 1070, 748 cm^{-1}; **HRMS** (ES) *m/z* calcd for $C_{16}H_{22}NO_3$ $[M+NH_4]^+$ 276.1594, found 276.1593.

***t*-Butyl(4-(ethoxymethoxy)-4-(2-(2-methyl-1,3-dioxolan-2-yl)ethyl)cyclopent-2-enyloxy)dimethylsilane (147)**

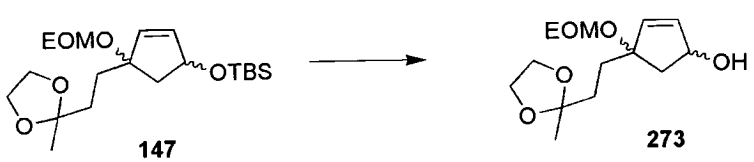


4-(*t*-Butyldimethylsilyloxy)-1-(2-(2-methyl-1,3-dioxolan-2-yl)ethyl)cyclopent-2-enol (**145**) (503 mg, 1.53 mmol, 1 equiv) was dissolved in dry DCM (25 mL), DIPEA (1.1 mL, 6.1 mmol, 4 equiv), DMAP (18 mg, 0.15 mmol, 0.1 equiv) and EOMCl (285

μL, 3.1 mmol, 2 equiv) was added and the resulting mixture was stirred at RT for 60 h. Saturated NH_4Cl solution (25 mL) was added, the organic layer was washed with H_2O and brine, dried over $MgSO_4$, filtered and solvent removed under reduced pressure. The resulting crude product was purified by flash column chromatography (SiO_2, hexanes/EtOAc 9:1) to yield cyclopentene (**147**) as a colourless oil (470 mg, 78% yield).

^{1}H NMR (360 MHz, $CDCl_3$) δ 5.85-5.80 (2 H, m, **HC**=C**H**), 4.78 (1 H, d, J_{AB}= 7.0 Hz, OC**H**$_2$O), 4.68 (1 H, d, J_{AB}= 7.0 Hz, OC**H**$_2$O), 4.65 (1 H, m, SiOC**H**), 3.95-3.90 (4 H, m, OC**H**$_2$C**H**$_2$O), 3.66-3.52 (2 H, m, CH$_3$C**H**$_2$O), 2.30 (1 H, dd, $J_{AB,\ AX}$= 14.1, 7.2 Hz, SiOCHC**H**$_2$), 1.85 (1 H, dd, $J_{AB,\ AX}$= 14.1, 4.4 Hz, SiOCHC**H**$_2$), 1.71-1.65 (4 H, m, OOCC**H**$_2$C**H**$_2$), 1.31 (3 H, s, C**H**$_3$), 1.19 (3 H, t, J= 7.1 Hz, C**H**$_3$CH$_2$O), 0.88 (9 H, s, SiC(C**H**$_3$)$_3$), 0.06 (6 H, s, Si(C**H**$_3$)$_2$); **^{13}C NMR** (90 MHz, $CDCl_3$) δ 136.8 (H**C**=CH), 136.4 (HC=**C**H), 109.9 (**C**OO), 90.0 (O**C**H$_2$O), 88.4 (HC=CH**C**OCH$_2$), 74.6 (SiO**C**H), 64.6 (O**C**H$_2$CH$_2$O), 63.0 CH$_3$**C**H$_2$O), 45.8 (SiO**C**CH$_2$), 34.7 (**C**H$_2$), 33.6 (**C**H$_2$), 25.9 (SiC(**C**H$_3$)$_3$), 23.8 (**C**H$_3$COO), 18.1 (Si**C**(CH$_3$)$_3$), 15.2 (**C**H$_3$CH$_2$O), -4.6 (Si(**C**H$_3$)$_2$); **IR** (thin film) ν 2955, 2931, 2882, 2857, 1371, 1253, 1101, 1031, 836 cm^{-1}; **HRMS** (ES) *m/z* calcd for $C_{20}H_{42}NO_5Si$ $[M+NH_4]^+$ 404.2827, found 404.2827.

4-(Ethoxymethoxy)-4-(2-(2-methyl-1,3-dioxolan-2-yl)ethyl)cyclopent-2-enol (273)



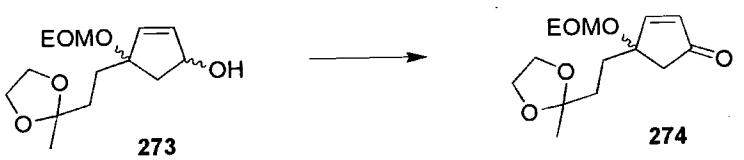
147 273

t-Butyl(4-(ethoxymethoxy)-4-(2-(2-methyl-1,3-dioxolan-2-yl)ethyl)cyclopent-2-enyloxy)dimethylsilane (**147**) (4.70 g, 12.2 mmol, 1 equiv) was dissolved in THF (200 mL) and TBAF (24.3 mL, 1 M in THF, 24.3 mmol, 2 equiv) was added before stirring the reaction mixture at RT for 2 h. Saturated NH_4Cl solution (200 mL) was added and the resulting mixture was transferred into a separating funnel containing Et_2O (200 mL). The aqueous layer was extracted twice with Et_2O and the combined

organic layers were dried over $MgSO_4$, filtered and the solvent was removed *in vacuo*. Purification by flash column chromatography (SiO_2, hexanes/EtOAc 7:3) furnished the secondary alcohol (**273**) as a pale yellow oil (3.31 g, 99% yield).

^{1}H NMR (360 MHz, $CDCl_3$) δ 6.18 (1 H, dd, *J*= 2.4, 5.6 Hz, COHCH=C**H**), 5.72 (1 H, d, *J*= 5.6 Hz, COHC**H**=CH), 4.94 (1 H, d, J_{AB}= 7.9 Hz, OC**H**$_2$O), 4.65 (1 H, d, J_{AB}= 7.9 Hz, OC**H**$_2$O), 4.58 (1 H, m, C**H**OH), 3.95-3.90 (4 H, m, OC**H**$_2$C**H**$_2$O), 3.81-3.49 (2 H, m, CH_3C**H**$_2$O), 2.24 (1 H, dd, $J_{AB,\ AX}$= 15.2, 7.6 Hz, CHOHC**H**$_2$), 1.95 (1 H, dd, $J_{AB,\ AX}$= 15.2, 1.8 Hz, CHOHC**H**$_2$), 1.73-1.67 (4 H, m, COOC**H**$_2$C**H**$_2$), 1.30 (3 H, s, C**H**$_3$), 1.19 (3 H, t, *J*= 7.1 Hz, C**H**$_3$CH$_2$O); **^{13}C NMR** (90 MHz, $CDCl_3$) δ 139.1 (**H**C=CHCOH), 135.4 (HC=**C**HCOH), 109.9 (**C**OO), 90.1 (**O**CH$_2$O), 88.5 (HC=CH**C**OCH$_2$), 75.1 (**C**HOH), 64.6 (**O**CH$_2$CH$_2$O), 62.9 (CH$_3$**C**H$_2$O), 44.5 (CHOH**C**H$_2$), 35.0 (**C**H$_2$), 33.6 (**C**H$_2$), 23.8 (**C**H$_3$), 14.6 (**C**H$_3$CH$_2$O); **IR** (thin film) ν 3433, 2976, 2881, 1094, 1031 cm^{-1}.

4-(Ethoxymethoxy)-4-(2-(2-methyl-1,3-dioxolan-2-yl)ethyl)cyclopent-2-enone (274)



273 274

4-(Ethoxymethoxy)-4-(2-(2-methyl-1,3-dioxolan-2-yl)ethyl)cyclopent-2-enol (**273**) (3.31 g, 12.2 mmol, 1 equiv) was dissolved in dry DCM (250 mL) and cooled to 0 °C. Following addition of PDC (6.86 g, 18.2 mmol, 1.5 equiv), the reaction mixture was stirred at RT for 18 h. Filtration through a celite plug followed by flash column chromatography (SiO_2, hexanes/EtOAc 7:3) afforded cyclopentenone (**274**) as a pale yellow oil (2.97 g, 91% yield).

^{1}H NMR (360 MHz, $CDCl_3$) δ 7.49 (1 H, d, *J*= 5.8 Hz, **H**C=CHCO), 6.20 (1 H, d, *J*= 5.8 Hz, HC=C**H**CO), 4.70 (1 H, d, J_{AB}= 7.7 Hz, OC**H**$_2$O), 4.64 (1 H, d, J_{AB}= 7.7 Hz, OC**H**$_2$O), 3.98-3.88 (4 H, m, OC**H**$_2$C**H**$_2$O), 3.59 (2 H, q, *J*= 7.1 Hz, CH$_3$C**H**$_2$O), 2.68 (1 H, d, J_{AB}= 18.7 Hz, COC**H**$_2$), 2.42 (1 H, d, J_{AB}= 18.7 Hz, COC**H**$_2$), 1.91-1.71 (4 H, m, COOC**H**$_2$C**H**$_2$), 1.31 (3 H, s, C**H**$_3$), 1.18 (3 H, t, *J*= 7.1 Hz, C**H**$_3$CH$_2$O); **^{13}C**

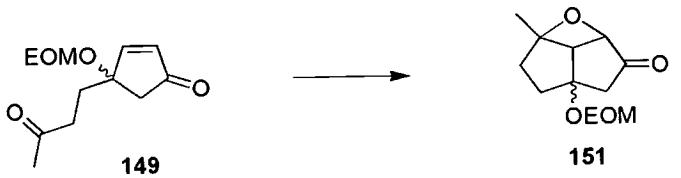
NMR (90 MHz, $CDCl_3$) δ 206.2 (**C**=O), 165.0 (**H**C=CHCO), 134.8 (HC=**C**HCO), 109.5 (**C**OO), 90.4 (O**C**H_2O), 83.4 (COCH_2**C**), 64.8 (O**C**H_2CH_2O), 63.5 (CH_3CH_2O), 45.9 (CO**C**H_2), 33.5 (**C**H_2), 33.2 (**C**H_2), 24.0 (**C**H_3), 15.1 (**C**H_3CH_2O); **IR** (thin film) ν 2977, 2935, 2883, 1720, 1027 cm^{-1}; **HRMS** (ES) *m/z* calcd for $C_{14}H_{22}NaO_5$ $[M+Na]^+$ 293.1359, found 293.1355.

4-(Ethoxymethoxy)-4-(3-oxobutyl)cyclopent-2-enone (149)

4-(Ethoxymethoxy)-4-(2-(2-methyl-1,3-dioxolan-2-yl)ethyl)cyclopent-2-enone (**274**) (170 mg, 0.63 mmol, 1 equiv) was dissolved in THF (10 mL), HCl solution (2 mL, 0.5 M) was added and the resulting solution was stirred at RT for 23 h. Following addition of saturated $NaHCO_3$ solution (10 mL) and DCM (10 mL), the organic layer was separated, dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Flash column chromatography (SiO_2, hexanes/EtOAc 1:1) furnished the title compound (**149**) as a colourless oil (109 mg, 76% yield).

1H NMR (360 MHz, CDCl3) δ 7.45 (1 H, d, *J*= 5.8 Hz, **H**C=CHCO), 6.20 (1 H, d, *J*= 5.8 Hz, HC=C**H**CO), 4.65 (1 H, d, J_{AB}= 7.7 Hz, OC**H**$_2$O), 4.60 (1 H, d, J_{AB}= 7.7 Hz, OC**H**2O), 3.56 (2 H, q, *J*= 7.1 Hz, CH$_3$C**H**$_2$O), 2.68 (1 H, d, J_{AB}= 18.7 Hz, COC**H**$_2$), 2.66-2.46 (2 H, m, C**H**$_2$), 2.36 (1 H, d, J_{AB}= 18.7 Hz, COC**H**$_2$), 2.15 (3 H, s, C**H**$_3$), 1.16 (3 H, t, *J*= 7.1 Hz, C**H**$_3$CH$_2$O); ^{13}**C NMR** (90 MHz, $CDCl_3$) δ 207.4 (**C**=O), 205.6 (**C**=O), 164.4 (H**C**=CHCO), 135.0 (HC=**C**HCO), 90.3 (O**C**H_2O), 82.9 (COCH_2**C**), 63.5 (CH_3CH_2O), 45.6 (COCH_2C) 38.1 (COCH_2CH_2C), 32.8 (COCH_2CH2C), 15.0 (CH_3); **IR** (thin film) ν 2975, 2932, 2888, 1720, 1354, 1105, 1026 cm^{-1}; **HRMS** (ES) *m/z* calcd for $C_{12}H_{22}O_4N$ $[M+NH_4]^+$ 244.1543, found 244.1543.

Oxetane (151)

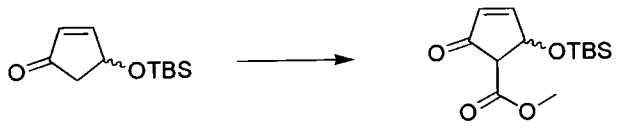


149 151

4-(Ethoxymethoxy)-4-(3-oxobutyl)cyclopent-2-enone (**149**) (55.3 mg, 0.24 mmol, 1 equiv) was dissolved in toluene (200 mL) and the solution deoxygenated using a flow of nitrogen gas for 90 minutes. The solution was immersed into an ice bath and irradiated with a 400 W medium pressure mercury lamp using a pyrex filter. The reaction was monitored by TLC and stopped after 1.5 h and the solvent was evaporated. Purification of the resulting residue by flash chromatography (SiO_2, hexanes/EtOAc 1:1) afforded oxetane (**151**) as a yellow oil (19 mg, 35% yield).

^{1}H NMR (360 MHz, $CDCl_3$) δ 4.76 (2 H, s, OCH_2O), 4.63 (1 H, d, J= 5.6 Hz, OCHC=O), 3.59 (2 H, q, J= 7.1 Hz, CH_3CH_2O), 3.03 (1 H, d, J= 5.6 Hz, CHCHC=O), 2.89 (1 H, d, J_{AB}= 17.6 Hz, CH_2C=O), 2.84 (1 H, d, J_{AB}= 17.6 Hz, CH_2C=O), 2.39 (1 H, m, CH_2), 2.19 (1 H, m, CH_2), 1.87 (2 H, m, CH_2), 1.63 (3 H, s, CH_3), 1.18 (3 H, t, J= 7.1 Hz, CH_3CH_2O); **^{13}C NMR** (90 MHz, $CDCl_3$) δ 210.5 (C=O), 95.3 (CH_3COC), 91.5 (OCH_2O), 90.0 (CCH_2C=O), 77.4 (OCHC=O), 63.6 (CH_3CH_2O), 58.2 (CHCHC=O), 55.2 (CH_2C=O), 39.0 (CH_2), 37.9 (CH_2), 23.7 (CH_3), 15.0 (CH_3CH_2O); **IR** (thin film) ν 2971, 2930, 1752, 1034 cm^{-1}; **HRMS** (ES) *m/z* calcd for $C_{12}H_{18}O_4Na$ $[M+Na]^+$ 249.1097, found 249.1094.

Methyl-2-(*tert*-butyldimethylsilyloxy)-5-oxocyclopent-3-enecarboxylate (155)



142 155

To a solution of *t*-butyldimethylsiloxy-2-cyclopenten-1-one (**142**) (194 mg, 0.92 mmol, 1 equiv) in anhydrous THF (5 mL) at -78 °C was added LHMDS (1.1 ml, 1.0 M in THF, 1.1 mmol, 1.2 equiv) and the resulting solution was stirred at -78 °C for 45 min. Following addition of HMPA (165 μL, 0.92 mmol, 1 equiv) and methyl cyanoformate (145 μL, 1.84 mmol, 2 equiv), the resulting mixture was stirred at -78 °C for a further 2.5 h before quenching with H_2O (10 mL). Ether extractions, followed by drying of the combined organic layers over MgSO4, filtering and removal of solvent under reduced pressure afforded the crude product which was purified by flash column chromatography (SiO_2, hexanes/EtOAc 8:2) to furnish a single diastereomer of ketoester (**155**) as a colourless oil (182 mg, 73% yield).

^{1}H NMR (360 MHz, $CDCl_3$) δ 7.48 (1 H, m, **H**C=CHCO), 6.17 (1 H, m, HC=C**H**CO), 5.29 (1 H, m, SiOC**H**), 3.78 (3 H, s, CO_2CH_3), 3.28 (1 H, m, COC**H**CO_2), 0.89 (9 H, s, SiC(CH_3)), 0.12 (3 H, s, SiCH_3), 0.09 (3 H, s, SiCH_3); **^{13}C NMR** (90 MHz, $CDCl_3$) δ 199.1 (**C**=O), 168.6 (CO_2), 163.5 (H**C**=CHCO), 132.5 (HC=**C**HCO), 72.3 (SiOCH), 61.7 (COCHCO_2), 52.6 (CO_2CH_3), 25.6 (SiC(CH_3)$_3$), 17.9 (Si**C**(CH_3)$_3$), -4.9 (Si(CH_3)$_2$); **IR** (thin film) ν 2854, 2931, 2857, 1745, 1721, 1260, 839 cm^{-1}; **HRMS** (ES) *m/z* calcd for $C_{13}H_{26}NO_4Si$ $[M+NH_4]^+$ 288.1626, found 288.1626.

5-Methyl-4-(*tert*-butyldimethylsilyloxy)cyclopent-2-enone (156)

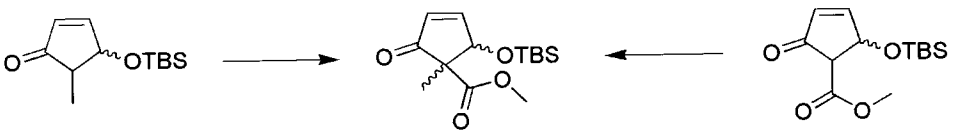
142 156

To a solution of *t*-butyldimethylsiloxy-2-cyclopenten-1-one (**142**) (178 mg, 0.84 mmol, 1 equiv) in anhydrous THF (5 mL) at -82 °C was added LHMDS (0.92 ml, 1.0

M in THF, 0.92 mmol, 1.1 equiv) and the resulting solution was stirred at -82 °C for 45 min. Following addition of HMPA (295 μL, 1.7 mmol, 2 equiv) and iodomethane (260 μL, 4.2 mmol, 5 equiv), the resulting mixture was stirred at -82 °C for 2.5 h before quenching with saturated NH_4Cl solution (10 mL). Ether extractions, followed by drying of the combined organic layers over $MgSO_4$, filtering and removal of solvent under reduced pressure afforded the crude product which was purified by flash column chromatography (SiO_2, DCM, 100%) to furnish a single diastereomer of the title compound (**156**) as a pale yellow oil (98 mg, 52% yield).

^{1}H NMR (360 MHz, $CDCl_3$) δ 7.39 (1 H, dd, *J*= 5.8, 2.3 Hz, COCH=C**H**), 6.15 (1 H, dd, *J*= 5.8, 1.2 Hz, COC**H**=CH), 4.92 (1 H, m, SiOC**H**), 2.47 (1 H, m, COC**H**CH_3),1.09-1.07 (3 H, d, *J*= 7.6 Hz, COCHC**H**$_3$), 0.90 (9 H, s, SiC(C**H**$_3$)$_3$), 0.13 (3 H, s, Si(C**H**$_3$)$_2$), 0.12 (3 H, s, Si(C**H**$_3$)$_2$); **^{13}C NMR** (90 MHz, $CDCl_3$) δ 210.4 (**C**=O), 162.7 (COCH=**C**H), 133.0 (CO**C**H=CH), 72.4 (SiO**C**H), 55.3 (CO**C**HCH$_3$), 25.7 (SiC(**C**H$_3$)$_3$, 18.2 (Si**C**(CH$_3$)$_3$, 11.5 (COCH**C**H$_3$), -4.7 (Si(**C**H$_3$)$_2$, -4.9 (Si(**C**H$_3$)$_2$; **IR** (thin film) ν 2925, 2854, 1711, 1255 cm^{-1}, **HRMS** (ES) *m/z* calcd for $C_{12}H_{23}O_2Si$ $[M+H]^+$ 227.1462, found 227.1464.

Methyl-2-(*tert*-butyldimethylsilyloxy)-1-methyl-5-oxocyclopent-3-enecarboxylate (157)



156 **157** **155**

Methyl-2-(*t*-butyldimethylsilyloxy)-5-oxocyclopent-3-enecarboxylate (**155**) (135 mg, 0.5 mmol, 1 equiv) was dissolved in anhydrous THF (5 mL) and cooled to -78 °C before addition of LHMDS (550 μL, 1.0 M in THF, 0.6 mmol, 1.1 equiv). The resulting solution was stirred at -78 °C for 40 min before addition of HMPA (88 μL, 0.50 mmol, 1 equiv) and iodomethane (63 μL, 1.00 mmol, 2 equiv). After stirring at -78 °C for a further 3 hours, the reaction mixture was allowed to warm to RT and was stirred for 18 h. Following aqueous workup and flash column chromatography (SiO_2,

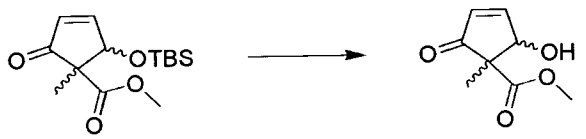
hexanes/EtOAc 8:2), the title compound (**157**) was obtained as a pale yellow oil (87 mg, 61% yield, 9:1 ratio of diastereomers).

Alternative method:

5-Methyl-4-(*t*-butyldimethylsilyloxy)cyclopent-2-enone (**156**) (47 mg, 0.21 mmol, 1 equiv) was dissolved in anhydrous THF (5 mL) and cooled to -78 °C before addition of LHMDS (320 μL, 1.0M in THF, 0.32 mmol, 1.5 equiv). The resulting mixture was stirred at -78 °C for 50 min before addition of HMPA (75 μL, 0.42 mmol, 2 equiv) and methylcyanoformate (85 μL, 1.05 mmol, 5 equiv). After stirring at -78 °C for a further 110 min, H_2O (5 mL) was added and the mixture was extracted with Et_2O, dried over $MgSO_4$, filtered and the solvent removed. Following flash column chromatography (SiO_2, hexanes/EtOAc 8:2), the title compound (**157**) was obtained as a colourless oil (32 mg, 54% yield, single diastereomer, identical by NMR to major diastereomer of first synthetic method).

^{1}H NMR (360 MHz, $CDCl_3$) major diastereomer δ 7.43 (1 H, dd, *J*= 5.7, 2.2 Hz, COHCH=C**H**), 6.17 (1 H, dd, *J*= 5.7, 1.6 Hz, COHC**H**=CH), 5.20 (1 H, dd, *J*= 2.2, 1.6 Hz, SiOC**H**), 3.72 (3 H, s, $CO_2C\mathbf{H_3}$), 1.28 (3 H, s, $COCC\mathbf{H_3}$), 0.91 (9 H, s, $OSiC(C\mathbf{H_3})_3$), 0.14 (3 H, s, $OSi(C\mathbf{H_3})_2$, 0.09 (3 H, s, $OSi(C\mathbf{H_3})_2$); **^{13}C NMR** (90 MHz, $CDCl_3$) major diastereomer δ 204.2 (**C**=O), 171.8 (O**C**=O), 163.4 (H**C**=CHCO), 131.3 (HC=**C**HCO), 76.5 (SiO**C**H), 60.1 (C=O**C**$(C)_3$), 52.6 ($CO_2\mathbf{C}H_3$), 25.7 ($SiC(\mathbf{C}H_3)_3$), 18.1 ($SiC(CH_3)_3$), 16.2 ($C{=}OC\mathbf{C}H_3$), -4.9 ($Si(\mathbf{C}H_3)_2$), -5.0 ($Si(\mathbf{C}H_3)_2$) ; **IR** (thin film) ν 2955, 2932, 2887, 2859, 1747, 1715, 1643, 1253, 1113, 838, 778 cm^{-1}; **HRMS** (ES) *m/z* calcd for $C_{14}H_{25}O_4Si$ $[M+H]^+$ 285.1517, found 285.1517.

Methyl-2-hydroxy-1-methyl-5-oxocyclopent-3-enecarboxylate (275)

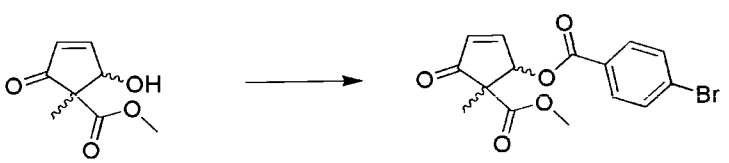


157 **275**

Methyl-2-(*t*-butyldimethylsilyloxy)-1-methyl-5-oxocyclopent-3-enecarboxylate (**157**) (55 mg, 0.19 mmol, 1 equiv) was dissolved in THF (5 mL) and cooled to 0 °C. Following addition of acetic acid (12 μL, 0.19 mmol, 1 equiv) and TBAF (190 μL, 1.0 M in THF, 0.19 mmol, 1 equiv) the resulting mixture was stirred first at 0 °C for 40 min, then at RT for 4 h before adding an excess of saturated NH_4Cl solution. Et_2O extractions, followed by drying, filtering and solvent removal afforded a crude mixture which was purified by flash column chromatography (SiO_2, hexanes/EtOAc 1:4) to afford secondary alcohol (**275**) as a colourless oil (24 mg, 73% yield).

^{1}H NMR (360 MHz, $CDCl_3$) δ 7.58 (1 H, dd, *J*= 5.8, 2.3 Hz, COCH=C**H**), 6.24 (1 H, dd, *J*= 5.8, 1.6 Hz, COC**H**=CH), 5.27 (1 H, m, HOC**H**), 3.72 (3 H, s, CO_2CH_3), 2.47 (1 H, m, **OH**), 1.35 (3 H, s, $COCCH_3$); **^{13}C NMR** (90 MHz, $CDCl_3$) δ 205.1 (**C**=O), 172.8 (CO_2), 163.4 (COCH=**C**H), 133.4 (**CO**CH=CH), 77.0 (**HO**CH), 60.3 ($COCCO_2$), 53.8 (CO_2CH_3), 16.6 ($COCCH_3$); **IR** (thin film) ν 3467, 2993, 2956, 1739, 1708, 1252, 845 cm^{-1}; **HRMS** (ES) *m/z* calcd for $C_8H_{14}NO_4$ $[M+NH_4]^+$ 188.0917, found 188.0916.

5-(Methoxycarbonyl)-5-methyl-4-oxocyclopent-2-enyl-4-bromobenzoate (276)



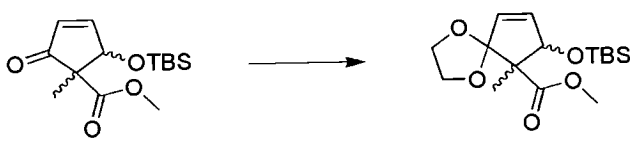
275 **276**

Methyl-2-hydroxy-1-methyl-5-oxocyclopent-3-enecarboxylate (**275**) (46 mg, 0.27 mmol, 1 equiv) was dissolved in anhydrous DCM (5 mL). Following addition of 4-bromobenzoylchloride (119 mg, 0.54 mmol, 2 equiv), DMAP (4 mg, 0.03 mmol, 0.1

equiv) and NEt_3 (45 μL, 0.32 mmol, 1.2 equiv), the solution was stirred at RT for 24 h. Saturated NH_4Cl solution was added, washed with DCM and the organic layer was washed with brine, dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Flash column chromatography (SiO_2, hexanes/EtOAc/hexane 9:1) afforded a crystalline, colourless solid (59 mg, 62% yield).

^{1}H NMR (360 MHz, $CDCl_3$) δ 7.91-7.87 (2 H, m, 2 x Ar**H**), 7.70 (1 H, dd, *J*= 5.8, 2.4 Hz, COCH=C**H**), 7.62-7.58 (2 H, m, 2 x Ar**H**), 6.41 (1 H, dd *J*= 5.8, 1.7 Hz, COC**H**=CH), 6.36 (1 H, m, CH=CHC**H**O), 3.79 (3 H, s, CO_2CH_3), 1.25 (3 H, s, $COCCH_3$); **^{13}C NMR** (90 MHz, $CDCl_3$) δ 202.6 (**C**=O), 170.3 (Ar**C**=O), 164.9 (CO_2CH_3), 158.6 (COCH=**C**H), 133.8 (CO**C**H=CH), 131.9 (2 x **ArC**H), 131.2 (2 x **ArC**H), 129.0 (**ArC**Br), 127.6 (**ArC**CO_2), 77.6 (OCHCH=CH), 58.2 (C=O**C**CH_3), 53.0 (CO_2CH_3), 15.6 (C=OCCH_3); **IR** (thin film) ν 2994, 2953, 1751, 1719, 1591, 1267, 1099, 1012 cm^{-1}; **HRMS** (EI) *m/z* calcd for $C_{15}H_{13}BrO_5$ $[M]^+$ 351.9941, found 351.9943; **MP** 91-92 °C.

Dioxolane (158)



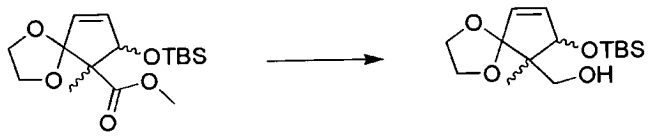
157 **158**

Methyl-2-(*t*-butyldimethylsilyloxy)-1-methyl-5-oxocyclopent-3-enecarboxylate (**157**) (244 mg, 0.86 mmol, 1 equiv) was dissolved in toluene and following addition of ethylene glycol (240 μL, 4.30 mmol, 5 equiv) and catalytic amount of tosic acid the mixture was refluxed under Dean-Stark conditions (oil bath temperature: 140 °C) for 48 h. After cooling to RT, the reaction mixture was washed with saturated sodium bicarbonate solution, dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. Flash column chromatography (SiO_2, hexanes/EtOAc 4:1) afforded dioxolane (**158**) as a pale yellow oil (107 mg, 38% yield).

^{1}H NMR (360 MHz, $CDCl_3$) δ 5.89 (1 H, dd, *J*= 5.9, 1.7 Hz, SiOCHC**H**=CH), 5.58 (1 H, dd, *J*= 5.9, 1.6 Hz, SiOCHCH=C**H**), 5.44 (1 H, t, J= 1.6 Hz, SiOC**H**CH=CH),

4.12 (1 H, m, $O(CH_2)_2O$), 3.98 (1 H, m, $O(CH_2)_2O$), 3.89-3.78 (2 H, m, $O(CH_2)_2O$), 3.71 (3 H, s, CO_2CH_3), 1.22 (3 H, s, $SiOCHCCH_3$), 0.91-0.87 (9 H, m, $SiC(CH_3)_3$), 0.15-0.06 (6 H, m, $Si(CH_3)_2$); **^{13}C NMR** (90 MHz, $CDCl_3$) δ 173.8 (CO_2), 138.7 ($SiOCHCH=CH$), 129.3 ($SiOCHCH=CH$), 118.1 (COO), 76.8 (SiOCH), 65.8 ($O(CH_2)_2O$), 65.1 ($O(CH_2)_2O$), 61.3 ($SiOCHCCH_3$), 51.8 (CO_2CH_3), 29.7 ($SiC(CH_3)_3$), 18.1 ($SiC(CH_3)_3$), 15.2 ($SiOCHCH_3$), -4.8 ($Si(CH_3)_2$), -4.9 ($Si(CH_3)_2$); **IR** (thin film) ν 2953, 2930, 2895, 2857, 1736, 1246, 1083 cm^{-1}; **HRMS** (ES) *m/z* calcd for $C_{16}H_{29}O_5Si$ $[M+H]^+$ 329.1779, found 329.1782.

Alcohol (277)

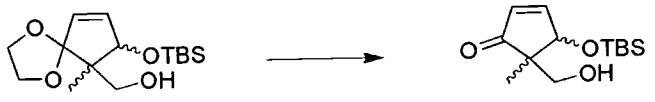


158 **277**

Dioxolane (**158**) (50 mg, 0.15 mmol, 1 equiv) was dissolved in anhydrous Et_2O (5 mL) and treated with $LiAlH_4$ powder (12 mg, 0.31 mmol, 2 equiv) at 0 °C. Following 10 min of stirring at at 0 °C, H_2O (25 μL) was carefully added, followed by NaOH solution (75 μL, 1 M) and H_2O (75 μL). The resulting slurry was allowed to stir for 20 min before addition of excess $MgSO_4$ and stirring for a further 20 min. Filtration, solvent removal and flash column chromatography (SiO_2, hexanes/EtOAc 3:2) afforded alcohol (**277**) as a colourless oil (34 mg, 76% yield).

^{1}H NMR (360 MHz, $CDCl_3$) δ 5.96 (1 H, dd, *J*= 6.0, 1.6 Hz, $CO_2CH=CH$), 5.69 (1 H, dd, *J*= 6.0, 1.6 Hz, $CO_2CH=CH$), 4.98 (1 H, m, SiOCH), 4.02-3.93 (4 H, m, OCH_2CH_2O), 3.65 (1 H, m, $HOCH_2C$), 3.47 (1 H, m, $OHCH_2C$), 0.89 (9 H, s, $SiC(CH_3)_3$), 0.84 (3 H, s, $SiOCHCCH_3$), 0.09 (6 H, s, $Si(CH_3)_2$); **^{13}C NMR** (90 MHz, $CDCl_3$) δ 139.3 ($SiOCH=CH$), 129.7 ($SiOCH=CH$), 119.5 (CO_2), 75.1 (SiOCH), 65.3 ($HOCH_2$), 64.8 ($O(CH_2)_2O$), 64.4 ($O(CH_2)_2O$), 53.5 ($SiOCHCCH_3$), 25.8 ($SiC(CH_3)_3$), 18.1 ($SiC(CH_3)_3$), 14.4 ($SiOCHCCH_3$), -4.7 ($Si(CH_3)_2$), -5.0 ($Si(CH_3)_2$); **IR** (thin film) ν 3541, 2954, 2930, 2885, 2857, 1718, 1255, 1084, 879cm^{-1}; **HRMS** (ES) *m/z* calcd for $C_{15}H_{29}O_4Si$ $[M+H]^+$ 301.1830, found 301.1831.

Enone (159)

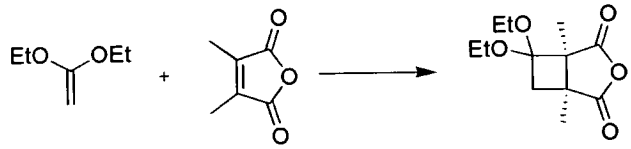


277 159

Alcohol (**277**) (34 mg, 0.11 mmol, 1 equiv), dissolved in a THF/H_2O mixture (5:1 mL), was treated with a catalytic amount of tosic acid and refluxed (oil bath temperature: 76 °C) for 2 h. After cooling to RT, H_2O (10 mL) and Et_2O (10 mL) was added, the organic layer was separated, dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Purification by flash column chromatography (SiO_2, hexanes/EtOAc 3:2) furnished enone (**159**) as a colourless oil (14 mg, 52% yield).

^{1}H NMR (360 MHz, $CDCl_3$) δ 7.34 (1 H, dd, *J*= 5.9, 2.1 Hz, COCH=C**H**), 6.16 (1 H, dd, *J*= 5.9, 1.4 Hz, COC**H**=CH), 4.92 (1 H, m, SiOC**H**), 3.83 (1 H, d, J_{AB}= 10.9 Hz, HOC$\mathbf{H}_2$), 3.53 (1 H, d, J_{AB}= 10.9 Hz, HOC$\mathbf{H}_2$), 0.95 (3 H, s, COCC$\mathbf{H}_3$), 0.91 (9 H, s, SiC(C$\mathbf{H}_3$)$_3$), 0.09 (3 H, s, Si(C$\mathbf{H}_3$)$_2$), 0.06 (3 H, s, Si(C$\mathbf{H}_3$)$_2$); **^{13}C NMR** (90 MHz, $CDCl_3$) δ 211.0 (**C**=O), 163.9 (COCH=**C**H), 132.3 (CO**C**H=CH), 74.4 (SiO**C**H), 65.2 (HO$\mathbf{C}H_2$), 55.0 (HO$\mathbf{C}H_2$C), 25.7 (SiC(**C**H_3)), 18.0 (Si**C**(CH_3)), 16.1 (COC**C**H_3), -4.7 (Si**C**H_3), -4.8 (Si**C**H_3); **IR** (thin film) ν 3433, 2930, 1715, 1118, 875 cm^{-1}; **HRMS** (ES) *m/z* calcd for $C_{13}H_{25}O_3Si$ $[M+H]^+$ 257.1567, found 257.1570.

6,6-Diethoxy-1,5-dimethyl-3-oxabicyclo[3.2.0]heptane-2,4-dione (173)



167 19 173

A solution of 2,3-dimethylmaleic anhydride (**19**) (2.01 g, 15.9 mmol, 1 equiv) and diethyl ketene acetal (**167**) (8.5 mL, 64 mmol, 4 equiv) in acetonitrile (370 mL) and acetone (40 mL) was degassed by bubbling a stream of N_2 through it for 45 min. Irradiation using a 400 W medium pressure mercury lamp with a pyrex filter for 12 h under water cooling, followed by solvent removal *in vacuo* afforded the crude product which was purified by flash column chromatography (SiO_2, hexanes/EtOAc 9:1), furnishing the title compound as a pale yellow oil (3.53 g, 91% yield).

^{1}H NMR (360 MHz, $CDCl_3$) δ 3.54-3.41 (4 H, m, 2 x OCH_2CH_3), 2.71 (1 H, d, J_{AB}= 13.2 Hz, CH_2COO), 2.26 (1 H, d, J_{AB}= 13.2 Hz, CH_2COO), 1.36 (3 H, s, CH_3), 1.32 (3 H, s, CH_3), 1.21 (3 H, t, J= 7.0 Hz, OCH_2CH_3), 1.15 (3 H, t, J= 7.0 Hz, OCH_2CH_3); **^{13}C NMR** (90 MHz, $CDCl_3$) δ 176.2 (C=O), 172.1 (C=O), 99.2 ($C(OCH_2CH_3)_2$), 59.6 (CCH_3), 58.6 (OCH_2CH_3), 58.4 (OCH_2CH_3), 41.9 (CH_2COO), 41.4 (CCH_3), 15.9 (CH_3), 14.9 (CH_3), 14.8 (CH_3), 10.2 (CH_3); **IR** (thin film) ν 2980, 2359, 1844, 1779, 963 cm^{-1}; **HRMS** (CI) *m/z* calcd for $C_{12}H_{19}O_5$ $[M+H]^+$ 243.1227, found 243.1227.

(2,2-Diethoxy-4-hydroxymethyl-1,4dimethylcyclobutyl)methanol (174)

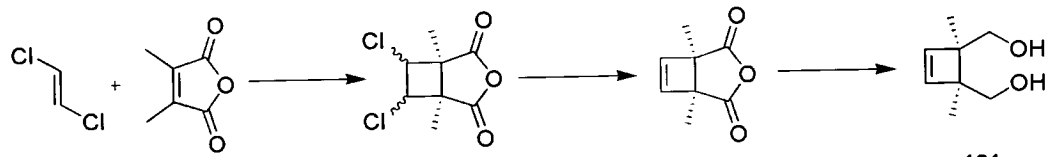
173 174

6,6-Diethoxy-1,5-dimethyl-3-oxabicyclo[3.2.0]heptane-2,4-dione (**173**) (13.4 g, 55.1 mmol, 1 equiv) in Et_2O (400 mL) was cooled to 0 °C and following careful addition of $LiAlH_4$ powder (8.36 g, 220 mmol, 4 equiv), the reaction mixture was stirred for 1 h at 0 °C, then at RT for a further 20 h. The resulting suspension was quenched by

addition of H_2O (4 mL), NaOH solution (1.0 M, 10 mL) and H_2O (10 mL) and dried by the addition of excess anhydrous $MgSO_4$. Filtration, removal of solvent under reduced pressure and flash column chromatography (SiO_2, hexanes/EtOAc 3:1) afforded diol (**174**) as a colourless semi-solid (11.7 g, 91% yield). Readily decomposes upon storage and prolonged contact with silica.

^{1}H NMR (360 MHz, $CDCl_3$) δ 4.07-3.99 (2 H, m, $HOCH_2$), 3.57-3.30 (6 H, m, $HOCH_2$, 2 x OCH_2CH_3), 1.88 (1 H, d, J_{AB}= 12.7 Hz, CH_2COO), 1.76 (1 H, d, J_{AB}= 12.7 Hz, CH_2COO), 1.19-1.13 (12 H, m, 2 x CH_3, 2 x OCH_2CH_3); **^{13}C NMR** (90 MHz, $CDCl_3$) δ 102.6 ($C(OCH_2CH_3)_2$), 69.0 ($HOCH_2$), 66.2 ($HOCH_2$), 57.8 (OCH_2CH_3), 57.1 (OCH_2CH_3), 52.6 ($HOCH_2C$), 38.3 (CH_2COO), 36.7 ($HOCH_2C$), 20.6 (CH_3), 16.0 (CH_3), 15.0 (CH_3), 14.9 (CH_3); **IR** (thin film) ν 3336, 2974, 2931, 1249, 1042 cm^{-1}; **HRMS** compound unstable, characterisation by mass spectrometry unsuccessful.

(4-Hydroxymethyl-1,4-dimethylcyclobut-2-enyl)-methanol (181)



46 19 47 180 181

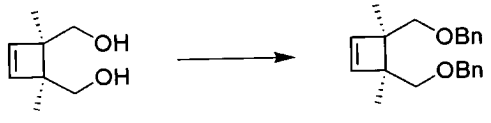
Dimethylmaleic anhydride (**19**) (20 g, 159 mmol, 1 equiv) and benzophenone (2.83 g, 15.5 mmol, 0.1 equiv) were dissolved in acetone (2.6 L) and the solution was degassed with N_2 for 1 h before addition of 1,2-*trans*-dichloroethene (**46**) (46.4 mL, 600 mmol, 4 equiv). The resulting solution was irradiated for 2.5 h under water cooling with a 400 W medium pressure mercury lamp, equipped with a pyrex filter. Following solvent removal *in vacuo*, the crude photo addition product (**47**) was obtained. Zn dust (260 g, 3.97 mol, 25 equiv) was activated by carefully washing with 1 M HCl solution followed by H_2O, EtOH and Et_2O and subsequently drying under vacuum. The activated zinc was placed in a three necked flask equipped with a condenser, stopper and mechanical stirrer and toluene (150 mL) and TMSCl (25.0 mL, 190.7 mmol, 1.2 equiv) were introduced. The crude photo addition product (**47**)

was then dissolved in toluene (150 mL) and acetic anhydride (180 mL, 1.91 mol, 12 equiv) and this solution was added to the three necked reaction vessel. The mixture was stirred at 140 rpm at 85 °C for 22 h before filtering through celite. The filtrate was evaporated to dryness and removal of all residual acetic anhydride was confirmed by crude ^{1}H-NMR. The crude mixture was suspended in THF (200 mL) and added to a suspension of $LiAlH_4$ (24.4 g, 636 mmol, 4 equiv) in THF (250 mL) at 0 °C under N_2 through a dropping funnel. The resulting slurry was agitated for 18 h at RT, cooled to 0 °C and quenched *via* careful addition of 1 M HCl solution (200 mL). After diluting the mixture to ~ 1 L with EtOAc, the organic layer was separated, washed with brine, dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Flash column chromatography (SiO_2, hexanes/EtOAc 3:2) followed by recrystallisation from hexanes afforded diol (**181**) as a plae yellow solid (12.84 g, 57% yield).

^{1}H NMR (250 MHz, $CDCl_3$) δ 6.00 (2 H, s, **HC=CH**), 3.88 (2 H, d, *J*= 11.4 Hz, CH_2OH), 3.47 (2 H, d, *J*= 11.4 Hz, CH_2OH), 3.28 (2 H, s, 2 x CH_2OH), 1.22 (6 H, s, 2 x CH_3); **^{13}C NMR** (63 MHz, $CDCl_3$) δ 140.9 (HC=CH), 68.1 (CH_2OH), 52.9 (q), 19.1 (CH_3).

The spectroscopic data were in agreement with those previously published.[22]

3,4-Bis-benzyloxymethyl-3,4-dimethylcyclobut-1-ene (182)



181 **182**

Sodium hydride (4.03 g, 60% dispersion in mineral oil, 100.6 mmol, 2.6 equiv) was suspended in THF (80 mL) and DMF (10 mL) and the resulting mixture cooled to 0 °C. Added to this was diol (**181**) (5.50 g, 38.7 mmol, 1 equiv) in THF (25 mL) *via* a cannula before addition of benzyl bromide (11.5 mL, 96.7 mmol, 2.5 equiv). The reaction mixture was stirred for 36 h and subsequently quenched by addition of H_2O. Following two EtOAc extractions, the organic layers were combined, washed with

brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Flash column chromatography (SiO_2, hexanes/EtOAc 9:1) afforded cyclobutene (**182**) as a colourless oil (12.4 g, quantitative yield).

^{1}H NMR (250 MHz, $CDCl_3$) δ 7.40-7.28 (10 H, m, **ArH**), 6.15 (2 H, s, **HC=CH**), 4.48 (2 H, s, 2 x Ar**C**H_2O), 4.47 (2 H, s, 2 x Ar**C**H_2O), 3.60 (2 H, d, *J*= 9.1 Hz, C**C**H_2O), 3.46 (2 H, d, *J*= 9.1 Hz, C**C**H_2O), 1.21 (6 H, s, 2 x **C**H_3); **^{13}C NMR** (63 MHz, $CDCl_3$) δ 141.1 (**HC=CH**), 138.8 (**ArCCH**$_2$), 128.2 (**ArCH**), 127.5 (**ArCH**), 127.3 (**ArCH**), 75.4 (**C**H_2), 73.2 (**C**H_2), 51.8 (q), 19.3 (**C**H_3).

The spectroscopic data were in agreement with those previously published.[22]

2,3-Bis-benzyloxymethyl-2,3-dimethylcyclobutanone (166)

Method 1

174 166

Diol (**174**) (11.7 g, 50.2 mmol, 1 equiv) and tetrabutyl ammonium iodide (catalytic amount) were dissolved in THF (250 mL) before adding NaH (5.1 g, 60% in mineral oil, 125 mmol, 2.5 equiv) and benzyl bromide (14.9 mL, 125 mmol, 2.5 equiv) and stirring the resulting mixture at RT for 66 h. Excess NaH was destroyed by addition of H_2O and extraction with Et_2O, drying of the organic layer with $MgSO_4$, filtration and removal of solvent *in vacuo* afforded a crude yellow oil. The crude was redissolved in MeCN (200 mL), H_2SO_4 (0.5 M solution, 50 mL) added and stirred at RT for 1 h. Addition of saturated $NaHCO_3$ solution and extraction with DCM, followed by drying of the organic phase with $MgSO_4$, filtration and removal of solvent under reduced pressure yielded a yellow oil. Purification by flash column chromatography (SiO_2, hexanes/EtOAc 9:1) afforded cyclobutanone (**166**) as a colourless oil (17.9 g, 99% yield).

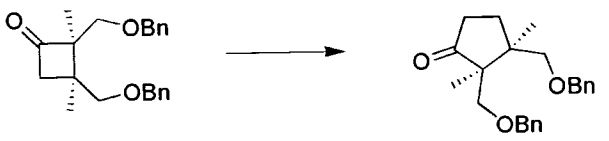
Method 2

182 **166**

A solution of cyclobutene (**182**) (5.61 g, 17.4 mmol, 1 equiv) in THF (150 mL) was treated with BH_3·THF complex (22.6 mL, 1 M solution in THF, 22.6 mmol, 1.3 equiv) at 0 °C and the resulting solution was stirred at RT for 18 h. Following the addition of NaOH solution (3 M, 20 mL) and 30% H_2O_2 solution (15 mL), the mixture was agitated for a further 30 min before pouring into a separating funnel containing brine (200 mL) and HCl (1 M, 50 mL). The solution was extracted thrice with EtOAc, the organic layers were combined, dried over $MgSO_4$, filtered and evaporated to dryness. The intermediate was redissolved in DCM (150 mL) and treated with PDC (7.51 g, 20 mmol, 1.5 equiv) at 0 °C for 3 h. The mixture was filtered through celite, the solvent removed under reduced pressure and subsequent flash column chromatography (SiO_2, hexanes/EtOAc 9:1) afforded cyclobutanone (**166**) as a colourless oil (2.58 g, 43% yield).

^{1}H NMR (360 MHz, $CDCl_3$) δ 7.33-7.27 (10 H, m, Ph**H**), 4.47 (1 H, d, J_{AB}= 12.2 Hz, OC**H**$_2$), 4.43 (1 H, d, J_{AB}= 12.2 Hz, OC**H**$_2$), 4.38 (2 H, s, OC**H**$_2$), 3.77 (1 H, d, J_{AB}= 9.0 Hz, OC**H**$_2$), 3.59 (2 H, s, OC**H**$_2$), 3.56 (1 H, d, J_{AB}= 9.0 Hz, OC**H**$_2$), 3.08 (1 H, d, J_{AB}= 16.8 Hz, C**H**$_2$COO), 2.59 (1 H, d, J_{AB}= 16.8 Hz, C**H**$_2$COO), 1.27 (3 H, s, C**H**$_3$), 1.15 (3 H, s, C**H**$_3$); **^{13}C NMR** (90 MHz, $CDCl_3$) δ 211.8 (**C**=O), 138.4 (**Ph**CCH_2), 138.0 (**Ph**CCH_2), 128.3 (**Ph**CH), 128.1 (**Ph**CH), 127.6 (**Ph**CH), 127.5 (**Ph**CH), 127.4 (**Ph**CH), 74.9 (OCH_2), 73.2 (OCH_2), 73.1 (OCH_2), 71.6 (OCH_2), 66.1 (H_3CC), 54.2 (CH_2CO), 36.1 (H_3CC), 21.0 (CH_3), 15.3 (CH_3); **IR** (thin film) ν 2856, 1777, 1454, 1095 cm^{-1}; **HRMS** (ES) *m/z* calcd for $C_{22}H_{30}O_3N$ $[M+NH_4]^+$ 356.2220, found 356.2219.

2,3-Bis-benzyloxymethyl-2,3-dimethylcyclopentanone (194)

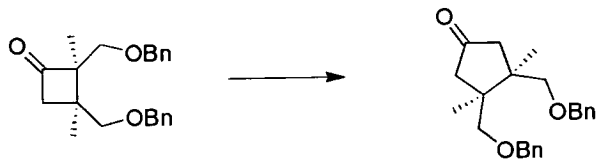


166 194

Cyclobutanone (**166**) (16.2 g, 47.6 mmol, 1 equiv) in DCM (550 mL) was cooled to 0 °C before dropwise addition of $BF_3{\cdot}OEt_2$ (30.3 mL, 238 mmol, 5 equiv) over a 5 min period. After allowing the mixture to stir for a further 5 min, ethyldiazoacetate (12.5 mL, 119 mmol, 2.5 equiv) was added dropwise and the resulting solution was stirred at 0 °C for 1.5 h. Saturated sodium bicarbonate solution and DCM was added and the organic layer was separated, dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The resulting crude oil was dissolved in DMSO (150 mL) and following addition of $MgCl_2{\cdot}6H_2O$, the reaction mixture was heated to 140 °C for 16 h. After addition of brine and EtOAc, the organic layer was separated, washed with brine, H_2O and brine, dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. Flash column chromatography (SiO_2, hexanes/EtOAc 9:1) furnished cyclopentanone (**194**) as a yellow oil (10.7 g, 68% yield). 1.20 g of the regioisomer (**196**), described below, was also obtained (7% yield). Overall yield 75%, 9:1 ratio of regioisomers.

^{1}H NMR (360 MHz, $CDCl_3$) δ 7.35-7.22 (10 H, m, Ar**H**), 4.39-4.28 (4 H, m, $H_3CCC\mathbf{H}_2O$, $ArC\mathbf{H}_2O$), 3.51 (1 H, d, J_{AB}= 9.4 Hz, $H_3CCC\mathbf{H}_2O$), 3.47 (1 H, d, J_{AB}= 9.4 Hz, $H_3CCC\mathbf{H}_2O$), 3.37 (2 H, s, $ArC\mathbf{H}_2O$), 2.40 (1 H, m, $C\mathbf{H}_2$), 2.26 (1 H, m, $C\mathbf{H}_2$), 2.00 (1 H, m, $C\mathbf{H}_2$), 1.68 (1 H, m, $C\mathbf{H}_2$), 1.08 (3 H, s, $C\mathbf{H}_3$), 1.07 (3 H, s, $C\mathbf{H}_3$); **^{13}C NMR** (90 MHz, $CDCl_3$) δ 222.0 (**C**=O), 138.3 (**Ar**CCH_2), 138.2 (**Ar**CCH_2), 128.3 (**Ar**CH), 127.5 (**Ar**CH), 127.4 (**Ar**CH), 127.3 (**Ar**CH), 127.2 (**Ar**CH), 77.2, (CH_2), 73.7 (CH_2), 73.3 (CH_2), 73.2 (CH_2), 54.0 (H_3C**C**), 45.1 (H_3C**C**), 35.5 (CH_2), 31.1 (CH_2), 21.2 (CH_3), 17.3 (CH_3); **IR** (thin film) ν 2827, 1734, 1454, 1095 cm^{-1}; **HRMS** (ES) *m/z* calcd for $C_{23}H_{32}NO_3$ $[M+NH_4]^+$ 370.2377, found 370.2379.

3,4-Bis-benzyloxymethyl-3,4-dimethylcyclopentanone (196)



166 196

Obtained as the undesired regioisomer in the ring expansion reaction of cyclobutanone (**166**), described above.

^{1}H NMR (250 MHz, $CDCl_3$) δ 7.67-7.35 (10 H, m, Ar**H**), 4.28 (4 H, s, 2 x Ar**CH$_2$**O), 3.54 (2 H, d, J_{AB}= 9.1 Hz, 2 x O**CH$_2$**C), 3.46 (2 H, d, J_{AB}= 9.1 Hz, 2 x O**CH$_2$**C), 2.58 (2 H, d, J_{AB}= 18.9 Hz, 2 x C=O**CH$_2$**), 2.20 (2 H, d, J_{AB}= 18.9 Hz, 2 x C=O**CH$_2$**), 1.22 (6 H, s, 2 x **CH$_3$**); **^{13}C NMR** (63 MHz, $CDCl_3$) δ 218.1 (**C**=O), 138.7 (Ar**C**CH_2), 128.7 (**ArC**H), 127.9 (**ArC**H), 76.7 (**C**H_2), 73.7 (**C**H_2), 50.7 (**C**H_2), 44.4 (H_3**C**C), 22.0 (**C**H_3); **IR** (thin film) ν 2925, 1739, 1454, 1273, 1097 cm^{-1}; **HRMS** (ES) *m/z* calcd for $C_{23}H_{29}O_3$ $[M+H]^+$ 353.2111, found 353.2108.

4,5-Bis-benzyloxymethyl-4,5-dimethylcyclopent-2-enone (165)

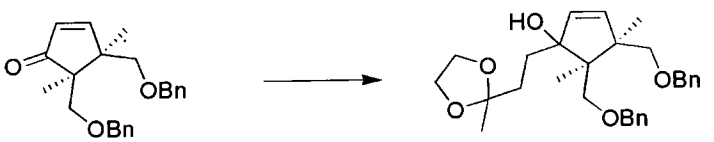
194 165

Cyclopentanone (**194**) (98 mg, 0.28 mmol, 1 equiv) in THF (2.5 mL) was cooled to -78 °C and LHMDS (420 μL, 1 M in THF, 0.42 mmol, 1.5 equiv) was slowly added. After stirring for 45 min at -78 °C, PhSeCl (80 mg, 0.42 mmol, 1.5 equiv) and HMPA (100 μL, 0.56 mmol, 2 equiv) in THF (2.5 mL) was added to the reaction mixture *via* a cannula. The resulting solution was subsequently stirred at -78 °C for 2.5 h before warming to RT, followed by addition of saturated NH_4Cl solution. The organic layer was washed with H_2O and brine, dried over $MgSO_4$ and the solvent removed under reduced pressure. The crude was subjected to flash column chromatography (SiO_2, hexanes/EtOAc 9:1) and the resulting brown oil was dissolved in DCM (15 mL) and 30% H_2O_2 solution (1 mL), was added. The reaction

mixture was stirred at RT for 80 min, quenched by addition of saturated sodium bicarbonate solution and extracted with DCM. The organic layer was washed with H_2O and brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Flash column chromatography (SiO_2, hexanes/EtOAc 9:1) furnished cyclopentenone (**165**) as a yellow oil (38 mg, 39% yield).

^{1}H NMR (360 MHz, $CDCl_3$) δ 7.38 (1 H, d, *J*= 5.9 Hz, COCH=C**H**), 7.33-7.14 (10 H, m, Ar**H**), 6.11 (1 H, d, *J*= 5.9 Hz, COC**H**=CH), 4.39 (1 H, d, J_{AB}= 12.1 Hz, H_3CCCH_2O), 4.35 (1 H, d, J_{AB}= 12.1 Hz, H_3CCCH_2O), 4.34 (2 H, s, $ArCH_2O$), 3.60 (1 H, d, J_{AB}= 9.4 Hz, H_3CCCH_2O), 3.56 (1 H, d, J_{AB}= 9.4 Hz, H_3CCCH_2O), 3.53 (2 H, s, $ArCH_2O$), 1.19 (3 H, s, CH_3), 1.16 (3 H, s, CH_3); **^{13}C NMR** (90 MHz, $CDCl_3$) δ 212.1 (**C**=O), 168.0 (COCH=**C**H), 138.3 (OCH_2**CAr**), 138.1 (OCH_2**CAr**), 130.4 (CO**C**H=CH), 128.3 (**ArC**H), 128.2 (**ArC**H), 127.8 (**ArC**H), 127.5 (**ArC**H), 127.4 (**ArC**H), 127.3 (**ArC**H), 74.5 (CH_2), 73.3 (CH_2), 73.2 (CH_2), 72.9 (CH_2), 53.9 (H_3CC), 51.6 (H_3CC), 19.8 (CH_3); **IR** (thin film) ν 2857, 2359, 1708, 1453, 1093 cm^{-1}; **HRMS** (ES) *m/z* calcd for $C_{23}H_{27}O_3$ $[M+H]^+$ 351.1955, found 351.1953.

4,5-Bis-benzyloxymethyl-4,5-dimethyl-1-[2-(2-methyl-[1,3]dioxolan-2-yl)ethyl]-cyclopent-2-enol (202)



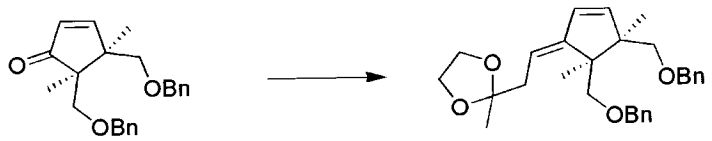
165 **202**

A solution of 2-(2-iodoethyl)-2-methyl-1,3-dioxolane (**144**) (386 mg, 1.60 mmol, 1.6 equiv) in dry Et_2O (10 mL) at -78 °C was treated with ^{t}butyl lithium (1.95 mL, 1.7 M solution in pentane, 3.30 mmol, 3.3 equiv) and the resulting mixture was stirred at -78 °C for 45 min, warmed to RT and stirred for a further 1 h. After re-cooling to -78 °C, the mixture was transferred into a solution of cyclopentenone (**165**) (349 mg, 1.0 mmol, 1 equiv) in Et_2O (10 mL) at -78 °C *via* a cannula and the reaction mixture was stirred for 2 h. Subsequently, a saturated solution of NH_4Cl was added, the mixture was extracted with EtOAc, the organic layers combined, washed with brine, dried

over $MgSO_4$, filtered and evaporated to dryness. Flash column chromatography afforded a single diastereomer of the tertiary alcohol (**202**) as a thick yellow oil (202 mg, 43% yield). The product was highly prone to elimination and decomposed upon standing at RT. The eliminated product (**203**) described below was also obtained (168 mg).

^{1}H NMR (360 MHz, $CDCl_3$) δ 7.35-7.25 (10 H, m, ArC**H**), 5.73 (1 H, d, *J*= 6.0 Hz, **H**C=CH), 5.64 (1 H, d, *J*= 6.0 Hz, HC=C**H**), 4.44-4.36 (4 H, m, C**H$_2$**), 3.96-3.86 (4 H, m, OC**H$_2$**C**H$_2$**O), 3.52-3.32 (4 H, m, C**H$_2$**), 2.00 (1 H, m, C**H$_2$**), 1.83-1.71 (3 H, m, C**H$_2$**, C**H$_2$**), 1.28 (3 H, s, COOC**H$_3$**), 1.18 (3 H, s, C**H$_3$**), 1.08 (3 H, s, C**H$_3$**); **^{13}C NMR** (90 MHz, $CDCl_3$) δ 138.9 (**H**C=CH), 138.6 (OC**H$_2$**C**Ar**), 138.5 (OC**H$_2$**C**Ar**), 133.6 (HC=C**H**), 128.2 (**ArCH**), 127.5 (**ArCH**), 127.4 (**ArCH**), 127.3 (**ArCH**), 110.2 (**C**OO), 86.9 (**C**OH), 75.7 (**CH$_2$**), 73.5 (**CH$_2$**), 73.2 (**CH$_2$**), 73.1 (**CH$_2$**), 64.6 (**CH$_2$**), 64.5 (**CH$_2$**), 53.1 (q), 52.9 (q), 33.5 (**CH$_2$**), 31.7 (**CH$_2$**), 23.8 (**CH$_3$**), 22.0 (**CH$_3$**), 17.1 (**CH$_3$**); **IR** (thin film) ν 3476, 2872, 2359, 1454, 1069 cm^{-1}; **HRMS** compound unstable, characterisation by mass spectrometry unsuccessful.

2-(2-[4,5-Bis-benzyloxymethyl-4,5-dimethylcyclopent-2-enylidene]ethyl)-2-methyl[1,3]dioxolane (203)



165 **203**

Eliminated product obtained from method described above.

^{1}H NMR (250 MHz, $CDCl_3$) δ 7.36 (10 H, m, ArC**H**), 6.37 (1 H, dd, *J*= 5.9, 0.9 Hz, CH=C**H**), 5.97 (1 H, dd, *J*= 5.9, 1.5 Hz, C**H**=CH), 5.06 (1 H, m, C=C**H**CH$_2$), 4.42 (2 H, s, ArCC**H$_2$**O), 4.39 (2 H, s, ArCC**H$_2$**O), 3.94-3.92 (4 H, m, OC**H$_2$**C**H$_2$**O), 3.50 (2 H, dd, *J*= 8.9, 4.2 Hz, CC**H$_2$**O), 3.39 (2 H, dd, *J*= 8.9, 4.2 Hz, CC**H$_2$**O), 2.46 (2 H, d, *J*= 7.8 Hz, C=CHC**H$_2$**), 1.28 (3 H, s, C**H$_3$**), 1.18 (3 H, s, C**H$_3$**), 1.10 (3 H, s, C**H$_3$**).

2,3-Bis-(4-methoxybenzyloxymethyl)-2,3-dimethylcyclobutanone (179)

174 **179**

Diol (**174**) (197 mg, 0.85 mmol, 1 equiv) in THF (10 mL) was treated with NaH (60% dispersion in mineral oil, 85 mg, 2.12 mmol, 2.5 equiv), catalytic amount of TBAI and paramethoxybenzyl chloride (254 μL, 1.87 mmol, 2.2 equiv). The resulting suspension was stirred at RT for 18 h and after a further addition of NaH (150 mg), the mixture was stirred for an additional 24 h. Quenching with saturated NH_4Cl solution, followed by extraction with Et_2O, drying over $MgSO_4$, filtering and removal of solvent under reduced pressure yielded a yellow oil. The crude was redissolved in MeCN (5 mL) and treated with H_2SO_4 (0.5 M, 2 mL) for 45 min at RT. The mixture was neutralised by addition of a saturated $NaHCO_3$ solution and extracted with Et_2O. The organic layers were combined, dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. Flash column chromatography (SiO_2, Hexane/EtOAc 4:1) yielded cyclobutanone (**179**) as a colourless oil (126 mg, 37 %).

^{1}H NMR (360 MHz, $CDCl_3$) δ 7.22-7.16 (4 H, m, Ph**H**), 6.89-6.85 (4 H, m, Ph**H**), 4.42-4.30 (4 H, m, PhC**H$_2$**O), 3.80 (3 H, s, PhOC**H$_3$**), 3.79 (3 H, s, PhOC**H$_3$**), 3.71 (1 H, d, J_{AB}= 9.0 Hz, CC**H$_2$**O),3.53 (2 H, s, CC**H$_2$**O) 3.50 (1 H, d, J_{AB}= 9.0 Hz, CC**H$_2$**O), 3.04 (1 H, d, J_{AB}= 16.8 Hz, COC**H$_2$**), 2.56 (1 H, d, J_{AB}= 16.8 Hz, COC**H$_2$**), 1.23 (3 H, s, C**H$_3$**), 1.12 (3 H, s, C**H$_3$**); **^{13}C NMR** (90 MHz, $CDCl_3$) δ 212.0 (**C**=O), 159.1 (**Ph**COCH$_3$), 159.0 (**Ph**COCH$_3$), 130.5 (**Ph**CCH$_2$O), 130.1 (**Ph**CCH$_2$O), 129.1 (**Ph**CH), 129.0 (**Ph**CH), 74.5 (**C**H$_2$), 72.8 (**C**H$_2$), 72.7 (**C**H$_2$), 71.2 (**C**H$_2$), 66.0 (q), 55.2 (PhOCH$_3$), 54.2 (**C**H$_2$), 36.0 (q), 21.0 (**C**H$_3$), 15.3 (**C**H$_3$); **IR** (thin film) ν 2934, 2856, 1776, 1513,1247 cm^{-1}; **HRMS** not obtained, compound unstable.

2,3-Bis-ethoxymethoxymethyl-2,3-dimethylcyclobutanone (178)

174 178

Diol (**174**) (6.21 g, 26.2 mmol, 1 equiv) was dissolved in anhydrous DCM (200 mL) and cooled to 0 °C. Following addition of diisopropyl ethylamine (11.4 mL, 65.5 mmol, 2.5 equiv) and ethoxymethylchloride (5.5 ml, 58.6 mmol, 2.2 equiv), the reaction mixture was warmed to RT and stirred for 36 h. TLC analysis showed remaining starting material. Further addition of diisopropyl ethylamine (4.6 mL, 26.2 mmol, 1 equiv) and ethoxymethylchloride (2.3 ml, 23.6 mmol, 0.9 equiv), followed by stirring at RT for 3 h, resulted in total consumption of starting material. The reaction mixture was washed with saturated NH_4Cl solution, H_2O and brine, dried over $MgSO_4$, filtered and evaporated to dryness. The resulting colourless oil was taken up in THF (100 mL) and treated with HCl solution (10 mL, 1 M) at RT for 22 h. The reaction mixture was neutralised *via* addition of saturated sodium bicarbonate solution and extracted with Et_2O. The organic layer was dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. Flash column chromatography (SiO_2, hexanes/EtOAc 4:1) afforded cyclobutanone (**178**) as a colourless oil (5.80 g, 82% yield).

^{1}H NMR (360 MHz, $CDCl_3$) δ 4.67 (1 H, s, OCH_2O), 4.60 (1 H, s, OCH_2O), 3.80 (1 H, d, *J*= 9.5 Hz, CH_2), 3.67 (1 H, d, *J*= 9.5 Hz, CH_2), 3.66 (2 H, s, CH_2), 3.58 (2 H, q, *J*= 7.1 Hz, CH_2CH_3), 3.54 (2 H, q, *J*= 7.1 Hz, CH_2CH_3), 3.03 (1 H, d, J_{AB}= 16.9 Hz, C=OCH_2), 2.59 (1 H, d, J_{AB}= 16.9 Hz, C=OCH_2), 1.23 (3 H, s, CH_3), 1.20 (3 H, t, *J*= 7.1 Hz, CH_2CH_3), 1.18 (3 H, t, *J*= 7.1 Hz, CH_2CH_3), 1.12 (3 H, s, CH_3); **^{13}C NMR** (90 MHz, $CDCl_3$) δ 211.3 (C=O), 95.4 (OCH_2O), 95.2 (OCH_2O), 72.6 (CH_2), 68.9 (CH_2), 65.7 (q), 63.4 (CH_2), 63.3 (CH_2), 54.1 (CH_2), 35.7 (q), 20.8 (CH_3), 15.1 (CH_3), 15.0 (CH_3); **IR** (thin film) ν 2975, 2876, 1779, 1112. 1045 cm^{-1};**HRMS** (ES) *m/z* calcd for $C_{14}H_{30}NO_5$ $[M+NH_4]^+$ 292.2118, found 292.2117.

2,3-Bis-hydroxymethyl-2,3-dimethylcyclobutanone (189)

178 189

Cyclobutanone (**178**) (1.07 g, 3.90 mmol, 1 equiv) was dissolved in THF (40 mL) and treated with concentrated HCl (5 mL) for 4 h. After addition of saturated $NaHCO_3$ solution, the mixture was extracted with EtOAc, the organic layers were combined, dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Flash column chromatography (SiO_2, hexanes/EtOAc 1:1) afforded diol (**189**) as a white solid (113 mg, 18% yield).

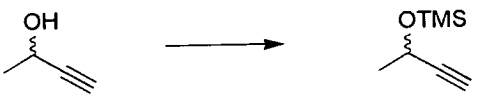
^{1}H NMR (250 MHz, $CDCl_3$) δ 4.13-3.89 (2 H, m, **CH_2**), 3.66 (1 H, d, *J*=11.5 Hz, **CH_2**), 3.49 (1 H, d, *J*=11.5 Hz, **CH_2**), 2.81 (1 H, d, *J*= 17.4 Hz, **CH_2**), 2.67 (1 H, d, *J*= 17.4 Hz, **CH_2**), 1.28 (3 H, s, **CH_3**), 1.20 (3 H, s, **CH_3**); **^{13}C NMR** (63 MHz, $CDCl_3$) δ 211.7 (**C**=O), 68.3 (**CH_2**), 68.0 (q), 63.6 (**CH_2**), 52.8 (**CH_2**), 37.2 (q), 20.5 (**CH_3**), 15.6 (**CH_3**).

A side product, tentatively assigned as 1,7-Dimethyl-3,5-dioxa-bicyclo[5.2.0]nonan-8-one (**278**), was also obtained (292 mg, 44% yield).

178 278

^{1}H NMR (360 MHz, $CDCl_3$) δ 5.02 (1 H, d, *J*= 6.7 Hz, O**CH_2**O), 4.53 (1 H, d, *J*= 6.7 Hz, O**CH_2**O), 4.06 (1 H, d, *J*= 12.9 Hz, **CH_2**), 3.89 (1 H, d, *J*= 12.9 Hz, **CH_2**), 3.79 (1 H, d, *J*= 12.9 Hz, **CH_2**), 3.52 (1 H, d, *J*= 12.9 Hz, **CH_2**), 3.46 (1 H, d, *J*= 17.4 Hz, **CH_2**), 2.61 (1 H, d, *J*= 17.4 Hz, **CH_2**), 1.16 (3 H, s, **CH_3**), 1.02 (3 H, s, **CH_3**); **^{13}C NMR** (90 MHz, $CDCl_3$) δ 212.3 (**C**=O), 99.3 (O**CH_2**O), 76.0 (**CH_2**), 74.6 (**CH_2**), 68.2 (q), 53.2 (**CH_2**), 38.5 (q), 20.3 (**CH_3**), 14.6 (**CH_3**).

Trimethyl-(1-methylprop-2-ynyloxy)silane (207)



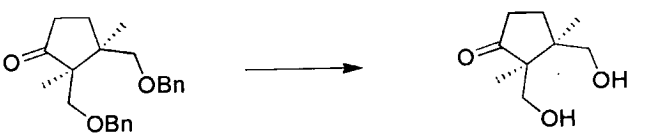
204 **207**

3-Butyn-2-ol (**204**) (2.0 mL, 25.5 mmol, 1 equiv) and HMDS (2.8 mL, 13.3 mmol, 0.52 equiv) were combined and heated to 110 °C for 18 h. The resulting brown mixture was filtered through a plug of silica to afford a pale yellow oil (3.17 g, 87% yield). No further purification was required, based on ^{1}H-NMR analysis.

^{1}H NMR (250 MHz, $CDCl_3$) δ 4.51 (1 H, dq, *J*= 6.5, 2.1 Hz, C**H**CH_2), 2.39 (1 H, d, *J*= 2.1 Hz, C≡C**H**), 1.43 (3 H, d, *J*= 6.5 Hz, CHC**H$_3$**), 0.18 (9 H, s, Si(C**H$_3$**)$_3$).

The spectroscopic data was in agreement with that of the commercially available compound, Registry Number 125494-93-1.

2,3-Bis-hydroxymethyl-2,3-dimethylcyclopentanone (198)



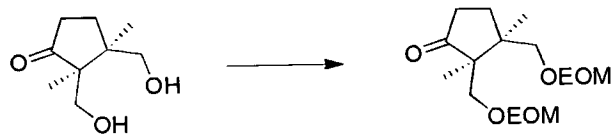
194 **198**

Cyclopentanone (**194**) (3.19 g, 9.05 mmol, 1 equiv) was dissolved in dry methanol (100 mL) and concentrated HCl (2 drops) and $Pd(OH)_2$ (255 mg, 20 %wt on C, 8 %wt equiv) was added. H_2 was bubbled through the suspension *via* a long needle for 10 min before placing the reaction mixture under a H_2 atmosphere, using a balloon, for 18 h. The catalyst was removed *via* filtration through celite and the solvent was removed *in vacuo*. Flash column chromatography (SiO_2, EtOAc, 100%) afforded diol (**198**) as a white solid (1.56 g, 99% yield).

^{1}H NMR (360 MHz, $CDCl_3$) δ 3.83-3.45 (4 H, m, C**H$_2$**OH), 2.40 (1 H, ddd, *J*= 19.6, 9.8, 8.1 Hz, C**H$_2$**), 2.29 (1 H, ddd, *J*= 19.6,10.2, 4.8 Hz, C**H$_2$**), 1.97 (1 H, ddd, *J*= 13.5, 9.8, 4.8 Hz, C**H$_2$**), 1.74 (1 H, ddd, *J*= 13.5, 10.2, 8.1 Hz, C**H$_2$**), 0.92 (3 H, s, C**H$_3$**), 0.92 (3 H, s, C**H$_3$**); **^{13}C NMR** (90 MHz, $CDCl_3$) δ 223.2 (**C**=O), 69.7 (CH_2),

63.9 (CH_2), 55.7 (q), 45.7 (q), 35.1 (CH_2), 30.7 (CH_2), 19.5 (CH_3), 17.2 (CH_3); **IR** (thin film) ν 3398, 2942, 2360, 2248, 1726, 1468, 1042 cm^{-1}; **HRMS** (ES) *m/z* calcd for $C_9H_{20}NO_3$ $[M+NH_4]^+$ 190.1438, found 190.1437.

2,3-Bis-ethoxymethoxymethyl-2,3-dimethylcyclopentanone (195)

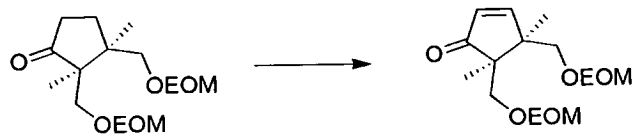


198 **195**

Diol (**198**) (4.50 g, 25.72 mmol, 1 equiv) was dissolved in anhydrous DCM (150 mL) and treated with diisopropyl ethylamine (11.2 mL, 64.30 mmol, 2.5 equiv) and ethoxymethylchloride (5.3 mL, 56.6 mmol, 2.2 equiv). The resulting reaction mixture was stirred at RT for 60 h. Following the addition of saturated NH_4Cl solution, the organic layer was separated, washed with H_2O and brine, dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. Flash column chromatography (SiO_2, hexanes/EtOAc 4:1) furnished cyclopentanone (**195**) as a colourless oil (6.76 g, 90% yield).

^{1}H NMR (360 MHz, $CDCl_3$) δ 4.62-4.59 (4 H, m, OCH_2O), 3.59-3.51 (8 H, m, CH_2), 2.37 (1 H, ddd, *J*= 18.0, 9.2, 6.3 Hz, CH_2), 2.27 (1 H, ddd, *J*= 15.8, 9.2, 5.5 Hz, CH_2), 2.00 (1 H, ddd, *J*= 13.1, 9.8, 5.5 Hz, CH_2), 1.68 (1 H, m, CH_2), 1.21 (3 H, t, *J*= 7.1 Hz, CH_2CH_3), 1.20 (3 H, t, *J*= 7.1 Hz, CH_2CH_3), 1.04 (3 H, s, CH_3), 1.03 (3 H, s, CH_3); **^{13}C NMR** (90 MHz, $CDCl_3$) δ 221.5 (C=O), 95.5 (OCH_2O), 95.4 (OCH_2O), 74.5 (CH_2), 71.0 (CH_2), 63.5 (CH_2), 63.4 (CH_2), 53.8 (q), 44.7 (q), 35.2 (CH_2), 30.8 (CH_2), 21.0 (CH_3), 16.8 (CH_3), 15.1 (CH_3); **IR** (thin film) ν 2975, 2877, 2359, 1738, 1044 cm^{-1}; **HRMS** (ES) *m/z* calcd for $C_{15}H_{29}O_5$ $[M+H]^+$ 289.2010, found 289.2012.

4,5-Bis-ethoxymethoxymethyl-4,5-dimethylcyclopent-2-enone (201)

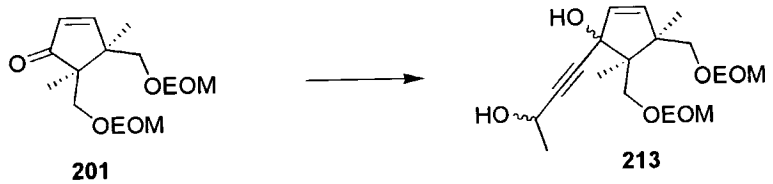


195 **201**

Cyclopentanone (**195**) (1.87 g, 6.50 mmol, 1 equiv) in anhydrous THF (40 mL) was cooled to -78 °C. LHMDS (9.8 mL, 1 M solution in THF, 9.75 mmol, 1.5 equiv) was added dropwise *via* a syringe and the resulting solution was stirred at -78 °C for 45 min. Addition of HMPA (2.3 mL, 13.0 mmol, 2 equiv) was followed by a solution of phenyl seleniumbromide (2.30 g, 9.75 mmol, 1.5 equiv) in anhydrous THF (20 mL) *via* a cannula. After stirring for a further 2 h at -78 °C, the solution was allowed to warm to RT before quenching with saturated NH_4Cl solution. Extraction with EtOAc afforded an organic layer, which was washed with H_2O and brine and evaporated to dryness. The crude intermediate selenide was redissolved in DCM (30 mL) and aqueous H_2O_2 (2.5 mL, 30% solution) was added. After stirring at RT for 1 h, the organic layer was washed with saturated NH_4Cl solution, H_2O and brine, dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. Flash column chromatography (SiO_2, hexanes/EtOAc 4:1) afforded cyclopentenone (**201**) as an orange oil (937 mg, 51% yield).

^{1}H NMR (360 MHz, $CDCl_3$) δ 7.35 (1 H, d, *J*= 5.9 Hz, COCHC**H**), 6.05 (1 H, d, *J*= 5.9 Hz COC**H**CH), 4.59-4.54 (4 H, m, OC**H$_2$**O), 3.64-3.47 (8 H, m, OC**H$_2$**), 1.15 (3 H, t, *J*= 7.1 Hz, $CH_2C\mathbf{H_3}$), 1.16 (3 H, t, *J*= 7.1 Hz, $CH_2C\mathbf{H_3}$), 1.13 (3 H, s, C**H$_3$**), 1.08 (3 H, s, C**H$_3$**); **^{13}C NMR** (90 MHz, $CDCl_3$) δ 211.7 (**C**=O), 167.8 (COCH**C**H), 130.3 (**C**OCHCH), 95.4 (O**C**H$_2$O), 95.2 (O**C**H$_2$O), 72.2 (**C**H$_2$), 70.9 (**C**H$_2$), 63.3 (**C**H$_2$CH$_3$), 53.6 (q), 51.1 (q), 19.8 (**C**H$_3$), 19.3 (**C**H$_3$), 15.0 (CH$_2$**C**H$_3$); **IR** (thin film) ν 2975, 2878, 1713, 1112, 1044 cm^{-1}; **HRMS** (ES) *m/z* calcd for $C_{15}H_{27}O_5$ $[M+H]^+$ 287.1853, found 287.1852.

4,5-Bis-ethoxymethoxymethyl-1-(3-hydroxybut-1-ynyl)-4,5-dimethylcyclopent-2-enol (213)

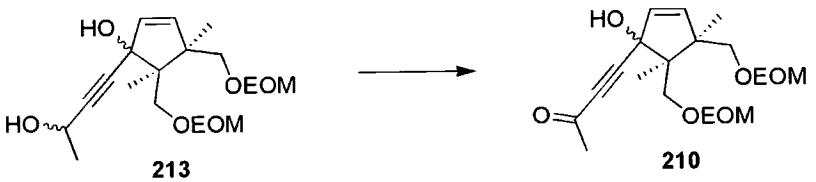


201 **213**

Trimethyl-(1-methyl-prop-2-ynyloxy)silane (**207**) (202 mg, 1.43 mmol, 3 equiv) in anhydrous THF (4 mL) was cooled to -42 °C before dropwise addition of *n*-butyl lithium (980 μL, 1.6 M solution in THF, 1.57 mmol, 3.3 equiv).The resulting solution was stirred at -42 °C for 30 min before transferring it into a solution of cyclopentenone (**201**) (136 mg, 0.48 mmol, 1 equiv) in anhydrous THF (5 mL) *via* a cannula. The reaction mixture was stirred at -42 °C for 30 min, allowed to warm to RT and stirred for a further 2 h. TMS deprotection was achieved by treating the reaction mixture at RT with HCl solution (2 mL, 1 M) for 30 min. The resulting mixture was extracted with Et_2O, the organic phase washed with H_2O and brine, dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. Flash column chromatography (SiO_2, hexanes/EtOAc 3:2) afforded diol (**213**) as a pale yellow oil (135 mg, 79% yield). Ratio of diastereomers by ^1H NMR ~ 8:1

^1H NMR (360 MHz, $CDCl_3$) major diastereomer δ 5.70 (1 H, dd, *J*= 5.7, 1.8 Hz, HC=C**H**), 5.60 (1 H, m, **H**C=CH), 4.73-4.68 (2 H, m, OC**H**$_2$O), 4.59 (2 H, s, OC**H**$_2$O), 4.52 (1 H, q, *J*= 6.6 Hz, C**H**OH), 3.94 (1 H, m, C**H**$_2$), 3.76 (1 H, m, C**H**$_2$), 3.66-3.50 (6 H, m, C**H**$_2$), 1.41 (3 H, d, *J*= 6.6 Hz, CHOHC**H**$_3$), 1.22 (3 H, t, *J*= 7.1 Hz, OCH$_2$C**H**$_3$), 1.19 (3 H, t, *J*= 7.1 Hz, OCH$_2$C**H**$_3$), 1.10 (3 H, s, C**H**$_3$), 1.05 (C**H**$_3$); **^{13}C NMR** (90 MHz, $CDCl_3$) major diastereomer δ 138.5 (H**C**=CH), 133.0 (HC=**C**H), 95.8 (O**C**H$_2$O), 95.1 (O**C**H$_2$O), 89.1 (**C**≡C), 85.9 (C≡**C**), 81.5 (HC=CH**C**OH), 72.3 (**C**H$_2$), 71.5 (**C**H$_2$), 63.5 (**C**H$_2$), 63.4 (**C**H$_2$), 58.0 (**C**HOH), 55.0 (q), 52.7 (q), 24.0 (**C**H$_3$), 19.2 (**C**H$_3$), 16.4 (**C**H$_3$); **IR** (thin film) ν 3409, 2977, 2878, 2360, 1044 cm^{-1}.

4-(4,5-Bis-ethoxymethoxymethyl-1-hydroxy-4,5-dimethylcyclopent-2-enyl)but-3-yn-2-one (210)



MnO_2 (650 mg, 7.46 mmol, 20 equiv) was added in one portion to a solution of diol (**213**) (133 mg, 0.37 mmol, 1 equiv) in DCM (10 mL) and the resulting suspension was stirred at RT for 45 min. Filtration through celite, removal of solvent *in vacuo* and flash column chromatography (SiO_2, hexanes/EtOAc 4:1) furnished alkynone (**210**) as a colourless oil (97 mg, 74% yield). Diastereomeric ratio 8:1 by ^{1}H-NMR.

^{1}H NMR (360 MHz, $CDCl_3$) major diastereomer δ 5.71 (1 H, d, *J*= 5.7 Hz, CHC**H**), 5.68 (1 H, d, *J*= 5.7 Hz, C**H**CH), 4.69 (2 H, s, OC**H$_2$**O), 4.61 (2 H, d, *J*= 2.1 Hz, OC**H$_2$**O), 3.93 (1 H, d, *J*= 9.6 Hz, C**H$_2$**), 3.62-3.52 (7 H, m, C**H$_2$**), 2.32 (3 H, s, COC**H$_3$**), 1.23-1.16 (6 H, m, CH$_2$C**H$_3$**), 1.12 (3 H, s, C**H$_3$**), 1.08 (3 H, s, C**H$_3$**); **^{13}C NMR** (90 MHz, $CDCl_3$) major diastereomer δ 183.8 (**C**=O), 140.3 (H**C**=CH), 131.4 (HC=**C**H), 95.8 (OCH$_2$O), 95.3 (OCH$_2$O), 92.8 (**C**≡C), 85.8 (C≡**C**), 81.8 (HO**C**), 72.4 (**C**H$_2$), 71.6 (**C**H$_2$), 63.6 (**C**H$_2$), 63.4 (**C**H$_2$), 55.6 (q), 55.1 (q), 32.5 (C=O**C**H$_3$), 19.2 (**C**H$_3$), 16.7 (**C**H$_3$), 15.1 (**C**H$_3$); **IR** (thin film) ν 3409, 2976, 2878, 2206, 1678, 1043 cm^{-1}; **HRMS** (ES) *m/z* calcd for $C_{19}H_{34}NO_6$ $[M+NH_4]^+$ 372.2381, found 372.2385.

tert-Butyldimethyl(1-methyl-prop-2-ynyloxy)silane (208)

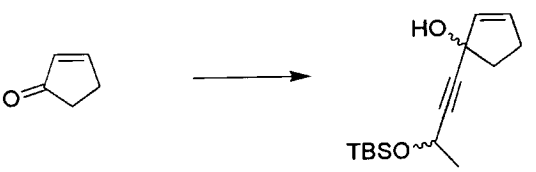
204 208

3-Butyn-2-ol (**204**) (4 mL, 51.4 mmol, 1 equiv), imidazole (4.2 g, 61.7 mmol, 1.2 equiv) and TBSCl (8.45 g, 56.6 mmol, 1.1 equiv) were dissolved in anhydrous DCM (50 mL) and stirred for 18 h. The reaction mixture was diluted with two volumes of DCM, washed with saturated NH_4Cl, H_2O and brine, dried over $MgSO_4$, filtered and the solvent was removed. Flash column chromatography (SiO_2, hexanes/EtOAc 9:1) furnished the title compound as a colourless oil (7.80 g, 83% yield).

^{1}H NMR (250 MHz, $CDCl_3$) δ 4.51 (1 H, dq, *J*= 2.1, 6.5 Hz, C**H**OSi), 2.37 (1 H, d, *J*= 2.1 Hz, C≡C**H**), 1.42 (3 H, d, *J*= 6.5 Hz, OCC**H$_3$**), 0.90 (9 H, s, SiC(C**H$_3$**)$_3$), 0.13 (3 H, s, Si(C**H$_3$**)$_2$), 0.12 (3 H, s, Si(C**H$_3$**)$_2$); **^{13}C NMR** (63 MHz, $CDCl_3$) δ 86.5 (**C**≡CH), 71.1 (C≡**C**H), 58.8 (**C**HOSi), 25.8 (SiC(**C**H$_3$)$_3$), 25.3 (CH**C**H$_3$), 18.2 (Si**C**(CH$_3$)$_3$), -4.7 (Si(**C**H$_3$)$_2$), -5.0 (Si(**C**H$_3$)$_2$).

The spectroscopic data were in agreement with those previously published.[74]

1-[3-(*tert*-Butyldimethylsilanyloxy)but-1-ynyl]cyclopent-2-enol (217)



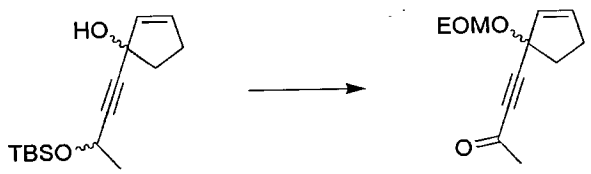
212 217

tert-Butyldimethyl(1-methyl-prop-2-ynyloxy)silane (**208**) (2.20 g, 11.94 mmol, 2 equiv) in THF (20 mL) was treated with *n*-butyl lithium (8.20 mL, 1.6 M solution in hexane, 13.1 mmol, 2.5 equiv) at -78 °C. After stirring for 45 min, the mixture was warmed to RT and transferred into a solution of cyclopentenone (**212**) (500 µL, 5.97 mmol, 1 equiv) in THF (20 mL) at -78 °C *via* a cannula over 30 min. After stirring for a further 45 min at -78 °C, the reaction mixture was allowed to warm to RT before quenching with saturated NH_4Cl solution. The ether extracts of this mixture

were washed with brine, dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Flash column chromatography (SiO_2, hexanes/EtOAc 8:2) afforded tertiary alcohol (**217**) as a colourless oil (0.94 g, 59% yield). 1:1 mix of diastereomers by ^{1}H-NMR.

^{1}H NMR (360 MHz, $CDCl_3$) δ 5.98-5.95 (2 H, m, HC=C**H**), 5.79-5.76 (2 H, m, **H**C=CH), 4.56 (1 H, q, *J*= 6.5 Hz, C**H**OSi), 4.55 (1 H, q, *J*= 6.5 Hz, C**H**OSi), 2.58-2.34 (6 H, m, C**H$_2$**C**H$_2$**), 2.18-2.04 (4 H, m, O**H**, CH$_2$C**H$_2$**), 1.39 (3 H, d, *J*= 6.5 Hz, CHC**H$_3$**), 1.39 (3 H, d, *J*= 6.5 Hz, CHC**H$_3$**), 0.89 (18 H, s, SiC(C**H$_3$**)$_3$), 0.11 (6 H, s, Si(C**H$_3$**)$_2$, 0.10 (6 H, s, Si(C**H$_3$**)$_2$; **^{13}C NMR** (90 MHz, $CDCl_3$) δ 134.8 (H**C**=CH), 134.7 (H**C**=CH), 134.7 (HC=**C**H), 134.7 (HC=**C**H), 87.0 (**C**≡C), 85.6 (C≡**C**), 77.8 (q), 59.0 (**C**HOSi), 40.9 (**C**H$_2$), 40.8 (**C**H$_2$), 31.0 (**C**H$_2$), 25.8 (SiC(**C**H$_3$)$_3$), 25.3 (CH**C**H$_3$), 18.2 (Si**C**(CH$_3$)$_3$), -4.6 (Si(**C**H$_3$)$_2$), -4.9 (Si(**C**H$_3$)$_2$); **IR** (thin film) ν 3366, 2930, 2857, 2360, 1254, 1102 cm^{-1}.

4-(1-Ethoxymethoxycyclopent-2-enyl)but-3-yn-2-one (220)



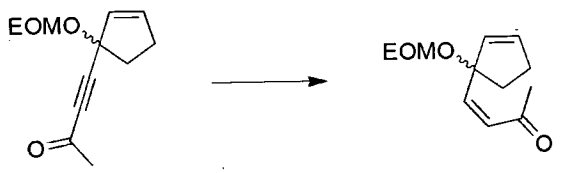
217 **220**

Enol (**217**) (940 mg, 3.52 mmol, 1 equiv), DMAP (43 mg, 0.35 mmol, 0.1 equiv), DIPEA (2.40 mL, 14.1 mmol, 4 equiv) and EOMCl (655 μL, 7.04 mmol, 2 equiv) were dissolved in DCM (40 mL) and heated to 40 °C for 18 hrs. After addition of saturated NH_4Cl solution, the mixture was extracted with Et_2O, the organic layers washed with brine, dried over $MgSO_4$, dried, filtered and evaporated to dryness. An aliquot of the crude intermediate (896 mg, 2.76 mmol, 1 equiv) was treated with TBAF (1 M solution in THF, 5.52 mL, 5.52 mmol, 2 equiv) in THF (15 mL) for 90 min. Following NH_4Cl quench, the reaction mixture was extracted with Et_2O, washed with brine, dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. After redissolving the intermediate propargyl alcohol (654 mg, 3.11 mmol, 1 equiv) in DCM (75 mL), MnO_2 (5.4 g, 62.20 mmol, 20 equiv) was added in one portion and

the resulting suspension was stirred at RT for 1 h. Purification by filtration through celite followed by flash column chromatography (SiO_2, hexanes/EtOAc 8:2) furnished alkynone (**220**) as a colourless oil (585 mg, 74% yield over 3 steps).

^{1}H NMR (360 MHz, $CDCl_3$) δ 6.06 (1 H, m, **H**C=CH), 5.86 (1 H, m, HC=C**H**), 4.92 (1 H, d, J_{AB}= 7.3 Hz, OC**H**$_2$O), 4.83 (1 H, d, J_{AB}= 7.3 Hz, OC**H**$_2$O), 3.65-3.21 (2 H, m, OC**H**$_2$CH$_3$), 2.57-2.26 (4 H, m, C**H**$_2$C**H**$_2$), 2.32 (3 H, s, COC**H**$_3$), 1.17 (3 H, t, J= 7.1 Hz, OCH$_2$C**H**$_3$); **^{13}C NMR** (90 MHz, $CDCl_3$) δ 184.0 (**C**=O), 136.8 (H**C**=CH), 132.2 (HC=**C**H), 91.7 (OCH$_2$O), 91.0 (q), 85.4 (**C**≡C), 82.6 (C≡**C**), 63.5 (OCH$_2$CH$_3$), 39.4 (**C**H$_2$CH$_2$), 32.6 (**C**H$_3$), 30.9 (CH$_2$**C**H$_2$), 14.9 (**C**H$_3$).

(Z)-4-(1-Ethoxymethoxycyclopent-2-enyl)but-3-en-2-one (222)



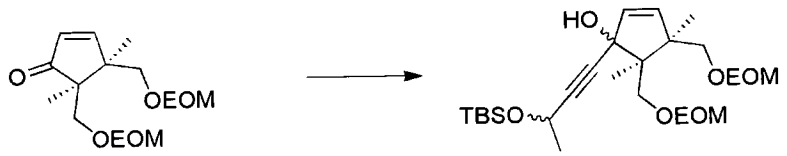
220 **222**

To alkynone (**220**) (144 mg, 0.69 mmol, 1 equiv) in EtOAc (10 mL) was added pyridine (50 μL), 1-octene (540 μL, 3.45 mmol, 5 equiv) and Lindlar's Catalyst (15 mg). After purging with H_2 for 5 min, the reaction mixture was stirred at RT under a H_2 atmosphere for 18 hrs. TLC analysis showed some starting material remaining and following further addition of Lindlar's Catalyst (35 mg), the reaction mixture was placed under a H_2 atmosphere for an additional 3 hours. Filtration through celite and evaporation of the solvents afforded the crude product which was purified by flash column chromatography (SiO_2, hexanes/EtOAC 9:1) to afford enone (**222**) as a colourless oil (92 mg, 63% yield).

^{1}H NMR (250 MHz, $CDCl_3$) δ 6.06 (1 H, m, HC=C**H**), 5.86 (1 H, d, J= 12.6 Hz, HC=C**H**), 5.74 (1 H, d, J= 12.6 Hz, **H**C=CH), 5.61 (1 H, m, **H**C=CH), 4.66 (1 H, d, J_{AB}= 7.3 Hz, OC**H**$_2$O), 4.54 (1 H, d, J_{AB}= 7.3 Hz, OC**H**$_2$O), 3.64-3.40 (2 H, m, OC**H**$_2$CH$_3$), 2.55-2.01 (4 H, m, C**H**$_2$C**H**$_2$), 2.23 (3 H, s, COC**H**$_3$), 1.14 (3 H, t, J= 7.1 Hz, OCH$_2$C**H**$_3$); **^{13}C NMR** (63 MHz, $CDCl_3$) δ 202.9 (**C**=O), 140.6 (H**C**=CH), 136.9

(HC=CH), 132.2 (HC=CH), 128.1 (HC=CH), 90.5 (q), 90.2 (OCH_2O), 63.3 (OCH_2CH_3), 37.0 (CH_2), 31.5 ($COCH_3$), 31.4 (CH_2), 15.0 (OCH_2CH_3).

1-[3-(*tert*-Butyldimethylsilanyloxy)but-1-ynyl]-4,5-bis-ethoxymethoxymethyl-4,5-dimethylcyclopent-2-enol (223)



201 **223**

tert-Butyl-dimethyl-(1-methyl-prop-2-ynyloxy)-silane (**208**) (739 mg, 4.01 mmol, 2.5 equiv) in THF (20 mL) was cooled to -42 °C and *n*-butyl lithium (2.50 mL, 1.6 M solution in hexane, 4.01 mmol, 2.5 equiv) was added dropwise. The resulting solution was stirred for 45 min at -42 °C. After warming to RT, the solution was slowly added to cyclopentenone (**201**) (460 mg, 1.60 mmol, 1 equiv) in THF (20 mL) at -42 °C *via* a cannula. The reaction mixture was stirred at -42 °C for 1 h, then warmed to RT over a further 1 h and quenched by addition of a saturated solution of NH_4Cl. The aqueous layer was extracted with EtOAc and the resulting organic layer was washed with brine, dried over $MgSO_4$, filtered and evaporated. Flash column chromatography (SiO_2, hexanes/EtOAc 9:1) afforded tertiary alcohol (**223**) as a colourless oil (131 mg, 80 % yield)

^{1}H NMR (360 MHz, $CDCl_3$) δ 5.69 (2 H, d, *J*= 5.7 Hz, 2 x **H**C=CH), 5.61 (1 H, d, *J*= 5.7 Hz, HC=C**H**), 5.60 (1 H, d, *J*= 5.7 Hz, HC=C**H**), 4.71-4.68 (4 H, m, OC**H$_2$**O), 4.60-4.58 (4 H, m, OC**H$_2$**O), 4.55 (1 H, q, *J*= 6.5 Hz, SiOC**H**), 4.54 (1 H, q, *J*= 6.5 Hz, SiOC**H**), 3.86 (1 H, d, *J*= 9.5 Hz, CC**H$_2$**O), 3.85 (1 H, d, *J*= 9.5 Hz, CC**H$_2$**O), 3.67-3.53 (14 H, m, CC**H$_2$**O), 1.39 (3 H, d, *J*= 6.5 Hz, SiOCHC**H$_3$**), 1.38 (3 H, d, *J*= 6.5 Hz, SiOCHC**H$_3$**), 1.22 (6 H, t, *J*=7.1 Hz, 2 x OCH_2C**H$_3$**), 1.19 (6 H, t, *J*=7.1 Hz, 2 x OCH_2C**H$_3$**), 1.10 (6 H, s, 2 x C**H$_3$**), 1.06 (6 H, s, 2 x C**H$_3$**), 0.88 (18H, s, 2 x $OSiC(CH_3)_3$), 0.10-0.08 (12 H, m, 2 x $OSi(CH_3)_2$); **^{13}C NMR** (90 MHz, $CDCl_3$) δ 138.6 (**H**C=CH), 138.5 (**H**C=CH), 133.0 (HC=**C**H), 132.9 (HC=**C**H), 95.9 (OCH_2O), 95.8 (OCH_2O), 95.3 (OCH_2O), 95.2 (OCH_2O), 89.4 (**C**≡C), 85.0 (C≡**C**),

81.6 (COH), 72.6 (CH_2), 72.5 (CH_2), 71.8 (CH_2), 63.4 (CH_2), 63.2 (CH_2), 63.1 (CH_2), 59.0 (CHOSi), 58.9 (CHOSi), 54.8 (q), 52.8 (q), 25.8 ($OSiC(CH_3)_3$), 25.4 (CH_3), 25.3 (CH_3), 19.3 (CH_3), 18.2 ($OSiC(CH_3)_3$), 16.5 (CH_3), 15.1 (CH_3), -4.5 ($OSi(CH_3)_2$), -4.6 ($OSi(CH_3)_2$), -4.9 ($OSi(CH_3)_2$), -5.0($OSi(CH_3)_2$); **IR** (thin film) ν 3434, 2360, 2341, 1101, 1043 cm^{-1}; **HRMS** (CI) *m/z* calcd for $C_{25}H_{45}O_6Si$ $[M-H]^+$ 469.2980, found 469.2986.

tert-Butyl-[3-(1-ethoxymethoxy-4,5-bis-ethoxymethoxymethyl-4,5-dimethylcyclopent-2-enyl)-1-methylprop-2-ynyloxy]dimethyl-silane (224)

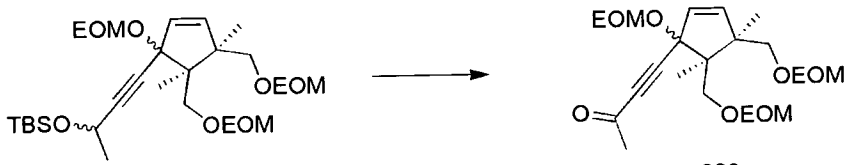
223 **224**

A solution of alcohol (**223**) (202 mg, 0.43 mmol, 1 equiv) in DCM (10 mL) was treated with DMAP (5 mg, 0.04 mmol, 0.1 equiv), DIPEA (295 μL, 1.72 mmol, 4 equiv) and EOMCl (80 μL, 0.86 mmol, 2 equiv). The resulting solution was heated to 40 °C under a N_2 atmosphere for 18 hrs. Following quenching with saturated NH_4Cl solution, the organice layer was washed with brine, dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Flash column chromatography (SiO_2, hexanes/EtOAc 19:1) furnished cyclopentenone (**224**) as a pale yellow oil (218 mg, 96% yield). 1:1 mixture of diastereomers by ^{1}H-NMR.

^{1}H NMR (360 MHz, $CDCl_3$) δ 5.86 (1 H, d, *J*= 5.9 Hz, **H**C=CH), 5.85 (1 H, d, *J*= 5.9 Hz, **H**C=CH), 5.72 (1 H, d, *J*= 5.9 Hz, HC=C**H**), 5.71 (1 H, d, *J*= 5.9 Hz, HC=C**H**), 5.14 (1 H, d, *J*= 7.0 Hz, OCH_2O), 5.13 (1 H, d, *J*= 7.0 Hz, OCH_2O), 4.75-4.61 (10 H, m, OCH_2O), 4.56 (1 H, q, *J*= 6.5 Hz, C**H**OSi), 4.55 (1 H, q, *J*= 6.5 Hz, C**H**OSi), 3.78-3.44 (20 H, m, CCH_2O), 1.40 (3 H, d, *J*= 6.5 Hz, $SiOHCCH_3$), 1.39 (3 H, d, *J*= 6.5 Hz, $SiOHCCH_3$), 1.22-1.15 (18 H, m, OCH_2CH_3), 1.14 (6 H, s, CH_3), 1.05 (6 H, s, CH_3), 0.87 (18 H, s, $OSiC(CH_3)_3$), 0.09-0.08 (12 H, m, $OSi(CH_3)_2$; **^{13}C NMR** (90 MHz, $CDCl_3$) δ 139.8 (H**C**=CH), 139.7 (H**C**=CH), 131.9 (HC=**C**H), 131.8 (HC=**C**H), 95.7 (OCH_2O), 95.4 (OCH_2O), 95.3 (OCH_2O), 92.1 (OCH_2O), 91.3

(CH=CH-C-O), 86.0 (C≡C), 85.9 (C≡C), 81.0 (C≡C), 80.9 (C≡C), 73.2 (CCH_2O), 73.1 (CCH_2O), 71.7 (CCH_2O), 71.6 (CCH_2O), 63.3 (CH_2), 63.2 (CH_2), 63.1 (CH_2), 63.0 (CH_2), 59.0 (CHOSi), 58.9 (CHOSi), 55.0 (q), 54.9 (q), 52.2 (q), 52.2 (q), 25.7 ($OSiC(CH_3)$), 25.3 (CH_3), 25.3 (CH_3), 20.0 (CH_3), 19.9 (CH_3), 18.1 ($OSiC(CH_3)$), 16.0 (CH_3), 15.9 (CH_3), 15.1 (CH_3), 15.0 (CH_3), -4.6 ($OSi(CH_3)_2$), -5.1 ($OSi(CH_3)_2$); **IR** (thin film) ν 2976, 2930, 2879, 1108, 1041 cm^{-1}; **HRMS** (ES) *m/z* calcd for $C_{28}H_{56}NO_7Si$ $[M+NH_4]^+$ 546.3821, found 546.3821.

4-(1-Ethoxymethoxy-4,5-bis-ethoxymethoxymethyl-4,5-dimethylcyclopent-2-enyl)but-3-yn-2-one (226)



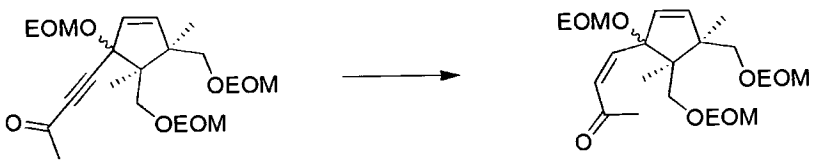
224 **226**

Cyclopentene (**223**) (575 mg, 1.08 mmol, 1 equiv) was dissolved in THF (20 mL) and TBAF (1 M solution in THF, 2.18 mL, 2.18 mmol, 2 equiv) was added. After stirring at RT for 1 h, NH_4Cl and Et_2O was added, the organic layer was washed with brine, dried over $MgSO_4$, filtered and evaporated to dr.ness. The resulting crude was taken up in DCM (40 mL) and treated with MnO_2 (1.88 g, 21.6 mmol, 20 equiv) at RT. After 4 hrs, the mixture was filtered through celite, evaporated *in vacuo* and purified by flash column chromatrography (SiO_2, hexanes/EtOAc 8:2) to afford alkynone (**226**) as a colourless oil (415 mg, 93% yield).

^{1}H NMR (360 MHz, $CDCl_3$) δ 5.87 (1 H, d, *J*= 5.7 Hz, HC=C**H**), 5.79 (1 H, d, *J*= 5.7 Hz, **H**C=CH), 5.05 (1 H, d, J_{AB}= 7.2 Hz, OCH_2O), 4.76 (1 H, d, J_{AB}= 7.2 Hz, OCH_2O), 4.62 (2 H, s, OCH_2O), 4.60 (2 H, s, OCH_2O), 3.71-3.49 (10 H, m, CCH_2O), 2.31 (3 H, s, $COCH_3$), 1.19-1.13 (9 H, m, OCH_2CH_3), 1.13 (3 H, s, CH_3), 1.05 (3 H, s, CH_3); **^{13}C NMR** (90 MHz, $CDCl_3$) δ 183.5 (C=O), 141.8 (HC=CH), 130.2 (HC=CH), 95.6 (OCH_2O), 95.3 (OCH_2O), 91.5 (OCH_2O), 89.5 (C≡C), 88.0 (C≡C), 85.7 (C≡C-C-C=C), 72.7 (CH_2), 71.2 (CH_2), 63.6 (CH_2), 63.4 (CH_2), 63.2 (CH_2), 55.8 (q), 52.4 (q), 32.6 ($C=OCH_3$), 20.1 (CH_3), 16.0 (CH_3), 15.1 (2 x CH_3),

14.9 (CH_3); **IR** (thin film) ν 2975, 2931, 2878, 2206, 1680, 1112, 1042 cm^{-1}; **HRMS** (ES) *m/z* calcd for $C_{22}H_{40}O_7Si$ $[M+NH_4]^+$ 430.2799, found 430.2795.

(Z)-4-(1-Ethoxymethoxy-4,5-bis-ethoxymethoxymethyl-4,5-dimethylcyclopent-2-enyl)but-3-en-2-one (227)

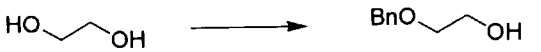


226 **227**

Alkynone (**226**) (204 mg, 0.49 mmol, 1 equiv) and 1-octene (390 μL, 2.47 mmol, 5 equiv) were dissolved in EtOAc (10 mL), Lindlar's Catalyst (57 mg) was added and the resulting mixture was purged with H_2 using a balloon for 5 min. The reaction mixture was stirred at RT under a H_2 for 100 min before removing the catalyst *via* filtration through celite. Following removal of the solvent under reduced pressure and flash column chromatography (SiO_2, hexanes/EtOAc 8:2), enone (**227**) was obtained as a colourless oil (188 mg, 92% yield).

^{1}H NMR (360 MHz, $CDCl_3$) δ 5.96 (1 H, d, *J*= 13.1 Hz, **H**C=CH), 5.87 (1 H, d, *J*= 6.1 Hz, **H**C=CH), 5.78 (1 H, d, *J*= 6.1 Hz, HC=C**H**), 5.71 (1 H, d, *J*= 13.1 Hz, HC=C**H**), 4.73 (1 H, d, *J*= 7.0 Hz, OC**H**$_2$O), 4.64-4.60 (5 H, m, OC**H**$_2$O), 3.61-3.47 (10 H, m, CC**H**$_2$O), 2.26 (3 H, s, COC**H**$_3$), 1.21 (3 H, t, *J*= 7.1 Hz, OCH$_2$C**H**$_3$), 1.20 (3 H, t, *J*= 7.1 Hz, OCH$_2$C**H**$_3$), 1.15 (3 H, t, *J*= 7.0 Hz, OCH$_2$C**H**$_3$), 1.14 (3 H, s, C**H**$_3$), 1.10 (3 H, s, C**H**$_3$); **^{13}C NMR** (90 MHz, $CDCl_3$) δ 203.3 (**C**=O), 141.0 (**H**C=CH), 136.4 (H**C**=CH), 130.3 (HC=**C**H), 130.2 (HC=**C**H), 95.6 (O**C**H$_2$O), 95.4 (O**C**H$_2$O), 92.0 (HC=CH-**C**-CH=CH), 91.2 (O**C**H$_2$O), 73.0 (**C**H$_2$), 71.5 (**C**H$_2$), 63.7 (**C**H$_2$), 63.5 (**C**H$_2$), 63.3 (**C**H$_2$), 55.0 (q), 52.4 (q), 31.4 (C=O**C**H$_3$), 20.8 (**C**H$_3$), 16.2 (**C**H$_3$), 15.1 (**C**H$_3$), 15.0 (**C**H$_3$); **IR** (thin film) ν 2974, 2927, 2876, 2359, 1700, 1040 cm^{-1}; **HRMS** (ES) *m/z* calcd for $C_{22}H_{39}O_7$ $[M+H]^+$ 415.2690, found 415.2687.

2-Benzyloxyethanol

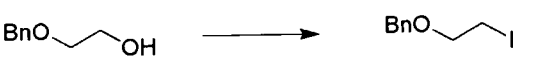


To a solution of ethylene glycol (22.3 mL, 400 mmol, 10 equiv) in DMF (10 mL) and MeOH (10 mL) was added NaH (2.0 g, 60% dispersion in oil, 50 mmol, 1.25 equiv). The resulting mixture was stirred at RT under a N_2 atmosphere for 7 h before dropwise addition of benzyl bromide (4.75 mL, 40 mmol, 1 equiv).After stirring under N_2 at RT for a further 18h, the reaction mixture was quenched *via* addition of a saturated 1 M HCl solution. The homogeneous mixture was extracted twice with EtOAc and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered and evaporated to dryness. Flash column chromatography (SiO_2, hexanes/EtOAc 1:1) afforded the title compound as a colourless oil (2.95 g, 48% yield).

^{1}H NMR (250 MHz, $CDCl_3$) δ 7.38-7.30 (5 H, m, Ar**H**), 4.58 (2 H, s, Ar**CH$_2$**O), 3.80-3.74 (2 H, m, **CH$_2$**), 3.62-3.58 (2 H, m, **CH$_2$**), 2.17 (1 H, s, O**H**); **^{13}C NMR** (63 MHz, $CDCl_3$) δ 137.9 (**Ar**CCH$_2$), 128.4 (**Ar**CH), 127.8 (**Ar**CH), 73.3 (**C**H$_2$), 71.3 (**C**H$_2$), 61.9 (**C**H$_2$).

The spectroscopic data was in agreement with that of commercially available 2-Benzyloxy-ethanol (CAS [622-08-2]).

(2-Iodoethoxymethyl)benzene (245)



245

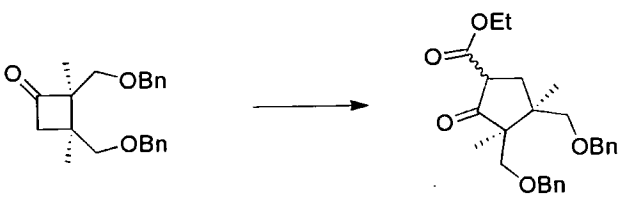
2-Benzyloxy-ethanol (1.06 g, 6.96 mmol, 1 equiv) was dissolved in anhydrous THF (20 mL) and PPh_3 (1.83 g, 6.96 mmol, 1 equiv), imidazole (949 mg, 13.9 mmol, 2 equiv) and iodine (1.77 g, 6.96 mmol, 1 equiv) were added portionwise. The reaction mixture was stirred at RT for 45 min before the solvent was removed *in vacuo*. The resulting residue was triturated thrice with Et_2O, the combined organic fractions were evaporated to dryness and purified by flash column chromatography (SiO_2,

haxanes/EtOAc 9:1) to afford the title compound as a colourless oil (1.66 g, 91% yield).

^{1}H NMR (250 MHz, $CDCl_3$) δ 7.38-7.28 (5 H, m, Ar**H**), 4.59 (2 H, s, Ar**C**H_2O), 3.75 (2 H, t, *J*= 6.7 Hz, **C**H_2), 3.23 (2 H, t, *J*= 6.7 Hz, **C**H_2); **^{13}C NMR** (63 MHz, $CDCl_3$) δ 137.7 (**ArC**CH_2), 128.4 (**ArC**H), 127.8 (**ArC**H), 127.7 (**ArC**H), 72.8 (**C**H_2), 70.7 (**C**H_2), 2.9 (**C**H_2).

The spectroscopic data were in agreement with those previously published.[94]

3,4-Bis-benzyloxymethyl-3,4-dimethyl-2-oxocyclopentanecarboxylic acid ethyl ester (190)



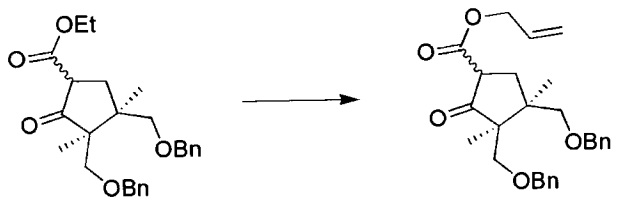
166 **190**

Cyclobutanone (**166**) (5.15 g, 15.2 mmol, 1 equiv) in DCM (200 mL) was cooled to 0 °C before dropwise addition of $BF_3{\cdot}OEt_2$ (4.87 mL, 38 mmol, 2.5 equiv). After stirring for 5 min, ethyldiazo acetate (8.0 mL, 76.07 mmol, 5 equiv) was added dropwise and the resulting solution was stirred at 0 °C for 50 min before allowing warming to RT. Following addition of saturated $NaHCO_3$ solution, the organic phase was seperated, dried over $MgSO_4$, dried and the solvent removed *in vacuo*. Flash column chromatography (SiO_2, hexanes/EtOAc 4:1) afforded cyclopentanone (**190**) as a colourless oil (5.70 g, 88% yield).

^{1}H NMR (360 MHz, $CDCl_3$) δ 7.39-7.17 (10 H, m, Ar**H**), 4.42-4.05 (6 H, m, 3 x **C**H_2), 3.59 (1 H, t, *J*= 9.8 Hz, **C**H), 3.54-3.49 (2 H, m, **C**H_2), 3.35 (1 H, d, *J*= 8.9 Hz, **C**H_2), 3.24 (1 H, d, *J*= 8.9 Hz, **C**H_2), 2.27-2.13 (2 H, m, C=OCHCH_2), 1.27 (3 H, t, *J*= 7.1 Hz, CH_2CH_3), 1.19 (3 H, s, **C**H_3), 1.08 (3 H, s, **C**H_3); **^{13}C NMR** (90 MHz, $CDCl_3$) δ 212.9 (**C**=O), 170.0 (**C**=O), 138.3 (**ArC**CH_2), 137.7 (**ArC**CH_2), 128.4 (**ArC**H), 128.2 (**ArC**H), 127.6 (**ArC**H), 77.4 (**C**H_2), 73.4 (**C**H_2), 73.3 (**C**H_2), 72.7 (**C**H_2), 61.3 (**C**H_2), 54.2 (**C**H), 53.4 (q), 43.9 (q), 36.2 (**C**H_2), 20.4 (**C**H_3), 17.2

(CH_3), 14.1 (CH_3); **IR** (thin film) ν 2981, 1749, 1722, 1454, 1096 cm^{-1}; **HRMS** (ES) *m/z* calcd for $C_{26}H_{36}O_5N$ $[M+NH_4]^+$ 442.2588, found 442.2589.

3,4-Bis-benzyloxymethyl-3,4-dimethyl-2-oxocyclopentanecarboxylic acid allyl ester (241)



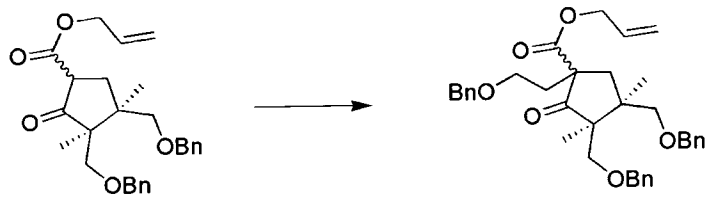
190 **241**

Cyclopentanone (**190**) (2.89 g, 6.81 mmol, 1 equiv) was dissolved in toluene (50 mL) and allyl alcohol (4.63 mL, 68.1 mmol, 10 equiv) and the resulting solution was heated to 120 °C for 38 h. After cooling to RT, the solvent was evaporated under reduced pressure and the crude product was purified by flash column chromatography (SiO_2, hexanes/EtOAC 4:1) to afford the title compound as a colourless oil (2.53 g, 85% yield).

Major isomer:

^{1}H NMR (360 MHz, $CDCl_3$) δ 7.43-7.24 (10 H, m, Ar**H**), 5.96 (1 H, m, CH_2CH=CH_2), 5.44-5.24 (2 H, m, CH_2CH=CH_2), 4.75-4.29 (6 H, m, 3 x CH_2), 3.71 (1 H, t, *J*= 9.9 Hz, C**H**), 3.61-3.54 (2 H, m, CH_2), 3.42 (1 H, d, *J*= 8.9 Hz, CH_2), 3.31 (1 H, d, *J*= 8.9 Hz, CH_2), 2.36-2.21 (2 H, m, CH_2), 1.26 (3 H, s, CH_3), 1.16 (3 H, s, CH_3); **^{13}C NMR** (90 MHz, $CDCl_3$) δ 212.7 (**C**=O), 169.7 (**C**=O), 138.3 (**Ar**CCH_2), 137.7 (**Ar**CCH_2), 131.8 (**C**H=CH_2), 138.4 (**Ar**CH), 128.2 (**Ar**CH), 127.6 (**Ar**CH), 127.5 (**Ar**CH), 118.3 (CH=**C**H_2), 77.4 (CH_2), 73.4 (CH_2), 73.3 (CH_2), 72.7 (CH_2), 65.8 (CH_2), 54.2 (CH), 53.3 (q), 43.9 (q), 36.2 (CH_2), 20.4 (CH_3), 17.3 (CH_3); **IR** (thin film) ν 2861, 1749, 1724, 1454, 1097 cm^{-1}; **HRMS** (ES) *m/z* calcd for $C_{27}H_{36}O_5N$ $[M+NH_4]^+$ 454.2588, found 454.2595.

1-(2-Benzyloxyethyl)-3,4-bis-benzyloxymethyl-3,4-dimethyl-2-oxocyclopentanecarboxylic acid allyl ester (236)



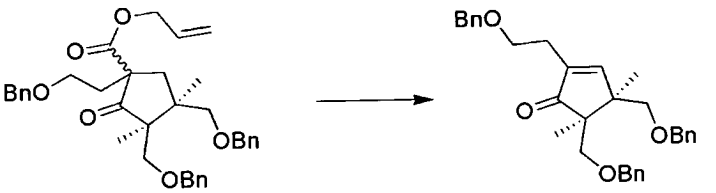
241 **236**

Cyclopentanone (**241**) (1.20 g, 2.74 mmol, 1 equiv) was dissolved in acetonitrile (5 mL) and K_2CO_3 (760 mg, 5.50 mmol, 2 equiv) and (2-iodo-ethoxymethyl)-benzene (**245**) (1.44 g, 5.50 mmol, 2 equiv) were added. The suspension was stirred under N_2 at 95 °C for 26 h, cooled to RT and EtOAc (10 mL) was added. Following washes with saturated NH_4Cl solution and brine, the organic layer was dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Flash column chromatography (SiO_2, DCM 100%) afforded the title compound as a pale yellow oil (928 mg, 76% yield).

Major isomer:

^{1}H NMR (360 MHz, $CDCl_3$) δ 7.34-7.20 (15 H, m, Ar**H**), 5.82 (1 H, m, C**H**=CH_2), 5.34-5.16 (2 H, m, CH=C**H$_2$**), 4.62-4.21 (8 H, m, 4 x **CH$_2$**), 3.71-3.28 (6 H, m, 3 x **CH$_2$**), 2.53 (1 H, d, *J*=13.7 Hz, **CH$_2$**), 2.39 (1 H, m, **CH$_2$**), 2.04 (1 H, d, *J*=13.7 Hz, **CH$_2$**), 1.98 (1 H, m, **CH$_2$**), 1.08 (3 H, s, **CH$_3$**), 1.04 (3 H, s, **CH$_3$**); **^{13}C NMR** (90 MHz, $CDCl_3$) δ 215.9 (**C**=O), 171.3 (**C**=O), 138.4 (**ArC**CH_2), 138.0 (**ArC**CH_2), 137.9 (**ArC**CH_2), 131.7 (**C**H=CH_2), 128.3 (**ArC**H), 128.2 (**ArC**H), 127.8 (**ArC**H), 127.7 (**ArC**H), 127.6 (**ArC**H), 127.5 (**ArC**H), 118.4 (CH=**C**H_2), 76.7 (**C**H_2), 74.6 (**C**H_2), 73.4 (**C**H_2), 73.2 (**C**H_2), 72.7 (**C**H_2), 66.9 (**C**H_2), 65.9 (**C**H_2), 57.9 (q), 55.3 (q), 42.5 (**C**H_2), 40.7 (q), 36.0 (**C**H_2), 22.1 (**C**H_3), 17.9(**C**H_3); **IR** (thin film) ν 2857, 1749, 1725, 1454, 1100 cm^{-1}; **HRMS** (ES) *m/z* calcd for $C_{36}H_{46}O_6N$ $[M+NH_4]^+$ 588.3320, found 588.3317.

2-(2-Benzyloxyethyl)-4,5-bis-benzyloxymethyl-4,5-dimethylcyclopent-2-enone (235)

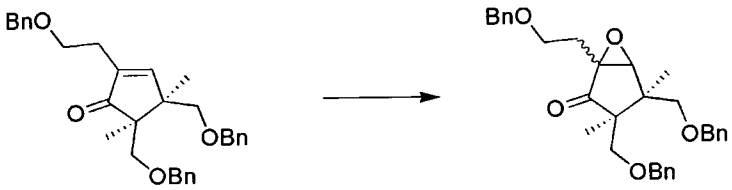


236 **235**

A acetonitrile solution (2.5 mL) of cyclopentanone (**236**) (106 mg, 0.18 mmol, 1 equiv) was added to a solution of $Pd(OAc)_2$ (5 mg, 0.02 mmol, 0.1 equiv) and PPh_3 (5 mg, 0.02 mmol, 0.1 equiv) in acetonitrile (2.5 mL) at 50 °C under a N_2 atosphere. The reaction mixture was then stirred at 95 °C for 5.5 h before allowing to cool to RT. Filtration through a plug of silica, removal of solvent and flash column chromatography (SiO_2, hexanes/EtOAc 9:1) furnished cyclopentenone (**235**) as a colourless oil (53 mg, 61% yield).

^{1}H NMR (360 MHz, $CDCl_3$) δ 7.33-7.18 (15 H, m, Ar**H**), 7.05 (1 H, s, C=C**H**), 4.44 (2 H, s, ArC**H$_2$**O), 4.38-4.29 (2 H, m, ArC**H$_2$**O), 4.31 (2 H, s, ArC**H$_2$**O), 3.61-3.47 (6 H, m, 3 x C**H$_2$**), 2.49 (2 H, dt, *J*= 1.0, 6.7 Hz, C**H$_2$**), 1.14 (3 H, s, C**H$_3$**), 1.12 (3 H, s, C**H$_3$**); **^{13}C NMR** (90 MHz, $CDCl_3$) δ 211.3 (**C**=O), 162.3 (C=**C**H), 139.2 (**Ar**CCH$_2$), 138.4 (**Ar**CCH$_2$), 138.3 (**Ar**CCH$_2$), 128.3 (**Ar**CH), 128.2 (**Ar**CH), 128.1 (**C**=CH), 127.6 (**Ar**CH), 127.4 (**Ar**CH), 127.3 (**Ar**CH), 127.2 (**Ar**CH), 74.8 (CH$_2$), 73.5 (CH$_2$), 73.2 (CH$_2$), 72.8 (CH$_2$), 72.7 (CH$_2$), 68.1 (CH$_2$), 54.1 (q), 49.6 (q), 25.3 (CH$_2$), 20.1 (CH$_3$), 19.9 (CH$_3$); **IR** (thin film) ν 2857, 1702, 1454, 1099 cm^{-1}; **HRMS** (ES) *m/z* calcd for $C_{32}H_{37}O_4$ $[M+H]^+$ 485.2686, found 485.2684.

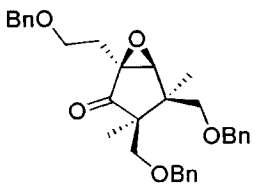
1-(2-Benzyloxyethyl)-3,4-bis-benzyloxymethyl-3,4-dimethyl-6-oxa-bicyclo[3.1.0]hexan-2-one (247)



235 **247**

Cyclopentenone (**235**) (272 mg, 0.56 mmol, 1 equiv) in MeOH (20 mL) was treated with H_2O_2 (190 μL, 30% wt solution in H_2O, 1.68 mmol, 3 equiv) and 1 M NaOH solution (1.68 mL, 1.68 mmol, 3 equiv) at 0 °C. The resulting solution was warmed to RT, stirred for 18 h and poured into a saturated NH_4Cl solution. The mixture was extracted with Et_2O, dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. Flash column chromatography (SiO_2, hexanes/EtOAc 9.5:0.5) afforded two diastereomers of the epoxide product (**247**) (**247β** - 85 mg, **247α** – 150 mg, 235 mg overall, 84% yield, 1.8:1 ratio of diastereomers)

Major Diastereomer

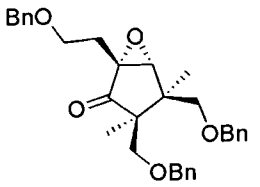


247α

^{1}H NMR (360 MHz, $CDCl_3$) δ 7.36-7.21 (15 H, m, Ar**H**), 4.53 (1 H, d, J_{AB}= 12.9 Hz, ArC**H**$_2$O), 4.47 (1 H, d, J_{AB}= 12.9 Hz, ArC**H**$_2$O), 4.45 (2 H, s, ArC**H**$_2$O), 4.39 (1 H, d, J_{AB}= 12.2 Hz, ArC**H**$_2$O), 4.34 (1 H, d, J_{AB}= 12.2 Hz, ArC**H**$_2$O), 3.74 (1 H, s, C=OCC**H**), 3.63-3.50 (5 H, m, 2 x C**H**$_2$, C**H**$_2$), 3.47 (1 H, d, J_{AB}= 8.8 Hz, C**H**$_2$), 2.36 (1 H, m, C=OCC**H**$_2$), 2.01 (1 H, m, C=OCC**H**$_2$), 1.08 (3 H, s, C**H**$_3$), 1.00 (3 H, s, C**H**$_3$); **^{13}C NMR** (90 MHz, $CDCl_3$) δ 211.2 (**C**=O), 138.4 (**Ar**CCH$_2$), 138.2 (**Ar**CCH$_2$), 138.0 (**Ar**CCH$_2$), 128.3 (**Ar**CH), 128.2 (**Ar**CH), 127.6 (**Ar**CH), 127.4 (**Ar**CH), 127.3 (**Ar**CH), 74.4 (**C**H$_2$), 73.4 (**C**H$_2$), 73.0 (**C**H$_2$), 72.9 (**C**H$_2$), 72.0 (**C**H$_2$), 67.4 (C=OCCH), 65.6 (**C**H$_2$), 62.1 (C=OCCH), 52.0 (q), 43.6 (q), 25.1

(CH_2), 18..8 (CH_3), 16.3 (CH_3); **IR** (thin film) ν 2859, 1740, 1454, 1097, 697 cm^{-1}; **HRMS** (ES) *m/z* calcd for $C_{32}H_{40}O_5N$ $[M+NH_4]^+$ 518.2901, found 518.2903.

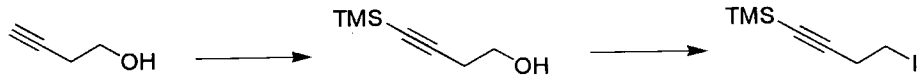
Minor Diastereomer



247β

^{1}H NMR (360 MHz, $CDCl_3$) δ 7.34-7.23 (13 H, m, Ar**H**), 7.13-7.01 (2 H, m, Ar**H**), 4.42 (1 H, d, J_{AB}= 12.0 Hz, Ar**C**H_2O), 4.32 (2 H, s, Ar**C**H_2O), 4.25 (1 H, d, J_{AB}= 12.0 Hz, Ar**C**H_2O), 3.57-3.40 (6 H, m, 2 x **C**H_2, **C**H_2, C=OCC**H**), 3.28 (1 H, d, J_{AB}= 12.0 Hz, **C**H_2), 2.21 (1 H, m, C=OCCH_2), 2.06 (1 H, m, C=OCCH_2), 1.31 (3 H, s, **C**H_3), 1.13 (3 H, s, **C**H_3); **^{13}C NMR** (90 MHz, $CDCl_3$) δ 212.1 (**C**=O), 138.4 (**ArC**CH_2), 138.3 (**ArC**CH_2), 137.6 (**ArC**CH_2), 138.3 (**ArC**H), 127.7 (**ArC**H), 127.6 (**ArC**H), 127.5 (**ArC**H), 127.4 (**ArC**H), 74.3 (**C**H_2), 73.5 (**C**H_2), 73.4 (**C**H_2), 73.0 (**C**H_2), 72.6 (**C**H_2), 68.8 (C=OCCH), 65.5 (**C**H_2), 62.8 (C=OCCH), 49.3 (q), 43.8 (q), 24.7 (**C**H_2), 21.6 (**C**H_3), 16.2 (**C**H_3); **IR** (thin film) ν 2860, 1737, 1454, 1099, 697 cm^{-1}; **HRMS** (ES) *m/z* calcd for $C_{32}H_{40}O_5N$ $[M+NH_4]^+$ 518.2901, found 518.2908.

(4-Iodobut-1-ynyl)trimethylsilane (250)



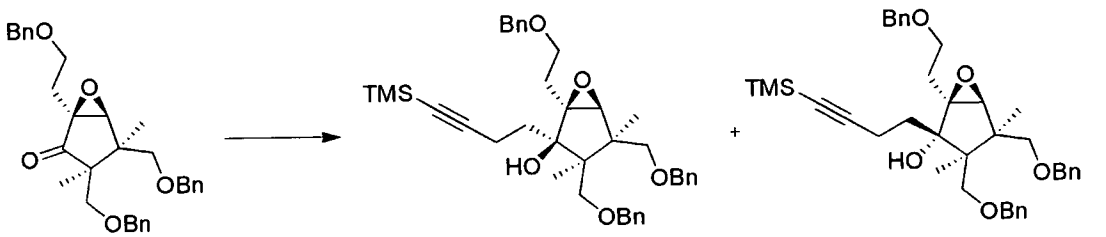
248 **249** **250**

3-Butyn-1-ol (**248**) (3 mL, 39.6 mmol, 1 equiv) in THF (100 mL) was cooled to -78 °C and ^{n}BuLi (54.5 mL, 87.2 mmol, 2.2 equiv) was added dropwise. After stirring at -78 °C for 20 min, agitation was continued at RT for a further 1 h. After re-cooling to -78 °C, TMSCl (11.1 mL, 87.2 mmol, 2.2 eqiv) was added and the resulting mixture was stirred at RT for 18 h. After addition of 1 M HCl solution (10 mL) and stirring for 5 min, the reaction mixture was extracted with EtOAc and the organic layer was washed with H_2O and brine before drying over $MgSO_4$, filtering and evaporating to dryness. Flash column chromatography (SiO_2, hexanes/EtOAc 7:3) afforded the intermediate 4-trimethylsilanyl-but-3-yn-1-ol (**249**) as a colourless oil (4.90 g, 87% yield). 4-Trimethylsilanyl-but-3-yn-1-ol (**249**) (4.54 g, 31.9 mmol, 1 equiv) in THF (100 mL) was then treated with PPh_3 (8.38 g, 31.9 mmol, 1 equiv), imidazole (4.35 g, 63.9 mmol, 2 equiv) and iodine (8.10 g, 31.9 mmol, 1 equiv) and the resulting solution was stirred at RT for 1 h. The solvent was removed *in vacuo* and the resulting brown residue triturated thrice with Et_2O. The combined organic fractions were evaporated to dryness and subsequent flash column chromatography (SiO_2, hexanes/EtOAc 9:1) furnished silane (**250**) as a pale pink oil (7.23 g, 90% yield, 78% yieled over 2 steps).

^{1}H NMR (360 MHz, $CDCl_3$) δ 3.18 (2 H, t, *J*= 7.5 Hz, **CH_2**), 2.76 (2 H, t, *J*= 7.5 Hz, **CH_2**), 0.13 (9 H, s, $Si(\mathbf{CH_3})_3$); **^{13}C NMR** (90 MHz, $CDCl_3$) δ 105.0 (**C**≡C), 86.7 (C≡**C**), 25.1 (**CH_2**), 1.0 (**CH_2**), -0.1 ($Si(\mathbf{CH_3})_3$).

The spectroscopic data were in agreement with those previously published.[95]

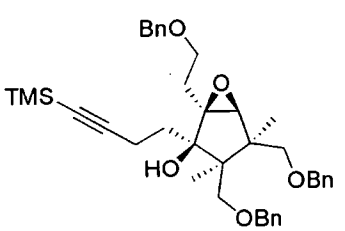
1-(2-Benzyloxyethyl)-3,4-bis-benzyloxymethyl-3,4-dimethyl-2-(4-trimethylsilanylbut-3-ynyl)6-oxabicyclo[3.1.0]hexan-2-ol (251αα)



247α **251αα** **251αβ**

A solution of (4-Iodo-but-1-ynyl)-trimethyl-silane (**250**) (59 mg, 0.22 mmol, 1.5 equiv) in dry Et_2O (5 mL) at -78 °C was treated with ^tBuLi (260 μL, 1.7 M solution in pentane, 0.44 mmol, 3 equiv) and stirred under a N_2 atmosphere for 1 h before warming to RT and stirring for a further 1 h. After re-cooling to -78 °C, the mixture was transferred into a Et_2O (10 mL) solution of epoxide (**247α**) (74mg, 0.14 mmol, 1 equiv) at -78 °C *via* a double tipped needle. The reaction mixture was then stirred for 2 h at -78 °C before warming to RT and quenching with saturated NH_4Cl solution. The organic layer was separated, washed with brine, dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Flash column chromatography (SiO_2, hexanes/EtOAc 9:1) furnished tertiary alcohols (**251αα**) and (**251αβ**) as a pale yellow oil (80 mg, 87% yield, 5:1 mixture of inseparable diastereomers).

Major diastereomer

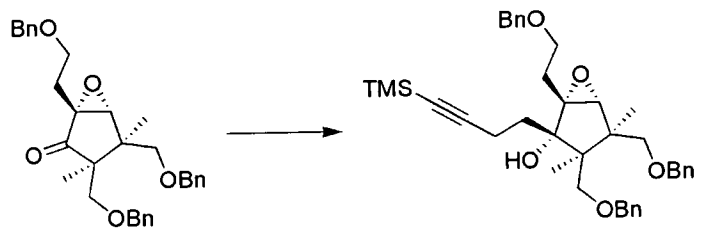


251αα

^{1}H NMR (360 MHz, $CDCl_3$) δ 7.33-7.22 (15 H, m, Ar**H**), 4.51-4.40 (5 H, m, 2 x Ar**CH$_2$**O, Ar**CH$_2$**O), 4.29 (1 H, d, J_{AB}= 11.7 Hz, Ar**CH$_2$**O), 3.71-3.53 (2 H, m, **CH$_2$**), 3.47-3.34 (4 H, m, 2 x **CH$_2$**), 3.20 (1 H, s, C=OCC**H**), 2.46-2.41 (2 H, m, **CH$_2$**), 2.31 (1 H, m, **CH$_2$**), 2.12 (1 H, m, **CH$_2$**), 1.96-1.89 (2 H, m, **CH$_2$**), 1.11 (3 H, s, **CH$_3$**), 1.09 (3 H, s, **CH$_3$**), 0.14 (9 H, s, Si(**CH$_3$**)$_3$); **^{13}C NMR** (90 MHz, $CDCl_3$) δ 138.3

(**Ar**CCH_2), 138.2 (**Ar**CCH_2), 137.8 (**Ar**CCH_2), 128.4 (**Ar**CH), 128.3 (**Ar**CH), 127.6 (**Ar**CH), 127.5 (**Ar**CH), 127.4 (**Ar**CH), 107.9 (Si**C**≡C), 84.1 (SiC≡**C**), 82.5 (HO**C**), 75.4 (CH_2), 73.3 (CH_2), 73.2 (CH_2), 73.1 (CH_2), 73.0 (CH_2), 69.1 (**CH**), 68.4 (HOCCCH_2), 65.9 (CH_2), 51.7 (q), 46.5 (q), 35.5 (CH_2), 28.1 (CH_2), 18.9 (CH_3), 18.2 (CH_3), 15.2 (CH_2), 0.17 (Si(CH_3)$_3$); **IR** (thin film) ν 3427, 2925, 2173, 1454, 1093, 841, 697 cm^{-1}; **HRMS** (ES) *m/z* calcd for $C_{39}H_{54}O_5NSi$ $[M+NH_4]^+$ 644.3766, found 644.3774.

1-(2-Benzyloxyethyl)-3,4-bis-benzyloxymethyl-3,4-dimethyl-2-(4-trimethylsilanylbut-3-ynyl)6-oxabicyclo[3.1.0]hexan-2-ol (251ββ)



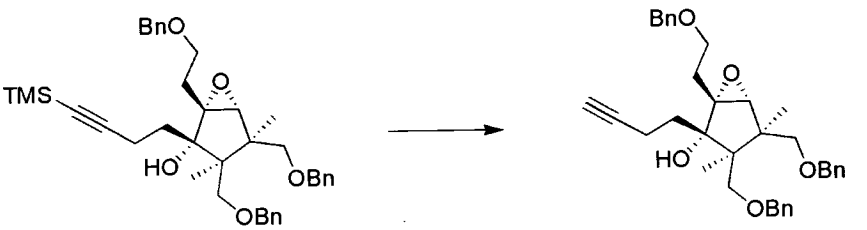
247β **251ββ**

A solution of (4-Iodo-but-1-ynyl)-trimethyl-silane (**250**) (73 mg, 0.27 mmol, 1.5 equiv) in dry Et_2O (5 mL) at -78 °C was treated with ^{t}BuLi (320 μL, 1.7 M solution in pentane, 0.55 mmol, 3 equiv) and stirred under a N_2 atmosphere for 1 h before warming to RT and stirring for a further 1 h. After re-cooling to -78 °C, the mixture was transferred into a Et_2O (10 mL) solution of epoxide (**247β**) (91mg, 0.18 mmol, 1 equiv) at -78 °C *via* a double tipped needle. The reaction mixture was then stirred for 2 h at -78 °C before warming to RT and quenching with saturated NH_4Cl solution. The organic layer was separated, washed with brine, dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Flash column chromatography (SiO_2, hexanes/EtOAc 9:1) furnished tertiary alcohol (**251ββ**) as a pale yellow oil (92 mg, 81% yield, single diastereomer).

^{1}H NMR (360 MHz, $CDCl_3$) δ 7.60-7.21 (15 H, m, Ar**H**), 4.40-4.32 (4 H, m, 2 x ArCH_2O), 4.26 (1 H, d, J_{AB}= 11.2 Hz, ArCH_2O), 4.16 (1 H, d, J_{AB}= 11.2 Hz, ArCH_2O), 3.42 (1 H, d, J_{AB}= 8.8 Hz, CH_2), 3.36 (1 H, d, J_{AB}= 8.8 Hz, CH_2), 3.33-3.14 (5 H, m, 2 x CH_2, C=OCC**H**), 2.76 (1 H, s, br, O**H**), 2.37 (2 H, m, CH_2), 2.16-2.10 (2 H, m, CH_2), 2.00-1.92 (2 H, m, CH_2), 1.11 (3 H, s, CH_3), 0.86 (3 H, s, CH_3),

0.17 (9 H, s, $Si(CH_3)_3$); **^{13}C NMR** (90 MHz, $CDCl_3$) δ 138.2 (**Ar**CCH_2), 138.1 (**Ar**CCH_2), 137.7 (**Ar**CCH_2), 128.3 (**Ar**CH), 128.2 (**Ar**CH), 127.7 (**Ar**CH), 127.6 (**Ar**CH), 127.5 (**Ar**CH), 108.3 (Si**C**≡C), 83.9 (SiC≡**C**), 81.3 (HO**C**), 74.3 (CH_2), 74.2 (CH_2), 73.3 (CH_2), 73.2 (CH_2), 72.9 (CH_2), 71.9 (HOCCCH_2), 71.1 (**C**H), 66.1 (CH_2), 45.2 (2 x q), 32.4 (CH_2), 27.4 (CH_2), 18.3 (2 xCH_3), 15.0 (CH_2), 0.22 ($Si(CH_3)_3$); **IR** (thin film) ν 3500, 2925, 2856, 2172, 1454, 1088, 841 cm^{-1}; **HRMS** (ES) *m/z* calcd for $C_{39}H_{54}O_5NSi$ $[M+NH_4]^+$ 644.3766, found 644.3770.

1-(2-Benzyloxyethyl)-3,4-bis-benzyloxymethyl-2-but-3-ynyl-3,4-dimethyl-6-oxa-bicyclo[3.1.0]hexan-2-ol (234ββ)



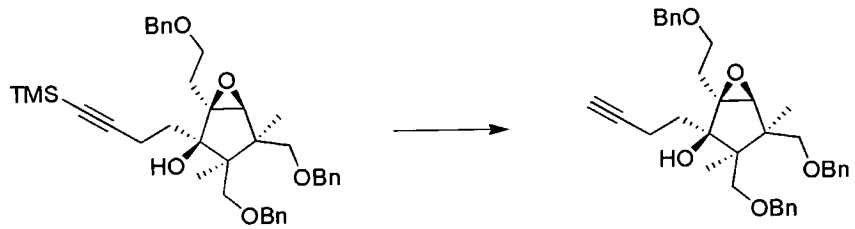
251ββ **234ββ**

Epoxide (**251ββ**) (80 mg, 0.13 mmol, 1 equiv) was dissolved in THF (5 mL) and treated with TBAF (140 μL, 1 M solution in THF, 0.14 mmol, 1.1 equiv) for 1 min. The reaction mixture was poured into a separating funnel containing saturated NH_4Cl solution, extracted with Et_2O and the organic layer washed with brine, dried over $MgSO_4$, filtered and evaporated to dryness. Flash column chromatography (SiO_2, hexanes/EtOAc 9:1) furnished the title compound (**234ββ**) as a colourless oil (64 mg, 91% yield).

^{1}H NMR (360 MHz, $CDCl_3$) δ 7.35-7.21 (15 H, m, Ar**H**), 4.39-4.31 (4 H, m, 2 x ArCH_2O), 4.27 (1 H, d, J_{AB}= 11.4 Hz, ArCH_2O), 4.16 (1 H, d, J_{AB}= 11.4 Hz, ArCH_2O), 3.43-3.14 (7 H, m, 3 x CH_2, C=OCC**H**), 2.77 (1 H, s, br, O**H**), 2.46-2.27 (2 H, m, CH_2), 2.14-2.10 (2 H, m, CH_2), 2.02-1.94 (3 H, m, CH_2, C≡C**H**), 1.11 (3 H, s, CH_3), 0.87 (3 H, s, CH_3); **^{13}C NMR** (90 MHz, $CDCl_3$) δ 138.2 (**Ar**CCH_2), 138.1 (**Ar**CCH_2),137.6 (**Ar**CCH_2), 128.3 (**Ar**CH), 138.2 (**Ar**CH), 127.7 (**Ar**CH), 127.6 (**Ar**CH), 127.5 (**Ar**CH), 85.4 (SiC≡**C**), 81.3 (HO**C**), 74.4 (CH_2), 74.2 (CH_2),73.3 (CH_2), 73.2 (CH_2), 72.8 (CH_2), 71.8 (HOCCCH_2), 71.2 (**C**H), 67.9 (H**C**≡C), 66.0 (CH_2), 45.2 (2 x q), 32.2 (CH_2), 27.4 (CH_2), 18.3 (2 xCH_3), 13.6 (CH_2); **IR** (thin

film) ν 3498, 3290, 2857, 1454, 1089, 697 cm^{-1}; **HRMS** (ES) *m/z* calcd for $C_{36}H_{46}O_5N$ $[M+NH_4]^+$ 572.3370, found 572.3372.

1-(2-Benzyloxyethyl)-3,4-bis-benzyloxymethyl-2-but-3-ynyl-3,4-dimethyl-6-oxa-bicyclo[3.1.0]hexan-2-ol (234αα)

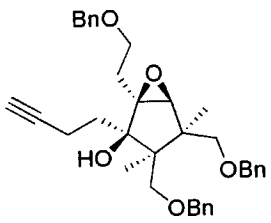


251αα
(+251αβ, not shown)

234αα
(+234αβ, not shown)

The inseparable 5:1 mixture of (**251αα/251αβ**) (41 mg, 0.07 mmol, 1 equiv) was dissolved in THF (3 mL) and treated with TBAF (72 μL, 1 M solution in THF, 0.07 mmol, 1.1 equiv) for 5 min. The reaction mixture was poured into a separating funnel containing saturated NH_4Cl solution, extracted with Et_2O and the organic layer washed with brine, dried over $MgSO_4$, filtered and evaporated to dryness. Flash column chromatography (SiO_2, hexanes/EtOAc 9:1) furnished an inseparable 5:1 mixture of (**234αα**) and (**234αβ**) as a colourless oil (33 mg, 92% yield).

Major diastereomer

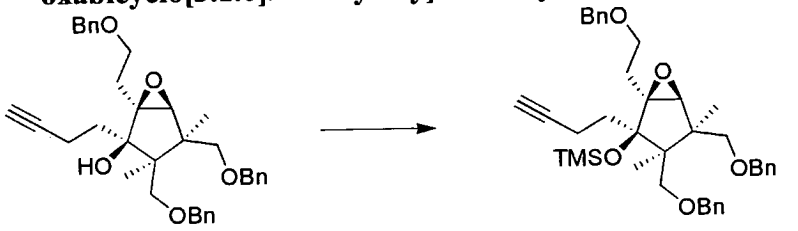


234αα

^{1}H NMR (360 MHz, $CDCl_3$) δ 7.34-7.26 (15 H, m, Ar**H**), 4.53-4.32 (6 H, 3 x Ar**CH$_2$**O), 3.73-3.38 (6 H, 3 x **CH$_2$**), 3.23 (1 H, s, C=OCC**H**), 2.45-2.30 (2 H, m, **CH$_2$**), 2.21-2.10 (2 H, m, **CH$_2$**), 2.01-1.94 (3 H, m, **CH$_2$**, C≡C**H**), 1.15 (3 H, s, **CH$_3$**), 1.11 (3 H, s, **CH$_3$**); **^{13}C NMR** (90 MHz, $CDCl_3$) δ 138.2 (**ArC**CH_2), 138.1 (**ArC**CH_2), 137.8 (**ArC**CH_2), 128.4 (**ArC**H), 128.3 (**ArC**H), 128.2 (**ArC**H), 127.6 (**ArC**H), 127.5 (**ArC**H), 127.5 (**ArC**H), 127.4 (**ArC**H), 85.2 (SiC≡**C**), 82.5 (HO**C**), 75.4 (**CH$_2$**), 73.3 (**CH$_2$**), 73.2 (**CH$_2$**), 73.2 (**CH$_2$**), 73.0(**CH$_2$**), 69.1 (HOCC**CH$_2$**), 68.4

(CH), 68.1 (HC≡C), 65.9 (CH_2), 51.7 (q), 46.5 (q), 35.4 (CH_2), 28.1 (CH_2), 19.0 (CH_3), 18.2 (CH_3), 13.8 (CH_2); **IR** (thin film) ν 3422, 3291, 2859, 1454, 1093, 697 cm^{-1}; **HRMS** (ES) *m/z* calcd for $C_{36}H_{43}O_5$ $[M+H]^+$ 555.3105, found 555.3106.

[1-(2-Benzyloxyethyl)-3,4-bis-benzyloxymethyl-2-but-3-ynyl-3,4-dimethyl-6-oxabicyclo[3.1.0]hex-2-yloxy]trimethylsilane (252ββ)



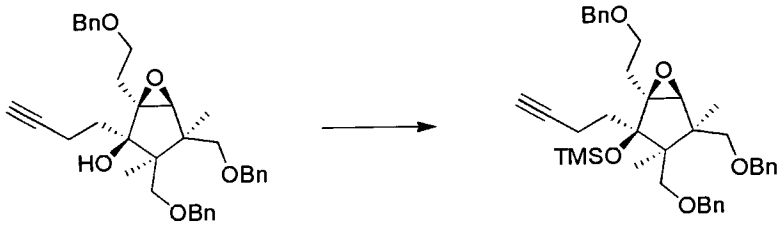
234ββ **252ββ** c

Epoxide (**234ββ**) (60 mg, 0.11 mmol, 1 equiv) was dissolved in DMF (2 mL) and TMSCl (77 μL, 0.61 mmol, 5.5 equiv), imidazole (51 mg, 0.75 mmol, 6.8 equiv) and DMAP (14 mg, 0.11 mmol, 1 equiv) were added. The resulting mixture was heated to 80 °C for 48 h, cooled to RT and worked up by addition of H_2O and EtOAc. The organic layer was separated, dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. Flash column chromatography (SiO_2, hexanes/EtOAc 9:1) afforded the title compound (**252ββ**) as a colourless oil (50 mg, 73% yield, 87% yield by recovery) with recovery of some unreacted starting material (10 mg).

^{1}H NMR (360 MHz, $CDCl_3$) δ 7.34-7.20 (15 H, m, Ar**H**), 4.40-4.29 (4 H, 2 x Ar**CH$_2$**O), 4.25 (1 H, d, J_{AB}= 11.4 Hz, Ar**CH$_2$**O), 4.16 (1 H, d, J_{AB}= 11.4 Hz, Ar**CH$_2$**O), 3.44 (1 H, d, J_{AB}= 8.8 Hz, **CH$_2$**), 3.36 (1 H, d, J_{AB}= 8.8 Hz, **CH$_2$**), 3.32-3.25 (3 H, m, **CH$_2$**, C=OCC**H**), 3.13-3.06 (2 H, m, **CH$_2$**), 2.35 (1 H, m, **CH$_2$**), 2.27-1.99 (4H, m, 2 x **CH$_2$**), 1.94 (1 H, m, C≡**CH**), 1.84 (1 H, m, **CH$_2$**), 1.11 (3 H, s, **CH$_3$**), 0.82 (3 H, s, **CH$_3$**), 0.17 (9 H, s, Si(**CH$_3$**)$_3$); **^{13}C NMR** (90 MHz, $CDCl_3$) δ 138.4 (**Ar**CCH$_2$), 138.4 (**Ar**CCH$_2$), 137.8 (**Ar**CCH$_2$), 128.3 (**Ar**CH), 128.0 (**Ar**CH),127.7 (**Ar**CH), 127.6 (**Ar**CH), 127.5 (**Ar**CH), 127.5 (**Ar**CH), 127.4 (**Ar**CH), 85.7 (SiC≡**C**), 85.1 (HO**C**), 74.8 (**CH$_2$**), 74.7(**CH$_2$**), 73.4 (**CH$_2$**), 73.3 (**CH$_2$**), 72.8 (**CH$_2$**), 69.5 (**CH**), 68.7 (H**C**≡C), 68.0 (**CH$_2$**), 66.2 (HOCCCH$_2$), 45.2 (2 x q), 35.9 (**CH$_2$**), 27.3 (**CH$_2$**), 18.0 (2 x **CH$_3$**), 14.3 (**CH$_2$**), 2.2 (Si(**CH$_3$**)$_3$); **IR** (thin

film) ν 3307, 2859, 1454, 1249, 1076, 838, 698 cm^{-1}; **HRMS** (ES) *m/z* calcd for $C_{39}H_{54}O_5NSi$ $[M+NH_4]^+$ 642.3766, found 642.3770.

[1-(2-Benzyloxyethyl)-3,4-bis-benzyloxymethyl-2-but-3-ynyl-3,4-dimethyl-6-oxabicyclo[3.1.0]hex-2-yloxy]trimethylsilane (252αα)

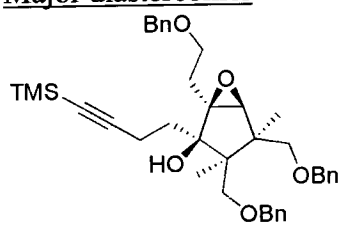


234αα
(+234αβ, not shown)

252αα
(+252αβ, not shown)

An inseparable 5:1 mixture of epoxides (**234αα/234αβ**) (33 mg, 0.06 mmol, 1 equiv) was dissolved in DMF (2 mL) and TMSCl (76 μL, 0.60 mmol, 10 equiv), imidazole (76 mg, 0.60 mmol, 10 equiv) and DMAP (8 mg, 0.06 mmol, 1 equiv) were added. The resulting mixture was heated to 80 °C for 50 h, cooled to RT and worked up by addition of H_2O and EtOAc. The organic layer was separated, dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. Flash column chromatography (SiO_2, hexanes/EtOAc 9:1) afforded an inseparable 5:1 mixture of (**252αα**) and (**234αβ**) as a colourless oil (20 mg, 54% yield, 80% yield by recovery) with recovery of some unreacted starting material (10 mg).

Major diastereomer

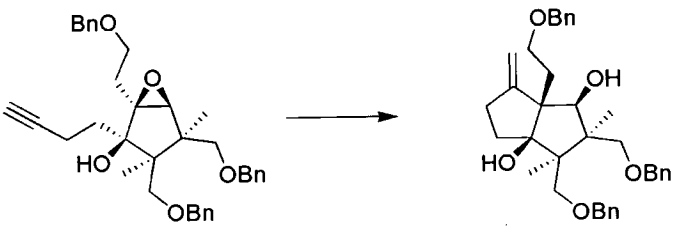


251αα

^{1}H NMR (360 MHz, $CDCl_3$) δ 7.33-7.20 (15 H, m, Ar**H**), 4.62 (1 H, d, J_{AB}= 12.3 Hz, ArCH_2O), 4.46-4.26 (5 H, m, 2 x ArCH_2O, ArCH_2**O**), 3.78 (1 H, m, CH_2), 3.64-3.30 (5 H, m, 2 x CH_2, C=OCC**H**), 3.13 (1 H, m, CH_2), 2.37-2.22 (2 H, m, CH_2), 2.17-1.98 (2 H, m, CH_2), 1.95 (1 H, m, C≡C**H**), 1.91-1.67 (2 H, m, CH_2), 1.12 (3 H, s,

CH_3),1.00 (3 H, s, CH_3), 0.17 (9 H, s, $Si(CH_3)_3$); ^{13}**C NMR** (90 MHz, $CDCl_3$) δ 139.3 (**Ar**CCH_2), 138.7 (**Ar**CCH_2), 138.2 (**Ar**CCH_2), 128.4 (**ArCH**), 128.2 (**ArCH**), 127.6 (**ArCH**), 127.6 (**ArCH**), 127.4 (**ArCH**), 127.3 (**ArCH**), 127.1 (**ArCH**),, 86.3 (Si**C**≡**C**), 84.7 (HO**C**), 73.2 (CH_2), 73.2 (CH_2), 73.1 (CH_2), 73.0 (CH_2), 72.9 (CH_2), 68.6 (**CH**), 68.5 (**HC**≡C), 68.2 (CH_2), 68.1 (HOCCCH_2), 46.0 (2 x q), 36.9 (CH_2), 28.7 (CH_2), 18.4 (CH_3), 18.1 (CH_3), 15.3 (CH_2), 2.2 ($Si(CH_3)_3$); **IR** (thin film) ν 3308, 2952, 1453, 1097, 838 cm^{-1}; **HRMS** (ES) *m/z* calcd for $C_{39}H_{54}O_5NSi$ $[M+NH_4]^+$ 644.3766, found 644.3769.

6a-(2-Benzyloxyethyl)-2,3-bis-benzyloxymethyl-2,3-dimethyl-6-methylenehexahydropentalene-1,3a-diol (233αα)



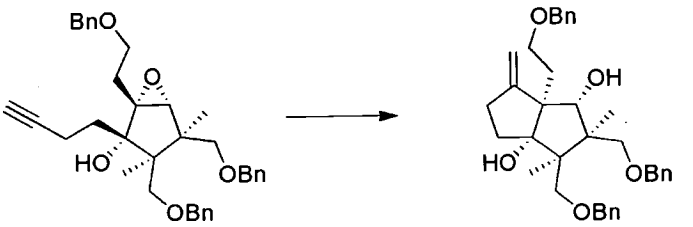
234αα
(+234αβ, not shown)

233αα

Cp_2TiCl_2 (115 mg, 0.46 mmol, 3.8 equiv) and Zn dust (91 mg, 1.39 mmol, 11.4 equiv) were placed in a round bottom flask and THF (5 mL) was added under rigorous exclusion of air by means of a N_2 atmosphere. The resulting suspension was stirred at RT for 1 h during which the colour of the mixture changed from red to green, indicating the formation of a low valent titanium complex. This suspension of Cp_2TiCl was then cannuled into a solution of the inseparable 5:1 mixture of (**234αα/234αβ**) (70 mg, 0.12 mmol, 1 equiv) in THF (5 mL) and the resulting green suspension was stirred at RT under a N_2 atmosphere for 1.5 h. H_2SO_4 (10% v/v, 10 mL) was added and the reaction mixture stirred for 22 h before extracting thrice with EtOAc. The organic layers were combind, washed with saturated $NaHCO_3$ solution and brie, dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. Flash column chromatography (SiO_2, hexanes/EtOAc 9:1) furnished the single diastereomer (**233αα**) as a colourless oil (34 mg, 51% yield, 60% yield by recovery) and recovery of unreacted starting material (14 mg).

^{1}H NMR (360 MHz, $CDCl_3$) δ 7.33-7.23 (15 H, m, Ar**H**), 4.91 (1 H, m, C=C**H$_2$**), 4.82 (1 H, m, C=C**H$_2$**), 4.77(1 H, s, **H**C-OH), 4.49-4.21 (6 H, m, 3 x ArC**H$_2$**O), 3.90-3.85 (2 H, m, OC**H$_2$**), 3.56-3.32 (4 H, m, 2 x OC**H$_2$**), 2.51-1.93 (6 H, m, 3 x C**H$_2$**), 1.11 (3 H, s, C**H$_3$**), 1.01 (3 H, s, C**H$_3$**); **^{13}C NMR** (90 MHz, $CDCl_3$) δ 160.4 (**C**=CH_2), 138.5 (**Ar**CCH_2), 137.7 (**Ar**CCH_2), 137.2 (**Ar**CCH_2), 128.5 (**Ar**CH), 128.4 (**Ar**CH), 128.3 (**Ar**CH), 128.1 (**Ar**CH), 127.9 (**Ar**CH), 127.6 (**Ar**CH), 127.5 (**Ar**CH), 106.9 (C=**C**H_2), 93.7 (**C**OH), 88.4 (H**C**OH), 74.2 (**C**H_2), 73.7 (**C**H_2), 73.3 (**C**H_2), 73.1 (**C**H_2), 67.9 (**C**H_2), 61.2 (q), 51.7 (q), 50.8 (q), 35.4 (**C**H_2), 37.7 (**C**H_2), 30.1 (**C**H_2), 21.9 (**C**H_3), 18.1 (**C**H_3); **IR** (thin film) ν 3425, 2927, 1454, 1072, 698 cm^{-1}; **HRMS** (ES) *m/z* calcd for $C_{36}H_{45}O_5$ $[M+H]^+$ 557.3262, found 557.3257.

6a-(2-Benzyloxyethyl)-2,3-bis-benzyloxymethyl-2,3-dimethyl-6-methylenehexahydropentalene-1,3a-diol (233ββ)

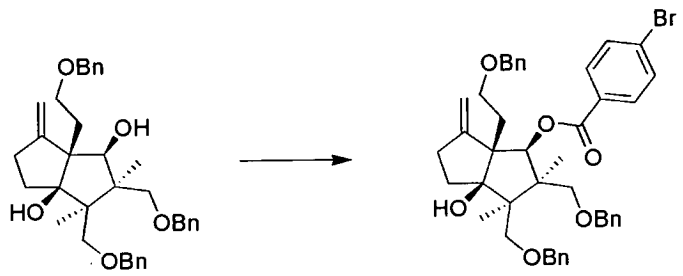


234ββ **233ββ**

Cp_2TiCl_2 (141 mg, 0.57 mmol, 3.8 equiv) and Zn dust (102 mg, 1.56 mmol, 10.4 equiv) were placed in a round bottom flask and THF (5 mL) was added under rigorous exclusion of air by means of a N_2 atmosphere. The resulting suspension was stirred at RT for 1 h during which the colour of the mixture changed from red to green, indicating the formation of a low valent titanium complex. This suspension of Cp_2TiCl was then cannuled into a solution of epoxide (**234ββ**) (83 mg, 0.15 mmol, 1 equiv) in THF (5 mL) and the resulting green suspension was stirred at RT under a N_2 atmosphere for 1.5 h. H_2SO_4 (10% v/v, 10 mL) was added and the reaction mixture stirred for 22 h before extracting thrice with EtOAc. The organic layers were combind, washed with saturated $NaHCO_3$ solution and brie, dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. Flash column chromatography (SiO_2, hexanes/EtOAc 9:1) furnished diol (**233ββ**) as a colourless oil (39 mg, 46% yield)

^{1}H NMR (360 MHz, $CDCl_3$) δ 7.31-7.25 (15 H, m, Ar**H**), 4.89 (1 H, m, C=C**H**$_2$), 4.72 (1 H, m, C=C**H**$_2$), 4.52-4.35 (6 H, m, 3 x ArC**H**$_2$O), 4.00 (1 H, s, br, O**H**), 3.80 (1 H, s, C**H**), 3.59-3.48 (2 H, m, OC**H**$_2$), 3.43-3.37 (4 H, m, 2 x OC**H**$_2$), 2.99 (1 H, s. br, O**H**), 2.45 (1 H, m, C**H**$_2$), 2.28 (1 H, m, C**H**$_2$), 2.14-1.90 (4 H, m, 2 x C**H**$_2$), 1.20 (3 H, s, C**H**$_3$), 1.19 (3 H, s, C**H**$_3$); **^{13}C NMR** (90 MHz, $CDCl_3$) δ 158.7 (**C**=CH$_2$), 138.4 (2 x **Ar**CCH$_2$), 137.2 (**Ar**CCH$_2$), 128.4 (**Ar**CH), 128.3 (**Ar**CH), 128.2 (**Ar**CH), 127.9 (**Ar**CH), 127.8 (**Ar**CH), 127.4 (**Ar**CH), 127.3 (**Ar**CH), 106.0 (C=**C**H$_2$), 92.4 (**C**-OH), 83.7 (HC-OH), 77.8 (**C**H$_2$), 74.5 (**C**H$_2$), 73.4 (2 x **C**H$_2$), 73.3 (**C**H$_2$), 67.5 (**C**H$_2$), 61.4 (q), 51.6 (q), 51.0 (q), 36.9 (**C**H$_2$), 31.9 (**C**H$_2$), 29.8 (**C**H$_2$), 17.0 (**C**H$_3$), 16.2 (**C**H$_3$); **IR** (thin film) ν 3429, 2862, 1454, 1072, 698 cm^{-1}; **HRMS** (ES) *m/z* calcd for $C_{36}H_{45}O_5$ $[M+H]^+$ 557.3262, found 557.3266.

4-Bromobenzoic acid-6a-(2-benzyloxy-ethyl)-2,3-bis-benzyloxymethyl-3a-hydroxy-2,3-dimethyl-6-methyleneoctahydropentalen-1-yl ester (269)

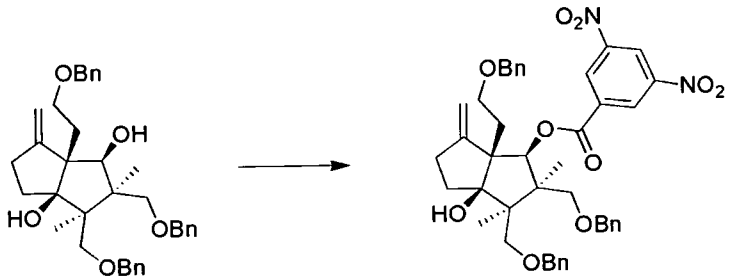


233αα **269**

Diol (**233αα**) (56mg, 0.1 mmol, 1 equiv) was dissolved in pyridine (3 mL), treated with *p*-Br-benzoyl chloride (220 mg, 1.0 mmol, 10 equiv) and heated to 100 °C for 36 h. The reaction mixture was poured into a saturated solution of NH_4Cl and extracted with EtOAc. The organic phase was washed with brine, dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. Flash column chromatography (SiO_2, hexanes/EtOAc 9:1) furnished the title compound (**269**) as a pale yellow oil (40 mg, 54% yield).

^{1}H NMR (360 MHz, $CDCl_3$) δ 7.91 (2 H, d, *J*= 8.5 Hz, *p*-BrAr**H**), 7.56 (2 H, d, *J*= 8.5 Hz, *p*-BrAr**H**), 7.33-7.15 (15 H, m, Ar**H**), 5.60 (1 H, s, C**H**), 5.20 (1 H, m, C=C**H**$_2$), 5.00 (1 H, m, C=C**H**$_2$), 4.54 (1 H, d, *J*= 11.4 Hz, ArC**H**$_2$), 4.42 (1 H, d, *J*= 12.1 Hz, ArC**H**$_2$), 4.32-4.19 (4 H, m, 2 x ArC**H**$_2$, ArC**H**$_2$), 3.65-3.26 (6 H, m, 3 x OC**H**$_2$), 2.54-2.32 (2 H, m, C**H**$_2$), 2.21 (1 H, m, C**H**$_2$), 2.10 (1 H, m, C**H**$_2$), 1.69-1.59 (2 H, m, 2 x C**H**$_2$), 1.14 (3 H, s ,C**H**$_3$), 1.04 (3 H, s ,C**H**$_3$); **^{13}C NMR** (90 MHz, $CDCl_3$) δ 165.3 (**C**=O), 160.6 (**C**=CH$_2$), 138.7 (**ArC**CH$_2$), 138.4 (**ArC**CH$_2$), 136.2 (**ArC**CH$_2$), 131.8 (*p*-Br**ArCH**), 131.2 (*p*-Br**ArCH**), 129.1 (*p*-Br**ArC**), 128.7 (**ArC**H), 128.5 (**ArC**H), 128.3 (**ArC**H), 128.2(**ArC**H), 128.2 (**ArC**H), 128.1 (*p*-Br**ArC**), 127.7 (**ArC**H), 127.6 (**ArC**H), 127.4 (**ArC**H), 127.3 (**ArC**H), 108.6 (C=**C**H$_2$), 93.5 (**C**OH), 88.7 (**C**H), 73.9 (**C**H$_2$), 73.2 (**C**H$_2$), 72.9 (**C**H$_2$), 72.8 (**C**H$_2$), 72.7 (**C**H$_2$), 68.0 (**C**H$_2$), 60.5 (q), 53.8 (q), 51.2 (q), 34.1 (**C**H$_2$), 32.1 (**C**H$_2$), 31.3 (**C**H$_2$), 22.3 (**C**H$_3$), 19.0 (**C**H$_3$); **IR** (thin film) ν 3377, 2925, 2858, 1718, 1271, 698 cm^{-1}; **HRMS** (ES) *m/z* calcd for $C_{43}H_{48}O_6Br^{79}$ $[M+H]^+$ 739.2629, found 739.2634.

3,5-Dinitro-benzoic acid-6a-(2-benzyloxyethyl)-2,3-bis-benzyloxymethyl-3a-hydroxy-2,3-dimethyl-6-methyleneoctahydropentalen-1-yl ester (270)



233αα **270**

Diol (**233αα**) (37mg, 0.06 mmol, 1 equiv) was dissolved in pyridine (3 mL), treated with 3,5-dinitrobenzoyl chloride (155 mg, 0.67 mmol, 10 equiv) and heated to 100 °C for 3.5 h. The reaction mixture was poured into a saturated solution of NH_4Cl and extracted with EtOAc. The organic phase was washed with brine, dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. Flash column chromatography (SiO_2, hexanes/EtOAc 9:1) furnished the title compound (**270**) as a pale yellow oil (27 mg, 54% yield).

^{1}H NMR (360 MHz, $CDCl_3$) δ 9.09-9.06 (3 H, m, 3,5-di-NO_2-Ar**H**), 7.36-7.07 (15 H, m, Ar**H**), 5.67 (1 H, s, C**H**), 5.49 (1 H, s, O**H**), 5.28 (1 H, m, =C**H**$_2$), 5.01 (1 H, m, =C**H**$_2$), 4.76 (1 H, d, *J*= 11.4 Hz, ArC**H**$_2$O), 4.37 (1 H, d, *J*= 12.0 Hz, ArC**H**$_2$O), 4.28-4.15 (4 H, m, 2 x ArC**H**$_2$O, ArC**H**$_2$O), 3.61-3.24 (6 H, m, 3 x OC**H**$_2$), 2.56-2.35 (2 H, m, C**H**$_2$), 2.22 (1 H, m, C**H**$_2$), 2.09 (1 H, m, C**H**$_2$), 1.74-1.66 (2 H, m, 2 x C**H**$_2$), 1.16 (3 H, s, C**H**$_3$), 1.10 (3 H, s, C**H**$_3$); **^{13}C NMR** (90 MHz, $CDCl_3$) δ 162.1 (**C**=O), 160.2 (**C**=CH$_2$), 148.4 (**ArC**-NO_2), 138.6 (**ArC**C), 137.9 (**ArC**C), 136.1 (**ArC**C), 134.1 (**ArC**C), 129.4 (**ArC**H), 128.6 (**ArC**H), 128.5 (**ArC**H), 128.3 (**ArC**H), 128.1 (**ArC**H), 127.7 (**ArC**H), 127.6 (**ArC**H), 127.5 (**ArC**H), 127.4 (**ArC**H), 122.1 (**ArC**H), 109.1 (C=**C**H$_2$), 93.6 (**C**OH), 90.6 (**C**H), 74.0 (**C**H$_2$), 73.2 (**C**H$_2$), 73.1 (**C**H$_2$), 72.7 (**C**H$_2$), 72.6 (**C**H$_2$), 67.7 (**C**H$_2$), 61.0 (q), 54.0 (q), 51.3 (q), 33.9 (**C**H$_2$), 31.9 (**C**H$_2$), 31.2 (**C**H$_2$), 22.2 (**C**H$_3$), 19.0 (**C**H$_3$); **IR** (thin film) ν 3375, 2924, 1732, 1545, 1344, 1074 cm^{-1}, **HRMS** (ES) *m/z* calcd for $C_{43}H_{47}N_2O_{10}$ $[M+H]^+$ 751.3225, found 751.3228.

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Abbreviations

Ac	acetyl
AD	Alzheimer's disease
AIBN	2,2-azobis(isobutyronitrile)
aq	aqueous
Bn	benzyl
br	broad
BTB	*bis*-(trifluoromethyl)benzyl
Bu	butyl
Bz	benzoyl
calcd	calculated
cat	catalytic
COSY	correlation spectroscopy
Cp	cyclopentadiene
CSA	camphorsulfonic acid
Cy	cyclohexyl
d	doublet
dba	dibenzylideneacetone
DBB	di-*tert*-butylbiphenylide
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCB	2,6-dichlorobenzyl
DCC	N,N-dicyclohexylcarbodiimide
DCM	dichloromethane
DEPT	distortionless enhancement by polarisation transfer
DIBALH	diisobutyl aluminium hydride
DIPEA	N,N-diisopropylethylamine
DMAP	dimethylaminopyridine
DMDO	dimethyldioxirane
DME	dimethoxyethane
DMF	dimethylformamide
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
DMSO	dimethylsulfoxide
dpm	dipivaloylmethanato
ee	enantiomeric excess
EI	electron impact ionisation
EOM	ethoxymethyl
ES	electrospray ionisation

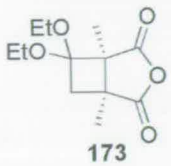
Et	ethyl
FAB	fast atom bombardment
g	gram(s)
HMPA	hexamethyl phosphoric acid triamide
hr	hour(s)
HRMS	high resolution mass spectrometry
HSQC	heteronuclear single quantum coherence
Hz	hertz
IBX	2-iodoxybenzoic acid
IR	infrared
J	coupling constant
LDA	lithium diisopropylamine
LDBB	lithium di-*tert*-butylbiphenylide
LHMDS	lithium hexamethyldisilazide
M	molar (moles per litre)
m	multiplet
m/z	mass to charge ratio
***m*CPBA**	*meta*-chloroperbenzoic acid
Me	methyl
min	minute(s)
MMPP	magnesium monoperoxyphthalate hexahydrate
MOM	methoxymethyl
mp	melting point
Ms	mesyl
MS	molecular sieves
NaHMDS	sodium hexamethyldisilazide
NMO	N-methylmorpholine
NMR	nuclear magnetic resonance
NOESY	nuclear overhauser effect spectroscopy
NTF	neurotrophic factor
°C	degree(s) celsius
PDC	pyridinium dichromate
PG	protecting group
Ph	phenyl
Piv	pivaloate
PMB	*para*-methoxybenzyl
ppm	parts per million
q	quartet

RT/rt	room temperature
SEM	β-trimethylsilylethoxymethyl
Sia	sialic acid
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide
TBS	*t*-butyldimethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC/tlc	thin layer chromatography
TMS	trimethylsilyl
TPAP	tetrapropylammonium perrutherate
TPPA	tetramethylphenylphosphoramide
Tr	trityl
Ts	p-toluenesulfonyl
UV	ultraviolet
δ	chemical shift

Appendix: Spectroscopic Data

6,6-Diethoxy-1,5-dimethyl-3-oxa-bicyclo[3.2.0]heptane-2,4-dione (173)

^{1}H-NMR (360 MHz, $CDCl_3$), ^{13}C-NMR (90 MHz, $CDCl_3$)



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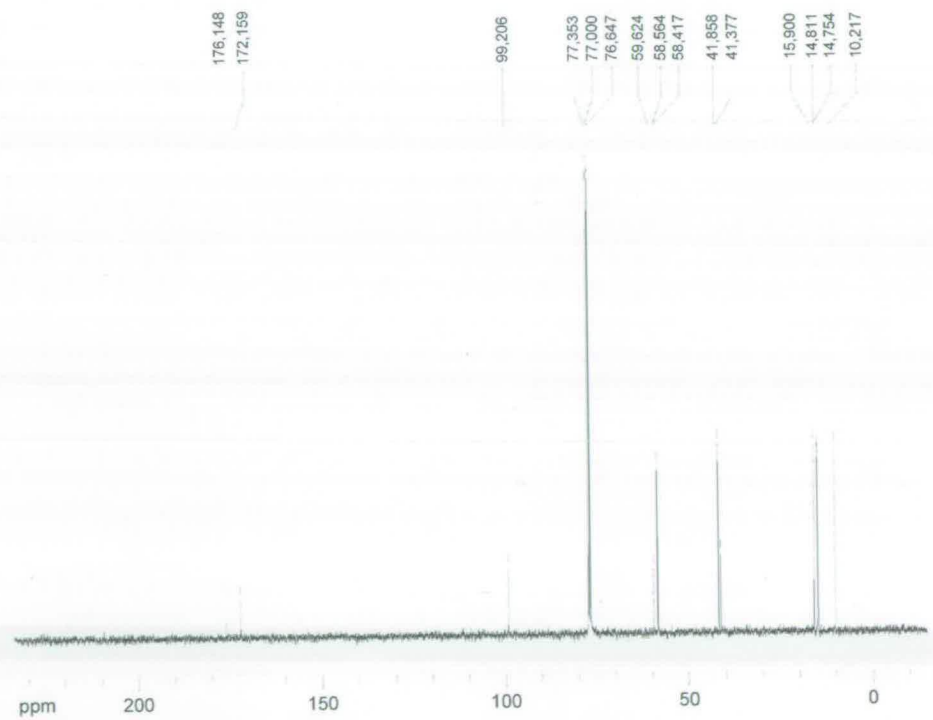
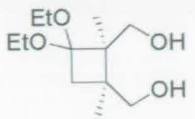


Diol (174)

^{1}H-NMR (360 MHz, $CDCl_3$), ^{13}C-NMR (90 MHz, $CDCl_3$)



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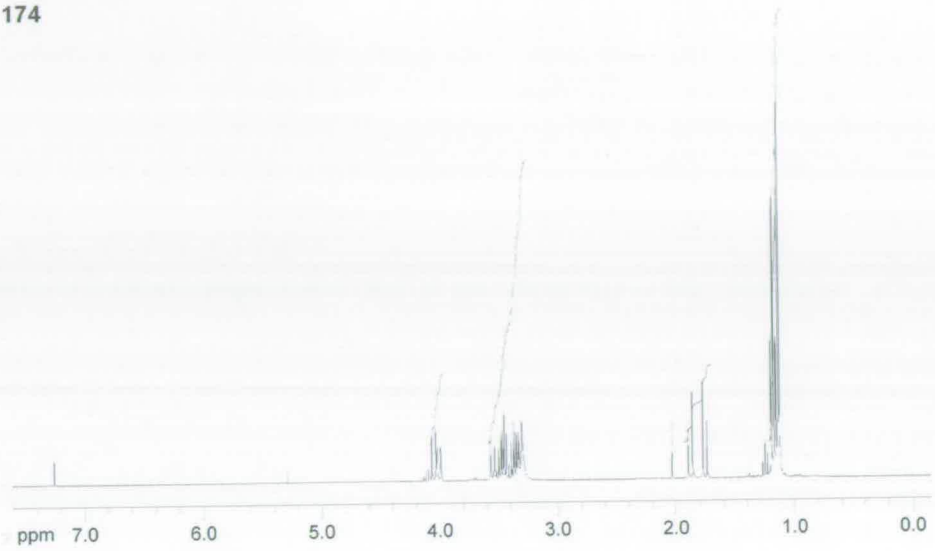
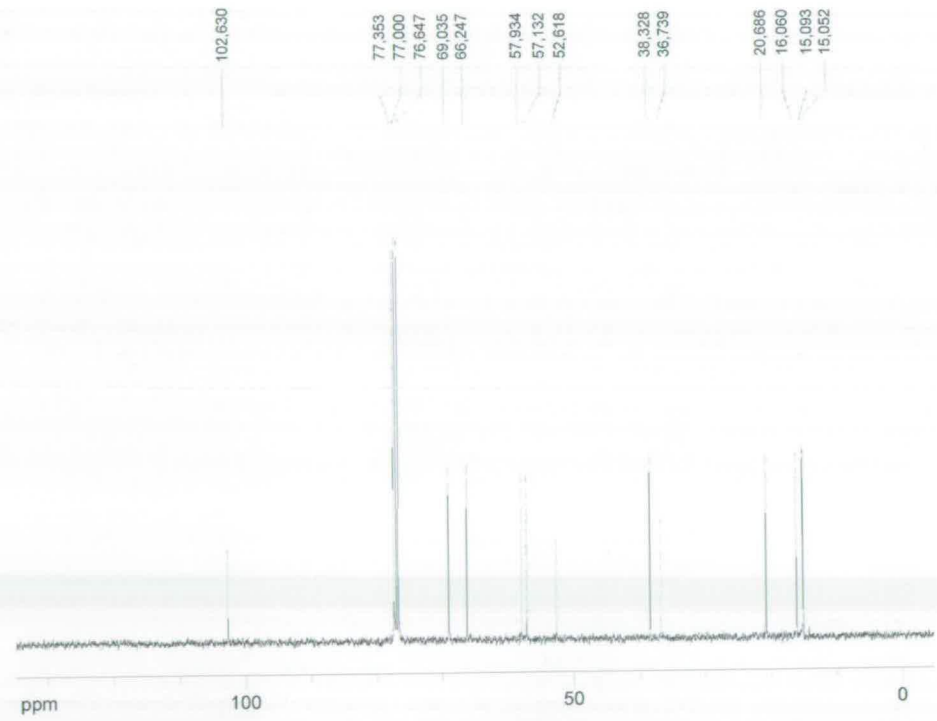
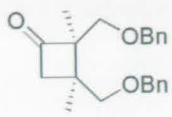




Cyclobutanone (166)

^{1}H-NMR (360 MHz, $CDCl_3$), ^{13}C-NMR (90 MHz, $CDCl_3$)



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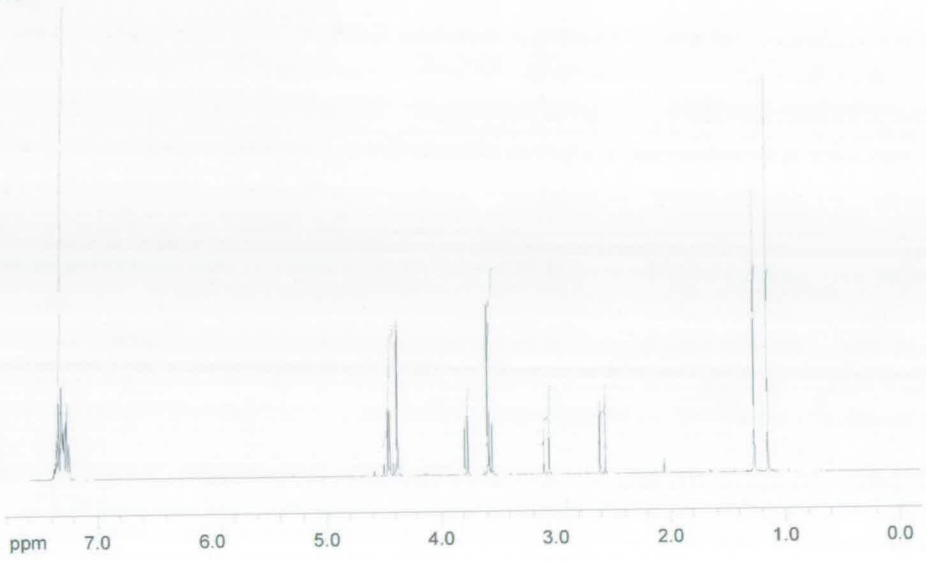
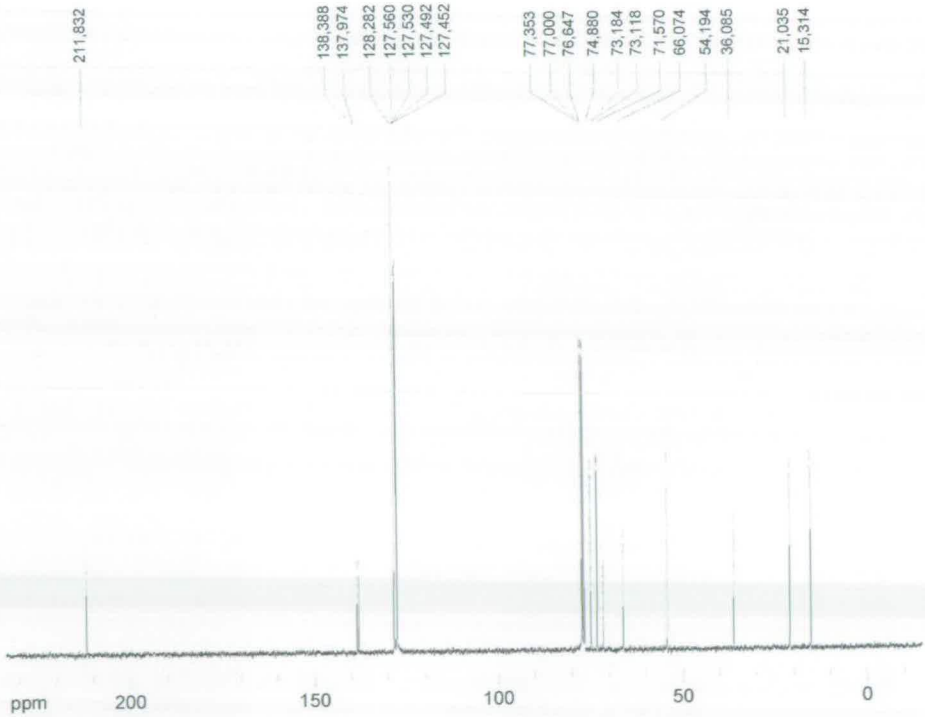
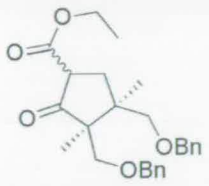




Ethyl ketoester (190)

^{1}H-NMR (360 MHz, $CDCl_3$), ^{13}C-NMR (90 MHz, $CDCl_3$)



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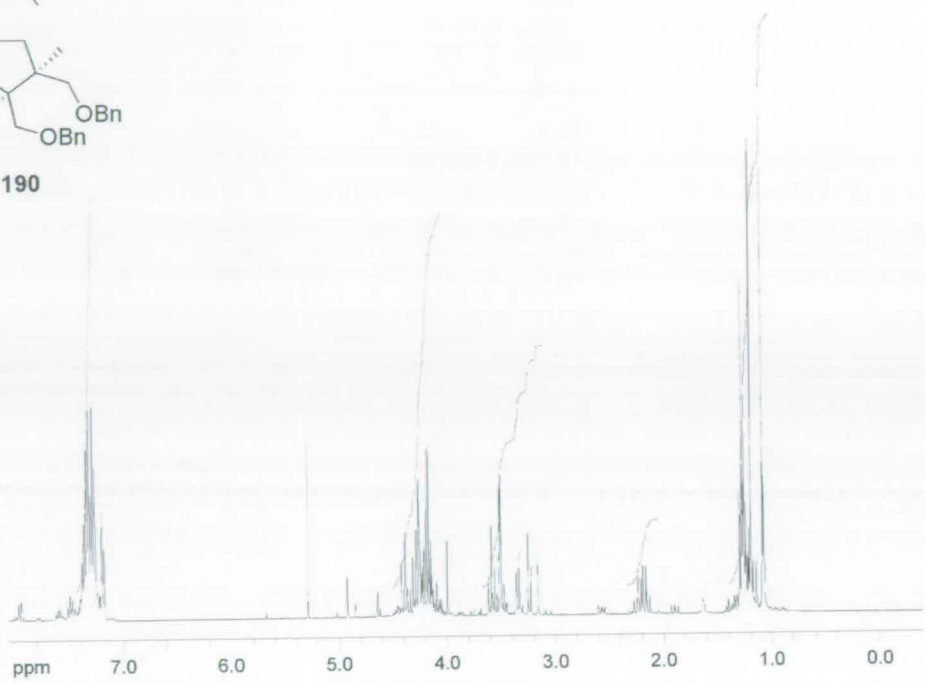
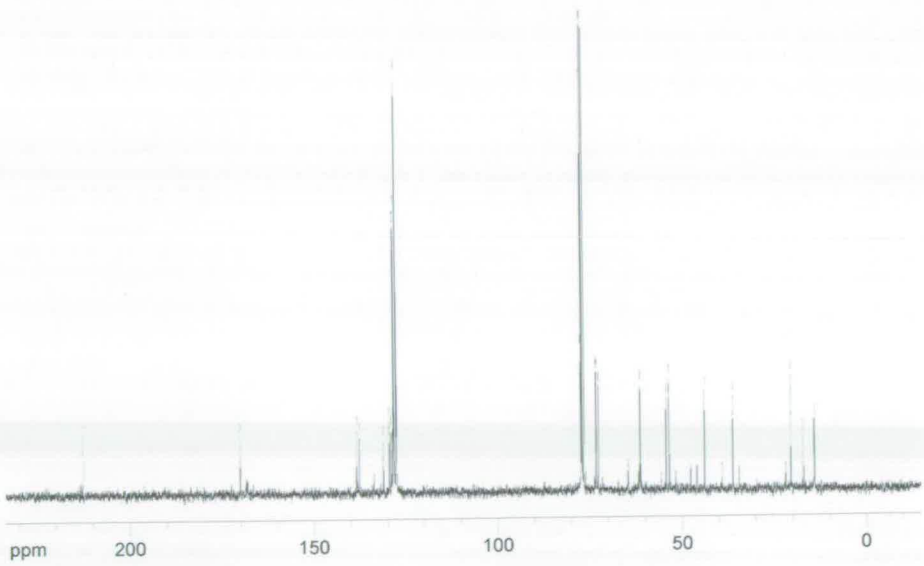
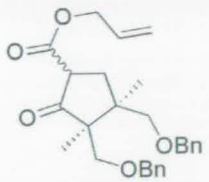




Allyl ketoester (241)

^{1}H-NMR (360 MHz, $CDCl_3$), ^{13}C-NMR (90 MHz, $CDCl_3$)



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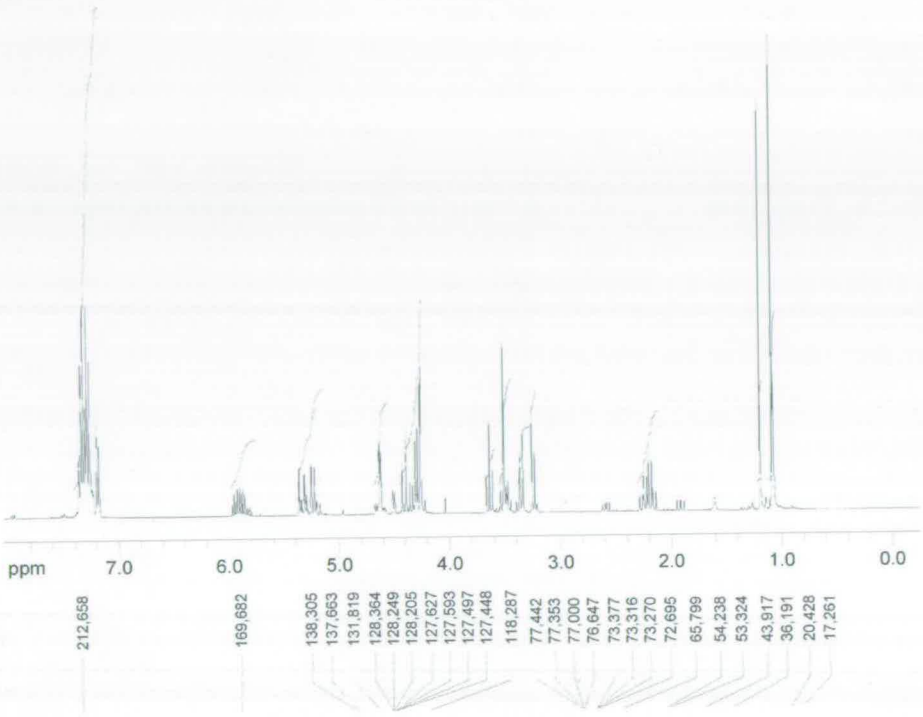
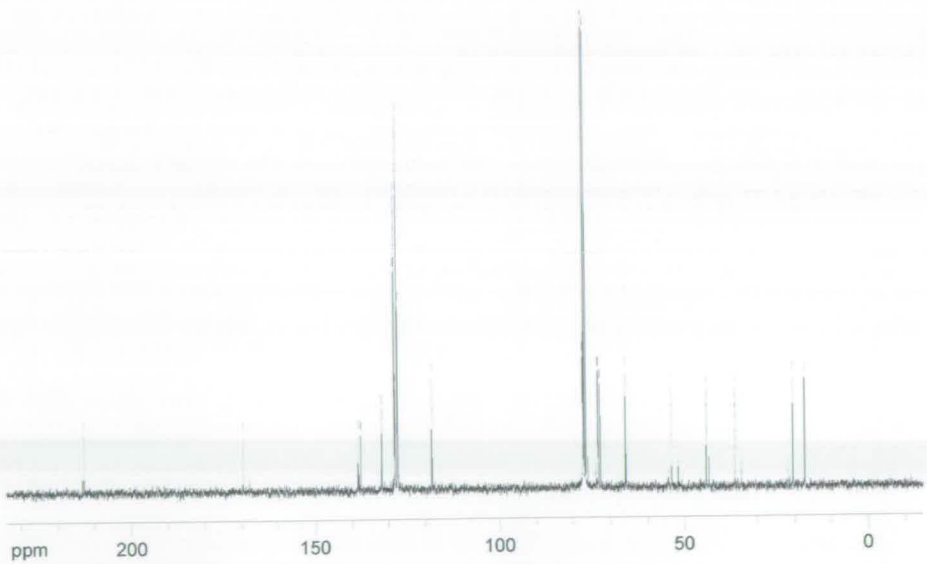
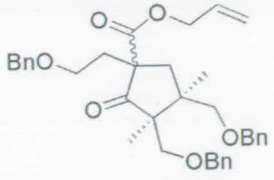




Cyclopentanone (236)

^{1}H-NMR (360 MHz, $CDCl_3$), ^{13}C-NMR (90 MHz, $CDCl_3$)



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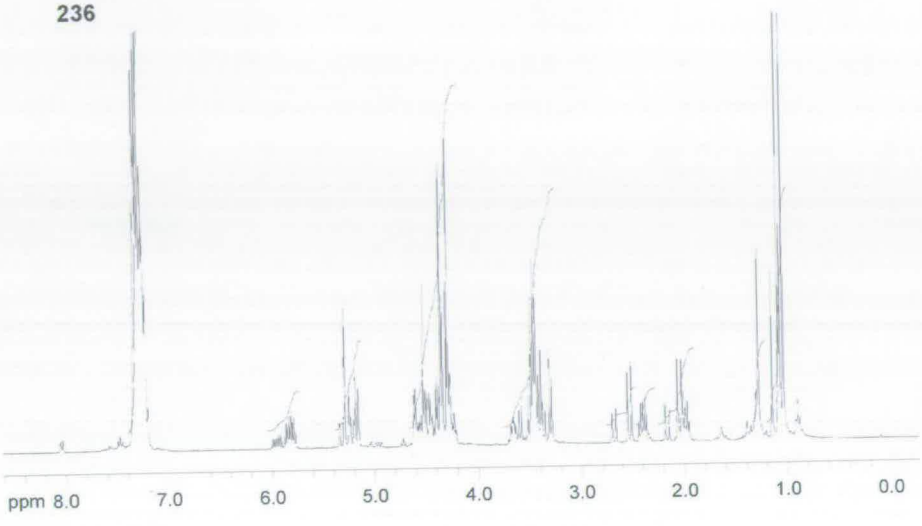
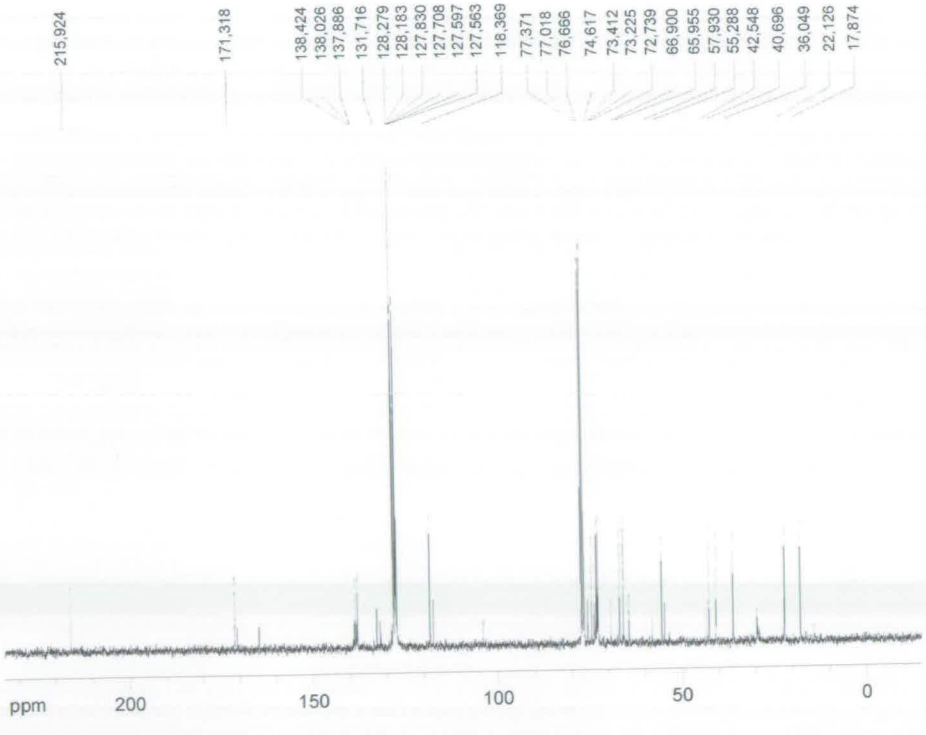
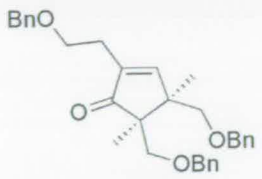




Cyclopentenone (235)

^{1}H-NMR (360 MHz, $CDCl_3$), ^{13}C-NMR (90 MHz, $CDCl_3$)



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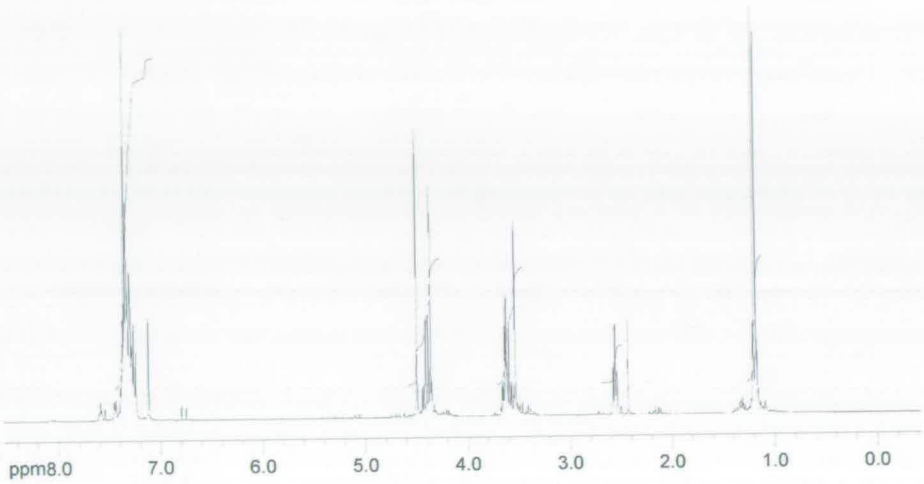
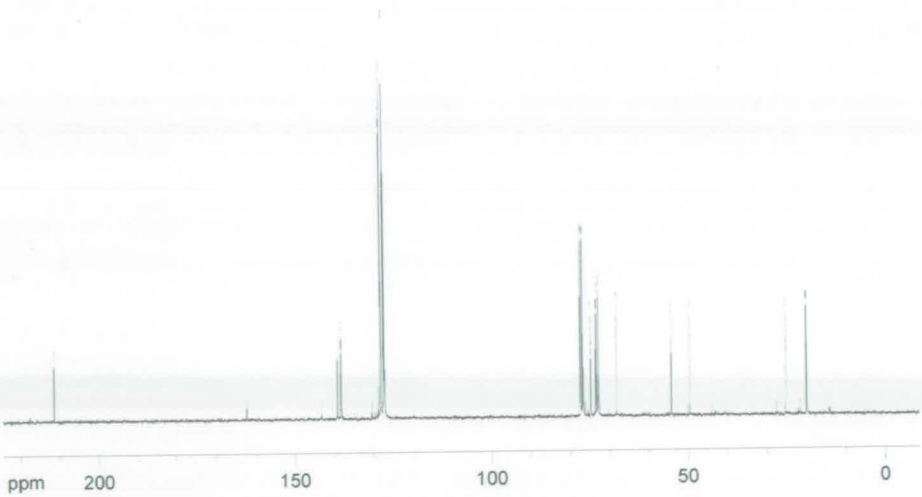
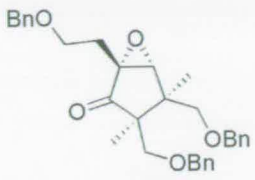




Epoxide (247β)

^{1}H-NMR (360 MHz, $CDCl_3$), ^{13}C-NMR (90 MHz, $CDCl_3$)



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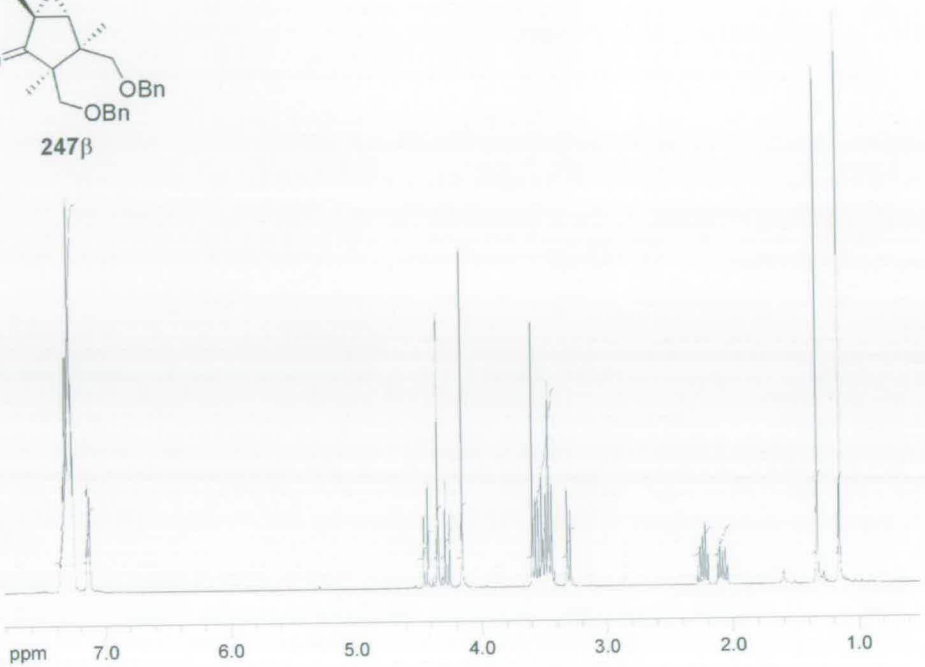
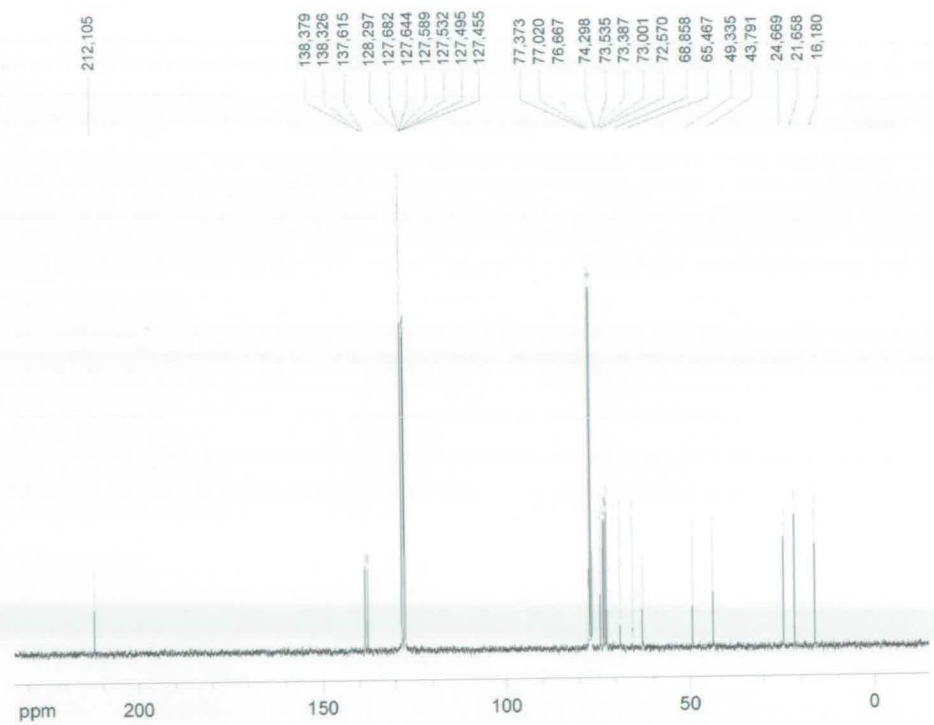
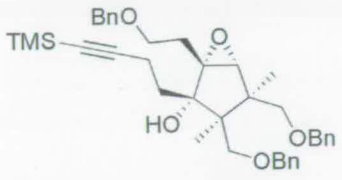




Tertiary alcohol (251ββ)

^{1}H-NMR (360 MHz, $CDCl_3$), ^{13}C-NMR (90 MHz, $CDCl_3$)



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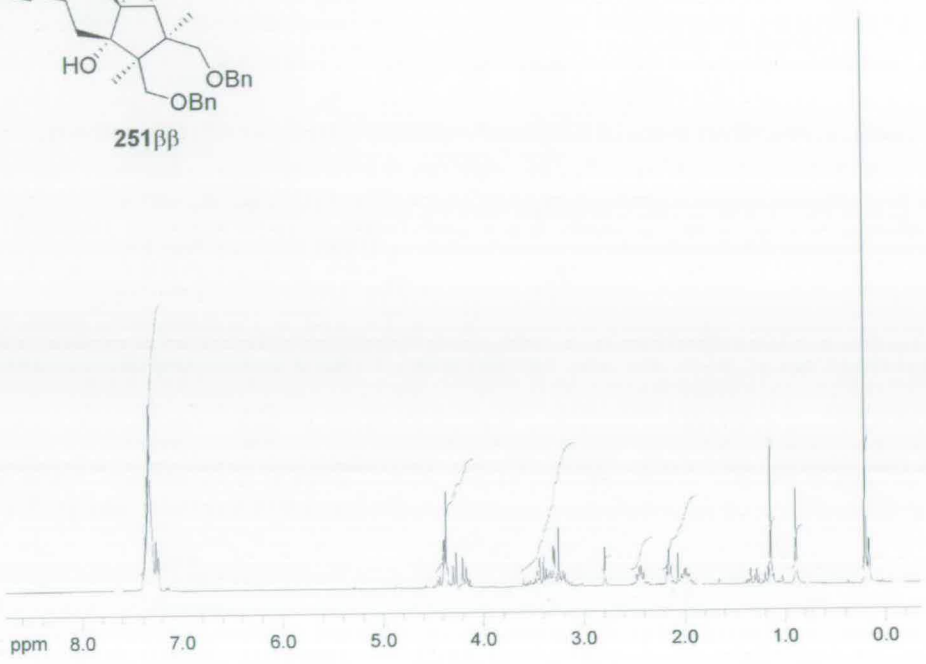
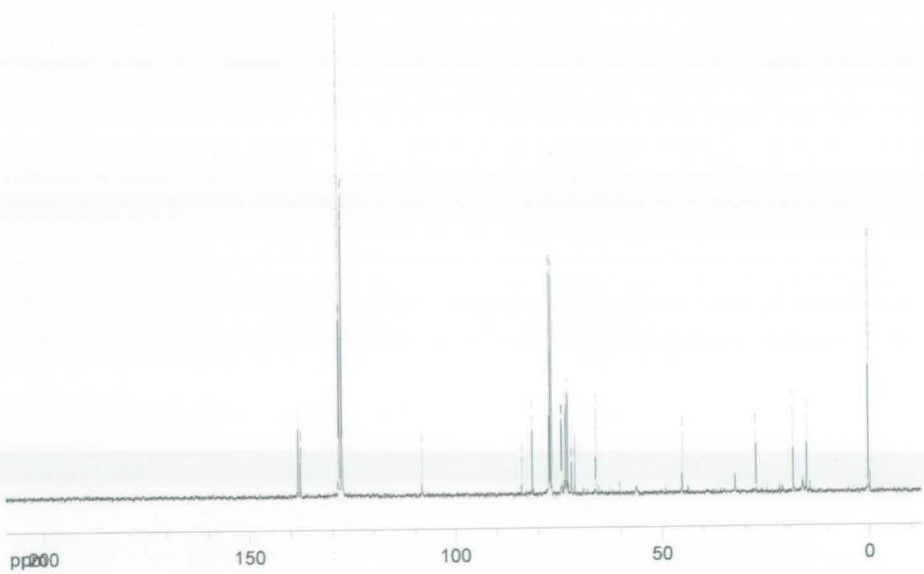
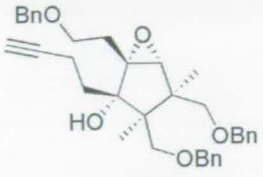




Tertiary alcohol (234ββ)

^{1}H-NMR (360 MHz, $CDCl_3$), ^{13}C-NMR (90 MHz, $CDCl_3$)



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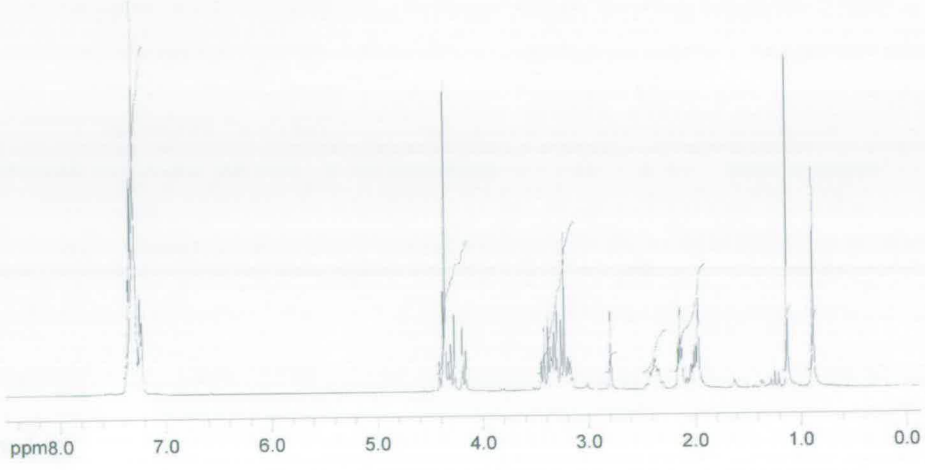
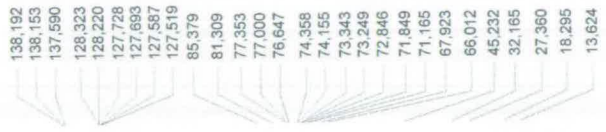
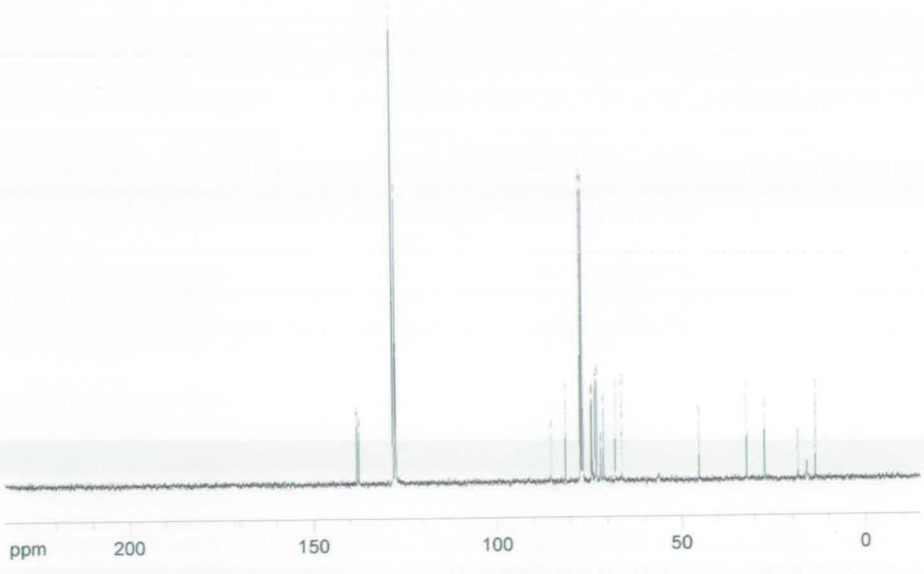
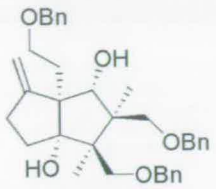






Diol (233ββ)

^{1}H-NMR (360 MHz, $CDCl_3$), ^{13}C-NMR (90 MHz, $CDCl_3$),



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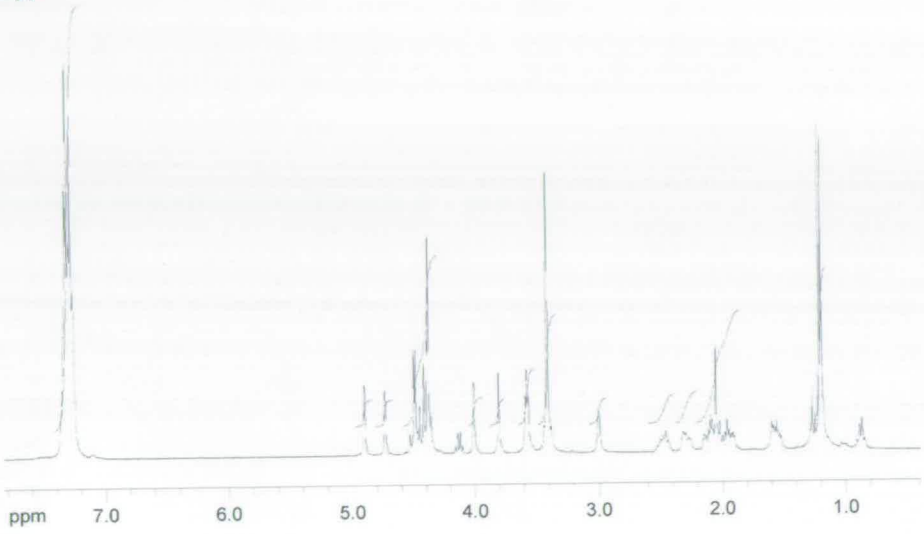

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