



**Total Synthesis of (\pm)-Merrilactone A and
(\pm)-Anislactone A**

Thesis Submitted in Accordance with the Requirement of the University
of Edinburgh for the Degree of Doctor of Philosophy

By

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December 2010

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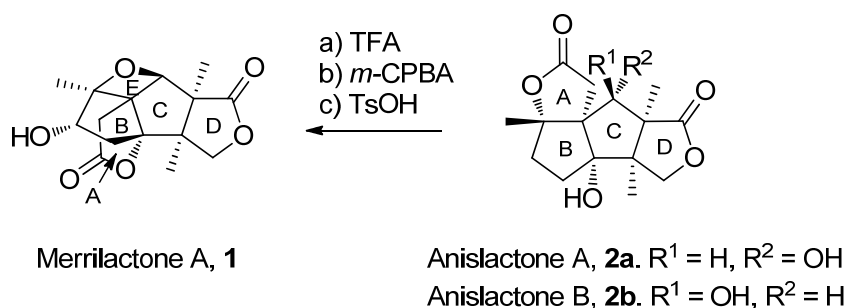
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2010

Abstract

Merrilactone A (**1**) was isolated in only 0.004% yield from the methanol extracts of the pericarps of *Illicium merrillianum*. 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. Merrilactone A also exhibits an important neurotrophic activity, significantly promoting neurite outgrowth in the primary cultures of foetal rat cortical neurons at very low concentrations.



Structurally, merrilactone A is related to anislactones A and B, a pair of epimeric sesquiterpene dilactones discovered ten years earlier by Kouno and co-workers from the related *Illicium anisatum* plant. Fukuyama has shown that anislactone B can be converted into merrilactone A using a simple three step sequence, suggesting that the anislactones may be biogenetic precursors to merrilactone A.

Described in this thesis are our research efforts directed towards developing a conceptually novel synthetic route enabling regiodivergent total synthesis of both anislactone A / B and merrilactone A. Our synthetic route (around 22 steps) features several key reactions, which include a [2+2] photo-cycloaddition reaction, Tiffeneau-Demjanov ring expansion and titanium(III) mediated radical cyclization.

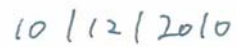
Declaration

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.

Signed



Lei Shi



10/12/2010

Lei Shi

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Contents

ABSTRACT	I
DECLARATION	II
ACKNOWLEDGEMENTS	III
1 INTRODUCTION	1
1.1 MERRILACTONE A AND ANISLACTONES: ORIGIN, STRUCTURE AND BIOLOGICAL ACTIVITY ...	1
1.2 BIOSYNTHESIS OF ANISLACTONE-TYPE SESQUITERPENES	3
1.3 CHEMICAL CONVERSION OF ANISLACTONE B TO MERRILACTONE A	4
1.4 PREVIOUS SYNTHESIS OF MERRILACTONE A	5
1.4.1 <i>Danishefsky's total syntheses of Merrilactone A</i>	6
1.4.1.1 Racemic total synthesis	6
1.4.1.2 Asymmetric formal synthesis	9
1.4.2 <i>Hirama's total syntheses of Merrilactone A</i>	12
1.4.2.1 Racemic total synthesis	12
1.4.2.2 Asymmetric total synthesis	15
1.4.2.3 Hirama's total synthesis of ent-(+)-Merrilactone A	18
1.4.3 <i>Metha's racemic total synthesis of Merrilactone A</i>	20
1.4.4 <i>Frontier's racemic total synthesis of Merrilactone A</i>	23
1.4.5 <i>Greaney's model study</i>	27
1.4.5.1 Unpublished work within Greaney's group	28
1.5 REFERENCES	30
2 TOTAL SYNTHESIS OF (±)-MERRILACTONE A	32
2.1 RETROSYNTHESIS ANALYSIS	32
2.2 SYNTHESIS OF SIMPLE MODEL SYSTEM	33
2.3 SYNTHESIS OF CYCLOPENTANONE	40
2.3.1 <i>Photochemical [2+2] route to cyclobutanone</i>	40
2.3.2 <i>Regioselective Tiffeneau-Demjanov ring expansion</i>	42
2.3.3 <i>Transesterification reaction</i>	44
2.3.4 <i>Alkylation of 1,3-ketoester and Tsuji-Trost reaction</i>	45
2.3.4.1 Mechanism of Tsuji-Trost reactions	45
2.3.4.2 Alkylation of 1,3-ketoester with protected 2-bromoethanol	47
2.3.4.3 Alkylation with methyl 2-bromoacetate	49
2.3.4.4 Alkylation with allyl bromide and optimization of Tsuij-Trost reaction	52
2.4 SYNTHESIS OF THE FUNCTIONALIZED CYCLOPENTANEONE	54
2.4.1 <i>Transformation of alkene to primary alcohol</i>	54
2.4.2 <i>Epoxidation and 1,2-organometallic addition</i>	59
2.4.2.1 Approach I, chelation controlled 1,2-addition	60
2.4.2.2 Approach II, steric controlled epoxidation	62

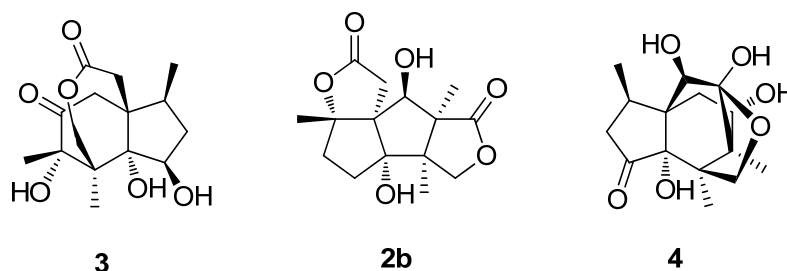
2.4.2.3	Stereoselective organometallic addition	67
2.5	TITANIUM(III)-MEDIATED RADICAL CYCLIZATION	70
2.5.1	<i>Radical cyclization in the synthesis of BC core of merrilactone A</i>	70
2.6	TOTAL SYNTHESIS OF MERRILACTONE A	74
2.6.1	<i>Synthesis of γ-lactone A in merrilactone A</i>	75
2.6.2	<i>Alkene isomerization</i>	77
2.6.3	<i>Formal total synthesis of merrilactone A</i>	80
2.7	CONCLUSION	82
2.8	REFERENCES	84
3	TOTAL SYNTHESIS OF ANISLACTONE A AND B	88
3.1	INTRODUCTION AND BACKGROUND OF ANISLACTONE A	88
3.2	ALUMINIUM TRIFLATE CATALYZED INTRAMOLECULAR HYDROALKOXYLATION REACTION ...	88
3.3	LACTONIZATION AND TOTAL SYNTHESIS OF ANISLACTONES	91
3.4	CONCLUSION	93
3.5	REFERENCES	94
4	CONCLUSIONS	95
5	EXPERIMENTAL	99
5.1	GENERAL PROCEDURES	99
5.2	EXPERIMENTAL PROCEDURES	99
6	ABBREVIATIONS	136
7	APPENDIX: SPECTROSCOPIC DATA	140

1 Introduction

1.1 Merrilactone A and Anislactones: Origin, Structure and Biological activity

The evergreen shrub or tree *Illicium* is the only genus member of the family Illiciaceae^[1], of which forty species have been found in eastern North America, Mexico, the West Indies and eastern Asia. The highest concentration of this species can be found in northern Myanmar and southern China, where almost thirty-five species have been documented. The *Illicium* species provides rich resources of neolignans and biosynthetically unique seco-prezizaane-type sesquiterpenes. Most importantly, some of these possess distinctive neurotoxic and neurotrophic properties^[2, 3].

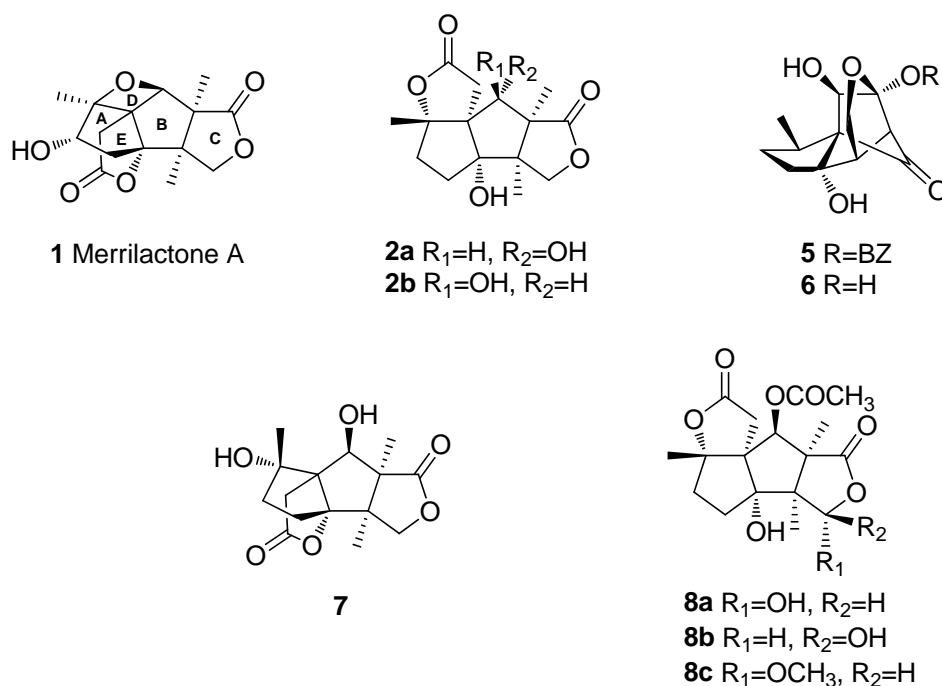
Based on their carbon skeleton, the *Illicium* sesquiterpenes have been classified into three categories^[3,4], a major class of seco-prezizaane-type sesquiterpenes, and two smaller classes, anislactone & allo-cedrane type sesquiterpenes. Scheme 1-1 shows representative examples of each of the above categories.



Scheme 1-1. Examples of seco-prezizaane-type (3), anislactone B (2b) and allo-cedrane type (4) sesquiterpenes.

Illicium merrillianum, an aboriginal plant of south-western China and Myanmar, occupies a significant taxonomical place as the first *Illicium* plant to yield a number of seco-prezizaane-type sesquiterpenes and allo-cedrane-type sesquiterpenes, including the biosynthetically essential tashiromin **5**, and 11-O-debenzoyltashiromin **6**. More importantly, *I. merrillianum* can produce a large number of anislactone-type compounds such as anislactone A and B (**3a** and **3b** respectively) and merrilactones A, B and C (**1**, **7** and **8** respectively), which possess a distinctive carbon skeleton consisting of two consecutive five-membered rings bearing two γ -lactones^[5-7]

(Scheme 1-2). They cannot therefore be categorised with the previously known seco-prezizaane-type sesquiterpenes. To date, thirty-six structurally novel sesquiterpenes have been isolated from this species.



Scheme 1-2. Illidium sesquiterpenes isolated from *I. merrillianum*.

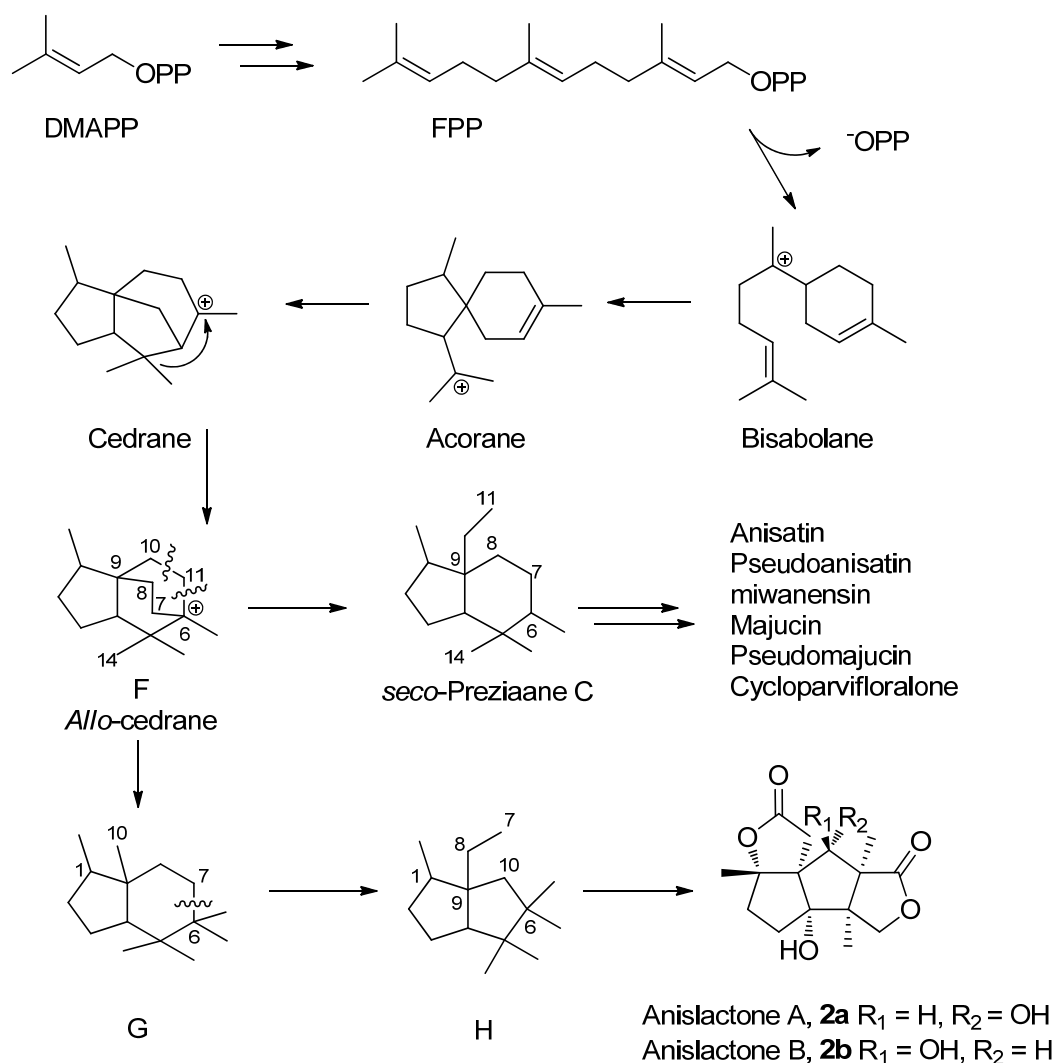
Merrilactone A (**1**) was isolated in only 0.004% yield from the methanol extracts of the pericarps of *I. merrillianum*. Its structure has been elucidated by means of extensive spectroscopic and X-ray crystallographic analysis and the absolute configuration established using the modified Mosher's method. Merrilactone A is a pentacyclic anisactone-type sesquiterpene fused with two γ -lactones and an oxetane ring. This densely oxygenated highly compact architecture also contains five contiguous quaternary centres and shows a cis-arrangement of the two angular methyl groups at the B-C junction, making it an attractive and challenging target for synthesis.

In addition to its attractive structure, merrilactone A also exhibits an important neurotrophic activity, significantly promoting neurite outgrowth in the primary cultures of foetal rat cortical neurons at very low concentrations from 10 $\mu\text{mol/L}$ to 0.1 $\mu\text{mol/L}$ ^[6]. Thus researchers believe that Merrilactone A may possess therapeutic potential in the treatment of neuro-degenerative diseases, such as Alzheimer's

disease and Parkinson's disease^[8].

1.2 Biosynthesis of Anislactone-type sesquiterpenes

These compounds originate from the mevalonic acid pathway, which affords dimethylallyl diphosphate (DMAPP) from acetyl-CoA. Three DMAPPs, or two IPPs (isopentenyl diphosphate) and one DMAPP, are formed into a farnesyl diphosphate (FPP), which is the essential precursor of sesquiterpenes. Then the cyclization of farnesyl diphosphate is promoted by sesquiterpene cyclase enzymes. The synthesis to this step is well studied, though the process after the first cyclization is unclear.



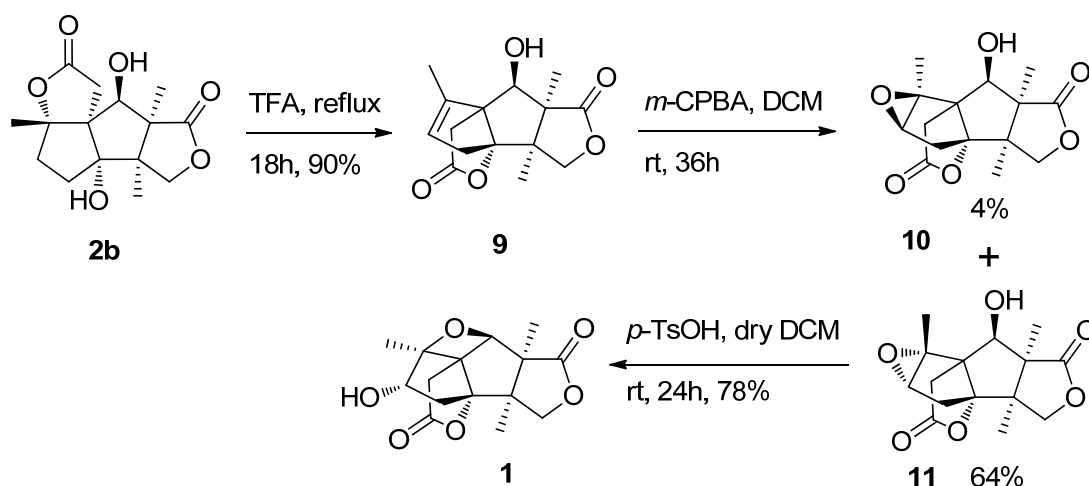
Scheme 1-3. Plausible biosynthetic route of anislactone-type sesquiterpenes.^[9]

After the bond cleavage between C6 and C11 of the molecule, the tricyclic carbon skeleton, *allo*-cedrane A, turns into *seco*-prezizaanes such as anisatin, pseudoanisatin,

miwanensin, pseudomajucin and cycloparvifloralone. As both anislactones and majucin possess the same γ -lactone motif, Kouno proposed that anislactones were from the majucin-type compound^[9]. However this biosynthetic assumption has some difficulties explaining some of the configurations and other features found in these molecules. Fukuyama proposed an alternative biogenetic pathway which led to anislactones from *allo*-cedrane A as shown in scheme 1-3^[5]. The bond breaking between C10 and C11 in *allo*-cedrane A gives rise to a bicyclic carbon skeleton G, which repeats the cleavage of the bond between C6 and C7 followed by the construction of five-membered ring between C6 and C10, resulting in the formation of anislactone-type carbon skeleton H. This newly proposed pathway is expected to be able to give a reasonable biosynthetic explanation to all characteristic sesquiterpenes in *Illicium* plants.

1.3 Chemical conversion of anislactone B to merrilactone A

Fukuyama and co-workers^[6] previously showed that anislactone B, which can be obtained from *Illicium merrillianum* in significant amounts, can be transformed to merrilactone A in three steps. At first, a solution of **2b** was refluxed in trifluoroacetic acid leading to the lactone transposition to the C-4 hydroxyl group. This was followed by the dehydration of the C-1 hydroxyl group, which gives rise to **9** in 90% yield. Secondly, treatment of **9** with *m*-chloroperoxybenzoic acid afforded the desired α -epoxidation product **11** in 64% yield, together with a separable β -epoxide **10** in 4% yield. The high stereoselectivity of epoxidation could be rationalized by a favorable attack of the peroxyacid from the less hindered convex face of **9**. Finally, **11** was treated with *p*-toluenesulfonic acid to produce **1** in 78% yield, which was identical in all respects to natural merrilactone A.



Scheme 1-4. Chemical conversion of Anislactone B to Merrilactone A

1.4 Previous syntheses of Merrilactone A

Merrilactone A's intriguing biological properties have attracted the attention of several research groups interested in the development of nonpeptidal neurotrophic agents. A total synthesis of merrilactone A and possible analogues would provide a route by which novel therapeutic agents could be investigated. In addition to its novel bioactivity, its unique structure has stimulated extensive efforts leading to several publications on its synthesis. Danishefsky^[10,11], Hirama^[12], and Mehta^[13] have completed three elegant syntheses of the natural product in the past eight years. Fukuyama^[14] reported one model study of this natural product. Very recently Frontier^[15,16] has reported a new synthetic approach.

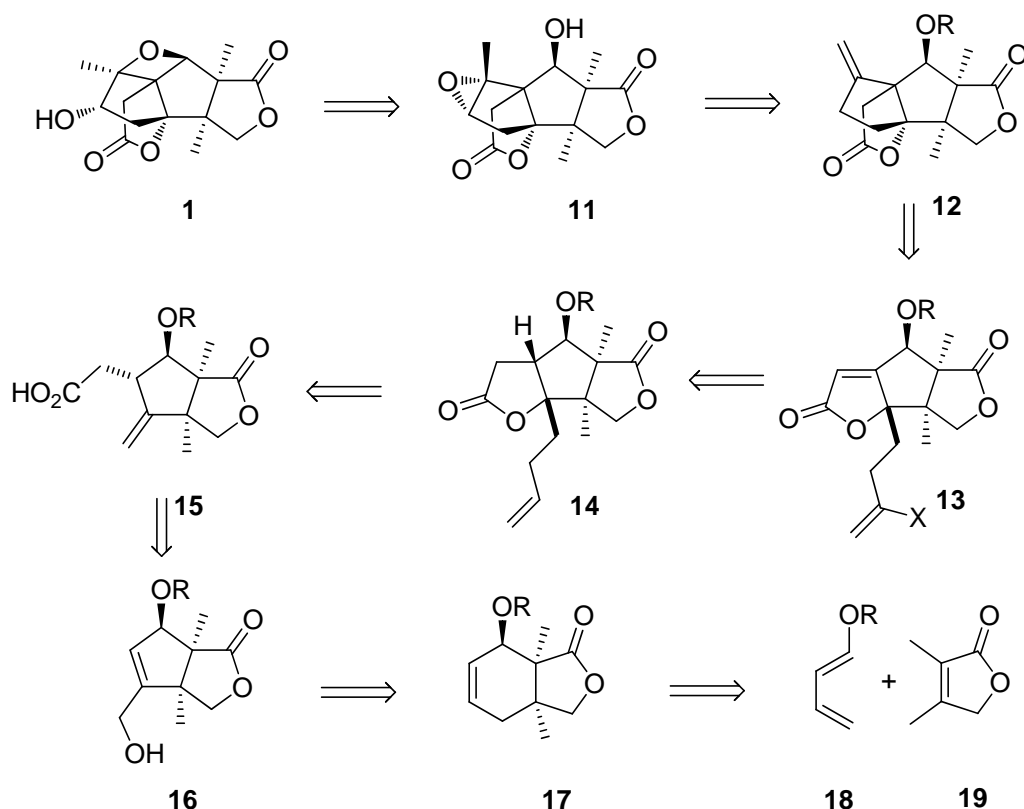
Scheme 1-5. Timeline of the different syntheses

2000	isolation		
2002	Samuel Danishefsky	Columbia U, US	<i>JACS</i> , 2002 , 2018
2003	Masahiro Hirama	Tohoku U, JP	<i>JACS</i> , 2003 , 10772
2006	Goverdhan Mehta	India Inst. Of Science, In	<i>ACIEE</i> , 2006 , 953
2007	Alison Frontier	University of Rochester, US	<i>JACS</i> , 2007 , 498
2010	Mike Greaney	Edinburgh U, UK	<i>ACIEE</i> , 2010 , 9250

1.4.1 Danishefsky's total syntheses of Merrilactone A

1.4.1.1 Racemic total synthesis

In 2002, the first racemic total synthesis of Merrilactone A was accomplished by Danishefsky and Birman successfully^[10]. The 20 step synthetic route afforded (±)-Merrilactone A in an impressive 10.7% overall yield. However, several problems of stereo- and regio- selectivity were encountered along the route. Scheme 1-6 shows the retro-synthetic analysis of the total synthesis.

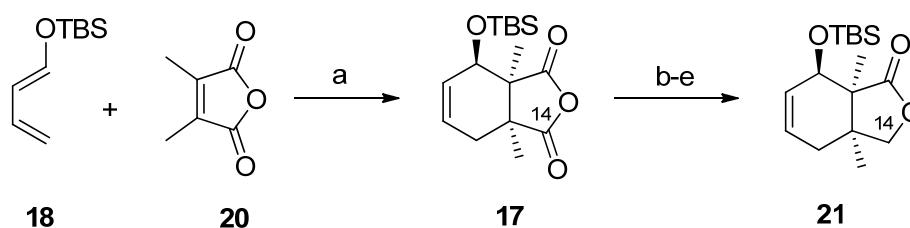


Scheme 1-6. Danishefsky's retrosynthetic analysis of Merrilactone A

The central oxetane motif in Merrilactone A is synthesized *via* a known, biomimetic *homo*-Payne-type rearrangement of epoxide **11**, which was obtained from the *exo*-olefin **12** *via* alkene isomerisation and epoxidation^[5]. A free radical cyclisation from **13** was anticipated to afford tetracycle **12**, setting a quaternary centre in a highly sterically crowded environment. The γ,δ -unsaturated acid **15** is a key intermediate, which could be elaborated into **14** *via* iodolactonisation reaction. Substrate **15** was believed to be obtainable by a Claisen rearrangement *via* **16**, which

in turn could be accessible from a ring contraction of bicycle **17**. The latter structure was a product of a Diels-Alder reaction of diene **18** and dienophile **19**.

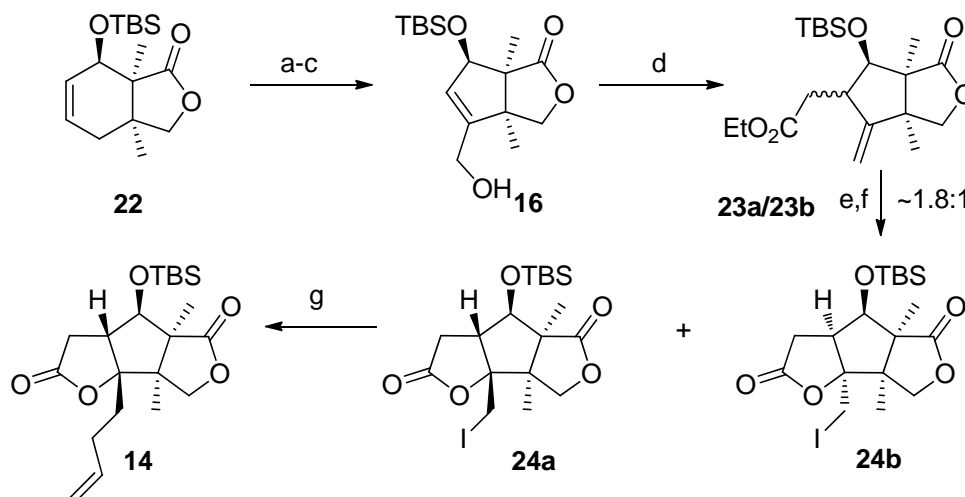
In the forward synthesis of merrilactone A, diene **18** reacts with 2,3-dimethylmaleic anhydride **20** at high temperature, affording bicycle **17** in 74% yield (Scheme 1-7) with high stereo- and regio-selectivity. Three stereocenters (including two quaternary) are created at the same time in this very early step.



a) 165 °C, mesitylene, 74%; b) NaOMe, MeOH; c) ClCO₂Me, THF, then NaBH₄, MeOH, -35 °C; d) aq. LiOH; e) LiBHET₃, THF, then TFA, DCM, 78% for 4 steps

Scheme 1-7. Diels-Alder reaction and regioselective C14 reduction

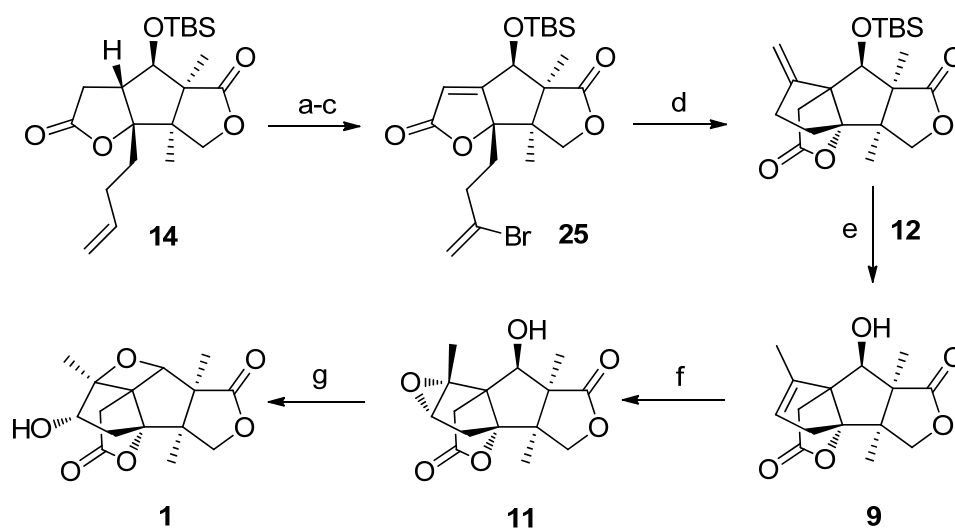
Selective reduction of C14 *via* conventional methods afforded a mixture of products due to regio-selectivity problems. Alternatively, a slight longer protocol could be applied to produce **21** in a reasonable 78% yield from **20** over four steps (b-e in Scheme 1-7).



a) O₃, PPh₃, DCM/MeOH; b) Bn₂NH.TFA, PhH, 65 °C, 94% over 2 steps; c) NaBH₄, DCM, MeOH, -78 °C, quant.; d) MeC(OEt)₃, mesitylene, PivOH, 135 °C, 92%; e) aq. LiOH, MeOH; f) I₂, NaHCO₃, THF, 59% **26** and 35% **25** over 2 steps; g) AllylSnBu₃, AIBN, PhH, 75%.

Scheme 1-8. Johnson-ortho-ester reaction and Keck C-allylation.

A ring contraction strategy was then employed *via* a ring opening-closing sequential reaction, which was initiated by ozonolysis of **22** followed by subsequent reductive workup. Reduction of the aldol condensation product between the resulting *di*-aldehyde produced the ring contracted bicyclic alcohol **16** in excellent yield. An *ortho*-ester Claisen rearrangement was then employed, producing a diastereomeric mixture of esters **23a** and **23b** in a moderate ratio (~1.8:1). The resulting ester mixture was hydrolysed into the corresponding acids which were subsequently iodolactonised into two chromatographically separable iodolactones **24b** and **24a** in 35% and 59% yield respectively. The tricyclic key intermediate **14** was synthesized from the desired diastereomer **24a** *via* Keck's C-allylation protocol^[17] of a three carbon chain elongation.



a) LHMDS, TMSCl, then PhSeCl; b) PhSeBr, MeCN; c) O₃, DCM, 1-hexene, PhH, NEt₃, reflux, 77% over 3 steps; d) Bu₃SnH, AIBN, PhH, 90%; e) TsOH.H₂O, PhH, reflux, 98%; f) *m*CPBA, DCM, 3.5:1 ratio of α/β epoxide, quant.; g) TsOH.H₂O, DCM, 71% over 2 steps.

Scheme 1-9. Free radical cyclisation and homo-Payne rearrangement

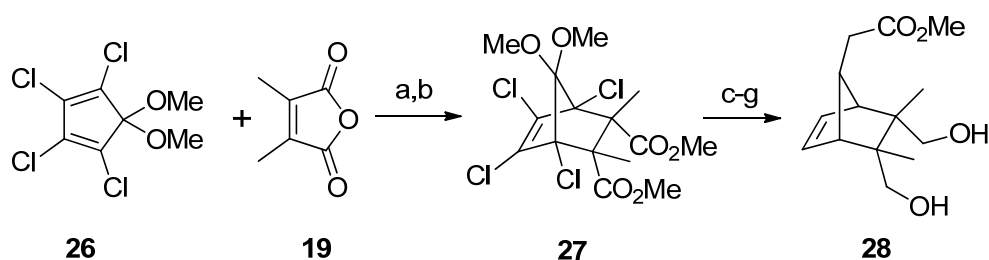
Selenylation of C10 of **14** *via* an intermediate silyl ketene acetal, then bromoselenylation of the pendant vinyl group, and subsequent concurrent oxidative deselenation yielded **25** with good yield over 3 steps. The tetracyclic **12** was then accessible from **25** *via* a radical cyclisation reaction in excellent yield. Subsequent isomerisation of the exocyclic methylene group and deprotection of the TBS group led to β -alcohol **9**. Hydroxyl groups usually act as *syn*-directing groups in epoxidations, however in this case the congested nature of the β -face of the double

bond dominates and the epoxidation occurs from the α -face (α/β epoxide = 3.5:1)^[18]. The total synthesis was then finished by conversion of the epoxidation **11** into (\pm)-Merrilactone A **1** via known *homo*-Payne rearrangement catalyzed by acid.

1.4.1.2 Asymmetric formal synthesis

In 2005, just three years after reporting their first racemic total synthesis of (\pm)-Merrilactone A, Danishefsky and co-workers reported an asymmetric variant. In order to resolve the various issues of selectivity in the racemic synthesis, a modified approach accessing either enantiomer of Merrilactone A was established.^[11] They concentrated attention on a stereocontrolled synthesis of key intermediate **24a**, since the transformation of this advanced intermediate into Merrilactone A had already been shown to be concise and high yielding.^[10] A substantial redesign of the previously racemic synthesis was necessary to tackle several multi-step sequences, such as transforming **17** into **21**, and lack of selectivity, for example the regioselective C14 reduction or the Claisen rearrangement of **16** which yielded a mixture of the diastereomeric esters **23a** and **23b**.

The starting point for the asymmetric route was the *endo*-selective Diels-Alder reaction at high temperature between the cyclic anhydride **19** and diene **26**. Deprotonation *via* lithiation and subsequent stereoselective methylation gave access to **27** in an 87% yield over two steps. **27** was then converted to *meso*-intermediate **28** efficiently through several standard transformations with an overall 48% yield over five steps (Scheme 1-10).

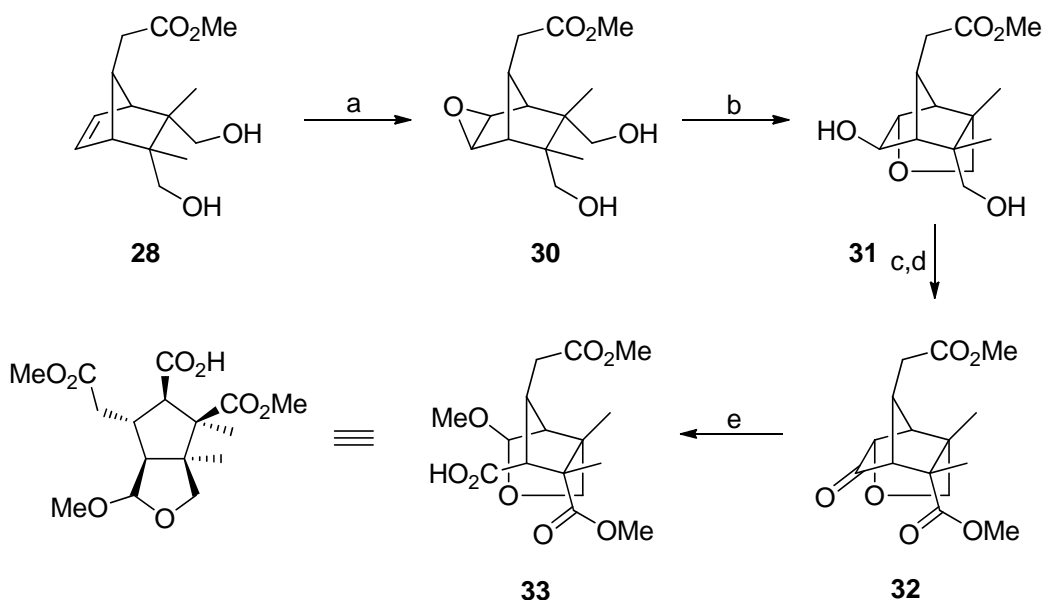


a) 180 °C, neat, then MeOH, reflux, PhH/MeOH, TMSCHN₂, 92%; b) LDA, HMPA, MeI, THF, -78 °C to RT, 95%; c) LiAlH₄, THF, reflux,; d) Na, NH₃, THF/EtOH, 72% over 2 stpes; e) 2,2-dimethoxypropane, acetone, TsOH; f) NaH, (EtO)₂POCH₂CO₂Et, THF, 86% over 2 stpes; g) Mg, MeOH, 77%.

Scheme 1-10. Endo-Diels Alder and conversion into meso 1,4-diol compound

Treatment of *meso*-compound **29** with dimethyldioxirane gave rise to the *exo*-epoxide **30**, setting the stage for the key steps in the asymmetric synthesis – a desymmetrisation of the epoxide **30** with Jacobsen's Co^{III} (salen) chiral catalyst. The desymmetrisation reaction was carried out by treatment of the epoxide **30** with a catalytic amount of (*S,S*)- $[\text{Co}^{\text{III}}$ (salen)]-OAc, as described by Jacobsen and co-workers^[20], successfully affording enantioenriched tricycle **31** in 86% yield and 86% ee. Similarly, using of the Jacobsen' catalyst (*R,R*)- $[\text{Co}^{\text{III}}$ (salen)]-OAc afforded *ent*-**31**, thereby setting up routes to the opposite enantiomer of Merrilactone A.

Oxidation of resulting diol **31** and subsequent esterification afforded ketoester **32** which in turn was substrate for Baeyer-Villiger oxidation. Exposure of intermediate **32** to standard Baeyer-Villiger oxidation condition gave access to carboxylic acid **33** in 63% yield over three steps.

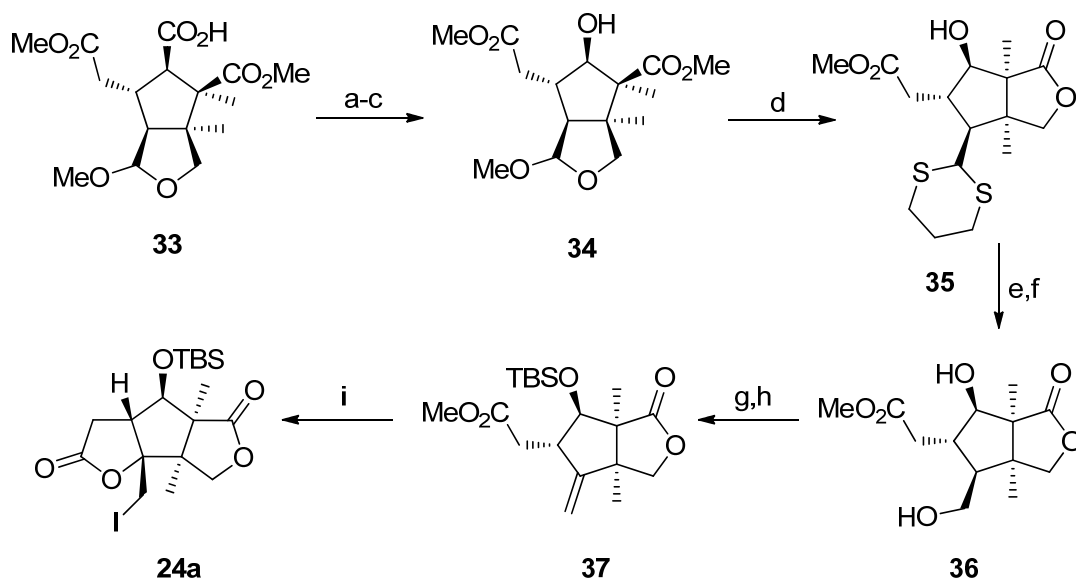


a) DMDO, DCM; b) (*s,s*)- $[\text{Co}^{\text{III}}$ (salen)]-OAc, -78 °C to -25 °C, THF, 86% for 2 stpes; c) PDC, DMF; d) K_2CO_3 , MeI, acetone, reflux, 70% over 2 stpes; e) MMPP, MeOH, 0 °C to RT, 88%

Scheme 1-11. Regio- and enantio-controlled chemical degradation pathway

The secondary alcohol **34** was obtained from carboxylic acid **33** in a three-step sequence with retention of stereochemistry (Scheme 1-12). Treatment of **34** with Lewis acid led to opening of the methoxy-tetrahydrofuran ring, subsequent trapping of the masked aldehyde, and lactonisation in a one-pot reaction to afford compound **35** which was then transformed into diol **36**. Selective reaction at the primary alcohol

in **36** was achieved by using the methodology developed by Grieco and co-workers to provide a transient selenide, which was converted to the desired exocyclic olefin **37** after oxidative elimination^[20]. The ester group of **37** was hydrolysed into carboxylic acid which underwent iodolactonisation, affording key intermediate **24a** (Scheme 1-12).



a) DCC, *m*CPBA, 0 °C to RT, 83%; b) PhH, reflux; c) K₂CO₃, MeOH, 70% for 2 stpes; d) BF₃.OEt₂, HS(CH₂)₃SH, DCM, 50%; e) PhI(OCOCF₃)₂, MeCN/H₂O, 50%; f) NaBH₄, MeOH, 0 °C; g) *o*-NO₂C₆H₄SeCN, Bu₃P, THF, then 30% H₂O₂, 86% for 2 steps; h) TBSOTf, Net₃, DCM, 76%; i) LiOH, H₂O/MeOH, then I₂, aq. NaHCO₃/THF, 75%

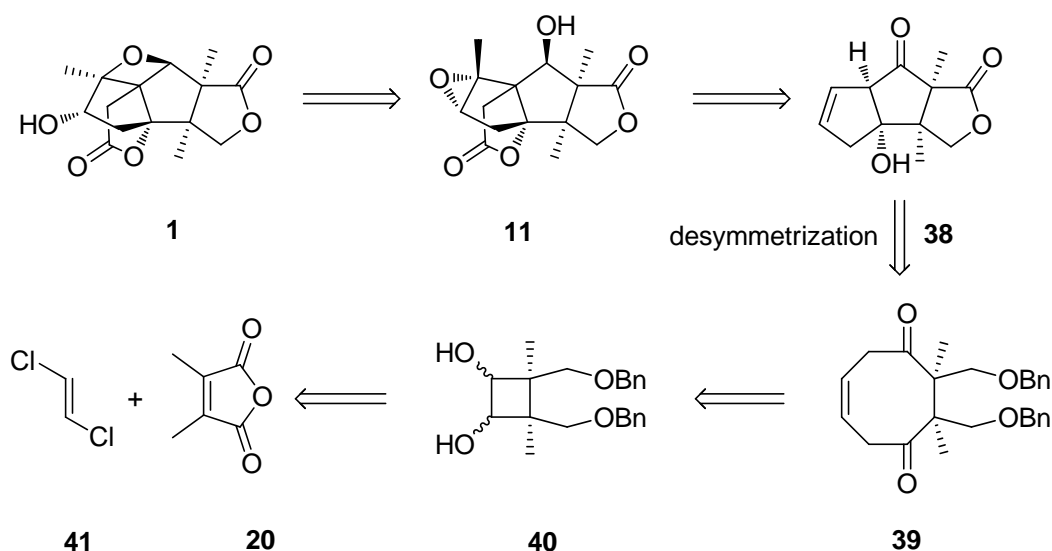
Scheme 1-12. Synthesis of entioenriched key intermediate

The enantiopure key intermediate **24a** could then be transformed into Merrilactone A through the known methodology reported in Danishefsky's racemic total synthesis of Merrilactone A^[10]. It is worthy of note that with this redesigned synthetic approach, the selectivity issues in the previous racemic route have been resolved successfully and for the first time enabled access to either enantiomer of the natural product. The key enantiopure intermediate **24a** was achieved *via* a 21 step synthetic route with an overall 6% yield, thus presenting the first formal asymmetric synthesis of this natural product.

1.4.2 Hirama's total syntheses of Merrilactone A

1.4.2.1 Racemic total synthesis

In 2003, Hirama and co-workers published the second total synthesis of (\pm)-Merrilactone A.^[12] They developed a totally new synthetic methodology for the construction of the core of the natural product. The 27 step racemic total synthesis was finished with an overall 1% yield. The retro-synthetic approach employed by Hirama and co-workers is shown in Scheme 1-13.



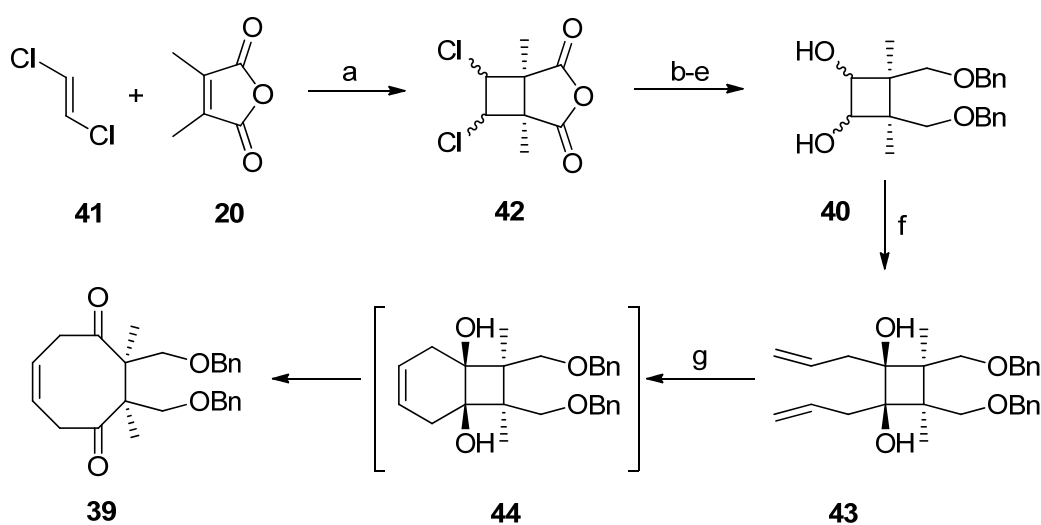
Scheme 1-13. Hirama's retrosynthesis of Merrilactone A

It was proposed that Merrilactone A would be prepared from precursor **11** *via* the known and previously successfully used *homo*-Payne rearrangement to install the oxetane moiety in the final step of the synthesis. Compound **11** was accessible from bicyclic compound **38** through a number of straightforward transformations. The key *cis*-bicyclo- [3.3.0]octane core was designed to be accessible *via* an impressive desymmetrisation reaction of the *meso*-diketone **39** by employing an intramolecular aldol reaction. The substrate **39** for this pivotal step would be accessible from a double allylation, ring closing metathesis and subsequent ring expansion of cyclobutane **40**. The latter would in turn be synthesized *via* a [2+2] photocycloaddition of *di*-haloalkene **41** and cyclic anhydride **20**.

In the forward synthesis, the envisioned [2+2] photocycloaddition was carried out under

irradiation of substrates **41** and **20** in the presence of the photosensitiser benzophenone to produce **42** in a stereospecific manner. The cycloadduct was subjected to dechlorination, anhydride reduction, di-benzylation of the resulting diol and dihydroxylation, affording the *meso*-diol **40** in a 47% yield over three steps.

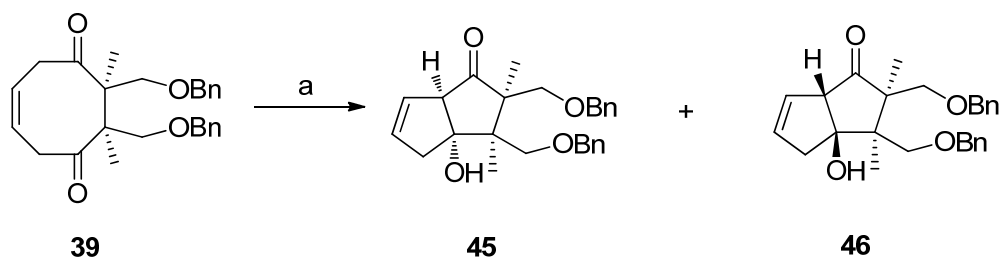
Exposure of cyclobutane **40** to a one-pot Swern oxidation and consecutive double *cis*-allylation afforded **43** as a major product in 78% yield. At this stage the ring closing metathesis reaction was applied, giving rise to the bicyclic [4.2.0]octyl system **44** effectively. Treatment of **44** with $\text{Pb}(\text{OAc})_4$ *in situ* formed the eight membered ring **39** in excellent yield (Scheme 1-14).



a) benzophenone, acetone, hv; b) Zn, TMSCl, Ac_2O , toluene, 85 °C; c) LiAlH_4 , THF, 47% for 3 stpes; d) BnBr , NaH , THF/DMF, 99%; e) OsO_4 , NMO, *t*BuOMe/*t*BuOH/ H_2O , 94%; f) $(\text{COCl})_2$, DMSO, NEt_3 , g) $(\text{PCy}_3)_2\text{Cl}_2\text{Ru}=\text{CHPh}$, DCM, reflux, then $\text{Pb}(\text{OAc})_4$, 95%.

Scheme 1-14. Synthesis of desymmetrisation substrate

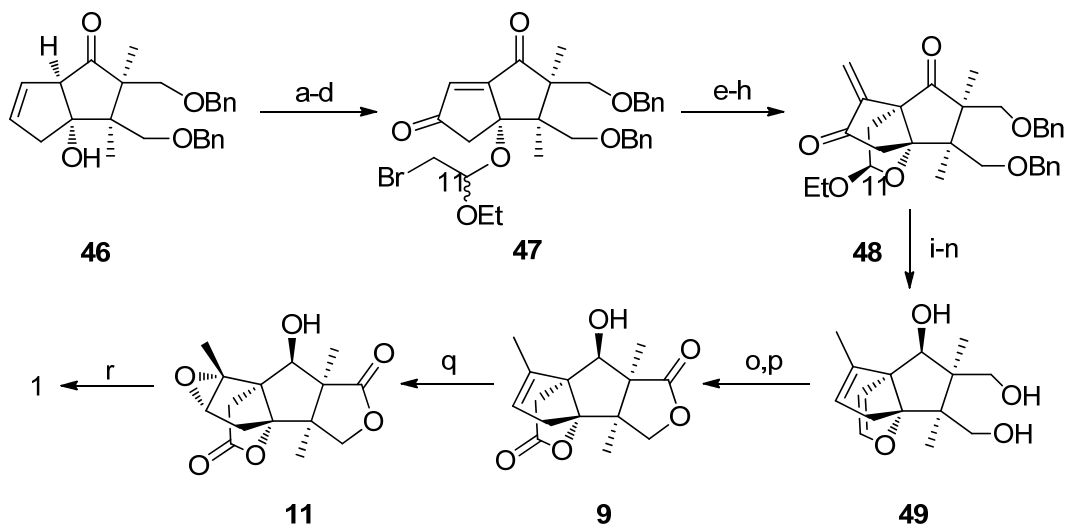
In the total synthesis' pivotal step, a base-induced intramolecular transannular aldol reaction promoted the desymmetrisation of *meso*-diketone **39** to afford the diastereometric bicycles in favor of desired **45** over undesired **46** in a ratio of 3.1:1 depending on the reaction condition. Interestingly in this desymmetrisation reaction, changing the condition by varying different bases giving access to the other diastereomer **46** as major product was also found to be feasible (Scheme 1-15).



a) LHDMS, THF, -100 °C, 45:56 ratio 3.1:1, 85%.

Scheme 1-15. Desymmetrisation via intramolecular aldol reaction

Epoxidation of the resulting aldol product **46** afforded the epoxide, which was subsequently opened by treating with DBU and then followed by oxidation to enone motif. An α -bromoacetal was introduced to afford **47** as a mixture of acetal diastereomers, setting the stage for radical cyclisation. Under standard radical conditions, cyclisation of **47** proceeded smoothly to give a 5-*exo*-trig product in good yield. Subsequent silyl enol ether formation followed by treatment with Eschenmoser's salt and *m*CPBA^[21] produced *exo*-alkene **48**. Selective reduction of ketone and hydrogenation to remove the benzyl groups led to triol **49** which, upon hydration and double Fetizon oxidation^[22] of the diol, underwent lactonisation yielding intermediate **9** and introducing the ring C in the natural product. Subsequent epoxidation afforded **11** and set the stage of final acid promoted Payne-type rearrangement to afford Merrilactone A (Scheme 1-16).



a) *m*CPBA, DCM, 81%; b) DBU, DCM, -40 °C, 81%; c) IBX, DMSO, 94%; d) BrCH₂CHBr(OEt), PhNMe₂, DCM, -78 °C to RT, 62%; e) Bu₃SnH, BEt₃/O₂, toluene, then CSA, EtOH, 71%; f) TMSOTf, DIPEA, DCM, -20 °C; g) Me₂NCH₂⁺I⁻, DCM; h) *m*CPBA, DCM, 70% over 3 setps; i) TFA/H₂O, 94%;

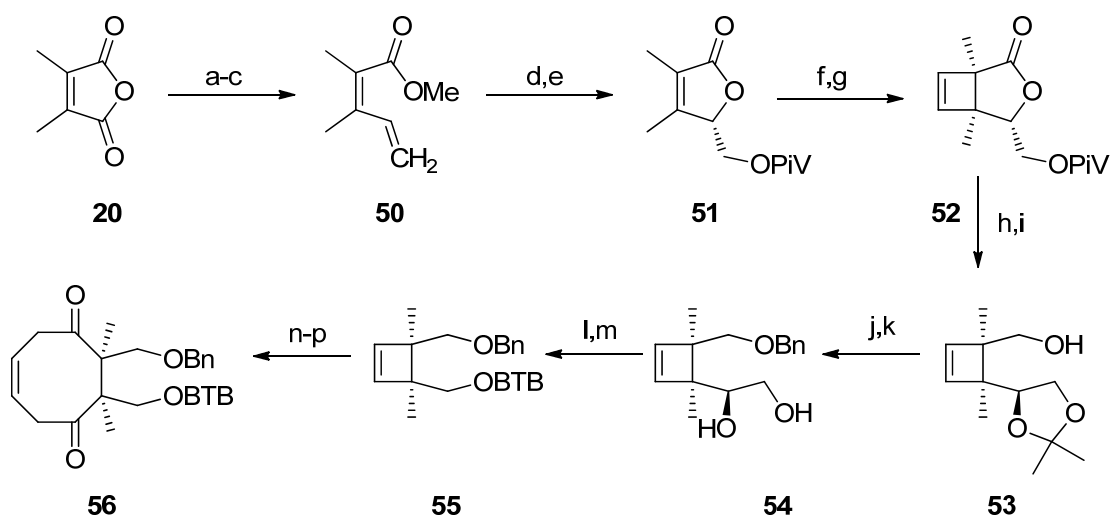
2-Tf₂N-5-chloropyridine, -78 °C, 99%; l) Pd(OAc)₂, PPh₃, NBU₃, HCOOH, DMF, 40 °C, 89%; m) DIBALH, DCM, -78 °C, 88%; n) Na, NH₃, THF/EtOH, -78 °C, 100%; o) DOWEX 50WX₂, THF/H₂O; p) Ag₂CO₃ on celite, toluene, 130 °C, 64 % for 2 steps; q) DMDO, DCM, 96%; r) TsOH, DCM, 81%.

Scheme 1-16. Completion of Merrilactone A synthesis

Hirama and co-workers's total synthesis of Merrilactone A utilized a novel desymmetrising intramolecular transannular aldol reaction to install two of the central five-membered carbocycles at the same time. As with Danishefsky's route, serious selectivity problems plague the synthesis at several stages, sffording racemic Merrilactone A in 27 steps and an overall yield of 1%.

1.4.2.2 Asymmetric total synthesis

Three years after their racemic synthesis of Merrilactone A, Hirama and co-workers reported an asymmetric version of their total synthesis in 2006^[23]. They successfully introduced a bulky protecting group to control the stereochemistry of intra-molecular aldol reaction, providing access to an enantioenriched analogue of the desymmetrisation substrate **39**. For preparing an enantioenriched analogue of **39** a novel route was developed, in which the two pendant alcohols were protected differentially. The new synthetic route began with the partial reduction of dimethyl maleic anhydride **20**, and consecutive Wittig olfination and esterification to afford **50** in 68% yield over three steps.



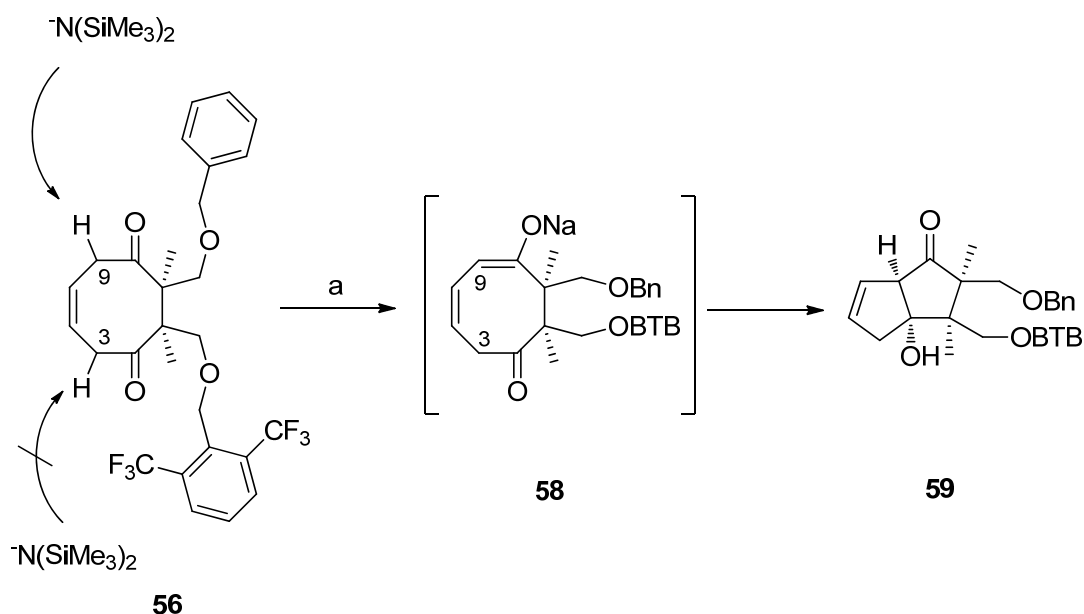
a) LiAlH(OtBu)₃, DME, -15 °C to RT, 85%; b) Ph₃PCH₃⁺Br⁻, tBuOK, 0 °C to RT, 87%; c) MeI, K₂CO₃, THF, 50 °C, 92%; d) AD-mix- α , tBuOH/H₂O, 0 °C, 65%, >99% ee after recrystallisation; e) PivCl, pyridine,

DMAP, DCM, 99%; f) *cis*-dichloroethylene, MeCN, -20 °C, hv; g) Zn, Ac₂O, toluene, 120 °C; h) LiAlH₄, Et₂O, 75% for 3 steps; i) Me₂C(OMe)₂, TsOH, DCM, 81%; j) BnBr, NaH, THF/DMF; k) 3M HCl, THF, 91% for 2 steps; l) Pd(OAc)₄, pyridine, DCM, -50 °C then DIBALH, -78 °C to -50 °C, 93%; m) BTBBr, KH, [18]crown-6, DMF; n) OsO₄, NMO, *t*BuOMe/*t*BuOH/H₂O, 94% over 2 steps; o) SO₃.py, DIPEA, DMSO, DCM, -15 °C then allylmagnesium bromide, -78 °C, ratio α/β 2.7:1, 78%; p) [(PCy₃)₂Cl₂Ru=CHPh], DCM, reflux then Pb(OAc)₄, 97%.

Scheme 1-17. Asymmetric synthesis of intramolecular aldol substrate

Sharpless asymmetric dihydroxylation reaction was employed on **50** to provide a diol in excellent enantioselectivity, which underwent *in situ* lactonisation. The resulting hydroxy- γ -lactone was protected as the pivaloate ester to afford **51**. Photo promoted [2+2] addition of 1,2-dichloroethylene and **51** and subsequent zinc mediated dechlorination afforded bicycle **52** in good yield. In order to install the anticipated differential protecting group pattern, **52** was then reduced and the resulting 1,2-diol was protected as its propylidene acetal to furnish **53**, and the remaining primary alcohol was protected as the benzyl ether. Key intermediate **55** was synthesized after removal of the acetal protecting group followed by cleavage of resulting diol and *in situ* reduction to primary alcohol which was subsequently protected as the *bis*-(trifluoromethyl)benzyl (BTB) ether (**60**). Further conversion of **55** to the aldol substrate **56** was achieved through steps similar to those used in the racemic synthesis (Scheme 1-17).

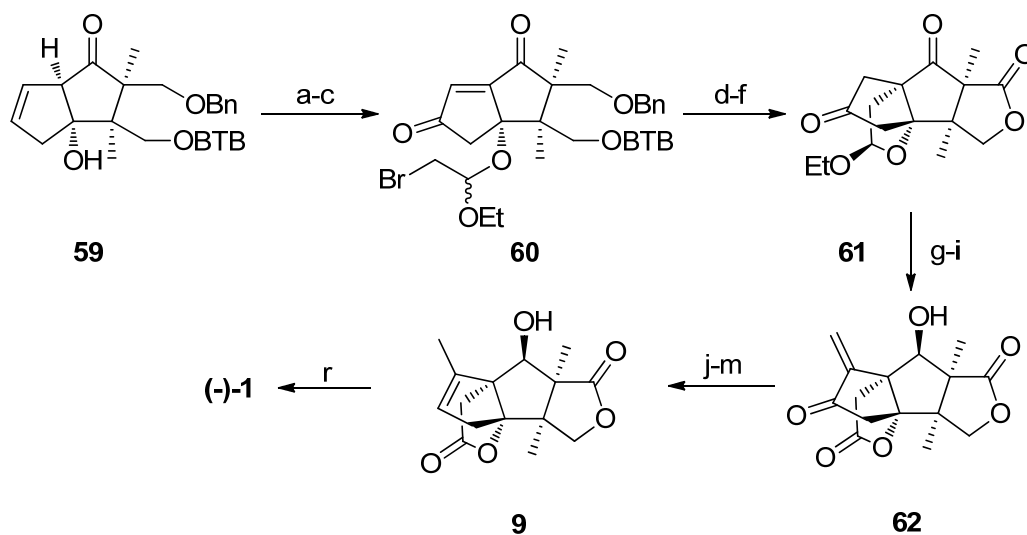
In order to control the regio-selectivity in the pivotal intra-molecular aldol reaction, the intermediate **56** was predominantly deprotonated at C9. The preference over C3 arose from unfavourable long range steric interaction between the base and trifluoromethyl substituents on the pendant BTB protecting group. Transannular aldol reaction of the resulting sodium enolate intermediate **58** proceeded smoothly with a highly stereoselectivity, constructing the desired [3.3.0]octane system **59** as the major enantiomer in 75% yield (Scheme 1-18).



a) NaHMDS, THF, $-100\text{ }^{\circ}\text{C}$, 97% overall, 75% yield for desired enantiomer **59**

Scheme 1-18. Asymmetric transannular aldol reaction

With an established synthetic route to the enantiopure **59**, the completion of the total synthesis closely followed the route developed in Hirama's racemic synthesis (cf. Scheme 1-16). Advanced enantioenriched intermediate **59** was thus converted into Merrilactone A in 15 steps as shown in Scheme 1-19.



a) *m*CPBA, DCM then florisil, DCM, 75%; b) IBX, DMSO, 91%; c) BrCH₂CHBr(OEt), PhNMe₂, DCM, $-78\text{ }^{\circ}\text{C}$ to RT, 92%; d) Bu₃SnH, AIBN, toluene, $85\text{ }^{\circ}\text{C}$, 73%; e) EtOSiMe₃, BF₃·Et₂O, DCM, 72%; f) Me₃SiOTf, NEt₃, DCM, $-20\text{ }^{\circ}\text{C}$; g) Me₂NCH₂⁺I⁻, MeCN; h) *m*CPBA, DCM, 64% over 3 steps; i) *m*CBPA, BF₃·OEt₂, DCM, $40\text{ }^{\circ}\text{C}$, 91%; j) LiBH(^tBu)₃, 2-Tf₂N-5-chloropyridine, THF, $-78\text{ }^{\circ}\text{C}$, 73%; k) Pd(OAc)₂, PPh₃, NBu₃, HCOOH, DMF, $40\text{ }^{\circ}\text{C}$, 91%; l) Na, NH₃, THF/EtOH, $-78\text{ }^{\circ}\text{C}$; m) Ag₂CO₃ on celite, toluene, $130\text{ }^{\circ}\text{C}$, 41 %

over 2 steps; n) DMDO, DCM, 91%; o) TsOH, DCM, 96%

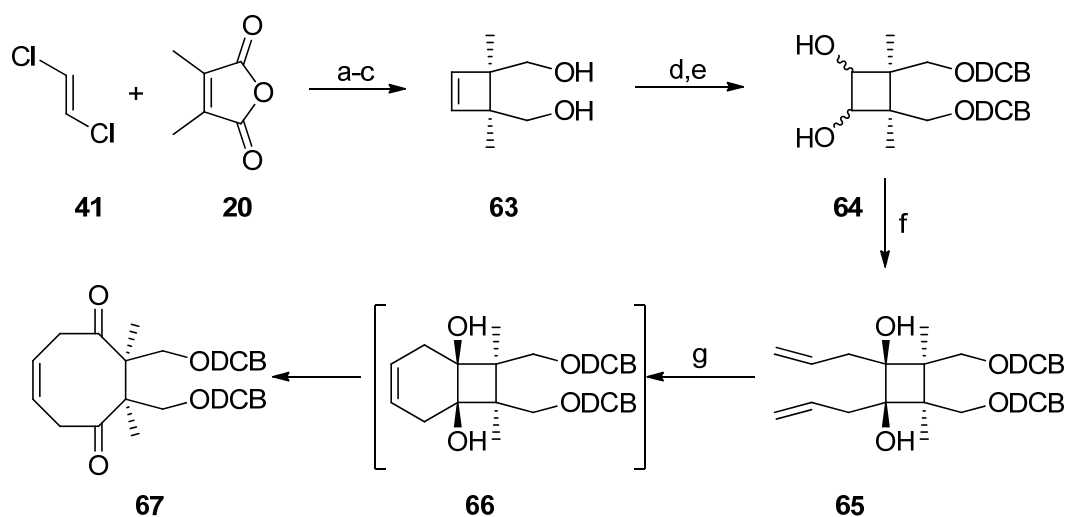
Scheme 1-19. Completion of the asymmetric total synthesis

The second asymmetric route to (-)-Merrilactone A has been achieved by Hirama and co-workers in 31 synthetic steps with an overall 1% yield. The long range steric effect of a novel bulky protecting group was employed in controlling the regio- and stereo-selectivity in their key intramolecular transannular aldol reaction to construct enantiopure *cis*-bicyclo[3.3.0]octane core in Merrilactone A. This methodology demonstrated impressive regio- and stereo-selective transformations, allowing the synthesis of the key intermediate **59** as a single enantiomer.

1.4.2.3 Hirama's total synthesis of *ent*-(+)-Merrilactone A

In 2007 Hirama and co-workers reported a modified version of their asymmetric synthesis providing access to unnatural enantiomer, *ent*-(+)-Merrilactone A^[24]. Compared with their previous methodology, employing differentially protected alcohol moieties to induce long range steric effects, this time they developed a novel desymmetrisation strategy applying a chiral lithium amide base in the key transannular aldol reaction to selectively deprotonate at C9 over C3. In order to avoid the requirement for the synthesis of differential protection upon the pendant alcohols, which was a long and cumbersome route employed in the previous asymmetric total synthesis (cf. Scheme 1-17), the key aldol substrate could be obtained *via* a similar approach to that reported in the racemic total synthesis (cf. Scheme 1-14).

The synthetic route began with the photochemical [2+2] reaction of 1,2-dichloroalkene **41** and 2,3-dimethylmaleic anhydride **20**. Subsequent dechlorination and anhydride reduction afforded diol **63**. Then the two hydroxyl moieties were protected as 2,6-dichlorobenzyl (DCB) ethers, which was found to provide the best selectivity in the key transannular aldol reaction. The dihydroxylation of **63** produced diol **64**, which was further elaborated into the anticipated diastereomer **65** *via* a one pot Swern oxidation with subsequent allylation to the transient 1,2 dione, analogous to the approach employed in the racemic synthesis. Ring closing metathesis and subsequent treatment with Pb(OAc)₄ then provided the key intermediate **67**, (Scheme 1-20).

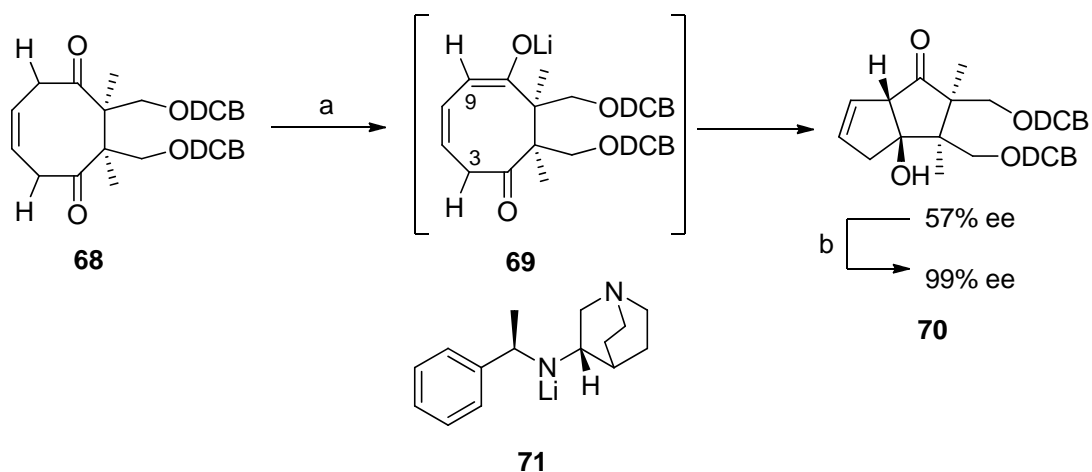


a) benzophenone, acetone, hv; b) Zn, TMSCl, Ac₂O, toluene, 85 °C; c) LiAlH₄, THF, 57% for 3 steps; d) DCBBr, NaH, THF/DMF; e) OsO₄, NMO, tBuOMe/tBuOH/H₂O, 91% over 2 steps; f) (COCl)₂, DMSO, NEt₃, DCM, -78 °C then allylmagnesium bromide, -78 °C, 70aa/70bb ratio 9:1, 80%; g) (PCy₃)₂Cl₂Ru=CHPh, DCM, reflux, then Pb(OAc)₄, 95%. DCCB = 2,6-dichlorobenzyl

Scheme 1-20. Preparation of DCB protected aldol substrate

The group then focused on the development of novel methodology to enable the regio- and enantio-selective transformation of aldol substrate **68**. Screening of a number of chiral lithium amide bases indicated that **71** could provide the desired enantiomer in good regio- and stereoselectivity over the other undesired enantio- and diastereomers. The transient intermediate lithium enolate **69**, which could be obtained *via* selective deprotonation at C9 over C3 dione **68** when treating it with chiral base **71**, underwent transannular aldol reaction in a stereoselective fashion to provide the enantioenriched **70** in 79% yield and 57% ee. The enantiomeric excess of **70** could be increased to 99% after a single recrystallisation step with a yield of 53% (Scheme 1-21).

With the enantiopure key intermediate **70** in hand, the total synthesis of *ent*-(+)-Merrilactone A could be achieved in analogy with the substrate preparation reported in the racemic total synthesis, outlined in Scheme 1-16 and the asymmetric variant described in Scheme 1-19. The conversion of **70** into the unnatural enantiomer of Merrilactone A was thereby completed in 16 steps and the total synthesis was achieved in 23 steps with an overall 1.3% yield.



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

Scheme 1-21. Enantioselective transannular aldol reaction using chiral base

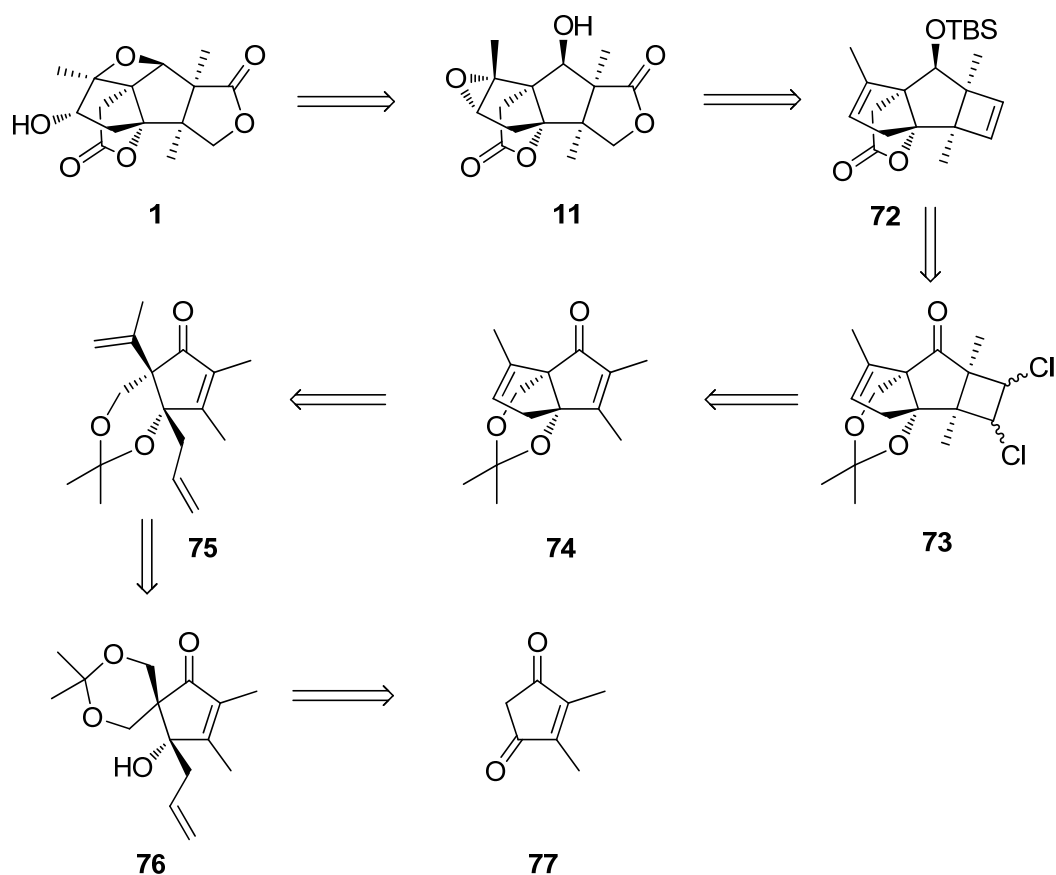
When the synthesis was finished, they also investigated the unnatural enantiomer's biological activity. Surprisingly, biological experiments revealed that the *ent*-(+)-Merrilactone A displayed similar level to stimulate neurite outgrowth as natural merrilactone A. This unexpected result presented an uncommon example of similar levels of biological activity being observed in both enantiomers of a natural product. Further research into the mechanism of this unexpected biological activity was reportedly currently ongoing.

Hirama's asymmetric total synthesis of both natural and unnatural enantiomers of Merrilactone A represented substantial efforts in developing the novel desymmetrisation strategy for the key intramolecular transannular aldol reaction. Enantioselective preparation of key intermediates *via* either selective deprotonation relying on the use of chiral bases, *or* by means of differential protection approach, provided a reliable and elegant approach towards the natural product.

1.4.3 Metha's racemic total synthesis of Merrilactone A

In 2005 Singh and Mehta published a model study on a novel synthesis of the core of Merrilactone A^[13a]. The key steps in the model study subsequently constituted the basis of the total synthesis of Merrilactone A, which was published in the following year^[13b]. As with the previous two total syntheses, the oxetane motif was constructed in the final step *via* the known *homo*-Payne rearrangement. Scheme 1-22 shows the

retrosynthetic approach adopted by Mehta and Singh.

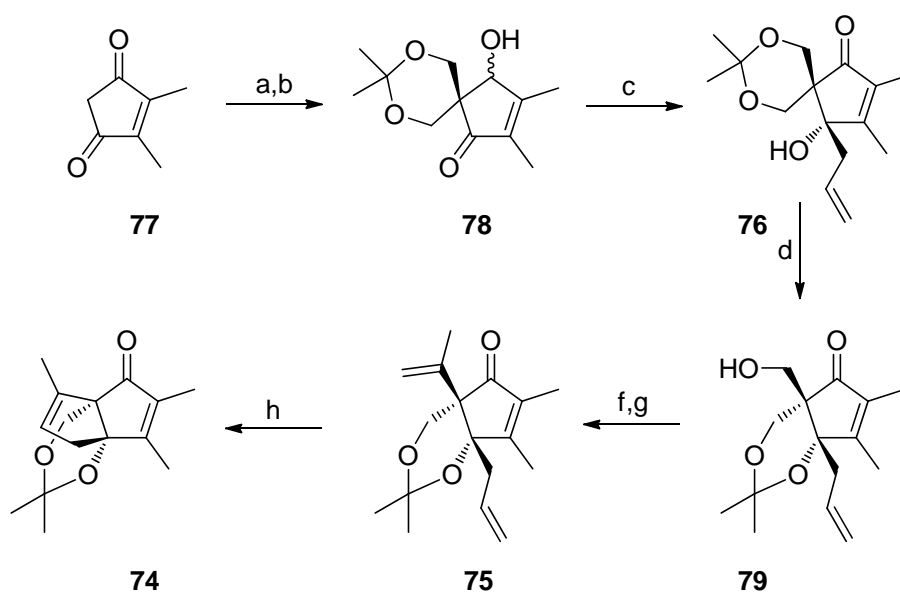


Scheme 1-22. Mehta and co-workers retrosynthesis

Relying on the acid promoted *homo*-Payne rearrangement in the final step of the synthesis of Merrilactone A, epoxide substrate **11** was anticipated to be accessible from **72** via ozonolysis and oxidation. Tetracycle **72** would be obtained from the [2+2] photo-addition product **73** by dehalogenation reaction. Compound **74** would be synthesized in a pivotal ring closing metathesis reaction of diene **75**, which was prepared from **76** through a multi-step sequence of deprotection-protection. Further analysis revealed that **77** is a suitable starting material for the total synthesis.

Double hydroxy-methylation of 1,4-dione **77** followed by acetonide protection and subsequent Luche reduction produced **78** in 77% yield over three steps. Successive allylation and oxidation furnished cyclopentenone **76** in high yield. Exposure of **76** to an acetonide deprotection-protection sequence afforded **79** thus setting the pivotal stage for the subsequent sequential annulation of carbocycle C and the γ -lactone ring D. The deprotection of **76** and reprotection under equilibrating conditions afforded

the desired **79** and **76** as a 1:1 mixture, with the latter isomer being readily recycled. Oxidation of the primary alcohol in **79** to the aldehyde and a subsequent multi-step sequence of methylation, oxidation and methylenation under Wittig conditions, afforded **75** in 36% yield over four steps. The key ring closing metathesis reaction on exposure to Grubbs' first generation catalyst was now applied to the *cis*-orientated allyl and propenyl side chains, furnishing bicycle core **74** in a good yield, and set the stage for the further [2+2] photo-addition reaction towards merrilactone A (Scheme 1-23).^[25]

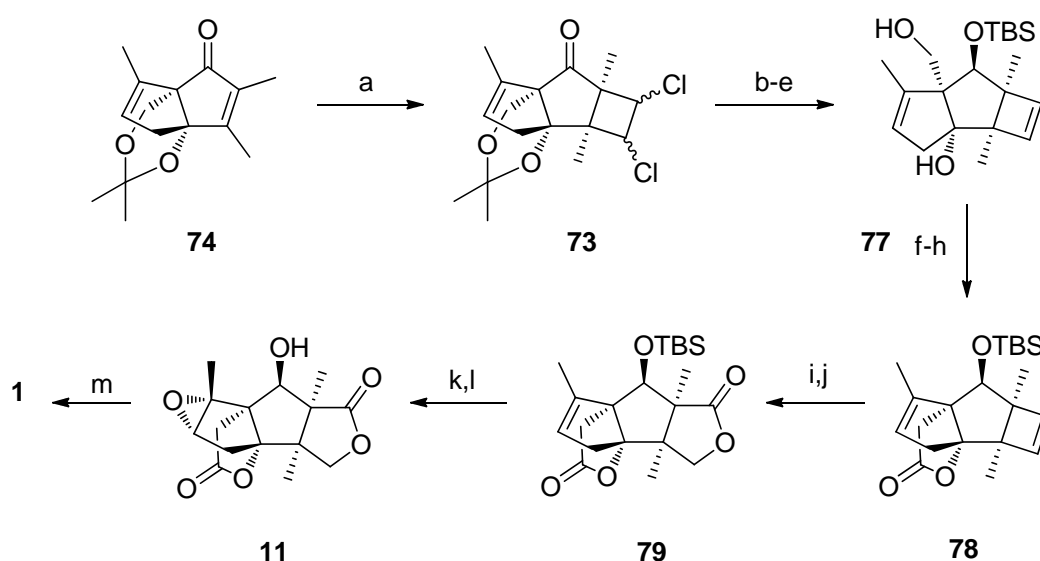


a) DBU, 40% HCHO, THF, 0 °C, 95%; b) acetone, MS, Amberlyst-15 then NaBH₄, CeCl₃, 0 °C, 83%; c) CeCl₃, allylmagnesium chloride, -78 °C, then MnO₂, DCM, 81%; d) 2M HCl, THF/H₂O, 90%; e) acetone, MS, amberlyst-15, 94%; f) PDC, DCM, then MeLi, Et₂O, 62%; g) PDC, DCM then Ph₃PCH₃Br, *t*BuOK, Et₂O, 55%; h) Grubbs' catalyst I, DCM, reflux, 76%

Scheme 1-23. Synthesis of RCM substrate and metathesis reaction

The photo [2+2]-cycloaddition reaction of intermediate **74** and 1,2-dichloroethylene proceeded in 65% yield, however it only gave a moderate degree of facial selectivity in favour of the desired β -face isomer **76** over the undesired diastereomer. After separation of the diastereomers, a number of straightforward transformations were applied, including reductive dehalogenation, DIBAL-H reduction, protection of the resulting alcohol with a TBS group, and subsequent acetonide deprotection to furnish the diol **77** in 54% yield over four steps. Conversion of **77** to **78** via a multi-step sequence of TPAP oxidation, Wittig methoxymethylenation, and consecutive

acid-mediated hydrolysis with simultaneous intramolecular hemiacetal formation and subsequent oxidation afforded **78** in good yield. Conversion of the cyclobutene ring of **75** into the right-hand γ -lactone ring was promoted by ozonolysis and successive *in situ* sodium borohydride reduction followed by oxidation to furnish the *bis*-lactone **79**. Elaboration of **79** into Merrilactone A was carried out by means of the well known Payne-type rearrangement strategy^[5] *via* deprotection of TBS, epoxidation and acid induced ring opening to finish the total synthesis of merrilactone A (see Scheme 1-24).



a) trans-dichloroethylene, hv, α/β face ratio 1:2. 65%; b) sodium naphthalenide, $-60\text{ }^\circ\text{C}$, 70%; c) DIBALH, $-78\text{ }^\circ\text{C}$, 95%; d) TBSOTf, NEt_3 , DCM, 86%; e) 2M HCl, THF/ H_2O , 95%; f) TPAP, DCM then $\text{Ph}_3\text{PCH}_3\text{OCH}_3$, tBuOK, THF, 54%; g) HClO_4 , DCM/THF; h) PCC, DCM, 62% for 2 steps; i) O_3 , MeOH, $-78\text{ }^\circ\text{C}$ then NaBH_4 , MeOH, $-78\text{ }^\circ\text{C}$, 45%; j) PCC, DCM, 80%; k) TBAF, AcOH, THF, 85%; l) DMDO, 95%; m) TsOH, DCM, 80%.

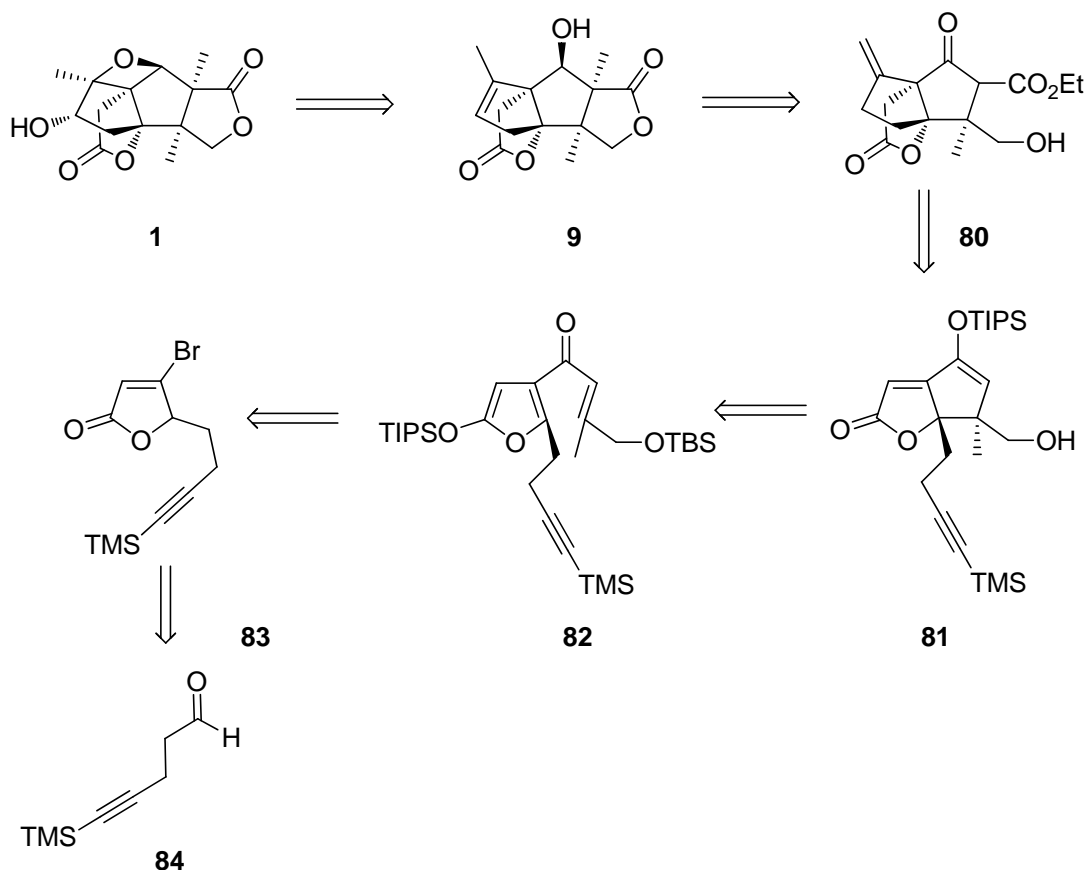
Scheme 1-24. Elaboration of key intermediate into Merrilactone A

In summary, Mehta and Singh have developed a route to Merrilactone A which was achieved in a 27 step sequence with an overall 0.4% yield. A number of selectivity issues may be noted such as the lack of stereoselectivity in the [2+2] photocycloaddition.

1.4.4 Frontier's racemic total synthesis of Merrilactone A

In 2007, Frontier's group published their total synthesis of (\pm)-Merrilactone A in communication form,^[15] and in the following year, a full account of their research

was reported describing their completion of the synthesis.^[16] Based on the well established methodology to install the oxetane in the final step, Frontier's group developed an impressive synthetic route involving a metal-catalyzed Nazarov cyclization reaction constructing the cyclopentane core of Merrilactone A.

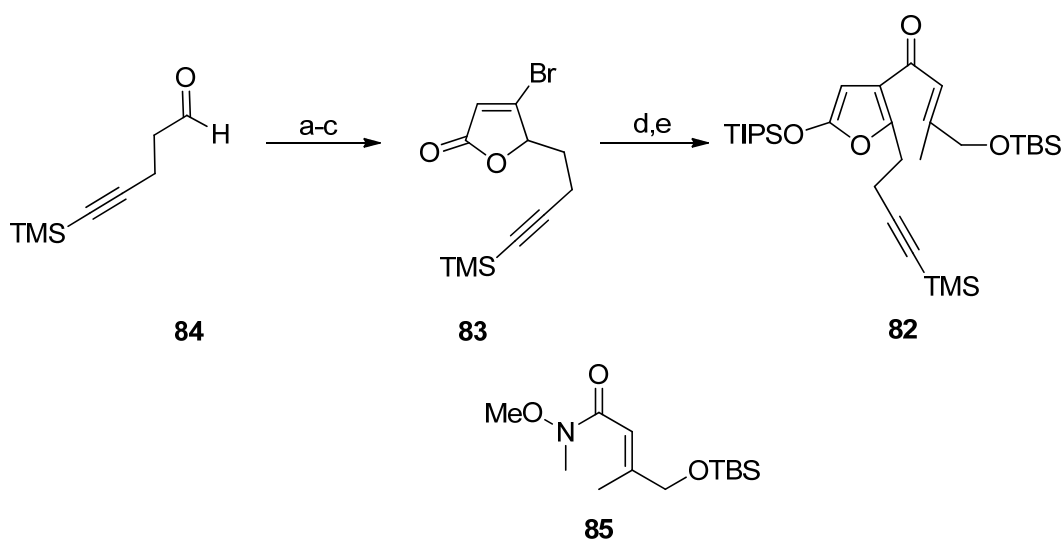


Scheme 1-25. Frontier's retrosynthetic analysis

Outline in Scheme 1-25 is the retrosynthetic approach adopted by Frontier and co-workers. Conversion of the advanced intermediate **9** into merrilactone A was to be achieved *via* the known epoxidation and *homo*-Payne rearrangement approach. The construction of the γ -lactone ring C would be achieved from alcohol **80** at a late stage. Subsequently, tricycle **80** would be accessible from **81** *via* a radical cyclisation reaction. Bicycle **81** would be prepared from compound **82** *via* a key Nazarov cyclisation reaction. Further analysis indicated that **82** was readily synthesized from **83** through a number of straightforward transformations. In turn, **84** was a suitable starting material for the total synthesis.

Outlined in Scheme 1-26 is the preparation towards the substrate for the pivotal

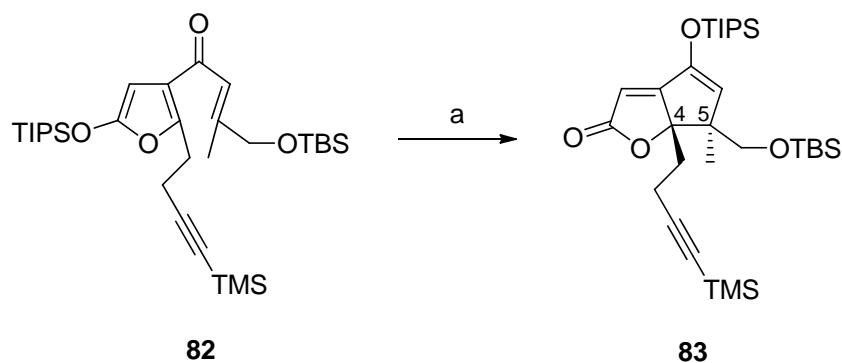
Nazarov cyclisation reaction. The synthesis began with the organometallic 1,2-addition reaction of lithiated ethyl propiolate to known aldehyde **84**. The lactonisation of resulting product proceeded smoothly followed by tin-bromide exchange producing the vinyl bromide **83** in excellent yield. Treatment of **83** with triethylamine and triisopropylsilyl triflate furnished silyloxyfuran in quantitative yield. The alkenyllithium derived from the silyloxyfuran was then added to a solution of Weinreb amide **85** to furnish the advanced intermediate **82**, the substrate for the next key Nazarov cyclization reaction.



a) ethyl propiolate, nBuLi, THF, -78 °C, 88%; b) Bu₃Sn(Bu)(CN)CuLi₂, THF/MeOH, -78 °C, 90%; c) Br₂, DCM, 93%; d) NEt₃, triisopropylsilyl triflate, DCM, -78 °C to 0 °C, quant.; e) tBuLi, Et₂O, then XX, 82%.

Scheme 1-26. Synthesis of key Nazarov substrate

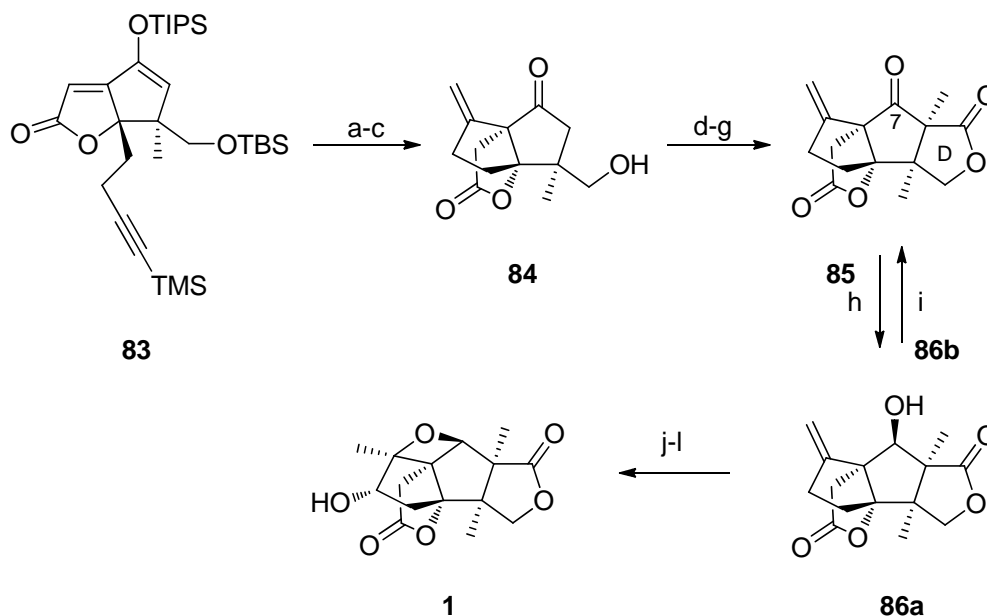
After careful screening of numerous model compounds closely related to **82** and adjusting subtly the structure of catalysts employed in the Nazarov cyclisation, the dicationic iridium catalyst - Ir(CO)(Me)(dppe)(DIB)²⁺ (BArF)₂⁻ emerged as the optimal catalyst for this system. Treatment of silyloxyfuran **82** with a dicationic iridium catalyst afforded the anticipated bicycle **83** as a single diastereomer - due to the conrotatory nature of the 4π electrocyclic pathway of the Nazarov cyclisation C₄ and C₅ are constructed in a stereospecific manner (Scheme 1-27).



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

Scheme 1-27. Nazarov cyclisation of silyloxyfuran

Following the successful Nazarov cyclisation, removal of the trimethylsilyl group of the resulting bicycle **83** set the stage for the radical cyclisation reaction. The desilylation product was exposed to tributyl tinhydride, followed by subsequent global silyl deprotection induced by TBAF to furnish alcohol **84** in excellent yield. The right-hand γ -lactone ring D was then constructed through transformation of the alcohol into the carbonate followed by an intramolecular nucleophilic lactonisation. Subsequently, methenylation, reduction of ketone to secondary alcohol and consecutive isomerisation of the *exo*-alkene provided the advanced common intermediate **86a**, which was previously transformed into merrilactone A by Danishefsky and co-workers in their racemic total synthesis.



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) NaBH₄, MeOH, ration 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.

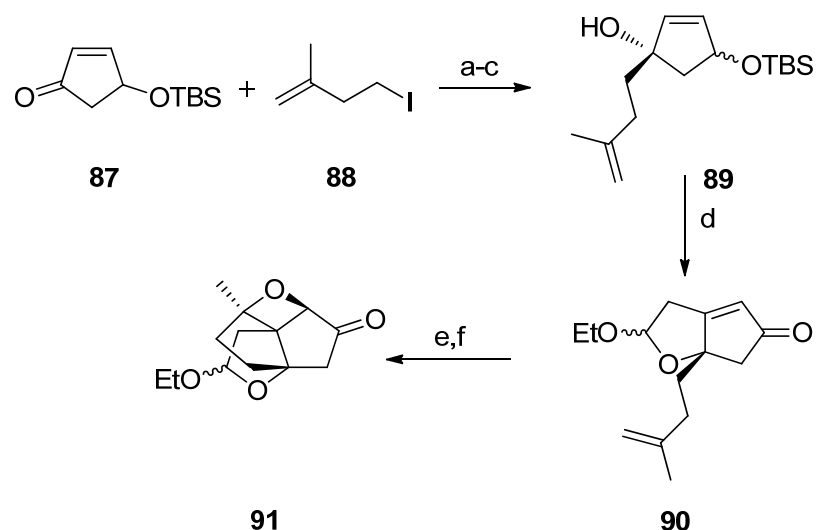
Scheme 1-28. Completion of the total synthesis

The stereoselective reduction at C7 proved to be somewhat problematic as it only gave moderate facial selectivity for desired **86a** over undesired product **86b** in a 1.2:1 ratio. The two diastereoisomers could be separated by column chromatography and the undesired isomer could be recycling by re-oxidation to ketone thus making the overall synthesis more efficient. The final established two steps were then carried out in analogy with all previous total syntheses; stereoselective epoxidation and *homo*-Payne rearrangement to furnish racemic merrilactone A (Scheme 1-28).

The efficient and elegant total synthesis of Merrilactone A involving a dicationic iridium catalyst promoting pivotal Nazarov cyclisation disclosed by Frontier and co-workers in only 17 steps presented a highly impressive overall yield of 10% and the research towards the asymmetric total synthesis with chiral catalyst is reportedly ongoing in the same group.

1.4.5 Greaney's model study

In 2005 Greaney and co-workers reported a conceptually different approach towards the synthesis of the core of Merrilactone A based on an intramolecular [2+2] Paternò-Büchi photoaddition strategy^[26]. In all previously reported total syntheses of Merrilactone A the central oxetane motif was constructed relying on a *homo*-Payne type rearrangement as the final step, However Greaney and co-workers employed an intramolecular [2+2] Paternò-Büchi photoaddition to create this key oxa-[3.3.3] structural motif **91** in a very high 93% yield. In addition, this work demonstrated a novel methodology to install the γ -lactone A ring *via* a tandem oxy-carbopalladation of enone approach (Scheme 1-29).



a) *t*BuLi, Et₂O, -78 °C, 89%; b) TBAF, THF; c) PDC, DCM, 62% over 2 steps; d) Pd(OAc)₂, CH₂=CHOEt, 65%; e) OsO₄, NaIO₄, THF/H₂O, 47%; f) *hν*, MeCN 93%.

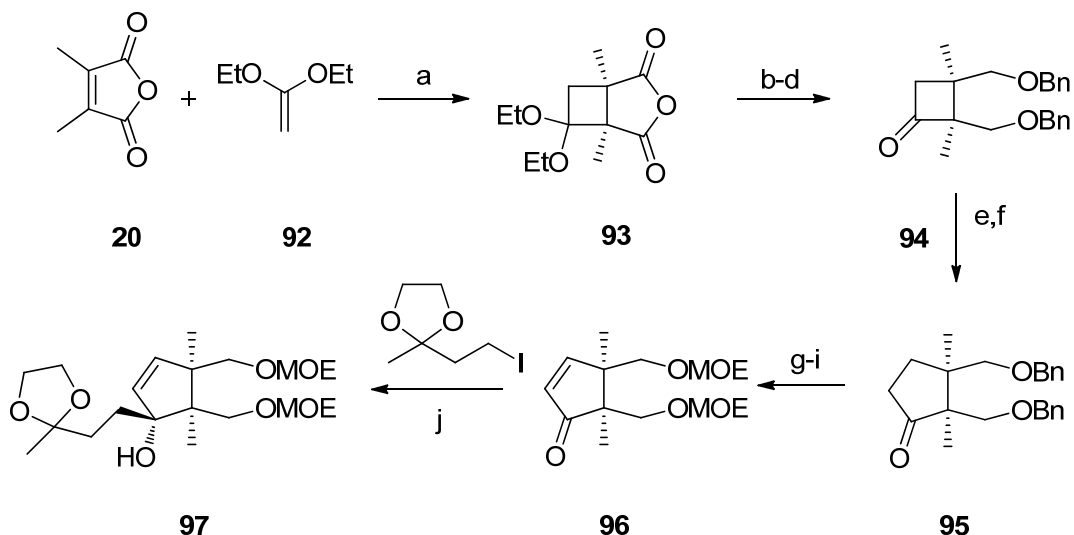
Scheme 1-29. Paternò-Büchi photoaddition in the synthesis of the core of Merrilactone A

1.4.5.1 Unpublished work within Greaney's group

The development of the Paterno-Buchi approach to Merrilactone A in the Greaney group proved ultimately unsuccessful^[27], but did lay the groundwork for a successful synthesis *via* alternative chemistry (*vide infra*). Our initial efforts at extending the Paterno-Buchi route focused on the installation of the two key *cis*-methyl quaternary centres using the [2+2] photocycloaddition route shown in Scheme 1-30. The two quaternary centres are set *via* photocycloaddition reaction between **20** and **92** in the very first step in the synthesis (Scheme 9-30).

The cyclobutane **93** is then taken through several standard transformations to afford **94**, where a key Tiffeneau-Demjanov ring expansion reaction had been employed to produce the cyclopentenone **95**. Critically, this reaction was found to be highly regioselective with the least-substituted carbon centre migrating. Exchange of benzyl for ethoxymethyl protecting groups was then necessary because benzyl groups were found to quench subsequent photocycloaddition reactions^[27]. Stereoselective 1, 2-addition of alkyllithium to cyclopentenone **96** proved to be very successful, proceeding in good selectivity (6 : 1) and excellent yield. Attempts at further manipulation of **95**, however, were unsuccessful due to the facile elimination of the

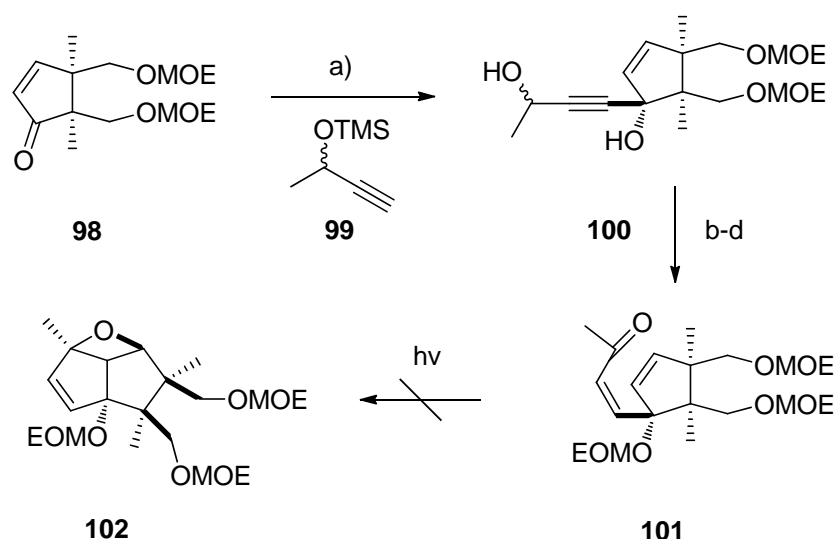
tertiary alcohol. Both the stereoselectivity of 1,2-addition to ketones such as **96**, and the instability of tertiary allylic alcohols such as **97**, proved to be major issues in the synthesis, and shaped all subsequent attempts at a stereocontrolled assembly of the central cyclopentane B ring.



a) $h\nu$, MeCN, acetone, 98%; b) LiAlH_4 , Et_2O ; c) NaH, BnBr, THF; d) H_2SO_4 , H_2O , MeCN, 71% over 3 steps; e) $\text{N}_2\text{CHCO}_2\text{Et}$, $\text{BF}_3 \cdot \text{OEt}_2$, f) $\text{MgCl}_2 \cdot 6\text{H}_2\text{O}$, DMSO, 54% over 2 steps; g) H_2 , Pd/C; h) EMOCl, NaH, THF; i) PhSeBr, LDA, then H_2O_2 , H_2O , DCM, 40% over 3 steps; j) $t\text{BuLi}$, Et_2O , -78°C .

Scheme 1-30. Paternò-Büchi photoaddition in the synthesis of Merrilactone A

In the Paternò-Büchi regime, the addition of the propargyllithium derived from **9** led to propargyl alcohol **100** that had no elimination mechanism available, representing a more tractable intermediate. Oxidation and Lindlar hydrogenation then afforded the cis-enone, a highly pre-organised substrate **101** for Paternò-Büchi photocycloaddition (Scheme 1-31). Unfortunately, all attempts at [2+2] cycloaddition failed. It appeared that the change of functional group in substrate **101** relative to the simpler model **90** (Scheme 1-29; enone in sidechain, alkene in ring ν ketone in side chain and enone in ring) was too drastic and the oxetane could not be constructed.



a) tBuLi, Et₂O, then HCl work up; b) PDC, DCM; c) Lindlar, H₂; d) EOMCl, NEt₃; e) hv

Scheme 1-31. Paternò-Büchi photoaddition in the synthesis of Merrilactone A

The aim of this PhD project is build on the foundations in previous years to finish the total synthesis of merrilactone A. Work will initially focus on the development of the methodology appropriate for 1) In corporation of C10 and C11 *via* Pd-catalyzed decarboxylation- dehydrogenation reaction, 2) construction of the bicyclic BC core *via* titanium(III) mediated radical epoxide opening and cyclization strategy. Finally regiodivergent synthesis of both anislactones and merrilactone A will be achieved by orthogonal lactonization sequences.

1.5 References

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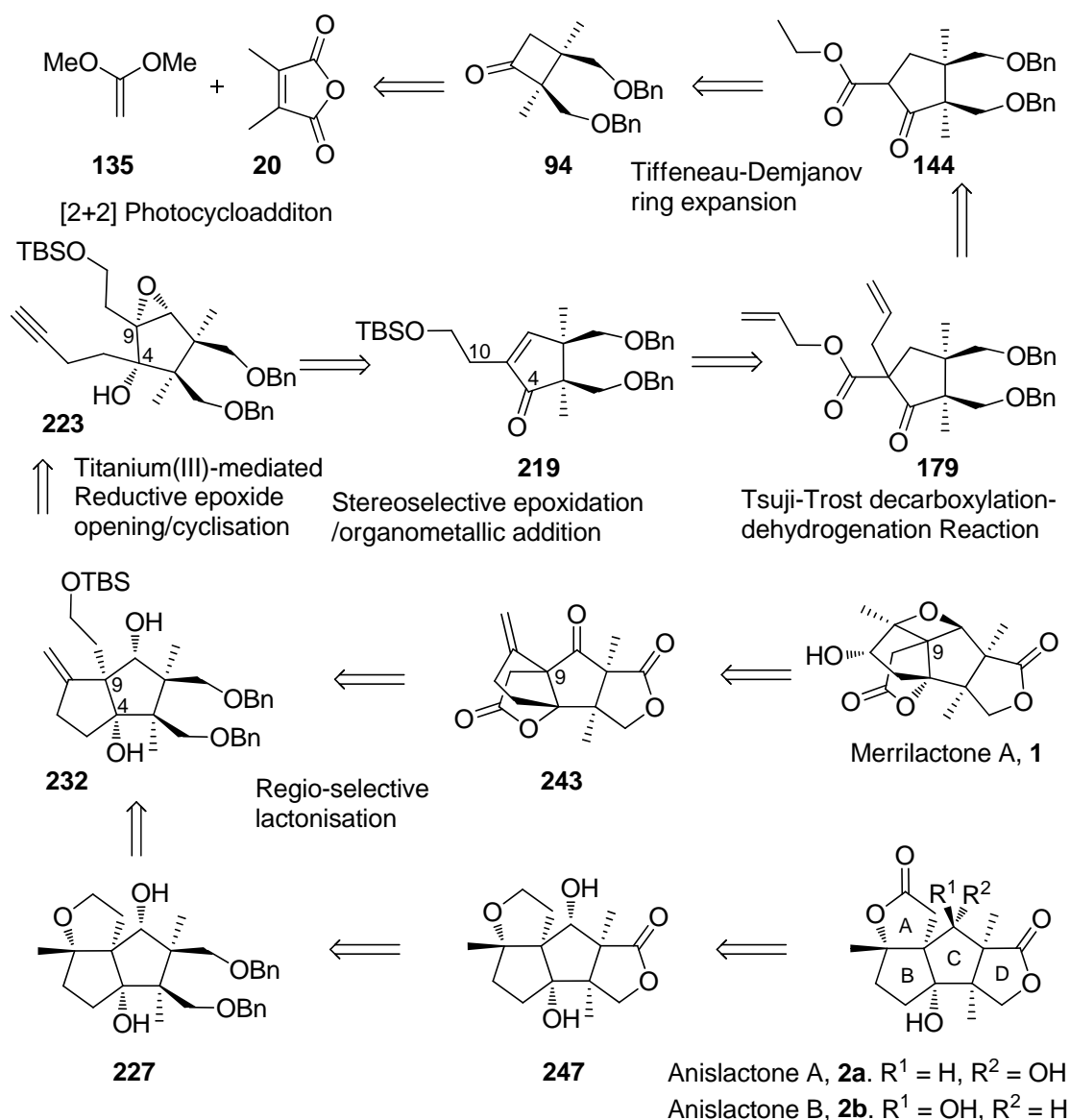
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2 Total synthesis of (\pm)-Merrilactone A

Merrilactone A's intriguing biological activity combined with its unique and challenging structure has made it a highly attractive target for total synthesis. Even though several fantastic and concise synthetic routes have been published in the leading journals^[1-9], its structure still challenges chemists to solve problems of C-C bond formation in stereochemically complex architectures.

2.1 Retrosynthesis analysis

The general features of our synthesis of Merrilactone A are based on the retrosynthetic analysis outlined in Scheme 2-1. We hoped to develop a synthetic route that could access both Merrilactone A and the related Anislactone structure. The core oxetane ring in Merrilactone A is generated from **243** via several well established procedures: the biomimetic *homo*-Payne rearrangement, selective epoxidation and isomerisation of the *exo*-alkene. Both γ -lactone rings A and D in (**1**) are disconnected by lactonization from **232**. The bicyclic BC core in **232** containing a highly congested C9 quaternary stereocentre would be installed *via* a pivotal titanium(III)-mediated reductive ring opening of epoxide and radical cyclization onto the pendant alkyne in **223**. This robust and efficient methodology will be the focus of a simple model study (*vide infra*). The tertiary alcohol at C4 would be constructed *via* a stereoselective 1,2-addition of an organometallic to the ketone in **219**. The alkyl chain in cyclopentenone **219** would be incorporated *via* a Pd-catalyzed decarboxylation-dehydrogenation reaction from cyclopentenone **179**, which would be prepared by transesterification and alkylation from **144**. The five-membered C ring at the core of natural product would be accessible by means of a key Tiffeneau-Demjanov ring expansion reaction from cyclobutane **94**. The *cis*-methyl quaternary centres in cyclobutane would be installed using a [2+2] photocycloaddition reaction at the first step in the synthesis route.

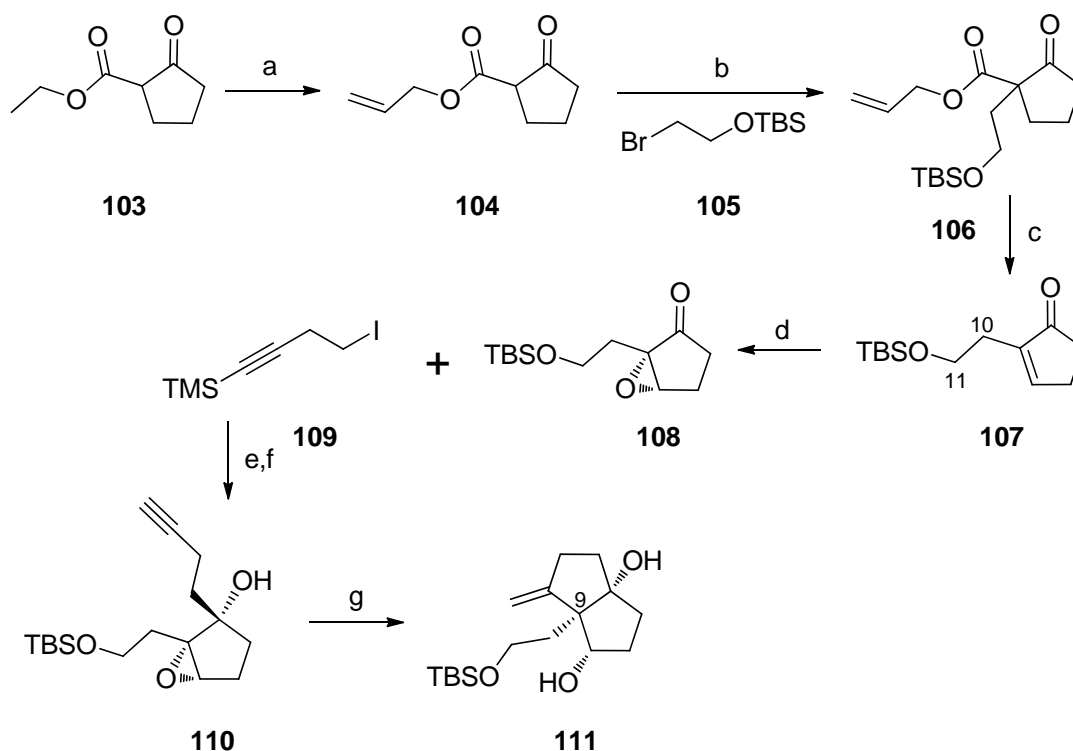


Scheme 2-1. Retrosynthesis for Merrilactone A and Anislactones

2.2 Synthesis of simple model system

In order to investigate the feasibility of the envisaged synthetic route, a simple model system was designed and carried out in which several key transformations were included (Scheme 2-2). Key amongst them was a Tsuji-Trost approach to the incorporation of C10 and C11, and the central reductive epoxide cyclisation reaction to install C9. The model system synthesis started with commercially available ethyl 2-oxocyclopentanecarboxylate **103**. After several attempts, it was discovered that by simply heating the substrate with allyl alcohol without any catalyst^[10-12], allylic

β -keto ester **104** could be readily prepared from ethyl 2-oxocyclopentanecarboxylate **103** in very high yield on 20g scale. The toluene and excess allyl alcohol were evaporated under reduced pressure and the crude allyl 2-oxocyclopentanecarboxylate **104** was subjected to the next step without further purification. An alkylation of the β -ketoester is required to install C10 and C11 of the natural product. The alkylation reaction proceeded slowly with TBS-protected 2-bromoethanol in refluxing acetone for 10 h producing **106** in 50% yield after two steps. Then it was ready for the next step: Tsuji-Trost reaction^[13-15]. Cyclopentanone **106** was treated with Pd(OAc)₂ and PPh₃ (1:1 ratio) in acetonitrile and the reaction mixture was heated to 70 °C under argon. TLC analysis indicated that reaction was normally completed in 1-2 hours, then a filtration through a short silica column to remove palladium furnished clean decarboxylation- dehydrogenation product **107** in 85-95% yield.



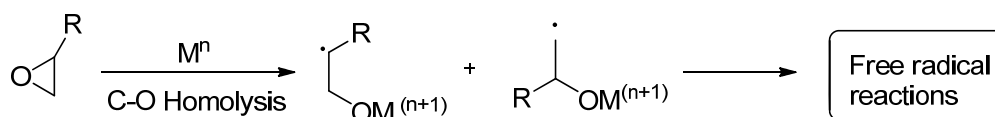
a) allyl alcohol, toluene, reflux; b) K₂CO₃, acetone, reflux, 46 % over 2 steps; c) Pd(OAc)₂, PPh₃, MeCN, reflux, 77 % yield; d) H₂O₂, NaOH, MeOH, 88 % yield; e) *t*-Buli, Et₂O, -78 °C; f) K₂CO₃, MeOH, 40 % over 2 steps, g) TiCp₂Cl₂, Zn, THF, 88 % yield.

Scheme 2-2. Model system for the constructions of AB ring in merrilactone A

Exposure of cyclopentanone **107** to H₂O₂ in MeOH gave the desired epoxide in good yield. 1,2-Addition was then carried out at -78 °C in diethyl ether where the

cyclopentenone **108** was treated with the organolithium compound generated *in situ* from (4-iodobut-1-ynyl)-trimethylsilane **109** and *t*-butyllithium^[16]. This afforded the tertiary alcohol in 30 min. Removal of TMS group using methanolic KOH^[17-19] afforded the epoxide product **110** in high yield, the substrate for the key radical cyclisation.

Background and mechanism of Ti(III) induced radical reaction. The utility of epoxide building blocks has received extensive attention, since they are highly versatile intermediates in the synthesis of natural products and biologically active compounds. With the rapid development of radical chemistry, the selective one-electron reduction of an epoxide to a radical intermediate represents a very useful synthetic tool, in which the generated radical intermediate could be trapped in subsequent reactions (Scheme 2-3).^[20-22]

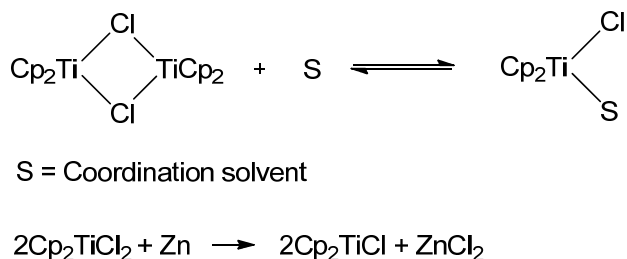


Scheme 2-3. One electron reduction of epoxide

Compared to reactions involving polar intermediates, another advantage of radical chemistry is the functional group tolerance. Sensitive functional groups such as esters, acetals, nitriles and ketone are tolerant to radical conditions while allylic ethers and aldehydes lead to reduced yields. Additionally, it should be expected that the product distribution will be different from those of classical reactions of epoxides. The regio- and stereochemistry of the epoxide opening *via* C-O homolysis is controlled by the relative stability of the intermediate radicals, which is affected by both substitution patterns (for example, tertiary > secondary > primary) and stereoelectronic factors.

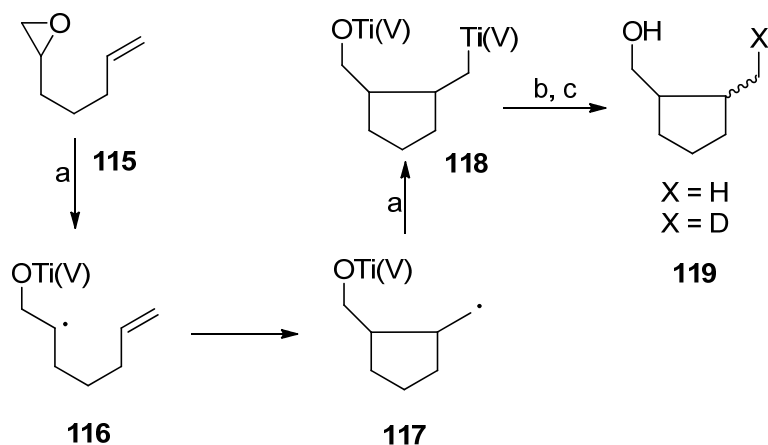
In 1972 Green and co-workers first reported bis(cyclopentadienyl) titanium(III) chloride,^[23] which in the solid state existed as a chloride-bridged dimer. In the presence of donor solvent such as THF, however, the dimer dissociates to produce the monomer species. The titanium(III) reagent was found to be able to promote the homolytic cleavage of epoxides with remarkable selectivity under room temperature.^[18-21] Isolation and purification of bis-(cyclopentadienyl)titanium(III)

chloride species was not necessary as the active reagent could be generated *in situ* by means of stirring a solution of the inexpensive, commercially available titanocene dichloride (red in THF) with activated powdered zinc metal (solution becomes green) (Scheme 2-4).



Scheme 2-4. Generation of titanium(III) species

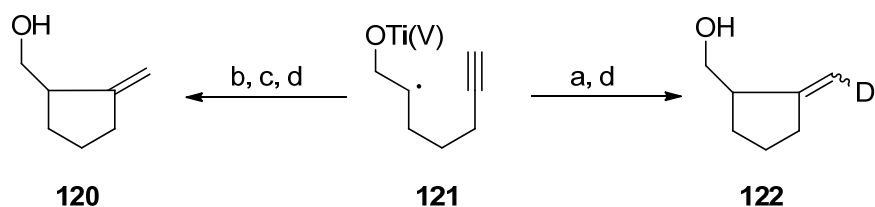
Titanium(III)-Mediated Epoxyolefin Cyclization. Titanium (III)-promoted radical carbon-carbon bond forming reactions have been investigated intensively since the 5-hexenyl radical cyclization is known to be a rapid and efficient process.^[24,25]



a) $\text{Cp}_2\text{TiCl}/\text{THF}/\text{rt}$. b) D_3O^+ . c) workup, H_3O^+

Scheme 2-5. Mechanism for the Ti(III) induced radical cyclization

In the case of intramolecular radical cyclization, 2 molar equivalents of Cp_2TiCl in THF was added to a solution of 6,7-epoxy-1-heptene **115** in THF, the green color of the titanium(III) species being rapidly discharged to a red color when subjected to the epoxide. Quenching the mixture with D_2SO_4 in D_2O afforded 2-methylcyclopentanemethanol **119** which was >85% monodeuterated at the methyl group in around 70% yield. This result suggested that hexenyl radical cyclization does indeed occur as proposed in Scheme 2-5.

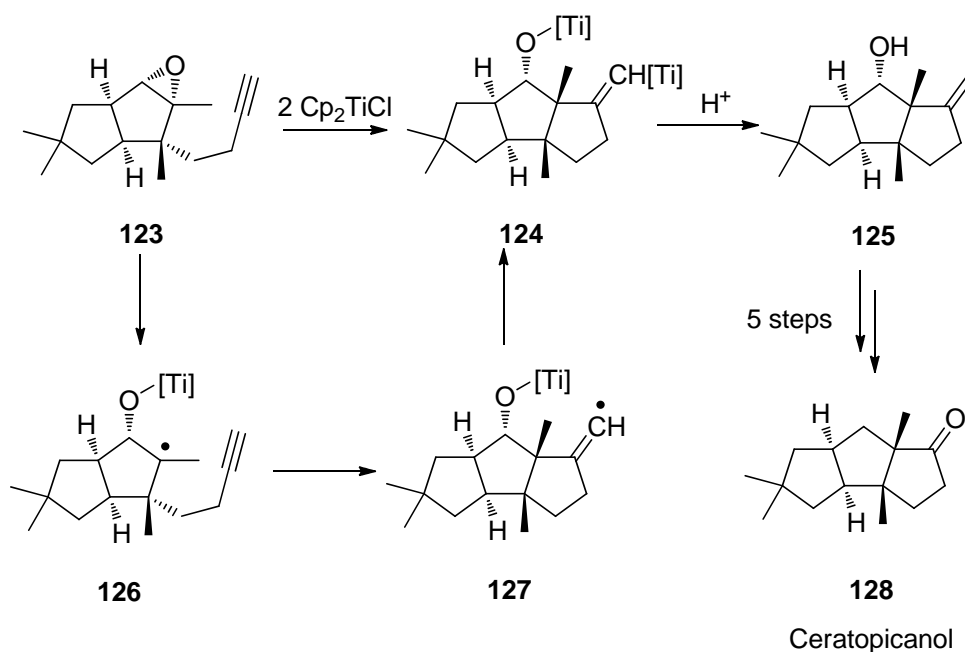


a) THF-d₈, RT; b) THF, RT; c) D₂O/D⁺; d) Workup (H₂O/H⁺)

Scheme 2-6. Mechanism for the Ti(III) induced radical cyclization

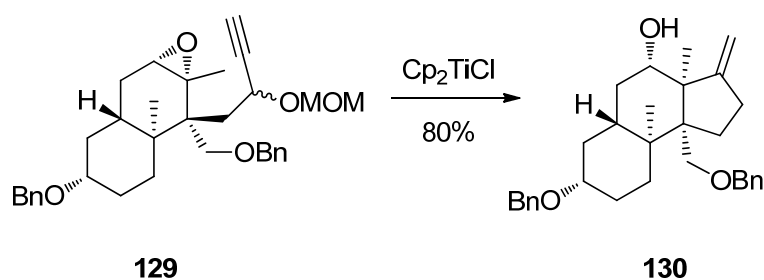
In contrast to these results, cyclization of 6,7-epoxy-1-heptyne **120** followed by deuterolysis afforded 2-methylenecyclopentanemethanol **120** containing no deuterium as the methylene group (Scheme 2-6). The initially formed vinyl radical would abstract a hydrogen atom from the THF solvent immediately due to its high reactivity. Using THF-d₈ as the solvent for the reaction, only one deuterated olefin **122** was obtained even after work up with H₂O. This further confirmed the free radical nature of the intermediates involved in these transformations.

Radical cyclization in natural products synthesis. Clive and co-workers applied this methodology in their total synthesis of (±)-ceratopicanol **128** (Scheme 2-7)^[26,27]. Exposure of the tricyclic epoxide **123** to Cp₂TiCl solution in THF led to regioselective, radical epoxide opening, affording the more substituted carbon radical **126**. Subsequent 5-exo-dig cyclisation of the radical **126** with the tethered terminal alkyne constructed a new carbon-carbon bond, resulting in intermediate radical **127**. Radical **127** was then quenched with a second equivalent of the titanocene reagent affording **124**. Finally acidic workup furnished the desired product **125** in 82% yield. A further five steps converted the product of the radical reaction **125** into ceratopicanol **128**.



Scheme 2-7. Radical cyclization in the synthesis of Ceratopicanol

Toyota and co-workers also published another example employing the radical epoxide opening methodology in cyclisations with alkynes in the study towards the synthesis of andrastins A–D (Scheme 2-8)^[28,29]. In this work, a highly stereoselective sequence of radical epoxide opening of the tricyclic epoxide **129** was followed by subsequent 5-*exo*-dig cyclization, affording the densely functionalised tricycle **130** as the sole product in 80% yield. Interestingly, under the reaction conditions the methoxymethyl ether group was removed.

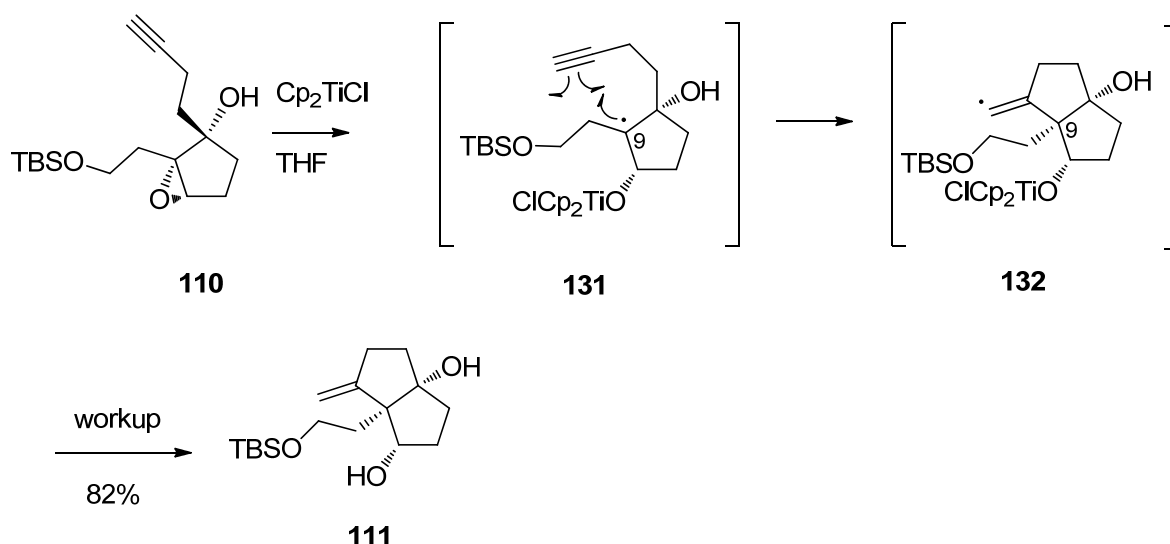


Scheme 2-8. Toyota and Roy's examples of radical epoxide opening methodology

As the examples of the application of titanium(III) mediated radical reaction in natural products synthesis demonstrate, there is some literature precedent for the formation of 5-membered carbocycles containing *exo*-alkenes. However, for the reaction related to the compounds similar to our substrates **110**, bearing a tertiary

alcohol adjacent to the carbon radical to be formed, no literature precedent could be found.

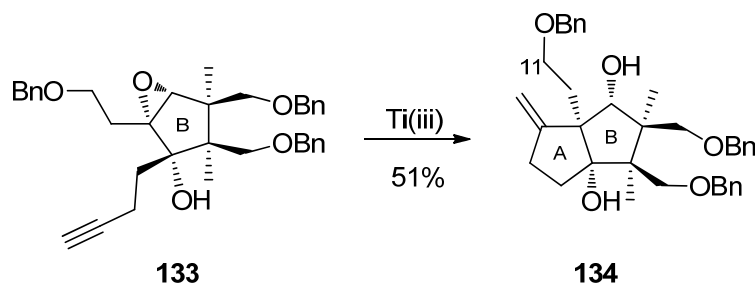
Radical cyclization in model system. At this stage we attempted the titanium(III) mediated reductive ring opening of epoxide and radical cyclization reaction^[20] on substrate **110**. It was expected that the more stable tertiary radical would be generated at C9, that would then undergo cyclisation to form the 5, 5 bicyclic system. The titanium(III) reagent was prepared by stirring a red THF solution of commercially available titanocene dichloride with activated powdered zinc metal. After 30 min, the red solution turned to lime green indicating formation of titanium(III). The clear green solution of titanium(III) was then transferred via cannula to the THF solution of compound **110**. In principle, the stability of the carbon radical generated in the reaction will be determined by the substitution pattern, for example, tertiary > secondary > primary. As expected, subjecting **110** to the solution of titanium(III) in THF led to selective scission of the C-O bond to form the more stable tertiary radical (Scheme 2-9). This was followed by 5-*exo*-dig cyclization onto the pendant alkyne furnishing bicyclic product **111** in 82% yield. The initially formed vinyl radical **132** abstracted a hydrogen atom from the THF solvent immediately.



Scheme 2-9. Proposed mechanism for the Ti(III) induced radical cyclization

Following this successful model radical cyclization reaction, the methodology was applied to the advanced intermediate **133** by co-worker Karsten Meyer (see Meyer, K.

PhD Thesis, University of Edinburgh, 2008). The reaction proceeded smoothly and the desired cyclisation product **134** was achieved in 51% yield. However further elaboration of **134** into the target natural product was unsuccessful as the OBn protection group on C11 was found to be difficult to remove under all conditions attempted.



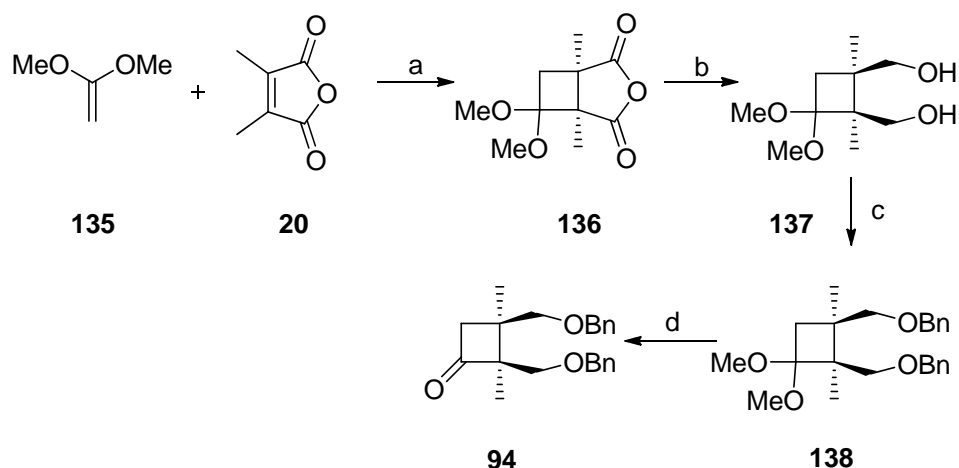
Scheme 2-10.

Nevertheless, the successful radical cyclization reaction constituted an important milestone in our route for the total synthesis of merrilactone A. Once this methodology had been effectively demonstrated we decided to prepare the key intermediate cyclobutane **94** in order to carry out the real total synthesis towards Merrilactone A (Scheme 2-11).

2.3 Synthesis of cyclopentanone

2.3.1 Photochemical [2+2] route to cyclobutanone

The commercially available compounds 2,3-dimethylmaleic anhydride **20** and dimethyl ketene acetal **135** were envisaged as the starting materials to undertake the synthesis of the sub-target cyclobutane through the strategy depicted in Scheme 2-11. Our plan involved four main transformations: (i) construction of cyclobutane **136** by a [2+2] photocycloaddition^[30] of **20** and **135**, (ii) reduction of anhydride **136** to diol **137**, (iii) subsequent protection of diols as their benzyl ethers **138**, (iv) deprotection of acetal by acid-catalysed hydrolysis furnishing the key intermediate cyclobutane **94**.



a) hv, MeCN, acetone, benzophenone, 94%; b) LiAlH₄, Et₂O; c) BnBr, NaH, Bu₄NI, THF; d) H₂SO₄, H₂O, 82% over 3 steps

Scheme 2-11. [2+2] photocycloaddition reaction

The [2+2] photocycloaddition reaction^[30] was performed *via* the irradiation of a solution of 2,3-dimethylmaleic anhydride **20** and dimethylketene acetal **135** in a solvent of acetone and acetonitrile using a 400 W medium pressure mercury lamp with a pyrex filter under water cooling. In the initial 5 hours the reaction proceeded smoothly and ¹H NMR analysis revealed that the conversion of 2,3-dimethylmaleic anhydride is over 60%. However the photoreaction became sluggish and lots of the starting 2,3-dimethylmaleic anhydride still remained even after irradiation for 20 hours. We found that the photocycloaddition reaction could be accelerated greatly by means of the use of benzophenone as a photosensitizer. This method effectively promoted the photocycloaddition reaction and resulted in 100% conversion of 2,3-dimethylmaleic anhydride in 20 hours. Needle crystals of photocycloaddition product **136** could be obtained *via* recrystallization from diethyl ether and hexane in 94% isolated yield, thus avoiding silica gel column chromatography.

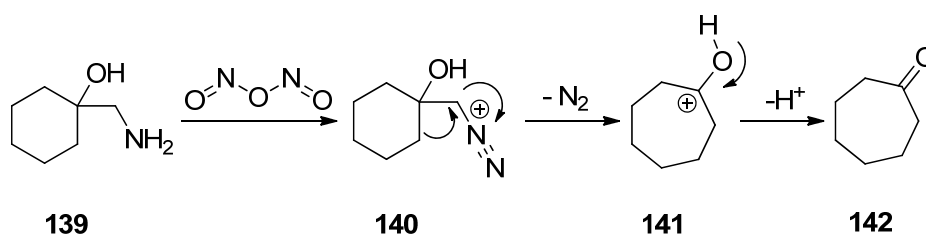
The key intermediate cyclobutanone **94** was prepared from **136** via three straightforward steps. Firstly, reduction of **136** on a 10 gram scale with lithium aluminium hydride (LiAlH₄) in diethyl ether furnished the diol **137** in quantitative yield (95% purity determined by ¹H NMR experiment), which was then directly used in the next step. Secondly, protection of diol with BnBr using NaH in THF and a catalytic amount of *n*Bu₄NI was monitored by TLC until the the reaction was completed. Subsequently, the reaction was quenched carefully with water and then

the pH of the reaction mixture was adjusted to 1 by adding H₂SO₄ solution to remove the acetal group. This three-step sequence produced the cyclobutanone **94** in 89% yield after purification by silica gel chromatography.

The advantage of this approach was that the challenging cis-methyl quaternary centres were set immediately by means of a [2+2] photocycloaddition reaction as the very first step in the synthesis. The key intermediate cyclobutanone **94** was accumulated on a large scale of around 30 grams in a short time *via* the effective and robust approach, requiring only one silica chromatography purification. With sufficient cyclobutanone **94** in hand our synthesis advanced to the next ring expansion stage.

2.3.2 Regioselective Tiffeneau-Demjanov ring expansion

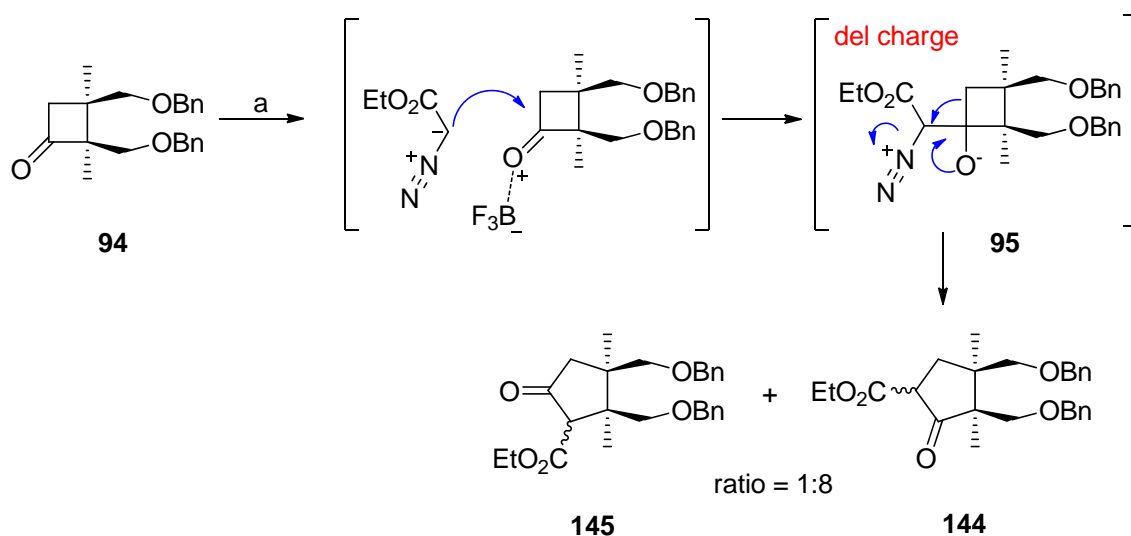
The classical Tiffeneau-Demjanov rearrangement (TDR) is the reaction^[31] of 1-aminomethyl cycloalkanols with nitrous acid to form an enlarged cycloketone. The TDR reaction was discovered by the Russian chemist Nikolai Demjanov and enlarged upon by Tiffeneau in 1903 and 1937, respectively. This reaction provides an easy way to expand a ring by one carbon. The starting ring can be between four and eight carbons giving good yields of product rings having five to nine carbons, while the yield decreases as initial ring size increases. The basic reaction mechanism is a diazotation of the amino group in **139** by nitrous acid followed by expulsion of nitrogen and formation of a carbocation **140**. A rearrangement reaction with ring expansion forms a more stable oxonium ion which is deprotonated to produce ring expansion product **142** (Scheme 2-12).



Scheme 2-12. Mechanism for the ring expansion reaction

For the synthesis of merrilactone A, a ketone group rather than a β -amino alcohol was present in the substrate and thus a modified TDR reaction has to be employed in

which ethyl diazoacetate is used as the ring expansion reagent^[34]. Ethyl diazoacetate was preferred over diazomethane for several reasons: Firstly, ethyl diazoacetate is easy to handle compared to diazomethane which possesses the unpleasant traits of explosiveness and difficulty of preparation and preservation. Secondly, ethyl diazoacetate affords a ring expanded β -ketoester which was to be employed for further elaboration. Finally, literature precedent was found where a greater regioselectivity was obtained in the rearrangement step with ethyl diazoacetate compared to diazomethane. Several examples were reported where this methodology has also been successfully employed in the expansion of cyclobutanones to cyclopentanones^[32,33].



a) $\text{N}_2\text{CHCO}_2\text{Et}$, $\text{BF}_3 \cdot \text{Et}_2\text{O}$, DCM, 0°C , 82%

Scheme 2-13. Tiffeneau-Demjanov ring expansion reaction

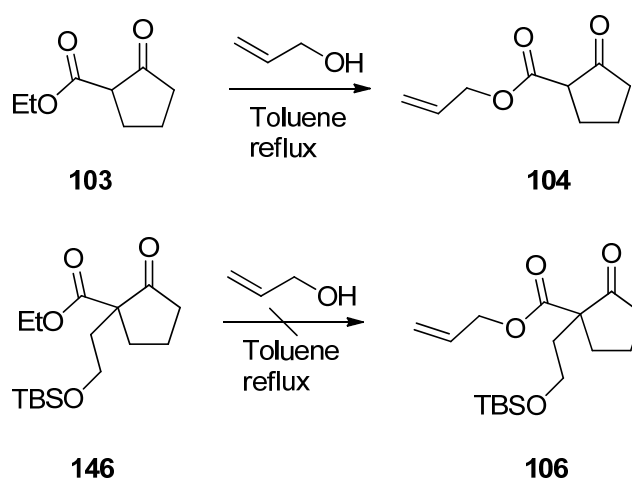
Due to the unsymmetrical nature of our substrate **94**, the carbon atom migration could occur on either side of the formed carbonyl motif, therefore giving two possible regioisomeric expansion products **145** and **144**. Additionally, the newly formed carbon stereocentre between ketone and ester group, was created without stereocontrol, thus forming diastereomeric mixtures of 1,3-ketoesters. Initial experimental studies on Tiffeneau-Demjanov ring enlargement reaction were carried out with the use of boron trifluoride etherate as the Lewis acid. Nucleophilic attack of ethyl diazoacetate onto an activated carbonyl group followed by loss of nitrogen with simultaneous ring expansion rearrangement resulted in desired product **144** in 82% yield (Scheme 2-13). A highly regioselective migration of the less-substituted

carbon atom centre was observed in this case. The byproduct suspected to be the undesired regioisomer **145** was collected in 10% yield but the structure was not confirmed due to the complicated ^1H NMR signals.

2.3.3 Transesterification reaction

Transesterification is one of the classic organic reactions having enjoyed numerous laboratory uses and industrial applications. It is more advantageous than ester synthesis from carboxylic acids and alcohols which require either harsh condition at high temperature or a coupling reagent such as DCC. These reactions are often catalyzed by the addition of an acid or base catalyst, or with the help of enzymes such as lipases.

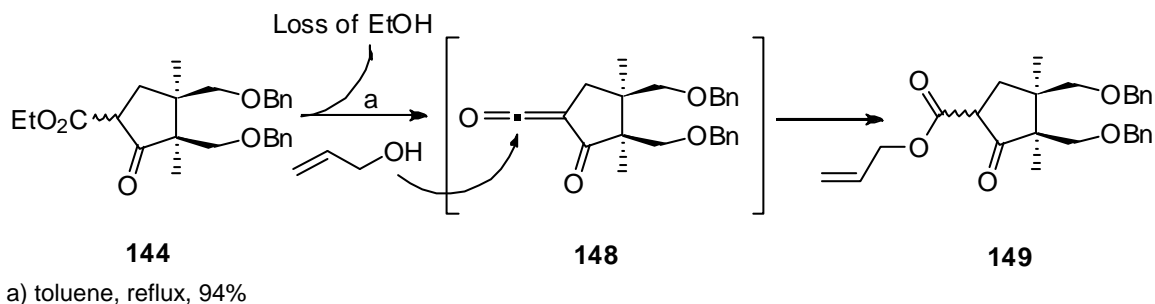
A search of the literature revealed several pertinent example of transesterification of a β -keto ester with an allylic alcohol proceeding in good yield^[10-12]. Mechanistic studies suggested that the transformation most likely proceeds *via* a ketene intermediate. In contrast to the model reaction (Scheme 2-14) in which substrate **103** underwent transesterification reaction smoothly, subjecting **146** to the same conditions gave no product even in refluxing toluene for one day. This control experiment further confirms the proposed mechanism involving a ketene intermediate pathway (not possible from **146**).



Scheme 2-14. Transesterification reaction in model system

This exceedingly simple, yet effective method was applied to our substrate **144**. The transesterification procedure was extremely simple experimentally: a mixture of **144**

and the allylic alcohol in toluene was merely heated to reflux, with a short tube in place of the usual condenser. The equilibrium was thus shifted to right due to the loss of the relatively volatile ethanol from the reaction mixture, furnishing the desired product **149** in 92% yield (Scheme 2-15).



Scheme 2-15. Transesterification reaction

Both ring expansion and transesterification reactions proceeded smoothly, thus sufficient materials could be accumulated in a short time to set the stage for the next alkylation and Tsuji-Trost reaction.

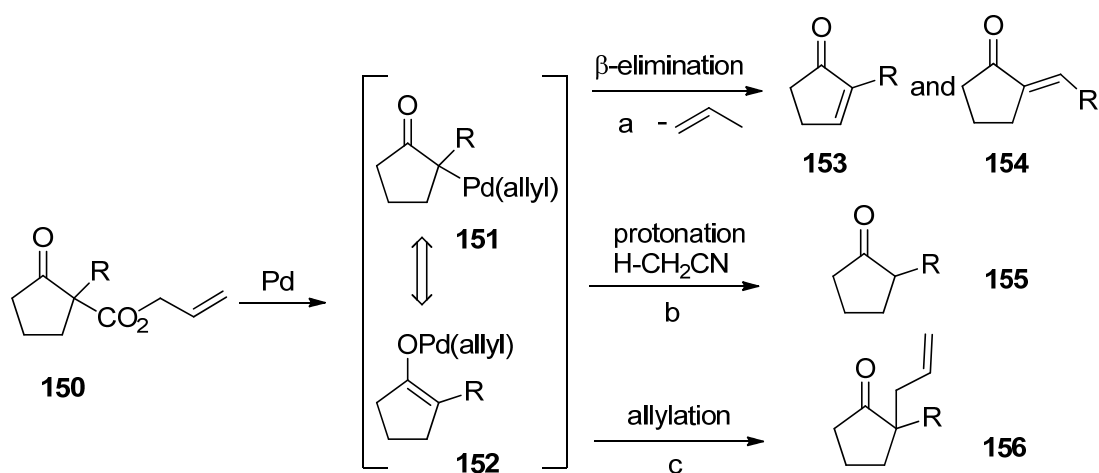
2.3.4 Alkylation of 1,3-ketoester and Tsuji-Trost reaction

2.3.4.1 Mechanism of Tsuji-Trost reactions

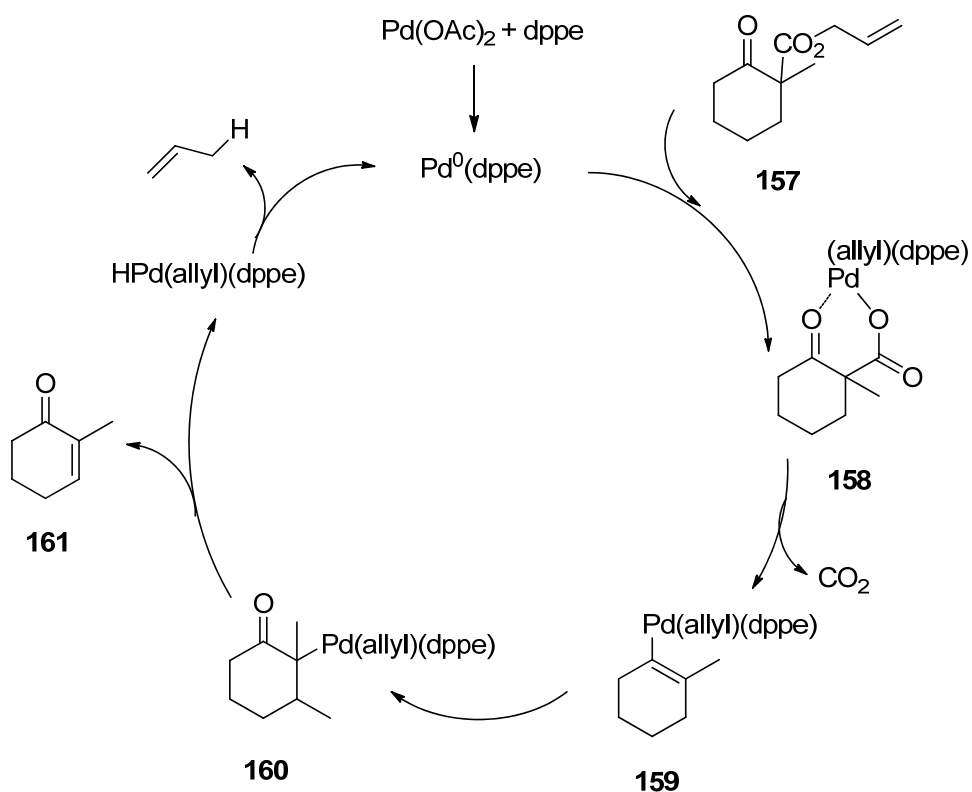
The palladium-catalyzed decarboxylation-dehydrogenation of allyl β -keto carboxylate to α -substituted α, β -unsaturated ketone was first reported by Jiro Tsuji in 1982.^[13-15] Three competitive reaction pathways catalyzed by palladium with substrate **150** are outlined in Scheme 2-16, including path **a**, decarboxylation-dehydrogenation to give 2-alkylcyclopentenone **153** or **154**, and path **b**, the decarboxylation-protonation to give 2-allyl-2-alkylcyclopentanone **155**, and path **c** the decarboxylation-allylation to give 2-allyl-2-alkylcyclopentanone **156**.

The three reaction pathways could be selectively controlled by different reaction conditions shown in Scheme 2-16. The decarboxylation dehydrogenation reaction was possible to be carried out as a main path under certain conditions. In attempts to improve the selectivity of the desired enone formation, the molar ratio of phosphine/palladium was found to be the key parameter in this reaction. In MeCN and using dppe, the enone formation becomes predominant when the molar ratio of

phosphine/palladium becomes lower than 1.



Scheme 2-16. Different pathway for the Tsuji-Trost reaction



Scheme 2-17. Mechanism for the Tsuji-Trost reaction

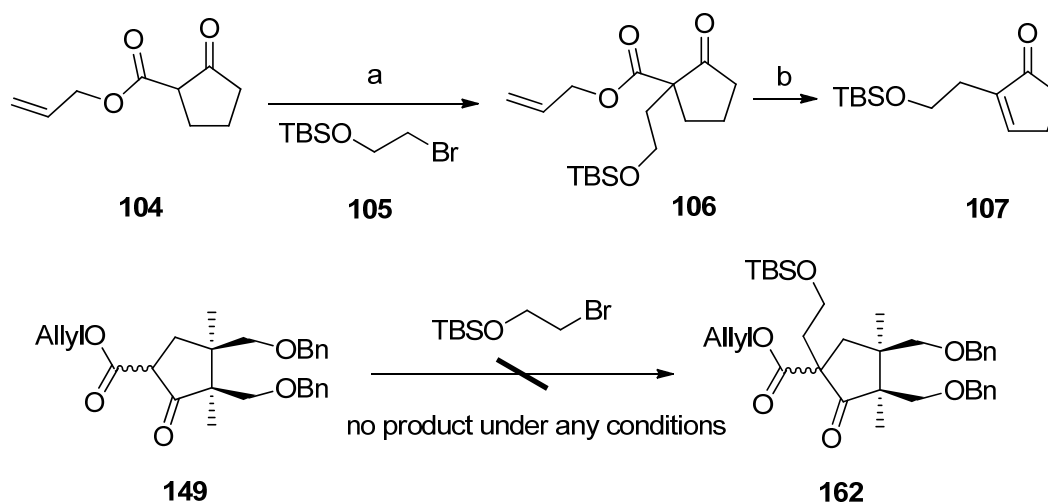
The mechanism of enone formation is explained in Scheme 2-17. Firstly the $\text{Pd}(0)$ species is generated in situ from $\text{Pd}(\text{OAc})_2$, which undergoes oxidative addition to the allyl ester affording allylpalladium β -keto carboxylate **158**. Subsequently, **158** undergoes decarboxylation to produce the allylpalladium enolate complex **159**,

which is in equilibrium with the carbon-bonded complex **160**. Then the enone is formed by means of the elimination of Pd-H from **160**. Finally the reductive elimination of the allylpalladium hydride complex produces propene and thus regenerates the Pd(0) species for the next reaction cycle.

2.3.4.2 Alkylation of 1,3-ketoester with protected 2-bromoethanol

With the ring expansion product in hand, the introduction of a quaternary centre at the 2-position of the 1,3 ketoester needed to be addressed prior to Tsuji-Trost reaction. We envisaged a direct introduction of a two carbon fragment for the carbon segment of γ -lactone *via* alkylation with an alkyl halide.

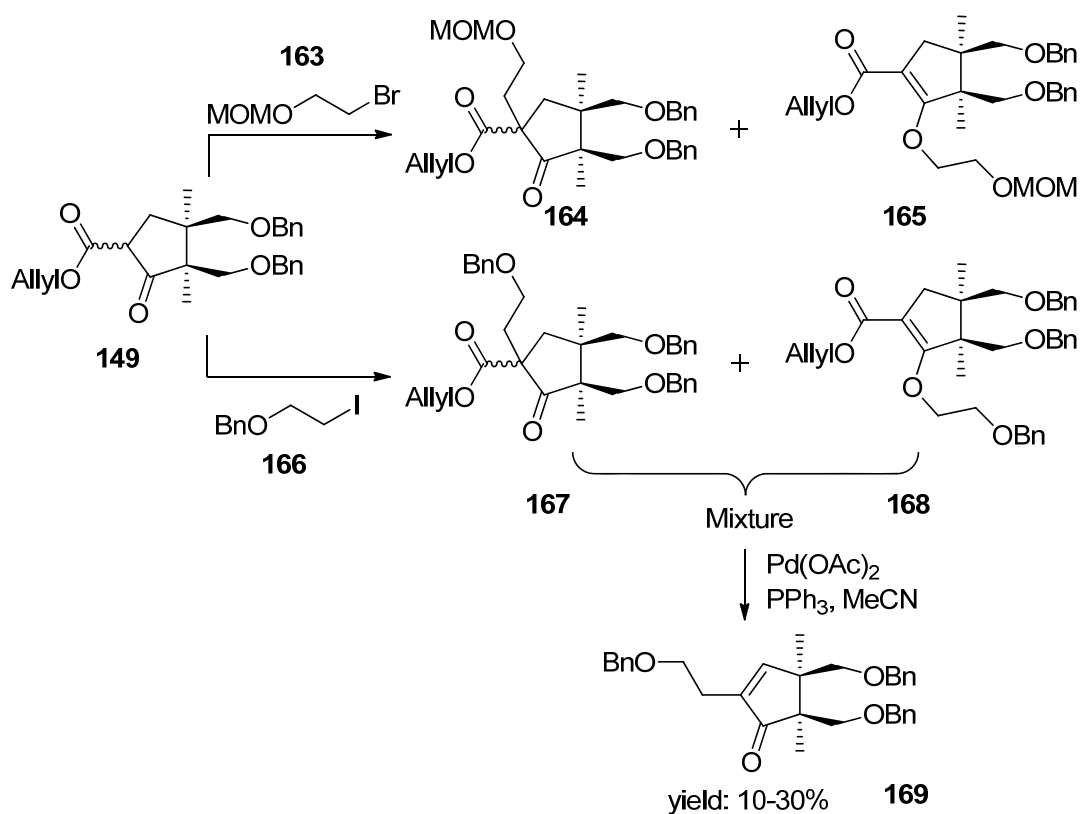
Initial attempts of such a transformation were carried out based on the TBS-protected 2-bromoethanol **105**, which was used in the model system successfully. Unfortunately, employing a range of conditions, no formation of the anticipated reaction product **162** from **149** could be achieved in our real synthesis (Scheme 2-18). This is likely due to increased steric hindrance between the two quaternary carbon centres and the TBS protecting group prevented the alkylation from occurring.



a) K_2CO_3 , acetone, reflux; b) $Pd(OAc)_2$, PPh_3 , MeCN, reflux

Scheme 2-18. Alkylation of 1,3-ketoester in the model system

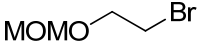
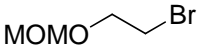
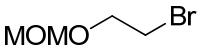
This result thus made us change our alkylation substrate from the bulky TBS group to less hindered protecting group such as **163** and **166**^[35]. Various conditions were screened and the results are shown in table 2-1.



Scheme 2-19. Alkylation of 1,3-ketoester with protected 2-bromoethanol

Table 2-1.

entry	Substrate	Conditions	Results
1		K ₂ CO ₃ , Acetone, RT	SM only
2		K ₂ CO ₃ , Acetone, reflux, 20h	Trace product
3		K ₂ CO ₃ , MeCN, reflux, 20h	Mixture, 60% yield
4		NaH, DMF, 120 °C, 10h	Decomposition
5		K ₂ CO ₃ , Acetone, HMPA (5 eq), RT	168 , 70% yield
6		Acetone, K ₂ CO ₃ , NaI, reflux, 40 h	SM only
7		MeCN, K ₂ CO ₃ , NaI, 80 °C,	Trace product
8		DMF or DMSO, K ₂ CO ₃ , 120 °C, 12h	Decomposition
9		Acetone, K ₂ CO ₃ , HMPA (5 eq), RT	165 , 60% yield

10		Acetone, K ₂ CO ₃ , HMPA (3 eq), RT	164 , 19% yield 165 , 40% yield
11		THF, NaH, NaI, HMPA (1 eq), RT	164 , 28% yield 165 , 40% yield
12		n-Bu ₂ O, NaH, 90 °C, 12 h	Trace product

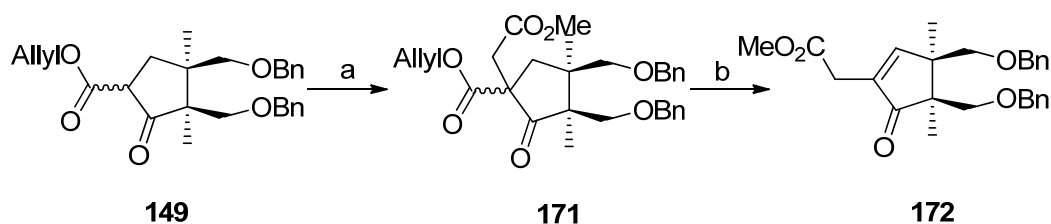
When reaction proceeded in acetone or acetonitrile below 80 °C without additive, only trace product was observed (entry 1, 2, 6, 7). Further increasing reaction temperature to reflux over 20 hours produced desired **167** and undesired byproduct **168** as an inseparable mixture (entry 3). This resulting mixture was subsequently treated with Pd(OAc)₂ and PPh₃ in refluxing MeCN to afford the desired product cyclopentanone **169** but in the very low yield of 10% after 2 steps. Carrying out the reaction in DMF or DMSO at high temperature over 120 °C gave no expected improvement but instead resulted in the decomposition of the starting materials (entry 4 and 8).

Hexamethylphosphoramide (HMPA) was found in the pertinent literature^[8,9] to be an effective additive to facilitate the alkylation reaction. In the presence of 5 equivalents of HMPA the alkylation reaction proceeded even at room temperature, however oxygen-alkylation pathway was found to occur predominantly over the desired carbon-alkylation pathway (entry 5 and 9). Decreasing loading of HMPA from 5 to 1 equivalents improved the formation of desired C-alkylation product **164** but the 28% yield was still not satisfactory (entry 9, 10, 11).

2.3.4.3 Alkylation with methyl 2-bromoacetate

The disappointing result let us slightly modify the approach for the alkylation reaction. In the alternative approach, represented in Scheme 2-20, methyl 2-bromoacetate was used as the alkylation reagent. Due to its high reactivity, the alkylation and Tsuji-Trost reaction preceded very well. Cyclopentanone **149** was treated with K₂CO₃ and methyl 2-bromoacetate in acetone, and the resulting suspension was stirred at room temperature for 24 h affording the alkylation product **171** in 92% yield, with just a trace of undesired O-alkylation product. This then set the stage for Tsuji-Trost reaction: cyclopentanone **171** was treated with Pd(OAc)₂ and PPh₃ in acetonitrile at 90 °C under an argon atmosphere. The resulting mixture

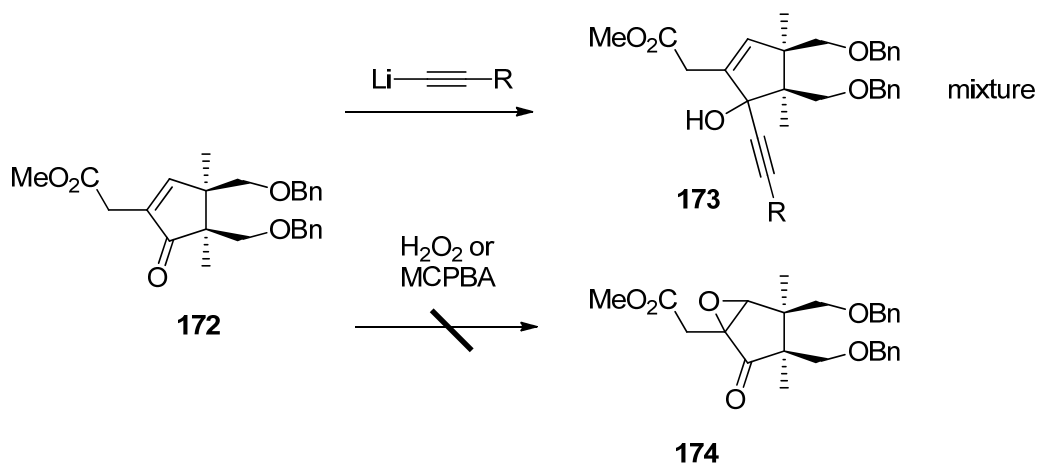
was then stirred for 3 h before being allowed to cool to room temperature furnishing cyclopentenone **172** in 90% yield.



a) methyl 2-bromoacetate, K_2CO_3 , acetone, 92%; b) $Pd(OAc)_2$, PPh_3 , MeCN, 90%

Scheme 2-20. Alkylation of 1,3-ketoester with methyl 2-bromoacetate

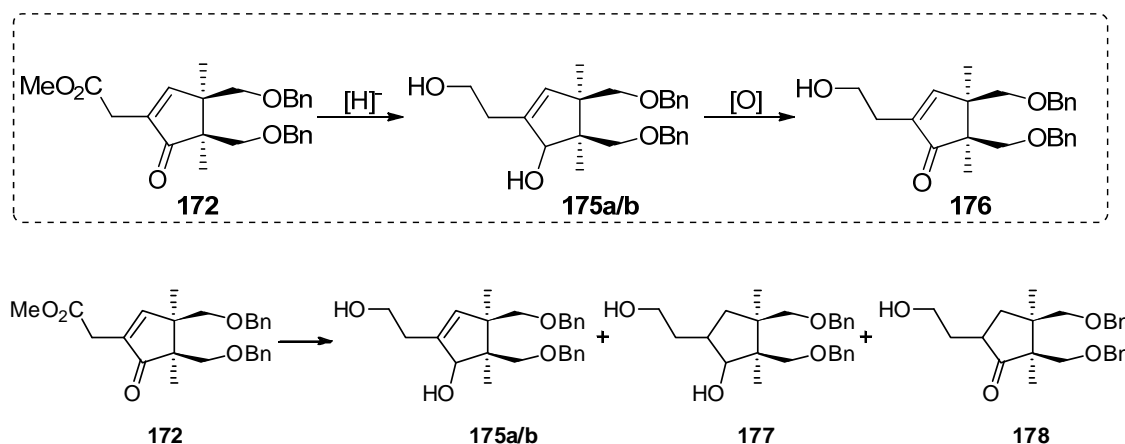
However the further elaboration of this substrate **172** was found to be difficult (Scheme 2-21). Subsequent 1,2-addition of organometallics to the ketone group was accompanied by competitive addition to the ester group without selectivity. Numerous efforts have been carried out attempting to control these addition reactions, such as slow addition of the substrate at low temperature. But all attempts proved to be fruitless and only gave complex mixtures of several unidentified products. Similarly, attempted epoxidation of the alkene with H_2O_2 led to rapid decomposition of substrate **172**.



Scheme 2-21. Further elaboration of cyclopentenone 147

To solve the chemoselectivity issue of having an ester and ketone group in the same molecule we reduced both moieties concurrently to diol **175** (Scheme 2-22). We envisaged that either the resulting allyl alcohol could be selectively oxidised to a ketone, or the less hindered primary alcohol group could be selectively protected. In

order to validate the viability of this redesigned route, a number of typical reducing reagents were screened and results are showed in table 2-2.



Scheme 2-22. Reduction of cyclopentenone 172

Table 2-2

Entry	Reducing reagent	175a/b	177	178
1	LAH	20-30%	trace	20%
2	DIBAL-H	0%	30-40%	trace
3	LiBH ₄			Mess on TLC
4	NaBH ₄ +CeCl ₃			No Reaction

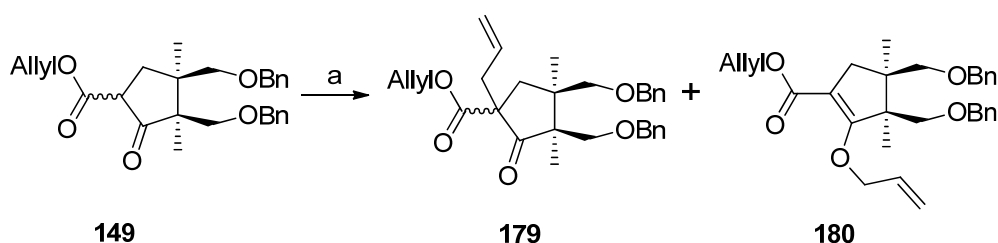
*the possible products **177** and **178** are not fully characterised

Lithium aluminium hydride (LAH) is a commonly used reducing reagent^[36,37] with good 1, 2 reduction selectivity for enones. Addition of LAH into the solution of **172** in diethyl ether did furnish the favored diol albeit in low yield of 20-30%, combined with several over reduction byproducts such as **177** and **178**. The structures of **177** and **178** were unconfirmed due to complicated ¹H NMR data. The byproduct **178** was suspected to be derived from the lithium enolate (the side product from 1,4-reduction of enone system of **172**), which resisted further reduction by LAH and delivered the ketone group after hydrolysis. Diisobutylaluminium hydride (DIBAL-H)^[38] is another excellent 1,2-reduction reagent. However in this case, none of the desired product **175** was obtained, only the unwanted **177**. It appears that the steric hindrance of the ketone group makes 1,4-reduction competitive over 1,2-reduction, producing **177** as the major product.

LuChé reduction^[39-40] is famous for its excellent 1,2- selectivity in enone reduction, and would not be expected to reduce the ester group. When applied to our substrate, however, the formation of the expected product **175** was not observed. Instead, the starting materials were fully recovered (entry 4). Other reducing reagent such as lithium borohydride (LiBH₄), aminoborohydrides or 9-borabicyclo(3.3.1)nonane (9-BBN) gave no improvement.

2.3.4.4 Alkylation with allyl bromide and optimization of Tsuji-Trost reaction

We turned our attention to alkylation of the β -ketoester **149** with allyl bromide which possesses high reactivity. The alkene is known to be convertible into the alcohol group easily *via* a standard multi-step sequence of dihydroxylation, oxidative cleavage and subsequent reduction of the resulting aldehyde to alcohol. Alkylation with allyl bromide could be achieved in analogy with the substrate preparation with methyl 2-bromoacetate. The substrate **149** (10 gram scale) was treated with K₂CO₃ in acetone and 2 equivalents of allyl bromide were added. The resulting suspension was stirred at room temperature for 10 hours furnishing the alkylation product **179** in 92% yield with only a trace of undesired O-alkylation product **180**. This nicely set the stage for the Tsuji-Trost reaction.

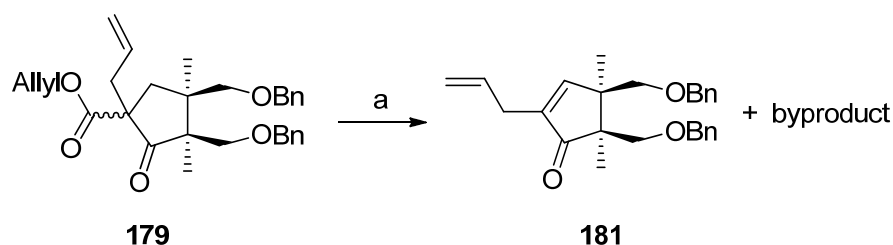


a) allyl bromide, K₂CO₃, acetone, **180**, 5%, **179**, 95%

Scheme 2-21. Alkylation of allyl bromide

Initial attempts at the Tsuji-Trost for synthesis of **181** were carried out using the same method as for the preparation of **171**. Treatment of **179** with catalytic Pd(OAc)₂ and PPh₃ in acetonitrile afforded the expected decarboxylation dehydrogenation product **181** but in an average yield of ~50%. The reaction was accompanied with formation of a large amount of unidentified byproduct, which was purified by column chromatography but the structure was unconfirmed due to a complex ¹H NMR spectrum. Extensive screening of mono- and bidentate phosphine ligands and

palladium sources proved fruitless and gave no increase of the yield. However a significant improvement was eventually achieved when we decreased the substrate concentration and catalyst loading. The formation of the byproduct was also suppressed efficiently. A number of reaction conditions has been screened and the results are presented in table 2-3.



a) Pd(OAc)₂, PPh₃, MeCN

Scheme 2-24. Optimization of Tsuji-Trost reaction

Table 2-3

entry	Catalyst Loading	Sub Concentration	Reaction Time	Yields
1	10%	0.2 [M]	0.5 h	45-64%
2	5%	0.2 [M]	1 h	76-82%
3	5%	0.08 [M]	1 h	79-86%
4	5%	0.04 [M]	2 h	87-92%
5	3%	0.04 [M]	> 4h	N/A

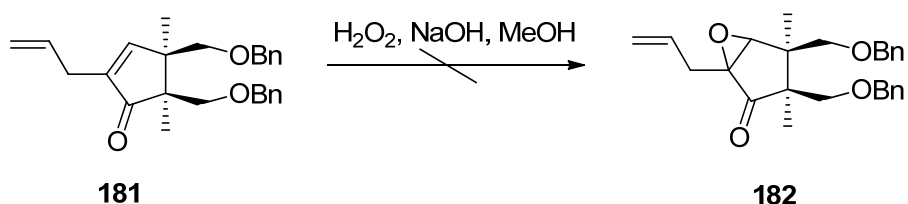
The reaction showed a remarkable dependence on the catalyst loading and substrate concentration. Under Tsuji's original conditions (0.2 [M] solution of substrate) with 10% catalyst loading, we were pleased to see the formation of desired product **181** but containing a large amount (30%) of an undesired byproduct (entry 1). When employing 5% catalyst loading (entry 2), the reaction proceeded smoothly in one hour with significant improvement of the formation of the desired product **181** with less undesired byproduct (10%). Further optimization by carrying out the reaction using a 0.08 [M] solution of substrate **179** afforded **181** with a slightly better yield of 86% after one hour (entry 3). The best yield was achieved using a 0.04 [M] solution of the starting material in MeCN, furnishing product **181** in 92% yield. Under these conditions the Tsuji-Trost reaction was proven to be reliable and effective, and could

be carried out on 5 gram scale of substrate furnishing the desired product smoothly in two hours combined with only trace amounts of byproduct. Further reducing catalyst loading from 5% mol to 3% mol was less efficient, with large amounts of substrate remaining even after several hours.

2.4 Synthesis of the functionalized cyclopentaneone

2.4.1 Transformation of alkene to primary alcohol

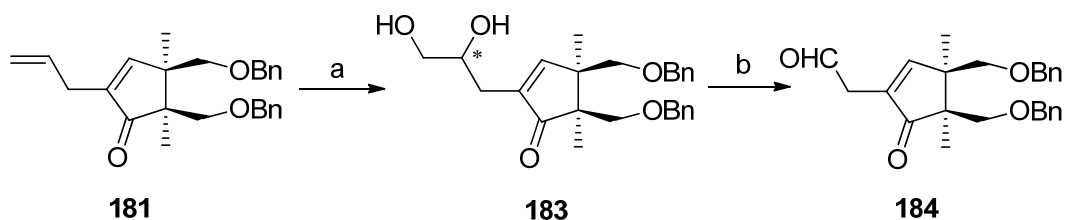
At this stage, we had to prepare the substrate for the key radical chemistry, requiring the alkene in the enone system of **181** to be selectively oxidized to an epoxide. The combination of hydrogen peroxide solution in methanol in the presence of sodium hydroxide is well known for its efficient epoxidation of enone systems. However initial experiments indicated that no formation of the desired epoxide **182** was observed when **181** was subjected to this condition, even at high temperatures and longer times. Attempts to apply *m*-chloroperoxybenzoic as oxidizing agent led to rapid decomposition of **181**. We felt that the terminal alkene in the side chain could be responsible for complications, so we decided to convert it into an alcohol.



Scheme 2-25. Epoxidation of cyclopentenone 181

Transformation of alkene to diol (Scheme 2-26) was effected by osmium tetroxide (OsO_4) and *N*-methylmorpholine *N*-oxide (NMO)^[45-46] as cooxidant. A catalytic amount of OsO_4 mediated mono-dihydroxylation^[41-44] of **181** with regioselectivity and led to a single diol **183** (precise stereochemistry of the 1,2-diol moiety not delineated). The excellent regioselectivity was probably derived from the stereo and electronic differences between the two alkenes. The terminal alkene was less hindered for access by osmium and was electronically rich compared to the alkene in the enone system. Accurate weighing of one equivalent of NMO was pivotal for this reaction since excess NMO led to double dihydroxylation of both alkene groups existing in the molecule. The resulting diol **183** was oxidatively cleaved to

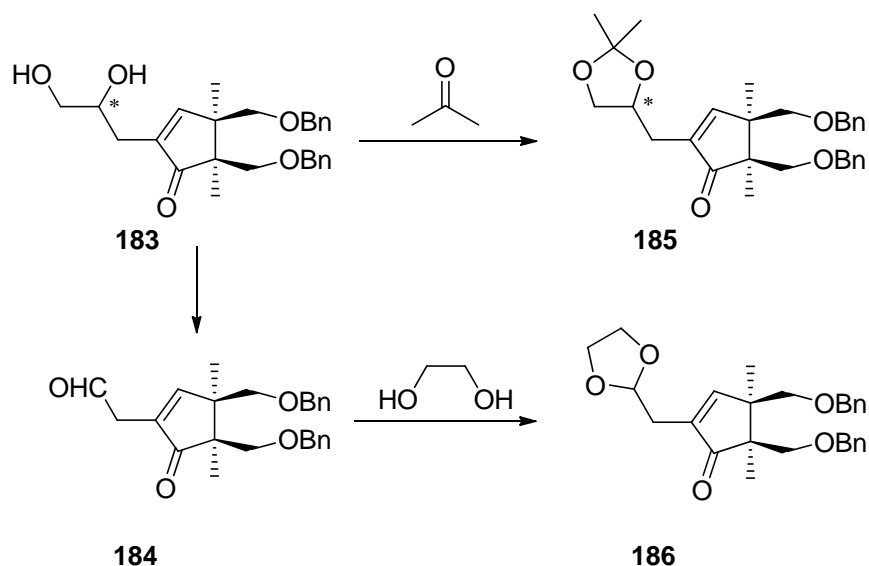
aldehyde by sodium metaperiodate in the solvent mixture of THF and water furnishing compound **184** with excellent yield.



a) OsO₄, NMO, H₂O, acetone, 92%; b) NaIO₄, THF, H₂O, 92%

Scheme 2-26. Transformation of alkene to primary alcohol

We then protected the aldehyde (also the diol precursor) as the dioxolane and acetonide respectively, as shown in Scheme 2-27. Protection of diol^[47] or aldehyde^[48] proceeded smoothly under standard conditions and produced corresponding products **185** and **186** in high yield.



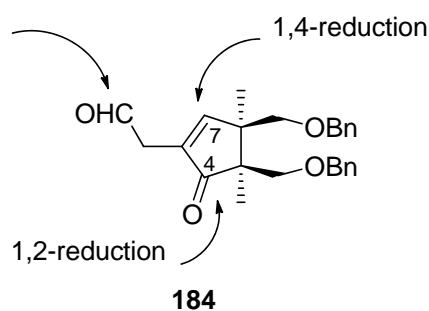
a) (EtO)₃CH, acetone, TsOH, 90%; b) TsOH, toluene, reflux, 99%

Scheme 2-27. Protection in dioxolane form

The advanced intermediates **185** and **186** were further functionalized into the substrates for the key radical cyclisation reaction in a reasonable number of steps. However these efforts were somewhat wasteful since the dioxolane group was found to be unstable and decomposed when subjected to radical conditions.

Attempts to reduce the aldehyde group were found to be somewhat problematic.

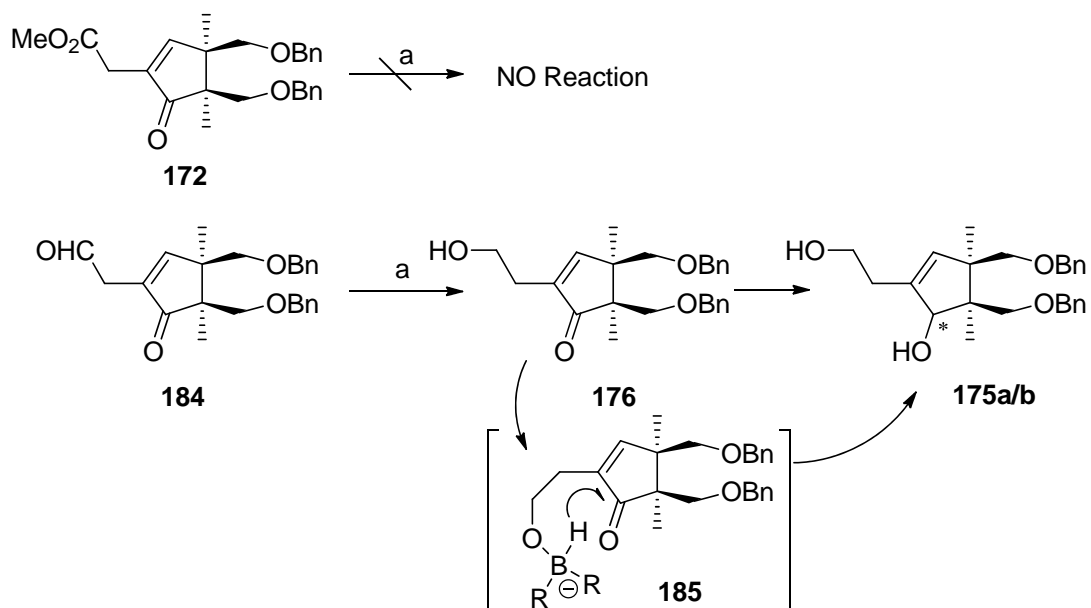
There were three potential reducible positions existing in this molecule (Scheme 2-28), including the aldehyde group, C7 of enone for 1,4-reduction and C4 of ketone for 1,2-reduction. Thus the control of selectivity was pivotal for the reduction reaction. Selective reduction of the aldehyde in the presence of ketone should be readily achieved *via* careful control of the reactivity of the reducing reagent, because the ketone is hindered and more stable than the aldehyde. 1,4-Reduction should be suppressed by selecting a reducing reagent with good regio-selectivity. In the event, the reduction reaction proved more complex than anticipated.



Scheme 2-28. Selectivity in reduction of 184

At first glance, the problem seems to be readily resolved if we could control the selectivity between aldehyde and 1,4-reduction of enone. A hint on how to achieve this came from the previous reduction of intermediate **172** (Scheme 2-20), where the Luche reduction was employed but no reaction occurred (including no 1,4-reduction). On the other hand, Luche reduction is known for selectively reducing ketones in the presence of an aldehyde. Bearing all this in mind, we attempted reduction under Luche conditions of sodium borohydride in methanol in the presence of cerium(III) chloride.

However three product spots appeared by TLC analysis: the aldehyde was reduced to a primary alcohol which was confirmed by HPLC-MS analysis and the ^1H NMR spectrum. Careful collection and separation of the other two by-products by column chromatography followed by further NMR analysis determined the structure to be the over reduced products **175a/b**. Obviously the ketone group was reduced to the allylic alcohol, however no 1,4-reduction product was observed due to the presence of cerium(III) chloride.



a) NaBH_4 , CeCl_3 , MeOH

Scheme 2-29. Possible pathway of ketone reduction

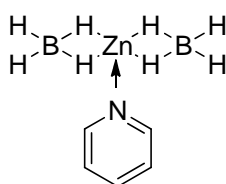
This result shown in Scheme 2-29 led us to a thorough investigation of the reduction. Firstly the aldehyde group was reduced to alcohol **176** in all cases. Nevertheless the reaction did not end at this stage and the product **175** appeared immediately after the primary alcohol **176** was formed. Various modifications of the system were made, such as changing the solvent to ethanol or *iso*-propanol, controlling the temperature at $0\text{ }^\circ\text{C}$, adding sodium borohydride carefully, but all proved unfruitful - the ketone group was always reduced. This result was quite surprising to us and was in contrast to the previous attempts to reduce **172**, where the ketone group was intact due to steric hindrance when Luche reduction conditions were employed.

A plausible account for this different activity may be derived from the presence of the free alcohol group contained in the molecule **176**. Thus we might predict a possible pathway shown in Scheme 2-29 for this result. While the aldehyde was reduced, the resulting free alcohol would coordinate to the boron and deliver a hydride to the ketone group *via* an intramolecular coordinate **185**. The presence of cerium(III) chloride could suppress the 1,4-reduction.

These unsuccessful attempts still gave us some constructive ideas; we need to choose

a suitable reducing reagent processing good selectivity through controllable reducing ability. In the optimised reaction, the aldehyde could be reduced exclusively while the ketone group could survive. LAH, DIBAL-H or similar reagents processing strong reducing ability were excluded firstly. 9-BBN, aminoborohydrides and $\text{LiAlH}(\text{O}^t\text{Bu})_3$ also failed on this substrate.

(Pyridine)(tetrahydroborato)zinc complex, $\text{Zn}(\text{BH}_4)_2(\text{Py})$ was reported by Behzad Zeynizadeh in 2003^[49] as a new reagent having great 1,2-reduction selectivity in the enone system, along with remarkable selectivity for reducing aldehydes in the presence of ketones. More interestingly, this reagent revealed alterable reducing ability in different solvents.



(Pyridine)(tetrahydroborato)zinc complex

Table 2-4 presents the results of reduction reactions with $\text{Zn}(\text{BH}_4)_2(\text{Py})$. In THF or diethyl ether (entry 2), the reduction gave **175a/b** as a major product. Then MeOH and EtOH were used as solvent and the reaction produced the desired **176** as major product with only trace formation of **175a/b** (entry 3). Eventually, we found that *iso*-PrOH or *tert*-BuOH as solvent gave solely the desired product **176**. The reaction was finished in 2 hours and then the excess $\text{Zn}(\text{BH}_4)_2(\text{Py})$ was quenched by several drops of HCl solution. Three steps (two pots) for the transformation of alkene to primary alcohol resulted in a 67% yield.

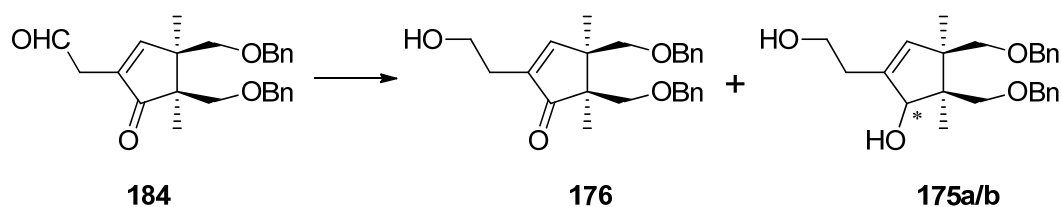


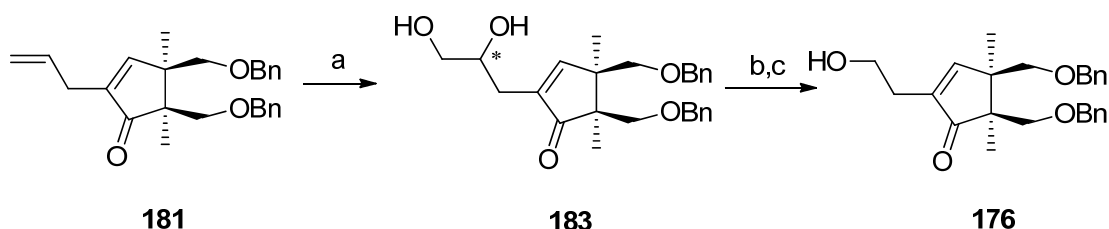
Table 2-4. $\text{Zn}(\text{BH}_4)_2(\text{Py})$ in reduction of aldehyde

entry	Reagent	Solvent	176	175a/b
1	NaBH_4 , CeCl_3	MeOH or EtOH	trace	major

2	Zn(BH ₄) ₂ (Py)	THF or Ether	trace	major
3	Zn(BH ₄) ₂ (Py)	MeOH or EtOH	major	much
4	Zn(BH ₄) ₂ (Py)	<i>iso</i> -PrOH or <i>t</i> -BuOH	sole product	N/A

* products were determined by TLC analysis

Obviously the direct alkylation of 1,3-ketoester **149** was the shortest pathway for the synthesis of **176**. However, as this approach was unsuccessful, we had to redesign our route to develop an alternative approach to advance our synthesis. Alkylation with allyl bromide was smooth. Conversion of alkene **181** to alcohol **176** required an extra three steps but afforded a good yield of 67% over three steps. This approach was reliable and robust, enabling the key intermediate **176** to be accumulated efficiently and our synthesis could advance to the next stage.

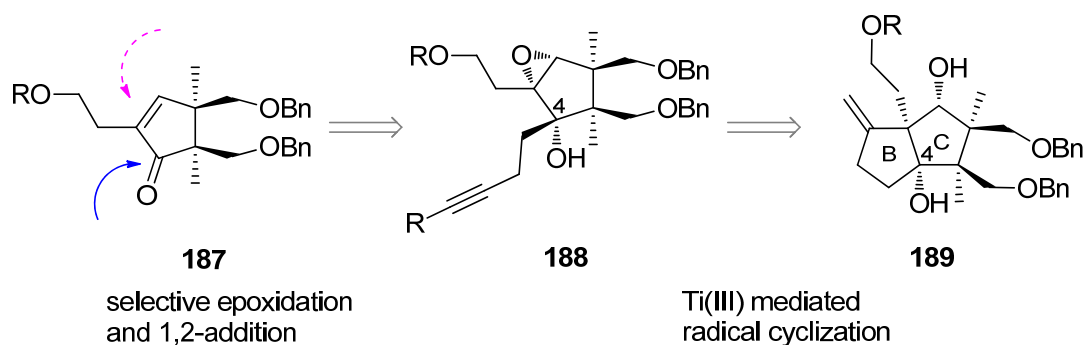


a) OsO₄, NMO, H₂O, acetone, 92% yield; b) i, NaIO₄, THF, ii, Zn(BH₄)₂.py, *i*-PrOH, 76% over 2 steps

Scheme 2-30. Transformation of alkene to alcohol

2.4.2 Epoxidation and 1,2-organometallic addition

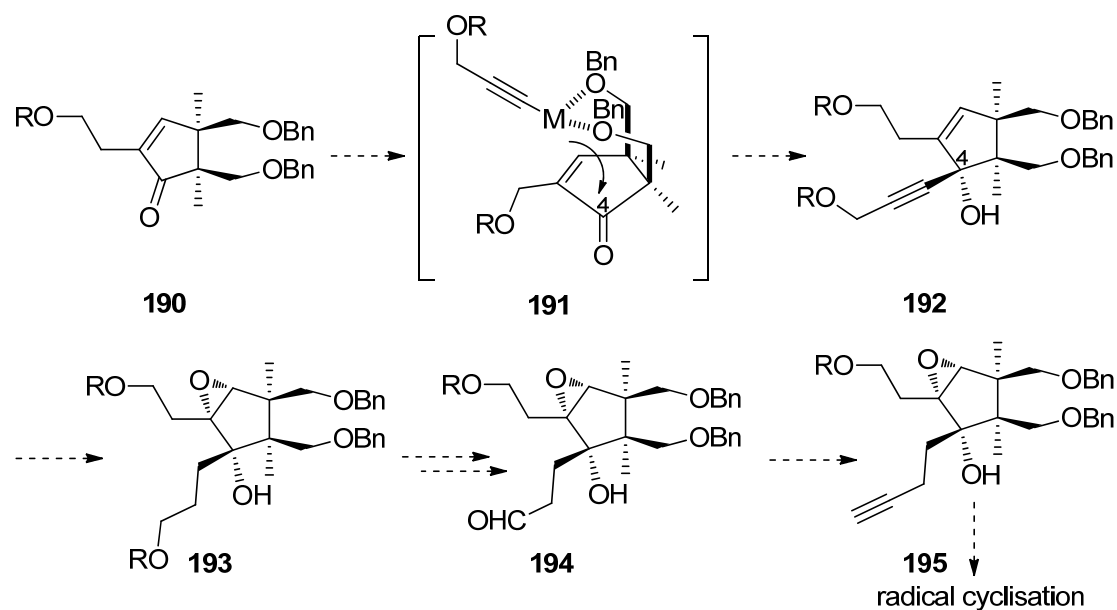
With an efficient synthesis of cyclopentenone **176** established, we next investigated the stereoselective epoxidation and 1,2-nucleophilic addition reactions which were required to set up the substrate for radical epoxide opening and cyclisation. As is evident from our retrosynthetic analysis (Scheme 2-24), we required the 1,2-nucleophilic addition to occur on the same face as the protected diol functionality of the cyclopentenone. This would set the correct stereochemistry at C4, eventually setting the scene for late stage lactonization of γ -lactone A.



Scheme 2-24. Selectivity in Epoxidation and 1,2-organometallic addition

2.4.2.1 Approach I, chelation controlled 1,2-addition

A short synthetic plan is outlined in Scheme 2-32 that describes a chelation controlled addition strategy. We expected that benzyl-protected hydroxyl groups could behave as weak *syn*-directing participating groups in 1,2-addition reaction^[50], thus creating the desired stereochemistry at C4. The nucleophile was chosen as an alkynyllithium, as sp^3 organometallics were expected to create elimination problems with the product tertiary alcohol (*vide supra*).

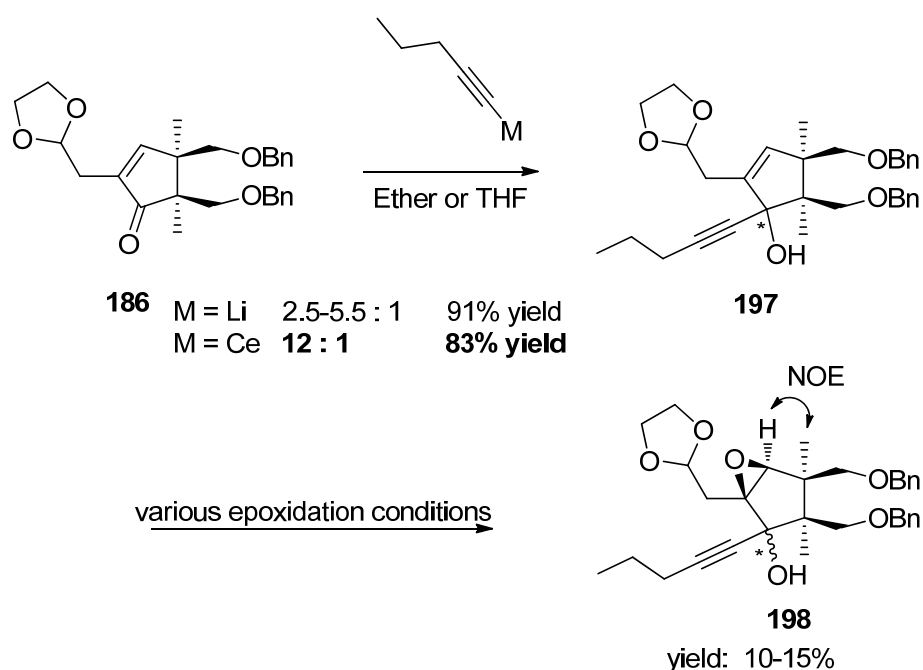


Scheme 2-32. Proposed chelation controlled 1,2-addition

Oxidation of the alkene to an epoxide and subsequent hydrogenation of the alkyne side chain could provide **193**. Deprotection and oxidation of the primary alcohol would result in an aldehyde which could be then converted consecutively to terminal alkyne **195** by Bestmann's reagent with potassium carbonate in methanol. This could

set the stage for radical cyclization.

To testify the feasibility of the proposed selective 1,2-addition and epoxidation approach, pentyne was selected as simple model substrate in the addition to **186** since it was commercially available as a liquid (Scheme 2-33). Deprotonation of the terminal alkyne using *n*-butyllithium and addition of cyclopentenone **186** afforded the tertiary alcohol **197** in excellent yield but only moderate selectivity (2.5-5.5 : 1). When exchanging the organolithium to the organocerium, the selectivity was improved to 12:1. Although the stereochemistry of the newly formed chiral centre C4 could not be determined at this stage as the NOESY and ¹H NMR proved non-conclusive, we advanced the material and attempted epoxidation of the alkene.



Scheme 2-33. Selective 1,2-organometallic addition and epoxidation

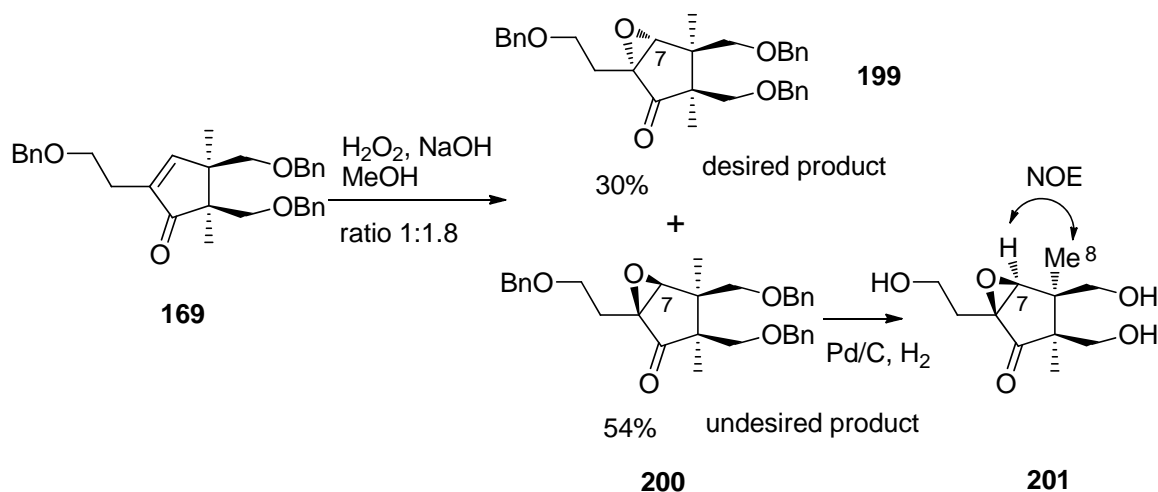
Exposure of **197** to *m*-chloroperoxybenzoic acid in dichloromethane afforded only low yields of the desired epoxidation product **198**, with slow decomposition of the substrate into complex mixtures being observed. Modifications such as increasing the temperature or increasing oxidative reagent loading, were not successful and only trace product was formed, along with the gradual decomposition of starting materials.

A number of reagents were screened for the epoxidation, *e.g.* buffered

trifluoroperoxyacetic acid, dimethyldioxirane, methyl(trifluoromethyl)dioxirane^[51-53], the peroxycarboximide derived from the combination of hydrogen peroxide and acetonitrile^[54], none of which were successful. We suspected that the tertiary alcohol moiety in **197** might be unstable in both basic and acid conditions. A NOESY analysis of **198** revealed that the newly formed epoxide was on the opposite face to the two methyl groups. However the stereochemistry of C4 remained unclear since there were no positive NOESY cross peaks that allowed confident assignment. The low yield of the epoxide product, and significant decomposition of the substrate, prompted us to seek an improved method to introduce the epoxide. As a result we turned our attention to the second approach - steric controlled epoxidation.

2.4.2.2 Approach II, steric controlled epoxidation

Treatment of cyclopentenone **169** with alkaline hydrogen peroxide in methanol afforded a very clean epoxidation reaction in 84% yield, furnishing the two diastereomers in a 1.8:1 ratio of **200** and **199** (Scheme 2-34). The two isomers were readily separated through column chromatography and the stereochemistry was assigned based on NOESY analysis of the downstream intermediate **201**. The key NOESY interaction observed was between the proton at C7 and the methyl group C8.



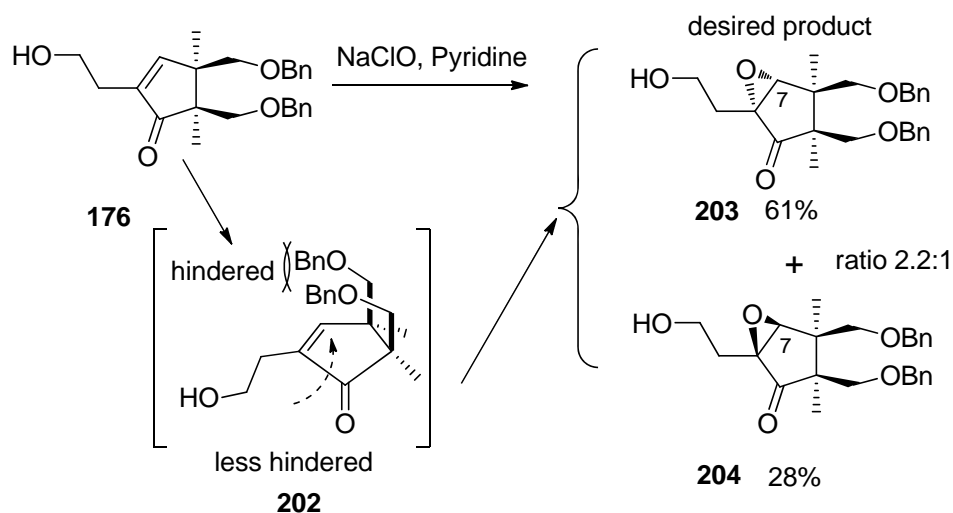
Scheme 2-34. Epoxidation with hydrogen peroxide

The facial selectivity apparent in the epoxidation reaction slightly favored the formation of undesired product **200**, in which the epoxide is introduced on the same

face as the bis-benzyl protected diol. We did not know the origin of this facial selectivity, but speculated that it could arise from the weak interaction of hydrogen bonding between hydrogen peroxide and BnO group. The configuration at C7 of the epoxide was not felt to be critical in itself in terms of the overall synthesis, as it could be manipulated in a variety of ways further down the line. However, the influence of the epoxide configuration on the subsequent 1,2 addition to the neighbouring ketone was thought to be highly important (*vide infra*). We required the epoxide to be formed on the opposite face of the protected diol in this context, ie **199**.

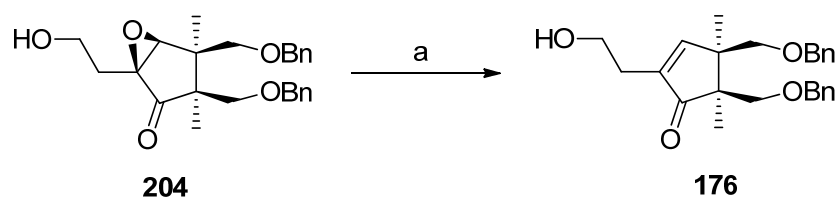
Obviously an improvement in the diastereoselectivity of the epoxidation was still required. Common epoxidation reagents known to afford good stereoselectivity in epoxidation reaction failed to promote the reaction. Using *m*CPBA, *t*-BuOOH and VO(acac)₂/*t*-BuOOH system^[55,56], no epoxidation product could be observed. This was speculatively attributed to the increased steric hindrance encountered by these larger epoxidation agents, preventing their approach, along with the electron-poor character of the carbon-carbon double bond of this system.

Sodium hypochlorite (NaClO), commonly known as bleach, was reported as an effective oxidizer in epoxidation reactions for the enone system affording excellent diastereoselectivity in the preceding literature^[57,58]. When sodium hypochlorite was used as epoxidation reagent in pyridine, the reaction worked well and furnished desired α -epoxide **203** as the major product (**203:204** = 2.2:1). The possible pathway for this reaction is shown in Scheme 2-35. In principle, the two BnO groups are larger than two methyl groups, and the epoxidation reagent attacks the enone from the less hindered face to produce corresponding epoxide **203**. Further optimization of the reaction conditions, such as screening the solvent (toluene, MeCN, DCM) or using NaBrO, gave no real improvement in the selectivity.



Scheme 2-35. Steric controlled epoxidation

The efficiency of the overall transformation could be improved by recycling the unwanted minor β -epoxide **204** through reductive deoxygenation. The deoxygenation of epoxides to alkenes is an important synthetic transformation in organic chemistry. It can be achieved by a number of methods,^[59-61] including $\text{FeCl}_3/\text{n-BuLi}$,^[62] $\text{NaOH}/\text{n-Bu}_4\text{NBr}$,^[63] $\text{Mo}(\text{CO})_6$,^[64] and SmI_2 ^[65] system. To our interest, the deoxygenation ability of $\text{Cp}_2\text{TiCl}_2/\text{Zn}$ has also been extensively studied, due to its unique features of high oxophilicity and reducing power. The low-valent titanium(III) species were readily generated as previously by the *in situ* reduction of bis(cyclopentadienyl)-titanium(IV) dichloride (Cp_2TiCl_2) with activated zinc powder in tetrahydrofuran for 1 hour at room temperature. This system is particularly effective if the olefin formed is a conjugated one.



a) TiCp_2Cl_2 , Zn, THF, 70%

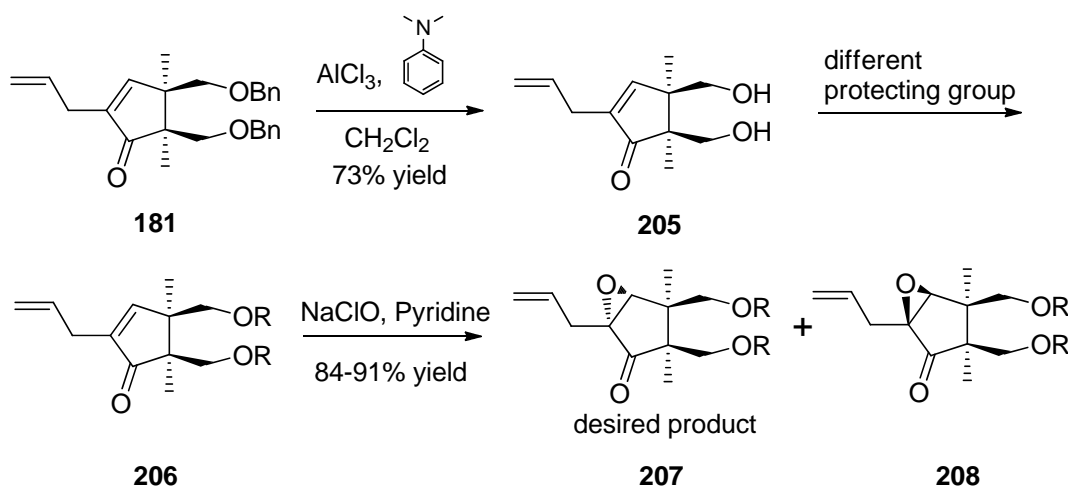
Scheme 2-36. Recovery of unwanted minor β -epoxide 204

Application of this methodology on our substrate **204** proved efficient: to a solution of the titanium(III) reagent, the substrate in tetrahydrofuran was added dropwise and stirring was continued for 10 hours at room temperature under argon. The deoxygenation product **176** was isolated in 70% yield, while other methods, such as

treatment with Mo(CO)₆ in refluxing benzene, only gave very low yields of the desired product.

Protection of diols with bulky silyl protecting groups.

A detailed investigation into stereocontrolled epoxidation was undertaken using bulkier protecting groups on the diol motif, which is briefly summarized below: if we could change the two OBn groups to bulkier protecting groups, such as silyl protecting groups, the diastereoselectivity of the epoxidation could possibly be improved. This proved to be the case. Debonylation and subsequent protection of diols with a series of different size silyl groups worked well. The results of diastereoselectivity in the epoxidation reaction are shown in table 2-5.



Scheme 2-37. Protection with different size silyl groups

Table 2-5

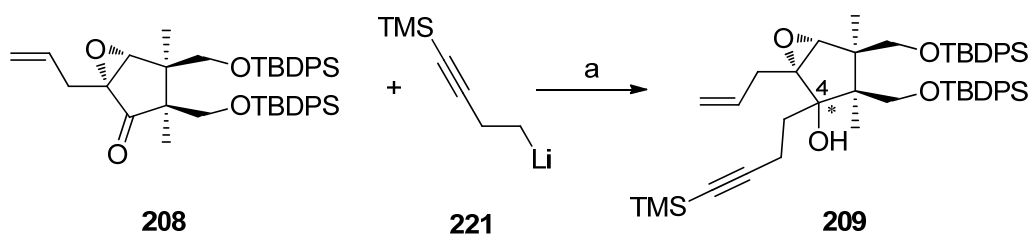
Entry	Protection group (R)	Ratio of 207 and 208
1	Bn	1.2 : 1
2	>Si(t-Bu) ₂	3.4 : 1
3	TBS	>10 : 1
4	TPS	SM decomposed
5	TBDPS	Sole product 207

*The ratio was determined by ¹H-NMR analysis

The diastereoselectivity of the epoxidation increased from 3.4 : 1 to 10 : 1 when

$>\text{Si}(\text{t-Bu})_2$ and TBS were used as protecting groups, respectively. TPS protection groups were found to be unstable in the epoxidation conditions and led to rapid decomposition of starting materials. Eventually, when TBDPS was used as protecting group the desired epoxidation product **207** was achieved as the sole product.

Unfortunately, the bulky TBDPS groups led to some problems in the following 1,2 addition reaction. Treatment of **208** with **221** produced the sole addition product **209** in high yield, however the newly formed chiral centre at C4 could not be assigned by nOe experiments at this stage. We expected that the epoxide group would be the dominant element of stereocontrol in 1,2 addition in general for this system (*vide infra*), but in the case of the very bulky TBDPS groups this epoxide control might be overwhelmed. Treatment of **209** with titanium(III) was fruitless and only the SM was fully recovered. Attempts to remove the TBDPS groups before 1,2-addition under various condition were also unsuccessful.



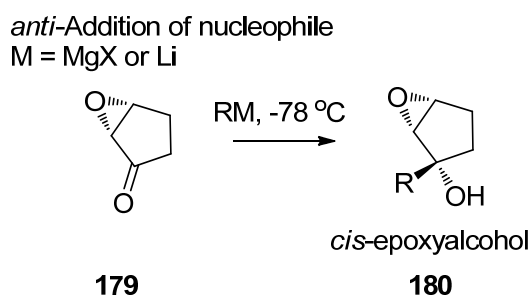
a) Et₂O, -78 °C

Scheme 2-38.

High selectivity (both regio and diastereo) of chemical reactions in total synthesis is certainly always preferred. In our case, using bulky TBDPS protection groups induced high diastereoselectivity for the epoxidation reaction, and we believed that the selectivity in the following 1,2-addition reaction and reactivity in the radical chemistry could possibly be solved by some method eventually. However, due to time restrictions and the fact that the benzyl groups were already proven as reliable in the synthesis (despite the moderate diastereoselectivity of the epoxidation reaction), under such circumstances we decided to advance our synthesis to the next step with benzyl groups.

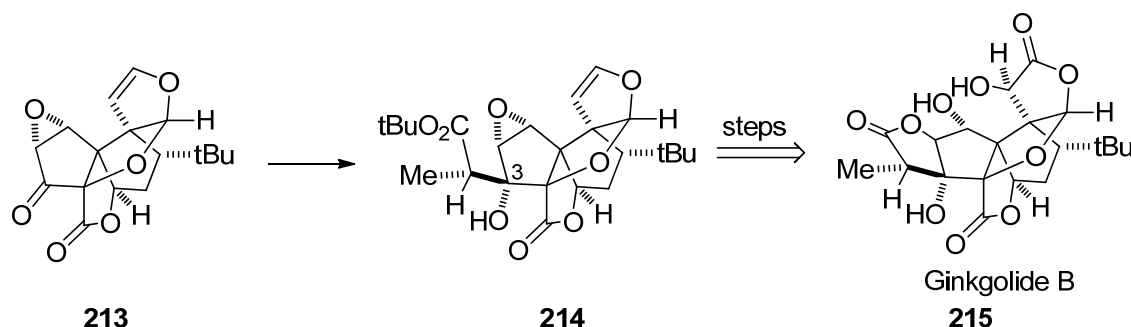
2.4.2.3 Stereoselective organometallic addition

With adequate quantities of α -epoxide **203** in hand we intended to carry out the introduction of the C15-C1-C2-C3 side-chain *via* organometallic addition. The epoxide group is known to exert powerful stereocontrol in this reaction for simple five-membered ring systems, enforcing exclusive *anti* addition of organometallics to the carbonyl group to produce the *cis*-epoxyalcohol (Scheme 2-39)^[66,67].



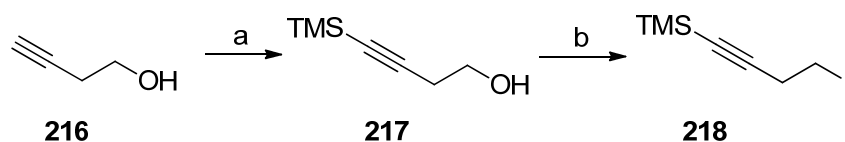
Scheme 2-39. Stereoselective 1,2-addition in the simple model system

A complex example in natural product synthesis could be found in the Corey's total synthesis of Ginkgolide B^[68]. Reaction of advanced intermediate **213** with 7 equivlant of the lithium enolate of *tert*-butyl propionate (from LDA) in 4:1 THF-hexamethyl-phosphoramidate (HMPA), furnished the desired aldol adduct **215** in 60% yield combined with a small amount of C3 epimer (ca. 7%).



Scheme 2-40. A complex example of stereoselective 1,2-addition

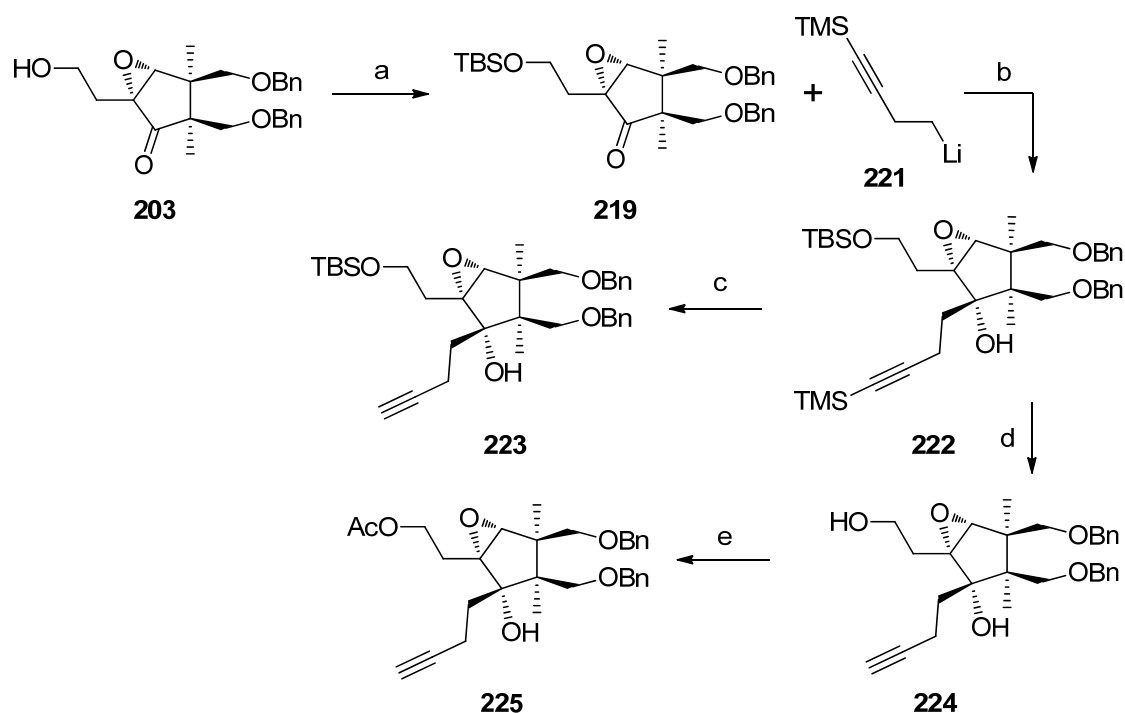
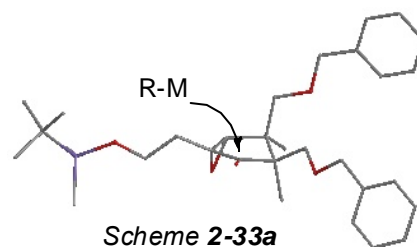
The side chain to be introduced was prepared in two steps as is outlined in Scheme 2-41. Treating 3-butyn-1-ol **216** with *n*-butyllithium and TMSCl furnished the intermediate alcohol **217** which was subsequently iodinated to afford **218** in good yield. Addition of *tert*-butyllithium to **218** would facilitate a lithium iodide exchange, generating organolithium **221** in high yield.



a) *n*BuLi, THF, -78 °C, then TMSCl, RT, 18 h; b) PPh₃, Imidazole, I₂, THF, RT, 1 h, 78% over 2 steps

Scheme 2-32. Synthesis of side-chain 218

We envisaged that the epoxide group would be the dominant element of stereocontrol in 1,2 addition to **219**, presenting a sterically more accessible convex face of the bicycle to the incoming nucleophile, anti to the epoxide C-O bond (see Scheme 2-33a for an MM2-minimised structure of **219**).

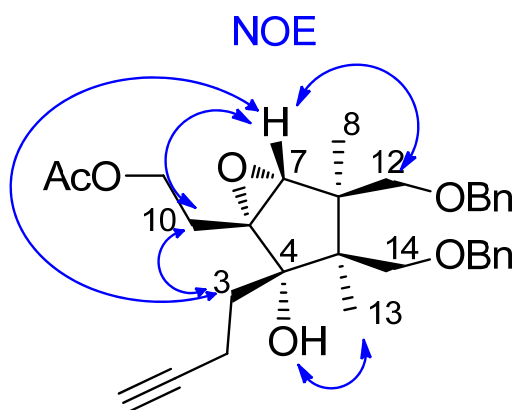


a) TBSCl, Et₃N, DCM, 91%; b) Et₂O, -78 °C, 94%; c) KOH, MeOH, 99%; d) TBAF, DCM; e) Ac₂O, pyridine, DCM 67%

Scheme 2-42. Stereoselective organometallic 1,2-addition

This proved to be the case – addition of excess homopropargyllithium reagent **221** to the highly hindered ketone proceeded in excellent yield and diastereoselectivity,^[16] affording the tertiary alcohol **222** as essentially a single stereoisomer in 94% yield (Scheme 2-42). The product of the organometallic addition reaction was then treated with KOH in MeOH^[19] or TBAF in DCM to remove the terminal alkyne protecting group and furnished **223** or **224** in 98% and 99% yield, respectively. The primary alcohol in **224** could be protected as an acetate when treated with Ac₂O in pyridine.

Once we successfully introduced the desired side-arm in excellent yield we set about demonstrating its relative stereochemistry. The use of X-ray crystallography proved unfeasible, as **225** was an oil. Nonetheless, the elucidation of the relative stereochemistry was achieved by means of extensive 1D and 2D-NMR spectroscopy (Scheme 2-43).



Scheme 2-43. nOe-signals observed for 1,2-addition product **225**

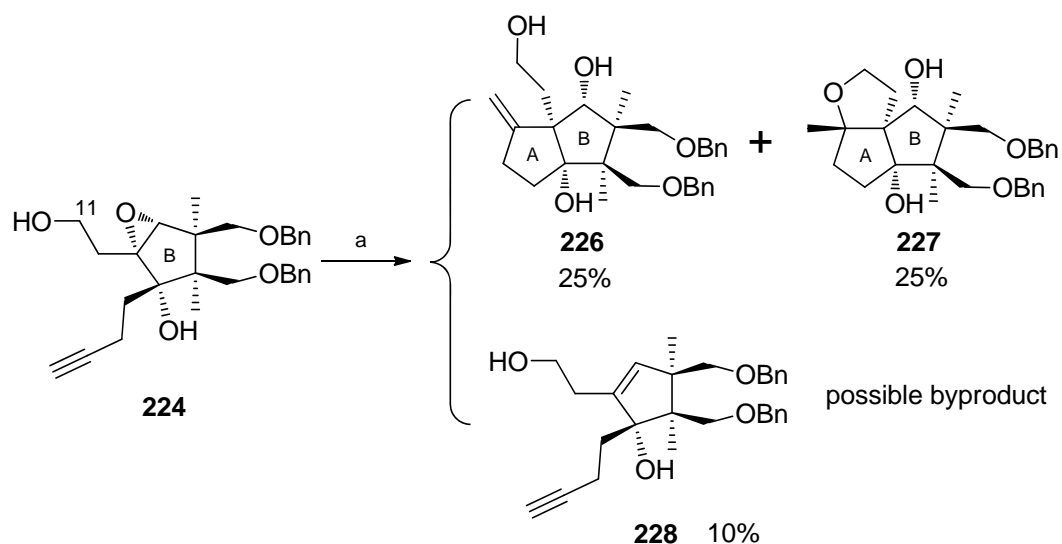
The crucial stereochemical configuration to be assigned was the orientation of the tertiary alcohol at C4. If we could demonstrate its location to be on the same face as the methyl substituents at C8 and C13, we would confirm the incoming nucleophile of 1,2-addition was anti to the epoxide C-O bond, thus constructing the correct stereochemistry at C4. Such proof was found in the nOe effect observed between the proton signals of the methyl substituent C13 and the proton of the tertiary alcohol at C4 as well as the nOe effect between C3 and C10. Both interactions strongly support our stereochemical assignment as indicated above. Furthermore the nOe correlations observed between the protons C7 and C12 confirmed the epoxide to be located on

the same face as the two methyl substituents, C8 and C13. Thus the stereochemistry of the epoxide **225** is correct.

2.5 Titanium(III)-Mediated Radical Cyclization

2.5.1 Radical cyclization in the synthesis of BC core of merrilactone A

As our successful preliminary reactions had been carried out on a model system (Scheme 2-9), initially we attempted this methodology on substrate **224** containing a free C11-OH group. The titanium(III) reagent was prepared *via* the following standard methods: to a flask containing titanocene dichloride (Cp_2TiCl_2) and excess activated zinc powder as the reducing agent was simply added anhydrous and degassed THF under a constant purge of argon. The resulting suspension was vigorously stirred for 60 min under an argon atmosphere with *rigorous* exclusion of oxygen, and the color changed from a dark red to a bright green, confirming the formation of the desired titanium(III) species. After the precipitation of unreacted zinc, the solution of titanium(III) was then transferred into a solution of substrate **224** in THF. The concentration of resulting substrate solution is [0.2] M. The reagent side product of ZnCl_2 contained in the reaction system appeared to have no detrimental effect on the radical cyclization reaction.

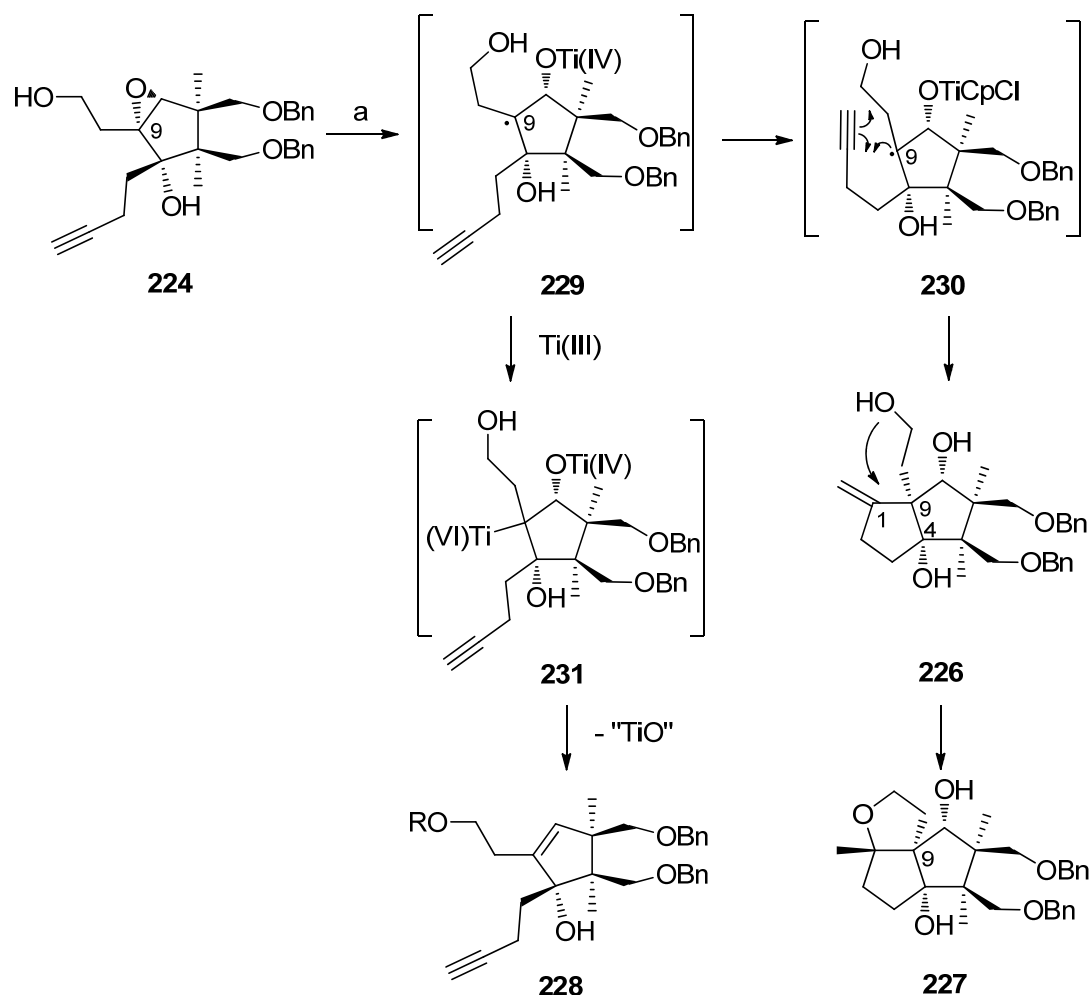


a) TiCp_2Cl_2 , Zn, THF

Scheme 2-44. Preliminary study of radical cyclisation

After 20 hours the reaction was quenched by adding several drops of water and the

excess titanium reagent was removed by filtration through a short silica pad. The crude product was purified by careful flash column chromatography to afford the major products **226** and **227** as a mixture of colourless oils in 50% yield. We were delighted to observe the successful formation of desired cyclization product **226**, accompanied with the formation of tricyclic product **227** in 1:1 ratio. Both structures were confirmed by ^1H NMR and ^{13}C NMR analysis (Scheme 2-44). Interestingly, the desired bicyclic product **226** underwent cyclization reaction to tricyclic **227** in CDCl_3 in the NMR tube after a period of several weeks. The formation of the minor byproduct was suspected to be **228** *via* a deoxygenation pathway. However the structure was not fully characterized due to the scarcity of materials and the unstable nature of this compound.

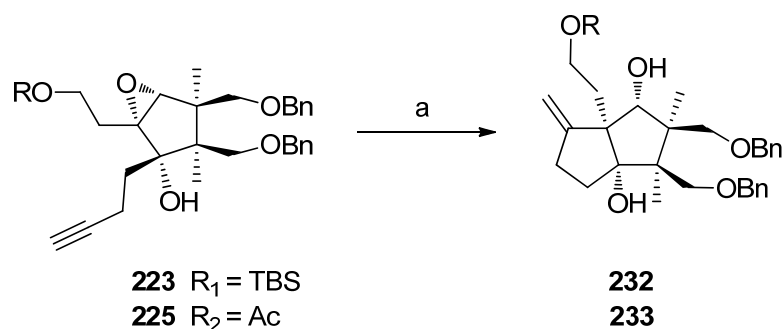


a) TiCp_2Cl_2 , Zn, THF

Scheme 2-45. Possible pathway for the formation of byproduct

Scheme 2-45 outlines the proposed mechanistic pathway for these radical transformations. Firstly, the titanium(III) mediated epoxide opening *via* regioselective C9-O homolysis generated the relative stable tertiary radical intermediate **229**, which underwent subsequent 5-*exo*-dig cyclization onto the pendant alkyne producing desired the bicyclic product **226** containing *exo*-alkene. Meanwhile the highly congested C9 quaternary stereo center was formed. It seemed that the steric conformation of **226** was appropriate for the consecutive alkene etherification reaction with free primary alcohol to produce **227**. The etherification was also possibly promoted by trace acid existing in the reaction system. Additionally, the etherification product **227** was very interesting to us as it possessed the fully carbon skeleton of the anisactone sesquiterpenes, thus **227** could possibly be converted into anisactones in a several-step sequence. This part will be discussed in detail in the following chapter of this thesis, The mechanism for the formation of byproduct **228** could be accounted for by the tertiary radical intermediate **229** reacting with a secondary titanium(III) equivalent to produce transient intermediate **231**, which subsequently lost one “TiO” to afford deoxygenation byproduct **228**.^[20] An analogous approach to deoxygenation has been employed by us earlier in the synthesis in recycling undesired epoxide **204** (Scheme 2-36).

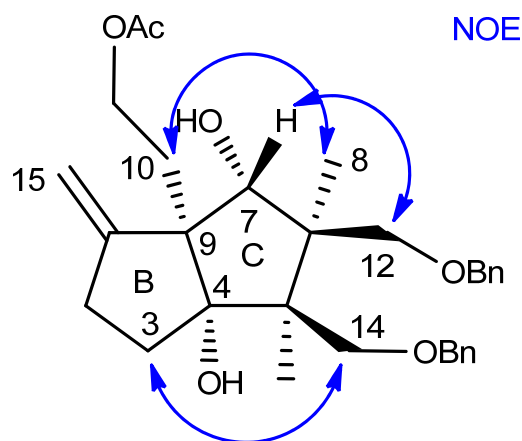
Although the desired bicyclic product **226** was achieved in only 25% yield and the reaction was accompanied by several unexpected pathways, this result still validated the feasibility of the radical epoxide opening and cyclisation methodology on our advanced complex intermediate **133**. Based on the understanding of the mechanism of the reaction, several modifications of the reaction condition could be made. Firstly, to circumvent the alkene etherification pathway we protected the primary alcohol as a TBS ether thus preventing the attack of free alcohol on the *exo*-alkene. Secondly, dilute conditions along with dropwise addition of titanium(III) reagent to epoxide, were found to be essential in minimizing the formation of deoxygenation product **228** over the course of the reaction.



a) TiCp_2Cl_2 , Zn, THF, 67-73%, 10% SM recovered

Scheme 2-46. Titanium(III) induced radical cyclization

Applying the modified conditions under dilute concentrations ^[60,61] ([0.04] M) of the substrates **223** and **225**, we were delighted to find that the reaction proceeded smoothly and furnished the bicyclic products **232** and **233** in 73% and 65% yield respectively, with the recovery of 10% starting materials over 20 hours. As before, the reaction was carried out under strict exclusion of oxygen throughout the course of the transformation. Initial formation of the low valent titanium reagent was achieved via treatment of titanocene with zinc dust and consecutive transfer of this reagent into a THF solution of substrate **223** and **225**, which resulted in the formation of the desired products **232** and **233**, respectively.



Scheme 2-47. nOe-signals observed for radical cyclisation product 233

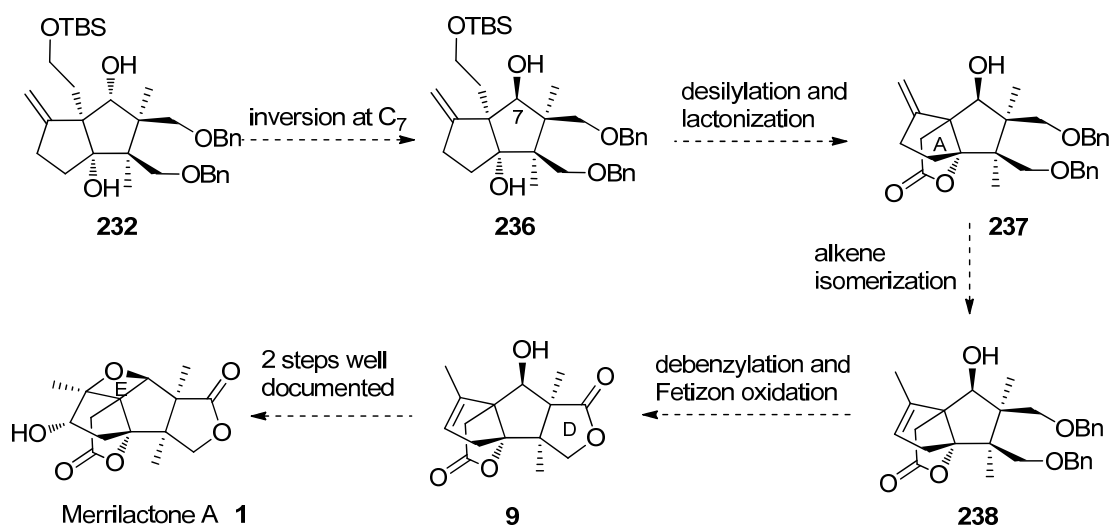
Once we had successfully employed the pivotal radical epoxide opening and cyclization strategy to our substrate **225** to afford the advanced bicyclic **233**, we set about demonstrating its relative stereochemistry (Scheme 2-47). The radical

cyclization product **233** could be fully characterized *via* 1D NMR spectroscopy techniques, however its relative stereochemistry proved difficult to elucidate by crystallographic methods, as it was an oil. Thus we turned our attention to 2D-NMR spectroscopy. Assignment of all ¹H NMR signals could be determined by COSY and HMQC experiments. Shown in Scheme 2-44 are the nOe interactions observed in the NOESY spectrum of **233**. Strong correlation peaks indicated a close spatial arrangement between the single proton at C7 and C12, suggesting that the secondary alcohol was on the same face as the *bis*-benzyl protected diol. Both nOe interactions between C8 and C10, C3 and C14 indicated that the newly formed B ring bearing an *exo*-alkene group was also on the same face as the *bis*-benzyl protected diol. These results were in accordance with our expectation and confirmed the stereochemistry of **233** to be as predicted.

It is worth noting that these nOe interactions outlined in Scheme 2-47 also confirmed the newly formed secondary alcohol at C7 to be on the opposite face of ring C with respect to the benzyl protected diol, as expected. This incorrect orientation of the hydroxyl group for merrilactone A required an inversion of stereochemistry, which would be achievable *via* an oxidation/reduction sequence.

2.6 Total synthesis of merrilactone A

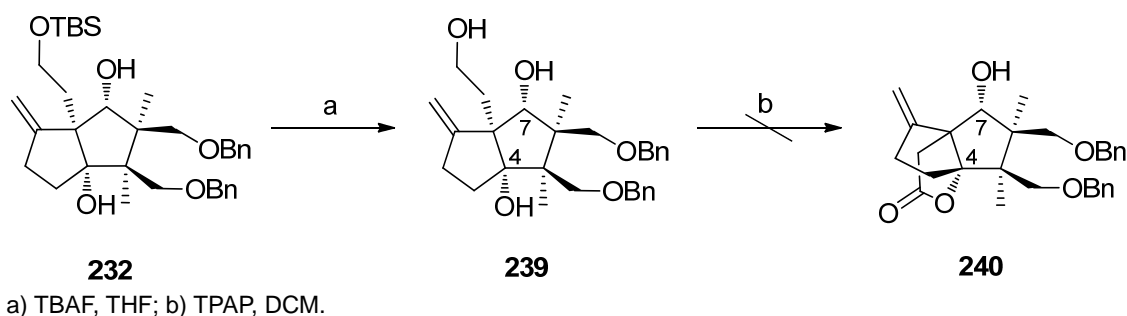
With the radical cyclization product **232** in hand, we were well placed to complete the synthesis as all C-C bond forming steps are complete. Considerable redox-adjustments were still required, however. The transformations shown in Scheme 2-48 were planned as the synthetic endgame: (i) inversion of the stereochemistry of the secondary alcohol at C7 of **236**, (ii) desilylation of TBS group and lactonization to form the left-hand γ -lactone A of **237**, (iii) debenzylolation and Fetizon oxidation of the diol to form right-hand γ -lactone D of **9**. Finally we anticipated to employ the known procedure of stereoselective epoxidation and *homo*-Payne rearrangement to construct the oxetane ring E.



Scheme 2-48. Synthesis plan for merrilactone A

2.6.1 Synthesis of γ -lactone A in merrilactone A

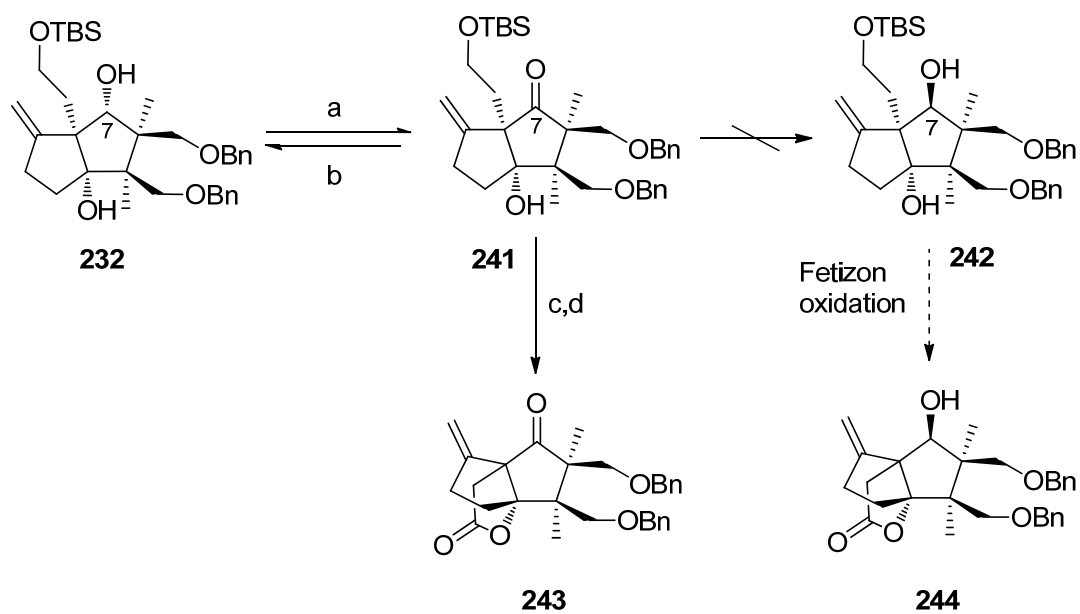
Several attempts to synthesize the γ -lactone A *via* different pathways were investigated in our synthesis (Scheme 2-49). Desilylation of **232** was straightforward, affording **239** in high yield. Subsequent oxidation with tetrapropylammonium perruthenate (TPAP) produced a mixture of several products based on TLC analysis. The lactonization reaction could undergo two competitive pathways with either the secondary alcohol at C7 or the tertiary alcohol at C4. Thus we decided to oxidize the secondary alcohol at C7 into a ketone to avoid the undesired lactonization pathway.



Scheme 2-49. Synthesis of γ -lactone A

Treatment of **232** with TPAP and excess NMO in dry DCM in the presence of molecular sieves afforded the ketone **241** smoothly (Scheme 2-50). Oxidation of **232** with Dess-Martin periodinane (DMP) also produced the desired ketone **241** but in low yield. At this stage we hoped to create the correct stereochemistry at the C7

secondary alcohol by means of reduction. A highly selective reduction had been achieved on an analogous structure in both Hirama and Metha's total synthesis of merrilactone A, where the bulky reducing reagent DIBAL-H demonstrated good selectivity in the reduction of ketone of **48** and **76** (Scheme 1-16 and 1-24). In turn we expected that Fetizon's oxidation could construct the γ -lactone A of **244** in the presence of secondary alcohol functionality (outlined in Scheme 2-50).



a) TPAP (50% mol), NMO (10 eq), DCM, 10 h, 76%; b) DIBALH or LiBH₄; c) TBAF, THF; d) TPAP (10 % mol), NMO (5 eq), 86% over 2 steps

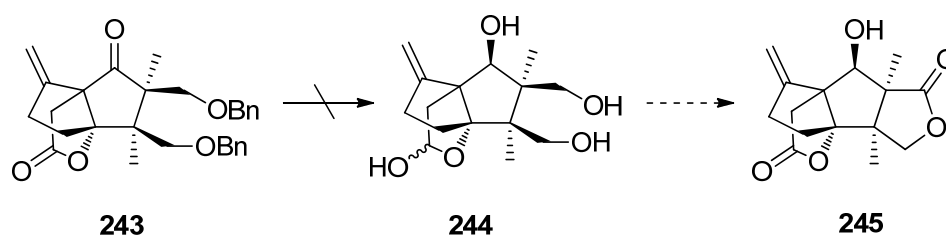
Scheme 2-50. Synthesis of γ -lactone A

However, to our surprise, slow addition of DIBAL-H into substrate **241** in toluene or dichloromethane at -78 °C only led to the recovery of the secondary alcohol **232**. No expected formation of secondary alcohol **242** was observed. We assumed that the benzyl ether groups could act as *syn*-directing participating groups *via* coordination with DIBAL-H, and then DIBAL-H delivered the hydride to the ketone from the same face of the benzyl group. Reduction with LiBH₄ produced the same product **232**. Other reduction reagents were investigated, including NaBH₄, Zn(BH₄)₂, and samarium(II) iodide (SmI₂), however the ketone group remained intact under such conditions indicating significant steric hindrance.

Currently we do not have an accurate explanation for the stereoselectivity of this

reduction reaction. As a result, we decided to employ an alternative synthetic approach based on compound **243** shown in Scheme 2-50. The γ -lactone A would be constructed first (**243**), then debenzoylation and stereoselective reduction of ketone would occur concurrently under dissolving metal conditions, a transformation based on precedent from Hirama's synthesis. The correct stereochemistry at C7 could be expected during the course of dissolving metal reduction. Treatment **241** with TBAF led to desilylation smoothly and subsequent lactonization with TPAP and excess NMO furnishing the γ -lactone A **243** in 86% yield over two steps. (Scheme 2-50)

Attempts at the debenzoylation of substrate **243** containing *exo*-alkene motif under dissolving metal condition were investigated subsequently at this stage. Accordingly, applications of Hirama's protocol of sodium in ammonia (*vide infra*) on **243** were carried out. Unfortunately these efforts were fruitless, as $^1\text{H-NMR}$ spectrum indicated that no desired product **224** was formed under this condition.



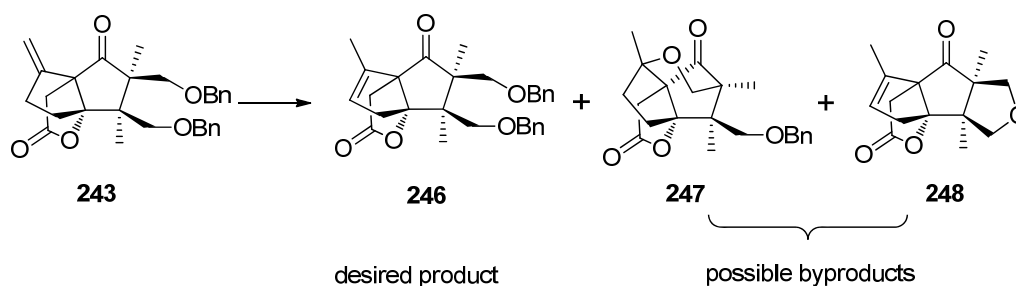
Scheme 2-51

As all of these attempts *via* different pathways to synthesize merrilactone A investigated above were unsuccessful, we directed our attention to the alkene isomerization reaction, in which the *exo*-alkene would be moved to an internal pattern.

2.6.2 Alkene isomerization

It was necessary to isomerize the *exo*-cyclic alkene into the B ring at this stage. The alkene isomerization reaction had been carried out by Danishefsky in the course of his merrilactone synthesis, albeit on a substrate differing in C-ring functionality. Using Danishefsky's conditions of *p*-toluenesulfonic acid in refluxing toluene for 4 hours afforded one major product accompanied by trace amounts of byproducts. The

major product, which was separated by silica column chromatography and characterized by ^1H NMR spectrum, however was not the desired olefin isomerization product **246**, and was suspected to be **247**. Mass spectrometry indicated that one benzyl protecting group had been removed in the reaction. The lability of the benzyl groups was confirmed by O-debenzylation products being observed even in refluxing dichloromethane with 1 equivalent p-toluenesulfonic acid. Debenzylation is known to be promoted by strong Bronsted acid or Lewis acid such as trifluoromethanesulfonic acid (TfOH), iron(III) chloride^[69,70] or tin(IV) chloride;^[71] however, O-debenzylation by TsOH is unusual in the literature^[72]. In order to access the desired olefin isomerization product, a number of modifications of the reaction conditions were made and the results are presented in the Table 2-6.



Scheme 2-52. Alkene isomerization

Table 2-6

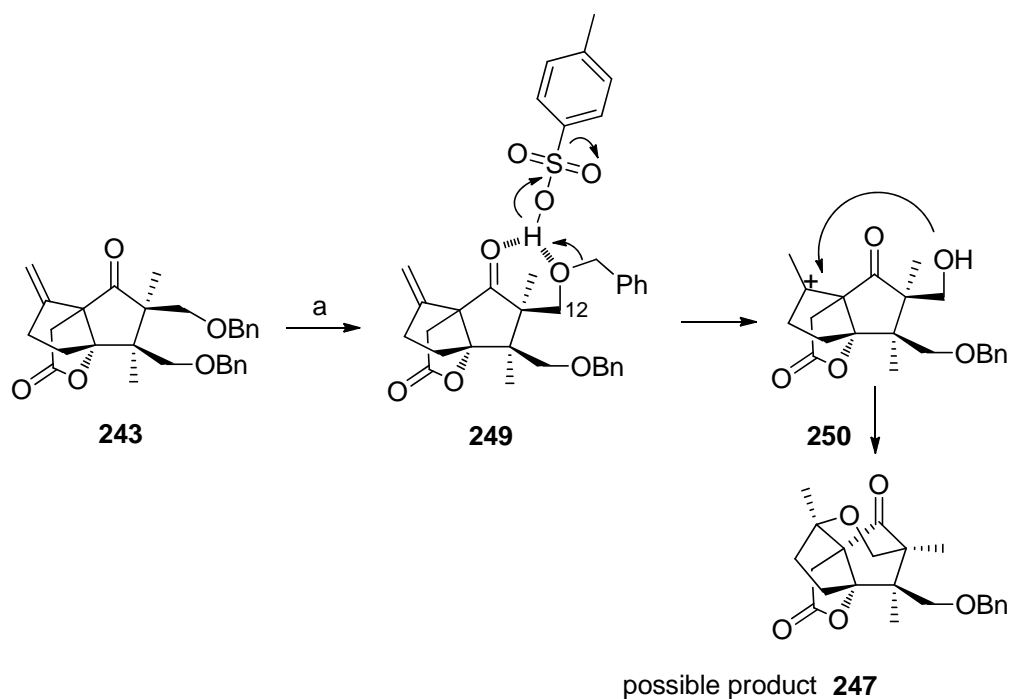
Entry	condition	results
1	TfOH, CH_2Cl_2	product 248
2	MsOH, CH_2Cl_2	two unidentified byproducts
3	TsOH, benzene, reflux	product 247
4	TsOH, CH_2Cl_2 , reflux or 40 °C	product 246 and 247
5	TsOH, CH_2Cl_2 , 30 °C	product 246 , reaction is slow
6	TsOH, AcOH, CH_2Cl_2 , 30 °C	2 days, product 246 , 92% yield
7	TFA, CH_2Cl_2	No Reaction
8	$\text{Rh}(\text{Ph}_3)_3\text{Cl}$, toluene, reflux	20h, product 246 , 10% conversion

*possible product **247** and **248** were not fully characterized

As shown in Table 2-6, treatment of substrate **243** with trifluoromethanesulfonic acid (TfOH) in dichloromethane produced rapid alkene isomerisation even at -78 °C.

However, deprotection of the benzyl ether group was followed by intramolecular S_N2 reaction immediately affording the cyclic ether **248** as the major product (entry 1). Exchanging to methanesulfonic acid (MsOH) led to two unidentified byproducts (entry 2). When *p*-toluenesulfonic acid was employed as catalyst for alkene isomerization in refluxing benzene, it only led to the formation of unexpected product **247** (entry 3). When reaction was carried out in refluxing dichloromethane, we did observe the formation of the expected product **246** albeit in low yield (entry 4). Further decreasing the temperature to 30 °C suppressed the unwanted debenzilation pathway and led to the formation desired product **246** (entry 5), but the reaction processed extremely slowly - probably due to the poor solubility of *p*-toluenesulfonic acid in dichloromethane at low temperature. Finally, using a solvent mixture of acetic acid and dichloromethane at 30 °C with *p*-toluenesulfonic acid was found to be effective for the alkene isomerization. The internal alkene **246** was obtained in high yield after 2 days while the O-debenzilation reaction was suppressed (entry 6). Transition metal rhodium-catalyzed alkene isomerization reaction was also investigated and the conversion was less than 10% even after 20 h (entry 8).

The detailed mechanism of the O-debenzilation etherification reaction remained unclear. However, the mild conditions using *p*-toluenesulfonic acid as catalyst at 30 °C led us to consider the mechanism of this reaction. Highly selective removal of the two benzyl protecting groups indicated some additional factor at work in this transformation; we suspected that the adjacent ketone group could participate in directing selective debenzilation *via* a proton chelating effect^[73].



a) TsOH, DCM

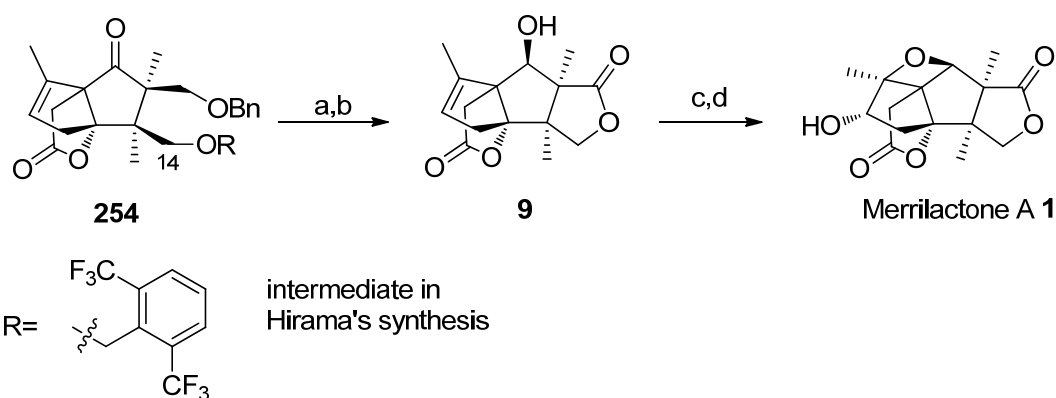
Scheme 2-53. Proposed chelation mechanism for selective debenzoylation reaction

The ketone oxygen could be capable of chelating the proton from *p*-toluenesulfonic acid which therein facilitated the acid-mediated debenzoylation *via* a six-membered cyclic intermediate **249**, as proposed in Scheme 2-53. A similar chelated intermediate has been put forward by Steven Fletcher to account for the trifluoroacetic acid mediated rapid O-debenzoylation of *ortho*-substituted phenols^[73]. Another analogous intermediate was also proposed by Baldwin for the MgBr₂-mediated debenzoylation reaction^[74]. Following debenzoylation, the free alcohol **250** attacked the *exo*-alkene to produce the stable six-membered cyclic ether.

Due to the the limited quantities of material and time restrictions, no further experiments were done to reinvestigate the mechanism for the formation of the products **247** and **248**. However, based on the results and preceding literature we believe that the account for this transformation is reasonable.

2.6.3 Formal total synthesis of merrilactone A

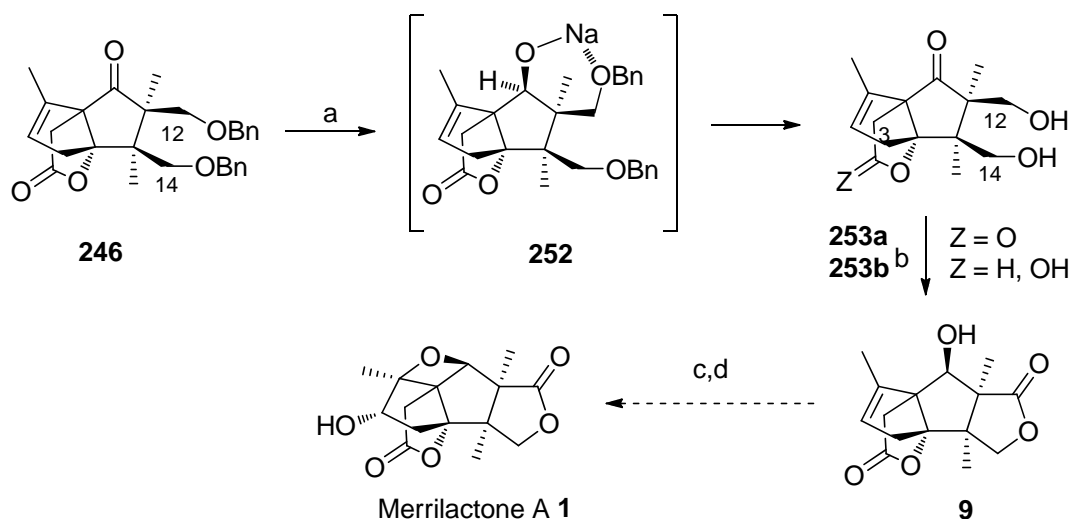
Compound **246** is very similar to a late-stage intermediate **254** in Inoue and Hirama's synthesis, differing only slightly in the protecting group at C14 (benzyl vs. substituted benzyl).



a) Na, NH₃, EtOH/THF, -78 °C; b) Ag₂CO₃, toluene, reflux, 41% over 2 steps; c) *m*CBPA, DCM, 91%; d) TsOH, DCM, 96%.

Scheme 2-54. Hirama's synthesis of merrilactone A

Accordingly, application of Hirama's two-step protocol (Scheme 2-55) of sodium in ammonia followed by Fetizon's reagent affected three transformations: first, the dissolving metal reduction effects debenzoylation and subsequent stereoselective reduction of the hindered ketone at C7 to the β -hydroxy group, presumably *via* **252** through a six-membered chelate. It is likely that the lactone A ring is also reduced to a lactol at this stage. Second, the mixture of lactols **253a/b** is oxidized with Fetizon's reagent^[75,76] – the weak oxidizing agent is selective for the sterically most accessible C12 primary alcohol – to produce the desired bis- γ -lactone **9** as a single isomer. This selectivity in the oxidative lactonization step is crucial to the success for the synthesis and was preceded in Hirama's work – molecular models of **246** shows that the C14 position is quite occluded by the sp³ C3 atom on the other side of the molecule. We were very happy to replicate the stereo- and regio-selectivity of this transformation. Unfortunately the isolated yield over the two steps was a poor 28% - considerably lower than that reported by Hirama, and we did not have the material to optimise this reaction further in our hands. Tetracycle **9** is the antepenultimate compound in all merrilactone A syntheses to date and the ¹H NMR, ¹³C NMR, IR, and HRMS spectra of **9** matches those reported in the previous literatures, thus represented a formal total synthesis of this natural product.



a) Na, NH₃, EtOH/THF, -78 °C; b) Ag₂CO₃, toluene, reflux, 28% over 2 steps; c) *m*CBPA, DCM; d) TsOH, DCM

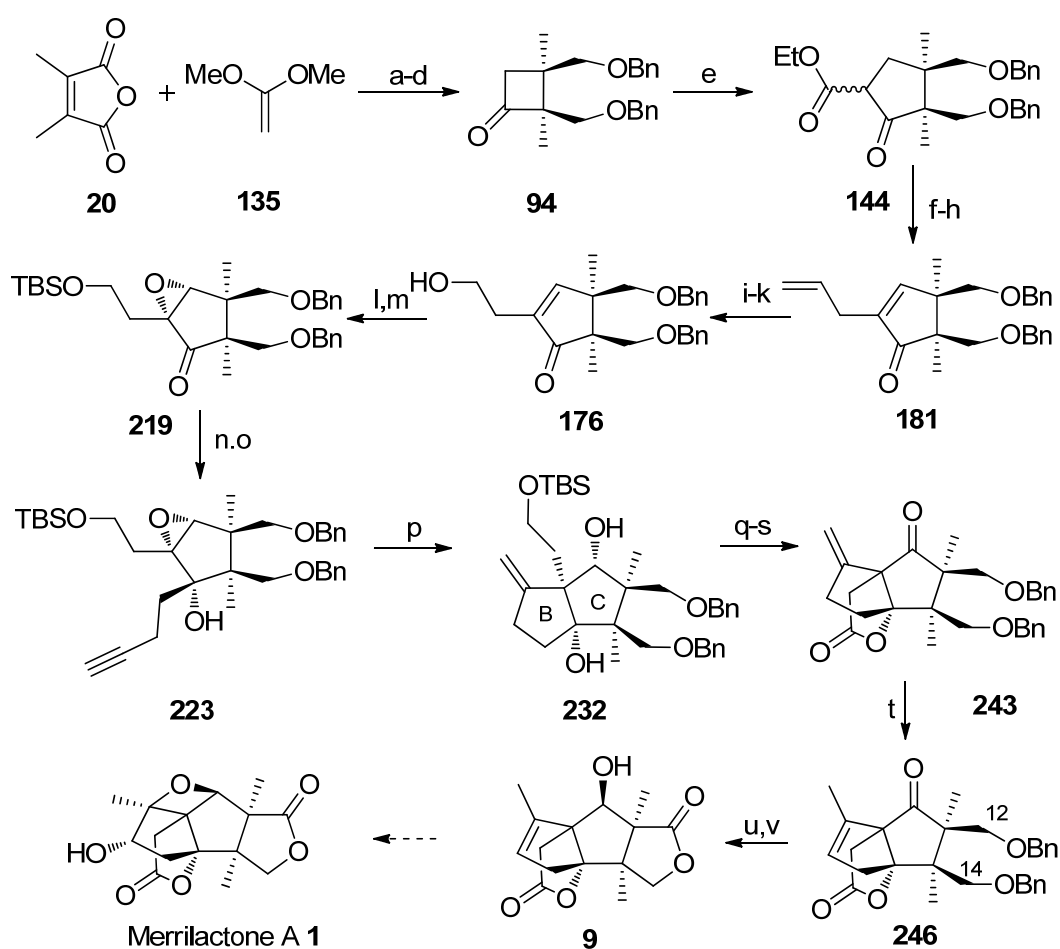
Scheme 2-55. Formal total synthesis of merrilactone A

2.7 Conclusion

We have achieved a formal total synthesis of the complex, neurotrophic sesquiterpenoid merrilactone A following the approach shown in Scheme 2-56.

The synthesis towards natural products began with [2+2] photocycloaddition of 4,5-dimethylmaleic anhydride **135** and dimethylketene acetal **20**. Reduction of the resulting anhydride, benzyl protection and ketal hydrolysis gave the cyclobutanone **94** in 83% yield over 4 steps. The required cyclopentanone **144** was achieved *via* a highly regioselective Tiffeneau-Demjanov rearrangement reacting with ethyl diazoacetate in the presence of BF₃·Et₂O. The ethyl ester group in **144** was then transesterified with allyl alcohol, followed by C-alkylation of the β-keto-ester with allyl bromide to set up a Tsuji-Trost decarboxylation-dehydrogenation sequence. Treatment with catalytic Pd(OAc)₂ and PPh₃ worked smoothly and gave the enone **181** in 90% yield. Oxidative cleavage of the terminal alkene followed by immediately reduction of the aldehyde with Zn(BH₄)₂(Py) complex gave the cyclopentanone **176** in 72% yield over 3 steps. The required α-epoxide **219** was prepared through NaOCl treatment of enone **176**, then addition of excess homopropargyl lithium reagent to the highly hindered ketone **219** proceeded in excellent yield and diastereoselectivity, affording the tertiary alcohol **223** as a single

stereoisomer in 94% yield. Treatment of **223** with Cp_2TiCl_2 and excess zinc promoted a reductive epoxide cleavage with titanium(III) and subsequent 5-*exo*-dig cyclisation onto the pendant alkyne resulted in successful formation of the BC bicycle **232** in 69% yield (79% brsm). Oxidation of the hindered secondary alcohol of **232**, desilylation and oxidative lactonization with TPAP afforded the tricyclic compound **243** in 71% yield over 3 steps. Careful treatment **243** with a mixture of TsOH and AcOH in DCM at 30 °C over 2 days afforded the internal alkene **246** in high yield. Compound **246** was very similar to a late stage intermediate in Inoue and Hirama's synthesis. Accordingly, application of Hirama's two step protocol of sodium in ammonia followed by Fetizon's reagent provided the tetracycle **9**.



a) hv, pyrex, MeCN/acetone (9:1), 96%; b) LiAlH_4 , Et_2O , 0 °C, 97%; c) BnBr, TBAI, NaH, THF; d) H_2SO_4 (aq), MeCN, 90% (two steps); e) $\text{N}_2\text{CHCO}_2\text{Et}$, $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (2.5 equiv), DCM, 0 °C, 88%; f) allyl alcohol, toluene, reflux, 93%; g) allyl bromide, K_2CO_3 , acetone, 89%; h) $\text{Pd}(\text{OAc})_2$ (5 mol%), PPh_3 (5 mol%), MeCN, reflux, 90%; i) OsO_4 (2 mol%), NMO (1 equiv), acetone / H_2O (4:1), 96%; j) NaIO_4 , THF/ H_2O (1:1),

k) ZnBH₄·py, isopropanol, 0 °C, 76% (2 steps). l) NaOCl (aq), pyridine, 0 °C, 90%, dr = 2.2:1; m) TBSCl, imidazole, DCM, 0 °C, 98%; n) **186**, *t*-BuLi, Et₂O, -78 °C, 94%; o) KOH, MeOH, 98%; p) Cp₂TiCl₂ (3 equiv), Zn (9 equiv), THF, ~69%, 10% SM recovered; q) TPAP (0.5 equiv), NMO, MS 4 Å, DCM, 82%; r) TBAF, THF; s) TPAP (0.1 equiv), NMO, MS 4 Å, DCM, 90% (2 steps); t) TsOH, AcOH/DCM (1:1), 30 °C, 78% (5% SM recovered); u) Na, liq NH₃, THF / EtOH (5:1), -78 °C; v) Ag₂CO₃ on celite, toluene, 130 °C, 28% (two steps);

Scheme 2-56

The key intermediate **9** was achieved *via* a 22 steps synthetic route with overall 2.4% yield. Tetracycle **9** is also the common intermediate in all merrilactone A syntheses to date, and represents a formal total synthesis of this natural product.

The novel synthetic route conceptualized here offers many avenues of diversity creation around the framework of this bioactive natural product. The strategy is also amenable towards accessing a pair of epimeric sesquiterpene, anislactone A and B *via* a regio- selective lactonization pathway. Detailed synthesis of anislactones will be discussed in the next chapter.

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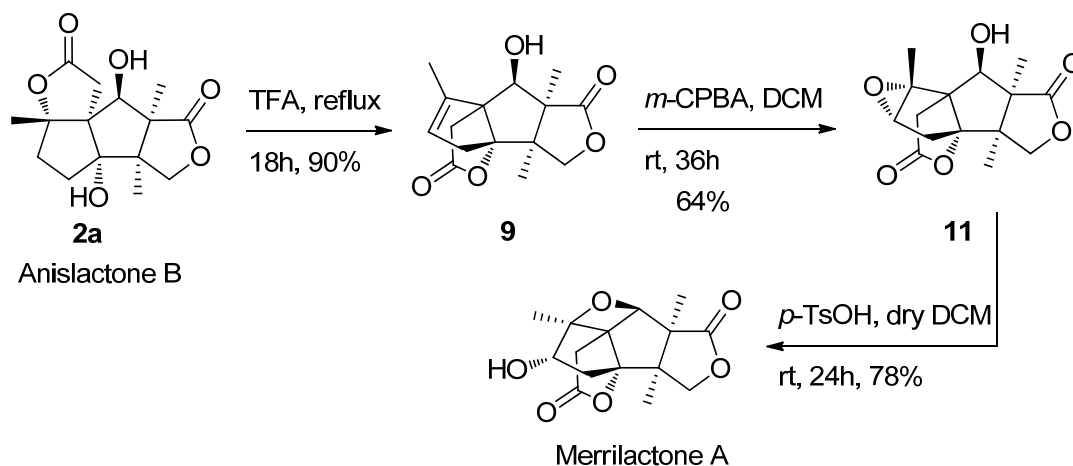
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3 Total synthesis of Anislactone A and B

3.1 Introduction and background of Anislactone A

In 1989 Kouno reported the isolation of anislactones A and B^[1], two novel sesquiterpene lactones that were isolated from the pericarps of *Illicium anisatum*. The structure of anislactone A was established from spectral data and X-ray crystallographic analysis. Anislactone B is an isomer of anislactone A, and its structure was determined by spectral data compared with those of anislactone A. Furthermore, anislactones A and B have an unique carbon skeleton, which consists of two consecutive five-membered ring frameworks fused with two γ -lactones.

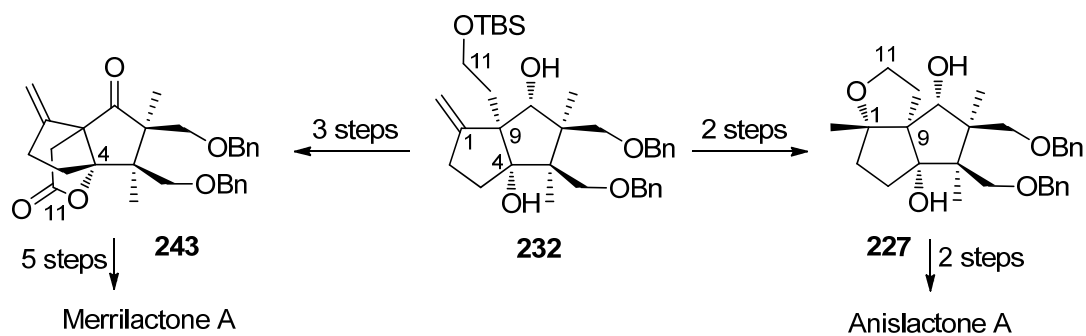
Interestingly, Fukuyama has shown that anislactone B can be converted into merrilactone A using a simple three-step sequence, suggesting that anislactones may be biogenetic precursors to merrilactone A. Anislactones A and B, by contrast to merrilactone A have received little attention from synthetic chemists with only a single report from Hong et al. on an approach to the tricyclic framework.^[2] This is presumably due to the lack of biological activity reported for the molecule, which was not subjected to any assay in Kuono's original report.



Scheme 3-1. Chemical conversion of anislactone B to merrilactone A

3.2 Aluminium triflate catalyzed intramolecular hydroalkoxylation reaction

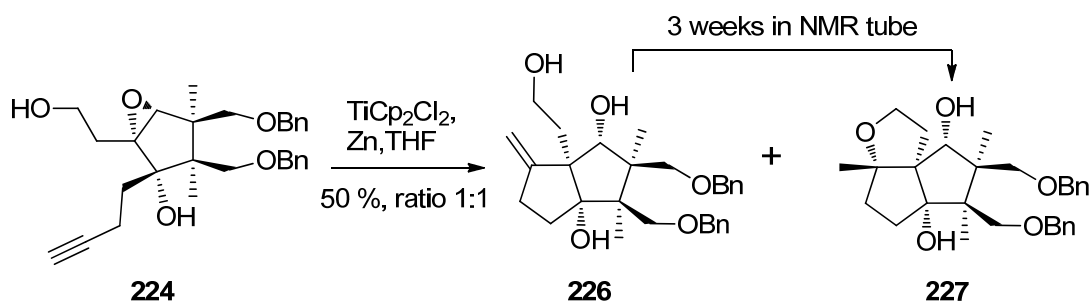
In order to access the anislactones it was necessary to install the regioisomeric γ -lactone between C1 and C9, as opposed to C4 and C9 in merrilactone A.



Scheme 3-2. Regio- selective lactonization for merrilactone A and anislactone A

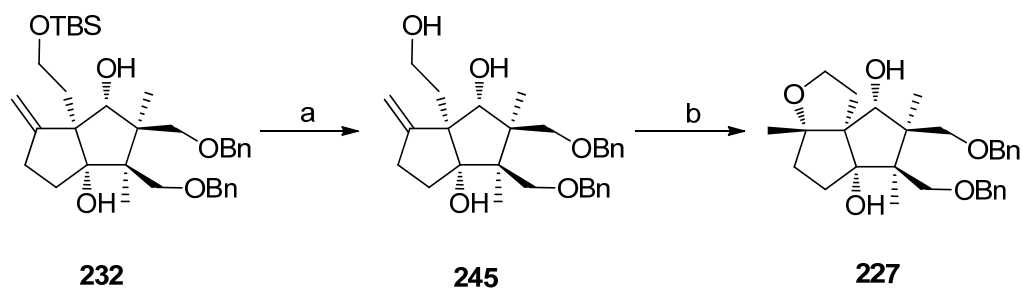
A hint on how to achieve this transformation came from our development of the earlier epoxide fragmentation/cyclization, where we observed a small amount of alkene etherification product being formed from substrates having a free C11-OH group. The etherification was possibly mediated by traces of acid existing in the reaction system and the resulting five-membered cyclic ether could be further oxidized to the γ -lactone D of anislactones.

As for merrilactone A, we prepared the titanium(III) reagent *via* the treatment of titanocene dichloride with activated zinc powder in anhydrous and degassed THF. The resulting suspension was vigorously stirred under argon atmosphere with *rigorous* exclusion of oxygen, and the color changed from dark red to bright green, confirming the formation of the desired titanium(III) species. The resulting titanium(III) complex was then transferred into a solution of **224**, containing the free primary alcohol, in THF and the resulting mixture was stirred for further 20 hours. Excess titanium reagent was removed using a silicon pad and the resulting reaction mixture was purified by column chromatography to furnish the radical cyclized products bicyclic **226** and tricyclic **227** as a mixture. Separation proved difficult by silica gel chromatography. ^1H NMR spectral data indicated that the ratio of the two products was roughly 1:1. Interestingly, bicyclic **226** underwent spontaneous etherification reaction in the NMR tube (in chloroform-d) and gradually transformed to tricyclic **227** in quantitative yield after several weeks.



Scheme 3-3.

In order to optimise the etherification reaction we screened various acid catalysts. Whilst strong Brønsted acids (TfOH, MsOH, TFA) all led to rapid decomposition, treatment of **226** with TsOH in DCM at 0 °C provided **227** but in low yield. Due to the unstable nature of the substrate **226** in the presence of Brønsted acids, we turned our attention to metal-catalyzed etherification reactions. Transition-metal catalysts such as $\text{Ce}^{\text{III}}/\text{NaI}^{\text{[4]}}$, $\text{Ru}^{\text{III}}/\text{Ag}^{\text{[5-7]}}$ and $\text{Au}^{\text{I}}/\text{Ag}^{\text{[8,9]}}$ systems, as well as Pt^{II} complexes, have recently been used as catalysts for the intramolecular etherification of unactivated alkenes to form cyclic ethers. Very recently, Elisabet Dunach *et al.* reported aluminium triflate as an efficient catalyst for the highly regioselective intramolecular hydroalkoxylation of unactivated olefins to afford the corresponding cyclic ether in excellent yield.^[10] This catalyst system provided one of the most straightforward routes to cyclic ethers with Markovnikov-type regioselectivity under very mild conditions.



a) TBAF, DCM; b) $\text{Al}(\text{OTf})_3$, DCM, 92% over 2 steps

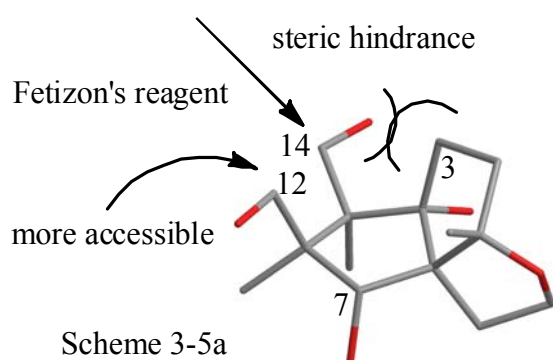
Scheme 3-4. $\text{Al}(\text{OTf})_3$ catalyzed intramolecular hydroalkoxylation reaction

Application of aluminium triflate on our substrate proved to be highly effective. We found it more efficient to effect radical cyclisation with the TBS-protected substrate as for Merrilactone A. Desilylation with tetra-*n*-butylammonium fluoride (TBAF)

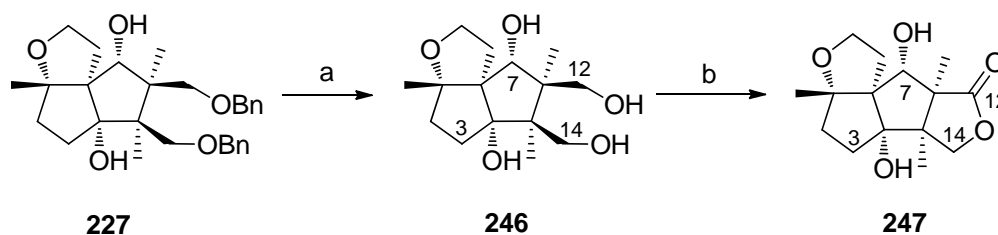
afforded **245**, the substrate for intramolecular hydroalkoxylation. The crude product **245** was redissolved in dichloromethane and treated with 0.05 equivalents of aluminium triflate. The resulting solution was stirred for 10 h at room temperature affording desired cyclic ether **227** in 88% yield over two steps, while the decomposition of substrate **245** was not observed.

3.3 Lactonization and total synthesis of anislactones

Removal of the benzyl protecting groups by hydrogenolysis was straightforward, setting the stage for two selective lactonizations (Scheme 3-5). First, the γ -lactone D was installed by regioselective oxidation of **246** with Fetizon's reagent. As previously found in this transformation, it appeared that the reactivity of the hydroxy group at C12 towards oxidation was higher than the one at C14. Molecular modeling (shown in Scheme 3-5a for an MM2-minimised structure of **246**) suggested that the steric hindrance between the protons at C3 and C14 impeded the attack of the bulky Fetizon's reagent, thus the weak oxidising agent was selective for the sterically most accessible C12 primary alcohol^[4b]. The secondary alcohol at C7 was intact and survived under these conditions due to the steric hindrance around C7 existing in the



molecule.

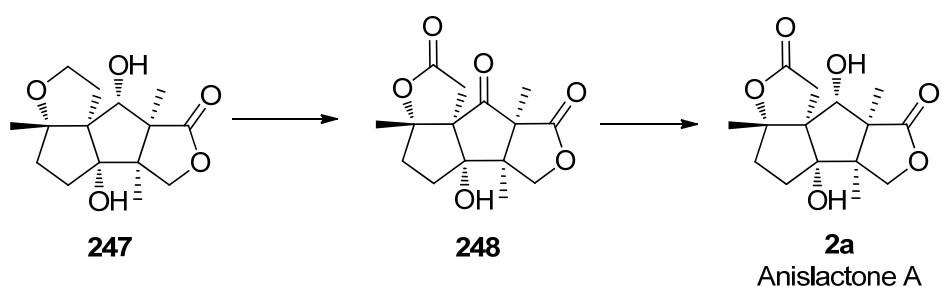


a) Pd/C, MeOH, H₂; b) Ag₂CO₃, toluene, 73% over 2 steps

Scheme 3-5. Selective lactonization of anislactones

The remaining γ -lactone A was anticipated to arise through oxidation at C11 of the cyclic ether. Using catalytic ruthenium tetroxide (RuO₄) and excess NaIO₄ in carbon

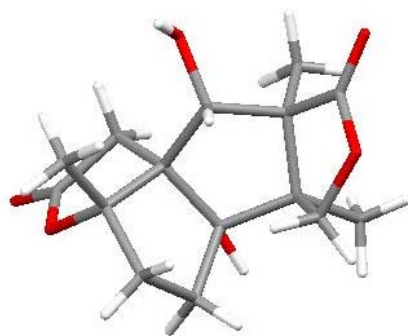
tetrachloride (CCl₄), the oxidation of **247** to **248** proved to be efficient. The reaction required several hours for completion with concomitant oxidation of the secondary alcohol to a ketone. Attempts to protect the secondary alcohol before oxidation were fruitless. Acetylation of **247** with 4-dimethylaminopyridine (DMAP), acetic anhydride and pyridine for three days yielded a tertiary alcohol protected monoacetyl derivative with the recovery of **247**. Similarly silylation with TMSCl or TMSOTf in the DCM was also unsuccessful, only furnishing mono-protected tertiary alcohol derivative, indicating the strongly hindered environment around the secondary alcohol group. Using harsh conditions, such as Ac₂O/Sc(OTf)₃/MeCN, or Ac₂O/cat. TMSOTf/DCM led to the rapid decomposition of the starting materials **247**.



a) RuO₄, NaIO₄, MeCN/CCl₄/H₂O, 75%; b) NaBH₄, THF, 98%, ratio 5:1

Scheme 3-6. Completion of anislactone A

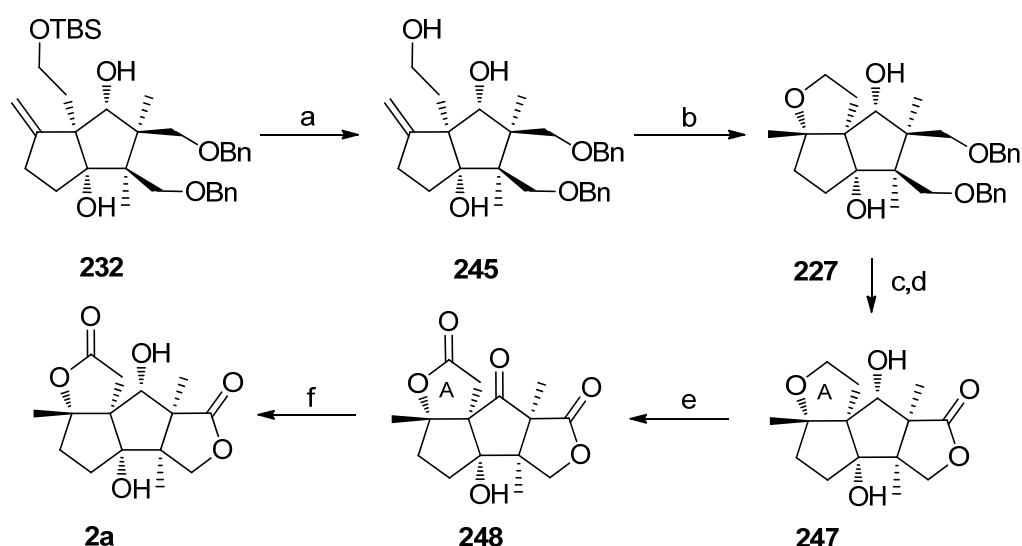
In the event, reduction of the ketone **248** with NaBH₄ was found to be efficient, delivering hydride from the more accessible β-face and producing anislactones A and B in 95% yielded as a 5:1 mixture, from which anislactone A could be purified. Synthetic **2a** matches ¹H NMR, ¹³C NMR, IR and HRMS spectra to the natural product, and the structure was confirmed unambiguously through X-ray crystallography of a single crystal which formed following chromatography (Scheme 3-7).



Scheme 3-7. X-Ray structure of Anisactone A

3.4 Conclusion

We have finished the first total synthesis of complex sesquiterpenoids anisactone A and B successfully in total 21 synthetic steps with an overall 5.6% yield.



a) TBAF, DCM/THF (5:1); b) $\text{Al}(\text{OTf})_3$ (5 mol%), DCM, 88% (two steps); c) H_2 , Pd/C, MeOH; d) Ag_2CO_3 on celite, toluene, 130 °C, 73% (two steps); e) RuCl_3 (0.5 equiv), NaIO_4 , MeCN/ $\text{CCl}_4/\text{H}_2\text{O}$ (1:1:1), 73%; f) NaBH_4 , THF, 95% (dr = 5:1)

Scheme 3-8. Total synthesis of anisactone A / B

Access to the anisactones was achieved from the common intermediate **232** via a regioselective lactonization pathway. A intramolecular etherification reaction catalyzed by $\text{Al}(\text{OTf})_3$ in DCM at room temperature afforded **227** in 88% yield. Hydrogenolysis of the benzyl protecting groups then region-selective oxidation with

Fetizon's reagent constructed the right-part γ -lactone D in **247**. The remaining γ -lactone A was then synthesised through RuO₄ oxidation at C11 of the cyclic ether, with concomitant oxidation of the secondary alcohol to a ketone. Reduction of this ketone with NaBH₄ delivered anisclactones A and B in 95% yield as a 5:1 mixture.

3.5 References

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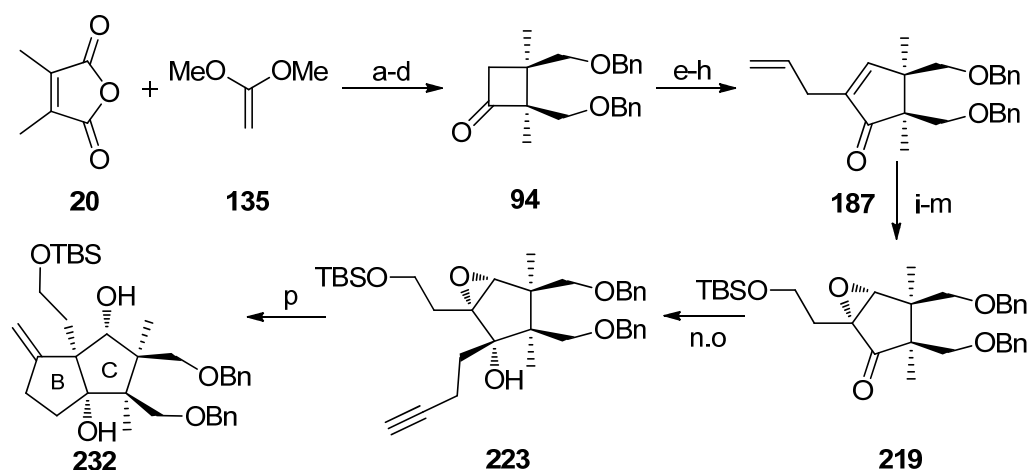
4 Conclusions

We have successfully achieved a formal total synthesis of the complex, neurotrophic sesquiterpenoid merrilactone A and the first total synthesis of anislactone A in the overall 2.2% yield (24 steps) and 5.6 % (21 steps), respectively. Our synthetic route is highly competitive with the four previous total syntheses of merrilactone A.

Table 4-1

2002	Danishefsky	20 steps	11%
2003	Hirama	27 steps	1%
2006	Mehta	27 steps	0.4%
2007	Frontier	20 steps	10%
2010	Greaney	24 steps	2.2%

One advantage of our synthetic route is that both natural products anislactone A / B and merrilactone A could be synthesized from the common intermediate **232**. We developed a concise and efficient route in 16 steps to the advanced BC intermediate **232** in overall 15.2% yield. The key transformations in our synthesis are shown in scheme 4-1.

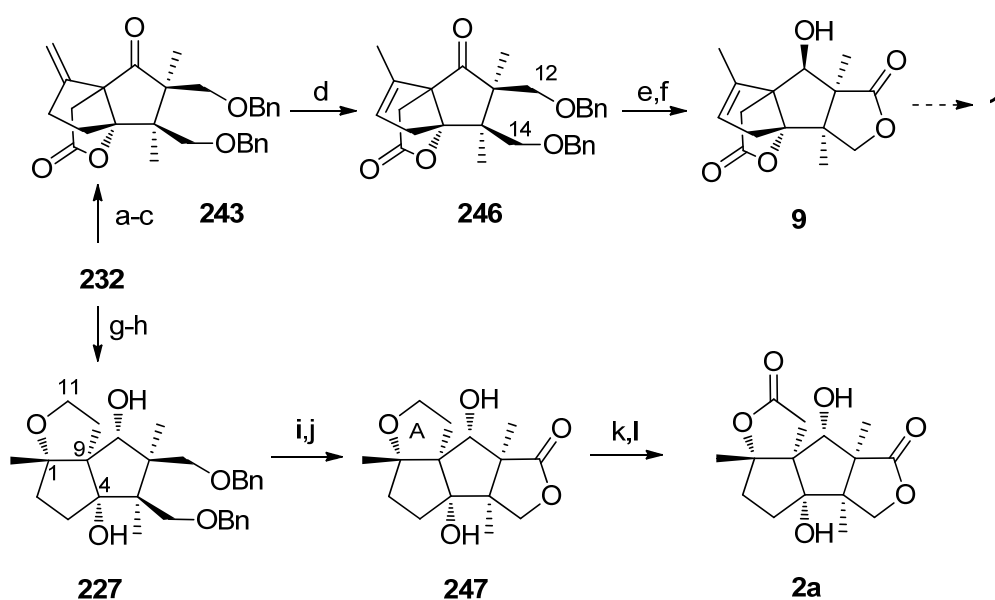


a) $h\nu$, pyrex, MeCN/acetone (9:1), 96%; b) LiAlH_4 , Et_2O , 0 °C 97%; c) BnBr, TBAI, NaH, THF; d) H_2SO_4 (aq), MeCN, 90% (two steps); e) $\text{N}_2\text{CHCO}_2\text{Et}$, $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (2.5 equiv), DCM, 0 °C, 88%; f) allyl alcohol, toluene, reflux, 93%; g) allyl bromide, K_2CO_3 , acetone, 89%; h) $\text{Pd}(\text{OAc})_2$ (5 mol%), PPh_3 (5 mol%), MeCN, reflux, 90%; i) OsO_4 (2 mol%), NMO (1 equiv), acetone / H_2O (4:1), 96%; j) NaIO_4 , THF/ H_2O (1:1), k) $\text{ZnBH}_4 \cdot \text{py}$, isopropanol, 0 °C, 76% (2 steps). l) NaOCl (aq), pyridine, 0 °C, 90%, dr = 2.2:1; m) TBSCl,

imidazole, DCM, 0 °C, 98%; n) **186**, *t*-BuLi, Et₂O, -78 °C, 94%; o) KOH, MeOH, 98%; p) Cp₂TiCl₂ (3 equiv), Zn (9 equiv), THF, ~69%, 10% SM recovered

Scheme 4-1

Cyclobutane **94** was achieved from a [2+2] photocycloaddition reaction. The five-membered C-ring **187** at the heart of the approach was synthesized through regionselective ring-expansion of cyclobutane **94**. The tertiary alcohol at C4 raised *via* a stereoselective epoxidation and organometallic 1,2-addition to the ketone in **219**. Reductive epoxide opening of **223** and radical cyclisation onto the pendant alkyne installed B/C bi-cyclic system **232** containing the highly congested C9 quaternary stereocenter. Compound **232** has the complete carbon skeleton of both anislactone A / B and merrillactone A and was directed to either one by orthogonal lactonization sequences.



a) TPAP (0.5 equiv), NMO, MS 4 Å, DCM, 82%; b) TBAF, THF; c) TPAP (0.1 equiv), NMO, MS 4 Å, DCM, 90% (2 steps); d) TsOH, AcOH/DCM (1:1), 30 °C, 78% (5% SM recovered); e) Na, liq NH₃, THF / EtOH (5:1), -78 °C; f) Ag₂CO₃ on celite, toluene, 130 °C, 28% (two steps); g) TBAF, DCM/THF (5:1); h) Al(OTf)₃ (5 mol%), DCM, 88% (two steps); i) H₂, Pd/C, MeOH; j) Ag₂CO₃ on celite, toluene, 130 °C, 73% (two steps); k) RuCl₃ (0.5 equiv), NaIO₄, MeCN/CCl₄/H₂O (1:1:1), 73%; l) NaBH₄, THF, 95% (dr = 5:1)

Scheme 4-2

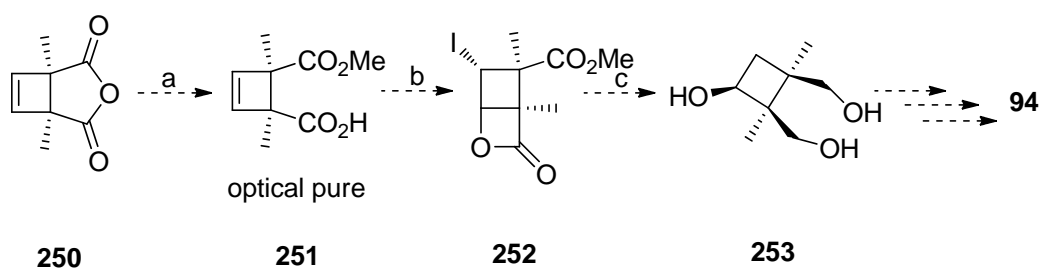
γ -Lactone A was achieved *via* a standard three-step-sequence from **232** as shown in Scheme 4-2. Careful treatment **243** with a mixture of TsOH and AcOH in DCM at 30 °C afforded the internal alkene **246** in high yield. Application of Hirama's two step

protocol of sodium in ammonia followed by Fetizon's reagent provided the tetracycle **9**. Tetracycle **9** is the common intermediate in all merrilactone A syntheses to date, and represents a formal total synthesis of this natural product. Access to the anislactones was achieved via a pivotal intramolecular etherification reaction catalyzed by Al(OTf)₃ in DCM at room temperature affording **227** in 88% yield. The remaining two γ -lactones were synthesized *via* Fetizon's oxidation and RuO₄ oxidation respectively.

High regio- and stereoselectivity in the chemical reaction is always desired in total syntheses as it directly affects the synthetic efficiency and overall yield of the final product. Our syntheses generally feature very high selectivities in the key steps, e.g. regioselective Tiffeneau-Demjanov ring expansion, stereoselective 1,2-addition to an epoxy-cyclopentanone and regioselective lactonization with Fetizon's reagent. Although the moderate diastereoselectivity (2.2 : 1) of the epoxidation reaction is not very satisfactory, the overall transformation is still very efficient as the undesired minor β -epoxide **204** could be recycled readily. Whilst we did solve this stereocontrol issue at the reaction level, we were unable to integrate the solution of using bulky silyl protecting groups to improve diastereoselectivity into the total synthesis as a whole. This was largely due to time restrictions, and it is possible that further work on this alternative route would improve the overall yield of the total synthesis.

In several events, the reactions proved more difficult than anticipated due to the complexity of the molecule, such as alkylation of 1,3-ketoester (scheme 2-19), Tsuij-Trost reaction (scheme 2-24), the reduction of aldehyde **184** (scheme 2-28), alkene isomerization (scheme 2-52) and intramolecular hydroalkoxylation (scheme 3-4). These challenges were surmounted eventually by careful optimization of reaction conditions and extensive screening of various reagents.

Our synthetic strategy is also amenable towards accessing both the enantiomers of the natural product, for example through desymmetrization during the early phase (Scheme 4-3)



a) chiral amine, MeOH; b) I₂, THF, NaHCO₃; c) LAH

Scheme 4-3. proposed asymmetric synthetic route

Treatment of the known anhydride **205** with chiral amine would lead to optically pure acid **251**. The resultant acid subjected to iodolactonization would produce iodolactone **252**. Reduction of iodolactone with LAH would afford triol **253** and the iodine atom would be removed concurrently. The resulting secondary alcohol would be selectively oxidised to a ketone in several steps and produce enantiopure intermediate **94**.

In summary, there were many surprises, disappointments and unexpected results that required more efforts to resolve. However, it was a great joy and learning experience in the area of contemporary total synthesis.

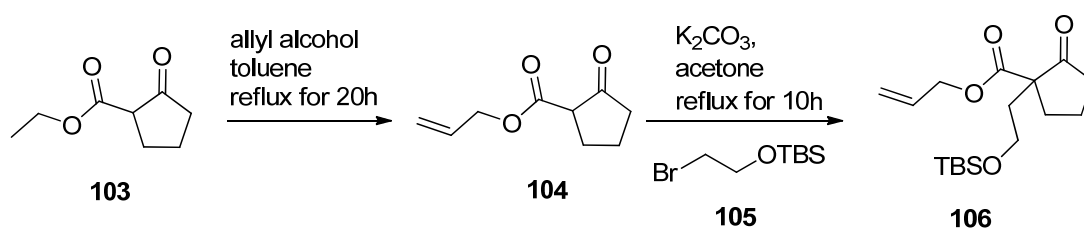
5 Experimental

5.1 General Procedures

General Methods: ^1H and ^{13}C NMR spectra were recorded on a Bruker 360 MHz, 500 MHz or 600 MHz instrument and are calibrated to residual solvent peaks (CDCl_3 7.26 ppm and 77.0 ppm). The data is reported as chemical shift (ppm) followed by peak signal shape with relevant coupling constants quoted to the nearest 0.1 Hertz. Infra-red spectra were recorded on a JASCO FT/IR-460 using sodium chloride disks or a PerkinElmer Spectrum One FT-IR Universal ATR sampling accessory instrument as a thin film. Electrospray high resolution mass spectrometry was performed by the EPSRC National Mass Spectrometry Service Centre, Swansea, using a Finigan MAT 900 XTL double focusing mass spectrometer. EI HRMS was carried out by the University of Edinburgh using a Kratos MS50 instrument. The data is recorded as the ionization method followed by the calculated and measured masses. T.L.C. was performed on Merck 60F₂₅₄ aluminium backed silica plates and visualized by UV light (both 254 nm and 365 nm). Final compounds were purified by wet flash chromatography using Merck Kieselgel 60 (particle size 35-70) silica under a positive pressure. All chemicals were purchased from a chemical supplier and used as received unless otherwise stated.

5.2 Experimental Procedures

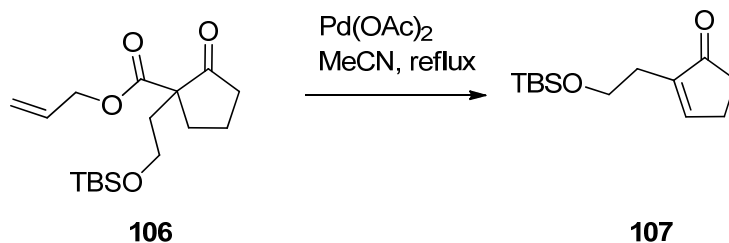
Allyl 1-(2-((tert-butyldimethylsilyl)oxy)ethyl)-2-oxocyclopentanecarboxylate (106)



Ethyl 2-oxocyclopentanecarboxylate **103** (3.12 g, 20.0 mmol, 1 equiv) was dissolved in toluene (100 mL) and allyl alcohol (11.6 mL, 200.0 mmol, 10 equiv) added. The resulting solution was heated to reflux for 20 h. After cooling to RT, the solvent was

evaporated under reduced pressure and the crude product **104** was used in the next step without further purification. Allyl 2-oxocyclopentanecarboxylate **104** (3.30 g, 20.0 mmol, 1 equiv) was dissolved in acetone (50 mL) and K_2CO_3 (5.40 g, 40.0 mmol, 2 equiv) and TBS-protected 2-bromoethanol **105** (9.6 g, 40.0 mmol, 2 equiv) were added. The suspension was refluxed for 24 h. After cooling down to RT the K_2CO_3 was removed by filtration through a short silica pad, the solvent removed *in vacuo* and the crude product then purified by flash column chromatography (SiO_2 , hexanes:EtOAc 20:1) to afford the product **106** as a colourless oil 3.0 g (46% yield for 2 steps). **106**: 1H NMR (500 MHz, $CDCl_3$) δ 5.92-5.83 (1 H, m), 5.30 (1 H, dq, $J = 17.2, 1.4$, Hz), 5.22 (1 H, dd, $J = 10.4, 1.2$ Hz), 4.59 (1 H, dd, $J = 5.6, 1.2$ Hz), 3.74-3.64 (2 H, m), 2.55-2.49 (1 H, m), 2.43-2.32 (2 H, m), 2.21-2.15 (1 H, m), 2.10-1.88 (4 H, m), 0.86 (9 H, s), 0.02 (6 H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.4, 170.7, 131.6, 118.4, 65.7, 59.5, 58.7, 37.7, 36.3, 32.6, 25.8, 19.7, 18.2, -5.5, -5.5; IR (thin film) ν_{max} 2956, 2929, 2886, 2857, 1755, 1728, 1471, 1464, 1256, 1223, 1099, 837, 777 cm^{-1} ; HRMS (ES) m/z calcd for $C_{17}H_{31}O_4Si$ $[M+H]^+$ 327.1986, found 327.1989.

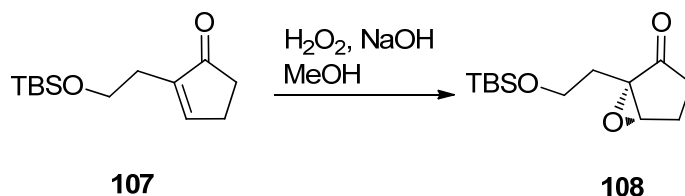
2-((Tert-butyldimethylsilyl)oxy)ethyl)cyclopent-2-enone (**107**)



A solution of cyclopentanone **106** (3.0 g, 9.1 mmol, 1 equiv) in acetonitrile (20 mL) was slowly added to a solution of $Pd(OAc)_2$ (101 mg, 0.455 mmol, 0.05 equiv) and PPh_3 (119 mg, 0.455 mmol, 0.05 equiv) in acetonitrile at 90 °C under Ar. The reaction mixture was then stirred at 90 °C for 3 h before being allowed to cool to RT. Filtration through a plug of silica, removal of solvent and flash column chromatography (SiO_2 , Hexanes/EtOAc 20:1) furnished cyclopentenone **107** 1.7 g, (77 % yield) as a colourless oil. **107**: 1H NMR (500 MHz, $CDCl_3$) δ 7.43 (1 H, tt, $J = 2.6, 1.1$, Hz), 3.71 (2 H, t, $J = 6.4$ Hz), 2.58-2.54 (2 H, m), 2.42-2.36 (4 H, m),

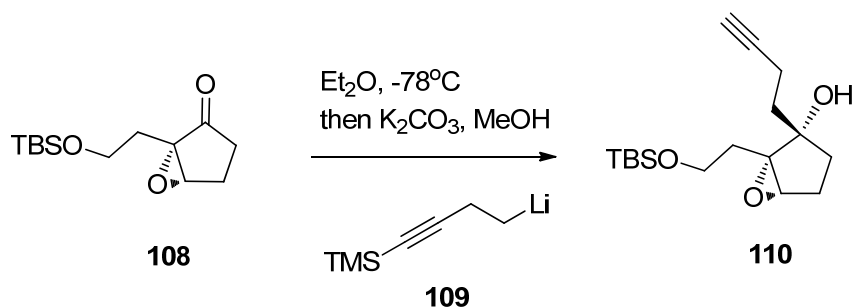
0.86 (9 H, s), 0.02 (6 H, s); ^{13}C NMR (125 MHz, CDCl_3) δ 209.8, 159.4, 143.2, 61.0, 34.3, 28.3, 26.6, 25.8, 18.2, -5.3; IR (thin film) ν_{max} 3419, 2925, 2694, 1629, 1442, 1348, 1253, 1048, 791 cm^{-1} ; HRMS (ES) m/z calcd for $\text{C}_{13}\text{H}_{25}\text{O}_2\text{Si}$ $[\text{M}+\text{H}]^+$ 241.1618, found 241.1620.

1-(2-((Tert-butyltrimethylsilyloxy)ethyl)-6-oxabicyclo[3.1.0]hexan-2-one (108)



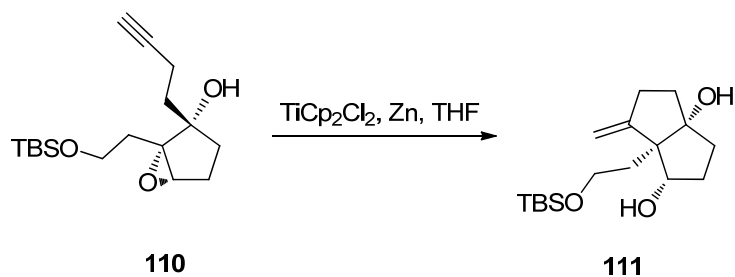
Cyclopentanone **107** (1.0 g, 4.1 mmol, 1 equiv) in MeOH (10mL) was added dropwise to H_2O_2 aqueous solution (1 mL, ~2 equiv) at 0 °C then NaOH (1 M) aqueous solution (0.5 mL) was added. The resulting solution was stirred for 10h after reaction was completed. Saturated NaHCO_3 solution (10 mL) was added, and the phase was extracted with ether (2 X 10 mL). The combined organic phase was removed under reduced pressure and flash column chromatography (SiO_2 , Hexanes/EtOAc 2:1) furnished epoxide product **108** as colourless oil 0.9 g (88 % yield). **108**: ^1H NMR (500 MHz, CDCl_3) δ 3.90 (1 H, s), 3.75 (1 H, ddd, $J = 10.2, 7.1, 5.3$ Hz), 3.66 (1 H, ddd, $J = 10.2, 6.4, 5.6$ Hz), 2.39-2.19 (3 H, m), 2.13-2.06 (1 H, m), 2.01-1.95 (1 H, m), 1.94-1.85 (1 H, m), 0.86 (9 H, s), 0.03 (3 H, s), 0.02 (3 H, s); ^{13}C NMR (125 MHz, CDCl_3) δ 210.6, 63.4, 61.7, 58.3, 31.4, 27.5, 25.8, 22.3, 18.1, -5.4, -5.5; IR (thin film) ν_{max} 2955, 2930, 2884, 2875, 1742, 1472, 1256, 1105, 838, 777 cm^{-1} ; HRMS (ES) m/z calcd for $\text{C}_{13}\text{H}_{25}\text{O}_3\text{Si}$ $[\text{M}+\text{H}]^+$ 257.1567, found 257.1570

2-(But-3-yn-1-yl)-1-(2-((tert-butyltrimethylsilyloxy)ethyl)-6-oxabicyclo[3.1.0]hexan-2-ol (110)



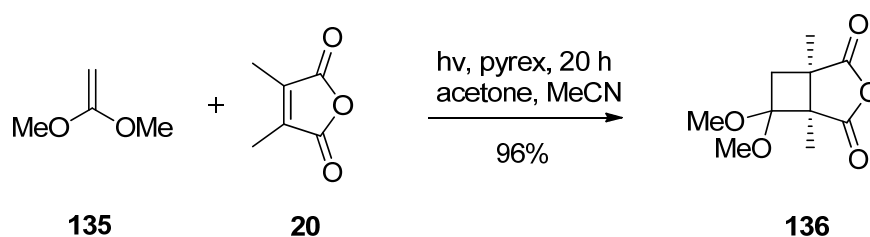
A solution of **109** (385 mg, 1.50 mmol, 1.5 equiv) in dry Et₂O 10 mL at -78 °C was treated with ^tBuLi (2.02 mL, 1.7M solution in pentane, 3.45 mmol, 3.45 equiv). The resulting mixture was stirred under Ar for 1 h before warming to RT and stirred for a further 2 h. After re-cooling to -78 °C, the mixture was transferred into an Et₂O solution of epoxide **108** (251 mg, 1.0 mmol, 1 equiv) at -78 °C *via* a double tipped needle. The reaction mixture was then stirred for 30 min and quenched with several drops water before warming up to RT. Filtration through a plug of silica to removed salt, removal of Et₂O under reduced pressure, the crude product as a colourless oil. The crude product obtained above was dissolved in MeOH 10 mL and treated with K₂CO₃ 70 mg. The resulting mixture was stirred for 10 h until reaction finished. The solvent was evaporated under reduced pressure and the crude product was purified by flash column chromatography (SiO₂, hexanes/EtOAc 20:1) to afford the product **110** as a colourless oil 120 mg (40% yield). **110**: ¹H NMR (500 MHz, CDCl₃) δ 4.18 (1 H, s), 3.92 (1 H, dt, *J* = 10.4, 2.5 Hz), 3.76 (1 H, td, *J* = 10.4, 4.1 Hz), 3.29 (1 h, s), 2.48-2.33 (2 H, m), 2.23 (1 H, dddd, *J* = 16.7, 10.7, 5.6, 2.6 Hz), 2.05-1.97 (2 H, m), 1.94 (1 H, t, *J* = 2.6, 2.6 Hz), 1.78-1.56 (3 H, m), 1.52-1.46 (2 H, m), 0.92 (9 H, s), 0.12 (3 H, s), 0.11 (3 H, s); ¹³C NMR (125 MHz, CDCl₃) δ 84.6, 78.8, 68.2, 68.0, 63.7, 60.2, 35.7, 30.8, 29.8, 25.8, 25.4, 18.2, 12.8, -5.4, -5.6; IR (thin film) ν_{max} 3426, 3313, 2954, 2884, 2857, 1471, 1256, 1099, 837, 626 cm⁻¹; HRMS (ES) *m/z* calcd for C₁₇H₃₁O₃Si [M+H]⁺ 311.2037, found 311.2041

6-(2-((Tert-butyl)dimethylsilyl)oxy)ethyl)-6-methyleneoctahydropentalene-1,3a-diol (111)



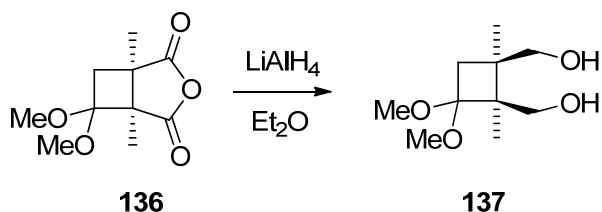
Cp_2TiCl_2 (176 mg, 0.70 mmol, 2 equiv) and Zn dust (65.0 mg, 2.13 mmol, 6 equiv) were placed in a dried round bottom flask and THF 5 mL was added under rigorous exclusion of air by means of an Ar atmosphere. The resulting suspension was stirred at RT for 1 h, during which the colour of the mixture was changed from red to green, indicating the formation of a low valent titanium complex. The suspension of Ti complex was then cannuled under Ar into a solution of the **110** (110 mg, 0.35 mmol, 1 equiv) in THF 5 mL and the resulting green solution was stirred at RT under an Ar for 2h. Then the excess Ti complex was removed by filtrated through a short silica pad and the solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography (SiO_2 , hexanes/EtOAc 20:1) to afford the product **111** as a colourless oil 90 mg (83% yield). **111**: $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 4.98 (1 H, t, $J = 1.9$ Hz), 4.75 (1 H, t, $J = 2.3$ Hz), 4.10 (1 H, m), 3.83 (1 H, ddd, $J = 10.8, 9.0, 1.9$ Hz), 3.74 (1 H, ddd, $J = 10.2, 6.4, 2.5$ Hz), 3.15 (1 H, s), 3.10 (1 H, d, $J = 4.6$ Hz), 2.46-2.40 (1 H, m), 2.31-2.24 (1 H, m), 2.09-2.03 (2 H, m), 1.89-1.77 (5 H, m), 1.65 (1 H, ddd, $J = 15.2, 6.4, 1.9$ Hz), 0.92 (9 H, s), 0.11 (3 H, s), 0.10 (3 H, s); $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 154.8, 108.1, 89.5, 80.7, 61.5, 59.6, 38.8, 35.6, 31.4, 31.1, 29.5, 25.8, 18.1, -5.6, -5.6; **IR** (thin film) ν_{max} 3383, 2952, 1716, 1652, 1455, 1214, 1033, 890 cm^{-1} ; **HRMS** (ES) m/z calcd for $\text{C}_{17}\text{H}_{33}\text{O}_3\text{Si}$ $[\text{M}+\text{H}]^+$ 313.2193, found 313.2196

6,6-Dimethoxy-1,5-dimethyl-3-oxabicyclo[3.2.0]heptane-2,4-dione (**136**)



A solution of 2,3-dimethylmaleic anhydride **20** (2.00 g 15.8 mmol, 1 equiv), dimethylketene acetal **135** (5.57 g, 63.2 mmol, 4 equiv) and benzophenone (287 mg, 1.58 mmol, 0.1 eq) in a mixed solvent of acetone (50 mL) and acetonitrile (350 mL) was degassed under a stream of N₂ for 30 min. The mixture was irradiated using a 400 W medium pressure mercury lamp with a pyrex filter for 24 h under water cooling. Solvent removal under reduced pressure followed by flash column chromatography (SiO₂, EtOAc/hexane 1:9) gave cyclobutane **136** as a pale yellow oil. Crystallization from Et₂O / hexane afforded the pure product (3.24 g, 15.1 mmol, 96% yield) as white needles. **136**: ¹H NMR (360 MHz, CDCl₃): δ 3.24 (3 H, s), 3.22 (3 H, s), 2.67 (1 H, d, *J* = 13.4, Hz), 2.24 (1 H, d, *J* = 13.4, Hz), 1.36 (3 H, s, Hz), 1.32 (3 H, s, Hz). ¹³C NMR (90 MHz, CDCl₃) δ 175.8, 171.9, 99.6, 59.2, 50.2, 50.1, 41.2, 41.0, 15.7, 10.2; IR (thin film) *v*_{max} 2949, 2841, 1846, 1779, 1448, 1385, 1272, 1255, 1144, 1094, 1060, 1029, 918, 834, 793, 752 cm⁻¹; HRMS (ES) *m/z* calcd for C₁₀H₁₅O₅ [M+H]⁺ 215.0914, found 215.0915.

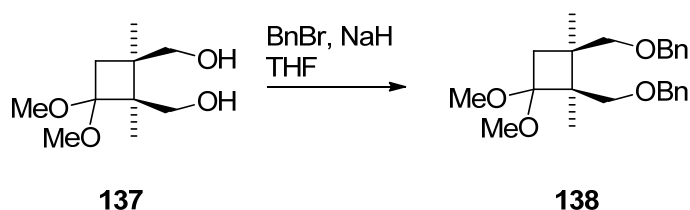
(3,3-Dimethoxy-1,2-dimethylcyclobutane-1,2-diol)dimethanol (**137**)



Anhydride **136** (7.00 g, 32.8 mmol, 1 equiv) in Et₂O (300 mL) was cooled to 0 °C and LiAlH₄ powder (2.20 g, 58.0 mmol, 2 equiv) carefully added in portions. The reaction mixture was then stirred for 5 h at 0 °C. The resulting suspension was quenched by addition of H₂O (2.2 mL), NaOH solution (1.0 M, 2.2 mL) and then H₂O (5 mL). Filtration and removal of solvent under reduced pressure afforded diol **137** as a colourless oil (6.5 g, 97% yield), which was used in the next step without further purification. **137**: ¹H NMR (360 MHz, CDCl₃) δ 4.07-3.94 (2 H, m), 3.57-3.48 (2 H, m), 3.45-3.42 (1 H, m), 3.32-3.26 (1 H, m), 3.17 (3 H, s), 3.12 (3 H, s), 1.81 (1 H, d, *J* = 12.6 Hz), 1.71 (1 H, d, *J* = 12.6 Hz), 1.14 (3 H, s), 1.12 (3 H, s); ¹³C NMR (90 MHz, CDCl₃) δ 102.8, 68.8, 65.7, 52.6, 50.0, 49.2, 37.6, 36.4, 20.6, 15.9; IR (thin film) *v*_{max} 3854, 3745, 3333, 2940, 2833, 1653, 1448, 1380, 1253, 1195,

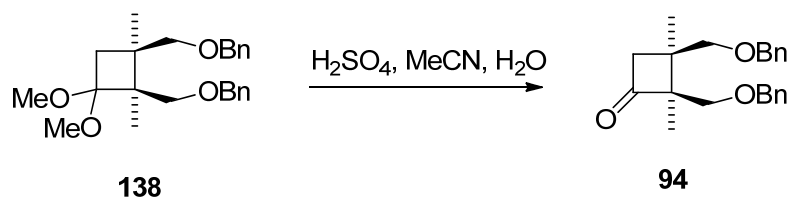
1111, 1065, 973, 916, 867, 826, 665 cm^{-1} ; HRMS (ES) m/z calcd for $\text{C}_{10}\text{H}_{20}\text{O}_4\text{Na}$ $[\text{M}+\text{Na}]^+$ 227.1254, found 227.1252.

(((3,3-Dimethoxy-1,2-dimethylcyclobutane-1,2-diyl)bis(methylene))bis(oxy))bis(methylene))dibenzene (138)



NaH (2.7 g, 60% in mineral oil, 70 mmol, 2.5 equiv) was added slowly to a solution of **137** (6.2 g, 30 mmol, 1 equiv) and Bu_4NI (1.1 g, 3.0 mmol, 0.1 equiv) in THF (200 mL) at 0°C , followed by the addition of benzyl bromide (7.2 mL, 6.2 mmol, 2.1 equiv). The reaction mixture was stirred at RT for 20 h and subsequently the excess NaH was quenched by addition of H_2O (50 mL). Following extraction with EtOAc ($\times 2$), the organic layers were combined, washed with brine and dried over MgSO_4 . Filtration and removal of solvent under reduced pressure afforded **138** as a yellow oil, which was used directly in the next step. **138**: ^1H NMR (360 MHz, CDCl_3) δ 7.40-7.29 (10 H, m), 4.57-4.45 (4 H, m), 3.60-3.50 (4 H, m), 3.25 (1 H, s), 3.15 (3 H, s), 2.14 (1H, d, $J = 12.6$ Hz), 1.77 (1H, d, $J = 12.6$ Hz), 1.25 (3 H, s, Hz), 1.175 (3 H, s); ^{13}C NMR (90 MHz, CDCl_3) δ 139.0, 138.8, 128.2, 128.1, 127.4, 127.3, 127.2, 102.8, 75.4, 73.1, 71.1, 52.1, 50.2, 48.9, 37.5, 35.8, 19.8, 15.8; IR (thin film) ν_{max} 3482, 3031, 2938, 1776, 1719, 1602, 1586, 1494, 1454, 1361, 1249, 828, 738, 698, 665 cm^{-1} .

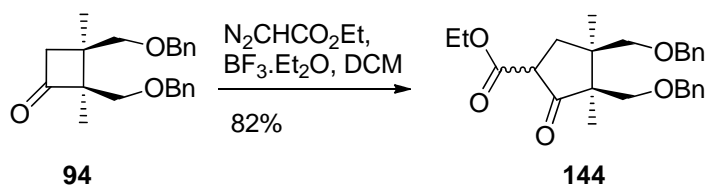
2,3-Bis((benzyloxy)methyl)-2,3-dimethylcyclobutanone (94)



Compound **138** (12.1g, 31.5 mmol) was dissolved in MeCN (50 mL), H_2SO_4 (0.5

M, 15 mL) added and the reaction stirred at RT for 5 h. The reaction was quenched with saturated NaHCO₃ solution, extracted with DCM, and the combined organic extracts dried with MgSO₄. Filtration and removal of solvent under reduced pressure afforded a yellow oil, which was purified by flash column chromatography (SiO₂, EtOAc/hexane 1:9) to give ketone **94** as a colourless oil (9.2 g, 90% yield for 2 steps). **94**: ¹H NMR (360 MHz, CDCl₃) δ 7.36-7.23 (10 H, m), 4.46 (1H, d, *J*_{ab}= 12.2 Hz), 4.42 (1H, d, *J*_{ab}= 12.2 Hz), 4.37 (2 H, s), 3.76 (1 H, d, *J*_{ab}= 9.0 Hz), 3.57 (2 H, s), 3.55 (1 H, d, *J*_{ab}= 9.0 Hz), 3.06 (1 H, d, *J* = 16.6 Hz), 2.58 (1 H, d, *J* = 16.6 Hz), 1.25 (3 H, s), 1.13 (3 H, s); ¹³C NMR (90 MHz, CDCl₃) δ 211.9, 138.3, 137.9, 128.2, 127.5, 127.4, 74.8, 73.1, 73.1, 71.5, 66.0, 54.2, 36.0, 21.0, 15.3; IR (thin film) ν_{max} 2871, 1775, 1496, 1454, 1378, 1273, 1095, 1028, 739, 699, 665 cm⁻¹; HRMS (ES) *m/z* calcd for C₂₂H₃₀O₃N [M+NH₄]⁺ 356.2220, found 356.2219.

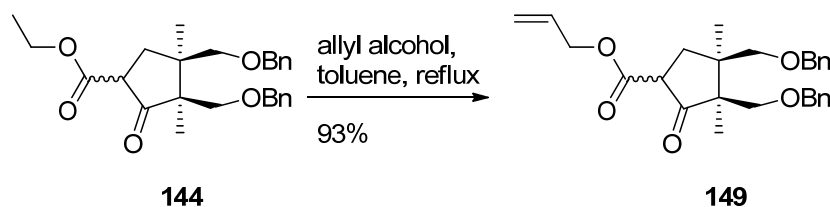
Ethyl 3,4-bis((benzyloxy)methyl)-3,4-dimethyl-2-oxocyclopentanecarboxylate (144)



Cyclobutanone **94** (5.15g, 15.2 mmol, 1 equiv) in DCM (200 mL) was cooled to 0 °C and BF₃·OEt₂ (4.87 mL, 38.0 mmol, 2.5 equiv) added dropwise. After stirring for 5 min, ethyl diazoacetate (4.0 mL, 38 mmol, 2.5 equiv) was added dropwise and the resulting solution was stirred at 0 °C for 2 h. Following addition of saturated NaHCO₃ solution, the organic phase was separated, dried over MgSO₄, and the solvent removed under reduced pressure. Flash column chromatography (SiO₂, hexanes/EtOAc 20:1) afforded cyclopentanone **144** as a colourless oil (mixture of diastereoisomers and tautomers, 5.60g, 88% yield). Major isomer **144**: ¹H NMR (360 MHz, CDCl₃) δ 7.39-7.17 (10 H, m), 4.42-4.05 (6 H, m), 3.59 (1 H, t, *J* = 9.8 Hz), 3.54-3.49 (2 H, m), 3.35 (1 H, d, *J* = 8.9 Hz), 3.24 (1 H, d, *J* = 8.9 Hz), 2.27-2.13 (2 H, m), 1.27 (3 H, t, *J* = 7.1 Hz), 1.19 (3 H, s), 1.08 (3 H, s); ¹³C NMR (90 MHz, CDCl₃) δ 212.8, 169.9, 138.2, 137.6, 128.3, 128.1, 127.5, 127.4, 127.2, 73.2, 73.1, 72.6, 61.2, 54.1, 53.3, 43.8, 36.1, 20.3, 17.1, 14.0; IR (thin film) ν_{max}

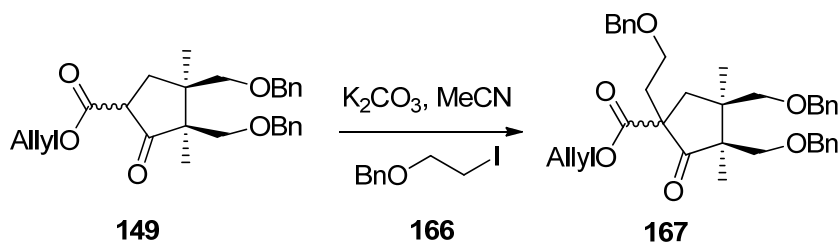
3030, 2981, 1719, 1495, 1454, 1367, 1207, 1097, 737, 698 cm^{-1} ; **HRMS** (ES) m/z calcd for $\text{C}_{26}\text{H}_{36}\text{NO}_5$ $[\text{M}+\text{NH}_4]^+$ 442.2588, found 442.2589

Allyl 3,4-bis((benzyloxy)methyl)-3,4-dimethyl-2-oxocyclopentanecarboxylate (149)



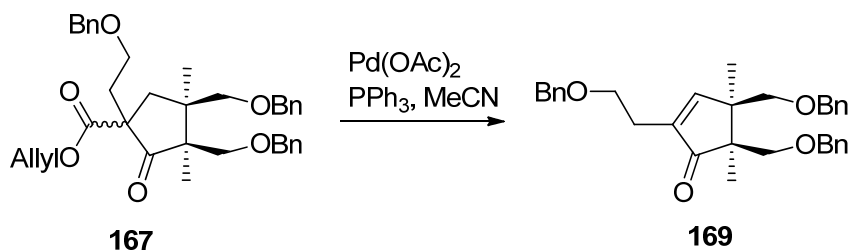
Cyclopentanone **144** (5.80 g, 13.6 mmol, 1 equiv) was dissolved in toluene (100 mL) and allyl alcohol (9.23 mL, 136 mmol, 10 equiv) added. The resulting solution was heated to reflux for 10 h. After cooling to RT, the solvent was evaporated under reduced pressure and the crude product was purified by flash column chromatography (SiO_2 , hexanes/EtOAc 20:1) to afford **149** as a colourless oil (5.5 g, 93% yield, mixture of diastereoisomers and tautomers). Major isomer **149**: ^1H NMR (360 MHz, CDCl_3) δ 7.36-7.16 (10 H, m), 5.95-5.83 (1 H, m), 5.33 (1 H, qd, $J = 17.2, 1.5$ Hz), 5.22 (1 H, dd, $J = 10.5, 2.3$ Hz), 4.66-4.57 (2 H, m), 4.41-4.27 (2 H, m), 4.24 (2 H, m), 3.64 (1 H, t, $J = 9.9$ Hz), 3.50 (2 H, m), 3.34 (1H, d, $J_{ab} = 9.0$ Hz), 3.24 (1 H, d, $J_{ab} = 9.0$ Hz), 2.61-1.83 (2 H, m), 1.19 (3 H, s), 1.08 (3 H, s); ^{13}C NMR (90 MHz, CDCl_3) δ 212.5, 169.6, 138.2, 137.5, 131.7, 118.2, 77.3, 73.2, 73.1, 72.6, 65.7, 54.1, 53.2, 43.8, 36.1, 20.3, 17.2; **IR** (thin film) ν_{max} 2861, 1749, 1724, 1454, 1097 cm^{-1} ; **HRMS** (ES) m/z calcd for $\text{C}_{27}\text{H}_{36}\text{NO}_5$ $[\text{M}+\text{NH}_4]^+$ 454.2588, found 454.2595.

Allyl-(2-(benzyloxy)ethyl)-3,4-bis((benzyloxy)methyl)-3,4-dimethyl-2-oxocyclopentanecarboxylate (167)



Cyclopentanone **149** (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-iodoethoxymethyl) benzene **166** (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 **167** as a pale yellow oil (928 mg, 76% yield, mixture of diastereoisomers, ratio = 2 : 1). Major isomer **167**: 1H NMR (360 MHz, $CDCl_3$) δ 7.34-7.20 (15 H, m), 5.82 (1 H, m), 5.34-5.16 (2 H, m), 4.62-4.21 (8 H, m), 3.71-3.28 (6 H, m), 2.53 (1 H, d, $J=13.7$ Hz), 2.39 (1 H, m), 2.04 (1 H, d, $J=13.7$ Hz), 1.98 (1 H, m), 1.08 (3 H, s), 1.04 (3 H, s); ^{13}C NMR (90 MHz, $CDCl_3$) δ 215.9, 171.3, 138.4, 138.0, 137.9, 131.7, 128.3, 128.2, 127.8, 127.7, 127.6, 127.5, 118.4, 76.7, 74.6, 73.4, 73.2, 72.7, 66.9, 65.9, 57.9, 55.3, 42.5, 40.7, 36.0, 22.1, 17.9; 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.

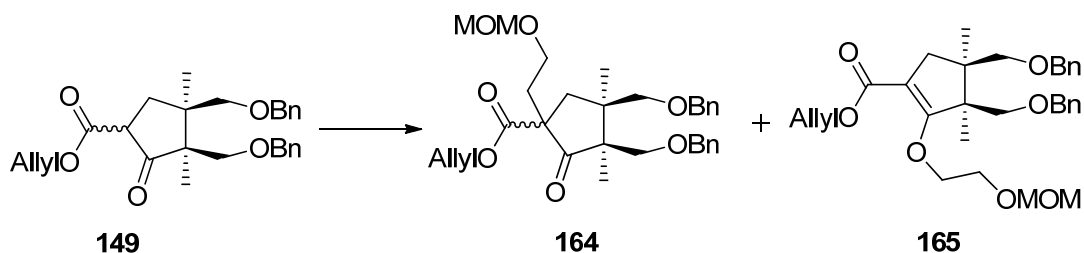
2-(2-(Benzyloxy)ethyl)-4,5-bis((benzyloxy)methyl)-4,5-dimethylcyclopent-2-enone (169)



An acetonitrile solution (2.5 mL) of cyclopentanone **167** (106 mg, 0.18 mmol, 1 equiv) was added to a solution of $Pd(OAc)_2$ (5.00 mg, 0.02 mmol, 0.1 equiv) and PPh_3 (5.00 mg, 0.02 mmol, 0.1 equiv) in acetonitrile (2.5 mL) at 50 °C under a N_2 atmosphere. 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 **169** as a colourless oil (17 mg, 20% yield). 1H NMR (360 MHz, $CDCl_3$) δ 7.33-7.18 (15 H, m), 7.05 (1 H, s), 4.44 (2 H, s), 4.38-4.29 (2 H, m), 4.31 (2 H, s), 3.61-3.47 (6 H, m),

2.49 (2 H, dt, $J = 1.0, 6.7$ Hz), 1.14 (3 H, s), 1.12 (3 H, s); ^{13}C NMR (90 MHz, CDCl_3) δ 211.3, 162.3, 139.2, 138.4, 138.3, 128.3, 128.2, 128.1, 127.6, 127.4, 127.3, 127.2, 74.8, 73.5, 73.2, 72.8, 72.7, 68.1, 54.1, 49.6, 25.3, 20.1, 19.9; IR (thin film) ν 2857, 1702, 1454, 1099 cm^{-1} ; HRMS (ES) m/z calcd for $\text{C}_{32}\text{H}_{37}\text{O}_4$ $[\text{M}+\text{H}]^+$ 485.2686, found 485.2684.

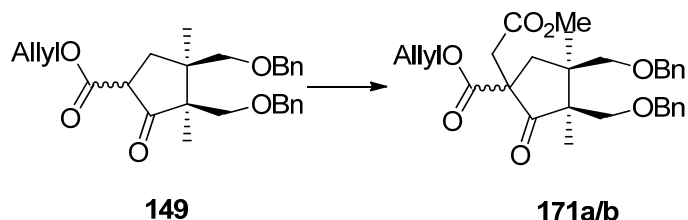
Allyl3,4-bis((benzyloxy)methyl)-1-(2-(methoxymethoxy)ethyl)-3,4-dimethyl-2-oxocyclopentanecarboxylate (164)



Cyclopentanone **149** (100 mg, 0.23 mmol, 1 equiv) was dissolved in acetonitrile (1 mL) and K_2CO_3 (65.0 mg, 0.46 mmol, 2 equiv) and 1-bromo-2-(methoxymethoxy)ethane **166** (76.0 mg, 0.46 mmol, 2 equiv) were added. The suspension was stirred under N_2 at 95°C for 26 h, cooled to RT and EtOAc (2 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 **164** as a pale yellow oil (12 mg, 10% yield, mixture of diastereoisomers, ratio = 2 : 1) and **165** (18 mg, 15% yield). Major isomer **164**: ^1H NMR (360 MHz, CDCl_3) δ 7.36-7.22 (10 H, m), 5.95-5.84 (1H, m), 5.36-5.31 (1H, m), 5.24-5.21 (1H, m), 4.62-4.57 (2H, m), 4.47 (2H, m), 4.34-4.27 (4H, m), 3.52-3.46 (4H, m), 4.34-4.31 (2H, m), 3.82 (3H, s), 2.52 (1 H, d, $J = 13.6$ Hz), 2.37 (1 H, td, $J = 13.8, 6.8$ Hz), 2.04 (1 H, d, $J = 13.7$ Hz), 1.96 (1 H, m), 1.08 (3H, s), 1.04 (3H, s); ^{13}C NMR (90 MHz, CDCl_3) δ 215.7, 171.2, 137.9, 137.8, 131.6, 128.6, 128.2, 128.1, 127.7, 127.6, 127.5, 127.5, 127.2, 118.4, 96.3, 96.1, 74.5, 73.3, 73.1, 73.0, 65.9, 64.1, 57.9, 55.2, 55.0, 42.4, 40.5, 35.8, 22.0, 17.8; IR (thin film) ν_{max} 3448, 2937, 2879, 1724, 1454, 1200, 1153, 1109, 1045, 918, 698 cm^{-1} ; HRMS (ES) m/z calcd for $\text{C}_{31}\text{H}_{44}\text{O}_7\text{N}_1$ $[\text{M}+\text{NH}_4]^+$ 542.3112, found 542.3113. **165**: ^1H NMR (360 MHz, CDCl_3) δ 7.34-7.29 (10 H, m), 6.04-5.85 (1 H, m), 5.31 (1 H, qd, $J = 17.2,$

1.6 Hz), 5.21 (1 H, qd, $J = 10.4, 1.3$ Hz), 4.62-4.60 (4H, m), 4.54 (1 H, ddd, $J = 11.4, 5.7, 3.3$ Hz), 4.40 (2 H, d, $J = 6.2$ Hz), 4.34 (2 H, d, $J = 11.7$ Hz), 4.21 (1 H, ddd, $J = 11.4, 5.9, 3.3$ Hz), 3.75-3.62 (2 H, m), 3.59 (1 H, d, $J = 8.8$ Hz), 3.44 (2 H, d, $J = 3.1$ Hz), 3.35 (1 H, d, $J = 8.8$ Hz), 3.33 (3 H, d, $J = 0.4$ Hz), 2.67 (1 H, d, $J = 14.0$ Hz), 2.16 (1 H, d, $J = 14.0$ Hz), 1.14 (3 H, s), 1.05 (3H, s); ^{13}C NMR (90 MHz, CDCl_3) δ 170.3, 164.7, 138.8, 138.5, 132.6, 128.1, 127.2, 117.4, 104.0, 96.3, 75.5, 74.0, 73.4, 73.0, 72.8, 66.6, 64.3, 55.0, 54.5, 43.0, 40.5, 22.2, 16.3; IR (thin film) ν_{max} 3423, 2933, 2860, 1703, 1624, 1454, 1373, 1321, 1267, 1227, 1200, 1171, 1153, 1111, 1028, 920, 737, 698 cm^{-1} ; HRMS (ES) m/z calcd for $\text{C}_{31}\text{H}_{44}\text{O}_7\text{N}_1$ $[\text{M}+\text{NH}_4]^+$ 542.3112, found 542.3113.

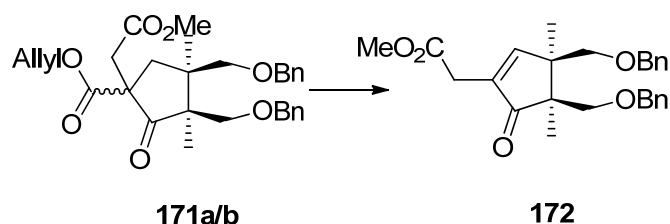
Allyl3,4-bis((benzyloxy)methyl)-1-(2-methoxy-2-oxoethyl)-3,4-dimethyl-2-oxocyclopentanecarboxylate (171)



Cyclopentanone **149** (5.00 g, 11.4 mmol, 1 equiv) was dissolved in acetone (100 mL) and K_2CO_3 (3.10 g, 22.4 mmol, 2 equiv) and methyl 2-bromoacetate (3.30 g, 22.4 mmol, 2 equiv) were added. The suspension was stirred at RT for 24 h. The K_2CO_3 was removed by filtration through a short silica pad, the solvent removed under reduced pressure and the crude product then purified by flash column chromatography (SiO_2 , hexanes/EtOAc 20:1) to afford the product **171a/b** as a colourless oil (5.2 g, 89% yield, mixture of diastereoisomers (ratio 2:1). Major isomer **171a**: ^1H NMR (360 MHz, CDCl_3) δ 7.35-7.18 (10 H, m), 5.86 (1 H, tdd, $J = 17.2, 10.5, 5.6, 5.6$ Hz), 5.29 (1 H, qd, $J = 17.2, 1.53$ Hz), 5.20 (1 H, ddd, $J = 10.4, 2.6, 1.2$ Hz), 4.60-4.59 (1 H, m), 4.59 (2 H, td, $J = 5.6, 1.3$ Hz), 4.35 (1 H, d, $J = 11.9$ Hz), 4.25 (3 H, m), 3.60 (3H, s), 3.47 (1 H, d, $J = 3.6$ Hz), 3.28 (1 H, d, $J = 1.5$ Hz), 3.15 (1 H, d, $J = 16.9$ Hz), 2.85 (2 H, m), 1.97 (1 H, d, $J = 14.4$ Hz), 1.14 (3 H, s), 1.12 (3 H, s); ^{13}C NMR (90 MHz, CDCl_3) δ 213.7, 172.0, 170.1, 137.8, 137.3, 131.6, 128.3, 128.2, 128.2, 128.1, 127.9, 127.8, 127.6, 127.5, 118.2, 77.1, 73.6, 73.3, 73.2, 66.2,

57.7, 55.1, 51.5, 42.6, 41.4, 40.4, 21.5, 18.0; **IR** (thin film) ν_{\max} 3030, 2949, 2862, 1732, 1455, 1417, 1358, 1267, 1206, 1098, 1058, 1029, 925, 738, 699 cm^{-1} ; **HRMS** (ES) m/z calcd for $\text{C}_{30}\text{H}_{40}\text{O}_7\text{N}_1$ $[\text{M}+\text{NH}_4]^+$ 526.2799, found 526.2800. Minor isomer **171b**: $^1\text{H NMR}$ (360 MHz, CDCl_3) δ 7.39-7.30 (10 H, m), 5.89-5.78 (1 H, m), 5.29 (1 H, qd, $J = 17.2, 1.53, 1.38$ Hz), 5.18 (1 H, ddd, $J = 10.4, 2.4, 1.1$ Hz), 4.53-4.41 (5 H, m), 4.31 (1 H, d, $J = 12.2$ Hz), 3.75 (1 H, d, $J = 9.0$ Hz), 3.69 (3 H, s), 3.49-3.42 (3 H, m), 3.37 (1 H, d, $J = 9.1$ Hz), 3.18 (1 H, d, $J = 14.5$ Hz), 2.48 (1 H, d, $J = 16.3$ Hz), 1.84 (1 H, d, $J = 14.5$ Hz), 1.23 (3 H, s), 1.09 (3 H, s); $^{13}\text{C NMR}$ (90 MHz, CDCl_3) δ 211.8, 170.9, 168.7, 138.0, 131.7, 128.2, 128.1, 127.4, 127.3, 127.2, 117.9, 75.5, 73.1, 72.8, 71.9, 66.1, 56.8, 56.7, 51.7, 42.6, 42.1, 39.8, 22.4, 16.9; **IR** (thin film) ν_{\max} 3030, 2951, 2862, 1739, 1454, 1414, 1355, 11275, 1205, 1098, 1029, 738, 698 cm^{-1} ; **HRMS** (ES) m/z calcd for $\text{C}_{30}\text{H}_{40}\text{O}_7\text{N}_1$ $[\text{M}+\text{NH}_4]^+$ 526.2799, found 526.2800.

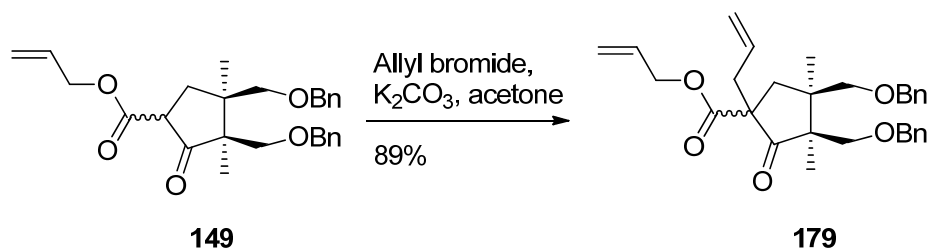
Methyl-(3,4-bis((benzyloxy)methyl)-3,4-dimethyl-5-oxocyclopent-1-en-1-yl)acetate (172)



An acetonitrile solution (2.5 mL) of cyclopentanone **171** (91.0 mg, 0.18 mmol, 1 equiv) was added to a solution of $\text{Pd}(\text{OAc})_2$ (5.00 mg, 0.02 mmol, 0.1 equiv) and PPh_3 (5.00 mg, 0.02 mmol, 0.1 equiv) in acetonitrile (2.5 mL) at 50 °C under a N_2 atmosphere. The reaction mixture was then stirred at 95 °C for 2 hours 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 **172** as a colourless oil (71 mg, 90% yield). **172**: $^1\text{H NMR}$ (360 MHz, CDCl_3) δ 7.39-7.23 (11 H, m), 4.43 (1 H, $J_{ab} = 10.8$ Hz), 4.38 (1 H, $J_{ab} = 10.8$ Hz), 4.37 (2 H, s), 3.70 (3H, s), 3.65 (1 H, $J_{ab} = 10.8$ Hz), 3.61 (1 H, $J_{ab} = 10.8$ Hz), 3.55 (2 H, s), 3.33-3.21 (2 H, m), 1.23 (3 H, s), 1.21 (3 H, s); $^{13}\text{C NMR}$ (90 MHz, CDCl_3) δ 210.0, 170.7, 163.2, 138.2, 138.1, 135.0, 128.1, 127.9, 127.3, 127.3, 127.1, 74.6, 73.1, 72.8, 54.0, 51.8, 49.9, 30.0, 19.9, 19.6; **IR** (thin film) ν_{\max} 2951, 2859, 1741, 1708, 1454,

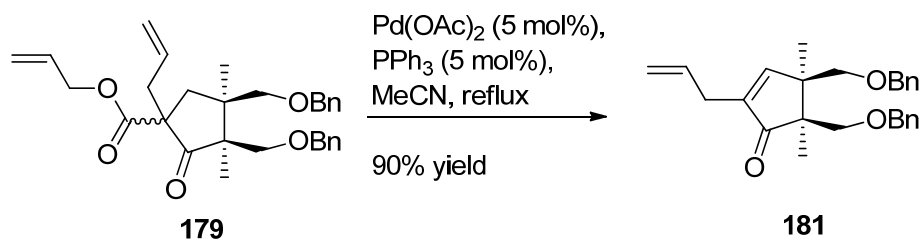
1436, 1376, 1361, 1305, 1257, 1204, 1167, 1094, 738, 698 cm^{-1} ; **HRMS** (ES) m/z calcd for $\text{C}_{26}\text{H}_{31}\text{O}_5$ $[\text{M}+\text{H}]^+$ 523.2166, found 523.2169.

Allyl 1-Allyl-3,4-bis((benzyloxy)methyl)-3,4-dimethyl-2-oxocyclopentane-carboxylate (179)



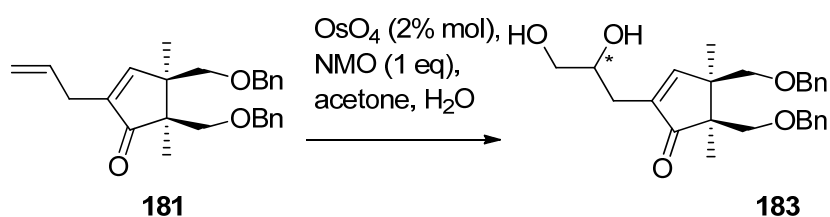
Cyclopentanone **149** (5.00 g, 11.4 mmol, 1 equiv) was dissolved in acetone (100 mL) and K_2CO_3 (3.10 g, 22.4 mmol, 2 equiv) and allyl bromide (2.68 g, 22.4, 2 equiv) were added. The suspension was stirred at RT for 24 h. The K_2CO_3 was removed by filtration through a short silica pad, the solvent removed under reduced pressure and the crude product then purified by flash column chromatography (SiO_2 , hexanes/EtOAc 20:1) to afford the product **179** as a colourless oil (4.8 g, 89% yield, mixture of diastereoisomers (ratio 2.5 : 1). Major diastereoisomer **179**: ^1H NMR (360 MHz, CDCl_3) δ 7.33-7.23 (10 H, m), 5.87 (1 H, tdd, $J = 17.0, 10.6, 5.7$ Hz), 5.62 (1 H, dddd, $J = 17.0, 10.3, 7.9, 6.8$ Hz), 5.32 (1 H, qd, $J = 17.2, 1.5$ Hz), 5.21 (1 H, dd, $J = 10.4, 1.3$ Hz), 4.94 (1 H, dd, $J = 10.1, 2.0$ Hz), 4.84 (1 H, dd, $J = 17.0, 1.8$ Hz), 4.59-4.56 (2 H, m), 4.36 (1 H, d, $J_{ab} = 11.9$ Hz), 4.29 (1 H, d, $J_{ab} = 11.9$ Hz), 4.27 (2 H, s), 3.50-3.46 (2 H, m), 3.40 (1 H, d, $J = 8.9$ Hz), 3.28 (1H, d, $J = 8.9$ Hz), 2.75 (1 H, dd, $J = 13.8, 6.8$ Hz), 2.41 (1 H, d, $J = 13.8$ Hz), 2.34 (1 H, dd, $J = 13.7, 8.0$ Hz), 1.96 (1 H, d, $J = 13.8$ Hz), 1.06 (3 H, s), 1.03 (3 H, s); ^{13}C NMR (90 MHz, CDCl_3) δ 215.4, 171.0, 137.9, 137.8, 133.4, 131.6, 128.2, 127.8, 127.7, 127.5, 127.5, 118.5, 118.0, 76.7, 74.5, 73.3, 73.2, 65.9, 59.4, 55.3, 42.4, 40.5, 39.9, 22.1, 17.8; **IR** (thin film) ν_{max} 3064, 3030, 2979, 2939, 2860, 1726, 1454, 1201, 1147, 1095, 920, 739, 698 cm^{-1} ; **HRMS** (ES) m/z calcd for $\text{C}_{30}\text{H}_{37}\text{O}_5$ $[\text{M}+\text{H}]^+$ 477.2636, found 477.2639.

2-Allyl-4,5-bis((benzyloxy)methyl)-4,5-dimethylcyclopent-2-enone (181)



A solution of cyclopentanone **179** (5.00 g, 10.5 mmol, 1 equiv) in acetonitrile (20 mL) was slowly added to a solution of Pd(OAc)_2 (117 mg, 0.52 mmol, 0.05 equiv) and PPh_3 (37.0 mg, 0.52 mmol, 0.05 equiv) in acetonitrile at 90 °C under Ar. The reaction mixture was then stirred at 90 °C for 3 h before being allowed to cool to RT. Filtration through a plug of silica, removal of solvent and flash column chromatography (SiO_2 , Hexanes/EtOAc 20:1) furnished cyclopentenone **181** (3.6 g, 90% yield) as a colourless oil. **181**: $^1\text{H NMR}$ (360 MHz, CDCl_3) δ 7.31-7.17 (10 H, m), 6.97 (1 H, t, $J = 1.4$ Hz), 5.83 (1 H, tdd, $J = 16.8, 10.1, 6.6$ Hz), 5.10-5.01 (2 H, m), 4.38 (1 H, d, $J_{ab} = 11.9$ Hz), 4.33 (1 H, d, $J_{ab} = 11.9$ Hz), 4.33 (2 H, s), 3.59 (1 H, d, $J_{ab} = 9.4$ Hz), 3.56 (1 H, d, $J_{ab} = 9.4$ Hz), 3.50 (1 H, d, $J_{ab} = 9.0$ Hz), 3.48 (1 H, d, $J_{ab} = 9.0$ Hz), 2.91 (1 H, ddd, $J = 6.6, 2.7, 1.3$ Hz), 1.15 (3 H, s), 1.13 (3 H, s); $^{13}\text{C NMR}$ (90 MHz, CDCl_3) δ 210.9, 161.4, 140.6, 138.3, 138.2, 134.4, 128.2, 128.1, 127.4, 127.3, 127.1, 116.4, 74.7, 73.5, 73.1, 72.8, 54.2, 49.5, 29.0, 20.1, 19.8; IR (thin film) ν_{max} 3064, 3030, 2979, 2858, 1705, 1454, 1360, 1093, 914, 737, 698 cm^{-1} ; HRMS (ES) m/z calcd for $\text{C}_{36}\text{H}_{31}\text{O}_3$ $[\text{M}+\text{H}]^+$ 391.2268, found 391.2273.

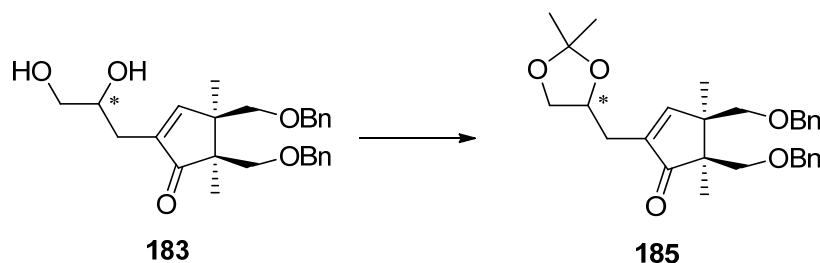
4,5-Bis((benzyloxy)methyl)-2-(2,3-dihydroxypropyl)-4,5-dimethylcyclopent-2-enone (**183**)



To a solution of cyclopentenone **181** (1.29 g, 3.30 mmol, 1 equiv) in water / acetone (7 mL / 28 mL) was added OsO_4 solution (0.67 mL of a 4 wt.% solution in water, 0.06 mmol, 0.02 equiv) and NMO (401 mg, 3.30 mmol, 1 equiv) at 0 °C. The reaction mixture was then stirred at RT for 20 h. A 5% aqueous solution of $\text{Na}_2\text{S}_2\text{O}_5$

(7 mL) was then added and the resulting mixture was stirred for a further 2 h. The solution was extracted with DCM (4 × 30 mL), and the combined organic phases were dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO₂, Hexanes/EtOAc 1:1) to give diol **183** (1.35 g, 96% yield, mixture of diastereoisomers) as a colourless oil (ratio = 1 : 1). **183**: ¹H NMR (360 MHz, CDCl₃) δ 7.40-7.22 (20H, m), 7.10 (1 H, m), 7.04 (1 H, m, C=CH), 4.44-4.39 (2 H, m), 4.33-4.21 (6 H, m), 3.77 (1 H, m), 3.67 (1 H, m), 3.59-3.45 (9 H, m), 3.41 (1 H, m), 3.31 (1 H, m), 3.10 (1 H, d, *J* = 4.2 Hz), 2.93 (1 H, d, *J* = 6.2 Hz), 2.69 (1 H, t, *J* = 6.1, 6.1 Hz), 2.57-2.27 (6 H, m), 1.20 (6 H, s), 1.19 (6 H, s); ¹³C NMR (90 MHz, CDCl₃) 213.3, 212.4, 164.8, 164.1, 138.7, 138.4, 137.9, 137.7, 137.4, 137.3, 128.3, 128.3, 128.3, 128.1, 127.9, 127.8, 127.8, 127.7, 127.6, 127.4, 73.7, 73.5, 73.4, 73.3, 73.2, 72.9, 70.3, 69.5, 65.5, 65.1, 54.1, 54.1, 50.0, 49.83, 29.8, 28.9, 20.2, 20.0, 19.9, 19.7; IR (thin film) ν 3408, 2922, 2862, 1701, 1454, 1361, 1090, 1028, 737, 698 cm⁻¹; HRMS (ES) *m/z* calcd for C₂₆H₃₃O₅ [M+H]⁺ 425.2323 found 425.2325.

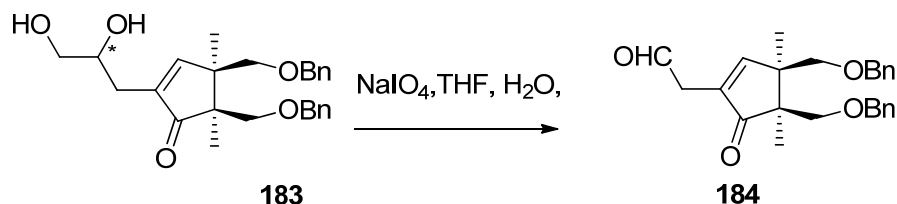
4,5-Bis((benzyloxy)methyl)-2-((2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-4,5-dimethylcyclopent-2-enone (185)



Compound **183** (150 mg, 0.35 mmol, 1 equiv) was dissolved in 1,1,1-trimethoxyethane (1 mL) and acetone (1 ml) and TsOH (6.0 mg, 0.1 equiv) was added. The solution was stirred for 10 h. The reaction mixture was then poured into a saturated aqueous solution of NaHCO₃ and extracted with DCM. The organic phase was washed with brine and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO₂, hexanes/EtOAc 5:1) to afford **185** as a colourless oil (149 mg, 98% yield, mixture of diastereoisomers, ratio = 1 : 1). **185**: ¹H NMR (360 MHz, CDCl₃) δ 7.38-7.24 (20 H, m), 7.14 (1 H, s), 7.12 (1 H,

s), 4.44-4.34 (8 H, m), 4.30-4.17 (2 H, m), 3.92 (1 H, dd, $J = 8.2, 5.9$ Hz), 3.83 (1 H, dd, $J = 8.1, 5.9$ Hz), 3.65-3.50 (10 H, m), 2.63-2.54 (2 H, m), 2.47-2.38 (2 H, m), 1.44 (3 H, s), 1.43 (3 H, s), 1.36 (3 H, s), 1.35 (3 H, s), 1.21 (3 H, s), 1.20 (3 H, s), 1.18 (3 H, s), 1.17 (3 H, s); ^{13}C NMR (90 MHz, CDCl_3) δ 212.3, 212.3, 164.2, 164.1, 139.3, 139.2, 139.2, 139.1, 129.3, 129.1, 128.9, 128.6, 128.6, 128.5, 128.4, 128.3, 109.9, 78.4, 78.2, 78.0, 77.8, 77.7, 75.6, 75.5, 75.5, 74.9, 74.5, 74.5, 74.3, 73.9, 70.0, 69.8, 55.1, 50.8, 50.8, 30.0, 29.6, 28.0, 27.9, 26.6, 26.6, 21.1, 21.1, 21.0, 20.9; IR (thin film) ν_{max} 3062, 3030, 2985, 2933, 2871, 1703, 1454, 1367, 1211, 1155, 1074, 1028, 737, 698 cm^{-1} ; HRMS (ES) m/z calcd for $\text{C}_{29}\text{H}_{37}\text{O}_5$ $[\text{M}+\text{H}]^+$ 465.2636, found 465.2643.

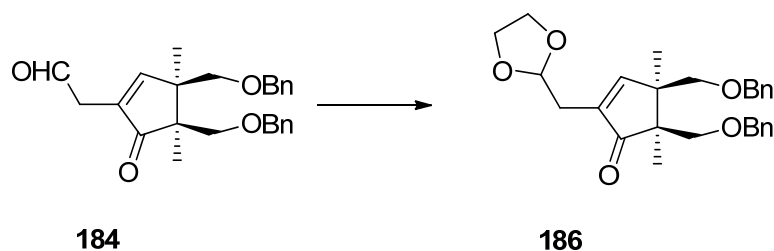
2-(3,4-Bis((benzyloxy)methyl)-3,4-dimethyl-5-oxocyclopent-1-en-1-yl)acetaldehyde (184)



To a solution of diol **183** (1.00 g, 2.35 mmol, 1 equiv) in THF (10 mL) was added a solution of NaIO_4 (1.0 g in water (10 mL), 2.7 mmol, 2 equiv), dropwise at 0 °C. The resulting mixture was stirred for 5 h, then extracted with EtOAc (2 × 50 mL). The combined organic phases were dried over MgSO_4 and concentrated under reduced pressure to give aldehyde **184** as a colourless oil. This crude product was used in the next step without further purification. **184**: ^1H NMR (360 MHz, CDCl_3) δ 9.60 (1 H, t, $J = 1.8$ Hz), 7.34-7.18 (11 H, m), 4.37 (1 H, d, $J_{ab} = 12.2$ Hz), 4.32 (1 H, d, $J_{ab} = 12.2$ Hz), 4.31 (1 H, s), 3.60 (1 H, d, $J_{ab} = 9.4$ Hz), 3.57 (1 H, d, $J_{ab} = 9.4$ Hz), 3.52 (1 H, d, $J_{ab} = 9.0$ Hz), 3.50 (1 H, d, $J_{ab} = 9.0$ Hz), 3.28 (2 H, m), 1.19 (3 H, s), 1.16 (3 H, s); ^{13}C NMR (90 MHz, CDCl_3) δ 210.5, 197.8, 164.4, 138.1, 138.0, 133.7, 128.2, 128.2, 127.5, 127.4, 127.2, 74.3, 73.2, 73.2, 72.8, 53.9, 50.3, 39.3, 19.9, 19.86; IR (thin film) ν_{max} 3427, 3062, 3030, 2968, 2858, 1724, 1705, 1454, 1361, 1093, 739, 698 cm^{-1} .

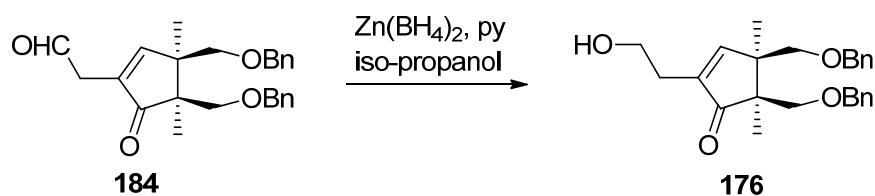
2-((1,3-Dioxolan-2-yl)methyl)-4,5-bis((benzyloxy)methyl)-4,5-dimethylcyclopent-

2-enone (186)



Compound **184** (100 mg, 0.25 mmol, 1 equiv) was dissolved in DCM (2 mL) and ethane-1,2-diol (155 mg, 10 equiv) and TsOH (4.3 mg, 0.1 equiv) was added. The solution was refluxed for 10 h. After cooling down to room temperature the reaction mixture was then poured into a saturated aqueous solution of NaHCO₃ and extracted with DCM. The organic phase was washed with brine and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO₂, hexanes/EtOAc 5:1) to afford **186** as a colourless oil (112 mg, 98% yield). **186**: ¹H NMR (360 MHz, CDCl₃) δ 7.38-7.25 (10 H, m), 7.22 (1 H, s), 5.03 (1 H, t, *J* = 4.8 Hz), 4.43 (1 H, *J*_{ab} = 10.8 Hz), 4.38 (2 H, s), 4.39 (1 H, *J*_{ab} = 14.4 Hz), 4.00-3.94 (2 H, m), 3.87-3.81 (2 H, m), 3.65 (1 H, *J*_{ab} = 10.8 Hz), 3.61 (1 H, *J*_{ab} = 7.8 Hz), 3.54 (1 H, *J*_{ab} = 9.0 Hz), 3.54 (1 H, *J*_{ab} = 9.0 Hz), 2.59 (2 H, dd, *J* = 4.8, 0.7 Hz), 1.21 (3 H, s), 1.09 (3 H, s); ¹³C NMR (90 MHz, CDCl₃) δ 211.0, 163.3, 138.4, 138.3, 136.8, 128.2, 128.2, 127.4, 127.3, 127.2, 102.5, 74.8, 73.4, 73.2, 72.8, 64.8, 54.0, 49.8, 29.4, 19.9; IR (thin film) ν_{max} 3480, 3030, 2874, 1704, 1496, 1454, 1362, 1271, 1206, 1092, 1028, 738, 698 cm⁻¹; HRMS (ES) *m/z* calcd for C₂₇H₃₃O₅ [M+H]⁺ 437.23225, found 437.23212.

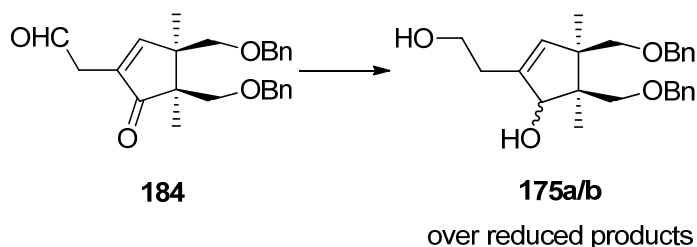
4,5-Bis((benzyloxy)methyl)-2-(2-hydroxyethyl)-4,5-dimethylcyclopent-2-enone (176)



The crude product **184** from the previous step was dissolved in *iso*-propanol (5 mL),

cooled to 0 °C and freshly prepared¹ Zn(BH₄)₂/ pyridine complex (400 mg, ~ 2.35 mmol, 1 equiv) added in one portion. The reaction mixture was stirred at 0 °C for 2 h and then quenched with saturated NH₄Cl aqueous (5 mL). The solution was extracted with EtOAc (2 × 10 mL), and the combined organic phases dried by MgSO₄ and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO₂, Hexanes:EtOAc 1:1) to afford **176** (0.70 g, 76% yield for 2 steps) as a colourless oil. **176**: ¹H NMR (600 MHz, CDCl₃) δ 7.32-7.16 (10 H, m), 6.98 (1 H, s), 4.34 (1 H, d, *J* = 12.0 Hz), 4.26 (1 H, d, *J* = 11.9 Hz), 4.25 (1 H, d, *J* = 11.9 Hz), 4.20 (1H, d, *J* = 11.9 Hz), 3.57 (2 H, dd, *J* = 11.1, 6.3 Hz), 3.53 (1 H, d, *J*_{ab} = 9.0 Hz), 3.51 (1 H, d, *J*_{ab} = 9.0 Hz), 3.45 (1 H, d, *J*_{ab} = 9.0 Hz), 3.41 (1 H, d, *J*_{ab} = 9.0 Hz), 2.49-2.45 (1 H, m), 2.41 (1 H, t, *J* = 6.2 Hz), 2.38-2.33 (1 H, m), 1.13 (3 H, s), 1.27 (3 H, s); ¹³C NMR (150 MHz, CDCl₃) δ 212.0, 163.4, 139.5, 137.9, 137.6, 128.3, 127.8, 127.7, 127.6, 73.8, 73.5, 73.3, 72.9, 60.0, 54.2, 49.7, 29.2, 20.1, 19.8; IR (thin film) ν_{max} 3423, 2871, 1701, 1454, 1361, 1074, 737, 698 cm⁻¹; HRMS (ES) *m/z* calcd for C₂₅H₃₁O₄ [M+H]⁺ 395.2217, found 395.2215.

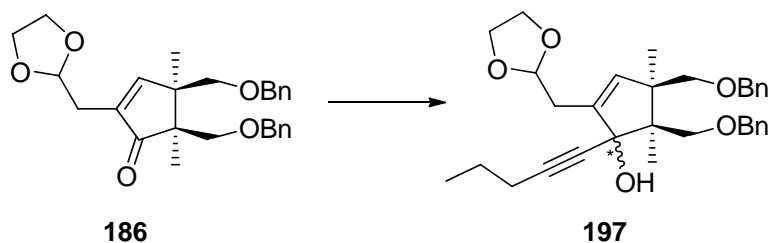
4,5-Bis((benzyloxy)methyl)-2-(2-hydroxyethyl)-4,5-dimethylcyclopent-2-enol (175)



(Ratio = 1 : 1) **175a**: ¹H NMR (600 MHz, CDCl₃) δ 7.37-7.22 (10 H, m), 5.18 (1 H, s), 4.48 (1 H, d, *J* = 12.1 Hz), 4.38 (1 H, d, *J* = 11.5 Hz), 4.32 (1 H, d, *J* = 12.1 Hz), 4.29 (1 H, d, *J* = 11.5 Hz), 4.05 (1 H, d, *J* = 10.8 Hz), 3.80 (1 H, d, *J* = 9.9 Hz), 3.77-3.72 (1 H, m), 3.59-3.53 (3 H, m), 3.44-3.41 (2 H, m), 3.11 (1 H, d, *J* = 9.3 Hz), 2.49 (1 H, ddd, *J* = 14.4, 5.1, 3.2 Hz), 2.32 (1 H, m), 1.07 (3 H, s), 0.96 (3 H, s); ¹³C NMR (150 MHz, CDCl₃) δ 143.0, 138.8, 136.6, 136.1, 128.5, 128.2, 128.1, 128.1, 127.6, 127.4, 85.6, 74.0, 73.3, 72.9, 62.0, 51.9, 48.7, 34.0, 22.4, 18.7; IR (thin film) ν_{max} 3405, 3029, 2858, 1495, 1454, 1362, 1073, 736, 698 cm⁻¹; HRMS (ES) *m/z*

calcd for $C_{25}H_{32}O_4Na$ $[M+Na]^+$ 419.2193, found 419.2192. **175b**: 1H NMR (600 MHz, $CDCl_3$) δ 7.38-7.26 (10 H, m), 5.30 (1 H, s), 4.68 (1 H, s), 4.46 (1H, d, J_{ab} = 12.0 Hz), 4.42 (1H, d, J_{ab} = 12.0 Hz), 4.36 (2 H, d, J = 1.4 Hz), 3.70 (1 H, td, J = 9.72, 4.71 Hz), 3.63 (1 H, m), 3.57 (1 H, d, J = 8.5 Hz), 3.51 (1 H, d, J = 8.5 Hz), 3.27 (1 H, d, J = 9.1 Hz), 3.20 (1 H, d, J = 9.1 Hz), 2.47 (1 H, td, J = 14.0, 3.8 Hz), 2.36 (1 H, ddd, J = 14.1, 9.4, 4.7 Hz), 1.07 (3 H, s), 1.04 (3 H, s); ^{13}C NMR (150 MHz, $CDCl_3$) δ 141.3, 138.4, 138.0, 134.6, 128.3, 128.3, 127.7, 127.5, 82.1, 75.7, 75.2, 73.4, 73.0, 60.6, 51.2, 51.2, 31.8, 20.0, 15.26; IR (thin film) ν_{max} 3375, 3029, 2857, 1495, 1454, 1362, 1206, 1073, 1028, 734, 697 cm^{-1} ; HRMS (ES) m/z calcd for $C_{25}H_{32}O_4Na$ $[M+Na]^+$ 419.2193, found 419.2192.

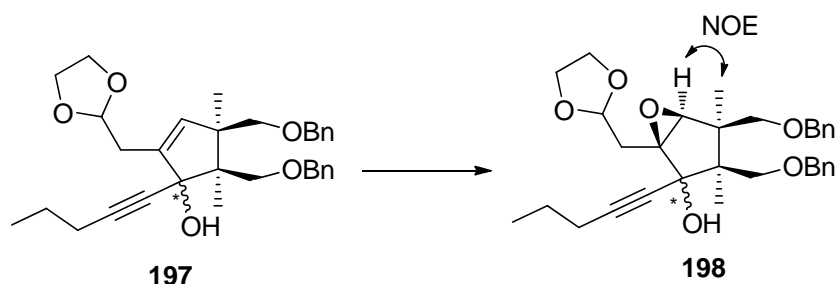
2-((1,3-Dioxolan-2-yl)methyl)-4,5-bis((benzyloxy)methyl)-4,5-dimethyl-1-(pent-1-yn-1-yl)cyclopent-2-enol (197)



Pent-1-yne (272 mg, 4.01 mmol, 2.5 equiv) in THF (20 mL) was cooled to -42 °C and *n*-butyllithium (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 **186** (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 **197** as a colourless oil (645 mg, 80 % yield). **197**: 1H NMR (360 MHz, $CDCl_3$) δ 7.39-7.31 (10 H, m), 5.56 (1 H, s), 5.14 (1 H, t, J = 4.8 Hz), 4.50-4.49 (4 H, m), 4.06-4.02 (2 H, m), 3.94-3.80 (2 H, m), 3.82 (1 H, d, J = 9.1 Hz), 3.72 (1 H, d, J = 7.0 Hz), 3.70 (1 H, d, J = 6.5 Hz), 3.57 (1 H, d, J = 8.6 Hz), 3.36 (1

H, s), 2.65 (2 H, dd, $J = 4.8, 1.0$ Hz), 2.17 (2 H, t, $J = 6.9$ Hz), 1.50 (2 H, dd, $J = 14.4, 7.2$ Hz), 1.23 (3 H, s), 1.14 (3 H, s), 1.00 (3 H, t, $J = 7.3$ Hz); ^{13}C NMR (90 MHz, CDCl_3) δ 138.9, 138.8, 138.6, 136.1, 128.1, 128.0, 127.3, 127.2, 127.1, 103.6, 86.5, 82.5, 81.9, 75.0, 74.7, 73.3, 73.0, 64.9, 64.7, 54.6, 51.2, 31.7, 22.1, 20.7, 20.4, 16.2, 13.5; IR (thin film) ν_{max} 3445, 2962, 2932, 2872, 1722, 1454, 1361, 1272, 1207, 1074, 1029, 737, 698 cm^{-1} ; HRMS (ES) m/z calcd for $\text{C}_{32}\text{H}_{40}\text{O}_5\text{Na}_1$ $[\text{M}+\text{Na}]^+$ 527.27680, found 527.27680.

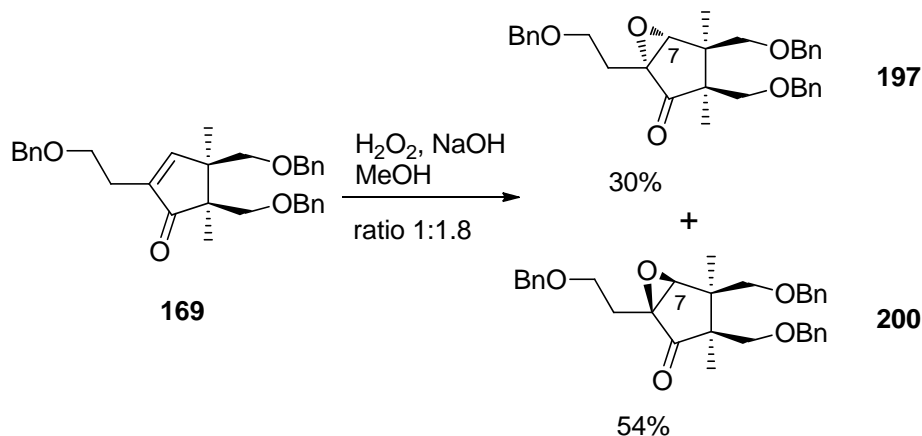
1-((1,3-Dioxolan-2-yl)methyl)-3,4-bis((benzyloxy)methyl)-3,4-dimethyl-2-(pent-1-yn-1-yl)-6-oxabicyclo[3.1.0]hexan-2-ol (198)



Compound **197** (50 mg, 0.1 mmol, 1 equiv) was dissolved in DCM (2 mL) and *m*CPBA (156 mg, 10 equiv) was added. The solution was stirred for 2 days. The reaction mixture was then poured into a saturated aqueous solution of NaHCO_3 and extracted with DCM. The organic phase was washed with brine and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO_2 , hexanes/ EtOAc 5:1) to afford **198** as a colourless oil (5 mg, 10% yield). **198**: ^1H NMR (360 MHz, CDCl_3) δ 7.40-7.30 (10 H, m), 5.13-5.11 (1 H, m), 4.57 (1 H, d, $J = 12.4$ Hz), 4.52 (1 H, d, $J = 11.9$ Hz), 4.45 (1 H, d, $J = 5.5$ Hz), 4.41 (1 H, d, $J = 4.9$ Hz), 4.07-4.02 (2 H, m), 3.94-3.90 (2 H, m), 3.74 (1 H, d, $J = 8.6$ Hz), 3.58 (1 H, d, $J = 8.9$ Hz), 3.53 (1 H, s), 3.46 (1 H, d, $J = 8.5$ Hz), 3.46 (1 H, s), 3.42 (1 H, d, $J = 8.9$ Hz), 2.75 (1 H, dd, $J = 14.7, 5.6$ Hz), 2.13-2.07 (3 H, m), 1.52-1.42 (2 H, m), 1.29 (3 H, s), 1.28 (3 H, s), 0.98 (3 H, t, $J = 7.3$ Hz); ^{13}C NMR (90 MHz, CDCl_3) δ 138.3, 137.6, 128.2, 128.2, 127.5, 127.5, 127.3, 101.8, 89.3, 81.2, 80.8, 75.2, 73.2, 72.8, 67.3, 66.6, 64.8, 64.5, 48.6, 46.4, 32.1, 21.9, 20.8, 18.6, 18.1, 13.5; IR (thin film) ν_{max} 3446, 2962, 2931, 2873, 1722, 1454, 1411, 1362, 1093, 1073, 1028, 738, 698 cm^{-1} ; HRMS (ES) m/z calcd for $\text{C}_{32}\text{H}_{40}\text{O}_6\text{Na}_1$ $[\text{M}+\text{Na}]^+$

543.27171, found 543.27171.

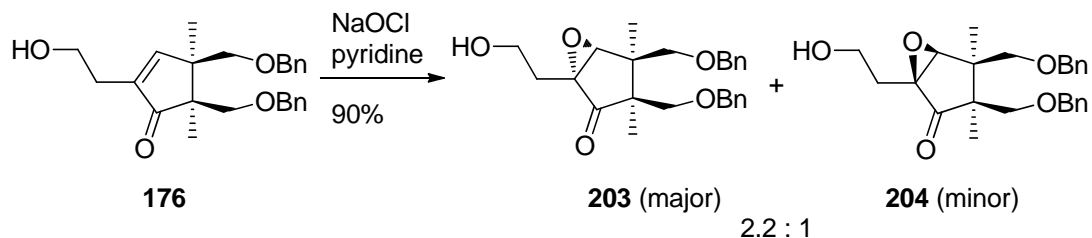
1-(2-(Benzyloxy)ethyl)-3,4-bis((benzyloxy)methyl)-3,4-dimethyl-6-oxabicyclo[3.1.0]hexan-2-one (197)



Cyclopentenone **169** (272 mg, 0.56 mmol, 1 equiv) in MeOH (20 mL) was treated with H₂O₂ (190 μL, 30% wt solution in H₂O, 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 NH₄Cl solution. The mixture was extracted with Et₂O, dried over MgSO₄, filtered and the solvent removed *in vacuo*. Flash column chromatography (SiO₂, hexanes/EtOAc 9.5:0.5) afforded two diastereomers of the epoxide product (**200** - 85 mg, **197** - 150 mg, 235 mg overall, 84% yield, 1.8:1 ratio of diastereomers). **200**: ¹H NMR (360 MHz, CDCl₃) δ 7.36-7.21 (15 H, m), 4.53 (1 H, d, *J*_{ab}= 12.9 Hz), 4.47 (1 H, d, *J*_{ab}= 12.9 Hz), 4.45 (2 H, s), 4.39 (1 H, d, *J*_{abB}= 12.2 Hz), 4.34 (1 H, d, *J*_{ab}= 12.2 Hz), 3.74 (1 H, s), 3.63-3.50 (4 H, m), 3.47 (1 H, d, *J*_{ab}= 8.8 Hz), 2.36 (1 H, m), 2.01 (1 H, m), 1.08 (3 H, s), 1.00 (3 H, s); ¹³C NMR (90 MHz, CDCl₃) δ 211.2, 138.4, 138.2, 138.0, 128.3, 128.2, 127.6, 127.4, 127.3, 74.4, 73.4, 73.0, 72.9, 72.0, 67.4, 65.6, 62.1, 52.0, 43.6, 25.1, 18.8, 16.3; IR (thin film) ν 2859, 1740, 1454, 1097, 697 cm⁻¹; HRMS (ES) *m/z* calcd for C₃₂H₄₀O₅N [M+NH₄]⁺ 518.2901, found 518.2903. **197**: ¹H NMR (360 MHz, CDCl₃) δ 7.34-7.23 (13 H, m), 7.13-7.01 (2 H, m), 4.42 (1 H, d, *J*_{ab}= 12.0 Hz), 4.32 (2 H, s), 4.25 (1 H, d, *J*_{ab}= 12.0 Hz), 3.57-3.40 (5 H, m), 3.28 (1 H, d, *J*_{ab}= 12.0 Hz), 2.21 (1 H, m), 2.06 (1 H, m), 1.31 (3 H, s), 1.13 (3 H, s); ¹³C NMR (90 MHz, CDCl₃) δ 212.1, 138.4, 138.3, 137.6, 138.3, 127.7, 127.6, 127.5, 127.4, 74.3, 73.5,

73.4, 73.0, 72.6, 68.8, 65.5, 62.8, 49.3, 43.8, 24.7, 21.6, 16.2; **IR** (thin film) ν 2860, 1737, 1454, 1099, 697 cm^{-1} ; **HRMS** (ES) m/z calcd for $\text{C}_{32}\text{H}_{40}\text{O}_5\text{N}$ $[\text{M}+\text{NH}_4]^+$ 518.2901, found 518.2908.

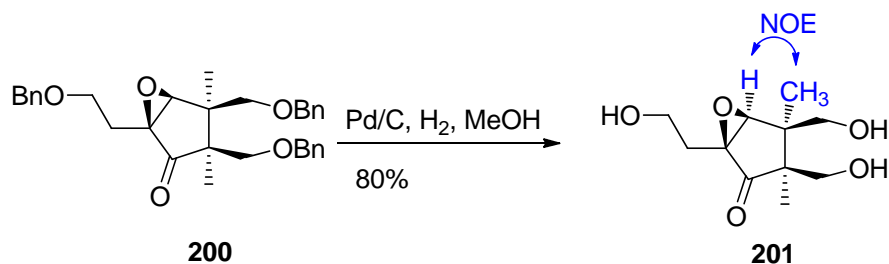
3,4-Bis((benzyloxy)methyl)-1-(2-hydroxyethyl)-3,4-dimethyl-6-oxabicyclo[3.1.0]hexan-2-one (203)



A solution of cyclopentanone **176** (1.0 g, 2.5 mmol, 1 equiv) in pyridine (10 mL) was treated with NaClO (14% active chlorine, 3 mL, *ca.* 10 equiv), dropwise, at 0 °C. The resulting solution was stirred for 5 h after which time the reaction was completed. Filtration through a plug of silica, removal of pyridine under reduced pressure and flash column chromatography (SiO_2 , Hexanes/EtOAc 2:1) furnished two diastereomeric epoxides **203** (633 mg, 62% yield) and **204** (276 mg, 27% yield), each as colourless oils. (dr = 2.2:1). Diastereomer **203**: **^1H NMR** (600 MHz, CDCl_3) δ 7.33-7.13 (10 H, m), 4.39 (1 H, d, $J = 12.0$ Hz), 4.17 (1 H, d, $J = 12.2$ Hz), 4.16 (1 H, d, $J_{ab} = 11.4$ Hz), 4.12 (1 H, d, $J_{ab} = 11.4$ Hz), 3.57-3.54 (4 H, m), 3.49 (1 H, d, $J = 9.3$ Hz), 3.40 (1 H, d, $J = 9.2$ Hz), 3.35 (1 H, d, $J = 9.4$ Hz), 2.91 (1 H, dd, $J = 7.4, 5.1$ Hz), 2.20 (1 H, td, $J = 14.5, 3.2, 3.2$ Hz), 1.75 (1 H, ddd, $J = 14.5, 9.5, 4.9$ Hz), 1.30 (3 H, s), 1.11 (3 H, s); **^{13}C NMR** (150 MHz, CDCl_3): δ 212.2, 138.0, 136.0, 128.4, 128.3, 128.2, 128.2, 127.6, 127.5, 127.3, 74.2, 73.3, 73.2, 73.1, 68.5, 62.9, 58.1, 49.4, 43.6, 28.9, 21.7, 16.2; **IR** (thin film) ν_{max} 3462, 3063, 3030, 2875, 1738, 1454, 1361, 1094, 739, 699 cm^{-1} ; **HRMS** (ES) m/z calcd for $\text{C}_{25}\text{H}_{31}\text{O}_5$ $[\text{M}+\text{H}]^+$ 411.2166, found 411.2162. Diastereomer **204**: **^1H NMR** (500 MHz, CDCl_3) δ 7.34-7.22 (10 H, m), 4.53 (1 H, d, $J_{ab} = 12.0$ Hz), 4.49 (1 H, d, $J_{ab} = 12.2$ Hz), 4.38 (2 H, d, $J = 1.9$ Hz), 3.75 (1 H, s), 3.78-3.71 (2H, m), 3.60 (1 H, d, $J = 9.0$ Hz), 3.58 (1 H, d, $J = 9.0$ Hz), 3.56 (1 H, d, $J = 9.0$ Hz), 3.49 (1 H, d, $J = 9.0$ Hz), 2.17-2.05 (2 H, m), 1.11 (3 H, s), 1.06 (3 H, s); **^{13}C NMR** (125 MHz, CDCl_3): δ 212.2, 138.2, 138.1, 128.3, 128.2, 127.5, 127.5, 127.4, 127.4, 74.1, 73.4, 73.0, 71.8, 67.5, 63.0,

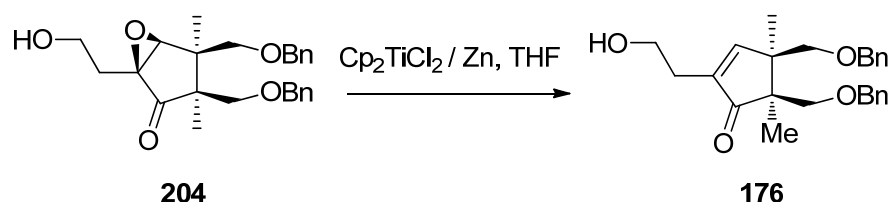
58.8, 52.1, 43.6, 28.1, 18.9, 16.3; **IR** (thin film) ν_{\max} 3460, 3030, 2862, 1739, 1496, 1454, 1361, 1272, 1073, 738, 698 cm^{-1} ; **HRMS** (ES) m/z calcd for $\text{C}_{25}\text{H}_{31}\text{O}_5$ $[\text{M}+\text{H}]^+$ 411.2166, found 411.2162.

1-(2-Hydroxyethyl)-3,4-bis(hydroxymethyl)-3,4-dimethyl-6-oxabicyclo[3.1.0]hexan-2-one (201)



To a solution of **200** (150 mg, 0.36 mmol) in MeOH (5 mL) was added Pd/C (15 mg) and the resulting mixture purged with H_2 for 5 min. The reaction mixture was then stirred under a hydrogen balloon at RT for 2 h, then filtered through a pad of silica and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2 , EtOAc) gave **201** as a colourless oil (63 mg, 80% yield). **201**: $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 4.16 (1 H, dd, $J = 11.7, 4.0$ Hz), 4.11 (1 H, dd, $J = 10.9, 4.7$ Hz), 3.79-3.71 (2 H, m), 3.65 (1 H, dd, $J = 11.7, 8.5$ Hz), 3.59 (1 H, s), 3.42 (1 H, dd, $J = 10.8, 5.5$ Hz), 3.26 (1 H, dd, $J = 8.5, 4.2$ Hz), 2.84 (1 H, t, $J = 5.2$, Hz), 2.13-2.10 (3 H, m), 1.12 (3 H, s), 1.11 (3 H, s); $^{13}\text{C NMR}$ (125 MHz, CDCl_3): δ 212.4, 67.9, 67.9, 66.2, 61.9, 58.5, 53.8, 44.6, 27.6, 19.2, 16.9; **IR** (thin film) ν_{\max} 3365, 2938, 1738, 1457, 1031, 879 cm^{-1} ; **HRMS** (ES) m/z calcd for $\text{C}_{11}\text{H}_{22}\text{O}_5\text{N}_1$ $[\text{M}+\text{NH}_4]^+$ 248.1492, found 248.1494

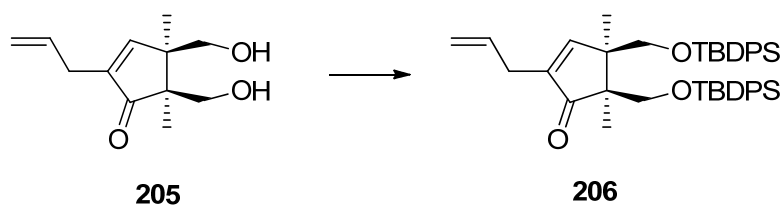
4,5-Bis((benzyloxy)methyl)-2-(2-hydroxyethyl)-4,5-dimethylcyclopent-2-enone (176)



Cp_2TiCl_2 (58.0 mg, 0.24 mmol, 2 equiv) and Zn dust (47 mg, 0.7 mmol, 6 equiv)

were placed in a dried round bottom flask and THF (2 mL) was added under an argon atmosphere. The resulting suspension was stirred at RT for 1 h, then cannulated under argon into a solution of epoxide **204** (50.0 mg, 0.13 mmol, 1 equiv) in THF (2 mL). The resulting green solution was stirred at RT under an argon atmosphere for 2 h. Then the catalyst was then removed by filtering through a short silica pad and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (SiO₂, hexanes/EtOAc 2:1) to afford the product **176** as a colourless oil (36 mg, 70% yield). **176**: ¹H NMR (600 MHz, CDCl₃) δ 7.32-7.16 (10 H, m), 6.98 (1 H, s), 4.34 (1 H, d, *J* = 12.0 Hz), 4.26 (1 H, d, *J* = 11.9 Hz), 4.25 (1 H, d, *J* = 11.9 Hz), 4.20 (1H, d, *J* = 11.9 Hz), 3.57 (2 H, dd, *J* = 11.1, 6.3 Hz), 3.53 (1 H, d, *J_{ab}* = 9.0 Hz), 3.51 (1 H, d, *J_{ab}* = 9.0 Hz), 3.45 (1 H, d, *J_{ab}* = 9.0 Hz), 3.41 (1 H, d, *J_{ab}* = 9.0 Hz), 2.49-2.45 (1 H, m), 2.41 (1 H, t, *J* = 6.2 Hz), 2.38-2.33 (1 H, m), 1.13 (3 H, s), 1.27 (3 H, s); ¹³C NMR (150 MHz, CDCl₃) δ 212.0, 163.4, 139.5, 137.9, 137.6, 128.3, 127.8, 127.7, 127.6, 73.8, 73.5, 73.3, 72.9, 60.0, 54.2, 49.7, 29.2, 20.1, 19.8; IR (thin film) ν_{max} 3423, 2871, 1701, 1454, 1361, 1074, 737, 698 cm⁻¹; HRMS (ES) *m/z* calcd for C₂₅H₃₁O₄ [M+H]⁺ 395.2217, found 395.2215.

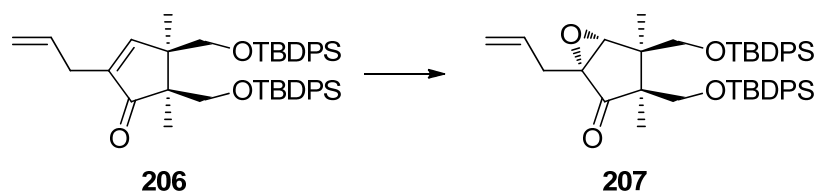
2-Allyl-4,5-bis(((tert-butyldiphenylsilyl)oxy)methyl)-4,5-dimethylcyclopent-2-ene one (206)



Compound **205** (1.0 g, 4.7 mmol, 1 equiv) in DCM (5 mL) was treated with TBDPSCl (2.80 g, 10.3 mmol, 2.2 equiv) and imidazole (958 mg, 14.1 mmol, 3.0 equiv) at 0 °C. The resulting solution was stirred for 5 h. Filtration through a plug of silica, removal of DCM under reduced pressure and flash column chromatography (SiO₂, hexanes/EtOAc 5:1) furnished product **206** (3.16g, 98% yield) as a colourless oil. **206**: ¹H NMR (600 MHz, CDCl₃) δ 7.56-7.24 (20 H, m), 6.83 (1 H, s), 5.83-5.76 (1 H, m), 5.07-5.04 (2 H, m), 3.99 (1 H, d, *J* = 10.4 Hz), 3.90 (1 H, d, *J* = 9.7 Hz), 3.76 (1 H, d, *J* = 3.3 Hz), 3.74 (1 H, d, *J* = 4.2 Hz), 2.85 (2 H, dddd, *J* = 46.0, 16.7, 6.8, 1.2 Hz), 1.16 (3 H, s), 1.08 (3 H, s), 0.99 (9 H, s), 0.96 (9 H, s); ¹³C NMR (150

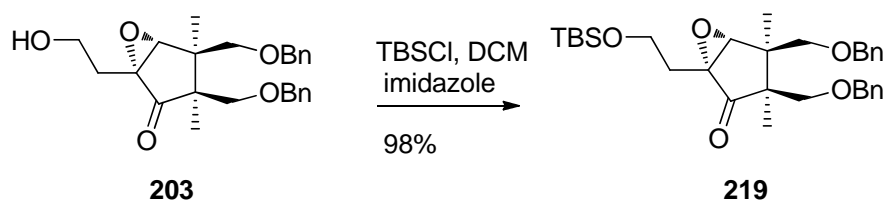
MHz, CDCl₃) δ 210.7, 161.2, 140.7, 135.7, 135.6, 135.5, 134.3, 133.2, 133.1, 129.6, 129.5, 127.5, 116.6, 68.6, 66.6, 55.3, 50.8, 29.3, 26.9, 26.7, 20.4, 19.2, 19.1, 19.0; **IR** (thin film) ν_{\max} 3072, 2930, 2857, 1708, 1471, 1472, 1113, 1080, 823, 739, 701 cm⁻¹; **HRMS** (ES) m/z calcd for C₄₄H₅₅O₃Si₂ [M+H]⁺ 687.3684, found 687.3680.

1-Allyl-3,4-bis(((tert-butyldiphenylsilyl)oxy)methyl)-3,4-dimethyl-6-oxabicyclo[3.1.0]hexan-2-one (207)



A solution of cyclopentanone **206** (50.0 mg, 0.07 mmol, 1 equiv) in pyridine (1 mL) was treated with NaClO (14% active chlorine, 0.1 mL, *ca.* 10 equiv) dropwise, at 0 °C. The resulting solution was stirred for 5 h after which time the reaction was completed. Filtration through a plug of silica, removal of pyridine under reduced pressure and flash column chromatography (SiO₂, Hexanes/EtOAc 2:1) furnished a mixture of two diastereomeric epoxides **207** (46 mg, 95% yield, ratio > 20 : 1) as colourless oils. **207**: ¹H NMR (600 MHz, CDCl₃) δ 7.55-7.24 (20 H, m), 5.58-5.51 (1 H, m), 5.02-4.99 (2 H, m), 3.89-3.87 (2 H, m), 3.76 (1 H, d, *J* = 10.2 Hz), 3.65 (1 H, d, *J* = 10.6 Hz), 3.53 (1 H, s), 2.64 (1 H, dd, *J* = 15.3, 6.2 Hz), 2.37 (1 H, dd, *J* = 15.3, 7.6 Hz), 1.26 (3 H, s), 1.22 (3 H, s), 1.00 (18 H, s); ¹³C NMR (150 MHz, CDCl₃) δ 212.40, 135.87, 135.80, 135.74, 135.59, 133.12, 133.04, 132.98, 132.57, 131.09, 129.88, 129.84, 129.67, 129.62, 127.72, 127.55, 118.56, 68.12, 66.48, 63.78, 50.63, 44.61, 28.45, 26.93, 26.76, 21.73, 19.13, 16.05; **IR** (thin film) ν_{\max} 2930, 2858, 1735, 1427, 1113, 1075, 997, 822, 701 cm⁻¹; **HRMS** (ES) m/z calcd for C₄₄H₅₈O₄Si₂N₁ [M+NH₄]⁺ 720.3899, found 720.3898.

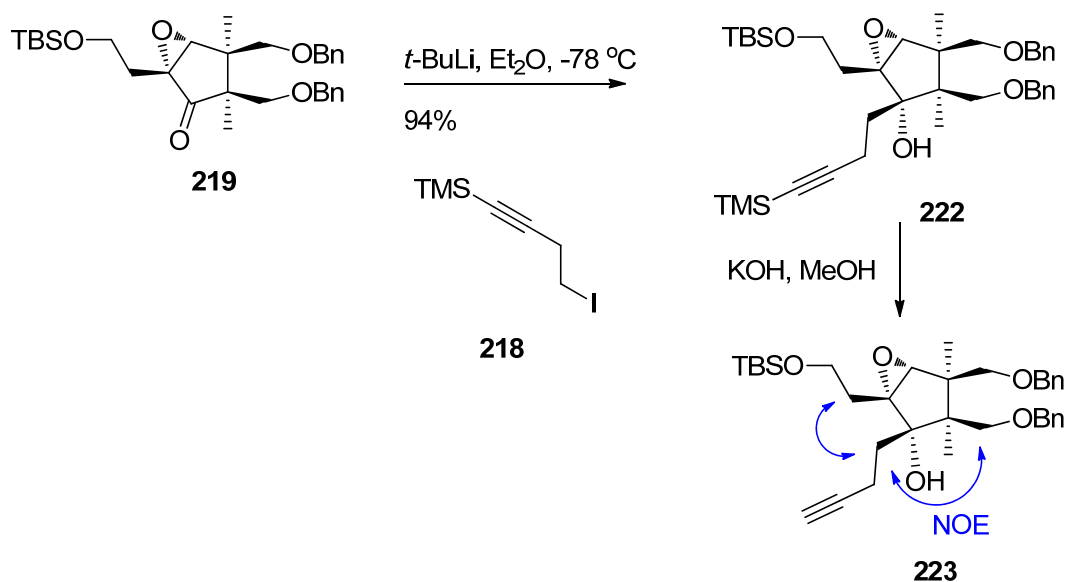
3,4-Bis((benzyloxy)methyl)-1-(2-(((tert-butyldimethylsilyl)oxy)ethyl))-3,4-dimethyl-1-6-oxabicyclo[3.1.0]hexan-2-one (209)



Epoxide **203** (1.0 g, 2.4 mmol, 1 equiv) in DCM (5 mL) was treated with TBSCl (432 mg, 2.88 mmol, 1.2 equiv) and imidazole (353 mg, 5.28 mmol, 2.2 equiv) at 0 °C. The resulting solution was stirred for 5 h. Filtration through a plug of silica, removal of DCM under reduced pressure and flash column chromatography (SiO₂, hexanes/EtOAc 2:1) furnished product **219** (1.26g, 98% yield) as a colourless oil.

187: ¹H NMR (500 MHz, CDCl₃) δ 7.34-7.14 (10 H, m), 4.40 (1 H, d, *J* = 12.0 Hz), 4.23 (1 H, d, *J* = 12.0 Hz), 4.22 (1 H, d, *J*_{ab} = 11.9 Hz), 4.16 (1 H, d, *J* = 11.9 Hz), 3.68 (1 H, td, *J* = 10.1, 6.6 Hz), 3.63-3.60 (1 H, m), 3.58 (1 H, s), 3.55 (1 H, d, *J* = 9.5 Hz), 3.53 (1 H, d, *J* = 9.3 Hz), 3.42 (1 H, d, *J* = 9.3 Hz), 3.30 (1 H, d, *J* = 9.3 Hz), 2.05 (2 H, t, *J* = 7.0, Hz), 1.31 (3 H, s), 1.42 (3 H, s), 0.86 (9 H, s), 0.01 (3 H, s), -0.01 (3 H, s); ¹³C NMR (125 MHz, CDCl₃): δ 212.2, 138.3, 137.5, 128.3, 128.2, 127.6, 127.6, 127.5, 74.3, 73.5, 73.3, 73.0, 68.8, 62.7, 58.4, 49.2, 43.7, 27.6, 25.8, 21.6, 18.1, 16.1, -5.4; IR (thin film) ν_{max} 3031, 2928, 2856, 1739, 1454, 1361, 1254, 1099, 1005, 836, 777 cm⁻¹; HRMS (ES) *m/z* calcd for C₃₁H₄₅SiO₅ [M+H]⁺ 525.3031, found 525.3028.

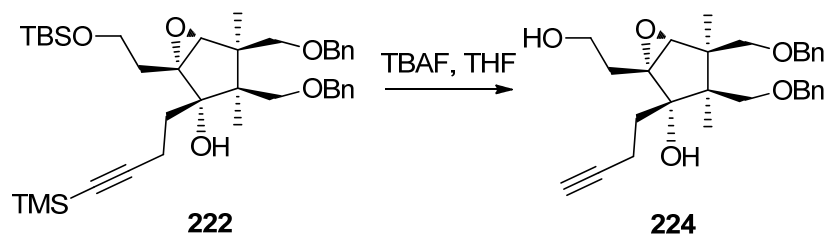
3,4-Bis((benzyloxy)methyl)-2-(but-3-yn-1-yl)-1-(2-((tert-butyldimethylsilyl)oxy)ethyl)-3,4-dimethyl-6-oxabicyclo[3.1.0]hexan-2-ol (223)



A solution of (4-iodobut-1-ynyl)trimethylsilane **218** (254 mg, 0.95 mmol, 5 equiv) in dry Et_2O (3 mL) at $-78\text{ }^\circ\text{C}$ was treated with $t\text{-BuLi}$ (1.23 mL, 1.7 M in pentane, 2.09 mmol, 11 equiv) and stirred under argon for 1 h before warming to RT and stirring for a further 2 h. After re-cooling to $-78\text{ }^\circ\text{C}$, the mixture was transferred into a solution of epoxide **219** (100 mg, 0.19 mmol, 1 equiv) in Et_2O at $-78\text{ }^\circ\text{C}$ via a double tipped needle. The reaction mixture was then stirred for 30 min and quenched with several drops of water before warming up to RT. The reaction mixture was filtered through a plug of silica, concentrated under reduced pressure and then purified by flash column chromatography (SiO_2 , hexanes/ EtOAc 20:1) to afford the product **222** as a colourless oil (116 mg, 94% yield). Product **222** (100 mg, 0.15 mmol, 1 equiv) was dissolved in MeOH (1 mL) and treated with KOH (10 mg). The resulting mixture was stirred for 10 h, then concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO_2 , hexanes/ EtOAc 20:1) to afford **223** as a colourless oil (89 mg, 98% yield). Product **223**: $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 7.36-7.24 (10 H, m), 4.36 (1 H, d, $J_{ab} = 12.0$ Hz), 4.34 (1 H, d, $J_{ab} = 12.0$ Hz), 4.28 (1 H, d, $J_{ab} = 11.5$ Hz), 4.23 (1 H, d, $J_{ab} = 11.5$ Hz), 3.54 (1 H, ddd, $J = 9.6, 7.7, 5.9$ Hz), 3.45-3.75 (3 H, m), 3.27 (1 H, d, $J_{ab} = 9.5$ Hz), 3.25 (1 H, s), 3.23 (1 H, d, $J_{ab} = 9.5$ Hz), 2.77 (1 H, s), 2.37 (1 H, dt, $J = 8.4, 2.6$ Hz), 2.11-1.92 (4 H, m), 1.95 (1 H, t, $J = 2.6, 2.6$ Hz), 1.10 (3 H, s), 0.879 (12 H, m), 0.02 (6H, s); $^{13}\text{C NMR}$ (125 MHz, CDCl_3): δ 138.1, 137.6, 128.3, 128.3, 128.0, 127.7, 127.6, 85.4,

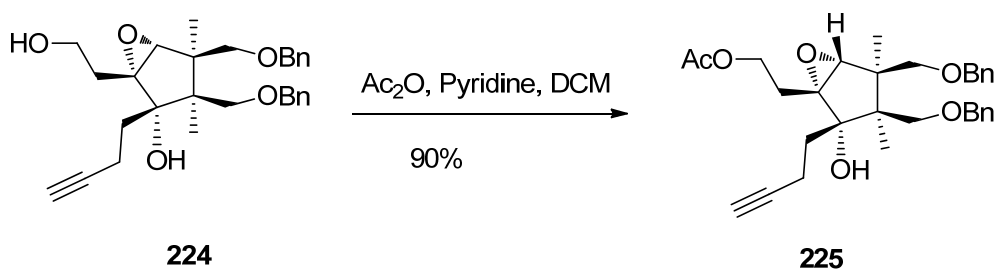
81.3, 74.3, 74.1, 73.3, 73.2, 71.6, 71.3, 67.8, 59.0, 45.4, 32.4, 30.5, 25.9, 18.2, 18.2, 13.6, -5.3; **IR** (thin film) ν_{\max} 3308, 2928, 2856, 1455, 1361, 1255, 1091, 837, 698 cm^{-1} ; **HRMS** (ES) m/z calcd for $\text{C}_{35}\text{H}_{51}\text{SiO}_5$ $[\text{M}+\text{H}]^+$ 579.3500, found 579.3506.

3,4-Bis((benzyloxy)methyl)-2-(but-3-yn-1-yl)-1-(2-hydroxyethyl)-3,4-dimethyl-6-oxabicyclo[3.1.0]hexan-2-ol (224)



Compound **222** (100 mg, 0.15 mmol, 1 equiv) was dissolved in DCM (2 mL) and treated with a solution of TBAF (0.76 mL, 1 M in THF, 5 equiv). The resulting mixture was stirred for 5 h. The solvent was evaporated under reduced pressure and the crude product was purified by flash column chromatography (SiO_2 , hexanes/EtOAc 20:1) to afford the product **224** as a colourless oil (68 mg, 95% yield). This compound decomposed over time so was immediately taken on to the next step.

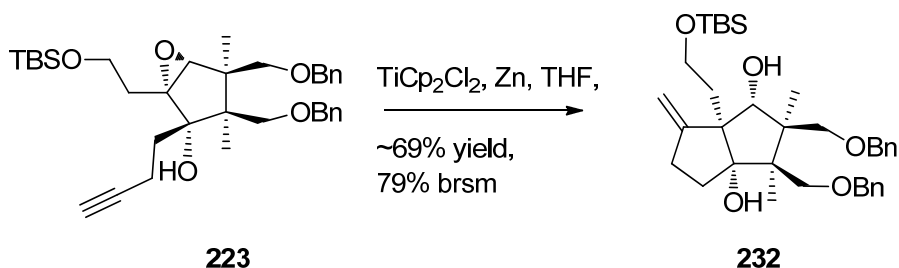
2-(3,4-Bis((benzyloxy)methyl)-2-(but-3-yn-1-yl)-2-hydroxy-3,4-dimethyl-6-oxabicyclo[3.1.0]hexan-1-yl)ethyl acetate (225)



Compound **224** (129 mg, 0.28 mmol, 1 equiv) in DCM (2 mL) was treated with Ac_2O (142 mg, 1.40 mmol, 5 equiv) and pyridine (79 mg, 2.8 mmol, 10 equiv) at 0 °C. The resulting solution was stirred for 5 h. Filtration through a plug of silica, removal of DCM under reduced pressure and flash column chromatography (SiO_2 , Hexanes/EtOAc 10:1) furnished product **225** (140 mg, 90% yield) as a colourless oil.

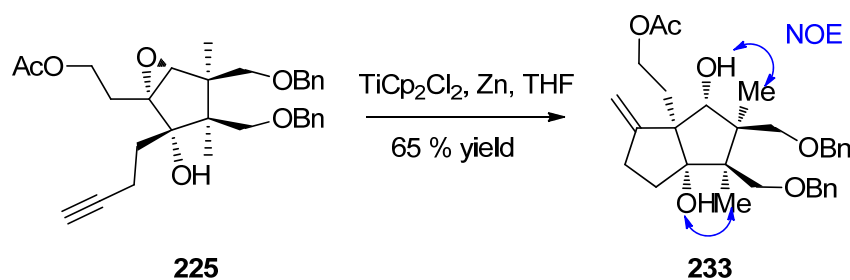
225: $^1\text{H NMR}$ (600 MHz, CDCl_3) δ 7.37-7.21 (10H, m), 4.41 (1 H, d, J_{ab} = 12.0 Hz), 4.36 (1 H, d, J_{ab} = 12.0 Hz), 4.24 (1 H, d, J_{ab} = 11.4 Hz), 4.16 (1 H, d, J_{ab} = 11.4 Hz), 3.85-3.81 (1 H, m), 3.68-3.64 (1 H, m), 3.44 (1 H, d, J_{ab} = 9.0 Hz), 3.36 (1 H, d, J_{ab} = 9.0 Hz), 3.32 (1 H, d, J_{ab} = 9.6 Hz), 3.22 (1 H, d, J_{ab} = 9.6 Hz), 3.20 (1 H, s), 2.67 (1 H, m), 2.45-2.39 (1 H, m), 2.34-2.28 (1 H, m), 2.14-2.08 (2 H, m), 2.02-1.99 (1 H, m), 1.98 (3 H, s), 1.96-1.92 (2 H, m), 1.12 (3H, s), 0.84 (3H, s); $^{13}\text{C NMR}$ (125 MHz, CDCl_3) 170.6, 138.0, 137.4, 128.4, 128.3, 128.3, 127.8, 127.7, 127.7, 127.6, 127.5, 85.2, 81.2, 74.3, 74.1, 73.4, 73.3, 70.7, 68.0, 60.3, 45.1, 31.9, 26.0, 20.9, 18.3, 13.5; **IR** (thin film) ν 3505, 3294, 3029, 2862, 1739, 1454, 1365, 1245, 1089, 738, 699 cm^{-1} ; **HRMS** (ES) m/z calcd for $\text{C}_{31}\text{H}_{39}\text{O}_6$ $[\text{M}+\text{H}]^+$ 507.2741 found 507.2748.

2,3-Bis((benzyloxy)methyl)-6a-(2-((tert-butyldimethylsilyl)oxy)ethyl)-2,3-dimethyl-6-methyleneoctahydropentalene-1,3a-diol (232)



Cp_2TiCl_2 (373 mg, 1.50 mmol, 3 equiv) and Zn dust (292 mg, 4.50 mmol, 9 equiv) were placed in a dried round bottom flask and THF (10 mL) was added under rigorous exclusion of air by means of an Ar atmosphere. The resulting suspension was stirred at RT for 1 h, during which time the colour of the mixture changed from red to green, indicating the formation of a low valent titanium complex. The suspension of Ti complex was then cannulated under Ar into a solution of **223** (250 mg, 0.44 mmol, 1 equiv) in THF (20 mL) and the resulting green solution was stirred at RT under an Ar for 30 h. The excess Ti complex was then removed by filtration through a short silica pad and the solvent removed under reduced pressure. The crude product was purified by flash column chromatography (SiO_2 , hexanes/EtOAc 20:1) to afford the product **232** (contaminated with a small amount of an unidentified by-product – suspected to be a deoxygenation product) as a colourless oil (180 mg, *ca.* 69% yield) plus recovery of unreacted starting material **5** (25 mg, 10%).

2-(1,2-Bis((benzyloxy)methyl)-3,6a-dihydroxy-1,2-dimethyl-4-methyleneoctahydro-pentalen-3a-yl)ethyl acetate (233)



Using the same procedure as above for TBS-protected **225**, Ac-protected **233** (80.0 mg, 0.16 mmol) was subjected to the radical cyclisation reaction to afford **233** (52 mg, 65% yield) as a colourless oil. In this case, the minor side-product could be easily removed by chromatography. **233**: $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 7.34-7.24 (10H, m), 4.94 (1 H, m), 4.87 (1 H, m), 4.43-4.32 (5 H, m), 4.11 (1 H, ddd, $J = 10.7, 9.4, 5.2$ Hz), 3.85 (1 H, d, $J = 4.1$ Hz), 3.52 (1 H, d, $J = 8.9$ Hz), 3.77-3.32 (3 H, m), 2.63-2.55 (1 H, m), 2.38-2.32 (1 H, m), 2.25 (1 H, s), 2.14 (1 H, d, $J = 4.17$ Hz), 2.11-2.04 (2 H, m), 2.03 (3 H, s), 2.00-1.98 (1 H, m), 1.61-1.57 (1 H, m), 1.24 (3H, s), 1.16 (3H, s); $^{13}\text{C NMR}$ (125 MHz, CDCl_3) 171.0, 157.3, 138.1, 138.1, 128.3, 128.2, 128.2, 127.5, 127.4, 127.4, 105.8, 92.5, 82.6, 77.3, 74.7, 73.4, 73.4, 63.3, 59.9, 50.7, 50.4, 37.2, 31.4, 28.7, 21.1, 17.7, 16.5; **IR** (thin film) ν 3522, 3064, 2935, 1733, 1454, 1364, 1252, 1072, 736, 699 cm^{-1} ; **HRMS** (ES) m/z calcd for $\text{C}_{31}\text{H}_{44}\text{O}_6\text{N}$ $[\text{M}+\text{NH}_4]^+$ 526.3163found 526.3162.

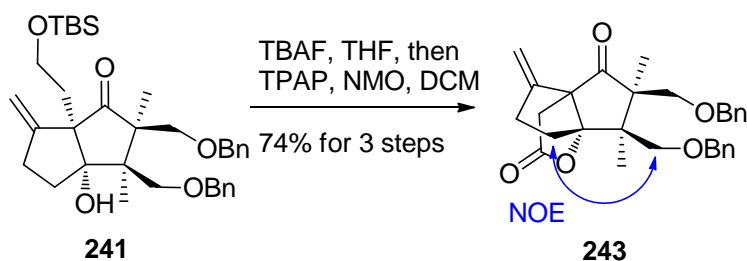
2,3-Bis((benzyloxy)methyl)-6a-(2-((tert-butyldimethylsilyloxy)ethyl)-3a-hydroxy-2,3-dimethyl-6-methylenehexahydro-pentalen-1(2H)-one (241)



The BC bicycle **232** (180 mg, *ca.* 0.30 mmol, *ca.* 1 equiv) in dry DCM (5 mL) was treated with TPAP (54.0 mg, 0.15 mmol, 0.5 equiv), NMO (181 mg, 1.55 mmol, 5

equiv) and MS 4Å (360 mg). The resulting solution was stirred for 5 h at RT. The sieves and catalyst were removed by filtration through a short silica pad and the solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography (SiO₂, hexanes/EtOAc 20:1) to afford the ketone **241** as a colourless oil (142 mg, 0.24 mmol, 82% yield). **241**: ¹H NMR (500 MHz, CDCl₃) δ 7.31-7.17 (10 H, m) 4.94 (1 H, m), 4.73 (1 H, m), 4.36 (1 H, d, *J* = 12.1 Hz), 4.30 (1 H, s), 4.24-4.21 (2 H, m), 4.14 (1 H, d, *J* = 11.9 Hz), 3.77 (1 H, dt, *J* = 10.4, 1.9 Hz), 3.67 (1 H, td, *J* = 10.4, 3.7 Hz), 3.53 (1 H, d, *J* = 9.5 Hz), 3.45 (1 H, d, *J* = 9.6 Hz), 3.42 (1 H, d, *J* = 9.5 Hz), 3.35 (1 H, d, *J* = 9.6 Hz), 2.43-2.37 (2 H, m), 2.29-2.22 (1 H, m), 2.13 (1 H, ddd, *J* = 14.2, 10.5, 3.4 Hz), 1.94 (1 H, ddd, *J* = 14.7, 4.1, 1.9 Hz), 1.71 (1 H, ddd, *J* = 14.4, 10.9, 7.9 Hz), 1.42 (3 H, s), 1.38 (3 H, s), 0.90 (9 H, s), 0.08 (3 H, s), 0.07 (3 H, s); ¹³C NMR (125 MHz, CDCl₃) δ 219.8, 152.4, 138.5, 137.6, 128.1, 128.0, 127.7, 127.6, 127.3, 107.4, 89.8, 74.2, 73.6, 73.2, 73.0, 66.2, 60.3, 56.0, 49.9, 39.8, 35.7, 31.4, 25.9, 19.9, 18.3, 15.4, -5.5, -5.5; IR (thin film) ν_{\max} 3408, 2929, 2858, 1731, 1456, 1361, 1258, 1076, 697 cm⁻¹; HRMS (ES) *m/z* calcd for C₃₅H₅₁SiO₅ [M+H]⁺ 579.3500, found 579.3500.

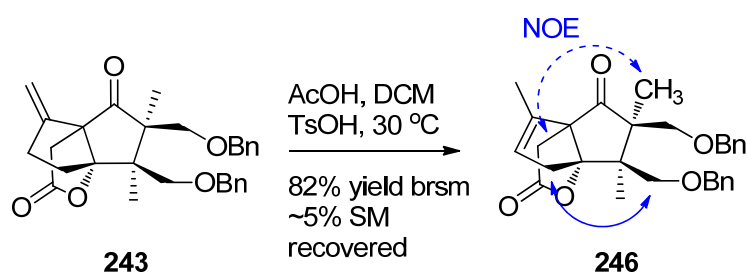
2,3-Bis((benzyloxy)methyl)-2,3-dimethyl-6-methylenetetrahydro-3a,6a-(epoxyethano)pentalene-1,8(4H)-dione (243)



To the solution of **243** (142 mg, 0.24 mmol) in DCM (5 mL) was added a solution of TBAF (0.48 mL, 1.0 M in THF, 2 equiv) and the resulting solution was stirred for 1 h. The solvent was then evaporated under reduced pressure and the solution filtered through a short silica pad (hexanes/EtOAc 1:1). The crude product was redissolved in DCM (5 mL) and treated with TPAP (9.0 mg, 24 μmol, 0.1 equiv), NMO (56.0 mg, 0.48 mmol, 2 equiv) and MS 4Å (200 mg). The resulting solution was stirred for 1 h at RT, then filtered through a short silica pad and the solvent evaporated under

reduced pressure. The crude product was purified by flash column chromatography (SiO₂, hexanes/EtOAc 10:1) to afford **243** as a colourless oil (102 mg, 90% yield for 2 steps). **243**: ¹H NMR (500 MHz, CDCl₃) δ 7.35-7.18 (10 H, m), 5.08 (1 H, m), 4.41 (1 H, d, *J*_{ab} = 12.5 Hz), 4.39 (1 H, d, *J*_{ab} = 12.5 Hz), 4.37 (2 H, s), 3.54 (1 H, d, *J*_{ab} = 9.2 Hz), 3.51 (1 H, *J*_{ab} = 9.2 Hz), 3.34 (1 H, d, *J*_{ab} = 9.0 Hz), 3.32 (1 H, d, *J*_{ab} = 9.0 Hz), 2.96-2.92 (1 H, m), 2.68 (1 H, d, *J*_{ab} = 19.0 Hz), 2.63-2.59 (1 H, m), 2.59 (1 H, d, *J*_{ab} = 19.0 Hz), 1.62 (3 H, m), 1.19 (3 H, s), 1.05 (3 H, s); ¹³C NMR (125 MHz, CDCl₃) δ 215.2, 175.1, 150.8, 137.4, 137.3, 128.3, 127.9, 127.9, 127.7, 127.7, 107.6, 102.9, 73.6, 73.4, 73.2, 72.5, 63.2, 58.4, 49.2, 42.4, 32.8, 32.8, 18.5, 17.5; IR (thin film) ν_{max} 2953, 2858, 1777, 1739, 1454, 1230, 1202, 1029, 946 cm⁻¹; HRMS (ES) *m/z* calcd for C₂₉H₃₆O₅N₁ [M+NH₄]⁺ 478.2588, found 478.2583

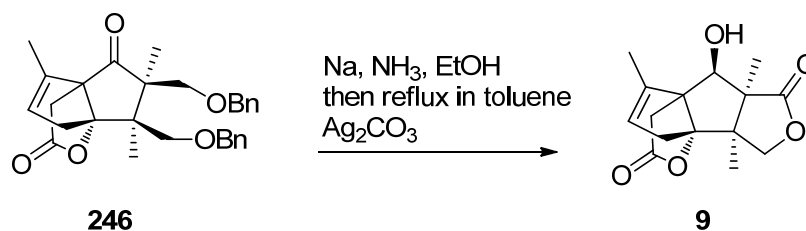
2,3-Bis((benzyloxy)methyl)-2,3,6-trimethyl-2,3-dihydro-3a,6a-(epoxyethano)pentalene-1,8(4H)-dione (246)



Compound **243** (10 mg, 21.7 μmol, 1 equiv) was dissolved in DCM (1 mL) and AcOH (1 mL) and TsOH (40 mg, 20 equiv) was added. The solution was stirred for 2 days, the temperature being carefully controlled below 30 °C. The reaction mixture was then poured into a saturated aqueous solution of NaHCO₃ and extracted with DCM. The organic phase was washed with brine and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO₂, hexanes/EtOAc 5:1) to afford unreacted starting material (0.5 mg, ~ 5%) and **246** as a colourless oil (7.8 mg, 78% yield, 82% brsm). **246**: ¹H NMR (500 MHz, CDCl₃) δ 7.35-7.18 (10 H, m), 5.08 (1 H, m), 4.41 (1 H, d, *J*_{ab} = 12.5 Hz), 4.39 (1 H, d, *J*_{ab} = 12.5 Hz), 4.37 (2 H, s), 3.54 (1 H, d, *J*_{ab} = 9.2 Hz), 3.51 (1 H, *J*_{ab} = 9.2 Hz), 3.34 (1 H, d, *J*_{ab} = 9.0 Hz), 3.32 (1 H, d, *J*_{ab} = 9.0 Hz), 2.96-2.92 (1 H, m), 2.68 (1 H, d, *J*_{ab} = 19.0 Hz), 2.63-2.59 (1 H, m), 2.59 (1 H, d, *J*_{ab} = 19.0 Hz), 1.62 (3 H, m), 1.19 (3 H,

s), 1.05 (3 H, s); $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 214.14 175.22 138.33 137.7, 137.4, 128.3, 128.3, 127.8, 127.7, 127.6, 127.6, 125.3, 99.4, 73.4, 73.3, 73.1, 72.3, 69.0, 59.2, 50.0, 42.2, 36.5, 17.9, 17.4, 12.9; **IR** (thin film) ν_{max} 2953, 2858, 1777, 1739, 1454, 1230, 1202, 1029, 946 cm^{-1} ; **HRMS** (ES) m/z calcd for $\text{C}_{29}\text{H}_{36}\text{O}_5\text{N}_1$ $[\text{M}+\text{NH}_4]^+$ 478.2588, found 478.2583

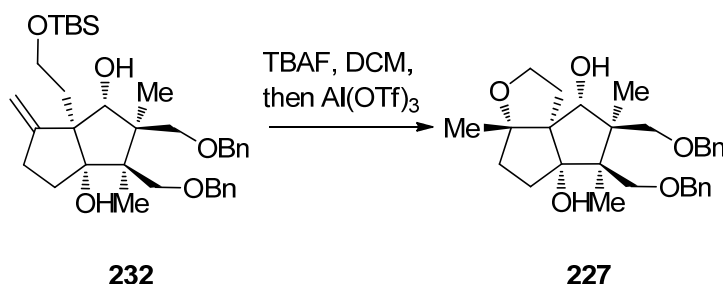
7-Hydroxy-3a,6,7a-trimethyl-3,3a,7,7a-tetrahydro-3b,6a-(epoxyethano)pentalen o[1,2-c]furan-1,9(4H)-dione (9)



To a solution of **246** (20 mg, 43 μmol) in THF (1.38 mL) and EtOH (0.36 mL) at -78 $^\circ\text{C}$ was added liquid ammonia (4.0 mL) followed by sodium (96.0 mg, 0.23 mmol) and the mixture stirred at -78 $^\circ\text{C}$ for 30 min. The reaction mixture was then quenched with ammonium chloride, stirred at -78 $^\circ\text{C}$ for 40 min, and then allowed to warm to RT. After the ammonia had boiled off, the resultant solution was filtered through a pad of silica to give the crude triol intermediate. This was taken into toluene (6 mL) and treated with Ag_2CO_3 on Celite (181 mg, 50%, 0.32 mmol) then heated to 130 $^\circ\text{C}$ for 4 h. The suspension was filtered through Celite, concentrated, and purified by flash column chromatography (hexane/EtOAc 2:1) to give bis-lactone **9** (2.9 mg, 28% for 2 steps). **9**: $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 5.39 (1 H, m), 4.20 (1 H, d, $J = 8.7$ Hz), 4.12 (1 H, d, $J = 5.6$ Hz), 3.95 (1 H, d, $J = 8.7$ Hz), 2.83 (1 H, d, $J = 19.0$ Hz), 2.78 (1 H, d, $J = 5.6$ Hz), 2.65 (1 H, d, $J = 19.0$ Hz), 2.57-2.46 (2 H, m), 1.82 (1 H, m), 1.23 (3 H, s), 1.23 (3 H, s); $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 178.3, 175.0, 141.0, 125.1, 104.4, 86.6, 73.6, 69.6, 61.9, 55.2, 41.0, 40.0, 16.7, 15.9, 15.1; $^1\text{H NMR}$ (500 MHz, Methanol- d_4) δ 5.34 (1 H, m), 4.17 (1 H, dd, $J = 8.6, 0.7$ Hz), 4.09 (1 H, s), 3.98 (1 H, d, $J = 8.6$ Hz), 2.89 (1 H, d, $J = 19.3$ Hz), 2.59-3.55 (1 H, m) 2.39-2.34 (1 H, m), 1.80 (3 H, dd, $J = 2.2, 3.8$ Hz), 1.20 (3 H, d, $J = 0.7$ Hz), 1.15 (3 H, s); $^{13}\text{C NMR}$ (125 MHz, Methanol- d_4) δ 180.2, 177.9, 143.8, 125.1, 106.5,

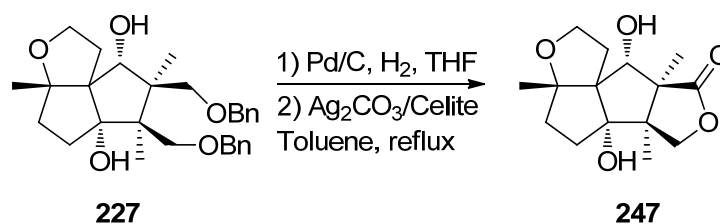
87.0, 74.4, 71.5, 64.0, 57.0, 41.9, 40.5, 16.9, 16.0, 15.0; **HRMS** (ES) m/z calcd for $C_{15}H_{18}O_5$ $[M]^+$ 278.11488, found 278.11519.

6,7-Bis((benzyloxy)methyl)-3a,6,7-trimethyloctahydro-1H-pentaleno[1,6a-b]furan-5a,8-diol (227)



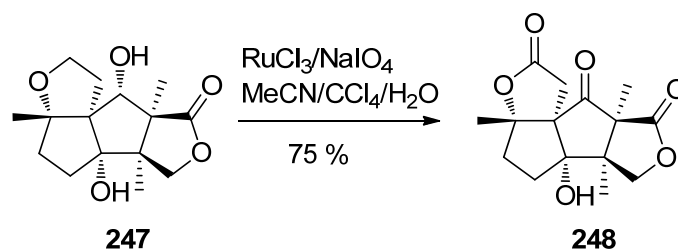
To the solution of **232** (65.0 mg, 0.12 mmol, 1 equiv) in DCM (1 mL) was added a solution of TBAF (0.24 mL, 1.0 M in THF, 2 equiv) and the resulting solution stirred for 1 h. The solvent was then evaporated under reduced pressure and the residue filtrated through a short silica pad using hexanes/EtOAc (1:1). The crude product was redissolved in DCM (5 mL) and treated with $Al(OTf)_3$ (2.5 mg, 5.0 μ mol, 0.05 equiv), then stirred for 10 h at RT. The reaction mixture was filtered through a short silica pad and the solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography (SiO_2 , hexanes/EtOAc 1:1) to afford the product **227** as colourless oil 44 mg (88% yield). **227**: 1H NMR (500 MHz, $CDCl_3$) δ 7.34-7.23 (10 H, m), 4.48 (1 H, d, $J_{ab} = 12.0$ Hz), 4.41 (1 H, d, $J_{ab} = 12.0$ Hz), 4.33 (1 H, d, $J_{ab} = 11.5$ Hz), 4.31 (1 H, d, $J_{ab} = 11.5$ Hz), 4.08 (1 H, d, $J = 2.3$ Hz), 3.89-3.85 (1 H, m), 3.81-3.76 (1 H, m), 3.61 (1 H, d, $J = 8.4$ Hz), 3.44 (1 H, d, $J = 8.4$ Hz), 3.38 (1 H, d, $J = 9.8$ Hz), 3.29 (1 H, d, $J = 9.8$ Hz), 2.65 (1 H, d, $J = 2.5$ Hz), 2.35 (1 H, td, $J = 12.8, 9.0$ Hz), 2.57-2.15 (2 H, m), 1.86 (1 H, ddd, $J = 13.2, 7.5, 3.9$ Hz), 1.72-1.66 (1 H, m), 1.52 (1 H, ddd, $J = 13.5, 9.9, 7.6$ Hz), 1.44 (1 H, s,), 1.21 (3 H, s), 1.06 (3 H, s), 0.98 (3 H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.0, 137.7, 128.4, 128.3, 127.6, 127.6, 127.4, 92.8, 91.1, 77.7, 74.9, 73.6, 73.1, 67.1, 66.5, 50.94, 50.1, 37.9, 36.5, 35.1, 26.9, 21.2, 16.1, 15.0; **IR** (thin film) ν_{max} 3436, 2929, 2871, 1713, 1454, 1362, 1275, 1207, 1072, 882 cm^{-1} ; **HRMS** (ES) m/z calcd for $C_{29}H_{38}O_5Na$ $[M+Na]^+$ 489.2611, found 489.2611.

5a,9-Dihydroxy-3a,5b,8a-trimethyloctahydro-1H-pentaleno[1,6a-b:4,5-c']difuran-8(2H)-one (247)



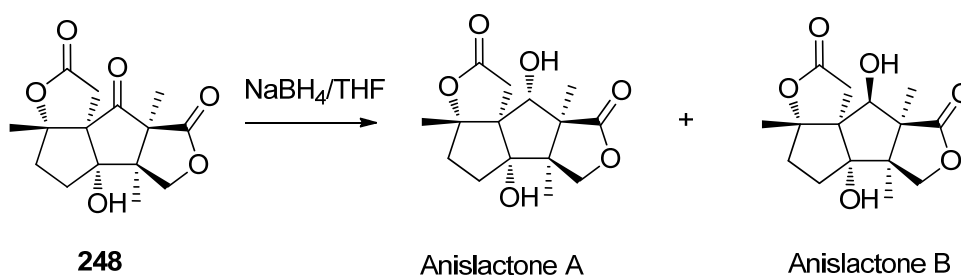
To a solution of **227** (230 mg, 0.50 mmol) in THF (5 mL) was added Pd/C (32 mg) and the resulting mixture purged with H₂ for 5 min. The reaction mixture was then stirred under a H₂ atmosphere (balloon) at RT for 3 h. The reaction mixture was filtered through a pad of silica and concentrated under reduced pressure to give the crude triol intermediate. This was taken into toluene (7.0 mL) and treated with Ag₂CO₃ on Celite (50%, 2.1 g) and heated to 130 °C for 4 h. The suspension was then filtered through Celite, concentrated under reduced pressure and purified by flash column chromatography (hexane/EtOAc 2:1) to give **247** as a white solid (102 mg, 73% yield for 2 steps). **247**: ¹H NMR (500 MHz, CDCl₃) δ 4.25 (1 H, d, *J* = 9.6 Hz), 3.98 (1 H, s), 3.92-3.86 (2 H, m), 3.84 (1 H, d, *J* = 9.6 Hz), 2.46 (1 H, ddd, *J* = 12.9, 9.6, 7.5 Hz), 2.21 (1 H, ddd, *J* = 12.8, 8.1, 4.6 Hz), 2.13 (1 H, ddd, *J* = 14.3, 8.2, 2.9 Hz), 1.89 (1 H, ddd, *J* = 14.1, 8.6, 3.0 Hz), 1.77 (1 H, ddd, *J* = 14.1, 10.0, 8.2 Hz), 1.60 (1 H, ddd, *J* = 14.3, 9.9, 8.8), 1.23 (3 H, s), 1.15 (3 H, s), 1.12 (3 H, s). ¹³C NMR (125 MHz, CDCl₃) δ 181.24, 92.57, 89.05, 74.17, 74.06, 70.06, 66.89, 56.50, 54.06, 37.56, 36.56, 25.66, 19.94, 17.42, 10.87; IR (KBr) ν_{max} 3445, 2926, 1750, 1459, 1387, 1082, 1002, 846 cm⁻¹; Mp: 218-220 °C, HRMS (ES) *m/z* calcd for C₁₅H₂₃O₅ [M+H]⁺ 283.15400, found 283.15337.

5a-Hydroxy-3a,5b,8a-trimethylhexahydro-1H-pentaleno[1,6a-b:4,5-c']difuran-2,8,9(8aH)-trione (248)



To a solution of **247** (15.0 mg, 52.8 μmol , 1 equiv) in a mixture of MeCN (0.8 mL), CCl_4 (0.8 mL), and H_2O (0.8 mL) was added NaIO_4 (60.0 mg, 0.25 mmol, 5 equiv) followed by $\text{RuCl}_3 \cdot \text{H}_2\text{O}$ (5.46 mg, 26.0 μmol , 0.5 equiv). The reaction mixture was stirred at RT for 20 h, then the reaction mixture was filtered through a pad of silica. Concentration under reduced pressure followed by flash column chromatography (hexane/EtOAc 1:1) gave the ketone **248** as a white solid (11.0 mg, 75% yield). **248**: $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 4.58 (1 H, d, $J = 10.1$ Hz), 4.01 (1 H, d, $J = 10.1$ Hz), 3.04 (1 H, d, $J = 17.7$ Hz), 2.78 (1 H, d, $J = 17.7$ Hz), 2.34 (1 H, ddd, $J = 13.6, 8.9, 7.7$ Hz), 2.23 (1 H, ddd, $J = 14.5, 9.0, 7.6$ Hz), 2.09 (1 H, ddd, $J = 14.5, 7.4, 5.5$ Hz), 2.00 (1 H, ddd, $J = 13.3, 6.6, 3.4$ Hz), 1.40 (3 H, s), 1.34 (3 H, s), 1.14 (3 H, s). $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 207.4, 173.6, 173.5, 95.6, 87.5, 73.3, 66.7, 62.1, 52.3, 38.2, 36.7, 36.1, 22.4, 16.2, 15.3, **IR** (KBr) ν_{max} 3484, 2952, 1774, 1713, 1456, 1394, 1232, 1215, 1086, 1052, 1012 cm^{-1} ; Mp: 202-204 $^\circ\text{C}$, **HRMS** (ES) m/z calcd for $\text{C}_{15}\text{H}_{19}\text{O}_6$ $[\text{M}+\text{H}]^+$ 295.11761, found 295.11809.

Anislactones



To a solution of **248** (5.0 mg, 17 μmol) in THF (2 mL) was added NaBH_4 (5.0 mg, 0.13 mmol). After 2 h, TLC indicated complete consumption of the starting materials. The reaction was quenched with several drops of saturated NH_4Cl solution and the suspension filtered through a Celite pad. Concentration under reduced pressure followed by flash column chromatography ($\text{CHCl}_3/\text{MeOH}$ 100:3) gave a mixture of

anis lactones A and B (4.6 mg, dr = 5:1, 95% yield). Further chromatographic purification of the two natural products enabled separation of anis lactone A, containing a trace amount of the B epimer, as a colourless film. A small single crystal of anis lactone A formed on standing that was suitable for X-ray crystallography.

Anis lactone A: $^1\text{H NMR}$ (500 MHz, $\text{C}_5\text{D}_5\text{N}$) δ 4.65 (1 H, d, $J = 6.1$ Hz), 4.54 (1 H, d, $J = 9.5$ Hz), 3.97 (1 H, d, $J = 9.5$ Hz), 3.65 (1 H, d, $J = 17.2$ Hz), 3.36 (1 H, d, $J = 17.1$ Hz), 2.41-2.37 (1 H, m), 2.16-2.01 (3 H, m), 1.65 (3 H, s), 1.45 (3 H, s), 1.31 (3 H, s). $^{13}\text{C NMR}$ (125 MHz, $\text{C}_5\text{D}_5\text{N}$) δ 181.0, 176.9, 95.9, 88.4, 73.7, 72.7, 68.3, 57.6, 55.5, 37.8, 36.4, 31.8, 21.0, 17.8, 11.1, $^1\text{H NMR}$ (500 MHz, CD_3OD) δ 4.34 (1 H, d, $J = 9.8$ Hz), 4.15 (1 H, s), 3.92 (1 H, d, $J = 9.7$ Hz), 3.07 (1 H, d, $J = 17.3$ Hz), 2.75 (1 H, d, $J = 17.3$ Hz), 2.30-2.58 (1 H, m), 1.99-1.94 (2 H, m), 1.79-1.74 (1 H, m), 1.46 (3 H, s), 1.12 (3 H, s), 1.04 (3 H, s). $^{13}\text{C NMR}$ (125 MHz, CD_3OD) δ 182.6, 179.3, 98.1, 89.0, 74.7, 73.4, 68.9, 58.2, 56.1, 38.2, 36.6, 32.0, 20.9, 17.4, 10.8, **IR** (KBr) ν_{max} 3398, 2926, 1736, 1458, 1270, 1084, 1009, 936 cm^{-1} **HRMS** (ES) m/z calcd for $\text{C}_{15}\text{H}_{21}\text{O}_6$ $[\text{M}+\text{H}]^+$ 297.13326, found 297.13311.

6 Abbreviations

Ac	acetyl
AD	Alzheimer's disease
AIBN	2,2-azobis(isobutyronitrile)
aq	aqueous
Bn	benzyl
br	broad
BTB	<i>bis</i> -(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- <i>tert</i> -butylbiphenylide
DBU	1,8-diazabicyclo-[5.4.0]-undec-7-ene
DCB	2,6-dichlorobenzyl
DCC	<i>N, N</i> -dicyclohexylcarbodiimide
DCM	dichloromethane
DEPT	distortionless enhancement by polarisation transfer
DIBALH	diisobutylaluminium hydride
DIPEA	<i>N,N</i> -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	hexamethylphosphoric 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- <i>tert</i> -butylbiphenylide
LHMDS	lithium hexamethyldisilazide
M	molar (moles per litre)
m	multiplet
<i>m/z</i>	mass to charge ratio
<i>m</i>CPBA	<i>meta</i> -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	<i>N</i> -methyilmorpholine
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	pivaloyl
PMB	<i>para</i> -methoxybenzyl
ppm	parts per million
q	quartet
RT/rt	room temperature
SEM	β -trimethylsilylethoxymethyl
Sia	sialic acid
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide
TBS	<i>t</i> -butyldimethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC/tlc	thin layer chromatography
TMS	trimethylsilyl
TPAP	tetrapropylammonium perruthenate
TPPA	tetramethylphenylphosphoramidate
Ts	<i>p</i> -toluenesulfonyl
UV	ultraviolet
δ	chemical shift

7 Appendix: Spectroscopic Data

