Studies towards the Total Synthesis of Samaderine C and Related Analogues

David James Burns

Thesis submitted in partial fulfilment of the requirements for the Degree of Doctor of Philosophy

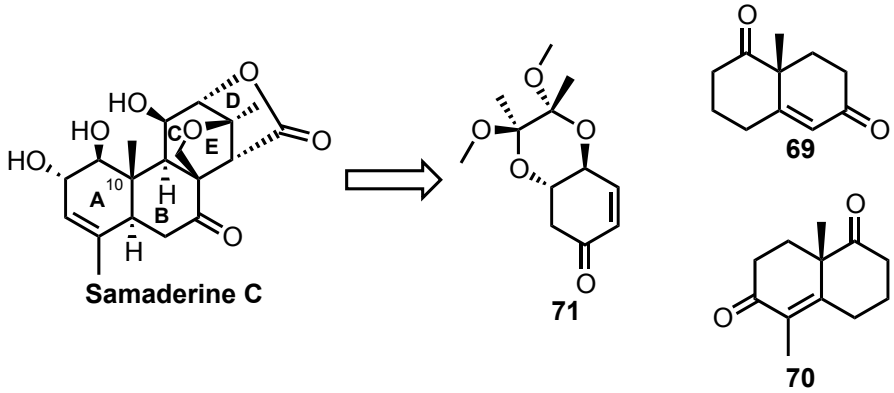
The University of York

Department of Chemistry

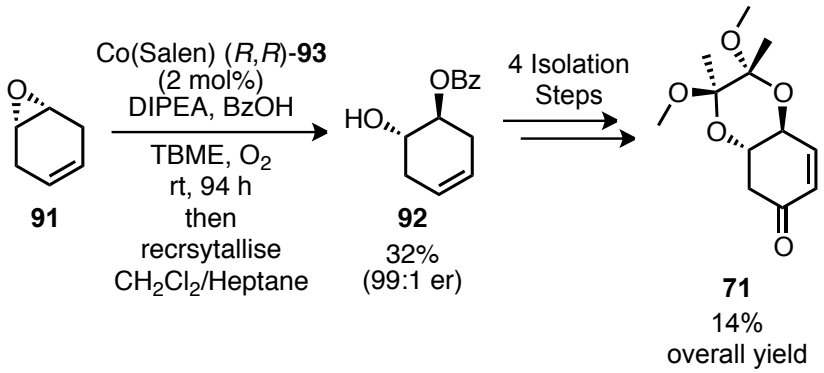
January 2013

Abstract

The samaderines are quassinoids isolated from *Samadera indica* plants and have been shown to possess a range of biological activity. Samaderine C is a cogent antifeedent (55.3% feeding inhibition) and shows a good level of toxicity in pupal mortality screens (54.1%). The aims of this project were to investigate synthetic approaches to samaderine C and to synthesise analogues of samaderine C in order to evaluate structure-activity aspects.

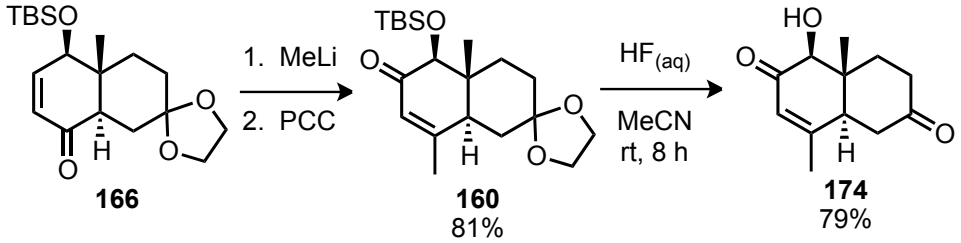


There were three main approaches considered for the synthesis of samaderine C. The first centred on a double 1,4-addition strategy to an enone starting material. Ultimately, model studies using organocuprate 1,4-additions highlighted shortcomings in this approach but we did develop a novel route to bicyclic enone **71** using desymmetrisation chemistry.



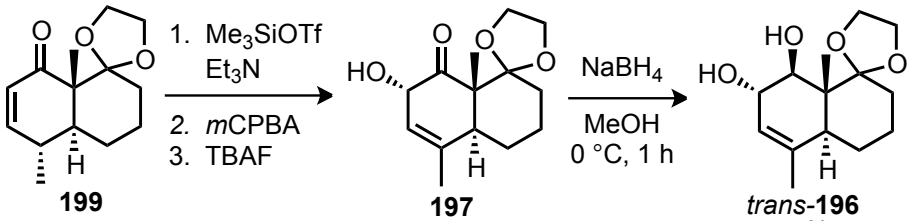
The second approach utilised the Wieland-Miescher ketone **69** as a scaffold for the synthesis of the *trans*-allylic diol AB-ring structure of samaderine C. From dione **69**, an enone **166** was synthesised and the plan was then for a diastereoselective reduction to give the *trans*-allylic diol motif. However, this approach was

unsuccessful. Using enone **160** we were able to globally deprotect to access a dione **174** which is a general quassinoid AB-ring motif.



166 **160** 81% **174** 79%

The final approach to access a *trans*-allylic diol AB-ring motif used the methyl-Wieland-Miescher ketone **70**. Using this starting material a *trans*-allylic diol AB-ring analogue was achieved using an α-hydroxylation reaction of enone **199** followed by reduction to give the *trans*-diol arrangement. To the best of our knowledge this represents the first synthesis of a quassinoidal *trans*-allylic diol AB-ring motif.



199 **197** 70% ***trans*-196** 80%

Contents

List of Figures

List of Tables

Acknowledgements

I would like to thank Richard and Peter for allowing me to occupy the twilight zone between their groups. They have both been a great encouragement and I have learnt so much over the last three years. In particular I would like to thank Peter for the attention he pays to the education of his group and the massive part he has played in my continued development as a synthetic chemist. To both groups, I can't thank you guys enough for the craic we have had, and the years have passed in a flash.

Thank you to all the great people I have lived with during my time in York (Phil, Jimmy, Laura, Pauline, Jon and Anthony (our honouree chemist/poet)). I have basically lived with nearly everyone in the group at some point and I count myself blessed as I have got on so well with all of them. Phil, never stop playing flat cricket and you know in a world without Ruth or Kat (a worse world I will admit…) we would still be living up the duel-screened-bachelor life together. Jimmy, you aren't happy just owning it in the science world you need to steal all my points on the PlayStation too! It was great fun living with you and I wish you every success in America. To the Claremont crew, remember 8.30 pm is always legitimate bedtime and there is nothing funny about someone who can't eat bitter cheesecake and laugh at the same time! Jon…. you're a legend and a ridiculous man. Sport is a massive deal to me, to put it lightly, and playing football in the organics 6-aside team as well as the 11-aside chemistry team got me through my PhD. Jimmy berating Rich, Will the toe-popping back post assassin and Al's bright read face every time I back healed the ball or threw in a step over in front of my own goal… are times I will always remember. Also thanks to Jon for all the banter we had either playing or training for golf. My game may have fallen apart during my stay in York but it definitely wasn't for the lack of effort on either of our parts!

Finally I want to thank my family. Thank you to my parents for being a constant source of encouragement and for everything they have sacrificed to get me to where I am today. Lastly, to my wonderful wife Kat. Being apart for three years was tough but thank you for the motivation you gave me to work hard and that despite being so far apart I knew you would always support me in whatever way I needed.

Declaration

The research presented in this Thesis was carried out at the University of York between October 2009 and September 2012. The work is, to the best of my knowledge, original except where due reference has been made to other workers.

Work published during PhD:

1. Burns, D. J.; Hachisu, S.; O'Brien, P.; Taylor, R. J. T. *Org. Biomol. Chem.* **2012**, *10*, 7666.
2. Burns, D. J.; Mommer, S.; O'Brien, P.; Taylor, R. J.; Whitwood, A. C.; Hachisu, S. *Org. Lett.* **2013**, *15*, 394.

David Burns

January 2013

Chapter 1. Introduction

1.1 Quassinoids

1.1.1 Introduction to Quassinoids

The bitter principles derived from the *Simaroubaceae* family are known as quassinoids. They are highly oxygenated terpenoids with either a tetra- or pentacyclic framework. Quassinoids are classed according to their basic skeleton and there are five main groups: C_{18}, C_{19}, C_{20}, C_{22} and C_{25}. The basic quassinoid skeletons can be seen in Figure 1.1. There are currently over 150 isolated and fully characterised compounds and dozens do not fit into these five structural groups. One such example is (+)-polyandrol (Figure 1.1).

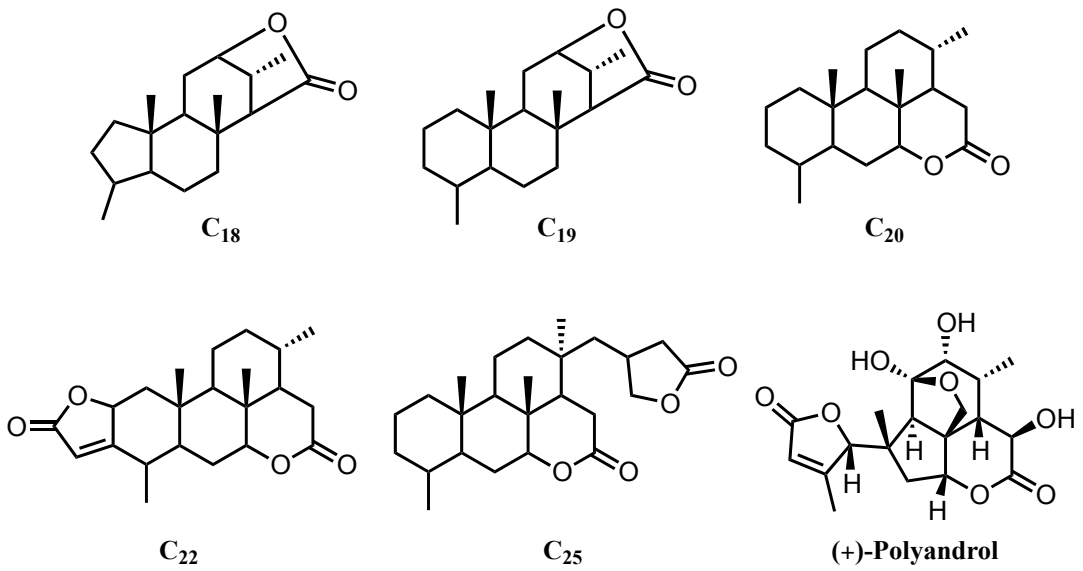


Figure 1.1: *Quassinoidal carbon skeletons and miscellaneous structures*

Quassin and neoquassin (Figure 1.2) were the first terpenoids of the class to be isolated. They were discovered in the early 1930s by Clark[1] from the bark of *Quassia Amara* but full structures were not determined until 1961 by Valenta.[2] This work marked the birth of quassinoid chemistry and even today new quassinoids are being isolated and characterised.[3]

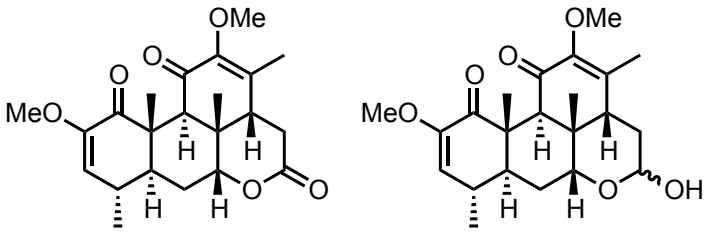


Figure 1.2: *The first quassinoids isolated*

1.1.2 Biological Activity of Quassinoids

The quassinoids represent a particularly biologically active group of compounds. The range of activity *in vivo* and/or *in vitro* includes insecticidal/antifeedant,[4,5] antiinflamatory,[6] amoebicidal[7,8] and antiviral (including anti-HIV).[9,10] However, interest in quassinoids has been intensified since the discovery of the significant antilukemic properties possessed by bruceatin.[11] There are numerous examples of cytotoxic quassinoids.[12-16] and this is by far the most studied and promising area of activity for this family of compounds.[17] Shown below (Figure 1.3, Table 1.1) are four of the most promising quassinoid members and their activity in screens as antileukemic agents.

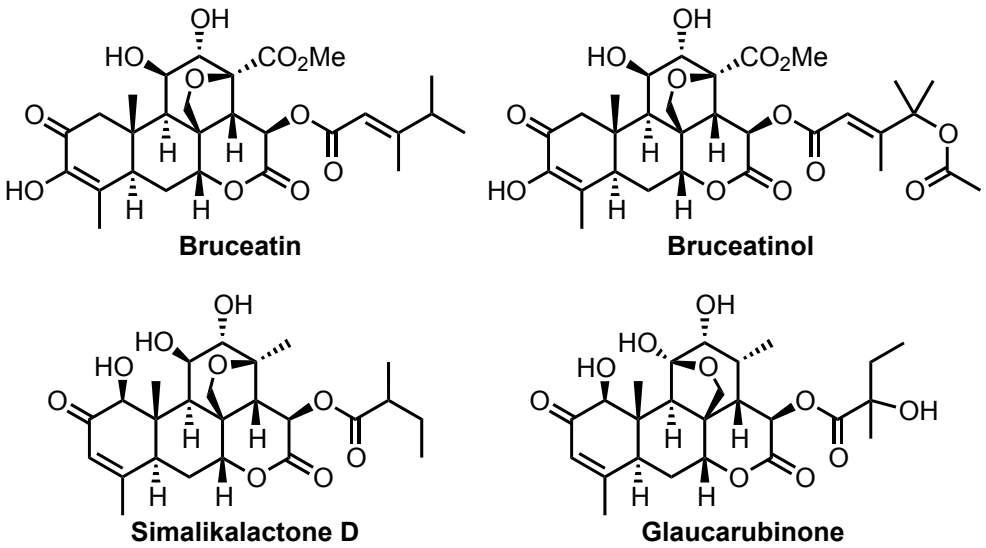


Figure 1.3: *Cytotoxicity of four quassinoids compounds*

Quassinoid	Optimal Dose (mg/kg)	T/C [a] (%)
Bruceatin	0.50	220
Bruceatinol	1.00	238
Glaucarubinone	0.25	177
Simalikalactone D	1.00	198

[a]Oncostatic parameter (T/C): the increase of life span of drug-treated animals *versus* controls in BDF1 mice with P-388 lymphocyctic leukaemia

Table 1.1: Cytotoxicity of four quassinoids compounds

Their mode of action is thought to be by inhibition of ribosomal peptidyl transferase leading to termination of chain elongation during the translation phase of protein biosynthesis.[18-20] Interestingly, this inhibition has been shown to occur only after one round of protein transcription. It was initially postulated that the inhibition mechanism may involve the action of the A-ring as a biological Michael-acceptor (Figure 1.4).[21] The most cytotoxic quassinoids possess a hydroxy-enone A-ring motif. A hydroxyl group in either the C-1 or C-3 positions is thought to modulate the β-terminus of the enone for action as a Michael-acceptor through a hydrogen bond interaction to the adjacent enone carbonyl (Figure 1.4). This hypothesis was supported by structure-activity studies.[22]

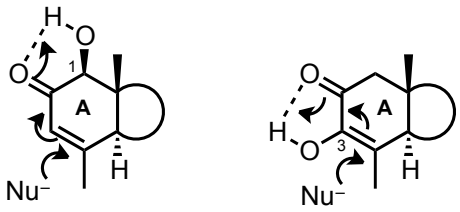
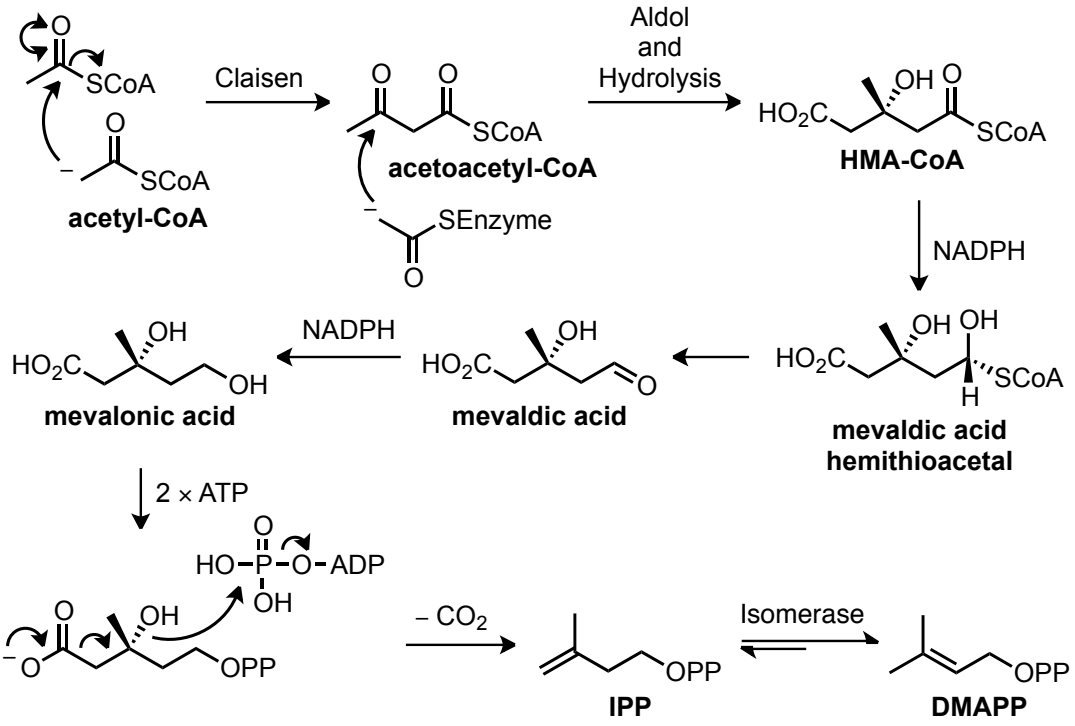


Figure 1.4: *Hydroxy ketone A-ring acting as a biological Michael-acceptor*

1.1.3 Biosynthesis of Quassinoids

The biosynthesis of quassinoids has not been fully established. It is generally thought they are derived from triterpenoid biogenetic pathways.[23-25] In particular, it has been speculated that these compounds might be products of a pathway closely resembling that of the limonoid terpenes. Cyclic terpenes are synthesised in a number of phases initiating from C5 subunits: isopentyl diphosphate (IPP) and dimethyl allyl diphosphate (DMAPP). These subunits can be synthesised *via* two separate biosynthetic pathways, with the preferred route dependent on the organism.[26,27] The most common pathway is that involving mevalonate (Scheme 1.1).

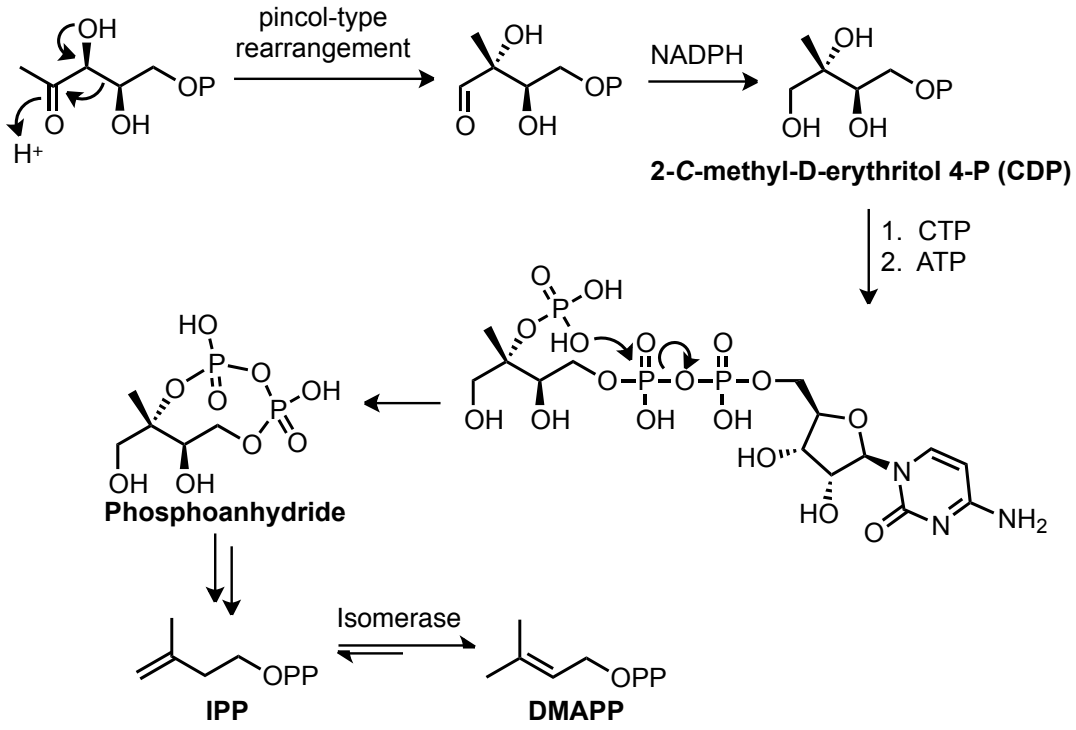


Scheme 1.1: *Activation of mevalonic acid and its synthetic pathway to IPP and DMAPP*

The first step in the mevalonate pathway is the Claisen-type reaction of two acetyl-coenzyme A (acetyl-CoA) units to give acetoacetyl-CoA (Scheme 1.2). An aldol reaction with an enzymic acetyl unit, after hydrolysis of the enzyme thiol ester, gives HMA-CoA. Then, an enzymatic reduction (NADPH) followed by collapse of the hemithioacetal gives mevaldic acid. A second NADPH reduction gives mevalonic acid. Phosphorylation of the primary alcohol to the diphoshpate then sets up a decarboxylative elimination to give IPP. The anticipated phosphorylation of the tertiary alcohol to aid this elimination does not seem to occur but it has been

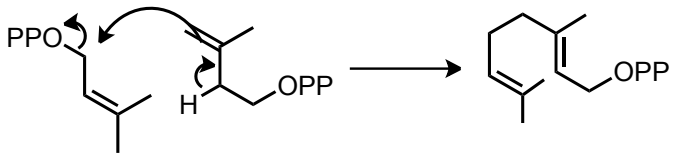
speculated that a third molecule of ATP may be involved.[27] Isomerase is then able to convert IPP into DMAPP.

The second biological route to IPP and DMAPP uses pyruvic acid-derived 1-deoxy-D-xylulose 5-P. The deoxyxylulose pathway begins with a pincol-type rearrangement of 1-deoxy-D-xylulose 5-P followed by an NADPH-mediated reduction (Scheme 1.2). The rearrangement and reduction occurs in the same biochemical step within a single enzyme without the release of any intermediates. Formation of a CDP intermediate followed by phosphorylation of the tertiary alcohol then sets up an intramolecular cyclisation to furnish a phosphoanhydride. Then, in a series of steps not entirely characterised, the phosphoanhyride is converted into IPP, which through enzymatic isomerisation, allows access to DMAPP.

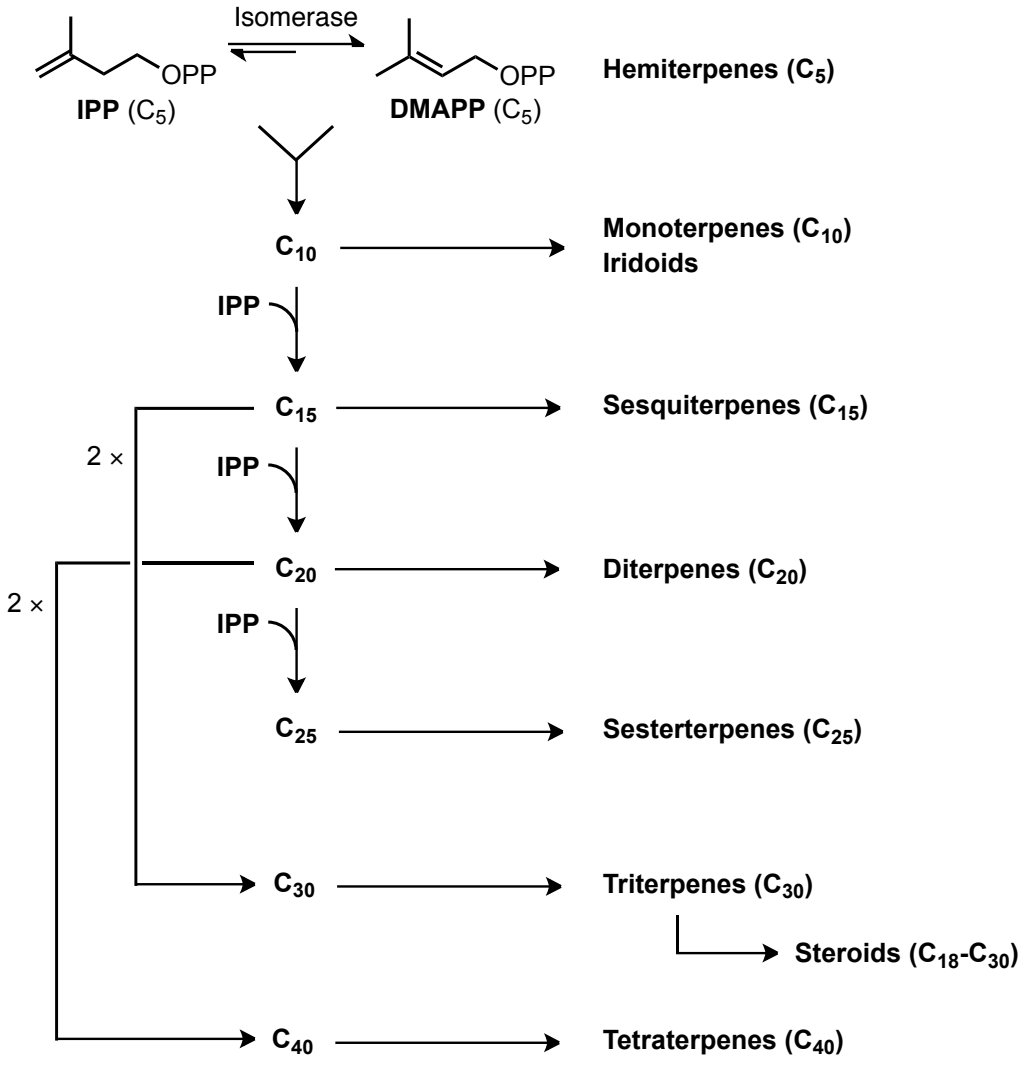


Scheme 1.2: *Deoxyxylulose pathway to IPP and DMAPP*

Polymerisation of the C5 units, IPP and DMAPP, can occur through ene-based reactions giving a series of aliphatic terpene products (Scheme 1.3). Further polymerisation builds up the carbon framework in units of five. These chains are then able to undergo a number of different cyclisation events often triggered by addition of an external electrophile. Secondary modifications, such as migrations and oxidations, as well as degradation reactions, lead to the variety inherent in cyclic terpenes and steroids. An overview is presented in Scheme 1.4.



Scheme 1.3: *Ene-based polymerisation mechanism example*

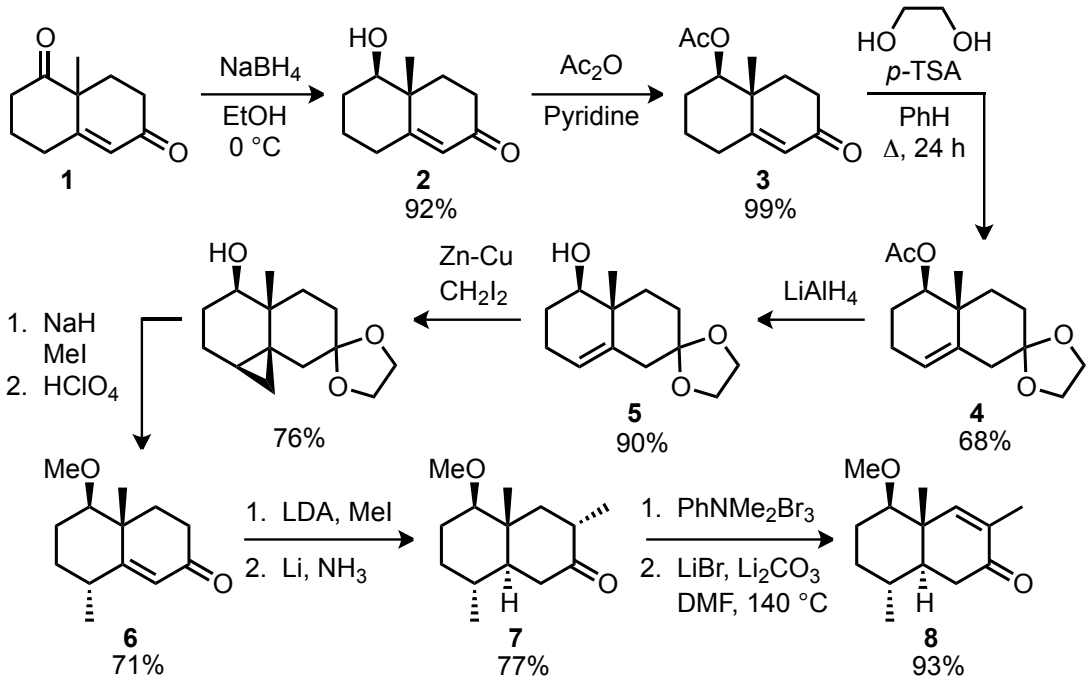


Scheme 1.4: *Polymerisation of C5 units and proliferation into higher order terpenes*

1.1.4 Total synthesis of Quassinoids

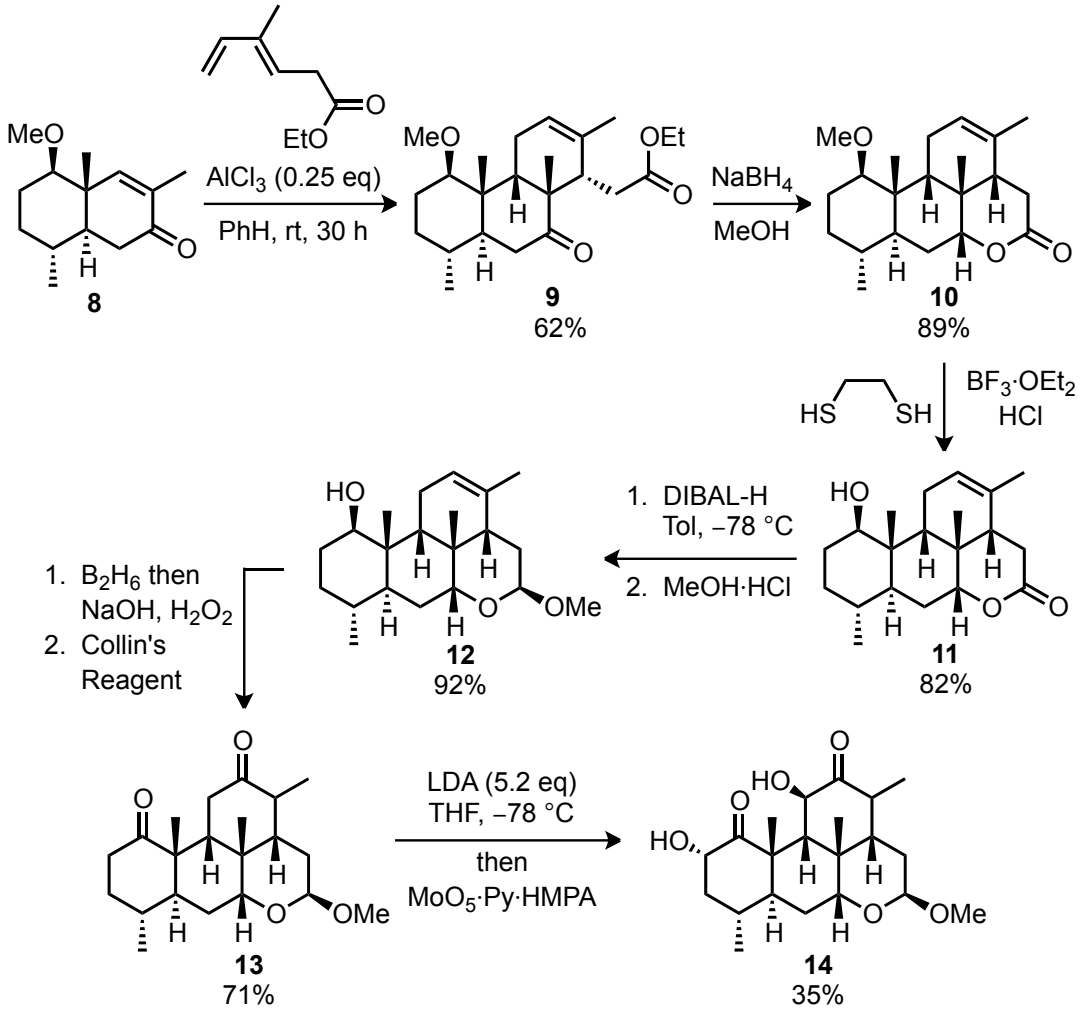
The quassinoids have not escaped significant synthetic focus with total syntheses of a number of tetracyclic and pentacyclic members; (±)-amarolide,[28] (±)-klaineanone,[29] (±)-castelanolide,[30] (±)- and (−)-chaparrinone,[31,32] (±)- and (−)-bruceantin,[33,34] (+)-picrasane B,[35] (+)-Δ2-picrasane B,[34] (±)-shinjulactone C,[36] shinjulactone D,[35] (±)-holacanthone,[37] (±)- and (−)-glaucarubolone,[31,36] (+)-simalikalactone D,[38] (±)-shinjudilactone,[39] (+)-quassimarin,[40] (+)-glucaruinone,[32] (±)-samaderine B,[41] (−)-samaderine Y,[42] (+)-quassin,[43] (±)-14β,15β-dihydroxyklaineanone,[44] (−)-peninsularinone[45] and (+)-des-*d*-chaparrinone.[46]

Grieco *et al*. reported the first total synthesis of a quassinoid. In 1980 they communicated the racemic synthesis of neoquassin and quassin[47] and one year later they published a full paper on their efforts.[48] Their route began from racemic enone **8** which they previously used in the synthesis of ivangulin, a secoeudesmanolide isolated from *Eriophyllum lanatum*.[49] Enone **8** was accessed from the Wieland-Miescher ketone **1** in 11 steps (Scheme 1.5). Starting from racemic Wieland-Miescher ketone **1**, the Grieco group used the reduction conditions of Boyce[50] to give alcohol **2** and then acetylation (to give acetate **3**) and isomerative ketalisation procedures outlined previously by Heathcock[51] gave ketal **4**. Acetate deprotection then gave alcohol **5**. Alcohol **5** was submitted to a cyclopropanation reaction. Then, treating the cyclopropane with perchloric acid removed the ketal protecting group and opened the cyclopropane to give enone **6**. Methylation followed by Birch-type reduction gave *trans*-decalone **7**. Then, a regioselective bromination and subsequent elimination gave α-methyl enone **8**.



Scheme 1.5: Synthesis of enone **8** starting material

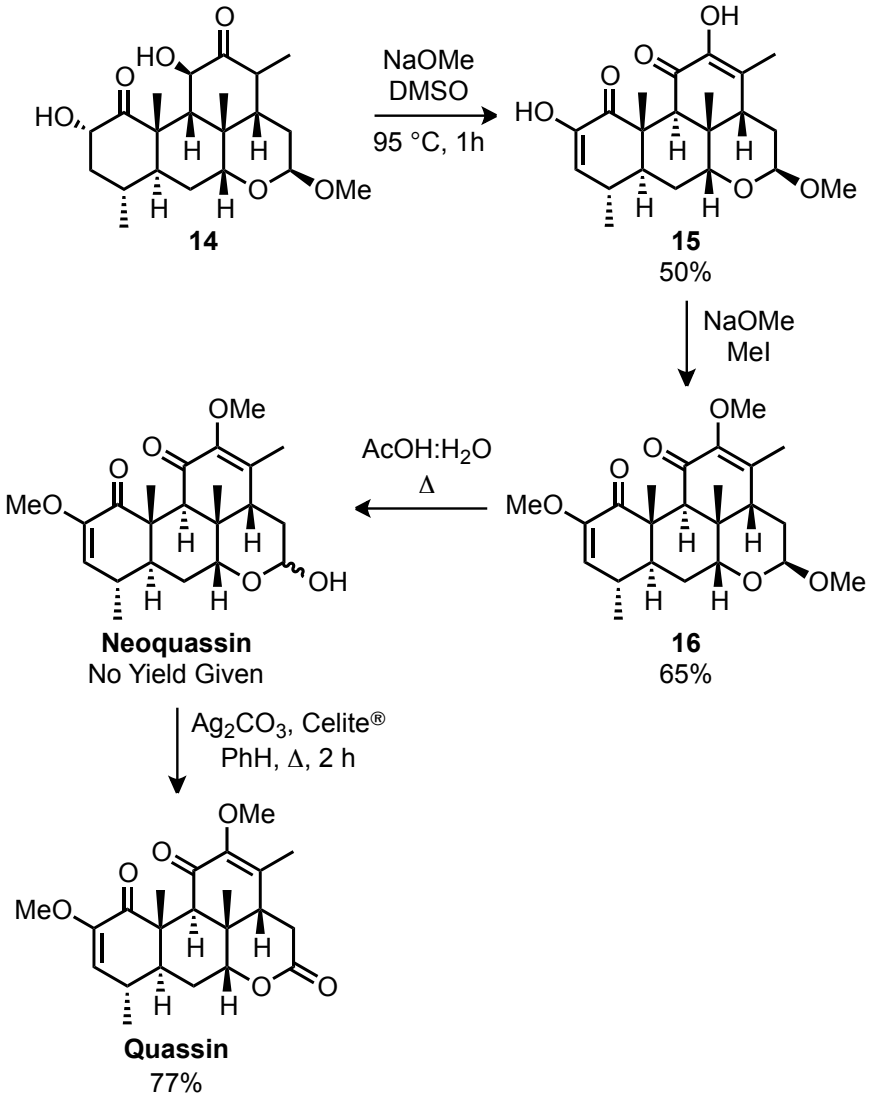
In the first step of Grieco's synthesis of neoquassin and quassin, reported in 1980, the C-ring was installed through a Diels-Alder cycloaddition (Scheme 1.6). Using sub-stoichiometric $AlCl_3$ a diene ester was annulated onto enone **8** in 62% yield. During the optimisation of this reaction it was found that higher quantities of the Lewis acid resulted in polymerisation of the diene. Chemoselective reduction of the ketone in **9** using $NaBH_4$ resulted in spontaneous lactonisation to give lactone **10**. Then, methyl ether cleavage was accomplished using ethane dithiol and $BF_3{\cdot}OEt_2$ to give alcohol **11**. Reduction of the lactone to the corresponding lactol (DIBAL-H) and methanolysis under acidic conditions furnished mixed acetal **12**. Hydroboration and oxidation of **12** gave diketone **13** in 71% yield. Then, diketone **13** was treated with excess LDA and the resulting dienolate was oxidised using MoOPH to give a diacyloin **14** in 35% yield.



Scheme 1.6: Conversion of known enone **8** to diacyloin **14**

In an interesting reaction, diacyloin **14** was oxidised to the bis(diosphenol) **15** using excess sodium methoxide in DMSO (Scheme 1.7). This transformation was first noticed as a side-product when isomerisation of the C-9 bridging position to the *trans*-ring junction using sodium methoxide in DMSO at rt was attempted. It was subsequently found that heating diacyloin **14** under the same general conditions induced the desired isomerisation and also led to oxidation to give bis(diosphenol) **15** in 50% yield.[52] More classical conditions for this transformation involve treating an acyloin with either bismuth(III) oxide[53,54] or potassium carbonate/potassium hydroxide in methanol/ethanol under an oxygen atmosphere.[55,56] Under an oxygen atmosphere, their reaction conditions resulted solely in decomposition. Methylation of both diosphenol hydroxyl groups gave bismethyl-enol-ether **16** which on hydrolysis then gave neoquassin. Finally, oxidation of the lactol to the lactone using

Fetizon's reagent gave quassin. The natural product quassin was therefore accessed in 12 steps in 3% overall yield starting from racemic enone **8**.



Scheme 1.7: Synthesis of quassin and neoquassin

1.2 Samaderines

1.2.1 Introduction to Samaderines

The samaderines are a subclass of the quassinoids characterised by their original isolation from *Samadera indica* plants. However, the samaderines were later discovered in a variety of other species including *Quassia indica.* To date, eight samaderines have been identified (Figure 1.5). Like all quassinoids, the samaderines are highly oxygenated terpenoids but they are distinguished as they contain a lactone ring and a tetrahydrofuran ring. The tetrahydrofuran ring is present throughout all samaderines and is fused between the C-8 and C-13 atoms. However, the lactone can have two forms. In samaderines A, B, C and D the lactone is a γ-lactone incorporated into the main carbon skeleton at the C-12 and C-14 positions. For samaderines E, X, Y and Z the lactone is a 6-membered δ-lactone from the C-14 anchor to the C-7 position.

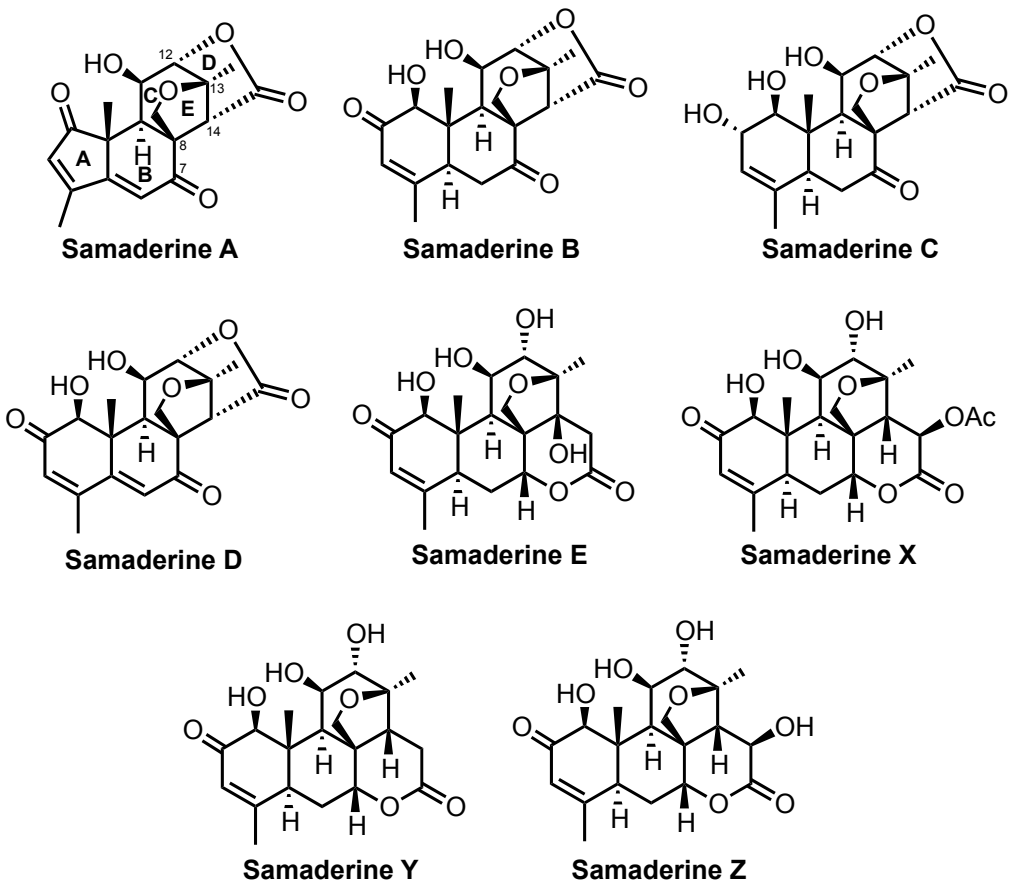


Figure 1.5: *The samaderines*

1.2.2 Biological Activity

The samaderines, like most other quassinoids, are biologically significant in their activity and showed promising activity in anti-tumour applications. Their cytotoxicity was reported by Kobayashi *et al.* in 1996 (Table 1.2). It was discovered that samaderines B, C, E, X, Y and Z show toxicity towards KB cells with the results for the B, E and X analogues being most pronounced with IC_{50} values of 0.07 μg/mL, 0.04 μg/mL and 0.02 μg/mL respectively. In the same publication, Kobayashi proved that these samaderines exhibit significant anti-malarial and anti-inflammatory attributes. A selection of the anti-malarial results are shown in Table 1.2. Samaderine E (entry 3) shows the most promising activity with an IC_{50} of 0.014 μM.

Entry	**Samaderine**	**IC_{50}** [a] (μM)	**IC_{90}** [a] (μM)
1	X	0.21	0.69
2	Z	0.056	0.093
3	E	0.014	0.069
4	B	0.071	0.19

[a]*IC values for inhibition of the growth of the chloroquine resistant strains of Plasmodium falciparum K1, at 0.1 μM concentration of samples*

Table 1.2: *Antimalarial properties of the samaderines*

As well as their anti-malarial facets, samaderines B and X also show marked anti-inflammatory properties. In Sprague-Dawley rats the exudate volume and the number of leukocytes in the pleural cavity were measured four hours after a carrageenan injection. Samaderines B and X were administered at 0 and 60 min after a carrageenan injection, at a dose of 1mg/kg. Samaderines B and X showed inhibition of the exudates volume by 78% and 79% respectively and a reduction in the number of leukocytes by 94% and 95% respectively.

In addition, samaderines A, B and C have been established as cogent antifeedants. Table 1,3 shows a collection of results highlighting the anitfeedant traits of these samaderines. Experiments to determine the growth regulatory potential are shown in Table 1.4. The results for azadirachtin A are included for comparison. Azadirachtin is a classical, potent, non-toxic antifeedant and is referenced here as a comparative standard. Samaderine B shows the most promising activity as an antifeedant (63.1% at 5 μg/cm^2)(Table 1.3). However, samaderine C displays the highest pupal toxicity with a mortality value of 54.1% (Table 1.4). Samaderine C's insectidical properties are directly comparable with azadiracthin A. In combination with the antifeedant activity shown by samaderine C, this samaderine analogue is probably the most promising lead for a commercial agrochemical application of a samaderine compound.

Concentration (μg/cm^2)	**Samaderine A**[a]	**Samaderine B**[a]	**Samaderine C**[a]	**Azadirachtin A**[a]
0.5	18.9	16.3	15.0	91.6
1.0	16.2	25.9	16.1	94.8
5.0	21.1	63.1	55.3	95.4

[a]*Antifeedant activity as percentage (area fed in treated / area fed in control) over 180 cm^2 castor leaf offered to Spodoptera litura*

Table 1.3: *Antifeedant activity of the Samaderines with Azadirachtin A as a standard*

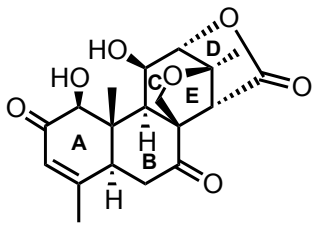
Compound	**Total Larval Duration**[a] (days)	**Pupal Duration**[a] (days)	**Pupal Mortality**[a] (%)
Control	14.5	8.4	7.1
Samaderine A	15.1	8.8	7.4
Samaderine B	15.6	9.3	37.5
Samaderine C	15.3	9.7	54.1
Azadirachtin A	16.1	9.3	62.5

[a]*Growth regulation and mortality of 25 Spodoptera litura individuals fed on castor leaf for 24h sprayed with 0.5* μg/cm^2 *test concentration*

Table 1.4: *Insectidical attributes of the samaderines*

1.2.3 Total Syntheses of Samaderines: Samaderine B

To date there have been numerous reported total syntheses of quassinoids. However, in contrast, the samaderine class has been significantly understudied with only two reported total syntheses. The first reported synthesis of a samaderine was that of racemic samaderine B (Figure 1.6) by Grieco and co-workers in 1994.[41] Grieco's contribution to the field of quassinoids has been significant and this paper is the culmination of a very large synthetic effort on his group's part. As a linear sequence of 47 steps from enone **17**, the route is not concise but it does overcome a number of synthetic difficulties.



Samaderine B

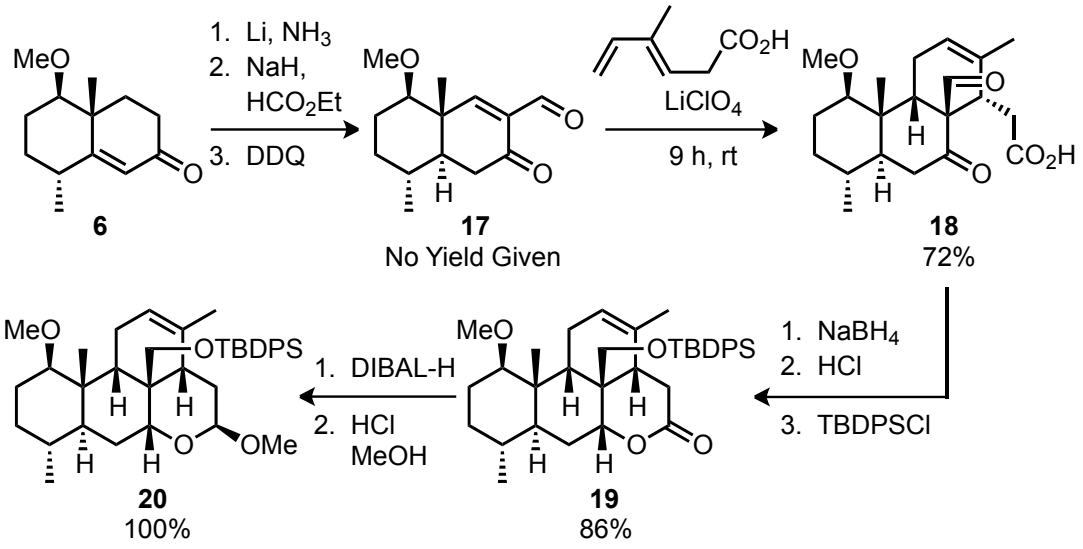
Figure 1.6: *Samaderine B*

Grieco's efforts began from enone **6** which was used in the synthesis of quassin and neoquassin described previously (see Scheme 1.5). As shown in Scheme 1.8, Birch-type reduction of the enone in **6** followed by formylation and DDQ oxidation gave enone **17**. In their efforts towards quassin and neoquassin, an $AlCl_3$-catalysed Diels-Alder annulation installed the C-ring system with subsequent epimerisation of the C-9 bridging position. In this case, $LiClO_4$-catalysed conditions, that had been previously studied within their group, were adopted.

In 1990, the Grieco group reported that use of $LiClO_4$ in diethyl ether led to a marked increase in reactivity as well as an increased tendency for *endo*-selectivity.[57] In [4+2] cycloaddition reactions, it had previously been established that aqueous reaction media[58-63] and high pressure reactions[58,64-66] produce increased reaction rates and improved stereoselectivity. The source of this reactivity is believed to be derived from the conditions forcing the dienophile and diene together lowering the reaction activation energy whilst driving a preference for the more structurally condensed

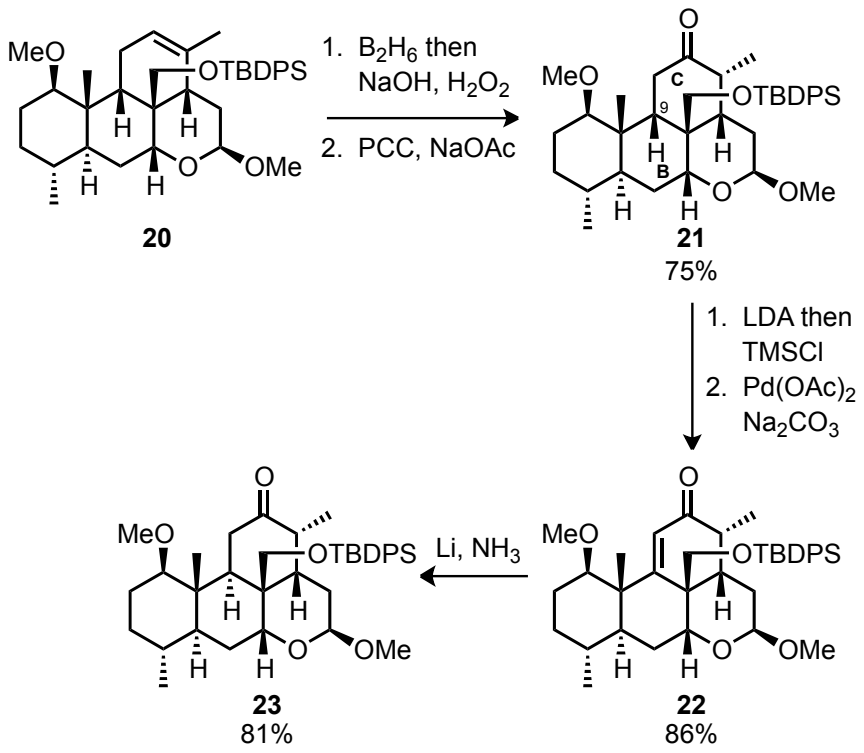
endo-reaction transition state. Grieco's $LiClO_4$ conditions, whilst not under pressure and in organic solvent, are thought to act in a similar fashion. Greico postulated the formation of a 'high internal solvent pressure' whereby the perchlorate ions confined solute movement preserving solvent ordering possibly by a micellar mechanism. Overall, this produced a similar physical effect as that in aqueous reaction media or under high physical pressure.

In the samaderine B synthesis, the Diels-Alder cycloaddition of racemic dienophile **17** with a diene under the $LiClO_4$ conditions gave the *endo*-adduct **18**. Then, reduction of the ketone and aldehyde carbonyls by $NaBH_4$ followed by lactonisation under acidic conditions and silyl protection of the primary alcohol furnished silyl ether **19**. Conversion of the lactone into the corresponding mixed acetal **20** was achieved by DIBAL-H reduction followed by methanolysis.



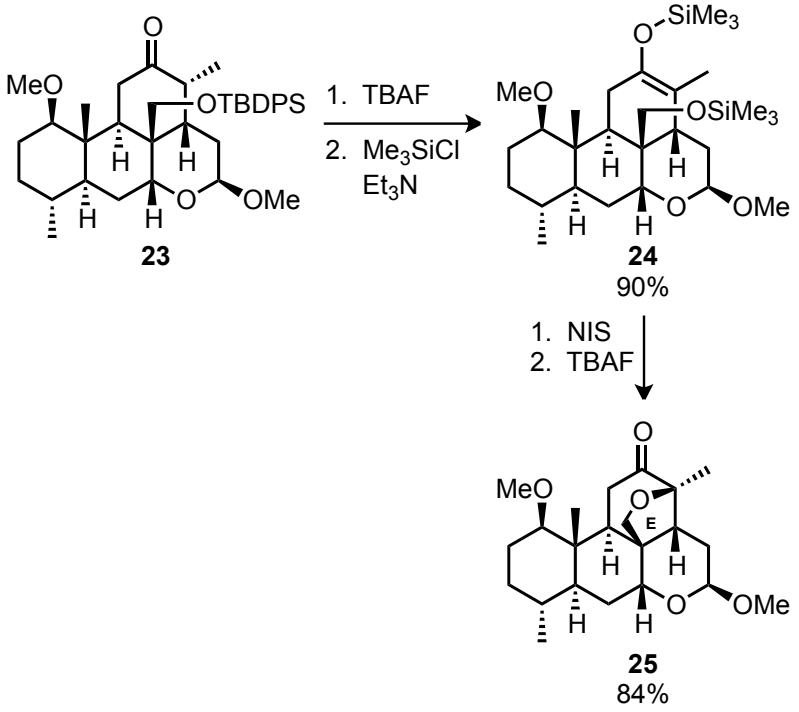
Scheme 1.8: *Diels-Alder annulation chemistry and conversion to mixed acetal* ***20***

Next, hydroboration of the C-ring alkene followed by oxidation gave ketone **21** (Scheme 1.9). In this context, a major limitation of a Diels-Alder annulation strategy is the stereospecific nature of the reaction. The result in this case was the *cis*-orientation of the B to C-ring junctions. This necessitated a C-9 epimerisation as required previously in Grieco's synthesis of quassin and neoquassin. When accessing quassin/neoquassin, this C-9 position was enolic and so epimerisation was readily achieved and also led to the discovery of the novel acyloin oxidation conditions. In the samaderine B synthesis the oxygenation pattern is different and a synthetically more laborious route was required. Using kinetic enolate forming conditions, the trimethylsilyl enol ether of **21** was formed and Saegusa oxidation resulted in enone **22**.[67] The desired *trans*-deaclin BC-ring junction in ketone **23** was achieved by a Birch-type reduction of enone **22**.



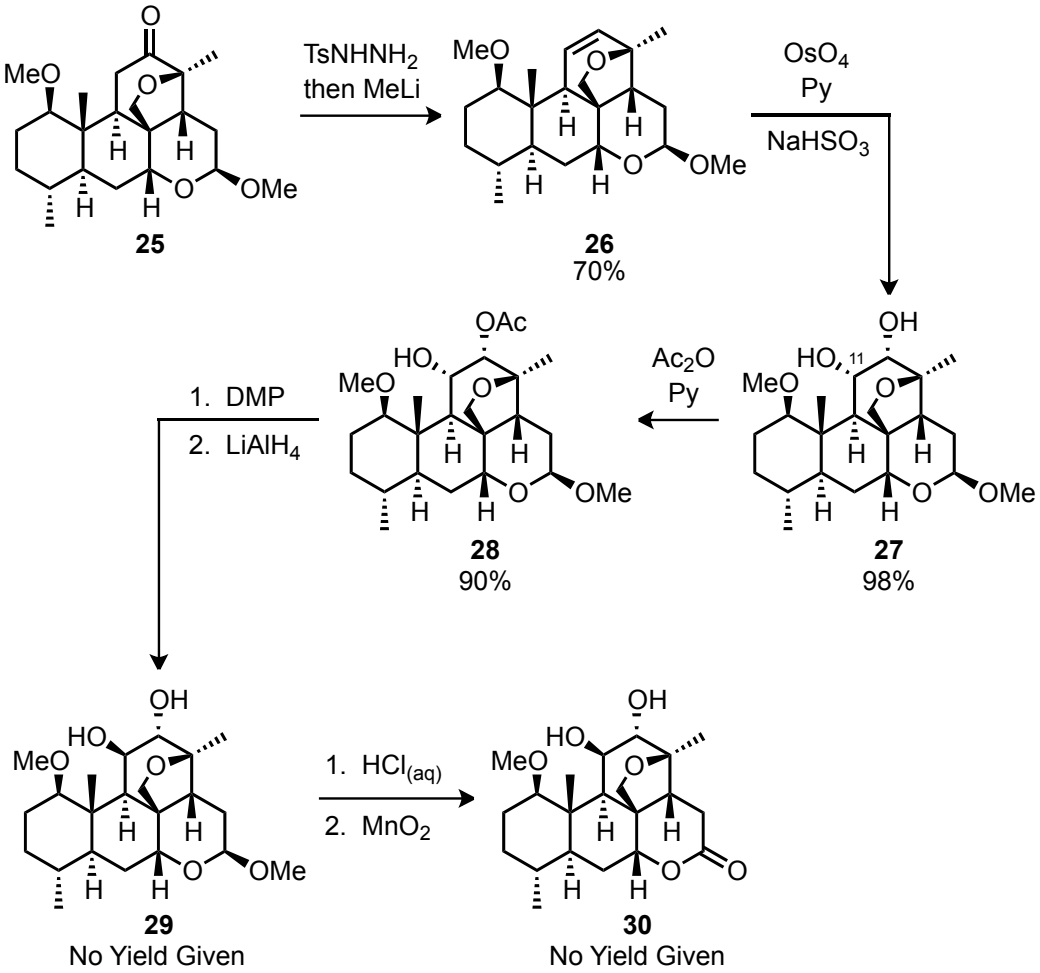
Scheme 1.9: *Epimerisation of the C-9 to give a trans-decalin ring junction*

The tetrahydrofuran E-ring was then installed (Scheme 1.10). TBAF cleavage of the TBDPS silyl ether revealed a primary alcohol. Formation of the thermodynamic silyl enol ether using Me_3SiCl and triethylamine gave disilyated adduct **24** in 90% yield. Iodination of the silyl enol ether moiety using NIS then allowed spontaneous etherification on treatment with TBAF to give the E-ring containing ketone **25**.



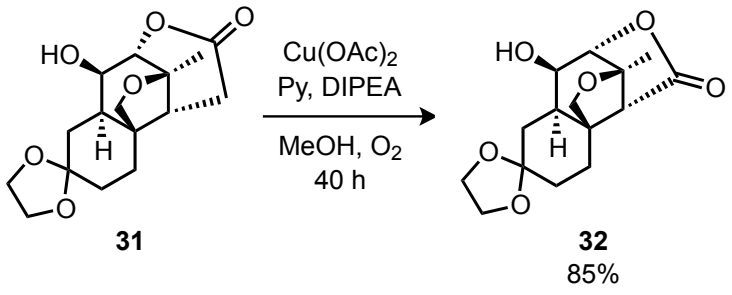
Scheme 1.10: *Hydofuryl E-ring formation*

Treating ketone **25** with tosyl-hydrazine and then methyllithium in a Shapiro reaction gave alkene **26** (Scheme 1.11).[68] A dihydroxylation reaction using stoichiometric osmium tetroxide was then carried out to give *cis*-diol **27** where osmylation occurred from the least hindered bottom face. A *trans*-diol moiety was required at this position and necessitated inversion of configuration at the C-11 hydroxyl. Grieco had previously demonstrated on related picrasane skeletons that the C-12 hydroxyl can be regioselectively protected as the acetate.[32] These conditions were employed giving acetate **28** which on oxidation using Dess-Martin periodinane (DMP) give an acyloin intermediate. Stereoselective reduction of the acyloin by $LiAlH_4$ from the least hindered bottom face gave *trans*-diol **29**. Then, hydrolysis of the mixed acetal to the lactol followed by manganese dioxide oxidation gave lactone **30**.



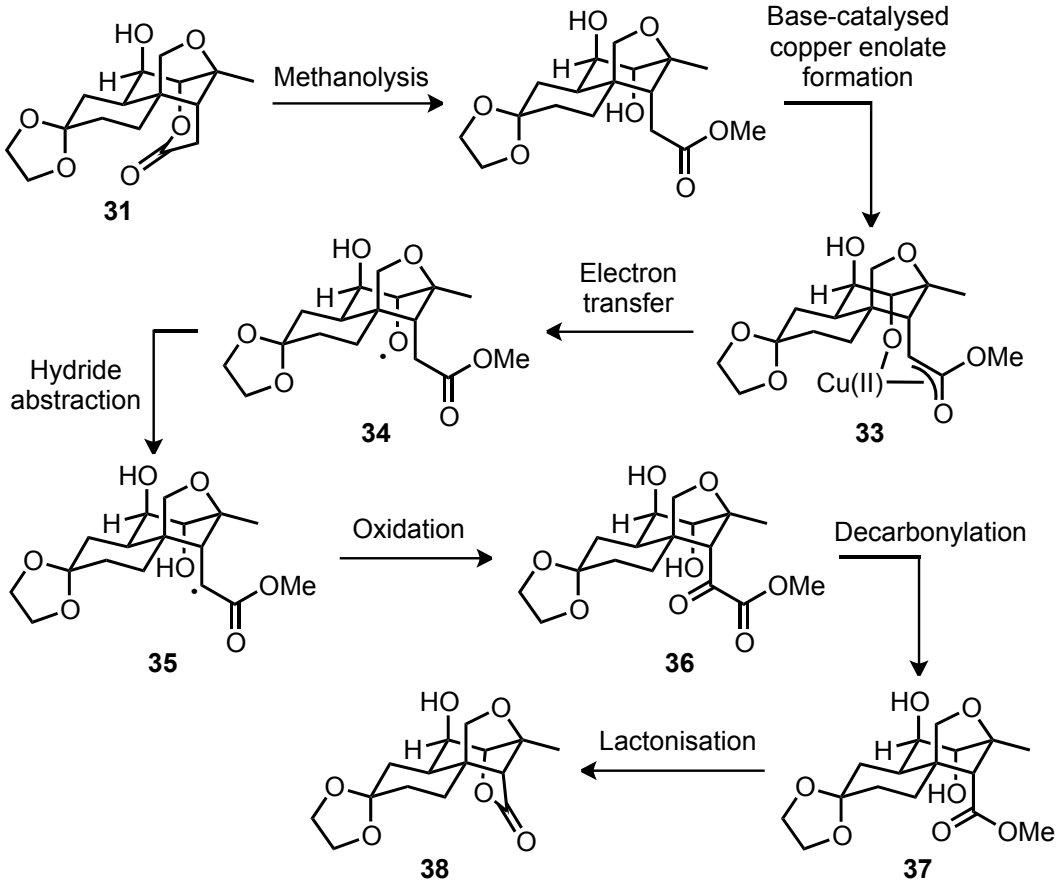
Scheme 1.11: *Trans-diol installation*

The centrepiece of this route was intended to be the formation of the C-12/C-14 γ-lactone using a copper(II)-mediated ring contraction which had previously been discovered by the Grieco group.[69] In this previous work, they had demonstrated the ability to convert δ-lactones such as **31** into γ-lactones such as **32** by bubbling oxygen through a solution of the δ-lactone in methanol in the presence of copper(II) acetate, Hünig's base (DIPEA) and pyridine (Scheme 1.12).



Scheme 1.12: *An exampled of the copper(II)-catalysed ring-contraction*

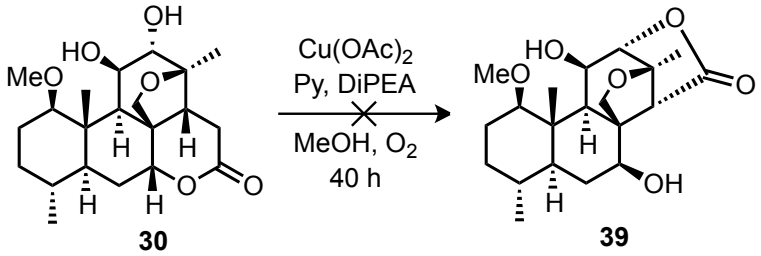
Based on the isolation of intermediates, the reaction mechanism is understood to proceed as outlined in Scheme 1.13. Methanolysis of the lactone gives a hydroxy-ester intermediate. A base-catalysed formation of a copper enolate (**33**) then occurs where the C-12 hydroxyl is coordinated to the copper metal. This coordination is believed to induce an electron transfer process giving oxo-radical **34** which then abstracts a hydrogen atom to give the keto-stablised radical **35**. Oxidation of this radical would give diketone **36** which on decarbonylation shortens the side-chain by one carbon to give ester **37** which would then spontaneously lactonise under the basic conditions to give the ring-contracted lactone **38**.



Scheme 1.13: *Copper(II)-catalysed ring contraction mechanism*

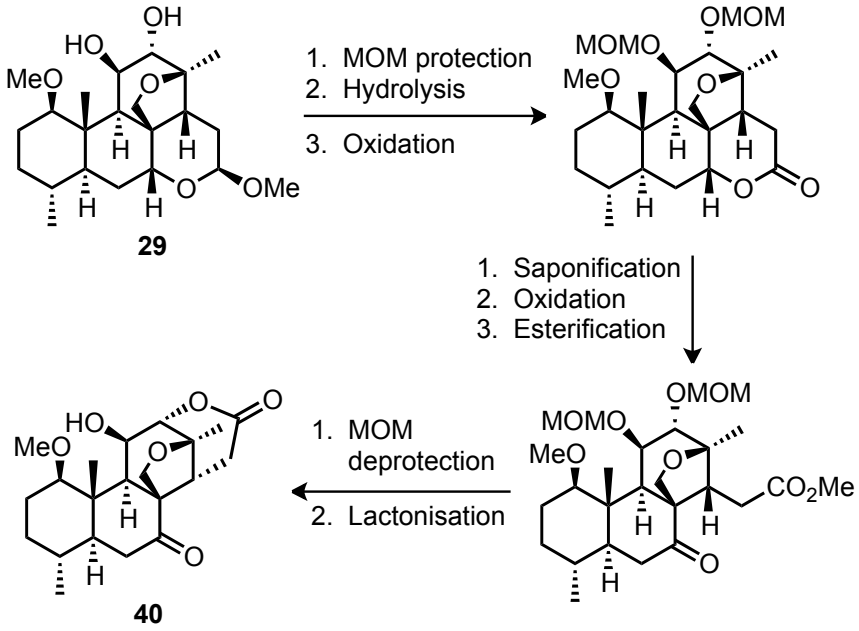
Unfortunately, in the projected samaderine B synthesis, application of **30** to the ring-contraction conditions had no affect on the substrate with quantitative recovery of starting material (Scheme 1.14). It was decided to attempt the ring-contraction on the isomeric pentacyclic γ-lactone **40**. All attempts at directly converting **30** into the desired isomer (**40**) by employing equilibrating conditions failed. The inability to cause the translactonisation may give an insight into the reason for the unsuccessful

copper(II)-catalysed ring-contraction reaction. During the proposed reaction mechanism, the first step requires the methanolic cleavage of the lactone. It is conceivable that in this system there is a thermodynamic drive towards the formation of the γ-lactone in its current position disfavouring both the ring-contraction chemistry as well as the translactonisation. The authors do not comment on the reason for the lack of reactivity.



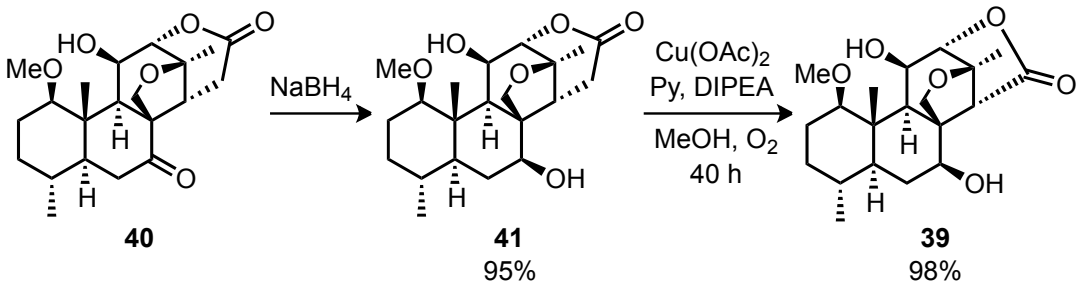
Scheme 1.14: *Attempted copper-catalysed ring contraction of* ***30***

Due to this lack of success, the synthesis underwent its most synthetically laborious sequence as the authors went back to **29** and attempted to construct the required γ-lactone **40** from this point. This seemingly simple transformation added eight more linear steps and the approach was not straightforward. The sequence used is summarised in Scheme 1.15.



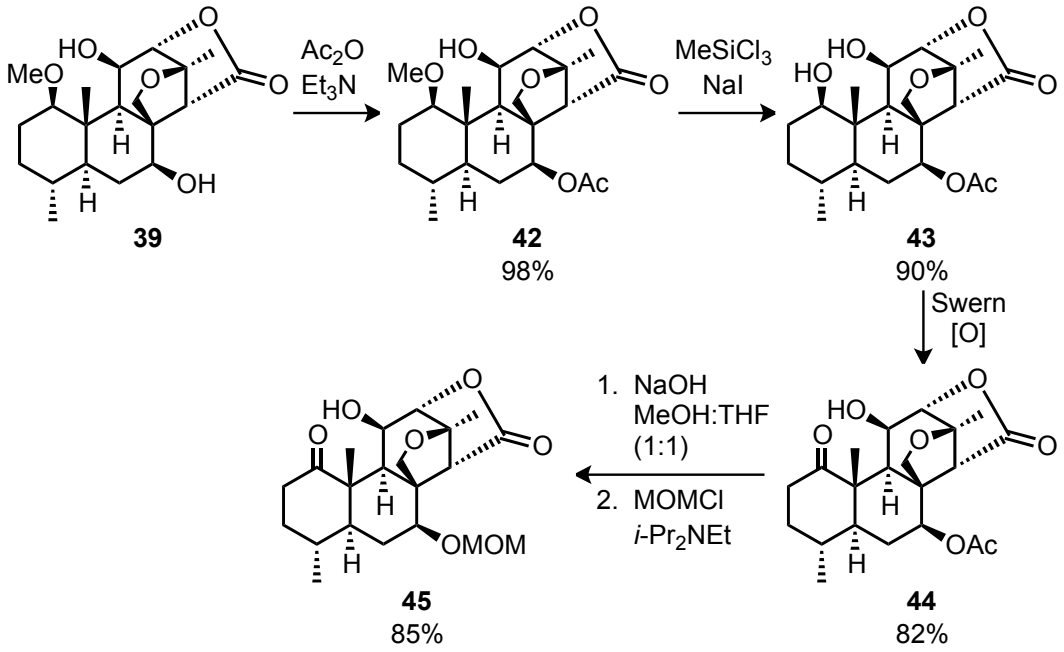
Scheme 1.15: *δ-Lactone isomerisation procedure*

With the desired γ-lactone isomer **40** in hand, Grieco's group reinvestigated the ring-contraction reaction. However, under the standard conditions (copper(II) acetate, pyridine, DIPEA and oxygen), no product was isolated. It was speculated that the ketone at C-7 was possibly causing 'conformational complications' which were not justified further. Fortunately, reduction of ketone **40** and reaction of the resultant alcohol **41** with copper(II) acetate and oxygen gave the desired product **39** in 98% yield (Scheme 1.16).



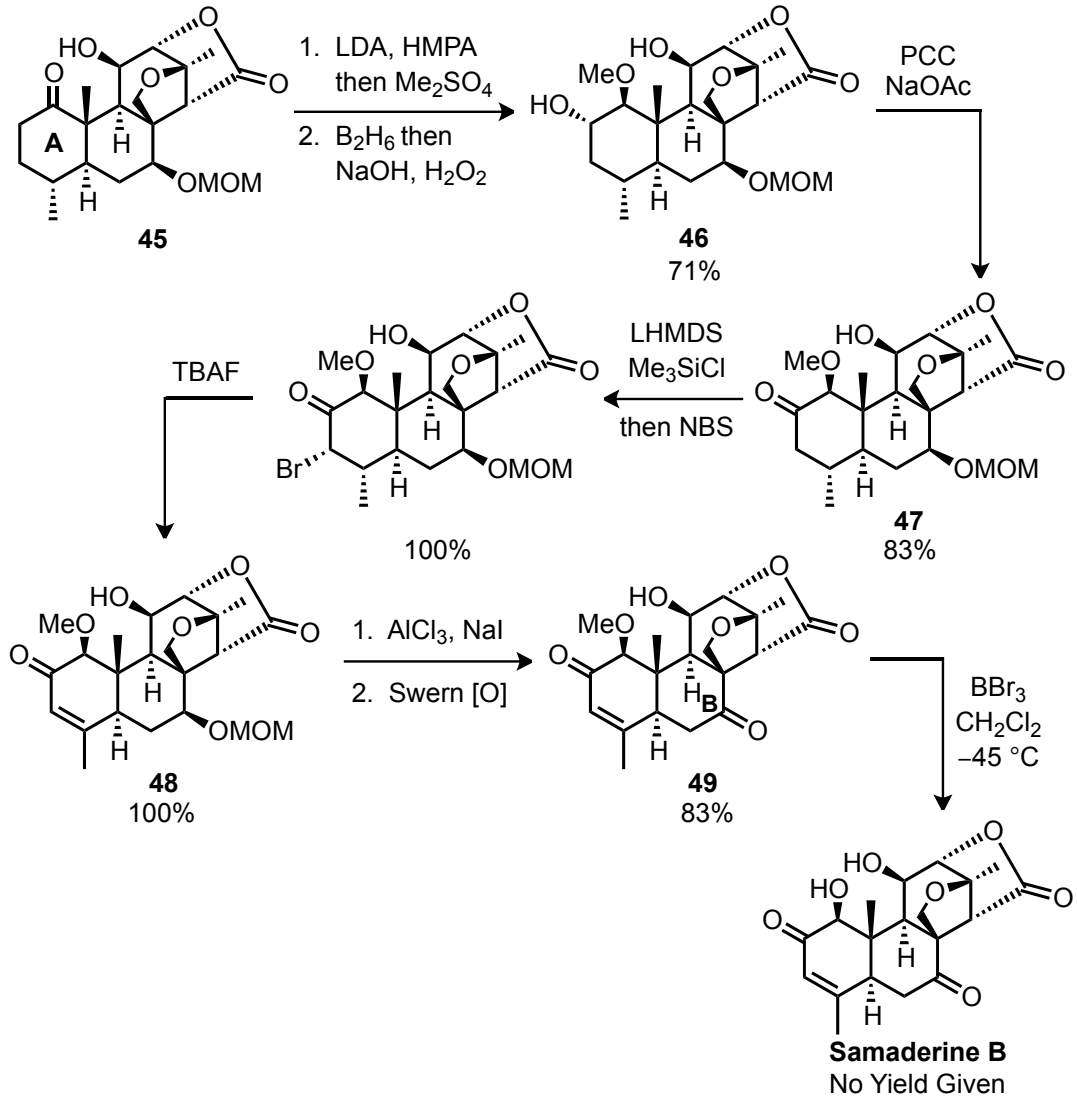
Scheme 1.16: *Copper(II)-mediated ring-contraction to a samaderine B precursor **39***

The final synthetic efforts focused on the functionalisation of the A-ring (Scheme 1.17). The B-ring alcohol of **39** was acetylated to give acetate **42**, which on deprotection of the methyl ether using Me_3SiCl and sodium iodide gave diol **43**. Swern oxidation of the least hindered A-ring alcohol gave ketone **44**. A protecting group switch from the acetate to the MOM ether then gave **45**.



Scheme 1.17: *Protecting group manipulations of A-ring functionalisation*

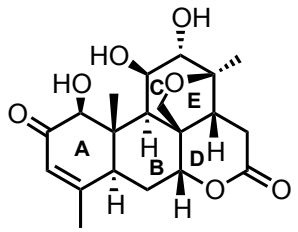
Treatment of **45** with LDA and trapping of the resulting A-ring enolate as the methyl enol ether allowed a hydroboration/oxidation reaction on the opposite face to the axial bridgehead methyl group to furnish *trans*-diol **46** (Scheme 1.18). The free A-ring alcohol was oxidised using PCC to give ketol **47**. Installation of the A-ring enone was achieved using enolate bromination and elimination to give enone **48**. The B-ring ketone was installed by deprotection of the MOM ether using $AlCl_3$ and sodium iodide and then a Swern oxidation to give ketone **49** in 83% yield. Finally, methyl ether deprotection using BBr_3 gave the racemic natural product samaderine B. This synthesis is long and was arranged to incorporate the copper(II)-catalysed ring-contraction chemistry despite there being numerous plausible methodologies for the installation of a γ-lactone. However, this work was the first synthesis of a samaderine, no mean task in itself.



Scheme 1.18: *A-ring functionalisation to furnish the natural product, samaderine B*

1.2.4 Total Syntheses of Samaderines: Samaderine Y

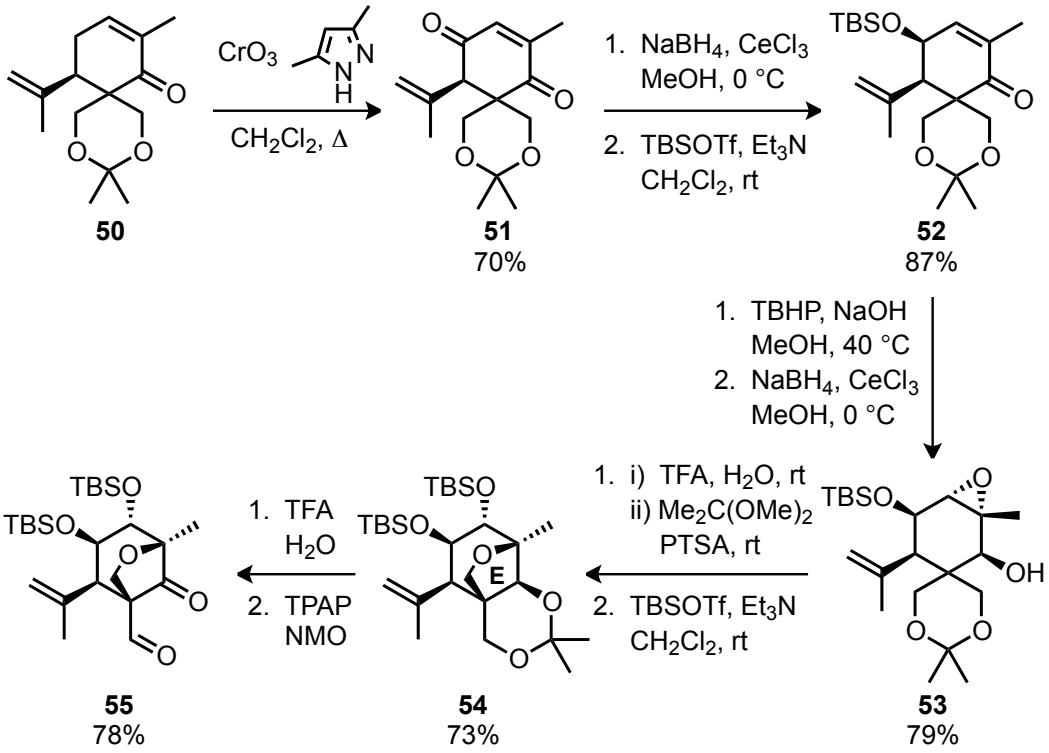
The second total synthesis of a samaderine was completed in 2005 by Shing and co-workers.[42] The synthesis of (−)-samaderine Y (Figure 1.7) was completed in 21 steps from the known enone **50** (derived from a chiral pool starting material) and represents a concise piece of modern synthesis. This samaderine analogue differs from samaderine B only in the size and position of the lactone but the strategy used is significantly different to Grieco's. Shing's route starts in the CE-rings and then used a Diels-Alder reaction to install the AB-rings. Grieco, in comparison, started the synthesis in the AB-rings and then used cycloaddition chemistry to generate the CE-rings.



Samaderine Y

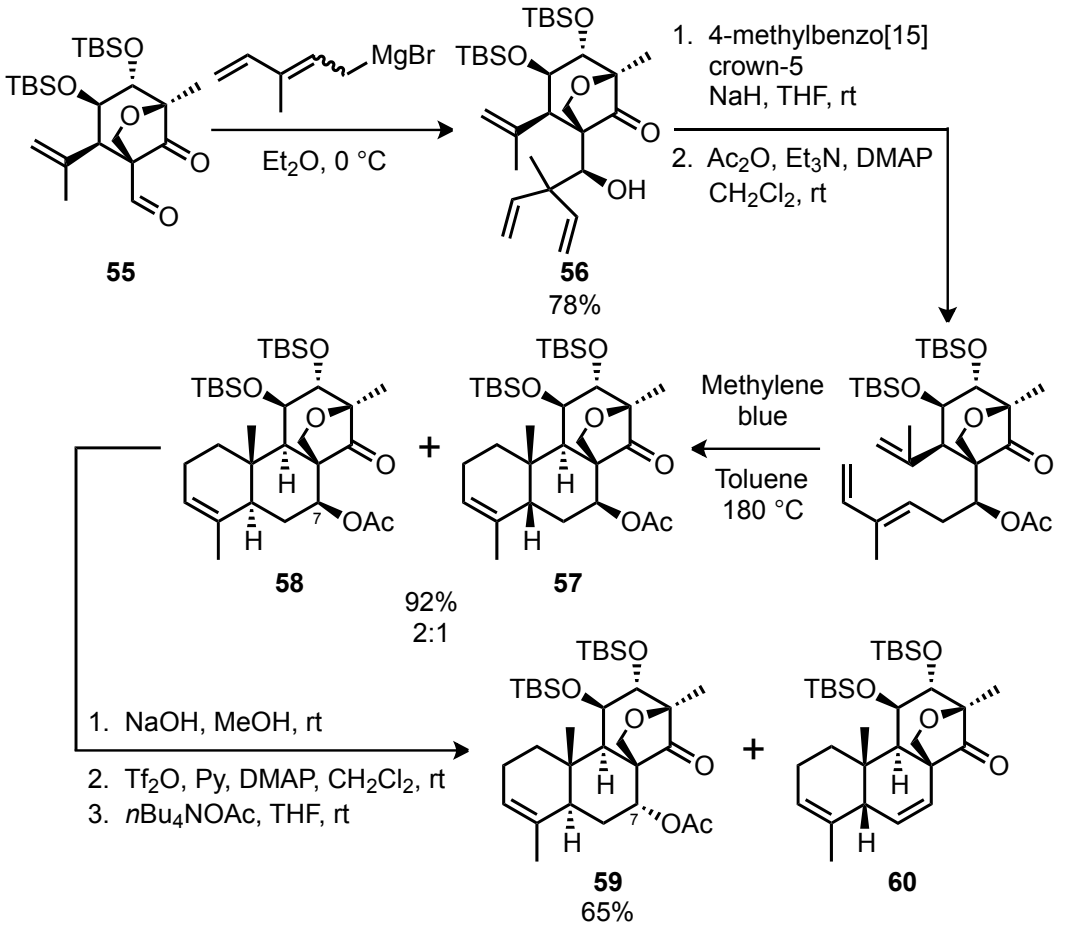
Figure 1.7: *Samaderine Y*

Shing's synthesis started from a known enone **50** which was previously used in their synthetic efforts the towards quassinoids simalikalactone D and quassimarin.[70] Enone **50** is readily available from (*S*)-(+)-carvone through a double aldol reaction with formaldehyde and ketalisation. Efforts towards samaderine Y proceeded *via* a relatively efficient sequence giving the CE-ring structures in eight steps (Scheme 1.19). Allylic oxidation of enone **50** using chromium trioxide gave ketone **51**. Ketone **51** was stereoselectively reduced under Luche conditions and the resultant alcohol was silyl-protected to give ketone **52**. Epoxidation of **52** occurred *trans*-to the bulky silyloxy group. This epoxide is important in effecting a chelation-controlled reduction of the ketone to give epoxy alcohol **53**. The next step was an acid-catalysed epoxide opening transketalisation to give the tetrahydrofuran E-ring. After silyl protection, ketal **54** was obtained. Ketal deprotection and TPAP oxidation then gave β-keto-aldehyde **55**.



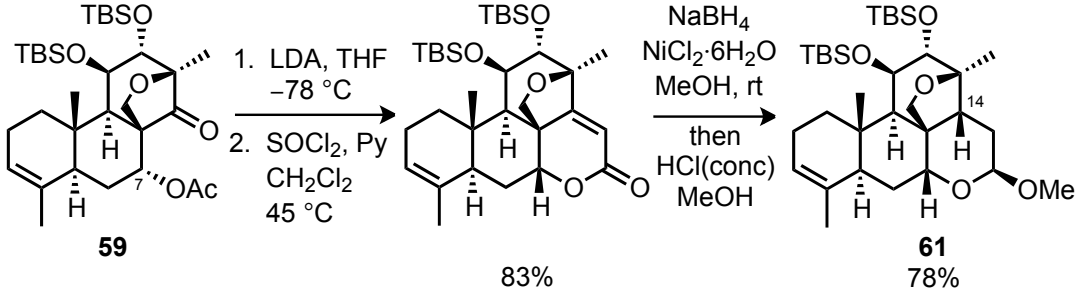
Scheme 1.19: *Synthesis of CE-ring structures of samaderine Y.*

From β-keto-aldehyde **55**, the A- and B-rings were formed. A diene Grignard addition to the aldehyde gave the undesired isomer, alcohol **56** (Scheme 1.20). The desired diene isomer was fortunately accessible using a base-mediated rearrangement followed by acetate formation.[71] An intramolecular Diels-Alder reaction then gave two diastereoisomers, acetates **57** and **58**, which proved to be inseparable. Next, inversion of the stereochemistry of the acetate at C-7 was required. The mixture of diastereomers, acetates **57** and **58**, were saponified and converted to the triflate, Then treatment with ammonium acetate caused the S_N2 inversion reaction. Due to conformational affects **57** eliminated to give **60** whereas **58** gave clean inversion to give **59** (with the desired stereochemistry). The two products **59** and **60** were now separable and the desired inverted acetate **59** was isolated in 65% yield.



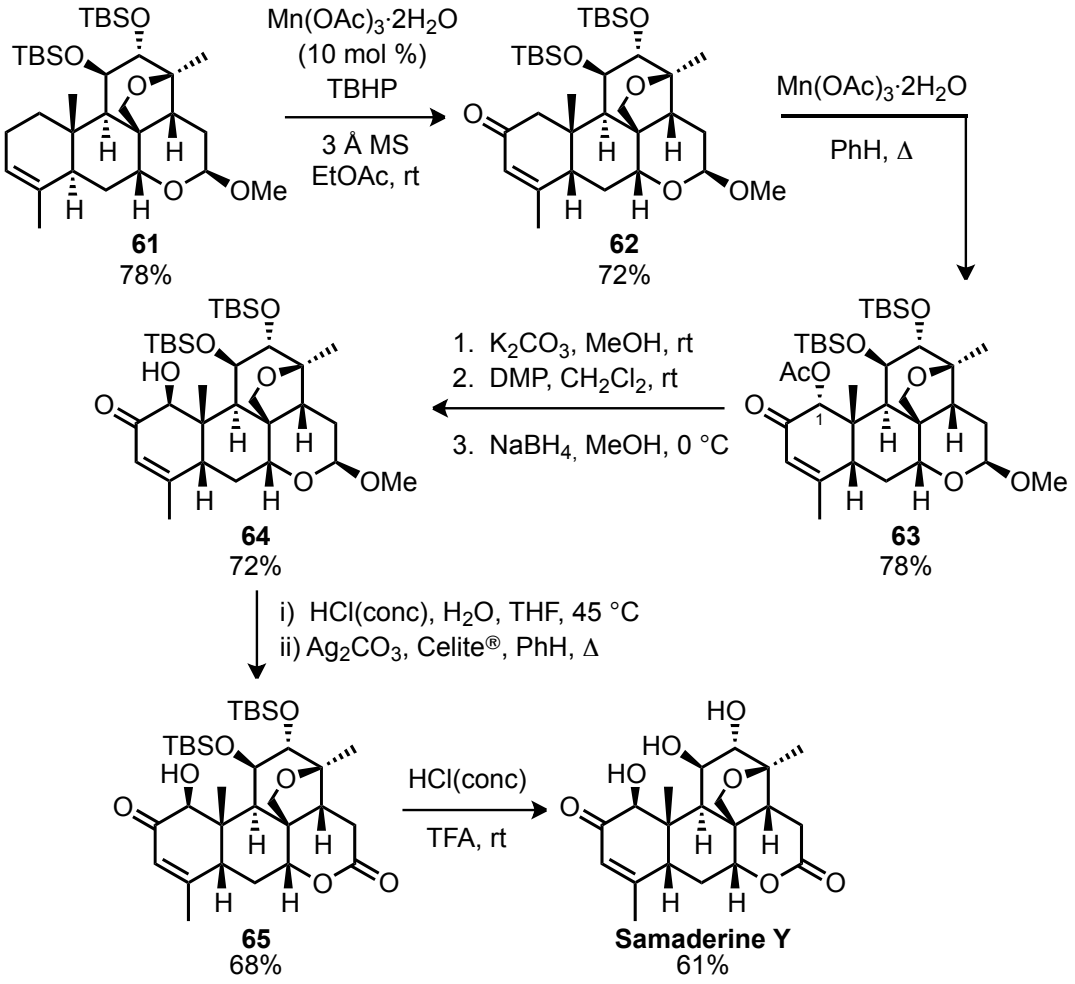
Scheme 1.20: *Synthesis of AB-ring structures of samaderine Y*

From keto acetate **59**, an intramolecular aldol condensation was used to form the D-ring (Scheme 1.21). The stereochemistry at the C-14 centre was introduced by 1,4-reduction of the enone double bond. Under the conditions, further reduction gave a lactol which was then converted into the mixed ketal **61** using concentrated HCl in methanol. The resulting structure now possessed all of the correct stereochemically-defined ring junctions.



Scheme 1.21: *Synthesis of the D-ring of samaderine Y*

As in Grieco's synthesis, Shing's end-game strategy involved the functionalisation of the samaderine A-ring (Scheme 1.22). Treating alkene **61** with catalytic manganese(III) acetate and a stoichiometric oxidant (TBHP), allylic oxidation to enone **62** was achieved. Subsequent α-keto acetoxylation using manganese(III) acetate in refluxing benzene gave α-acetoxy enone **63** in 78% yield.[72] Direct epimerisation of the C-1 position of α-acetoxy enone **63** to the desired diastereomer under both acidic and basic conditions were unsuccessful. Instead, a three-step protocol was required: acetate cleavage, oxidation to the dione followed by chemo- and stereoselective reduction to give α-hydroxy enone **64**. Finally, establishing the correct oxidation state of the D-ring was reached by ketal cleavage and oxidation to give lactone **65**, after which acidic deprotection of the silyl protecting groups gave the natural product as a single enantiomer, (−)-samaderine Y. Shing's approach was more concise (21 steps) than Grieco's, representing a modern example of total synthesis.



Scheme 1.22: *A-ring functionalisation to furnish the natural product, (−)-samaderine Y*

1.3 Samaderine C: Project Outline

Samaderine C (Figure 1.8) was first isolated by Polonsky in 1964 from the bark and seed kernels of the *Samadera indica* plant found primarily in Madagascar and South East Asia.[73] As already highlighted, it displays a range of biological activity including antifeedant and insecticidal properties as well as herbicidal activity.

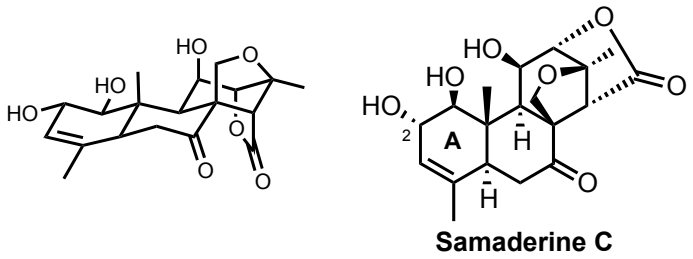
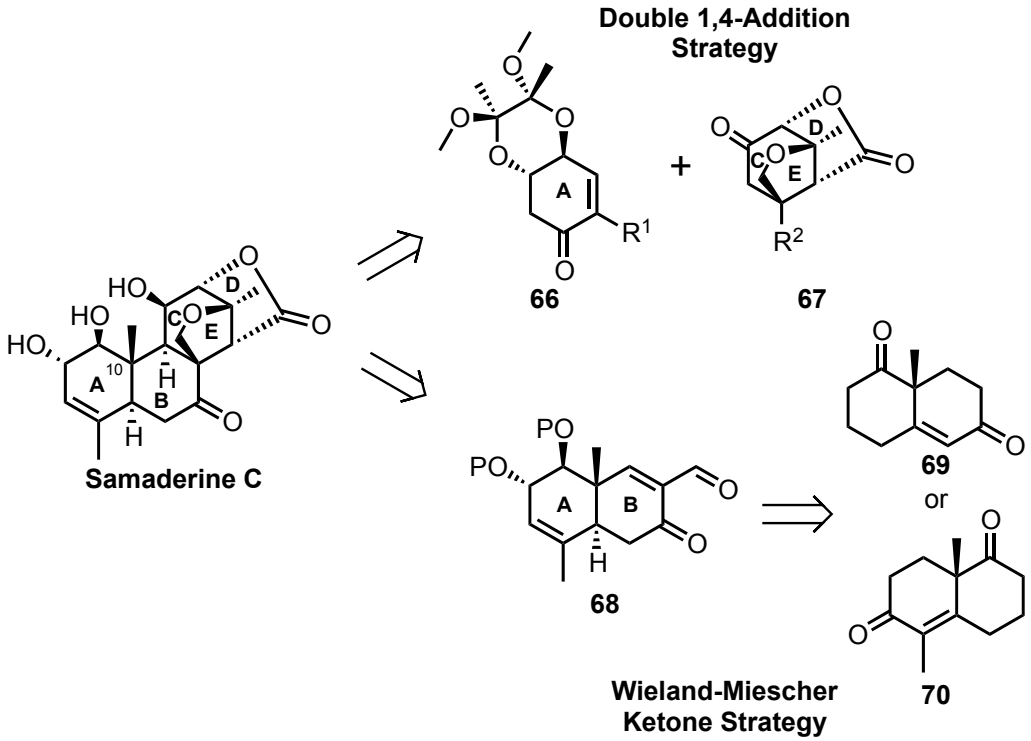


Figure 1.8: *Samaderine C*

Structurally, samaderine C resembles samaderine B almost entirely with the exception of the oxidation state at the C-2 centre. Synthetically, samaderine C poses a challenge with ten contiguous stereocentres of which three are quaternary. However, it is only on examining the literature that the most challenging structural motif is revealed. Despite its prevalence in the quassinoid family,[74] the *trans*-allylic diol A-ring motif has never previously been synthesised in a quassinoidal structure.[75-82] In general, quasinoid diol A-rings of all diastereomeric configurations are prevalent and yet there has only been one reported total synthesis of a quassinoid containing a diol A-ring.[30] From the outset, one of our main goals was achieving structures containing the A-ring *trans*-diol oxygenation motif.

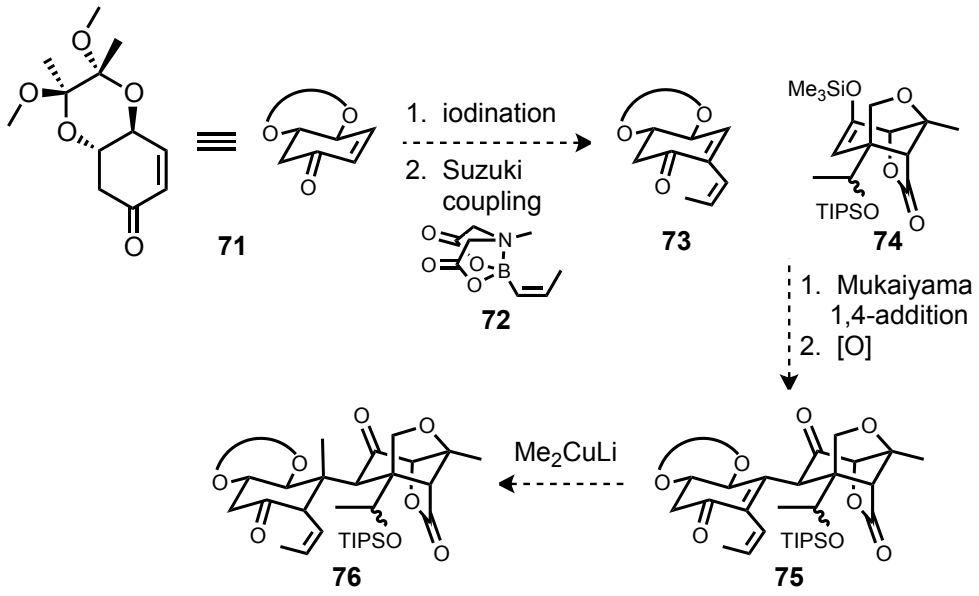
Biologically, samaderine C has been shown to posses promising activity as an agrochemical (see Table 1.4). Although studies have been devoted to investigating the quassinoids mode of action as cytotoxic agents, no such work has been carried out to ascertain the mechanism of the samaderine's action as an agrochemical. The aim of this project was therefore to develop a synthetic route to samaderine C and any analogues that may help build a structure-activity profile for this compound's action as an agrochemical. We particularly focused on the synthesis of structures containing the previously unrealised *trans*-allylic diol A-ring motif.

There have been two distinct approaches undertaken during the course of the studies described in this thesis and an overview of the retrosynthetic analysis of each is shown in Scheme 1.23. One route centred on a double 1,4-addition procedure to form the quaternary C-10 bridgehead between the A-ring and the B-rings. A B-ring disconnection would allow a convergent strategy in which an enone A-ring structure **66** would be appended to a CDE-ring cluster **67** *via* a 1,4-conjugate addition of an enolate derived from **67**. The C-10 axial methyl group would be installed using a second 1,4-addition of a methyl nucleophile (Me_2CuLi or Me_2Zn). The double 1,4-addition strategy offered a unique opportunity to probe the structure-activity relationship of samaderine C as an agrochemical. The convergent nature of this route would allow the rapid synthesis of analogues with the express purpose of under pinning the structural requirements for activity. In a totally different approach, the AB-ring system of samaderine C would be derived from either the Wieland-Miescher ketone **69** or its methyl analogue **70**. We envisaged that following Grieco's precedent in the synthesis of samaderine B and quassin, a Diels-Alder annulation would introduce the C-ring system onto a dieneophile such as **68**.



Scheme 1.23: *Retrosynthetic analysis of the two planned approaches to samaderine C*

We proposed that a route to samaderine C from the double 1,4-addition approach would take the form of that outlined in Scheme 1.24. The starting materials, enone **71** and silyl enol ether **74**, would require synthesis. From enone **71**, iodination and palladium-mediated Suzuki coupling would install the propenyl metathesis handle to give α-propenyl enone **73**. Under Mukaiyama-1,4-addition-type conditions, silyl enol ether **74** would undergo a 1,4-addition reaction with enone **73** and, after enolate oxidation, would give enone **75**. This is the key convergent step. Regeneration of the cyclohexenone in ring A will be achieved ideally in the same process. In a second 1,4-addition step (Me_2CuLi), the quaternary C-10 methyl-bridgehead stereocentre would be formed giving advanced intermediate **76**. We anticipated that protonation of the resulting enolate would occur pseudo-axial and *trans*-to the methyl group. This would become important in the future for formation of the required *trans*-decalin AB-ring junction.

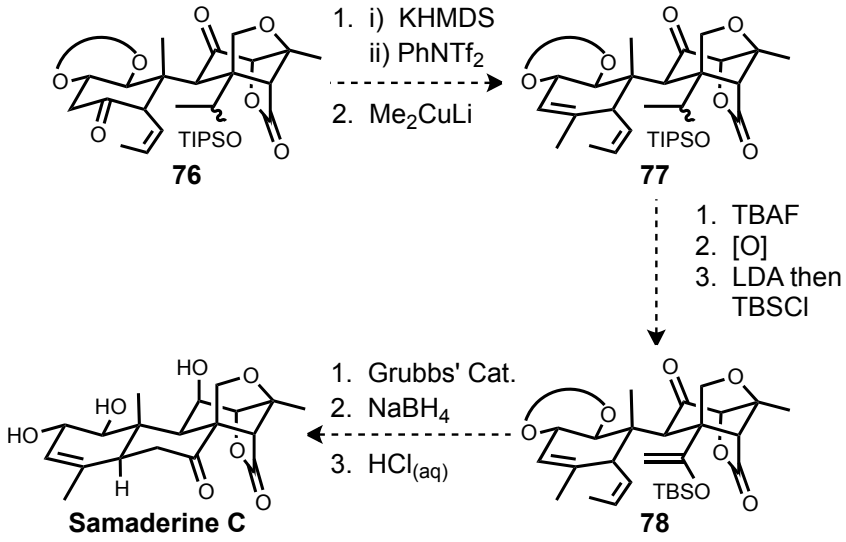


71 72 73 74 75 76

Scheme 1.24: *Forward synthesis via the double 1,4-addition approach: the convergent step*

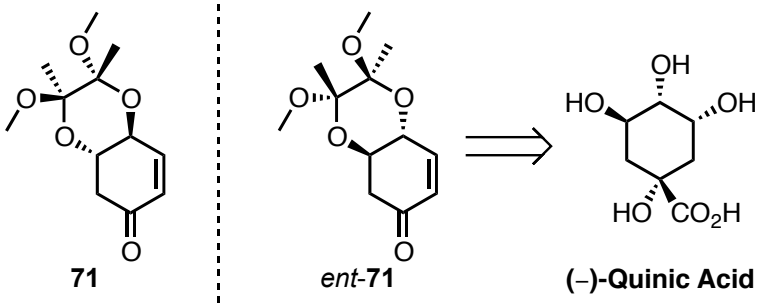
The end-game of this synthesis would involve methyl alkene formation and B-ring completion (Scheme 1.25). Methyl alkene formation would be achieved using cross-coupling of an enol triflate and Me_2CuLi to give diene **77**. Silyl cleavage of the TIPS ether, oxidation of the resultant alcohol and silyl enol ether formation would give **78**. The ring-closing metathesis (RCM) of silyl enol ether alkenes is precedented.[83] We therefore proposed that the carbon-framework of samaderine C could be completed using such a process to give the B-ring containing compound which on reduction of

the C-ring ketone and global deprotection would give the natural product, samaderine C.



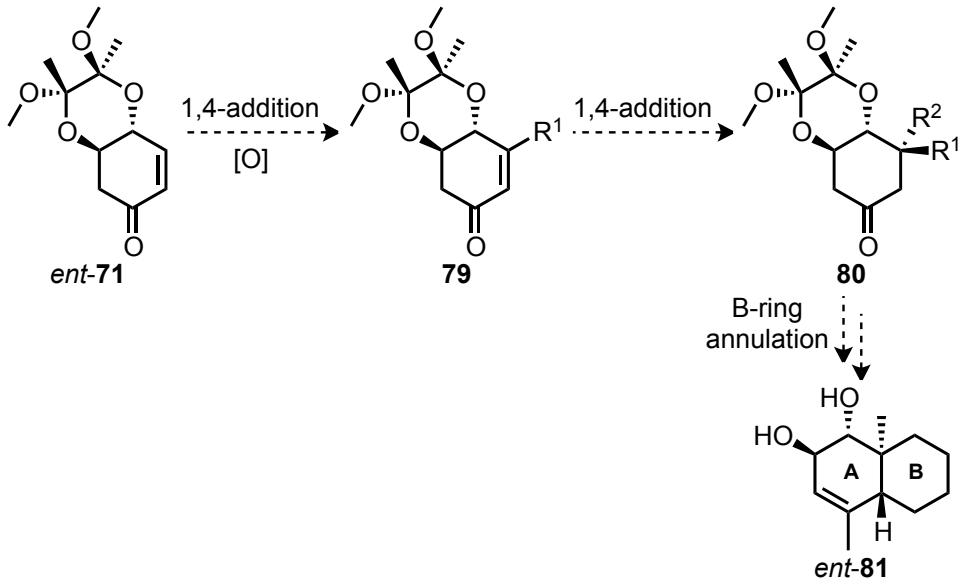
Scheme 1.25: *Forward synthesis via the double 1,4-addition approach: the end-game*

Thus, enone **71** plays a pivotal role in this route. However, at the beginning of our studies, no route to enone **71** in the desired enantiomeric series existed. However, a synthesis of the antipode, *ent*-**71** was well established starting from (−)-quinic acid (Scheme 1.26). As a result, the development of a route to the required enantiomer, enone **71**, was a primary objective of this project. However, due to the ease of preparation of multi-gram quantities of *ent*-**71**, most of the methodology development was carried out in the "wrong" enantiomeric series for samaderine C synthesis.



Scheme 1.26: *Enone 71 and its antipode ent-71 from (−)-quinic acid*

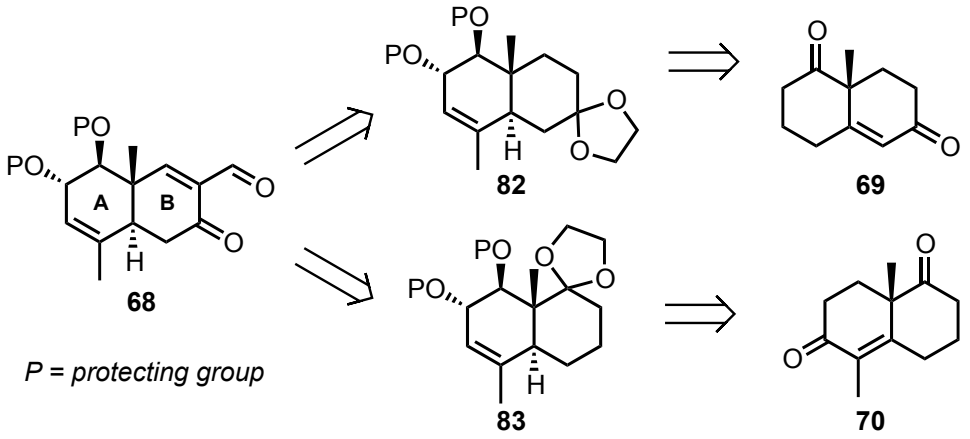
Our efforts on the double 1,4-addition route towards samaderine C covered three main areas of investigation. In chapter 2, the development of a synthesis of enone **71** in the required enantiomeric series and diastereoselective reactions of *ent*-**71** are described. The reasons for selecting the butane diacetal protecting group are discussed in chapter 2. Chapter 3 focused on the synthesis of β-substituted enones such as **79**, their 1,4-addion reactions to give **80** and attempted conversion into AB-ring analogues such as *ent*-**81** (Scheme 1.27).



Scheme 1.27: *Double 1,4-addition strategy and B-ring annulation chemistry investigated*

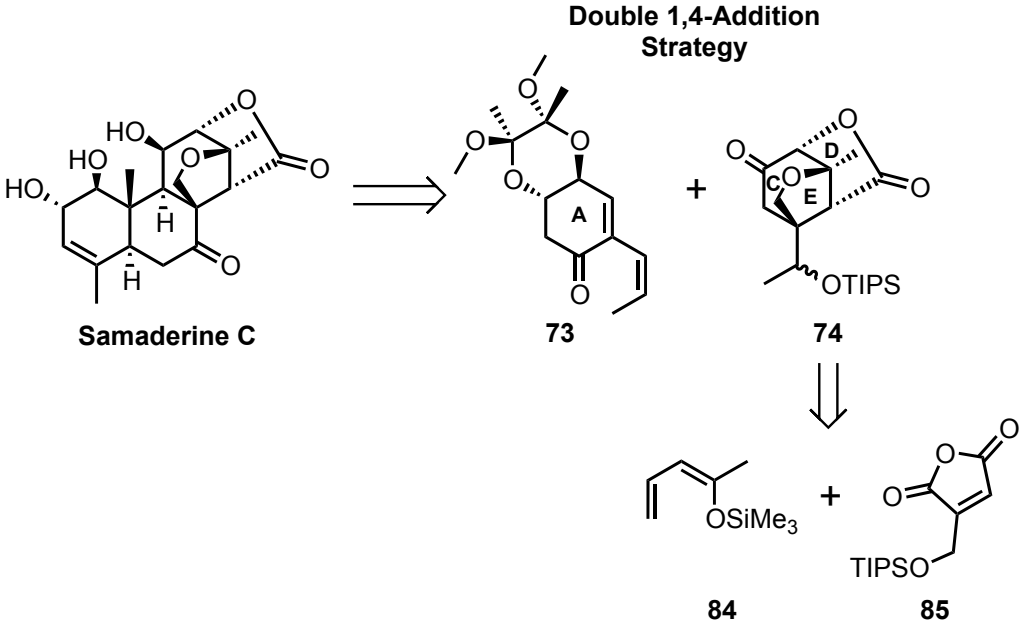
During the course of our studies, an alternative strategy towards the total synthesis of samaderine C was also investigated. This approach centred on the use of Wieland-Miescher ketone **69** and its methyl analogue **70** as starting materials (Scheme 1.28). In contrast to the original convergent route, the *trans*-decalone AB-ring system of samaderine C would be furnished early in the synthesis through the use of these bicyclic starting materials. The Wieland-Miescher ketone and its analogues[84] have been widely-used in the synthesis of quassinoids[30,31,33,39-41,47,49] and a range of other compounds sharing similar carbon frameworks.[85-90] Thus, they were an attractive starting point for our synthesis. We envisaged that a Diels-Alder, CDE-ring disconnection in line with that previously outlined in Grieco's synthesis of samaderine B would make dieneophile **68** an appropriate AB-ring target. Dieneophile **68** could be achieved from either AB-ring structures **82** or **83** which we then envisaged accessing from the Wieland-Miescher ketone **69** of its methyl

analogue **70** (Scheme 1.28). The results with ketones **69** and **70** are described in chapters 4 and 5 respectively.



Scheme 1.28: *Approaches toward dienophile **68** from the Wieland-Miescher ketones **69** and **70***

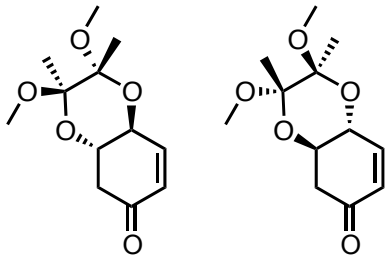
Due to the lack of literature precedent, we prioritised the synthesis of fragments containing the *trans*-allylic diol A-ring motif. However, if time permitted, we also planned to investigate the synthesis of CDE-ring-type structures. In the convergent 1,4-addition strategy, disconnection across the B-ring would give an α-propenyl enone fragment **73** and a CDE-ring structure **74** (Scheme 1.29). We envisaged that the CDE-fragment could be disconnected *via* a retro-Diels-Alder reaction to diene **84** and substituted maleic anhydride **85**. Some preliminary work was carried out on this topic and is summarised in chapter 6.



Scheme 1.29: *Convergent strategy to a CDE-ring cluster derived from a Diels-Alder cycloaddition*

Chapter 2: The Synthesis and Diastereoselective Reactions of a Bicyclic Cyclohexenone

As outlined in section 1.3, bicyclic enone **71** plays a pivotal role in our proposed double 1,4-addition strategy to the AB-rings of samaderine C. This chapter outlines the character of the known enone *ent*-**71** and then discusses the synthesis of enone *ent*-**71** and *rac*-**71**. The chemistry developed towards enone **71** in the required enantiomeric series *via* a desymmetrisation route is also presented. Finally, investigations of diastereoselective reactions of bicyclic cyclohexenone *ent*-**71** with a view to their use in samaderine C synthesis and the preparation of other, simpler natural product targets are described.



71 *ent*-**71**

Figure 2.1: *Enones 71 and ent-71*

2.1 Synthesis of a (−)-Quinic Acid Derived Bicyclic Cyclohexenone and its Enantiocomplementary Variant

2.1.1 Relevant Background Literature

The known enone, *ent*-**71**, is a bicyclic cyclohexenone with the *trans*-diol group protected as a diacetal. Diacetals are diequatorial 1,2-diol-specific protecting groups that were first reported in 1938.[91] Since then, they have been used regularly but particularly in carbohydrate chemistry where the need for 1,2-diequatorial protecting groups is perhaps greatest.[92-95] Ley *et al.*[96] are attributed to the development of the butane diacetal (BDA) present in enone *ent*-**71**. There have been a range of diacetal variants developed, such as dispiroacetals[97] and cyclohexane diacetals (CDA)[95] (Figure 2.2).

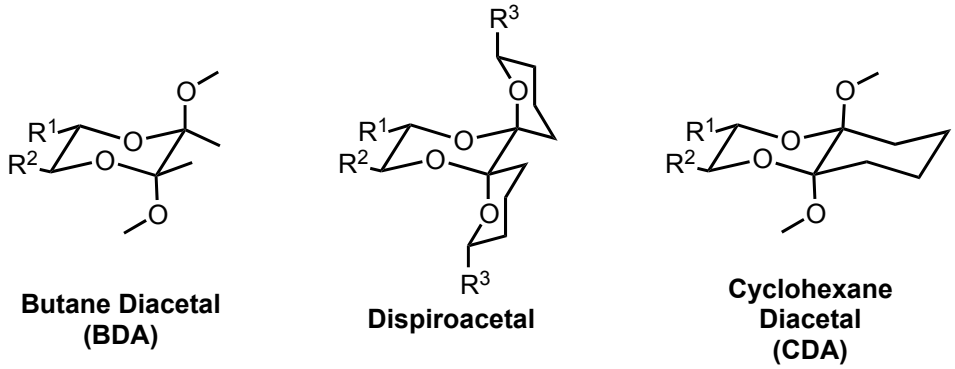


Figure 2.2: *Examples of diacetal protecting groups*

The usefulness of such diacetal protecting groups derives from their structural rigidity. For enone *ent*-**71** (Figure 2.3), this inflexibility will result in a conformational lock of the cyclohexenone ring. The diequatorial requirement for protection locks the diol in this *trans*-decalin-type arrangement and hence removes the ability of the cyclohexenone to ring-flip completely from one chair conformer to the other. In addition, there is a double anomeric effect present in the backbone of the protecting group. This effect causes the methoxy groups to be placed in the stabilised axial-positions. The diequatorial requirement in combination with the steroelectronic preference ensures the conformation of enone *ent*-**71**. It was hoped that rigidity would make it easier to determine the stereoselectivity of 1,4-addition reactions as the product diastereomers could be assigned using coupling constant values in the ^{1}H NMR spectra. It was also hoped that the locking of the ring might aid stereocontrol in any 1,4-addition processes.

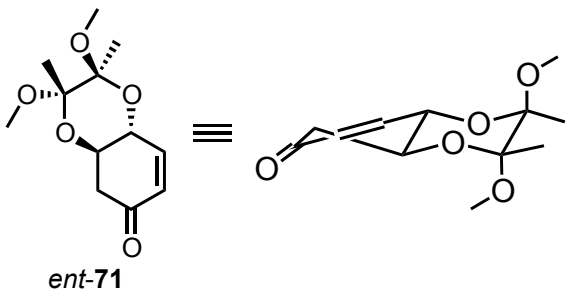
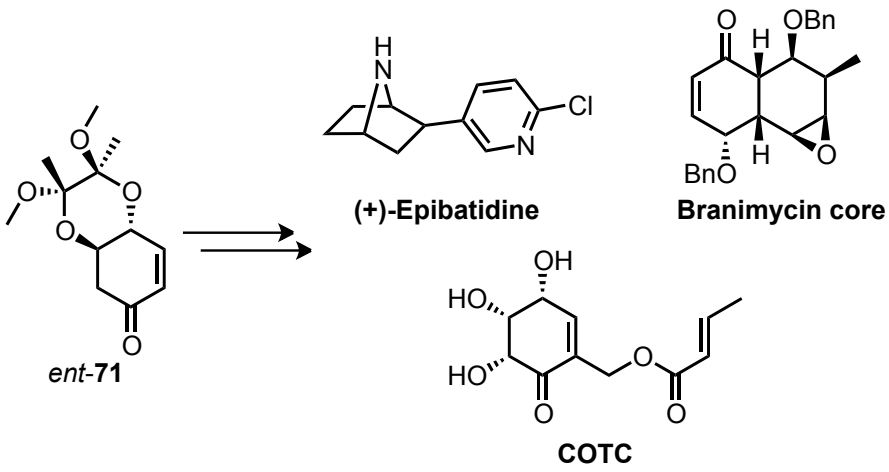


Figure 2.3: *Conformational analysis of enone ent-**71***

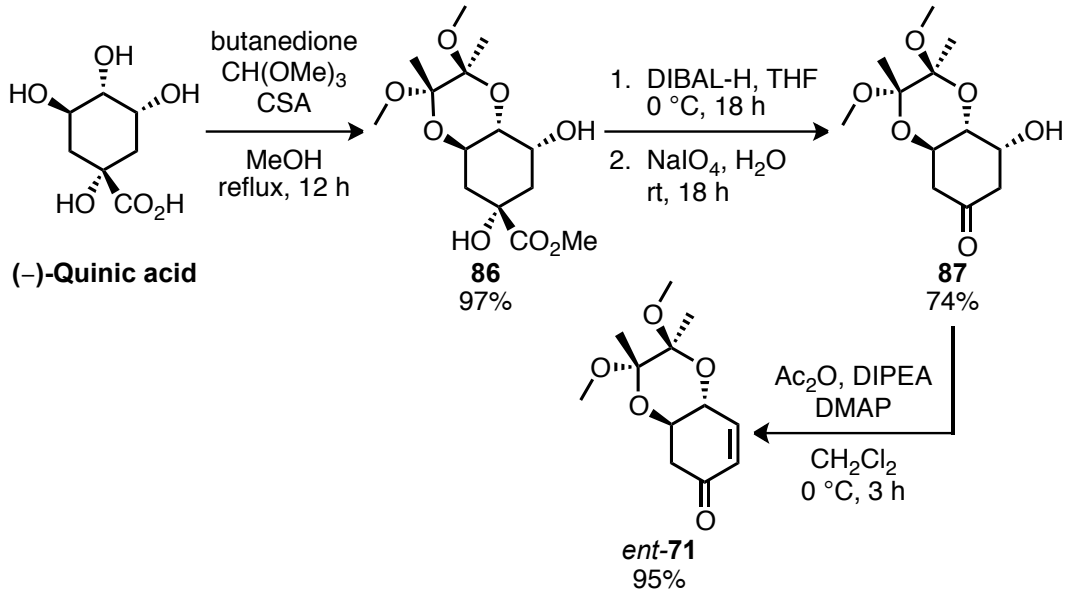
Enone *ent*-**71** has been used in many previous synthetic efforts (Scheme 2.1), including studies by Maycock towards (+)-epibatidine *via* a Stille coupling approach.[98] In addition, Enev and co-workers used enone *ent*-**71** in studies toward

the core of branimycin[99] while Whitehead's group used enone *ent*-**71** to synthesise the anti-tumour lead COTC.[100]



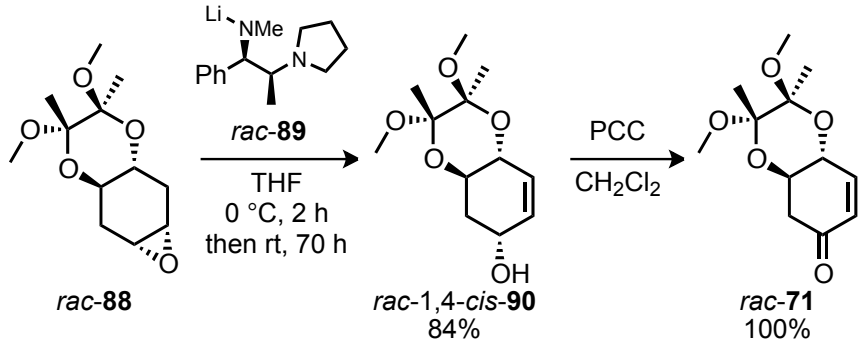
Scheme 2.1: *Previous syntheses utilising enone ent-71*

As previously highlighted, there has been no reported synthesis of **71** in the desired enantiomeric series. However, the synthesis of *ent*-**71** was reported by Maycock *et al.* in 2001[98] and a route to the racemic enone *rac*-**71** was described by the O'Brien group in 2000.[101] The procedure used by Maycock *et al.* (Scheme 2.2), developed from a general route by Brükner,[102] uses a chiral pool starting material, (–)-quinic acid. Their first step was the BDA protection of the *trans*-diol of (–)-quinic acid and methyl ester formation to give ester **86**. Reduction of the ester group and periodate cleavage of the subsequent diol gave hydroxy enone **87**. An elimination reaction then gave enone *ent*-**71**.



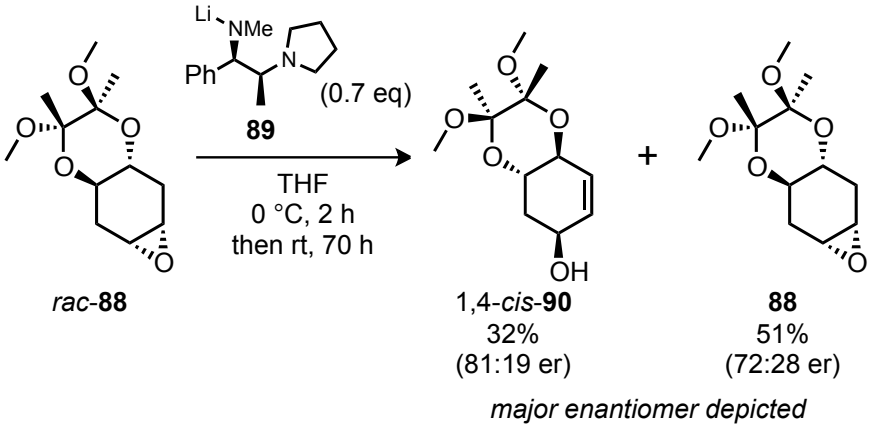
Scheme 2.2: *Route to enone ent-71*

The O'Brien group's route to enone *rac*-**71** started from C_2 symmetric and racemic epoxide *rac*-**88** (derived from 1,4-cylcohexadiene) (Scheme 2.3). These studies were focused on the use of lithium amide bases for diastereoselective rearrangements of epoxides. However, use of a racemic lithium amide base *rac*-**89** gave a route to racemic enone *rac*-**71**. Treating racemic epoxide *rac*-**88** with a racemic lithium amide base *rac*-**89** resulted in allylic alcohol *rac*-1,4-*cis*-**90** that was then oxidised to give enone *rac*-**71**.



Scheme 2.3: *O'Brien's route to enone intermediate rac-71*

Within this publication, the possibility of accessing the desired enone enantiomer **71** was described *via* the use of an enantiopure lithium amide base **89** in a kinetic resolution process (Scheme 2.4). Treating racemic epoxide *rac*-**88** with a single enantiomer of lithium amide base **89** gave enantioenriched allylic alcohol **90** (81:19 er). The starting epoxide **88** was also recovered enantioenriched (72:28 er). Although allylic alcohol **90** was not oxidised to the desired enone **71**, the precedent is evident and so opens up a possible synthetic route to enone **71** with the required configuration.



Scheme 2.4: *O'Brien's kinetic resolution route to allylic alcohol 1,4-cis-**90***

The necessity for a robust and scalable route to the desired enantiomer of enone **71** is restricted by the lack of (+)-quinic acid in nature. Many synthetically or biologically important compounds can be derived from chiral pool starting materials.[42,103] A significant challenge for synthetic chemists is when the desired enantiomeric series is not available from the chiral pool. As examples, proline and carvone are chiral pool starting materials that are available in both enantiomeric series while quinic acid is available in only one series (Figure 2.4).

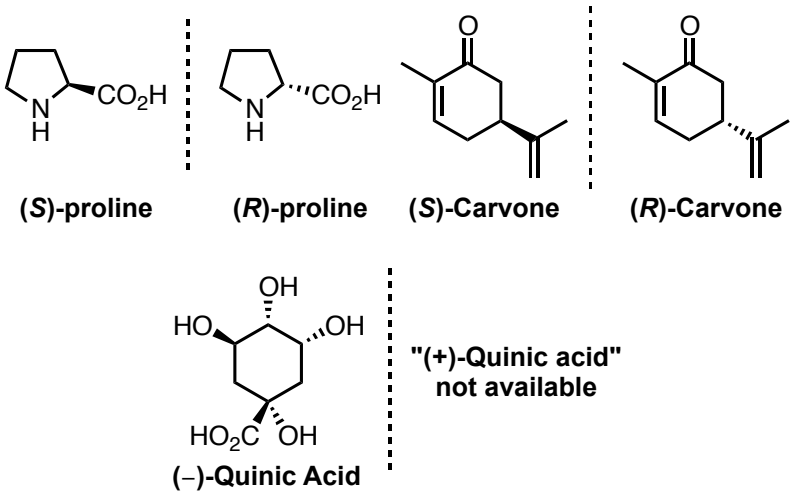


Figure 2.4: *Chiral pool starting materials and the availability of both enantiomers*

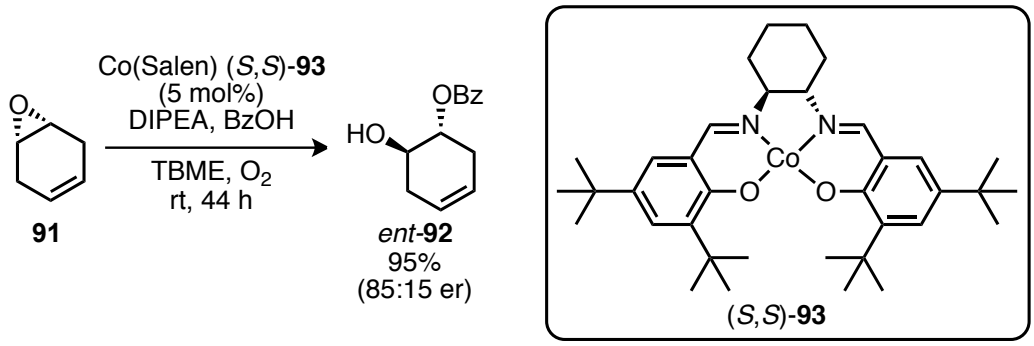
We therefore needed to develop a route to enone **71**. The requirements for such a route were as follows:

1. *Concise*: as with any synthetic route its brevity not only adds to the elegance of any procedure but also the economy. This is particularly important for our purposes as enone **71** is to form a crucial starting material in a convergent route to samaderine C.
2. *Asymmetry introduced early*: this can be achieved most readily by the use of a chiral pool starting material which removes the need for an enantiodetermining step. However, we identified early on that this was not the most viable method for our purposes. We therefore needed our enantiodetermining step to be as early in the route as feasible in order to minimise waste of material and reagents in the preceding steps.
3. *Gives a single enantiomer*: Whatever the chosen method of enantioinduction, we wanted to synthesise a single enantiomer. A single

enantiomer could be achieved by using a recrystallisation step but this would require solid material for successful results.

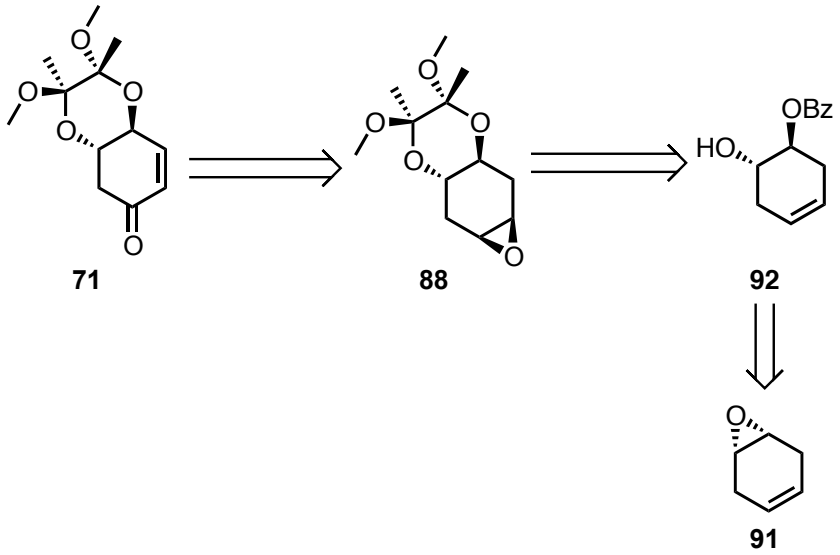
4. *Scalable*: As enone **71** is to be a starting material we wanted to be able to achieve multi-gram quantities.
5. *Economical*: Chemistry is not immune to the global economic climate. We therefore desired a route that would minimise the use of expensive reagents or catalysts (and, where possible, they should be recoverable and recyclable).

With these goals in mind we identified that the general route used by the O'Brien group was a suitable backbone for our synthesis of enone **71** with the requisite configuration. However, we wished to move the enantiodetermining step earlier in the synthesis. We therefore considered incorporating a desymmetrisation reaction published by Jacobsen *et al.* in 1997.[104] The Jacobsen group reported taking *meso*-epoxide **91** and treating it with cobalt catalyst (*S*,*S*)-**93** in the presence of benzoic acid and DIPEA base under an oxygen atmosphere. This gave enantioenriched hydroxy benzoate **92** in excellent yield (85:15 er) (Scheme 2.5).



Scheme 2.5: *Jacobsen's desymmetrisation reaction to give hydroxy benzoate **92***

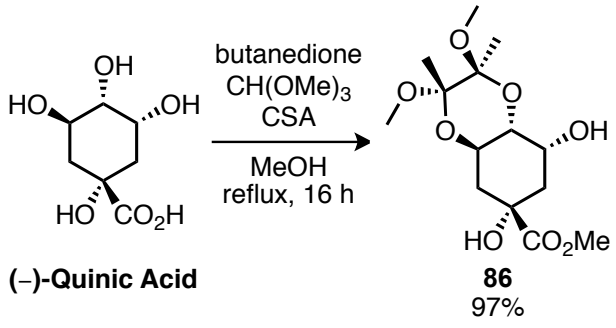
With Jacobsen's desymmetrisation chemistry in mind, Scheme 2.6 outlines a proposed retrosynthetic approach to enone **71**. Synthesis of enone **71** would be achieved from epoxide **88** where the epoxide rearrangement reaction could be carried out using LDA. Epoxide **88** would be generated from hydroxy benzoate **92**, which is the product of the Jacobsen desymmetrisation of *meso*-epoxide **91** using benzoic acid in the presence of a chiral Co-salen catalyst. Ultimately, this became our planned route to enone **71** in the desired enantiomeric series.



Scheme 2.6: *Retrosynthesis of enone **71** incorporating the Jacobsen's desymmetrisation reaction*

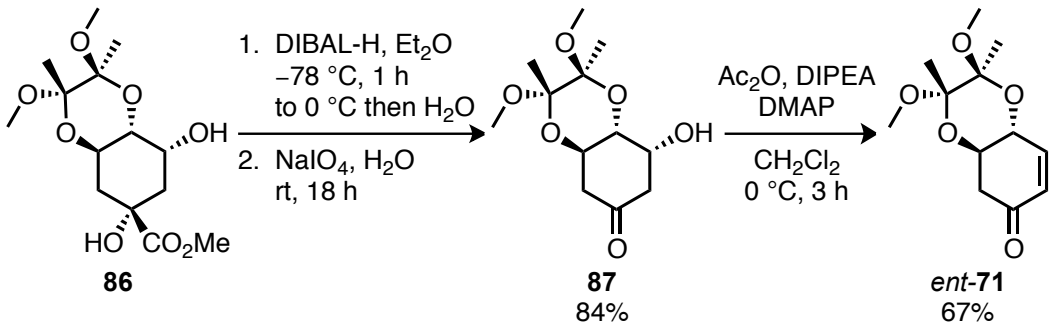
2.1.2 Synthesis of (−)-Quinic Acid Derived Bicyclic Cyclohexanone

The methodology development described in subsequent chapters was undertaken in the "wrong" enantiomeric series using (–)-quinic acid derived enone *ent*-**71**. Starting from (–)-quinic acid made the route synthetically and commercially attractive for the purposes of our model studies. We therefore initiated our studies by preparing enone *ent*-**71** from (–)-quinic acid using Maycock's route.[98] The BDA protecting group was installed onto (–)-quinic acid along with esterification in a single step using trimethylorthoformate, butanedione and CSA in MeOH at reflux to give protected diacetal **86** in 97% yield (Scheme 2.7).



Scheme 2.7: *Installation of the diacetal protecting group*

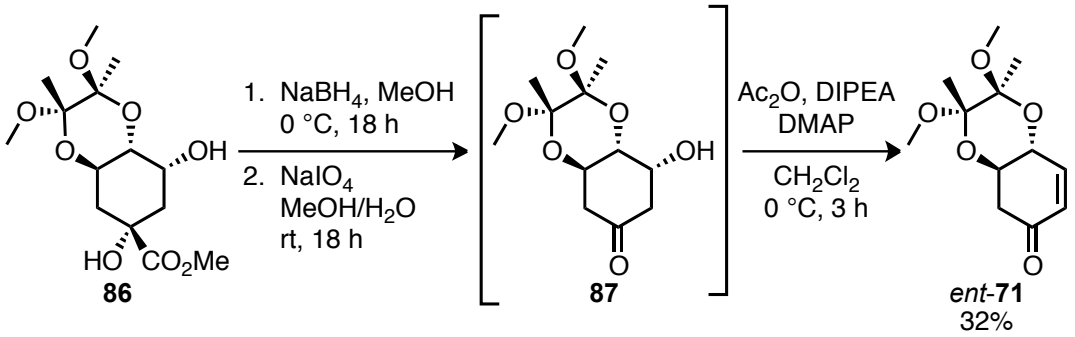
Initial efforts trialled the use of DIBAL-H as a reducing agent for the conversion of the hydroxy ester moiety into an alcohol. Subsequent cleavage using sodium periodate gave hydroxy ketone **87** (Scheme 2.8). It was found that an aqueous quench of the reduction step resulted in a viscous gel containing aluminium salts. This gel required further extraction with water and then diol cleavage gave hydroxy ketone **87** in 84% yield over the two steps. Although the yield was high, it was felt that on scale-up this extraction process would be laborious and potentially problematic. Rochelle's salt is a widely employed method for breaking up aluminium-based emulsions.[105] This salt was incorporated into the work-up procedure for the DIBAL-H reduction step but, although the aluminium-based gum was dispersed, the extraction process was made more difficult because of the formation of an emulsion between the organic and aqueous layers. Ultimately, hydroxy ketone **87** was isolated in a disappointing 44% yield. The elimination to give enone *ent*-**71** was facile and proceeded with moderate yield using an acylation-elimination sequence (Scheme 2.8). Treatment of hydroxy ketone **87** with acetic anhydride and base gave enone *ent*-**71** in 67% yield (Scheme 2.8). Enone *ent*-**71** was therefore accessed readily from (–)-quinic acid in four steps with 55% overall yield. However, the DIBAL-H reduction was anticipated to be problematic on scale-up and an alternative reduction method was sought.



Scheme 2.8: *Initial synthesis of enone ent-**71**.*

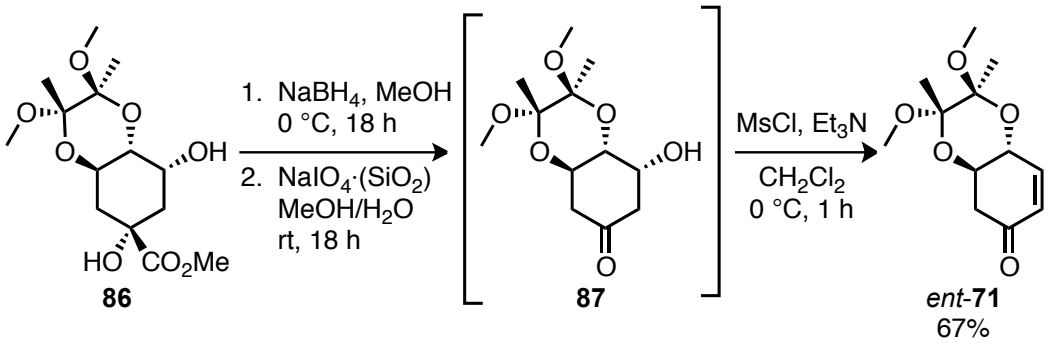
Previous syntheses have shown that the α-hydroxy ester functionality in **86** was sufficiently activated to be reduced using $NaBH_4$.[100,106] Use of this reduction methodology would avoid the problematic DIBAL-H reduction as well as allowing a more telescoped synthetic sequence. This type of pathway to enone *ent*-**71** was previously published in 2004 by the O'Brien group with a 90% yield over the three steps required.[106] Our initial effort using $NaBH_4$ is shown in Scheme 2.9. Reduction

of hydroxy ester **86** with $NaBH_4$ in MeOH at 0 °C and subsequent diol cleavage using sodium periodate and a telescoped elimination gave enone *ent*-**71**. The overall yield for the three steps (32%) was disappointing and fell short of the yield previously published.



Scheme 2.9: *Telescoped $NaBH_4$ reduction process to enone ent-71*

Another method published at the same time as these studies attracted our attention.[107] The method involved quenching the $NaBH_4$ reduction and then evaporating the mixed organic and aqueous solvents. Successive washes of the resultant solid gave a crude diol on evaporation of washings. Cleavage of the crude diol using silica-supported sodium periodate gave crude hydroxy ketone **87** which, under modified elimination conditions, gave an improved overall yield of enone *ent*-**71** (67%) in a more telescoped approach (Scheme 2.10). This route proved to be the most reproducible in our hands and was consequently scaled-up and used to prepare multi-gram quantities of enone *ent*-**71**. For example, 3.13 g of *ent*-**71** was prepared in one batch. Enone *ent*-**71** was ultimately used in most of our methodology development studies as it was so easy to prepare.

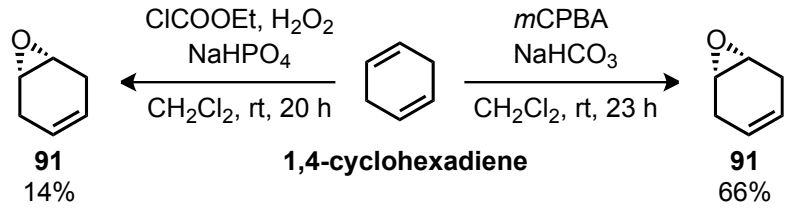


Scheme 2.10: *Optimised route to enone ent-71*

2.1.3 Synthesis of Racemic Bicyclic Cyclohexenone

We then investigated the synthesis of enone **71** as a racemate using a route based on that previously used by the O'Brien group during their chiral lithium amide base studies.[101] This route is essentially the same as that designed for the asymmetric synthesis of enone **71** but would access racemic diol *rac*-**71** instead of the desymmetrised enantioenriched material. We felt that initially working in the racemic sense would give experience of this chemistry whilst using less precious starting materials.

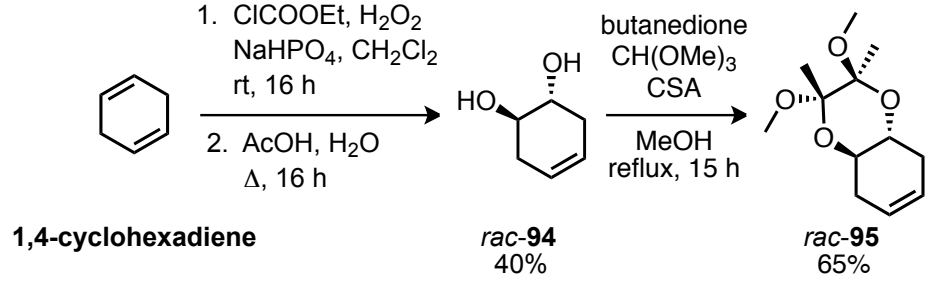
Epoxide **91** has been synthesised previously by epoxidation of 1,4-cyclohexadiene using a peracid formed *in situ* from ethyl chloroformate and hydrogen peroxide.[108] Our efforts to reproduce this method were inhibited by purification problems. Epoxide **91** can be distilled at 36 °C and 15 mbar of pressure but this led to the co-distillation of side-products. Pure epoxide **91** could only be achieved through careful fractional distillation using a Vigreux column but in a disappointing 14% yield (Scheme 2.11). A more recent report for the synthesis of epoxide **91** employed *m*CPBA as the oxidant.[109] Crude epoxide from this reaction was distilled with standard apparatus at 46 °C and under 409 mbar of pressure to give *meso*-epoxide **91** in a dramatically improved 66% yield (Scheme 2.11).



Scheme 2.11: *Epoxidation of 1,4-cyclohexadiene to meso-epoxide **91***

Isolation problems could also be easily remedied by telescoping the epoxide formation with the subsequent acid-catalysed epoxide opening. After epoxidation using ethyl chloroformate and hydrogen peroxide, the crude epoxide was heated under reflux in water and acetic acid. Continuous extraction by refluxing CH_2Cl_2 through the aqueous hydrolysis mixture using a heavier-than-water liquid-liquid extraction set-up gave a 40% yield of diol *rac*-**94**. Diol *rac*-**94** was then BDA-

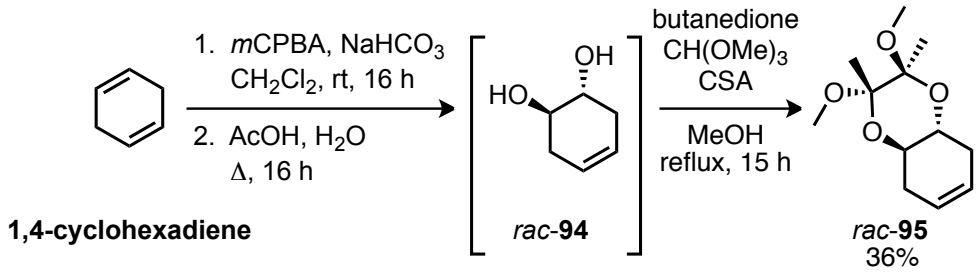
protected under standard conditions to furnish BDA-protected cyclohexene diol *rac*-**95** in 65% yield (Scheme 2.12).



Scheme 2.12: *Telescoped epoxidation/epoxide opening route to BDA protected cyclohexene rac-**95***

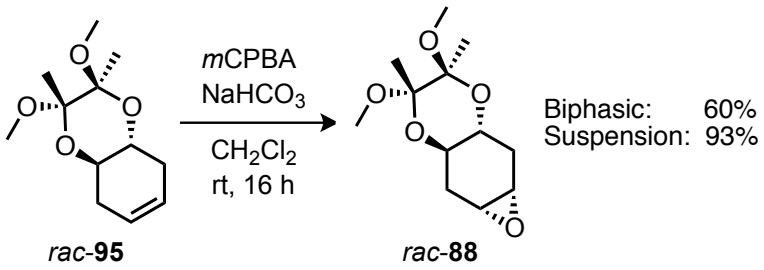
A major drawback of this telescoped method was the need for a continuous extraction. This necessity undoubtedly accounted for the relatively low yield despite the clean conversion of the 1,4-cyclohexadiene into diol *rac*-**96** observed by analysis of the ^{1}H NMR spectrum of the crude product. It was hoped that avoiding a continuous liquid-liquid extraction might improve the yield.

Switching to the preferred *m*CPBA epoxidation of 1,4-cyclohexadiene followed by hydrolysis using acetic acid/water produced an aqueous reaction mixture. The solvent was removed under reduced pressure and the resulting colourless solid was successively washed with ether. After the organic solvent was removed from the washings, diol *rac*-**96** was obtained as a colourless solid. Without further purification, diol *rac*-**96** was BDA-protected to deliver *ca*. 10 g of BDA-protected cyclohexene diol *rac*-**95** in 36% yield over this sequence (Scheme 2.13).



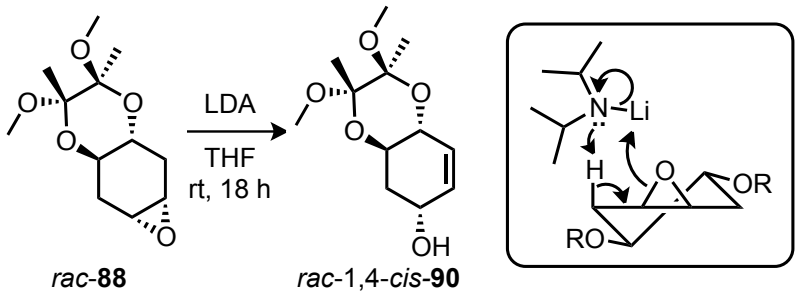
Scheme 2.13: *mCPBA/epoxide opening telescoped route to BDA protected cyclohexene rac-**95***

Protected diol *rac*-**95** was then treated with *m*CPBA to give epoxide *rac*-**88** (Scheme 2.14). Initial attempts at this transformation followed a biphasic procedure. Stirring *rac*-**95** and *m*CPBA in CH_2Cl_2 with $NaHCO_{3(aq)}$ gave consistently poor yields (60%). However, altering the conditions to use of solid $NaHCO_3$ as a suspension in CH_2Cl_2 improved the yield to 93%.



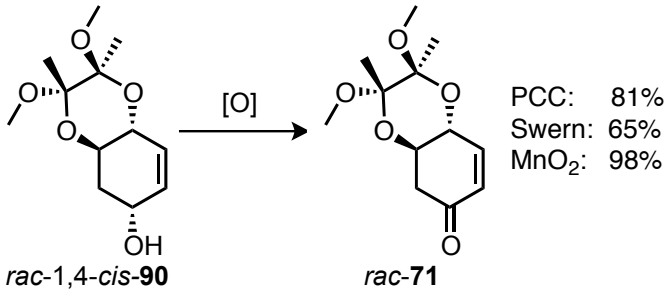
Scheme 2.14: *Epoxidation of BDA protected diol* ***97***

The subsequent epoxide rearrangement reaction of *rac*-**88** was induced using LDA. Reaction of epoxide *rac*-**88** with LDA in THF gave allylic alcohol *rac*-1,4-*cis*-**90** in 55% yield (Scheme 2.15). This reaction proceeded to give only the depicted diastereomer. The rearrangement of epoxides using lithium amide bases has been well-studied[110-113] including the more recent use of chiral lithium amides.[101,114-116] Rickborn first established that such processes are stereospecific *cis*-β-eliminations, proceeding *via* the mechanism included in Scheme 2.15.[117] A six-membered transition state is favoured in which the *pseudo*-axial β-hydrogen that is *syn* to the epoxide oxygen is abstracted in a cyclic transition state. In our system, the rearrangement of epoxide *rac*-**88** therefore affords the diastereomer *rac*-1,4-*cis*-**90** as a single product as the BDA group prevents a ring-flip to place the other β-hydrogen in the required *pseudo*-axial arrangement.



Scheme 2.15: *Stereospecific rearrangement of epoxide rac-***97**

The final step in the sequence was oxidation of the allylic alcohol *rac*-1,4-*cis*-**90** to the enone *rac*-**71** (Scheme 2.16). Following a literature procedure, allylic alcohol *rac*-1,4-*cis*-**90** was oxidised using PCC to give enone *rac*-**71** in 81% yield. Changing to a Swern oxidation resulted in a lower 65% yield. Our best oxidation conditions proved to be manganese dioxide. Stirring allylic alcohol *rac*-1,4-*cis*-**90** and manganese dioxide as a suspension in CH_2Cl_2 at rt gave enone *rac*-**71** in 98% yield.



Scheme 2.16: *Oxidation of allylic alcohol rac-1,4-cis-**90** to enone ent-**71***

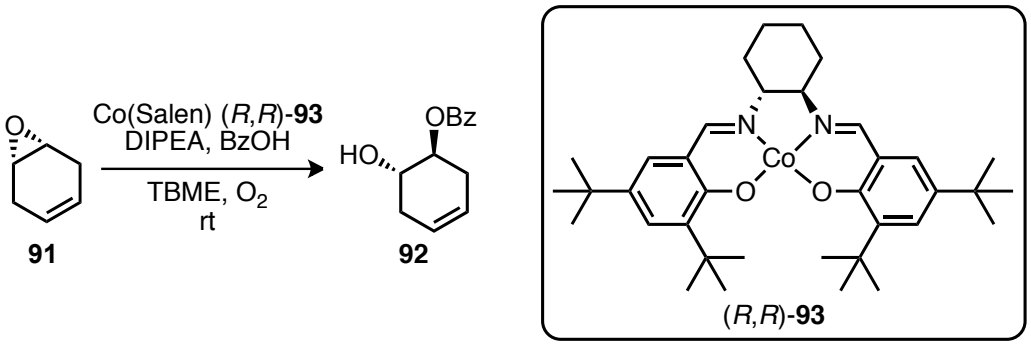
Using this approach, racemic enone *rac*-**71** was thus synthesised on a multi-gram scale. The overall yield for the sequence was 18% over the four steps.

*2.1.4 Synthesis of Enone **71***

The work in the racemic series then provided the perfect platform in order to access enone **71** in the desired enantiomeric series. An enantioselective synthesis of diol **96** would allow a route to enone **71** (see Scheme 2.6). Diol **94** could be formed *via* the desymmetrisation of *meso*-epoxide **91**, which itself could be readily obtained from commercially available 1,4-cyclohexadiene as previously shown.

The desymmetrisation of *meso*-epoxide **91** by a cobalt salen catalyst using benzoic acid to give an enantioenriched hydroxy-benzoate is known.[104] Following the procedure outlined by the Jacobsen group, cobalt salen catalyst (*R*,*R*)-**93** was preactivated by stirring under an oxygen atmosphere. *meso*-Epoxide **91** was then stirred with the actived catalyst in the presence of benzoic acid and DIPEA. This resulted in benzoate **92** (Scheme 2.17). We have found this reaction to not only be amenable to scale-up but also to remain a viable process even when lowering the

catalyst loadings. The results of a study on catalyst loading and reaction time are shown in Table 2.1.



Scheme 2.17: *Desymmetrisation of meso-epoxide **91** to give enantioenriched benzoate **92***

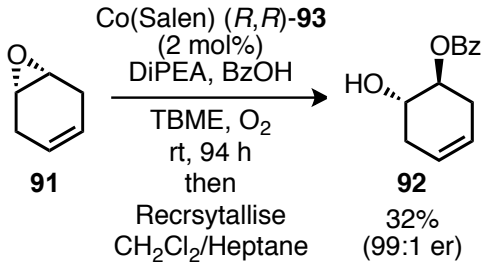
Entry	Mol% (*R*,*R*)-**94**	Time (h)	Yield[a] (%)	er[b]
1	5	53	74	83:17
2	2.5	90	79	85:15
3	2	94	85	85:15
4	1	120	70	79:21
5	0	140	0	N/A

[a]Yield after purification by chromatography. [b]Enantiomer ratio (er) determined by CSP-HPLC on a Chiralpak AS column; major enantiomer is (*S*,*S*)-**93**.

Table 2.1: *Desymmetrisation of meso-epoxide **91** to give enantioenriched benzoate **92***

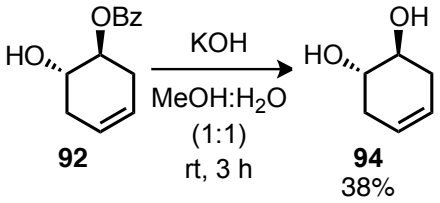
As shown in Table 2.1, lowering the loading of the catalyst did not appear to impact drastically on either the yield or the enantioselectivity. Loadings as low as 1 mol% (entry 4) were tolerated but required extended reaction times (120 h). The flexibility of this reaction appears to be due to the high catalyst turnover number and the lack of background reactivity. The lack of reactivity was proven as there was no reaction in the absence of catalyst (entry 5). We found the optimised reaction conditions to be a catalyst loading of 2 mol% (entry 3). At this loading, the reaction proceeded to give an 80% yield of hydroxy benzoate **92** in 85:15 er after 94 h.

From the outset, the goal was the synthesis of a single enantiomer of enone **71**. We anticipated that recrystallisation of hydroxy benzoate **92** could be possible and would give highly enantioenriched hydroxy benzoate **92**. The recrystallisation of such an early stage intermediate would ensure the maximum efficiency of our route. Fortunately, suitable conditions were found (Scheme 2.18). Recrystallisation of **92** from hot CH_2Cl_2 and heptane gave hydroxy benzoate **92** of 99:1 er by CSP-HPLC in 32% overall yield from *meso*-epoxide **92**. Accessing enantiopure material allows the possibility of seeding future recrystallisation procedures although this was not attempted during the course of these studies.



Scheme 2.18: *Desymmetrisation of meso-epoxide **91** and recrystallisation to give benzoate **92***

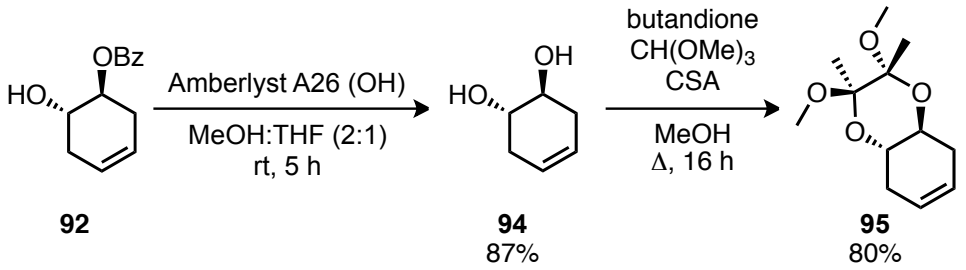
We had previously postulated that the lower isolated yields of diol *rac*-**96** were due to the difficulty in its isolation due to its hydrophilicity. We experienced similar problems on saponification of hydroxy benzoate **92** to diol **94**. Under hydroxide cleavage conditions, only a 38% yield of **94** was obtained even after continuous extraction overnight (Scheme 2.19).



Scheme 2.19: *Saponification of benzoate **92** under hydroxide conditions*

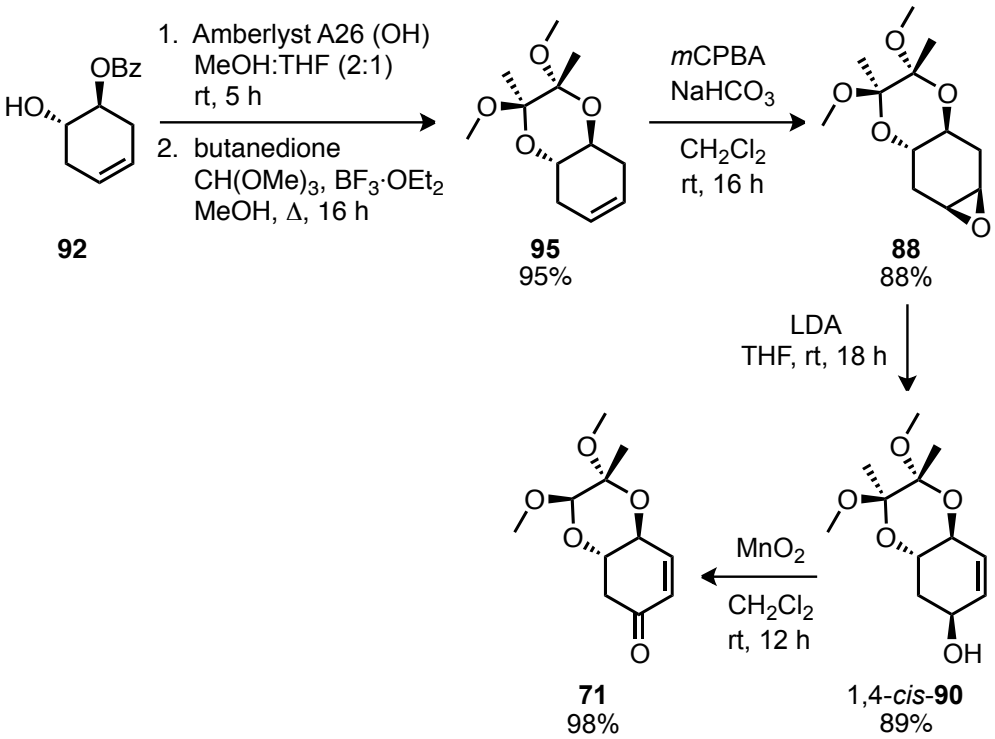
We found, in an optimised procedure, that use of the polymer-supported reagent Amberlyst A26 (OH) hydrolysed the benzoate and removed the requirement for an aqueous work-up (Scheme 2.20). Stirring hydroxy benzoate **92** with the Amberlyst beads in a MeOH/THF mixed solvent system cleaved the benzoate. The solvent was

removed under reduced pressure to give diol **94** in 87% yield. The free diol **94** was then successfully protected to give BDA-protected diol **95** in 80% yield.



Scheme 2.20: *Saponification of benzoate **93** using Amberlyst A26 (OH) reagent*

The saponification and BDA protection reactions were then telescoped to give BDA protected diol **95** in 95% yield from hydroxy benzoate **92** (Scheme 2.21). From this point, the route followed the procedures used in the synthesis of racemic enone *rac*-**71**. Epoxidation of **95** using *m*CPBA furnished epoxide **88** in 88% yield. Epoxide **88** was converted regiospecifically into allylic alcohol 1,4-*cis*-**90** (89% yield) on treatment with LDA. Finally, oxidation to the desired enone **71** was achieved using the manganese dioxide conditions in 98% yield. The expected absolute configuration was proven by comparison of its optical rotation value ($[\alpha]_D$ –72.0 (*c* 1.0 in $CHCl_3$)) with that of *ent*-**71** prepared from (−)-quinic acid ($[\alpha]_D$ +60.4 (*c* 0.5 in $CHCl_3$)).



Scheme 2.21: *Application of developed chemistry to access enone 71*

In summary we, attained enone **71** in six isolation steps and 14% overall yield from a commercial starting material. This is the first route to enone **71** in this configuration and has been published.[118] During the course of our route, we successfully addressed the five main goals of this synthesis:

1. *Concise*: the route is only six isolation steps long.
2. *Asymmetry introduced early*: our enantiodetermining reaction is the second step of the reaction.
3. *Gives a single enantiomer*: a recrystallisation of an early intermediate minimised waste whilst giving access to a single enantiomer.
4. *Scalable*: enone **71** was achieved on a gram-scale but a larger scale synthesis should also be possible.
5. *Economical*: by telescoping a number of steps we minimised the need for purification. The cobalt catalyst (*R*,*R*)-**93** is recoverable from the desymmetrisation reaction and the desymmetrisation was shown to be reliable with catalyst loadings as low as 1 mol%.

2.2 Diastereoselective Reactions of a (−)-Quinic Acid Derived Enone

2.2.1 Introduction to the (−)-Quinic Acid Derived Enone

The chiral pool provides a rich and diverse starting point for many synthetic endeavours. As discussed in section 2.1, enone *ent*-**71** has proven an invaluable tool in the synthesis of natural products and biologically active compounds. Enone *ent*-**71** has proved a versatile intermediate due to a range of possible reactivity despite only having a single cyclohexane backbone. Previous examples had shown the ability to functionalise the enone in the α-position[98,119] as well as formation of a Diels-Alder adduct.[120] Functionalisation of enone *ent*-**71** using enolate chemistry also exists in the literature.[100,107,120] We began our studies using enone *ent*-**71** by investigating the expansion of its reactivity profile, with a long-term view towards the total synthesis of samaderine C using this enone (Figure 2.5).

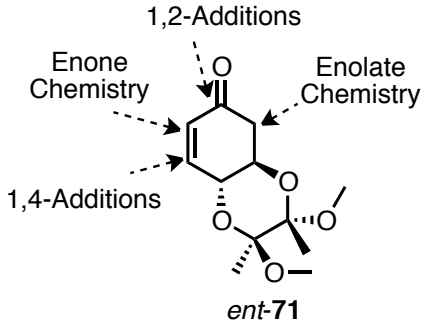


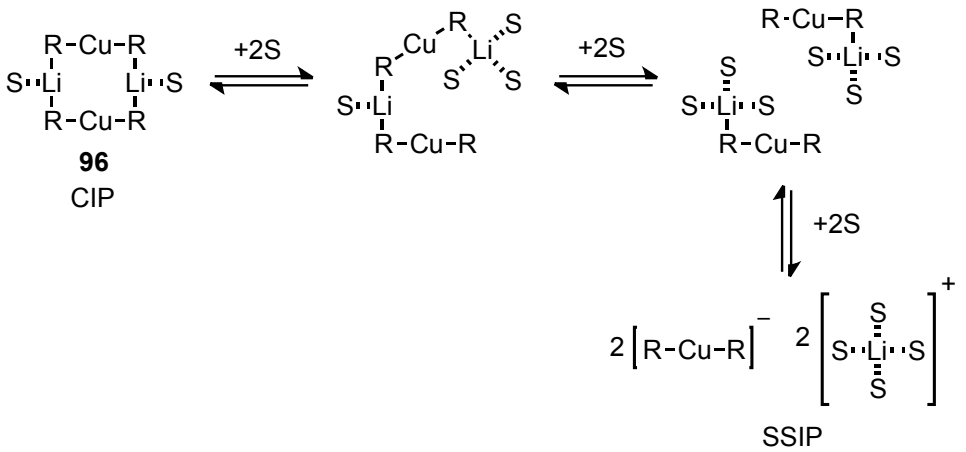
Figure 2.5: *Possible sites of reactivity of enone ent-71*

Enone **71** provides a structurally intriguing case study for investigating the stereoselective reactions of a conformationally locked system. The following section discusses the stereoselective reactions of enone *ent*-**71** and the synthesis of some small cyclohexanone natural products. Although a few examples were known, we felt that 1,2-additions to the ketone functionality in enone *ent*-**71** deserved further study. No examples of a 1,4-addition to enone *ent*-**71** exist and so we also set about using enone *ent*-**71** in 1,4-addition chemistry.[121-123] Since we planned to use a double 1,4-addition strategy to access the AB-rings of samaderine C, our initial efforts focused on using organocuprates and copper-catalysed Grignard additions for 1,4-addition to enone *ent*-**71**.

2.2.2 1,4-Additions of Diorganocuprates to a (−)-Quinic Acid Derived Enone

Organocopper chemistry has a long and successful history[124,125] and 1,4-additions of organocuprates (R_2CuLi) has been an invaluable tool to synthetic chemists.[126,127] The chemoselectivity of additions to enones by alkyl lithiums (1,2-addition) in comparison to organocuprates (1,4-additions) is often rationalised by a hard *versus* soft rationale. In reality, the mechanism of the 1,4-addition of an organocuprate to an enone is much more involved than a "soft" alkyl nucleophile engaging the enone moiety in a Michael-addition fashion. Since organocopper chemistry is key to our projected samaderine C synthesis, some of the important factors are presented here.

The reactivity of organocuprates can be dependent on the stoichiometry between the organometallic reagent and the copper salt. For our purposes, we used the most reactive cuprate species, diorganocuprate $R_2CuLi{\cdot}LiX$, formed from two equivalents of alkyl lithium and a copper salt. The homocuprate species $R_2CuLi{\cdot}LiX$ has a linear C-Cu-C structure with a metal counter ion. Theoretical studies suggest that such species exist as a bimetallic dimer **96** but higher order complexation is anticipated (Scheme 2.22).[128-133] This arrangement is supported by several crystal structures.[134,135]



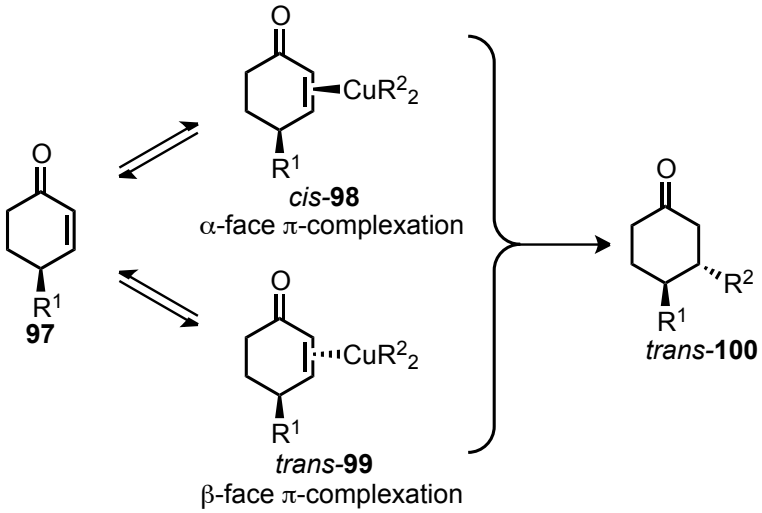
Scheme 2.22: *CIP and SSIP structures observed*

However, the solution structure of organocuprates has been difficult to establish. It is thought that solvent molecules can break up the organometallic clusters into fragments of various sizes and stoichiometry. The parent organometallic clusters are often referred to as contact ion pairs (CIP) and are thought to be the most reactive

form (Scheme 2.22).[136-138] The solvated fragments are known as solvent separated ion pairs (SSIP) and can have a range of reactivity and structural arrangements. In the reaction system there is probably a dynamic equilibrium between CIPs and SSIPs with the equilibrium dictated by a number of factors (additives, solvent, copper salt).

The range of reactivity and structural characteristics of so many organocuprate forms has made it difficult to determine the mechanism of 1,4-additions of organocuprates. The overall mechanism has only recently become more rigorously established and was the accumulation of a vast amount of both experimental and theoretical investigations. The earliest kinetic studies showed a first order dependence on the enone concentration but a more complex relationship to the cuprate dimer.[139] Later kinetic experiments at low temperature (−60 °C) and with an excess of cuprate showed that there was also a first order dependence on the cuprate species.[140]

The kinetic results also suggested the reversible formation of a cuprate-enone complex. The nature of this complexation is understood to be a η^2 π-complex formed through the interaction of the R_2Cu^- HOMO ($3d_{xz}$) and the enone LUMO (π*). This theory is supported by the observed weakening of the enone C=C bond.[141-144] Subsequently, rapid injection NMR spectroscopic studies of a substituted enone **97** revealed the existence two types of η^2 π-complex.[145-147] These observed complexes are attributed to an α-face complex *cis*-**98** and a β-face *trans*-**99** complex (Scheme 2.23). Interestingly, product analysis indicated the exclusive formation of 1,4-addition product *trans*-**100** arising from the β-face complex *trans*-**99**. This evidence supports the reversibility of the η^2 π-complexation.



Scheme 2.23: *π-Complexation in the reaction mechanism*

The involvement of an η^1 β-cuprio(III)enolate species had long been speculated.[148,149] Kinetic isotope experiments involving ^{13}C labelling of the β-enone terminus and the α-carbon of a cuprate nucleophile indicated that the rate-determining step was probably a reductive elimination-type process of an η^1 β-cuprio(III)enolate species.[150] Its existence was recently established by NMR spectroscopy by the observation of η^1 β-cuprio(III)enolate species **101** (Figure 2.6).[145,147]

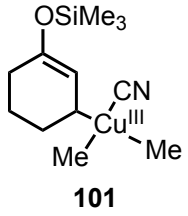
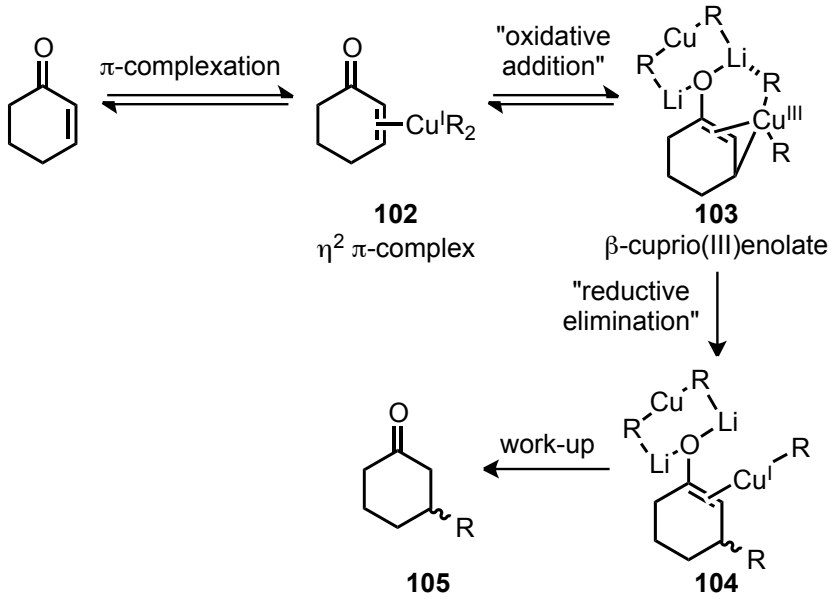


Figure 2.6: *The β-cuprio(III)enolate species **101** observed by NMR spectroscopy*

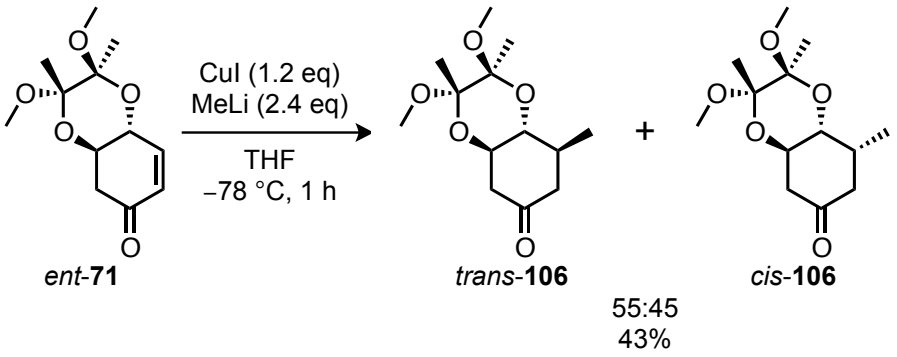
Based on all this previous work, the current understanding of the mechanism of 1,4-addition of cuprates to enones is shown in Scheme 2.24. A π-complexation process gives copper-enone η^2 π-complex **102**. Formation of a β-cuprio(III)enolate species **103** then occurs through an oxidative addition-type process (two SET process had been postulated[151-153] but this has since been refuted[154-157]). A reductive elimination-type process (the rate-determining step) gives an enolate **104** that on work-up collapses to give the 1,4-addition product **105**.



Scheme 2.24: *Proposed cuprate 1,4-addition mechanism (solvation omitted for clarity)*

We therefore began our 1,4-addition studies with the reaction of simple organocuprates (R_2CuLi) with enone *ent*-**71**. Our efforts were always focused on the delivery of a methyl cuprate in a *cis*-orientation to the adjacent CHO group as this would give the desired axial C-10 methyl substituent for the planned synthesis of samaderine C. It was important to ascertain the diastereoselectivity of the 1,4-addition of cuprates to enone *ent*-**71** before the more challenging double 1,4-addition strategy was explored.

The preferred solvent for cuprate reaction is Et_2O over THF. Cuprate reactions in THF causes the formation of less reactive SSIPs. However, enone *ent*-**71** was not sufficiently soluble in Et_2O and so necessitated the use of THF. Therefore, the cuprate species was preformed using 1.2 eq. of CuI and 2.4 eq. of MeLi in THF at –78 °C. Enone *ent*-**71** was then added as a THF solution. The result was an inseparable 55:45 mixture of diastereomeric β-substituted ketones *trans*-**106** and *cis*-**106** in 43% yield (Scheme 2.25). Compounds *trans*-**106** and *cis*-**106** are named based on the relative stereochemistry of the methyl group and the adjacent alkoxy group.



Scheme 2.25: *First methyl cuprate addition to enone ent-**71***

Using the ^{1}H NMR spectrum of the products, the magnitude of the ^{3}J coupling constant between H-3 and the adjacent CH proton (H-4) at the new stereogenic centre was used to assign the stereochemistry of *trans*-**106** and *cis*-**106** (Figure 2.7). This was facilitated by the conformation-locking BDA protecting group. A larger ^{3}J value indicated the *trans*-diaxial arrangement of the protons as found in *trans*-**106**. For *trans*-**106**, a ^{3}J value of 9.5 Hz was measured. The axial-equatorial ^{3}J coupling constant present in *cis*-**106** could not be measured because of overlapping of the diagnostic signals.

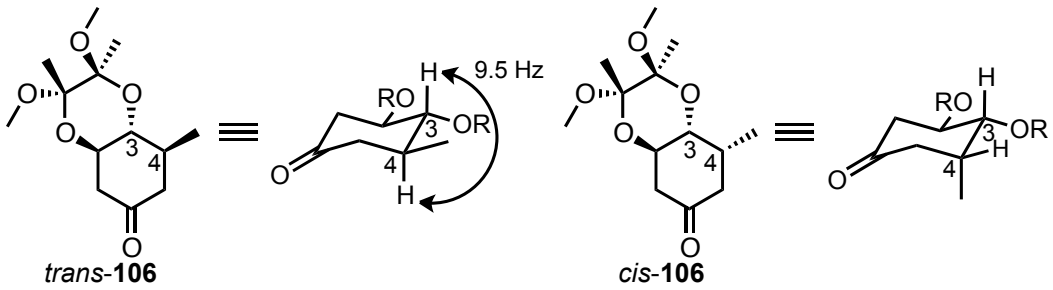


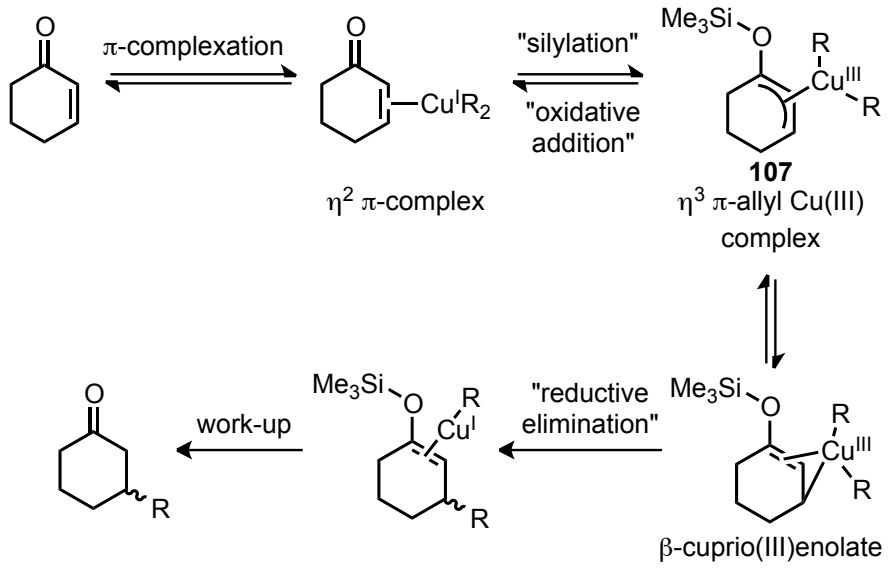
Figure 2.7: *Observed ^{3}J value and assignment of trans-**71** and cis-**71***

This reaction using a CuI-derived methyl cuprate was interesting but conditions were sought to give higher yield and diastereoselectivity. In particular, we studied the use of CuCN (including the mixing time for reacting the organolithium with CuCN) and the use of the additive Me_3SiCl. The reasons for selecting these variables are summarised below.

Numerous published examples have shown that copper salt optimisation is crucial.[158] In particular, the use of CuCN and the reactivity of cuprates derived from this salt led

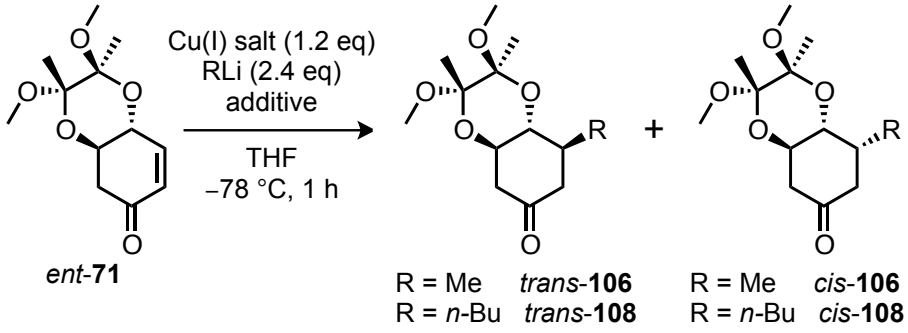
Lipshutz to postulate the existence of "higher order" cuprates ($R_2Cu(CN)Li_2$).[159,160] Lipshutz hypothesised that higher order cuprates possess a tricoordinate copper(I) centre in which the cyano ligand imparts a lowering of π-acidity in order to facilitate the unusual coordination state.[125] Later work disputed the structural attributes of cuprates derived from CuCN.[161] However, structural studies have shown the propensity of cyano-Gilman cuprates to form higher aggregate structures[138,162,163] while theoretical studies have indicated that in S_N2 alkylation reactions of cyano-Gilman cuprates the nitrile ligand facilitates formation of bridged complexes which have lower activation energies for displacement.[164] It has been suggested that the increased reactivity of cyano-Gilman cuprates in 1,4-additions could be derived from similarly lowered energy transition states.[161,165] The marked distinction in the reactivity and stereoselectivity observed for cyano-Gilman cuprates is irrefutable and highlights the importance of the copper salt counter ion. For this reason, we carried out a number of cuprate additions to enone *ent*-**71** using diorganocuprates derived from the CuCN salt.

In addition to the CuCN salt, we investigated the use of an additive to this reaction. Me_3SiCl has been previously shown to be significant in not only improving the rates and yields of cuprate addition reactions[166] but also affecting diastereoselectivity.[167,168] The mechanistic origin for this acceleration effect is not yet fully understood.[145,169-172] An experimental study revealed that the reaction involved the silylation of the copper-enone π-complex[145] (such as **107**) and kinetic isotope studies have shown this silylation to be crucial.[173,174] Recent NMR spectroscopy studies have shown the existence of a silylated η^3 π-allyl Cu(III) complex such as **107** when a silane is present in the reaction.[147] This result may shed some light on the mechanistic rationale behind the difference in Me_3SiCl promoted 1,4-additions of cuprates. A proposed mechanism is summarised in Scheme 2.26.



Scheme 2.26: *Proposed mechanism involving η^3 π-allyl Cu(III) complex **107***

The results for the addition of CuCN-derived methyl and *n*-butyl cuprates to enone *ent*-**71** are shown below in Scheme 2.27 and Table 2.2. The addition of both of these cuprates in the presence of the Me_3SiCl additive were also investigated.



Scheme 2.27: *Cuprate additions to enone ent-**71***

Entry	R	Cu(I) Salt	Additive	Product	Yield (%)[a]	dr (*trans:cis*)[b]
1	Me	CuI	None	**106**	43	55:45
2	Me	CuCN	None	**106**	70	60:40
3	*n*-Bu	CuCN	None	**108**	74	>99:1
4	Me	CuCN	Me_3SiCl[c]	**106**	96	>99:1
5	*n*-Bu	CuCN	Me_3SiCl[c]	**108**	98	>99:1

[a]Yield of product after chromatography [b]Ratio of trans- and cis-diastereomers by ^{1}H NMR spectroscopy after chromatography [c]TBAF desilylation after an aqueous work-up

Table 2.2: *Cuprate additions to enone ent-**71***

Both methyl cuprate and *n*-butyl cuprate addition to enone *ent*-**71** were studied. We found changing the salt from CuI to CuCN in the methyl cuprate reaction caused an increase in yield from 43% (entry 1) to 70% (entry 2). Using a CuCN derived *n*-butyl cuprate gave *n*-butyl β-substituted ketone *trans*-**108** as a single diastereomer in 74% yield (entry 3). As precedented in the literature, it was found that using Me_3SiCl resulted in drastic improvements in yield for both methyl cuprate (96%, entry 4) and *n*-butyl cuprate (98%, entry 5). Interestingly, the methyl cuprate addition in the presence of Me_3SiCl not only improved in yield but also the diastereoselectivity: *trans*-**106** was isolated as a single diastereomer (>99:1 dr).

The preferential formation of *trans*-**106** and *trans*-**108** as the major diastereomers can be rationalised through a steric clash leading to a facial preference during the π-complexation phase.[169,175-178] We propose that enone **71**'s lowest energy conformation will be a flattened half chair geometry as consistent with other conformationally locked cyclohexenones (Figure 2.8).[179] This conformation is the only available geometry available to enone *ent*-**71**. The BDA-group infers a strong *trans*-diequatorial diol requirement while the enone π-system will be planar to maximise π-orbital overlap. The sofa conformer resembles the envelope conformer adopted by five-membered rings and so has two distinct facial environments: a convex face and a concave face. π-Complexation to the convex face will be preferred on steric grounds and would subsequently lead to the *trans*-adducts, *trans*-**106** and *trans*-**108**, as the major products. The difference in diastereoselectivity between *n*-butyl cuprate and methyl cuprate can therefore be explained be an increased facial selectivity for the sterically larger *n*-butyl cuprate.

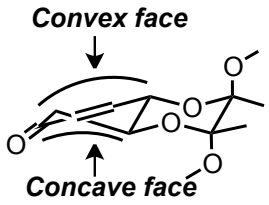


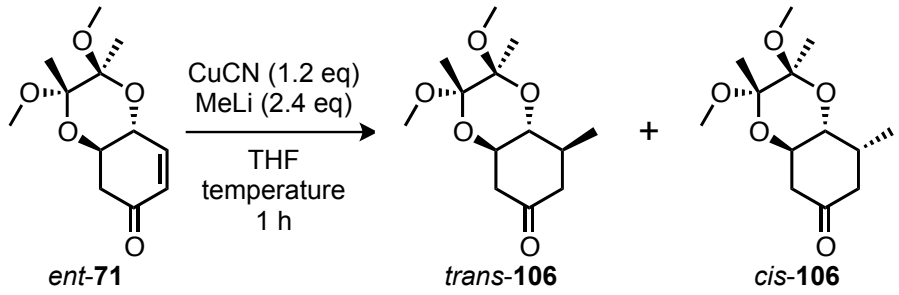
Figure 2.8: *Convex/concave faces of enone ent-**71***

Our explanation for the improved yield and diastereoselectivity in the presence of Me_3SiCl is as follows. The Me_3SiCl additive is known to be more than a simple trap

for the enolate formed post-addition (see Scheme 2.26) and so can be involved in a significant capacity to induce such a change in stereoselectivity.[161] It is plausible that the formation of the η^3 π-allyl Cu(III) complex (see Scheme 2.26) on the least hindered convex face acts as a kinetic trap preventing reversal of complexation and recoordination on the concave face.

The negative effects of THF as a solvent in conjugate additions of cuprates has been shown (CIPs *versus* SSIPs). Solvent separated ion pairs (SSIP) are thought to be less reactive and more susceptible to breakdown. The breakdown of the cuprate was investigated by using a varied mixing time for reacting MeLi with CuCN. After addition of the organolithium reagent to a solution of the copper salt, the resulting mixture was allowed to stir during a mixing time. This period was generally 20 min but, by altering the time, the breakdown of the cuprate could be monitored and assessed through the yield of product.

Reactions of enone *ent*-**71** with dimethyl cuprate generated from CuCN (with different mixing times) in the presence or absence of Me_3SiCl were therefore investigated. The results are shown in Scheme 2.28 and Table 2.3. A brief foray into altering mixing times can be seen in entries 1, 2 and 3 of Table 2.3. These entries do show a trend towards cuprate degradation but it is felt that at such low temperatures degradation is slow and not appreciable to impact on the choice of THF as solvent in terms of yield.



Scheme 2.28: *Altering mixing time and temperature for methyl cuprate additions to enone ent-**71***

Entry	Mixing Time	Temperature (°C)	Additive	Yield (%)[a]	dr (*trans:cis*)[b]
1	5	−78	Me_3SiCl[c]	96	>99:1
2	20	−78	Me_3SiCl[c]	89	>99:1
3	60	−78	Me_3SiCl[c]	85	>99:1
4	20	−40	None	90	27:73
5	20	−40	Me_3SiCl[c]	97	>99:1
6	20	0	None	77	33:67
7	20	0	Me_3SiCl[c]	89	75:25

[a]*Yield and dr of product after chromatography* [b]*Ratio of trans- and cis-diastereomers by* ^{1}*H NMR spectroscopy after chromatography* [c]*TBAF desilylation after an aqueous work-up where required*

Table 2.3: *Altering mixing time and temperature for methyl cuprate additions to enone ent-**71***

It was postulated that altering the temperature could increase complexation to the less favoured concave face of the enone π-system. At –40 °C, the reaction with Me_3SiCl (entry 5) mirrored the result at –78 °C (entry 2) i.e. both gave *trans*-**106** in >99:1 dr. However, at –40 °C, the reaction without Me_3SiCl (entry 4) showed a switch in stereoselectivity in favour of *cis*-**106** (73:27 dr). On raising the reaction temperature to 0 °C in the absence of Me_3SiCl, *cis*-**106** (67:33 dr) was preferentially formed (entry 6). At raised temperatures even in the presence of Me_3SiCl (entry 7), the diastereoselectivity was eroded from being almost totally selective at –78 °C (entry 2) to 75:25 dr (*trans*:*cis*) at 0 °C.

There are two explanations for the erosion of stereoselectivity at higher temperatures. The first is simply the change in the energetics of the transition states making

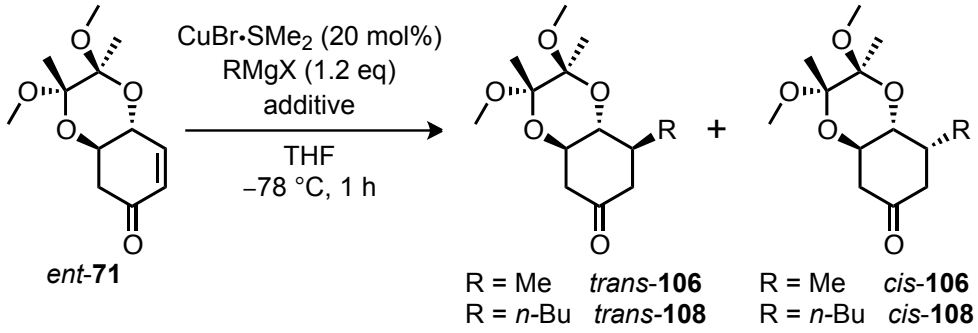
concave complexation more favoured. The second is that the conformation of the enone changes at higher temperatures, possibly through breaking of the planarity of the enone π-system. The reason for the diastereoselectivity change remains unclear but these results highlight the importance of temperature in these reactions.

Overall, the organocuprate 1,4-additions studies have revealed several useful results for the future synthesis of samaderine C through the double 1,4-addition strategy. We discovered that the best conditions for 1,4-additions to enone *ent*-**71** were the use of CuCN as a copper source in the presence of a Me_3SiCl additive. The results showed a trend towards the *trans*-addition products in very good yields.

2.2.3 Copper-Catalysed 1,4-Addition of Grignard Reagents

In 1941, Kharasch and Tawney showed that the presence of just 1 mol% of CuCl dramatically influenced the regioselectivity in the addition of MeMgBr to an enone.[180] A switch from 1,2-addition to a completely selective 1,4-addition reaction with the salt present was observed. With the desire for a *cis*-selective addition process in mind, reactions were carried out using a copper-catalysed Grignard addition to compare the reactivity and stereoselectivity of this reaction to those of the organocuprates already presented.

To investigate this 1,4-addition method, a Grignard reagent was added to a suspension of substoichiometric $CuBr.SMe_2$[125] (20 mol%) and a solution of enone *ent*-**71** (premixed with Me_3SiCl where appropriate) was then added to give the product. This reaction process was carried out for both *n*-butyl and methyl Grignard reagents (Scheme 2.29 and Table 2.4).



Scheme 2.29: *Copper-catalysed Grignard additions to enone ent-**71***

Entry	Grignard Reagent	Additive	Product	Yield (%)[a]	dr (*trans:cis*)[b]
1	MeMgCl	None	**106**	31	50:50
2	MeMgCl	Me_3SiCl[c]	**106**	75	45:55
3	*n*-BuMgBr	None	**108**	31	50:50
4	*n*-BuMgBr	Me_3SiCl[c]	**108**	74	56:44

[a]*Yield and dr of product after chromatography* [b]*Ratio of trans- and cis-diastereomers by* ^1H *NMR spectroscopy after chromatography* [c]*TBAF desilylation after an aqueous work up where required.*

Table 2.4: *Copper-catalysed Grignard additions to enone ent-**71***

Using MeMgCl, a 31% yield of β-substituted enones *trans*-**106** and *cis*-**106** was achieved in a 50:50 dr (*trans*:*cis*) in the absence of Me_3SiCl (entry 1). In the presence of Me_3SiCl, the yield increased (75%) but the reaction was equally unselective (45:55, *trans*:*cis*, entry 2). For the addition of *n*-butyl Grignard, it might be expected that addition of the bulkier reagent would lead to increased stereoselectivity in line with our previous cuprate results but this was not found to be the case. The reaction in the absence of Me_3SiCl gave a 50:50 mixture of *trans*-**108** and *cis*-**108** in 31% yield (entry 3). Use of a Me_3SiCl additive with *n*-butyl cuprate (entry 4) showed an increase in yield (74%) but with no significant diastereoselectivity observed (56:44 dr).

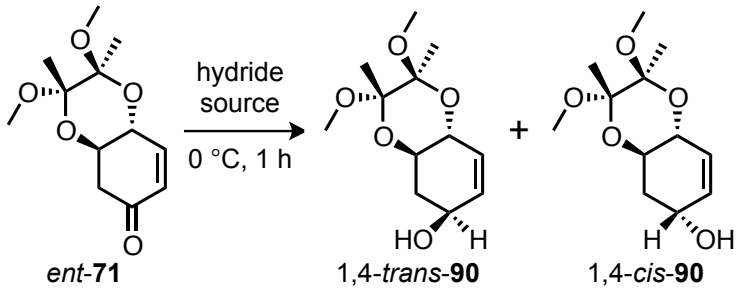
Overall, Me_3SiCl showed improvements in yield but the influence on stereoselectivity was less pronounced than had been seen with the cuprate results. The increase in yield supports research by Nakamura and Kuwajuma who showed the accelerative effects of Me_3SiCl for copper-catalysed Grignard additions. The

poor stereoselectivity we observed is also in line with previous work.[181] In a review by Feringa, he describes that copper-catalysed Grignard additions to enones are "sensitive to every parameter in the reaction protocol (i.e., stoichiometry, solvent, counterion and various reaction conditions, including the use of chiral or achiral additives and Lewis acids)".[182] The exact reason for the low stereoselectivity is not understood. However, previous studies have already shown the advantageous use of Gilman-style cuprates over catalytic Grignard additions.[182]

The copper-catalysed Grignard additions in Table 2.4 were repeated many times in an attempt to check for experimental error but the results always gave lower yields and worse diastereoselectivity compared to these observed using the diorganocuprates. For this reason, we identified the conditions previously developed (CuCN, alkyllithium with Me_3SiCl) as the preferred cuprate addition conditions in the future development of the double 1,4-addition strategy towards the total synthesis of samaderine C.

2.2.4 Nucleophilic Additions of Organometallic Reagents to a (−)-Quinic Acid Derived Enone

While not directly relevant to our proposed total synthesis of samaderine C, the high yields and intriguing diastereoselectivity observed in our cuprate addition studies prompted us to further explore the reactivity of enone *ent*-**71**. Due to the lack of reported examples, we next investigated the diastereoselectivity of 1,2-additions to enone *ent*-**71**. Our study included hydride sources (reduction), organolithium reagents and Grignard reagents. The reduction of enone *ent*-**71** was first investigated where enone *ent*-**71** was reacted with a hydride source to give allylic alcohol products (Scheme 2.30 and Table 2.5).



Scheme 2.30: *Reductions of enone ent-71*

Entry	Reagent	Yield (%)[a]	dr (*1,4-trans*:*1,4-cis*)[b]
1	$NaBH_4$	92	90:10
2	$NaBH_4$, $CeCl_3 \cdot 7H_2O$	93	90:10
3	L-selectride	77	50:50

[a]*Yield of product after chromatography* [b]*Ratio of trans- and cis-diastereomers by* ^{1}*H NMR spectroscopy after chromatography.*

Table 2.5: *Reductions of enone ent-71*

Reduction of the enone carbonyl was first carried out by treatment of enone *ent*-**71** with $NaBH_4$ (entry 1). This gave a 90:10 mixture of diastereomers *1,4-cis*-**90** and *1,4-trans*-**90** in 93% yield. These products are named based on the relative orientation of the allylic substituents. The assignment of the products 1,4-*trans*-**90** and 1,4-*cis*-**90** was achieved using the ^3J coupling constants of allylic proton H-6 and the adjacent CH_2 protons H-1a and H-1b (Figure 2.9). The H-1a proton in the major product shows three large couplings (13, 12 and 10 Hz). These correlated to a ^2J geminal coupling to the H-1b proton and two *trans*-diaxial ^3J couplings to protons H-6 and H-2. The minor diastereomer showed two 13 Hz couplings corresponding to the ^2J geminal coupling and the *trans*-diaxial ^3J coupling to H-2. There was then a smaller 5 Hz coupling attributed to the diequatorial ^3J coupling to the allylic H-6 proton. Based on this analysis, the major product was assigned as 1,4-*trans*-**90** while the minor product was attributed to 1,4-*cis*-**90**.

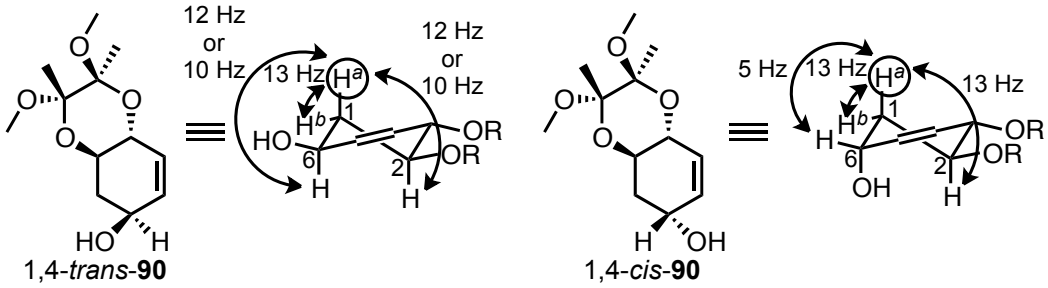
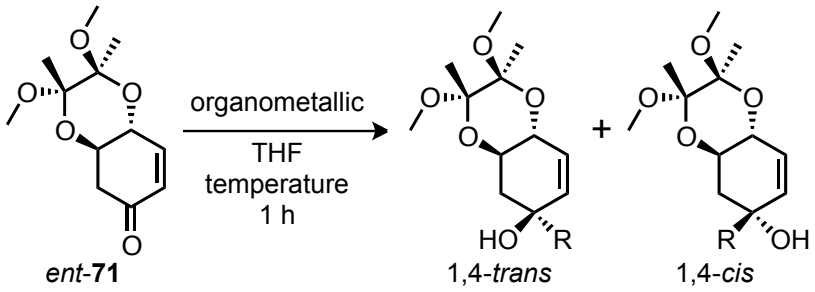


Figure 2.9: *Assignment of reduction products 1,4-trans-**90** and 1,4-cis-**90***

Enone *ent*-**71** was then reduced using $NaBH_4$ under Luche conditions ($CeCl_3 \cdot 7H_2O$) (entry 2). This also gave a 90:10 mixture (1,4-*trans*:1,4-*cis*) of **90** in 93% yield. We speculate that preference for the 1,4-*trans*-product is based on the small hydride nucleophile preferentially attacking the carbonyl of enone *ent*-**71** on a *pseudo*-axial approach as would traditionally be expected.[183] Support for this hypothesis was provided by the result using the bulky reducing agent, L-selectride (entry 3). This hydride source resulted in a lowering of the stereoselectivity as a 50:50 mixture of 1,4-*cis*-**90** and 1,4-*trans*-**90** was isolated in 77% yield. Smaller reducing agents ($NaBH_4$) are less impacted by 1,3-diaxial interactions and so prefer a *pseudo*-axial approach to place the alcohol group in an equatorial position. Larger nucleophiles (L-selectride) are affected more by steric contributions and so are forced into the least hindered pathway (*pseudo*-equatorial approach).

It is important to highlight the diastereo-complementary synthesis of allylic alcohols 1,4-*trans*-**90** and 1,4-*cis*-**90**. We have shown a desymmetrisation and epoxide rearrangement route to 1,4-*cis*-**90** as a single diastereomer (see Scheme 2.16). Now, using a $NaBH_4$ reduction, the complementary diastereomer, 1,4-*trans*-**90**, can be accessed in high yield (93%) and dr (90:10).

Following on from these results, the addition of organometallics to enone *ent*-**71** was next investigated (Scheme 2.31 and Table 2.6). Enone *ent*-**71** was used as a solution in THF and reacted with an organometallic reagent at low temperature.



Scheme 2.31: *1,2-additions of organometallics to enone ent-**71***

Entry	Reagent	Temperature (°C)	Product	Yield (%)[a]	dr (*1,4-trans*:*1,4-cis*)[b]
1	MeLi	0	**109**	90	66:34
2	MeMgBr	−78	**109**	68	83:17
3	MeMgBr	0	**109**	93	75:25
4	PhLi	0	**110**	98	>99:1
5	AllylMgCl	0	**111**	98	79:21

[a]Yield of product after chromatography [b]Ratio of trans- and cis-diastereomers by ^{1}H NMR spectroscopy after chromatography

Table 2.6: *1,2-additions of organometallics to enone ent-**71***

The addition of MeLi to enone *ent*-**71** was known.[122] In studies towards the natural product neoaltuene, the Podlech group added MeLi to enone *ent*-**71** at 0 °C in THF. They obtained a 60% yield of a 60:40 mixture in which they assigned 1,4-*cis*-**109** as the major diastereomer through nOe experiments. We repeated this experiment (entry 1) and obtained a 68% yield of an 83:17 mixture of inseparable diastereomers. On comparison of experimental data, our major product matched their major product (1,4-*cis*-**109**). However, we sought to ratify the Podlech group's assignment. Using our own nOe experiments (Figure 2.10), the allylic methyl group and the CHO signal belonging to axial protons H-2 showed a positive nOe leading us to assign 1,4-*trans*-**109** as the major product. Conclusive evidence was achieved by recrystallisation of the 83:17 mixture of products from Et_2O. This gave the major product as a single diastereomer which on X-ray crystallographic analysis was unequivocally shown to be 1,4-*trans*-**109** (Figure 2.11), indicating that Podlech's assignment was incorrect.

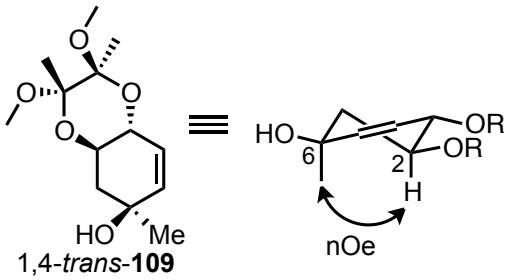


Figure 2.10: *nOe assignment of alcohol 1,4-trans-**109***

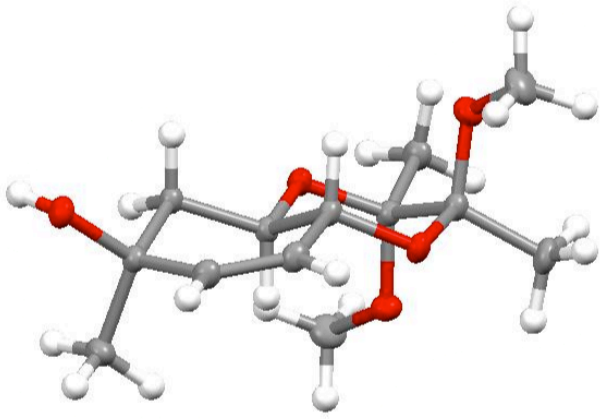
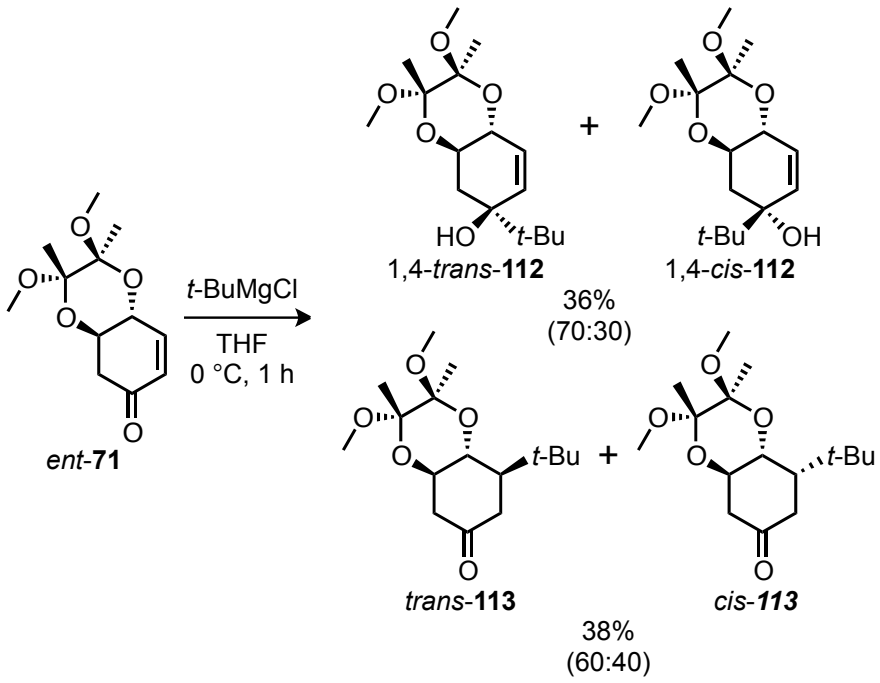


Figure 2.11: *X-ray crystal structure of major diastereomer 1,4-trans-**109***

Investigation of addition of MeMgBr also carried out. At −78 °C (entry 2), a 63% yield of an 83:17 mixture (1,4-*trans*:1,4-*cis*) was obtained. Raising the reaction temperature to 0 °C (entry 3) lowered the diastereoselectivity to 75:25 but increased the yield to 93%. The addition of a phenyl group using PhLi gave a 98% yield of 1,4-*trans*-**110** as a single diastereomer (entry 4). The addition of an allyl Grignard reagent (entry 5) gave product 1,4-*trans*-**111** in a high yield (98%) as an inseparable 79:21 mixture of diastereomers (1,4-*trans*:1,4-*cis*). The major allylic phenyl (1,4-*trans*-**110**) and allyl products (1,4-*trans*-**111**) were assigned using the analogous nOe enhancements used in the assignment the methyl addition product 1,4-*trans*-**109**. Finally, treating enone *ent*-**71** with *t*-BuMgCl resulted in 1,2-addition products 1,4-*trans*-**112** and 1,4-*cis*-**112** (70:30) in 36% yield together with the 1,4-addition products *trans*-**113** and *cis*-**113** (60:40) in 38% yield (Scheme 2.32).



Scheme 2.32: *Addition of t-butyl Grignard reagent to enone ent-**71***

It is clear that for 1,2-additions to enone *ent*-**71**, despite the steric size of the incoming nucleophiles, the preferred orientation for attack on the carbonyl group is *pseudo*-axial. We tentatively suggest two explanations for the stereoselectivity of these reactions. Equatorial addition would result in Felkin-type torsional strain as the transition state requires the carbonyl to eclipse the adjacent hydrogen. Cyclohexenones only possess a single 1,3-diaxial clash between the incoming nucleophile and the corresponding CH which is normally detrimental to axial attack, particularly with large nucleophiles. Finally, it is possible that a Cieplak CH *sigma-sigma* donation promotes axial addition (Figure 2.12).[184,185] The enone double bond may also facilitate the axial approach of the nucleophile on stereoelectronic grounds.

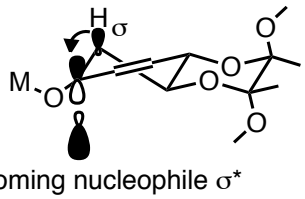
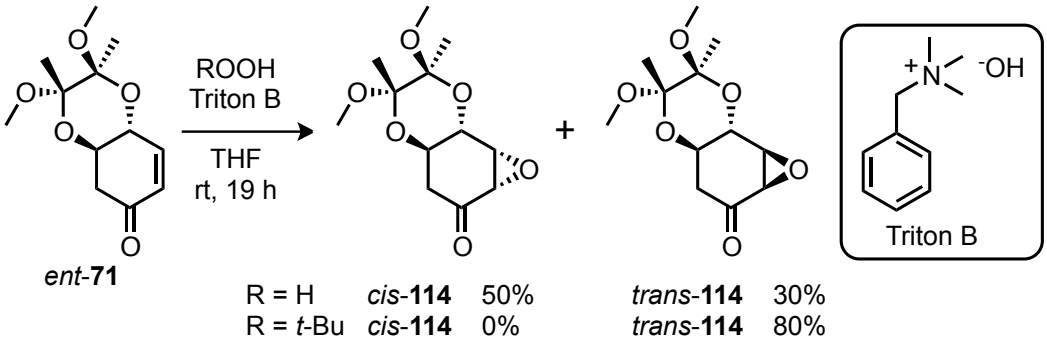


Figure 2.12: *Cieplak interaction to account for axial attack on enone ent-**71***

2.2.5 Epoxidation of a (−)-Quinic Acid Derived Enone

We wished to further explore the reactivity of enone *ent*-**71** and identified the double bond as a target for further elaboration. Previously, the enone moiety had been used in a Diels-Alder reaction[120] and a cyclopropanation reaction.[186] In contrast, nucleophilic epoxidation remained unstudied.

To that end, enone *ent*-**71** was treated with hydrogen peroxide and Triton B base to give a 65:35 ratio of *cis*-**114**:*trans*-**114** by analysis of the ^{1}H NMR spectrum of the crude product (Scheme 2.33). Isolation by flash column chromatography gave *cis*-**114** in 50% yield while *trans*-**114** was obtained in 30% yield. The relative stereochemistry was proved by obtaining an X-ray crystal structure of *cis*-**114** (Figure 2.13). Interestingly, we found that changing the peroxide species to the more sterically hindered *t*-butyl hydrogen peroxide gave *trans*-**114** as a single diastereomer in 81% yield. These epoxidation conditions allowed complementary access to either diastereomer *cis*-**114** or *trans*-**114** as the major product.



Scheme 2.33: *Nucelophilic epoxidation of enone ent-**114***

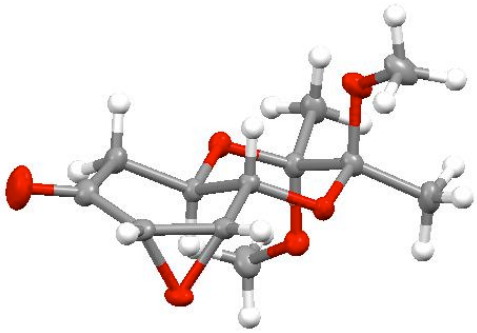


Figure 2.13: *X-ray crystal structure of epoxide cis-**114***

2.2.6 Synthesis of Natural Products Using the (−)-Quinic Acid Derived Enone and its Enantiomer

The reactivity of enone *ent*-**71** spurred us on to investigate the synthesis of some simple natural products using either of the available enone enantiomers *ent*-**71** and **71**. To highlight our synthesis of enone **71** *via* the novel desymmetrisation route, we selected the synthesis of theobroxide-related natural products.

Theobroxide-related natural products, β-methyl enone **115** and *ent*-**115** as well as α-methyl enone **116**, were isolated from the mycelia of *Lasiodiplodia theobromae* OCS71 and are structurally related to theobroxide (Figure 2.14).[187,188] Compounds of this class have been shown to stimulate tuber formation in potato (*Solanum tuberosum*) while in morning glory (*Pharbitis nil*), they exhibit stimulation of flower bud formation. They also inhibit stem elongation through gibberellin biosynthesis suppression. Surprisingly, β-methyl enones **115** and *ent*-**115** were present in nature as a 7:5 mixture.

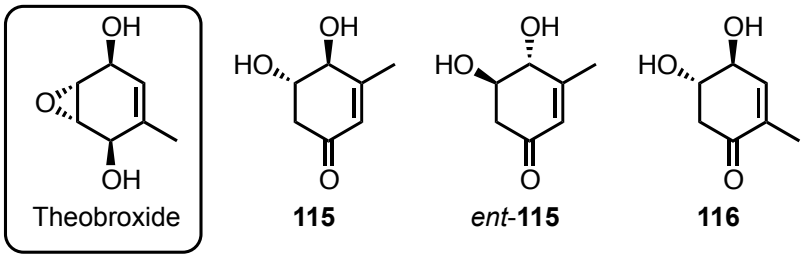
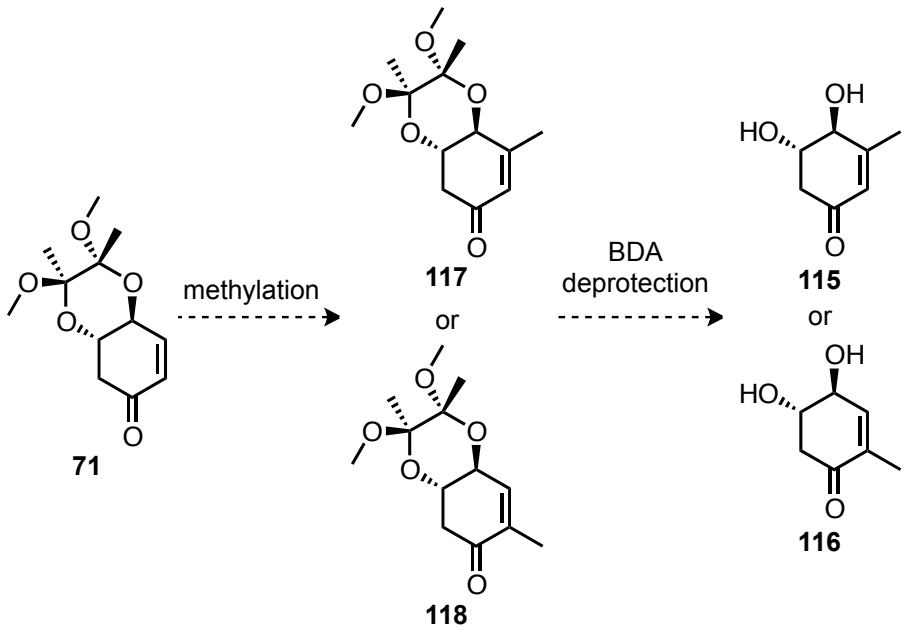


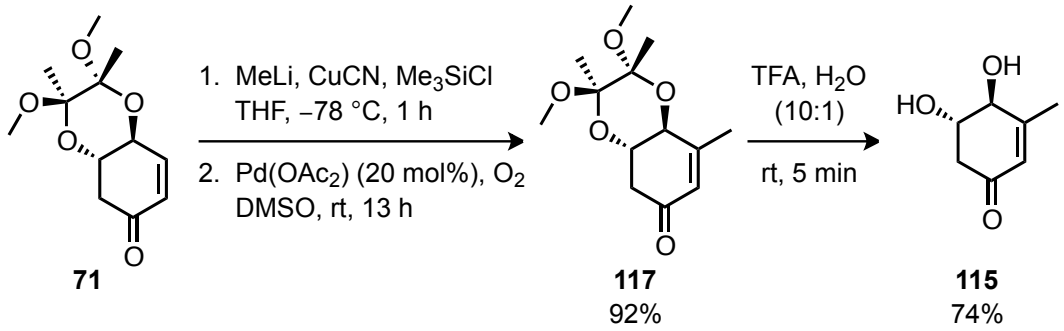
Figure 2.14: *Natural products isolated from Lasiodiplodia theobromae OCS71*

It was envisaged that both the α-methyl and β-methyl natural products could be accessed from enone **71** (Scheme 2.34). Starting from **71**, an α-or β-methylation of the enone double bond would give the methyl adducts **117** or **118** which on deprotection of the BDA protecting group would furnish the relevant natural product.

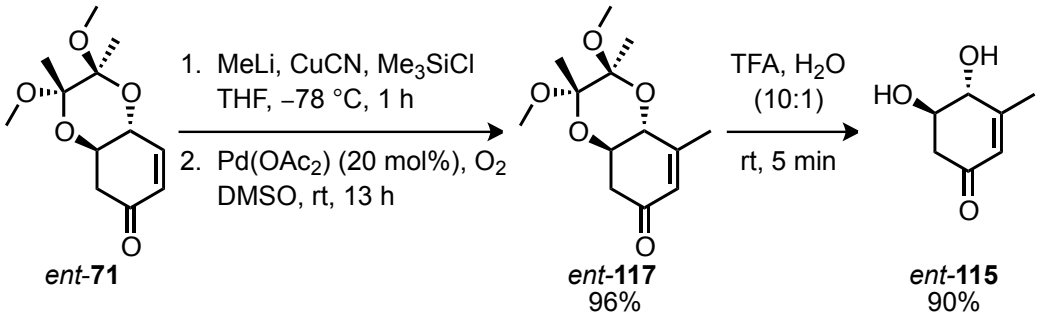


Scheme 2.34: *Methylation and deprotection to give theobroxide-related natural products*

The synthesis of the β-methyl natural products **115** and *ent*-**115** were first studied. Starting from enone **71**, addition of methyl cuprate, promoted by Me_3SiCl, and subsequent Saegusa oxidation of the silyl enol ether intermediate gave the β-methyl enone **117** in 92% yield (Scheme 2.35). Butane diacetal deprotection of **117** with TFA gave the desired β-methyl natural product **115** in 74% yield. The corresponding enantiomer *ent*-**115** was accessed using the (−)-quinic acid derived enone *ent*-**71** (Scheme 2.36). Following the same methyl cupate/Saegusa oxidation procedure, β-methyl enone *ent*-**117** was synthesised in 96% yield. BDA deprotection using TFA gave β-methyl natural product *ent*-**115** in 90% yield. The spectroscopic data and specific rotation for both stereoisomers matched those reported in the isolation paper.[188]

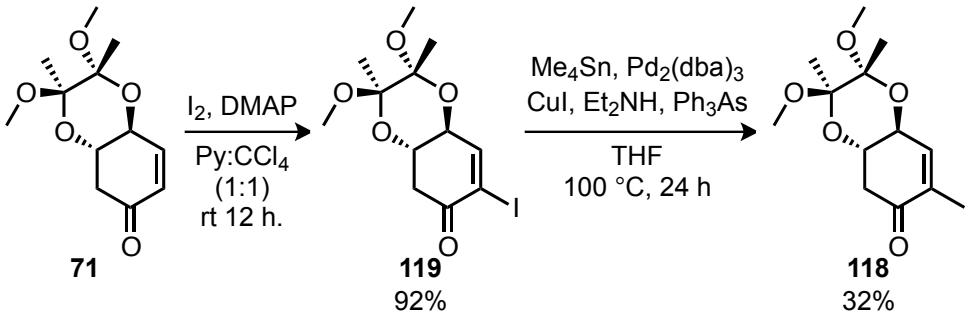


Scheme 2.35: *Conversion of enone **71** into β-methyl natural product **115***

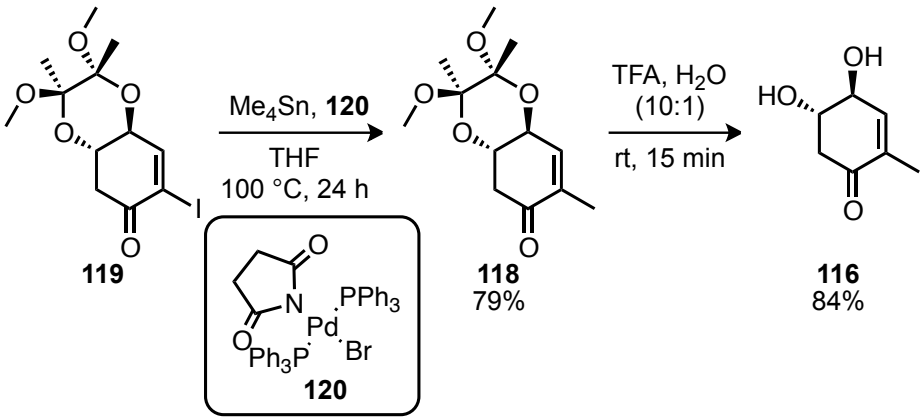


Scheme 2.36: *Conversion of enone ent-**71** into β-methyl natural product ent-**115***

Next, the synthesis of the α-methyl natural product **116** was studied using palladium coupling chemistry. The BDA protected α-methyl enone **119** is known in the opposite enantiomeric series.[119] Using the literature conditions, enone **71** was iodinated using iodine and DMAP to give iodoenone **119** in 92% yield (Scheme 2.37). The literature example then reported a 99% yield for a methyl coupling reaction using Me_4Sn, Ph_3As, CuI, diethylamine and $Pd_2(dba)_3$ with iodoenone **119** as a solution in THF. This solution was then heated at 100 °C in a sealed tube. However, in our hands these reactions conditions gave α-methyl enone **118** in only 32% yield as the best yield after multiple attempts (Scheme 2.37). However, we found that the use of NBS palladium precatalyst **120** (previously developed by the Taylor and Fairlamb groups)[189] gave BDA protected α-methyl enone **118** in 79% yield (Scheme 2.38). BDA deprotection of α-methyl enone **118** then gave diol **116** in 84% yield. The spectroscopic data recorded matched those reported ($[\alpha]_D$ +141.4 (*c* 0.7 in MeOH))(Lit.,[190] +11.3 (*c* 0.01 in MeOH)).[187]



Scheme 2.37: *Synthesis of iodoenone **119** and palladium coupling under literature conditions*

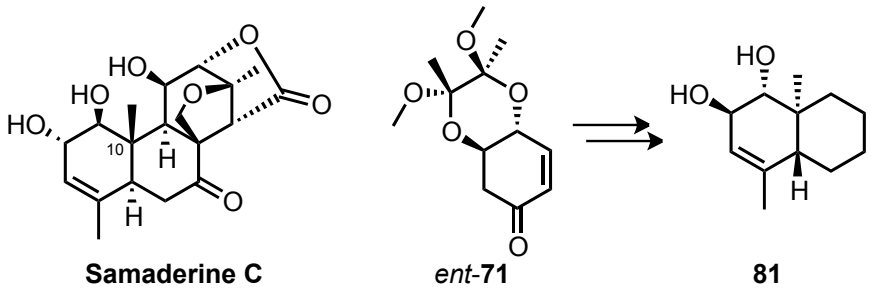


Scheme 2.38: *Conversion of iodoenone **119** to α-methyl natural product **116***

In conclusion, a commercially available starting material we have developed a convenient and scalable synthesis of a useful chiral intermediate and using both enone enantiomers we have synthesised therobroxide related natural products.

Chapter 3: Efforts Towards the AB-Rings of Samaderine C: the Double 1,4-Addition Approach

This chapter describes our efforts to develop a strategy for the synthesis of the AB-rings of samaderine C (Scheme 3.1). The plan was to introduce the two substituents at C-10 in the A-ring of samaderine C *via* a double 1,4-addition approach to a suitable enone *ent*-**71** (the synthesis of which was described in the previous chapter). However, since enone *ent*-**71** can be readily prepared from (−)-quinic acid, all initial synthetic work in this chapter was carried out in effectively the "wrong" enantiomeric series for samaderine C synthesis. Specifically, efforts were focused on the conversion of enone *ent*-**71** into the *trans*-decalin-diol **81**, a compound that we felt was a suitable model of the AB-ring system of samaderine C. This chapter describes our efforts towards the synthesis of diol **81**.

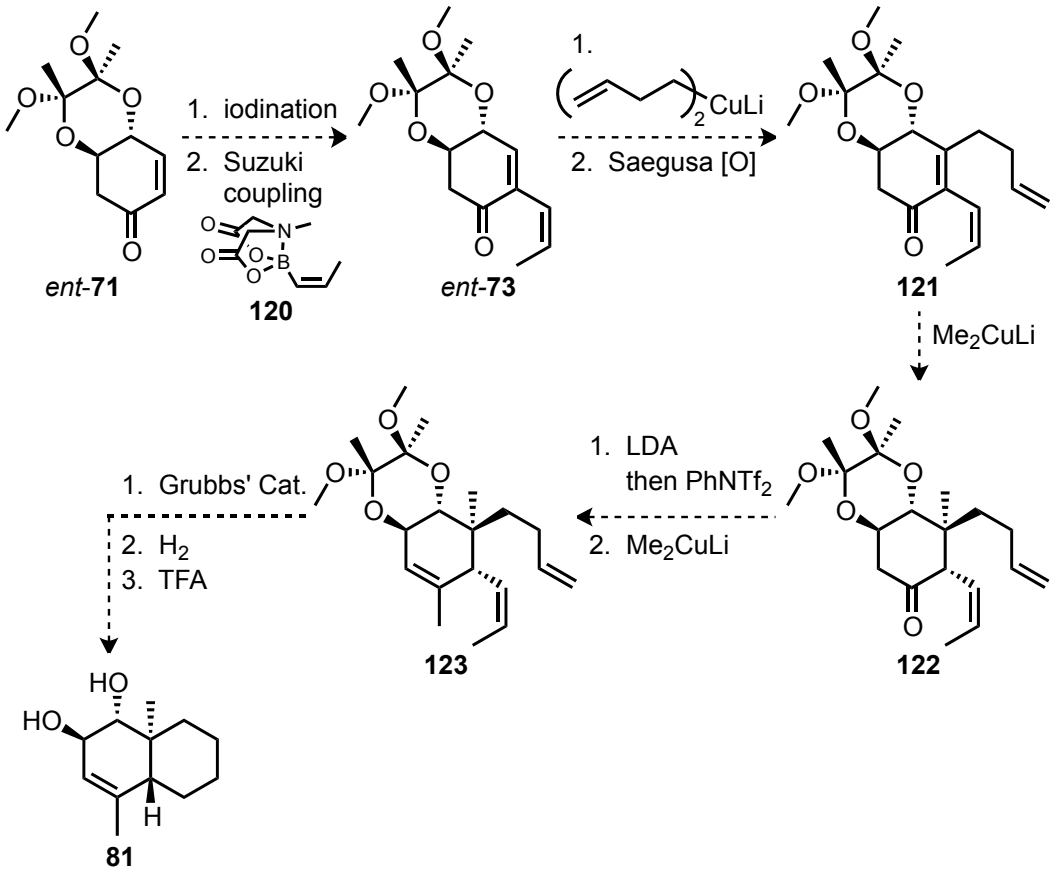


Scheme 3.1: *Synthesis of AB-ring model* ***81*** *from enone ent-**71***

3.1 Strategy Towards the AB-Ring Model Compound

Our initially proposed route for the synthesis of *trans*-decalin-diol **81** is summarised in Scheme 3.2. The route would start with iodination of *ent*-**71** in the α-position followed by a Suzuki cross-coupling with MIDA-boronate **72** to give α-propenyl enone *ent*-**73**. In this approach, a butenyl cuprate will represent the CDE-ring cluster. The 1,4-addition of a butenyl group to enone *ent*-**73** would form an enolate which we hoped to utilise to reform the enone oxidation state. This could be accomplished by trapping the enolate *in situ* as the silyl enol ether, which on Saegusa oxidation would

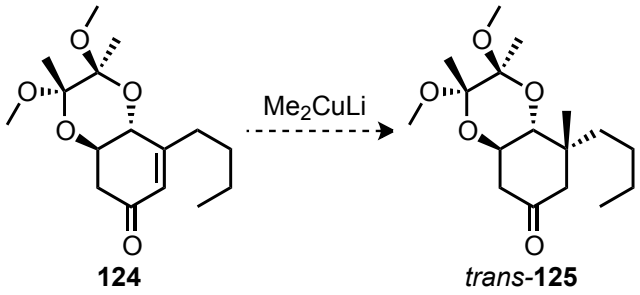
furnish β-butenyl enone **121**. It was envisaged that the addition of a methyl cuprate would then give β-disubstituted ketone **122**. The diastereoselectivity of this second cuprate addition is a key aspect of this route and the sense and degree of stereoselectivity would need to be investigated. In particular, we anticipated that the order of introducing the butenyl and methyl groups could be reversed in order to access the desired diastereomer. The A-ring methyl alkene would then be formed. Kinetic enolate formation and trapping as the enol triflate followed by cross-coupling with Me_2CuLi would then give methyl alkene **123**. Completion of the B-ring would be achieved by RCM, selective hydrogenation and diol deprotection to give the *trans*-decalin-diol **81**.



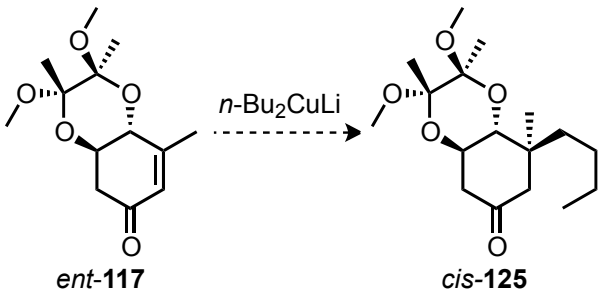
Scheme 3.2: *Proposed synthesis of AB-ring model **81***

3.2 1,4-Additions of Organocuprates to β-Substituted Enones

In order to investigate the diastereoselectivity of the 1,4-addition of cuprates to β-substituted enones, a methyl/*n*-butyl model study was devised as shown in Schemes 3.3 and 3.4. The previous cuprate additions to unsubstituted enone *ent*-**71** gave *trans*-selective additions (*trans* to the adjacent alkoxy moiety) to give the cuprate substituent in the equatorial position. If the same sense of induction occurred in the addition of Me_2CuLi to *n*-butyl β-substituted enone **124** then β-disubstituted ketone *trans*-**125** should be the major product (Scheme 3.3) i.e. Me_2CuLi adds *trans* to the adjacent oxygen. By ananlogy, addition of *n*-Bu_2CuLi to methyl β-substituted enone *ent*-**117** should give the other diastereomer, β-disubstituted ketone *cis*-**125** as the major product (Scheme 3.4).

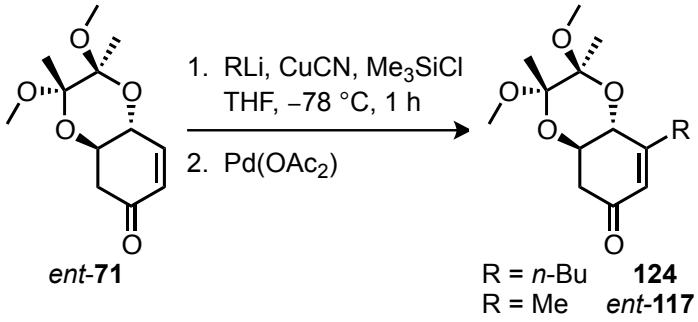


Scheme 3.3: *Methyl cuprate addition to β-substituted enone **124***



Scheme 3.4: *n-Butyl cuprate addition to β-substituted enone ent-**117***

The methyl and *n*-butyl β-substituted enones *ent*-**117** and **124** were synthesised using a cuprate reaction in the presence of Me_3SiCl and the resulting silyl enol ether was then oxidised using a Saegusa reaction to give the products (Schemes 3.5 and Table 3.1).



Scheme 3.5: *Synthesis of methyl and butyl β-substituted enones from enone ent-**71***

Entry	R	$Pd(OAc)_2$ Loading	Product	Yield[a] (%)
1	*n*-Bu	1.2 eq.[b]	**124**	56
2	Me	1.2 eq.[b]	*ent*-**117**	61
3	*n*-Bu	0.2 eq.[c]	**124**	82
4	Me	0.2 eq.[c]	*ent*-**117**	96

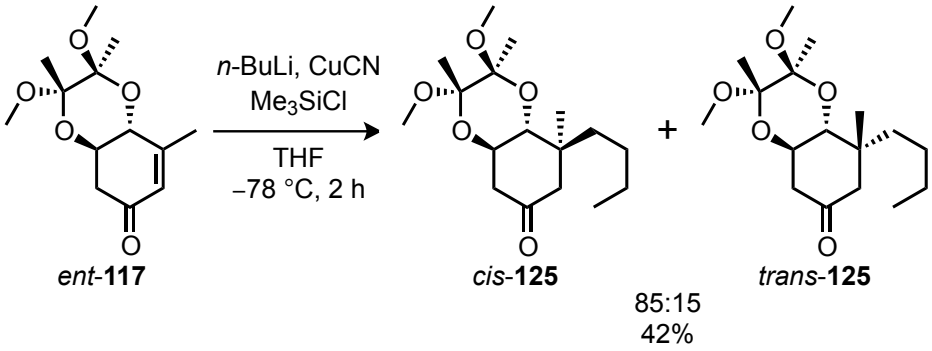
[a]Yield after purification by chromatography. [b]Conditions: $Pd(OAc)_2$ (1.2 eq.), under Ar, MeCN, rt, 20 h.[c]Conditions: $Pd(OAc)_2$ (0.2 eq.), under O_2, DMSO, rt, 20 h

Table 3.1: *Synthesis of methyl and butyl β-substituted enones from enone ent-**71***

Thus, *n*-butyl cuprate was reacted with enone *ent*-**71** and the resulting silyl enol ether was submitted to the stoichiometric Saegusa oxidation. This gave β-*n*-butyl enone **124** in 56% yield (entry 1). Using the same method with methyl cuprate gave β-methyl enone *ent*-**117** in 61% yield (entry 2). The catalytic Saegusa reaction was also screened. This method involved bubbling oxygen gas through a solution of the trimethylsilyl enol ether and $Pd(OAc_2)$ (0.1 eq.) for 30 min and then stirring at rt under an oxygen atmosphere for 20 h. The catalytic method resulted in a consistently higher yield (82%) of β-*n*-butyl enone **124** (entry 3). The catalytic oxidation also proved successful after a methyl cuprate addition to give methyl β-methyl enone *ent*-**117** in an excellent 96% yield (entry 4).

With both β-substituted enones *ent*-**117** and **124** in hand, the appropriate cuprate additions were undertaken. In the absence of Me_3SiCl, the cuprate additions to both β-substituted enones *ent*-**117** and **124** resulted in none of the desired products.

Instead, some 1,2-addition side-products were detected. These initial results showed that cuprate additions to β-substituted enones are challenging in line with previous studies.[191,192] Hence, reactions in the presence of Me_3SiCl were investigated with more promising results. *n*-Butyl cuprate addition to β-methyl enone **124** gave a 42% yield of β-disubstituted ketones *cis*-**125** and *trans*-**125** as an inseparable 85:15 mixture of diastereomers (Scheme 3.6). The *cis*-diastereomer was obtained as the major product in line with previous results suggesting the preference for *trans*-cuprate additions placing the *n*-butyl substituent in the equatorial position. The major diastereomer was assigned as *cis*-**125** by nOe experiments (Figure 3.1). Irradiation of the H-2 proton showed a positive enhancement with the axial methyl group.



Scheme 3.6: *n-Butyl cuprate addition to β-methyl enone ent-**117***

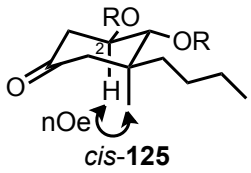
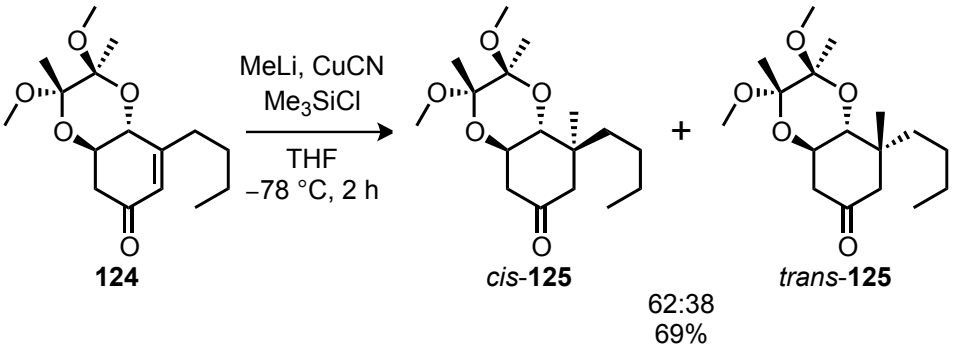


Figure 3.1: *Assignment of cis-**125** through nOe enhancement*

It was therefore expected that addition of a methyl cuprate to β-*n*-butyl enone **124** should give the complementary diastereoisomer *trans*-**125** as the major product with equatorial *trans*-addition of the methyl cuprate. Surprisingly, addition of methyl cuprate to β-*n*-butyl enone **124** gave the same major diastereomer, *cis*-**125** in 69% yield as an inseparable 62:38 mixture. The higher yield for the addition of the smaller methyl cuprate to the sterically hindered β-substituted enone was expected. The reduced diastereoselectivity for methyl cuprate *versus n*-butyl cuprate additions was similar to that observed in the 1,4-additions to enone *ent*-**71**. However, the same major *cis*-diastereomer for both of these reactions was completely unexpected.

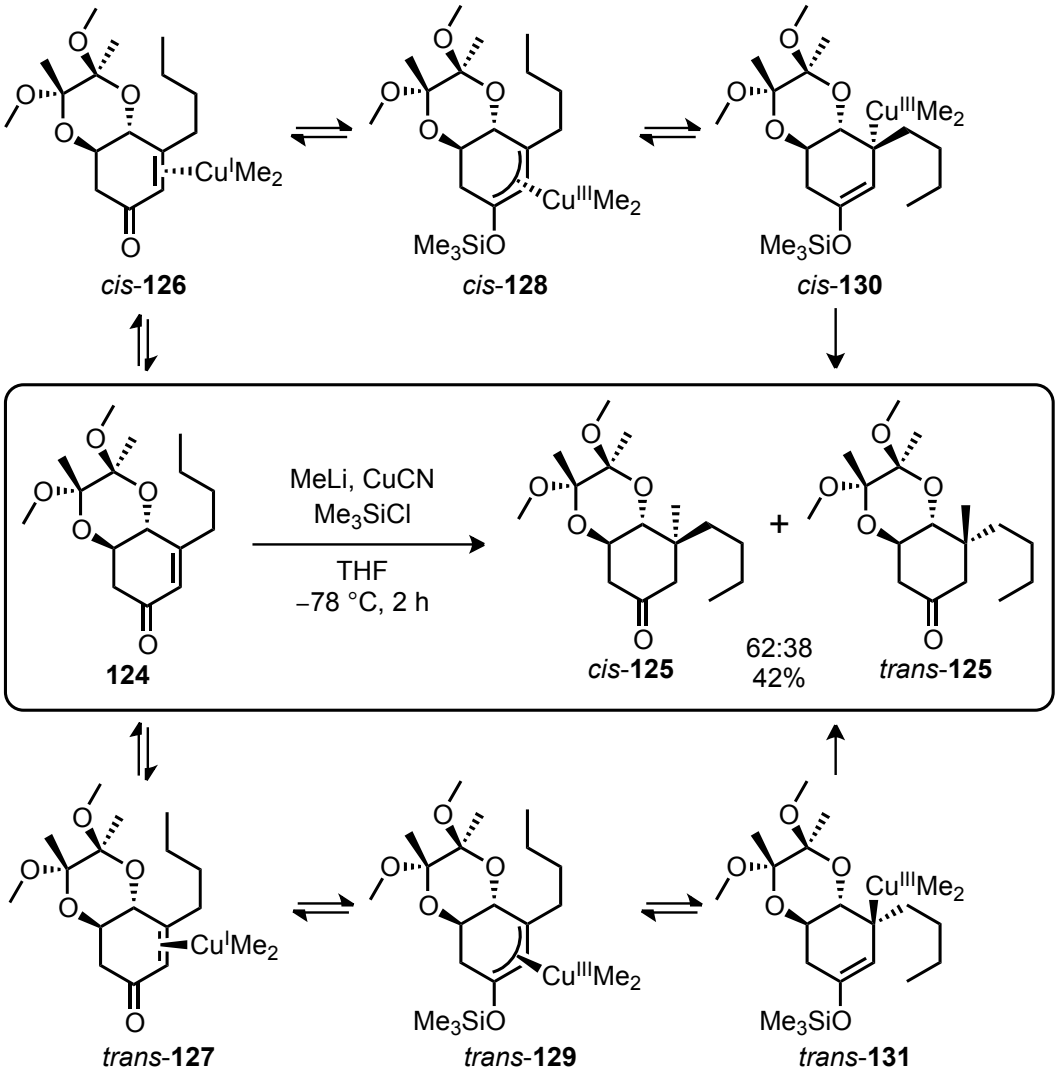


Scheme 3.7: *Methyl cuprate addition to β-n-butyl enone **124***

The same major product regardless of the addition order suggests that additions to β-substituted enones of this system type are dependent on more than just the steric hindrance during the π-complexation phase of the reaction mechanism. If we make the assumption that the reaction pathway is reversible until the final carbon-carbon bond forming event then the reaction mechanism for a methyl cuprate addition to β-*n*-butyl enone **124** will be as outlined in Scheme 3.8.[193]

We believe that the reaction pathway will follow that previously outlined (see Scheme 2.26) with π-complexation to give either η^2 π-complexes *cis*-**126** or *trans*-**127** (Scheme 3.8). Formation of the η^3 π-allyl Cu(III) complexes (*cis*-**128** or *trans*-**129**) is thought to occur spontaneously in the presence of Me_3SiCl. Before the irreversible reductive elimination-type process to give the final products, both η^3 π-allyl Cu(III) complexes (*cis*-**128** or *trans*-**129**), must pass through the η^1 β-cuprio(III)enolates (*cis*-**130** or *trans*-**131**) and it is here that we speculate a rationale for the diastereoselectivity observed. Addition of cuprates to tri- or tetrasubstituted enones has been a significant challenge to synthetic chemists attributed to the steric congestion and the formation of a quaternary centre.[191,192] If the barrier (activation energy) to the carbon-carbon bond-forming reductive elimination step is very high and every step preceding it is reversible to some extent then a dynamic kinetic process could be set up. The relative activation energies from the η^1 β-cuprio(III)enolates (*cis*-**130** or *trans*-**131**) to copper enolate product precursors would be key. We suggest that the transition state which places the smallest group in the axial position and the largest group in the equatorial arrangement would be favoured. Therefore, regardless of the order of addition in our double 1,4-addiiton sequence,

formation of *cis*-**130** with an axial methyl and equatorial *n*-butyl group would be favoured.



Scheme 3.8: *Methyl cuprate addition to enone **124** and associated mechanistic pathways*

We suggest this mechanistic rationale but recognise the limitations of our analysis, such as an assumption of reversibility between the intermediates of cuprate 1,4-additions in the presence of Me_3SiCl. Our explanation here ignores the importance of π-complexation shown by our previous results as well as the literature.[127,141,193] Regardless of the mechanistic rationale for these results the synthetic opportunity offered is promising since either order of addition could be used to access the desired diastereomer. Further studies towards samaderine C will have a choice of routes available to suit the synthetic needs. The methyl group could be installed either

initially and carried through as a methyl β-substituted enone or added in a later step as a methyl cuprate.

3.3 Studies Towards the Synthesis of the AB-Ring Model Compound

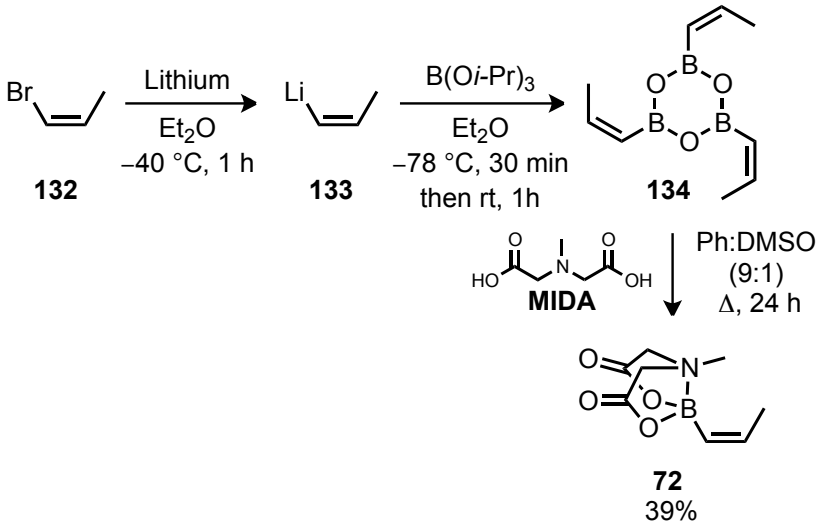
The stereochemical outcome of cuprate additions to our system may not be fully understood but by achieving the desired *cis*-methyl orientation, work could now progress towards the synthesis of the AB-ring system diol **81**. Our intention was to use a ring-closing metathesis to furnish the completed B-ring structure after the double 1,4-addition approach. Based on the methyl/*n*-butyl addition results, we believed the double 1,4-addition strategy should deliver the desired diastereomer regardless of the order of addition (Scheme 3.2). Enone *ent*-**71** provides the A-ring with correctly defined diol stereocentres and a cuprate addition process has been shown to be a suitable methodology to install the methyl group at the C-10 bridgehead position. The challenge now became developing the annulation process to furnish the B-ring.

3.3.1 Investigation of Ring-Closing Metathesis Annulation Strategy

The annulation methodology for constructing the AB-rings initially investigated was RCM as its precedence for six-membered ring formation is excellent.[194-196] For this method, we required the installation of an alkene in the appropriate α-position of an enone. The palladium couplings of iodoenones in similar scenarios have been shown to be a robust coupling protocol for α-functionalisation of enones.[98,119,197,198] We therefore investigated the synthesis of α-propenyl enone *ent*-**73** using palladium chemistry to append the propenyl RCM handle.

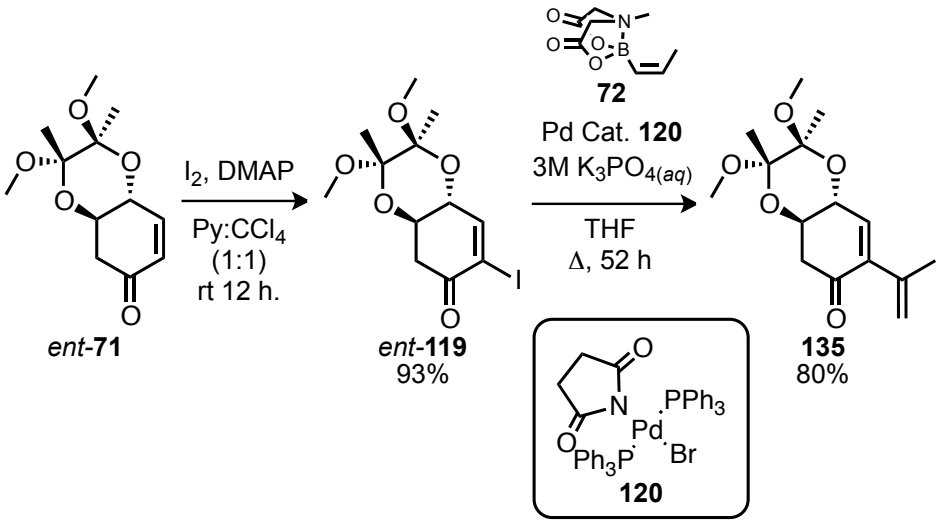
cis-Propenyl MIDA boronate **72** would be used to functionalise iodoenone **119** through a Suzuki–Miyaura coupling. MIDA boronates have become synthetically very useful. The MIDA moiety derived from *N*-methyliminodiacetic acid (MIDA) stabilises otherwise air- and moisture-sensitive boronic acids as the corresponding esters, which are bench-stable. Hydrolysis of the MIDA boronates *in situ*, then

provides a slow release of the boronic acid coupling partner. *cis*-Propenyl MIDA boronate **72** is commercially available but this commercial material often comes as an mixture of *cis*- and *trans*-isomers. We therefore investigated the synthesis of MIDA boronate **72**. A previous synthesis of **72** exists.[199] Following this procedure, vinyl bromide **132** underwent a halogen-lithium exchange to give vinyl lithium **133** which was trapped using triisopropyl borate to give boroxin **134**. Boroxin **134** then formed the desired *cis*-propenyl MIDA boronate **72** on reaction with MIDA under Dean-Stark conditions. *cis*-Propenyl MIDA boronate **72** was thus synthesised in 39% yield over the three required steps (Scheme 3.9).

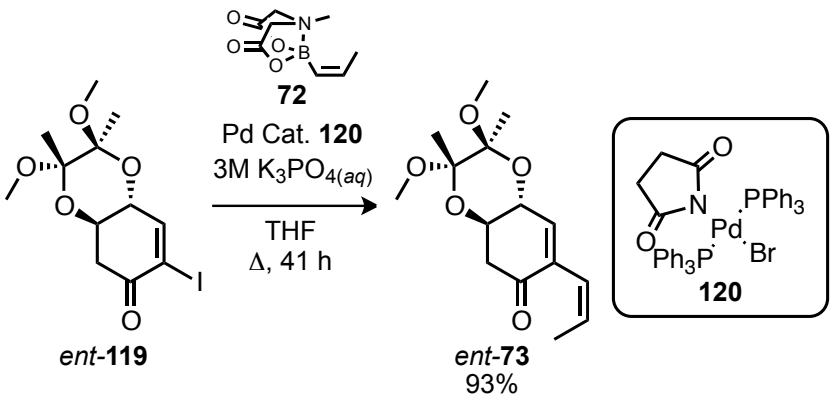


Scheme 3.9: *Synthesis of cis-propenyl MIDA boronate 72*

Treatment of enone *ent*-**71** with iodine and DMAP gave iodoenone *ent*-**119** in 93% yield. The palladium catalyst, *trans*-bromo[*N*-succinimidyl-bis(triphenylphosphine)] -palladium(II) **120**, developed by the Fairlamb and Taylor groups,[189] was employed to carry out the Suzuki–Miyaura coupling. The coupling step initially proved capricious with an alkene isomerisation occurring somewhere in the reaction pathway to give α-vinyl enone *ent*-**73** in 80% yield (Scheme 3.10). However, it was found that the rate of stirring influenced the formation of this side-product. It was postulated that more vigorous stirring reduced the formation of "hot spots" within the reaction vessel, which are tentatively attributed to lead to the formation of α-vinyl enone **135**. Stirring the reaction vigorously gave α-propenyl enone *ent*-**73** (93% yield) with no detectable presence of **135** (Scheme 3.11).

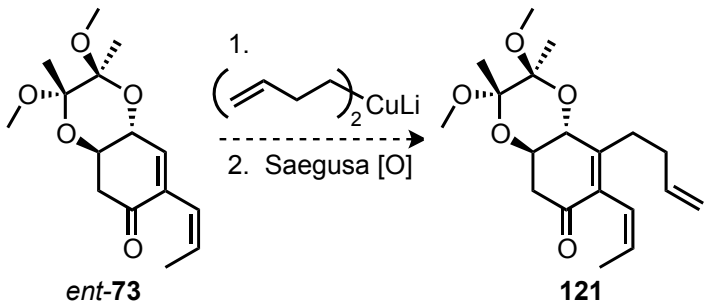


Scheme 3.10: *Synthesis of unexpected α-vinyl enone **135***



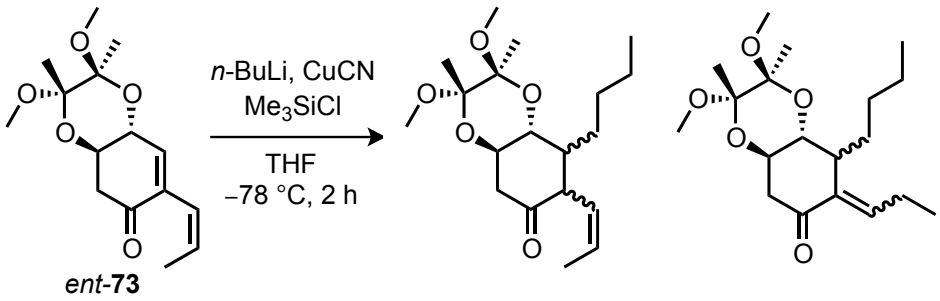
Scheme 3.11: *Suzuki-Miyaura coupling process to form enone ent-**73***

With one alkene for the RCM installed, efforts were then made to investigate cuprate additions to α-propenyl enone *ent*-**73** with a vision towards attaching a butenyl side-chain followed by oxidation to give RCM precursor **121**. Our planned approach is shown in Scheme 3.12.



Scheme 3.12: *Proposed route to RCM precursor **121***

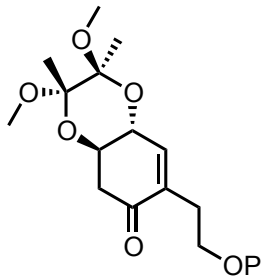
The bromide precursor to the proposed butenyl cuprate was reasonably expensive and the formation and use of a butenyl cuprate up to this point was unstudied. *n*-Butyl cuprate was therefore used to initially investigate cuprate additions to α-propenyl enone *ent*-**73**. Treatment of α-propenyl enone *ent*-**73** with *n*-BuLi, CuCN and Me_3SiCl at –78 °C in THF gave a complex mixture of isomeric products (Scheme 3.13). No single product was able to be isolated pure but analysis by ^1H NMR spectroscopy showed the presence of several alkene-containing products. The definitive assignment of the products shown was never achieved as we were unable to isolated any pure compounds.



Scheme 3.13: *Possible mixture of alkene isomers on cuprate addition to ent-73*

The possible alkene isomers that may result from this cuprate addition are shown in Scheme 3.13. Cuprate additions to a cross-conjugated enone such as *ent*-**73** would result in a trimethylsilyl enol ether or enolate species which could quench *via* more than one pathway, either an exocyclic proton quenching pathway through a conjugated diene side chain to give isomeric exocyclic enone products or in the enolic α-position in an *pseudo*-axial or equatorial fashion. Similarly mixed results were obtained on trying a Saegusa oxidation on the trimethylsilyl enol ether trapped from the *n*-butyl cuprate addition to *ent*-**73**. No single enone product was identifiable from a complex mixture of isomeric products.

The limitation of cuprate additions to the cross-conjugated α-propenyl enone *ent*-**73** severely hampers the RCM approach as a plausible B-ring annulation method. Continuing with this methodology would require masking the alkene substituent as in enone **136** (Figure 3.2) in order to remove the problem of cross conjugation. At this point, it was deemed that synthetic efforts would be best spent in assessing other annulation methods rather than investing time in masking an RCM handle.

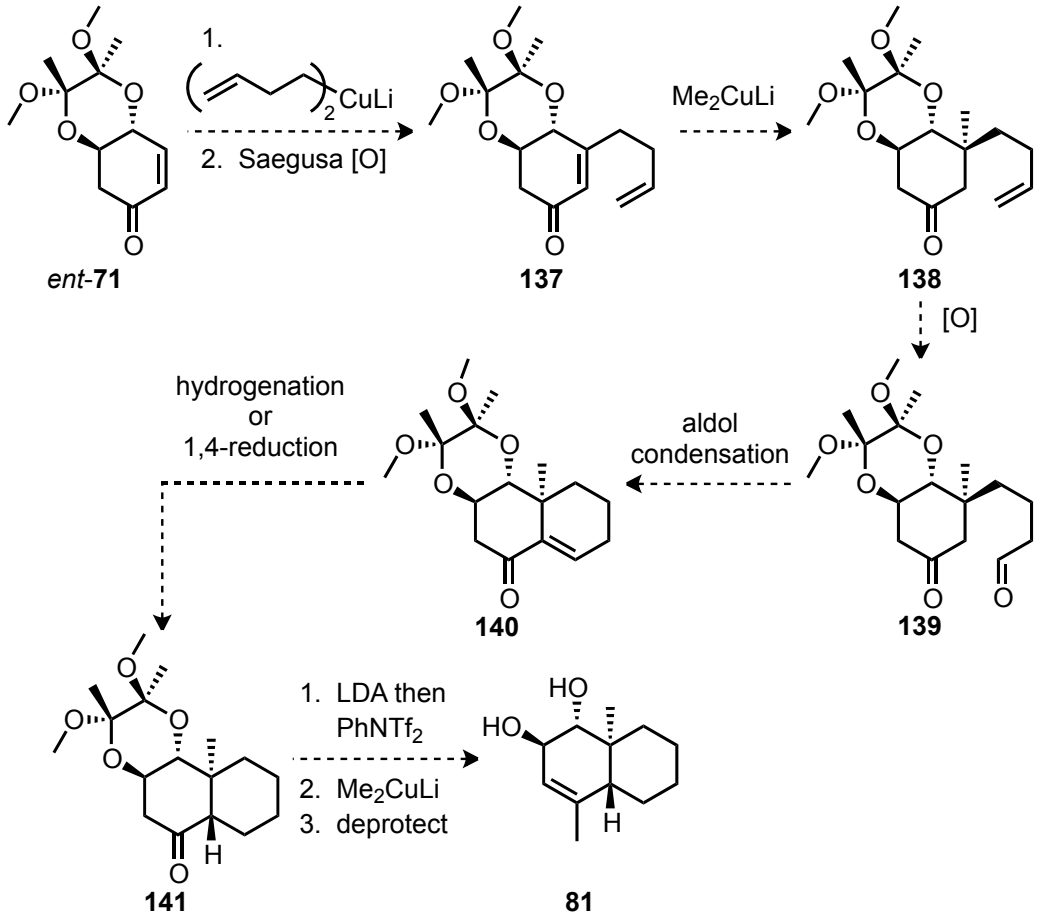


136

Figure 3.2: *Possible masked alkene analogue*

3.3.2 Investigation of an Aldol-Based B-ring Annulation Strategy

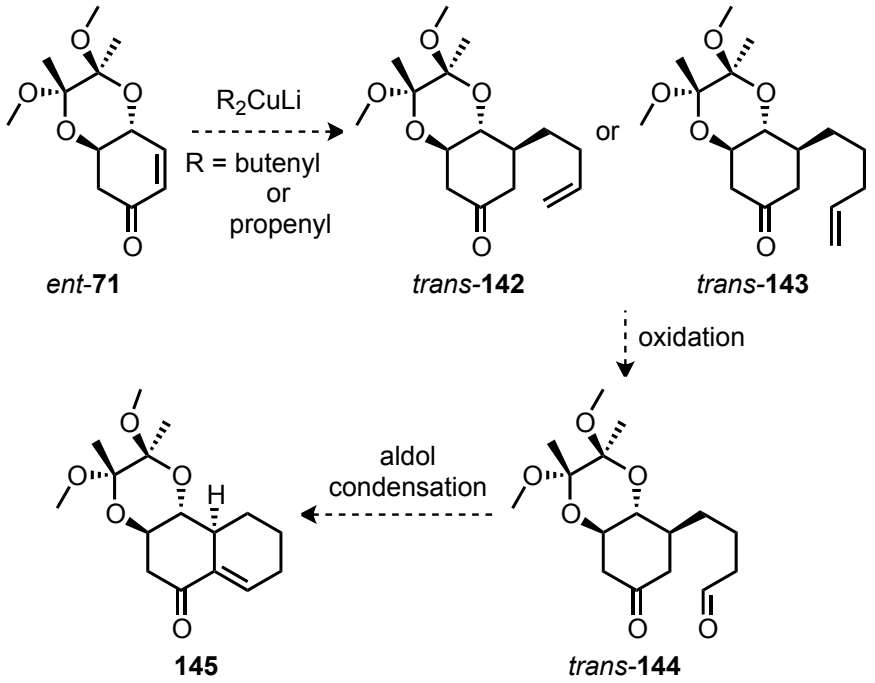
The RCM-based B-ring annulation approach was ruled out in the short-term. Therefore, an alternative annulation method was sought. We next investigated an aldol-based approach (Scheme 3.14). It was hoped that synthesis of a butenyl adduct **138** by methyl cuprate 1,4-addition to β-pentenyl enone **137** would occur with the stereochemistry predicted from our earlier studies. Then, hydroboration and oxidation to keto aldehyde **139** would allow evaluation of an aldol condensation ring-closing approach. We envisaged that the *trans*-decalin ring junction of **141** would be formed by hydrogenation or a 1,4-reduction of enone **140**. The methyl alkene in **81** would be installed using enol triflate formation and cross-coupling with Me_2CuLi.



Scheme 3.14: *Aldol condensation route to AB-ring model compound* ***81***

In order to investigate the aldol-based annulation chemistry, most of our investigations were *via* mono β-substituted keto aldehydes (Scheme 3.15). Shortening the route would allow more expedient investigation of the crucial aldol

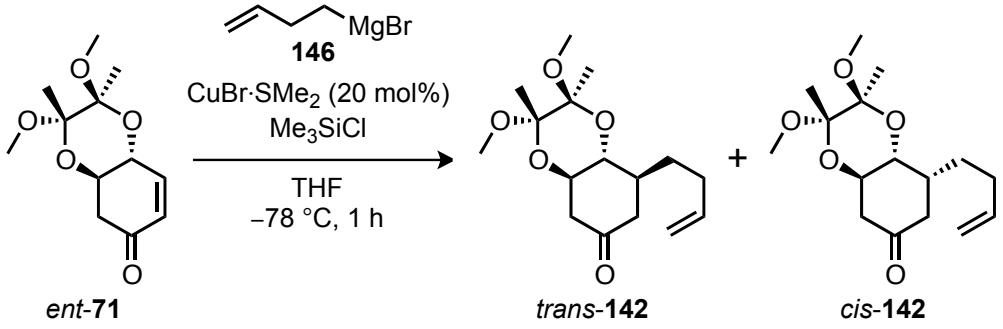
condensation step as well as aiding in assignment of diastereomers using the coupling constants present in the ^{1}H NMR spectra. Hence, the reaction of enone *ent*-**71** with butenyl or propenyl cuprate would be expected to give the *trans*-addition products, *trans*-**142** or *trans*-**143**. Oxidation of this pendant side chain (either by hydroboration-oxidation of *trans*-**142** or by ozonolysis of *trans*-**143**) would then give a keto-aldehyde **144** which could be used to assess the aldol condensation annulation approach to give bicyclic enone **145**.



Scheme 3.15: *Aldol condensation route to enone **145***

The envisaged synthesis of butenyl intermediate *trans*-**142** involved addition of a butenyl cuprate to enone *ent*-**71**. The butenyl cuprate would be made from a butenyllithium and CuCN under our standard cuprate conditions. However, butenyllithium is not commercially available and needed to be prepared from 4-bromo-1-butene. Several examples of the use of butenyllithium have been reported.[200-202] Unfortunately, in our hands, titrations indicated that formation of the lithiated species was not occurring. Several attempts at forming butenyllithium and adding its cuprate to enone *ent*-**71** failed.

Our previous studies had shown that copper-catalysed addition of Grignard reagents to enone *ent*-**71** were successful, although the diastereoselectivity of these reactions was poor. Nevertheless, the corresponding butenyl Grignard reagent **146** was investigated as other options were not available. Grignard reagent **146** was formed by reacting 4-bromo-1-butene with magnesium turnings in THF at reflux. In the presence of $CuBr.SMe_2$ (20 mol%), addition of butenyl Grignard reagent **146** to enone *ent*-**71** under standard conditions was successful (Scheme 3.16 and Table 3.2).



Scheme 3.16: *Copper-catalysed butenyl Grignard addition to enone ent-71*

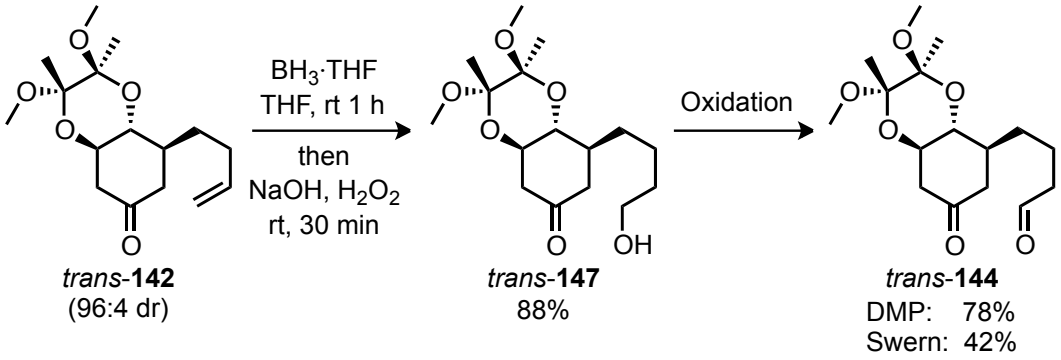
Entry	**Scale**[a] (mmol)	**Yield**[b] (%)	**dr**[c] (*trans*:*cis*)
1	0.41	92[d]	96:4
2	0.41	64[d]	56:44
3	8.26	49[d]	55:45

[a]Scale of enone ent-71 [b]Yield of product after chromatography [c]Ratio of trans- and cis-diastereomers by ^{1}H NMR spectroscopy after chromatography [d]TBAF desilylation after an aqueous work-up

Table 3.2: *Copper-catalysed butenyl Grignard addition to enone ent-71*

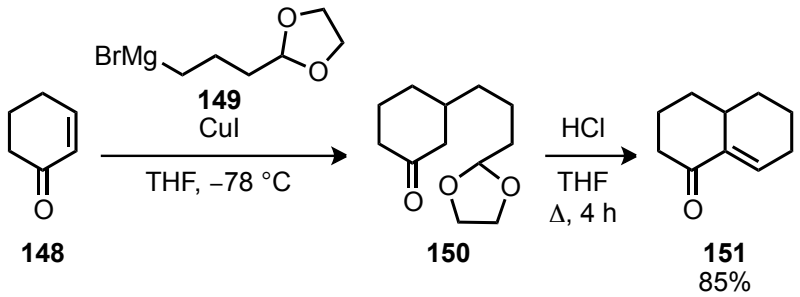
The first reaction with 100 mg of enone *ent*-**71** (0.41 mmol) gave a 92% yield of a 96:4 mixture of butenyl β-substituted enones *trans*-**142** and *cis*-**142** which were tentatively assigned by ^{1}H NMR (entry 1). However, repeating this experiment on the same scale and under supposedly identical conditions gave 64% yield but only 56:44 dr (entry 2). Scaling the reaction up to 2.0 g of enone *ent*-**71** (8.26 mmol) also gave poor diastereoselectivity and a lower yield (49%, entry 3). This experiment was repeated further on a range of scales with the same overall molarity of solutions and rates of additions with no discernable trend in diastereoselectivity and yield. In line with previous Grignard additions to enone *ent*-**71**, results were variable both in terms of yield and diastereoselectivity on a range of scales.

The oxidation of the pendant side-chain was then attempted using the 94:6 mixture of butenyl β-substituted enones *trans*-**142** and *cis*-**142** (Scheme 3.17). A hydroboration reaction was successful and gave alcohol *trans*-**147** in 88% yield as a single diastereomer (tentatively assigned by ^{1}H NMR). Oxidation of alcohol *trans*-**147** using DMP gave aldehyde *trans*-**144** in good yield (78%). The analogous Swern oxidation of *trans*-**147** gave aldehyde *trans*-**144** in only 42% yield.



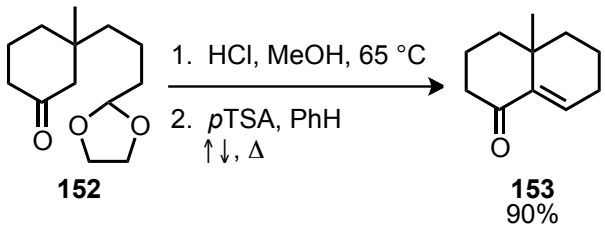
Scheme 3.17: *Synthesis of aldehyde trans-**144** from a 96:4 mixture of trans-**142** and cis-**142***

We next investigated the aldol condensation process. Aldol cyclisations are well precedented and the Helquist annulation, in particular, closely resembles the desired synthetic route to model compound **81**.[203] In their studies into palladium-catalysed arylation−dehydroaromatisation reactions, the Maier group used a Helquist annulation to achieve enone **151** (Scheme 3.18).[204] The Helquist annulation is the copper-catalysed 1,4-addition of an acetal-protected Grignard reagent (such as **149**) to an enone (**148**) to give an acteal adduct **150**. Subsequent deprotection under acidic conditions gives an enone (**151**) or an aldol products (*via* aldol cyclisation).



Scheme 3.18: *The Maier group's use of the Helquist annulation*

Another example of a related aldol condensation reaction has been reported. In 2000, the Tanaka group used an aldol condensation strategy in studies towards (±)-scopadulin.[205] The reaction used by the Tanaka group is outlined in Scheme 3.19, where acetal cleavage of **152** resulted in an aldol condensation under the acidic conditions to give the bicyclic enone **153** in 90% yield.

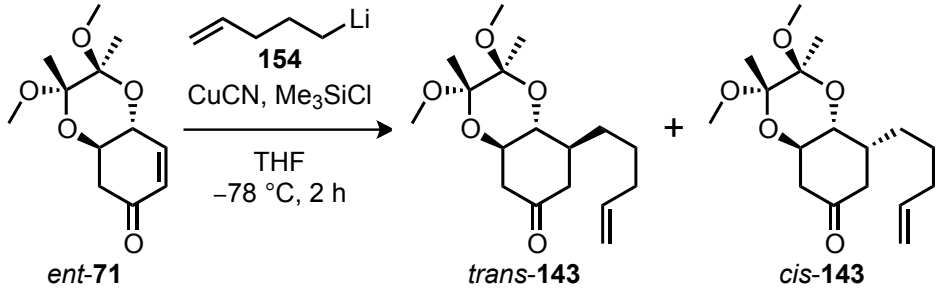


Scheme 3.19: *The Tanaka group's synthesis of a methyl dealcone* ***153***

With this encouraging precedent, the first steps in our aldol annulation route were taken. Following Tanaka's procedure, *trans*-**144** was stirred with catalytic HCl in MeOH at rt.[205] The result was discernable aldol products but multiple isomers were present (as shown in the ^{1}H NMR spectrum of the crude product). No starting material remained but the result was a complex mixture of products including some aromatised compounds (by ^{1}H NMR spectroscopy). Unfortunately, it was not possible to isolate any pure compounds from this experiment. We speculate that milder cyclisation conditions were needed to preserve the acid-labile BDA protecting group.

Our studies were limited by the amount of diastereomerically enriched keto-aldehyde *trans*-**144** available to us. Aldol reactions were attempted on the *ca* 50:50 mixtures of *trans*-**144** and *cis*-**144** (obtained from the poorly diastereoselective additions of the butenyl Grignard) but the aldol step gave increased complexity due to the diastereomeric mixtures possible. We really needed *trans*-**144** in >90:10 dr. Thus, we decided to investigate the previously more reliable alkyllithium-derived cuprate. The use of pentenyllithium in a cuprate reaction would give pentenyl adduct **143** which on oxidative alkene cleavage would give the same keto aldehyde **144**.

As with butenyllithium, pentenyllithium is not commercially available and so required synthesis from the corresponding 5-bromopentene *via* a halogen-lithium exchange reaction. The halogen-lithium exchange reaction to form pentenyllithium **154** was successful resulting in titrateable pentenyllithium as a solution in Et_2O. Pentenyllithium was then used in a cuprate addition reaction with enone *ent*-**71**. A typical pentenyl cuprate reaction with enone *ent*-**71** was carried out using the following procedure. Pentenyllithium was freshly prepared by a halogen-lithium exchange reaction between lithium wire and 5-bromopentene. The organolithium was titrated using *N*-benzylbenzamide three times and an average of the titres taken. Pentenyllithium (2.4 eq.) was then added to CuCN (1.2 eq.) in THF at −78 °C. On formation of the cuprate species, a solution of enone *ent*-**71** in THF was added dropwise. Products *trans*-**143** and *cis*-**143** were isolated as inseparable mixtures of diastereomers for which the dr was determined by analysis of the ^{1}H NMR spectra of the isolated mixtures. Following this procedure, the results for four reactions are presented in Table 3.3.



Scheme 3.20: *Pentenyl cuprate additions enone ent-71*

Entry	Yield[a] (%)	dr[b] (*trans*:*cis*)
1	83[c]	50:50
2	89[c]	50:50
3	87[c]	93:7
4	91[c]	77:23

[a]*Yield of product after chromatography* [b]*Ratio of trans- and cis-diastereomers by* ^{1}*H NMR spectroscopy after chromatography* [c]*TBAF desilylation after an aqueous work-up*

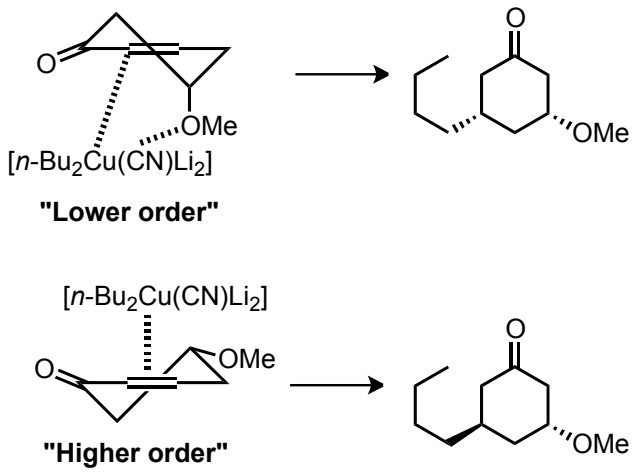
Table 3.3: *Pentenyl cuprate additions enone ent-71*

All attempts showed good isolated yields of pentenyl adducts (83–91%), but diastereoselectivity varied from 93:7 of *trans*-**143** and *cis*-**143** (entry 3) to a 50:50 mixture of *trans*-**143** and *cis*-**143** (entry 1). Many reactions under seemingly identical conditions were attempted with no reproducible diastereoselectivity established. For all these reactions, a rt solution of enone *ent*-**71** had been added dropwise *via* a syringe and syringe-pump set-up. The rate of addition was altered to investigate if this was the source of the variation. Numerous repetitions at a range of addition rates showed no trend in the resulting diastereoselectivity.

Cooled solutions of enone *ent*-**71** at −78 °C were cannula-transferred in an attempt to control the reaction temperature more effectively. These attempts were hindered by the limited solubility of enone *ent*-**71** at −78 °C resulting in a blockage of the cannula. At decreased solution concentrations, blockage was prevented but reactions did not follow any discernable pattern in diastereoselectivity. Several reactions were attempted in which the solution of enone *ent*-**71** was added down the inside of the reaction flask with the aim of controlling temperature without the need to decrease the enone solution concentration. The diastereoselectivity of these reactions was also variable.

We investigated the pentenyllithium formation in more detail as we suspected that this could be the source of the variability. The halogen-lithium exchange would result in a lithium bromide by-product. In addition, quenching of pentenyllithium would also result in lithium hydroxide as a side-product. Salt additives have proven important in determining the diastereoselectivity of a number of reactions.[158] To investigate the importance of either of these salts in our pentenyl process, cuprate reactions were doped with ten equivalents of both salts. Results initially indicated no diastereoselectivity for the reactions carried out in the presence of lithium hydroxide or lithium bromide. However, on repeating these experiments, both reactions gave a modest dr in favour of *trans*-**143**.

The diastereoselectivity for cuprate reactions has been shown, in certain systems, to vary with the stoichiometry of the cuprate species. Higher order cuprates [$R_2Cu(CN)Li_2$] have been shown to proceed to give the expected kinetic cuprate product while lower order species [RCu(CN)Li] are considered coordinatively unsaturated and hence under chelation control can give products not normally expected for a kinetically-determined reaction. This process has been demonstrated by a number of groups and an example from the Sato group is shown in Scheme 3.21.[206]



Scheme 3.21: *Sato's observed coordination of lower order cuprates*

Whilst the existence of a distinct higher order species is disputed, the results found in the literature undeniably point to the importance of the stoichiometry used in formation of the cuprate. Due to this precedent, reactions were carried out using altered stoichiometry of CuCN and organolithium. However, a reaction with a higher pentenyllithium loading gave the same 99:1 diastereoselectivity as a reaction containing a higher loading of CuCN. These reactions were undertaken using pentenyllithium from the same halogen-lithium exchange reaction. Using this same pentenyllithium material, two reactions under standard stoichiometry were undertaken side-by-side as controls. Both these reactions gave poor yields with no diastereoselectivity.

It is also worth considering the affect of the alkene present in the cuprate side chain. A study by Yamamoto showed the importance of a secondary π-interaction with the

cuprate species (Figure 3.3). The π-interaction investigated by Yamamoto was a substrate-controlled interaction of an alkyne with dimethyl cuprate. The interaction of the less Lewis acidic pentenyl alkene would be less pronounced than an alkyne. Also, as part of the cuprate complex we do not suggest that it is a directed effect causing diastereomeric complications. However, the ability of a diorganocuprate complex to interact through multiple π-interactions would suggest that a dipentenyl cuprate species could have multiple π-interactions between the alkene moieties and the copper centres. This would affect not only the aggregate state of the copper clusters but also the ability of the copper complexes to undergo the necessary π-complexation to enone *ent*-**71**. The structure of the cuprate complex has already been shown to be highly dependent on various factors (additives, solvent, salts). Any π-complexation may accentuate the variability in the structural characteristics of the cuprate complex and hence the reactivity exhibited by these structures.

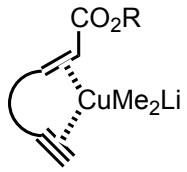
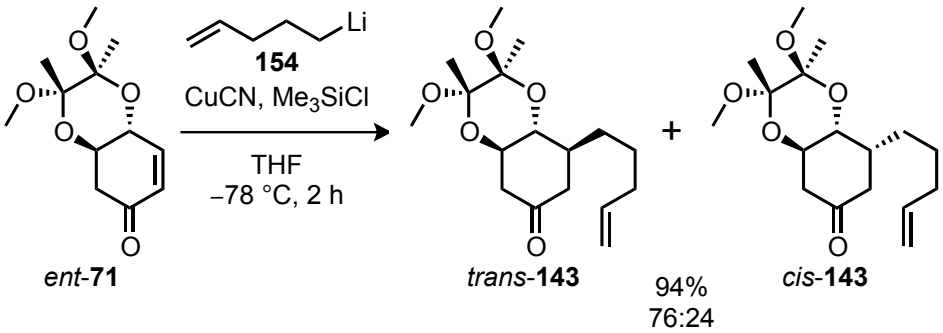


Figure 3.3: *π-π Chelation-control of cuprate 1,4-addition*

In a final attempt to produce reproducible diastereoselectivity, the halogen-lithium exchange reaction was filtered prior to titration in order to remove the soluble salts. A cuprate reaction under standard conditions with this organolithium gave a 94% yield and 76:24 dr (*trans*-**143**:*cis*-**143**). Two repetitions did give similar results (75:25 dr) but not with the high diastereoselectivity (93:7 dr) of the first reaction.

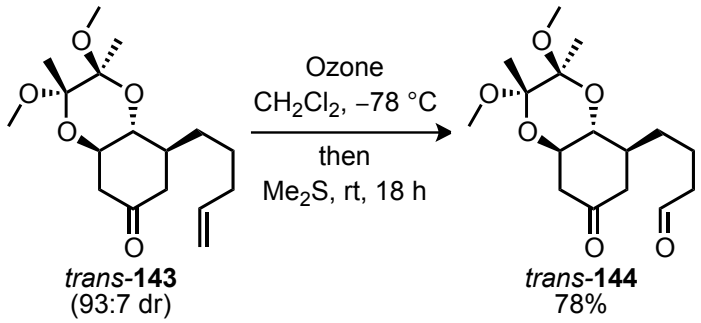


Scheme 3.22: *Filtered pentenyl cuprate addition result*

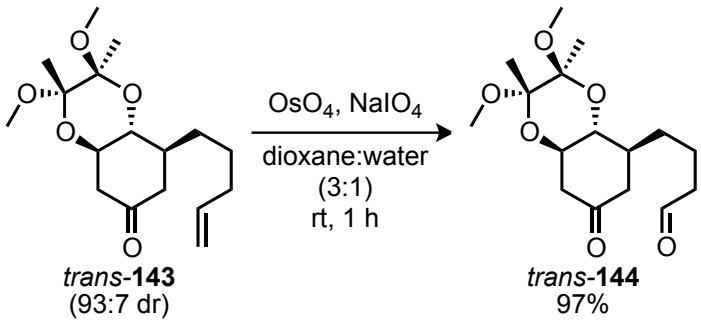
At this point, further studies into the diastereoselectivity of pentenyl cuprate additions to enone *ent*-**71** were halted. In the proposed route to bicyclic model compound **81**, the pentenyl addition adduct would be oxidised, resulting in the removal of the β-stereocentre. We therefore continued with the diasteromerically enriched material to investigate the aldol condensation reaction with a view towards the assessing the aldol condensation reaction.

3.3.3 Investigations into an Aldol-Based B-ring Annulation Approach

Our previous attempts at an acid-catalysed aldol condensation had resulted in a complex mixture of aldol products as well as some aromatised side products. It was hoped that through a screen of reaction conditions we could establish conditions that would resolve the current limitations. Oxidative alkene cleavage of *trans*-**143** was first required. Fortunately, using *trans*-**143** (93:7 dr), ozonolysis afforded aldehyde **144** in 78% yield (Scheme 3.23). Alternatively, under Lemieux–Johnson conditions of osmium tetroxide and sodium periodate,[207] alkene *trans*-**143** (93:7 dr) was converted into keto aldehyde *trans*-**144** in 97% yield (Scheme 3.24). In both cases the aldehyde product *cis*-**144** from *cis*-**143** was not observed.

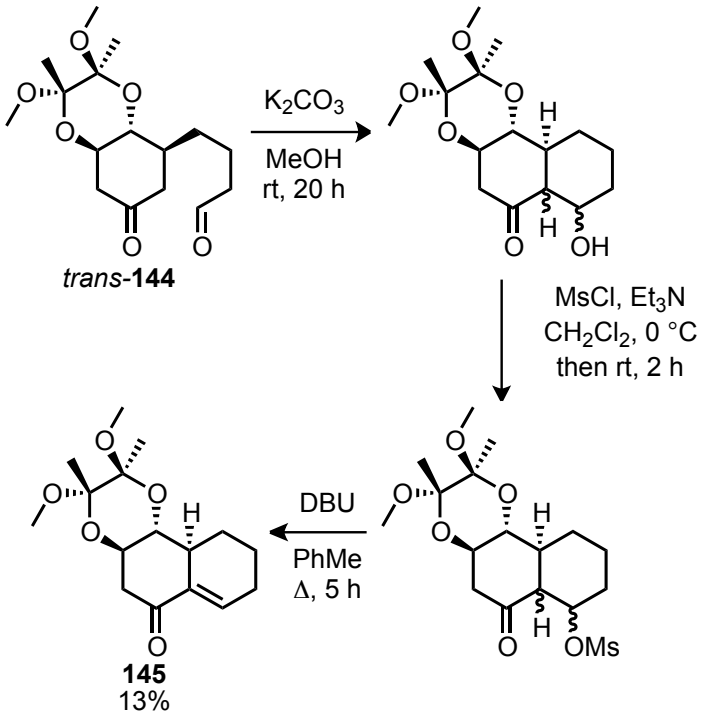


Scheme 3.23: *Ozonolysis oxidative alkene cleavage of trans-**143***



Scheme 3.24: *Lemieux-Johnson oxidative alkene cleavage of trans-**143***

Aldehyde *trans*-**144** was stirred at rt in MeOH in the presence of K_2CO_3 to give a complex mixture of aldol products (Scheme 3.25). The crude mixture was treated with mesyl chloride to give a mixture of mesylated adducts with a trace of enone **145** present on analysis of the ^1H NMR spectrum of the crude product. The crude mesylated material and DBU were then heated at reflux in toluene over 5 h and, after purification, a 13% yield of the desired enone **145** was obtained. The harsh elimination conditions could be responsible for the lack of recovered material as enone **145** was the only isolated compound.



Scheme 3.25: *Aldol condensation to give enone **145***

The reluctance of the aldol products to undergo a condensation reaction suggested that the stereochemistry defined in the aldol reaction may not have the required antiperiplanar arrangement of the hydroxyl/mesylate and the adjacent enolic-hydrogen to facilitate an E_2 or E_{1cb} elimination pathway. Both acid- and base-catalysed aldol condensation processes were investigated with numerous attempts made. Results were complex and never yielded higher than the 13% of enone **145**. Alternative aldol condensation reactions were sought and organocatalytic aldol chemistry was therefore attempted.

Organocatalysis has become increasing prevalent in all areas of synthetic chemistry,[208] and examples include proline-catalysed aldol processes.[209-211] It was postulated that using a chiral organocatalyst the preferential formation of a single aldol product could be achieved. Proline-mediated aldol chemistry offered an attractive starting point. If a chelation-controlled aldol reaction did occur then the use of either commercially available proline enantiomer should, following a Houk-type mechanism,[212] dictate the facial selectivity and therefore diastereoselectivity of the reaction (Figure 3.4).

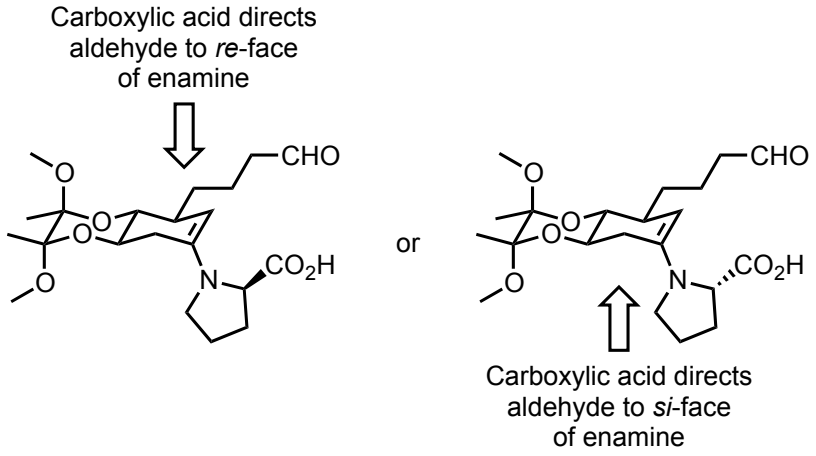
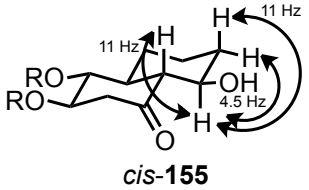


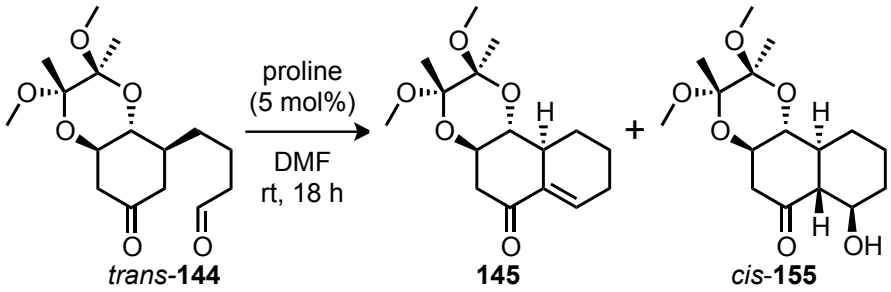
Figure 3.4: *Houk-type mechanism for proline-catalysed intramolecular aldol condensation*

Using (*R*)- or (*S*)-proline, the aldol condensations were attempted (Scheme 3.25 and Table 3.4). In two reactions, aldehyde *trans*-**144** was treated with either (*R*)- or (*S*)-proline in DMF. After 17 h, (*R*)-proline gave enone **145** in 35% yield along with a 22% isolated yield of aldol product *cis*-**155** (tentatively assigned by ^{1}H NMR) (entry 1). (*S*)-Proline gave enone **145** but in a lower 19% yield along with a 46% yield of aldol product *cis*-**155** (entry 2). Aldol adduct *cis*-**155** was assigned by the C*H*OH proton. It is present as a triplet of doublets with two large 11 Hz *trans*-diaxial couplings and a smaller 4.5 Hz axial-equatorial coupling (Figure 3.4).



cis-**155**

Figure 3.4: *^{3}J couplings of cis-**155***



Scheme 3.25: *Proline-catalysed aldol condensation of keto aldehyde trans-**144***

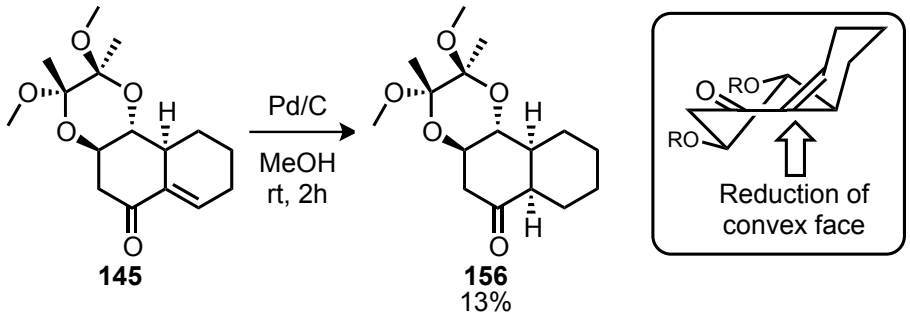
Entry	Proline Enantiomer	Yield 145[a] (%)	Yield 155[a] (%)
1	*R*	35	22
2	*S*	19	46

[a]*Yield of product after chromatography*

Table 3.4: *Proline catalysed aldol condensation of keto aldehyde trans-**144***

We tentatively postulate that the (*R*)-proline-catalysed aldol reaction results in two diastereomeric aldol products. The major aldol product undergoes an elimination reaction resulting in enone **145**. The minor aldol product is *cis*-**155** which does not undergo an elimination process. The same two aldol diastereomers are formed in the (*S*)-proline reaction but in the opposite ratio leading to a greater formation of the aldol *cis*-**155** over enone **145**.

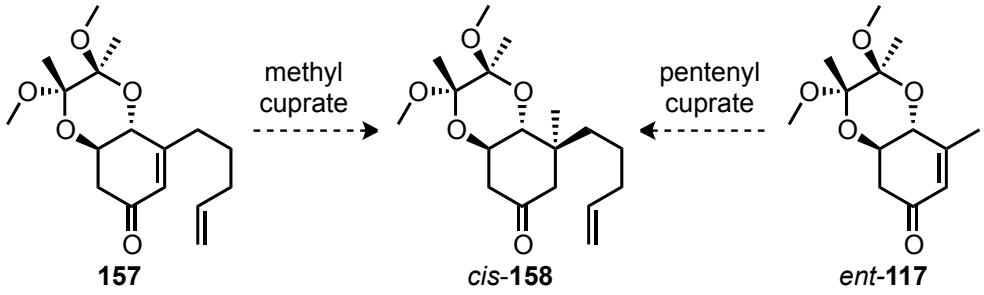
In the proposed synthesis of *trans*-decalin-diol **81**, the enone intermediate resulting from an aldol condensation annulation would be required to undergo a stereoselective reduction to give a *trans*-decalone **81**. Thus, enone **145** was stirred with palladium on carbon under a hydrogen atmosphere. This resulted in a 13% yield of a decalone that is tentatively assigned by analysis of the ^{1}H NMR spectrum, as *cis*-decalone **156** (Scheme 3.26). Decalone **156** decomposed on standing overnight. The hydrogenation of bridgehead enones has a precedence for reduction to a *cis*-decalin-type structure based on the bowl-shape of the enone starting material.[213-215]



Scheme 3.26: *Hydrogenation of enone **145***

3.4 Efforts Towards an AB-ring Compound from β-Disubstituted Ketones

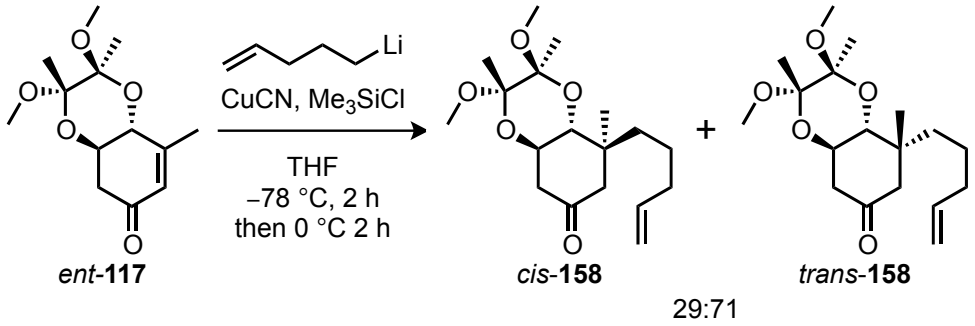
Finally, we investigated the synthesis of a β-disubstituted ketone with the methyl and pentenyl group with a view to the synthesis of the AB-ring model compound **81**. Previous reactions had indicated that a methyl cuprate addition to a β-substituted enone (**157**) should result in the same major diastereomer (*cis*-**158**) as the pentenyl cuprate addition to β-methyl enone *ent*-**117** (Scheme 3.27).



Scheme 2.27: *Methyl and pentenyl cuprate options towards β-disubstituted ketone cis-**158***

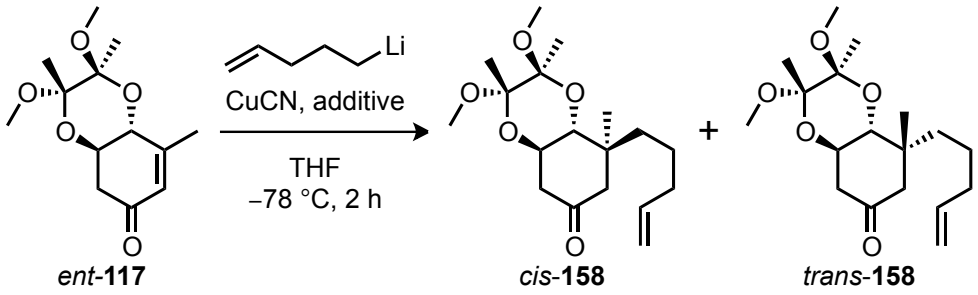
Following the method previously developed, β-methyl enone *ent*-**117** was reacted with a pentenyl cuprate in the presence of Me_3SiCl (Scheme 3.28). After 2 h at −78 °C, the reaction showed no sign of product by TLC analysis. Warming to 0 °C and stirring for 2 h showed the formation of some product. On purification, adduct *trans*-**158** was isolated in 20% yield but was assigned tentatively based on ^{1}H NMR. The stereochemistry of this adduct was determined by ^{1}H NMR nOe experiments. From the chromatography another fraction was isolated which contained an 86:14 mixture of starting enone *ent*-**117** and *cis*-**158**. The adducts isolated gave *trans*-**158** and *cis*-**158** in a ratio of 29:71. These results are surprising as they give the opposite major diastereomer to that predicted based on the *n*-butyl/methyl model study. This

reaction was only carried out once and with the capricious nature of pentenyl cuprate additions in our systems, the diastereoselectivity observed cannot be drawn as definitive.



Scheme 3.28: *Pentenyl cuprate addition towards β-disubstituted ketone* ***158***

If sufficient amounts of *cis*-**158** could be obtained then efforts could progress towards a bicyclic model compound. In an effort to improve the yield of the process, pentenyl cuprate additions to β-methyl enone *ent*-**117** where carried out in the presence of additives (Scheme 3.29, Table 3.5) at −78 °C. In the presence of HMPA and Me_3SiCl, a 50:50 inseparable mixture of *trans*-**158** and *cis*-**158** was isolated in 55% yield (entry 1). The increased yield demonstrates that HMPA leads to increased reactivity of the cuprate.[125,216] Another effective additive in these reactions is $BF_3{\cdot}OEt_2$.[125,217,218] In the presence of $BF_3{\cdot}OEt_2$, a 50:50 mixture of *trans*-**158** and *cis*-**158** were isolated in 65% yield (entry 2). Both additives improve the yield of product but there was no diastereoselectivity. It is not clear if this is a result of a less diastereoselective but more reactive cuprate species being formed in the presence of the additive or the result of the capricious nature of the pentenyl cuprate reactions in general.



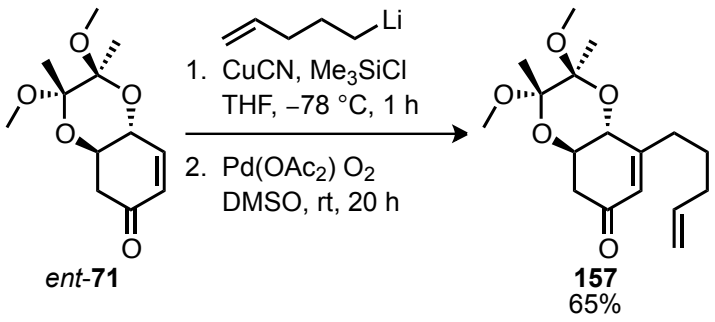
Scheme 3.29: *Pentenyl cuprate addition to β-methyl enone ent-**117***

Entry	Additive	Yield 158[a] (%)	dr[b] (*trans*-**158** : *cis*-**158**)	Starting material[a] (%)
1	HMPA, Me_3SiCl	55[c]	50:50	32
2	$BF_3{\cdot}OEt_2$	65	50:50	14

[a]Yield of product after chromatography [b]Ratio of trans- and cis-diastereomers by ^{1}H NMR spectroscopy after chromatography [c]TBAF desilylation after an aqueous work-up where required.

Table 3.5: *Pentenyl cuprate addition to β-methyl enone ent-**117***

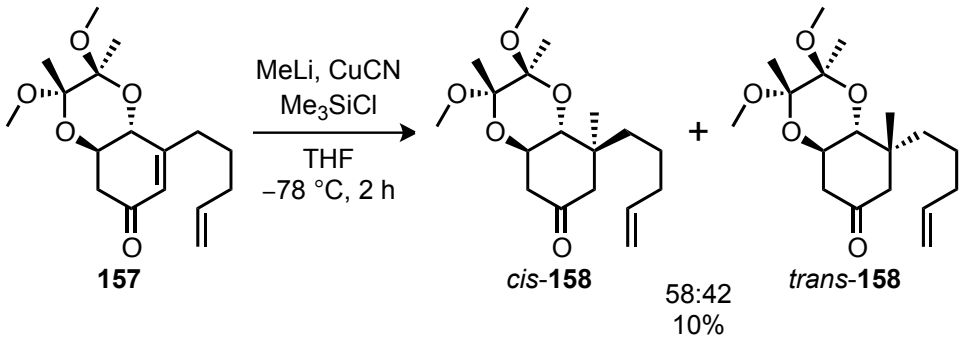
The addition of methyl cuprate to β-pentenyl enone **157** was investigated next. Preparation of a β-pentenyl enone **157** was required. Thus, addition of a pentenyl cuprate to enone *ent*-**71** in the presence of Me_3SiCl and Saegusa oxidation of the resulting silyl enol ether gave β-pentenyl enone **157** in 65% yield (Scheme 3.30).



Scheme 3.30: *Formation of β-pentenyl enone **157***

Enone **157** was then reacted with a methyl cuprate. Under standard conditions, methyl cuprate was reacted with β-pentenyl enone **157** at −78 °C. Unfortunately, the reaction proceeded slowly and gave a 58:42 mixture of *trans*-**158** and *cis*-**158** in only 10% yield (62% of starting enone **157** was recovered) (Scheme 3.31). The use of additives did not increase the overall yield in this case with no product isolated and

complete recovery of starting material in the presence of HMPA. A $BF_3.OEt_2$-promoted reaction led to compete decomposition of starting material.

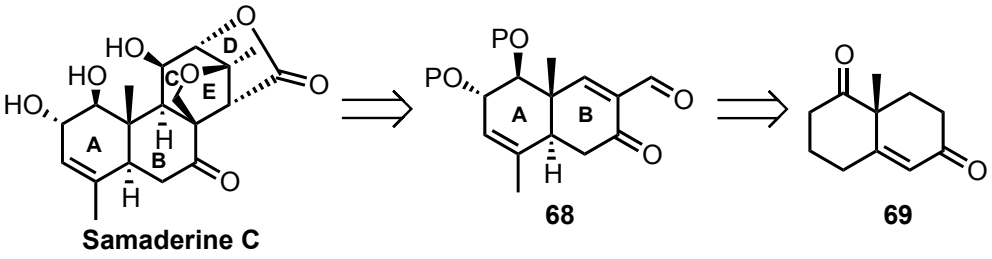


Scheme 3.31: *Methyl cuprate addition to β-pentenyl enone **157***

At this stage, we halted further study into the double 1,4-addition route to a model compound. The route did allow access to a de-methylated bicyclic structure **145**. However, we have identified a number of limitations with our double conjugate addition methodology. The yields from the second conjugate addition to the β-substituted enone were generally low or with poor diastereoselectivity. However, we did discover some interesting diastereoselectivity in a simplified *n*-butyl/methyl system. The RCM approach would need to be investigated further to overcome the problem of 1,4-additions to a cross conjugated enone. The aldol condensation method suffered from poor yields of the desired enone while a successful method of selective reduction to the *trans*-decalin still needed to be established. Due to these limitations and the time remaining for these studies, further work into the synthesis of AB-ring model compound **81** *via* a double conjugate addition process was paused while an alternative strategy was investigated.

Chapter 4: Samaderine C AB-Ring Synthesis: The Wieland-Miescher Ketone Approach

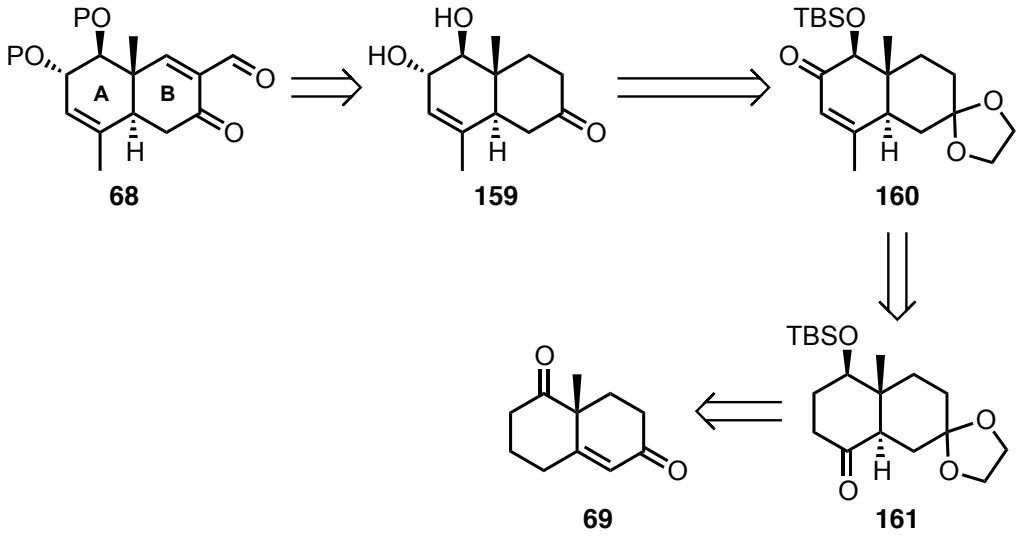
At this point, it was clear that the double 1,4-addition strategy to an AB-ring model of samaderine C may not prove fruitful. We therefore turned our attention to an approach from the Wieland-Miescher ketone **69** (Scheme 4.1). Our alternative approach to samaderine C hinged on the synthesis of an AB-ring structure such as dienophile **68** and its ultimate reaction in a Diels-Alder annulation.



Scheme 4.1: *Retrosynthesis of samaderine C back to Wieland-Miescher ketone* ***69***

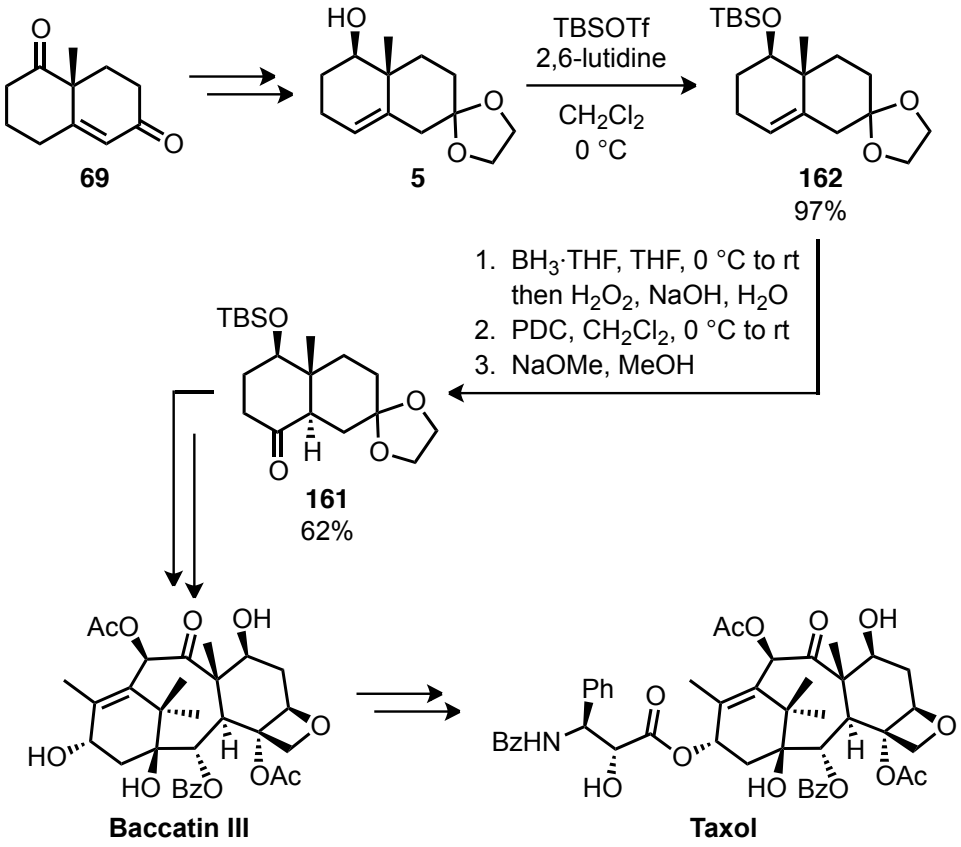
4.1. Strategy to AB-ring Structures from the Wieland-Miescher Ketone

A retrosynthetic analysis of dienophile **68** is outlined in Scheme 4.2. We foresaw that α-formyl enone **68** would be accessed from ketone **159** using the chemistry mirroring Grieco's approach in the synthesis of samaderine B (see Scheme 1.5). The biggest challenge with this route was anticipated to be the diastereoselective reduction of a protected α-hydroxy enone **160**. We recognised from the outset that reduction of the enone carbonyl must occur on the same face as the axial bridgehead methyl group to give the required *trans*-diol configuration. We hoped that the inherent steric substrate control could be overturned using an asymmetric reductant. Enone **160** would be gained from a 1,3-carbonyl transposition *via* addition of a methyl nucleophile and oxidation with PCC from known ketone **161**.[219] Following established chemistry, ketone **161** would be reached from the Wieland-Miescher ketone **69**.



Scheme 4.2: *Retrosynthesis of dienophile **68** back to the Wieland-Miescher ketone **69***

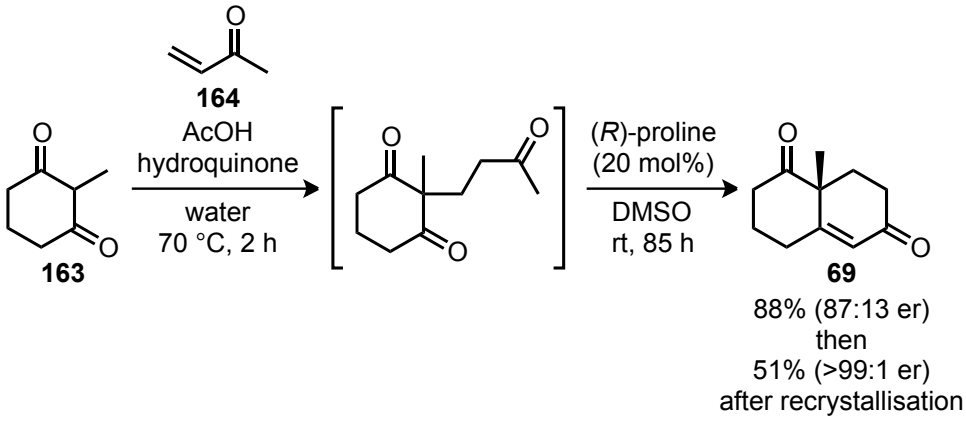
Known ketone **161** was a key intermediate in Danishefsky's famous synthesis of baccatin III and taxol.[219] Its synthesis shares chemistry used in Grieco's synthesis of neoquassin and quassin (see Scheme 1.5). As shown in Scheme 4.3, Danishefsky started from the Wieland-Miescher ketone **69** and used the reduction/acetylation chemistry developed by Boyce[50] and the isomerative ketalisation step outlined by Heathcock to give alcohol **5**. Silyl protection as the TBS ether then gave ether **162**.[51] Oxygenation of the A-ring was achieved using a hydroboration reaction, which on oxidative work up, PDC oxidation and sodium methoxide mediated isomerisation gave ketone **161**. Further steps then gave baccatin III and taxol in this historic piece of organic synthesis.



Scheme 4.3: *Danishefsky's route to ketone **161**, used to access Baccatin III and Taxol*

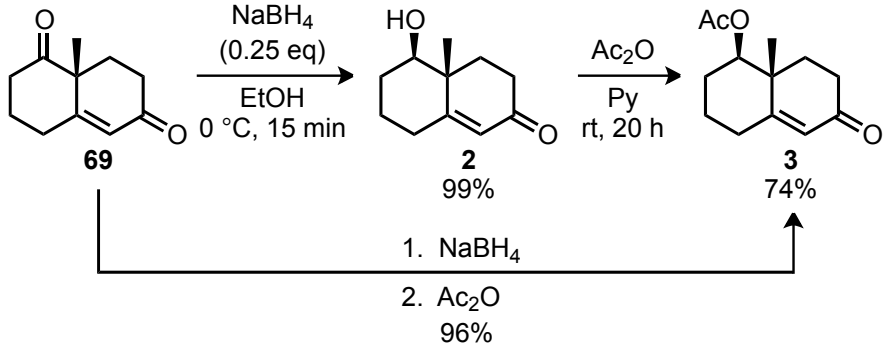
4.2 Synthesis of a β-Methyl Enone and Investigation of its Reduction

Our efforts began with the synthesis of Wieland-Miescher ketone **69** following a literature procedure.[220] 2-Methyl-1,3-cyclohexanone **163** and methyl vinyl ketone **164** were stirred in water at 75 °C for 2 h in the presence of acetic acid and hydroquinone (Scheme 4.4). The resulting Michael product was then treated with (*R*)-proline in DMSO at 40 °C to furnish ketone **69** in 88% yield and 87:13 er by CSP-HPLC. Both yield and enantioselectivity were commensurate with that previously reported.[220] The Wieland-Miescher ketone **69** (20.0 g) was then recrystallised once from hot Et_2O to give **69** (10.3 g) as a single enantiomer (>99:1 er by CSP-HPLC) in 51% yield over the Hajos-Parish reaction and recrystallisation procedure.



Scheme 4.4: *Hajos-Parish reaction to give Wieland-Miescher ketone* ***69***

With *ca.* 10 g of Wieland Miescher ketone **69** in hand, work could now begin on the synthesis of dienophile **68**. Following a method developed by Boyce and Whitehurst, ketone **69** was reduced with 0.25 eq. of $NaBH_4$ to alcohol **2** in excellent yield (99%) and with complete diastereoselectivity for the equatorial alcohol (Scheme 4.5).[50] Figure 4.1 depicts the source of stereoselectivity in this reaction. It can be rationalised by preferential attack of the borohydride reagent on the ketone carbonyl in a *pseudo*-axial manner, an approach that would minimise steric interactions with the adjacent axial methyl group. Alcohol **2** was protected as the acetate by treatment with acetic anhydride in pyridine, giving acetate **3** in 74% yield.[51] A better procedure involved protecting the crude alcohol **2** as the acetate. This telescoped method gave acetate **3** in 96% yield, over the two steps (Scheme 4.5).



Scheme 4.5: *Reduction and acetylation to acetate* ***3***

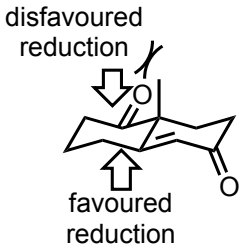
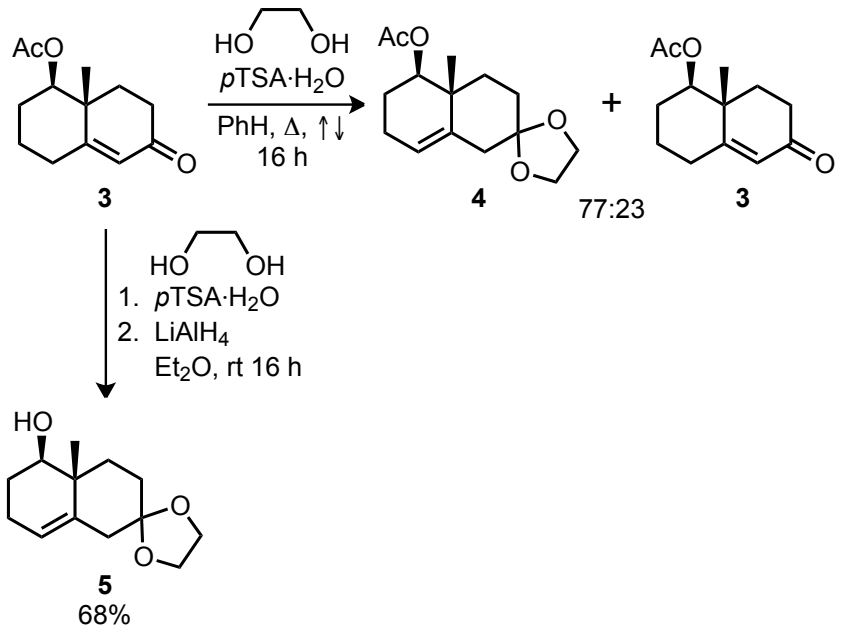


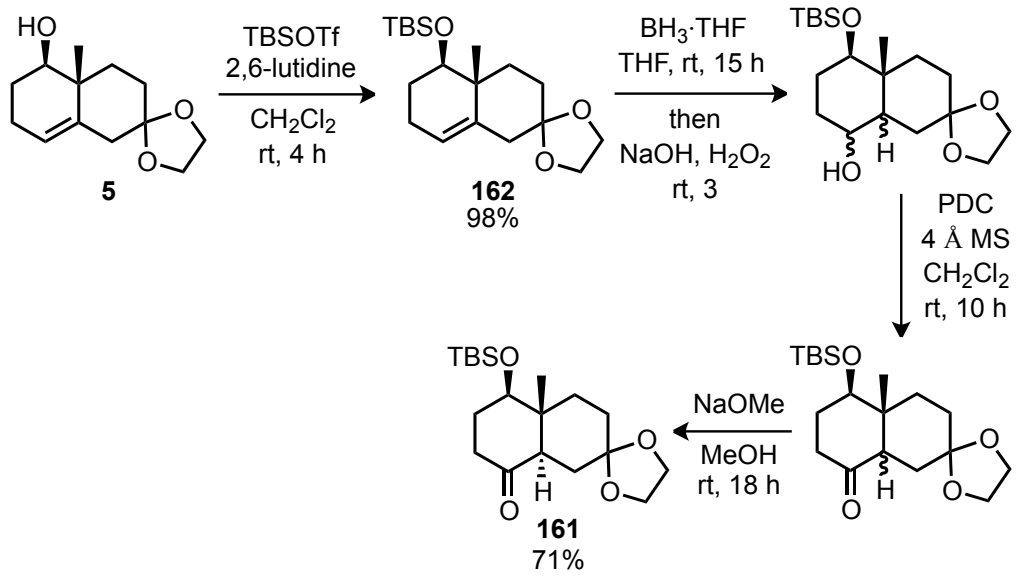
Figure 4.1: *Axial bridgehead methyl-directed reduction of Wieland-Miescher ketone* ***69***

Next, the isomerative ketalisation reaction of acetate **3** to ketal **4** was investigated (Scheme 4.6). However, this step proved synthetically inconvenient as the reaction did not proceed to completion. Instead, a 77:23 mixture of ketal **4** and starting acetate **3** was obtained. Separation of the desired ketal **4** from the starting acetate **3** proved difficult. An improved procedure involved telescoping the crude mixture from the isomerative ketalisation reaction into a deprotection step using $LiAlH_4$. This procedure provided alcohol **5** in 68% yield over both steps (Scheme 4.6).[51]



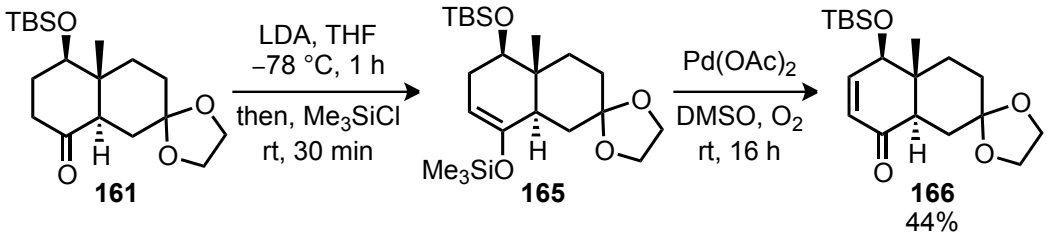
Scheme 4.6: *Isomerative ketalisation and telescoped procedure to alcohol* ***5***

Alcohol **5** was silylated using TBSOTf and 2,6-lutidine to give TBS ether **162** in near-quantitative yield (98%). Then, following Danishefsky's procedure,[219] the alkene in **162** was hydroborated with $BH_3 \cdot THF$ and subsequent oxidative work-up gave a crude alcohol product (Scheme 4.7). This crude alcohol was oxidised using PDC and then epimerised to *trans*-decalone **161** in 71% isolated yield over the three steps.



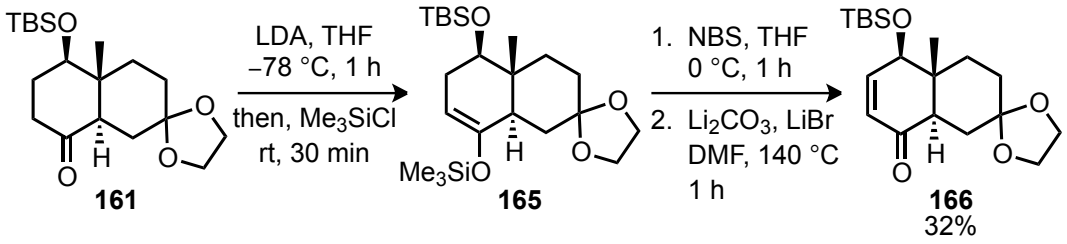
Scheme 4.7: *Hydroboration-oxidation-epimerisation procedure to ketone **161***

The first novel step in our approach to the AB-rings of samaderine C required an oxidation of ketone **161** to enone **166** (Scheme 4.8). Oxidation of silyl enol ethers using $Pd(OAc)_2$ had previously proven successful within the project so this approach was examined first. The formation of the kinetic enolate from ketone **161** and trapping with Me_3SiCl would give a silyl enol ether which on treatment with $Pd(OAc)_2$ would oxidise to the desired enone **166**. Therefore, enone **161** was treated with LDA at −78 °C and trapped with Me_3SiCl to give silyl enol ether **165**. This crude intermediate was then submitted to a catalytic Saegusa oxidation resulting in formation of enone **166** in 44% yield. Since analysis of the ^1H NMR spectrum of the crude silyl enol ether **165** showed complete conversion, the oxidation step appears to be the cause of the low yield. As a result, other methods for this functional group interconversion were explored.



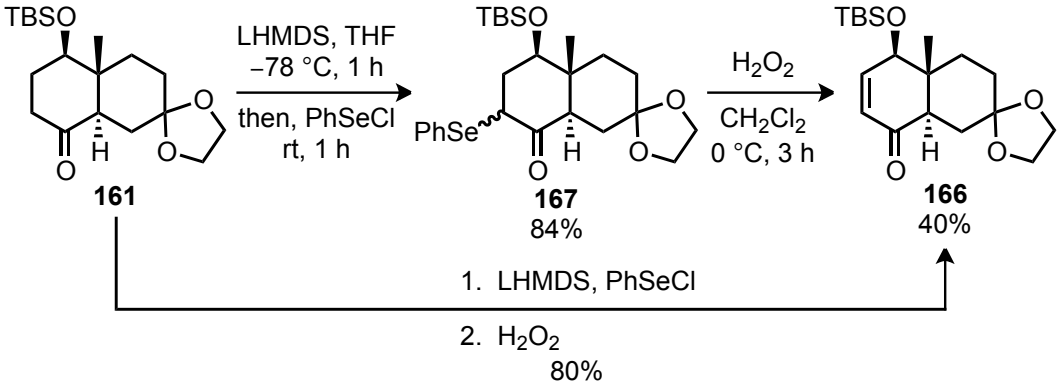
Scheme 4.8: *Saegusa oxidation to enone **166***

A bromination-elimination route to enone **166** was also investigated (Scheme 4.9). Using the same kinetic enolate forming conditions, silyl enol ether **165** was formed. Bromination using recrystallised NBS gave a bromide of undetermined diastereomeric composition. This crude bromide was then eliminated using Li_2CO_3 and LiBr in DMF at high temperature to give enone **166** in a disappointing 32% yield. A higher yielding method into convert ketone **161** to enone **166** was still required.



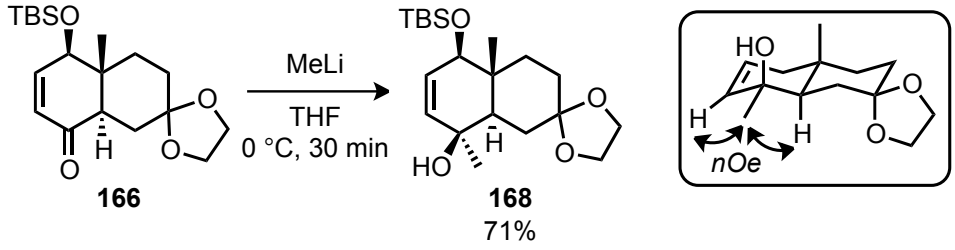
Scheme 4.9: *Bromide formation and elimination to enone **166***

The formation of keto selenides and β-elimination of the corresponding selenoxides is an alternative methodology for the conversion of ketones into enones.[221] Therefore, ketone **161** was deprotonated using LHMDS at –78 °C and reacted with phenylselenyl chloride to form a 50:50 diastereomeric mixture of selenides **167** in 84% isolated yield (tentatively assigned by ^{1}H NMR) (Scheme 4.10). Oxidation of the mixture of selenides **167** using hydrogen peroxide gave apparently complete conversion to enone **166** (by analysis of the ^{1}H NMR spectrum of the crude material) but enone **166** was isolated in a low 40% yield. A better yield was obtained if the mixture of selenides was not isolated. Ketone **161** was deprotonated using LHMDS and quenched with phenylselenium chloride to give the crude mixture of selenides **167**. This crude mixture was then oxidised using hydrogen peroxide to give enone **166** in 80% yield over the two steps (Scheme 4.10).



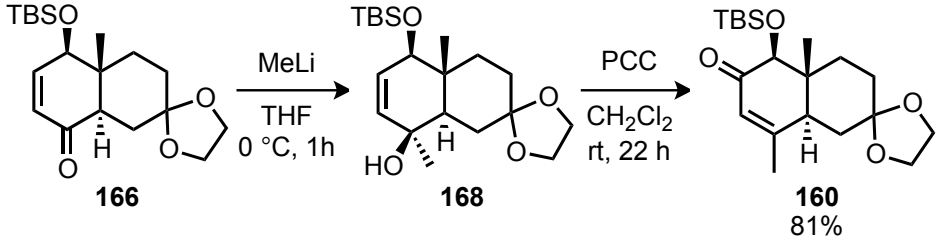
Scheme 4.10: *Selenide formation and oxidation to enone* ***166***

We were now set to address the key 1,3-carbonyl transposition process. It was hoped that the methyl group could be installed at the same time to give a β-methyl enone. The reaction envisaged was a Dauben oxidation[222] of the tertiary alcohol, formed from a 1,2-addition of MeLi with ketone **166**. To that affect, MeLi was added to enone **166** in THF at 0 °C to give tertiary alcohol **168** as a single diastereomer on analysis of the ^{1}H NMR spectrum of the crude product (Scheme 4.11). Alcohol **168** was isolated in 71% yield. The allylic stereochemistry could be assumed based on literature precedent in structurally similar systems[223,224] and a 1,3-diaxial clash of the incoming methyl nucleophile and the axial bridgehead methyl group. However, further evidence of this product was obtained through nOe experiments. Irradiation of the allylic methyl group showed interactions only with the adjacent vinylic and bridgehead hydrogens (Scheme 4.11).



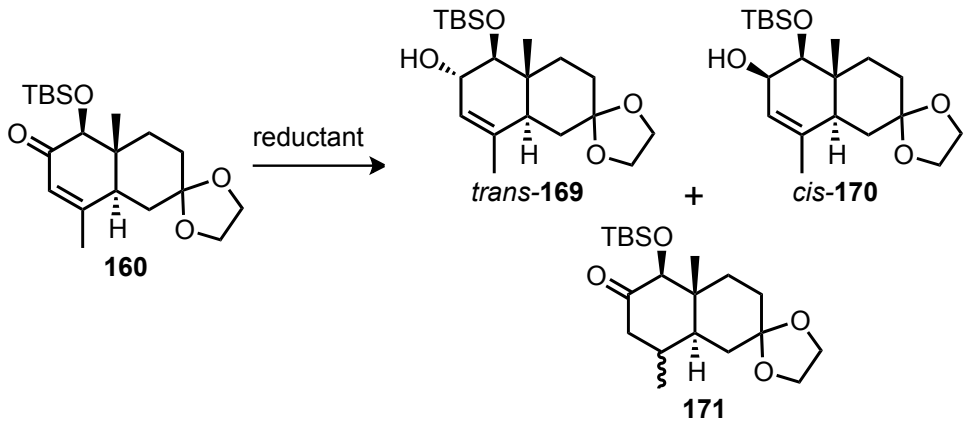
Scheme 4.11: *Isolation of allylic alcohol* ***168***

The formation of tertiary alcohol **168** was sufficiently clean to allow the use of the crude tertiary alcohol material in the Dauben oxidation step (Scheme 4.12). Methyllithium was added to enone **166** and, without purification, alcohol **168** was submitted to the Dauben oxidation reaction (PCC in CH_2Cl_2 at rt for 22 h). The reaction proceeded to completion and, to our delight, afforded an 81% yield of β-methyl enone **160**.



Scheme 4.12: *MeLi addition to enone **166** and Dauben oxidation to β-methyl enone **160***

As discussed previously, it was hoped that the stereoselective reduction β-methyl enone **160** would give a *trans*-allylic diol A-ring as present in **159**. With this in mind, a series of reductions of β-methyl enone **160** was attempted (Scheme 4.13 and Table 4.1). These reactions were carried out on a 10 mg scale (0.03 mmol), with the crude mixtures analysed ^{1}H NMR spectroscopy. Assignment of *trans*-diol products and *cis*-diol products was relatively straightforward. A larger (*ca*. 9 Hz) ^3J *trans*-diaxial coupling was expected for the *trans*-diol **169** product while the *cis*-diol product **170** should show a smaller ^3J diequatorial coupling (*ca*. 5 Hz).



Scheme 4.13: *Reduction of β-methyl enone* ***160***

Entry	Reduction Method	*trans*-**169**	*cis*-**170**	1,4-Reduction Product 171	Starting Material
1	$NaBH_4$[a]	×	✓	×	×
2	$NaBH_4$ $CeCl_3 \cdot 7H_2O$[a]	×	✓	✓	×
3	DIBAL-H[b]	×	✓	×	×
4	$LiAlH_4$[b]	×	✓	×	×
5	L-Selectride[b]	×	✓	✓	×
6	BH_3·THF[b]	×	✓	×	×
7	SmI_2[b]	×	×	×	✓
8	$Al(O\textit{i}\text{-}Pr)_3$, *i*-PrOH, Δ	×	×	×	✓
9	Li*t*-BuO_3AlH[b]	×	×	×	✓

[a]*Conditions: MeOH 0 °C.* [b]*Conditions: THF, 0 °C*

Table 4.1: *Reduction of β-methyl enone* ***160***

Unfortunately, none of the reduction methods attempted showed any evidence of reduction to diol *trans*-**169**. Standard reducing agents such as $NaBH_4$, $NaBH_4/CeCl_3$, DIBAL-H and $LiAlH_4$ (entries 1-4) showed complete conversion with diol *cis*-**170** as the major product. Interestingly, addition of the $CeCl_3$ for the Luche reduction (entry 2) altered the selectivity towards a 1,4-reduction. The 1,4-reduction product was identified using a doublet of 3H integration (CH*Me*) but we were unable to

determine the configuration. L-selectride also showed substantial amounts of 1,4-reduction (entry 5).

We had originally foreseen the difficulty in reduction to a *trans*-diol product. However, we had hoped that use of an asymmetric reductant would overcome the inherent substrate control. Disappointingly, both CBS- and alpineborane-based methods resulted in only starting material. Figure 4.2 highlights the difficulty in the attempted diastereoselective reduction to diol *trans*-**169**. In a similar way to enone *ent*-**71**, β-methyl enone **160** will sit in a flattened half chair conformation. The ring is puckered at the methyl bridgehead position placing the methyl group over the desired reduction face of the enone carbonyl.

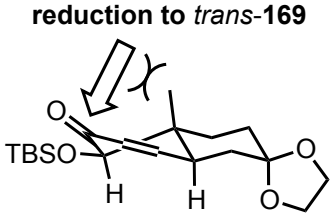
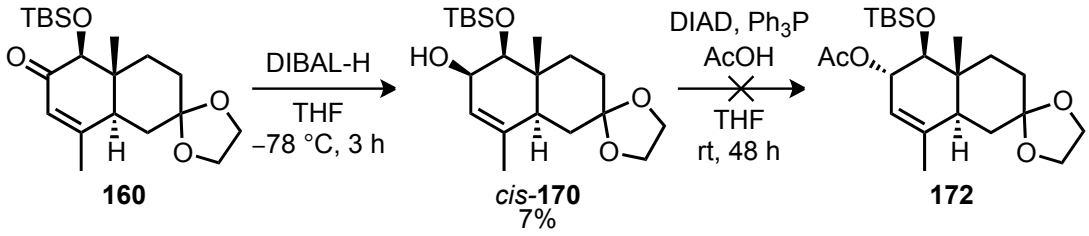


Figure 4.2: *Reduction of β-methyl enone **60** to diol trans-**169***

We briefly investigated the possibility of converting diol *cis*-**170** into the desired diol *trans*-**169** as shown in Scheme 4.14. Analysis of the ^{1}H NMR spectrum of the crude material in the reduction study showed that the DIBAL-H reduction was the "cleanest". Enone **160** was therefore reduced with DIBAL-H at −78 °C in THF. Disappointingly, this resulted in only 7% yield of diol *cis*-**170**. The product was assigned a *cis*-diol due to the CHO/CHO ^{3}J axial-equatorial coupling of 5.5 Hz. We have no explanation for the very low yield obtained from this reaction, other than the possible instability of the product on silica, as the ^{1}H NMR spectra of the crude material showed clean conversion to diol *cis*-**170**. Diol *cis*-**170** was then subjected to a Mitsunobu inversion reaction.[225] However, this reaction resulted in complete recovery of the starting diol. It is conceivable that the formation of the required Mitsunobu intermediate (oxyphosphonium ion) was disfavoured by 1,3-diaxial interactions between the allylic hydroxyl and the bridgehead methyl group.



Scheme 4.14: *DIBAL-H reduction Mitsunobu approach to a trans-diol* ***172***

Ultimately, we were unable to utilise a diastereoselective reduction of β-methyl enone **160** to achieve the desired *trans*-diol motif. This chemistry was not, however, fruitless. We have developed an efficient route to β-methyl enone **160** using Dauben oxidation conditions. Furthermore, it was hoped that alkyl lithium addition to enone **166** and subsequent Dauben rearrangement would provide a general route to β-substituted quassinoidal A-ring structures.

4.3 Synthesis of General Quassinoid AB-ring Motif and Analogues

Before exploring alternative routes to the required *trans*-diol present in the AB-rings of samaderine C, we briefly explored the synthesis of other quassinoid AB-ring analogues. This is because β-methyl enone **160** can be regarded as a general quassinoid AB-ring structure (Figure 4.3). Structure-activity studies had shown the importance of the hydroxy enone A-ring motif as a biological Michael-acceptor in their action as cytotoxic agents (see Figure 1.4).

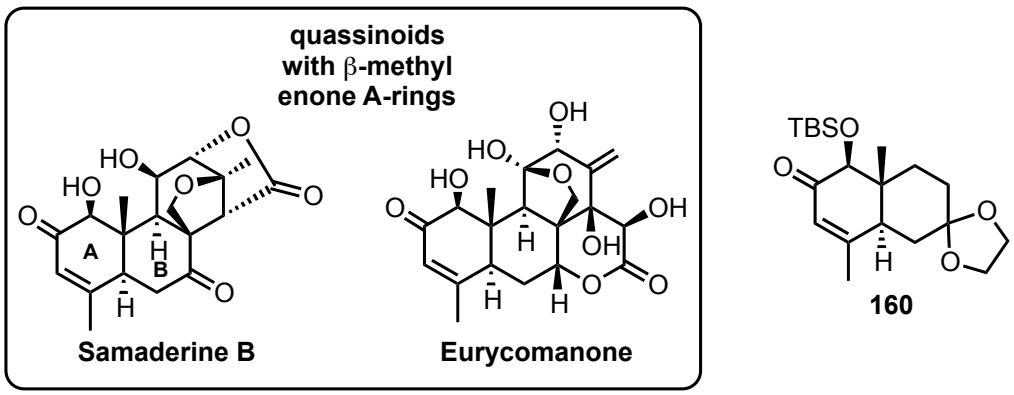
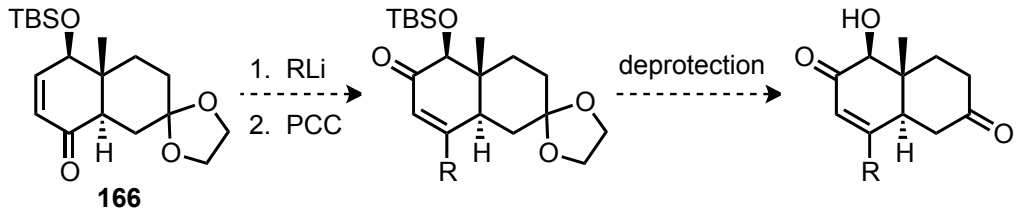


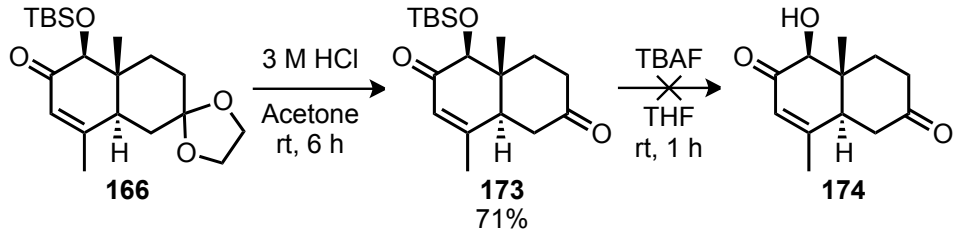
Figure 4.3: *β-Methyl enone* ***160*** *as a general quassinoid AB-ring structure*

We identified that our 1,3-carbonyl transposition chemistry opened a novel route to quassinoidal hydroxy enone A-rings where the substitution of the enone β-terminus could be altered by varying the organometallic reagent added in a 1,2-fashion to enone **166** prior to Duaben oxidation (Scheme 4.15). Variation of the enone β-terminus could modulate this motif's activity as a biological Michael-acceptor. Studies thus turned to finding a deprotection method to allow access to dione AB-ring models. Once this was established, we planned to investigate altering the organometallic reagent used in the 1,3-carbonyl transposition chemistry.



Scheme 4.15: *Use of the Duaben oxidation to quassinoid AB-ring analogues*

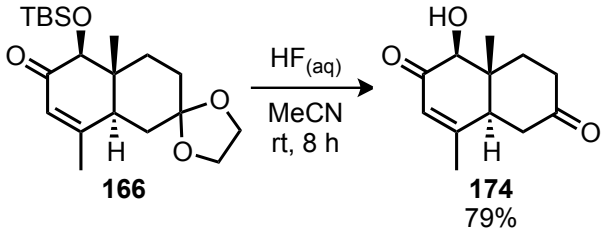
A sequential deprotection strategy was initiated, starting with removal of the ketal from **166** (Scheme 4.16). The ketal was readily cleaved by stirring ketal **166** in acetone with 3 M $HCl_{(aq)}$ to give dione **173** in 71% yield. Unfortunately, we were then unable to deprotect the TBS ether. Deprotection using TBAF at rt over 1 h led to complete decomposition of starting material.



Scheme 4.16: *Sequential deprotection strategy towards quassinoid AB-ring model **174***

A global deprotection method was then investigated. Ketal **166** was stirred in MeCN at rt in the presence of $HF_{(aq)}$ over 8 h (Scheme 4.17). Under these conditions, both the TBS and the ketal protecting groups were removed to give dione **174** in 79% yield. An X-ray crystal structure of dione **174** (Figure 4.4) proves the connectivity and relative stereochemistry. Hydroxy dione **174** represents a general quassionoidal

AB-ring ring structure and opens up the possibility of the synthesis of future quassinoids with this hydroxy enone A-ring motif *via* a 1,3-transposition procedure.



Scheme 4.17: *Global deprotection strategy towards quassinoid AB-ring model* ***174***

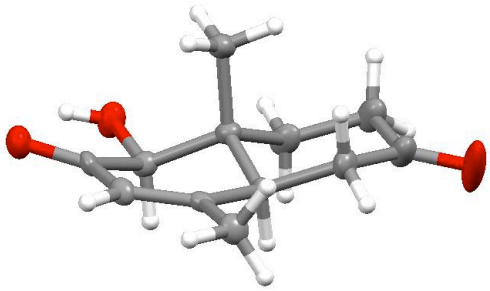
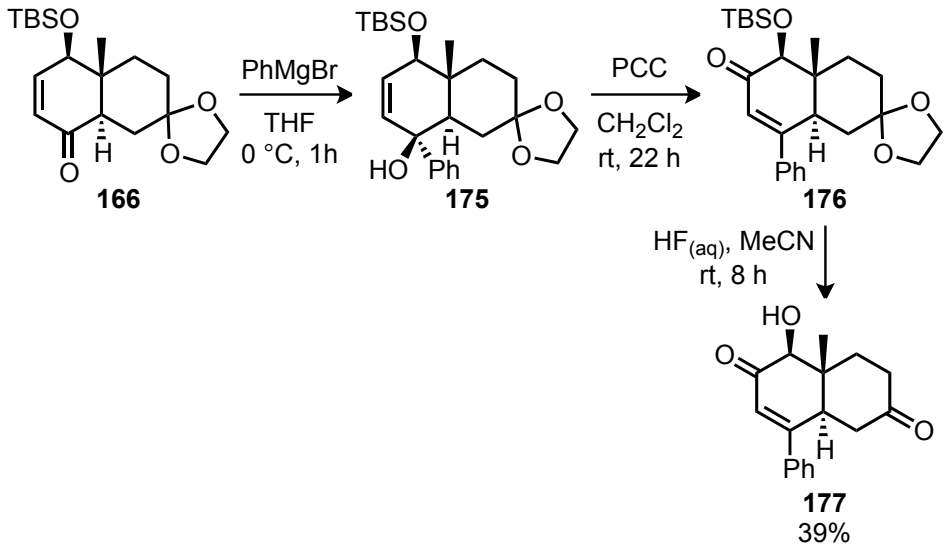


Figure 4.4: *Crystal structure of quassinoid AB-ring model* ***174***

The success of $HF_{(aq)}$ for global deprotection then allowed variation of the organometallic reagent used prior to the Dauben oxidation to be investigated as shown in Scheme 4.18. Thus, enone **166** was reacted with PhMgBr to give a single diastereomer of tertiary allylic alcohol **168** (relative stereochemistry assumed to be as shown). The crude tertiary allylic alcohol **175** was then submitted to the PCC oxidative transposition reaction and resulted in β-phenyl enone **176**. The crude β-phenyl enone **176** was then globally deprotected using $HF_{(aq)}$ to give the β-phenyl quassinoidal AB-ring analogue **177** in 39% yield over the three steps from enone **166**.

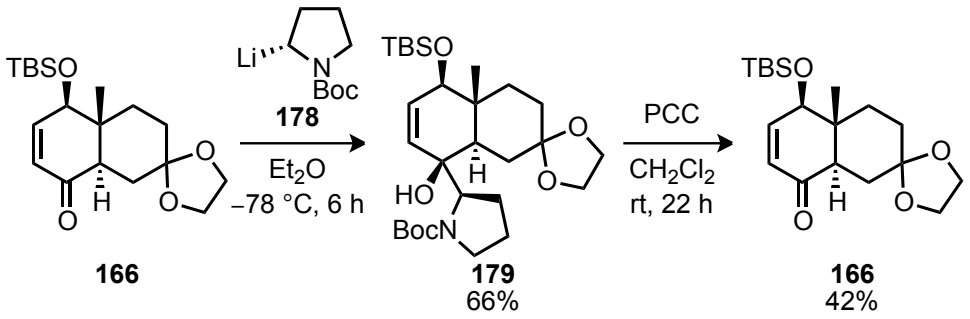


Scheme 4.18: *1,3-Transposition procedure towards phenyl-quassinoid AB-ring model* ***177***

Building on this success, a more complex organometallic reagent was investigated. Lithiation of small *N*-Boc-protected nitrogen heterocycles has proven an invaluable tool for the asymmetric synthesis of chiral building blocks and has been well-studied in our group.[226,227] We therefore trialled the addition of lithiated *N*-Boc pyrrolidine **178** to enone **166** in an attempt in introduce a potentially biologically significant nucleophile to our 1,3-transposition procedure.

N-Boc pyrrolidine was lithiated in Et_2O at −78 °C using *s*-BuLi and (−)-sparteine to produce a chiral organolithium **178** according to Beak's original procedure (Scheme 4.19).[228] To this species, enone **166** in Et_2O was added and the reaction was stirred at −78 °C for 6 h. Analysis of the ^{1}H NMR spectrum of the crude product showed only one discernable product. Purification by flash column chromatography gave a product that was tentatively assigned by ^{1}H NMR as amino alcohol **179** (66% yield). The stereochemistry of the alcohol stereocentre is assumed to be that from a *pseudo*-axial delivery of the nucleophile on the carbonyl face opposite to the bridgehead methyl group. The pyrrolidine stereocentre depicted is that expected from the lithiation in the presence of (−)-sparteine. Unfortunately, subjection of amino alcohol **179** to the PCC transposition reaction resulted in cleavage of the newly-formed carbon-carbon bond to give enone **166** in 42% yield and no other products were isolated. This reaction may be considered to proceed in glycol cleavage-type fashion

after deprotection of the Boc protecting group under the reaction conditions. There is literature precedent for the glycol-type cleavage of 1,2-amino alcohols with PCC[229] while 1,2-amino alcohol cleavage is known when using sodium periodate.[230,231]

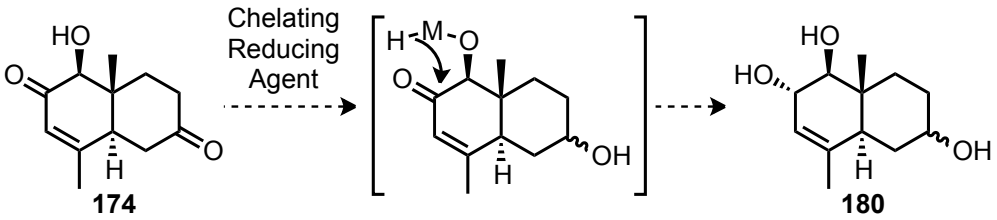


Scheme 4.19: *Synthesis of amino alcohol **179** and attempted 1,3-transposition*

Despite this setback, with two successful examples, we felt that the transposition-deprotection procedure was a viable route to quassinoidal β-subsituted hydroxy enone A-rings. Therefore, we returned to the unresolved synthetic challenge, the synthesis of a *trans*-allylic diol A-ring motif.

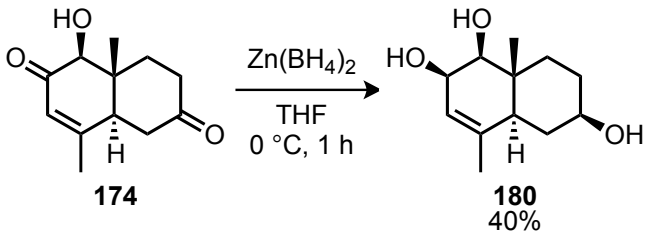
4.4 Chelation Controlled Reduction route to a trans-Diol Motif

Our success in the synthesis of general quassinoidal AB-ring structures spurred us on to study the conversion of a hydroxy enone such as **174** into a *trans*-allylic diol compound (Scheme 4.20). It was envisaged that the adjacent hydroxyl group could facilitate a directed or chelation-controlled reduction onto the desired carbonyl face on the enone. We recognised that reduction of the ketone carbonyl was almost certainly unavoidable. However, the resulting triol could potentially be protected and selectively oxidised.



Scheme 4.20: *Directed reduction of dione **174** to give triol **180***

There is significant historical precedence for chelation-controlled reductions using zinc borohyride and the ability of this reagent to drastically change the stereochemical outcome of reactions.[178,232,233] Dione **174** was therefore reacted with zinc borohydride, which was freshly prepared from $NaBH_4$ and dry zinc chloride (Scheme 4.21). The result indicated formation of *cis*-triol **180** but there was no evidence for production the *trans*-diol. Purification by flash column chromatography then gave triol **180** in 40% yield. The product is tentatively assigned as triol **80** as it decomposed in the NMR solvent on standing overnight preventing further characterisation. The configuration of *cis*-triol **180** was assigned using the 5.5 Hz ^3J equatorial-axial coupling between the two C*H*OH protons (Figure 4.5). The third alcohol stereocentre was assigned by the evidence for an axial C*H*OH proton. It appears as a triplet of triplets with 11 Hz and 5 Hz couplings. This splitting pattern can be rationalised by two ^3J axial-axial couplings (11 Hz) and two ^3J axial-equatorial couplings (5 Hz).



Scheme 4.21: *Chelation-controlled reduction of β-methyl enone **174** using zinc borohydride*

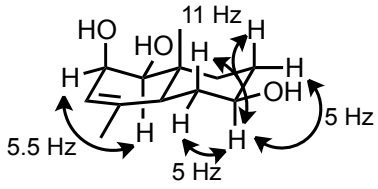
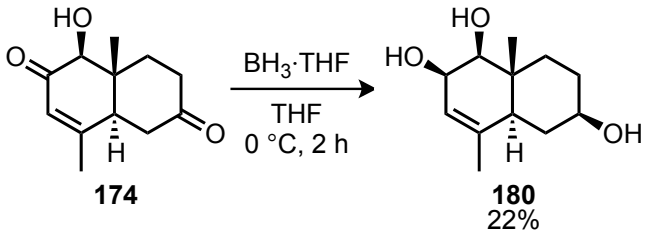


Figure 4.5: *Assignment of triol **180***

Finally, the precedented chelation-controlled reduction of a hydroxy enone using borane was investigated.[234] Dione **174** was treated with BH_3·THF to give *cis*-triol **180** in 22% yield (Scheme 4.22). No chelation-controlled reduction product (*trans*-diol) was indicated in the ^{1}H NMR spectrum of the crude material. Once again, the yield was disappointing based on the cleanness of the reaction.

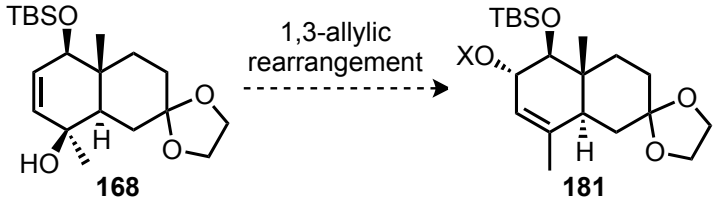


Scheme 4.22: *Chelation controlled reduction of β-methyl enone **174** using borane*

We therefore abandoned the used β-methyl enone **160** as an intermediate to a *trans*-diol-type compound. Instead, previous intermediates in this route were studied as a way of accessing the desired *trans*-diol configuration.

4.5 1,3-Allylic Rearrangement to a trans-Diol Motif

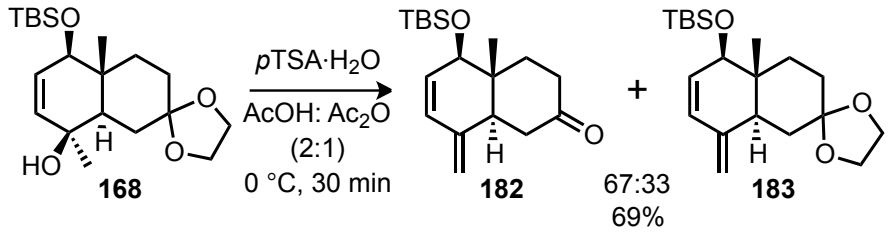
Tertiary alcohol **168** was an intermediate used in the Dauben oxidative 1,3-carbonyl transposition to give β-methyl enone **160** (see Scheme 4.12). We proposed that a 1,3-allylic alcohol transposition of alcohol **168** could result in a *trans*-diol product (Scheme 4.23). Reaction processes that were not *syn*-stereospecific in their mechanism but more S_N2'-like were investigated. A *syn*-stereospecific 1,3-allylic rearrangements would result in the undesired *cis*-diol. It was hoped that the addition would occur on the allylic face opposite the axial bridgehead methyl group to give *trans*-diol **181**.



Scheme 4.23: *Proposed 1,3-allylic rearrangement to a trans-diol motif*

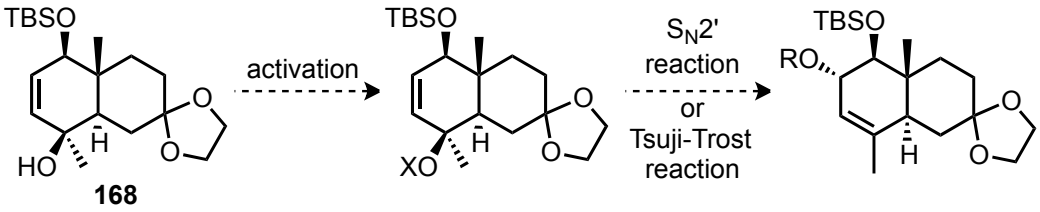
The first conditions undertaken for the 1,3-allylic transposition were the precedented acid-catalysed rearrangement of an allylic acetate (Scheme 4.24).[235,236] Acetic acid and acetic anhydride were added to alcohol **168** and catalytic *p*TSA. It was envisaged that alcohol **168** would form an allylic acetate on reaction with the acetic anhydride and subsequent substitution in an S_N2' fashion would form a 1,3-transposed product. However, using allylic alcohol **168**, only exocyclic methylene compounds **182** and

183 were isolated as a 67:33 (69% yield). It seems that under the strongly acidic conditions elimination of allylic alcohol or the intermediate allylic acetate occurs with formation of a conjugated exocyclic double bond. Some of the ketal group was also removed under the acidic conditions to give ketone **182**.



Scheme 4.24: *Acid-catalysed 1,3-rearrangement to exocyclic methylene compounds **182** and **183***

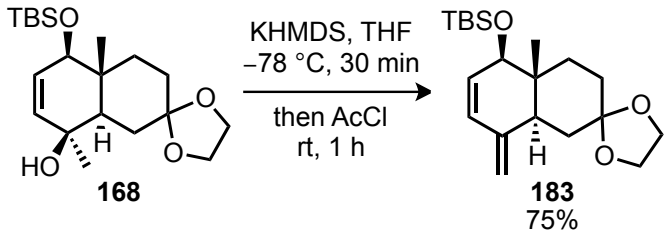
It was unclear whether the elimination experienced by alcohol **168** under the acidic conditions was directly from the allylic alcohol/acetate (tertiary form) or if the 1,3-transposition reaction occurred and then, under the acidic conditions, the transposed product was unstable and eliminated to the exocyclic products. Therefore, alternative, stepwise conditions were sought. It was predicted that if the allylic alcohol could be activated as a leaving group it would allow a sequential S_N2' process or a Tsuji-Trost reaction to give a *trans*-diol product (Scheme 4.25). The Tsuji-Trost reaction would require an inner-sphere reaction process to achieve the *trans*-diol product.[237]



Scheme 4.25: *S_N2' or Tsuji-Trost approaches to a trans-diol compound*

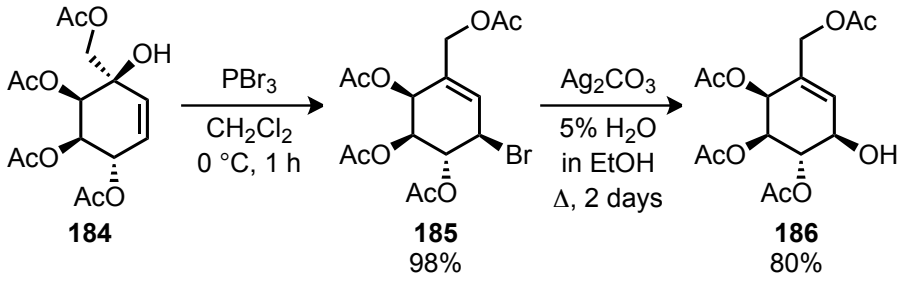
We briefly investigated these routes with the initial formation of allylic acetate **184**. Treating alcohol **168** with acetic anhydride in pyridine at rt for 48 h showed no evidence of the acetate product with only starting material observed. In more forcing conditions, allylic acetate **184** was deprotonated using KHMDS base. The resulting alkoxide was then acetylated using acetyl chloride. These conditions resulted in exocyclic methylene **183** being isolated as the sole product in 75% yield (assigned by ^{1}H NMR only) (Scheme 4.26). Further efforts to activate allylic alcohol **168** were

made with the attempted formation of a carbonate, xanthate, mesylate or tosylate. All gave either decomposition or the formation of exocyclic methylene compound **183**. Alternative approaches were therefore sought.



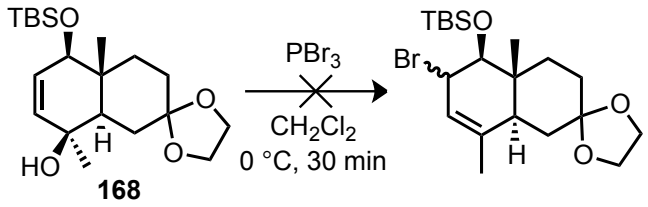
Scheme 4.26: *Attempted acetylation of alcohol **168***

An interesting allylic-transposed bromination reaction was reported by Kim in 2009.[238] Specifically Kim used the 1,3-transposed bromination of a tertiary alcohol to access the natural product (+)-MK7606 which had been isolated from cultures of *Curvularia eragrostidis* D2452. The allylic-transposed bromination is a known process[239,240] and in Kim's case they used the allylic-transposed bromination reaction of tertiary alcohol **184** to give bromide **185**. Subsequent hydrolysis of bromide **185** gave a *trans*-diol product **186** (Scheme 4.27). It was hoped that the same reaction sequence on tertiary alcohol **168** would result in the formation of a *trans*-diol product.



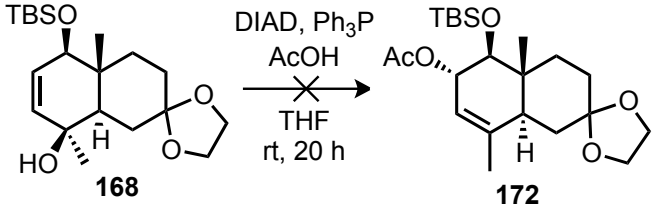
Scheme 4.27: *Kim's allylic-transposed bromination route to (+)-MK7607*

Thus, allylic alcohol **168** was stirred with PBr_3 at 0 °C for 30 min (Scheme 4.28). Unfortunately, no brominated products were observed. No new products were seen on TLC analysis or in the ^{1}H NMR spectrum of the crude product which showed only decomposition. In case the bromide was unstable, the reaction was repeated and the crude product was taken directly to the hydrolysis step. However, no *trans*-diol products were observed.



Scheme 4.28: *Attempted allylic-transposed bromination of* ***168***

In a final attempt to achieve the 1,3-allylic transposition, an allylic Mitsunobu reaction was attempted. This type of reaction is well-precedented.[241-244] Allylic alcohol **168** was treated under standard Mitsunobu conditions (Scheme 4.29). However, this resulted in complete recovery of the starting material. Presumably, 1,3-diaxial interactions disfavour the formation of the Mitsunobu intermediate.

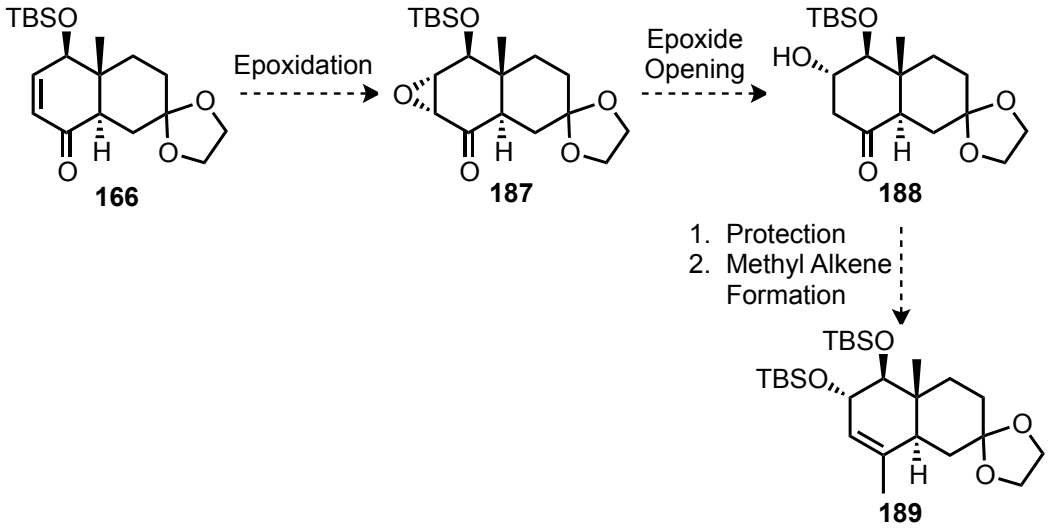


Scheme 4.29: *Attempted Mitsunobu allylic substitution reaction of* ***186***

A 1,3-transposition of the allylic alcohol **186** to give a *trans*-diol motif ultimately proved unsuccessful. These results have shown the favourable formation of the undesired exocyclic methylene motif. Therefore, at this stage transposition-based routes were abandoned.

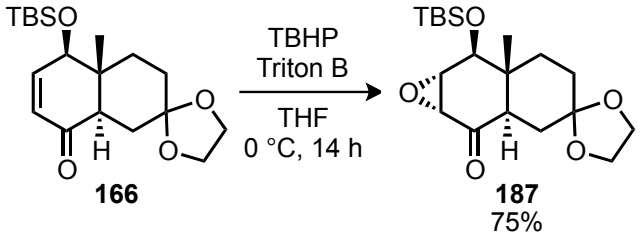
4.6 Epoxide-Opening Route to a trans-Diol Motif

With little success so far, an epoxide-opening route was devised and is summarised in Scheme 4.30. Starting from enone **166**, diastereoselective epoxidation should give epoxy ketone **187**. A reductive epoxide-opening reaction would then give a *trans*-diol aldol product **188**. Subsequent protection and methyl alkene formation, would give the *trans*-allylic diol **189**. Studies began with investigation of the diastereoselective epoxidation of enone **166**.



Scheme 4.30: *Proposed epoxide-opening route to protected trans-diol* ***189***

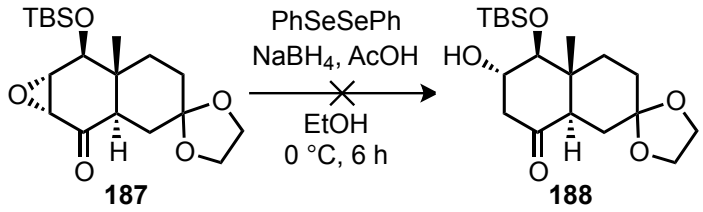
There are a number of methods for diastereo- or enantioselective nucleophilic epoxidations.[245-247] Our previous results had shown the importance of the axial bridgehead methyl group on the steric hindrance of the A-ring top face. Based on literature precedent,[248-252] we therefore identified the nucleophilic epoxidation of enone **166** using the bulky reagent *tert*-butyl hydrogen peroxide (TBHP) as a possible route to keto epoxide **187**. Thus, enone **166** was treated with TBHP and Triton B base to give a single epoxy ketone **187** in 75% yield (Scheme 4.31). The product stereochemistry was assumed based on the preferential epoxidation of enone **166**'s bottom face as the top should be blocked by the axial bridgehead methyl group.



Scheme 4.31: *Epoxidation of enone* ***166***

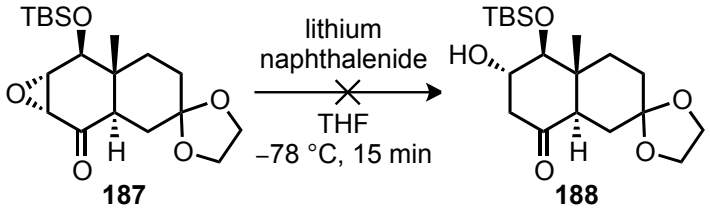
With epoxy ketone **187** in hand, a number of reductive-epoxide opening reactions were attempted. First, the phenylselenide anion was explored. This reaction was first developed by the Yoshikoshi group as a synthetic alternative to stereoselective aldol reactions.[253] Since then, the phenylselenide anion has been widely used for the

reductive opening of epoxides.[254-256] The anion itself is generally generated *in situ* by reduction of diphenyl diselenide with $NaBH_4$. Therefore, diphenyl diselenide in EtOH was reduced by $NaBH_4$ to give a solution of the selenide anion. To this mixture, epoxy ketone **187** was added (Scheme 4.32). After 6 h at 0 °C, only quantitative recovery of the starting material was observed. The reaction was attempted numerous times with different batches of diphenyl diselenide with only starting material recovered. It is possible that the axial methyl group may be preventing the necessary S_N2-type opening of the epoxide group by blocking the top face of keto epoxide **187**.



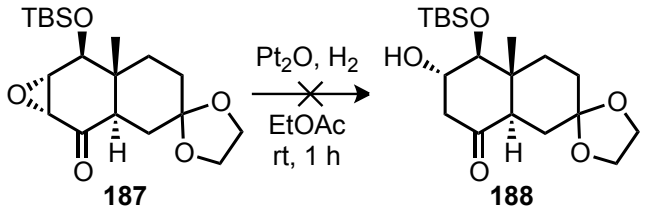
Scheme 4.32: *Attempted reductive epoxide-opening of **187** using phenyl selenide anion*

If steric congestion was the main issue, a smaller reductant may be beneficial and, therefore, single electron reduction was explored using lithium naphthalenide. Following a literature procedure,[257] lithium naphthalenide was prepared by dissolving lithium metal in a naphthalene/THF solution and epoxy ketone **187** was added (Scheme 4.33). The result was a very complex mixture of products from which no compound could be isolated.



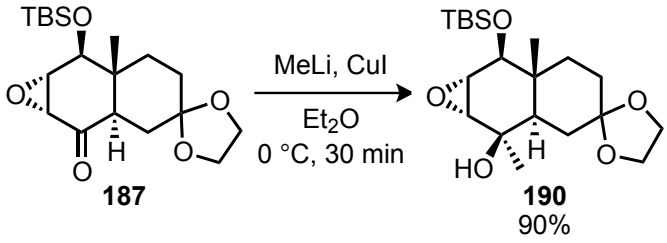
Scheme 4.33: *Attempted reductive epoxide-opening of **166** using lithium naphthalenide*

The next strategy employed was hydrogenation of epoxy ketone **187**. There are examples of the hydrogenation of α,β-epoxy ketones to give aldol-type products.[258,259] However, stirring epoxy ketone **187** with platinum(II) oxide under a hydrogen atmosphere gave an unidentifiable product which on standing overnight decomposed (Scheme 4.34).



Scheme 4.34: *Attempted reductive epoxide-opening of **187** using hydrogenation*

The final reductive epoxide-opening technique investigated used dimethyl cuprate, which had reported shown to induce the desired reaction.[260-262] Formation of dimethyl cuprate was achieved using MeLi (2.4 eq.) and CuI (1.2 eq.). To this cuprate solution was added epoxy ketone **187**. The result was the formation of epoxy alcohol **190** as a single diastereomer in 90% yield (Scheme 4.35).



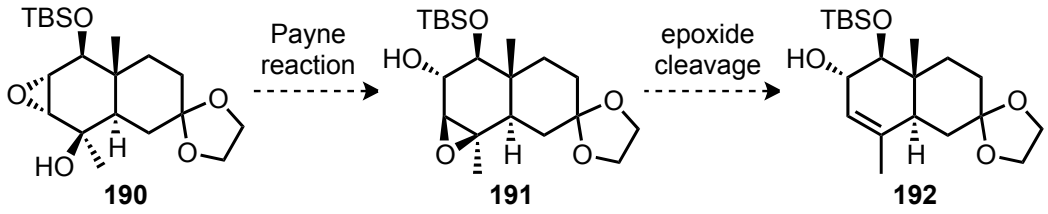
Scheme 4.35: *Attempted reductive epoxide-opening of **187** using dimethylcuprate*

It was clear that the reductive opening of epoxy ketone **187** to give the desired *trans*-diol product was not straightforward. However, the formation of epoxy alcohol **190** inspired our next approach to the desired *trans*-diol A-ring motif.

4.7 Payne Rearrangement Approach to a trans-Diol Motif

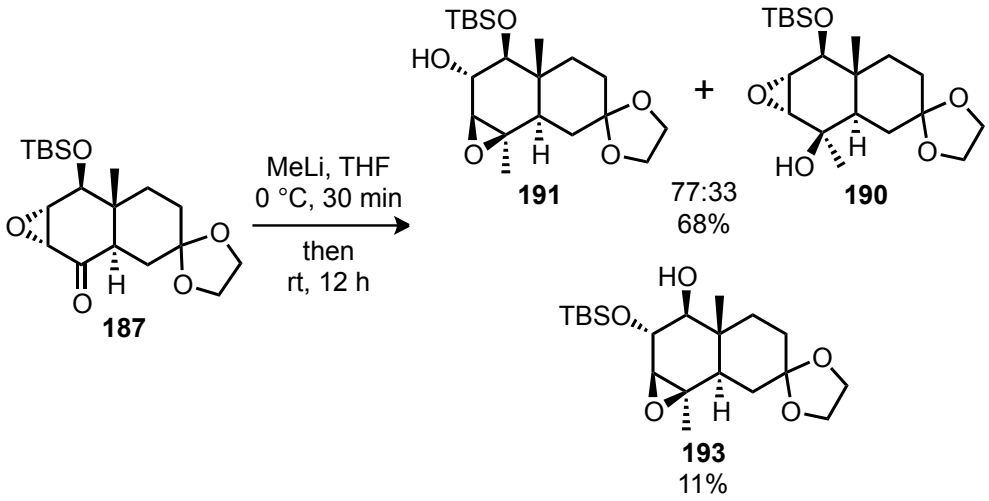
On inspection of the structure of epoxy alcohol **190**, we realised that it had the appropriate alcohol and epoxide arrangement to facilitate a Payne rearrangement.[263-265] The Payne reaction is known to be an equilibrium between the starting epoxy alcohol and the resulting product epoxy alcohol. The equilibrium position, and hence the major product, is the result of the thermodynamic stability of the two compounds.[264] It has been demonstrated that the equilibrium of a Payne rearrangement of cyclic epoxy alcohols will result in the product with an equatorial alcohol.[266] We therefore proposed a route to protected *trans*-diol **192** based on a

Payne rearrangement reaction (Scheme 4.36). From epoxy alcohol **190** a Payne rearrangement would give epoxy alcohol **191** which we hoped would be favoured as the alcohol group is equatorial. Epoxy alcohol **190** would then be subjected to an epoxide cleavage reaction to give protected *trans*-diol **192**.



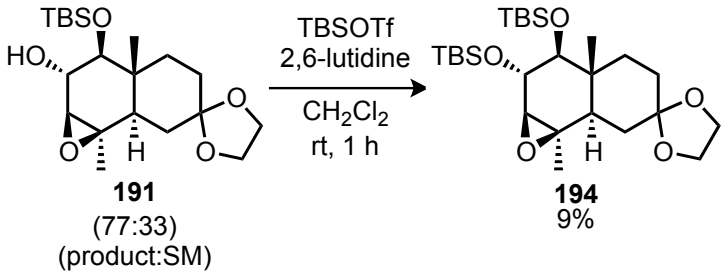
Scheme 4.36: *Proposed Payne rearrangement approach*

To this end, epoxy ketone **187** was treated with MeLi at 0 °C and then allowed to stir at rt overnight (Scheme 4.37). This resulted in epoxy alcohol **193** in 11% yield where a silyl transfer reaction had occurred from the neopentyl alcohol to the newly-formed equatorial alcohol. We also isolated a 68% yield of an inseparable 77:23 mixture of the Payne rearranged product **191** and the epoxy alcohol **190**. The spontaneous nature of the Payne rearrangement was a pleasing result. However, the non-rearranged epoxy alcohol **190** could be obtained as the sole product in high yield (92%) if the reaction was halted after 30 min at 0 °C. The assignment of the TBS regioisomers **191** and **193** is tentative. These products differ only in their R_F and the chemical shifts of the C*H*O signals. Assignment is based on a 2.5 Hz coupling shown in **193** by the C*H*OH to the alcohol proton. The *trans*-diol configuration of both regioisomers **191** and **193** was confirmed in the axial-axial ^3J coupling of the C*H*OH protons (8.0 Hz for **191** and 8.5 Hz for **193**). Consequently, this helps confirm the configuration of epoxy ketone **187** as a *trans*-relationship between the epoxide and the axial bridgehead methyl group. Nevertheless, the spontaneity of the rearrangement reaction was a welcomed shortening of the proposed route.

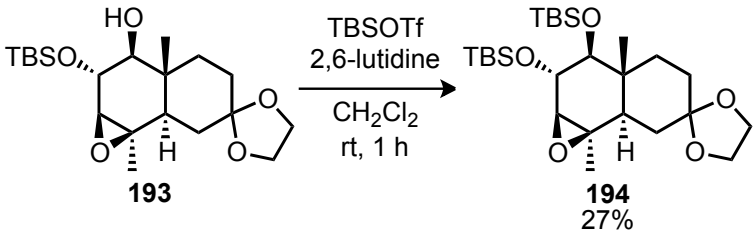


Scheme 4.37: *Payne rearrangement to epoxides **191** and **193***

In order to prepare substrates for epoxide removal, the free hydroxyl groups of regioisomers **191** and **193** were protected as TBS ethers. Initially, TBS protection of both regioisomers using TBSCl and DMAP showed no product after 24 h. Changing to more forcing TBSOTf conditions gave the diTBS adduct **194** from both epoxy alcohol starting materials. The TBS protection of epoxy alcohol **191** gave diTBS adduct **194** in 9% yield (Scheme 4.38) while epoxy alcohol **193** gave a 27% yield diTBS adduct **194** (Scheme 4.39). No other products were isolated in both cases.

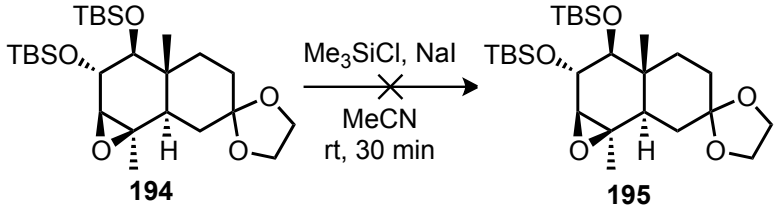


Scheme 4.38: *TBS protection of **191** to disilyl ether **194***

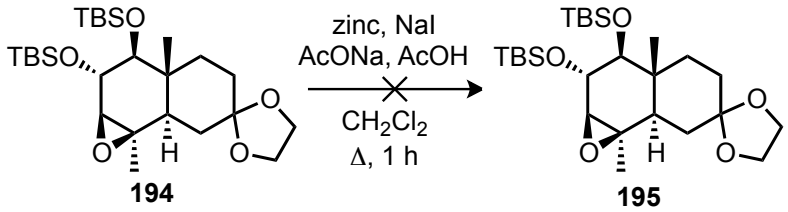


Scheme 4.39: *TBS protection of **193** to disilyl ether **194***

There have been a number of conditions published for the removal of epoxides to give alkenes. These include the use of Me_3SiI,[267,268] zinc and sodium iodide,[269,270] lithium,[271] and titanocene chloride.[272] The Me_3SiI conditions, first developed in 1981,[267] were widely-used and were amongst the mildest conditions available. The attempted removal of the epoxide from the diTBS protected compound **194** was therefore attempted under these conditions (Scheme 4.39). Iodotrimethylsilane was prepared *in situ* from Me_3SiCl and sodium iodide. Addition of epoxide **194** to this solution resulted in complete decomposition of the starting material with no product present by TLC analysis or in the ^1H NMR spectrum of the crude material. Changing to the zinc and sodium iodide reaction conditions gave only decomposition (Scheme 4.40).



Scheme 4.40: *Attempted epoxide removal from **194** using Me_3SiI*



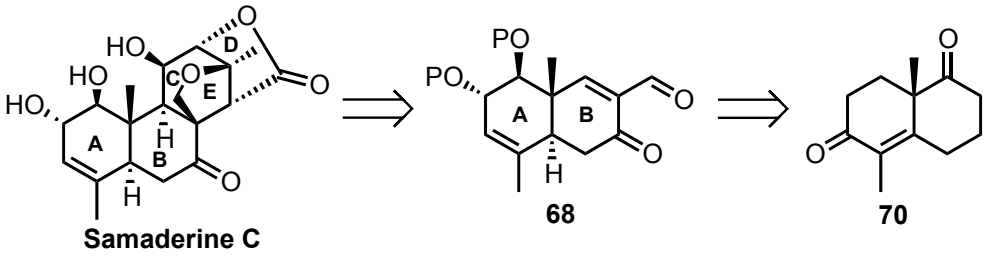
Scheme 4.41: *Attempted epoxide removal from **194** using zinc/sodium iodide*

At this point, the use of a Payne rearrangement approach to the *trans*-diol motif was halted. The success of this route in achieving the *trans*-diol motif was promising but subsequent removal of the epoxide to give the *trans*-allylic diol **195** was unsuccessful. With time pressures mounting and, as of yet, no structure possessing the desired *trans*-allylic diol A-ring motif being obtained, we drew a line under the approach using the Wieland-Miescher ketone **69** for now.

In summary, our studies towards a compound with the *trans*-diol A-ring motif using the Wieland-Miescher ketone **69** as a starting material has been in-depth and varied. Unfortunately, we were unable to achieve the desired *trans*-allylic diol configuration using the diastereoselective reduction of β-methyl enone **166**. Efforts using a 1,3-allylic alcohol transposition were also fruitless due to favourable formation of an exocyclic-methylene motif as well as detrimental 1,3-diaxial influences. The epoxide-opening approach was also unsuccessful. The Payne rearrangement approach did give the *trans*-diol configuration but epoxide removal could not be achieved. Our attention now turned a related approach using the methyl-Wieland-Miescher ketone **70** which was designed to utilise the axial bridgehead methyl group to direct the formation of the *trans*-allylic diol motif.

Chapter 5: Samaderine C AB-Ring Synthesis: The Methyl-Wieland-Miescher Ketone Approach

The lack of success using the Wieland-Miescher ketone **70** to access the *trans*-diol motif present in the AB-rings of samaderine C was disappointing. However, through this study much was learned about the synthesis of the samaderine C AB-rings. The steric hindrance of the A-ring top face by the axial bridgehead methyl group was evident. We sought a new approach to the AB-ring dienophile **68** that utilised the strereo-directing ability of the bridgehead methyl group to our advantage in setting up the *trans*-diol motif. An alternative Wieland-Miescher ketone approach was therefore devised and centred on the use of methyl-Wieland-Miescher ketone analogue **70** (Scheme 5.1).

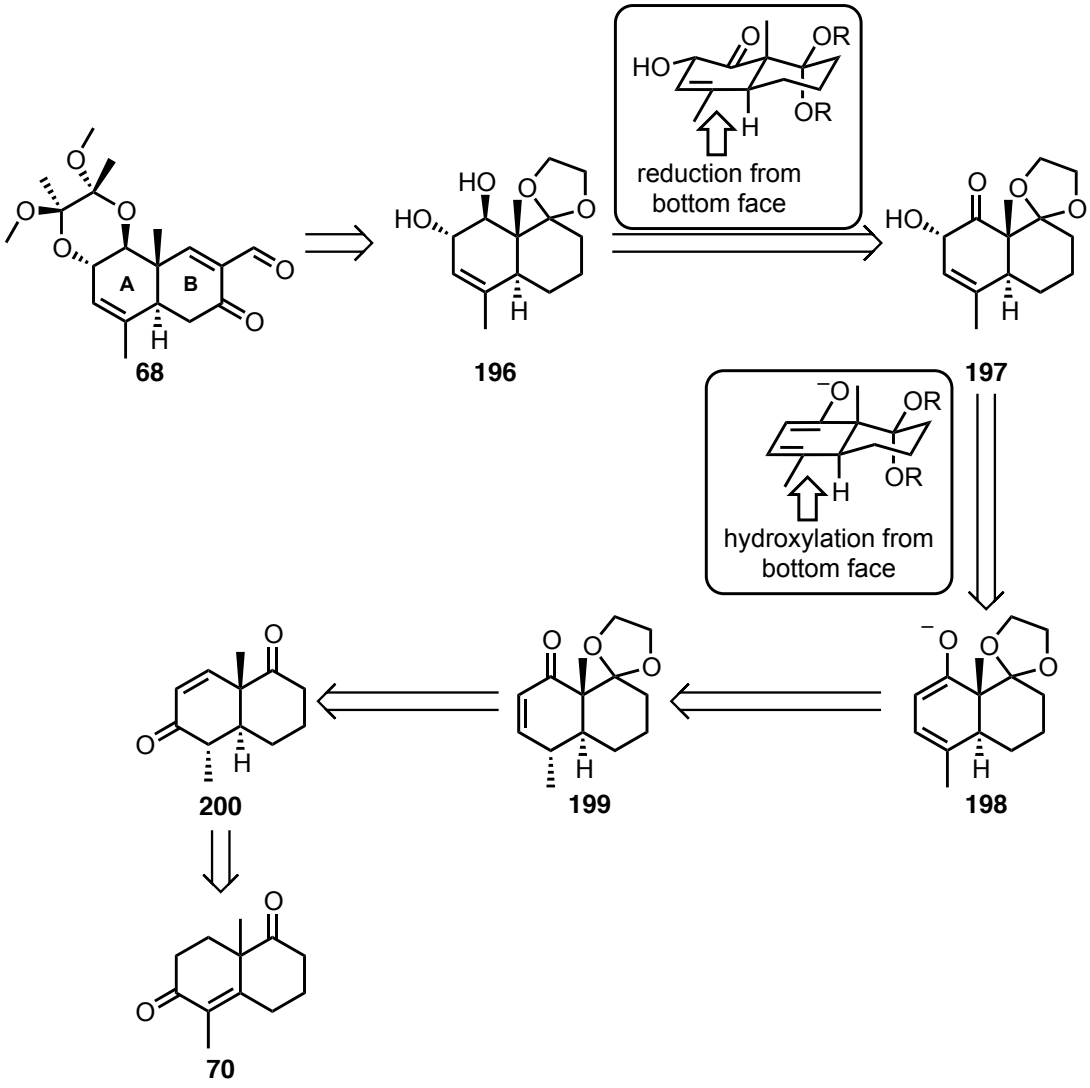


Scheme 5.1: *Retrosynthesis of samaderine C to methyl-Wieland-Miescher ketone **70***

5.1. Strategy to AB-ring Structures from the Methyl-Wieland-Miescher Ketone

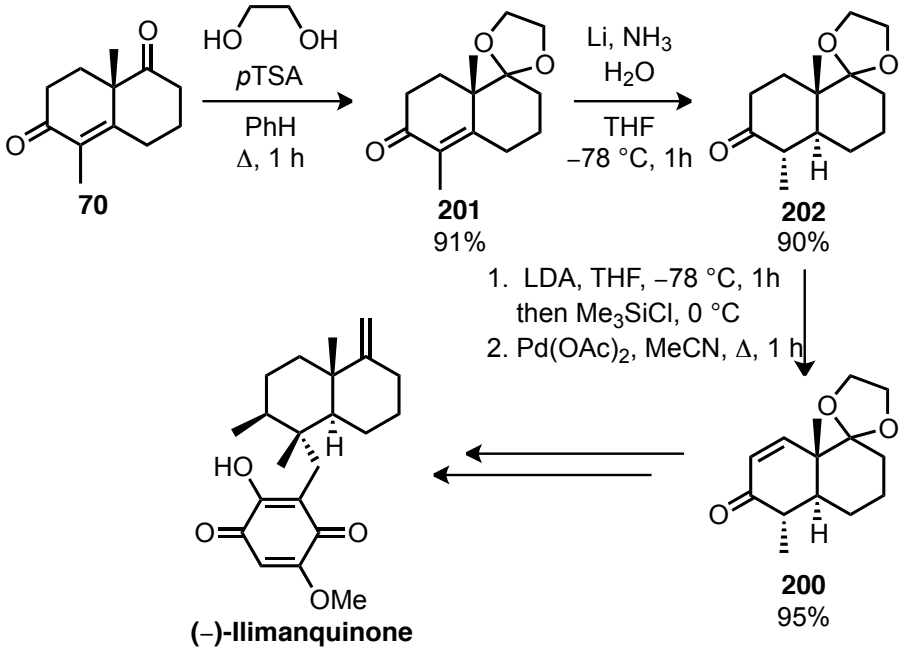
The plan was to access dienophile **68**, in which the A-ring would now be constructed from the Wieland-Miescher enone ring and the B-ring would be formed from the ketone ring. This is in complete contrast to the ring pattern in the Wieland-Miescher ketone approach described in Chapter 4. Scheme 5.2 highlights the proposed synthesis a diol *trans*-**196** from the methyl-Wieland-Miescher ketone **70**. Using the bridgehead methyl group to direct reduction to the bottom face, diol *trans*-**196** would be achieved from hydroxy ketone **197**. The hydroxy ketone **197** would itself be realised by the α-hydroxylation of an extended enolate **198**, where the oxidising

agent would be directed to the A-ring bottom face by the bridgehead methyl group. Enolate **198** would be formed by γ-deprotonation of enone **199**. A 1,3-carbonyl transposition would be employed on enone **200**. The known[273] enone **200** would be reached from methyl-Wieland-Miescher ketone analogue **70**.



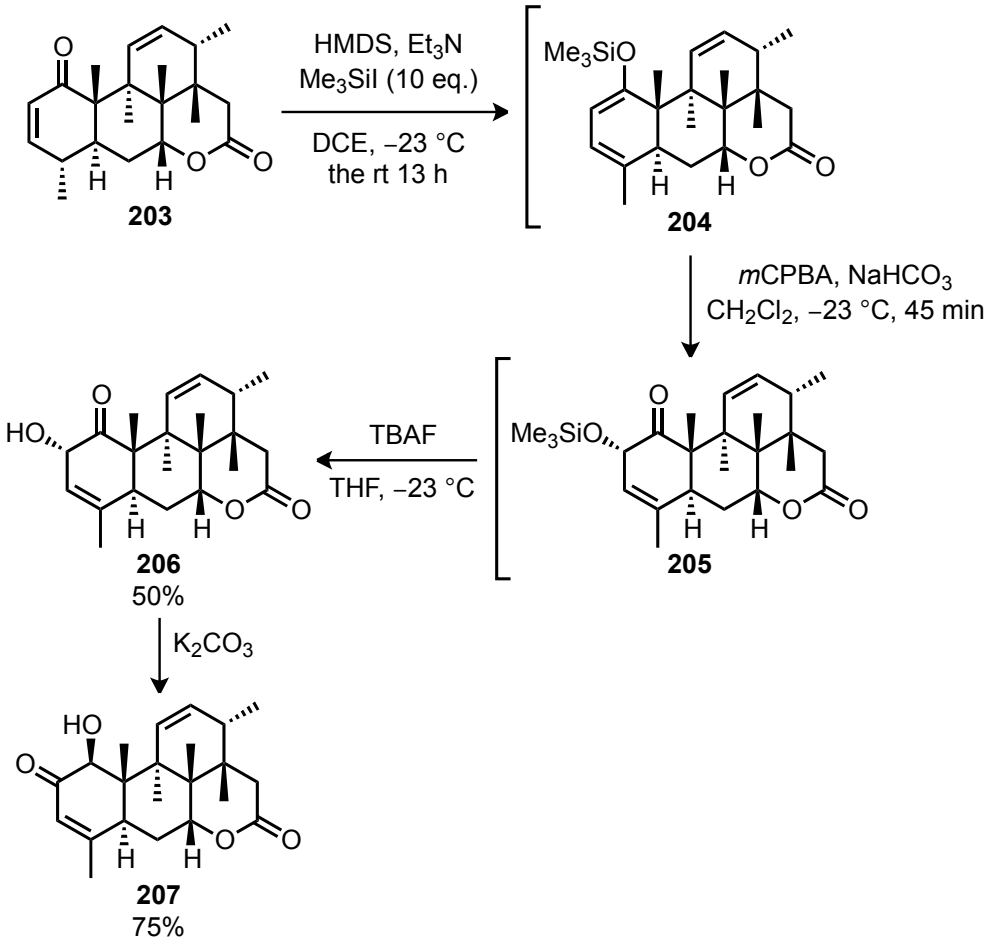
Scheme 5.2: *Retrosynthesis of dienophile **68** to methyl-Wieland-Miescher ketone **70***

Known enone **200** was an intermediate in Samadi's synthesis of (−)-ilimaquinone (Scheme 5.3).[273] Starting from methyl-Wieland-Miescher ketone analogue **70**, chemoselective ketalisation gave ketal **201**. The *trans*-decalin ring junction was then established by Birch-type reduction of enone **201** to give ketone **202**. Ketone **202** was submitted to kinetic enolate formation and quenching with Me_3SiCl then gave a silyl enol ether which on Saegusa oxidation delivered enone **200**. Seven further steps including a benzylic alkylation and two Wittig olefinations gave the natural product (−)-ilimaquinone.



Scheme 5.3: *Samadi's route to enone **200**, an intermediate in the synthesis of (−)-ilimaquinone*

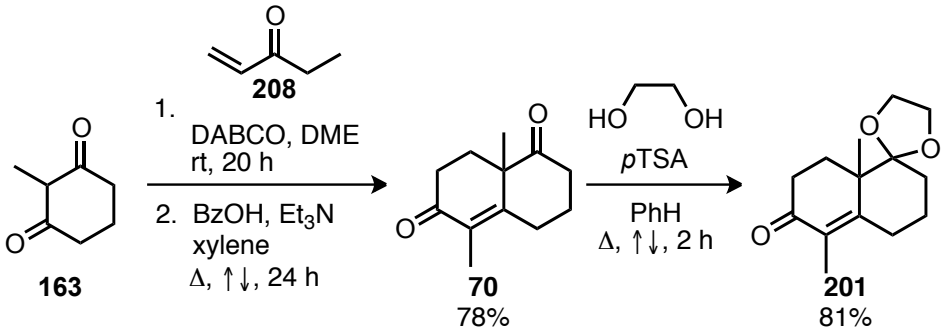
The envisaged α-hydroxylation method was based on chemistry previously used by Grieco in his work towards (±)-klaineanone (Scheme 5.4).[29] Grieco treated late-stage intermediate enone **203** with HMDS, triethylamine and Me_3SiI to give an extended silyl enol ether **204**. Silyl enol ether **204** was then used in a Rubottom-type reaction.[274] Treating the extended silyl enol ether **204** with *m*CPBA epoxidised the more electron-rich double bond, which on work-up gave α-silyloxy ketone **205**. This intermediate was cleaved using TBAF to give hydroxy ketone **206** in 50% yield from enone **203**. α-Hydroxy ketone was then used in a α-ketol isomerisation to give β-methyl enone **207**. We felt that intercepting an appropriate α-hydroxy enone intermediate would allow reduction to give the desired *trans*-diol motif and efforts commenced to that end.



Scheme 5.4: *Extended enolate formation and Rubottom oxidation to hydroxy ketone* ***206***

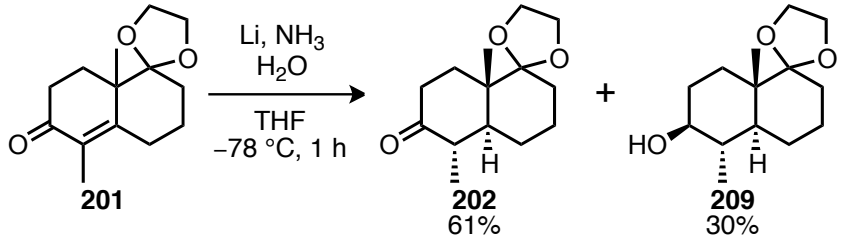
5.2 Synthesis of the trans-Diol Motif in the AB-Rings of Samaderine C

Efforts began towards the diol *trans*-**196** from the methyl-Wieland-Miescher ketone **70**. The first goal was the repetition of Samadi's route to enone **200**. The methyl-Wieland-Miescher ketone **70** was synthesised in racemic form and all the synthetic work described in this chapter was carried out with racemic compounds.[275] The starting material 2-methyl-1,3-cyclohexadione **163** was reacted with ethyl vinyl ketone **208** in the presence of DABCO base to form the Michael adduct (Scheme 5.5). This Michael adduct was then cyclised to complete the Robinson annulation in 78% yield from the dione starting material **70**. Heating **70** under Dean-Stark conditions in the presence of *p*TSA and ethylene glycol gve ketal **201** in 81% yield where the ketone carbonyl has been protected in preference to the enone carbonyl.

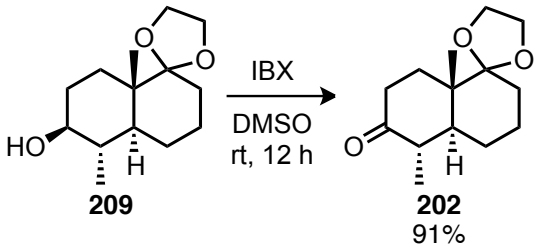


Scheme 5.5: *Synthesis of ketal **201***

The *trans*-ring junction was then established using a Birch reduction. Enone **201** was reacted with lithium in ammonia. The reaction was quenched with ammonium chloride to give ketone **202** in 61% yield with an over-reduction product, alcohol **209**, isolated in 30% yield (Scheme 5.6). Fortunately, to aid in the progress of material, alcohol **209** could be cleanly converted back into ketone **202** by IBX oxidation in 87% yield (Scheme 5.7).

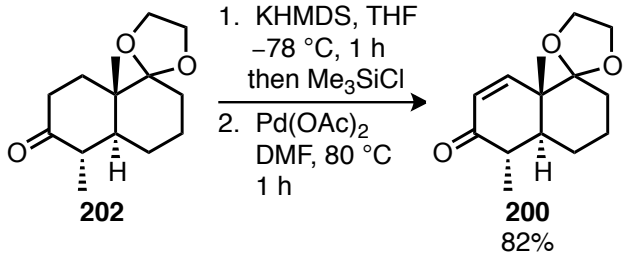


Scheme 5.6: *Synthesis of ketone **202** and over-reduction product alcohol **209***



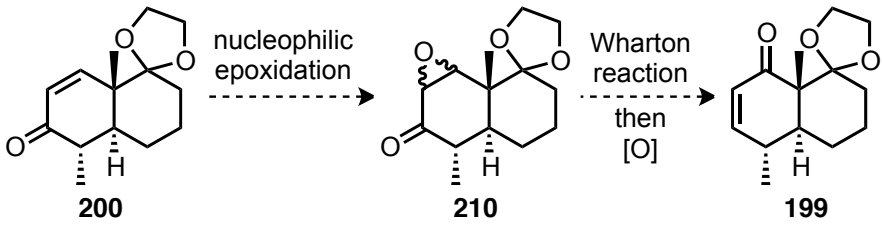
Scheme 5.7: *Oxidation of alcohol **209** to ketone **202***

The final step of Samadi's route was the stiochiometric Saegusa oxidation of ketone **202** to enone **200**. The kinetic enolate of **202** was formed using KHMDS as base at −78 °C. The resulting enolate was trapped with Me_3SiCl and the silyl enol ether was treated with $Pd(OAc_2)$ in DMF at 80 °C over 1 h to give enone **200** in 82% yield (Scheme 5.8).



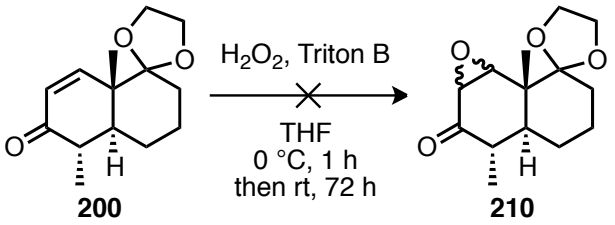
Scheme 5.8: *Saegusa oxidation of ketone **202** to enone **200***

We envisaged at this point that a Wharton rearrangement would facilitate the desired 1,3-transposition (Scheme 5.9).[276] Nucleophilic epoxidation of enone **200** would give epoxy ketone **210**. The Wharton reaction involves treating an epoxy ketone with hydrazine to give a 1,3-transposed allylic alcohol product. In this case, the resulting alcohol intermediate would be oxidized to give enone **199**. Thus, over these three steps, enone **200** has undergone a formal 1,3-carbonyl transposition.



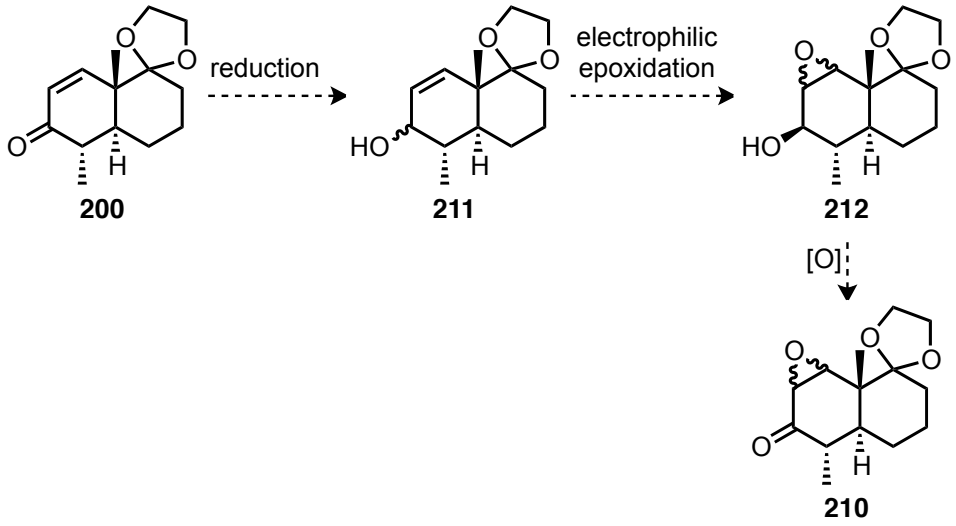
Scheme 5.9: *Proposed synthesis of epoxy ketone **210** and subsequent Wharton-reaction*

Before the Wharton reaction could be attempted, epoxy ketone **210** needed to be synthesised. To that end, enone **200** was submitted to the Weitz-Scheffer-style nucleophilic epoxidation reaction as shown in Scheme 5.10.[277] Stirring enone **200** with hydrogen peroxide and Triton B base resulted in complete recovery of starting material with no epoxy ketone **210** detected. The base was altered in subsequent attempts but with no success. The difficulty of nucleophilic epoxidation of the A-ring enone is speculated to be due to steric encumbrance of the enone β-terminus by the adjacent quaternary centre as well as the ketal group, which is also in close proximity. The lack of reactivity of an enone of this type is in line with an example from the Ling group.[278]



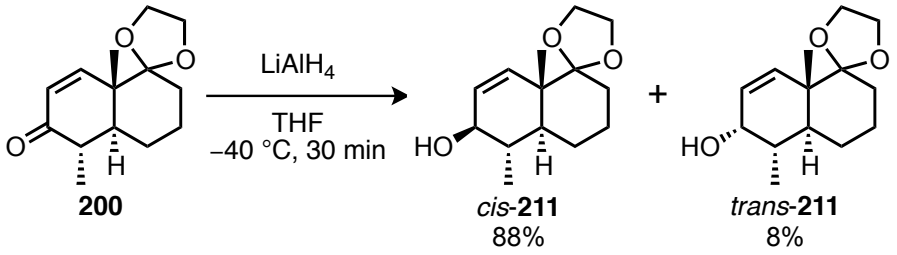
Scheme 5.10: *Attempted nucleophilic epoxidation of enone **200***

An electrophilic epoxidation procedure was therefore used to overcome this lack of reactivity. The plan was to reduce enone **200** to allylic alcohol **211**. This allylic alcohol would then be treated with an electrophilic epoxidation reagent (*m*CPBA) to give an epoxy alcohol **212**, which, on oxidation, would furnish the required epoxy ketone **210** (Scheme 5.11).



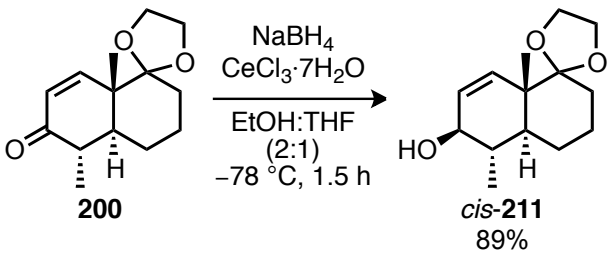
Scheme 5.11: *Electrophilic epoxidation approach to epoxy ketone **210***

Enone **200** was therefore reduced with $LiAlH_4$ at −40 °C to give an 87:13 mixture (from the ^1H NMR spectrum of the crude material) of allylic alcohols *cis*-**211** and *trans*-**211** (Scheme 5.12). The stereochemical labels refer to the relative orientation of the alcohol group to the axial-bridgehead methyl group. Purification by flash column chromatography gave *cis*-**211** in 88% yield while diastereoisomer *trans*-**211** was obtained in 8% yield.



Scheme 5.12: *$LiAlH_4$ reduction of enone **200***

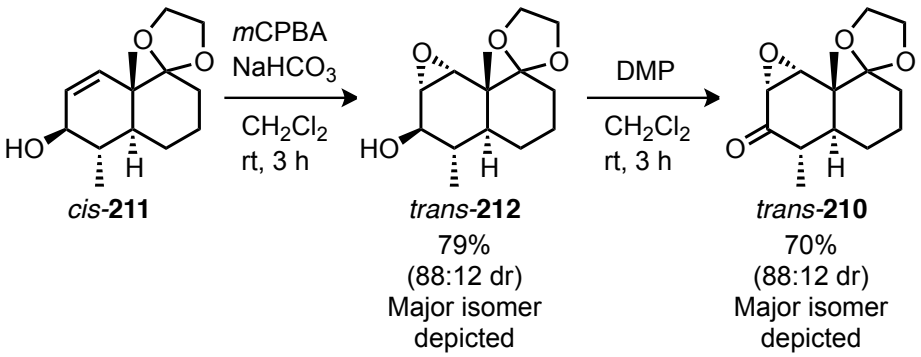
For comparison, enone **200** was then reduced with $NaBH_4$ under Luche conditions (Scheme 5.13). Reacting enone **200** with $NaBH_4$ in the presence of $CeCl_3 \cdot 7H_2O$ at −78 °C gave a 94:6 mixture of allylic alcohols *cis*-**211** and *trans*-**211**. Purification by flash column chromatography gave only *cis*-**211** in 89% yield.



Scheme 5.13: *$NaBH_4$ reduction of enone **200***

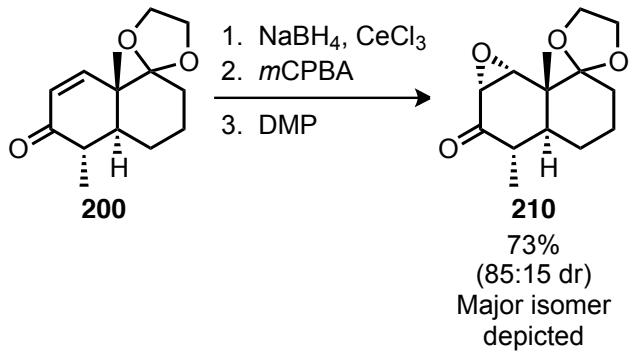
The electrophilic epoxidation reaction was then examined using allylic alcohol *cis*-**211**. Reaction of allylic alcohol *cis*-**211** with *m*CPBA gave epoxy alcohols *trans*-**212** and *cis*-**212** in 79% yield as an 88:12 mixture of diastereomers, which were inseparable by column chromatography (Scheme 5.14). The diastereomer depicted (*trans*-**212**) is the assumed major product. The assignment is based only on the previously observed predominance of the axial bridgehead methyl group to direct reactions onto the bottom face of the A-ring. We recognise the ability of the equatorial alcohol in *cis*-**211** to facilitate a hydrogen bonding-directed epoxidation

event and we propose that such an effect is responsible for formation of the minor diastereomer.[279] In the interests of achieving the *trans*-diol motif in the AB-ring compound *trans*-**196**, the stereochemistry is ultimately unimportant (*vida infra*). Hence, epoxy alcohols, *trans*-**212** and *cis*-**212** (88:12 dr) were oxidised using DMP to give the epoxy ketones *trans*-**210** and *cis*-**210** in 70% yield with retention of the diastereomeric mixture (88:12 dr).



Scheme 5.14: *Electrophilic epoxidation and oxidation to epoxy ketone **120***

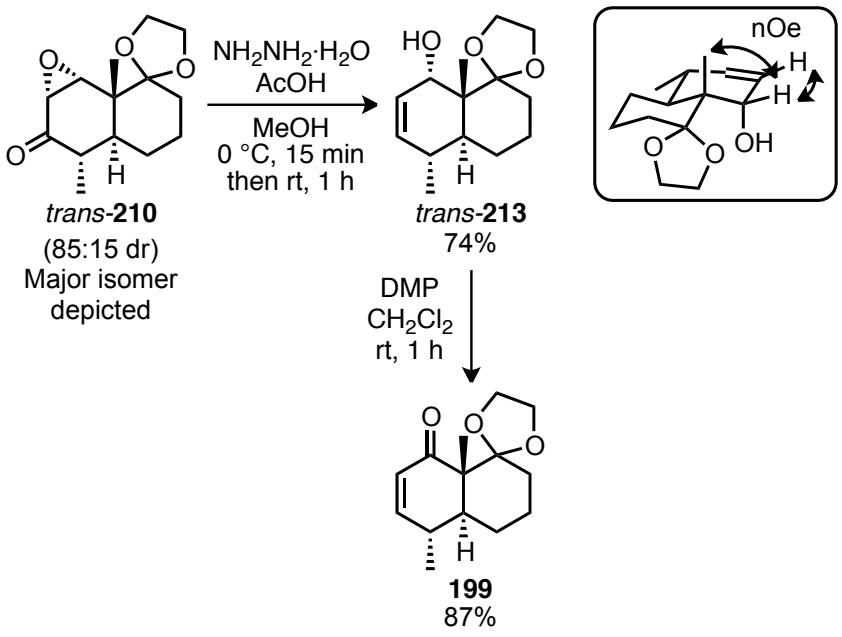
We found that this three-step reduction-epoxidation-oxidation route could be telescoped to save on purification (Scheme 5.15). Enone **200** was reduced using $NaBH_4$. The resulting crude allylic alcohols were epoxidised using *m*CPBA and subsequently oxidised using DMP to give epoxy ketone *trans*-**210** in 73% yield from enone **200** and as an 85:15 mixture of inseparable diastereomers.



Scheme 5.15: *Telescoped electrophilic epoxidation approach to epoxy ketone trans-**210***

Epoxy ketone mixture *trans*-**210** and *cis*-**210** (85:15 dr) was then used in the Wharton reaction. In the presence of acetic acid, epoxy ketones mixture, *trans*-**210** and *cis*-**210**, were treated with hydrazine monohydrate at 0 °C. After 1 h, the reaction was quenched to give a mixture of allylic alcohols in a 96:4 ratio by analysis of the

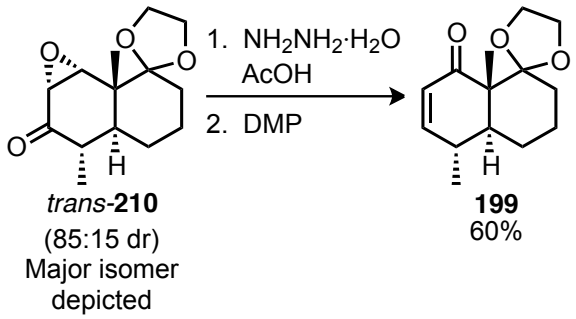
^{1}H NMR spectrum of the crude material. Purification gave only allylic alcohol *trans*-**213** (74% yield). The stereochemical label is the relative arrangement of the alcohol group and the adjacent bridgehead methyl group. Allylic alcohol *trans*-**213** was identical to the major diastereomer observed in the ^{1}H NMR spectrum of the crude material. The assignment of the stereochemistry in *trans*-**213** is based on nOe studies, which showed an nOe enhancement of the equatorial hydrogen to the adjacent vinylic hydrogen and the axial methyl group (Scheme 5.16). The diastereomeric enrichment observed (85:15 dr starting material to 94:6 dr product) was unexpected. There are two plausible explanations. The first involves the isomerisation of allylic alcohol products under the acidic reaction conditions and the second rationale is based on the selective decomposition of the minor diastereomer under the reaction conditions. To complete the 1,3-transposition pathway, allylic alcohol *trans*-**213** was oxidised (Scheme 5.16). The oxidation was carried out using DMP to give enone **199** in 87% yield.



Scheme 5.16: *Wharton reaction of epoxy ketone trans-**210** and oxidation to give ketone **199***

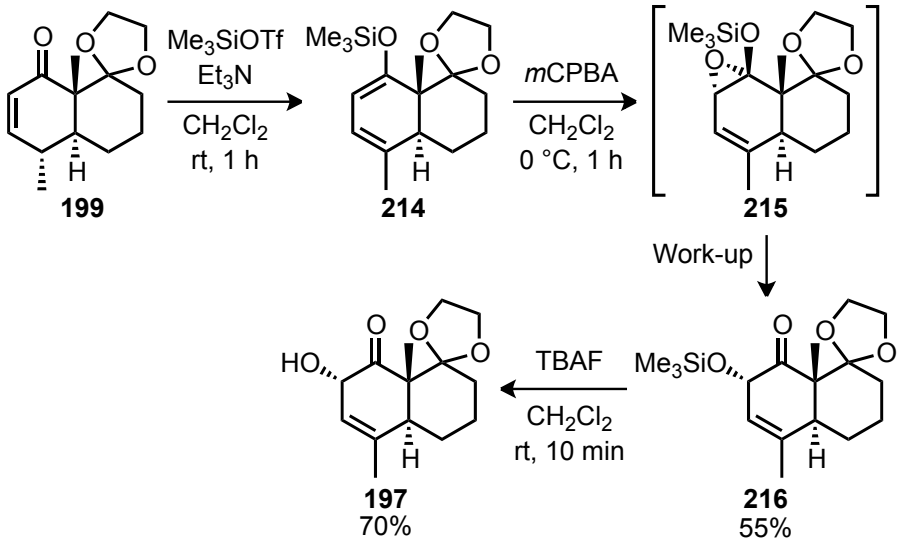
We discovered that the 1,3-transposition route was amenable to a telescoped procedure (Scheme 5.17). Epoxy ketone *trans*-**210** was treated with hydrazine in the Wharton reaction and the resulting crude mixture of allylic alcohols was oxidised using DMP. This furnished enone **199** in 60% yield from epoxy ketone *trans*-**210**

without the need for purification of the intermediate allylic alcohols. We were now ready to investigate the key α-hydroxylation of enone **199**.



Scheme 5.17: *Telescoped Wharton reaction and DMP oxidation to enone **199***

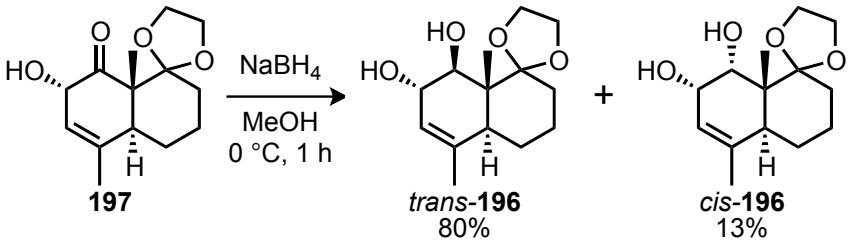
We followed Grieco's general approach for the α-hydroxylation (see Scheme 5.4), using modified conditions to effect the α-hydroxylation of enone **199** (Scheme 5.18). The extended silyl enol ether **214** was formed by treating enone **199** with Me_3SiOTf to form an oxonium species which, in the presence triethylamine, was deprotonated in the γ-position. The resulting extended silyl enol ether **214** was then reacted with purified *m*CPBA at 0 °C to give the Rubottom-type adduct **215**, which on work-up was expected to collapse to α-siloxy ketone **216**.[264,274] The epoxidation was diastereoselective with only one α-siloxy ketone **216** compound observed in the ^1H NMR spectrum of the crude material. The axial bridgehead methyl group is expected to direct the *m*CPBA reagent onto the bottom face of the most electron rich silyl enol ether double bond of extended silyl enol ether **214**. Therefore, the stereospecific collapse of epoxy silyl ether **215** gives a single diastereomer, α-siloxy ketone **216**, which was isolated in 59% yield. This compound was not fully characterised and was assigned by ^1H NMR only. Using TBAF, the silyl protecting group was removed to give hydroxy ketone **197** in a pleasing 70% yield. The stereochemistry in α-hydroxy ketone **197** was proved subsequently (*vida infra*).



Scheme 5.18: *Extended enolate formation/oxidation and cleavage to give α-hydroxy ketone **197***

Achieving hydroxy enone **197** was an excellent result considering the poor yields obtained by Grieco, the number of steps and the sensitivity of the intermediates used. However, we were surprised at the stability of the α-siloxy ketone **216**. Ultimately, all of the steps were telescoped: enone **199** was reacted under the same conditions to give crude α-siloxy ketone **216** which was then used in the TBAF deprotection step to give hydroxy ketone **197** in 70% yield from enone **199**.

With hydroxy ketone **197** in hand, studies progressed to investigating its diastereoselective reduction to give diol *trans*-**196** (Scheme 5.19). Hydroxy enone **197** was reduced using $NaBH_4$ in MeOH at 0 °C to give an 82:18 mixture of *trans*-**196** and *cis*-**196**. These diastereomers were separated by flash column chromatography to give *trans*-**196** in 80% yield and *cis*-**196** in 13% yield. Initially, these products were not readily identifiable. There was expected to be a large *trans*-diaxial ^3J coupling (*ca* 9 Hz) of the two CHO protons in the ^{1}H NMR spectrum of the *trans*-**196**. A smaller ^3J coupling axial-equatorial coupling was expected the same signals in *cis*-**196**. Comparison of these coupling constants should have made characterisation straightforward. However, in both products, the relevant CHO protons where obscured by the broad ketal multiplets.



Scheme 5.20: *$NaBH_4$ reduction of hydroxy ketone **197***

Ultimately, confirmation of the structure of the diastereomers was obtained by X-ray crystallography of a crystal grown from the major product. This confirmed the major product to be *trans*-**196** (Figure 5.1). As expected, reduction of hydroxy ketone **197** by $NaBH_4$ was directed primarily onto the bottom face of the carbonyl group to give the desired *trans*-allylic diol product *trans*-**196** (Figure 5.2). Finally, after much effort, we had successfully synthesised a compound which contained the *trans*-diol motif in the AB-rings of samaderine C.

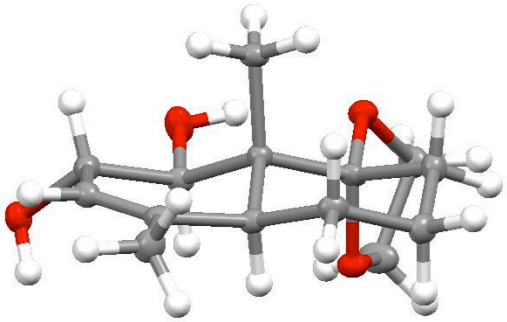


Figure 5.1: *Crystal structure of trans-diol trans-**196***

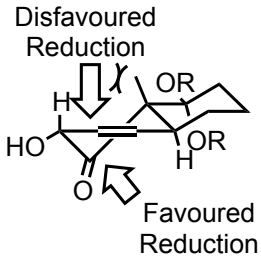
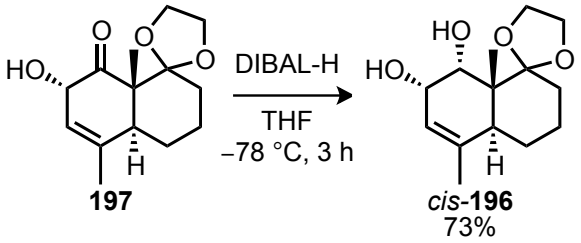


Figure 5.2: *Facial selectivity on reduction of hydroxy ketone **197***

We were slightly surprised, that the axial bridgehead methyl group did not cause complete diastereoselectivity in favour of the *trans*-allylic diol product *trans*-**196**. A completely diastereoselective reduction of hydroxy ketone **197** was ideally desired. We speculated that a larger reducing agent would suffer from increased steric clash

with the axial bridgehead methyl group and so would be more selective for reduction on the bottom face of the ketone carbonyl group. To this end, hydroxy ketone **197** was reduced with DIBAL-H. Under these conditions, the sole product observed was *cis*-allylic diol *cis*-**196**, obtained in 73% yield after purification. A crystal structure of *cis*-**196** was obtained using this material (Figure 5.3). The stereochemical outcome of this reaction is discussed later with other related reduction results.



197 *cis*-**196** 73%

Scheme 5.21: *DIBAL-H reduction of hydroxy ketone **197***

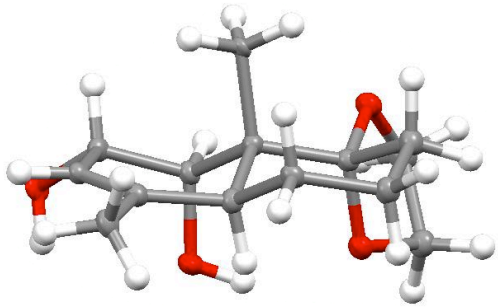


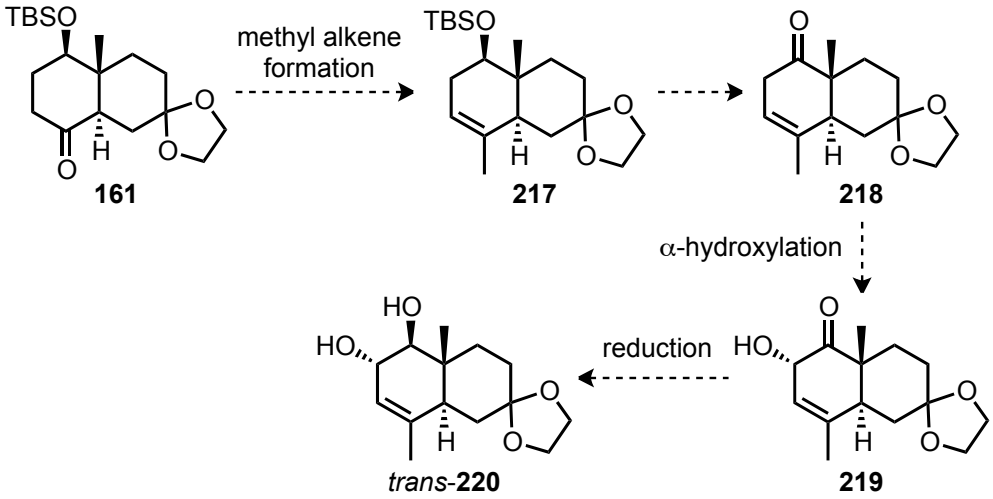
Figure 5.3: *Crystal structure of cis-allylic diol cis-**196***

To our knowledge, this constitutes the first synthesis of a quassinoidal *trans*-allylic diol motif. We anticipate that a ketone (obtained by ketal deprotection) will allow elaboration towards the total synthesis of samaderine C using Diels-Alder chemistry.

5.3. α-Hydroxylation Approach Using the Wieland-Miescher ketone 69

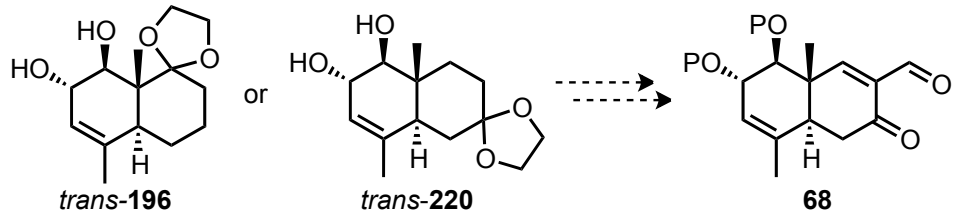
With development of a successful strategy for forming the AB-ring *trans*-diol motif now in place, we were intrigued to see if the key α-hydroxylation method could also be employed starting from Wieland-Miescher ketone **69** (Scheme 5.22). We anticipated that the route from Wieland-Miescher ketone **69** could be intercepted at ketone **161**. Formation of the methyl alkene would then give alkene **217**. Deprotection and oxidation of alkene **217** would give ketone **218**. We hoped that the

α-hydroxylation procedure would then give hydroxy ketone **219**, which would be reduced to give diol *trans*-**220**.



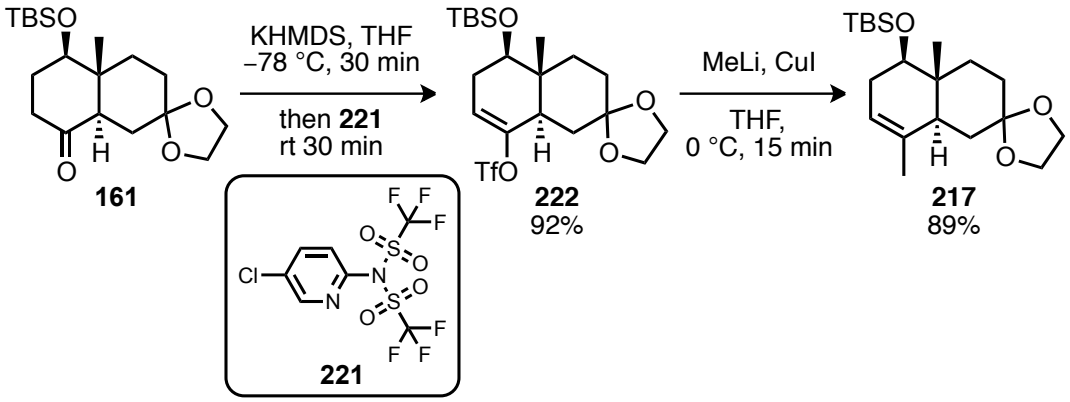
Scheme 5.22: *α-Hydroxylation approach from ketone **161***

Diols *trans*-**196** and *trans*-**220** are regioisomeric compounds which are different only by the position of their ketal groups (Scheme 5.23). However, it was hoped that conversion of *trans*-**220** into dienophile **68** may be more straightforward as the ketal oxygenation is already in the correct position. In contrast, achieving dienophile **68** from *trans*-**196** would require another 1,3-oxygentation transposition.



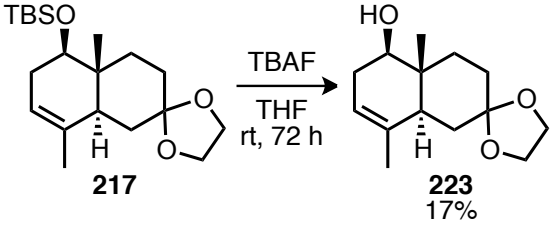
Scheme 5.23: *Dieneophile **68** from either trans-**196** or trans-**220***

An organometallic approach to the methyl alkene was planned *via* the formation of an enol triflate and copper-catalysed cross coupling with dimethyl cuprate (Scheme 5.24). Ketone **161** was deprotonated using KHMDS at −78 °C to furnish the kinetic enolate, which was trapped using Comins' reagent **221** to give enol triflate **222** in 92% yield. Dimethyl cuprate was formed from MeLi and CuI and was then reacted with enol triflate **222** to successfully give methyl alkene **217** as a single regioisomer in 89% yield.



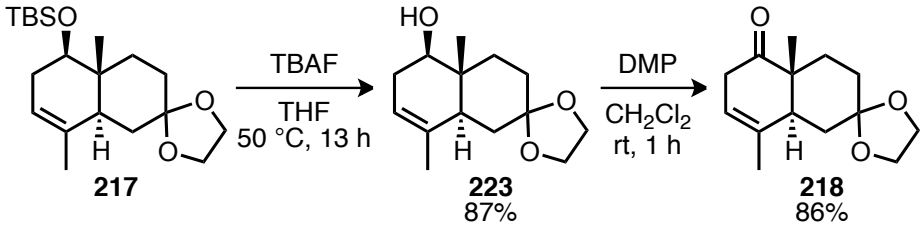
Scheme 5.24: *Methyl alkene formation from ketone **217***

To achieve the desired ketone **218**, the TBS group needed to be removed to facilitate oxidation to ketone **218**. Initial attempts to deprotect TBS ether **217** with TBAF at rt over 72 h resulted in only a 17% yield of the deprotected alcohol **223** with the starting material recovered in 56% yield (Scheme 5.25). From here, various TBS deprotection conditions were trialled with no success. Efforts included TBAF and AcOH,[280] HF in pyridine,[219] refluxing in $LiAlH_4$,[281] TFA in dry CH_2Cl_2,[282] NIS,[283] Me_3SiOTf/MeOH,[284] refluxing in NaOH,[282] and silica-supported polymolybdic acid.[285] All efforts resulted in either no deprotection with complete recovery of starting material or deprotection of both the TBS ether and the ketal group.



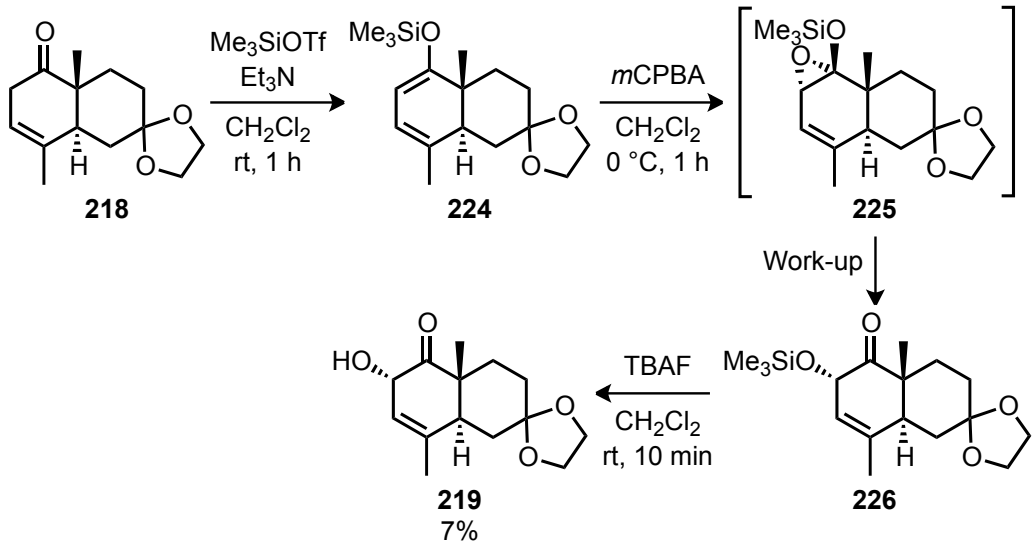
Scheme 5.25: *Room temperature TBS cleavage using TBAF*

Fortunately, we returned to the TBAF-based conditions. It was found that heating TBAF and TBS ether **217** at 50 °C for 13 h gave alcohol **223** in 87% yield (Scheme 5.26). Oxidation of this alcohol gave 86% yield of ketone **218** under DMP conditions.



Scheme 5.26: *TBS cleavage and oxidation to ketone **218***

The α-hydroxylation method with ketone **218** could now be assessed. Ketone **218** was treated with Me_3SiOTf to give the extended silyl enol ether **224** (Scheme 5.27). This step showed complete conversion by analysis of the ^1H NMR spectrum of the crude material with only the desired extended silyl enol ether present as a single product. Treating the extended silyl enol ether with purified *m*CPBA gave complete conversion into the epoxy silyl ether **225** which then collapsed on work-up to α-siloxy ketone **226**, as a single product on analysis of the ^1H NMR spectrum of the crude material. Unfortunately, in this case, deprotection using TBAF resulted in spontaneous formation of a bright purple solution which on work-up and purification gave hydroxy ketone **219** in only 7% yield. Full characterisation of hydroxy ketone **219** was not possible due to decomposition in the NMR tube overnight.

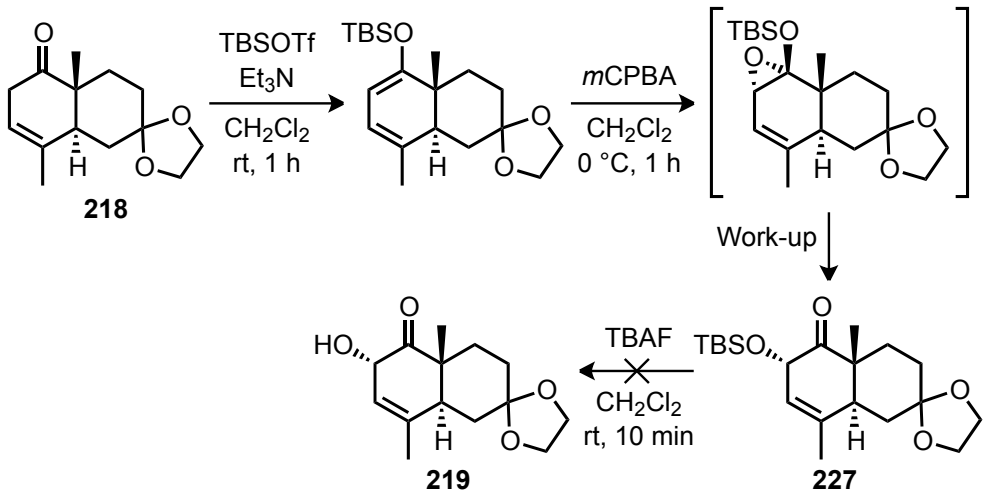


Scheme 5.27: *α-Hydroxylation approach from ketone **218***

The reaction process proceeded cleanly until the silyl deprotection step from α-siloxy ketone **226**. The ^1H NMR spectrum of the crude material post-TBAF cleavage showed product **219** but also may other unidentifiable products some of which

appeared to be aromatic. We explored the use of cold (0 °C) 1 M $HCl_{(aq)}$ for deprotection but this resulted in complete decomposition with no product observed.

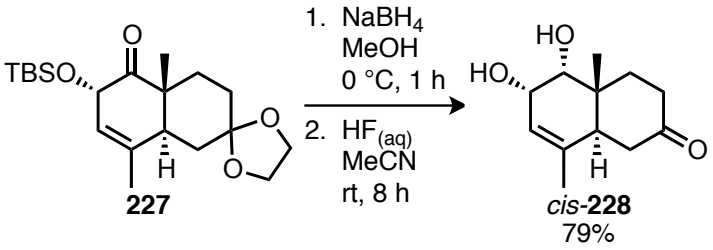
There was literature precedent for the use of bulkier silyl groups in Rubottom oxidation procedures, where the newly-formed hydroxyl group retains the silyl group rather than being completely removed.[286,287] We hoped that the TBS α-silyoxy ketone would prove more stable towards decomposition in our system. Using TBSOTf, the same process was undertaken as shown in Scheme 5.28. Each step proceeded with full conversion by analysis of the ^1H NMR spectra of the crude intermediates until TBS α-siloxy ketone **227**. Unfortunately, once again, TBAF cleavage of the α-siloxy ketone **227** resulted mostly decomposition with the TBS protected hydroxy ketone **227** recovered in only 10% yield.



Scheme 5.28: *TBS mediated α-hydroxylation approach with ketone **218***

At this point, we have no clear explanation as to why the α-hydroxylation methodology works for enone **199** but not for ketone **161**. There was sufficient TBS protected hydroxy ketone **227** remaining to attempt a $NaBH_4$ reduction. α-Siloxy ketone **227** was therefore treated with $NaBH_4$ in an attempt to achieve the desired *trans*-diol motif. However, using TBS protected α-hydroxy ketone **227**, reaction with $NaBH_4$ resulted in the formation of the *cis*-diol product as a single diastereomer (Scheme 5.29). Due to limitations on the quantity of material, the crude *cis*-diol was globally deprotected using $HF_{(aq)}$ to give diol **228** in 79% yield over the two steps.

The relative stereochemistry of *cis*-**228** arrangement was confirmed by X-ray crystallography (Figure 5.4).



Scheme 5.29: *Reduction and global deprotection to diol cis-**228***

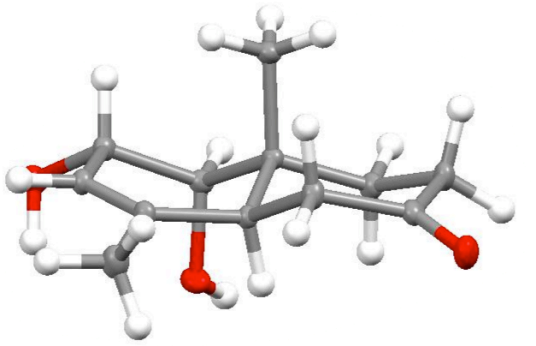
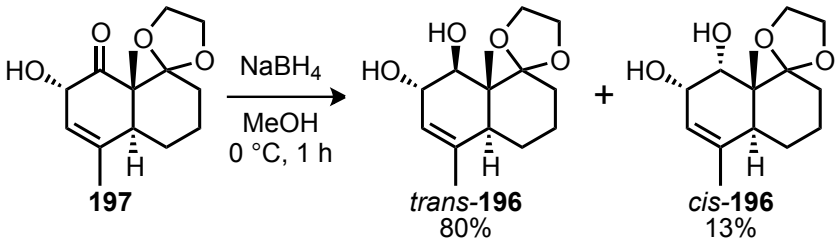
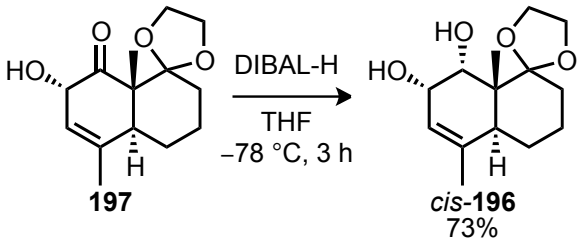


Figure 5.4: *X-ray structure of diol cis-**228***

Therefore, including the reduction just presented in Scheme 5.29, we have investigated the reduction of three similar α-functionalised ketone compounds. The reduction of α-hydroxy ketone **197** with $NaBH_4$ (Scheme 5.30) proceeded to give primarily the *trans*-diol product, *trans*-**196**. Conversely, the other two attempted reductions resulted in *cis*-diol motifs, the $NaBH_4$ reduction of TBS α-siloxy ketone **227** (see Scheme 5.29) and the DIBAL-H-mediated reduction of α-hydroxy ketone **197** (Scheme 5.31). We tentatively suggest a plausible reason for the observed diastereoselectivity.



Scheme 5.30: *$NaBH_4$ reduction of hydroxy ketone **197***



Scheme 5.31: *DIBAL-H reduction of hydroxy ketone **197***

Reduction of the α-hydroxy ketone **197** will initially result in the formation of an α-alkoxy ketone as the reducing agent abstracts the alcohol proton to form an alkoxide species. A second equivalent of the reducing agent would then perform the ketone reduction. In the case of $NaBH_4$, the α-alkoxy ketone formed will be a sodium alkoxide, while DIBAL-H reduction will result in a di*iso*-butyl aluminium alkoxide. We suggest that the DIBAL-H reduction results in an alkoxy species that resembles the TBS α-siloxy ketone **227** i.e. a bulky alkoxy substituent. Both the DIBAL-H reduction and the $NaBH_4$ reduction of TBS α-siloxy ketone **227** result in *cis*-diol products. It is plausible that these bulkier alkoxy species adopt a conformation placing the bulky alkoxy group in a position that blocks the A-ring carbonyl's bottom face forcing reduction to occur on the top face to give a *cis*-diol. However, the smaller corresponding sodium alkoxide formed from the $NaBH_4$ reduction does not facilitate the same alkoxy-mediated inhibition of the A-ring bottom bottom face (Figure 5.5).

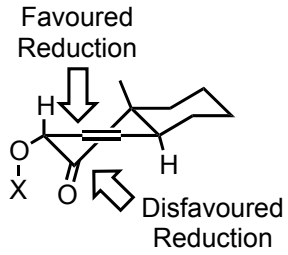
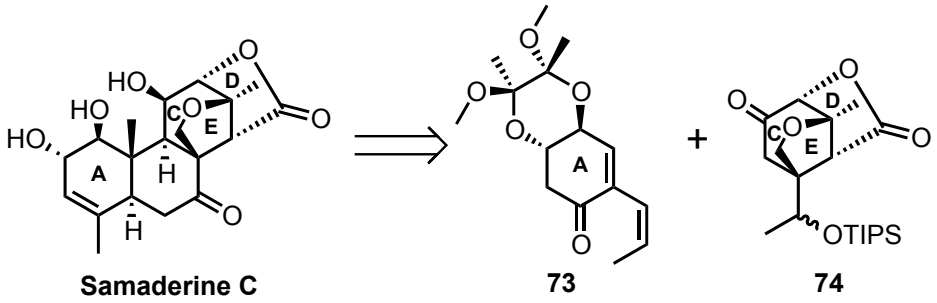


Figure 5.5: *Reversal in the reduction selectivity leading to cis-diol products*

While we could not achieve a *trans*-allylic diol compound using the Wieland-Miescher ketone **69** as the starting material, use of the methyl-Wieland-Miescher ketone **70** has provided a route to *trans*-allylic diol *trans*-**196**. To the best of our knowledge this it the first synthesis of a *trans*-allylic diol quassinoidal AB-ring compound. Furthermore, *trans*-**196** is, in principle, suitable for use in a total synthesis of samaderine C.

Chapter 6: Samaderine C CDE-Ring Synthesis: Diels-Alder Approach

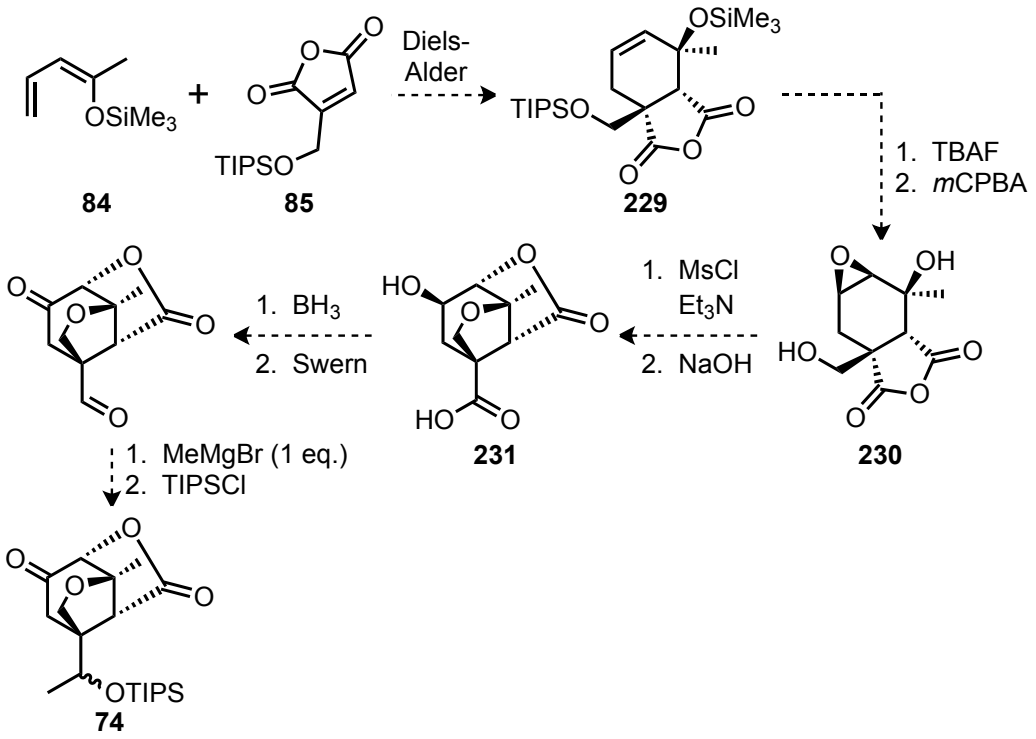
Studies up to this point had focused solely on the synthesis of the samaderine C AB-ring motif. Work now turned to the synthesis of the CDE-ring cluster of samaderine C. The proposed double 1,4-addition strategy used a CDE-ring cluster **74** which would be converted into an enolate and then added in a 1,4-fashion to enone **73** (Scheme 6.1). This chapter describes our preliminary efforts towards a synthesis of ketone **74**.



Scheme 6.1: *Disconnection of samaderine C disconnected in a 1,4-fashion to a CDE-ring compound 74*

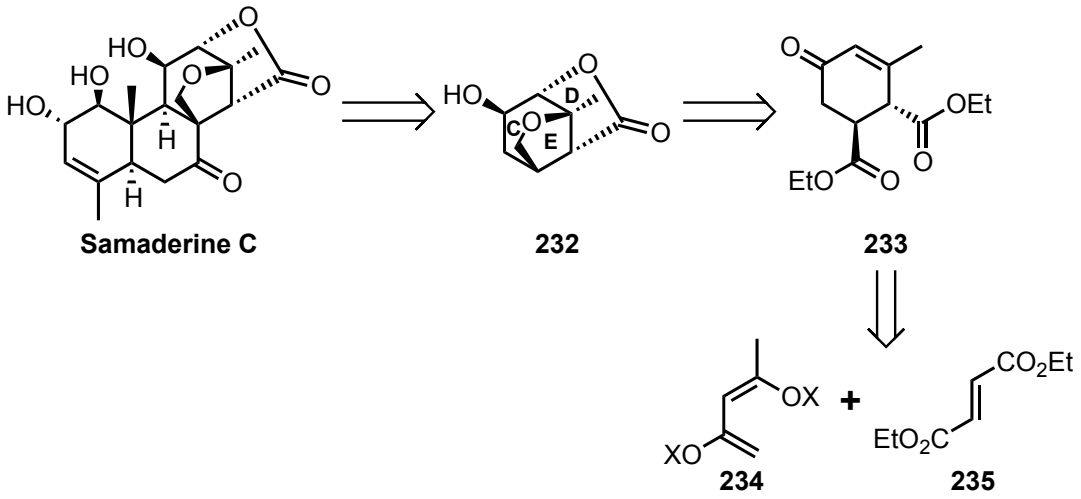
6.1 Strategy to CDE-Ring Structures

It was envisaged that CDE-ring system **74** could be accessed using a Diels-Alder strategy. The proposed forward synthesis of the CDE-ring structure **74** is shown in Scheme 6.2. An *endo*-selective Diels-Alder cycloaddition reaction of diene **84** and maleic anhydride **85** would furnish adduct **229**. Silyl cleavage would then give a diol intermediate which would then undergo a directed epoxidation to give epoxide **230**. We predict that treatment of epoxide **230** with mesyl chloride will selectively mesylate the primary alcohol and, on hydroxide-opening of the anhydride, will allow an intramolecular epoxide-opening cascade to give hydroxy acid **231**. Subsequent manipulation of the pendant carboxylic acid and the ring alcohol would ultimately lead to the desired CDE-ring compound **74**.



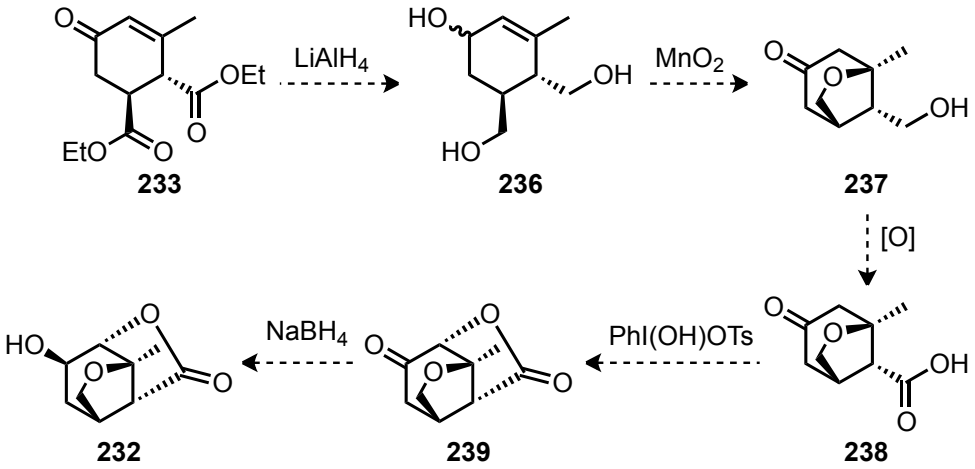
Scheme 6.2: *Proposed route to CDE-ring compounds **74** via an epoxide-opening cascade*

However, before exploring this approach we simplified the CDE-ring structure further and investigated an alternative strategy. By removing the pendent carboxylic acid we decided to attempt the synthesis of CDE-fragment **232** (Scheme 6.3). We anticipated that this tricyclic fragment could be formed from enone **233** which itself would be accessed from a Diels-Alder cycloaddition. A dienol ether-type diene such as **234** would undergo a [4+2] cycloaddition with commercially available diethyl fumerate **235**, that on elimination would give the enone **233**.



Scheme 6.3: *Simplified CDE-ring structure **232***

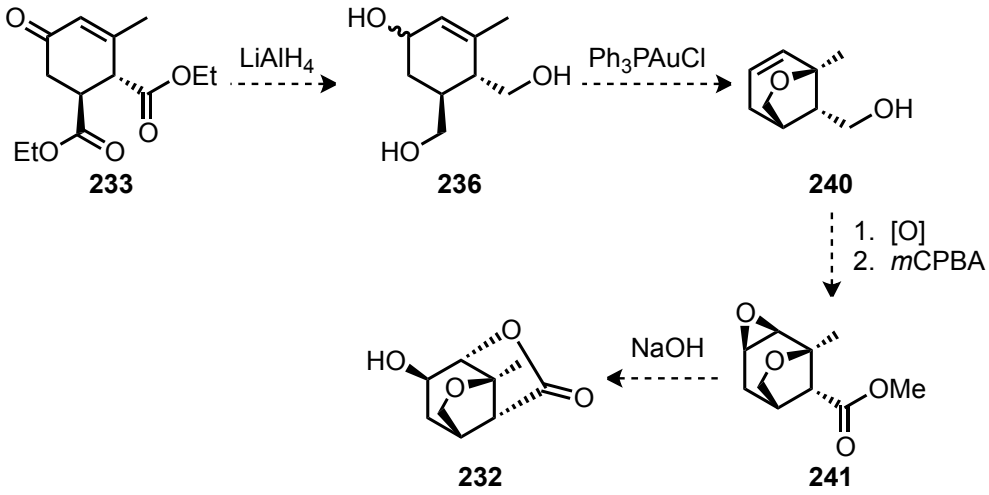
From enone **233**, we imagined two possible routes to the CDE-fragment **232**. The first route incorporates an oxy-Michael reaction to form the E-ring tetrahydrofuran (Scheme 6.4). Complete reduction of enone **233** would give triol **236**. It was hoped that preferential oxidation of the activated allylic alcohol using manganese dioxide would form an enone which, dependent on the diol conformation, would undergo an oxy-Michael reaction to give ketone **237**. An oxidation would then give acid **238**. In 1990, Moriarty published a convenient hypervalent iodine method for coupling carboxylic acids onto enolic positions.[288-290] Following these conditions (*e.g.* PhI(OH)OTs, or use of modern variants), we envisaged accessing ketone **239**. The regioselectively for this process is not assured. We speculate that the desired enolic position will be more acidic since the axial enolic hydrogen is antiperiplanar to the β-etheryl oxygen. Finally, a chemoselective reduction of ketone **239** would give the desired CDE-ring compound **232**.



Scheme 6.4: *Oxy-Michael route to CDE-ring analogue **232***

The second route also uses enone **233** but would proceed *via* an alternative etherification reaction to form the E-ring (Scheme 6.5). Global reduction of enone **233** to triol **236** would allow a nucleophilic substitution-type etherification. Gold has been reported to be an effective catalyst in such intramolecular etherification events.[291-294] However, no examples of intramolecular gold-catalysed processes, to give a bicyclic motif, have been described. A related study that produces a fused [5.5.0] system is known.[295] We envisaged that application of triol **236** to these conditions would give alcohol **240**. Oxidation of alcohol **240** to the methyl ester should be feasible and epoxidation using *m*CPBA should then give epoxy ester **241**.

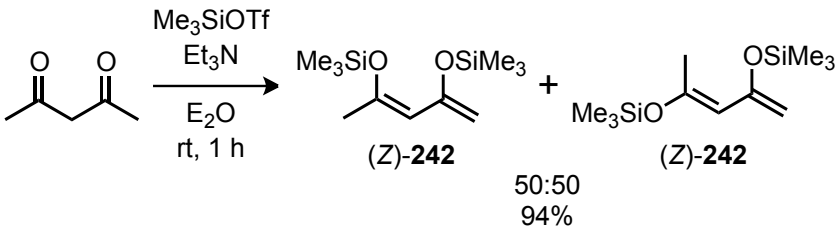
We hoped that treatment of epoxy ester **241** with hydroxide would result in either saponification of the methyl ester or an epoxide-opening reaction (*trans*-diaxial-opening). In either case the resulting intermediate should cyclise to give the CDE-ring fragment **232**.



Scheme 6.5: *Gold-catalysed etherification route to CDE-ring analogue **232***

6.2 Investigation of an Oxy-Michael Approach to a CDE-ring Compound

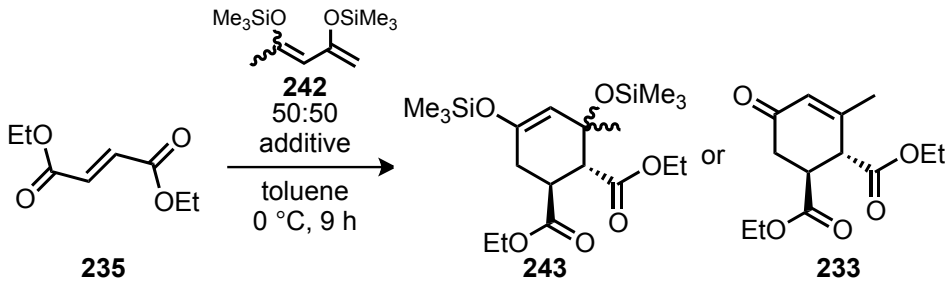
We began this section of our studies by attempting the synthesis of enone **233** using Diels-Alder chemistry. First, the synthesis of an appropriate diene Diels-Alder partner **242** was required. Its synthesis is outlined in Scheme 6.6. Acetylacetone was used in a *bis*-silylation reaction using 2 eq. of Me_3SiOTf following the conditions described by Demark *et al*.[296] The diene **242** was obtained as a 50:50 mixture of geometrical isomers (*Z*)-**242** and (*E*)-**242** in 94% yield after bulb-to-bulb distillation.



Scheme 6.6: *Bis-silylation of acetylacetone to give dienes (Z)-**242** and (E)-**242***

Diene **242** had previously been used in Diels-Alder cycloaddition processes.[297-300] It was therefore known that the reaction of diene **242** typically required the use of a

Lewis acid or high temperatures to induce the desired [4+2] reaction. The Diels-Alder reaction between the diene mixture **242** and diethyl fumerate **235** was therefore screened with Lewis acid additives. Dienes **242** were stirred with diethyl fumerate **235** in toluene at 0 °C for 9 h in the presence of a Lewis acid (Scheme 6.7 and Table 6.1). The reactions were analysed for either the Diels-Alder adduct **243** or the eliminated product β-methyl enone **233**.



Scheme 6.7: *Diels-Alder reactions of diene **242** with diethylfumerate **235***

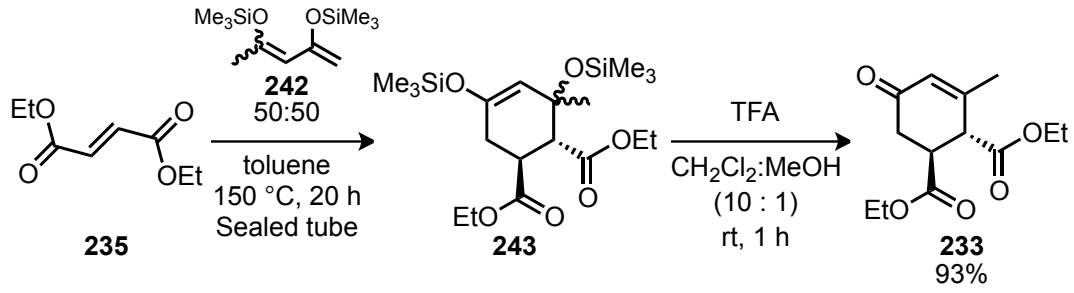
Entry	Additive	Result	Yield[a] (%)
1	None	SM	N/A
2	$ZnCl_2$	SM	N/A
3	$TiCl_4$	SM	N/A
4	$BF_3{\cdot}OEt_2$	Decomp.	N/A
5	$AlCl_3$	Decomp.	N/A
6	$AlMe_3/AlBr_3$	**233**	70%

[a]Yield after purification by chromatography.

Table 6.1: *Diels-Alder reactions of diene **242** with diethylfumerate **235***

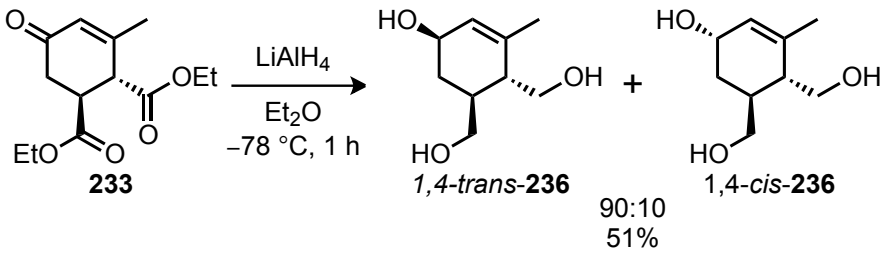
In the absence of a Lewis acid catalyst, the cycloaddition reaction was found not to occur, returning only starting material (entry 1). Similarly, the use of $ZnCl_2$ (entry 2) and $TiCl_4$ (entry 3) proved ineffective with only starting material observed. With $BF_3{\cdot}OEt_2$ (entry 4) or $AlCl_3$ (entry 5), the reaction did proceed with consumption of both starting materials. However, no enone product **233** or the Diels-Alder adduct **243** were isolated. Fortunately, the use of a mixed aluminium catalyst ($AlMe_3/AlBr_3$)[301] did give the desired β-methyl enone **233** in 70% yield with no intermediate Diels-Alder adduct **243** observed (entry 6).

The mixed $AlMe_3/AlBr_3$ conditions indicated that the Diels-Alder reaction of these two partners was possible. We sought to find a higher yielding process and one that would hopefully remove the need for toxic Lewis acid catalysts. Therefore, the thermal Diels-Alder process was attempted. The mixture of dienes **242** was heated with diethyl fumerate **235** in toluene in a sealed tube at 150 °C to give a mixture of Diels-Alder adducts **243** (Scheme 6.8). This Diels-Alder mixture was then treated with TFA in CH_2Cl_2-MeOH (10:1) to give β-methyl enone **233** in 93% yield over both the cycloaddition and elimination steps.



Scheme 6.8: *Sealed tube Diels-Alder reaction of dienes **242** with diethylfumerate **235***

Triol **236** was a proposed intermediate in both the oxy-Michael (see Scheme 6.4) and etherification (see Scheme 6.5) routes to CDE-ring compound **232**. Global reduction of both esters and the enone carbonyl should give the desired triol **236**. Using $LiAlH_4$, β-methyl enone **233** was reduced. The reaction mixture was carefully quenched using Glauber's salt ($Na_2SO_4{\cdot}H_2O$) in order to avoid an aqueous work-up. This procedure gave a mixture of triol diastereomers (Scheme 6.9). A 90:10 mixture of triols 1,4-*trans*-**236** and 1,4-*cis*-**236** was isolated in 51% yield. Other unidentifiable products were also obtained.



Scheme 6.9: *Reduction of enone **233** to triol products*

The assignment of relative stereochemistry was achieved using the coupling constants present in the ^{1}H NMR spectrum of the product mixture. The axial proton of 1,4-*trans*-**236**, highlighted in Figure 6.1, shows three characteristic couplings. The largest coupling is the 12.5 Hz ^{2}J coupling to the geminal proton. There are also two large couplings, 10 Hz and 8 Hz, which correspond to two *trans*-diaxial ^{3}J couplings. The corresponding signals in the minor diastereomer, 1,4-*cis*-**236**, show the large ^{2}J geminal coupling (13 Hz), a large ^{3}J *trans*-diaxial coupling (8 Hz) and a smaller ^{3}J axial-equatorial coupling (4 Hz).

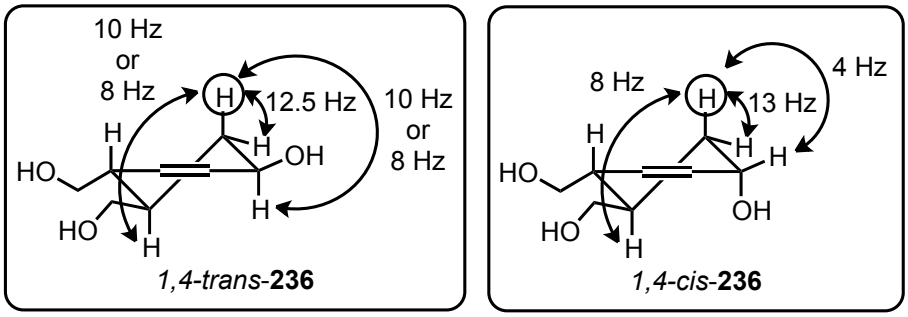
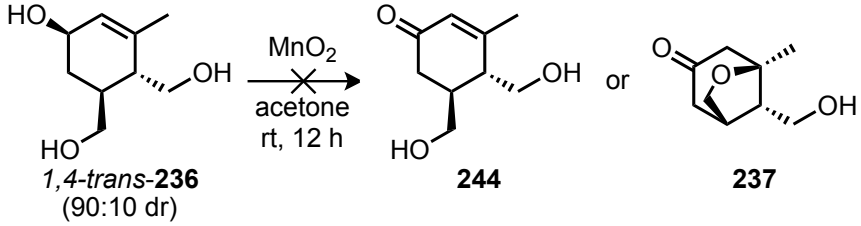


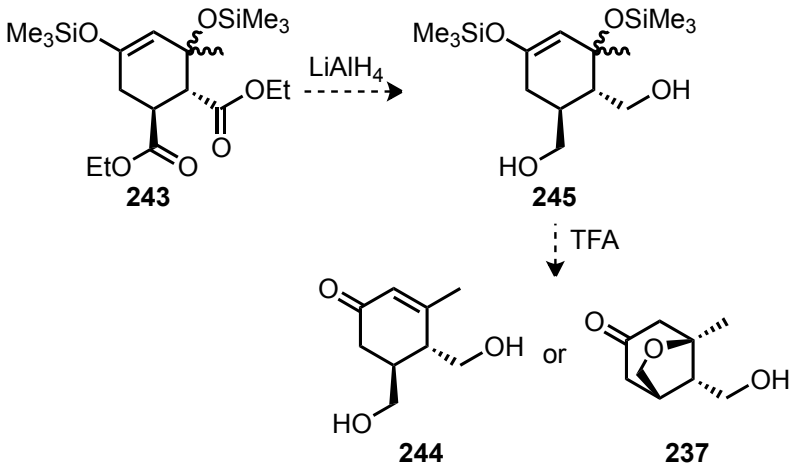
Figure 6.1: *Diagnostic coupling constants for assignment of 1,4-trans-**236** and 1,4-cis-**236***

The oxy-Michael approach was the first to be investigated using triol **236**. We hoped that selective oxidation of the allylic alcohol would give diol **244**, which could undergo the desired oxy-Michael reaction to give ketone **237** based on a literature example (Scheme 6.10).[302] Following the literature conditions, triols 1,4-*trans*-**236** and 1,4-*cis*-**236** (90:10 dr) were submitted to manganese dioxide oxidation. Unfortunately, none of the desired products, ketone **237** or enone **244**, were formed. The result was a mixture of products which, surprisingly, contained mainly aldehydes suggesting that oxidation of the primary alcohol(s) had occurred.



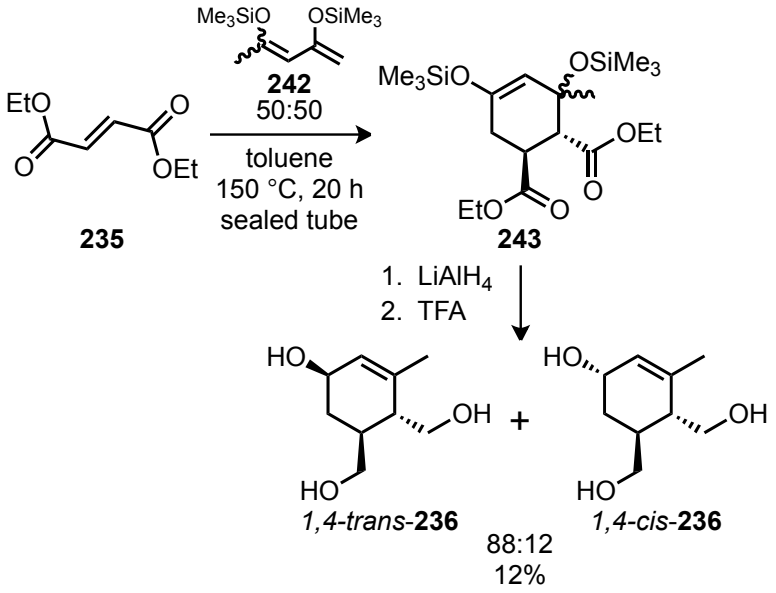
Scheme 6.10: *Attempted allylic oxidation/Michael addition to **237***

In an effort to obtain diol **244** or ketone **237**, we investigated using the Diels-Alder adduct **243** as a synthetic intermediate (Scheme 6.11). The plan was that the silyl enol ether in **243** would act as a suitable ketone protecting group. Treatment of **243** with $LiAlH_4$ should reduce only the ester groups to give diol **245** and on elimination of the β-silyl ether using TFA, enone **244** or ketone **237** could be formed



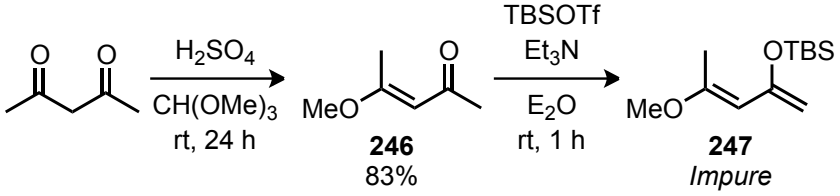
Scheme 6.11: *Proposed use of a silyl enol ether as a ketone protecting group*

Following the Diels-Alder conditions previously used, diethyl fumerate **235** was reacted with the mixture of dienes **242** in a sealed tube at 150 °C to give the Diels-Alder adducts **243** (Scheme 6.12). This crude material was then used in a reduction reaction with $LiAlH_4$ and worked-up using Glauber's salt. This crude reduction mixture was then submitted to the TFA elimination conditions. However, analysis of the ^1H NMR spectrum of the crude material showed a very complex mixture that, on isolation, produced the previously obtained triols 1,4-*trans*-**236** and 1,4-*cis*-**236** (88:12 dr) in 12% yield.



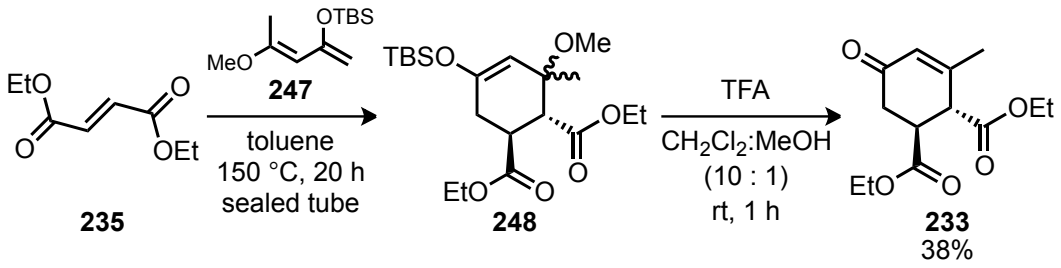
Scheme 6.12: *Attempted use of a silyl enol ether protected intermediate **245***

It appears that, under the $LiAlH_4$ reduction conditions used, the trimethylsilyl enol ether moiety was cleaved and subsequent reduction of the enone carbonyl was inevitable. We hoped that the use of a more robust silyl enol ether (*e.g.* TBS) would facilitate our planned route. The synthesis of a TBS enol ether equivalent was therefore attempted and is outlined in Scheme 6.13. TBS-methoxy diene **247** is known but no synthetic details have been described.[303,304] We adapted a method that was reported for the corresponding trimethylsilyl methoxy ether.[305] Thus, acetylacetone was stirred neat in trimethylorthoformate with catalytic sulfuric acid to give methoxy enol ether **246** as a single geometric isomer in 83% yield after distillation. The second enol ether was formed using TBSOTf. Diene **247** was obtained, but, after three successive distillations, we were unable to separate the diene from TBS-related impurities. The crude TBS diene **247** was therefore used in further reactions.



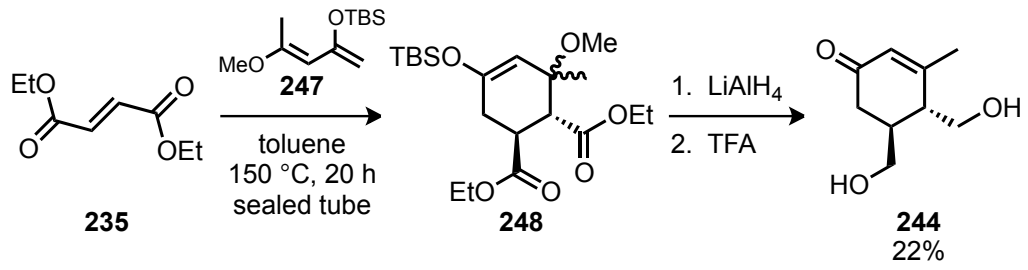
Scheme 6.13: *Synthesis of TBS-methoxy diene **247***

Using TBS diene **247** in the planned procedure to β-methyl enone **233** would establish the applicability of the diene in the Diels-Alder process. Therefore, TBS diene **247** was reacted with diethyl fumerate **235** in toluene in a sealed tube at 150 °C (Scheme 6.14). The reaction was successful with TBS Diels-Alder adduct **248** observed, which on TFA cleavage gave β-methyl enone **233** in 38% yield. The yield was lower than we hoped but may be due to the use of impure diene **247**. Two equivalents of TBS diene **247** were used but the purity of the diene could have been even less than 50%. Analysis of the crude TBS Diels-Alder adducts **248** by ^{1}H NMR spectroscopy indicated the presence of unreacted diethyl fumerate **235** but no TBS diene **247** remained.



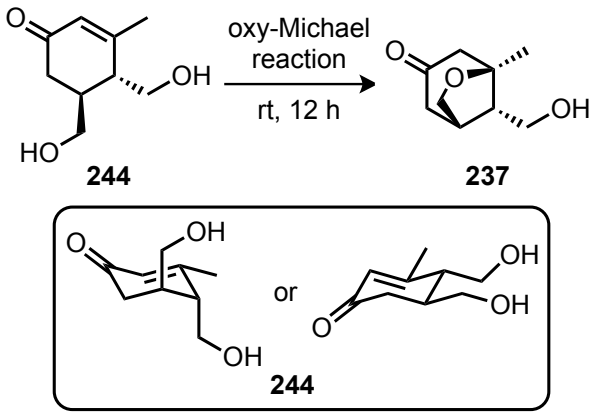
Scheme 6.14: *Sealed tube Diels-Alder reactions of TBS diene **247** with diethylfumerate **235***

The successful synthesis of β-methyl enone **233** proved the ability of diene **247** to react in the cycloaddition reaction. We therefore returned to the tandem Diels-Alder/*in situ* ketone protection/reduction process. The cycloaddition reaction using diene **247** and diethyl fumerate **235** gave TBS Diels-Alder adduct **248** (Scheme 6.15). Subsequent $LiAlH_4$ reduction and Glauber's salt work-up presumably gave a diol TBS enol ether which was then eliminated using TFA. Diol **244** was formed in 22% yield as the only isolated product. We feel the impurity of diene **247** may be responsible for the low yield.



Scheme 6.15: *Synthesis of oxy-Michael precursor **244***

Since diol **244** was isolated, the oxy-Michael reaction was not spontaneous as first hoped. Conditions to induce this oxy-Michael reaction were therefore investigated (Scheme 6.16 and Table 6.2). Use of NaOMe (entry 1) or K_2CO_3 (entry 2) in MeOH gave no conversion with only starting material present. Use of DBU (entry 3) and NaOH (entry 4) also gave starting material. We were concerned that diol **244** may not be able to ring-flip into the conformation required for cyclisation. Therefore, **244** was heated in MeOH at reflux with NaOMe (entry 5). However, this resulted in only starting material. Under acidic conditions, HCl in Et_2O (entry 6), the result was decomposition of the starting material to methylene-containing products.



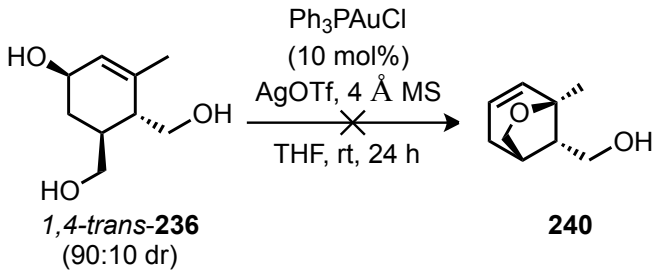
Scheme 6.16: *Attempted at an oxy-Michael reaction with diol **244***

Entry	Conditions	Result
1	NaOMe, MeOH, rt	SM
2	K_2CO_3, MeOH, rt	SM
3	DBU, CH_2Cl_2, rt	SM
4	NaOH, H_2O, rt	SM
5	NaOMe, MeOH, Δ	SM
6	HCl in Et_2O, rt	Decomp.

Table 6.2: *Attempted oxy-Michael reaction with diol **244***

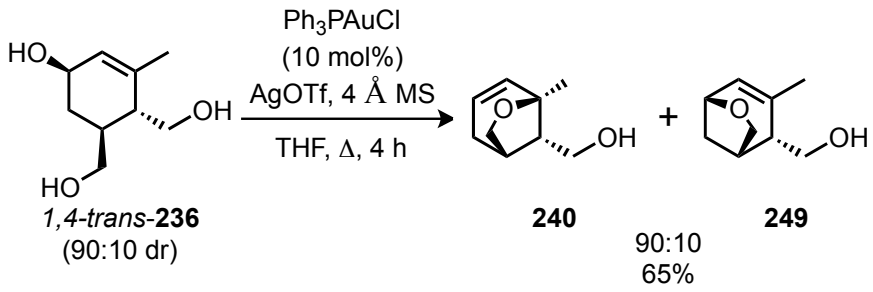
6.3 Investigation of Nucleophilic-Substitution Etherification Approach to a CDE-Ring Compound

With the time for these studies running out, we abandoned the oxy-Michael approach and investigated the etherification route. The formation of the E-ring ether was proposed using gold chemistry (see Scheme 6.5). The triol mixture 1,4-*trans*-**236** 1,4-*cis*-**236** (90:10 dr) was therefore reacted with a gold triphenylphosphine chloride catalyst at rt in the presence of silver triflate and molecular sieves (Scheme 6.17). Disappointingly, stirring at rt for 24 h resulted only in starting material being recovered.



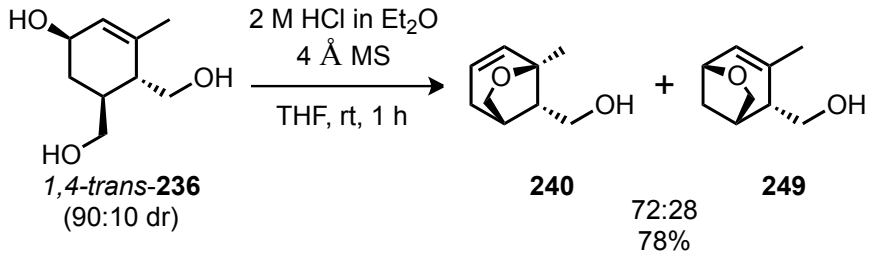
Scheme 6.17: *Attempted gold-catalysed etherification to ether **240***

However, we were able to effect the desired etherification reaction by using the same reagents at reflux for 4 h (Scheme 6.18). An inseparable mixture of two ether products **240** and **249** were formed in 65% yield. Products **240** and **249** were tentatively assigned by ^{1}H NMR only. Fortunately, the major product (90:10 ratio **240** and **249**) was our desired ether **240**. The characterisation of the two regioisomers is based on the number of alkene signals present for each product i.e. product **240** shows two alkene signals while ether **249** possesses only one.



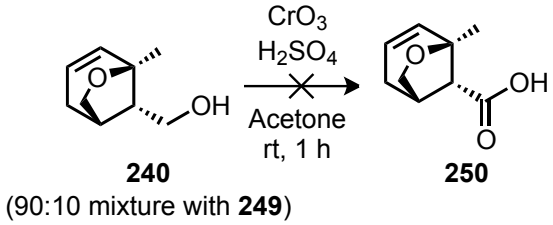
Scheme 6.18: *Heated gold-catalysed etherification of triol **236***

The requirement for this reaction to be heated caused us to question the gold-catalysed aspect of this process. We speculated that trace amounts of triflic acid may form under these conditions and the resulting etherification event could proceed *via* a Bronsted acid-promoted S_N2'-type reaction. To test this theory, we reacted a 90:10 mixture of triols 1,4-*trans*-**236** and 1,4-*cis*-**236** (90:10 dr) under acidic conditions (HCl in Et_2O) at rt (Scheme 6.19). Under these conditions, a 72:28 mixture of **240** and **249** was obtained in 78% yield. Although this reaction was carried out only once and on a small-scale, it suggests that the ether formation does not necessarily require the presence of the gold catalyst.



Scheme 6.19: *Acid-catalysed etherification of triol **236***

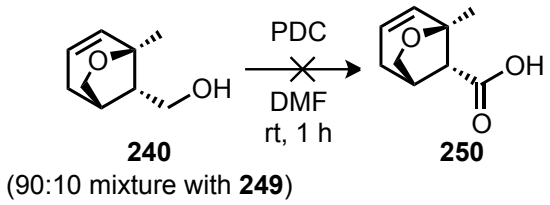
Following the proposed route (see Scheme 6.5), oxidation of the primary alcohol to the carboxylic acid was attempted. Direct conversion of alcohol **240** (90:10 mixture with **249**) into acid **250** using Jones oxidation conditions was unsuccessful, resulting in decomposition of the starting material (Scheme 6.20). The Jones oxidation conditions are harsh, with sulfuric acid present and it was not surprising that alcohol **240** was sensitive under these conditions.



Scheme 6.20: *Attempted Jones oxidation of alcohol **240***

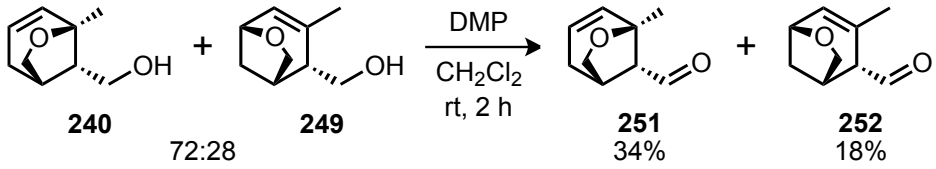
A milder route to convert alcohol **240** into acid **250** was briefly explored. Corey had developed conditions for the direct oxidation of primary alcohols to acids using PDC in wet DMF.[306] Application of alcohol **240** (90:10 mixture with **249**) to these

conditions did not give the desired acid **250** but resulted in decomposition of the starting alcohol (Scheme 6.21).



Scheme 6.21: *Attempted PDC oxidation of alcohol **240** to acid **250***

A sequential oxidation route to carboxylic acid **250** should be possible. With this in mind, oxidation of alcohol **240** to the aldehyde would then allow subsequent Pinnick oxidation to give the carboxylic acid **250**. To that end, alcohol mixture, **240** and **249** (72:28) were oxidised using DMP to give a mixture of aldehydes. Purification by flash column chromatography gave two aldehydes. Aldehyde **251** was obtained in 34% yield and isomeric aldehyde **252** was isolated in 18% yield (Scheme 6.22).

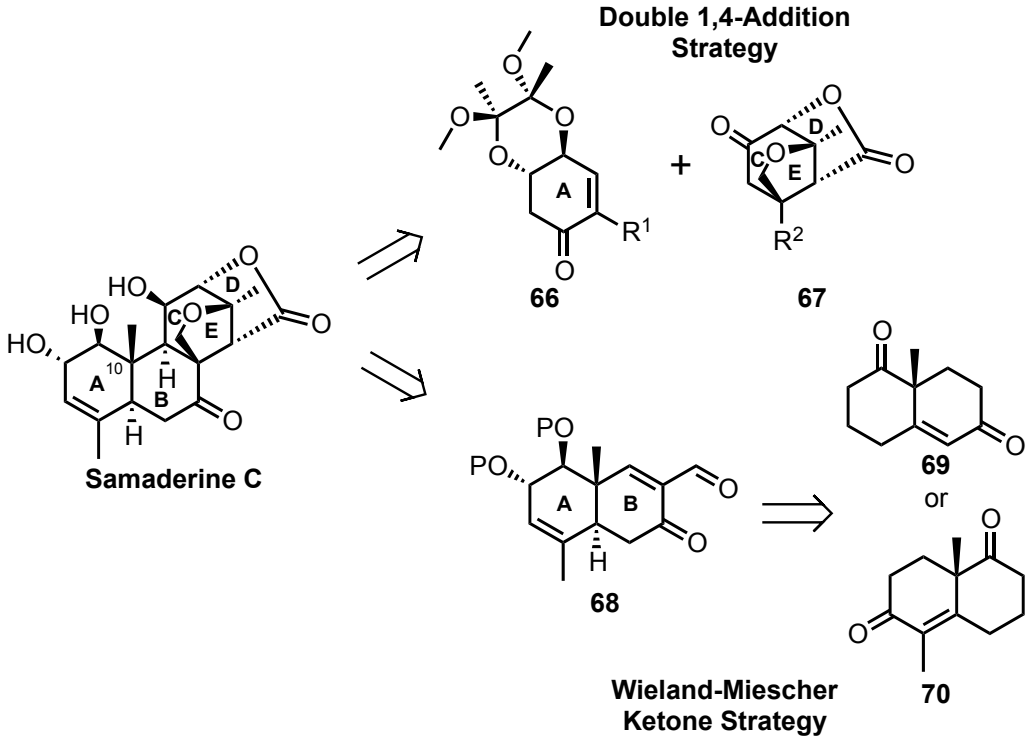


Scheme 6.22: *DMP oxidation of alcohols **240** and **249***

At this point, further studies were not possible due to material and time restrictions. However, this route does look promising for access to CDE-ring analogues of samaderine C. The etherification reaction does form the hydrofuran E-ring and, with further development, the synthesis of the lactone D-ring is conceivable from this point.

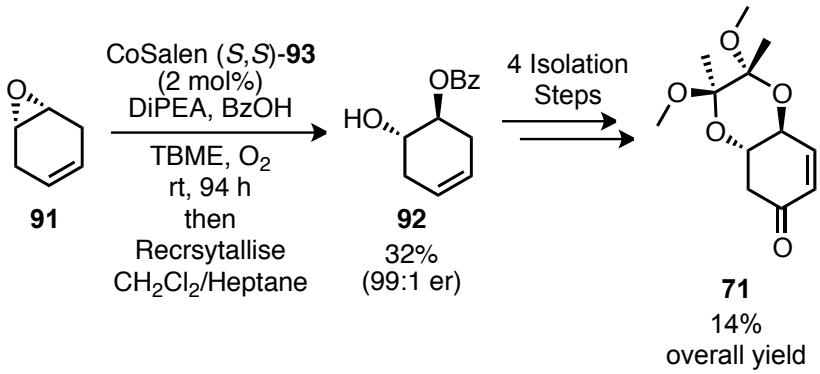
Chapter 7: Conclusions and Future Work

Over the course of these studies, we have investigated two main approaches for the total synthesis of samaderine C (Scheme 7.1). The first route hinged around a double 1,4-addition strategy, combining the enolate of CDE-ring fragment **67** with an A-ring enone **66**. The second approach utilised the Wieland-Miescher ketone **69** and its methyl analogue **70** in an attempt to reach a Diels-Alder dienophile **68**.



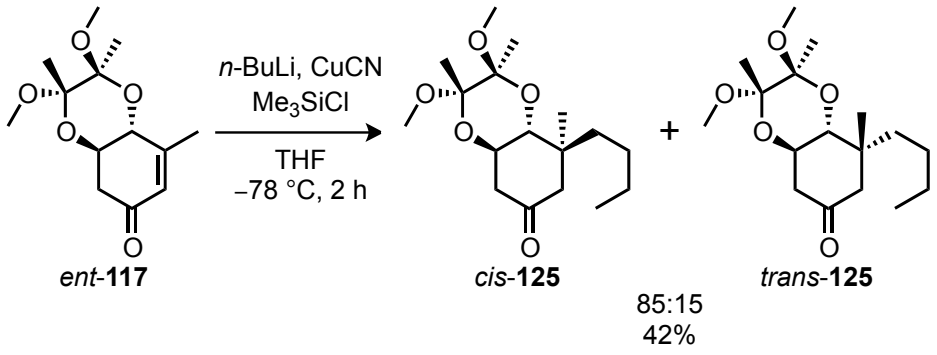
Scheme 7.1: *Retrosynthetic analysis of the two planned approaches*

In chapter 2 the synthesis of diol enone **71** was described. This enone is the enantiomer of known enone *ent*-**71** which can be synthesised from the chiral pool starting material, (−)-quinic acid. With no (+)-quinic acid available from nature we utilised the desymmetrisation chemistry shown in Scheme 7.2 to access hydroxy benzoate **92**. After a recrystallisation, hydroxy benzoate **92** was obtained in 32% yield as a single enantiomer. In a further four isolation steps, enone **71** was synthesised. The overall yield was 14% from a commercial starting material (1,4-cyclohexadiene).

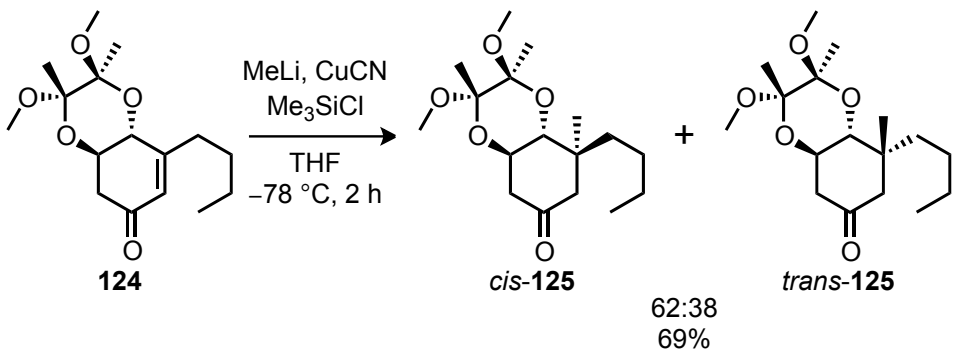


Scheme 7.2: *Synthesis of enone **71***

Chapter 3 highlighted our attempts at using the double 1,4-addition procedure to access the AB-ring structure of samaderine C. Unfortunately, a suitable B-ring annulation method could not be found. However, during the course of our cuprate addition studies to β-substituted adducts derived from enone *ent*-**71**, we observed interesting diastereoselectivity (Scheme 7.3 and Scheme 7.4). We found that addition of methyl/*n*-butyl cuprates to the complementary β-substituted enones surprisingly resulted in the same major diastereomer *cis*-**125**.

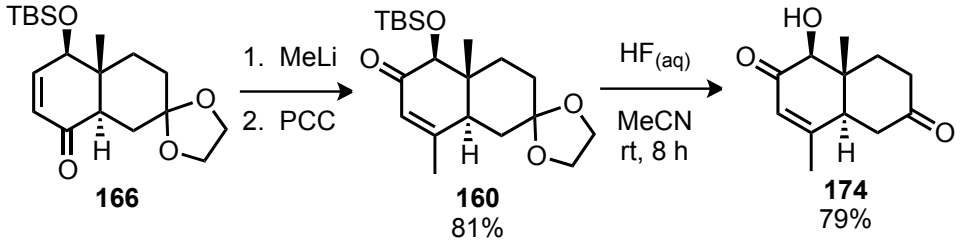


Scheme 7.3: *n-Butyl cuprate addition to β-methyl enone ent-**117***



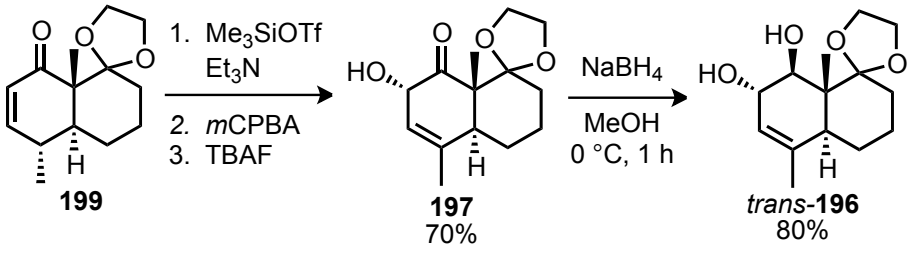
Scheme 7.4: *Methyl cuprate addition to β-n-butyl enone **124***

With no success with the double 1,4-addition approach, we then turned our attention to the use of the Wieland-Miescher ketone **69** to access the samaderine C *trans*-diol A-ring motif (Chapter 4). In the main result of this chapter, we utilised the addition of MeLi to enone **166** to form a tertiary alcohol, which was subsequently rearranged in a Dauben oxidation to give β-methyl enone **160** (Scheme 7.5). The original plan was to diastereoselectively reduce β-methyl enone **160** to give the *trans*-diol motif. Unfortunately, all efforts to achieve this reduction were unsuccessful as the axial bridgehead methyl group directed reduction to form the *cis*-diol adduct. We were, however, able to globally deprotect β-methyl enone **160** using $HF_{(aq)}$ to give **174**, which represents the AB-ring structure of a large number of quassinoid natural products (e.g. samaderines B, D, E, X, Y and Z).



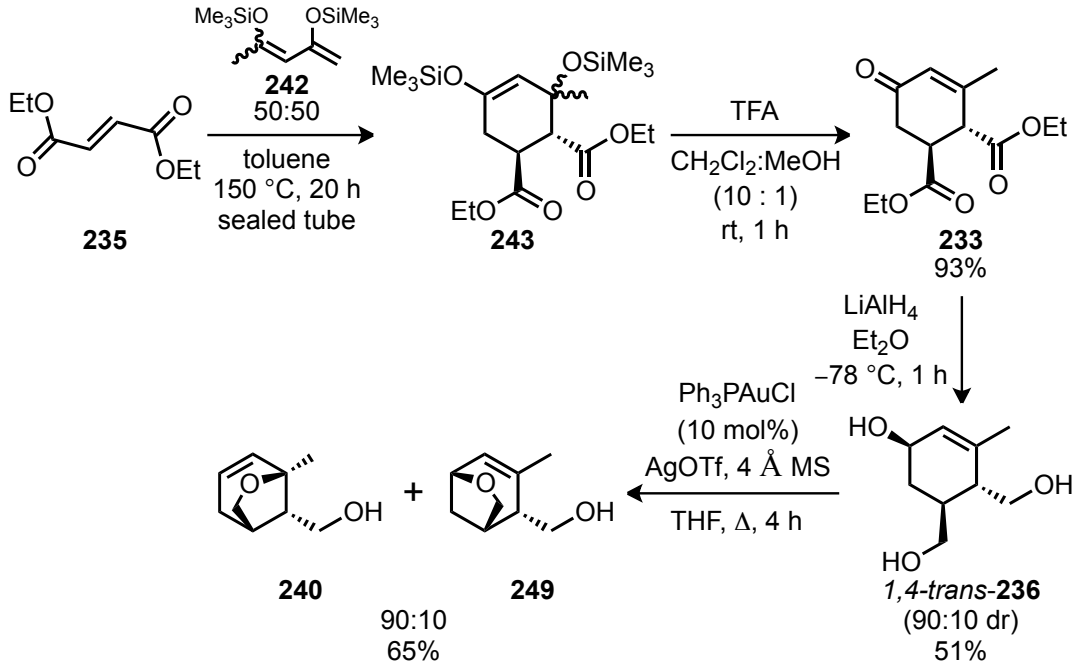
Scheme 7.5: *β-Methyl enone **160** synthesis and global deprotection to dione **174***

Chapter 5 centred on the use of the methyl-Wieland-Miescher ketone analogue **70** with the specific goal of using the axial bridgehead methyl group to direct the stereoselective formation of the *trans*-diol motif. From this starting point, we were able to synthese enone **199** (Scheme 7.6). Enone **199** was then used to form an extended enolate from which α-hydroxylation gave hydroxy ketone **197**. Diastereoselective reduction of hydroxy ketone **197** then gave diol *trans*-**196**. To the best of our knowledge, this represents the first approach to give the quassinoid *trans*-diol A-ring motif.



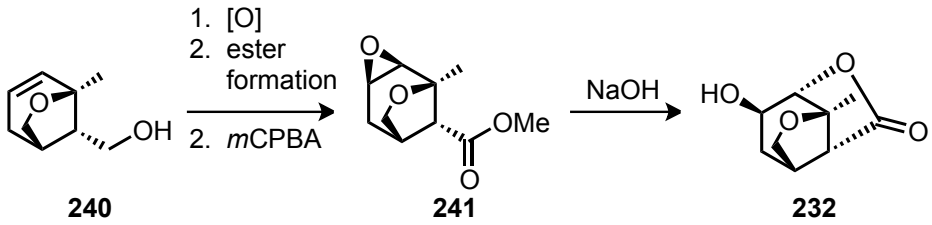
Scheme 7.6: *Synthesis of diol trans-**196***

We then briefly studied the synthesis of a CDE-ring analogue as described in Chapter 6. Diels-Alder cycloaddition of diethylfumerate **235** and dienes **242** gave Diels-Alder adducts **243**, which were then eliminated using TFA to give β-methyl enone **233** (Scheme 7.7). Global reduction using $LiAlH_4$ gave triols 1,4-*trans*-**236** and 1,4-*trans*-**236** (90:10 dr). An etherification reaction under gold catalysed conditions then gave alcohol **240**, representing the CE-rings of samaderine C.



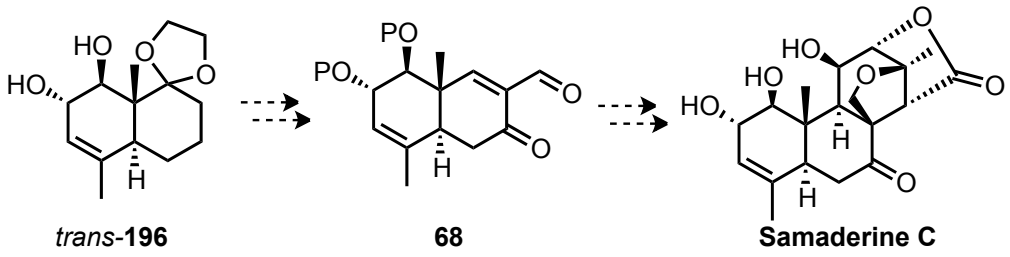
Scheme 7.7: *CE-ring analogue **240** synthesis*

In future, efforts should continue on the synthesis of the CDE-ring analogue **232**. Scheme 7.8 shows the steps remaining. Alcohol **240** still needs to be oxidised to a methyl ester, where upon, epoxidation would then give epoxy ester **241**. Treating epoxy ester **241** with hydroxide will hopefully result in the formation of the CDE-ring analogue alcohol **232**.



Scheme 7.8: *Conversion of alcohol **240** into CDE-ring analogue **232***

In addition to the CDE-ring analogue we feel the precedent of quassinoidal CDE-ring structures from a Diels-Alder annulation strategy is strong. Therefore, from the diol *trans*-**196** we would endeavour to complete the total synthesis of samaderine C. Appropriate protection of the *trans*-diol moiety would be followed by a ketal deprotection, a 1,3-carbonyl transposition and α-formylation and enone formation to give the dienophile **68** (Scheme 7.9). We envisage a Diels-Alder strategy followed by further elaboration would give the CDE-rings of samaderine C. We also recognise the possibility of re-ordering the synthesis of samaderine C. Initial CDE-ring functionalisation would then allow the use of our α-hydroxylation/reduction methodology to give the A-ring *trans*-diol motif as the end game strategy.



Scheme 7.9: *Total synthesis of samaderine C from trans-**196***

Chapter 8: Experimental

8.1 General

Except where specified, all reagents were purchased from commercial sources and were used without further purification. All procedures were carried out in an atmosphere of argon. Where necessary, solvents were dried on an MBraun SPS solvent purification system. Anhydrous tetrahydrofuran (THF) was obtained by distillation over sodium benzophenone. Petroleum ether (petrol) refers to light petroleum ether, bp 40–60 °C. Flash column chromatography was performed using Fluka silica gel 60 at a low positive pressure, unless otherwise stated. Analytical thin layer chromatography was performed on aluminium sheets pre-coated with Merck silica gel 60 F254 and visualised with ultraviolet light (254 nm), aqueous potassium permanganate or anisaldehyde solutions where appropriate. All melting points were taken on a Gallenkamp apparatus. Proton magnetic resonance (^{1}H NMR) spectra were recorded at 400 MHz on a JEOL ECX 400 spectrometer or at 270 MHz on a JEOL ECX 270 spectrometer and are reported as follows: chemical shift δ (ppm) (multiplicity, coupling constant *J* (Hz), number of protons, assignment). The coupling constants are quoted to the nearest 0.5 Hz (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br. = broad) and are reported as measured splitting of each individual resonance. The residual protic solvent $CHCl_3$ (δ_H = 7.26 ppm) was used as an internal reference while in CD_3OD the corresponding reference (δ_H = 3.34 ppm) was used. ^{13}C NMR spectra were recorded at 100 MHz on a JEOL ECX 400 spectrometer. The central reference of $CDCl_3$ (δ_C = 77.0 ppm) was used as an internal reference for NMR experiments in $CDCl_3$ while in CD_3OD the corresponding reference (δ_C = 49.9 ppm) was used. ^{13}C spectra were assigned using DEPT experiments where necessary. Chemical shifts are reported in parts per million (ppm) to the nearest 0.01 ppm for ^{1}H and the nearest 0.1 ppm for ^{13}C. Infrared spectra were carried out on a ThermoNicolet IR100 spectrometer and are recorded as a thin film or Nujol© mull between NaCl disks. Absorption maxima are reported in wavenumbers (cm^{-1}) and only selected absorbances are reported. Mass spectra and accurate mass measurements were recorded on a Micromass Autospec spectrometer.

General procedure A: Co-salen desymmetrisation of *meso*-epoxide **91**

A solution of (*R*,*R*)-Co-salen **93** (1–5 mol%) and benzoic acid (140 mg, 1.15 mmol, 1.1 eq.) in TBME (1 mL) were stirred under O_2 for 1 h. The solvent was then evaporated under reduced pressure to give the oxidised catalyst as a red slurry. To the catalyst slurry, DIPEA (199 μL, 1.15 mmol, 1.1 eq.), TBME (1 mL) and *meso*-epoxide **91** (100 mg, 1.05 mmol, 1.0 eq.) were added. The resulting solution was stirred at rt under O_2 for 53–120 h. Then, Et_2O (10 mL) and 3 M $HCl_{(aq)}$ (10 mL) were added and the layers separated and the aqueous layer was extracted with Et_2O (5 × 10 mL). The combined organic extracts were washed with saturated $NaHCO_{3(aq)}$, dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product.

General procedure B: Addition of cuprate to enone in the absence of of additive *e.g*. Me_3SiCl

Organolithium reagent (0.99 mmol, 2.4 eq.) was added dropwise over 15 min to a vigorously stirred suspension of CuI or CuCN (0.50 mmol, 1.2 eq.) in THF (5 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C, –40 °C or 0 °C for 20 min. Then, a solution of an enone (0.413 mmol, 1.0 eq.) in THF (6 mL) was added dropwise over 10 min to give a yellow solution. After stirring at –78 °C, –40 °C or 0 °C for 1 h, saturated $NH_4Cl_{(aq)}$ (20 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product.

General procedure C: Addition of cuprate to enone in the presence of additive *e.g*. Me_3SiCl

Organolithium reagent (0.99 mmol, 2.4 eq.) was added dropwise over 15 min to a vigorously stirred suspension of CuCN (0.50 mmol, 1.2 eq.) in THF (5 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C, –40 °C or 0 °C for 20 min. Then, a premixed solution of an enone (0.41 mmol, 1.0 eq.) and Me_3SiCl (105 μL, 0.83 mmol, 2.0 eq.) in THF (6 mL) was added dropwise over 10 min to give a yellow

solution. After stirring at –78 °C, –40 °C or 0 °C for 1 h, saturated $NH_4Cl_{(aq)}$ (20 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude silyl enol ether. TBAF (1.0 M solution in THF, 0.45 mmol, 1.1 eq.) was added dropwise to a stirred solution of crude silyl enol ether in CH_2Cl_2 (10 mL) at 0 °C under Ar. After stirring for 30 min, saturated $NH_4Cl_{(aq)}$ (20 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product.

General procedure D: Copper catalysed addition of Grignard reagents to enone in the absence of Me_3SiCl

Grignard reagent (0.99 mmol, 2.4 eq.) was added dropwise over 15 min to a vigorously stirred suspension of CuBr·SMe_2 or CuCN (0.08 mmol, 0.2 eq.) in THF (5 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 20 min. Then, a solution of an enone (0.41 mmol, 1.0 eq.) in THF (6 mL) was added dropwise over 30 min to give a yellow solution. After stirring for 1 h, saturated $NH_4Cl_{(aq)}$ (20 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product.

General procedure E: Copper catalysed addition of Grignard reagents to enone in the presence of Me_3SiCl

Grignard reagent (0.99 mmol, 2.4 eq.) was added dropwise over 15 min to a vigorously stirred suspension of CuBr·SMe_2 or CuCN (0.08 mmol, 0.2 eq.) in THF (5 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 20 min. Then, a premixed solution of an enone (0.41 mmol, 1.0 eq.) and Me_3SiCl (0.83 mmol, 2.0 eq. or 0.41 mmol, 1.0 eq.) in THF (6 mL) was added dropwise over 15 min to give a yellow solution. After stirring for 1 h, saturated $NH_4Cl_{(aq)}$ (20 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give

the crude silyl enol ether. TBAF (1.0 M solution in THF, 0.45 mmol, 1.1 eq.) was added dropwise to a stirred solution of crude silyl enol ether in CH_2Cl_2 (10 mL) at 0 °C under Ar. After stirring for 30 min, saturated $NH_4Cl_{(aq)}$ (20 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product.

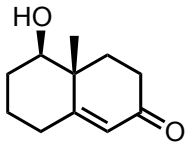
General procedure F: Preparation of Grignard reagent

Alkyl halide (0.20 mmol, 1.0 eq.) was added dropwise to a stirred suspension of magnesium turnings (0.30 mmol, 1.5 eq.) in THF (10 mL) under Ar. The resulting mixture was sonicated (to initiate Grignard formation) and then stirred and heated at reflux for 30 min. Then the mixture was cooled to 0 °C.

General procedure G: Preparation of alkyllithium reagent

Alkyl halide (1.0 mmol, 1.0 eq.) was added dropwise to a stirred suspension of lithium granules (2.2 mmol, 2.2 eq.) in Et_2O (10 mL) at rt under Ar. The resulting mixture was sonicated (to initiate organolithium formation) and then stirred at 0 °C for 1 h. The molarity was determined by titration with *N*-benzylbenzamide.[307]

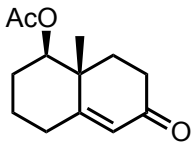
(4a*R*,5*R*)-5-Hydroxy-4a-methyl-4,4a,5,6,7,8-hexahydronaphthalen-2(3*H*)-one 2



A solution of $NaBH_4$ (32 mg, 0.84 mmol) in EtOH (8 mL) was added dropwise to a stirred solution of ketone **69** (500 mg, 2.81 mmol) in EtOH (4 mL) at 0 °C under Ar over 1 h. The resulting mixture was stirred at 0 °C for 15 min. Then, acetic acid (803 μL, 14.0 mmol) was added and the mixture was allowed to warm to rt. The solvent was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with petrol-EtOAc (2:3) as eluent gave alcohol **2** (501 mg, 99%) as a white solid, R_F (2:3 petrol-EtOAc) 0.29; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.58 (d, *J* = 1.5 Hz, 1H, C=CH), 3.44 (dd, *J* = 11.5, 4.3 Hz, 1H, C*H*OH), 2.65–2.23 (m, 5H), 2.11–1.66 (m, 5H), 1.51–1.46 (m, 1H), 1.23 (s, 3H, Me); MS (ESI) 181 [$(M + H)^+$, 100], 163 (41). Spectroscopic data are consistent with those reported in the literature.[50]

Lab book reference: djbI/6

(1*R*,8a*R*)-8a-Methyl-6-oxo-1,2,3,4,6,7,8,8a-octahydronaphthalen-1-yl acetate 3



A solution of $NaBH_4$ (582 mg, 15.4 mmol) in EtOH (135 mL) was added dropwise to a stirred solution of ketone **69** (9.14 g, 51.9 mmol) in EtOH (65 mL) at 0 °C under Ar over 1 h. The resulting mixture was stirred at 0 °C for 15 min. Then, acetic acid (14.7 mL, 256.4 mmol) was added and the mixture was allowed to warm to rt. The solvent was evaporated under reduced pressure to give the crude alcohol **2**. Acetic anhydride (20.9 mL, 205.1 mmol) was added dropwise to a stirred solution of the crude alcohol **2** in pyridine (35 mL) at rt under Ar. The resulting mixture was stirred at rt for 20 h. Then, 10% $H_2SO_{4(aq)}$ (50 mL) and CH_2Cl_2 (50 mL) were added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL).

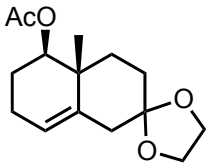
The combined organics were washed with saturated $NaHCO_{3(aq)}$ (300 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 300 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with petrol-EtOAc (2:3) as eluent gave acetate **3** (11.0 g, 96%) as a white solid, mp 82–83 °C (lit.,[31] 63–64 °C); $[\alpha]_D$ −113.1 ((*c* 1.0 in $CHCl_3$)(lit.,[31] −111.7 (*c* 1.54 in $CHCl_3$)); R_F (2:3 petrol-EtOAc) 0.59; IR (Thin Film) 2947, 1730 ($C{=}O_{ester}$), 1678 ($C{=}O_{ketone}$), 1620 (C=C), 1372, 1037, 864 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 5.78 (d, *J* = 1.5 Hz, 1H, =CHCO), 4.62 (dd, *J* = 11.5, 4.0 Hz, 1H, CHO), 2.39–2.30 (m, 3H), 2.25–2.21 (m, 1H), 2.05 (s, 3H, MeCO), 1.96–1.67 (m, 5H), 1.54–1.40 (m, 1H), 1.26 (s, 3H, Me); ^{13}C NMR (100.6 MHz; $CDCl_3$) δ: 199.0 (C=O), 170.5 (C=O), 166.9 (*C*=CHCO), 125.9 (=*C*HCO), 79.3 (CHO), 40.5 (*C*Me), 34.0 (CH_2), 33.6 (CH_2), 31.8 (CH_2), 26.9 (CH_2), 23.0 (*Me*CO) 21.2 (CH_2), 16.7 (Me); MS (ESI) 245 [$(M + Na)^+$, 49], 223 [$(M + H)^+$, 100], 163 (19); HRMS (ESI) *m/z* calcd for $C_{13}H_{18}O_3$ $(M + Na)^+$ 245.1148 found 245.1148 (0.1 ppm error), *m/z* calcd for $C_{13}H_{18}O_3$ $(M + H)^+$ 223.1329 found 223.1333 (−2.1 ppm error). Spectroscopic data are consistent with those reported in the literature.[313]

Lab book reference: djbI/83 djbi77/1

Acetic anhydride (1.06 mL, 11.22 mmol) was added dropwise to a stirred solution of alcohol **2** (501 mg, 2.80 mmol) in pyridine (2 mL) at rt under Ar. The resulting mixture was stirred at rt for 20 h. Then, 10% $H_2SO_{4(aq)}$ (10 mL) and CH_2Cl_2 (10 mL) were added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organics were washed with saturated $NaHCO_{3(aq)}$ (100 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with petrol-EtOAc (2:3) as eluent gave acetate **3** (460 mg, 74%) as a white solid.

Lab book reference: djbI/6

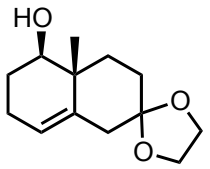
(4a'*R*,5'*R*)-4a'-Methyl-3',4',4a',5',6',7'-hexahydro-1'*H*-spiro[[1,3]dioxolane-2,2'-naphthalene]-5'-yl acetate 4



Ethylene glycol (2.44 mL, 43.90 mmol) was added to a stirred solution of acetate **3** (976 mg, 4.39 mmol) and *p*TSA·H_2O (8 mg, 0.04 mmol) in benzene (10 mL) at rt under Ar. The resulting mixture was stirred and heated at reflux under a soxhlet extractor filled with 4 Å molecular sieves (50 g) and a condenser for 16 h. Then, saturated $NaHCO_{3(aq)}$ (20 mL) and CH_2Cl_2 (20 mL) were added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (5 × 10 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with petrol-EtOAc (2:3) as eluent gave (by ^{1}H NMR spectroscopy) a 77:23 mixture of ketal **4** and starting acetate **3** (847 mg, 55% of ketal **4**) as a yellow oil, R_F (2:3 petrol-EtOAc) 0.56; data for ketal **4** ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.33–5.29 (m, 1H, CH=C), 4.79 (dd, *J* = 11.5, 4.5 Hz, 1H, CHO), 4.10–3.86 (m, 4H, OCH_2CH_2O), 2.50 (ddd, *J* = 14.0, 5.5, 3.0 Hz, 1H), 2.29–2.16 (m, 2H), 2.10–1.99 (m, 1H), 2.05 (s, 3H, MeCO), 1.81–1.61 (m, 5H), 1.51–1.40 (m, 1H), 1.13 (s, 3H, Me); MS (EI) 266 [$(M)^{\bullet+}$, 72], 99 (100). Spectroscopic data are consistent with those reported in the literature.[51]

Lab book reference: djbI/96

(4a*R*,5*R*)-5-Hydroxy-4a-methyl-4,4a,5,6,7,8-hexahydronaphthalen-2(3*H*)-one 5

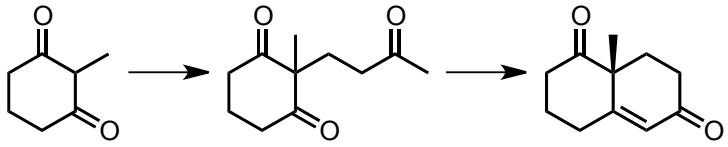


Ethylene glycol (2.50 mL, 45.02 mmol) was added to a stirred solution of acetate **3** (1 g, 4.50 mmol) and *p*TSA·H_2O (9 mg, 0.05 mmol) in benzene (22 mL) at rt under

Ar. The resulting mixture was stirred and heated at reflux under a soxhlet extractor filled with 4 Å molecular sieves (250 g) and a condenser for 26 h. Then, saturated $NaHCO_3$(aq) (50 mL) and CH_2Cl_2 (50 mL) were added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (5 × 50 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give (by ^{1}H NMR spectroscopy) a 77:23 mixture of ketal **4** and starting acetate **3**. $LiAlH_4$ (171 mg, 4.50 mmol) was added to a stirred solution of the crude mixture in Et_2O (50 mL) at rt under Ar. The resulting mixture was stirred at rt for 16 h. Then, 1 $M_{(aq)}$ NaOH (50 mL) and CH_2Cl_2 (50 mL) were added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude mixture as a yellow solid. Purification by flash column chromatography on silica with petrol–EtOAc (1:1) as eluent gave alcohol **5** (687 mg, 68%) as a colourless oil, mp 77-79 °C (lit.,[51] 84–85 °C); $[\alpha]_D$ +71.9 ((*c* 1.1 in $CHCl_3$)(lit.,[31] +62.9 (*c* 1.0 in $CHCl_3$)); R_F (1:1 petrol-EtOAc) 0.36; IR (Thin Film) 3297 (OH), 2937, 1102, 801 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.31 (dt, *J* = 5.0, 3.0 Hz, 1H, HC=), 4.03–3.89 (m, 4H, OCH_2CH_2O), 3.59 (td, *J* = 8.0, 5.5 Hz, 1H, C*H*OH), 2.52 (dq, *J* = 14.0, 3.0 Hz, 1H), 2.24–2.14 (m, 2H), 2.08–2.00 (m, 1H), 1.95 (ddd, *J* = 13.0, 4.0, 3.0 Hz, 1H), 1.80 (td, *J* = 13.5, 4.0 Hz, 1H), 1.74–1.68 (m, 3H), 1.45 (td, *J* = 13.5, 4.5 Hz, 1H), 1.38 (d, *J* = 5.5 Hz, 1H), 1.08 (s, 3H, Me); ^{13}C NMR (100.6 MHz; $CDCl_3$) δ: 138.9 (CH=*C*), 121.9 (*C*H=C), 109.5 (OCO), 77.7 (COH), 64.6 (CH_2), 64.4 (CH_2), 41.3 (CH_2), 39.2 (C), 35.3 (CH_2), 30.9 (CH_2), 27.3 (CH_2), 24.9 (CH_2), 16.8 (Me); MS (ESI) 247 [(M + Na)$^+$, 76], 225 [(M + H)$^+$, 100], 207 (32); HRMS (ESI) *m/z* calcd for $C_{13}H_{20}O_3$ (M + Na)$^+$ 247.1305 found 247.1308 (−1.2 ppm error), *m/z* calcd for $C_{13}H_{20}O_3$ (M + H)$^+$ 225.1485 found 225.1489 (−1.6 ppm error). Spectroscopic data are consistent with those reported in the literature.[314]

Lab book reference: djbI/23

(*R*)-8a-Methyl-3,4,8,8a-tetrahydronaphthalene-1,6(2*H*,7*H*)-dione 69

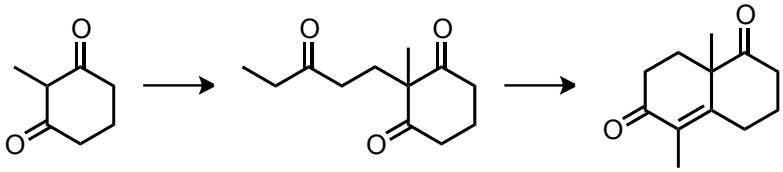


Methyl vinyl ketone **164** (66.0 mL, 0.79 mol) was added to a stirred solution of 2-methyl-1,3-cyclohexadione **163** (50.0 g, 0.40 mol), acetic acid (916 μL, 16.0 mmol) and hydroquinone (440 mg, 4.00 mmol) in water (120 mL) at rt under Ar. The resulting mixture was stirred and heated at 75 °C for 2 h. Then, saturated brine (200 mL) was added and the mixture was extracted with EtOAc (5 × 200 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude Michael product, R_F (2:3 petrol-EtOAc) 0.45; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.77-2.58 (m, 4H, CH_2CO), 2.34 (t, J = 7.5 Hz, 2H, CH_2COMe), 2.10 (s, 3H, Me), 2.80-1.84 (m, 4H), 1.24 (s, 3H, Me); MS (EI) 196 [$(M)^{\bullet+}$, 8], 111 (67), 55 (100). (*R*)-Proline (2.3 g, 20.0 mmol) was added to a stirred solution of the crude Michael product in DMSO (390 mL) at rt under Ar. The resulting mixture was stirred at rt for 85 h. Then, water (500 mL) and EtOAc (500 mL) were added and the layers were separated. The aqueous layer was extracted with EtOAc (5 × 500 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with petrol-EtOAc (2:3) as eluent gave Wieland-Miescher ketone **69** (62.4 g, 88%, 87:13 er by CSP-HPLC) as a yellow solid, mp 43–44 °C (lit.,[312] 49–50 °C); $[\alpha]_D$ −80.7 ((*c* 1.3 in $CHCl_3$)(lit.,[312] −104 (*c* 1.0 in $CHCl_3$) for **69** of 91:9 er); R_F (2:3 petrol-EtOAc) 0.45; IR (Thin Film) 2952, 1711 (C=O), 1668 (C=O), 1236, 940 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.85 (d, J = 2.0 Hz, 1H, =CH), 2.76–2.66 (m, 2H), 2.53–2.40 (m, 4H), 2.18–2.06 (m, 3H), 1.76–1.64 (m, 1H), 1.42 (s, 3H, CMe); ^{13}C NMR (100.6 MHz; $CDCl_3$) δ: 211.3 (C=O), 198.5 (C=O), 166.0 (*C*=CHCO), 126.0 (C=*C*HCO), 50.8 (*C*Me), 37.8 (CH_2), 33.8 (CH_2), 31.9 (CH_2), 29.8 (CH_2), 23.5 (C*Me*), 23.1 (CH_2); MS (ESI) 179 [$(M + H)^+$, 100], 201 (26); HRMS (ESI) *m/z* calcd for $C_{11}H_{14}O_2$ $(M + H)^+$ 179.1067 found 179.1070 (−2.2 ppm error); CSP-HPLC: Chiralcel OD (5:1 *iso*-Hexane-IPA, 0.5 mL min^{-1}) (*S*)-**69** 19.1 min, (*R*)-**69** 20.1 min. Spectroscopic data are consistent with those reported in the literature.[312]

Wieland-Miescher ketone **69** (20.0 g) was recrystallised from Et_2O to give **69** (10.3 g, 51%, >99:1 er by CSP-HPLC) as white needles, mp 48–49 °C (lit.,[312] 49–50 °C); $[\alpha]_D$ −111.8 ((*c* 1.1 in $CHCl_3$)(lit.,[312] −104 (*c* 1.0 in $CHCl_3$) for **69** of 91:9 er); CSP-HPLC: Chiralcel OD (5:1 *iso*-Hexane-IPA, 0.5 mL min^{-1}) (*R*)-**69** 21.1 min.

Lab book reference: djbI/71

(*RS*)-5,8a-Dimethyl-3,4,8,8a-tetrahydronaphthalene-1,6(2*H*,7*H*)-dione 70

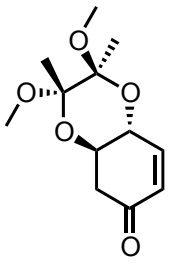


DABCO (4.93 g, 55.1 mmol) and ethyl vinyl ketone **208** (3.65 mL, 44.3 mmol) were added in one portion to a stirred suspension of 2-methyl-1,3-cyclohexanedione **163** (5.04 g, 40.0 mmol) in DME (50 mL) at rt. The resulting mixture was stirred at rt for 20 h. The mixture was cooled to 0 °C. Then, 3 M $HCl_{(aq)}$ (50 mL) was added and the mixture was stirred at 0 °C for 10 min. The mixture was extracted with Et_2O (4 × 50 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude Michael adduct as a colourless oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.75–2.53 (m, 4H), 2.39–2.23 (m, 4H), 2.06–1.78 (m, 4H), 1.21 (s, 3H, Me), 0.99 (t, *J* = 7.5 Hz, 3H, CH_2*Me*). Et_3N (4.46 mL, 32.0 mmol) and benzoic acid (5.37 g, 44.0 mmol) were added to a stirred solution of the crude Michael adduct in xylene (75 mL) at rt. The resulting solution was stirred and heated at reflux for 24 h using a Dean-Stark trap. The reaction mixture was allowed to cool to rt and then saturated $NaHCO_{3(aq)}$ (50 mL) was added and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 50 mL). The combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with petrol–EtOAc (1:1) as eluent gave enone **70** (5.97 g, 78%) as a colourless oil, R_F (2:3 petrol–EtOAc) 0.41; IR (Thin Film) 2952, 2873, 1711 (C=O), 1663 (C=O), 1610 (C=C), 1449, 1422, 1357, 1329, 1310, 1241, 1201, 1162, 1112, 1094, 1010, 742 cm^{-1}; ^{1}H NMR (400

MHz, $CDCl_3$) δ: 2.85 (dt, *J* = 16.0, 5.0 Hz, 1H), 2.66 (ddd, *J* = 16.0, 11.0, 6.0 Hz, 1H), 2.53–2.33 (m, 4H), 2.17–1.99 (m, 3H), 1.79 (s, 3H, MeC=), 1.77–1.67 (m, 1H), 1.40 (s, 3H, Me); MS (ESI) 215 [$(M + Na)^+$]; HRMS (ESI) *m/z* calcd for $C_{12}H_{16}O_2$ $(M + Na)^+$ 215.1043 found 215.1047 (−1.9 ppm error). Spectroscopic data are consistent with those reported in the literature.[275]

Lab book reference: djb4/32

(2*S*,3*S*,4a*R*,8a*R*)-2,3-Dimethoxy-2,3-dimethyl-2,3,4a,5-tetrahydrobenzo [*b*][1,4]dioxin-6(8a*H*)-one *ent*-**71**



$NaBH_4$ (2.57 g, 67.8 mmol) was added portionwise to a stirred solution of bis acetal **86** (3.07 g, 9.42 mmol) in MeOH (40 mL) at 0 °C under Ar. When the effervescence ceased, the resulting mixture was allowed to warm to rt and stirred at rt for 18 h. Then, water (40 mL) and $NaIO_4$ (11.08 g, 51.8 mmol) were added and the resulting suspension was stirred at rt for 18 h. Saturated $NH_4Cl_{(aq)}$ (30 mL) was added and the mixture was extracted with CH_2Cl_2 (10 × 50 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude hydroxy ketone. DMAP (58 mg, 0.47 mmol), DIPEA (3.45 mL, 19.78 mmol) and acetic anhydride (1.06 mL, 11.30 mmol) were added to a stirred solution of the crude hydroxy ketone in CH_2Cl_2 (30 mL) at 0 °C under Ar. The resulting mixture was stirred at 0 °C for 3 h. Then, saturated $NH_4Cl_{(aq)}$ (30 mL) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (5 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with petrol-EtOAc (4:1) as eluent gave enone *ent*-**71** (729 mg, 32%) as a white solid, mp 180–183 °C (lit.,[98] 182–184 °C); $[\alpha]_D$ +60.4 (*c* 0.5 in CH_2Cl_2) (lit.,[98] +64.4, (*c* 0.39 in CH_2Cl_2)); R_F (1:1 petrol-EtOAc) 0.24; IR (Thin Film) 1675 (C=O), 1377,

1248, 1127, 1070, 1033, 883, 848, 782 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 6.87 (dd, *J* = 10.5, 1.5 Hz, 1H, =CH), 6.01 (dd, *J* = 10.5, 2.5 Hz, 1H, =CH), 4.51 (ddd, *J* = 9.0, 2.5, 1.5 Hz, 1H, CHO), 4.05 (ddd, *J* = 13.5, 9.0, 5.0 Hz, 1H, CHO), 3.33 (s, 3H, OMe), 3.27 (s, 3H, OMe), 2.74 (dd, *J* = 16.5, 5.0 Hz, 1H, CH_AH_B), 2.49 (dd, *J* = 16.5, 13.5 Hz, 1H, CH_AH_B), 1.37 (s, 3H, Me), 1.34 (s, 3H, Me). ^{13}C NMR (100.6 MHz; $CDCl_3$) δ: 196.6 (C=O), 148.4 (=CH), 129.9 (=CH), 100.6 (OCO), 99.5 (OCO), 69.1 (CHO), 67.9 (CHO), 48.0 (OMe), 47.9 (OMe), 41.8 (CH2), 17.6 (Me), 17.5 (Me); MS (ESI) 265 [(M + Na)+, 100], 211 (61); HRMS (ESI) *m/z* calcd for $C_{12}H_{18}O_5$ $(M + Na)^+$ 265.1046 found 265.1051 (−0.4 ppm error); CSP-HPLC: CHIRALPAK® AS column (95:5 *iso*-Hexane-EtOAc, 0.5 mL min^{-1}) (*R*,*R*)-**71** 4.1 min. Spectroscopic data are consistent with those reported in the literature.[98]

Lab book reference: djb1/14

$NaBH_4$ (6.84 g, 180.70 mmol) was added portionwise to a stirred solution of bis acetal **86** (8.27 g, 25.80 mmol) in MeOH (60 mL) at 0 °C under Ar. When the effervescence ceased, the resulting mixture was allowed to warm to rt and stirred at rt for 18 h. Saturated $NH_4Cl_{(aq)}$ (30 mL) was added and the resulting mixture was stirred at rt for 15 min. Then, the solvent was evaporated under reduced pressure to give the crude product. EtOAc (30 mL) was added and the suspended solid was removed by filtration. This process was repeated (6 × 30 mL of EtOAc). The combined organic filtrates were evaporated under reduced pressure to give the crude triol. $NaIO_4$ (11.1 g, 5.19 mmol) was dissolved in water (50 mL) with gentle warming. To the resulting solution, silica gel (30 g) was added with vigorous stirring. The solvent was evaporated under reduced pressure to give silica-supported $NaIO_4$ as a free-flowing solid which was then added to a stirred solution of the crude triol in CH_2Cl_2 (50 mL) at rt. After stirring for 2 h the solids were removed from the heterogeneous mixture by filtration. The filtrate was dried ($MgSO_4$) and evaporated under reduced pressure to give the crude hydroxy ketone (5.03 g, 19.36 mmol). To a stirred solution of the crude hydroxy ketone in CH_2Cl_2 (50 mL) at 0 °C under Ar was added mesyl chloride (1.65 mL, 21.3 mmol) and Et_3N (8.10 mL, 58.08 mmol). The resulting mixture was stirred at 0 °C for 1 h. Then, saturated $NH_4Cl_{(aq)}$ (30 mL) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2

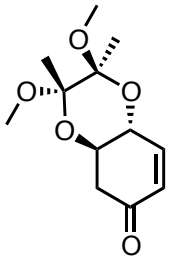
(5 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with petrol-EtOAc (4:1) as eluent gave enone *ent*-**71** (3.13 g, 67%) as a white solid.

Lab book reference: djb2/50

DMAP (36 mg, 0.29 mmol), DIPEA (2.14 mL, 12.26 mmol) and acetic anhydride (660 μL, 7.01 mmol) were added to a stirred solution of hydroxy ketone **87** (1.52 g, 5.84 mmol) in CH_2Cl_2 (20 mL) at 0 °C under Ar. The resulting solution was stirred at 0 °C for 3 h. Then, saturated $NH_4Cl_{(aq)}$ (30 mL) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (5 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with petrol-EtOAc (4:1) as eluent gave enone *ent*-**71** (943 mg, 67%) as a white solid.

Lab book reference: djb1/7

(2*RS*,3*RS*,4a*SR*,8a*SR*)-2,3-Dimethoxy-2,3-dimethyl-2,3,4a,5-tetrahydrobenzo [*b*][1,4]dioxin-6(8a*H*)-one *rac*-**71**



PCC (880 mg, 3.99 mmol) was added to a stirred solution of allylic alcohol *rac*-1,4-*cis*-**90** (570 mg, 2.66 mmol) in CH_2Cl_2 (10 mL) at rt under Ar. The resulting orange suspension was stirred at rt for 5 h. Then, Celite® (1 g) and Et_2O (10 mL) were added and the solids were removed by filtration through a Celite® pad. The Celite® pad was washed with Et_2O (5 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give enone *rac*-**71** (518 mg,

81%) as an off-white solid, mp 180–183 °C (lit.,[98] 182–184 °C). Spectroscopic data are consistent with those reported in the literature.[98]

Lab book reference: djb3/8

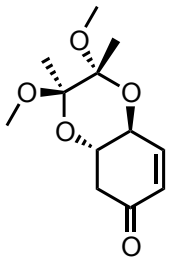
MnO_2 (3.98 g, 38.91 mmol) was added to a stirred solution of allylic alcohol *rac*-1,4-*cis*-**90** (1.90 g, 7.78 mmol) in CH_2Cl_2 (110 mL) at rt under Ar. The resulting suspension was stirred at rt for 7 h. TLC analysis showed starting material remained and therefore more MnO_2 (3.98 g, 38.91 mmol) was added. The resulting suspension was stirred at rt for 7 h. Then, Et_2O (10 mL) was added and the mixture filtered through a Celite® pad. The Celite® pad was washed with Et_2O (5 × 100 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give enone *rac*-**71** (1.69 g, 98%) as an off-white solid.

Lab book reference: djb3/23

DMSO (45 μL, 0.63 mmol) was added dropwise to a stirred solution of oxalyl chloride (27 μL, 0.32 mmol) in CH_2Cl_2 (2 mL) at –78 °C under Ar. After stirring for 30 min, a solution of allylic alcohol *rac*-1,4-*cis*-**90** (58 mg, 0.24 mmol) in CH_2Cl_2 (5 mL) was added dropwise and the solution was stirred for 30 min. Then, Et_3N (166 μL, 1.19 mmol) was added and the solution was stirred for 15 min. Then, the solution was allowed to warm to rt and stirred at rt for 1 h. Then, saturated brine (10 mL) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (5 × 10 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with petrol-EtOAc (4:1) as eluent gave enone *rac*-**71** (37 mg, 65%) as an off-white solid.

Lab book reference: djb3/27

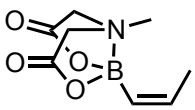
(2*R*,3*R*,4a*S*,8a*S*)-2,3-Dimethoxy-2,3-dimethyl-2,3,4a,5-tetrahydrobenzo[*b*][1,4]dioxin-6(8a*H*)-one 71



MnO_2 (1.64 g, 18.84 mmol) was added to a stirred solution of allylic alcohol 1,4-*cis*-**90** (920 mg, 3.77 mmol) in CH_2Cl_2 (17 mL) at rt under Ar. The resulting suspension was stirred at rt for 12 h. Then, Et_2O (10 mL) was added and the solids were removed by filtration through a Celite® pad. The Celite® pad was washed with Et_2O (5 × 100 mL). The combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with petrol-EtOAc (4:1) as eluent gave enone **71** (898 mg, 98%, 99:1 er by CSP-HPLC) as a white solid, mp 180–183 °C (lit.,[2]182–184 °C); $[\alpha]_D$ –72.0 (*c* 1.0 in $CHCl_3$)(Lit.,[2] +64.4 (*c* 0.39 in $CHCl_3$) for *ent*-**71**); Anal. Calcd. for $C_{12}H_{18}O_5$: C, 59.49; H, 7.49. Found: C, 59.46; H, 7.40. CSP-HPLC: Chiral Pak As column (95:5 *iso*-Hexane-EtOAc, 0.5 mL min^{-1}) (*R,R*)-**71** 4.4 min, (*S,S*)-**71** 7.2 min. Spectroscopic data are consistent with those reported in the literature.[98]

Lab book reference: djbI/26

(*Z*)-Prop-1-enyl MIDA boronic ester 72

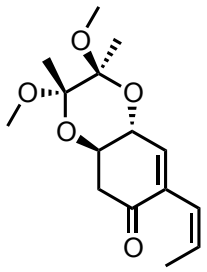


(*Z*)-Propenylbromide **132** (3.45 mL, 40.09 mmol) was added dropwise to a stirred suspension of lithium granules (715 mg, 120.27 mmol) in Et_2O (40 mL) at –40 °C under Ar. The reaction was initiated with sonication and then stirred at –40 °C for 1 h. The solids were removed by canula filtration to give (*Z*)-propenyl lithium **133** as a colourless solution. (*Z*)-Propenyl lithium **133** was added dropwise over 10 min to a stirred solution of triisopropyl boronate (4.49 mL, 41.6 mmol) at –78 °C under Ar.

The resulting solution was stirred at –78 °C for 30 min and then allowed to warm to rt and stirred for 1 h. Then, 1 M $HCl_{(aq)}$ (100 mL) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (5 × 10 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude (*Z*)-propenyl boroxin **134** (1.06 g, 5.17 mmol) as a yellow oil. Methyliminodiacetic acid (MIDA) (2.74 g, 18.61 mmol) was added to a stirred solution of crude (*Z*)-propenyl boroxin **134** (1.06 g, 5.17 mmol) in benzene and DMSO (9:1, 300 mL) at rt under Ar. The resulting mixture was stirred and heated at reflux under Dean-Stark conditions for 24 h. Then, saturated brine (300 mL) and EtOAc (200 mL) were added and the layers were separated. The aqueous layer was extracted with EtOAc (8 × 200 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give a DMSO solution of crude (*Z*)-propenyl MIDA boronic ester. The crude product was absorbed onto silica and purified by flash column chromatography on silica with EtOAc-MeCN (9:1) as eluent to give (*Z*)-propenyl MIDA boronic ester **72** (3.06 g, 39%) as a white solid, mp 110-112 °C (lit.,[199] 99–110 °C); R_F (9:1 EtOAc-MeCN) 0.47; IR (Thin Film) 1737 (C=O), 1637 (C=C), 1376, 1131, 855 cm^{-1}; ^1H NMR (400 MHz, CD_3CN) δ: 6.31 (br s, 1H, =CHB), 5.29 (dq, *J* = 14.0, 2.0 Hz, 1H, =C*H*Me), 3.94 (d, *J* = 17.0 Hz, 2H, C$H_A$$H_B$), 3.78 (d, *J* = 17.0 Hz, 2H, C$H_A$$H_B$), 2.80 (s, 3H, NMe), 1.77 (dd, *J* = 7.0, 2.0 Hz, 3H, =CH*Me*); ^{13}C NMR (100.6 MHz; CD_3CN)(=*C*HB resonance not resolved) δ:170.0 (C=O), 143.1 (Me*C*H=), 62.5 (CH_2), 47.4 (NMe), 17.0 (=CH*Me*). Spectroscopic data are consistent with those reported in the literature.[199]

Lab book reference: djb1/67, djb1/72, djb1/74

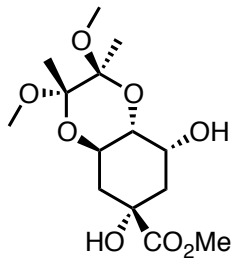
(2*S*,3*S*,4a*R*,8a*R*)-2,3-Dimethoxy-2,3-dimethyl-7-((*Z*)-prop-1-enyl)-2,3,4a,5-tetrahydrobenzo[*b*][1,4]dioxin-6(8a*H*)-one ***ent*-73**



(*Z*)-Propenyl MIDA boronic ester **72** (118 mg, 0.60 mmol), palladium catalyst **120** (22 mg, 0.03 mmol) and K_3PO_4 (1.4 mL of a 3 M solution in water, 4.20 mmol) were added sequentially to a vigorously stirred solution of iodoenone ***ent*-119** (200 mg, 0.54 mmol) in THF (15 mL) at rt under Ar. The resulting mixture was stirred and heated at reflux for 41 h. Then, water (10 mL) and CH_2Cl_2 (10 mL) were added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (5 × 10 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with CH_2Cl_2-Et_2O (99:1) as eluent gave propenyl enone ***ent*-73** (2.82 g, 93%) as a yellow oil, R_F (99:1 CH_2Cl_2-Et_2O) 0.52; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.70 (br s, 1H, =CH), 6.06 (dq, *J* = 12.0, 2.0 Hz, 1H, *H*C=CHMe), 5.83 (dq, *J* = 12.0, 7.0 Hz, 1H, HC=C*H*Me), 4.48 (br d, *J* = 9.0 Hz, 1H, CHO), 4.01 (ddd, *J* = 13.5, 9.0, 5.0 Hz, 1H, CHO), 3.30 (s, 3H, OMe), 3.26 (s, 3H, OMe), 2.77 (dd, *J* = 16.5, 5.0 Hz, 1H, CH_AH$_B$), 2.48 (dd, *J* = 16.5, 13.5 Hz, 1H, CH$_A$$H_B$), 1.75 (dd, *J* = 7.0, 2.0, 3H, =CH*Me*), 1.35 (s, 3H, Me), 1.31 (s, 3H, Me); ^{13}C NMR (100.6 MHz; $CDCl_3$) δ: 195.9 (C=O), 144.3 (=CH), 135.9 (=C), 129.9 (=CH), 122.1 (=CH), 100.7 (OCO), 99.6 (OCO), 69.3 (CHO), 67.7 (CHO), 48.1 (OMe), 47.9 (OMe), 41.9 (CH_2), 17.7 (Me), 17.6 (Me), 14.9 (Me); MS (ESI) 305 [$(M + Na)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{15}H_{22}O_5$ $(M + Na)^+$ 305.1359, found 305.1358 (2.6 ppm error).

Lab book reference: djb1/65

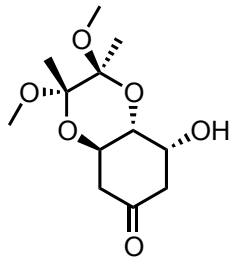
(2*S*,3*S*,4a*R*,6*S*,8*R*,8a*R*)-Methyl 6,8-dihydroxy-2,3-dimethoxy-2,3-dimethyloctahydrobenzo[*b*][1,4]dioxine-6-carboxylate 86



2,3-Butanedione (2.55 mL, 29.06 mmol), trimethylorthoformate (9.50 mL, 86.72 mmol) and CSA (688 mg, 2.98 mmol) were added to a stirred solution of (–)-quinic acid (5.06 g, 26.31 mmol) in MeOH (50 mL) at rt under Ar. The resulting mixture was stirred and heated at reflux for 16 h. The resulting mixture was allowed to cool to rt and Et_3N (0.5 mL, 6.86 mmol) was added. The solvent was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with petrol-EtOAc (1:1) as eluent gave bis acetal **86** (8.07 g, 97%) as a pale yellow solid, mp 130–132 °C (lit.,[308] 139.8–140.2 °C); $[\alpha]_D$ +118.1 (*c* 1.0 in CH_2Cl_2) (lit.,[308] $[\alpha]_D$ +116.3 (*c* 1.06 in CH_2Cl_2)); R_F (1:1 petrol-EtOAc) 0.26; IR (Thin Film): 3444 (OH), 3330 (OH), 2990, 2955, 2929, 2894, 2844, 2820, 1730 (C=O); ^{1}H NMR (400 MHz; $CDCl_3$) δ: 4.30 (ddd, *J* = 12.5, 10.0, 4.5 Hz, 1H, CHO), 4.18 (q, *J* = 3.0 Hz, 1H, C*H*OH), 3.78 (s, OMe), 3.59 (dd, *J* = 10.0, 3.0 Hz, 1H, CHO), 3.26 (s, 3H, OMe), 3.25 (s, 3H, OMe), 2.18 (dt, *J* = 12.5, 3.0 Hz, 1H, CH_AH$_B$), 2.10 (ddd, *J* = 12.5, 4.5, 3.0 Hz, 1H, CH_AH$_B$), 2.04 (dd, *J* = 15.0, 3.0 Hz, 1H, CH$_A$$H_B$), 1.92 (t, *J* = 12.5 Hz, 1H, CH$_A$$H_B$), 1.31 (s, 3H, OMe), 1.27 (s, 3H, OMe); ^{13}C NMR (100.6 MHz; $CDCl_3$) δ: 174.3 (C=O), 100.3 (OCO), 99.7 (OCO), 75.8 (COH), 72.7 (CHO), 69.2 (CHO), 62.4 (CHO), 52.9 (CO_2*Me*), 47.9 (OMe), 47.8 (OMe), 38.6 (CH_2), 37.3 (CH_2), 17.8 (Me), 17.6 (Me); MS (ESI) 343 [(M + Na)$^+$, 100], 289 (32); HRMS (ESI) *m/z* calcd for $C_{14}H_{24}O_8$ (M + Na)$^+$ 343.1363 found 343.1363 (0.0 ppm error). Spectroscopic data are consistent with those reported in the literature.[308]

Lab book reference: djb1/3

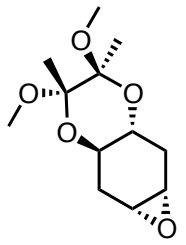
(2*S*,3*S*,4a*R*,8*R*,8a*R*)-8-Hydroxy-2,3-dimethoxy-2,3-dimethylhexahydrobenzo [*b*][1,4]dioxin-6(7*H*)-one 87



DIBAL-H (7.80 mL of a 1.0 M solution in hexane, 7.80 mmol) was added dropwise to a stirred solution of bis acetal **86** (500 mg, 1.56 mmol) in Et_2O (50 mL) at –78 °C under Ar. The resulting mixture was stirred at –78 °C for 1 h and then allowed to warm to 0 °C. Water (30 mL) was added and the solid was removed from the gelatinous mixture by filtration. Water (100 mL) was added to the solid and the resulting suspension was stirred at rt for 1 h. The solids were removed by filtration and washed with water (20 mL.). The combined filtrates were extracted with EtOAc (5 × 50 mL). The combined organic extracts were evaporated under reduced pressure to give crude triol. The triol and $NaIO_4$ (601 mg, 2.81 mmol) were dissolved in MeOH (30 mL) and water (20 mL) and stirred at rt for 18 h. Then, saturated $NH_4Cl_{(aq)}$ (30 mL) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (5 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give hydroxy ketone **87** (341 mg, 84%) as a white solid, mp 147–151 °C (lit.,[98] 163–165 °C); $[\alpha]_D$ +134.8 (*c* 0.6 in CH_2Cl_2) (lit.,[98] $[\alpha]_D$ +159.8 (*c* 0.59 in CH_2Cl_2)); R_F (95:5 CH_2Cl_2-MeOH) 0.31; IR (Thin Film) 3477 (OH), 1722 (C=O), 1108, 999, 844 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 4.20–4.14 (m, 2H, CHO + C*H*OH), 3.78 (dd, *J* = 10.0, 2.5 Hz, 1H, CHO), 3.20 (s, 3H, OMe), 3.13 (s, 3H, OMe), 2.56–3.35 (m, 4H, 2 x CH_2), 1.25 (s, 3H, Me), 1.20 (s, 3H, Me); ^{13}C NMR (100.6 MHz; $CDCl_3$) δ: 205.7 (C=O), 100.2 (OCO), 99.2 (OCO), 72.3 (CHO), 67.5 (CHO), 63.3 (CHO), 48.1 (OMe), 47.9 (OMe), 46.4 (CH_2), 44.7 (CH_2), 17.7 (Me), 17.5 (Me); MS (ESI) 283 [$(M + Na)^+$, 100], 229 (32); HRMS (ESI) *m/z* calcd for $C_{12}H_{20}O_6$ $(M + Na)^+$ 283.1152 found 283.1154 (−0.7 ppm error). Spectroscopic data are consistent with those reported in the literature.[98]

Lab book reference: djb1/5

(1aS*R*,2aS*R*,4R*S*,5R*S*,6aS*R*,7aR*S*)-4,5-Dimethoxy-4,5-dimethyloctahydrooxireno [2',3':4,5]benzo[1,2-*b*][1,4]dioxine *rac*-**88**



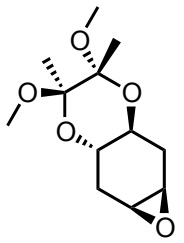
*m*CPBA (10.18 g, 41.30 mmol) was added in 2 g portions over 45 min to a stirred suspension of alkene *rac*-**95** (4.71 g, 20.65 mmol) and $NaHCO_3$ (6.93 g 82.60 mmol) in CH_2Cl_2 (62 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 1 h and then at rt for 16 h. Saturated $Na_2S_2O_{3(aq)}$ (20 mL) was added and the bisphasic mixture was stirred at 0 °C for 1 h. Then, saturated $NaHCO_{3(aq)}$ (100 mL) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (5 × 100 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with petrol-EtOAc (4:1) as eluent gave epoxide *rac*-**88** (4.68 g, 93%) as a colourless oil, R_F (1:1 petrol-EtOAc) 0.43; IR (Thin Film) 2991, 1441, 1124, 1037, 911, 846 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 3.67 (td, *J* = 10.5, 5.5 Hz, 1H, CHO), 3.55 (td, *J* = 10.5, 7.0 Hz, 1H, CHO), 3.25 (s, 3H, OMe), 3.23 (s, 3H, OMe), 3.23–3.19 (m, 1H, $CHO_{epoxide}$), 3.14–3.10 (m, 1H, $CHO_{epoxide}$), 2.42 (dddd, *J* = 14.5, 5.5, 2.0, 1.0 Hz, 1H, CH_{eq}), 2.25 (ddd, *J* = 15.0, 7.0, 5.5 Hz, 1H, CH_{eq}), 1.96 (dd, *J* = 14.5 10.5 Hz, 1H CH_{ax}), 1.81 (ddd, *J* = 15.0, 10.5, 2.0 Hz, 1H, CH_{ax}), 1.27 (s, 6H, 2 × Me); ^{13}C NMR (100.6 MHz; $CDCl_3$) δ: 99.2 (OCO), 99.0 (OCO), 67.3 (CHO), 65.3 (CHO), 53.2 ($CHO_{epoxide}$), 50.6 ($CHO_{epoxide}$), 47.94 (OMe), 47.90 (OMe), 29.4 (CH_2), 29.1 (CH_2), 17.77 (Me), 17.75 (Me); MS (ESI) 267 [$(M + Na)^+$, 100], 213 (74); HRMS (ESI) *m/z* calcd for $C_{12}H_{20}O_5$ $(M + Na)^+$ 267.1203 found 267.1196 (2.6 ppm error).

Lab book reference: djb3/20

*m*CPBA (2.81 g, 11.40 mmol) was added to a stirred solution of alkene *rac*-**88** (1.30 g, 5.70 mmol) in CH_2Cl_2 (7 mL) and saturated $NaHCO_{3(aq)}$ (5 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 1 h and then at rt for 16 h. Saturated $Na_2S_2O_{3(aq)}$ (20 mL) was added and the bisphasic mixture was stirred at 0 °C for 1 h. Then, saturated $NaHCO_{3(aq)}$ (100 mL) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (5 × 100 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with petrol-EtOAc (4:1) as eluent gave epoxide *rac*-**88** (835 mg, 60%) as a colourless oil.

Lab book reference: djb3/5

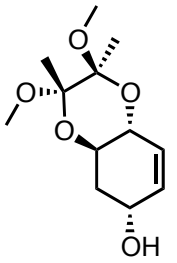
(1a*R*,2a*S*,4*R*,5*R*,6a*S*,7a*S*)-4,5-Dimethoxy-4,5-dimethyloctahydrooxireno [2',3':4,5]benzo[1,2-*b*][1,4]dioxine 88



*m*CPBA (189 mg, 0.66 mmol) was added to a stirred suspension of alkene **95** (100 mg, 0.44 mmol) and $NaHCO_3$ (74 mg, 0.88 mmol) in CH_2Cl_2 (2 mL) at 0 °C under Ar. The resulting mixture was stirred at 0 °C for 1 h and then at rt for 16 h. Saturated $Na_2S_2O_{3(aq)}$ (10 mL) was added and the biphasic mixture was stirred at 0 °C for 1 h. Then, saturated $NaHCO_{3(aq)}$ (10 mL) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (5 × 10 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with petrol-EtOAc (4:1) as eluent gave epoxide **88** (94.3 mg, 88%) as a white solid, mp 113–114 °C; $[\alpha]_D$ –170.5 (*c* 1.0 in $CHCl_3$).

Lab book reference: djbI2/59

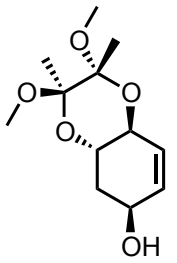
(2*SR*,3*SR*,4a*RS*,6*RS*,8a*RS*)-2,3-Dimethoxy-2,3-dimethyl-2,3,4a,5,6,8a-hexahydrobenzo[*b*][1,4]dioxin-6-ol *rac*-1,4-*cis*-**90**



n-BuLi (11.47 mL of a 2.5 M solution in hexanes, 28.67 mmol) was added dropwise over 10 min to a stirred solution of DIPA (4.25 mL, 30.11 mmol) in THF (60 mL) at 0 °C under Ar. After stirring at 0 °C for 30 min, a solution of epoxide *rac*-**88** (3.50 g, 14.34 mmol) in THF (60 mL) was added dropwise by means of a cannula. After stirring for 1 h, the solution was allowed to warm to rt and stirred at rt for 18 h. Then, saturated $NH_4Cl_{(aq)}$ (100 mL) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (5 × 100 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with petrol-EtOAc (4:1) as eluent gave allylic alchol *rac*-1,4-*cis*-**90** (1.91 g, 55%) as a white solid, mp 96–97 °C; mp 99-100 °C; $[\alpha]_D$ –213.7 (*c* 1.0 in $CHCl_3$); R_F (1:1 petrol-EtOAc) 0.23; IR (NaCl) 3610 (OH), 3016, 2931, 1375, 1237, 1200, 1048 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 5.77 (br s, 2H, 2 × =CH), 4.37 (br s, 1H, CHO*H*), 4.13 (d, *J* = 9.0 Hz, 1H, CHO), 3.9 (ddd, *J* = 13.0, 9.0, 3.5 Hz, 1H, CHO), 3.28 (s, 3H, OMe), 3.27 (s, 3H, OMe), 2.01 (br dd, *J* = 13.0, 3.5 Hz, 1H, CH_AH_B), 1.84 (td, *J* = 13.0, 5.0 Hz, 1H, H-CH_AH_B), 1.34 (s, 3H, Me), 1.33 (s, 3H, Me); ^{13}C NMR (100.6 MHz; $CDCl_3$) δ: 130.2 (=CH), 129.1 (=CH), 100.4 (OCO), 100.0 (OCO), 69.7 (CHO), 65.5 (CHO), 64.9 (CHO), 47.96 (OMe), 47.90 (OMe), 34.6 (CH_2), 17.9 (Me), 17.8 (Me); MS (ESI) 267 [$(M + Na)^+$, 100], 213 (64); HRMS (ESI) *m/z* calcd for $C_{12}H_{20}O_5$ $(M + Na)^+$ 267.1203 found 267.1201 (0.9 ppm error).

Lab book reference: djb3/22

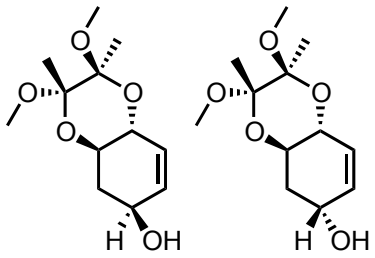
(2*R*,3*R*,4a*S*,6*S*,8a*S*)-2,3-Dimethoxy-2,3-dimethyl-2,3,4a,5,6,8a-hexahydrobenzo [*b*][1,4]dioxin-6-ol 1,4-*cis*-**90**



n-BuLi (1.98 mL of a 1.6 M solution in hexanes, 3.17 mmol) was added dropwise over 10 min to a stirred solution of DIPA (560 μL, 3.28 mmol) in THF (5 mL) at 0 °C under Ar. After stirring at 0 °C for 30 min, a solution of epoxide **88** (250 mg, 1.02 mmol) in THF (5 mL) was added dropwise by means of a cannula. After stirring for 1 h, the solution was allowed to warm to rt and stirred at rt for 18 h. Then, saturated $NH_4Cl_{(aq)}$ (50 mL) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (5 × 50 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with petrol-EtOAc (4:1) as eluent gave allylic alcohol 1,4-*cis*-**90** (242 mg, 89%) as a white solid, mp 99–100 °C; $[\alpha]_D$ –213.7 (*c* 1.0 in $CHCl_3$).

Lab book reference: djbI2/61

(2*S*,3*S*,4a*R*,6*S*,8a*R*)-and (2*S*,3*S*,4a*R*,6*R*,8a*R*)-2,3-Dimethoxy-2,3-dimethyl-2,3,4a,5,6,8a-hexahydrobenzo[*b*][1,4]dioxin-6-ol 1,4-*trans*-**90 and** 1,4-*cis*-**90**



1,4-*trans* 1,4-*cis*

Table 2.5, entry 1

$NaBH_4$ (312 mg, 8.26 mmol) was added to a stirred solution of enone *ent*-**71** (1.0 g, 0.413 mmol) in MeOH (30 mL) at 0 °C under Ar. The resulting solution was stirred at 0 °C for 1 h. The solvent was evaporated under reduced pressure. Then, saturated $NH_4Cl_{(aq)}$ (30 mL) and CH_2Cl_2 (30 mL) were added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give (by ^{1}H NMR spectroscopy) the crude product as an 90:10 mixture of alcohols 1,4-*trans*-**90** and 1,4-*cis*-**90**. Purification by flash column chromatography on silica with petrol-EtOAc (1:1) as eluent gave (by ^{1}H NMR spectroscopy) an 90:10 mixture of alcohols 1,4-*trans*-**90** and 1,4-*cis*-**90** (931 mg, 92%) as a white solid, mp 148–149 °C; $[\alpha]_D$ +137.8 (*c* 1.0 in $CHCl_3$); R_F (2:1 petrol-EtOAc) 0.19; IR (Thin Film) 3478 (OH), 2938, 1459, 1130, 1034 895 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.74–5.70 (m, 1H, =CH), 5.67–5.61 (m, 1H, =CH), 4.49–4.44 (m, 0.9H, $CHO_{1,4\text{-}trans}$), 4.37–4.30 (m, 0.1H, $CHOH_{1,4\text{-}cis}$), 4.29–4.24 (m, 0.9H, $CHO_{1,4\text{-}trans}$), 4.12–4.07 (m, 0.1H, $CHO_{1,4\text{-}cis}$), 3.87 (ddd, *J* = 13.0, 9.0, 3.0 Hz, 0.1H, $CHO_{1,4\text{-}cis}$), 3.68 (ddd, *J* = 13.0, 9.0, 3.0 Hz, 0.9H, $CHO_{1,4\text{-}trans}$), 3.25 (s, 0.3H, $OMe_{1,4\text{-}cis}$), 3.25 (s, 2.7H, $OMe_{1,4\text{-}trans}$), 3.25 (s, 2.7H, $OMe_{1,4\text{-}trans}$), 3.23 (s, 0.3H, $OMe_{1,4\text{-}cis}$), 2.31–2.25 (m, 0.9H, CH_AH_B), 2.02–1.96 (m, 0.1H, CH_AH_B), 2.02–1.92 (br s, 1H, OH), 1.81 (td, *J* = 13.0, 5.0 Hz, 0.1H, $CH_AH_{B,\ 1,4\text{-}cis}$), 1.63 (ddd, *J* = 13.0, 12.0, 10.0 Hz, 0.9H, $CH_AH_{B,\ 1,4\text{-trans}}$), 1.31 (s, 2.7H, $Me_{1,4\text{-}trans}$), 1.30 (s, 0.3H, $Me_{1,4\text{-}cis}$), 1.29 (s, 0.3H, $Me_{1,4\text{-}cis}$), 1.29 (s, 2.7H, $Me_{1,4\text{-}trans}$); ^{13}C NMR (100.6 MHz; $CDCl_3$) δ: 132.0 ($=CH_{1,4\text{-}trans}$), 130.3 ($=CH_{1,4\text{-}cis}$), 129.3 ($=CH_{1,4\text{-}cis}$), 128.3 ($=CH_{1,4\text{-}trans}$), 100.6 ($OCO_{1,4\text{-}cis}$), 100.4 ($OCO_{1,4\text{-}trans}$), 100.2 ($OCO_{1,4\text{-}cis}$), 100.0 ($OCO_{1,4\text{-}trans}$), 69.9 ($CHO_{1,4\text{-}cis}$), 69.3 ($CHO_{1,4\text{-}trans}$), 68.2 ($CHO_{1,4\text{-}$

trans), 67.6 ($CHO_{1,4\text{-}trans}$), 65.6 ($CHO_{1,4\text{-}cis}$), 65.0 ($CHO_{1,4\text{-}cis}$), 48.1 (2 × $OMe_{1,4\text{-}cis}$, 48.0 (2 × $OMe_{1,4\text{-}trans}$), 36.7 ($CH_{2,\ 1,4\text{-}trans}$), 34.8 ($CH_{2,\ 1,4\text{-}cis}$), 18.00 ($Me_{1,4\text{-}cis}$), 17.96 ($Me_{1,4\text{-}trans}$ + $Me_{1,4\text{-}cis}$), 17.93 ($Me_{1,4\text{-}trans}$); MS (ESI) 267 [$(M + Na)^+$, 100], 213 (28), 101 (70); HRMS (ESI) *m/z* calcd for $C_{12}H_{20}O_5$ $(M + Na)^+$ 267.1203, found 267.1195 (3.1 ppm error).

Lab book reference: djb3/87/1

Table 2.5, entry 2

$NaBH_4$ (312 mg, 8.26 mmol) was added to a stirred solution of enone *ent*-**71** (1.0 g, 0.413 mmol) in MeOH (30 mL) at 0 °C under Ar. The resulting solution was stirred at 0 °C for 1 h. The solvent was evaporated under reduced pressure. Then, saturated $NH_4Cl_{(aq)}$ (30 mL) and CH_2Cl_2 (30 mL) were added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give (by ^1H NMR spectroscopy) the crude product as an 90:10 mixture of alcohols 1,4-*trans*-**90** and 1,4-*cis*-**90**. Purification by flash column chromatography on silica with petrol-EtOAc (1:1) as eluent gave (by ^1H NMR spectroscopy) an 90:10 mixture of alcohols 1,4-*trans*-**90** and 1,4-*cis*-**90** (933 mg, 93%) as a white solid.

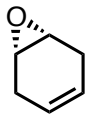
Lab book reference djb3/88/1

Table 2.5, entry 3

L-Selectride (826 μL of a 1.0 M solution in THF, 0.83 mmol) was added dropwise over 15 min to a stirred solution of enone *ent*-**71** (100 mg, 0.41 mmol) in THF (3 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 2 h. Then, saturated $NH_4Cl_{(aq)}$ (5 mL) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (5 × 5 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with petrol-EtOAc (1:1) as eluent gave (by ^1H NMR spectroscopy) an 50:50 mixture of alcohols 1,4-*trans*-**90** and 1,4-*cis*-**90** (77 mg, 77%) as a white solid.

Lab book reference: djb4/11

(1*R*,6*S*)-7-Oxabicyclo[4.1.0]hept-3-ene 91



*m*CPBA (43.3 g, 0.25 mol) was added in 1 g portions over 45 min to a stirred biphasic solution of 1,4-cyclohexadiene (25 mL, 0.26 mol) and $NaHCO_3$ (33.3 g, 0.40 mol) in CH_2Cl_2 (330 mL) and water (198 mL) at 0 °C under Ar. The resulting suspension was allowed to warm to rt and stirred at rt for 23 h. Saturated $Na_2S_2O_{3(aq)}$ (100 mL) was added and the mixture was stirred at rt for 1 h. The two layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 300 mL). The combined organic extracts were washed with saturated $NaHCO_{3(aq)}$ (300 mL), dried ($MgSO_4$) and evaporated under reduced pressure (> 400 mbar and < 40 °C) to give the crude epoxide. Purification by vacuum distillation gave *meso*-epoxide **91** (16.9 g, 66%) as a colourless liquid, bp 46 °C/469 mbar (lit.,[1] 43–45 °C/14 mmHg); R_F (1:1 petrol-EtOAc) 0.57; ^{1}H NMR (400 MHz; $CDCl_3$) δ: 5.42– 5.44 (m, 2H, =CH), 3.25–3.23 (m, 2H, CHO), 2.57 (br d, J = 18.0 Hz, 2H, CH_AH$_B$), 2.44 (br d, J = 18.0 Hz, 2H, CH$_A$$H_B$); ^{13}C NMR (100.6 MHz; $CDCl_3$) δ: 121.5 (=CH), 60.0 (CHO), 24.9 (CH_2); MS (ESI) 135 (100). Spectroscopic data are consistent with those reported in the literature.[109]

Lab book reference: djbI/3

(1*S*,6*S*)-6-Hydroxycyclohex-3-enyl benzoate 92

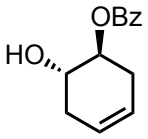


Table 2.1, entry 3

Using general procedure A, (*R*,*R*)-**93** (2.1 g, 3.40 mmol, 2.0 mol%), benzoic acid (23.3 g, 0.19 mol), TBME (50 mL), DIPEA (33.3 mL, 0.19 mol) and *meso*-epoxide **91** (16.7 g, 0.17 mol) for 94 h gave the crude product. Purification by flash column chromatography on silica with petrol-EtOAc (1:1) as eluent gave hydroxy benzoate **92** (32.4 g, 85%, 85:15 er by CSP-HPLC) as a brown solid. The solid was dissolved

in the minimum amount of hot CH_2Cl_2 and heptane was added. The resulting off-white crystals were collected by filtration. The same recrystallisation procedure was repeated once more to give hydroxy benzoate **92** (12.07 g, 32%, 98.5:1.5 er by CSP-HPLC) as yellow needles, mp 58–59 °C; $[\alpha]_D$ +138.6 (c 1.0 in $CHCl_3$); R_F (1:1 petrol-EtOAc) 0.46; IR (Thin Film) 3455 (OH), 3033, 1715 (C=O), 1316, 1118, 1069, 1027, 975, 671 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ: 8.03–7.99 (m, 2H, *o*-Ph), 7.55–7.49 (m, 1H, *p*-Ph), 7.42–7.36 (m, 2H, *m*-Ph), 5.65–5.08 (m, 2H, =CH), 5.17–5.08 (m, 1H, CHO), 4.03 (td, *J* = 8.5, 6.0 Hz, 1H, CHO), 2.98 (br s, 1H, OH), 2.72–2.49 (m, 2H, CH), 2.26–2.12 (m, 2H, CH); ^{13}C NMR (100.6 MHz; $CDCl_3$) δ: 166.5 (C=O), 133.1 (Ph CH), 130.1 (Ph C), 129.6 (Ph CH), 128.3 (Ph CH), 124.3 (=CH), 123.7 (=CH), 74.7 (CHO), 68.9 (CHO), 32.9 (CH_2), 30.1 (CH_2); MS (ESI) 241 [(M + Na)+, 100], 219 [(M + H)+, 17]; HRMS (ESI) *m/z* calcd for $C_{12}H_{20}O_4$ $(M + Na)^+$ 241.0835 found 241.0825 (4.1 ppm error); CSP-HPLC:Chiral Pak AS column (95:5 *iso*-hexane-EtOAc, 0.5 mL min^{-1}) (*S*,*S*)-**92** 3.1 min, (*R*,*R*)-**92** 5.3 min.

Lab book reference: djbI2/22

Table 2.1, entry 1

Using general procedure A, (*R*,*R*)-**93** (31 mg, 0.05 mmol, 5.0 mol%), benzoic acid (140 mg, 1.15 mmol), TBME (1 mL), DIPEA (199 μL, 1.15 mmol) and *meso*-epoxide **91** (100 mg, 1.05 mmol) for 53 h gave the crude product. Purification by flash column chromatography on silica with petrol-EtOAc (1:1) as eluent gave hydroxy benzoate **92** (167 mg, 74%, 83:17 er by CSP-HPLC) as a brown solid.

Lab book reference: djb2/93

Table 2.1, entry 2

Using general procedure A, (*R*,*R*)-**93** (880 mg, 1.46 mmol, 2.5 mol%), benzoic acid (7.83 g, 64.13 mmol), TBME (10 mL), DIPEA (11.1 mL, 64.13 mmol), and *meso*-epoxide **91** (5.60 g, 58.30 mmol) for 90 h gave the crude product. Purification by flash column chromatography on silica with petrol-EtOAc (1:1) as eluent gave hydroxy benzoate **92** (9.99 g, 79%, 85:15 er) as a brown solid.

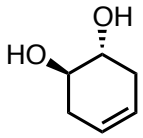
Lab book reference: djb3/1

Table 2.1, entry 4

Using general procedure A, (*R*,*R*)-**93** (6 mg, 0.01 mmol, 1.0 mol%), benzoic acid (140 mg, 1.15 mmol), TBME (1 mL), DIPEA (199 μL, 1.15 mmol) and *meso*-epoxide **91** (100 mg, 1.05 mmol) for 120 h gave the crude product. Purification by flash column chromatography on silica with petrol-EtOAc (1:1) as eluent gave hydroxy benzoate **92** (158 mg, 70%, 79:21 er by CSP-HPLC) as a brown solid.

Lab book reference: djb2/98

(1*SR*,2*SR*)-Cyclohex-4-ene-1,2-diol *rac*-**94**

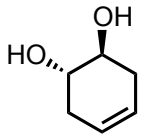


A solution of ethyl chloroformate (2.54 mL, 26.63 mmol) and 1,4-cyclohexadiene (2.36 mL, 24.21 mmol) in CH_2Cl_2 (15 mL) was added to a stirred solution of $NaHPO_4$ (10.31 g, 72.63 mmol) in hydrogen peroxide (24.7 mL of a 30% w/v solution in water, 217.89 mmol) at rt under Ar. The resulting mixture was stirred at rt for 20 h. The two layers were separated and the aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organic extracts were evaporated under reduced pressure to *ca*. 25% of the original volume. Acetic acid (1.38 mL, 24.21 mmol) and water (30 mL) were added to the solution at rt. The resulting mixture was stirred and heated at reflux for 16 h. The resulting mixture was cooled to rt and $NaHCO_3$ (2.24 g, 26.63 mmol) was added portionwise. The two layers were separated and the aqueous layer was continuously extracted with CH_2Cl_2 for 24 h. The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give diol *rac*-**94** (1.10 g, 40 %) as a white solid, mp 91–93 °C (lit.,[309] 95 °C); R_F (1:1 petrol-EtOAc) 0.17; IR (Thin Film) 3326 (OH), 1268, 1052, 995, 924, 782, 675, 599 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ: 5.43–5.40 (m, 2H, =CH), 4.66 (br s, 2H, OH), 3.60–3.55 (m, 2H, CHO), 2.33–2.23 (m, 2H, CH), 1.92–1.80 (m, 2H, CH); ^{13}C NMR (100.6 MHz; $CDCl_3$) δ: 124.2 (=CH), 70.2 (CHO), 31.7 (CH_2); MS (ESI) 137 [$(M + Na)^+$, 100], 191 (38), 241 (37); HRMS (ESI) *m/z* calcd for $C_6H_{10}O_2$ $(M + Na)^+$

137.0573 found 137.0570 (1.9 ppm error). Spectroscopic data are consistent with those reported in the literature.[309]

Lab book reference: djb2/83

(1*S*,2*S*)-Cyclohex-4-ene-1,2-diol 94



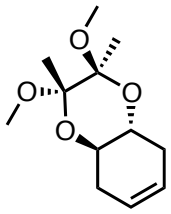
Amberlyst A26 OH resin (600 mg) was added to a stirred solution of hydroxy benzoate **92** (99:1 er) (240 mg, 1.10 mmol) in MeOH (2 mL) and THF (1 mL) at rt. The resulting mixture was stirred at rt for 5 h. Then, the polymer was removed by filtration and washed with CH_2Cl_2 (5 × 20 mL). The combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give diol **94** (109 mg, 87%) as a white solid, mp 91–93 °C (lit.,[309] 95 °C); $[\alpha]_D$ +86.05 (*c* 1.15 in MeOH) (lit.,[310] $[\alpha]_D$ +43.9 (*c* 0.60 in MeOH)). Spectroscopic data are consistent with those reported in the literature.[309]

Lab book reference: djb3/4

KOH (1.53 mL of a 1 M solution in MeOH and water (1:1), 1.53 mmol) was added to a stirred solution of benzoate **92** (190 mg, 0.88 mmol) in MeOH (2 mL) at rt. The resulting mixture was stirred at rt for 3 h. Then, saturated $NH_4Cl_{(aq)}$ (10 mL). The aqueous mixture was continuously extracted with CH_2Cl_2 (20 mL) for 18 h. The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give diol **94** (33 mg, 38%) as a white solid.

Lab book reference: djb2/96

(2*SR*,3*SR*,4a*RS*,8a*RS*)-2,3-Dimethoxy-2,3-dimethyl-2,3,4a,5,8,8a-hexahydrobenzo [*b*][1,4]dioxine *rac*-**95**



2,3-Butanedione (0.85 mL, 9.73 mmol), trimethyl orthoformate (2.97 mL, 26.55 mmol) and CSA (206 mg, 0.89 mmol) were added to a stirred solution of diol *rac*-**94** (1.01 g, 8.85 mmol) in MeOH (50 mL) at rt under Ar. The resulting mixture was stirred and heated at reflux for 15 h. The resulting mixture was allowed to cool to rt and Et_3N (0.5 mL, 6.86 mmol) was added. The solvent was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with petrol-EtOAc (4:1) as eluent gave BDA protected diol *rac*-**95** (1.31 g, 65%) as a pale yellow solid, mp 57–60 °C; R_F (1:1 petrol-EtOAc) 0.71; IR (Thin Film) 2931, 1446, 1139, 1079, 977, 899 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 5.57–5.54 (m, 2H, CH=CH), 3.82–3.77 (m, 2H, 2 × CHO), 3.28 (s, 6H, 2 × OMe), 2.37–3.25 (m, 2H, 2 × CH), 2.23–2.10 (m, 2H, 2 × CH), 1.58 (s, 6H, 2 × OMe); ^{13}C NMR (100.6 MHz; $CDCl_3$) δ: 124.5 (C=C), 99.2 (2 × OCO), 68.4 (2 × CHO), 47.9 (2 × OMe), 30.5 (2 × CH_2), 17.9 (2 × Me); MS (ESI) 251 [$(M + Na)^+$, 100], 101 (77); HRMS (ESI) *m/z* calcd for $C_{12}H_{20}O_4$ $(M + Na)^+$ 251.1254 found 251.1252 (0.7 ppm error); MS (ESI) 251 [$(M + Na)^+$, 100], 101 (71); HRMS (ESI) *m/z* calcd for $C_{12}H_{20}O_4$ $(M + Na)^+$ 251.1254 found 251.1250 (0.3 ppm error).

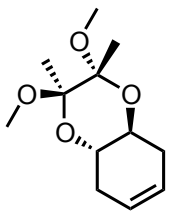
Lab book reference: djb2/86

*m*CPBA (30.76 g, 124.80 mmol) was added in 1 g portions over 45 min to a stirred biphasic solution of 1,4-cyclohexadiene (11.81 mL, 124.80 mmol) and $NaHCO_3$ (20.97 g, 249.60 mmol) in CH_2Cl_2 (156 mL) and water (100 mL) at 0 °C under Ar. The resulting suspension was allowed to warm to rt and stirred at rt for 23 h. Saturated $Na_2S_2O_{3(aq)}$ (50 mL) was added and the mixture was stirred at rt for 1 h. The two layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were washed with saturated $NaHCO_{3(aq)}$

(100 mL), dried ($MgSO_4$) and evaporated under reduced pressure (> 400 mbar and < 40 °C) to *ca*. 25% of the original volume. Acetic acid (7.14 mL, 124.80 mmol) and water (50 mL) were added to the solution at rt. The resulting mixture was stirred and heated at reflux for 16 h. The resulting mixture was cooled to rt and $NaHCO_3$ (11.53 g, 137.28 mmol) was added portionwise. The solvent was evaporated under reduced pressure to give a white solid. Et_2O (100 mL) was added and the solid residue was removed by filtration. This process was repeated a further 7 times. The combined filtrates were dried ($MgSO_4$) and evaporated under reduced pressure to give crude diol. 2,3-Butanedione (12 mL, 137.28 mmol), trimethylorthoformate (41.8 mL, 374.39 mmol) and CSA (2.9 g, 12.48 mmol) were added to a stirred solution of the crude diol *rac*-**95** in MeOH (100 mL) at rt under Ar. The resulting mixture was stirred and heated at reflux for 15 h. The resulting mixture was allowed to cool to rt and Et_3N (2 mL, 27.44 mmol) was added. The solvent was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with petrol-EtOAc (4:1) as eluent gave BDA protected diol *rac*-**95** (10.13 g, 36%) as a pale yellow solid.

Lab book reference: djb3/13

(2*R*,3*R*,4a*S*,8a*S*)-2,3-Dimethoxy-2,3-dimethyl-2,3,4a,5,8,8a-hexahydrobenzo[*b*][1,4]dioxine 95



Amberlyst A26 (OH form) resin (10 g) was added to a stirred solution of benzoate **92** (99:1 er) (5.0 g, 22.91 mmol) in MeOH (57 mL) and THF (28 mL) at rt. The resulting mixture was stirred at rt for 5 h. Then, the polymer was removed by filtration and washed with CH_2Cl_2 (5 × 100 mL). The combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude diol as a white solid. 2,3-Butanedione (2.20 mL, 25.20 mmol), trimethyl orthoformate (7.57 mL, 68.73 mmol) and $BF_3.OEt_2$ (369 μL, 2.29 mmol) were added to a stirred solution of

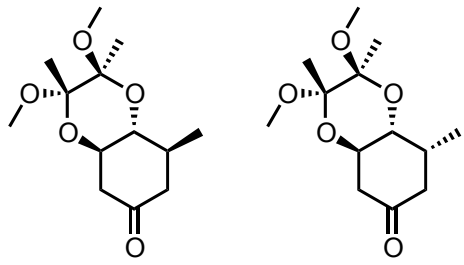
the crude diol in MeOH (50 mL) at rt under Ar. The resulting mixture was stirred at rt for 16 h. Then, the mixture was evaporated under reduced pressure to *ca.* 25 mL. Then, saturated $NaHCO_{3(aq)}$ (500 mL) and CH_2Cl_2 (100 mL) were added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with petrol-EtOAc (3:2) as eluent gave BDA-protected diol **95** (4.96 g, 95%) as a white solid, mp 78–79 °C; $[\alpha]_D$ –139.9 (*c* 1.0 in $CHCl_3$).

Lab book reference: djbI/49

2,3-Butanedione (2.71 mL, 31.03 mmol), trimethyl orthoformate (9.45 mL, 84.63 mmol) and CSA (655 mg, 2.82 mmol) were added to a stirred solution of diol **94** (99:1 er) (3.22 g, 28.21 mmol) in MeOH (60 mL) at rt under Ar. The resulting mixture was stirred and heated at reflux for 15 h. The resulting mixture was allowed to cool to rt and Et_3N (0.5 mL, 6.86 mmol) was added. The solvent was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with petrol-EtOAc (4:1) as eluent gave BDA protected diol **95** (5.14 g, 80%) as a pale yellow solid.

Lab book reference: djb3/10

(2*S*,3*S*,4a*R*,8*S*,8a*R*)-and (2*S*,3*S*,4a*R*,8*R*,8a*R*)-2,3-Dimethoxy-2,3,8-trimethylhexahydrobenzo[*b*][1,4]dioxin-6(7*H*)-one *trans*-106 and *cis*-106



trans *cis*

Table 2.2, entry 1

Using general procedure B at –78 °C, MeLi (1.24 mL of a 1.55 M solution in Et_2O, 1.98 mmol), CuI (189 mg, 0.99 mmol) in THF (10 mL) and enone *ent*-**71** (200 mg, 0.82 mmol) in THF (7 mL) gave the crude product. Purification by flash column chromatography on silica with petrol-EtOAc (4:1) as eluent gave (by ^{1}H NMR spectroscopy) a 55:45 mixture of β-substituted ketones *trans*-**106** and *cis*-**106** (92 mg, 43%) as a white solid, R_F (4:1 petrol-EtOAc) 0.31; IR (Thin Film) 2956, 2913, 1720 (C=O), 1378, 1213, 850 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.96–3.92 (m, 0.9H, CHO_{cis} and CHO_{cis}), 3.75 (ddd, J = 12.5, 9.5, 6.0 Hz, 0.55H, CHO_{trans}), 3.48 (t, J = 9.5 Hz, 0.55H, CHO_{trans}), 3.26 (s, 1.65H, OMe_{trans}), 3.26 (s, 1.35H, OMe_{cis}), 3.21 (s, 1.65H, OMe_{trans}), 3.19 (s, 1.35H, OMe_{cis}), 2.59–2.43 (m, 2.45H), 2.39 (ddd, J = 15.0, 4.5, 2.0 Hz, 0.55H, $CH_AH_{B,\ trans}$), 2.33–2.26 (m, 0.9H), 2.06 (t, J = 15.0 Hz, 0.55H, $CH_AH_{B,\ trans}$), 1.84 (ddqd, J = 12.5, 9.5, 6.5, 4.5 Hz, 0.55H, $CH_AH_{B,\ trans}$), 1.31 (s, 1.35H, Me_{cis}), 1.28 (s, 3.3H, 2 × Me_{trans}), 1.26 (s, 1.35H, Me_{cis}), 1.07 (d, J = 6.5 Hz, 1.65H, $CHMe_{trans}$), 0.94 (d, J = 6.5 Hz, 1.35H, $CHMe_{cis}$); ^{13}C NMR (100.6 MHz; $CDCl_3$) δ: 207.6 ($C{=}O_{cis}$), 206.3 ($C{=}O_{trans}$), 99.8 (OCO_{cis}), 99.6 (OCO_{trans}), 99.5 (OCO_{trans}), 99.2 (OCO_{cis}), 74.8 (CHO), 71.4 (CHO), 68.3 (CHO), 64.2 (CHO), 48.1 (OMe), 48.03 (OMe), 48.00 (OMe), 47.9 (OMe), 47.8 (CH_2), 46.9 (CH_2), 45.2 (CH_2), 45.1 (CH_2), 31.9 (CH), 29.7 (CH), 17.8 (Me), 17.8 (Me), 17.74 (Me), 17.72 (Me), 17.1 (Me), 13.5 (Me); MS (ESI) 281 [$(M + Na)^+$, 100], 227 (48), 101 (62); HRMS (ESI) *m/z* calcd for $C_{13}H_{22}O_5$ $(M + Na)^+$ 281.1359, found 281.1351 (2.9 ppm error).

Lab book ref: djb1/18

Table 2.2, entry 2

Using general procedure B at −78 °C, MeLi (0.62 mL of a 1.55 M solution in Et_2O, 0.99 mmol) and CuCN (44 mg, 0.50 mmol) in THF (5 mL), and enone *ent*-**71** (100 mg, 0.41 mmol) in THF (4 mL) gave the crude product. Purification by flash column chromatography on silica with petrol-EtOAc (4:1) as eluent gave (by ^{1}H NMR spectroscopy) a 60:40 mixture of β-substituted ketones *trans*-**106** and *cis*-**106** (94 mg, 70%) as a white solid.

Lab book ref: djb1/19

Table 2.2, entry 4

Using general procedure C at −78 °C, MeLi (0.62 mL of a 1.55 M solution in Et_2O, 0.99 mmol) and CuCN (44 mg, 0.50 mmol) in THF (5 mL), and a premixed solution of enone *ent*-**71** (100 mg, 0.41 mmol) and Me_3SiCl (105 μL, 0.83 mmol) in THF (4 mL), followed by TBAF (454 μL of a 1.0 M solution in THF, 0.45 mmol) in CH_2Cl_2 (10 mL) gave the crude product. Purification by flash column chromatography on silica with petrol-EtOAc (4:1) as eluent gave (by ^{1}H NMR spectroscopy) β-substituted ketone *trans*-**106** (102 mg, 96%) as a white solid, mp 125–130 °C; $[\alpha]_D$ +191.5 (*c* 0.5 in CH_2Cl_2), R_F (4:1 petrol-EtOAc) 0.31; IR (Thin Film) 2956, 2913, 1720 (C=O), 1378, 1213, 850 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.73 (ddd, *J* = 12.5, 9.5, 6.0 Hz, 1H, CHO), 3.47 (t, *J* = 9.5 Hz, 1H, CHO), 3.26 (s, 3H, OMe), 3.21 (s, 3H, OMe), 2.58–2.45 (m, 2H, CH_AH$_B$ and CH_AH$_B$), 2.38 (ddd, *J* = 15.0, 4.5, 2.5 Hz, 1H, CH$_A$$H_B$), 2.05 (t, *J* = 12.5 Hz, 1H, CH$_A$$H_B$), 1.89–1.77 (m, 1H, C*H*Me), 1.30 (s, 3H, Me), 1.27 (s, 3H, Me), 1.06 (d, *J* = 6.5 Hz, 3H, CH*Me*); ^{13}C NMR (100.6 MHz; $CDCl_3$) δ: 206.2 (C=O), 99.5 (OCO), 99.4 (OCO), 74.7 (CHO), 68.2 (CHO), 47.9 (OMe), 47.8 (OMe), 47.7 (CH_2), 45.0 (CH_2), 31.8 (CH), 17.7 (Me), 17.6 (Me), 17.0 (Me); MS (ESI) 281 [(M + Na)$^+$, 100], 227 (98), 101 (78); HRMS (ESI) *m/z* calcd for $C_{13}H_{22}O_5$ (M + Na)$^+$ 281.1359, found 281.1354 (2.1 ppm error).

Lab book ref: djb2/32

Table 2.3, entry 4

Using general procedure B at −40 °C, MeLi (0.62 mL of a 1.55 M solution in Et_2O, 0.99 mmol) and CuCN (44 mg, 0.50 mmol) in THF (5 mL), and enone *ent*-**71** (100 mg, 0.41 mmol) in THF (4 mL) gave the crude product. Purification by flash column chromatography on silica with petrol-EtOAc (4:1) as eluent gave (by ^{1}H NMR spectroscopy) a 27:73 mixture of β-substituted ketones *trans*-**106** and *cis*-**106** (94 mg, 70%) as a white solid.

Lab book ref: djb2/37

Table 2.3, entry 5

Using general procedure C at −40 °C, MeLi (0.62 mL of a 1.55 M solution in Et_2O, 0.99 mmol) and CuCN (44 mg, 0.50 mmol) in THF (5 mL), and a premixed solution of enone *ent*-**71** (100 mg, 0.41 mmol) and Me_3SiCl (105 μL, 0.83 mmol) in THF (4 mL), followed by TBAF (454 μL of a 1.0 M solution in THF, 0.45 mmol) in CH_2Cl_2 (10 mL) gave the crude product. Purification by flash column chromatography on silica with petrol-EtOAc (4:1) as eluent gave β-substituted ketone *trans*-**106** (104 mg, 97%) as a white solid.

Lab book ref: djb2/36

Table 2.3, entry 6

Using general procedure B at 0 °C, MeLi (0.62 mL of a 1.55 M solution in Et_2O, 0.99 mmol) and CuCN (44 mg, 0.50 mmol) in THF (5 mL), and enone *ent*-**71** (100 mg, 0.41 mmol) in THF (4 mL) gave the crude product. Purification by flash column chromatography on silica with petrol-EtOAc (4:1) as eluent gave (by ^{1}H NMR spectroscopy) a 33:67 mixture of β-substituted ketones *trans*-**106** and *cis*-**106** (71 mg, 77%) as a white solid.

Lab book ref: djb2/39

Table 2.3, entry 7

Using general procedure C at 0 °C, MeLi (0.62 mL of a 1.55 M solution in Et_2O, 0.99 mmol) and CuCN (44 mg, 0.50 mmol) in THF (5 mL), and a premixed solution of enone *ent*-**71** (100 mg, 0.41 mmol) and Me_3SiCl (105 μL, 0.83 mmol) in THF (4 mL), followed by TBAF (454 μL of a 1.0 M solution in THF, 0.45 mmol) in CH_2Cl_2 (10 mL) gave the crude product. Purification by flash column chromatography on silica with petrol-EtOAc (4:1) as eluent gave (by ^{1}H NMR spectroscopy) a 75:25 mixture of β-substituted ketones *trans*-**106** and *cis*-**106** (95 mg, 89%) as a white solid.

Lab book ref: djb2/38

Table 2.4, entry 1

Using general procedure D, MeMgCl (166 μL of a 2.98 M solution in THF, 1.98 mmol), CuBr·SMe_2 (20 mg, 0.05 mmol) in THF (5 mL), and a premixed solution of and enone *ent*-**71** (100 mg, 0.41 mmol) in THF (4 mL) gave the crude product. Purification by flash column chromatography on silica with petrol-EtOAc (4:1) as eluent gave (by ^{1}H NMR spectroscopy) a 50:50 mixture of β-substituted ketones *trans*-**106** and *cis*-**106** (33 mg, 31%) as a white solid.

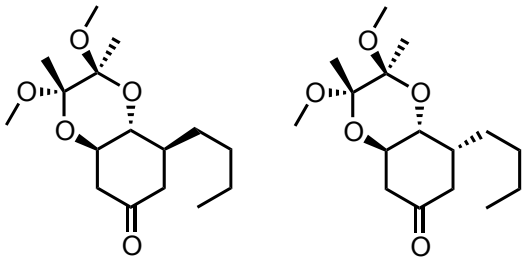
Lab book ref: djb1/97

Table 2.4, entry 2

Using general procedure E, MeMgCl (166 μL of a 2.98 M solution in THF, 1.98 mmol), CuBr·SMe_2 (20 mg, 0.05 mmol) in THF (5 mL), and a premixed solution of and enone *ent*-**71** (100 mg, 0.41 mmol) and Me_3SiCl (55 μL, 0.41 mmol) in THF (4 mL) followed by TBAF (454 μL of a 1.0 M solution in THF, 0.45 mmol) in CH_2Cl_2 (10 mL) gave the crude product. Purification by flash column chromatography on silica with petrol-EtOAc (4:1) as eluent gave (by ^{1}H NMR spectroscopy) a 55:45 mixture of β-substituted ketones *trans*-**106** and *cis*-**106** (79 mg, 75%) as a white solid.

Lab book ref: djb1/97

(2*S*,3*S*,4a*R*,8*S*,8a*R*)-and (2*S*,3*S*,4a*R*,8*R*,8a*R*)-8-Butyl-2,3-dimethoxy-2,3-dimethylhexahydrobenzo[*b*][1,4]dioxin-6(7*H*)-one *trans*-108 and *cis*-108



trans *cis*

Table 2.2, entry 3

Using general procedure B at −78 °C, *n*-BuLi (1.28 mL of a 1.53 M solution in hexanes, 1.98 mmol), and CuCN (89 mg, 0.99 mmol) in THF (10 mL), and enone *ent*-**71** (200 mg, 0.83 mmol) in THF (7 mL) gave the crude product. Purification by flash column chromatography on silica with petrol-EtOAc (4:1) as eluent gave β-substituted ketone *trans*-**108** (181 mg, 74%) as a colourless oil, $[\alpha]_D$ +172.2 (*c* 1.8 in CH_2Cl_2); R_F (4:1 petrol-EtOAc) 0.33; IR (Thin Film) 2954, 1721 (C=O), 1462, 1376, 1264, 1214, 1121, 1050, 963, 934 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 3.69 (ddd, *J* = 12.5, 9.5, 6.0 Hz, 1H, CHO), 3.51 (t, *J* = 9.5 Hz, 1H, CHO), 3.22 (s, 3H, OMe), 3.15 (s, 3H, OMe), 2.52–2.41 (m, 3H), 1.93 (t, *J* = 15.0 Hz, 1H, CH_AH$_B$), 1.89–1.82 (m, 1H), 1.73–1.63 (m, 1H), 1.34–1.16 (m, 3H), 1.26 (s, 3H, Me), 1.22 (s, 3H, Me), 1.15–1.01 (m, 2H), 0.82–0.78 (m, 3H, CH_2*Me*); ^{13}C NMR (100.6 MHz; $CDCl_3$) (CH_2 resonance not resolved) δ: 206.3 (C=O), 99.3 (OCO), 99.2 (OCO), 73.3 (CHO), 68.2 (CHO), 47.8 (OMe), 44.7 (CH_2), 36.5 (OMe), 30.4 (CH_2), 28.1 (CH_2), 22.6 (CH_2), 17.6 (Me), 17.4 (Me), 13.8 (CH_2*Me*); MS (ESI) 323 [$(M + Na)^+$, 100], 269 (35); HRMS (ESI) *m/z* calcd for $C_{16}H_{28}O_5$ $(M + Na)^+$ 323.1829, found 323.1817 (3.6 ppm error).

Lab book ref: djb1/26

Table 2.2, entry 5

Using general procedure C at −78 °C, *n*-BuLi (1.28 mL of a 1.53 M solution in hexanes, 1.98 mmol) and CuCN (89 mg, 0.99 mmol) in THF (10 mL), and a

premixed solution of enone *ent*-**71** (200 mg, 0.83 mmol) and Me_3SiCl (105 μl, 0.83 mmol) in THF (7 mL), followed by TBAF (454 μL, of a 1.0 M solution in THF, 0.45 mmol) in CH_2Cl_2 (10 mL) gave the crude product. Purification by flash column chromatography on silica with petrol-EtOAc (4:1) as eluent gave β-substituted ketone *trans*-**108** (243 mg, 98%) as a colourless oil.

Lab book ref: djb1/55

Table 2.4, entry 3

Using general procedure D, *n*-BuMgBr (2.86 mL of a 0.43 M solution in THF, 1.23 mmol) [prepared from bromobut-1-ane (466 μL, 4.30 mmol), magnesium turnings (156 mg, 6.44 mmol) in THF (10 mL) according to general procedure F], and $CuBr{\cdot}SMe_2$ (10 mg, 0.05 mmol) in THF (5 mL) and a solution of enone *ent*-**71** (100 mg, 0.41 mmol) in THF (4 mL) gave the crude product. Purification by flash column chromatography on silica with petrol-EtOAc (4:1) as eluent gave (by ^1H NMR spectroscopy) a 50:50 mixture of β-substituted ketones *trans*-**108** and *cis*-**108** (38 mg, 31%) as a colourless oil, ^1H NMR (400 MHz, $CDCl_3$) Diagnostic signals for *cis*-**108** δ: 3.97–3.90 (m, 1H, CHO_{cis} and CHO_{cis}).

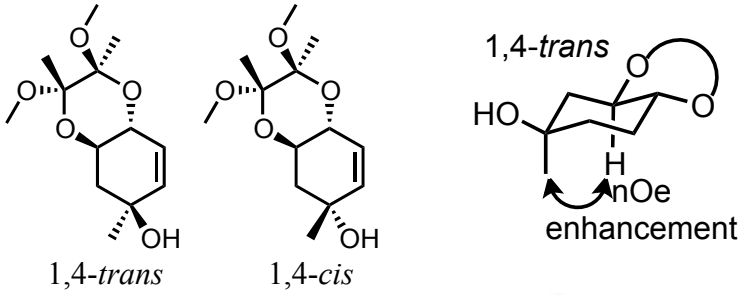
Lab book ref: djb2/1

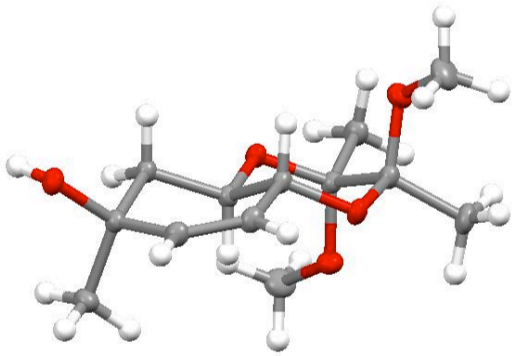
Table 2.4, entry 4

Using general procedure E, *n*-BuMgBr (2.86 mL of a 0.43 M solution in THF, 1.23 mmol) [prepared from bromobut-1-ane (466 μL, 4.30 mmol), magnesium turnings (156 mg, 6.44 mmol) in THF (10 mL) according to general procedure F], and $CuBr{\cdot}SMe_2$ (10 mg, 0.05 mmol) in THF (5 mL) and a premixed solution of enone *ent*-**71** (100 mg, 0.41 mmol) with Me_3SiCl (78 μL, 0.62 mmol) in THF (4 mL), followed by TBAF (454 μL, 0.45 mmol) in CH_2Cl_2 (10 mL) gave the crude product. Purification by flash column chromatography on silica with petrol-EtOAc (4:1) as eluent gave (by ^1H NMR spectroscopy) a 56:44 mixture of β-substituted ketones *trans*-**108** and *cis*-**108** (92 mg, 74%) as a colourless oil.

Lab book ref: djb2/16

(2*S*,3*S*,4a*R*,6*R*,8a*R*)- and (2*S*,3*S*,4a*R*,6*S*,8a*R*)-2,3-Dimethoxy-2,3,6-trimethyl-2,3,4a,5,6,8a-hexahydrobenzo[*b*][1,4]dioxin-6-ol 1,4-*trans*-**109 and** 1,4-*cis*-**109**





X-ray crystal structure of 1,4-trans-109

Table 2.6, entry 2

MeMgBr (275 μL of a 3 M solution in Et_2O, 0.825 mmol) was added dropwise over 15 min to a stirred solution of enone *ent*-**71** (100 mg, 0.413 mmol) in THF (6 mL) at –78 °C under Ar. gave the crude product. The resulting solution was stirred at –78 °C for 2 h. Then, saturated $NH_4Cl_{(aq)}$ (5 mL) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (5 × 5 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with petrol-EtOAc (1:1) as eluent gave (by ^{1}H NMR spectroscopy) a 83:17 mixture of alcohols 1,4-*trans*-**109** and 1,4-*cis*-**109** (72 mg, 68%) as a white solid, R_F (1:1 petrol-EtOAc) 0.52; IR (Thin Film) 3355 (OH), 2905, 1437, 1116, 968 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.59–5.45 (m, 2H, HC=CH), 4.18 (dd, J = 9.0, 1.0 Hz, 0.83H, $CHO_{1,4\text{-}trans}$), 4.05 (dd, J = 9.0, 1.0 Hz, 0.17H, $CHO_{1,4\text{-}cis}$), 3.84 (ddd, J = 13.0, 9.0, 3.5 Hz, 0.17H, $CHO_{1,4\text{-}cis}$), 3.65 (ddd, J = 13.0, 9.0, 3.5 Hz, 0.83H, $CHO_{1,4\text{-}trans}$), 3.21-3.20 (m, 6H, 2 × OMe), 2.09 (br s, 1H, OH), 2.00 (ddd, J = 13.0, 3.5, 1.5 Hz, 0.83H, $CH_AH_{B,\ 1,4\text{-}trans}$), 1.93 (ddd, J = 13.0, 3.5, 1.5 Hz, 0.17H, $CH_AH_{B,\ 1,4\text{-}cis}$), 1.81 (t, J = 13.0 Hz, 0.83H, $CH_AH_{B,\ 1,4\text{-}trans}$), 1.61 (t, J = 13.0 Hz, 0.17H, $CH_AH_{B,\ 1,4\text{-}cis}$) 1.31 (s,

2.49H, $Me_{1,4\text{-}trans}$), 1.27-1.25 (m, 6.51H, $Me_{1,4\text{-}cis}$, 2 × Me); ^{13}C NMR (100.6 MHz; $CDCl_3$)($Me_{1,4\text{-}trans}$ resonance not resolved) δ: 135.6 (=$CH_{1,4\text{-}cis}$), 134.2 (=$CH_{1,4\text{-}trans}$), 127.8 (=$CH_{1,4\text{-}trans}$), 126.2 (=$CH_{1,4\text{-}cis}$), 100.5, ($OCO_{1,4\text{-}trans}$), 100.4 ($OCO_{1,4\text{-}cis}$), 100.04 ($OCO_{1,4\text{-}trans}$), 100.01 ($OCO_{1,4\text{-}cis}$), 72.1 (*C*OH$Me_{1,4\text{-}cis}$), 70.5 (*C*OH$Me_{1,4\text{-}trans}$), 69.8 ($CHO_{1,4\text{-}trans,\ 1\text{-}4,\text{-}cis}$), 68.1 ($CHO_{1,4\text{-}cis}$), 66.4 ($CHO_{1,4\text{-}trans}$), 48.0 ($OMe_{1,4\text{-}trans}$), 47.9 ($OMe_{1,4\text{-}trans,\ 1,4\text{-}cis}$), 47.89 ($OMe_{1,4\text{-}cis}$), 42.4 ($CH_{2,\ 1,4\text{-}cis}$), 40.6 ($CH_{2,\ 1,4\text{-}trans}$), 30.0 (COH*Me*$_{1,4\text{-}trans}$), 29.5 (COH*Me*$_{1,4\text{-}cis}$), 17.93 ($Me_{1,4\text{-}trans}$), 17.90 ($Me_{1,4\text{-}cis}$), 17.88 ($Me_{1,4\text{-}cis}$); MS (ESI) 281 [$(M + Na)^+$, 100]; ESI-MS *m/z* calcd for $C_{13}H_{22}O_5$ $(M + Na)^+$ 281.1359, found 281.1354 (1.3 ppm error). Spectroscopic data are consistent with those that reported in the literature.[122]

Crystal structure determination of alcohol 1,4-*trans*-109

$C_{13}H_{22}O_5$, M = 258.31, monoclinic, a = 13.3877(9), b = 6.7900(5), c = 15.7945(13) Å, β = 103.153°, U = 1398.10(19) $Å^3$, T = 110(10) K, space group $P2_1$, Z = 4, μ(Mo-Kα) = 0.096 mm^{-1}, 8616 reflections measured, 5081 unique (R_{int} = 0.0461) which were used in calculations. The final R1 was 0.0478 ($I>2\sigma_I$) and wR2 was 0.1337 (all data).

Lab book ref: djb1/21

Table 2.6, entry 3

MeMgBr (275 μL of a 3 M solution in Et_2O, 0.825 mmol) was added dropwise over 15 min to a stirred solution of enone *ent*-**71** (100 mg, 0.413 mmol) in THF (6 mL) at 0 °C under Ar. The resulting solution was stirred at 0 °C for 2 h. Then, saturated $NH_4Cl_{(aq)}$ (5 mL) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (5 × 5 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with petrol-EtOAc (1:1) as eluent gave (by ^1H NMR spectroscopy) a 75:25 mixture of alcohols 1,4-*trans*-**109** and 1,4-*cis*-**109** (100 mg, 93%) as a colourless oil. The 75:25 mixture of alcohols 1,4-*trans*-**109** and 1,4-*cis*-**109** was recrystallised from hot heptane twice to give alcohol 1,4-*trans*-**109**.

Lab book ref: djb1/24

Table 2.6, entry 1

MeLi (388 μL of a 1.6 M solution in Et_2O, 0.825 mmol) was added dropwise over 15 min to a stirred solution of enone *ent*-**71** (100 mg, 0.413 mmol) in THF (6 mL) at 0 °C. The resulting solution was stirred at 0 °C for 2 h. Then, saturated $NH_4Cl_{(aq)}$ (5 mL) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (5 × 5 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with petrol-EtOAc (1:1) as eluent gave (by ^1H NMR spectroscopy) a 66:34 mixture of alcohols 1,4-*trans*-**109** and 1,4-*cis*-**109** (96 mg, 90%) as a colourless oil.

Lab book ref: djb1/22

(2*S*,3*S*,4a*R*,6*S*,8a*R*)-2,3-Dimethoxy-2,3-dimethyl-6-phenyl-2,3,4a,5,6,8a-hexahydrobenzo[*b*][1,4]dioxin-6-ol 1,4-*trans*-**110**

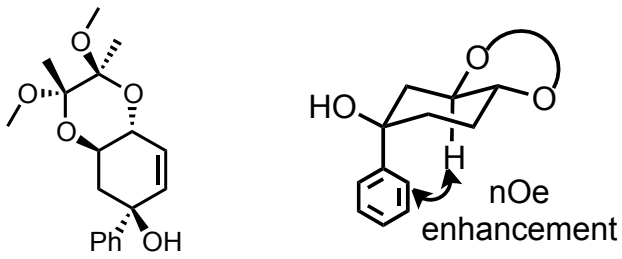


Table 2.6, entry 4

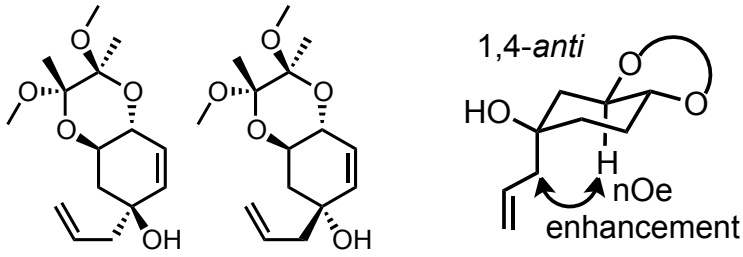
PhMgCl (413 μL of a 2 M solution in Et_2O, 0.826 mmol) was added dropwise over 15 min to a stirred solution of enone *ent*-**71** (100 mg, 0.413 mmol) in THF (6 mL) at 0 °C under Ar. The resulting solution was stirred at 0 °C for 2 h. Then, saturated $NH_4Cl_{(aq)}$ (5 mL) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (5 × 5 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with petrol-EtOAc (4:1) as eluent gave (by ^1H NMR spectroscopy) alcohol 1,4-*trans*-**110** (130 mg, 98%) as a white solid, mp 117–120 °C; $[\alpha]_D$ +170.8 (*c* 1.15 in $CHCl_3$), R_F (4:1 petrol-EtOAc) 0.12; IR (Thin Film) 3457 (OH), 2950, 1450, 1036, 936 cm^{-1}; ^1H NMR (400 MHz,

$CDCl_3$) δ: 7.53 (dd, *J* = 7.0, 1.5 Hz, 2H, *o*-Ph), 7.53 (t, *J* = 7.0 Hz, 2H, *m*-Ph), 7.53 (tt, *J* = 7.0, 1.5 Hz, 1H, *p*-Ph), 5.90 (dd, *J* = 10.0, 1.5 Hz, 1H, =CH), 5.70 (ddd, *J* = 10.0, 2.5, 1.5 Hz, 1H, =CH), 4.35 (ddd, *J* = 9.0, 2.5, 1.5 Hz, 1H, CHO), 3.65 (ddd, *J* = 13.0, 9.0, 3.0 Hz, 1H, CHO), 3.30 (s, 3H, OMe), 2.99 (s, 3H, OMe), 2.30 (ddd, *J* = 13.0, 3.0, 1.5 Hz, 1H, CH_AH_B), 2.14 (t, *J* = 13.0 Hz, 1H, CH_AH_B), 2.05 (br s, 1H, OH), 1.33 (s, 3H, Me), 1.25 (s, 3H, Me); ^{13}C NMR (100.6 MHz; $CDCl_3$) (COH resonance not resolved) δ: 146.0 (*i*-Ph), 133.2 (=CH), 128.2 (*m*-Ph), 128.0 (=CH), 127.4 (*p-Ph*), 125.6 (*o*-Ph), 100.2 (OCO), 99.7 (OCO), 69.8 (CHO), 66.4 (CHO), 47.8 (OMe), 47.5 (OMe), 43.0 (CH_2), 17.7 (Me), 17.6 (Me); MS (ESI) 343 [(M + Na)$^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{18}H_{24}O_5$ (M + Na)$^+$ 343.1516, found 343.1392 (3.3 ppm error).

The relative stereochemistry was assigned by the nOe enhancement indicated.

Lab book ref: djb1/24

(2*S*,3*S*,4a*R*,6*S*,8a*R*)-and (2*S*,3*S*,4a*R*,6*R*,8a*R*)-6-Allyl-2,3-dimethoxy-2,3-dimethyl-2,3,4a,5,6,8a-hexahydrobenzo[*b*][1,4]dioxin-6-ol 4-*trans*-**111 and** 1,4-*cis*-**111**



1,4-*trans* 1,4-*cis*

Table 2.6, entry 5

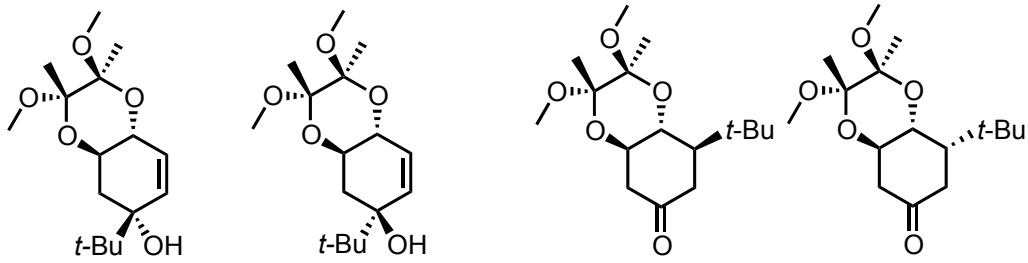
AllylMgCl (826 μL of a 1.0 M solution in Et_2O, 0.826 mmol) was added dropwise over 15 min to a stirred solution of enone *ent*-**71** (100 mg, 0.413 mmol) in THF (6 mL) at 0 °C under Ar. The resulting solution was stirred at 0 °C for 2 h. Then, saturated $NH_4Cl_{(aq)}$ (5 mL) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (5 × 5 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with petrol-EtOAc (4:1) as

eluent gave (by ^{1}H NMR spectroscopy) an 80:20 mixture of allyl alcohols 1,4-*trans*-**111** and 1,4-*cis*-**111** (114 mg, 98%) as a colourless oil, R_F (1:1 petrol-EtOAc) 0.40; IR (Thin Film) 3434 (OH), 2992 1455 1036 847 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.92–5.81 (m, 0.8H, C*H*=$CH_{2,\ 1,4\text{-}trans}$), 5.80–5.72 (m, C*H*=$CH_{2,\ 1,4\text{-}cis}$), 5.69 (dd, *J* = 10.0, 1.5 Hz, 0.2H, =$CH_{1,4\text{-}cis}$), 5.64 (dd, *J* = 10.0, 1.5 Hz, 0.8H, =$CH_{1,4\text{-}trans}$), 5.56 (ddd, *J* = 10.0, 2.5, 2.0 Hz, 0.2H, =$CH_{1,4\text{-}cis}$), 5.51 (ddd, *J* = 10.0, 2.5, 2.0 Hz, 0.8H, =$CH_{1,4\text{-}trans}$), 5.19–5.07 (m, 2H, CH=C*H*$_2$), 4.25 (ddd, *J* = 9.0, 2.5, 1.5 Hz, 0.8H, $CHO_{1,4\text{-}trans}$), 4.09 (ddd, *J* = 9.0, 2.5, 1.5 Hz, 0.2H, $CHO_{1,4\text{-}cis}$), 3.91 (ddd, *J* = 12.5, 9.0, 4.0 Hz, 0.2H, $CHO_{1,4\text{-}cis}$), 3.72 (ddd, *J* = 13.0, 9.0, 3.5 Hz, 0.8H, $CHO_{1,4\text{-}trans}$), 3.26 (s, 3H, OMe), 3.24 (s, 3H, OMe), 2.43-2.30 (m, 2H, C*H*$_2$CH=CH_2), 2.13 (ddd, *J* = 12.5, 4.0, 1.5 Hz, 0.8H, C*H*$_A$$H_{B,\ 1,4\text{-}trans}$), 1.89 (ddd, *J* = 13.0, 4.0, 2.0 Hz, 0.2H, C*H*$_A$$H_{B,\ 1,4\text{-}cis}$), 1.81–1.72 (m, 1H, CH_AH_B), 1.32 (s, 0.6H, $Me_{1,4\text{-}cis}$), 1.32 (s, 2.4H, $Me_{1,4\text{-}trans}$), 1.30 (s, 0.6H, $Me_{1,4\text{-}cis}$), 1.30 (s, 2.4H, $Me_{1,4\text{-}trans}$); ^{13}C NMR (100.6 MHz; $CDCl_3$) δ: 134.1, 132.8 (=$CH_{1,4\text{-}trans}$), 132.6 (=$CH_{1,4\text{-}cis}$), 132.5 (=$CH_{1,4\text{-}cis}$), 128.9 (=$CH_{1,4\text{-}cis}$), 127.4 (=$CH_{1,4\text{-}trans}$), 119.5 (=$CH_{2,\ 1,4\text{-}trans}$), 119.4 (=$CH_{2,\ 1,4\text{-}trans}$), 100.4 ($OCO_{1,4\text{-}cis}$), 100.3 ($OCO_{1,4\text{-}trans}$), 99.9 ($OCO_{1,4\text{-}cis}$), 99.8 ($OCO_{1,4\text{-}trans}$), 73.1 (Allyl*C*$OH_{1,4\text{-}trans}$), 72.1 (Allyl*C*$OH_{1,4\text{-}cis}$), 69.6 ($CHO_{1,4\text{-}cis}$), 69.5 ($CHO_{1,4\text{-}trans}$), 67.4 ($CHO_{1,4\text{-}trans}$), 66.2 ($CHO_{1,4\text{-}cis}$), 48.08 ($OMe_{1,4\text{-}cis}$), 48.02 ($OMe_{1,4\text{-}cis,\ 1,4\text{-}trans}$), 47.86 ($OMe_{1,4\text{-}trans}$), 47.0 (*C*$H_2$CH=$CH_{2,\ 1,4\text{-}cis}$), 46.4 (*C*$H_2$CH=$CH_{2,\ 1,4\text{-}trans}$), 39.6 ($CH_{2,\ 1,4\text{-}trans}$), 38.4 ($CH_{2,\ 1,4\text{-}trans}$), 17.83 ($Me_{1,4\text{-}cis}$), 17.80 ($Me_{1,4\text{-}trans,\ 1,4\text{-}cis}$), 17.7 ($Me_{1,4\text{-}trans}$); MS (ESI) 307 [(M + Na)$^+$, 86], 135 (100); HRMS (ESI) *m/z* calcd for $C_{15}H_{24}O_5$ (M + Na)$^+$ 307.1506, found 307.1516 (3.3 ppm error).

The relative stereochemistry was assigned by the nOe enhancement indicated.

Lab book reference: djb1/40

(2*S*,3*S*,4a*R*,6*S*,8a*R*)- and (2*S*,3*S*,4a*R*,6*R*,8a*R*)-6-(*tert*-butyl)-2,3-dimethoxy-2,3-dimethyl-2,3,4a,5,6,8a-hexahydrobenzo[*b*][1,4]dioxin-6-ol 1,4-*trans*-**112 and** 1,4-*cis*-**112 and (2*S*,3*S*,4a*R*,8*S*,8a*R*)- and (2*S*,3*S*,4a*R*,8*R*,8a*R*)-8-*Tert*-Butyl-2,3-dimethoxy-2,3-dimethylhexahydrobenzo[*b*][1,4]dioxin-6(7*H*)-one** *trans*-**113 and** *cis*-**113**



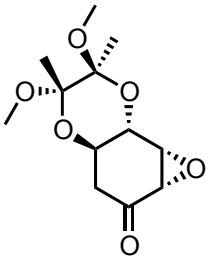
1,4-trans-**112** 1,4-*cis*-**112** 1,4-*trans*-**113** 1,4-*cis*-**113**

t-BuMgCl (413 μL of a 2 M solution in Et_2O, 0.826 mmol) was added dropwise over 15 min to a stirred solution of enone *ent*-**71** (100 mg, 0.413 mmol) in THF (6 mL) at 0 °C under Ar. The resulting solution was stirred at 0 °C for 2 h. Then, saturated $NH_4Cl_{(aq)}$ (5 mL) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (5 × 5 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with petrol-EtOAc (4:1) as eluent gave (by ^{1}H NMR spectroscopy) a 60:40 mixture of β-substituted ketones *trans*-**112** and *cis*-**112** (47 mg, 38%) as a colourless oil, R_F (1:1 petrol-EtOAc) 0.58; IR (Thin Film) 2952, 1720 (C=O), 1374 1119, 852 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.34 (td, J = 11.0, 6.0 Hz, 0.4H, CHO_{cis}), 4.11 (dd, J = 11.0, 5.0 Hz, 0.4H, CHO_{cis}), 3.94 (t, J = 10.0 Hz, 0.6H, CHO_{trans}), 3.82 (ddd, J = 12.0, 10.0, 6.0 Hz, 0.6H, CHO_{trans}), 3.38 (s, 1.8H, OMe_{trans}), 3.26 (s, 1.2H, OMe_{cis}), 3.23 (s, 1.2H, OMe_{cis}), 3.22 (s, 1.8H OMe_{trans}), 2.68–2.60 (m, 0.6H), 2.58–2.34 (m, 2.8H), 2.11 (dd, J = 15.0, 12.0 Hz, 0.6H, CH_AH_{Btrans}), 2.06 (ddd, J = 7.0, 5.5, 2.5 Hz, 0.3H, C*Ht*-Bu_{cis}), 1.70 (ddd, J = 16.0, 10.0, 5.0 Hz, 0.6H, C*Ht*-Bu_{trans}), 1.31 (s, 1.8H, Me_{trans}), 1.28 (s, 1.8H, Me_{trans}), 1.276 (s, 1.2H, Me_{cis}), 1.271 (s, 1.2H, Me_{cis}), 1.00 (s, 5.4H, *t*-Bu_{trans}), 0.99 (s, 3.6H, *t*-Bu_{cis}); ^{13}C NMR (100.6 MHz; $CDCl_3$) δ: 209.1 ($C{=}O_{cis}$), 208.2 ($C{=}O_{trans}$), 99.8 (OCO_{trans}), 99.6 (OCO_{cis}), 99.2, (OCO_{trans}), 99.0 (OCO_{cis}), 74.0 (CHO_{cis}), 72.3 (CHO_{trans}), 68.4 (CHO_{trans}), 64.5 (CHO_{cis}), 49.5 (OMe_{trans}), 48.2 (OMe_{trans}), 48.1 (OMe_{cis}), 48.0 (OMe_{cis}), 45.4 (C*Ht*-Bu_{trans}), 45.1 (C*Ht*-Bu_{cis}), 45.0 ($CH_{2,\ cis}$), 44.6 ($CH_{2,\ trans}$), 43.4 ($CH_{2,\ cis}$), 42.1 ($CH_{2,\ trans}$), 34.8 (CMe_{3cis}), 33.4

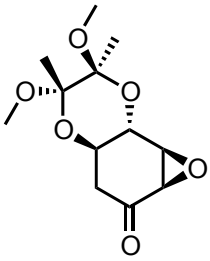
(*C*Me$_{3trans}$), 30.6 (C*Me*$_{3cis}$), 28.5 (*C*Me$_{3trans}$), 18.0 (Me$_{trans}$), 17.9 (Me$_{trans}$), 17.8 (Me$_{cis}$), 17.7 (Me$_{cis}$); MS (ESI) 323 [(M + Na)$^+$, 100], 269 (51); HRMS (ESI) *m/z* calcd for $C_{16}H_{28}O_5$ (M + Na)$^+$ 323.1829, found 323.1830 (−0.3 ppm error) and gave (by ^{1}H NMR spectroscopy) a 70:30 mixture of *t*-butyl alcohols 1,4-*trans*-**113** and 1,4-*cis*-**113** (44 mg, 36%) as a colourless oil, R_F (1:1 petrol-EtOAc) 0.50; IR (Thin Film) 3509 (OH), 2954, 1466 1127 949 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.81–5.71 (m, 2H, HC=CH), 4.23 (ddd, *J* = 9.0, 2.5, 1.0 Hz, 0.7H, CHO$_{1,4\text{-}trans}$), 4.07 (dd, *J* = 8.5, 1.0 Hz, 0.3H, CHO$_{1,4\text{-}cis}$), 3.89 (dd, *J* = 17.0, 8.5 Hz, 0.3H, CHO$_{1,4\text{-}cis}$), 3.73 (ddd, *J* = 13.5, 9.0, 4.5 Hz, 0.7H, CHO$_{1,4\text{-}trans}$), 3.27 (s, 4,2H), 3.24 (s, 1.8H), 2.46 (ddd, *J* = 13.5, 4.5, 1.0 Hz, 0.7H, C*H*$_A$H$_{B,\ 1,4\text{-}trans}$), 1.85 (d , *J* = 9.0 Hz, 0.3H C*H*$_A$H$_{B,\ 1,4\text{-}cis}$), 1.60 (t , *J* = 13.5 Hz, 0.7H, CH$_A$*H*$_{B,\ 1,4\text{-}trans}$), 1.53 (br s, 0.3H, OH$_{1,4\text{-}cis}$), 1.44 (br s, 0.7H, OH$_{1,4\text{-}trans}$), 1.33 (s, 0.9H, Me$_{1,4\text{-}cis}$), 1.32 (s, 0.9H, Me$_{1,4\text{-}cis}$), 1.31 (s, 2.1H, Me$_{1,4\text{-}trans}$) 1.30 (s, 2.1H, Me$_{1,4\text{-}trans}$), 0.99 (s, 6.3H, *t*-Bu$_{1,4\text{-}trans}$), 0.93 (s, 2.7H, *t*-Bu$_{1,4\text{-}cis}$); ^{13}C NMR (100.6 MHz; $CDCl_3$) δ: 131.0 (=CH$_{1,4\text{-}trans}$), 130.5 (=CH$_{1,4\text{-}cis}$), 129.8 (=CH$_{1,4\text{-}trans}$), 129.5 (=CH$_{1,4\text{-}cis}$), 100.3 (OCO$_{1,4\text{-}cis}$), 100.1 (OCO$_{1,4\text{-}trans}$), 99.9 (OCO$_{1,4\text{-}cis}$), 99.7 (OCO$_{1,4\text{-}trans}$), 77.2 (HO*Ct*-Bu$_{1,4\text{-}cis}$), 77.1 (HO*Ct*-Bu$_{1,4\text{-}trans}$), 69.5 (CHO$_{1,4\text{-}cis}$), 69.2 (CHO$_{1,4\text{-}trans}$), 68.5 (CHO$_{1,4\text{-}trans}$), 67.1 (CHO$_{1,4\text{-}cis}$), 48.0 (OMe$_{1,4\text{-}cis}$), 47.9 (OMe$_{1,4\text{-}cis}$), 47.8 (OMe$_{1,4\text{-}trans}$), 47.7 (OMe$_{1,4\text{-}trans}$), 38.4 (CH$_{2,\ 1,4\text{-}trans}$), 37.4 (CH$_{2,\ 1,4\text{-}cis}$), 37.1 (*C*Me$_{3,\ 1,4\text{-}trans}$), 34.5 (*C*Me$_{3,\ 1,4\text{-}cis}$), 25.5 (C*Me*$_{3,\ 1,4\text{-}trans}$), 24.7 (C*Me*$_{3,\ 1,4\text{-}trans}$), 17.9 (Me$_{1,4\text{-}cis}$), 17.8 (Me$_{1,4\text{-}cis,\ 1,4\text{-}trans}$), 17.7 (Me$_{1,4\text{-}trans}$); MS (ESI) 323 [(M + Na)$^+$, 87], 283 (58) 269 (100); HRMS (ESI) *m/z* calcd for $C_{16}H_{28}O_5$ (M + Na)$^+$ 323.1829, found 323.1824 (1.6 ppm error).

Lab book ref: djb1/39

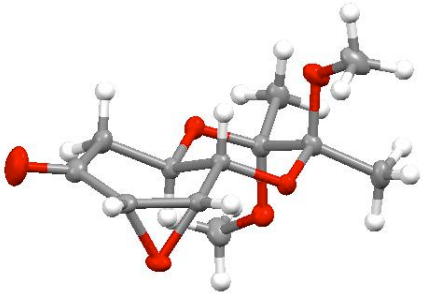
(1a*S*, 3a*R*,5*S*,6*S*,7a*S*,7b*S*) and (1a*R*, 3a*R*,5*S*,6*S*,7a*S*,7b*R*)-5,6-Dimethoxy-5,6-dimethyl-hexahydro-1,4,7-trioxa-cyclopropa[*a*]napthalen-2-one *cis*-114 and *trans*-114



cis



trans



X-ray crystal structure of cis-114

Hydrogen peroxide (750 μL of a 30% w/v solution in water, 6.61 mmol) and Triton B (29 μL of a 40% w/w solution MeOH, 0.05 mmol) were added to a stirred solution of enone *ent*-**71** (200 mg, 0.83 mmol) in THF (2 mL) at 0 °C under Ar. The resulting mixture was allowed to warm to rt and stirred for 19 h. Then, saturated $NH_4Cl_{(aq)}$ (5 mL) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (5 × 5 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product which contained a 65:35 mixture of epoxides *cis*-**114** and *trans*-**114** (by ^{1}H NMR spectroscopy). Purification by flash column chromatography on silica with petrol-EtOAc (1:1) as eluent gave epoxide *trans*-**114** (64 mg, 30%) as a white solid, mp 130–132 °C; $[\alpha]_D$ +180.3 (*c* 1.0 in $CHCl_3$); R_F (1:1 petrol-EtOAc) 0.65; IR (Thin Film) 2951, 1720 (C=O), 1377, 1143, 1113, 883 cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ: 4.06 (dd, *J* = 9.5, 1.0 Hz, 1H, CHO), 3.81 (ddd, *J* = 14.5, 9.5, 3.5 Hz, 1H, CHO), 3.48 (d, *J* = 3.0 Hz, 1H, $CHO_{epoxide}$), 3.36 (s, OMe), 3.28 (dt, *J* = 3.0, 1.0 Hz, 1H, $CHO_{epoxide}$), 3.23 (s, 3H, OMe), 2.59 (t, *J* = 14.5 Hz, 1H, CH_AH_B), 2.40 (ddd, *J* = 14.5, 3.5, 1.0 Hz, 1H, CH_AH_B), 1.36 (s, 3H, Me), 1.30 (s, 3H, Me); ^{13}C NMR (100.6 MHz; $CDCl_3$) δ: 202.5 (C=O), 100.5 (OCO), 99.9 (OCO), 68.8 (CHO), 67.7 (CHO), 57.1 (CHO), 54.7 (CHO), 48.3 (OMe), 48.2 (OMe), 38.9 (CH_2), 17.6 (Me), 17.5 (Me); MS (ESI) 281 [(M + Na)$^+$, 14], 259 [(M + H)$^+$, 14], 227 (100); HRMS (ESI) *m/z* calcd for $C_{12}H_{18}O_6$ (M + H)$^+$ 259.1176, found 259.1171 (1.8 ppm error) and epoxide *cis*-**114** (106 mg, 50%) as a white solid, mp 142–144 °C; $[\alpha]_D$ +87.4 (*c* 1.0 in $CHCl_3$); R_F (1:1 petrol-EtOAc) 0.55; IR (Thin Film) 2950, 1722 (C=O), 1379, 1135, 856 cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ: 4.30 (ddd, *J* = 11.5, 9.5, 6.5 Hz, 1H, CHO), 4.06 (d, *J* = 9.5

Hz, 1H, CHO), 3.61 (d, J = 4.0 Hz, 1H, $CHO_{epoxide}$), 3.39 (d. J = 4.0 Hz, 1H, $CHO_{epoxide}$), 3.32 (s, OMe), 3.26 (s, 3H, OMe), 2.72 (dd, J = 19.0, 6.5 Hz, 1H, CH_AH_B), 2.31 (dd, J = 19.0, 11.5 Hz, 1H, CH_AH_B), 1.39 (s, 3H, Me), 1.29 (s, 3H, Me); ^{13}C NMR (100.6 MHz; $CDCl_3$) δ: 201.5 (C=O), 100.3 (OCO), 99.4 (OCO), 68.2 (CHO), 60.5 (CHO), 55.8 (CHO), 55.1 (CHO), 48.2 (OMe), 48.0 (OMe), 40.7 (CH_2), 17.7 (Me), 17.6 (Me); MS (ESI) 281 [$(M + Na)^+$, 14], 227 (100); HRMS (ESI) *m/z* calcd for $C_{12}H_{18}O_6$ $(M + Na)^+$ 281.0996, found 281.0995 (0.2 ppm error).

Crystal structure determination of epoxide *cis*-114

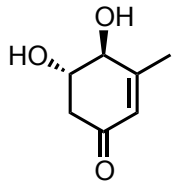
$C_{12}H_{18}O_6$, M = 258.26, monoclinic, a = 6.84156(13), b = 7.72334(13), c = 12.3930(2) Å, β = 93.6531°, U = 653.51(2) Å^3, T = 110(10) K, space group $P2_1$, Z = 4, μ(Mo-Kα) = 0.096 mm^{-1}, 8114 reflections measured, 3594 unique (R_{int} = 0.0251) which were used in calculations. The final R1 was 0.0390 ($I>2\sigma_I$) and wR2 was 0.0993 (all data).

Lab Book Ref: djb2/79

tert-Butyl hydrogen peroxide (12 μL of a 6.0 M solution in decane, 2.07 mmol) and Triton B (12 μL of a 40% w/w solution MeOH, 0.03 mmol) were added to a stirred solution of enone *ent*-**71** (100 mg, 0.41 mmol) in THF (2 mL) at 0 °C under Ar. The resulting mixture was allowed to warm to rt and stirred for 19 h. Then, saturated $NH_4Cl_{(aq)}$ (5 mL) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (5 × 5 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with petrol-EtOAc (1:1) as eluent gave epoxide *trans*-**114** (86 mg, 80%) as a white solid.

Lab book reference: djb4/8

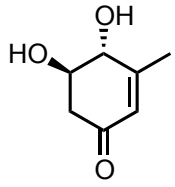
(4*S*,5*S*)-4,5-Dihydroxy-3-methylcyclohex-2-enone 115



A solution of β-methyl enone **117** (89 mg, 0.35 mmol) in TFA (2 mL) and water (200 μL) was stirred at rt for 15 min. The solvent was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with EtOAc as eluent gave diol **115** (36 mg, 74%) as a colourless oil, $[\alpha]_D$ +107.0 (*c* 1.0 in MeOH))((Lit.,[3] +11.3 (*c* 0.01 in MeOH) for a ~60:40 mixture of (*S*,*S*)-**115** and (*R*,*R*)-**115** isolated from *Lasiodiplodia theobromae*); R_F (EtOAc) 0.19; IR (Thin Film) 3324 (OH), 1631 (C=O), 1266, 1053 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ: 5.86–5.83 (m, 1H, =CH), 4.09 (d, *J* = 7.0 Hz, 1H, CHO), 3.90 (ddd, *J* = 10.0, 7.0, 4.5 Hz, 1H, CHO), 2.68 (dd, *J* = 16.5, 4.5 Hz, 1H, CH_AH_B), 2.40 (dd, *J* = 16.5, 10.0 Hz, 1H, CH_AH_B), 2.05 (s, 3H, Me). ^{13}C NMR (100.6 MHz; CD_3OD) δ: 198.4 (C=O), 163.5 (=*C*Me), 126.0 (=CH), 73.5 (CHO), 71.4 (CHO), 43.3 (CH_2), 19.5 (Me); MS (ESI) 279 [$(M + Na)^+$, 75], 257 [$(M + H)^+$, 100], 225 (71), 193 (55); HRMS (ESI) *m/z* calcd for $C_7H_{10}O_3$ $(M + H)^+$ 143.0703, found 143.0703 (−0.3 ppm error), calcd for $C_7H_{10}O_3$ $(M + Na)^+$ 165.0521, found 165.0522 (0.7 ppm error). Spectroscopic data are consistent with those reported in the literature.[311]

Lab book reference: djbI3/37

(4*R*,5*R*)-4,5-Dihydroxy-3-methylcyclohex-2-enone *ent*-115

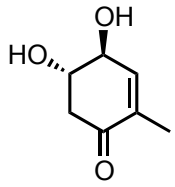


A solution of β-methyl enone *ent*-**117** (30 mg, 0.12 mmol) in TFA (2 mL) and water (200 μL) was stirred at rt for 15 min. The solvent was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with EtOAc as eluent gave diol *ent*-**115** (15 mg, 90%) as a colourless oil, $[\alpha]_D$

−166.8 (*c* 0.5 in MeOH)((Lit.,[311] +11.3 (*c* 0.01 in MeOH) for a ~60:40 mixture of (*S*,*S*)-**115** and (*R*,*R*)-**115** isolated from *Lasiodiplodia theobromae*); R_F (EtOAc) 0.19.

Lab book reference: djbI3/22

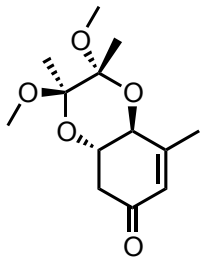
(4*S*,5*S*)-4,5-Dihydroxy-2-methylcyclohex-2-enone 116



A solution of α-methyl enone **118** (15 mg, 0.06 mmol) in TFA (1 mL) and water (100 μL) was stirred at rt for 15 min. The solvent was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with EtOAc as eluent gave diol **116** (7 mg, 84%) as a colourless oil, $[\alpha]_D$ +141.4 (*c* 0.7 in MeOH)(Lit.,[190] +11.3 (*c* 0.01 in MeOH)); R_F (EtOAc) 0.16; IR (Thin Film) 3327 (OH), 1642 (C=O), 1051, 883 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ: 6.62 (dq, *J* = 2.5, 1.5 Hz, 1H, =CH), 4.21–4.17 (m, 1H, CHO), 3.79 (ddd, *J* = 11.5, 7.5, 4.5 Hz, 1H, CHO), 2.69 (dd, *J* = 16.0, 4.5 Hz, 1H, CH_AH$_B$), 2.39 (dd, *J* = 16.0, 11.5 Hz, 1H, CH$_A$$H_B$), 1.73 (dd, *J* = 2.0, 1.5 Hz, 3H, Me); ^{13}C NMR (100.6 MHz; CD_3OD) δ: 198.5 (C=O), 146.8 (=CH), 135.4 (=*C*Me), 72.3 (CHO), 72.1 (CHO), 44.1 (CH_2), 13.9 (Me); MS (ESI) 296 (34), 200 (63), 143 [$(M + H)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_7H_{10}O_3$ $(M + H)^+$ 143.0703, found 143.0698 (3.6 ppm error). Spectroscopic data are consistent with those reported in the literature.[190]

Lab book reference: djbI3/40

(2*R*,3*R*,4a*S*,8a*S*)-2,3-Dimethoxy-2,3,8-trimethyl-2,3,4a,5-tetrahydrobenzo[*b*][1,4]dioxin-6(8a*H*)-one 117

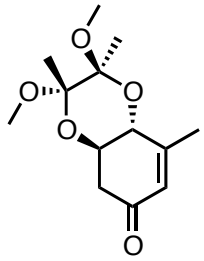


MeLi (620 μL of a 1.6 M solution in hexanes, 0.99 mmol) was added dropwise over 15 min to a vigorously stirred suspension of CuCN (44 mg, 0.50 mmol) in THF (2 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 20 min. Then, a premixed solution of enone **71** (100 mg, 0.41 mmol) and Me_3SiCl (63 μL, 0.50 mmol) in THF (5 mL) was added dropwise over 30 min to give a yellow solution. After stirring for 1 h saturated $NaHCO_{3(aq)}$ (10 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude silyl enol ether. $Pd(OAc)_2$ (9 mg, 0.08 mmol) was added to a stirred solution of the crude silyl enol ether in DMSO (2 mL) and the resulting mixture was stirred at rt under O_2 for 20 h. Then, saturated $NH_4Cl_{(aq)}$ (10 mL) and CH_2Cl_2 (10 mL) were added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (5 × 10 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with petrol-EtOAc (4:1) as eluent gave β-substituted enone **117** (97 mg, 92%) as a white solid, mp 130–132 °C; $[\alpha]_D$ −121.1 (*c* 1.0 in $CHCl_3$); R_F (4:1 petrol-EtOAc) 0.22; IR (Thin Film) 2946, 2846, 2809, 1642 (C=O), 1359, 1108, 1065 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 5.85 (dq, *J* = 2.5, 1.0 Hz, 1H, =CH), 4.39 (ddq, *J* = 9.0, 2.5, 1.0 Hz, 1H, CHO), 4.05 (ddd, *J* = 13.5, 9.0, 5.0 Hz, 1H, CHO), 3.31 (s, 3H, OMe), 3.26 (s, 3H, OMe), 2.70 (ddd, *J* = 16.0, 5.0, 1.0 Hz, 1H, CH_AH$_B$), 2.48 (dd, *J* = 16.0, 13.5 Hz, 1H, CH$_A$$H_B$), 2.05 (t, *J* = 1.0 Hz, 3H, Me), 1.37 (s, 3H, Me), 1.33 (s, 3H, Me); ^{13}C NMR (100.6 MHz; $CDCl_3$) δ: 196.0 (C=O), 160.4 (=*C*Me), 127.5 (=CH), 100.7 (OCO), 99.7 (OCO), 71.0 (CHO), 67.8 (CHO), 48.19 (OMe), 48.16 (OMe), 42.2 (CH_2), 18.1 (Me), 17.8 (2 × Me); MS (ESI) 279 [$(M + Na)^+$, 75], 257 [$(M + H)^+$, 100], 225 (71), 193 (55); HRMS (ESI) *m/z* calcd for $C_{13}H_{20}O_5$ $(M + H)^+$

257.1384, found 257.1383 (0.3 ppm error).

Lab book reference: djbI3/36

(2*S*,3*S*,4a*R*,8a*R*)-2,3-Dimethoxy-2,3,8-trimethyl-2,3,4a,5-tetrahydrobenzo[*b*][1,4]dioxin-6(8a*H*)-one ***ent*-117**



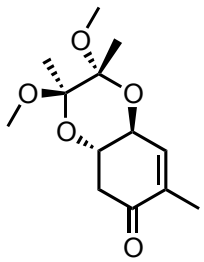
MeLi (3.18 mL of a 1.53 M solution in hexanes, 4.96 mmol) was added dropwise over 15 min to a vigorously stirred suspension of CuCN (222 mg, 2.48 mmol) in THF (25 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 20 min. Then, a premixed solution of enone *ent*-**71** (500 mg, 2.07 mmol) and Me_3SiCl (314 μL, 2.48 mmol) in THF (17 mL) was added dropwise over 30 min to give a yellow solution. After stirring for 1 h, a mixture of saturated $NaHCO_{3(aq)}$ and Et_3N (30:1, 50 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude silyl enol ether. $Pd(OAc)_2$ (93 mg, 0.41 mmol) was added to a stirred solution of the crude silyl enol ether in DMSO (20 mL) at rt under O_2. The resulting mixture was stirred at rt for 20 h under O_2. Then, saturated $NH_4Cl_{(aq)}$ (50 mL) and CH_2Cl_2 (30 mL) were added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (5 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with petrol-EtOAc (4:1) as eluent gave β-substituted enone *ent*-**117** (507 mg, 96%) as a white solid, mp 130–132 °C; $[\alpha]_D$ +116.2 (*c* 0.9 in CH_2Cl_2); R_F (4:1 petrol-EtOAc) 0.22.

Lab book reference: djb2/49

MeLi (744 μL of a 1.6 M solution in hexanes, 1.19 mmol) was added dropwise over 15 min to a vigorously stirred suspension of CuCN (44 mg, 0.50 mmol) in THF (5 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 20 min. Then, a premixed solution of enone *ent*-**71** (100 mg, 0.41 mmol) and Me_3SiCl (108 μL, 0.99 mmol) in THF (5 mL) was added dropwise over 30 min to give a yellow solution. After stirring for 30 min, a mixture of saturated $NaHCO_{3(aq)}$ and Et_3N (30:1, 20 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude silyl enol ether. $Pd(OAc)_2$ (111 mg, 0.50 mmol) was added to a stirred solution of the crude silyl enol ether in MeCN (5 mL) at rt under Ar. The resulting mixture was stirred at rt for 20 h. Then, saturated $NH_4Cl_{(aq)}$ (20 mL) and CH_2Cl_2 (20 ml) were added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (5 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with petrol-EtOAc (4:1) as eluent gave β-substituted enone *ent*-**117** (64 mg, 61%) as a colourless oil.

Lab book reference: djb2/90

(2*R*,3*R*,4a*S*,8a*S*)-2,3-Dimethoxy-2,3,7-trimethyl-2,3,4a,5-tetrahydrobenzo[*b*][1,4]dioxin-6(8a*H*)-one 118



Palladium catalyst **120** (20 mg, 0.03 mmol) was added to a stirred solution of iodoenone **119** (90 mg, 0.25 mmol) and Me_4Sn (136 μL, 0.98 mmol) in THF (5 mL) at rt under Ar in a sealed tube. The resulting mixture was heated at 100 °C for 24 h. After cooling to rt, saturated $Na_2S_2O_{3(aq)}$ (10 mL) was added. The mixture was extracted with Et_2O (3 × 10 mL) and the combined organics were extracted with 10% $KF_{(aq)}$ (30 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the

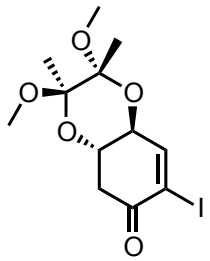
crude product. Purification by flash column chromatography on silica with petrol-EtOAc (4:1) as eluent gave α-methyl enone **118** (50 mg, 79%) as a white solid, mp 193 °C; $[\alpha]_D$ −30.1 (*c* 0.5 in $CHCl_3$); R_F (4:1 petrol-EtOAc) 0.38; IR (Thin Film) 1648 (C=O), 1131, 1019, 880 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 6.61 (q, *J* = 1.5 Hz, 1H, =CH), 4.44 (d, *J* = 9.0, 2.0 Hz, 1H, CHO), 3.98 (ddd, *J* = 13.5, 9.0, 5.0 Hz, 1H, CHO), 3.30 (s, 3H, OMe), 3.24 (s, 3H, OMe), 2.74 (dd, *J* = 16.5, 5.0 Hz, 1H, CH_AH$_B$), 2.46 (dd, *J* = 16.5, 13.5 Hz, 1H, CH$_A$$H_B$), 1.77 (dd, *J* = 2.0, 1.5 Hz, 1H, =CMe), 1.35 (s, 3H, Me), 1.32 (s, 3H, Me); ^{13}C NMR (100.6 MHz; CDCl3) δ: 196.9 (C=O), 143.5 (=CH), 136.9 (=*C*Me), 100.7 (OCO), 99.8 (OCO), 69.3 (CHO), 68.3 (CHO), 48.21 (OMe), 48.14 (OMe), 41.9 (CH_2), 17.9 (Me), 17.8 (Me), 15.4 (Me); MS (ESI) 320 (25), 279 [$(M + Na)^+$, 18], 266 (100), 257 (51); HRMS (ESI) *m/z* calcd for $C_{13}H_{20}O_5$ $(M + H)^+$ 257.1384, found 257.1377 (2.4 ppm error), calcd for $C_{13}H_{20}O_5$ $(M + Na)^+$ 279.1203, found 279.1208 (−1.9 ppm error).

Lab book reference: djbI3/45

Ph_3As (18 mg, 0.06 mmol), $Pd_2(dba)_3$ (26 mg, 0.03 mmol), CuI (20 mg, 0.11 mmol) and Et_2NH (84 μL, 0.81 mmol) were added to a stirred solution of iodoenone **119** (100 mg, 0.27 mmol) in THF (5 mL), at rt under Ar in a sealed tube. After stirring for 10 min, Me_4Sn (150 μL, 1.08 mmol) was added and the resulting mixture was stirred and heated at 100 °C for 72 h. After cooling, 10% $Na_2SO_{3(aq)}$ (10 mL) and Et_2O (10 mL) were added and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 10 mL) and the combined organics were extracted with 10% $KF_{(aq)}$ (30 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with petrol-EtOAc (4:1) as eluent gave α-methyl enone **118** (22 mg, 32%) as a white solid and enone **71** (17 mg, 17%).

Lab book reference: djbI3/38

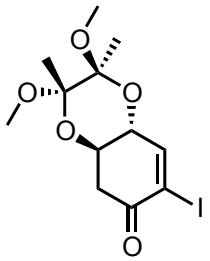
(2*R*,3*R*,4a*S*,8a*S*)-7-Iodo-2,3-dimethoxy-2,3-dimethyl-2,3,4a,5-tetrahydrobenzo[*b*][1,4]dioxin-6(8a*H*)-one 119



Iodine (419 mg, 1.65 mmol) and DMAP (1 crystal) were added to a stirred solution of enone **71** (200 mg, 0.83 mmol) in pyridine and CCl_4 (1:1, 5 mL) at rt. The resulting mixture was stirred at rt for 2 h. Then, saturated $Na_2S_2O_{3(aq)}$ (20 mL) and Et_2O (20 mL) were added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with petrol-EtOAc (4:1) as eluent gave iodoenone **119** (278 mg, 92%) as a white solid, mp 188–190 °C; $[\alpha]_D$ −55.9 (*c* 1.0 in $CHCl_3$); R_F (4:1 petrol-EtOAc) 0.70; IR (Thin Film) 1654 (C=O), 1125, 881, 786 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.63 (d, *J* = 2.0 Hz, 1H, =CH), 4.48 (dd, *J* = 9.0, 2.0 Hz, 1H, CHO), 4.06 (ddd, *J* = 13.5, 9.0, 5.0 Hz, 1H, CHO), 3.31 (s, 3H, OMe), 3.26 (s, 3H, OMe), 2.98 (dd, *J* = 16.5, 5.0 Hz, 1H, CH_AH$_B$), 2.62 (dd, *J* = 16.5, 13.5 Hz, 1H, CH$_A$$H_B$), 1.36 (s, 3H, Me), 1.33 (s, 3H, Me); ^{13}C NMR (100.6 MHz; $CDCl_3$) δ: 189.7 (C=O), 156.6 (=CH), 103.6 (=CI), 100.8 (OCO), 99.6 (OCO), 71.0 (CHO), 67.4 (CHO), 48.14 (OMe), 48.04 (OMe), 39.7 (CH_2), 17.49 (Me), 17.42 (Me); MS (ESI) 390 [$(M + Na)^+$, 22], 369 [$(M + H)^+$, 25], 432 (100); HRMS (ESI) *m/z* calcd for $C_{12}H_{17}IO_5$ $(M + H)^+$ 369.0193, found 369.0202 (−2.4 ppm error). Spectroscopic data are consistent with those reported in the literature.[119]

Lab book reference: djbI3/35

(2*S*,3*S*,4a*R*,8a*R*)-7-Iodo-2,3-dimethoxy-2,3-dimethyl-2,3,4a,5-tetrahydrobenzo[*b*][1,4]dioxin-6(8a*H*)-one *ent*-119



Iodine (4.20 g, 16.52 mmol) and DMAP (1 crystal) were added to a stirred solution of enone *ent*-**71** (2.0 g, 4.26 mmol) in pyridine and CCl_4 (1:1, 20 mL) at rt. The resulting mixture was stirred at rt for 2 h. Then, saturated $Na_2S_2O_{3(aq)}$ (30 mL) and Et_2O (30 mL) were added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (5 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to gave the crude product. Purification by flash column chromatography on silica with petrol-EtOAc (4:1) as eluent gave iodoenone *ent*-**119** (2.82 g, 93%) as a white solid, mp 188–190 °C (lit.,[98] 190–192 °C); $[\alpha]_D$ +62.4 (*c* 0.5 in CH_2Cl_2) (lit.,[98] +64.4, (*c* 0.39 in CH_2Cl_2)); MS (ESI) 390 [$(M + Na)^+$, 22], 369 [$(M + H)^+$, 25], 432 (100); HRMS (ESI) *m/z* calcd for $C_{12}H_{17}IO_5$ $(M + H)^+$ 369.0193, found 369.0202 (−2.4 ppm error). Spectroscopic data are consistent with those reported in the literature.[98]

Lab book reference: djb1/47

(2*S*,3*S*,4a*R*,8a*R*)-8-Butyl-2,3-dimethoxy-2,3-dimethyl-2,3,4a,5-tetrahydrobenzo[*b*][1,4]dioxin-6(8a*H*)-one 124

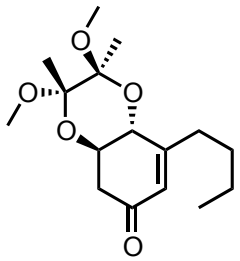


Table 3.1, entry 3

n-BuLi (3.24 mL of a 1.53 M solution in hexanes, 4.96 mmol) was added dropwise over 15 min to a vigorously stirred suspension of CuCN (222 mg, 2.48 mmol) in THF (25 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 20 min. Then, a premixed solution of enone *ent*-**71** (500 mg, 2.07 mmol) and Me_3SiCl (314 μL, 2.48 mmol) in THF (17 mL) was added dropwise over 30 min to give a yellow solution. After stirring for 30 min, a mixture of saturated $NaHCO_{3(aq)}$ and Et_3N (30:1, 50 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude silyl enol ether. $Pd(OAc)_2$ (93 mg, 0.41 mmol) was added to a stirred solution of the crude silyl enol ether in DMSO (20 mL) at rt under O_2. The resulting mixture was stirred at rt for 20 h under O_2. Then, saturated $NH_4Cl_{(aq)}$ (50 mL) and CH_2Cl_2 (30 mL) were added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (5 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with petrol-EtOAc (4:1) as eluent gave β-substituted enone **124** (507 mg, 82%) as a colourless oil, $[\alpha]_D$ +98.1 (*c* 0.9 in CH_2Cl_2); R_F (4:1 petrol-EtOAc) 0.41; IR (Thin Film) 2956, 1677 (C=O), 1378, 1270, 1082, 886 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 5.83 (dq, *J* = 2.5, 1.0 Hz, 1H, =CH), 4.45 (ddt, *J* = 9.0, 2.5, 1.0 Hz, 1H, CHO), 4.04 (ddd, *J* = 13.5, 9.0, 5.0 Hz, 1H, CHO), 3.33 (s, 3H, OMe), 3.26 (s, 3H, OMe), 2.69 (ddd, *J* = 16.0, 5.0, 1.0 Hz, 1H, C*H*$_A$H$_B$), 2.49–2.31 (m, 2H), 2.47 (dd, *J* = 16.0, 13.5 Hz, 1H, CH$_A$*H*$_B$), 1.55–1.28 (m, 4H), 1.37 (s, 3H, Me), 1.33 (s, 3H, Me), 0.92 (t, *J* = 7.0 Hz, 3H, CH_2*Me*); ^{13}C NMR (100.6 MHz; $CDCl_3$) δ: 196.1 (C=O), 164.3 (=C), 125.9 (=CH), 100.5 (OCO), 99.4 (OCO), 70.2 (CHO), 67.8 (CHO), 48.3 (OMe), 48.0

(OMe), 42.0 (*C*H_2CO), 30.7 (CH_2), 29.1 (CH_2), 22.4 (CH_2), 17.7 (Me), 17.6 (Me), 13.8 (CH_2*Me*); MS (ESI) 321 [$(M + Na)^+$, 58], 299 [$(M + H)^+$, 100], 267 (32), 235 (50); HRMS (ESI) *m/z* calcd for $C_{16}H_{26}O_5$ $(M + H)^+$ 299.1853, found 299.1852 (0.5 ppm error).

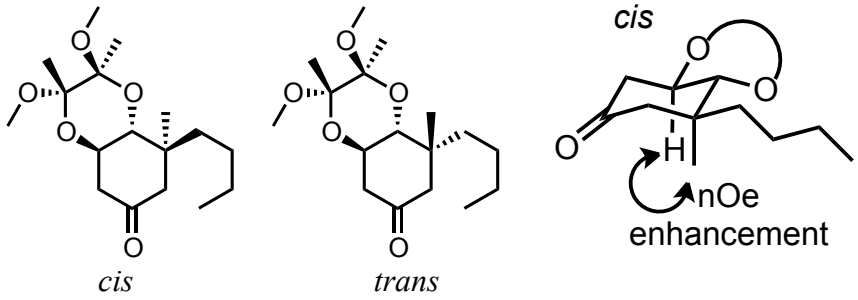
Lab book reference: djb1/43

Table 6.1, entry 1

n-BuLi (744 μL of a 1.6 M solution in hexanes, 1.19 mmol) was added dropwise over 15 min to a vigorously stirred suspension of CuCN (44 mg, 0.50 mmol) in THF (5 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 20 min. Then, a premixed solution of enone *ent*-**71** (100 mg, 0.41 mmol) and Me_3SiCl (108 μL, 0.99 mmol) in THF (5 mL) was added dropwise over 30 min to give a yellow solution. After stirring for 30 min, a mixture of saturated $NaHCO_{3(aq)}$ and Et_3N (30:1, 20 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude silyl enol ether. $Pd(OAc)_2$ (111 mg, 0.50 mmol) was added to a stirred solution of the crude silyl enol ether in MeCN (5 mL) at rt under Ar. The resulting mixture was stirred at rt for 20 h. Then, saturated $NH_4Cl_{(aq)}$ (20 mL) and CH_2Cl_2 (20 ml) were added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (5 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with petrol-EtOAc (4:1) as eluent gave β-substituted enone **124** (69 mg, 56%) as a colourless oil.

Lab book reference: djb1/38

(2*S*,3*S*,4a*R*,8*R*,8a*R*)- and (2*S*,3*S*,4a*R*,8*S*,8a*R*)-8-Butyl-2,3-dimethoxy-2,3,8-trimethylhexahydrobenzo[b][1,4]dioxin-6(7H)-one *cis*-125 and *trans*-125



Using general procedure C at −78 °C, *n*-BuLi (2.07 mL of a 2.5 M solution in hexanes, 5.18 mmol) and CuCN (233 mg, 2.60 mmol) in THF (26 mL), and a premixed solution of enone *ent*-**117** (555 mg, 2.17 mmol) and Me_3SiCl (550μL, 4.33 mmol) in THF (19 mL), followed by TBAF (2.4 mL of a 1.0 M solution in THF, 2.4 mmol) in CH_2Cl_2 (10 mL) gave the crude product. Purification by flash column chromatography on silica with petrol-EtOAc (4:1) as eluent gave (by ^1H NMR spectroscopy) an 85:15 mixture of β-disubstituted ketones *cis*-**125** and *trans*-**125** (287 mg, 42%) as a colourless oil, R_F (4:1 petrol-EtOAc) 0.43; IR (Thin Film) 2955, 1720 (C=O), 1461, 1378, 1212, 1121, 1048, 884 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 4.01 (ddd, J = 12.0, 10.0, 6.0 Hz, 0.15H, CHO_{trans}), 3.98 (ddd, J = 12.0, 10.0, 6.0 Hz, 0.85H, CHO_{cis}), 3.77 (d, J = 10.0 Hz, 0.85H, CHO_{cis}), 3.71 (d, J = 10.0 Hz, 0.15H, CHO_{trans}), 3.29 (s, 2.55H, OMe_{cis}), 3.28 (s, 0.45H, OMe_{trans}), 3.22 (s, 0.45H, OMe_{trans}), 3.21 (s, 2.55H, OMe_{cis}), 2.61–2.09 (m, 4H), 1.62–0.83 (m, 18H); ^{13}C NMR (100.6 MHz; $CDCl_3$) (OMe_{trans}, 3 × Me and 2 × CH_2 resonances not resolved) δ: 207.5 ($C{=}O_{cis}$), 207.1 ($C{=}O_{trans}$), 99.9 (OCO_{cis}), 99.8 (OCO_{trans}), 99.5 (OCO_{cis}), 99.4 (OCO_{trans}), 74.7 (CHO_{cis}), 77.3 (CHO_{trans}), 65.6 (CHO_{cis}), 65.2 (CHO_{trans}), 51.3 (CH_{2cis}), 48.1 (OMe_{cis}), 47.9 (OMe_{cis}), 47.8 (OMe_{trans}), 45.2 (CH_{2cis}), 39.4 (C_{cis}), 38.1 (C_{trans}), 37.9 (CH_{2cis}), 32.0 (CH_{2trans}), 25.7 (CH_{2trans}), 25.4 (CH_{2cis}), 24.1 (CH_{2trans}), 23.4 (CH_{2cis}), 18.6 (Me_{cis}), 17.8 (Me_{cis}), 17.7 (Me_{trans}), 14.2 (Me_{trans}), 14.1 (Me_{cis}); MS (ESI) 337 [$(M + Na)^+$, 100], 283 (44); HRMS (ESI) *m/z* calcd for $C_{17}H_{30}O_5$ $(M + Na)^+$ 337.1985, found 37.1997 (−3.3 ppm error).

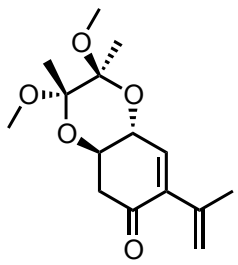
The relative stereochemistry was assigned by the nOe enhancement indicated.

Lab book ref: djb2/51/2

Using general procedure C at −78 °C, MeLi (2.7 mL of a 1.5 M solution in Et_2O, 4.05 mmol) and CuCN (182 mg, 2.03 mmol) in THF (20 mL), and a premixed solution of enone **124** (200 mg, 1.69 mmol) and Me_3SiCl (429 μL, 3.38 mmol) in THF (15 mL) followed by TBAF (1.9 mL of a 1.0 M solution in THF, 1.90 mmol) in CH_2Cl_2 (10 mL) gave the crude product. Purification by flash column chromatography on silica with petrol-EtOAc (4:1) as eluent gave (by ^{1}H NMR spectroscopy) a 62:38 mixture of β-disubstituted ketones *cis*-**125** and *trans*-**125** (364 mg, 69%) as a colourless oil**.**

Lab book ref: djb2/52

(2*S*,3*S*,4a*R*,8a*R*)-2,3-Dimethoxy-2,3-dimethyl-7-(prop-1-en-2-yl)-2,3,4a,5-tetrahydrobenzo[*b*][1,4]dioxin-6(8a*H*)-one 135

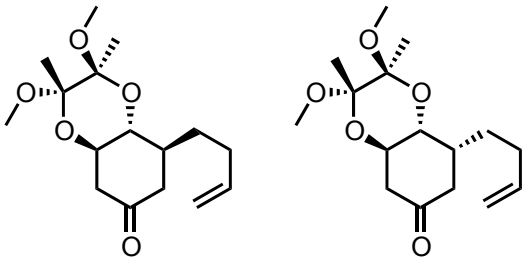


(*Z*)-Propenyl MIDA boronic ester **72** (42 mg, 0.22 mmol), palladium catalyst **120** (8 mg, 0.01 mmol) and K_3PO_4 (504 μL of a 3 M solution in water, 1.51 mmol) were added sequentially to a stirred solution of iodoenone *ent*-**199** (72 mg, 0.20 mmol) in THF (7 mL) at rt under Ar. The resulting mixture was stirred and heated at reflux for 52 h. Then, water (10 mL) and CH_2Cl_2 (10 mL) were added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (5 × 10 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with CH_2Cl_2-Et_2O (99:1) as eluent gave propenyl enone **135** (44 mg, 80%) as a yellow oil, R_F (4:1 petrol-EtOAc) 0.33; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.72 (d, J = 2.0 Hz, 1H, CH=CCO), 5.21 (s, 1H, =CH_AH$_B$), 5.09 (t, J = 2.0 Hz, 1H, =CH$_A$$H_B$), 4.49 (dd, J = 9.0, 2.0 Hz, 1H, CHO), 4.02 (ddd, J = 13.5, 9.0, 5.0 Hz, 1H, CHO), 3.33 (s, 3H, OMe), 3.27 (s, 3H, OMe), 2.79 (dd, J = 16.5, 5.0 Hz, 1H, CH_AH$_B$), 2.50 (dd, J = 16.5, 13.5 Hz, 1H, CH$_A$$H_B$), 1.89 (br s, 3H, =CMe), 1.37 (s, 3H, Me), 1.33 (s, 3H,

Me); ^{13}C NMR (100.6 MHz; $CDCl_3$) δ: 195.6 (C=O), 143.3 (*C*H=CCO), 142.0 (=C), 139.8 (=C), 117.1 (=CH_2), 100.2 (OCO), 99.6 (OCO), 69.2 (CHO), 67.6 (CHO), 48.2 (OMe), 48.1 (OMe), 42.5 (CH_2), 22.2 (=CMe), 17.7 (Me), 17.6 (Me); MS (ESI) 305 [$(M + Na)^+$, 100], 322 (16); HRMS (ESI) *m/z* calcd for $C_{15}H_{22}O_5$ $(M + Na)^+$ 305.1359, found 305.1355 (1.6 ppm error).

Lab book reference: djb1/54

(2*S*,3*S*,4a*R*,8*S*,8a*R*)- and (2*S*,3*S*,4a*R*,8*R*,8a*R*)-8-(But-3-enyl)-2,3-dimethoxy-2,3-dimethylhexahydrobenzo[*b*][1,4]dioxin-6(7*H*)-one *trans*-142 and *cis*-142



trans *cis*

Table 3.2, entry 1

Using general procedure E, butenyl magnesium bromide **146** (12 mL of a 0.08 M solution in THF, 0.99 mmol) [prepared from bromobut-1-ene (101 μL, 0.99 mmol) and magnesium turnings (36 mg, 1.49 mmol) in THF (12 mL) according to general procedure F] and CuBr·SMe_2 (17 mg, 0.08 mmol) in THF (5 mL), and a premixed solution of enone *ent*-**71** (100 mg, 0.41 mmol) and Me_3SiCl (57 μL, 0.45 mmol) in THF (4 mL), followed by TBAF (454 μL of a 1.0 M solution in THF, 0.45 mmol) in CH_2Cl_2 (10 mL) gave the crude product. Purification by flash column chromatography on silica with petrol-EtOAc (4:1) as eluent gave (by ^{1}H NMR spectroscopy) a 96:4 mixture of β-substituted ketones *trans*-**142** and *cis*-**142** (113 mg, 92%) as a colourless oil, R_F (4:1 petrol-EtOAc) 0.31; data for *trans*-**142** ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.74 (ddt, *J* = 17.0, 10.0, 6.0 Hz, 1H, C*H*=CH_2), 4.98 (ddd, *J* = 17.0, 3.0, 1.5 Hz, 1H, =C$H_A$$H_B$), 4.73 (br d, *J* = 10.0 Hz, 1H, =CH_AH_B), 3.74 (ddd, *J* = 12.5, 10.0, 6.0 Hz, 1H, CHO), 3.57 (t, *J* = 10.0 Hz, 1H, CHO), 3.27 (s, 3H, OMe), 3.20 (s, 3H, OMe), 2.58–2.37 (m, 3H), 2.17–1.88 (m, 4H), 1.84–1.72 (m, 1H), 1.35–1.16 (m, 7H).

Lab book reference: djb2/9

Table 3.2, entry 2

Using general procedure E, butenyl magnesium bromide **146** (12 mL of a 0.08 M solution in THF, 0.99 mmol) [prepared from bromobut-1-ene (101 μL, 0.99 mmol) and magnesium turnings (36 mg, 1.49 mmol) in THF (12 mL) according to general procedure F] and CuCN (8 mg, 0.08 mmol) in THF (5 mL), and a premixed solution of enone *ent*-**71** (100 mg, 0.41 mmol) and Me_3SiCl (57 μL, 0.45 mmol) in THF (4 mL), followed by TBAF (454 μL of a 1.0 M solution in THF, 0.45 mmol) in CH_2Cl_2 (10 mL) gave the crude product. Purification by flash column chromatography on silica with petrol-EtOAc (4:1) as eluent gave (by ^1H NMR spectroscopy) a 56:44 mixture of β-substituted ketones *trans*-**142** and *cis*-**142** (78 mg, 64%) as a colourless oil, R_F (4:1 petrol-EtOAc) 0.31; R_F (4:1 petrol-EtOAc) 0.31; ^1H NMR (400 MHz, $CDCl_3$) δ: 5.79–5.08 (m, 1H, C*H*=CH_2), 5.01–4.94 (m, 1H, =C$H_A$$H_B$), 4.94–4.90 (m, 1H, =$CH_A$$H_B$), 3.98–3.88 (m, 0.88 H, 2 × CHO_{cis}), 3.74 (ddd, *J* = 12.5, 10.0, 6.0 Hz, 0.56H, CHO_{trans}), 3.57 (t, *J* = 10.0 Hz, 0.56H, CHO_{trans}), 3.27 (s, 1.68H, OMe_{trans}), 3.26 (s, 1.32H, OMe_{cis}), 3.20 (s, 1.68H, OMe_{trans}), 3.18 (s, 1.32H, OMe_{cis}), 2.58–2.37 (m, 3H), 2.17–1.88 (m, 4H), 1.84–1.72 (m, 1H), 1.35–1.16 (m, 1H), 1.31 (s, 1.68H, Me_{trans}), 1.28 (s, 1.68H, Me_{trans}), 1.27 (s, 1.32H, Me_{cis}), 1.26 (s, 1.32H, Me_{cis}).

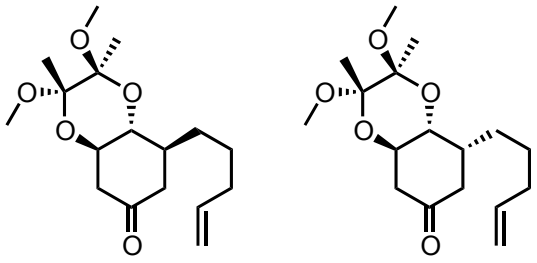
Lab book reference: djb2/8

Table 3.2, entry 3

Using general procedure E, butenyl magnesium bromide **146** (60 mL of a 0.17 M solution in THF, 9.91 mmol) [prepared from bromobut-1-ene (1.34 mL, 9.91 mmol) and magnesium turnings (361 mg, 14.86 mmol) in THF (60 mL) according to general procedure F] and CuBr·SMe_2 (340 mg, 1.65 mmol) in THF (100 mL), and a premixed solution of enone *ent*-**71** (2.0 g, 8.26 mmol) and Me_3SiCl (1.15 mL, 9.09 mmol) in THF (66 mL), followed by TBAF (9.91 mL of a 1.0 M solution in THF, 9.91 mmol) in CH_2Cl_2 (50 mL) gave the crude product. Purification by flash column chromatography on silica with petrol-EtOAc (4:1) as eluent gave (by ^1H NMR spectroscopy) a 55:45 mixture of β-substituted ketones *trans*-**142** and *cis*-**142** (1.21 g, 49%) as a colourless oil.

Lab book reference: djb2/18

(2*S*,3*S*,4a*R*,8*S*,8a*R*)- and (2*S*,3*S*,4a*R*,8*R*,8a*R*)-2,3-Dimethoxy-2,3-dimethyl-8-(pent-4-enyl)hexahydrobenzo[*b*][1,4]dioxin-6(7*H*)-one *trans*-143 and *cis*-143



trans *cis*

Table 3.3, entry 1

Using general procedure C at –78 °C, pentenyllithium (13.6 mL of a 0.73 M solution in Et_2O, 9.91 mmol) [prepared from bromopent-1-ene (1.19 mL, 10.06 mmol) and lithium granules (132 mg, 22.14 mmol) in Et_2O (15 mL) according to general procedure G], and CuCN (444 mg, 4.96 mmol) in THF (50 mL), and a premixed solution of enone *ent*-**71** (1.0 g, 4.13 mmol) and Me_3SiCl (1.05 mL, 8.26 mmol) in THF (33 mL), followed by TBAF (4.54 mL of a 1.0 M solution in THF, 4.53 mmol) in CH_2Cl_2 (20 mL) gave the crude product. Purification by flash column chromatography on silica with petrol-EtOAc (4:1) as eluent gave (by ^{1}H NMR spectroscopy) a 50:50 mixture of β-substituted ketones *trans*-**143** and *cis*-**143** (1.01 g, 83%) as a colourless oil, R_F (4:1 petrol-EtOAc) 0.47; IR (Thin Film) 2945, 1721 (C=O), 1650 (C=C), 1458, 1121, 1050, 912 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.85–5.73 (m, 1H, C*H*=CH_2), 5.02–4.91 (m, 2H, CH=CH_2), 4.00–3.90 (m, 1H, CHO_{cis} and CHO_{cis}), 3.77 (ddd, *J* = 12.5, 9.5, 6.0 Hz, 0.5H, CHO_{trans}), 3.59 (t, *J* = 9.5 Hz, 0.5H, CHO_{trans}), 3.30 (s, 1.5H, OMe), 3.29 (s, 1.5H, OMe), 3.24 (s, 1.5H, OMe), 3.22 (s, 1.5H, OMe), 2.62–2.41 (m, 3.5H), 2.11–1.90 (m, 3.5H), 1.84–1.73 (m, 1H), 1.55–1.36 (m, 1H), 1.36–1.11 (m, 7.5H), 0.99–0.88 (m, 0.5H), ^{13}C NMR (100.6 MHz; $CDCl_3$) (OMe resonance not resolved) δ: 207.4 ($C{=}O_{cis}$), 206.3 ($C{=}O_{trans}$), 138.4 ($CH{=}CH_{2cis}$), 138.3 ($CH{=}CH_{2trans}$), 114.5 ($CH{=}CH_{2trans}$), 114.4 ($CH{=}CH_{2cis}$), 99.6 (OCO_{cis}), 99.5 (OCO_{trans}), 99.3 (OCO_{trans}), 98.9 (OCO_{cis}), 73.3 (CHO_{trans}), 71.7 (CHO_{cis}), 68.3 (CHO_{trans}), 64.5 (CHO_{cis}), 47.88 (OMe), 47.85 (OMe), 47.79 (OMe), 44.84 (CH_2), 44.82 (CH_2), 44.79 (CH_2), 43.9 (CH_2), 36.7 (CH_{cis}), 36.4 (CH_{trans}), 33.7 (CH_2), 33.5 (CH_2), 30.4 (CH_2), 27.0 (CH_2), 26.4 (CH_2), 25.4 (CH_2), 17.64 (Me), 17.59 (Me), 17.57 (Me), 17.52 (Me); MS (ESI) 335 [$(M + Na)^+$, 26], 281 (100);

HRMS (ESI) *m/z* calcd for $C_{17}H_{28}O_5$ $(M + Na)^+$ 335.1829, found 335.1826 (0.9 ppm error).

Lab book reference: djb2/46, djb2/47

Table 3.3, entry 2

Using general procedure C at –78 °C, pentenyllithium (7.00 mL of a 0.70 M solution in Et_2O, 4.90 mmol) [prepared from bromopent-1-ene (1.19 mL, 10.06 mmol) and lithium granules (132 mg, 22.14 mmol) in Et_2O (15 mL) according to general procedure G], and CuCN (219 mg, 2.45 mmol) in THF (25 mL), and a premixed solution of enone *ent*-**71** (494 mg, 2.04 mmol) and Me_3SiCl (519 μL, 4.08 mmol) in THF (16 mL), followed by TBAF (2.25 mL of a 1.0 M solution in THF, 2.25 mmol) in CH_2Cl_2 (40 mL) gave the crude product. Purification by flash column chromatography on silica with petrol-EtOAc (4:1) as eluent gave (by ^1H NMR spectroscopy) a 50:50 mixture of β-substituted ketones *trans*-**143** and *cis*-**143** (571 mg, 89%) as a colourless oil.

Lab book reference: djb2/62, djb2/61

Table 3.3, entry 3

Using general procedure C at –78 °C, pentenyllithium (8.75 mL of a 0.62 M solution in Et_2O, 5.46 mmol) [prepared from bromopent-1-ene (1.19 mL, 10.06 mmol) and lithium granules (132 mg, 22.14 mmol) in Et_2O (15 mL) according to general procedure G], and CuCN (244 mg, 2.73 mmol) in THF (27 mL), and a premixed solution of enone *ent*-**71** (551 mg, 2.28 mmol) and Me_3SiCl (577 μL, 4.55 mmol) in THF (18 mL), followed by TBAF (2.50 mL of a 1.0 M solution in THF, 2.50 mmol) in CH_2Cl_2 (40 mL) gave the crude product. Purification by flash column chromatography on silica with petrol-EtOAc (4:1) as eluent gave (by ^1H NMR spectroscopy) a 93:7 mixture of β-substituted ketones *trans*-**26** and *cis*-**26** (617 mg, 87%) as a colourless oil.

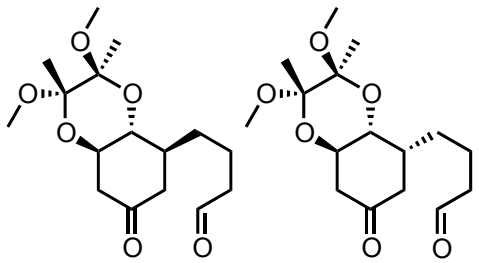
Lab book reference: djb2/69, djb2/70

Table 3.3, entry 4

Using general procedure C at –78 °C pentenyllithium (10.0 mL of a 0.84 M solution in Et_2O, 8.40 mmol) [prepared from bromopent-1-ene (1.19 mL, 10.06 mmol) and lithium granules (132 mg, 22.14 mmol) in Et_2O (15 mL) according to general procedure G] and CuCN (376 mg, 4.20 mmol) in THF (42 mL), and a premixed solution of enone *ent*-**71** (847 mg, 3.50 mmol) and Me_3SiCl (888 μL, 7.00 mmol) in THF (28 mL), followed by TBAF (3.85 mL of a 1.0 M solution in THF, 3.85 mmol) in CH_2Cl_2 (40 mL) gave the crude product. Purification by flash column chromatography on silica with petrol-EtOAc (4:1) as eluent gave (by ^{1}H NMR spectroscopy) a 77:23 mixture of β-substituted ketones *trans*-**143** and *cis*-**143** (993 mg, 91%) as a colourless oil.

Lab book reference: djb2/71 djb2/72

4-((2*S*,3*S*,4a*R*,5*S*,8a*R*)- and 4-((2*S*,3*S*,4a*R*,5*R*,8a*R*)-2,3-Dimethoxy-2,3-dimethyl-7-oxooctahydrobenzo[*b*][1,4]dioxin-5-yl)butanal *trans*-144 and *cis*-144



OsO_4 (101 μL of a 0.0984 M solution in *t*-BuOH, 0.01 mmol) and $NaIO_4$ (274 mg, 1.28 mmol) were added to a stirred solution of a 93:7 mixture of pentenyl β-substituted ketones *trans*-**143** and *cis*-**143** (100 mg, 0.32 mmol) in dioxane and water (3:1, 2.36 mL) at rt under Ar. The resulting suspension was stirred for 1 h at rt. Then, 3 M $HCl_{(aq)}$ (20 mL) and CH_2Cl_2 (20 mL) were added and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with petrol-EtOAc (4:1) as eluent gave aldehyde *trans*-**144** (390 mg, 97%) as a colourless oil, R_F (1:1 petrol-EtOAc) 0.37; IR (Thin Film) 1722 (C=O), 1377, 1212, 1122, 1049 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ:

9.69–9.67 (m, 1H, CHO), 3.93 (dd, J = 10.0, 4.5 Hz, 0.07H, CHO_{cis}), 3.85 (ddd, J = 11.5, 10.0, 5.5 Hz, 0.07H, CHO_{cis}), 3.70 (ddd, J = 12.0, 10.0, 6 Hz, 0.93H, CHO_{trans}), 3.53 (t, J = 9.5 Hz, 0.93H, CHO_{trans}), 3.22 (s, 3H, OMe_{trans} and OMe_{cis}), 3.17 (s, 2.79H, OMe_{trans}), 3.15 (s, 0.21H, OMe_{cis}) 2.55–2.31 (m, 5H), 2.06–1.89 (m, 2H), 1.82–1.67 (m, 2H), 1.58–1.43 (m, 1H), 1.26–1.22 (s, 6H, 2 × Me), 0.91–0.81 (m, 1H); ^{13}C NMR (100.6 MHz; $CDCl_3$) (OMe resonance not resolved) δ: 207.1 (C=O), 205.9 (C=O), 202.1 (CHO), 201.9 (CHO), 99.8 (OCO), 99.6 (OCO), 99.4 (OCO), 99.1 (OCO), 73.4 (CHO), 71.6 (CHO), 68.3 (CHO), 64.6 (CHO), 48.0 (OMe), 47.9 (OMe), 47.9 (OMe), 44.9 (CH_2), 44.9 (CH_2), 44.8 (CH_2), 43.9 (CH_2), 43.8 (CH_2), 43.75 (CH_2), 36.8 (CH), 36.5 (CH), 30.6 (CH_2), 26.6 (CH_2), 20.2 (CH_2), 18.8 (CH_2), 17.74 (Me), 17.72 (Me), 17.63 (Me), 17.60 (Me); MS (ESI) 315 [$(M + H)^+$, 11], 283 (100); HRMS (ESI) *m/z* calcd for $C_{16}H_{26}O_6$ $(M + H)^+$ 315.1802, found 315.1806 (−1.3 ppm error).

Lab book reference: djb2/63

Ozone gas was bubbled through a solution of a 93:7 mixture of pentenyl β-substituted ketones *trans*-**143** and *cis*-**143** (1.01 g, 3.23 mmol) in CH_2Cl_2 (50 mL) at –78 °C (the exhaust gas was quenched in a Drechsel Bottle containing saturated $KI_{(aq)}$ solution). Ozone gas was bubbled through the solution until a blue colour persisted. Then, O_2 was bubbled through the solution until the blue colour subsided. Then, SMe_2 (15 mL, 210.16 mmol) was added and the mixture was then allowed to warm to rt. The resulting solution was stirred at rt for 18 h. The solvent was evaporated under reduced pressure to give aldehyde *trans*-**144** (788 mg, 78%) as a colourless oil.

Lab book reference: djb2/53

DMP (64 mg, 0.15 mmol) was added to a stirred solution of β-substituted keto alcohol *trans*-**147** (41 mg, 0.13 mmol) in CH_2Cl_2 (3 mL) at rt under Ar. The resulting solution was stirred at rt for 2 h. Then, saturated $NaHCO_{3(aq)}$ (5 mL) and saturated $Na_2S_2O_{3(aq)}$ (5 mL) were added and the resulting biphasic mixture was stirred at rt for 1 h. Then, CH_2Cl_2 (10 mL) was added and the layers were separated. The aqueous

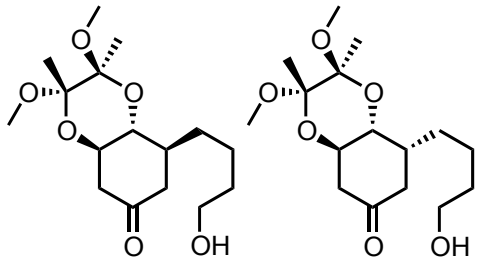
layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with EtOAc as eluent gave keto aldehyde *trans*-**144** (31 mg, 78%) as a colourless oil, R_F (EtOAc) 0.62; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.75 (t, *J* = 1.5 Hz, 1H, CHO), 3.76 (ddd, *J* = 12.5, 9.5, 5.5 Hz, 1H, CHO), 3.59 (t, *J* = 9.5 Hz, 1H, CHO), 3.28 (s, 3H, OMe), 3.23 (s, 3H, OMe), 2.55–2.31 (m, 5H), 2.06–1.89 (m, 2H), 1.82–1.67 (m, 2H), 1.58–1.43 (m, 1H), 1.32 (s, 3H, Me), 1.30 (s, 3H, Me), 0.91–0.81 (m, 1H).

Lab book reference: djb2/30

DMSO (508 μL, 7.16 mmol) was added dropwise to a stirred solution of oxalyl chloride (303 μL, 3.58 mmol) in CH_2Cl_2 (14 mL) at –78 °C under Ar. After stirring for 30 min, a solution of a 96:4 mixture of keto alcohols *trans*-**147** and *cis*-**147** (1.03 g, 3.26 mmol) in CH_2Cl_2 (10 mL) was added dropwise and the solution was stirred for 30 min. Then, Et_3N (2.27 mL, 16.28 mmol) was added and the solution was stirred for 15 min. Then, the reaction was allowed to warm to rt and stirred for 1 h. Then, saturated brine (20 mL) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give (by ^{1}H NMR spectroscopy) a 50:50 mixture of keto aldehydes *trans*-**144** and *cis*-**144** (433 mg, 42%) as a colourless oil.

Lab book reference: djb2/40

(2S,3*S*,4a*R*,8*S*,8a*R*)- and (2*S*,3*S*,4a*R*,8*R*,8a*R*)-8-(4-Hydroxybutyl)-2,3-dimethoxy-2,3-dimethylhexahydrobenzo[*b*][1,4]dioxin-6(7*H*)-one *trans*-147 and *cis*-147



trans *cis*

BH_3·THF (180 μL of a 1.0 M solution in THF, 0.18 mmol) was added dropwise to a stirred solution of a 96:4 mixture of β-substituted ketones *trans*-**142** and *cis*-**142** (44 mg, 0.15 mmol) in THF (3 mL) at rt under Ar. The resulting solution was stirred at rt for 1 h. Then, NaOH (74 μL of a 3 M solution in water, 0.22 mmol) was added dropwise followed by H_2O_2 (77 μL of a 30% w/v solution in water, 0.66 mmol). After stirring for 30 min, saturated brine (10 mL) and CH_2Cl_2 (10 mL) were added and the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with petrol-EtOAc (1:1) as eluent gave (by ^{1}H NMR spectroscopy) alcohol *trans*-**147** (41 mg, 88%) as a colourless oil, R_F (1:1 petrol-EtOAc) 0.34; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.74–3.67 (m, 1H, CHO), 3.62 (t, J = 6.5 Hz, 2H, CH_2OH), 3.53 (ddd, J = 12.0, 9.5, 4.0 Hz, 1H, CHO), 3.24 (s, 3H, OMe), 3.23 (s, 3H, OMe), 2.13–1.96 (m, 2H), 1.98–0.98 (m, 16H).

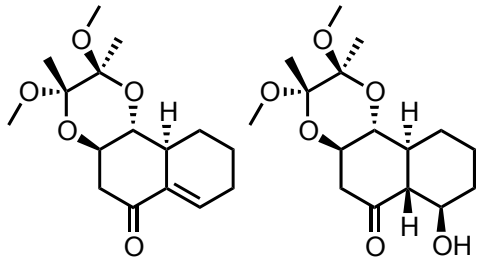
Lab book reference: djb/28

BH_3·THF (4.83 mL of a 1.0 M solution in THF, 4.83 mmol) was added dropwise to a stirred solution of a 55:45 mixture of β-substituted ketones *trans*-**142** and *cis*-**142** (1.2 g, 4.83 mmol) in THF (20 mL) at rt under Ar. The resulting solution was stirred at rt for 1 h. Then, NaOH (6.04 mL of a 3 M solution in water, 18.11 mmol) was added dropwise followed by H_2O_2 (2.05 mL of a 30% w/v solution in water, 18.11 mmol). After stirring for 30 min, saturated brine (50 mL) and CH_2Cl_2 (50 mL) were

added and the mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with petrol-EtOAc (1:1) as eluent gave (by ^{1}H NMR spectroscopy) a 55:45 mixture of β-substituted keto alcohols *trans*-**147** and *cis*-**147** (1.03 g, 81%) as a colourless oil, R_F (1:1 petrol-EtOAc) 0.34; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.20–4.11 (m, 0.45H, CHO_{cis}), 3.99–3.91 (m, 0.45H, CHO_{cis}), 3.74–3.67 (m, 0.55H, CHO_{trans}), 3.64–3.60 (m, 2H, CH_2OH), 3.60–3.54 (m, 0.55H, CHO_{trans}), 3.31 (s, 1.35H, OMe_{cis}), 3.29 (s, 1.35H, OMe_{cis}), 3.24 (s, 1.65H, OMe_{trans}), 3.23 (s, 1.65H, OMe_{trans}), 2.13–1.96 (m, 2H), 1.98–0.98 (m, 16H).

Lab book reference: djb/31

(2*S*,3*S*,4a*R*,10a*S*,10b*R*)-2,3-Dimethoxy-2,3-dimethyl-2,3,4a,5,8,9,10,10a-octahydronaphtho[1,2-*b*][1,4]dioxin-6(10b*H*)-one 145 and (2*S*,3*S*,4a*R*,6a*R*,7*R*,10a*S*,10b*R*)-7-Hydroxy-2,3-dimethoxy-2,3-dimethyldecahydronaphtho[1,2-*b*][1,4]dioxin-6(10b*H*)-one *cis*-155



145 *cis*-**155**

K_2CO_3 (409 mg, 2.96 mmol) was added to a stirred solution of *trans*-**144** (932 mg, 2.96 mmol) in MeOH (50 mL) at rt under Ar. The resulting mixture was stirred at room temperature for 20 h. Then, saturated brine (50 mL) and CH_2Cl_2 (50 mL) were added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product (802 mg), which contained a mixture of diastereomeric aldol products (by ^{1}H NMR spectroscopy).

Mesyl chloride (237 μL, 3.06 mmol) and Et_3N (1.07 mL, 7.65 mmol) were added to a stirred solution of the crude aldol product (802 mg, 2.55 mmol) in CH_2Cl_2 (10 mL)

at 0 °C. The resulting mixture was then allowed to warm to rt and stirred at rt for 2 h. Then, saturated $NaHCO_{3(aq)}$ (20 mL) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product which contained a mixture of diastereomeric mesylates and a trace amount of an enone (by ^{1}H NMR spectroscopy).

DBU (381 μL, 2.55 mmol) was added to a stirred solution of the crude mesylates in benzene (100 mL) at rt under Ar. The resulting mixture was stirred and heated at reflux for 5 h. Then, saturated brine (20 mL) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with petrol-EtOAc (4:1) as eluent gave enone **145** (110 mg, 13%) as a colourless foam, $[\alpha]_D$ +133.2 (*c* 0.9 in CH_2Cl_2); R_F (1:1 petrol-EtOAc) 0.48; IR (Thin Film) 1692 (C=O), 1617 (C=C) cm^{-1}; ^{1}H NMR (400 MHz; $CDCl_3$) δ: 6.85–6.83 (m, 1H, C=CH), 3.89 (ddd, *J* = 12.5, 10.0, 5.0 Hz, 1H, CHO), 3.43 (dd, *J* = 11.0, 10.0 Hz, 1H, CHO), 3.24 (s, 3H, OMe), 3.23 (s, 3H, OMe), 2.73 (dd, *J* = 17.0, 5.0 Hz, 1H, CH_AH$_B$), 2.42 (dd, *J* = 17.0, 12.5 Hz, 1H, CH$_A$$H_B$), 2.41–2.11 (m, 4H), 1.89–1.78 (m, 1H), 1.50–1.37 (m, 1H), 1.31 (s, 3H, Me), 1.28 (s, 3H, Me), 1.21–1.06 (m, 1H); ^{13}C NMR (100.6 MHz; $CDCl_3$) δ: 196.6 (C=O), 139.5 (C=*C*H), 135.9 (*C*=CH), 99.1 (OCO), 98.9 (OCO), 73.2 (CHO), 66.3 (CHO), 47.9 (OMe), 47.7 (OMe), 43.2 (CH_2), 37.4 (CH), 25.7 (CH_2), 25.2 (CH_2), 20.4 (CH_2), 17.6 (Me), 17.5 (Me); MS (ESI) 297 [(M + H)$^+$, 23], 265 (100); HRMS (ESI) *m/z* calcd for $C_{16}H_{24}O_5$ (M + H)$^+$ 297.1697, found 297.1701 (−1.7 ppm error).

Lab book reference: djb2/66

(*R*)-Proline (17 mg, 0.02 mmol) was added to a stirred solution of *trans*-**144** (96 mg, 0.31 mmol) in DMF (2 mL) at rt under Ar. The resulting mixture was stirred at rt for 17 h. Then, saturated brine (10 mL) and CH_2Cl_2 (10 mL) were added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude enone product. Purification by flash column

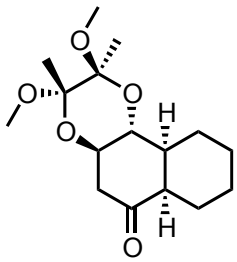
chromatography on silica with petrol-EtOAc (4:1) as eluent gave enone **145** (32 mg, 35%) as a colourless foam and gave aldol *cis*-**155** (21 mg, 22%) as a colourless oil, R_F (Et_2O) 0.30; ^1H NMR (400 MHz; $CDCl_3$) δ: 4.00 (dd, *J* = 11.0, 9.5 Hz, 1H, CHO), 3.89 (td, *J* = 11.0, 4.5 Hz, 1H, CHOH), 3.69 (ddd, *J* = 13.5, 9.5, 5.0 Hz, 1H, CHO), 3.28 (s, 3H, OMe), 3.20 (s, 3H, OMe), 2.76 (dd, *J* = 14.5, 13.5 Hz, 1H, CH_AH_BCO), 2.55 (ddd, *J* = 14.5, 5.0, 1.0 Hz, 1H, CH_AH_BCO), 2.31 (ddd, *J* = 10.5, 5.5, 1.0 Hz, 1H), 2.20–1.81 (m, 4H), 1.72–1.30 (m, 3H), 1.52–1.22 (m, 7H).

Lab book reference: djb3/36

(*S*)-Proline (17 mg, 0.02 mmol) was added to a stirred solution of (93:7 dr) *trans*-**144** (96 mg, 0.31 mmol) in DMF (2 mL) at rt under Ar. The resulting mixture was stirred at rt for 17 h. Then, saturated brine (10 mL) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with petrol-EtOAc (4:1) as eluent gave enone **145** (17 mg, 19%) as a colourless foam and gave aldol *cis*-**155** (44 mg, 46%) as a colourless oil.

Lab book reference: djb2/37

(2*S*,3*S*,4a*R*,6a*R*,10a*S*,10b*R*)-2,3-Dimethoxy-2,3-dimethyldecahydronaphtho[1,2-*b*][1,4]dioxin-6(10b*H*)-one 156

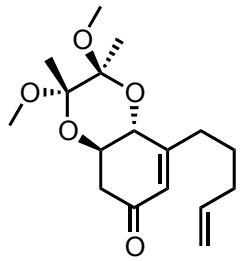


Palladium on carbon (10 mg) was added to a stirred solution of enone **145** (93 mg, 0.31 mmol) in methanol (5 mL) at rt under hydrogen. The resulting mixture was stirred at rt for 2 h. The reaction was filtered to remove solids and the solvent removed under reduced pressure to give the crude product. Purification by flash

column chromatography on silica with petrol-EtOAc (4:1) as eluent gave *cis*-decalone **156** (10 mg, 13%) as a colourless foam, mp 132–135 °C, $[\alpha]_D$ +153.2 (*c* 0.7 in CH_2Cl_2); R_F (1:1 petrol-EtOAc) 0.61; IR (Thin Film) 1712 (C=O) 1369, 995, 882 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ: 3.74 (ddd, *J* = 12.0, 10.0, 6.5 Hz, 1H, CHO), 3.60 (dd, *J* = 10.0, 9.5 Hz, 1H, CHO), 3.26 (s, 3H, OMe), 3.20 (s, 3H, OMe), 2.60–2.49 (m, 2H), 2.30 (br d, *J* = 12.5 Hz, 1H, COCH), 2.40–1.89 (m, 2H), 1.80–1.69 (m, 2H), 1.41–0.92 (m, 11H). *Product decomposed on standing overnight.*

Lab book reference: djb3/41

(2*S*,3*S*,4a*R*,8a*R*)-2,3-Dimethoxy-2,3-dimethyl-8-(pent-4-enyl)-2,3,4a,5-tetrahydrobenzo[*b*][1,4]dioxin-6(8a*H*)-one 157

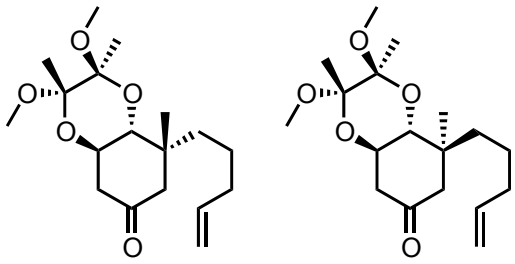


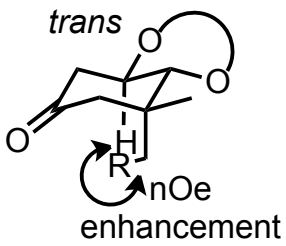
Pentenyllithium (1.90 mL of a 0.5 M solution in Et_2O, 0.95 mmol) [prepared from bromopent-1-ene (1.19 mL, 10.06 mmol) and lithium granules (132 mg, 22.14 mmol) in Et_2O (15 mL) according to general procedure G] was added dropwise over 15 min to a vigorously stirred suspension of CuCN (43 mg, 0.48 mmol) in THF (10 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 20 min. Then, a premixed solution of enone *ent*-**71** (96 mg, 0.40 mmol) and Me_3SiCl (100 μL, 0.79 mmol) in THF (10 mL) was added dropwise over 30 min to give a yellow solution. After stirring for 1 h, a mixture of saturated $NaHCO_{3(aq)}$ and Et_3N (30:1, 10 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude silyl enol ether. $Pd(OAc)_2$ (18 mg, 0.08 mmol) was added to a stirred solution of the crude silyl enol ether in DMSO (10 mL) at rt under O_2. The resulting mixture was stirred at rt for 20 h under O_2. Then, saturated $NH_4Cl_{(aq)}$ (20 mL) and CH_2Cl_2 (30 ml) were added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (5 × 20 mL). The combined organic extracts were

dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with petrol-EtOAc (4:1) as eluent gave β-substituted enone **157** (80 mg, 65%) as a colourless oil, $[\alpha]_D$ +93.8 (*c* 0.9 in CH_2Cl_2); R_F (4:1 petrol-EtOAc) 0.17; IR (Thin Film) 2949, 1677 (C=O), 1377, 1132, 910 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 5.81–5.78 (m, 1H, CH=C), 5.81–5.70 (m, 1H, C*H*=CH_2), 5.02–4.87 (m, 2H, CH=CH_2), 4.41 (dd, *J* = 9.0, 1.0 Hz, 1H, CHO), 4.00 (ddd, *J* = 13.5, 9.0, 5.0 Hz, 1H, CHO), 3.29 (s, 3H, OMe), 3.22 (s, 3H, OMe), 2.66 (ddd, *J* = 16.5, 5.0, 1.0 Hz, 1H, C$H_A$$H_B$CO), 2.44 (dd, *J* = 16.5, 13.5 Hz, 1H, $CH_A$$H_B$CO), 2.55–2.28 (m, 2H), 2.12–2.02 (m, 2H), 1.67–1.48 (m, 2H), 1.33 (s, 3H, Me), 1.28 (s, 3H, Me); ^{13}C NMR (100.6 MHz; $CDCl_3$) δ: 196.1 (C=O), 163.9 (CH=*C*), 137.8 (*C*H=CH_2), 126.1 (*C*H=C), 115.3 (CH=*C*H_2), 100.7 (OCO), 99.5 (OCO), 70.3 (CHO), 67.8 (CHO), 48.5 (OMe), 48.1 (OMe), 42.1 (CH_2), 33.3 (CH_2), 30.6 (CH_2), 26.4 (CH_2), 17.8 (Me), 17.7 (Me); MS (ESI) 333 [$(M + Na)^+$, 65], 279 (49), 179 (100); HRMS (ESI) *m/z* calcd for $C_{17}H_{26}O_5$ $(M + Na)^+$ 333.1672, found 333.1681 (−2.5 ppm error).

Lab book reference: djb3/29

(2*S*,3*S*,4a*R*,8*S*,8a*R*) and (2*S*,3*S*,4a*R*,8*R*,8a*R*)-2,3-Dimethoxy-2,3,8-trimethyl-8-(pent-4-enyl)hexahydrobenzo[*b*][1,4]dioxin-6(7*H*)-one *cis*-158 and *trans*-158





Using general procedure C at 0 °C, pentenyllithium (2.5 mL of a 0.18 M solution in Et_2O, 0.47 mmol) [prepared from bromopent-1-ene (510 μL, 4.31 mmol) and lithium granules (66 mg, 9.49 mmol) in Et_2O (15 mL) according to general procedure G], CuCN (21 mg, 0.23 mmol) in THF (10 mL), and a premixed solution of enone *ent*-**117** (50 mg, 0.20 mmol) and Me_3SiCl (49 μL, 0.39 mmol) in THF (5 mL), followed by TBAF (2.25 mL of a 1.0 M solution in THF, 2.25 mmol) in CH_2Cl_2 (10 mL) gave

the crude product. Purification by flash column chromatography on silica with petrol-EtOAc (4:1) as eluent gave β-disubstituted ketone *trans*-**158** (13 mg, 20%) as a colourless oil, R_F (4:1 petrol-EtOAc) 0.65; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.77 (ddt, *J* = 17.0, 10.0, 6.5 Hz, 1H, C*H*=CH_2), 4.97 (ddd, *J* = 17.0, 3.5, 1.5 Hz, 1H, CH=C$H_A$$H_B$), 4.94–4.90 (m, 1H, CH=$CH_AH_B$), 4.00 (ddd, *J* = 12.0 10.0 6.0 Hz, 1H, CHO), 3.70 (d, *J* = 10.0 Hz, 1H, CHO), 3.27 (s, 3H, OMe), 3.21 (s, 3H, OMe), 2.57 (ddd, *J* = 14.0, 6.0, 2.5 Hz, 1H, C$H_A$$H_B$), 2.49 (ddd, *J* = 14.0, 12.0, 1.0 Hz, 1H, CH_AH_B), 2.38 (dd, *J* = 14.5, 2.5 Hz, 1H, C$H_A$$H_B$), 2.13 (dd, *J* = 14.5, 1.0 Hz, CH_AH_B), 2.16–1.92 (m, 2H), 1.64–1.54 (m, 1H), 1.42–1.29 (m, 2H), 1.29 (s, 3H, Me), 1.28 (s, 3H, Me), 1.10–1.00 (m, 1H) 1.08 (s, 3H, Me) and (by ^{1}H NMR spectroscopy) an 86:14 mixture of enone *ent*-**117** and *cis*-**158** (31 mg, 8% of *cis*-**158**) as a colourless oil, R_F (4:1 petrol-EtOAc) 0.55; data for *cis*-**158**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.76 (ddt, *J* = 17.0, 10.0, 6.5 Hz, 1H, C*H*=CH_2), 4.96 (ddd, *J* = 17.0, 3.5, 1.5 Hz, 1H, CH=C$H_A$$H_B$), 4.92–4.91 (m, 1H, CH=$CH_AH_B$), 4.00 (ddd, *J* = 12.0 10.0 6.0 Hz, 1H, CHO), 3.70 (d, *J* = 10.0 Hz, 1H, CHO), 3.27 (s, 3H, OMe), 3.21 (s, 3H, OMe), 2.57 (ddd, *J* = 14.0, 6.0, 2.0 Hz, 1H, C$H_A$$H_B$), 2.49 (ddd, *J* = 14.0, 12.0, 1.0 Hz, 1H, CH_AH_B), 2.26 (d, *J* = 14.0 Hz, 1H, C$H_A$$H_B$), 2.17 (dd, *J* = 14.0, 2.0 Hz, CH_AH_B), 2.16–1.92 (m, 2H), 1.64–1.54 (m, 1H), 1.42–1.29 (m, 2H), 1.29 (s, 3H, Me), 1.28 (s, 3H, Me), 1.10–1.00 (m, 1H), 0.89 (s, 3H, Me).

The relative stereochemistry was assigned by the nOe enhancement indicated.

Lab book reference: djb3/46

Using general procedure C at −78 °C, pentenyllithium (2.5 mL of a 0.18 M solution in Et_2O, 0.47 mmol) [prepared from bromopent-1-ene (510 μL, 4.31 mmol) and lithium granules (66 mg, 9.49 mmol) in Et_2O (15 mL) according to general procedure G], CuCN (21 mg, 0.23 mmol) and HMPA (102 μL, 0.59 mmol) in THF (10 mL), and a premixed solution of enone *ent*-**117** (50 mg, 0.20 mmol) and Me_3SiCl (49 μL, 0.39 mmol) in THF (5 mL), followed by TBAF (2.25 mL of a 1.0 M solution in THF, 2.25 mmol) in CH_2Cl_2 (10 mL) gave the crude product. Purification by flash column chromatography on silica with petrol-EtOAc (4:1) as eluent gave (by ^{1}H NMR spectroscopy) a 50:50 mixture of β-disubstituted ketones *cis*-**158** and *trans*-

158 (35 mg, 55%) as a colourless oil and starting enone *ent*-**117** (16 mg, 32%) as a colourless solid.

Lab book reference: djb3/47

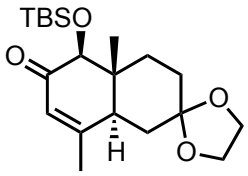
Using general procedure C at −78 °C, pentenyllithium (2.5 mL of a 0.18 M solution in Et_2O, 0.47 mmol) [prepared from bromopent-1-ene (510 μL, 4.31 mmol) and lithium granules (66 mg, 9.49 mmol) in Et_2O (15 mL) according to general procedure G], CuCN (21 mg, 0.23 mmol) and $BF_3.OEt_2$ (48 μL, 0.89 mmol) in THF (10 mL), and a premixed solution of enone *ent*-**117** (50 mg, 0.20 mmol) and Me_3SiCl (49 μL, 0.39 mmol) in THF (5 mL), followed by TBAF (2.25 mL of a 1.0 M solution in THF, 2.25 mmol) in CH_2Cl_2 (10 mL) gave the crude product. Purification by flash column chromatography on silica with petrol-EtOAc (4:1) as eluent gave (by ^1H NMR spectroscopy) a 50:50 mixture of β-disubstituted ketones *cis*-**158** and *trans*-**158** (41 mg, 65%) as a colourless oil and starting enone *ent*-**117** (7 mg, 14%) as a colourless oil.

Lab book reference: djb3/48

Using general procedure C at −78 °C, MeLi (241 μL of a 1.6 M solution in hexanes, 0.39 mmol), CuCN (21 mg, 0.23 mmol) in THF (10 mL), and a premixed solution of enone **157** (50 mg, 0.20 mmol) and Me_3SiCl (49 μL, 0.39 mmol) in THF (5 mL), followed by TBAF (193 mL of a 1.0 M solution in THF, 0.19 mmol) in CH_2Cl_2 (10 mL) gave the crude product. Purification by flash column chromatography on silica with petrol-EtOAc (4:1) as eluent gave (by ^1H NMR spectroscopy) a 58:42 mixture of β-disubstituted ketones *cis*-**158** and *trans*-**158** (5 mg, 10%) as a colourless oil and starting enone **157** (31 mg, 62%) as a colourless oil.

Lab book reference: djb3/32

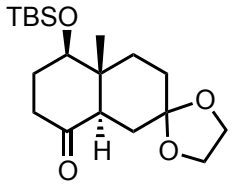
(4a'*R*,5'*S*,8a'*S*)-5'-(*tert*-Butyldimethylsilyloxy)-4a',8'-dimethyl-3',4',4a',5'-tetrahydro-1'*H*-spiro[[1,3]dioxolane-2,2'-naphthalen]-6'(8a'*H*)-one 160



MeLi (256 μL of a 1.6 M solution in hexanes, 0.41 mmol) was added dropwise to a stirred solution of enone **166** (69 mg, 0.20 mmol) in THF (3 mL) at 0 °C under Ar. The resulting mixture was stirred at 0 °C for 1 h. Then, water (10 mL) and CH_2Cl_2 (10 mL) were added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude tertiary alcohol **168**. PCC (88 mg, 0.41 mmol) was added to a stirred solution of the crude tertiary alcohol **168** in CH_2Cl_2 (10 mL) at rt under Ar. The resulting mixture was stirred at rt for 22 h. Then, Celite® (1 g) and Et_2O (10 mL) were added and the solids were removed by filtration through a Celite® pad. The Celite® pad was washed with Et_2O (5 × 20 mL). The combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with petrol-EtOAc (4:1) as eluent gave β-methyl enone **160** (58 mg, 81%) as a colourless oil, $[\alpha]_D$ −7.2 (*c* 0.9 in $CHCl_3$); R_F (1:1 petrol-EtOAc) 0.28; IR (Thin Film) 2952, 1687 (C=O), 1626 (C=C), 1100, 966, 943, 778 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 5.85–5.82 (m, 1H, =CH), 4.01–3.96 (m, 4H, OCH_2CH_2O), 3.91 (s, 1H, CHO), 2.72–2.65 (m, 1H, =CMeC*H*), 1.91–1.85 (m, 2H), 1.85 (t, *J* = 1.5 Hz, 3H), 1.71–1.43 (m, 4H), 0.91 (s, 9H, Si*t*-Bu), 0.82 (s, 3H, CMe), 0.19 (s, 3H, SiMe), 0.01 (s, 3H, SiMe); ^{13}C NMR (100.6 MHz; $CDCl_3$) δ: 198.0 (C=O), 160.7 (Me*C*=CH), 126.1 (MeC=*C*H), 108.8 (OCO), 84.3 (CHO), 64.5 (OCH_2), 64.3 (OCH_2), 45.6 (*C*Me), 43.6 (=CMe*C*H), 34.0 (CH_2), 33.2 (CH_2), 30.4 (CH_2), 25.8 (CMe_3) 21.6 (*Me*C=), 18.7 (CMe_3), 9.8 (Me), –3.9 (SiMe), –5.5 (SiMe); MS (ESI) 389 [$(M + Na)^+$, 82], 367 [$(M + H)^+$, 100); HRMS (ESI) *m/z* calcd for $C_{20}H_{34}O_4Si$ $(M + H)^+$ 367.2299 found 367.2289 (2.8 ppm error).

Lab book reference: djbI/50

(4a'*R*,5'*R*,8a'*R*)-5'-(*tert*-Butyldimethylsilyloxy)-4a'-methylhexahydro-1'*H*-spiro[[1,3]dioxolane-2,2'-naphthalen]-8'(8a'*H*)-one 161

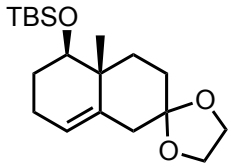


BH_3·THF (18.9 mL, 18.9 mmol) was added dropwise to a stirred solution of alkene **162** (5.34 g, 15.8 mmol) in THF (50 mL) at 0 °C under Ar. The resulting mixture was stirred at 0 °C for 1 h and then at rt for 15 h. The mixture was cooled to 0 °C and NaOH (24 mL of a 3 M solution, 0.072 mol) was added dropwise followed by H_2O_2 (24 mL of a 30% w/v solution in water, 0.21 mol). After stirring for 1 h at 0 °C, the mixture was allowed to warm to rt and stirred at rt for 3 h. Then, CH_2Cl_2 (100 mL) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (5 × 100 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude alcohol. PDC (11.0 g, 31.5 mmol) was added in portions (1 g) to a stirred solution of the crude alcohol and 4 Å sieves (12.0 g) in CH_2Cl_2 (100 mL) at 0 °C under Ar. The resulting mixture was stirred at 0 °C for 1 h and then allowed to warm to rt and stirred at rt for 10 h. Then, Celite® (10 g) and Et_2O (100 mL) were added and the solids were removed by filtration through a Celite® pad. The Celite® pad was washed with Et_2O (5 × 200 mL). The combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude ketone. NaOMe (10 mL of a 25% wt. solution in MeOH, 36.65 mmol) was added dropwise to a stirred solution of the crude ketone in MeOH (43 mL) at rt under Ar. The resulting mixture was stirred at rt for 18 h. The solvent was evaporated under reduced pressure and water (100 mL) and Et_2O (100 mL) were added to the resulting residue. The two layers were separated and the aqueous layer was extracted with Et_2O (5 × 100 mL). The combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with petrol-EtOAc (4:1) as eluent gave ketone **161** (3.81 g, 71%) as a colourless oil, $[\alpha]_D$ −8.6 ((*c* 1.0 in $CHCl_3$)(lit.,[219] +11.1 (*c* 1.8 in $CHCl_3$)) for *S*-**161**); R_F (4:1 petrol-EtOAc) 0.45; IR (Thin Film) 2908, 1690 (C=O), 1236, 824 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 3.97–3.87 (m, 4H, OCH_2CH_2O), 3.79 (dd, *J* = 11.0, 5.0 Hz, 1H, CHO), 2.47 (dd, *J* = 12.5, 3.5 Hz, 1H,

COCH), 2.41–2.27 (m, 2H), 2.00–1.79 (m, 3H), 1.75–1.58 (m, 4H), 1.46–1.38 (m, 1H), 0.88 (s, 9H, Si*t*-Bu), 0.78 (s, 3H, Me), 0.08 (s, 3H, SiMe), 0.06 (s, 3H, SiMe); ^{13}C NMR (100.6 MHz; $CDCl_3$) δ: 210.5 (C=O), 109.2 (OCO), 77.5 (CHO), 64.44 (OCH_2), 64.34 (OCH_2), 52.3 (CH), 42.5 (CMe), 39.0 (CH_2), 35.2 (CH_2), 30.88 (CH_2), 30.69 (CH_2), 29.8 (CH_2), 25.9 (C*Me*$_3$), 18.1 (*C*Me$_3$), 10.7 (Me), −3.9 (SiMe), −4.6 (SiMe); MS (ESI) 377 [$(M + Na)^+$, 39], 355 [$(M + H)^+$, 100], 339 (22); HRMS (ESI) *m/z* calcd for $C_{19}H_{34}O_4$ $(M + Na)^+$ 377.2119 found 377.2111 (2.0 ppm error), *m/z* calcd for $C_{19}H_{34}O_4$ $(M + H)^+$ 355.2299 found 355.2296 (1.0 ppm error). Spectroscopic data are consistent with those reported in the literature.[219]

Lab book reference: djbI/33

***tert*-Butyldimethyl((4a'*R*,5'*R*)-4a'-methyl-3',4',4a',5',6',7'-hexahydro-1'*H*-spiro[[1,3]dioxolane-2,2'-naphthalene]-5'-yloxy)silane 162**

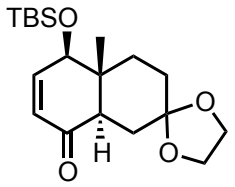


TBSOTf (4.95 mL, 21.6 mmol) was added dropwise to a stirred solution of alcohol **5** (3.22 g, 14.4 mmol) and 2,6-lutidine (3.34 mL, 28.7 mmol) in CH_2Cl_2 (25 mL) at 0 °C under Ar. The resulting mixture was stirred at 0 °C for 4 h. Then, saturated $NaHCO_{3(aq)}$ (20 mL) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with petrol-EtOAc (1:1) as eluent gave silyl ether **162** (4.74 g, 98%) as a colourless oil, $[\alpha]_D$ +38.8 (*c* 1.1 in $CHCl_3$); R_F (1:1 petrol-EtOAc) 0.74; IR (Thin Film) cm^{-1}; 2949, 1466, 1253, 865, 697 cm^{-1}, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.29–5.26 (m, 1H, CH=C), 4.00–3.91 (m, 4H, OCH_2CH_2O), 3.54 (dd, *J* = 12.0, 3.5 Hz, 1H, CHO), 2.49 (dq, *J* = 14.0, 3.0 Hz, 1H), 2.17–2.08 (m, 2H), 2.02–1.96 (m, 1H), 1.88 (ddd, *J* = 13.0, 4.0, 3.0 Hz, 1H), 1.78 (td, *J* = 13.5, 4.0 Hz, 1H), 1.72–1.63 (m, 2H), 1.59–1.54 (m, 2H), 1.32 (td, *J* = 13.5, 4.5 Hz, 1H), 1.05 (s, 3H, Me), 0.88 (s, 9H, Si*t*-Bu), 0.04 (s, 3H, SiMe), 0.02 (s, 3H, SiMe); ^{13}C NMR (100.6 MHz; $CDCl_3$) δ: 139.6 (CH=*C*), 121.6 (*C*H=C), 109.7

(OCO), 78.2 (CHO), 64.6 (OCH_2), 64.4 (OCH_2), 41.4 (CH_2), 39.8 (C), 35.8 (CH_2), 31.1 (CH_2), 27.7 (CH_2), 26.0 (CMe_3), 24.9 (CH_2), 18.2 (CMe_3), 17.2 (Me), −3.9 (SiMe), −4.7 (SiMe); MS (ESI) 361 [$(M + Na)^+$, 14], 339 [$(M + H)^+$, 100], 207 (34); HRMS (ESI) *m/z* calcd for $C_{19}H_{34}O_3$ $(M + Na)^+$ 361.2169 found 361.2160 (2.7 ppm error), *m/z* calcd for $C_{19}H_{34}O_3$ $(M + H)^+$ 339.2350 found 339.2349 (0.3 ppm error).

Lab book reference: djbI2/8

(4a'*R*,5'*R*,8a'*R*)-5'-(*tert*-Butyldimethylsilyloxy)-4a'-methyl-3',4',4a',5'-tetrahydro-1'*H*-spiro[[1,3]dioxolane-2,2'-naphthalen]-8'(8a'*H*)-one 166



LHMDS (4.44 mL of a 1.0 M solution in THF, 4.44 mmol) was added dropwise to a stirred solution of ketone **161** (500 mg, 1.48 mmol) in THF (5 mL) at –78 °C under Ar. The resulting mixture was stirred at –78 °C for 1 h. Then, a solution of PhSeCl (850 mg, 4.44 mmol) in THF (15 mL) was added and the reaction was allowed to warm to rt and stirred for 1 h. Saturated $NH_4Cl_{(aq)}$ (50 mL) and CH_2Cl_2 (50 mL) were added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude selenides. Hydrogen peroxide (670 μL of a 30% w/v solution in water, 5.91 mmol) was added dropwise to a stirred solution of the crude selenides in CH_2Cl_2 (10 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 3 h. Then, saturated brine (20 mL) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with petrol-EtOAc (4:1) as eluent gave enone **166** (396 mg, 80%) as a colourless oil, $[\alpha]_D$ −69.8 (*c* 1.0 in $CHCl_3$); R_F (4:1 petrol-EtOAc) 0.29; IR (Thin Film) 2952, 1685 (C=O), 1256, 1128, 1018, 838, 775 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 6.55 (dd, *J* = 10.5, 1.5 Hz, 1H, C*H*=CHCO), 5.92 (dd, *J* = 10.5, 2.5 Hz, 1H, CH=C*H*CO), 4.33 (dd, *J* =

2.5, 1.5 Hz, 1H, CHO), 4.10–3.99 (m, 4H, OCH_2CH_2O), 2.48 (dd, *J* = 12.5, 3.5 Hz, 1H, COCH), 2.04 (ddd, *J* = 14.0, 3.5, 2.5 Hz, 1H, CH_AH_B), 1.84 (ddd, *J* = 12.5, 4.0, 2.5 Hz, 1H, CH_AH_B), 1.73–1.49 (m, 4H), 0.91 (s, 9H, Si*t*-Bu), 0.85 (s, 3H, CMe), 0.11 (s, 3H, SiMe), 0.09 (s, 3H, SiMe); ^{13}C NMR (100.6 MHz; $CDCl_3$) δ: 200.0 (C=O), 151.9 (*C*H=CHCO), 128.3 (CH=*C*HCO), 108.9 (OCO), 78.0 (CHO), 64.5 (OCH_2), 64.4 (OCH_2), 51.3 (CO*C*H), 44.6 (*C*Me), 35.3 (CH_2), 30.8 (CH_2), 30.0 (CH_2), 25.9 (C*Me*$_3$), 18.2 (*C*Me$_3$), 10.7 (Me), –4.2 (SiMe), –4.8 (SiMe); MS (ESI) 375 [$(M + Na)^+$, 17], 353 [$(M + H)^+$, 100], 339 (25); HRMS (ESI) *m/z* calcd for $C_{19}H_{32}O_4Si$ $(M + Na)^+$ 375.1962 found 375.1940 (5.9 ppm error), *m/z* calcd for $C_{19}H_{32}O_4Si$ $(M + H)^+$ 353.2143 found 353.2127 (4.5 ppm error).

Lab book reference: djbI/54

n-BuLi (617 μL of a 1.6 M solution in hexanes, 0.99 mmol) was added dropwise to a stirred solution of DIPA (145 μL, 1.04 mmol) in THF (5 mL) at 0 °C under Ar. The resulting mixture was stirred at 0 °C for 30 min. The freshly prepared LDA solution was added dropwise to a stirred solution of ketone **161** (92 mg, 0.26 mmol) in THF (5 mL) at –78 °C under Ar. The resulting mixture was stirred at –78 °C for 1 h. Then, freshly distilled Me_3SiCl (53 μL, 0.42 mmol) was added and the resulting mixture was allowed to warm to rt and stirred at rt for 30 min. Then, saturated $NaHCO_{3(aq)}$ (10 mL) and CH_2Cl_2 (10 mL) were added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (5 × 10 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude silyl enol ether **165**. $Pd(OAc)_2$ (12 mg, 0.05 mmol) was added to a stirred solution of the crude silyl enol ether **165** in DMSO (5 mL) at rt under O_2. The resulting mixture was stirred at rt for 16 h. Then, saturated brine (10 mL) and CH_2Cl_2 (10 mL) were added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (5 × 10 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with petrol-EtOAc (1:1) as eluent gave enone **166** (41 mg, 44%) as a colourless oil.

Lab book reference: djbI2/87

n-BuLi (1.12 mL of a 1.6 M solution in hexanes, 1.79 mmol) was added dropwise to a stirred solution of DIPA (265 μL, 1.89 mmol) in THF (10 mL) at 0 °C under Ar. The resulting mixture was stirred at 0 °C for 30 min. The freshly prepared LDA solution was added dropwise to a stirred solution of ketone **161** (167 mg, 0.47 mmol) in THF (10 mL) at –78 °C under Ar. The resulting mixture was stirred at –78 °C for 1 h. Then, freshly distilled Me_3SiCl (96 μL, 0.75 mmol) was added and the resulting mixture was allowed to warm to rt and stirred at rt for 30 min. Then, saturated $NaHCO_{3(aq)}$ (20 mL) and CH_2Cl_2 (20 mL) were added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (5 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude silyl enol ether **165**. Recrystallised NBS (54 mg, 0.30 mmol) was added to a stirred solution of the crude silyl enol ether **165** in THF (10 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 1 h. Then, saturated brine (20 mL) and CH_2Cl_2 (20 mL) were added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (5 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude bromide. Li_2CO_3 (46 mg, 0.63 mmol) and LiBr (44 mg, 0.50 mmol) were added to a stirred solution of the crude bromide in DMF (5 mL) at rt. The resulting suspension was stirred and heated at 140 °C for 1 h. Then, saturated brine (20 mL) and CH_2Cl_2 (20 mL) were added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (5 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with petrol-EtOAc (1:1) as eluent gave enone **166** (53 mg, 32%) as a colourless oil.

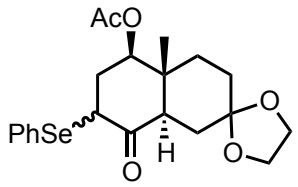
Lab book reference: djbI2/80

Hydrogen peroxide (670 μL of a 30% w/v solution in water, 5.91 mmol) was added dropwise to a stirred solution of selenides **167** in CH_2Cl_2 (10 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 2 h. Then, saturated brine (10 mL) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column

chromatography on silica with petrol-EtOAc (4:1) as eluent gave enone **166** (210 mg, 40%) as a colourless oil

Lab book reference: djbI/46

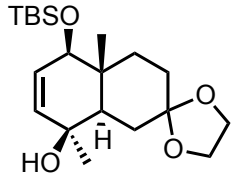
(4a'*R*,5'*R*,7'*SR*,8a'*R*)-4a'-Methyl-8'-oxo-7'-(phenylselanyl)octahydro-1'*H*-spiro[[1,3]dioxolane-2,2'-naphthalen]-5'-yl acetate 167



LHMDS (6.34 mL of a 0.7 M solution in THF, 4.44 mmol) was added dropwise to a stirred solution of ketone **161** (500 mg, 1.48 mmol) in THF (15 mL) at –78 °C under Ar. The resulting mixture was stirred at –78 °C for 1 h. Then, a solution of PhSeCl (289 mg, 1.48 mmol) in THF (15 mL) was added and the reaction was allowed to warm to rt and stirred for 1 h. Saturated $NH_4Cl_{(aq)}$ (50 mL) and CH_2Cl_2 (50 mL) were added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with petrol-EtOAc (4:1) gave (by ^{1}H NMR spectroscopy) a 50:50 mixture of diastereomeric selenides **167** (616 mg, 84%) as a yellow oil, R_F (4:1 petrol-EtOAc) 0.38; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.58–7.10 (m, 5H, Ph), 3.96–3.90 (m, 4H, OCH_2CH_2O), 3.83–3.78 (m, 1H), 3.68 (dd, *J* = 11.0, 4.5 Hz, 0.5H), 3.52 (dd, *J* = 10.5, 5.5 Hz, 0.5H), 3.28 (dd, *J* = 12.0, 4.0 Hz, 0.5H), 2.61–2.32 (m, 1.5H), 2.21–1.08 (m, 1H), 1.89 (dd, *J* = 15.0, 5.0 Hz, 0.5H), 1.81–1.37 (m, 8.5H), 0.86 (s, 4.5H, Si*t*-Bu), 0.78 (s, 4.5H, Si*t*-Bu), 0.09 (s, 1.5H, SiMe), 0.08 (s, 1.5H, SiMe), 0.04 (s, 1.5H, SiMe), 0.00 (s, 1.5H, SiMe).

Lab book reference: djbI/41

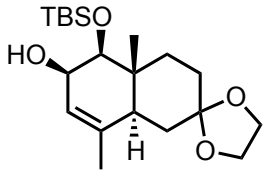
(4a'*R*,5'*R*,8'*S*,8a'*R*)-5'-((*tert*-Butyldimethylsilyl)oxy)-4a',8'-dimethyl-3',4',4a',5',8',8a'-hexahydro-1'*H*-spiro[[1,3]dioxolane-2,2'-naphthalen]-8'-ol 168



MeLi (213 μL of a 1.6 M solution in Et_2O, 0.34 mmol) was added dropwise to a stirred solution of enone **166** (100 mg, 0.14 mmol) in THF (2 mL) at 0 °C under Ar. The resulting mixture was stirred at 0 °C for 30 min. Then, saturated NH_4Cl (10 mL) and CH_2Cl_2 (10 mL) were added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with petrol-EtOAc (4:1) as eluent gave alcohol **168** (74 mg, 71%) as a white solid, mp 90–91 °C; $[\alpha]_D$ −22.5 (*c* 0.5 in $CHCl_3$); R_F (Et_2O) 0.46; IR (Thin Film) 3437 (OH), 2908, 1235, 1086, 762 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 5.55 (dd, *J* = 10.0, 2.0 Hz, 1H, CH=), 5.43 (dd, *J* = 10.0, 1.5 Hz, 1H, CH=), 3.99–3.90 (m, 4H, OCH_2CH_2O), 3.83 (s, 1H, CHO), 1.85–1.58 (m, 6H), 1.19 (s, 3H, Me), 0.95 (s, 3H, Me), 0.88 (s, 9H, Si*t*-Bu), 0.05 (s, 3H, SiMe), 0.03 (s, 3H, SiMe); ^{13}C NMR (100.6 MHz; $CDCl_3$) δ: 133.2 (CH=), 131.7 (CH=), 109.8 (OCO), 77.9 (CHO), 69.0 (Me*C*OH), 64.35 (OCH_2), 64.32 (OCH_2), 45.7 (CH), 37.2 (*C*Me), 36.4 (CH_2), 30.81 (CH_2), 30.80 (CH_2), 28.5 (Me), 26.0 (C*Me*$_3$), 18.2 (*C*Me$_3$), 12.2 (C*Me*), −4.1 (SiMe), −4.7 (SiMe); MS (ESI) 391 (16), 351 (100); HRMS (ESI) *m/z* calcd for $C_{20}H_{36}O_4Si$ $(M + Na)^+$ 391.2281 found 391.2262 (−1.2 ppm error).

Lab book reference: djbI2/5

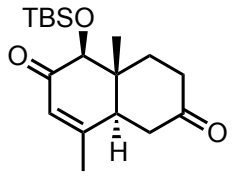
(4a'*R*,5'*S*,6'*R*,8a'*S*)-5'-((*tert*-Butyldimethylsilyl)oxy)-4a',8'-dimethyl-3',4',4a',5',6',8a'-hexahydro-1'*H*-spiro[[1,3]dioxolane-2,2'-naphthalen]-6'-ol *cis*-**170**



DIBAL-H (655 μL of a 1.0 M solution in toluene, 0.66 mmol) was added dropwise to a stirred solution of enone **160** (80 mg, 0.22 mmol) in THF (2 mL) at −78 °C under Ar. The resulting mixture was stirred at −78 °C for 3 h. Then, a 20% aqueous solution of Rochelle's $salt_{(aq)}$ (10 mL) was added and the biphasic mixture was stirred at rt for 1 h. Then CH_2Cl_2 (10 mL) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with petrol-EtOAc (4:1) as eluent gave diol *cis*-**170** (6 mg, 7%) as a colourless oil, R_F (1:1 petrol:EtOAc) 0.66; IR (Thin Film) 3553 (OH), 2953, 1467, 1255, 1106, 865, 777, 733 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 5.63–5.61 (m, 1H, =CH), 4.05–4.02 (m, 1H, C*H*OH), 4.02–3.91 (m, 4H, OCH_2CH_2O), 3.49 (d, *J* = 5.5 Hz, 1H, CHO), 2.82 (br s, 1H, CHO*H*), 2.21–2.15 (m, 1H), 1.83–1.55 (m, 9H), 0.93 (s, 9H, Si*t*-Bu), 0.91 (s, 3H, Me), 0.11 (s, 3H, SiMe), 0.10 (s, 3H, SiMe); ^{13}C NMR (100.6 MHz; $CDCl_3$) δ: 138.0 (=*C*Me), 122.6 (=CH), 109.4 (OCO), 78.9 (CHOH), 66.7 (CHO), 64.4 (OCH_2), 64.3 (OCH_2), 44.0 (CH), 37.1 (*C*Me), 33.7 (CH_2), 33.4 (CH_2), 30.2 (CH_2), 26.0 (C*Me*$_3$), 21.0 (=C*Me*), 18.2 (*C*Me$_3$), 10.9 (C*Me*), −4.2 (SiMe), −4.6 (SiMe); MS (ESI) 391 [$(M+Na)^+$, 63], 351 (100); HRMS (ESI) *m/z* calcd for $C_{20}H_{36}O_4$ $(M + Na)^+$ 391.2275 found 391.2256 (4.8 ppm error).

Lab book reference: djbI/70

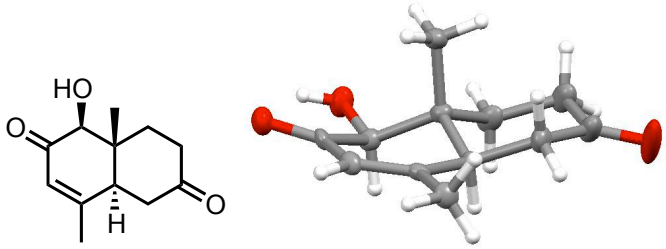
(4a*R*,5*S*,8a*S*)-5-((*tert*-Butyldimethylsilyl)oxy)-4a,8-dimethyl-1,3,4,4a,5,8a-hexahydronaphthalene-2,6-dione 173



3 M $HCl_{(aq)}$ (330 μL) was added to a stirred solution of ketal **160** (56 mg, 0.15 mmol) in acetone (1 mL) at rt. The resulting mixture was stirred at rt for 6 h. Then, water (5 mL) and CH_2Cl_2 (5 mL) were added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with petrol-EtOAc (4:1) as eluent gave dione **173** (35 mg, 71%) as a colourless oil, R_F (1:1 petrol-EtOAc) 0.53; IR (Thin Film) 2953, 1713 (C=O), 1687 (C=O), 1252, 1140, 837, 778 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 5.92–5.89 (m, 1H, CH=C), 3.95 (s, 1H, CHO), 2.80–2.73 (m, 1H), 2.65 (dd, *J* = 15.0, 4.0 Hz, 1H), 2.47–2.34 (m, 3H), 2.27–2.20 (m, 1H), 1.85 (t, *J* = 1.5 Hz, 3H), 1.69–1.59 (m, 1H), 1.01 (s, 3H, CH=C*Me*), 0.92 (s, 9H, Si*t*-Bu), 0.19 (s, 3H, Me), 0.01 (s, 3H, Me); ^{13}C NMR (100.6 MHz; $CDCl_3$) δ: 209.5 (C=O), 197.4 (C=O), 158.4 (Me*C*=CH), 126.8 (MeC=*C*H), 83.8 (CHO), 47.4 (=CMe*C*H), 43.5 (*C*Me), 39.7 (CH_2), 37.4 (CH_2), 35.9 (CH_2), 26.1 (C*Me*$_3$), 21.4 (*Me*C=), 18.8 (*C*Me$_3$), 10.2 (CMe), –3.7 (SiMe), –5.3 (SiMe); MS (ESI) 345 [$(M + Na)^+$, 100], 323 [$(M + H)^+$, 43]; HRMS (ESI) *m/z* calcd for $C_{18}H_{30}O_3Si$ $(M + Na)^+$ 345.1856 found 345.1846 (3.1 ppm error), *m/z* calcd for $C_{18}H_{30}O_3Si$ $(M + H)^+$ 323.2037 found 323.2033 (1.2 ppm error).

Lab book reference: djbI/51

(4a*R*,5*S*,8a*S*)-5-Hydroxy-4a,8-dimethyl-1,3,4,4a,5,8a-hexahydronaphthalene-2,6-dione 174



X-ray crystal structure of 174

$HF_{(aq)}$ (5 μL of a 40 wt% aqueous solution, 0.12 mmol) was added to a stirred solution of ketal **166** (29 mg, 0.12 mmol) in MeCN (1 mL) at rt in a plastic reaction vessel. The resulting mixture was stirred at rt for 8 h. Then, saturated $NaHCO_{3(aq)}$ (10 mL) and CH_2Cl_2 (10 mL) were added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with petrol-EtOAc (1:1) as eluent gave dione **174** (13 mg, 79%) as a white solid, mp 106–107 °C; $[\alpha]_D$ +50.0 (*c* 0.5 in $CHCl_3$); R_F (1:1 petrol–EtOAc) 0.17; IR (Thin Film) 3394 (OH), 2927, 1683 (C=O), 1645 (C=O), 1112 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 6.07 (dq, *J* = 3.0, 1.5 Hz, 1H, C*H*=CMe), 3.94 (s, 1H, CHO), 3.76 (s, 1H, OH), 2.85–2.78 (m, 1H, =CMeC*H*), 2.71 (ddd, *J* = 15.0, 4.0, 1.0 Hz, 1H), 2.49–2.36 (m, 3H), 2.32–2.25 (m, 1H), 1.92 (t, *J* = 1.5 Hz, 3H), 1.84–1.76 (m, 1H), 0.97 (s, 3H, CMe); ^{13}C NMR (100.6 MHz; $CDCl_3$) δ: 209.0 (C=O), 198.3 (C=O), 162.1 (CH=*C*Me), 124.8 (*C*H=CMe), 81.8 (*C*HOH), 47.2 (CH), 43.5 (*C*Me), 39.6 (CH_2), 37.2 (CH_2), 35.1 (CH_2), 21.9 (CH=C*Me*), 9.7 (C*Me*); MS (ESI) 231 [$(M + Na)^+$, 100], 209 [$(M + H)^+$, 38]; HRMS (ESI) *m/z* calcd for $C_{12}H_{16}O_3$ $(M + Na)^+$ 231.0992 found 231.0990 (0.6 ppm error), *m/z* calcd for $C_{12}H_{16}O_3$ $(M + H)^+$ 209.1172 found 209.1175 (−1.3 ppm error).

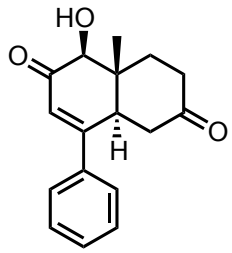
Crystal structure determination of dione 174

$C_{12}H_{16}O_4$, *M* = 208.25, monoclinic, *a* = 8.9705(6), *b* = 6.9768(6), *c* = 17.0416(13) Å, *β* = 91.631°, *U* = 1066.12(14) $Å^3$, *T* = 110(10) K, space group $P2_1$, *Z* = 4, *μ*(Mo-Kα) = 0.096 mm^{-1}, 6678 reflections measured, 6678 unique (R_{int} = 0.0000) which were

used in calculations. The final R1 was 0.06480 ($I>2\sigma_I$) and wR2 was 0.1557 (all data).

Lab book reference: djbI/57

(4a*R*,5*S*,8a*S*)-5-Hydroxy-4a-methyl-8-phenyl-1,3,4,4a,5,8a-hexahydronaphthalene-2,6-dione 177

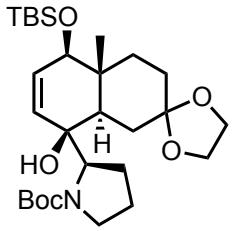


PhMgBr (153 μL of a 3.0 M solution in Et_2O, 0.46 mmol) was added dropwise to a stirred solution of enone **166** (80 mg, 0.23 mmol) in THF (3 mL) at 0 °C under Ar. The resulting mixture was stirred at 0 °C for 1 h. Then, saturated $NH_4Cl_{(aq)}$ (10 mL) and CH_2Cl_2 (10 mL) were added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude tertiary alcohol **175**. PCC (98 mg, 0.41 mmol) was added to a stirred solution of the crude tertiary alcohol **175** in CH_2Cl_2 (10 mL) at rt under Ar. The resulting mixture was stirred at rt for 22 h. Then, Celite® (1 g) and Et_2O (10 mL) were added and the solids were removed by filtration through a Celite® pad. The Celite® pad was washed with Et_2O (5 × 20 mL). The combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude enone **176**. $HF_{(aq)}$ (16 μL of a 40 wt% aqueous solution, 0.38 mmol) was added to a stirred solution of the crude enone **176** in MeCN (1 mL) at rt in a plastic reaction vessel. The resulting mixture was stirred at rt for 8 h. Then, saturated $NaHCO_{3(aq)}$ (10 mL) and CH_2Cl_2 (10 mL) were added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with Et_2O as eluent gave dione **177** (24 mg, 39%) as a white solid, mp 163–164 °C (Decomposed); $[\alpha]_D$ +290.8 (*c* 1.2 in $CHCl_3$); R_F (Et_2O) 0.29; IR (Thin Film)

3364 (OH), 1684 (C=O), 1651 (C=O), 1113, 758 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.42–7.36 (m, 3H, Ar), 7.20–7.15 (m, 2H, Ph), 6.20 (d, *J* = 2.9 Hz, 1H, CH=), 4.15 (s, 1H, CHO), 3.80 (s, 1H, OH), 3.34 (ddd, *J* = 14.0, 4.0, 3.0 Hz, 1H, =CCH), 2.58–2.32 (m, 4H), 2.11 (dd, *J* = 15.5, 14.0 Hz, 1H), 1.91 (td, *J* = 12.5, 6.5 Hz, 1H), 1.06 (s, 3H, CMe); ^{13}C NMR (100.6 MHz; $CDCl_3$) δ: 209.0 (C=O), 198.6 (C=O), 163.0 (CH=*C*), 137.6 ($C_{i\text{-}Ph}$), 129.4 (CH), 128.9 (CH), 126.7 (CH), 125.8 (CH), 81.5 (CHO), 45.5 (=C*C*H), 43.6 (*C*Me), 40.6 (CH_2), 37.0 (CH_2), 34.7 (CH_2), 9.7 (C*Me*); MS (ESI) 293 [$(M + Na)^+$, 64], 271 [$(M + H)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{17}H_{18}O_3$ $(M + Na)^+$ 293.1148 found 293.1149 (−0.4 ppm error), *m/z* calcd for $C_{17}H_{18}O_3$ $(M + H)^+$ 271.1329 found 271.1331 (−0.7 ppm error).

Lab book reference: djbI2/27

(*R*)-*tert*-Butyl 2-((4a'*R*,5'*R*,8'*S*,8a'*R*)-5'-((*tert*-Butyldimethylsilyl)oxy)-8'-hydroxy-4a'-methyl-3',4',4a',5',8',8a'-hexahydro-1'*H*-spiro[[1,3]dioxolane-2,2'-naphthalen]-8'-yl)pyrrolidine-1-carboxylate 179

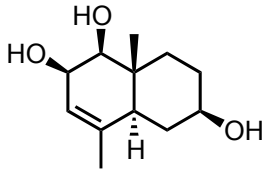


s-BuLi (213 μL of a 1.3 M solution in cyclohexane, 0.28 mmol) was added dropwise to a stirred solution of *N*-Boc pyrrolidine (38 μL, 0.28 mmol) and (−)-sparteine (64 μL, 0.28 mmol) in Et_2O (1 mL) at −78 °C under Ar. The resulting mixture was stirred at −78 °C for 1 h. Then, a solution of enone **166** (50 mg, 0.14 mmol) in Et_2O (1 mL) was added dropwise over 15 min. The resulting mixture was stirred at −78 °C for 6 h. Then, saturated $NH_4Cl_{(aq)}$ (10 mL) and CH_2Cl_2 (10 mL) were added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with petrol-EtOAc (4:1) as eluent gave alcohol **179** (49 mg, 66%) as a colourless oil, R_F (Et_2O) 0.71; ^1H NMR (400 MHz, $CDCl_3$) δ: 5.48 (d, *J* = 10.5 Hz, 1H, =CH), 5.37 (dd, *J* = 10.5, 2.0 Hz, 1H, =CH), 3.97–3.89 (m, 5H, OCH_2CH_2O + CHN), 3.69 (dd, *J*

= 2.0, 1.5 Hz, 1H, CHO), 3.67–3.59 (m, 1H, CHN), 3.21 (ddd, *J* = 11.0, 8.5, 6.5 Hz, 1H, CH_AH_BN), 2.01–1.45 (m, 10H), 1.45 (s, 9H, NBoc), 1.27–1.15 (m, 1H), 0.94 (s, 3H, Me), 0.88 (s, 9H, Si*t*-Bu), 0.05 (s, 3H, SiMe), 0.03 (s, 3H, SiMe);

Lab book reference: djbI2/17

(1*S*,2*R*,4a*S*,6*R*,8a*R*)-4,8a-Dimethyl-1,2,4a,5,6,7,8,8a-octahydronaphthalene-1,2,6-triol 180



BH_3·THF (48 μL of a 1.0 M solution in THF, 0.05 mmol) was added to a stirred solution of enone **174** (9 mg, 0.04 mmol) in THF (1 mL) at 0 °C under Ar. The resulting mixture was stirred at 0 °C for 2 h. Then, saturated $NaHCO_{3(aq)}$ (5 mL) and CH_2Cl_2 (5 mL) were added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with petrol-EtOAc (1:10) as eluent gave dione **180** (2 mg, 22%) as a colourless oil, R_F (1:10 petrol-EtOAc) 0.16; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.64–5.61 (m, 1H, =CH), 4.16–4.12 (m, 1H, C*H*OH), 3.62 (tt, *J* = 11.0, 5.0 Hz, 1H, C*H*OH), 3.33 (d, *J* = 5.5 Hz, 1H, C*H*OH), 2.06 (dddd, *J* = 12.0, 5.0, 3.0, 2.0 Hz, 1H), 1.98 (ddd, *J* = 13.5, 5.0, 3.0 Hz, 1H), 1.89–1.82 (m, 2H), 1.69 (q, *J* = 1.5 Hz, 3H, =CMe), 1.53–1.44 (m, 1H), 1.32 (ddd, *J* = 13.0, 12.0, 11.0 Hz, 1H), 1.21–1.13 (m, 1H), 0.85 (s, 3H, Me). *Product decomposed on standing overnight.*

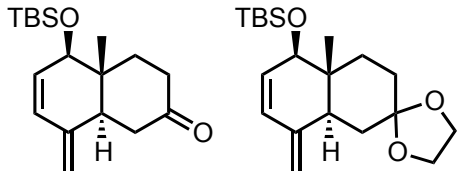
Lab book reference: djbI/74

$NaBH_4$ (9 mg, 0.24 mmol) was added to a stirred solution of dried $ZnCl_2$ (16 mg, 0.12 mmol) in THF (2 mL) at rt under Ar. The resulting mixture was stirred at rt for 6 h. The $Zn(BH_4)_2$ solution was cooled to 0 °C and a solution enone **174** (25 mg, 0.12 mmol) in THF (1 mL) was added dropwise over 5 min. The resulting mixture

was stirred at 0 °C for 1 h. Then, saturated $NH_4Cl_{(aq)}$ (5 mL) and CH_2Cl_2 (5 mL) were added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with petrol-EtOAc (1:10) as eluent gave dione **180** (6 mg, 40%) as a colourless oil. *Product decomposed on standing overnight.*

Lab book reference: djbI2/58

(4a*R*,5*R*,8a*S*)-5-((*tert*-Butyldimethylsilyl)oxy)-4a-methyl-8-methylene-3,4,4a,5,8,8a-hexahydronaphthalen-2(1*H*)-one 182 and *tert*-Butyldimethyl(((4a'*R*,5'*R*,8a'*S*)-4a'-methyl-8'-methylene-3',4',4a',5',8',8a'-hexahydro-1'*H*-spiro[[1,3]dioxolane-2,2'-naphthalen]-5'-yl)oxy)silane 183

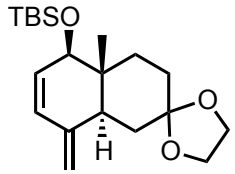


182 **183**

*p*TSA·H_2O (11 mg, 0.06 mmol) was added to a stirred solution of alcohol **168** (74 mg, 0.23 mmol) in acetic acid (1 mL) and Ac_2O (500 μL) at 0 °C under Ar. The resulting mixture was stirred at 0 °C for 30 min. Then, saturated $NaHCO_{3(aq)}$ (10 mL) and CH_2Cl_2 (10 mL) were added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with petrol-EtOAc (4:1) as eluent gave (by ^{1}H NMR spectroscopy) a 67:33 mixture of ketone **182** and ketal **183** (44 mg, 69%) as a colourless oil, R_F (Et_2O) 0.31; ^{1}H NMR (400 MHz) δ: 6.10 (dd, *J* = 10.0, 2.5 Hz, 0.67H, =$CH_{\mathbf{182}}$), 6.05 (dd, *J* = 10.0, 2.5 Hz, 0.33H, =$CH_{\mathbf{183}}$), 5.49 (d, *J* = 10.0 Hz, 0.67H, =$CH_{\mathbf{182}}$), 5.43 (d, *J* = 10.0 Hz, 0.33H, =$CH_{\mathbf{183}}$), 4.95 (s, 0.67H, =CH_AH$_{B\mathbf{182}}$), 4.86 (s, 0.33H, =CH_AH$_{B\mathbf{183}}$), 4.72 (s, 1H, =CH$_A$$H_{B\mathbf{182+183}}$), 4.09 (s, 1H, CHO), 4.00–3.92 (m, 1.32H, $OCH_2CH_2O_{\mathbf{183}}$), 2.54–1.41 (m, 10H), 0.91 (s, 6.03H, Si*t*-$Bu_{\mathbf{182}}$), 0.89 (s, 2.97H, Si*t*-$Bu_{\mathbf{183}}$), 0.10 (s, 2.01H, $SiMe_{\mathbf{182}}$), 0.07 (s, 0.99H, $SiMe_{\mathbf{183}}$), 0.06 (s, 2.01H, $SiMe_{\mathbf{182}}$), 0.05 (s, 0.99H, $SiMe_{\mathbf{183}}$).

Lab book reference: djbI2/6

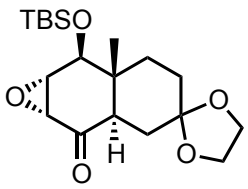
tert-Butyldimethyl(((4a'*R*,5'*R*,8a'*S*)-4a'-methyl-8'-methylene-3',4',4a',5',8',8a'-hexahydro-1'*H*-spiro[[1,3]dioxolane-2,2'-naphthalen]-5'-yl)oxy)silane 183



KHMDS (109 μL of a 0.7 M solution in THF, 0.08 mmol) was added dropwise to a stirred solution of alcohol **168** (12 mg, 0.04 mmol) in THF (1 mL) at −78 °C under Ar. The resulting mixture was stirred at −78 °C for 30 min. Then, freshly distilled AcCl (4 μL, 0.05 mmol) was added and the resulting mixture was allowed to warm to rt and stirred at rt for 1 h. Then, saturated $NaHCO_{3(aq)}$ (5 mL) and CH_2Cl_2 (5 mL) were added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (5 × 5 mL). The combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with petrol-EtOAc (4:1) as eluent gave diene **183** (10 mg, 75%) as a colourless oil, R_F (Et_2O) 0.31; ^{1}H NMR (400 MHz) δ: 6.10 (ddd, J = 10.0, 2.5, 0.5 Hz, 1H, =CH), 5.49 (d, J = 10.0 Hz, 1H, =CH), 4.95 (s, 1H, =CH_AH$_B$), 4.72 (s, 1H, =CH$_A$$H_B$), 4.11–4.07 (m, 1H, CHO), 4.00–3.92 (m, 4H, OCH_2CH_2O), 2.54–1.41 (m, 10H), 0.91 (s, 9H, Si*t*-Bu), 0.10 (s, 3H, SiMe), 0.06 (s, 3H, SiMe).

Lab book reference: djbI2/13

(1a'*R*,2a'*R*,6a'*R*,7'*S*,7a'*S*)-7'-((*tert*-Butyldimethylsilyl)oxy)-6a'-methylhexahydro-1a'*H*-spiro[[1,3]dioxolane-2,4'-naphtho[2,3-b]oxiren]-2'(5'*H*)-one 187

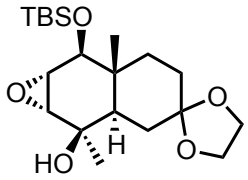


TBHP (234 μL of a 6.0 M solution in decane, 1.41 mmol) and Triton B (2 μL, 0.01 mmol) were added to a stirred solution of enone **166** (99 mg, 0.28 mmol) in THF (5 mL) at 0 °C under Ar. The resulting mixture was stirred at 0 °C for 2 h and then

allowed to warm to rt and stirred for 14 h. Then, saturated brine (10 mL) and CH_2Cl_2 (10 mL) were added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with petrol-EtOAc (4:1) as eluent gave epoxy ketone **187** (77 mg, 75%) as a colourless oil, R_F (4:1 petrol-EtOAc) 0.34; IR (Thin Film) 2953, 1714 (C=O), 1258, 872 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 3.96–3.85 (m, 5H, OCH_2CH_2O + CHOTBS), 3.29 (d, J = 3.5 Hz, 1H, $CHO_{epoxide}$), 3.26 (dd, J = 3.5, 0.5 Hz, 1H, $CHO_{epoxide}$), 2.73 (dd, J = 10.0, 7.0 Hz, 1H, COCH), 1.75–1.48 (m, 6H), 0.91 (s, 9H, Si*t*-Bu), 0.80 (s, 3H, CMe), 0.17 (s, 3H, SiMe), 0.11 (s, 3H, SiMe); ^{13}C NMR (100.6 MHz; $CDCl_3$) δ: 206.8 (C=O), 108.6 (OCO), 76.4 (CHO), 64.5 (OCH_2), 64.4 (OCH_2), 62.4 ($CHO_{epoxide}$), 55.2 ($CHO_{epoxide}$), 44.6 (*C*Me), 44.3 (CO*C*H), 35.8 (CH_2), 30.4 (CH_2), 29.2 (CH_2), 25.9 (C*Me*$_3$), 18.1 (*C*Me$_3$), 12.5 (C*Me*), −4.2 (SiMe), −4.9 (SiMe); MS (ESI) 391 [$(M + Na)^+$, 11], 369 [$(M + H)^+$, 100)]; HRMS (ESI) *m/z* calcd for $C_{19}H_{32}O_5Si$ $(M + Na)^+$ 391.1911 found 391.1902 (2.2 ppm error), *m/z* calcd for $C_{19}H_{32}O_5Si$ $(M + H)^+$ 369.2092 found 369.2077 (4.1 ppm error).

Lab book reference: djbI2/57

(1a'*R*,2'*R*,2a'*R*,6a'*R*,7'*S*,7a'*S*)-7'-((*tert*-Butyldimethylsilyl)oxy)-2',6a'-dimethyloctahydro-1a'*H*-spiro[[1,3]dioxolane-2,4'-naphtho[2,3-*b*]oxiren]-2'-ol 190

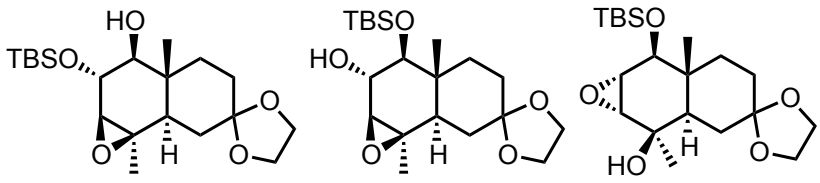


MeLi (143 μL of a 1.6 M solution in Et_2O, 0.23 mmol) was added to a stirred suspension of CuI (22 mg, 0.11 mmol) in THF (5 mL) at 0 °C. The resulting solution was stirred at 0 °C for 15 min. Then, a solution of epoxy ketone **187** (21 mg, 0.06 mmol) in THF (5 mL) was added dropwise over 15 min and the resulting mixture was stirred at 0 °C for 30 min. Then, saturated $NH_4Cl_{(aq)}$ (10 mL) and CH_2Cl_2 (10

mL) were added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (5 × 10 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with petrol-EtOAc (4:1) as eluent gave epoxy alcohol **190** (20 mg, 90%) as a colourless oil, $[\alpha]_D$ −19.7 (*c* 1.0 in $CHCl_3$); R_F (Et_2O) 0.41; IR (Thin Film) 3440 (OH), 2906, 1442, 1235, 1088, 858, 763 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 3.97–3.89 (m, 4H, OCH_2CH_2O), 3.33 (s, 1H, CHO), 3.03 (d, *J* = 0.5 Hz, 2H, 2 × $CHO_{epoxide}$), 1.81–1.68 (m, 2H), 1.65–1.55 (m, 3H), 1.36 (d, *J* = 3.5 Hz, 1H), 1.29 (s, 3H, *Me*COH), 1.20–1.12 (m, 1H), 0.97 (s, 3H, CMe), 0.91 (s, 9H, Si*t*-Bu), 0.13 (s, 3H, SiMe), 0.06 (s, 3H, SiMe); ^{13}C NMR (100.6 MHz; $CDCl_3$) δ: 109.6 (OCO), 77.9 (CHO), 69.9 (Me*C*OH), 64.4 (OCH_2), 64.3 (OCH_2), 60.1 ($CHO_{epoxide}$), 59.0 ($CHO_{epoxide}$), 41.6 (CH), 37.3 (CH_2), 36.1 (*C*Me), 30.5 (CH_2), 30.0 (CH_2), 26.2 (*Me*COH), 25.9 (C*Me*$_3$), 18.1 (*C*Me$_3$), 13.2 (C*Me*), −4.3 (SiMe), −5.0 (SiMe); MS (ESI) 385 [$(M + H)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{20}H_{36}O_5Si$ $(M + H)^+$ 385.5901 found 385.2396 (−0.5 ppm error).

Lab book reference: djbI2/79

(1a'*S*,2'*R*,3'*S*,3a'*R*,7a'*R*,7b'*R*)-2'-((*tert*-Butyldimethylsilyl)oxy)-3a',7b'-dimethyloctahydro-1a'*H*-spiro[[1,3]dioxolane-2,6'-naphtho[1,2-*b*]oxiren]-3'-ol 193 and (1a'*S*,2'*S*,3'*S*,3a'*R*,7a'*R*,7b'*R*)-3'-((*tert*-Butyldimethylsilyl)oxy)-3a',7b'-dimethyloctahydro-1a'*H*-spiro[[1,3]dioxolane-2,6'-naphtho[1,2-*b*]oxiren]-2'-ol 191 and (1a'*R*,2'*R*,2a'*R*,6a'*R*,7'*S*,7a'*S*)-7'-((*tert*-Butyldimethylsilyl)oxy)-2',6a'-dimethyloctahydro-1a'*H*-spiro[[1,3]dioxolane-2,4'-naphtho[2,3-*b*]oxiren]-2'-ol 190

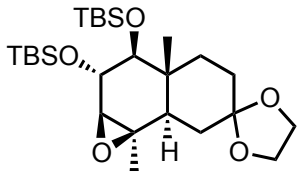


193 **191** **190**

MeLi (344 μL of a 1.6 M solution in Et_2O, 0.41 mmol) was added to a stirred solution of epoxy ketone **187** (76 mg, 0.21 mmol) in THF (5 mL) at rt under Ar. The resulting mixture was stirred at 0 °C for 30 min. The mixture was then allowed to warm to rt and stirred for 12 h. Then, saturated $NH_4Cl_{(aq)}$ (10 mL) and CH_2Cl_2 (10 mL) were added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (5 × 10 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with petrol-EtOAc (4:1) as eluent gave epoxy alcohol **193** (9 mg, 11%) as a colourless oil, R_F (4:1 petrol:EtOAc) 0.31; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.99–3.94 (m, 4H, OCH_2CH_2O), 3.88 (d, J = 8.5 Hz, 1H, CHO), 3.11 (dd, J = 8.5, 2.5 Hz, 1H, C*H*OH), 2.74 (s, 1H, $CHO_{epoxide}$), 1.96–1.92 (m, 1H), 1.90–1.88 (m, 1H), 1.84–1.62 (m, 5H), 1.57 (s, 3H, *Me*CHO), 1.25 (s, 3H, Me), 0.93 (s, 9H, Si*t*-Bu), 0.17 (s, 3H, SiMe), 0.15 (s, 3H, SiMe) and gave (by ^{1}H NMR spectroscopy) a 77:23 mixture of epoxy alcohol **191** and epoxy alcohol **190** (54 mg, 68%) as a colourless oil, R_F (4:1 petrol:EtOAc) 0.15; ^{1}H NMR (400 MHz, $CDCl_3$)(data for **191**) δ: 4.00–3.90 (m, 5H, OCH_2CH_2O + C*H*OH), 3.13 (d, J = 8.0 Hz, 1H, CHO), 2.85 (s, 1H, $CHO_{epoxide}$), 2.1–1.56 (m, 7H), 1.25 (s, 3H, *Me*CHO), 0.92 (s, 3H, Me), 0.89 (s, 9H, Si*t*-Bu), 0.11 (s, 3H, SiMe), 0.06 (s, 3H, SiMe).

Lab book reference: djbI2/60

(((1a'*S*,2'*S*,3'*S*,3a'*R*,7a'*R*,7b'*R*)-3a',7b'-Dimethyloctahydro-1a'*H*-spiro[[1,3]dioxolane-2,6'-naphtho[1,2-*b*]oxirene]-2',3'-diyl)bis(oxy))bis(*tert*-butyldimethylsilane) 194



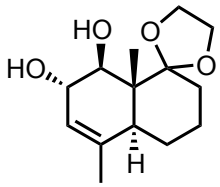
TBSOTf (7 μL, 0.04 mmol) was added to a stirred solution of epoxy alcohol **193** (9 mg, 0.02 mmol) and 2,6-lutidine (6 μL, 0.05 mmol) in THF (1 mL) at rt under Ar. The resulting mixture was stirred at rt for 1 h. Then, saturated $NaHCO_{3(aq)}$ (5 mL) and CH_2Cl_2 (5 mL) were added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (5 × 5 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with petrol-EtOAc (4:1) as eluent gave epoxide **194** (1 mg, 9%) as a colourless oil, R_F (4:1 petrol:EtOAc) 0.39; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.90–3.85 (m, 5H, OCH_2CH_2O + CHO), 3.08 (d, J = 8.0 Hz, 1H, CHO), 2.67 (s, 1H, $CHO_{epoxide}$), 1.87–1.41 (m, 10H), 1.15 (s, 3H, Me), 0.89 (s, 9H, Si*t*-Bu), 0.80 (s, 9H, Si*t*-Bu), 0.11 (s, 3H, SiMe), 0.05 (s, 3H, SiMe), 0.00 (s, 3H, SiMe), 0.06 (s, 3H, SiMe); MS (ESI) 499 [$(M + H)^+$, 9], 481 (100); HRMS (ESI) *m/z* calcd for $C_{26}H_{50}O_5Si_2$ $(M + H)^+$ 499.3270 found 499.3287 (−3.4 ppm error). *Note: Epoxide **194** decomposed on standing.*

Lab book reference: djbI2/66

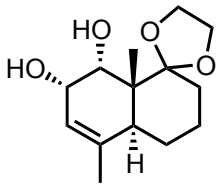
TBSOTf (49 μL, 0.21 mmol) was added to a stirred solution of a 77:23 mixture of epoxy alcohol **191** and epoxy alcohol **190** (54 mg, 0.14 mmol) and 2,6-lutidine (33 μL, 0.28 mmol) in THF (5 mL) at rt under Ar. The resulting mixture was stirred at rt for 1 h. Then, saturated $NaHCO_{3(aq)}$ (10 mL) and CH_2Cl_2 (10 mL) were added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (5 × 10 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with petrol-EtOAc (4:1) as eluent gave epoxide **194** (19 mg, 27%) as a colourless oil. *Product decomposed on standing.*

Lab book reference: djbI2/67

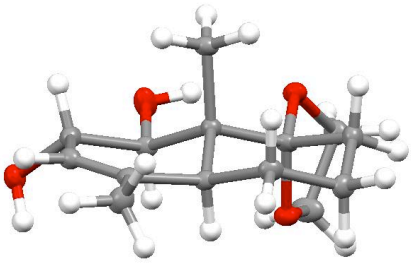
(4a'*S,7'*S**,8'*R**,8a'*R**)- and (4a'*S**,7'*S**,8'S*,8a'R*)-5',8a'-Dimethyl-3',4',4a',7',8',8a'-hexa- hydro-2'*H*-spiro[[1,3]dioxolane-2,1'-naphthalene]-7',8'-diol *trans*-196 and *cis*-196**



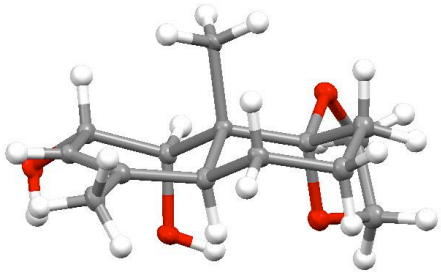
trans-**196**



cis-**196**



X-ray crystal structure of *trans*-196



X-ray crystal structure of *trans*-196

$NaBH_4$ (19 mg, 0.49 mmol) was added to a stirred solution of α-hydroxy-ketone **197** (31 mg, 0.12 mmol) in MeOH (5 mL) at 0 °C under Ar. The resulting mixture was stirred at 0 °C for 1 h. Then, saturated $NH_4Cl_{(aq)}$ (10 mL) was added and the mixture was extracted with Et_2O (3 × 5 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude products which contained an 82:18 mixture of diols *trans*-**196** and *cis*-**196** (by ^1H NMR spectroscopy). Purification by flash column chromatography on silica with petrol–EtOAc (2:3) as eluent gave diol *cis*-**196** (4 mg, 13%) as a white solid, mp 140–146 °C; R_F (2:3 petrol–EtOAc) 0.25; IR (Thin Film) 3415 (OH), 2904 1420, 1063, 997, 855 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 5.34–5.31 (m, 1H, =CH), 4.15–3.91 (m, 6H, OCH_2OCH_2 + 2 × C*H*OH), 2.64–2.61 (m, 1H), 1.83 (dq, *J* = 13.0, 3.0 Hz, 1H), 1.76–1.67 (m, 5H), 1.64–1.44 (m, 2H), 1.32–1.21 (m, 1H), 0.92 (s, 3H, CMe); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 136.6 (=*C*Me), 123.9 (=CH), 114.6 (OCO), 70.5 (CHOH), 67.6 (CHOH), 65.0 (OCH_2), 64.0 (OCH_2), 45.7 (*C*Me), 38.8 (CH), 29.4 (CH_2), 22.9 (CH_2), 21.9 (CH_2), 21.4 (=C*Me*), 15.1 (C*Me*); MS (ESI) 277 [(M + $Na)^+$]; HRMS (ESI) *m/z* calcd for $C_{14}H_{22}O_4$ $(M + Na)^+$ 277.1410 found 277.1408 (0.7 ppm error) and gave diol *trans*-**196** (25 mg, 80%) as a white solid, mp 145–147 °C; R_F (2:3 petrol–EtOAc) 0.11; IR (Thin Film) 3396 (OH), 2905, 1419, 1181, 1060, 720 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 5.32–5.29 (m, 1H, =CH), 4.14–3.89 (m,

6H, OCH_2CH_2O + 2 × C*H*OH), 2.46–2.42 (m, 1H), 1.75–1.22 (m, 9H), 1.06 (s, 3H, CMe); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 136.9 (=*C*Me), 122.3 (=CH), 114.2 (OCO), 76.8 (CHOH), 73.3 (CHOH), 64.6 (OCH_2), 63.6 (OCH_2), 45.2 (*C*Me), 44.4 (CH), 28.4 (CH_2), 22.7 (CH_2), 22.2 (CH_2), 21.2 (=C*Me*), 10.1 (C*Me*); MS (ESI) 277 [(M + Na)$^+$]; HRMS (ESI) *m/z* calcd for $C_{14}H_{22}O_4$ (M + Na)$^+$ 277.1410 found 277.1405 (1.5 ppm error).

Crystal structure determination of diol *cis*-196

$C_{14}H_{22}O_4$, M = 254.32, monoclinic, a = 7.1504(3), b = 7.1378(3), c = 24.5830(13) Å, β = 96.665°, U = 1246.19(10) Å^3, T = 110(10) K, space group Pn, Z = 4, μ(Mo-Kα) = 0.098 mm^{-1}, 18108 reflections measured, 4557 unique (R_{int} = 0.0644) which were used in calculations. The final R1 was 0.0932 (I>2σ$_I$) and wR2 was 0.2180 (all data).

Crystal structure determination of diol *trans*-196

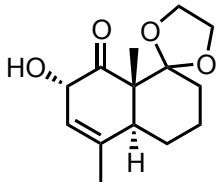
$C_{14}H_{22}O_4$, M = 254.32, monoclinic, a = 11.9035(6), b = 9.1144(4), c = 12.4728(7) Å, β = 110.195°, U = 1270.02(11) Å^3, T = 110(10) K, space group P2$_1$/n, Z = 4, μ(Mo-Kα) = 0.096 mm^{-1}, 4830 reflections measured, 2374 unique (R_{int} = 0.0248) which were used in calculations. The final R1 was 0.0545 (I>2σ$_I$) and wR2 was 0.1065 (all data).

Lab book reference: djbI3/88

DIBAL-H (183 μL of a 1.0 M solution in toluene, 0.18 mmol) was added dropwise to a stirred solution of α-hydroxy ketone **197** (15 mg, 0.06 mmol) in THF (5 mL) at −78 °C under Ar. The resulting solution was stirred at −78 °C for 3 h. Then, saturated $NH_4Cl_{(aq)}$ (10 mL) was added and the mixture was extracted with Et_2O (3 × 5 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with petrol–EtOAc (2:3) as eluent gave diol *cis*-**196** (11 mg 73%) as a white solid.

Lab book reference: djbI3/60

(4a'*S,7'*S**,8a'*R**)-7'-Hydroxy-5',8a'-dimethyl-4',4a',7',8a'-tetrahydro-2'*H*-spiro[[1,3]-dioxolane- 2,1'-naphthalen]-8'(3'*H*)-one 197**



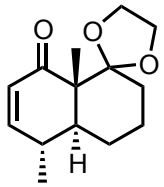
Et_3N (196 μL, 1.41 mmol) and Me_3SiOTf (127 μL, 0.70 mmol) were added to a stirred solution of enone **199** (83 mg, 0.35 mmol) in CH_2Cl_2 (6 mL) at rt under Ar. The resulting mixture was stirred at rt for 1 h. Then, saturated $NaHCO_{3(aq)}$ (10 mL) was added and the mixture was extracted with CH_2Cl_2 (4 × 5 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude silyl enol ether **214**. Then, $NaHCO_3$ (118 mg, 1.41 mmol) and purified *m*CPBA (61 mg, 0.35 mmol) were added to a stirred solution of the crude silyl enol ether **214** in CH_2Cl_2 (6 mL) at 0 °C under Ar. The resulting mixture was stirred at 0 °C for 1 h. After being allowed to warm to rt, $NaHCO_{3(aq)}$ (10 mL) was added and the mixture was extracted with CH_2Cl_2 (4 × 5 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude α-siloxy ketone **216**. Then, TBAF (703 μL of a 1 M solution in THF, 0.70 mmol) was added to a stirred solution of the crude epoxy silyl ether in CH_2Cl_2 (6 mL) at rt under Ar. The resulting mixture was stirred at rt for 10 min. Then, staturated $NH_4Cl_{(aq)}$ (10 mL) was added and the mixture was extracted with CH_2Cl_2 (4 × 5 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with petrol–EtOAc (4:1) as eluent gave α-hydroxy ketone **197** (63 mg, 70%) as a colourless oil, R_F (2:3 petrol–EtOAc) 0.45; IR (Thin Film) 3397 (OH), 2904, 1700 (C=O), 1073, 862 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 5.53 (tq, J = 3.0, 1.5 Hz, 1H, =CH), 4.66–4.63 (m, 1H, C*H*OH), 4.32–4.16 (m, 2H, OCH_2), 4.02–3.94 (m, 2H, OCH_2), 2.88–2.84 (m, 1H, CH), 1.82–1.44 (m, 10H), 1.37 (s, 3H, CMe); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 208.3 (C=O), 138.1 (=*C*Me), 122.5 (=CH), 110.5 (OCO), 70.2 (CHOH), 65.7 (OCH_2), 65.3 (OCH_2), 54.6 (*C*Me), 47.1 (CH), 31.2 (CH_2), 22.5 (CH_2), 22.4 (CH_2), 21.1 (=C*Me*), 15.5 (C*Me*); MS (ESI) 275 [$(M + Na)^+$]; HRMS (ESI) *m/z* calcd for $C_{14}H_{20}O_4$ $(M + Na)^+$ 275.1254 found 275.1247 (+1.2 ppm error).

Lab book reference: djbI3/62

TBAF (508 μL of a 1 M solution in THF, 0.51 mmol) was added to a stirred solution of α-siloxy ketone **216** (45 mg, 0.14 mmol) in CH_2Cl_2 (6 mL) at rt under Ar. The resulting mixture was stirred at rt for 10 min. Then, staturated $NH_4Cl_{(aq)}$ (10 mL) was added and the mixture was extracted with CH_2Cl_2 (4 × 5 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with petrol–EtOAc (4:1) as eluent gave α-hydroxy ketone **197** (25 mg, 70%) as a colourless oil.

Lab book reference: djbI3/59

(4a'*RS,5'*RS**,8a'*RS**)-5',8a'-Dimethyl-3',4',4a',5'-tetrahydro-2'*H*-spiro-[[1,3]dioxolane-2,1'naphthalen]- 8'(8a'*H*)-one 199**



DMP (71 mg, 0.17 mmol) was added to a stirred solution of allylic alcohol *trans*-**213** (27 mg, 0.11 mmol) in CH_2Cl_2 (2 mL) at rt under Ar. The resulting mixture was stirred at rt for 1 h. Then, saturated $NaHCO_{3(aq)}$ (5 mL) and saturated $Na_2S_2O_{3(aq)}$ (5 mL) were added and the resulting biphasic mixture was stirred at rt for 1 h. Then, CH_2Cl_2 (10 mL) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with petrol–EtOAc (4:1) as eluent gave enone **199** (23 mg, 87%) as a colourless oil, R_F (2:3 petrol– EtOAc) 0.58; IR (Thin Film) 2901, 1658 (C=O), 1172, 898, 821 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 6.51 (ddd, J = 10.0, 2.5, 0.5 Hz, 1H, COCH=C*H*), 5.75 (dd, J = 10.0, 2.5 Hz, 1H, COC*H*=CH), 4.35–4.30 (m, 1H, OCH_AH_B), 4.05–3.88 (m, 3H, OCH_2 + OCH_AH_B), 2.24 (dqt, J = 10.0, 7.5, 2.5 Hz, 1H, C*H*Me), 1.97 (ddd, J = 12.5, 10.0, 3.5 Hz, 1H CH), 1.80–1.73 (m, 1H), 1.70–1.45 (m, 4H), 1.33–1.25 (m, 1H), 1.22 (s, 3H, Me), 1.12 (d, J = 7.5 Hz, 3H, CH*Me*);.^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 201.5 (C=O), 152.5 (COCH=*C*H), 128.2 (CO*C*H=CH), 111.5 (OCO), 65.8 (OCH_2), 64.7 (OCH_2), 52.1 (*C*Me), 46.8 (*C*HMe), 33.4 (CH), 32.4 (CH_2), 23.9 (CH_2), 22.5 (CH_2),

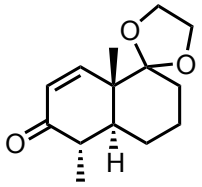
19.0 (CH*Me*), 13.9 (C*Me*); MS (ESI) 259 [$(M + Na)^+$]; HRMS (ESI) *m/z* calcd for $C_{14}H_{20}O_3$ $(M + Na)^+$ 259.1305 found 259.1303 (0.2 ppm error).

Lab book reference: This reaction was carried out by Stefan Mommer sm1/34

$NH_2NH_2{\cdot}H_2O$ (89 μL of a 50% solution in water, 1.43 mmol) was added to a stirred solution of an 85:15 mixture of epoxy ketones *trans*-**210** and *cis*-**210** (300 mg, 1.19 mmol) in MeOH (10 mL) at 0 °C under Ar. The resulting mixture was stirred at 0 °C for 15 min. Then, AcOH (136 μL, 2.38 mmol) was added and the mixture was allowed to warm to rt over 1 h. Then, $NaHCO_{3(aq)}$ (10 mL) and CH_2Cl_2 (10 mL) were added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude allylic alcohols. DMP (1.0 g, 2.38 mmol) was added to a stirred solution of the crude allylic alcohols in CH_2Cl_2 (10 mL) at rt under Ar. The resulting mixture was stirred at rt for 1 h. Then, saturated $NaHCO_{3(aq)}$ (10 mL) and saturated $Na_2S_2O_{3(aq)}$ (10 mL) were added and the resulting biphasic mixture was stirred at rt for 1 h. Then, CH_2Cl_2 (20 mL) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with petrol–EtOAc (4:1) as eluent gave enone **199** (185 mg, 60%) as a colourless oil.

Lab book reference: djbI3/54

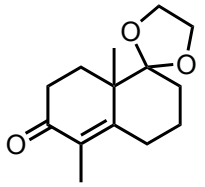
(4a'*RS,5'*RS**,8a'*RS**)-5',8a'-Dimethyl-3',4',4a',5'-tetrahydro-2'*H*-spiro[[1,3]dioxolane-2,1'-naph-thalen]-6'(8a'*H*)-one 200**



KHMDS (6.00 mL of a 0.7 M solution in toluene, 4.20 mmol) was added dropwise to a stirred solution of ketone **202** (500 mg, 2.10 mmol) in THF (10 mL) at −78 °C under Ar. The resulting solution was stirred at –78 °C for 1 h. Me_3SiCl (533 μL, 4.20 mmol) was added and the solution was stirred at –78 °C for 30 min. Then, $NaHCO_{3(aq)}$ (20 mL) and CH_2Cl_2 (20 mL) were added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude silyl enol ether. $Pd(OAc)_2$ (518 mg, 2.31 mmol) was added to a stirred solution of the crude silyl enol ether in MeCN (10 mL) at rt under Ar. The resulting mixture was stirred and heated at 80 °C for 1 h. After being allowed to cool to rt, the solids were removed by filtration and the filtrate was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with petrol–EtOAc (4:1) as eluent gave enone **200** (405 mg, 82%) as a colourless oil, R_F (2:3 petrol–EtOAc) 0.60; IR (Thin Film) 1676 (C=O), 1184, 875 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.01 (d, *J* = 10.0 Hz, 1H, COCH=C*H*), 5.87 (d, *J* = 10.0 Hz, 1H, COC*H*=CH), 4.04–3.91 (m, 4H, OCH_2CH_2O), 2.25 (dq, *J* = 13.0, 6.5 Hz, 1H, C*H*Me), 2.04 (td, *J* = 13.0, 3.0 Hz, 1H, CH), 1.73–1.43 (m, 5H), 1.32–1.20 (m, 1H), 1.16 (s, 3H, CMe), 1.09 (d, *J* = 6.5 Hz, 3H, CH*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 201.6 (C=O), 155.5 (COCH=*C*H), 127.6 (CO*C*H=CH), 111.5 (OCO), 65.3 (OCH_2), 64.8 (OCH_2), 45.8 (CH), 45.3 (*C*Me), 42.0 (CO*C*H), 29.2 (CH_2), 23.8 (CH_2), 22.7 (CH_2), 16.1 (Me), 12.4 (C*Me*); MS (ESI) 237 [$(M + H)^+$]; HRMS (ESI) *m/z* calcd for $C_{14}H_{20}O_3$ $(M + H)^+$ 237.1485 found 237.1485 (–1.5 ppm error). Spectroscopic data are consistent with those reported in the literature.[273]

Lab book reference: djbI3/9

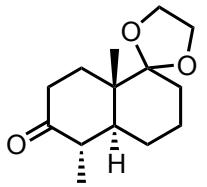
(*RS*)-5',8a'-Dimethyl-3',4',8',8a'-tetrahydro-2'*H*-spiro[[1,3]dioxolane-2,1'-naphthalen]-6'(7'*H*)-one 201



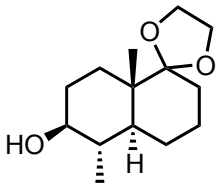
*p*TSA·H_2O (0.12 g, 0.72 mmol) and ethylene glycol (25.1 mL, 0.45 mol) were added to a stirred solution of enone **70** (5.97 g, 31.0 mmol) in benzene (50 mL) at rt. The resulting mixture was stirred and heated at reflux for 2 h using a Dean-Stark trap. The reaction mixture was allowed to cool to rt. Saturated $NaHCO_{3(aq)}$ (50 mL) was added and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 50 mL). The combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with petrol–EtOAc (1:1) as eluent gave ketal **201** (5.92 g, 81%) as a colourless oil, R_F (2:3 petrol–EtOAc) 0.56; IR (Thin Film) 2950, 2879, 1663 (C=O), 1610 (C=C), 1457 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 4.00–3.88 (m, 4H, OCH_2CH_2O), 2.75–2.67 (m, 1H), 2.49–2.32 (m, 2H), 2.26–2.03 (m, 2H), 1.92–1.78 (m, 2H), 1.76 (d, *J* = 1.5 Hz, 3H, MeC=), 1.71–1.53 (m, 3H), 1.31 (s, 3H, Me); ^{13}C NMR (100.6 MHz; $CDCl_3$) δ: 198.8 (C=O), 160.3 (CMe=*C*), 130.2 (*C*Me=C), 112.9 (OCO), 65.4 (OCH_2), 65.2 (OCH_2), 45.4 (*C*Me), 33.8 (CH_2), 29.8 (CH_2), 26.6 (CH_2), 26.5 (CH_2), 21.5 (CH_2), 20.9 (C*Me*=C), 11.6 (C*Me*); MS (ESI) 259 [$(M + Na)^+$]; HRMS (ESI) *m/z* calcd for $C_{14}H_{20}O_3$ $(M + Na)^+$ 259.1305 found 259.1302 (1.1 ppm error). Spectroscopic data are consistent with those reported in the literature.[273]

Lab book reference: This reaction was carried out by Stefan Mommer sm1/7

(4a'*RS*,5'*RS*,8a'*RS*)-5',8a'-Dimethylhexahydro-2'*H*-spiro[[1,3]dioxolane-2,1'-naphthalen]-6'(7'*H*)-one 202 and **((4a'*RS*,5'*RS*,6'*RS*,8a'*RS*)-5',8a'-Dimethyloctahydro-2'*H*-spiro[[1,3]dioxolane-2,1'-naphthalen]-6'-ol 209**



202



209

A solution of enone **201** (5.92 g, 25.0 mmol) and H_2O (450 μL, 25.0 mmol) in THF (50 mL) was added dropwise to a stirred solution of lithium wire (890 mg, 125 mmol) in liquid NH_3 (125 mL) at −78 °C over 30 min. The mixture was allowed to warm to rt and stirred for 1 h. Then, $NH_4Cl_{(s)}$ was added and NH_3 was allowed to evaporate. Then, saturated brine (50 mL) and CH_2Cl_2 (50 mL) were added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with petrol–EtOAc (1:1) as eluent gave ketone **202** (3.59 g, 61%) as a colourless oil, R_F (2:3 petrol-EtOAc) 0.59; IR (Thin Film) 2949, 1708 (C=O), 1185 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 3.96–3.81 (m, 4H, OCH_2CH_2O), 2.45–2.17 (m, 3H), 1.89 (tdd, *J* = 13.5, 5.5, 0.5 Hz, 1H), 1.75–1.39 (m, 7H), 1.25–1.17 (m, 4H), 0.96 (d, *J* = 6.5 Hz, 3H, Me); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 213.0 (C=O), 112.7 (OCO), 65.2 (OCH_2), 65.1 (OCH_2), 48.2 (CO*C*H), 45.1 (CH), 42.5 (*C*Me), 37.7 (CH_2), 30.8 (CH_2), 30.1 (CH_2), 25.1 (CH_2), 22.8 (CH_2), 14.3 (CH*Me*), 11.8 (C*Me*); MS (ESI) 261 [$(M + Na)^+$]; HRMS (ESI) *m/z* calcd for $C_{14}H_{22}O_3$ $(M + Na)^+$ 261.1461 found 261.1460 (0.0 ppm error) and gave alcohol **209** (1.80 g, 30%) as a white solid, R_F (2:3 petrol–EtOAc) 0.40; IR (Thin Film) 3390 (OH), 2945, 1451, 1377, 1353, 1282, 1239, 1165, 1136, 951, 867 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 3.99–3.79 (m, 4H, OCH_2CH_2O), 3.10 (td, *J* = 9.5, 5.0 Hz, 1H, C*H*OH), 1.87–1.79 (m, 1H), 1.75–1.35 (m, 10H), 1.29–1.20 (m, 2H), 1.00 (s, 3H, Me), 0.96 (d, *J* = 6.0 Hz, 3H, *Me*CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 113.1 (OCO), 76.3 (CHOH), 65.2 (OCH_2), 65.0 (OCH_2), 45.8 (CH), 42.3 (*C*Me), 39.2 (CH_2), 30.6 (CH_2), 30.1 (CH_2), 28.3 (CH_2), 23.6 (CH), 23.0 (CH_2), 15.3 (Me), 14.9 (Me); MS (ESI) 241 [$(M + H)^+$]; HRMS

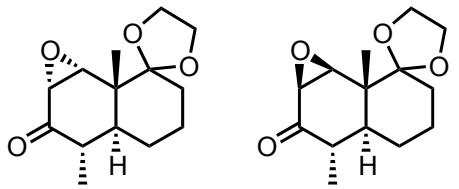
(ESI) *m/z* calcd for $C_{14}H_{24}O_3$ $(M + H)^+$ 241.1798 found 241.1802 (−1.7 ppm error). Spectroscopic data are consistent with those reported in the literature.[273]

Lab book reference: djbI/85

IBX (116 mg, 0.42 mmol) was added to a stirred solution of alcohol **209** (50 mg, 0.21 mmol) in DMSO (1.5 mL) at rt under Ar. The resulting mixture was stirred at rt for 20 h. Then, saturated $NaHCO_{3(aq)}$ (10 mL) was added and the mixture was extracted with CH_2Cl_2 (4 × 15 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with petrol–EtOAc (4:1) as eluent gave ketone **202** (46 mg, 91%) as a colourless oil.

Lab book reference: djbI4/56

(1a'*RS,3'*RS**,3a'*RS**,7a'*RS**,7b'*RS**)- and (1a'*RS**,3'*RS**,3a'*RS**,7a'*RS**,7b'*RS**)-3',7a'-Dimethylhexahydro- 1a'*H*-spiro[[1,3]-dioxolane-2,7'-naphtho[1,2-*b*]oxiren]-2'(3'*H*)-one *trans*-210 and *cis*-210**



trans *cis*

DMP (103 mg, 0.24 mmol) was added to a stirred solution of an 88:12 mixture of epoxy alcohols *trans*-**212** and *cis*-**212** (41 mg, 0.16 mmol) in CH_2Cl_2 (2 mL) at rt under Ar. The resulting mixture was stirred at rt for 30 min. Then, saturated $NaHCO_{3(aq)}$ (10 mL) and saturated $Na_2S_2O_{3(aq)}$ (10 mL) were added and the resulting biphasic mixture was stirred at rt for 1 h. Then, CH_2Cl_2 (10 mL) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude products which contained an 88:12 mixture of epoxy

ketones *trans*-**210** and *cis*-**210** (by ^{1}H NMR spectroscopy). Purification by flash column chromatography on silica with petrol–EtOAc (4:1) as eluent gave an 88:12 mixture (by ^{1}H NMR spectroscopy) of epoxy ketones *trans*-**210** and *cis*-**210** (29 mg, 70%) as a white solid, mp 86–88 °C; R_F (2:3 petrol–EtOAc) 0.60; IR (Thin Film) 2908, 1686 (C=O), 1171, 1043, 847 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.14–3.91 (m, 4H, OCH_2CH_2O), 3.58 (d, J = 4.0 Hz, 0.12H, CHO_{cis}), 3.52 (d, J = 4.0 Hz, 0.88H, CHO_{trans}), 3.24 (d, J = 4.0 Hz, 1H, $CHO_{trans + cis}$), 2.59 (dq, J = 13.5, 7.0 Hz, 0.88H, C*H*Me_{trans}), 2.13 (ddd, J = 13.0, 10.5, 3.5 Hz, 0.12H, CH_{cis}), 1.89 (td, J = 13.0, 3.0 Hz, 0.88H, CH_{trans}), 1.85–1.78 (m, 0.12H, CH_{cis}), 1.74–1.30 (m, 6H), 1.26 (s, 2.64H, Me_{trans}), 1.15 (d, J = 7.0 Hz, 0.36H, CHMe_{cis}), 0.99 (s, 0.36H, Me_{cis}), 0.88 (d, J = 7.0 Hz, 2.64H, CHMe_{trans}); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 209.7 ($C{=}O_{trans}$), 208.7 ($C{=}O_{cis}$), 112.1 (OCO_{trans}), 111.6 (OCO_{cis}), 65.0 (OCH_{2cis}), 64.9 (OCH_{2trans}), 64.8 (OCH_{2cis}), 64.5 (OCH_{2trans}), 64.0 (CHO_{trans}), 59.9 (CHO_{cis}), 55.6 (CHO_{trans}), 54.5 (CHO_{cis}), 49.0 (CH_{trans}), 44.1 (CH_{cis}), 42.8 (*C*Me_{cis}), 42.5 (*C*Me_{trans}), 38.6 (CH_{cis}), 38.0 (CH_{trans}), 30.1 (CH_{2cis}), 29.0 (CH_{2trans}), 24.5 (CH_{2cis}), 22.8 (CH_{2trans}), 22.6 (CH_{2trans}), 22.5 (CH_{2cis}), 16.5 (CHMe_{cis}), 14.1 (CHMe_{cis}), 13.1 (CMe_{trans}), 10.4 (CMe_{trans}); MS (ESI) 253 [$(M + H)^+$]; HRMS (ESI) *m/z* calcd for $C_{14}H_{20}O_4$ $(M + H)^+$ 253.1434 found 253.1437 (–1.2 ppm error).

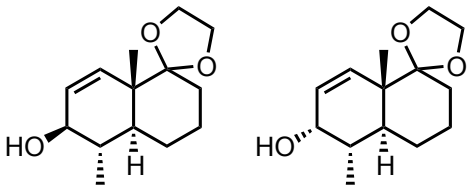
Lab Book Reference: This reaction was carried out by Stefan Mommer sm1/29

$CeCl_3{\cdot}7H_2O$ (1.26 g, 3.39 mmol) was added to a stirred solution of enone **200** (400 mg, 1.69 mmol) in EtOH-THF (2:1, 28 mL) at rt under Ar. The resulting mixture was stirred at rt for 10 min. After cooling to –78 °C, $NaBH_4$ (128 mg, 3.39 mmol) was added and the mixture was stirred at –78 °C for 1.5 h. Then, saturated $NH_4Cl_{(aq)}$ (10 mL) and CH_2Cl_2 (10 mL) were added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (5 × 10 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude allylic alcohols. *m*CPBA (834 mg of approx. 70% purity, 3.29 mmol) was added to a stirred suspension of the crude allylic alcohols and $NaHCO_3$ (569 mg, 6.77 mmol) in CH_2Cl_2 (25 mL) at 0 °C under Ar. The resulting mixture was stirred at 0 °C for 10 min and then rt for 22 h. Saturated $Na_2S_2O_{3(aq)}$ (10 mL) was added and the biphasic mixture was stirred at 0 °C for 1 h. Then, $NaHCO_{3(aq)}$ (20 mL) was

added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude epoxy alcohols. DMP (1.44 g, 3.39 mmol) was added to a stirred solution of the crude epoxy alcohols in CH_2Cl_2 (25 mL) at rt under Ar. The resulting mixture was stirred at rt for 2 h. Then, saturated $NaHCO_{3(aq)}$ (10 mL) and saturated $Na_2S_2O_{3(aq)}$ (10 mL) were added and the resulting biphasic mixture was stirred at rt for 1 h. Then, CH_2Cl_2 (20 mL) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude products which contained an 85:15 mixture of epoxy ketones *trans*-**210** and *cis*-**210** (by ^{1}H NMR spectroscopy). Purification by flash column chromatography on silica with petrol–EtOAc (4:1) as eluent gave an 85:15 mixture (by ^{1}H NMR spectroscopy) of epoxy ketones *trans*-**210** and *cis*-**210** (310 mg, 73%) as a white solid.

Lab book reference: djbI3/43

(4a'*RS,5'*RS**,6'*RS**,8a'*RS**)- and (4a'*RS**,5'*RS**,6'*RS**,8a'*RS**)-5',8a'-Dimethyl-3',4',4a',5',6',8a'-hexa- hydro-2'*H*-spiro-[[1,3]dioxolane-2,1'-naphthalen]-6'-ol *trans*-211 and *cis*-211**



trans *cis*

A solution of enone **200** (50 mg, 0.21 mmol) in THF (1 mL) was added dropwise to a stirred suspension of $LiAlH_4$ (8 mg, 0.21 mmol) in THF (1.5 mL) at –40 °C under Ar. The resulting mixture was stirred at –40 °C for 30 min. After being allowed to warm to 0 °C, 2 M $NaOH_{(aq)}$ (5 mL) was added dropwise. Then, saturated brine (10 mL) and Et_2O (10 mL) were added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude products which contained an 87:13 mixture of alcohols *trans*-**211** and *cis*-**211** (by ^{1}H NMR spectroscopy).

Purification by flash column chromatography on silica with petrol–EtOAc (3:2) as eluent gave *trans*-**211** (45 mg, 88%) as a colourless oil, R_F (2:3 petrol–EtOAc) 0.43; IR (Thin Film) 3344 (OH), 2905, 1421, 1022, 726 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 5.82 (dd, *J* = 10.0, 2.0 Hz, 1H, COHC*H*=CH), 5.55 (dd, *J* = 10.0, 2.0 Hz, 1H, COHCH=C*H*), 4.00–3.88 (m, 4H, OCH_2CH_2O), 3.76 (dt, *J* = 8.5, 2.0 Hz, 1H, C*H*OH), 1.72–1.40 (m, 8H), 1.19–1.12 (m, 1H), 1.07 (s, 3H, CMe), 1.01 (d, *J* = 6.5 Hz, 3H, CH*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 135.0 (COH*C*H=CH), 129.0 (COHCH=*C*H), 112.3 (OCO), 75.0 (CHOH), 65.2 (OCH_2), 64.9 (OCH_2), 44.9 (*C*Me), 43.9 (*C*HMe), 37.5 (CH), 29.7 (CH_2), 23.0 (CH_2), 22.6 (CH_2), 18.6 (CH*Me*), 15.8 (C*Me*); MS (ESI) 261 [$(M + Na)^+$]; HRMS (ESI) *m/z* calcd for $C_{14}H_{22}O_3$ $(M + Na)^+$ 261.1461 found 261.1456 (+1.9 ppm error) and gave alcohol *cis*-**211** (4 mg, 8%) as a colourless oil, R_F (2:3 petrol–EtOAc) 0.31; IR (Thin Film) 3380 (OH), 2907, 1246 727 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 5.94 (d, *J* = 10.0 Hz, 1H, CHOHC*H*=CH), 5.78 (dd, *J* = 10.0, 5.0 Hz, 1H, CHOHCH=C*H*), 4.00–3.90 (m, 4H, OCH_2CH_2O), 3.82 (t, *J* = 5.0 Hz, 1H, C*H*OH), 1.84–1.43 (m, 8H), 1.20–1.09 (m, 1H), 1.01 (s, 3H, CMe), 0.99 (d, *J* = 6.5 Hz, 3H, CH*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 137.3 (CHOH*C*H=CH), 127.1 (CHOHCH=*C*H), 112.5 (OCO), 68.7 (CHOH), 65.3 (OCH_2), 64.9 (OCH_2), 45.4 (*C*Me), 38.8 (*C*HMe), 33.4 (CH), 29.7 (CH_2), 23.1 (CH_2), 22.2 (CH_2), 17.2 (CH*Me*), 14.7 (C*Me*); MS (ESI) 261 [$(M + Na)^+$]; HRMS (ESI) m/z calcd for $C_{14}H_{22}O_3$ $(M + Na)^+$ 261.1461 found 261.1456 (2.1 ppm error).

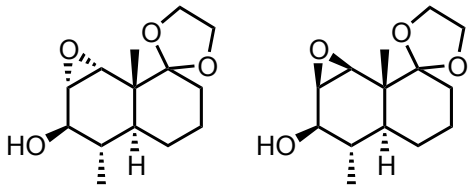
Lab book reference: This reaction was carried out by Stefan Mommer sm/26

$CeCl_3.7H_2O$ (118 mg, 0.32 mmol) was added to a stirred solution of enone **200** (50 mg, 0.21 mmol) in EtOH-THF (2:1, 3 mL) at rt under Ar. The resulting mixture was stirred at rt for 10 min. After cooling to –78 °C, $NaBH_4$ (12 mg, 0.32 mmol) was added and the mixture was stirred at –78 °C for 1.5 h. Then, saturated $NH_4Cl_{(aq)}$ (10 mL) and CH_2Cl_2 (10 mL) were added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude products which contained a 94:6 mixture of alcohols *trans*-**211** and *cis*-**211** (by ^1H NMR

spectroscopy). Purification by flash column chromatography on silica with petrol–EtOAc (3:2) as eluent gave alcohol *trans*-**211** (45 mg, 89%) as a colourless oil.

Lab book reference: This reaction was carried out by Stefan Mommer sm1/28

(1a'*RS,2'*RS**,3'*RS**,3a'*RS**,7a'*RS**,7b'*RS**)- and (1a'*RS**,2'*RS**,3'*RS**,3a'*RS**,7a'*RS**,7b'*RS**)-3',7a'- Dimethyloctahydro-1a'*H*-spiro-[[1,3]dioxolane-2,7'-naphtho[1,2-b]oxiren]-2'-ol *trans*-212 and *cis*-212**



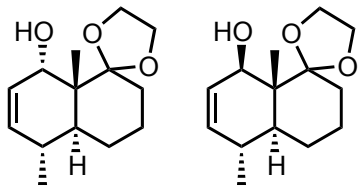
trans *cis*

*m*CPBA (187 mg of approx. 70% purity, 0.76 mmol) and was added to a stirred suspension of alcohol *trans*-**211** (45 mg, 0.19 mmol) and $NaHCO_3$ (128 mg, 1.52 mmol) in CH_2Cl_2 (2 mL) at 0 °C under Ar. The resulting mixture was stirred at 0 °C for 10 min and then at rt for 22 h. Saturated $Na_2S_2O_{3(aq)}$ (10 mL) was added and the biphasic mixture was stirred at 0 °C for 1 h. Then, $NaHCO_3$(aq) (10 mL) and CH_2Cl_2 (10 mL) were added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude products which contained an 88:12 mixture of epoxy alcohols *trans*-**212** and *cis*-**212** (by ^{1}H NMR spectroscopy). Purification by flash column chromatography on silica with petrol–EtOAc (3:2) as eluent gave an 88:12 mixture (by ^{1}H NMR spectroscopy) of epoxy alcohols *trans*-**212** and *cis*-**212** (38 mg, 79%) as a colourless oil, R_F (2:3 petrol–EtOAc) 0.30; IR (Thin Film) 3392 (OH), 2907, 1038, 725 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.08–3.91 (m, 4H, OCH_2CH_2O), 3.52 (d, J = 8.5 Hz, 0.12H, C*H*OH_{cis}), 3.42 (dd, J = 8.5, 2.0 Hz, 0.88H, CHO_{trans}), 3.34 (d, J = 4.0 Hz, 0.88H, CHO_{trans}), 3.29 (dd, J = 4.0, 2.5 Hz, 0.88H, CHO_{trans}), 3.18 (d, J = 4.0 Hz, 0.12H, CHO_{cis}), 2.99 (d, J = 4.0 Hz, 0.12H, CHO_{cis}), 1.79 (br s, 1H, $OH_{cis\ +\ trans}$), 1.72-1.10 (m, 8H), 1.09 (s, 0.36H, Me_{cis}), 1.07 (s, 2.64H, Me_{trans}), 0.93 (d, J = 6.5 Hz, 3H, $CHMe_{cis\ +\ trans}$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 112.8 (OCO_{trans}), 112.3 (OCO_{cis}), 76.2 ($CHOH_{trans}$), 72.4 ($CHOH_{cis}$), 65.2 (OCH_{2cis}), 64.9 (OCH_{2trans}), 64.8 (OCH_{2cis}), 64.5 (OCH_{2trans}), 61.4

(CHO_{trans}), 57.2 (CHO_{cis}), 56.9 (CHO_{trans}), 54.2 (CHO_{cis}), 44.7 (CH_{trans}), 42.4 (CMe_{cis}), 41.6 (CMe_{trans}), 36.2 (CH_{cis}), 35.8 (CH_{cis}), 33.5 (CH_{trans}), 30.9 (CH_{2cis}), 29.2 (CH_{2trans}), 22.9 (CH_{2trans}), 22.5 (CH_{2cis}), 22.4 (CH_{2cis}), 21.8 (CH_{2trans}), 17.2 (Me_{cis}), 14.8 (Me_{cis}), 14.7 (Me_{trans}), 13.1 (Me_{trans}); MS (ESI) 255 [$(M + Na)^+$]; HRMS (ESI) *m/z* calcd for $C_{14}H_{22}O_4$ $(M + Na)^+$ 277.1410 found 277.1414 (–1.3 ppm error).

Lab book reference: This reaction was carried out by Stefan Mommer sm1/33

(4a'*RS,5'*RS**,8'*RS**,8a'*RS**)- and (4a'*RS**,5'*RS**,8'*RS**,8a'*RS**)-5',8a'-Dimethyl-3',4',4a',5',8',8a'-hexa-hydro-2'*H*-spiro[[1,3]dioxolane-2,1'-naphthalen]-8'-ol *trans*-213 and *cis*-213**



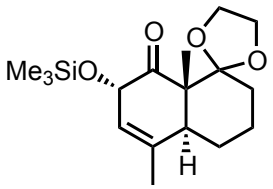
trans *cis*

$NH_2NH_2{\cdot}H_2O$ (8 μL of a 50% solution in water, 0.13 mmol) was added to a stirred solution of an 85:15 mixture of epoxy ketones *trans*-**210** and *cis*-**210** (29 mg, 0.11 mmol) in MeOH (1 mL) at 0 °C under Ar. The resulting mixture was stirred at 0 °C for 15 min. Then, AcOH (13 μL, 0.23 mmol) was added and the mixture was allowed to warm to rt over 1 h. Then, $NaHCO_{3(aq)}$ (10 mL) and CH_2Cl_2 (10 mL) were added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude products which contained a 96:4 mixture of alcohols *trans*-**213** and *cis*-**213** (by ^1H NMR spectroscopy). Purification by flash column chromatography on silica with petrol–EtOAc (4:1) as eluent gave allylic alcohol *trans*-**213** (20 mg, 74%) as a colourless oil, R_F (2:3 petrol–EtOAc) 0.52; IR (Thin Film) 3481 (OH), 2906, 1235, 1167, 1066, 1022, 934 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 5.46–5.40 (m, 2H, HC=CH), 4.65 (d, *J* = 3.5 Hz, 1H, C*H*OH), 4.14–3.90 (m, 4H, OCH_2CH_2O), 3.41 (s, 1H, OH), 1.87–1.79 (m, 1H), 1.76–1.58 (m, 4H), 1.57–1.46 (m, 1H), 1.39 (ddd, *J* = 12.0, 9.5, 4.0 Hz, 1H), 1.26–1.12 (m, 1H), 1.05 (s, 3H, Me), 0.96 (d, *J* = 7.0 Hz, 3H CH*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 132.2

(CHOH*C*H=CH), 128.4 (CHOHCH=*C*H), 114.4 (OCO), 69.8 (CHOH), 64.9 (OCH_2), 63.5 (OCH_2), 44.3 (CH), 44.2 (*C*Me), 33.6 (CH), 29.0 (CH_2), 24.0 (CH_2), 22.2 (CH_2), 19.5 (CH*Me*), 9.7 (C*Me*); MS (ESI) 261 [$(M + Na)^+$]; HRMS (ESI) *m/z* calcd for $C_{14}H_{22}O_3$ $(M + Na)^+$ 261.1461 found 261.2464 (–1.9 ppm error). *The major diastereomer is assumed to be obtained through retention of stereochemistry of the epoxy alcohol starting material. It is noted that the dr increases (85:15 to 96:4) suggesting the stereochemical outcome is not that straightforward.*

Lab book reference: This reaction was carried out by Stefan Mommer sm1/32

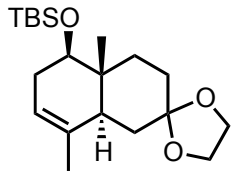
(4a'*S*,7'*S*,8a'*R*)-5',8a'-Dimethyl-7'-((trimethylsilyl)oxy)-4',4a',7',8a'-tetrahydro-2'*H*-spiro[[1,3]dioxolane-2,1'-naphthalen]-8'(3'*H*)-one 216



Et_3N (142 μL, 1.02 mmol) and Me_3SiOTf (92 μL, 0.51 mmol) were added to a stirred solution of enone **199** (60 mg, 0.25 mmol) in CH_2Cl_2 (5 mL) at rt under Ar. The resulting mixture was stirred at rt for 1 h. Then, saturated $NaHCO_{3(aq)}$ (10 mL) was added and the mixture was extracted with CH_2Cl_2 (4 × 5 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude silyl enol ether **214**. Then, $NaHCO_3$ (43 mg, 0.51 mmol) and purified *m*CPBA (44 mg, 0.25 mmol) were added to a stirred solution of the crude silyl enol ether in CH_2Cl_2 (5 mL) at 0 °C under Ar. The resulting mixture was stirred at 0 °C for 1 h. After being allowed to warm to rt, $NaHCO_{3(aq)}$ (10 mL) was added and the mixture was extracted with CH_2Cl_2 (4 × 5 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with petrol–EtOAc (4:1) as eluent gave α-siloxy ketone **216** (45 mg, 59%) as a colourless oil, R_F (4:1 petrol–EtOAc) 0.40; ^1H NMR (400 MHz, $CDCl_3$) δ: 5.40 (tq, J = 3.0, 1.5 Hz, 1H, =CH), 4.64 (dq, J = 5.0, 2.5 Hz, 1H, CHO), 4.33–4.20 (m, 2H, OCH_2), 4.00–3.87 (m, 2H, OCH_2), 2.91–2.86 (m, 1H, CH), 1.79–1.64 (m, 6H), 1.59–1.40 (m, 3H), 1.31 (s, 3H, CMe), 0.14 (s, 9H, $SiMe_3$).

Lab book reference: djbI3/59

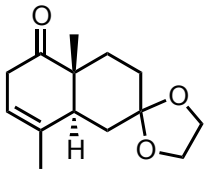
***tert*-Butyl(((4a'*R*,5'*R*,8a'*S*)-4a',8'-dimethyl-3',4',4a',5',6',8a'-hexahydro-1'*H*-spiro[[1,3]dioxolane-2,2'-naphthalen]-5'-yl)oxy)dimethylsilane 217**



MeLi (13.7 mL of a 1.6 M solution in Et_2O, 21.95 mmmol) was added to a stirred solution of CuI (2.61 g, 13.72 mmol) in THF (5 mL) at 0 °C. The resulting suspension was stirred at 0 °C for 15 min. Then, a solution of enol triflate **222** (643 mg, 1.37 mmol) in THF (5 mL) was added dropwise over 15 min and the resulting solution was stirred at 0 °C for 15 min. Then, saturated $NH_4Cl_{(aq)}$ (10 mL) and CH_2Cl_2 (10 mL) were added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (5 × 10 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with petrol-EtOAc (4:1) as eluent gave methyl alkene **217** (430 mg, 89%) as a colourless oil, $[\alpha]_D$ −27.9 (*c* 1.0 in $CHCl_3$); R_F (4:1 petrol-EtOAc) 0.53; IR (Thin Film) 2907, 1442, 1232, 1090, 762 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 5.25–5.24 (m, 1H, =CH), 3.99–3.92 (m, 4H, OCH_2CH_2O), 3.50 (dd, *J* = 9.5, 6.5 Hz, 1H, CHO), 2.21–2.09 (m, 2H), 2.00–1.92 (m, 1H), 1.83–1.62 (m, 4H), 1.56–1.48 (m, 4H), 1.17 (td, *J* = 13.5, 4.5 Hz, 1H), 0.86 (s, 9H, Si*t*-Bu), 0.78 (s, 3H, Me), 0.00 (s, 6H, 2 × SiMe); ^{13}C NMR (100.6 MHz; $CDCl_3$) δ: 134.5 (=*C*Me), 120.4 (=CH), 109.7 (OCO), 76.3 (CHO), 64.4 (OCH_2), 64.3 (OCH_2), 44.0 (CH), 37.6 (*C*Me), 33.6 (CH_2), 33.5 (CH_2), 33.4 (CH_2), 30.9 (CH_2), 26.0 (C*Me*$_3$), 20.9 (=C*Me*) 18.2 (*C*Me$_3$), 9.1 (C*Me*), –3.9 (SiMe), –4.7 (SiMe); MS (ESI) 353 [$(M + H)^+$, 100], 221 (90); HRMS (ESI) *m/z* calcd for $C_{20}H_{36}O_3Si$ $(M + H)^+$ 353.2506 found 353.2508 (−0.5 ppm error).

Lab book reference: djbI3/11

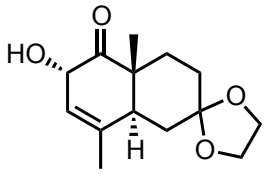
(4a'*R*,8a'*S*)-4a',8'-Dimethyl-4',4a',6',8a'-tetrahydro-1'*H*-spiro[[1,3]dioxolane-2,2'-naphthalen]-5'(3'*H*)-one 218



DMP (534 mg, 1.26 mmol) was added to a stirred solution of alcohol **223** (200 mg, 0.84 mmol) in CH_2Cl_2 (5 mL) at rt under Ar. The resulting suspension was stirred at rt for 2 h. Then, saturated $NaHCO_{3(aq)}$ (10 mL) and saturated $Na_2S_2O_{3(aq)}$ (10 mL) were added and the resulting biphasic mixture was stirred at rt for 1 h. Then, CH_2Cl_2 (10 mL) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with petrol-EtOAc (4:1) as eluent gave ketone **218** (171 mg, 86%) as a colourless oil, $[\alpha]_D$ −9.4 (*c* 1.6 in $CHCl_3$); R_F (Et_2O) 0.58; IR (Thin Film) 2904, 1685 (C=O), 1080, 860 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 5.43–5.38 (m, 1H, =CH), 3.93–3.81 (m, 4H, OCH_2CH_2O), 2.96–2.88 (m, 1H), 2.70–2.55 (m, 2H), 1.78 (ddd, J = 13.0, 4.0, 2.0 Hz, 1H), 1.70–1.57 (m, 8H), 0.99 (s, 3H, Me); ^{13}C NMR (100.6 MHz; $CDCl_3$) δ: 213.7 (C=O), 135.8 (=*C*Me), 118.5 (=CH), 108.6 (OCO), 64.3 (OCH_2), 64.2 (OCH_2), 45.6 (*C*Me), 42.3 (CH), 38.4 (CH_2), 33.3 (CH_2), 30.0 (CH_2), 28.9 (CH_2), 20.4 (=C*Me*), 14.4 (C*Me*); MS (ESI) 300 (28), 259 [$(M + Na)^+$, 27], 237 [$(M + H)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{14}H_{20}O_3$ $(M + Na)^+$ 259.1305 found 259.1303 (0.5 ppm error), *m/z* calcd for $C_{14}H_{20}O_3$ $(M + H)^+$ 237.1485 found 237.1481 (0.5 ppm error).

Lab book reference: djbI3/39

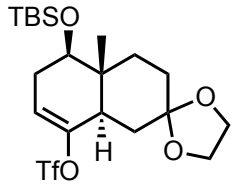
(4a'*R*,6'*S*,8a'*S*)-6'-Hydroxy-4a',8'-dimethyl-4',4a',6',8a'-tetrahydro-1'*H*-spiro[[1,3]dioxolane-2,2'-naphthalen]-5'(3'*H*)-one 219



Et_3N (77 μL, 0.42 mmol) and $MeSi_3OTf$ (118 μL, 0.85 mmol) were added to a stirred solution of ketone **218** (50 mg, 0.21 mmol) in CH_2Cl_2 (5 mL) at rt under Ar. The resulting mixture was stirred at rt for 15 min. Then, saturated $NaHCO_{3(aq)}$ (10 mL) and CH_2Cl_2 (10 mL) were added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude silyl enol ether **224**. $NaHCO_3$ (71 mg, 0.85 mmol) and purified *m*CPBA (37 mg, 0.21 mmol) were added to a stirred solution of the crude silyl enol ether in CH_2Cl_2 (5 mL) at 0 °C under Ar. The resulting mixture was stirred at 0 °C for 30 min. After being allowed to warm to rt, $NaHCO_{3(aq)}$ (10 mL) was added the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude α-siloxy ketone **226**. TBAF (423 μL of a 1.0 M solution in THF, 0.42 mmol) was added to a stirred solution of the crude epoxy silyl ether in CH_2Cl_2 (5 mL) at rt under Ar. The resulting mixture was stirred at rt for 15 min. Then, saturated $NH_4Cl_{(aq)}$ (10 mL) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with petrol–EtOAc (4:1) as eluent gave α-hydroxy ketone **219** (4 mg, 7%) as a colourless oil, R_F (Et_2O) 0.26; IR (Thin Film) 3391 (OH), 2911, 1693 (C=O), 1078, 979 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 5.62–5.58 (m, 1H, =CH), 4.79–4.76 (m, 1H, CHO), 4.02–3.90 (m, 4H, OCH_2CH_2O), 2.62–5.58 (m, 1H), 2.07–1.99 (m, 1H), 1.86–1.58 (m, 9H), 1.24 (d, J = 0.5 Hz, 3H, Me); MS (ESI) 275 [$(M + Na)^+$ 100]; HRMS (ESI) *m/z* calcd for $C_{14}H_{20}O_4$ $(M + Na)^+$ 275.1254 found 275.1249 (1.9 ppm error).

Lab book reference djbI3/67

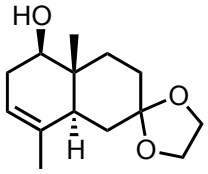
(4a'*R*,5'*R*,8a'*R*)-5'-((*tert*-Butyldimethylsilyl)oxy)-4a'-methyl-3',4',4a',5',6',8a'-hexahydro-1'*H*-spiro[[1,3]dioxolane-2,2'-naphthalen]-8'-yl trifluoromethanesulfonate 222



KHMDS (5.38 mL of a 0.7 M solution in toluene, 3.77 mmol) was added dropwise to a stirred solution of ketone **161** (534 mg, 1.51 mmol) in THF (5 mL) at −78 °C under Ar. The resulting solution was stirred at −78 °C for 30 min. Then, a solution of Comin's reagent **221** (888 mg, 2.62 mmol) in THF (5 mL) was added dropwise and the resulting solution was allowed to warm to rt and stirred at rt for 30 min. Then, saturated $NaHCO_{3(aq)}$ (10 mL) and CH_2Cl_2 (10 mL) were added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (5 × 10 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with petrol-EtOAc (4:1) as eluent gave enol triflate **222** (643 mg, 92%) as a colourless oil, $[\alpha]_D$ −11.8 (*c* 1.5 in $CHCl_3$); R_F (4:1 petrol-EtOAc) 0.56; IR (Thin Film) 2909, 1397, 1191, 861 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 5.62 (dt, *J* = 5.5, 2.5 Hz, 1H, =CH), 4.01–3.91 (m, 4H, OCH_2CH_2O), 3.55 (dd, *J* = 9.5, 6.5 Hz, 1H, CHO), 2.70–2.64 (m, 1H), 2.39–2.30 (m, 1H), 2.19–2.10 (m, 1H), 1.85–1.77 (m, 3H), 1.67 (ddt, *J* = 13.0, 4.5, 2.0 Hz, 1H), 1.62–1.56 (m, 2H), 1.25 (s, 3H, CMe), 0.88 (s, 9H, Si*t*-Bu), 0.04 (s, 3H, SiMe), 0.03 (s, 3H, SiMe); ^{13}C NMR (100.6 MHz; $CDCl_3$) δ: 149.1 (*C*OTf), 116.3 (=CH), 118.6 (q, *J* = 320 Hz, CF_3), 108.5 (OCO), 74.4 (CHO), 64.6 (OCH_2), 64.3 (OCH_2), 42.8 (CH), 39.2 (*C*Me), 33.1 (CH_2), 31.4 (CH_2), 31.0 (CH_2), 30.7 (CH_2), 25.9 (C*Me*$_3$), 18.1 (*C*Me$_3$), 9.1 (C*Me*), –4.0 (SiMe), –4.7 (SiMe); ^{19}F NMR (282 MHz, $CDCl_3$) δ: –73.75; MS (ESI) 550 (42), 487 [$(M + H)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{20}H_{33}F_3O_4SSi$ $(M + H)^+$ 487.1792 found 487.1779 (2.6 ppm error).

Lab book reference: djbI3/10

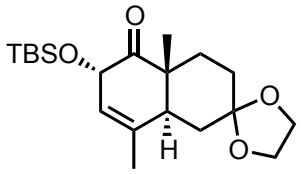
(4a'*R*,5'*R*,8a'*S*)-4a',8'-Dimethyl-3',4',4a',5',6',8a'-hexahydro-1'*H*-spiro[[1,3]dioxolane-2,2'-naphthalen]-5'-ol 223



TBAF (2.0 mL of a 1.0 M solution in THF, 1.99 mmol) was added to a stirred solution of silyl ether **222** (351 mg, 1.00 mmol) in THF (15 mL) at rt under Ar. The resulting solution was stirred and heated at 50 °C for 13 h. Then, saturated NH_4Cl (20 mL) and CH_2Cl_2 (20 mL) were added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with Et_2O as eluent gave alcohol **223** (206 mg, 87%) as a colourless oil, $[\alpha]_D$ −17.9 (*c* 1.0 in $CHCl_3$); R_F (Et_2O) 0.36; IR (Thin Film) 3399 (OH), 2907, 1415, 1087, 866 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 5.28–5.23 (m, 1H, =CH), 3.94–3.89 (m, 4H, OCH_2CH_2O), 3.52 (dd, J = 10.0, 6.5 Hz, 1H, CHO), 2.29–2.17 (m, 2H), 1.96–1.89 (m, 2H), 1.81–1.60 (m, 4H), 1.55–1.47 (m, 4H), 1.27 (td, J = 12.9, 4.9 Hz, 1H), 0.76 (s, 3H, Me); ^{13}C NMR (100.6 MHz; $CDCl_3$) δ: 134.6 (=*C*Me), 120.0 (=CH), 109.4 (OCO), 75.9 (CHO), 64.3 (OCH_2), 64.2 (OCH_2), 43.8 (CH), 37.2 (*C*Me), 33.2 (CH_2), 32.6 (CH_2), 32.5 (CH_2), 30.6 (CH_2), 20.8 (=C*Me*), 8.7 (C*Me*); MS (ESI) 239 $[(M + H)^+$, 221 (32); HRMS (ESI) *m/z* calcd for $C_{14}H_{22}O_3$ $(M + H)^+$ 239.1642 found 239.1640 (0.6 ppm error).

Lab book reference: djbI3/28

(4a'*R*,6'*S*,8a'*S*)-6'-((*tert*-Butyldimethylsilyl)oxy)-4a',8'-dimethyl-4',4a',6',8a'-tetrahydro-1'*H*-spiro[[1,3]dioxolane-2,2'-naphthalen]-5'(3'*H*)-one 227

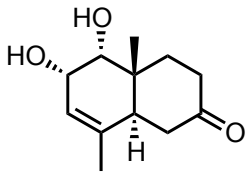


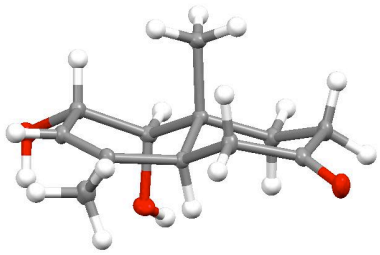
Et_3N (189 μL, 1.86 mmol) and TBSOTf (214 μL, 0.93 mmol) were added to a stirred solution of ketone **218** (110 mg, 0.47 mmol) in CH_2Cl_2 (5 mL) at rt under Ar. The resulting mixture was stirred at rt for 15 min. Then, $NaHCO_{3(aq)}$ (10 mL) was added the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude silyl enol ether. $NaHCO_3$ (157 mg, 1.86 mmol) and purified *m*CPBA (161 mg, 0.93 mmol) were added to a stirred solution of the crude silyl enol ether in CH_2Cl_2 (5 mL) at 0 °C under Ar. The resulting mixture was stirred at 0 °C for 30 min. After being allowed to warm to rt, $NaHCO_{3(aq)}$ (10 mL) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the α-siloxy ketone. TBAF (932 μL of a 1.0 M solution in THF, 0.93 mmol) was added to a stirred solution of the crude epoxy TMS ether in CH_2Cl_2 (5 mL) at rt under Ar. The resulting mixture was stirred at rt for 15 min. Then, saturated $NH_4Cl_{(aq)}$ (10 mL) was added and the mixture was extracted with CH_2Cl_2 (4 × 5 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with petrol–EtOAc (4:1) as eluent gave α-siloxy ketone **227** (17 mg, 10%) as a colourless oil, $[\alpha]_D$ −7.0 (*c* 0.1 in $CHCl_3$); R_F (Et_2O) 0.26; IR (Thin Film) 2908, 1701, 1444, 1079, 821 cm^{-1}; ^1H NMR (400 MHz, CDCl3) δ: 5.48–5.45 (m, 1H, =CH), 4.84–4.82 (m, 1H, CHO), 3.99–3.88 (m, 4H, OCH_2CH_2O), 2.71–2.64 (m, 1H), 1.99–1.90 (m, 1H), 1.83–1.77 (m, 1H), 1.74–1.64 (m, 6H), 1.62–1.55 (m, 1H), 1.18 (s, 3H, CMe), 0.91 (s, 9H, Si*t*-Bu), 0.14 (s, 3H, SiMe), 0.06 (s, 3H, SiMe); ^{13}C NMR (100.6 MHz; $CDCl_3$) δ: 210.3 (C=O), 138.0 (=*C*Me), 124.7 (=CH), 108.5 (OCO), 72.0 (CHO), 64.5 (OCH_2), 64.4 (OCH_2), 48.0 (*C*Me), 45.2 (CH), 33.3 (CH_2), 29.8 (CH_2), 28.5 (CH_2), 26.0 (C*Me*$_3$), 20.6 (=C*Me*), 18.8 (*C*Me$_3$), 15.2 (C*Me*), −4.2 (SiMe), −5.2 (SiMe); MS (ESI) 389 [$(M + Na)^+$ 100];

HRMS (ESI) m/z calcd for $C_{20}H_{34}O_4Si$ $(M + Na)^+$ 389.2119 found 389.2101 (4.6 ppm error).

Lab book reference: djbI3/70

(4a*R*,5*R*,6*S*,8a*S*)-5,6-Dihydroxy-4a,8-dimethyl-1,4,4a,5,6,8a-hexahydronaphthalen-2(3*H*)-one *cis*-228





X-ray crystal structure of *cis*-228

$NaBH_4$ (17 mg, 0.44 mmol) was added to a stirred solution of α-siloxy ketone **227** (55 mg, 0.22 mmol) in MeOH (5 mL) at 0 °C under Ar. The resulting mixture was stirred at 0 °C for 1 h. Then, saturated $NH_4Cl_{(aq)}$ (10 mL) was added and the mixture was extracted with Et_2O (3 × 5 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude alcohol. $HF_{(aq)}$ (5 μL of a 40 wt% aqueous solution, 0.12 mmol) was added to a stirred solution of the crude mixture in MeCN (1 mL) at rt in a plastic reaction vessel. The resulting solution was stirred at rt for 8 h. Then, saturated $NaHCO_{3(aq)}$ (10 mL) and CH_2Cl_2 (10 mL) added dropwise and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organics were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with EtOAc as eluent gave diol *cis*-**228** (13 mg, 79%) as a colourless oil, $[\alpha]_D$ +17.0 (*c* 0.1 in $CHCl_3$); R_F (EtOAc) 0.32; IR (Thin Film) 3288 (OH), 2874, 1670, 1028 836 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 5.34–5.30 (m, 1H, HC=), 4.37–4.36 (m, 1H, C*H*OH), 3.59 (d, *J* = 4.0 Hz, 1H, C*H*OH), 2.71–2.65 (m, 1H), 2.61 (dddd, *J* = 15.0, 4.0, 1.5, 1.0 Hz, 1H), 2.56–2.41 (m, 2H), 2.32–2.17 (m, 2H), 2.05–1.95 (m, 3H), 1.65 (q, *J* = 1.5 Hz, 3H, =CMe), 1.56 (ddd, *J* = 13.0, 7.0, 2.5 Hz, 1H), 0.99 (d, *J* = 0.5 Hz, 3H, Me); ^{13}C NMR (100.6 MHz; $CDCl_3$) δ: 211.0 (C=O), 137.3 (=*C*Me), 122.8 (=CH), 74.6 (CHO), 67.4 (CHO), 39.5 (CH_2), 39.1 (CH), 38.8 (CH_2), 37.2 (*C*Me), 32.9 (CH_2), 20.7 (=C*Me*), 15.2 (C*Me*);

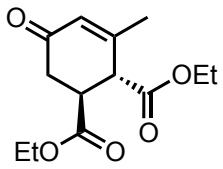
MS (ESI) 233 [(M + Na)$^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{12}H_{18}NaO_3$ (M + Na)$^+$ 233.1148 found 233.1156 (−3.3 ppm error).

Crystal structure determination of diol *cis*-228

$C_{12}H_{18}O_3$, M = 210.26, orthorhombic, a = 6.1186(5), b = 12.2742(4), c = 14.054(3) Å, U = 1055.4(2) Å^3, T = 110(10) K, space group $P2_12_12_1$, Z = 4, μ(Mo-Kα) = 0.096 mm^{-1}, 10017 reflections measured, 3408 unique (R_{int} = 0.0298) which were used in calculations. The final R1 was 0.0384 (I>2σ$_I$) and wR2 was 0.0945 (all data).

Lab book reference: djbI3/71

(1*SR*,2*RS*)-Diethyl 3-methyl-5-oxocyclohex-3-ene-1,2-dicarboxylate 233



Diethyl fumerate (804 μL, 4.92 mmol) was added to a stirred solution of a 50:50 mixture of dienes (*E*)-**242** and (*Z*)-**242** (2.40 g, 9.83 mmol) in toluene (5 mL) at rt under Ar in a sealed tube. The resulting mixture was stirred and heated at 150 °C for 20 h. After being allowed to cool to rt, the solvent was evaporated under reduced pressure to give the crude Diels-Alder adduct **243**. TFA (5 mL) was added to a stirred solution of the crude Diels-Alder adduct **243** in CH_2Cl_2 (10 mL) and MeOH (1 mL) at rt. The resulting mixture was stirred at rt for 1 h. Then, the solvent was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with petrol-EtOAc (4:1) as eluent gave enone **233** (1.16 g, 93%) as a colourless oil, R_F (4:1 petrol-EtOAc) 0.19; IR (Thin Film) 2938, 1706 (C=O), 1652 (C=O), 1232, 1173, 1013, 721 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.93 (quintet, J = 1.5 Hz, 1H, =CH), 4.22 (q, J = 7.0 Hz, 2H, OCH_2Me), 4.14 (q, J = 7.0 Hz, 2H, OCH_2Me), 3.71 (d, J = 5.5 Hz, 1H, =CMeC*H*), 3.47 (dt, J = 6.5, 5.5 Hz, 1H, CH), 2.74 (dd, J = 17.0, 5.5 Hz, 1H, CH_AH$_B$), 2.68 (dd, J = 17.0, 6.5 Hz, 1H, CH$_A$$H_B$), 2.04 (d, J = 1.5 Hz, 3H, =CMe), 1.29 (t, J = 7.0 Hz, 3H, OCH$_2$*Me*), 1.22 (t, J = 7.0 Hz, 3H, OCH$_2$*Me*); ^{13}C NMR (100.6 MHz; $CDCl_3$) δ: 195.6 (C=O$_{enone}$), 172.1 (C=O$_{ester}$), 170.6 (C=O$_{ester}$), 155.7 (=*C*Me), 128.2 (=CH), 61.9 (O*C*H$_2$Me), 61.7

(O*C*H_2Me), 48.3 (CH), 42.8 (CH), 36.5 (CH_2), 23.7 (=C*Me*), 14.2 (OCH$_2$*Me*), 14.1 (OCH$_2$*Me*); MS (ESI) 347 (20), 277 [$(M + Na)^+$, 100], 255 [$(M + H)^+$, 68]; HRMS (ESI) *m/z* calcd for $C_{13}H_{18}O_5$ $(M + Na)^+$ 277.1046 found 277.1038 (3.2 ppm error), calcd for $C_{13}H_{18}O_5$ $(M + H)^+$ 255.1227 found 255.1223 (1.6 ppm error).

Lab book reference: djbI4/36

Table 6.1, entry 2

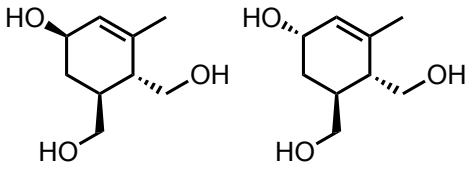
$AlMe_3$ (20 μL of a 2.0 M solution in hexanes, 0.04 mmol), $AlBr_3$ (52 mg, 0.20 mmol) and diethylfumerate **235** (64 μL, 0.39 mmol) were added to a stirred solution of a 50:50 mixture of dienes (*E*)-**242** and (*Z*)-**242** (380 mg, 1.56 mmol) in toluene (1 mL) at 0 °C under Ar. The resulting mixture was stirred at 0 °C for 9 h. Then, the solvent was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with petrol-EtOAc (4:1) as eluent gave enone **233** (69 mg, 70%) as a colourless oil.

Lab book reference: djbI4/25

Diethyl fumerate **235** (27 μL, 0.17 mmol) was added to a stirred solution of impure diene **247** (75 mg, 0.33 mmol, assuming 100% purity) in toluene (1 mL) at rt under Ar in a sealed tube. The resulting mixture was stirred and heated at 150 °C for 27 h. After being allowed to cool to rt, the solvent was evaporated under reduced pressure to give the crude Diels-Alder adduct **248**. TFA (1 mL) was added to a stirred solution of the crude Diels-Alder adduct **248** in CH_2Cl_2 (2 mL) and MeOH (200 μL) at rt. The resulting mixture was stirred at rt for 1 h. Then, the solvent was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with petrol-EtOAc (4:1) as eluent gave enone **233** (16 mg, 38%) as a colourless oil. *Note: Diene **247** of unkown purity and this could explain the low yield of this reaction.*

Lab book reference: djbI4/43

((1*SR*,2*RS*,5*RS*)- and ((1*SR*,2*RS*,5*SR*)-5-Hydroxy-3-methylcyclohex-3-ene-1,2-diyl)dimethanol 1,4-*trans*-**236 and** 1,4-*cis*-**236**



1,4-trans 1,4-*cis*

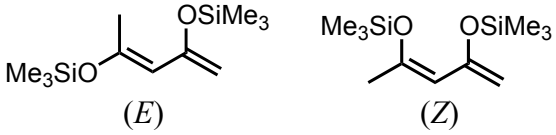
$LiAlH_4$ (224 mg, 5.90 mmol) was added to a stirred solution of the enone **233** (500 mg, 1.97 mmol) in Et_2O (10 mL) at −78 °C under Ar. The resulting mixture was stirred at −78 °C for 1 h. Then, Glaubert's salt ($Na_2SO_4 \cdot 10H_2O$) was added slowly until effervescence ceased. The mixture was allowed to warm to rt and the solid was removed by filtration and washed with EtOAc (10 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with CH_2Cl_2-MeOH (10:1) as eluent gave (by ^1H NMR spectroscopy) a 90:10 mixture of triols 1,4-*trans*-**236** and 1,4-*cis*-**236** (170 mg, 51%) as a colourless oil, R_F (10:1 CH_2Cl_2-MeOH) 0.11; IR (Thin Film) 3310 (OH), 2889, 1420, 1035, 1017, 941 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ: 5.56-5.50 (m, 1H, =CH), 4.14-4.08 (m, 1H, C*H*OH), 3.75-3.48 (m, 4H, 2 × CH_2OH), 2.21-2.14 (m, 0.1H, =CMeC$H_{1,4\text{-}cis}$), 2.06 (dtd, J = 12.5, 4.0, 0.5 Hz, 0.9H, =CMeC$H_{1,4\text{-}trans}$), 1.96-1.89 (m, 1.9H), 1.87-1.80 (m, $0.1H_{1,4\text{-}cis}$), 1.75-1.74 (m, 3H, =CMe), 1.63 (ddd, J = 13.0, 8.0, 4.0 Hz, 0.1H, C$H_A H_{B1,4\text{-}cis}$), 1.34 (ddd, J = 12.5, 10.0, 8.0 Hz, 0.9H, C$H_A H_{B1,4\text{-}trans}$); ^{13}C NMR (100.6 MHz; CD_3OD) δ: 135.9 (=*C*$Me_{1,4\text{-}cis}$), 135.3 (=*C*$Me_{1,4\text{-}trans}$), 128.9 (=$CH_{1,4\text{-}trans}$), 126.8 (=$CH_{1,4\text{-}cis}$), 65.6 ($CHOH_{1,4\text{-}trans}$), 64.7 ($CH_2OH_{1,4\text{-}trans}$), 63.73 ($CHOH_{1,4\text{-}cis}$), 63.70 ($CH_2OH_{1,4\text{-}cis}$), 61.8 ($CH_2OH_{1,4\text{-}cis}$), 60.5 ($CH_2OH_{1,4\text{-}trans}$), 43.5 ($CH_{1,4\text{-}trans}$), 43.4 ($CH_{1,4\text{-}cis}$), 35.7 ($CH_{1,4\text{-}trans}$), 35.5 ($CH_{1,4\text{-}cis}$), 33.6 ($CH_{2\ 1,4\text{-}trans}$), 30.1 ($CH_{2\ 1,4\text{-}cis}$), 21.2 (=C*Me*$_{1,4\text{-}cis}$), 20.7 (=C*Me*$_{1,4\text{-}trans}$); MS (ESI) 367 [(2 × M + Na)$^+$, 68], 195 [(M + Na)$^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{18}H_{32}O_6$ (2 × M + Na)$^+$ 367.2091 found 367.2078 (3.6 ppm error), calcd for $C_9H_{16}O_3$ (M + Na)$^+$ 195.0992 found 195.0996 (−2.0 ppm error).

Lab book reference: djbI4/37

Diethyl fumerate **235** (200 μL, 1.23 mmol) was added to a stirred solution of a 50:50 mixture of dienes (*E*)-**242** and (*Z*)-**242** (601 mg, 2.46 mmol) in toluene (5 mL) at rt under Ar in a sealed tube. The resulting mixture was stirred and heated at 150 °C for 20 h. After being allowed to cool to rt, the solvent was evaporated under reduced pressure to give the crude Diels-Alder adduct **243**. $LiAlH_4$ (187 mg, 4.92 mmol) was added to a stirred solution the crude Diels-Alder adduct **243** in Et_2O (10 mL) at −78 °C under Ar. The resulting mixture was stirred at −78 °C for 1 h. Then, Glaubert's salt ($Na_2SO_4 \cdot 10H_2O$) was added slowly until effervescence ceased. The mixture was allowed to warm to rt and the solid was removed by filtration and washed with EtOAc (10 × 20 mL) The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude silyl enol ether **245**. TFA (5 mL) was added to a stirred solution of the crude silyl enol ether **245** in CH_2Cl_2 (10 mL) and MeOH (1 mL) at rt. The resulting mixture was stirred at rt for 1 h. Then, the solvent was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with petrol-EtOAc (4:1) as eluent gave (by ^{1}H NMR spectroscopy) an 90:10 mixture of triols 1,4-*trans*-**236** and 1,4-*cis*-**236** (26 mg, 12%) as a colourless oil.

Lab book reference: djbI4/30

(*E*)-and (*Z*)-2,2,4,8,8-Pentamethyl-6-methylene-3,7-dioxa-2,8-disilanon-4-ene (*E*)-242 and (*Z*)-242

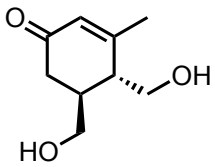


Me_3SiOTf (5.0 mL, 27.6 mmol) was added dropwise to a stirred solution of acetylacetone (941 μL, 9.21 mmol) and Et_3N (5.14 mL, 36.8 mmol) in Et_2O (10 mL) at rt under Ar. The resulting mixture was stirred at rt for 1 h. Then, saturated $NaHCO_{3(aq)}$ (20 mL) and pentane (20 mL) were added and the layers were separated. The aqueous layer was extracted with pentane (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by bulb-to-bulb distillation gave (by ^{1}H NMR

spectroscopy) a 50:50 mixture of dienes (*E*)-**242** and (*Z*)-**242** (2.11 g, 94%), bp 72–78 °C/0.1 mmHg); IR (Thin Film) 2914, 1627 (C=C), 1315, 1232, 1006, 833, 743 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 5.19 (s, 0.5H), 4.75-4.74 (m, 0.5H), 4.74 (s, 0.5H), 4.31 (d, *J* = 1.5 Hz, 0.5H), 4.14 (s, 0.5H), 4.09 (s, 0.5H), 2.01 (s, 1.5H, Me), 1.85 (s, 1.5H, Me), 0.23 (s, 4.5H, $SiMe_3$), 0.22 (s, 4.5H, $SiMe_3$), 0.20 (s, 4.5H, $SiMe_3$), 0.19 (s, 4.5H, $SiMe_3$); ^{13}C NMR (100.6 MHz; $CDCl_3$) δ: 154.6 (C), 152.8 (C), 152.5 (C), 150.8 (C), 108.7 (=CH), 107.2 (=CH), 93.5 (2 × $=CH_2$), 23.9 (Me), 20.1 (Me), 1.0 ($SiMe_3$), 0.5 ($SiMe_3$), 0.3 ($SiMe_3$), 0.2 ($SiMe_3$); MS (ESI) 245 [$(M + H)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_{11}H_{24}O_2Si_2$ $(M + H)^+$ 245.1388 found 245.1377 (4.4 ppm error).

Lab book reference: djbI4/33

(4*RS*,5*SR*)-4,5-Bis(hydroxymethyl)-3-methylcyclohex-2-enone 244

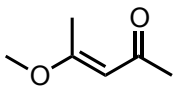


Diethyl fumerate **235** (425 μL, 2.59 mmol) was added to a stirred solution of diene **247** (1.18 g, 5.19 mmol, assuming 100% purity) in toluene (4 mL) at rt under Ar in a sealed tube. The resulting mixture was stirred and heated at 150 °C for 24 h. After being allowed to cool to rt, the solvent was evaporated under reduced pressure to give the crude Diels-Alder adduct **248**. $LiAlH_4$ (491 mg, 12.95 mmol) was added to a stirred solution of the crude Diels-Alder adduct **248** in Et_2O (10 mL) at −78 °C under Ar. The resulting mixture was stirred at −78 °C for 1 h. Then, Glauber's salt ($Na_2SO_4 \cdot 10H_2O$) was added slowly until effervescence ceased. The mixture was allowed to warm to rt and the solid was removed by filtration and washed with EtOAc (10 × 20 mL). The combined organic extracts were evaporated under reduced pressure to give the crude diol. TFA (10 mL) was added to a stirred solution of the crude diol in CH_2Cl_2 (20 mL) and MeOH (2 mL) at rt. The resulting mixture was stirred at rt for 1 h. Then, the solvent was evaporated under reduced pressure to give the crude producr. Purification by flash column chromatography on silica with CH_2Cl_2-MeOH (10:1) as eluent gave enone **244** (97 mg, 22%) as a colourless oil, R_F

(10:1 CH_2Cl_2-MeOH) 0.17; IR (Thin Film) 3309 (OH), 2894, 1621 (C=O), 1035, 709 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ: 5.87 (d, *J* = 0.5 Hz 1H, =CH), 3.83–3.76 (m, 2H, CH_2OH), 3.52–3.43 (m, 2H, CH_2OH), 2.64 (dd, *J* = 17.5, 5.5 Hz, 1H, CH_AH$_B$), 2.49–2.39 (m, 2H), 2.29 (dd, *J* = 17.5, 4.5 Hz, 1H, CH$_A$$H_B$), 2.02 (t, *J* = 0.5 Hz, 3H, =Cme); ^{13}C NMR (100.6 MHz; CD_3OD) δ: 200.1 (C=O), 163.4 (=*C*me), 126.8 (=CH), 63.4 (CH_2OH), 61.7 (CH_2OH), 44.3 (CH), 38.0 (CH), 35.9 (CH_2), 22.5 (=C*me*); MS (ESI) 193 [$(M + H)^+$, 52], 171 [$(M + H)^+$, 100]; HRMS (ESI) *m/z* calcd for $C_9H_{14}O_3$ $(M + Na)^+$ 193.0835 found 193.0836 (−0.5 ppm error), calcd for $C_9H_{14}O_3$ $(M + H)^+$ 171.1016 found 171.1010 (3.2 ppm error). *Note: Diene **247** of unkown purity and this could explain the low yield of this reaction.*

Lab book reference: djbI4/45

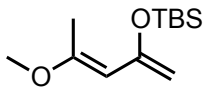
(*E*)-4-Methoxypent-3-en-2-one 246



Concentrated H_2SO_4 (3 drops) was added to a stirred solution of acetylacetone (6.12 mL, 59.9 mmol) in trimethylorthoformate (6.56 mL, 59.9 mmol) at rt under Ar. The resulting mixture was stirred at rt for 24 h. Then, 2 M $NaOH_{(aq)}$ (50 mL) and Et_2O (50 mL) were added and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 50 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by fractional distillation gave methyl enol ether **246** (5.69 g, 83%) as a colourless oil, bp 50–55 °C/6 mmHg (lit.[315] bp 43–47 °C/4 mmHg); ^1H NMR (400 MHz, $CDCl_3$) δ: 5.46 (s, 1H, =CH), 3.64 (s, 3H, OMe), 2.27 (s, 3H, *Me*COMe=), 2.16 (s, 3H, COMe). Spectroscopic data are consistent with those reported in the literature.[315]

Lab book reference: djbI3/98

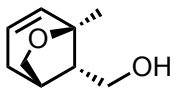
(*E*)-*tert*-Butyl((4-methoxypenta-1,3-dien-2-yl)oxy)dimethylsilane 247



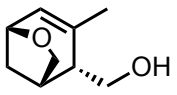
TBSOTf (1.51 mL, 6.58 mmol) was added dropwise to a stirred solution of methyl enol ether **246** (500 mg, 4.38 mol) and Et_3N (1.22 mL, 8.77 mmol) in Et_2O (5 mL) at rt under Ar. The resulting mixture was stirred at rt for 1 h. Then, saturated $NaHCO_{3(aq)}$ (10 mL) and pentane (10 mL) were added and the layers were separated. The aqueous layer was extracted with pentane (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by bulb-to-bulb distillation three times gave impure diene **247** (1.26 g) as an orange oil, bp 72–78 °C/0.1 mmHg. *Note: Diene **247** was contaminated by impurities and its purity is unkown,*

Lab book reference: djbI4/43

((1*SR*,5*RS*,8*SR*)-5-Methyl-6-oxabicyclo[3.2.1]oct-3-en-8-yl)methanol 240 and ((1*SR*,2*RS*,5*RS*)-3-Methyl-6-oxabicyclo[3.2.1]oct-3-en-2-yl)methanol 249



240



249

Ph_3PAuCl (139 mg, 0.28 mmol) and AgOTf (72 mg, 0.28 mmol) was added to a stirred solution of an 90:10 mixture of triols 1,4-*trans*-**236** and 1,4-*cis*-**236** (484 mg, 2.81 mmol) and 4 Å MS (500 mg) in THF (10 mL) at rt under Ar. The resulting mixture was stirred and heated at reflux for 4 h. Then, the mixture was filtered through a Celite® plug and washed with EtOAc (10 × 10 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with CH_2Cl_2-MeOH (10:1) as eluent gave (by ^1H NMR spectroscopy) a 90:10 mixture of alcohols **240** and **249** (280 mg, 65%) as a colourless oil, R_F (10:1 CH_2Cl_2-MeOH) 0.35; ^1H NMR (400 MHz, CD_3OD) δ: 5.81-5.77 (m, 0.1H, $=CH_{\mathbf{249}}$), 5.74 (dddd, J = 9.5, 4.0, 2.5, 1.5 Hz, 0.9H, $=CH_{\mathbf{240}}$), 5.57 (ddd, J = 9.5, 3.0, 2.0 Hz, 0.9H, $=CH_{\mathbf{240}}$),

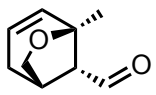
4.25 (t, J = 5.5 Hz, 0.1H, CHO_{249}), 4.04-3.96 (m, 0.9H, CHO_{240}), 3.84 (dd, J = 11.0, 3.5 Hz, 0.1H, CHO_{249}), 3.78-3.59 (m, 2.9H, 3 × CHO_{240} + 2 × CHO_{249}), 2.75-2.71 (m, 0.1H, CH_{249}), 2.62-2.56 (m, 0.9H, CH_{240}), 2.37-2.30 (m, 0.9H_{240}), 2.19-2.15 (m, 0.1H_{249}), 2.04-2.01 (m, 0.9H_{240}), 2.00-1.96 (m, 0.1H_{249}), 1.66 (s, 0.3H, =CMe_{249}), 1.31 (s, 2.7H, =CMe_{240}); MS (ESI) 309 (66), 279, (71), 155 [$(M + H)^+$, 18], 107 (100); HRMS (ESI) *m/z* calcd for $C_9H_{15}O_2$ $(M + H)^+$ 155.1067 found 155.1073 (−4.1 ppm error).

Lab book reference: djbI4/52

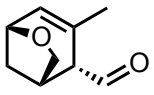
HCl (5 μL of a 2.0 M solution in Et_2O, 0.01 mmol) was added to a stirred solution of an 90:10 mixture of triols 1,4-*trans*-**236** and 1,4-*cis*-**236** (10 mg, 0.06 mmol) and 4 Å MS (100 mg) in THF (5 mL) at rt under Ar. The resulting mixture was stirred at rt for 1 h. Then, the solvent was evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with CH_2Cl_2-MeOH (10:1) as eluent gave (by ^{1}H NMR spectroscopy) a 72:28 mixture of alcohols **240** and **249** (7 mg, 78%) as a colourless oil.

Lab book reference: djbI4/50

(1*SR*,5*RS*,8*RS*)-5-Methyl-6-oxabicyclo[3.2.1]oct-3-ene-8-carbaldehyde 251 and (1*SR*,2*RS*,5*RS*)-3-Methyl-6-oxabicyclo[3.2.1]oct-3-ene-2-carbaldehyde 252



251



252

DMP (347 mg, 0.82 mmol) was added to a stirred solution of a 72:18 mixture of alcohols **240** and **249** (63 mg, 0.41 mmol) in CH_2Cl_2 (5 mL) at rt under Ar. The resulting suspension was stirred at rt for 2 h. Then, saturated $NaHCO_{3(aq)}$ (10 mL) and saturated $Na_2S_2O_{3(aq)}$ (10 mL) were added and the resulting biphasic mixture was stirred at rt for 1 h. Then, CH_2Cl_2 (10 mL) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the

crude product. Purification by flash column chromatography on silica with Et_2O as eluent gave aldehyde **251** (21 mg, 34%) as a colourless oil, R_F (Et_2O) 0.46; IR (Thin Film) 2922, 2882, 2832, 1690 (C=O), 1095, 1020, 977, 844 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 9.67 (d, J = 2.0 Hz, 1H, CHO), 5.79 (s, 2H, 2 × =CH), 4.04 (ddd, J = 8.5, 5.5, 2.5 Hz, 1H, CH_AH$_B$O), 3.61 (d, J = 8.5 Hz, 1H, CH$_A$$H_B$O), 2.91–2.85 (m, 1H, CHCO), 2.50–2.43 (m, 2H, CH_AH$_B$ + CH), 2.08 (dt, J = 18.5, 2.5 Hz, 1H, CH$_A$$H_B$), 1.43 (s, 3H, Me); ^{13}C NMR (100.6 MHz; $CDCl_3$) δ: 201.2 (CHO), 133.5 (=CH), 129.6 (=CH), 73.9 (CH_2O), 59.0 (CH), 37.3 (*C*HCO), 32.1 (CH_2), 22.9 (Me); MS (ESI) 252 (64), 150 [$(M + NH)^+$, 58], 135 (100); HRMS (ESI) *m/z* calcd for $C_9H_{12}O_2$ $(M + H)^+$ 153.0910 found 153.0925 (−10.1 ppm error) and gave aldehyde **252** (11 mg, 18%) as a colourless oil, R_F (Et_2O) 0.40; IR (Thin Film) 2916, 2829, 1695 (C=O), 1424, 1060, 1028, 869 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 9.76 (d, J = 1.0 Hz, 1H, CHO), 5.97–5.95 (m, 1H, =CH), 4.35 (t, J = 5.0 Hz, 1H, CHO), 4.05 (dd, J = 8.0, 6.5 Hz, 1H, CH_AH$_B$O), 3.71 (d, J = 8.0 Hz, 1H CH$_A$$H_B$O), 2.94–2.89 (m, 1H, CHCO), 1.86–1.71 (m, 6H); ^{13}C NMR (100.6 MHz; $CDCl_3$) δ: 200.3 (CHO), 132.4 (=*C*Me), 129.7 (=CH), 72.0 (CH_2O), 71.2 (CHO), 61.9 (*C*HCO), 35.0 (CH), 31.9 (CH_2), 21.6 (=C*Me*); MS (ESI) 153 [$(M + H)^+$, 87], 135 (100); HRMS (ESI) *m/z* calcd for $C_9H_{12}O_2$ $(M + H)^+$ 153.0910 found 154.0910 (0.1 ppm error).

Lab book reference: djbI4/48

Appendix

Organic & Biomolecular Chemistry

Cite this: *Org. Biomol. Chem.*, 2012, **10**, 7666

www.rsc.org/obc

COMMUNICATION

Catalytic asymmetric synthesis of butane diacetal-protected (4*S*,5*S*)-dihydroxycyclohexen-1-one and use in natural product synthesis†

David J. Burns,[a] Shuji Hachisu,[b] Peter O'Brien*[a] and Richard J. K. Taylor[a]

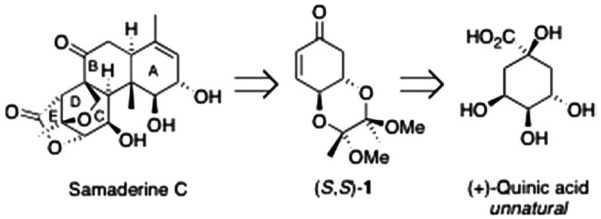
Received 19th July 2012, Accepted 17th August 2012
DOI: 10.1039/c2ob26406d

Due to the lack of availability of unnatural (+)-quinic acid as a starting material, a 6-step synthesis of butane diacetal-protected (4*S*,5*S*)-dihydroxycyclohexen-1-one (formally derived from (+)-quinic acid) has been devised. The key catalytic asymmetric step involves a chiral Co-salen-catalysed epoxide ring-opening reaction. (4*S*,5*S*)-Dihydroxycyclohexen-1-one was utilised in the synthesis of two cyclohexenone natural products isolated from the mycelia of *Lasiodiplodia theobromae*.

Synthesis employing chiral pool starting materials such as amino acids and sugars represents one of the seminal strategies for the preparation of enantiopure natural products and pharmaceuticals. Nowadays, despite the plethora of asymmetric synthesis methods that are at our disposal, readily available chiral pool compounds are still important for the total synthesis of complex natural products. A representative recent example is provided by Gademann's total synthesis of cyrneine A from (*R*)-carvone.[1] Notwithstanding the numerous successful examples of chiral pool syntheses, a significant limitation is the commercial availability of only one, naturally occurring stereoisomer.[2] We encountered exactly this problem during the development of methodology for a projected total synthesis of samaderine C. Our plan (Scheme 1) was to construct the A ring of samaderine C starting from (4*S*,5*S*)-dihydroxycyclohexen-1-one (*S*,*S*)-**1** with the *trans*-diol functionality conveniently protected as a butane diacetal (BDA)[3] which could, in principle, be derived from (+)-quinic acid, the unnatural and unavailable stereoisomer.

Enone (*R*,*R*)-**1**, prepared in three steps from (−)-quinic acid,[4] is a well-established chiral building block used in a number of synthetic applications.[4b,c,5] Indeed, we have previously used enone (*R*,*R*)-**1** to prepare the cyclohexenone core of scyphostatin.[6] However, the lack of availability of (+)-quinic acid means that enone (*S*,*S*)-**1** has not previously been considered a viable starting material in synthesis. To address this issue, we report herein the development of a catalytic asymmetric synthetic route to enone (*S*,*S*)-**1** and demonstrate its usefulness in the preparation of naturally occurring methylated enones (*S*,*S*)-**2**[7] and (*S*,*S*)-**3**,[8] structurally related to theobroxide (Fig. 1).

Our synthetic approach to enone (*S*,*S*)-**1** is outlined in Scheme 2. It was envisaged that (*S*,*S*)-**1** would be prepared from BDA-protected chiral epoxide **4** *via* lithium amide-mediated epoxide rearrangement[9–11] and oxidation of the allylic alcohol. Epoxide **4** would be generated from mono-protected dihydroxycyclohexene (*S*,*S*)-**5** which would in turn be the product of a Jacobsen desymmetrisation of *meso*-epoxide **6** using benzoic acid in the presence of a chiral Co-salen catalyst.[12]



Scheme 1

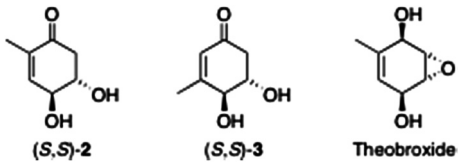
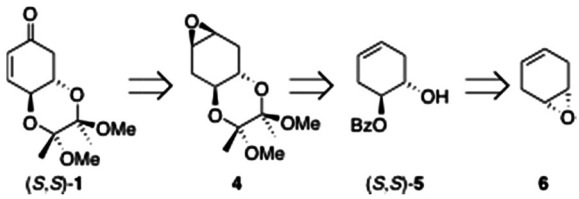


Fig. 1 Theobroxide-related natural products.

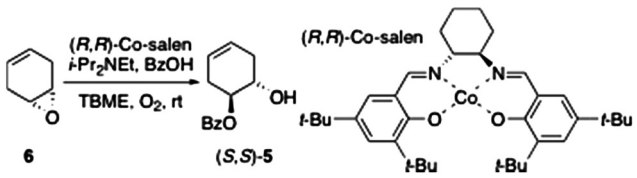


Scheme 2

[a]*Department of Chemistry, University of York, Heslington, York YO10 5DD, UK. E-mail: peter.obrien@york.ac.uk; Fax: +44 (0)1904 322516; Tel: +44 (0)1904 322535*
[b]*Syngenta, Jealott's Hill International Research Centre, Bracknell, Berkshire RG42 6EY, UK*

† Electronic supplementary information (ESI) available: Full experimental procedures and copies of $^{1}H/^{13}C$ NMR spectra and CSP-HPLC data. See DOI: 10.1039/c2ob26406d

Table 1 Desymmetrisation of *meso*-epoxide **6**



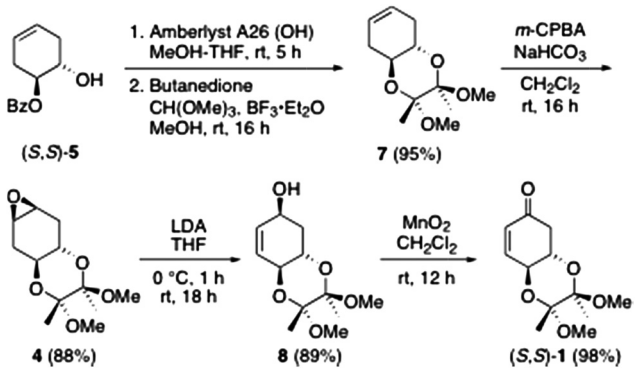
Entry	Mol% (*R*,*R*)-Co-salen	Time (h)	Yield[a] (%)	er[b]
1	5	53	74	83 : 17
2	2.5	90	79	85 : 15
3	2	94	85	85 : 15
4	1	120	70	79 : 21
5	0	140	0	n/a

[a] Yield after purification by chromatography. [b] Enantiomer ratio (er) determined by CSP-HPLC on a Chiralpak AS column; major enantiomer is (*S*,*S*)-**5**.

To start with, *meso*-epoxide **6** was prepared by epoxidation of 1,4-cyclohexadiene using *m*-CPBA in $NaHCO_3$-buffered dichloromethane.[13] Purification by distillation gave **6** in 67% yield. Next, the Jacobsen desymmetrisation step was evaluated. Based on precedent,[12] the (*R*,*R*)-Co-salen was selected as we anticipated that this should deliver (*S*,*S*)-**5**. Ultimately, this was proven to be the case by conversion of (*S*,*S*)-**5** into enone (*S*,*S*)-**1** (*vide infra*). Following the literature protocol,[12] the (*R*,*R*)-Co-salen (1–5 mol%) was oxidatively pre-activated by stirring under an oxygen atmosphere in TBME. Then, i-Pr_2NEt, additional TBME solvent and *meso*-epoxide **6** were added and the reaction was stirred for 53–120 h. The results of this study are presented in Table 1. Using 5 mol% (*R*,*R*)-Co-salen for 53 h, benzoate (*S*,*S*)-**5** was isolated in 74% yield and 83 : 17 er (entry 1). A similarly high yield and enantioselectivity were obtained at 2.5, 2.0 and 1.0 mol% loadings of the (*R*,*R*)-Co-salen catalyst, but longer reaction times were required (90–120 h) (entries 2–4). These results are consistent with the lack of a background reaction between benzoic acid and epoxide **6** under these conditions: a reaction in the absence of catalyst yielded no product (entry 5). Based on these results, a reaction using 2 mol% (*R*,*R*)-Co-salen was scaled up. Thus, 16.7 g of **6** delivered 32.4 g (85% yield) of benzoate (*S*,*S*)-**5** in 85 : 15 er. Crucially, recrystallisation from dichloromethane and heptane gave 12.1 g (32%) of (*S*,*S*)-**5** in 98.5 : 1.5 er.

With benzoate (*S*,*S*)-**5** of high er in hand, conversion into the desired enone (*S*,*S*)-**1** was carried out (Scheme 3). Initial attempts at saponification of benzoate (*S*,*S*)-**5** using KOH led to low yields due to problems in isolating the water-soluble diol product. Instead, use of the polymer-supported Amberlyst A26 (OH form) in MeOH cleaved the ester and removed the need for an aqueous work-up. The crude diol thus obtained was then BDA-protected using butanedione, trimethyl orthoformate and $BF_3{\cdot}Et_2O$ to give **7** in 95% yield over the 2 steps. Subsequent epoxidation proceeded uneventfully to give BDA-protected epoxide **4** in 88% yield.

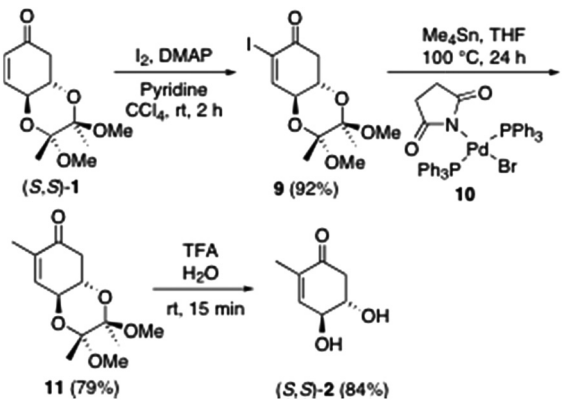
Treatment of epoxide **4** with LDA in THF led to efficient epoxide rearrangement to give allylic alcohol **8** in 89% yield (Scheme 3). The BDA group locks the protected diol in **4** in a *trans*-diequatorial arrangement and the stereospecific preference



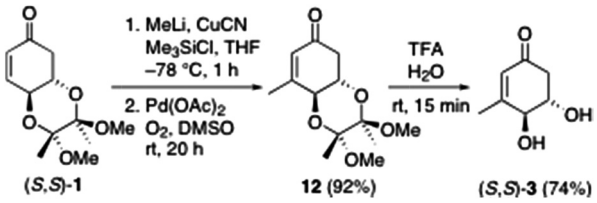
Scheme 3

for removal of an axial proton that is *syn* to the epoxide leads to the generation of a single diastereomeric allylic alcohol.[11] Finally, oxidation using MnO_2 in dichloromethane gave enone (*S*,*S*)-**1** in 98% yield. The absolute stereochemistry of our synthesised enone **1** was established as (*S*,*S*) by comparison of its optical rotation ($[\alpha]_D$ −72.0 (*c* 1.0 in $CHCl_3$)) with that of (*R*,*R*)-**1** ($[\alpha]_D$ +64.4 (*c* 0.39 in $CHCl_3$)) prepared from (−)-quinic acid.[4a] We also confirmed that (*S*,*S*)-**1** was formed in 98.5 : 1.5 er using CSP-HPLC. Our synthesis of the previously unknown enone (*S*,*S*)-**1** proceeds in 6 steps and 14% overall yield.

To demonstrate the synthetic utility of enone (*S*,*S*)-**1**, it was used in the first syntheses of two theobroxide-related natural products, (*S*,*S*)-**2** and (*S*,*S*)-**3** (Fig. 1). α-Methyl-dihydroxyenone (*S*,*S*)-**2** was isolated from the mycelia of *Lasiodiplodia theobromae*, a common pathogenic fungus found in the tropics and subtropics.[7] In terms of biological activity, (*S*,*S*)-**2** showed potato micro-tuber-inducing activity at a concentration of 10^{-3} M which compared well with other theobroxide-related natural products. Our synthesis of (*S*,*S*)-**2** is shown in Scheme 4. First, iodination of enone (*S*,*S*)-**1** was carried out in 92% yield to give iodide **9** which was subjected to Stille coupling with tetramethyltin to produce α-methyl enone **11**. In our hands, use of Pd_2dba_3, $AsPh_3$, CuI and Et_2NH (THF, 100 °C, sealed tube, 24 h)[14] was only moderately successful (32% yield of **11**). In contrast, replacing this cocktail of reagents with NBS palladium precatalyst **10**[15] led to efficient Stille coupling under similar conditions. In this way, α-methyl enone **11** was formed in 79% yield. Then, BDA-deprotection using TFA–water gave naturally occurring



Scheme 4



Scheme 5

(*S*,*S*)-**2** in 84% yield which exhibited $[\alpha]_D$ +141.4 (*c* 0.7 in MeOH) (lit.,[8] $[\alpha]_D$ +128 (*c* 0.21 in MeOH)).

Our attention then turned to structurally related β-methyl enone (*S*,*S*)-**3** (Fig. 1). This enone was also isolated from the pathogenic fungus *Lasiodiplodia theobromae* and showed growth inhibitory effects on seedlings of *Nicotiana tabacum*.[8] Surprisingly, the enone was isolated from *Lasiodiplodia theobromae* as a mixture of enantiomers (~60 : 40 mixture of (*S*,*S*)-**3** and (*R*,*R*)-**3**). The plan was to utilise enone (*S*,*S*)-**1** in a synthesis of the major enantiomer in the naturally occurring mixture. Thus, Me_3SiCl-promoted conjugate addition of lithium dimethylcuprate to enone (*S*,*S*)-**1** gave an intermediate silyl enol ether. Subsequent Saegusa oxidation using catalytic $Pd(OAc)_2$ in the presence of oxygen[16] delivered β-methyl enone **12** in 92% yield (Scheme 5). Then, the BDA group was removed using TFA–water to give (*S*,*S*)-**3** in 74% yield. Our synthesised (*S*,*S*)-**3** exhibited $[\alpha]_D$ +107.0 (*c* 1.0 in MeOH) (lit.,[9] $[\alpha]_D$ +11.3 (*c* 0.01 in MeOH) for a ~60 : 40 mixture of (*S*,*S*)-**3** and (*R*,*R*)-**3** isolated from *Lasiodiplodia theobromae*).

In conclusion, a 6-step, catalytic asymmetric synthesis of butane diacetal-protected (4*S*,5*S*)-dihydroxycyclohexen-1-one (*S*,*S*)-**1** has been developed and utilised in the synthesis of two cyclohexenone natural products isolated from *Lasiodiplodia theobromae*. Enone (*S*,*S*)-**1** can now be considered a useful starting material for future synthetic endeavours.

Acknowledgements

We thank Syngenta and The University of York for funding.

Notes and references

1 E. Elamparuthi, C. Fellay, M. Neuburger and K. Gademann, *Angew. Chem., Int. Ed.*, 2012, **51**, 4071.
2 J. M. Finefield, D. H. Sherman, M. Creitman and R. M. Williams, *Angew. Chem., Int. Ed.*, 2012, **51**, 4082.
3 S. V. Ley, D. K. Baeschlin, D. J. Dixon, A. C. Foster, S. J. Ince, H. W. M. Priepke and D. J. Reynolds, *Chem. Rev.*, 2000, **101**, 53.
4 (*a*) O. Gebauer and R. Brückner, *Liebigs Ann.*, 1996, 1559; (*b*) M. T. Barros, C. D. Maycock and M. R. Ventura, *J. Chem. Soc., Perkin Trans. 1*, 2001, 166; (*c*) C. L. Arthurs, N. S. Wind, R. C. Whitehead and I. J. Stratford, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 553.
5 (*a*) S. Marchart, J. Mulzer and V. S. Enev, *Org. Lett.*, 2007, **9**, 813; (*b*) M. Shan and G. A. O'Doherty, *Org. Lett.*, 2008, **10**, 3381; (*c*) M. Altemöller and J. Podlech, *Eur. J. Org. Chem.*, 2009, 2275; (*d*) H. Schuster, R. Martinez, H. Bruss, A. P. Antonchick, M. Kaiser, M. Schurmann and H. Waldmann, *Chem. Commun.*, 2011, **47**, 6545.
6 L. M. Murray, P. O'Brien and R. J. K. Taylor, *Org. Lett.*, 2003, **5**, 1943.
7 R. Takei, K. Takahashi, H. Matsuura and K. Nabeta, *Biosci., Biotechnol., Biochem.*, 2008, **72**, 2069.
8 N. Kitaoka, K. Nabeta and H. Matsuura, *Biosci., Biotechnol., Biochem.*, 2009, **73**, 1890.
9 (*a*) J. K. Whitesell and S. W. Felman, *J. Org. Chem.*, 1980, **45**, 755; (*b*) J. K. Crandall and M. Apparu, *Org. React. (N. Y.)*, 1983, **29**, 345.
10 For our previous work on epoxide rearrangement reactions using lithium amide bases, see: (*a*) P. O'Brien and P. Poumellec, *Tetrahedron Lett.*, 1996, **37**, 8057; (*b*) P. O'Brien and P. Poumellec, *J. Chem. Soc., Perkin Trans. 1*, 1998, 2435; (*c*) S. E. de Sousa, P. O'Brien and H. C. Steffens, *Tetrahedron Lett.*, 1999, **40**, 8423; (*d*) S. Barrett, P. O'Brien, H. C. Steffens, T. D. Towers and M. Voith, *Tetrahedron*, 2000, **56**, 9633; (*e*) E. Baron, P. O'Brien and T. D. Towers, *Tetrahedron Lett.*, 2002, **43**, 723; (*f*) S. E. de Sousa, P. O'Brien and C. D. Pilgram, *Tetrahedron*, 2002, **58**, 4643; (*g*) P. O'Brien and C. D. Pilgram, *Org. Biomol. Chem.*, 2003, **1**, 523; (*h*) S. J. Oxenford, J. M. Wright, P. O'Brien, N. Panday and M. R. Shipton, *Tetrahedron Lett.*, 2005, **46**, 8315.
11 A. Kee, P. O'Brien, C. D. Pilgram and S. T. Watson, *Chem. Commun.*, 2000, 1521.
12 E. N. Jacobsen, F. Kakiuchi, R. G. Konsler, J. F. Larrow and M. Tokunaga, *Tetrahedron Lett.*, 1997, **38**, 773.
13 Q. Tan and M. Hayashi, *Org. Lett.*, 2009, **11**, 3314.
14 M. T. Barros, C. D. Maycock, M. I. Madureira and M. R. Ventura, *Chem. Commun.*, 2001, 1662.
15 (*a*) C. M. Crawforth, S. Burling, I. J. S. Fairlamb, R. J. K. Taylor and A. C. Whitwood, *Chem. Commun.*, 2003, 2194; (*b*) C. M. Crawforth, S. Burling, I. J. S. Fairlamb, A. R. Kapdi, R. J. K. Taylor and A. C. Whitwood, *Tetrahedron*, 2005, **61**, 9736; (*c*) M. J. Burns, I. J. S. Fairlamb, A. R. Kapdi, P. Sehnal and R. J. K. Taylor, *Org. Lett.*, 2007, **9**, 5397. NBS palladium precatalyst **10** is available from Aldrich: catalogue number 643742.
16 (*a*) Y. Ito, T. Hirao and T. Saegusa, *J. Org. Chem.*, 1978, **43**, 1011; (*b*) R. C. Larock, T. R. Hightower, G. A. Kraus, P. Hahn and D. Zheng, *Tetrahedron Lett.*, 1995, **36**, 2423.

ORGANIC LETTERS

2013
Vol. 15, No. 2
394–397

Stereocontrolled Synthesis of the AB Rings of Samaderine C

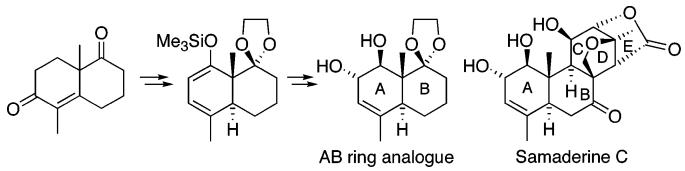
David J. Burns,[†] Stefan Mommer,[†] Peter O'Brien,*[,†] Richard J. K. Taylor,[†] Adrian C. Whitwood,[†] and Shuji Hachisu[‡]

Department of Chemistry, University of York, Heslington, York YO10 5DD, U.K., and Syngenta, Jealott's Hill International Research Centre, Bracknell, Berkshire, RG42 6EY, U.K.

peter.obrien@york.ac.uk

Received December 11, 2012

ABSTRACT

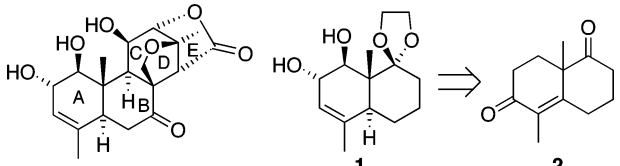


A concise synthesis of the AB rings of samaderine C (12 steps, 8 isolation steps, 7.8% overall yield), a quassinoid with antifeedant and insecticidal activity, is described. The development of the first general approach to the *trans*-1,2-diol A-ring motif in samaderine C and other quassinoids is a key feature. The *trans*-1,2-diol is crafted *via* stereoselective α-hydroxylation (of a silyl enol ether) and reduction, a strategy that has much potential for quassinoid synthesis.

Samaderine C (Scheme 1) is a highly oxygenated, polycyclic quassinoid isolated from the bark and seed kernels of the *samadera indica* plant found primarily in Madagascar and southeast Asia.[1,2] One of eight isolated samaderines, our interest in samaderine C was initiated by its reported antifeedant and insecticidal properties.[3] To date, there have been rather limited synthetic efforts on the samaderines, with only two reported total syntheses. In 1994, Grieco et al. disclosed a racemic total synthesis (> 30 steps) of samaderine B.[4] More, recently, Shing and co-workers reported a 21-step synthesis of (−)-samaderine Y starting from (+)-carvone.[5]

As there have been no previous synthetic studies on samaderine C, and to explore possible agrochemical structure−activity relationships, we focused on the synthesis of analogues of the AB rings of samaderine C. In particular,

Scheme 1. Samaderine C and **1**, an AB Ring Analogue



we sought a general strategy for constructing the *trans*-1,2-diol A-ring motif present in samaderine C and other quassinoids. Indeed, we could find no previous syntheses of such *trans*-1,2-diols in the quassinoid literature. Diol **1** was chosen as a suitable AB ring analogue of samaderine C, and herein we describe a concise, stereocontrolled synthesis starting from the known[6] bicyclic enone **2** (Scheme 1).

Our retrosynthetic analysis of diol **1** is summarized in Scheme 2. Our long-term plan had protected enone **3** serving as an advanced intermediate from which the CDE rings of samaderine C would be elaborated. Enone **3** would

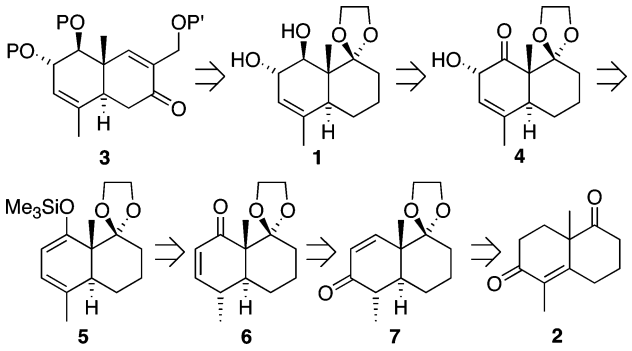
[†] University of York.
[‡] Syngenta.

(1) Zylber, J.; Polonsky, J. *Bull. Chim. Soc. Fr.* **1964**, 2016.
(2) Malathi, R.; Rajan, S. S.; Suresh, G.; Krishnakumari, G. N.; Gopalakrishnan, G. *Acta Crystallogr.* **2003**, *C59*, 416.
(3) Govindachari, T. R.; Krishnakumari, G. N.; Gopalakrishnan, G.; Suresh, G.; Wesley, S. D.; Sreelatha, T. *Fitoterapia* **2001**, *72*, 568.
(4) Grieco, P. A.; Pineiro-Nunez, M. M. *J. Am. Chem. Soc.* **1994**, *116*, 7606.
(5) Shing, T. K. M.; Yeung, Y. Y. *Angew. Chem., Int. Ed.* **2005**, *44*, 7981.
(6) Ziegler, F. E.; Hwang, K.-J.; Kadow, J. F.; Klein, S. I.; Pati, U. K.; Wang, T.-F. *J. Org. Chem.* **1986**, *51*, 4573.

10.1021/ol303385a
Published on Web 01/09/2013

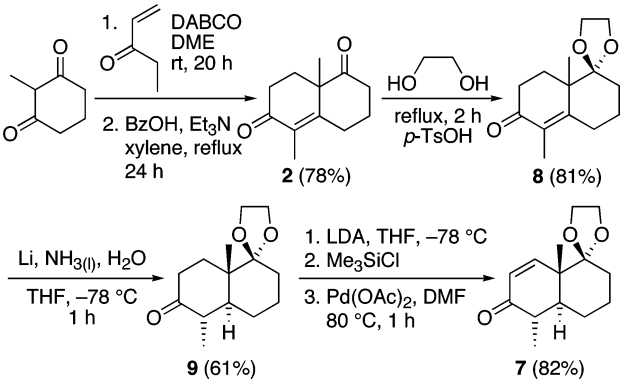
in turn be prepared from diol **1** by diol protection, ketal deprotection, 1,3-carbonyl transposition, enone formation, and enone α-functionalization. It was our intention that the bridgehead axial methyl group would control the configuration of the diol functionality in **1**: reduction of hydroxy ketone **4** (→ **1**) and α-hydroxylation of silyl enol ether **5** (→ **4**) should both occur on the face opposite to the axial methyl group to deliver the requisite *trans*-1,2-diol motif. Silyl enol ether **5** would be derived from enone **6** (by γ-enolization), itself obtained from enone **7** *via* a 1,3-carbonyl transposition (Wharton rearrangement of an epoxy ketone[7] was envisaged). Previously, Grieco had developed an approach for the α-hydroxylation of enones such as **6**,[8] and the preparation of enone **7** from bicyclic enone **2** has been described.[9]

Scheme 2. Detailed Retrosynthetic Analysis of Diol **1**



Multigram quantities of racemic enone **7** were prepared as outlined in Scheme 3. First, 2-methyl-1,3-cyclohexadione and ethyl vinyl ketone were reacted in a DABCO-mediated Robinson annelation[6] to give, after elimination, bicyclic enone **2** in 78% yield. Ketal formation to give **8** (81% yield) was accomplished using ethylene glycol and catalytic *p*-TsOH under Dean–Stark conditions. Next, stereoselective reduction of enone **8** using lithium in ammonia (in the presence of 1 equiv of H_2O) gave ketone **9** in 61% yield. Over-reduction to the secondary alcohol was a complicating factor although the alcohol could be isolated and oxidized to give additional quantities of **9**. Finally, the enone in **7** was constructed using a stoichiometric $Pd(OAc)_2$-mediated oxidation[10] of an intermediate silyl enol ether (formed by regioselective deprotonation of ketone **9** using LDA), as developed by Saegusa.[9] This delivered a single diastereomer of enone **7** in 82% yield. Using the Larock modification[11] of the Saegusa oxidation (catalytic $Pd(OAc)_2$/oxygen), none of **7** was formed and a Nicolaou-style[12] IBX-mediated oxidation of ketone **9** gave only a 14% yield of enone **7**.

Scheme 3. Synthesis of Bicyclic Enone **7**



Next, we needed to carry out a 1,3-carbonyl transposition on enone **7** to place the ketone adjacent to the bridgehead methyl group (as in **6**). For this, a nucleophilic epoxidation of enone **7** and a Wharton rearrangement–oxidation were planned. However, all attempts at directly epoxidizing **7** (e.g., H_2O_2 and NaOH or Triton B) met with failure, presumably due to steric hindrance from the neighboring methyl and ketal groups. Instead, we resorted to a three-step reduction, *m*-CPBA epoxidation, and oxidation which, although it involved more steps, was efficient and was ultimately telescoped successfully.

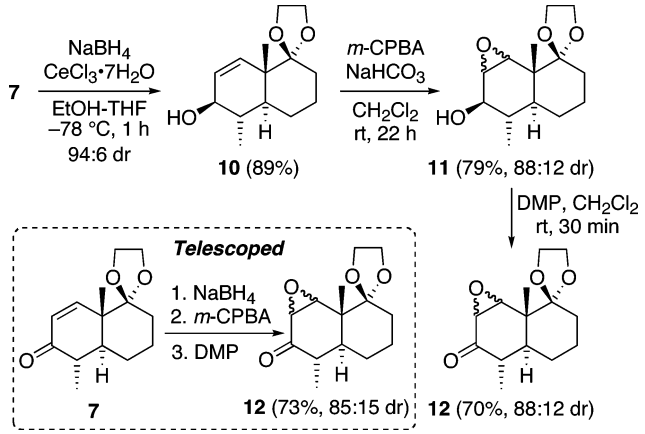
Initially, the steps were separately explored (Scheme 4). Luche reduction ($NaBH_4/CeCl_3 \cdot 7H_2O$) of enone **7** gave a 94:6 mixture of diastereomeric alcohols from which an 89% yield of alcohol **10**[13] was isolated. Then, *m*-CPBA epoxidation of allylic alcohol **10** gave an inseparable 88:12 mixture of epoxides **11** in 79% yield. The relative stereochemistry of epoxides **11** is of no consequence (*vide infra*) and remains unassigned.[14] Oxidation with Dess-Martin periodinane (DMP) delivered an 88:12 mixture of epoxy-ketones **12** (70% yield). A more efficient synthesis of **12** was achieved by telescoping these three reactions. By working-up the first two reactions and carrying the crude products forward without purification, an 85:15 mixture of epoxy-ketones **12** was obtained after chromatography (73% yield from **7**) (Scheme 4).

Treatment of the 85:15 mixture of diastereomeric epoxy-ketones **12** with hydrazine hydrate (50% aqueous solution) and acetic acid led to the allylic alcohols **13** (characterized

(7) Wharton, P. S.; Bohlen, D. H. *J. Org. Chem.* **1961**, *26*, 3615.
(8) (a) Spohn, R. F.; Grieco, P. A.; Nargund, R. P. *Tetrahedron Lett.* **1987**, *28*, 2491. (b) Grieco, P. A.; Collins, J. L.; Moher, E. D.; Fleck, T. J.; Gross, R. S. *J. Am. Chem. Soc.* **1993**, *115*, 6078.
(9) Poigny, S.; Guyot, M.; Samadi, M. *J. Org. Chem.* **1998**, *63*, 5890.
(10) Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011.
(11) Larock, R. C.; Hightower, T. R.; Kraus, G. A.; Hahn, P.; Zheng, D. *Tetrahedron Lett.* **1995**, *36*, 2423.
(12) Nicolaou, K. C.; Zhong, Y.-L.; Baran, P. S. *J. Am. Chem. Soc.* **2000**, *122*, 7596.

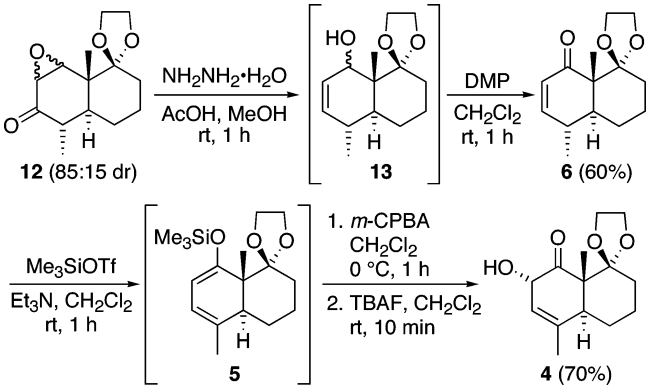
(13) The relative configuration of alcohol **10** was assigned as shown due to the presence of a characteristic *trans*-diaxial ^3J coupling between the C*H*OH and C*H*Me protons in the ^{1}H NMR spectrum (^3J = 8.5 Hz).
(14) It is tempting to assign the major epoxide as being *trans* to the axial methyl group in a sterically controlled epoxidation of **10**. However, there is also the potential of hydrogen-bonded directed epoxidation *cis* to the hydroxyl group (and hence *cis* to the methyl group), and this should not be ruled out given the enhanced *cis*-directing potential of an *equatorial* hydroxyl group. See: (a) Chamberlain, P.; Roberts, M. L; Whitham, G. G. *J. Chem. Soc. (B)* **1970**, 1374. (b) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307.

Scheme 4. Telescoped Synthesis of Epoxy-Ketone **12**



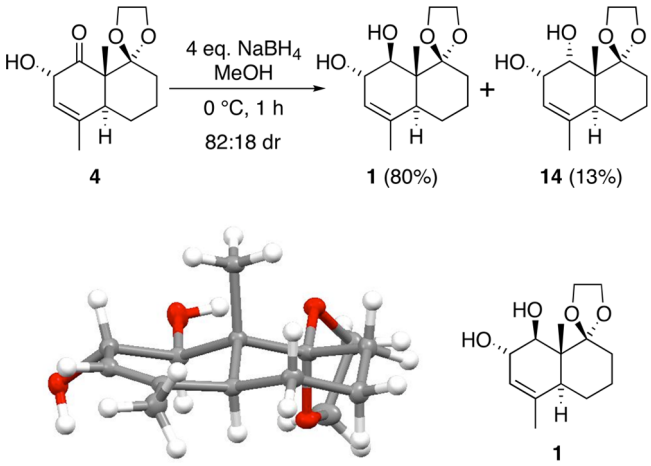
in a separate experiment) *via* a Wharton rearrangement (Scheme 5).[7] Workup and subjection of the crude allylic alcohols **13** to Dess-Martin periodinane oxidation gave enone **6** in 60% yield over the two steps. γ-Enolization of enone **6** was achieved using Et_3N and Me_3SiOTf and gave extended silyl enol ether **5**. Based on Grieco's precedent,[8] *in situ* oxidation with purified *m*-CPBA followed by stirring with TBAF generated α-hydroxy ketone **4** as a single diastereomer in 70% yield. The stereochemistry of **4** was confirmed by X-ray crystal structures of diols **1** and **14** (*vide infra*) which indicated that the oxidation had, as expected, occurred opposite to the bridgehead axial methyl group.

Scheme 5. Synthesis of α-Hydroxy Ketone **4**

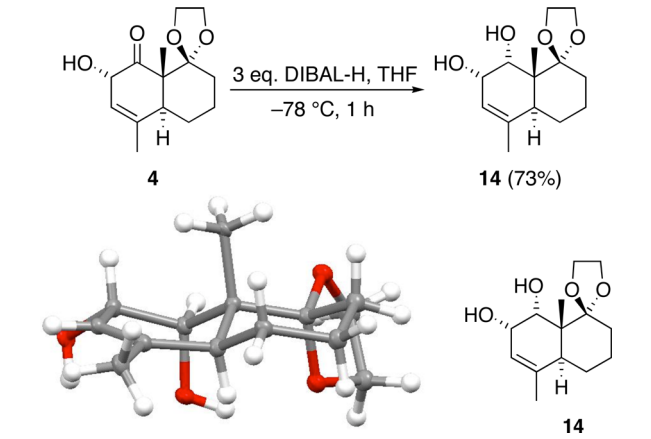


Finally, the reduction of α-hydroxy ketone **4** was explored. Using 4 equiv of $NaBH_4$ in MeOH at 0 °C, an 82:18 mixture of alcohols **1** and **14** were generated. After chromatography, *trans*-1,2-diol **1** was isolated in 80% yield and *cis*-1,2-diol **14** in 13% yield. As predicted, steric hindrance led to a preferred hydride attack on the face opposite to the methyl group. Unequivocal proof of the structure of *trans*-1,2-diol **1** was obtained by X-ray crystallography (Scheme 6).

Scheme 6. Stereoselective Synthesis and X-ray Crystal Structure of *trans*-1,2-Diol **1**



Scheme 7. Stereoselective Synthesis and X-ray Crystal Structure of *cis*-1,2-Diol **14**



In contrast, and somewhat surprisingly, reduction of α-hydroxy ketone **4** using 3 equiv of DIBAL-H in THF at −78 °C led to the preferred formation of *cis*-1,2-diol **14** which was isolated in 73% yield. Structural proof was obtained by X-ray crystallography (Scheme 7). There was no evidence of the formation of *trans*-1,2-diol **1** in this reaction. Our conjecture is that, with DIBAL-H, an aluminum alkoxide forms which, if it adopts an axial position, can coordinate to the axial oxygen of the ketal group. This would lead to a conformational change of the A-ring, exposing the other carbonyl face to the excess DIBAL-H that is present. Notably, the complementary diastereoselectivity produced with $NaBH_4$ and DIBAL-H facilitates synthetic access to either *trans*-or *cis*-1,2-diols in the quassinoid family of natural products.

In summary, a concise synthesis of the AB rings of samaderine C has been developed (12 steps, 8 isolation steps, 7.8% overall yield). In particular, we have successfully implemented a strategy for the stereoselective synthesis of the *trans*-1,2-diol motif present in samaderine C (and a range

of other quassinoids). Our approach includes a stereoselective α-hydroxylation (of an extended silyl enol ether) and a reduction. A complementary route to a *cis*-1,2-diol, a motif that is present in other quassinoid natural products such as castelanolide,[15] has also been discovered. We believe that these new aspects have great potential for quassinoid total synthesis.

(15) Grieco, P. A.; Lis, R.; Ferrino, S.; Yan, J. *J. Org, Chem.* **1984**, *49*, 2342.

Acknowledgment. We thank Syngenta and the University of York for funding.

Supporting Information Available. Full experimental procedures, characterization data, and copies of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

Abbreviations

Ac	Acetyl
Ac_2O	Acetic anhydride
acac	Acetylacetone
aq.	Aqueous
Ar	Aryl
Bn	Benzyl
Boc	*tert*-butoxycarbonyl
br	Broad
CAN	Cerium ammonium nitrate
Cbz	Carbobenzyloxy
COSY	Correlation spectroscopy
$Cu(OTf)_2$	Coppper(II) trifluoromethanesulfonate
d	Doublet
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-Dichloroethane
DEAD	Diethyl azodicarboxylate
DIBAL	Di*iso*butylaluminium hydride
DIPA	Di*iso*propylamine
DIPEA	Di*iso*propylethylamine
DMAP	4-*N*,*N*-Dimethylaminopyridine
DMF	*N*,*N*-Dimethylformamide
DMP	Dess-Martin periodinane
DMPU	1,3-Dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone

DMSO	Dimethyl sulfoxide
equiv	Equivalent
ESI	Electrospray ionisation
Et	Ethyl
Ether	Diethyl ether
EtOAc	Ethyl acetate
HMBC	Heteronulcear multiple bond correlation
HMDS	Hexamethyldisilazane
HMPA	Hexamethylphosphoramide
HRMS	High resolution mass spectrometry
HSQC	Heteronuclear single quantum correlation
HWE	Horner-Wadsworth-Emmons
Hz	Hertz
i	*Iso*
IR	Infra-red
J	Coupling constant in Hz
KHMDS	Potassium hexamethyldisilazane
KO*t*-Bu	Potassium *tert*-Butoxide
LDA	Lithium di*iso*propylamine
LHMDS	Lithium hexamethyldisilazane
m	Multiplet
M	Molar
m/z	Mass to charge ratio
M^+	Molecular ion
Me	Methyl

MeCN	Acetonitrile
min.	Minute(s)
mL	Millilitre
mmol	Millimole
MoOPH	$MoO_5 \cdot H_2O \cdot HMPA$
mp.	Melting point
Ms	Methanesulfonyl
MS	Mass spectrometry
Nap	Napthyl
NBS	*N*-Bromosuccinimide
n-BuLi	*n*-Butyllithium
NCS	*N*-Chlorosuccinimide
n-Hex	*n*-Hexyl
NMR	Nuclear magnetic resonance
nOe	Nuclear Overhauser effect
n-Pr	*n*-Propyl
p	*para*
Petrol	Petroleum ether (Fraction which boils at 40-60 °C)
Ph	Phenyl
PhMe	Toluene
PMB	*para*-methoxybenzyl
ppm	Parts per million
PPTS	Pyridinium *p*-toluenesulfonate
Pr	Propyl
*p*TSA	*para*-Toluenesulfonic acid

Py	Pyridine
q	Quartet
Quant.	Quantitative
R	Alkyl group (undefined)
R_f	Retention factor
RSM	Recovered starting material
rt	Room temperature
s	Singlet
SAR	Structure activity relationship
s-BuLi	*sec*-Butyllithium
SM	Starting material
t	Triplet
TBAF	Tertabutylammonium fluoride
TBS	*tert*-butyldimethylsilyl
TBSCl	*tert*-butyldimethylsilyl chloride
TBSOTf	*tert*-butyldimethylsilyl trifluoromethanesulfonate
t-Bu	*tert*-Butyl
t-BuLi	*tert*-Butyllithium
Tf	Trifluoromethanesulfonyl
Tf_2O	Trifluoromethanesulfonic anhydride
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
TfOH	Trifluoromethanesulfonic acid
THF	Tetrahydrofuran
THP	Tetrahydropyran

TLC	Thin layer chromatography
TMEDA	Tetramethylethylenediamine
TMS	Trimethylsilyl
TMSOTf	Trimethylsilyl trifluoromethanesulfonate
Ts	*p*-Toluenesulfonyl
δ	Chemical shift
Δ	Heat
µL	Microlitre
µW	Microwave

References

(1) Clark, E. P. *J. Am. Chem. Soc.* **1937**, *59*, 927.

(2) Valenta, Z.; Papadopoulos, S.; Podešva, C. *Tetrahedron* **1961**, *15*, 100.

(3) Liu, J.-H.; Zhao, N.; Zhang, G.-J.; Yu, S.-S.; Wu, L.-J.; Qu, J.; Ma, S.-G.; Chen, X.-G.; Zhang, T.-Q.; Bai, J.; Chen, H.; Fang, Z.-F.; Zhao, F.; Tang, W.-B. *J. Nat. Prod.* **2012**, *75*, 683.

(4) Daido, M.; Ohno, N.; Imamura, K.; Fukamiya, N.; Hatakoshi, M.; Yamazaki, H.; Tagahara, K.; Lee, K.-H.; Okano, M. *Biosci. Biotechnol. Biochem.* **1995**, *59*, 974.

(5) Polonsky, J.; Bhatnagar, S. C.; Griffiths, D. C.; Pickett, J. A.; Woodcock, C. M. *J. Chem. Ecol.* **1989**, *15*, 993.

(6) Kitagawa, I.; Mahmud, T.; Yokota, K.-i.; Nakagawa, S.; Mayumi, T.; Kobayashi, M.; Shibuya, H. *Chem. Pharm. Bull.* **1996**, *44*, 2009.

(7) Wright, C. W.; O'Neill, M. J.; Phillipson, J. D.; Warhurst, D. C. *Antimicrob. Agents Chemother.* **1988**, *32*, 1725.

(8) Gillin, F. D.; Reiner, D. S.; Suffness, M. *Antimicrob. Agents Chemother.* **1982**, *22*, 342.

(9) Pierré, A.; Robert-Géro, M.; Tempête, C.; Polonsky, J. *Biochem. Biophys. Res. Commun.* **1980**, *93*, 675.

(10) Okano, M.; Fukamiya, N.; Tagahara, K.; Cosentino, M.; Lee, T. T.-Y.; Morris-Natschke, S.; Lee, K.-H. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 701.

(11) Kupchan, S. M.; Britton, R. W.; Ziegler, M. F.; Sigel, C. W. *J. Org. Chem.* **1973**, *38*, 178.

(12) Fukamiya, N.; Okano, M.; Miyamoto, M.; Tagahara, K.; Lee, K.-H. *J. Nat. Prod.* **1992**, *55*, 468.

(13) Ohnishi, S.; Fukamiya, N.; Okano, M.; Tagahara, K.; Lee, K.-H. *J. Nat. Prod.* **1995**, *58*, 1032.

(14) Fukamiya, N.; Okano, M.; Tagahara, K.; Aratani, T.; Muramoto, Y.; Lee, K.-H. *J. Nat. Prod.* **1987**, *50*, 1075.

(15) Fukamiya, N.; Okano, M.; Tagahara, K.; Aratani, T.; Lee, K.-H. *J. Nat. Prod.* **1988**, *51*, 349.

(16) Lumonadio, L.; Atassi, G.; Vanhaelen, M.; Vanhaelen-Fastre, R. *J. Ethnopharmacol.***1991**, *31*, 59.

(17) Investigational Drug Branch, C. T. E. P., Division of Cancer Treatment, National Cancer Institute, *Bruceantin,* 1978, Clinical Brochure. Investigational Drug Branch, C. T. E. P., Division of Cancer Treatment, National Cancer Institute, *Annual Report to the FDA,* 1984.

(18) Hall, I. H.; Liou, Y. F.; Lee, K. H.; Chaney, S. G.; Willingham, W. *J. Pharm. Sci.* **1983**, *72*, 626.

(19) Lia0O, L.-L.; Kupchan, S. M.; Horwitz, S. B. *Mol. Pharmacol.* **1976**, *12*, 167.

(20) Hall, I. H.; Liou, Y. F.; Okano, M.; Lee, K. H. *J. Pharm. Sci.* **1982**, *71*, 345.

(21) Kupchan, S. M.; Lacadie, J. A. *J. Org. Chem.* **1975**, *40*, 654.

(22) Valeriote, F. A.; Corbett, T. H.; Grieco, P. A.; Moher, E. D.; Collins, J. L.; Fleck, T. J. *Oncol. Res.* **1998**, *10*, 201.

(23) Polonsky, J. *Fortschr Chem. Org. Naturst.* **1973**, *30*, 101.

(24) Clayton, R. B. *Q. Rev. Chem. Soc.* **1965**, *19*, 168.

(25) Clayton, R. B. *Q. Rev. Chem. Soc.* **1965**, *19*, 201.

(26) Eisenreich, W.; Rohdich, F.; Bacher, A. *Trends Plant Sci.* **2001**, *6*, 78.

(27) Dewick, P. M. *Medicinal Natural Products: A Biosynthetic Approach*; 2 ed.; John *Wiley* and Sons: Chichester, 2002.

(28) Hirota, H.; Yokoyama, A.; Miyaji, K.; Nakamura, T.; Igarashi, M.; Takahashi, T. *J. Org. Chem.* **1991**, *56*, 1119.

(29) Grieco, P. A.; Parker, D. T.; Nargund, R. P. *J. Am. Chem. Soc.* **1988**, *110*, 5568.

(30) Grieco, P. A.; Lis, R.; Ferrino, S.; Law, J. Y. *J. Org. Chem.* **1984**, *49*, 2342.

(31) Grieco, P. A.; Collins, J. L.; Moher, E. D.; Fleck, T. J.; Gross, R. S. *J. Am. Chem. Soc.* **1993**, *115*, 6078.

(32) Gross, R. S.; Grieco, P. A.; Collins, J. L. *J. Am. Chem. Soc.* **1990**, *112*, 9436.

(33) VanderRoest, J. M.; Grieco, P. A. *J. Am. Chem. Soc.* **1993**, *115*, 5841.
(34) Sasaki, M.; Murae, T.; Takahashi, T. *J. Org. Chem.* **1990**, *55*, 528.
(35) Kim, M.; Kawada, K.; Gross, R. S.; Watt, D. S. *J. Org. Chem.* **1990**, *55*, 504.
(36) Collins, J. L.; Grieco, P. A.; Gross, R. S. *J. Org. Chem.* **1990**, *55*, 5816.
(37) Fleck, T. J.; Grieco, P. A. *Tetrahedron Lett.* **1992**, *33*, 1813.
(38) Moher, E. D.; Collins, J. L.; Grieco, P. A. *J. Am. Chem. Soc.* **1992**, *114*, 2764.
(39) Grieco, P. A.; Collins, J. L.; Huffman, J. C. *J. Org. Chem.* **1998**, *63*, 9576.
(40) Moher, E. D.; Grieco, P. A.; Collins, J. L. *J. Org. Chem.* **1993**, *58*, 3789.
(41) Grieco, P. A.; Pineiro-Nunez, M. M. *J. Am. Chem. Soc.* **1994**, *116*, 7606.
(42) Shing, T. K. M.; Yeung, Y. Y. *Angew. Chem., Int. Ed.* **2005**, *44*, 7981.
(43) Shing, T. K. M.; Jiang, Q.; Mak, T. C. W. *J. Org. Chem.* **1998**, *63*, 2056.
(44) Grieco, P. A.; Cowen, S. D.; Mohammadi, F. *Tetrahedron Lett.* **1996**, *37*, 2699.
(45) Moher, E. D.; Reilly, M.; Grieco, P. A.; Corbett, T. H.; Valeriote, F. A. *J. Org. Chem.* **1998**, *63*, 3508.
(46) Grieco, P. A.; Speake, J. D. *J. Org. Chem.* **1998**, *63*, 5929.
(47) Grieco, P. A.; Ferrino, S.; Vidari, G. *J. Am. Chem. Soc.* **1980**, *102*, 7586.
(48) Vidari, G.; Ferrino, S.; Grieco, P. A. *J. Am. Chem. Soc.* **1984**, *106*, 3539.
(49) Grieco, P. A.; Oguri, T.; Wang, C.-L. J.; Williams, E. *J. Org. Chem.* **1977**, *42*, 4113.
(50) Boyce, C. B. C.; Whitehurst, J. S. *J. Chem. Soc.* **1960**, 2680.
(51) Heathcock, C. H.; Ratcliffe, R. *J. Am. Chem. Soc.* **1971**, *93*, 1746.
(52) Grieco, P. A.; Ferrino, S.; Vidari, G.; Huffman, J. C. *J. Org. Chem.* **1981**, *46*, 1022.
(53) Cram, D. J.; Allinger, N. L. *J. Am. Chem. Soc.* **1956**, *78*, 2518.

(54) Nace, H. R.; Nelander, D. H. *J. Org. Chem.* **1964**, *29*, 1677.

(55) Clarke, R. L. *J. Am. Chem. Soc.* **1960**, *82*, 4629.

(56) Barton, D. H. R.; Eastham, J. F. *J. Chem. Soc.* **1953**, 424.

(57) Grieco, P. A.; Nunes, J. J.; Gaul, M. D. *J. Am. Chem. Soc.* **1990**, *112*, 4595.

(58) Blokzijl, W.; Blandamer, M. J.; Engberts, J. B. F. N. *J. Am. Chem. Soc.* **1991**, *113*, 4241.

(59) Pindur, U.; Lutz, G.; Otto, C. *Chem. Rev.* **1993**, *93*, 741.

(60) Rideout, D. C.; Breslow, R. *J. Am. Chem. Soc.* **1980**, *102*, 7816.

(61) Grieco, P. A.; Garner, P.; He, Z.-m. *Tetrahedron Lett.* **1983**, *24*, 1897.

(62) Breslow, R.; Maitra, U.; Rideout, D. *Tetrahedron Lett.* **1983**, *24*, 1901.

(63) Grieco, P. A.; Yoshida, K.; Garner, P. *J. Org. Chem.* **1983**, *48*, 3137.

(64) Dauben, W. G.; Kozikowski, A. P. *J. Am. Chem. Soc.* **1974**, *96*, 3664.

(65) Van Eldik, R.; Asano, T.; Le Noble, W. J. *Chem. Rev.* **1989**, *89*, 549.

(66) Ballerini, E.; Minuti, L.; Piermatti, O. *J. Org. Chem.* **2010**, *75*, 4251.

(67) Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011.

(68) Shapiro, R. H.; Lipton, M. F.; Kolonko, K. J.; Buswell, R. L.; Capuano, L. A. *Tetrahedron Lett.* **1975**, *16*, 1811.

(69) Inanaga, J.; Sasaki, S.; Grieco, P. A.; Kim, H. *J. Am. Chem. Soc.* **1985**, *107*, 4800.

(70) Shing, T. K. M.; Zhu, X. Y.; Yeung, Y. Y. *Chem. Eur. J.* **2003**, *9*, 5489.

(71) Wilson, S. R.; Mao, D. T.; Jernberg, K. M.; Ezmirly, S. T. *Tetrahedron Lett.* **1977**, *18*, 2559.

(72) Cambie, R. C.; Hay, M. P.; Larsen, L.; Rickard, C. E. F.; Rutledge, P. S.; Woodgate, P. D. *Aust. J. Chem.* **1991**, *44*, 821.

(73) Polonsky, J.; Zylber, J. *Bull. Soc. Chim. Fr.* **1964**, *8*.

(74) Fiaschetti, G.; A. Grotzer, M.; Shalaby, T.; Castelletti, D.; Arcaro, A. *Curr. Med. Chem.* **2011**, *18*, 316.

(75) Bhatnagar, S. C.; Caruso, A. J.; Polonsky, J.; Rodriguez, B. S. *Tetrahedron* **1987**, *43*, 3471.

(76) Chan, K. L.; Lee, S.; Sam, T. W.; Han, B. H. *Phytochemistry* **1989**, *28*, 2857.

(77) Casinovi, C. G.; Ceccherelli, P.; Fardella, G.; Grandolini, G. *Phytochemistry* **1983**, *22*, 2871.

(78) Ham, E. A.; Schafer, H. M.; Denkewalter, R. G.; Brink, N. G. *J. Am. Chem. Soc.* **1954**, *76*, 6066.

(79) Joshi, B. C.; Pandey, A.; Prakash Sharma, R.; Khare, A. *Phytochemistry* **2003**, *62*, 579.

(80) Caruso, A. J.; Poplonsky, J.; Rodriguez, B. S. *Tetrahedron Lett.* **1982**, *23*, 2567.

(81) Muhammad, I.; Bedir, E.; Khan, S. I.; Tekwani, B. L.; Khan, I. A.; Takamatsu, S.; Pelletier, J.; Walker, L. A. *J. Nat. Prod.* **2004**, *67*, 772.

(82) Le Van, T.; Nguyen Ngoc, S. *J. Org. Chem.* **1970**, *35*, 1104.

(83) Aggarwal, V. K.; Daly, A. M. *Chem. Commun.* **2002**, 2490.

(84) Bradshaw, B.; Bonjoch, J. *Synlett* **2012**, *2012*, 337.

(85) Smith, A. B.; Mewshaw, R. *J. Org. Chem.* **1984**, *49*, 3685.

(86) Shishido, K.; Tokunaga, Y.; Omachi, N.; Hiroya, K.; Fukumoto, K.; Kametani, T. *J. Chem. Soc., Chem. Commun.* **1989**, 1093.

(87) Dzierba, C. D.; Zandi, K. S.; Möllers, T.; Shea, K. J. *J. Am. Chem. Soc.* **1996**, *118*, 4711.

(88) An, J.; Wiemer, D. F. *J. Org. Chem.* **1996**, *61*, 8775.

(89) Kende, A. S.; Deng, W.-P.; Zhong, M.; Guo, X.-C. *Org. Lett.* **2003**, *5*, 1785.

(90) Hanessian, S.; Boyer, N.; Reddy, G. J.; Deschênes-Simard, B. t. *Org. Lett.* **2009**, *11*, 4640.

(91) Böeseken, J.; Tellegen, F. *Recl. Trav. Chim. Pays-Bas* **1938**, *57*, 133.

(92) Entwistle, D. A.; Hughes, A. B.; Ley, S. V.; Visentin, G. *Tetrahedron Lett.* **1994**, *35*, 777.

(93) Ley, S. V.; Owen, D. R.; Wesson, K. E. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2805.

(94) Ley, S. V.; Priepke, H. W. M.; Warrine, S. L. *Angew. Chem., Int. Ed. Engl.***1994**, *33*, 2290.

(95) Ley, S. V.; Priepke, H. W. M. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2292.

(96) Ley, S. V.; Baeschlin, D. K.; Dixon, D. J.; Foster, A. C.; Ince, S. J.; Priepke, H. W. M.; Reynolds, D. J. *Chem. Rev.* **2000**, *101*, 53.

(97) Ley, S. V.; Woods, M.; A, Z.-G. *Synthesis* **1992**.

(98) Barros, M. T.; Maycock, C. D.; Ventura, M. R. *J. Chem. Soc., Perkin Trans. 1* **2001**, 166.

(99) Marchart, S.; Mulzer, J.; Enev, V. S. *Org. Lett.* **2007**, *9*, 813.

(100) Arthurs, C. L.; Wind, N. S.; Whitehead, R. C.; Stratford, I. J. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 553.

(101) Kee, A.; O'Brien, P.; Pilgram, C. D.; Watson, S. T. *Chem. Commun.* **2000**, 1521.

(102) Gebauer, O.; Brückner, R. *Liebigs Ann. Chem.* **1996**, *1996*, 1559.

(103) Cuthbertson, J. D.; Godfrey, A. A.; Taylor, R. J. K. *Org. Lett.* **2011**, *13*, 3976.

(104) Jacobsen, E. N.; Kakiuchi, F.; Konsler, R. G.; Larrow, J. F.; Tokunaga, M. *Tetrahedron Lett.* **1997**, *38*, 773.

(105) Klooster, v. *J. Chem. Educ.* **1959**, *36*, 314.

(106) Murray, L. M.; O'Brien, P.; Taylor, R. J. K.; Wünnemann, S. *Tetrahedron Lett.* **2004**, *45*, 2597.

(107) Schuster, H.; Martinez, R.; Bruss, H.; Antonchick, A. P.; Kaiser, M.; Schurmann, M.; Waldmann, H. *Chem. Commun.* **2011**, *47*, 6545.

(108) Costero, A. M.; Rodriguez, S. *Tetrahedron Lett.* **1992**, *33*, 623.

(109) Tan, Q.; Hayashi, M. *Org. Lett.* **2009**, *11*, 3314.

(110) Kissel, C. L.; Rickborn, B. *J. Org. Chem.* **1972**, *37*, 2060.

(111) Magnus, A.; Bertilsson, S. K.; Andersson, P. G. *Chem. Soc. Rev.* **2002**, *31*, 223.

(112) Morgan, K. M.; Gronert, S. *J. Org. Chem.* **2000**, *65*, 1461.

(113) Satoh, T. *Chem. Rev.* **1996**, *96*, 3303.

(114) O'Brien, P. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1439.

(115) Seki, A.; Asami, M. *Tetrahedron* **2002**, *58*, 4655.

(116) Whitesell, J. K.; Felman, S. W. *J. Org. Chem.* **1980**, *45*, 755.

(117) Thummel, R. P.; Rickborn, B. *J. Am. Chem. Soc.* **1970**, *92*, 2064.

(118) Burns, D. J.; Hachisu, S.; O'Brien, P.; Taylor, R. J. K. *Org. Biomol. Chem.***2012**, *10*, 7666.

(119) Barros, M. T.; Maycock, C. D.; Madureira, M. I.; Ventura, M. R. *Chem. Commun.* **2001**, 1662.

(120) Murray, L. M.; O'Brien, P.; Taylor, R. J. K. *Org. Lett.* **2003**, *5*, 1943.

(121) Shan, M.; O'Doherty, G. A. *Org. Lett.* **2008**, *10*, 3381.

(122) Altemöller, M.; Podlech, J. *Eur. J. Org. Chem.* **2009**, *2009*, 2275.

(123) Shih, T.-L.; Liang, M.-T.; Wu, K.-D.; Lin, C.-H. *Carbohydr. Res.* **2011**, *346*, 183.

(124) Krause, N. *Modern Organocopper Chemistry*; John Wiley & Sons, 2002.

(125) Taylor, R. J. K. *Organocopper Reagents: A Practical Approach*; Oxford University Press, USA, 1995.

(126) Perlmutter, P. *Conjugate addition reactions in organic synthesis*; Pergamon, 1992.

(127) Nakamura, E.; Mori, S. *Angew. Chem., Int. Ed.* **2000**, *39*, 3750.

(128) Snyder, J. P.; Tipsword, G. E.; Spangler, D. P. *J. Am. Chem. Soc.* **1992**, *114*, 1507.

(129) Snyder, J. P.; Spangler, D. P.; Behling, J. R.; Rossiter, B. E. *J. Org. Chem.* **1994**, *59*, 2665.

(130) Boehme, M.; Frenking, G.; Reetz, M. T. *Organometallics* **1994**, *13*, 4237.

(131) Stemmler, T. L.; Barnhart, T. M.; Penner-Hahn, J. E.; Tucker, C. E.; Knochel, P.; Boehme, M.; Frenking, G. *J. Am. Chem. Soc.* **1995**, *117*, 12489.

(132) Snyder, J. P.; Bertz, S. H. *J. Org. Chem.* **1995**, *60*, 4312.

(133) Bertz, S. H.; Vellekoop, A. S.; Smith, R. A. J.; Snyder, J. P. *Organometallics* **1995**, *14*, 1213.

(134) Lorenzen, N. P.; Weiss, E. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 300.

(135) Olmstead, M. M.; Power, P. P. *J. Am. Chem. Soc.* **1990**, *112*, 8008.

(136) John, M.; Auel, C.; Behrens, C.; Marsch, M.; Harms, K.; Bosold, F.; Gschwind, R. M.; Rajamohanan, P. R.; Boche, G. *Chem. Eur. J.* **2000**, *6*, 3060.

(137) Gschwind, R. M.; Rajamohanan, P. R.; John, M.; Boche, G. *Organometallics* **2000**, *19*, 2868.

(138) Xie, X.; Auel, C.; Henze, W.; Gschwind, R. M. *J. Am. Chem. Soc.* **2003**, *125*, 1595.

(139) Krauss, S. R.; Smith, S. G. *J. Am. Chem. Soc.* **1981**, *103*, 141.

(140) Canisius, J.; Gerold, A.; Krause, N. *Angew. Chem., Int. Ed.* **1999**, *38*, 1644.

(141) Henze, W.; Gärtner, T.; Gschwind, R. M. *J. Am. Chem. Soc.* **2008**, *130*, 13718.

(142) Hallnemo, G.; Olsson, T.; Ullenius, C. *J. Organomet. Chem.* **1985**, *282*, 133.

(143) Christenson, B.; Olsson, T.; Ullenius, C. *Tetrahedron* **1989**, *45*, 523.

(144) Eriksson, J.; Davidsson, Ö. *Organometallics* **2001**, *20*, 4763.

(145) Bertz, S. H.; Cope, S.; Murphy, M.; Ogle, C. A.; Taylor, B. J. *J. Am. Chem. Soc.* **2007**, *129*, 7208.

(146) Murphy, M. D.; Ogle, C. A.; Bertz, S. H. *Chem. Commun.* **2005**, 854.

(147) Bertz, S. H.; Hardin, R. A.; Murphy, M. D.; Ogle, C. A.; Richter, J. D.; Thomas, A. A. *J. Am. Chem. Soc.* **2012**, *134*, 9557.

(148) Posner, G. *Org. React.* **1972**, *19*, 1.

(149) Yamamoto, Y. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 947.

(150) Frantz, D. E.; Singleton, D. A.; Snyder, J. P. *J. Am. Chem. Soc.* **1997**, *119*, 3383.

(151) House, H. O. *Acc. Chem. Res.* **1976**, *9*, 59.

(152) House, H. O.; Umen, M. J. *J. Am. Chem. Soc.* **1972**, *94*, 5495.

(153) House, H. O.; Snoble, K. *J. Org. Chem.* **1976**, *41*, 3076.

(154) Hannah, D. J.; Smith, R. A. J. *Tetrahedron Lett.* **1975**, *16*, 187.

(155) Smith, R. A. J.; Hannah, D. J. *Tetrahedron* **1979**, *35*, 1183.

(156) Casey, C. P.; Boggs, R. A. *Tetrahedron Lett.* **1971**, *12*, 2455.

(157) Whitesides, G. M.; Kendall, P. E. *J. Org. Chem.* **1972**, *37*, 3718.

(158) Palais, L.; Alexakis, A. *Tetrahedron: Asymmetry* **2009**, *20*, 2866.

(159) Lipshutz, B. H.; Wilhelm, R. S.; Kozlowski, J. A. *Tetrahedron* **1984**, *40*, 5005.

(160) Lipshutz, B. H.; Parker, D. A.; Kozlowski, J. A.; Nguyen, S. L. *Tetrahedron Lett.* **1984**, *25*, 5959.

(161) Nakamura, E.; Yoshikai, N. *Bull. Chem. Soc. Jpn.* **2004**, *77*, 1.

(162) Gschwind, R. M.; Xie, X.; Rajamohanan, P. R.; Auel, C.; Boche, G. *J. Am. Chem. Soc.* **2001**, *123*, 7299.

(163) Henze, W.; Vyater, A.; Krause, N.; Gschwind, R. M. *J. Am. Chem. Soc.* **2005**, *127*, 17335.

(164) Nakamura, E.; Yamanaka, M.; Yoshikai, N.; Mori, S. *Angew. Chem., Int. Ed.* **2001**, *40*, 1935.

(165) Yamanaka, M.; Mori, S.; Nakamura, E. *Bull. Chem. Soc. Jpn.* **2002**, *75*, 1815.

(166) Christenson, B.; Ullenius, C.; H»kansson, M.; Jagner, S. *Tetrahedron* **1992**, *48*, 3623.

(167) Alexakis, A.; Sedrani, R.; Mangeney, P. *Tetrahedron Lett.* **1990**, *31*, 345.

(168) Fleming, I.; Barbero, A.; Walter, D. *Chem. Rev.* **1997**, *97*, 2063.

(169) Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1985**, *26*, 6015.

(170) Horiguchi, Y.; Komatsu, M.; Kuwajima, I. *Tetrahedron Lett.* **1989**, *30*, 7087.

(171) Lipshutz, B. H.; Dimock, S. H.; James, B. *J. Am. Chem. Soc.* **1993**, *115*, 9283.

(172) Bertz, S. H.; Miao, G.; Rossiter, B. E.; Snyder, J. P. *J. Am. Chem. Soc.* **1995**, *117*, 11023.

(173) Eriksson, M.; Johansson, A.; Nilsson, M.; Olsson, T. *J. Am. Chem. Soc.* **1996**, *118*, 10904.

(174) Frantz, D. E.; Singleton, D. A. *J. Am. Chem. Soc.* **2000**, *122*, 3288.

(175) Dirat, O.; Elliott, J. M.; Jelley, R. A.; Jones, A. B.; Reader, M. *Tetrahedron Lett.* **2006**, *47*, 1295.

(176) Büchel, K. H. *Methods of Organic Chemistry (Houben-Weyl)*; G. Thieme, 1997.

(177) Nogradi, M. *Stereoselective Synthesis: A Practical Approach*; Wiley, 2008.

(178) Trost, B. M.; Fleming, I. *Comprehensive Organic Synthesis: Selectivity, Strategy, and Efficiency in Modern Organic Chemistry*; Pergamon Press, 1991.

(179) Lightner, D. A.; Gurst, J. E. *Organic Conformational Analysis and Stereochemistry from Circular Dichroism Spectroscopy*; Wiley, 2000.

(180) Kharasch, M. S.; Kleiger, S. C.; Martin, J. A.; Mayo, F. R. *J. Am. Chem. Soc.* **1941**, *63*, 2305.

(181) Horiguchi, Y.; Matsuzawa, S.; Nakamura, E.; Kuwajima, I. *Tetrahedron Lett.* **1986**, *27*, 4025.

(182) Harutyunyan, S. R.; den Hartog, T.; Geurts, K.; Minnaard, A. J.; Feringa, B. L. *Chem. Rev.* **2008**, *108*, 2824.

(183) Clayden, J.; Greeves, N.; Warren, S.; Worthers, P. *Organic Chemistry*. Oxford University Press, 2001.

(184) Cieplak, A. S. *J. Am. Chem. Soc.* **1981**, *103*, 4540.

(185) Cieplak, A. S. *Chem. Rev.* **1999**, *99*, 1265.

(186) Arthurs, C. L.; Morris, G. A.; Piacenti, M.; Pritchard, R. G.; Stratford, I. J.; Tatic, T.; Whitehead, R. C.; Williams, K. F.; Wind, N. S. *Tetrahedron* **2010**, *66*, 9049.

(187) Takei, R.; Takahashi, K.; Matsuura, H.; Nabeta, K. *Biosci. Biotechnol. Biochem.* **2008**, *advpub*, 0807040957.

(188) Kitaoka, N.; Nabeta, K.; Matsuura, H. *Biosci. Biotechnol. Biochem.* **2009**, *advpub*, 0907061520.

(189) Crawforth, C. M.; Burling, S.; Fairlamb, I. J. S.; Taylor, R. J. K.; Whitwood, A. C. *Chem. Commun.* **2003**, 2194.

(190) Takei, R.; Takahashi, K.; Matsuura, H.; Nabeta, K. *Biosci. Biotechnol. Biochem.* **2008**, *72*, 2069.

(191) Christoffers, J.; Baro, A.; Ley, S. V. *Quaternary Stereocenters*; John Wiley & Sons, 2006.

(192) Hawner, C.; Alexakis, A. *Chem. Commun.* **2010**, *46*, 7295.

(193) Nakamura, E.; Mori, S.; Morokuma, K. *J. Am. Chem. Soc.* **1997**, *119*, 4900.

(194) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012.

(195) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413.

(196) Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2036.

(197) Burns, A. R.; McAllister, G. D.; Shanahan, S. E.; Taylor, R. J. K. *Angew. Chem., Int. Ed.* **2010**, *49*, 5574.

(198) Graham, A. E.; Taylor, R. J. K. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1087.

(199) Knapp, D. M.; Gillis, E. P.; Burke, M. D. *J. Am. Chem. Soc.* **2009**, *131*, 6961.

(200) Xu, S. L.; Xia, H.; Moore, H. W. *J. Org. Chem.* **1991**, *56*, 6094.

(201) Negishi, E.; Swanson, D. R.; Rousset, C. J. *J. Org. Chem.* **1990**, *55*, 5406.

(202) Hwang, J.-l.; Hong, Y.-T.; Kim, S. *Adv. Synth. Catal.* **2005**, *347*, 1513.

(203) Bal, S. A.; Marfat, A.; Helquist, P. *J. Org. Chem.* **1982**, *47*, 5045.

(204) Varseev, G. N.; Maier, M. E. *Org. Lett.* **2005**, *7*, 3881.

(205) Rahman, S. M. A.; Ohno, H.; Maezaki, N.; Iwata, C.; Tanaka, T. *Org. Lett.* **2000**, *2*, 2893.

(206) Hareau-Vittini, G.; Hikichi, S.; Sato, F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2099.

(207) Pappo, R.; Allen, J. D. S.; Lemieux, R. U.; Johnson, W. S. *J. Org. Chem.* **1956**, *21*, 478.

(208) Berkessel, A.; Gröger, H.; MacMillan, D. *Asymmetric Organocatalysis: From Biomimetic Concepts to Applications in Asymmetric Synthesis*; John Wiley & Sons, 2006.

(209) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615.

(210) Panday, S. K. *Tetrahedron: Asymmetry* **2011**, *22*, 1817.

(211) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471.

(212) Bahmanyar, S.; Houk, K. N. *J. Am. Chem. Soc.* **2001**, *123*, 12911.

(213) Chen, K.; Baran, P. S. *Nature* **2009**, *459*, 824.

(214) Schow, S. R.; Rossignol, D. P.; Lund, A. E.; Schnee, M. E. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 181.

(215) Snider, B. B.; Vo, N. H.; Foxman, B. M. *J. Org. Chem.* **1993**, *58*, 7228.

(216) Trost, B. M.; Fleming, I, *Additions to and Substitutions at C-C Bonds: 4*; Pergamon Press, 1991.

(217) Boga, C.; Savoia, D.; Umani-Ronchi, A. *Tetrahedron: Asymmetry* **1990**, *1*, 291.

(218) Lipshutz, B. H.; Ellsworth, E. L.; Siahaan, T. J. *J. Am. Chem. Soc.* **1988**, *110*, 4834.

(219) Danishefsky, S. J.; Masters, J. J.; Young, W. B.; Link, J. T.; Snyder, L. B.; Magee, T. V.; Jung, D. K.; Isaacs, R. C. A.; Bornmann, W. G.; Alaimo, C. A.; Coburn, C. A.; Di Grandi, M. J. *J. Am. Chem. Soc.* **1996**, *118*, 2843.

(220) Buchschacher, P.; Fürst, A.; Gutzwiller, J. *Org. Synth.* **1990**, *7*, 368.

(221) Reich, H. J.; Renga, J. M.; Reich, I. L. *J. Am. Chem. Soc.* **1975**, *97*, 5434.

(222) Dauben, W. G.; Michno, D. M. *J. Org. Chem.* **1977**, *42*, 682.

(223) Uyanik, M.; Ishihara, K.; Yamamoto, H. *Org. Lett.* **2006**, *8*, 5649.

(224) Orru, R. V. A.; Wijnberg, J. B. P. A.; de Groot, A. *J. Org. Chem.* **1995**, *60*, 4233.

(225) Mitsunobu, O.; Yamada, M. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 2380.

(226) Clayden, J. *Organolithium: Selectivity for Synthesis*; Elsevier Science & Tech, 2002.

(227) Wu, G.; Huang, M. *Chem. Rev.* **2006**, *106*, 2596.

(228) Beak, P.; Kerrick, S. T.; Wu, S.; Chu, J. *J. Am. Chem. Soc.* **1994**, *116*, 3231.

(229) Cisneros, A.; Fernández, S.; Hernández, J. E. *Synth. Commun.* **1982**, *12*, 833.

(230) House, H. O.; Berkowitz, W. F. *J. Org. Chem.* **1963**, *28*, 2271.

(231) Kovar, J.; Blaha, K. *Coll. Czech. Chem. Commun.* **1963**, *28*, 2199.

(232) Katritzky, A. R.; Meth-Cohn, O.; Ley, S. V.; Rees, C. W. *Synthesis: Carbon with One Heteroatom Attached by a Single Bond: Carbon with One Heteroatom Attached by a Single Bond*; Pergamon Press, 1995.

(233) Smith, M. B. *Organic Synthesis*; Elsevier Science, 2011.

(234) Woo, C. M.; Lu, L.; Gholap, S. L.; Smith, D. R.; Herzon, S. B. *J. Am. Chem. Soc.* **2010**, *132*, 2540.

(235) Izzo, I.; De Riccardis, F.; Massa, A.; Sodano, G. *Tetrahedron Lett.* **1996**, *37*, 4775.

(236) Babler, J. H.; Olsen, D. O.; Arnold, W. H. *J. Org. Chem.* **1974**, *39*, 1656.

(237) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395.

(238) Lim, C.; Baek, D. J.; Kim, D.; Youn, S. W.; Kim, S. *Org. Lett.* **2009**, *11*, 2583.

(239) Babler, J. H. *J. Org. Chem.* **1976**, *41*, 1262.

(240) Bakkestuen, A. K.; Gundersen, L.-L.; Petersen, D.; Utenova, B. T.; Vik, A. *Org. Biomol. Chem.***2005**, *3*, 1025.

(241) Lumin, S.; Falck, J. R.; Capdevila, J.; Karara, A. *Tetrahedron Lett.* **1992**, *33*, 2091.

(242) Myers, A. G.; Zheng, B. *Tetrahedron Lett.* **1996**, *37*, 4841.

(243) Kwon, Y.-U.; Chung, S.-K. *Org. Lett.* **2001**, *3*, 3013.

(244) Swamy, K. C. K.; Kumar, N. N. B.; Balaraman, E.; Kumar, K. V. P. P. *Chem. Rev.* **2009**, *109*, 2551.

(245) Nemoto, T.; Ohshima, T.; Yamaguchi, K.; Shibasaki, M. *J. Am. Chem. Soc.* **2001**, *123*, 2725.

(246) Corey, E. J.; Zhang, F.-Y. *Org. Lett.* **1999**, *1*, 1287.

(247) Marigo, M.; Franzén, J.; Poulsen, T. B.; Zhuang, W.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 6964.

(248) Yadav, V. K.; Kapoor, K. K. *Tetrahedron* **1995**, *51*, 8573.

(249) Knight, S. D.; Overman, L. E.; Pairaudeau, G. *J. Am. Chem. Soc.* **1993**, *115*, 9293.

(250) Shenvi, R. A.; Guerrero, C. A.; Shi, J.; Li, C.-C.; Baran, P. S. *J. Am. Chem. Soc.* **2008**, *130*, 7241.

(251) Shing, T. K. M.; Zhu, X. Y.; Mak, T. C. W. *Tetrahedron: Asymmetry* **1996**, *7*, 673.

(252) Grieco, P. A.; Ohfune, Y.; Majetich, G. F.; Wang, C. L. J. *J. Am. Chem. Soc.* **1982**, *104*, 4233.

(253) Miyashita, M.; Suzuki, T.; Yoshikoshi, A. *Tetrahedron Lett.* **1987**, *28*, 4293.

(254) Quesada, E.; Stockley, M.; Taylor, R. J. K. *Tetrahedron Lett.* **2004**, *45*, 4877.

(255) Rodeschini, V.; Boiteau, J.-G.; Van de Weghe, P.; Tarnus, C.; Eustache, J. *J. Org. Chem.* **2003**, *69*, 357.

(256) Nicolaou, K. C.; Sasmal, P. K.; Roecker, A. J.; Sun, X.-W.; Mandal, S.; Converso, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 3443.

(257) Jankowska, R.; Liu, H.-J.; L. Mhehe, G. *Chem. Commun.* **1999**, 1581.

(258) Lei, X.; Zaarur, N.; Sherman, M. Y.; Porco, J. A. *J. Org. Chem.* **2005**, *70*, 6474.

(259) Su, S.; Acquilano, D. E.; Arumugasamy, J.; Beeler, A. B.; Eastwood, E. L.; Giguere, J. R.; Lan, P.; Lei, X.; Min, G. K.; Yeager, A. R.; Zhou, Y.; Panek, J. S.; Snyder, J. K.; Schaus, S. E.; Porco, J. A. *Org. Lett.* **2005**, *7*, 2751.

(260) Bull, J. R.; Lachmann, H. H. *Tetrahedron Lett.* **1973**, *14*, 3055.

(261) Szajewski, R. P. *J. Org. Chem.* **1978**, *43*, 1819.

(262) Bell, R. P. L.; Sobolev, A.; Wijnberg, J. B. P. A.; de Groot, A. *J. Org. Chem.* **1998**, *63*, 122.

(263) Payne, G. B. *J. Org. Chem.* **1962**, *27*, 3819.

(264) Li, J. J. *Name Reactions: A Collection of Detailed Reaction Mechanisms and Synthetic Applications*; Springer-Verlag Berlin Heidelberg, 2009.

(265) Nowrouzi, F.; Janetzko, J.; Batey, R. A. *Org. Lett.* **2010**, *12*, 5490.

(266) Mubarak, A.; Fraser-Reid, B. *J. Org. Chem.* **1982**, *47*, 4265.

(267) Caputo, R.; Mangoni, L.; Neri, O.; Palumbo, G. *Tetrahedron Lett.* **1981**, *22*, 3551.

(268) Li, M.; Yu, B. *Org. Lett.* **2006**, *8*, 2679.

(269) Li, Y.; Feng, J.-P.; Wang, W.-H.; Chen, J.; Cao, X.-P. *J. Org. Chem.* **2007**, *72*, 2344.

(270) Cane, D. E.; Yang, G.; Coates, R. M.; Pyun, H. J.; Hohn, T. M. *J. Org. Chem.* **1992**, *57*, 3454.

(271) Gurudutt, K. N.; Ravindranath, B. *Tetrahedron Lett.* **1980**, *21*, 1173.

(272) Fernández-Mateos, A.; de la Nava, E. M.; Coca, G. P.; Silvo, A. R.; González, R. R. *Org. Lett.* **1999**, *1*, 607.

(273) Poigny, S.; Guyot, M.; Samadi, M. *J. Org. Chem.* **1998**, *63*, 5890.

(274) Rubottom, G. M.; Vazquez, M. A.; Pelegrina, D. R. *Tetrahedron Lett.* **1974**, *15*, 4319.

(275) Ziegler, F. E.; Hwang, K. J.; Kadow, J. F.; Klein, S. I.; Pati, U. K.; Wang, T. F. *J. Org. Chem.* **1986**, *51*, 4573.

(276) Wharton, P.; Bohlen, D. *J. Org. Chem.* **1961**, *26*, 3615.

(277) Weitz, E.; Scheffer, A. *Chem. Ber.* **1921**, *54*, 2327.

(278) Ling, T.; Rivas, F.; Theodorakis, E. A. *Tetrahedron Lett.* **2002**, *43*, 9019.

(279) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307.

(280) Kocieński, P. J. *Protecting Groups*; Georg Thieme, 2005.

(281) Zhang, J.; Xu, X. *Tetrahedron Lett.* **1998**, *39*, 6525.

(282) David Crouch, R. *Tetrahedron* **2004**, *60*, 5833.

(283) Karimi, B.; Zamani, A.; Zareyee, D. *Tetrahedron Lett.* **2004**, *45*, 9139.

(284) Hunter, R.; Hinz, W.; Richards, P. *Tetrahedron Lett.* **1999**, *40*, 3643.

(285) Kishore Kumar, G. D.; Baskaran, S. *J. Org. Chem.* **2005**, *70*, 4520.

(286) Kusama, H.; Hara, R.; Kawahara, S.; Nishimori, T.; Kashima, H.; Nakamura, N.; Morihira, K.; Kuwajima, I. *J. Am. Chem. Soc.* **2000**, *122*, 3811.

(287) Paquette, L. A.; Hartung, R. E.; Hofferberth, J. E.; Vilotijevic, I.; Yang, J. *J. Org. Chem.* **2004**, *69*, 2454.

(288) Moriarty, R. M.; Vaid, R. K.; Hopkins, T. E.; Vaid, B. K.; Prakash†, O. *Tetrahedron Lett.* **1990**, *31*, 201.

(289) Uyanik, M.; Yasui, T.; Ishihara, K. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3848.

(290) Merritt, E. A.; Olofsson, B. *Synthesis* **2011**, *2011*, 517.

(291) Aponick, A.; Biannic, B. *Org. Lett.* **2011**, *13*, 1330.

(292) Ghebreghiorgis, T.; Biannic, B.; Kirk, B. H.; Ess, D. H.; Aponick, A. *J. Am. Chem. Soc.* **2012**, *134*, 16307.

(293) Unsworth, W. P.; Stevens, K.; Lamont, S. G.; Robertson, J. *Chem. Commun.* **2011**, *47*, 7659.

(294) Aponick, A.; Li, C.-Y.; Biannic, B. *Org. Lett.* **2008**, *10*, 669.

(295) Lin, C.-C.; Teng, T.-M.; Odedra, A.; Liu, R.-S. *J. Am. Chem. Soc.* **2007**, *129*, 3798.

(296) Denmark, S. E.; Heemstra, J. R. *J. Org. Chem.* **2007**, *72*, 5668.

(297) Barbero, A.; Pulido, F. J. *Synthesis* **2004**, *2004*, 401.

(298) Ward, D. E.; Shen, J. *Org. Lett.* **2007**, *9*, 2843.

(299) Ahmed, Z.; Langer, P. *Tetrahedron Lett.* **2006**, *47*, 417.

(300) Büttner, S.; Kelzhanova, N. K.; Abilov, Z. A.; Villinger, A.; Langer, P. *Tetrahedron* **2012**, *68*, 3654.

(301) Jung, M. E.; Ho, D.; Chu, H. V. *Org. Lett.* **2005**, *7*, 1649.

(302) Inoue, T.; Oritani, T. *Biosci. Biotechnol. Biochem.* **2000**, *64*, 1071.

(303) Chen, D.; Wang, J.; Totah, N. I. *J. Org. Chem.* **1999**, *64*, 1776.

(304) Seth, P. P.; Chen, D.; Wang, J.; Gao, X.; Totah, N. I. *Tetrahedron* **2000**, *56*, 10185.

(305) Huang, Y.; Feng, X.; Wang, B.; Zhang, G.; Jiang, Y. *Synlett* **2002**, *2002*, 2122.

(306) Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, *20*, 399.

(307) Burchat, A. F.; Chong, J. M.; Nielsen, N. *J. Organomet. Chem.* **1997**, *542*, 281.

(308) Alves, C.; Barros, M. T.; Maycock, C. D.; Ventura, M. R. *Tetrahedron* **1999**, *55*, 8443.

(309) Jiang, L.; Martinelli, J. R.; Burke, S. D. *J. Org. Chem.* **2002**, *68*, 1150.

(310) Koreeda, M.; Yoshihara, M. *J. Chem. Soc., Chem. Commun.* **1981**, 974.

(311) Kitaoka, N.; Nabeta, K.; Matsuura, H. *Biosci. Biotechnol. Biochem.* **2009**, *73*, 1890.

(312) Mori, K.; Katoh, T.; Suzuki, T.; Noji, T.; Yamanaka, M.; Akiyama, T. *Angew. Chem., Int. Ed.* **2009**, *48*, 9652.

(313) Lo, L.-C.; Shie, J.-J.; Chou, T.-C. *J. Org. Chem.* **2001**, *67*, 282.

(314) Ducrot, P.-H.; Hervier, A.-C.; Lallemand, J.-Y. *Synth. Commun.* **1996**, *26*, 4447.

(315) Curini, M.; Epifano, F.; Genovese, S. *Tetrahedron Lett.* **2006**, *47*, 4697.